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An Investigation of (*R*)-(+)-1-(1-Naphthyl)ethylimines and (*R*)-(+)-1-(Phenyl)ethylimines as Chiral Templates in the Staudinger Reaction

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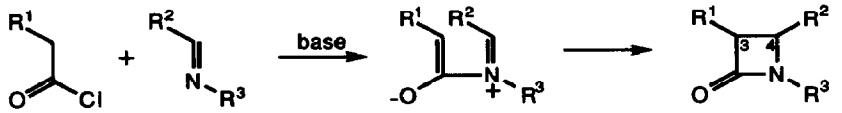
Abstract: *(R)-(+)-1-(1-Naphthyl)ethylimines were found to be moderately better chiral templates in the Staudinger reaction in comparison to (R)-(+)-1-(phenyl)ethylimines. The best diastereoselectivities and yields were obtained with (R)-(+)-1-(1-naphthyl)ethylimines when toluene was used as the solvent. The resulting diastereomeric cis β-lactams were separated by silica gel flash column chromatography or recrystallization.*

Impressive progress has been made in recent years with regard to the asymmetric synthesis of β-lactams.[1,2] In particular, the asymmetric version of the Staudinger reaction has been explored extensively and successfully.[3,4] Broadly speaking, the annulation of a carboxylic acid chloride in the presence of base (formation of a ketene) and an imine is referred to as the Staudinger reaction. Asymmetric induction has been achieved by placing chiral auxiliaries at the acid chloride (R^1), the acid chloride carbonyl (iminium salts), and the imine (R^2 and R^3 in **Scheme 1**).[1]

Scheme 1



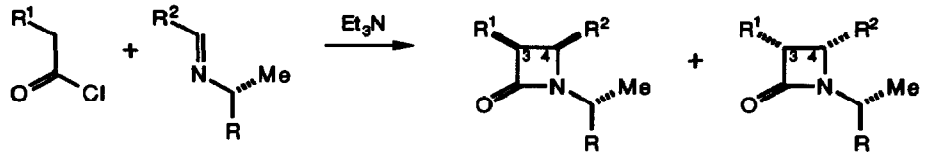
The best stereochemical results were achieved when the chiral auxiliary was attached at the acid chloride (R^1) or at the imine carbon (R^2).[3] With few exceptions[3,5] stereocontrol was poor when the chiral auxiliary was located at the imine nitrogen (R^3). This is presumably due to the relatively large distance between the nitrogen substituents and the carbon-carbon bond forming reaction centers of the zwitterionic intermediate (**Scheme 1**). Placing the chiral auxiliary at the imine nitrogen provides the best flexibility with regard to the introduction of various substituents at the β-lactam ring system (positions 3 and 4). Therefore, it is of continuing interest to find chiral auxiliaries which would facilitate high stereocontrol in the Staudinger reaction and which could be removed in one step from the β-lactam nitrogen. *N*-Unsubstituted β-lactams (R^3=H) are important building blocks for the synthesis of β-lactam antibiotics[1,2] and useful chiral building blocks for β-amino acids.[6]

Our studies in this area were prompted by a report from Aszodi *et al.* who disclosed that reaction between the ketene derived from phthalimidoacetyl chloride and the imine, obtained from chloroacetaldehyde and 1-(phenyl)ethylamine, gave a 90:10 ratio of diastereomeric cis β-lactams.[7] We therefore reasoned that the sterically more demanding 1-(1-naphthyl)ethylimines would provide even better diastereocontrol in the Staudinger reaction.

Imines **2** and **3** were synthesized from various aldehydes and (*R*)-(+)-1-(1-naphthyl)ethylamine and (+)-1-

(phenyl)ethylamine respectively.[8] The crude reaction products were typically used without purification in the Staudinger reaction. Initially we investigated (**Scheme 2**) the reaction of phenoxyacetyl chloride **1a** (R^1 = PhO) with naphthylethylimine **2a** (R=1-naphthyl, R^2 = styryl) in the presence of triethylamine and dichloromethane as the solvent (**Table I**, entry 1). Dichloromethane is often the solvent of choice for the Staudinger reaction.[3] The two diastereomeric cis products **4a** and **5a** (R^1 = PhO, R^2 = styryl) were obtained in a ratio of 75:25 and in 56% yield. The exclusive formation of cis products was expected because a Bose-Evans ketene and a *C*-ethenyl-*N*-alkyl imine was used in the Staudinger reaction.[3] Since the diastereomeric product distribution in the Staudinger reaction is dependent on solvent effects, we investigated the influence of solvents on the diastereoselectivity of the reaction (**Table I**). Reaction in chloroform provided an improved diastereomeric ratio of 85:15, but only 14% yield. The chemical yield was improved to 60% with ten equivalents of the acid chloride. Utilizing carbon tetrachloride as the solvent (entry 3, **Table I**) provided the same diastereomeric ratio as the reaction dichloromethane but gave a better yield. Good diastereoselectivities (83:17) and chemical yields (71%) were observed in benzene and toluene (entries 4 and 5, **Table I**).[9] The best chemical yield (90%) but low diastereoselectivity (60:40 ratio) was obtained in dimethylformamide (entry 7, **Table I**).

Scheme 2



1a R^1 = PhO
1b R^1 = Phth

2 R = 1-naphthyl
3 R = phenyl

4

5

Table I. Effect of different solvents on the formation of diastereomeric β-lactams **4a** and **5a** (R^1 = PhO, R^2 = styryl, R = 1-naphthyl) from phenoxyacetyl chloride (**1a**) and imine **2a** (R=1-napthyl, R^2=styryl)

entry	solvent	ratio of 4a:5a	yield (%)
1	dichloromethane	75:15	56
2	chloroform	85:15	14 (60)
3	carbon tetrachloride	75:25	77
4	benzene	83:17	72
5	toluene	83:17	71
6	nitrobenzene	67:33	69
7	dimethylformamide	60:40	90
8	cyclohexane	70:30	55

β-Lactams **4a** and **5a** (R=1-naphthyl, R^1=PhO, R^2=styryl) can be separated either by silica gel column chromatography or by recrystallization. The absolute stereochemistry of the reaction products **4a** and **5a** was determined by comparison with (1'*R*,3*S*,4*R*)-*N*-[1'-(1-naphthyl)ethyl]-3-phenoxy-4-chlorophenyl-2-azetidinone **4i** for which the absolute stereochemistry had been determined by single crystal X-ray analysis.[10,11] Since the diastereomeric product distribution in the Staudinger reaction is also influenced by substituent effects, we investigated a variety of different acid chlorides and imines (**Table II**), utilizing toluene as the solvent. Reaction between phthalimidoacetyl chloride (**1b**, R^1=phthalimindo) and imine **2a** (entry 2, **Table II**) gave a similar product distribution (85:15 ratio of **4b** and **5b**) as observed with phenoxyacetyl chloride (**1a**) and imine **2a** (entry

1, **Table II**). A decrease in diastereoselectivity was observed when the styryl group (entry 1, **Table II**) of imine **2a** was replaced by a phenyl group (imine **2b**, entry 3, **Table II**). The introduction of a 4-nitrophenyl group (imine **2c**) in place of a phenyl group reversed the diastereomeric ratio of **4** and **5**. Isomer **5d** (R=1-naphthyl, R^1=PhO, R^2=4-NO_2Ph) was now found to be the major product (entry 4, **Table II**).

Table II. Influence of different substituents on the diastereoselectivity of the Staudinger reaction with (*R*)-(+)-1-(1-naphthyl)ethylimines **2** and toluene as the solvent

entry	imine	β-lactams **4** and **5**	R^1	R^2	ratio of **4**:**5**	yield (%)
1	**2a**	**4a**, **5a**	PhO	styryl	83:17	71
2	**2a**	**4b**, **5b**	Phth	styryl	85:15	71
3	**2b**	**4c**, **5c**	PhO	Ph	70:30	10
4	**2c**	**4d**, **5d**	PhO	4-O_2NPh	40:60	42
5	**2d**	**4e**, **5e**	PhO	4-MePh	71:29	30

Since the diastereoselectivities observed in our study were lower than expected, we decided to repeat the studies reported by Aszodi *et al.*[7] and to compare the ability of naphthylethylimines **2** and phenylethylimines **3** (**Table III**) to induce asymmetry in the Staudinger reaction under identical conditions. We prepared imines **2d** (R=1-naphthyl, R^2=chloromethyl) and **3a** (R=phenyl, R^2=chloromethyl) from chloroacetaldehyde, (*R*)-(+)-1-(1-naphthylethyl)amine, and (*R*)-(+)-1-phenylethylamine and subjected them to the Staudinger reaction under the conditions reported by Aszodi *et al.*[7] (entries 1 and 5, **Table III**).[12] In our hands, however, reaction of phenylethylimine **3a** (R=phenyl, R^2=chloromethyl) with phthalimidoacetyl chloride (**1b**) yielded a 80:20 ratio of diastereoisomers (entry 5, **Table III**) instead of the reported 90:10 ratio. A comparison between the two imines (entries 1 and 5, **Table III**) revealed that naphthylethylimine **2d** (R=1-naphthyl, R^2=chloromethyl) was only slightly superior (83:17 diastereomeric ratio) to phenylethylimine **3a** (R=phenyl, R^2=chloromethyl).

Table III. A comparison of naphthylethylimines **2** and phenylethylimines **3** in the Staudinger reaction

entry	imine	β-lactams **4** and **5**	R	R^1	R^2	solvent	ratio of **4**:**5**	yield (%)
1	**2d**	**4f**, **5f**	1-naphthyl	Phth	chloromethyl	chloroform	83:17	46
2	**2a**	**4a**, **5a**	1-naphthyl	PhO	styryl	toluene	83:17	71
3	**2a**	**4a**, **5a**	1-naphthyl	PhO	styryl	dichloromethane	75:15	56
4	**2a**	**4a**, **5a**	1-naphthyl	PhO	styryl	chloroform	83:17	14
5	**3a**	**4g**, **5g**	phenyl	Phth	chloromethyl	chloroform	80:20	20
6	**3b**	**4h**, **5h**	phenyl	PhO	styryl	toluene	67:33	59
7	**3b**	**4h**, **5h**	phenyl	PhO	styryl	dichloromethane	67:33	92
8	**3b**	**4h**, **5h**	phenyl	PhO	styryl	chloroform	71:29	57

We investigated additional imines and different solvents (**Table III**) and found in all instances that the naphthylethylimines **2** gave better diastereoselectivities than the phenylethylimines **3** (entries 1-8, **Table III**). The best solvent for the reaction of naphthylethylimines **2** was toluene (entry 2, **Table III**), providing good diastereoselectivity (83:17) and good yield (71%). Chloroform as the solvent also gave good diastereoselectivity but the yields were typically low (entries 1 and 4, **Table III**). For phenylethylimines **3** the best diastereoselectivities were achieved with chloroform as the solvent (entries 5 and 8, **Table III**).

In addition to providing better diastereoselectivities in the Staudinger reaction, the diastereoisomers of *N*-naphtylethyl-β-lactams can be more easily separated by silica gel flash column chromatography than the corresponding *N*-phenylethyl-β-lactams. The *N*-phenylethyl and the *N*-naphthylethyl groups can be removed reductively (Li/ammonia) from the β-lactam nitrogen.[13-15]

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(8) Preparation of (*R*)-*N*-1-(1-naphthyl)ethylcinnamylideneimine **2a**: *trans*-Cinnamaldehyde (2.2 mL, 17.07 mmol, 1.1 eq), $MgSO_4$ (3 g), and HOAc (0.5 mL) were added to a solution of **1** (2.5 mL, 15.52 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 5 hr, and then filtered. After removal of the solvent under reduced pressure (rotary evaporator), the residue was kept under vacuum (0.2 mm Hg) overnight to yield 4.5 g of the crude imine. Crystallization from CH_2Cl_2/hexanes gave (*R*)-*N*-1-(1-naphthyl)ethylcinnamylideneimine as brown crystals: m.p. 101.5 °C; $[\alpha]_D$ -260.4° (c=1, $CHCl_3$).
(9) *N*-[1-(1-Naphthyl)ethyl]-3-phenoxy-4-styryl-2-azetidinones (**4a** and **5a**, entry 5, **Table I**). To a solution of phenoxyacetyl chloride (0.16 mL, 1.16 mmol, 1.1 eq) in anhydrous toluene (5 mL) at -78 °C (argon atmosphere) was added dropwise triethylamine (0.18 mL, 1.26 mmol, 1.2 eq). After stirring at -78 °C for 15 min, a solution of (*R*)-*N*-1-(1-naphthyl)ethylcinnamylideneimine (300 mg, 1.05 mmol) in toluene (2 mL) was added slowly over a time period of ten minutes. The reaction mixture was then stirred for 0.5 hr at -78 °C and at room temperature for 8 hr. After quenched with ice, the reaction mixture was extracted with EtOAc. The organic layer was washed sequentially with saturated $NaHCO_3$ and H_2O, and then dried ($MgSO_4$) and evaporated. The crude products were purified by column chromatography (silica gel, hexanes:EtOAc=4:1) to yield the two cis isomers (297 mg, 71 %, major:minor=82:18). These two isomers can be separated by either crystallization (EtOAc/hexanes) or chromatography (silica gel, hexanes:EtOAc=4:1). Major isomer, (1'*R*,3*S*,4*R*)-*N*-[1'-(1-naphthyl)ethyl]-3-phenoxy-4-styryl-2-azetidinone (**4a**): m.p. 135-136 °C; $[\alpha]_D$ -98.3° (c=1.3, $CHCl_3$). Minor isomer, (1'*R*,3*R*,4*S*)-*N*-[1'-(1-naphthyl)ethyl]-3-phenoxy-4-styryl-2-azetidinone (**5a**): m.p. 120-121 °C; $[\alpha]_D$ -72.6° (c=0.95, $CHCl_3$).
(10) The absolute configuration of all products was assigned by comparison of their ^1H NMR spectra, and circular dichroism spectra with the data for (1'*R*,3*S*,4*R*)-*N*-[1'-(1-naphthyl)ethyl]-3-phenoxy-4-chlorophenyl-2-azetidinone **4i** for which the absolute configuration was determined by X-ray crystallography. This β-lactam was prepared in a 53:47 ratio of **4i** and **5i** as described in (9) using 4-chlorobenzaldehyde instead of cinnamaldehyde, and dichloromethane as the solvent for β-lactam formation. Another distinguishing feature between the major isomers **4** and the minor isomers **5** was the R_f value. The major isomers **4** invariably displayed higher R_f values during silica gel thin layer chromatography, using hexanes/EtOAc (4:1) as the mobile phase.
(11) We would like to thank Dr. Fusao Takusagawa from the Department of Chemistry at the University of Kansas for performing the single crystal X-ray analysis of **4i**.
(12) The chloromethylimines **2d** and **3a** (used in entries 1 and 5, **Table III**) were prepared according to the reported procedure,[7] using 4 Å sieves instead of Drierite as the drying agent for the imines.
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