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Do Reaction Conditions Affect the Stereoselectivity in the Staudinger Reaction?

Yikai Wang, Yong Liang, Lei Jiao, Da-Ming Du, and Jiaxi Xu*

Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, People's Republic of China

jxxu@pku.edu.cn

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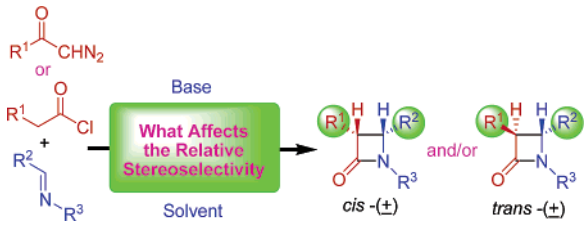

The stereochemistry is one of the critical issues in the Staudinger reaction. We have proposed the origin of the stereoselectivity recently. The effects of solvents, additives, and pathways of ketene generation on the stereoselectivity were investigated by using a clean Staudinger reaction, which is a sensitive reaction system to the stereoselectivity. The results indicate that the additives, usually existed and generated in the Staudinger reaction, and the pathways of the ketene generation do not generally affect the stereoselectivity. The solvent affects the stereoselectivity. The polar solvent is favorable to the formation of trans-β-lactams. The addition orders of the reagents affect the stereoselectivity in the Staudinger reaction between acyl chlorides and imines. The addition of a tertiary amine into a solution of the acyl chloride and the imine generally decreases the stereoselectivity, which is affected by the interval between additions of the acyl chloride and the tertiary amine, and the imine substituents. Our current results provide further understanding on the stereochemistry of the Staudinger reaction between acyl chlorides and imines and on the factors affecting the stereochemistry and also provide a method to prepare β-lactams with the desired relative configuration via rationally tuning the stereoselectivity-controlling factors in the Staudinger reaction.

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 synthetic and pharmaceutical fields.[2−4] The reaction of a ketene with an imine usually produces two new stereocenters (C_3 and C_4 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 has been considered as one of the critical issues in the Staudinger reaction.[5] Much attention has been paid to the experimental[6] and theoretical[7] investigations into the stereoselectivity of the β-lactam formation in the Staudinger

* Corresponding author. Phone: +86-10-6275-1497. Fax: +86-10-6275-1708.

(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. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Curr. Med. Chem.* **2004**, *11*, 1837−1879.

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reaction during the past decades. Recently, we have proposed a model that successfully explains and predicts the relative stereoselectivity in the Staudinger reaction on the basis of a kinetic analysis of the cis/trans ratio of reaction products.[8]

In the Staudinger reaction, ketenes are generated in situ mainly via three ways: (1) the elimination of acyl chlorides or related derivatives in the presence of a base,[6a,b,9] (2) the photolysis of metal−carbene complexes,[6k,10] and (3) the Wolff rearrangement of α-diazocarbonyl compounds under thermal, photo, or microwave irradiation conditions.[8,11] Thus, reaction conditions,[5] such as temperature,[8] solvent,[7e,12a] base,[12b] the chloride anion,[6c,6k,7e] and the metal[6k,7f] may affect the stereochemical outcomes. Moreover, Arrieta et al.[7e] pointed out that the different stereoselectivites of the Staudinger reaction depended on the methods used in the generation of the active species on the basis of their computational investigations and predicted that when the ketene was formed before the cycloaddition, the β-lactam product was predominantly cis, while when the imine reacted directly with the acyl chloride, the subsequent intramolecular S_N2 displacement determined the final trans selectivity. Thus, the addition order of reagents could also obviously affect the stereochemical outcomes in the Staudinger reaction between acyl chlorides and imines. To understand the influence of the reaction conditions on the stereoselectivity better, a comprehensive comparison of the "origin" ketene−imine reaction[13] and the "modified" ketene−imine reaction, especially the most widely used Staudinger reaction between acyl chlorides and imines, is required. Fortunately, we have found a clean ketene−imine reaction system,[8] which provides an efficient and sensitive platform to study the influence of the reaction conditions on the stereoselectivity. Herein, we present our experimental results and hope to provide a deeper understanding of the stereoselectivity in the Staudinger reaction, especially the Staudinger reaction involving acyl chlorides and imines.

Results and Discussion

Influence of Solvents on the Stereoselectivity in the Staudinger Reaction. The Staudinger reaction is a stepwise reaction involving the nucleophilic attack of an imine to a ketene giving rise to a zwitterionic intermediate and a subsequent ring closure of the zwitterionic intermediate producing the β-lactam product.[5] When the direct ring closure of the zwitterionic intermediate is fast enough, the final β-lactam product is cis, while when the direct ring closure is not so fast, the isomerization of the imine moiety in the zwitterionic intermediate occurs to form a sterically more favorable intermediate, which produces the final trans-β-lactam product. The relative (cis/trans) 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.[8] The competition is mainly controlled by the electronic effect of the substituents of ketenes and imines and the steric hindrance of the N-substituent of imines.[8] However, solvents possibly affect the stability and half-life of the zwitterionic intermediate, resulting in the change of the stereoselectivity. Arrieta et al. concluded previously that the polarity of the solvent enhanced the diastereomeric excess of the Staudinger reaction according to their computational results.[7e]

In our previous work, the reaction of *S*-phenyl 2-diazoethanethioate (**1**) with a series of *N*-isopropyl imines **2a**−**f** in toluene at 80 °C was well studied.[8] This clean reaction is a quite efficient and sensitive to the stereoselectivity, which could produce β-lactam products from predominately trans to mainly cis isomers depending on the electronic effect of the imine substituents. To investigate the influence of solvents on the stereoselectivity, we conducted these reactions at 80 °C in different solvents (Table 1, entries 1−7). It is notable that the cis/trans[14] ratios of products correlate well with the Hammett constants[15] (σ) (Table 1, entries 1−7, and Figure 1). Moreover, it is found that increasing the polarity of the solvent does not enhance the stereoselectivity. For instance, the stereoselectivities

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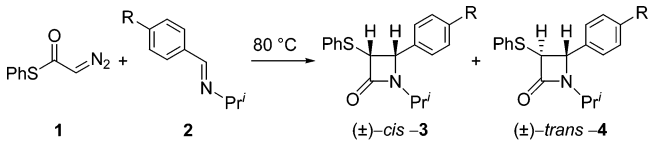
TABLE 1. Influence of Solvents and Additives on the Stereoselectivity in the Staudinger Reaction



a: R=MeO, **b**: R=Me, **c**: R=H, **d**: R=Cl, **e**: R=CF_3, **f**: R=NO_2

			cis/trans[a]							
entry	solvent	additive	**3a**:**4a**	**3b**:**4b**	**3c**:**4c**	**3d**:**4d**	**3e**:**4e**	**3f**:**4f**	ρ	R^2
1	toluene		4:96	7:93	12:88	17:83	42:58	73:27	1.62	0.98
2	MeCN		3:97	7:93	11:89	15:85	40:60	71:29	1.66	0.97
3	cyclohexane		2:98	6:94	10:90	26:74	55:45	84:16	2.13	0.99
4	*n*-octane		5:95	9:91	12:88	22:78	49:51	82:18	1.72	0.98
5	$ClCH_2CH_2Cl$		2:98	4:96	8:92	13:87	36:64	74:26	1.87	0.98
6	$(CH_3OCH_2)_2$		4:96	7:93	13:87	18:82	39:61	72:28	1.56	0.97
7	*o*-$C_6H_4Cl_2$		2:98	5:95	10:90	16:84	41:59	75:25	1.83	0.97
8	toluene	Et_3N·HCl	4:96	6:94	11:89	18:82	46:54	74:26	1.71	0.99
9	toluene	TEBA	6:94	7:93	12:88	18:82	48:52	70:30	1.50	0.98
10	toluene	$(C_4H_9)_4N^+Br^-$	4:96	8:92	18:82	20:80	40:60	67:33	1.46	0.95
11	toluene	Et_3N	3:97	5:95	8:92	12:88	40:60	76:24	1.84	0.97
12	toluene	pyridine	3:97	7:93	10:90	16:84	40:60	72:28	1.67	0.97
13	toluene	$Cr(CO)_6$	3:97	7:93	10:90	17:83	43:57	79:21	1.84	0.97

[a] Determined by ^{1}H NMR of the crude reaction mixture.

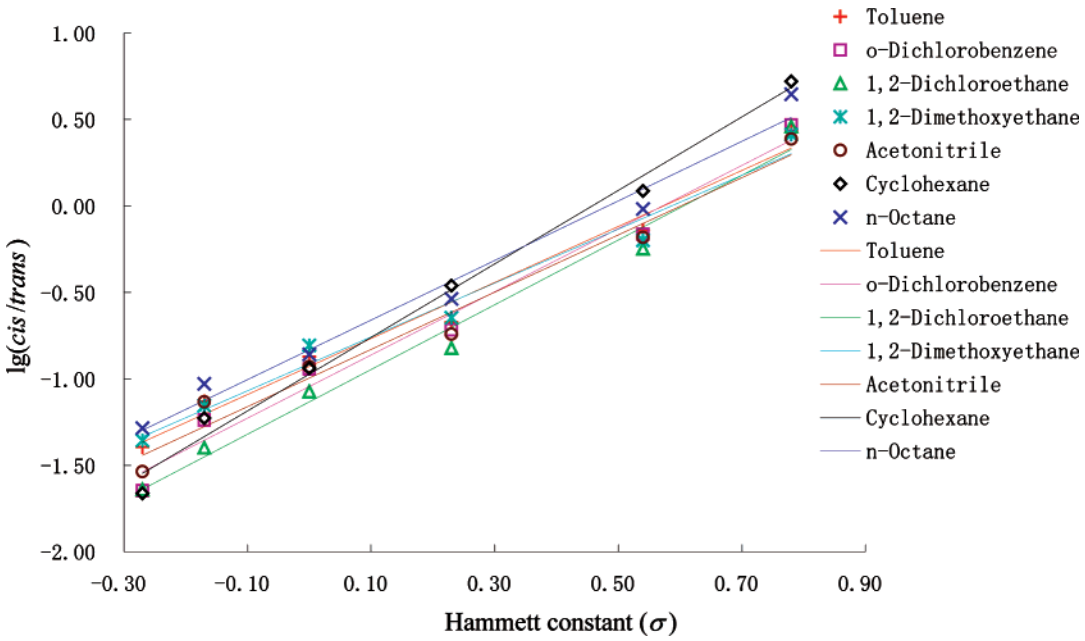


FIGURE 1. Influence of solvents on the stereoselectivity in the Staudinger reaction.

in acetonitrile (the typical polar solvent, Table 1, entry 2) are almost the same as those in toluene in each of the cases. However, oppositely, the amounts of cis-β-lactam products increase in the nonpolar solvents (cyclohexane and *n*-octane, Table 1, entries 3 and 4). These results indicate that the nonpolar solvents cannot stabilize the zwitterionic intermediates, facilitating the direct ring closure to form cis products, while the polar solvents can stabilize the zwitterionic intermediates and increase their half-life, increasing the isomerization of the imine moiety to generate trans products. It is quite different from the previous computational results[7e] that the polarity of the solvent enhanced the cis selectivity (diastereomeric excess) in the ketene−imine reaction. On the basis of our experimental results, the computational results of Arrieta et al. are incompletely correct.[7e] The incompletely correct computational results were obtained possibly because the computational model systems were too simplified, and although the cis transition structures in the formation of β-lactam are more polar than their trans congeners on the basis of calculation, the energy difference between these two types of transition structures is possibly not a major factor in the solvent effect on the stereoselectivity. The real influence of solvents on the stereoselectivity is that the polar solvent is generally favorable to increase the formation of trans-β-lactam

(14) 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 to ~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 the ^{1}H NMR spectra of crude reaction mixtures.

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

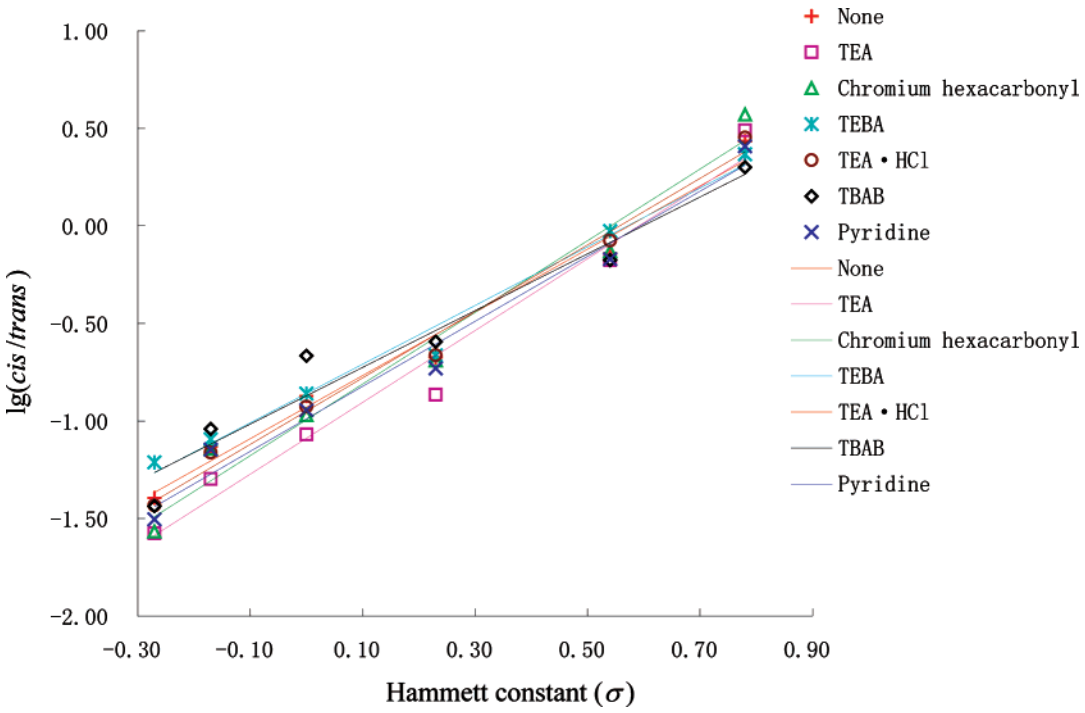


FIGURE 2. Influence of additives on the stereoselectivity in the Staudinger reaction.

products. That is, for the Staudinger reactions with trans-β-lactams as major products, the polarity of the solvent enhances their diastereomeric excesses, while for the Staudinger reactions with cis-β-lactams as major products, the polarity of the solvent decreases their diastereomeric excesses.

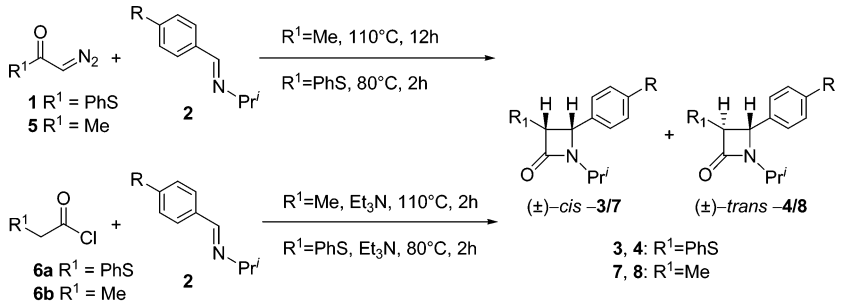
Influence of Additives on the Stereoselectivity in the Staudinger Reaction. For the Staudinger reaction involving ketenes generated via the elimination of acyl chlorides or related derivatives in the presence of a base,[6a,b,9] and via the photolysis of metal−carbene complexes,[6k,10] there are some additives (nucleophiles, such as chloride anion and tertiary amines, and electrophilic metal carbonyl complexes) that may affect the cis/trans ratio of the β-lactam products,[5,6c,6k,7e,f,12b] in the reaction system.

To investigate the influence of additives on the stereoselectivity, we also chose the reactions of **1** with **2a**−**f** in toluene at 80 °C as standard reactions, and then conducted the same reactions in the presence of different additives, which usually exist in the "modified" ketene−imine reaction (Table 1, entries 8−13). It is found that the cis/trans ratios of products also correlate well with the Hammett constants (σ) (Table 1, entries 8−13, and Figure 2), and the stereoselectivities in the presence of additives are almost the same as those in the standard reactions. This indicates that, when the active species in the Staudinger reaction are ketenes, the usually existed additives in the reaction system do not affect the stereoselectivity obviously.

Influence of the Pathways of the Ketene Generations on the Stereoselectivity in the Staudinger Reaction. Because the elimination of acyl chlorides and the Wolff rearrangement of α-diazo carbonyl compounds are two major methods to generate ketenes, to study the formation pathways of ketenes on the stereoselectivity in the Staudinger reaction, we conducted two series of Staudinger reactions in which the ketenes were generated either via the thermal Wolff rearrangement of α-diazo carbonyl compounds [*S*-phenyl 2-diazoethanethioate (**1**) and 1-diazoacetone (**5**)] or via the elimination of acyl chlorides [phenylthioacetyl chloride (**6a**) and propionyl chloride (**6b**)], respectively (Table 2, entries 1, 2, 5, and 6, and Figure 3). For the elimination of acyl chlorides, a solution of an acyl chloride was added into a solution of an imine and triethylamine (named as the addition mode A). The cis/trans ratios of products also correlate well with the Hammett constants (σ) (Table 2 and Figure 3). The results indicate that in the addition mode A (Table 2, entries 2 and 6), their stereoselectivities are similar with those of the corresponding standard ketene−imine reactions (Table 2, entries 1 and 5). The formation pathways of ketenes do not really affect the stereoselectivity obviously in most cases. This further confirms the conclusion of Lynch et al.:[6j] when the acyl chloride is added over a solution of the imine and a tertiary amine, the formation of the corresponding ketene occurs prior to the cycloaddition. Meanwhile, this confirms our conclusion again:[8] when the active species in the Staudinger reaction are ketenes, the stereoselectivity is mainly determined by the electronic effect of the ketene and imine substituents and the steric hindrance of the N-substituents of imines.

Influence of Addition Modes on the Stereoselectivity in the Staudinger Reaction. In the literature,[6] there are usually two different addition modes in the Staudinger reaction between acyl chlorides and imines: (1) the acyl chloride is added dropwise over a solution of the imine and a tertiary amine (the addition mode A) and (2) the tertiary amine is added dropwise over a mixture of the imine and the acyl chloride (named as the addition mode B). The different addition orders of the reagents affect the stereoselectivity because of the different reaction processes.[5,6] According to a calculation investigation,[7e] it was concluded that in the addition mode A, the cis-β-lactam was the major or exclusive stereoisomer due to the formation of the ketene prior to the cycloaddition, while in the addition mode B, the trans-β-lactam was the major or exclusive stereoisomer, because the imine reacted directly with the acyl chloride

TABLE 2. Influence of the Pathways of the Ketene Generations and Addition Modes on the Stereoselectivity in the Staudinger Reaction



a: R=MeO, **b**: R=Me, **c**: R=H, **d**: R=Cl, **e**: R=CF_3, **f**: R=NO_2

entry	ketene precursor	reaction temperature (°C)	addition mode[a]	*cis*-**3**/*trans*-**4** or *cis*-**7**/*trans*-**8**[b]						ρ	R^2
				a	**b**	**c**	**d**	**e**	**f**		
1	**1**	80		4:96	7:93	12:88	17:83	42:58	73:27	1.62	0.98
2	**6a**	80	A	7:93	10:90	14:86	20:80	48:52	81:19	1.57	0.96
3	**6a**	80	B	8:92	19:81	18:82	21:79	51:49	81:19		
4	**6a**	80	C	21:79	32:68	32:68	38:62	41:59	58:42		
5	**5**	110		1:99	3:97	6:94	6:94	13:87	29:71	1.22	0.91
6	**6b**	110	A	2:98	2:98	5:95	6:94	19:81	40:60	1.40	0.97
7	**6b**	110	B	6:94	8:92	5:95	4:96	19:81	41:59		

[a] A: A solution of acyl chloride in toluene was added into a solution of an imine and triethylamine in toluene. B: A solution of triethylamine in toluene was added into a solution of an imine and acyl chloride in toluene immediately. C: A solution of triethylamine in toluene was added after the solution of an imine and acyl chloride in toluene was stirred for 4 h at 80 °C. [b] Determined by ^{1}H NMR of the crude reaction mixture.

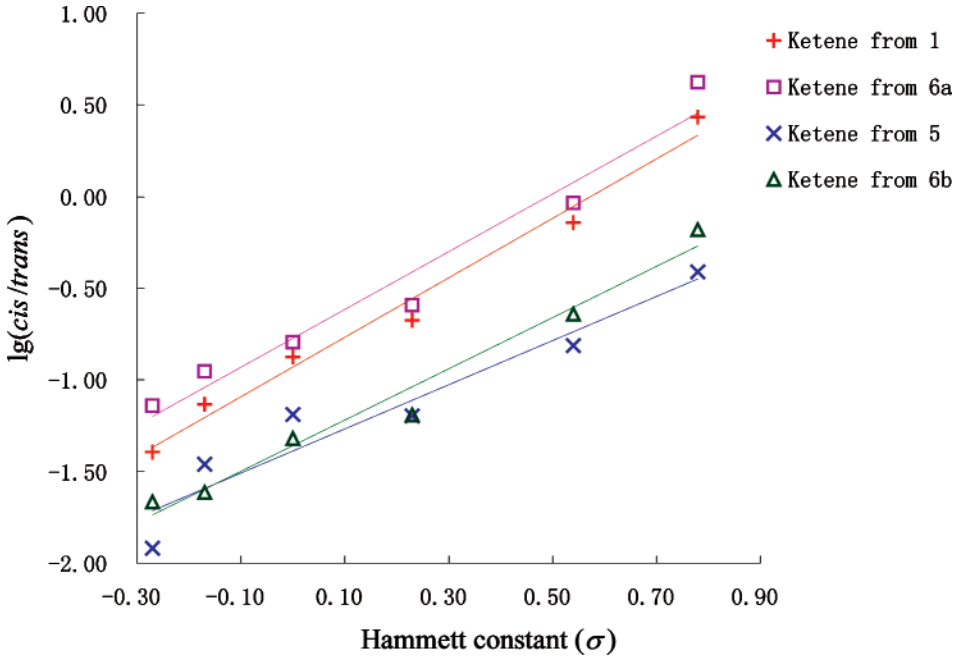
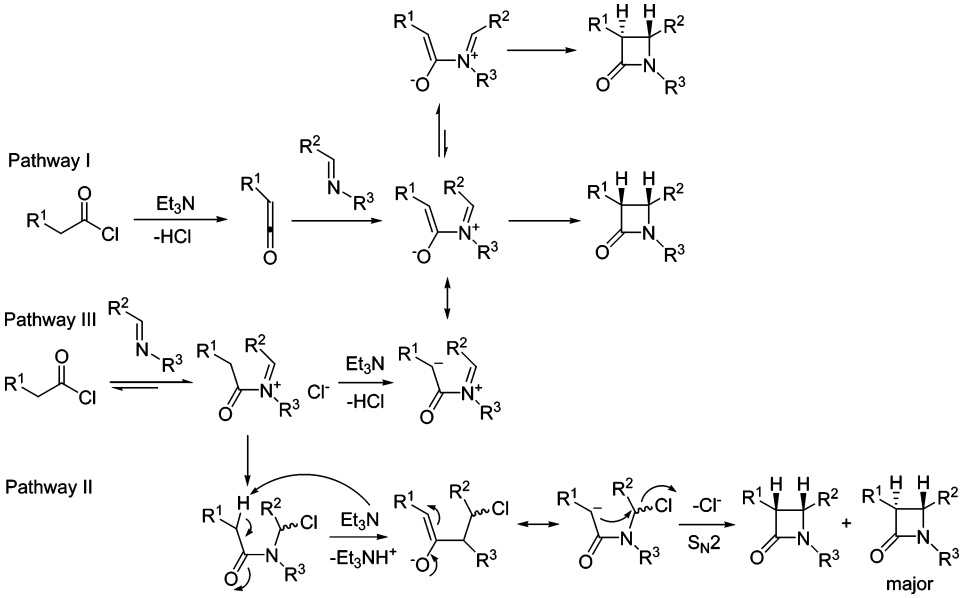


FIGURE 3. Influence of the pathways of the ketene generations on the stereoselectivity in the Staudinger reaction.

to give rise to a chloro amide, and the subsequent intramolecular S_N2 displacement determined the final trans selectivity.

To further investigate the influence of the addition modes on the stereoselectivity in the Staudinger reaction, we conducted two series of reactions involving various imines **2a**−**f** and phenylthioacetyl chloride (**6a**) via the addition modes A and B, respectively (Table 2, entries 2 and 3). The results indicate that the stereoselectivities in the reactions involving imines **2b**,**c** with **6a** in the addition mode B are different from those in the addition mode A. It seems that the electronic effect of the substituents in imines **2b**−**d** has no relationship with the cis/trans ratios of the products (the cis/trans ratios are nearly the same, all about 20:80). But for imines **2a** and **2f**, the stereoselectivities in the addition mode B are still consistent with those in the addition mode A, respectively. So it can be concluded that the chloro amide reaction pathway possibly occurs in the addition mode B for the reactions of imines **2b**−**d**. However, for the reaction of **6a** and **2a** with the strong electron-donating group *p*-MeO, the electron-rich group increases the nucleophilicity of the imine to the ketene but decreases the possibility of the nucleophilic addition of the chloride anion to the imine moiety in the formed acyl iminium chloride. After the addition of triethylamine the acyl iminium chloride could directly undergo a hydrogen abstraction to give rise to the zwitterionic intermediate, which further produces the β-lactam. For reactions of **6a** and **2e**−**f** with the strong electron-withdrawing groups

SCHEME 1. Three Different Possible Pathways in the Reaction between Acyl Chlorides and Imines with Triethylamine



(CF_3 and NO_2), the electron-withdrawing groups decrease the nucleophilicity of the imines to ketene to generate acyl iminium chlorides incompletely. When triethylamine is added, acyl chloride **6a** undergoes an elimination of hydrogen chloride to produce phenylthioketene directly. Thus, the ketene−imine cycloaddition is a major pathway in these cases. This is the reason that imines **2a** and **2e**,**f** show similar stereoselectivities in the addition modes A and B.

To observe the chloro amide reaction pathway obviously, we conducted another series of reactions, in which a solution of the acyl chloride and the imine in toluene was first stirred for 4 h and then triethylamine was added (named as the addition mode C). The stereoselectivities in the addition mode C (Table 2, entry 4) are quite different from those in the addition modes A and B. For the reactions of phenylthioacetyl chloride (**6a**) with imines **2** in the addition mode C, all reactions give similar stereoselectivities although they show obviously different stereoselectivities in both addition modes A and B. This indicates that in the addition mode C the imines **2** react directly with phenylthioacetyl chloride (**6a**) first to give rise to the corresponding chloro amides, the subsequent intramolecular S_N2 displacement of the chloro amides in the presence of triethylamine determines the stereochemical outcomes. Because all imines **2** have similar structural features, the chloro amides with similar structural features give similar stereoselectivities in the intramolecular S_N2 displacement.

On the basis of previous investigations[6] and our experimental results, we can conclude that there are three different possible pathways, which compete with each other, in reactions between acyl chlorides and imines with triethylamine (Scheme 1). In pathway I the acyl chloride first reacts with triethylamine to generate the ketene, and then the ketene reacts with the imine to form a zwitterionic intermediate, which undergoes a direct ring closure to produce a cis-β-lactam or an isomerization of its imine moiety and a subsequent ring closure to yield a trans-β-lactam. The ratio of cis/trans is mainly dominated by the electronic effects of the ketene and imine substituents and the steric hindrance of the imine N-substituent. In pathway II the acyl chloride reacts directly with the imine to form an acyl iminium chloride. The chlorine anion attacks the acyl iminium to afford a chloro amide, which could undergo a hydrogen abstraction to give rise to a carbanion after addition of triethylamine. The carbanion undergoes an intramolecular S_N2 displacement to generate the β-lactam. The ratio of cis/trans is predominantly controlled by the steric hindrance during the S_N2 displacement. In pathway III the acyl iminium formed as in pathway II directly undergoes a hydrogen abstraction after addition of triethylamine to give rise to the zwitterionic intermediate, which produces the β-lactam as in pathway I.

For the addition mode A, pathway I is a major process because the reactions in the addition mode A show almost the same stereoselectivity as the corresponding reactions involving the ketenes generated from α-diazo carbonyl compounds (Table 2, entries 1, 2, 5, and 6). For the addition mode B, pathway I is still a major process. But pathway II occurs in some cases. However, for imines with strong electron-donating or electron-withdrawing groups pathway II hardly occurs. For the addition mode C, the stereoselectivities become lower and incline to the same value in most cases, which indicates that pathway II is a major process and the chloro amides predominately form after stirring for 4 h in the absence of triethylamine. However, for the imines with electron-withdrawing groups, they hardly react with the acyl chloride to generate the acyl iminium chlorides completely. After addition of triethylamine, the unreacted acyl chlorides produce the ketenes directly. Thus, pathway I is also an important process. For the imines with strong electron-donating C-substituents, their acyl iminiums could not be attacked by the chlorine anion to afford the chloro amides. Pathway III may be a major process.

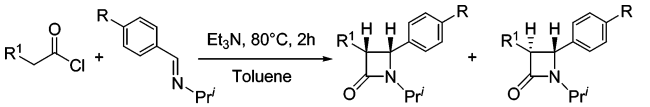
To identify whether the lower and similar stereoselectivities come from base-promoted equilibrium between the cis- and trans-β-lactams in the addition mode C, separated pure cis-β-lactams **11c** and **11f** were stirred in toluene in the presence of triethylamine at 80 °C for 6 h. No epimerization was observed on ^{1}H NMR analysis of the crude reaction mixtures. It is in good agreement with the reported results that cis-β-lactams cannot epimerize in the presence of triethylamine.[6i]

Chloro amides generated from chloro- and cyanoacetyl chlorides with imines could produce β-lactams in the presence of triethylamine.[6a,b,e] However, Lynch et al. found that a

β-trialkylsilyloxy-substituted chloro alkanamide cannot yield a β-lactam in the presence of triethylamine.[6j] On the basis of detailed studies via low-temperature FT-IR, they concluded that the formation of β-lactams proceeded entirely through ketene intermediates.[6j] According to these reported results,[6a,b,e,j] it seems that the reactions of alkanoic acid chlorides with imines cannot undergo chloro amide pathway to give rise to β-lactams. To further confirm this assumption, we conducted two series of reactions involving imines **2a**−**f** and propionyl chloride (**6b**) via the addition modes A and B, respectively. The results indicate that the stereoselectivities have no obvious change in the addition modes A and B (Table 2, entries 6 and 7). We also conducted the reaction in the addition mode C. However, the reaction became messy. It is difficult to determine the cis/trans ratio accurately because of low yields of β-lactams. This indicates that the reactions hardly undergo chloro amide pathway to yield β-lactams, which is in good accordance with reported result.[6j] It is possibly due to the weak acidity of the α-hydrogen in chloro alkanamides. Reviewing the above results, we can conclude that the chloro amides with a strong acidic α-hydrogen can undergo an intramolecular S_N2 displacement to yield β-lactams in the presence of triethylamine, while the chloro amides with a weak acidic α-hydrogen cannot generally. Thus, the reactions of aliphatic carboxylic chlorides and imines undergo only ketene and/or acyl iminium chloride intermediates to yield β-lactams in the presence of triethylamine because the α-hydrogen in acyl chlorides and acyl iminiums shows stronger acidic character than that in chloro amides due to strong electron-withdrawing chlorine and iminium groups attached to the carbonyl group in acyl chlorides and acyliminiums.

Influence of the Addition Modes on the Stereoselectivity in the Staudinger Reaction for Different Acyl Chlorides and Imines. Because different ketenes affect the stereoselectivity in the Staudinger reaction,[8] the different acyl chlorides should affect the stereoselectivity in the Staudinger reaction in different addition modes. We have found that the two different addition orders of reagents in the reaction between acyl chlorides and imines could even result in different products.[9g] To investigate the generality, we conducted a series of reactions in which the representative acyl chlorides and imines were selected and used via different addition modes of reagents. To study the influence of the chloro amide pathway in the addition mode B, we also conducted a series of experiments in the addition mode C. The results are compiled in Table 3. The results indicate that low stereoselectivities were obtained in the addition mode C in most cases and trans-β-lactam products increase generally from the addition mode A to C. This provides a route to prepare the trans-β-lactams as the desired products for the reactions, which yield the cis-β-lactams as major products in the addition mode A.

TABLE 3. Influence of the Addition Modes on the Stereoselectivity in the Staudinger Reaction for Different Acyl Chlorides and Imines



2a: R=MeO, **2c**: R=H, **2f**: R=NO_2 (±)–*cis* – **9,11,13,15** (±)–*trans* – **10,12,14,16**

6c: R^1=Ph, **9, 10**: R^1=Ph,
6d: R^1=PhO, **11, 12**: R^1=PhO,
6e: R^1=PhthN, **13, 14**: R^1=PhthN,
6f: R^1=Cl **15, 16**: R^1=Cl

entry	R	addition mode[a]	cis/trans[b] **9**:**10**	**11**:**12**	**13**:**14**	**15**:**16**
1	MeO	A	35:65	90:10	84:16[c]	57:43
2	MeO	B	22:78	81:19	79:21	46:54
3	MeO	C[d]	14:86	49:51	54:46	36:64
4	H	A	55:45	97:3	87:13	71:29
5	H	B	54:46	98:2	88:12	72:28
6	H	C[d]	42:58	53:47	53:47	54:46
7	NO_2	A	85:15	>99:1	>99:1	87:13
8	NO_2	B	83:17	>99:1	98:2	87:13
9	NO_2	C[d]	67:33	67:33	55:45	52:48

[a] A: A solution of acyl chloride in toluene was added into a solution of an imine and triethylamine in toluene. B: A solution of triethylamine in toluene was added into a solution of an imine and acyl chloride in toluene immediately. C: A solution of triethylamine in toluene was added after the solution of an imine and acyl chloride in toluene was stirred for 4 h at 80 °C. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Ref 16. [d] β-Lactam products were obtained in relatively low yields compared to those in the addition modes A and B. *N*-Isopropyl amide and (substituted) benzaldehydes were also obtained in low yields from the hydrolysis of *N*-acyl iminium chlorides during workup as reported previously (ref 17).

Conclusion

In summary, the effects of solvents, additives, pathways of the ketene generation, and the addition orders of an acyl chloride and triethylamine on the stereoselectivity were investigated systematically. The results indicate that nonpolar solvents are favorable to the formation of cis-β-lactams, while polar solvents are favorable to the formation of trans-β-lactams. The additives and the pathways of the ketene generation do not affect the stereoselectivity obviously. The addition order of the reagents affects the stereoselectivity in the Staudinger reaction between acyl chlorides and imines. For the reactions involving addition of a tertiary amine into a solution of an acyl and an imine, the interval between additions of the acyl chloride and the tertiary amine into the solution really influences the stereoselectivity, which is also affected by the imine substituents because the reaction between the acyl chloride and the imine with the tertiary amine could undergo three different pathways to produce β-lactams.

For the "origin" Staudinger reaction, we can tune its stereoselectivity via changing the reaction conditions such as solvent and temperature.[8] For the Staudinger reactions between acyl chlorides and imines, we can tune its stereoselectivity via changing the addition order of the reagents. Generally, addition of a tertiary amine to a stirred solution of an imine and an acyl chloride increases the proportion of trans-β-lactam and decreases the stereoselectivity. In this addition mode the yields of the minor isomer of β-lactams could increase compared to those of other addition modes. We hope that our current results could provide some useful information to understand the stereochemistry of the Staudinger reaction between acyl chlorides and imines and the factors affecting the stereochemistry and also provide some useful information to use the Staudinger reaction to prepare β-lactams with the desired relative configuration via rationally tuning the stereoselectivity-controlling factors.

Experimental Section

General Procedure for the Reactions of α-Diazo Carbonyl Compounds 1 or 5 with Imines 2. A flame-dried round-bottom flask was charged with a solution of imine (0.15 mmol) in 1 mL of dry toluene. A solution of α-diazo carbonyl compound **1** or **5** (0.195 mmol) in 0.5 mL of dry toluene was then added via a syringe. The flask was immersed in an oil-bath, preheated to the desired temperature, and stirred for 2 h at the same temperature (80 °C for 2 h for compound **1** and 110 °C for 12 h for compound **5**). After

removal of the solvent, the residue was directly submitted to NMR analysis to determine the cis/trans ratio of β-lactams. Column chromatography of the crude mixture on silica gel afforded the corresponding cis- and/or trans-β-lactam products.

General Procedure (Mode A) for the Reactions of Acyl Chlorides 6 with Imines 2. A flame-dried round-bottom flask was charged with a solution of imine (0.15 mmol) and triethylamine (20 mg, 0.195 mmol) in 1 mL of dry toluene. The flask was immersed in an oil-bath preheated to the desired temperature. A solution of the desired acyl chloride (0.195 mmol) in 0.5 mL of dry toluene was then added through a syringe during 2 min. 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 β-lactams. Column chromatography of the crude mixture on silica gel afforded the corresponding cis- and/or trans-β-lactam products.

General Procedure (Mode B) for the Reactions of Acyl Chlorides 6 with Imines 2. A flame-dried round-bottom flask was charged with a solution of imine (0.15 mmol) and the desired acyl chloride (0.195 mmol) in 1 mL of dry toluene. The flask was immersed in an oil-bath preheated to the desired temperature. A solution of triethylamine (20 mg, 0.195 mmol) in 0.5 mL of dry toluene was then added dropwise through a syringe in less than 2 min. 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 β-lactams. Column chromatography of the crude mixture on silica gel afforded the corresponding cis- and/or trans-β-lactam products.

General Procedure (Mode C) for the Reactions of Acyl Chlorides 6 with Imines 2. A flame-dried round-bottom flask was charged with a solution of imine (0.15 mmol) and the desired acyl chloride (0.195 mmol) in 1 mL of dry toluene. The flask was immersed in an oil-bath preheated to the desired temperature. After the solution was stirred for 4 h at the same temperature, a solution of triethylamine (20 mg, 0.195 mmol) in 0.5 mL of dry toluene was then added dropwise through 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 β-lactams. Column chromatography of the crude mixture on silica gel afforded the corresponding cis- and trans-β-lactam products.

(±)-*cis*-1-Isopropyl-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (11f). Colorless crystals, mp 156−157 °C. IR (KBr) ν (cm^{-1}): 1745 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (d, J = 6.6 Hz, 3H), 1.32 (d, J = 6.6 Hz, 3H), 3.92 (heptet, J = 6.6 Hz, 1H), 5.07 (d, J = 4.1 Hz, 1H), 5.42 (d, J = 4.1 Hz, 1H), 6.69−7.15 (m, 5H), 7.59 (d, J = 8.6 Hz, 2H), 8.15 (d, J = 8.6 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.3, 21.3, 45.4, 60.1, 80.9, 115.2, 122.3, 123.3, 129.3, 129.5, 142.3, 148.0, 156.4, 165.0. MS (EI) m/z (rel intensity, %): 326 (M^+, 0.4), 241 (100), 194(13), 165(13), 105-(22), 94(12), 77(28). Anal. Calcd for $C_{18}H_{18}N_2O_4$ (326.35): C, 66.25; H, 5.56; N, 8.58. Found: C, 65.93; H, 5.69; N, 8.31.

(±)-*trans*-1-Isopropyl-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (12f). Colorless crystals, mp 105−106.5 °C. IR (KBr) ν (cm^{-1}): 1766 (C═O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (d, J = 6.6 Hz, 3H), 1.34 (d, J = 6.6 Hz, 3H), 3.83 (heptet, J = 6.6 Hz, 1H), 4.67 (d, J = 1.5 Hz, 1H), 4.95 (d, J = 1.5 Hz, 1H), 6.74−7.27 (m, 5H), 7.59−7.63 (m, 2H), 8.29−8.34 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.2, 21.2, 45.6, 61.7, 86.6, 115.2, 122.4, 124.4, 127.8, 129.6, 144.8, 148.3, 156.8, 164.9. MS (ESI) m/z: 349 ($M + Na^+$). Anal. Calcd for $C_{18}H_{18}N_2O_4$ (326.35): C, 66.25; H, 5.56; N, 8.58. Found: C, 65.96; H, 5.56; N, 8.58.

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Supporting Information Available: Analytic data and copies of ^{1}H NMR and ^{13}C NMR spectra of all unknown β-lactam products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The ratio of **13a**:**14a** here shows some difference from our previous datum in ref 8. The reason is not clear until now. The datum reported herein was confirmed several times. We were concerned that the amount of triethylamine affected the ratio and conducted a series of experiments with different equivalents of triethylamine. When the molar ratio of R^1CH_2COCl **6e** to imine **2a** was 1.3:1.0, ratios of **13a**:**14a** were obtained in 80:20, 84:16, 85:15, 84:16, and 78:22, respectively, in the presence of 1.0, 1.3, 1.5, 2.0, and 2.6 equiv of triethylamine. On the basis of the above results, the amount of triethylamine does not affect the ratio of products obviously.

(17) Jiao, L.; Liang, Y.; Wu, C. Z.; Huang, X.; Xu, J. X. *Chem. Res. Chin. Univ.* **2005**, *21*, 59−64.