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1-(2,6-Dichlorophenyl)ethylamine: a New and Efficient Chiral Auxiliary for the Staudinger β-Lactam Synthesis

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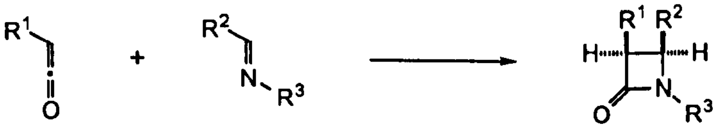
Abstract: The diastereoselective synthesis of β-lactams by the Staudinger reaction was examined using chiral imines, derived from substituted 1-phenylethylamines. Among them, 1-(2,6-dichlorophenyl)ethylamine was found to be a new and efficient chiral auxiliary, and the corresponding *cis*-β-lactams were obtained in good to excellent yields with high diastereoselectivity.

β-Lactams are precursors of biologically and clinically important antibiotics such as penicillins and thienamycins, and a number of accounts and articles have been published.[1] The asymmetric synthesis of β-lactam ring systems is worthwhile objective, and the Staudinger reaction is the most extensively developed method (Scheme 1).



Scheme 1

In recent years, we have been designing and resolving new types of artificial chiral auxiliaries,[2,3] and found that optically pure *erythro*-2-amino-1,2-diphenylethanol (ADPE) showed effective asymmetric induction in several organic reactions.[3] The Staudinger reaction was also tried using a chiral imine, derived from optically pure ADPE and aldehydes. However, since the attempt resulted in a low diastereoselectivity, we focused on the utilization of other artificial chiral compounds. Usually, the asymmetric Staudinger reaction, controlled by a chiral *N*-substituent on imines (R^3), is difficult to achieve high diastereoselectivity, because of the relatively long distance between the chiral auxiliary and the reaction centers, and only a few particular examples of high stereoselection have been reported.[4] Recently, Georg and Wu have reported a β-lactam synthesis using *N*-(1-naphthylethyl)imines.[5] However, the method was also poor in generality; high diastereoselectivity was observed only for restricted imine substrates. Here, we would like to describe the widely applicable and highly diastereoselective Staudinger reaction using a simple 1-phenylethylamine derivative as a chiral auxiliary on imines.

At first, in order to find out a suitable chiral auxiliary, imines **1** were prepared from 1-arylethylamine derivatives[6] and benzaldehyde. The Staudinger reaction of **1** with phenoxyketene was performed under usual conditions (CH_2Cl_2, 0 °C). The results are summarized in Table 1. As can be seen from Table 1, the reaction with an imine, derived from 1-phenyl- or 1-(1-naphthyl)ethylamine, gave a mixture of *cis*-β-lactams **3** and **4** with almost no diastereoselectivity (entries 1 and 2). However, upon introducing a substituent at the *ortho*-position of the phenyl group of 1-phenylethylamine, the diastereoselectivity was slightly improved (entries 3-8).

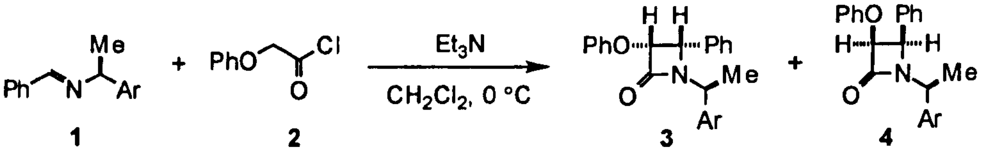


Table 1. The Asymmetric Staudinger Reaction Using 1-Arylethylamines as Chiral Auxiliaries

entry	Ar	time / h	yield / %	3 : 4 [a]
1	Ph	3.0	83	58 : 42
2	1-Naphthyl	3.0	86	59 : 41
3	2-MeC$_6$H$_4$	4.0	92	65 : 35
4	2-PhC$_6$H$_4$	4.0	87	62 : 38
5	2-MeOC$_6$H$_4$	6.0	97	68 : 32
6	2-FC$_6$H$_4$	8.0	83	60 : 40
7	2-ClC$_6$H$_4$	6.5	87	71 : 29
8	2-BrC$_6$H$_4$	4.0	91	63 : 37
9	2,6-Cl$_2$C$_6$H$_3$	3.0	94	83 : 17

[a] Determined by HPLC.

Among the *ortho*-substituted 1-phenylethylamines, *ortho*-chloro derivative gave the best result (entry 7). On the basis of these results, we employed 1-(2,6-dichlorophenyl)ethylamine[7] as a chiral auxiliary (entry 9) to achieve the highest diastereoselectivity. The stereochemical assignment of the diastereomers for each reaction was made by HPLC and/or NMR comparison with those obtained by the reaction of entry 9; the relative configuration of major product **3** (Ar=2,6-Cl$_2$C$_6$H$_3$) was determined by X-ray crystallography [8]

In order to rationalize the dramatic inprovement of stereoselectivity by introducing chlorine substituents, we calculated transition states for the reaction of imine **1** (Ar=Ph, 2,6-Cl$_2$C$_6$H$_3$) with phenoxyketene based on the semi-empirical MO calculational method reported by Cossio *et al.*[9] In the case of the non-substituted derivative (Ar=Ph), free energy difference ($\Delta\Delta G^{\ddagger}$) between two diastereomeric transition states was 0.13 kcal·mol^{-1} at 273 K, which corresponds to a diastereoselectivity of 56 : 44. On the other hand, the calculation for the dichloro-substituted derivative (Ar=2,6-Cl$_2$C$_6$H$_3$) resulted in $\Delta\Delta G^{\ddagger} = 0.66$ kcal·mol^{-1} at 273 K to give a diastereoselectivity of 77 : 23. These results are in good agreement with the observed values (Table 1) The

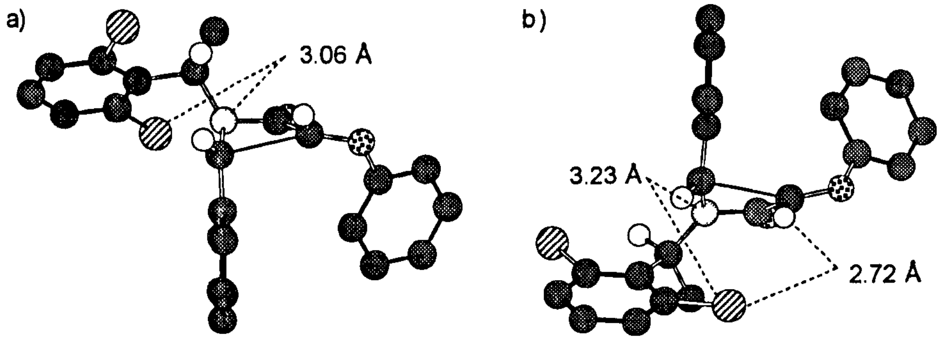


Figure 1. Calculated transition state structures for the Staudinger reaction of **1** (Ar=2,6-Cl$_2$C$_6$H$_3$) with phenoxyketene leading to a) the major product and b) the minor product.

larger energy deference between the dichloro-substituted transition states would be explained by an electrostatic attractive interaction between the chlorine and the partially positive charged nitrogen (distance: 3.06 Å)[9b] in the transition state leading to the major product (Fig. 1a). In the transition state of higher energy (Fig. 1b), this effect was suppressed (distance: 3.23 Å) due to a steric repulsion between the ketene hydrogen and the chlorine (distance: 2.72 Å).

Next, the effects of solvent and temperature were examined using imine 1 ($Ar=2,6\text{-}Cl_2C_6H_3$). The effects were not so large as that of the substituent on the nitrogen of the imine, although the reaction in a non-polar solvent, such as toluene or hexane, provided somewhat higher stereoselectivity but in lower chemical yield. From the viewpoints of chemical yield, diastereoselectivity, and suppression of the concomitant formation of by-products, we chose propionitrile as a solvent and carried out reactions at 0 °C.

Under the optimized reaction conditions, various β-lactams were synthesized using imines **5** having 1-(2,6-dichlorophenyl)ethyl group on the nitrogen. The results are shown in Table 2 In each case, a [2+2] cyclization reaction proceeded smoothly to give the corresponding mixture of *cis*-β-lactams **6** and **7**, and no *trans*-isomer was detected as reported for the usual Staudinger reaction. The good yield and high diastereoselectivity were maintained, even when an electron-donating or withdrawing group was introduced on the aromatic ring of the aldehyde moiety (entries 2 and 3). As well as aromatic imines, olefinic and aliphatic imines having no α-proton also gave satisfactory results (entries 4 and 5). Thus, the present method was found to have wide applicability in the Staudinger reaction.

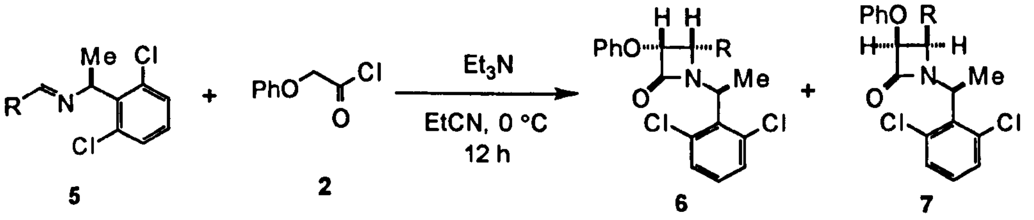


Table 2. The Asymmetric Staudinger Reaction of *N*-[1-(2,6-Dichlorophenyl)ethyl]imines

entry	R	yield / %	6 : 7[a]
1	Ph	89	85 : 15
2	4-$MeOC_6H_4$	76	88 : 12
3	4-ClC_6H_4	83	85 : 15
4	PhCH=CH	60	88 : 12
5	^{t}Bu	56	91 : 9

[a] Determined by HPLC.

A representative procedure of the Staudinger reaction giving a mixture of β-lactam **6** and **7** (R=Ph) is as follows. To a mixture of triethylamine (0.42 mmol) and imine **5** (R=Ph) (0.30 mmol) in propionitrile (3 mL) was added dropwise a solution of phenoxyacetyl chloride (**2**) (0.36 mmol) in propionitrile (2 mL) under argon at 0 °C, and the reaction mixture was stirred for 3 h at the same temperature. After being quenched with water (*ca.* 5 mL), the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4. After removal of the solvent, the resulting crude product was purified by PTLC on silica gel (15% AcOEt/hexane) to give a mixture of two diastereomers of β-lactam **6** and **7** (R=Ph) in 89% yield. Each β-lactam had *cis*-configuration on the lactam ring, and no *trans*-isomer was detected. The diastereomer ratio was determined to be 85.15 by HPLC.

In conclusion, we developed a new artificial chiral auxiliary, 1-(2,6-dichlorophenyl)ethylamine, which was effective in the Staudinger reaction with high stereoselectivity and high yield. The method would provide a useful route for the synthesis of optically active *β*-lactams.

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6. Although racemic 1-arylethylamines were used throughout the investigation, the optically pure amines were highly anticipated to give the same results according to the reaction mechanism. Deprotective method of the 1-arylethyl group from *β*-lactams was well established. See, for example, Hattori, K., Yamamoto, H *Synlett*, **1993**, 239. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.*, **1985**, *26*, 3783

7 Polniaszek, R. P.; Licht, C. F. *Synth. Commun.* **1992**, *22*,171. By their method, optically active 1-(2,6-dichlorophenyl)ethylamine could be prepared, but the operations were somewhat laborious. We also developed a new route to synthesize racemic 1-(2,6-dichlorophenyl)ethylamine from 2,6-dichlorobenzaldehyde with a high conversion on a large scale [(i) MeMgBr, (ii) HBr, (iii) NaN_3, (iv) $LiAlH_4$], and the optical resolution of the racemic product is now under investigation.

8 Crystal data for **3** (Ar=2,6-$Cl_2C_6H_3$): $C_{23}H_{19}Cl_2NO_2$, *Mw*=412.31, monoclinic, space group $P2_1/c$, *a*=18.513(4) Å, *b*=6.701(1) Å, *c*=18.204(3) Å, *β*=116 06(1)°, *V*=2028.6(7) Å^3, *Z*=4, *Dc*=1.35 gcm^{-3}, *R*=0.071, *Rw*=0 071, reflections used=2249

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