Diastereoselective Hydrochlorination of Acrylylurea Derivatives Using Titanium Tetrachloride and Alcohol. Chelation-Controlled Michael Addition of Chloride and Intramolecular Proton Transfer to the α-Position

Keiki Kishikawa,* Atsuko Furusawa, Shigeo Kohmoto, Makoto Yamamoto, and Kazutoshi Yamada

Department of Materials Science, Faculty of Engineering, Chiba University, 1-33 Yayoi-cho, Inage-Ku, Chiba 263, Japan

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Michael addition to α,β-unsaturated carboxylic acid derivatives has proven to be a useful vehicle for asymmetric induction at the β-carbon in numerous investigations.[1] However, the asymmetric hydrochlorination of α,β-unsaturated carboxylic acid derivatives has yet to be demonstrated. Moreover, stereoselective hydrochlorination of acrylic acid derivatives has been discussed in only a few reports with only moderate selectivity: (1) hydrochlorination of 2-butenoic acid using hydrogen chloride and α-cyclodextrin (64% ee, Tanaka et al., 1990[2] (34% ee based on our calculation[3])), and (2) hydrochlorination of acrylylureas using titanium tetrachloride and 2-propanol (66% de, Kishikawa et al., 1990[4]). In this article we describe our further investigations of our hydrochlorination,[4] elucidation of its mechanism, improvement of the diastereoselectivity, and determination of the absolute configurations of the products.

Acrylylurea **1a** was hydrochlorinated under a variety of conditions using titanium tetrachloride and 2-propanol. Thus, to a solution of **1a** in toluene was added a solution of titanium tetrachloride in toluene, followed by 1 equiv of 2-propanol. After stirring for 1 h, the reaction was quenched by the addition of water. A plot of yields (**2a**) versus amounts of reagents ($TiCl_4$/*i*-PrOH = 1:1) are shown in Figure 1. The best yield was observed when a ratio of $TiCl_4$/*i*-PrOH/**1a** = 1:1:1 was used. Yields of **2a** with varying amounts of 2-propanol and 1 equiv of $TiCl_4$ are shown in Figure 2. Reactions with more than 1 equiv of 2-propanol proceeded quantitatively. Figure 3 shows yields of **2a** resulting from reaction temperatures of −70 °C to about 20 °C. Higher temperatures produced better yields.

Yields in various solvents were investigated by carrying out the reaction of **1a** in toluene, carbon tetrachloride, chloroform, and methylene chloride (Table I). In toluene and chloroform, the reaction provided the product in 100% yield. In carbon tetrachloride and methylene chloride, the products were obtained in moderate yields (71 and 78%). Solvent polarity showed no distinct effect on the reactivity in this selection of solvents.

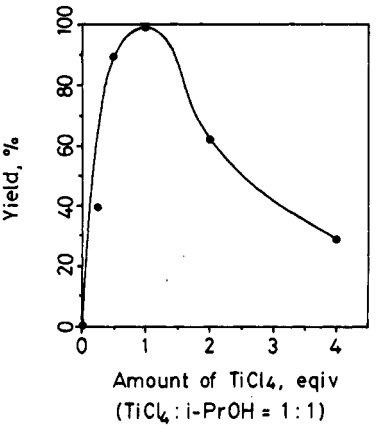


Figure 1. Plot of yield (**2a**) versus amount of titanium tetrachloride for the hydrochlorination of **1a**.

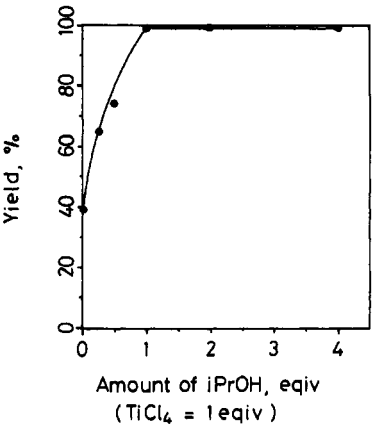


Figure 2. Plot of yield (**2a**) versus amount of 2-propanol (titanium tetrachloride = 1 equiv) for the hydrochlorination of **1a**.

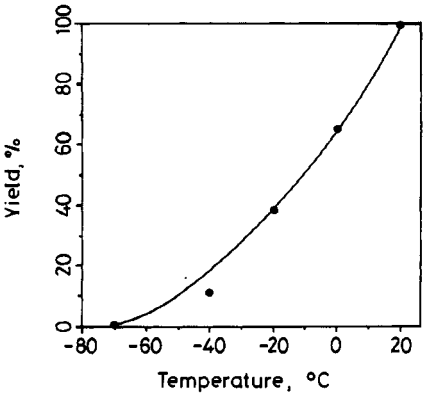


Figure 3. Plot of yield (**2a**) versus reaction temperature for the hydrochlorination of **1a**.

Among the alcohols (methanol, ethanol, 2-propanol, *tert*-butyl alcohol and benzyl alcohol), reaction with 2-propanol resulted in the best yield. The steric character of 2-propanol might be most suitable for the acceleration of the reaction.

In order to determine which proton moves to the α-position, a series of deuterium exchange experiments was attempted by addition of CD_3OD and/or D_2O to the

(1) (a) Davies, S. G.; Easton, R. J. C.; Walker, J. C.; Warner, P. *Tetrahedron* **1986**, *42*, 175. (b) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035. (c) Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369. (d) Alexakis, A.; Sedrani, R.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 4411. (e) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611. (f) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992, p 199.

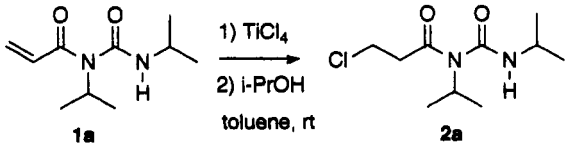
(2) Tanaka, Y.; Sakuraba, H.; Nakanishi, H. *J. Org. Chem.* **1990**, *55*, 564.

(3) The enantio excess of (*R*)-3-chlorobutyric acid was based on $[\alpha]^{20}_D$ of the optically pure acid (+21.5°).

(4) Kishikawa, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1990**, 1123.

0022-3263/93/1958-7296$04.00/0

Table I. Hydrochlorination of 1a[a]

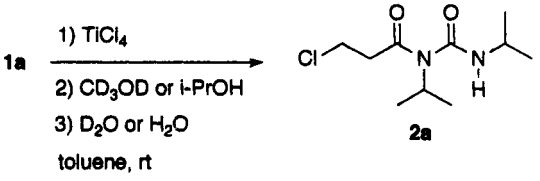


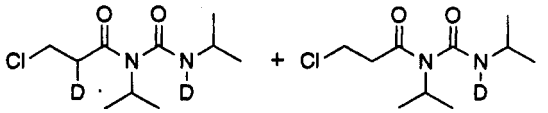
1a 2a

entry	solvent	alcohol	yield (%)[b]
1	toluene	*i*-PrOH	100
2	CCl_4		71
3	$CHCl_4$		100
4	CH_2Cl_2		78
5	toluene	MeOH	64
6		EtOH	75
7		*i*-PrOH	100
8		*t*-BuOH	59
9		BnOH	73

[a] The reaction was carried out at room temperature. After addition of titanium tetrachloride (1 equiv) to the solution of **1a**, alcohol (1 equiv) was added and stirred for 1 h. [b] Determined by ^1H NMR spectroscopy.

Table II. Hydrochlorination with Methanol-d_4 and/or Quenching with D_2O[a]





2b 2c

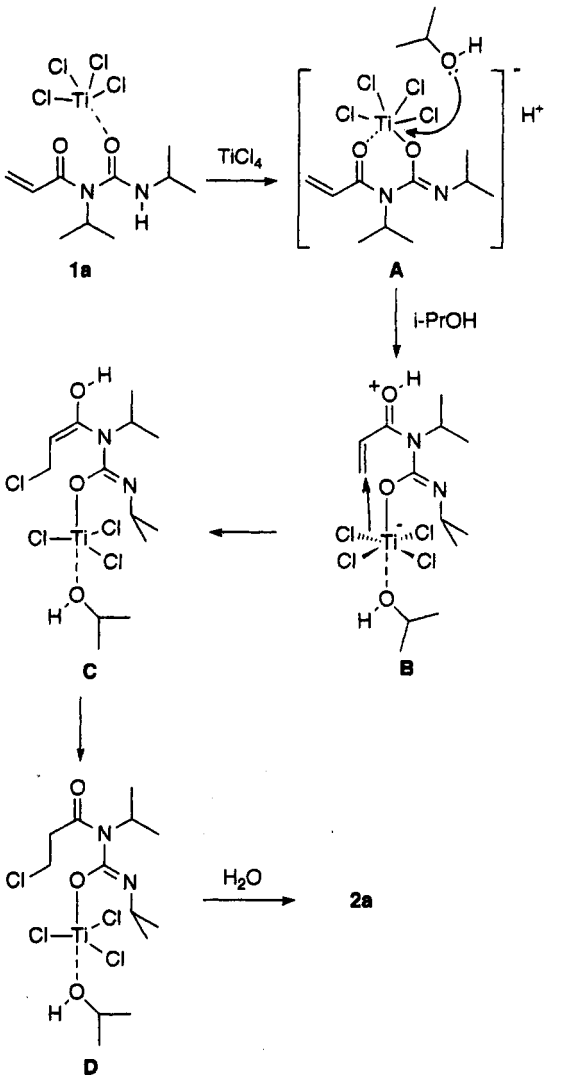
entry	starting material	alcohol	water	product (%)[b] 2a/2b/2c
1	**1a**	CD_3OD	H_2O	100:0:0
2		iPrOH	D_2O	0:22:78
3		CD_3OD	D_2O	0:20:80
4	**2a**	iPrOH	D_2O	0:10:90

[a] After addition of titanium tetrachloride (1 equiv) to the solution of toluene, alcohol (1 equiv) was added and the solution was stirred for 1 h. [b] Determined by ^1H NMR spectroscopy.

reaction (Table II). The ratio of **2a**/**2b**/**2c** was determined by ^1H NMR spectroscopy. In all cases the reactions proceeded quantitatively. Addition of CD_3OD followed by quenching with H_2O did not afford the α-deuterioacylurea **2b** (entry 1). On the other hand, quenching with D_2O gave **2b** in 22% yield (entry 2). Accordingly, the 22% deuterium at the α-position of **2b** originates in the process of quenching with water. The addition of CD_3OD followed by quenching with D_2O gave **2b** and **2c** in 20 and 80% yields, respectively (entry 3). Thus, the proton at the nitrogen of **1a** is transferred to the α-position of the product during the reaction.

To explain these results, the following mechanism (Scheme I) for the hydrochlorination can be suggested. First, the titanium of $TiCl_4$ chelates with the two carbonyl oxygens of **1a**. Then, the amide proton undergoes an intramolecular transfer to the Cl ligands on titanium (**A**). Attack of 2-propanol at titanium with ligand exchange of the acylyl carbonyl oxygen results in a hexavalent titanium species. This undergoes a conformational change so as to locate a Cl ligand near the β-carbon of the acrylyl group (**B**), and it attacks the β-carbon after protonation of the carbonyl oxygen. After hydrochlorination, ketonization

Scheme I

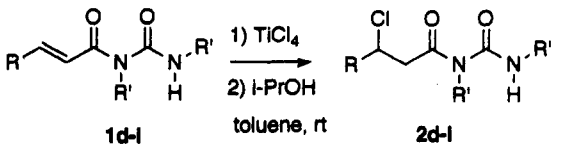


of **C** yields **D**. To confirm the occurrence of acid-catalyzed isomerization upon quenching, a toluene solution of **2a** was stirred with $TiCl_4$ for 1 h and then was quenched by addition of D_2O. Deuterium exchange amounting to 10% was observed. Not unexpectedly, quenching with water generated HCl, which caused the observed acid-catalyzed keto–enol isomerization.

Intermediate **B** from the above mechanism suggested that introduction of bulky chiral substituents at the nitrogen atoms, one of which is positioned near the titanium atom in **B**, could result in highly diastereoselective hydrochlorination. Acrylylureas **1d–i** (Table III) were prepared from β-substituted acrylic acids and chiral carbodiimides (*N*,*N*′-bis[(*S*)-1-phenylethyl]carbodiimide (**3a**),[6] *N*,*N*′-bis[(*S*)-1-(1-naphthyl)ethyl]carbodiimide (**3b**) and *N*,*N*′-bis[(*R*)-1-(1-naphthyl)ethyl]carbodiimide (**3c**)). The hydrochlorination of **1d–f** (R = (*S*)-1-phenylethyl) using 1 equiv of 2-propanol gave the products with poor to moderate diastereoselectivity (entries 1, 3, 5). The yields were increased by the addition of 1 equiv more of 2-propanol (entries 2, 4, 6). The selectivity was improved by substitution of the *N*-(1-arylethyl) groups with the bulkier *N*-[1-(1-naphthyl)ethyl] group (entries 7–9). In particular, 2-butenoylurea **1g** gave **2g** in 78% de.

The absolute configuration of **2g** was determined by comparison of its spectral data with an authentic sample prepared by an independent route. Optical resolution of

Table III. Diastereoselective Hydrochlorination[a]



1d-l 2d-l

entry	starting material	R	R′	product	% yield[b]	% de (major isomer)[c]
1[d]	1d	Me	(*S*)-1-phenylethyl	2d	16	56 (3*S*)
2					50	32 (3*S*)
3[d]	1e	Et		2e	44	14 (3*S*)
4[e]					86	66 (3*S*)
5[d]	1f	Pr		2f	14	0 (–)
6[e]					72	10 (3*S*)
7	1g	Me	(*S*)-1-(1-naphthyl)-ethyl	2g	54	78 (3*S*)
8	1h	Et	(*R*)-1-(1-naphthyl)-ethyl	2h	50	60 (3*R*)
9	1i	Pr		2i	29	48 (3*R*)

[a] After addition of titanium tetrachloride (1 equiv) to the solution of 1 in toluene, 2-propanol (2 equiv) was added and stirred at room temperature for 1 h. The reaction was quenched by addition of water. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy. [d] One equivalent of 2-propanol was added. [e] Reference 4.

3-chlorobutyric acid using (–)-quinine was carried out to obtain (*R*)-3-chlorobutyric acid, which showed a greater specific rotation ($[\alpha]^{20}_D$ +13.71° (*c* = 9.55, diethyl ether)) than that previously reported ($[\alpha]^{20}_D$ +11.5° (*c* = 10, diethyl ether)[5]), notwithstanding that the purity was 64% ee. The enantiomeric excess of the (*R*)-acid was determined as follows. The optically-resolved acid was derivatized to the corresponding acylurea by the reaction with *N*,*N*′-bis[(*S*)-1-(1-naphthyl)ethyl]carbodiimide. The diastereomer ratio of **2g** ((3*R*)-form/(3*S*)-form = 82:18) was determined by ^{1}H NMR spectroscopy. The minor diastereomer (3*S*)-**2g** was identical to the major diastereomer of **2g** obtained in entry 7 of Table II. Thus, the absolute configuration of the major product **2g** is unequivocally established as the (3*S*)-form. The estimated $[\alpha]^{20}_D$ for the (*R*)-acid is ca. +21.5°, which was calculated from the value +13.71° at 64% ee.

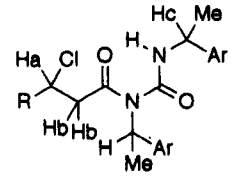
The configurations of the other products (**2d–f, h, i**) were tentatively assigned by comparison with the ^{1}H NMR spectra of **2g** (Table IV). The Ha-peak of the major diastereomers occurs at higher field than that of the minor diastereomers. One of the methylene Hb-peaks of the major products appears in the range of 2.55 to 2.70 ppm, and the other in the range of 2.90 to 3.30 ppm. In the minor products, both of the methylene Hb-peaks appear in the narrow range of 2.88 to 2.96 ppm. Further, the Hc-peak of the major products is at lower field than that of the major products. Accordingly, all of the pairs of major and minor products have similar chemical shift relationships. Therefore, the absolute configuration of the major product is the (3*S*,1′*S*,1″*S*)-form for **2d–g** and the (3*R*,1′*R*,1″*R*)-form for **2h–i**. The stereochemistry of the minor product is (3*R*,1′*S*,1″*S*)-form for **2d–g** and the (3*S*,1′*R*,1″*R*)-form for **2h,i**.

The transition states **I** and **II** of the diastereoselective hydrochlorination are depicted in Scheme II. The conformation of the 1-(1-naphthyl)ethyl moiety is fixed by the steric hindrance presented by the titanium group. One of the Cl atoms attacks the β-carbon atom of the propenoylurea. In transition state **I**, considerable steric repulsion between the naphthyl and R group would arise. Reaction from the less hindered state **II** is preferable to that from **I**, resulting in the (3*S*)-form as the major product.

In summary, the diastereoselectivity in hydrochlorination can be explained by the mechanism proposed in this study. It was confirmed that the hydrochlorination using titanium tetrachloride and alcohol is promoted by the two carbonyl groups and the amide proton of the acrylylureas.

(5) Levene, P. A.; Haller, H. L. *J. Biol. Chem.* **1929**, *81*, 425.

Table IV. List of Chemical Shifts of 3-Chloroacylureas



2d: R = Me, Ar = Ph
2e: R = Et, Ar = Ph
2f: R = Pr, Ar = Ph
2g: R = Me, Ar = 1-naphthyl
2h: R = Et, Ar = 1-naphthyl
2i: R = Pr, Ar = 1-naphthyl

product	chemical shift (δ) Ha	Hb	Hc	configuration
2d (major)	4.50	2.58, 2.95	4.95	3*S*, 1′*S*, 1″*S*
2d (minor)	4.63	2.90, 2.96	4.87	3*R*, 1′*S*, 1″*S*
2e (major)	4.33	2.56, 2.92	4.96	3*S*, 1′*S*, 1″*S*
2e (minor)	4.48	2.90, 2.96	4.87	3*R*, 1′*S*, 1″*S*
2f (major)	4.39	2.55, 2.95	5.02	3*S*, 1′*S*, 1″*S*
2f (minor)	4.52	2.91, 2.95	4.82	3*R*, 1′*S*, 1″*S*
2g (major)	4.55	2.69, 3.03	5.60	3*S*, 1′*S*, 1″*S*
2g (minor)	4.80	2.90, 2.96	5.43	3*R*, 1′*S*, 1″*S*
2h (major)	4.35	2.70, 2.98	5.60	3*R*, 1′*R*, 1″*R*
2h (minor)	4.65	2.93, 2.95	5.40	3*S*, 1′*R*, 1″*R*
2i (major)	4.40	2.65, 2.90	5.60	3*R*, 1′*R*, 1″*R*
2i (minor)	4.75	2.88, 2.96	5.35	3*S*, 1′*R*, 1″*R*

Experimental Section

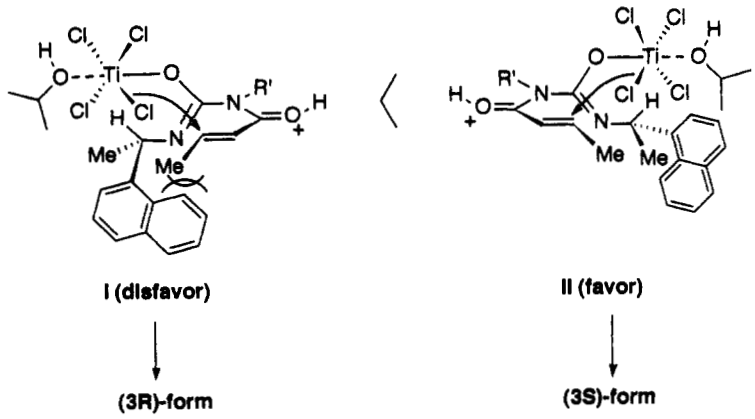
Preparation of *N*-(2-propyl)acrylylurea **1a** and *N*-(1-phenylethyl)acrylylureas **1d–f**, and the hydrochlorination were carried out by the methods in our precedent papers.[4,6d] Preparation of *N*-[(1-naphthyl)ethyl]acrylylureas **1g–i** and the hydrochlorination were also performed by the same procedures.

***N*,*N*′-Bis[(*S*)-1-(1-naphthyl)ethyl]-*N*′-(2-butenoyl)urea (1g)**: 99% yield; mp 121–122 °C; IR (KBr) 3284, 3012, 1705, 1665, 1625, 1520, 1375, 1245, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.46 (d, *J* = 7.7 Hz, 3H), 1.78 (dd, *J* = 7.7, 1.4 Hz, 3H), 1.80 (d, *J* = 7.7 Hz, 3H), 5.61 (dq, *J* = 7.7, 7.7 Hz, 1H), 6.15 (dd, *J* = 15.0, 1.4 Hz, 1H), 6.50 (q, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 6.90 (dt, *J* = 15.0, 7.7 Hz, 1H), 6.95–7.01 (m, 1H), 7.15 (m, 3H), 7.33–7.55 (m, 5H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.80–7.95 (m, 3H); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 18.08 (q), 21.09 (q), 46.21 (d), 49.49 (d), 121.93 (d), 122.98 (d), 124.02 (d), 124.77 (d), 125.24 (d), 125.60 (d), 125.72 (d), 126.41 (d), 126.82 (d), 127.99 (d), 128.56 (d), 128.76 (d), 129.91 (d), 130.49 (s), 131.18 (s), 133.60 (s), 133.84 (s), 137.51 (s), 143.17 (d), 153.91 (s), 166.54 (s); HRMS (FAB) (*m*/*z*) foun (MH)$^+$ 437.2222, calcd for $C_{29}H_{29}N_2O_2$ (MH) 437.2215.

***N*,*N*′-Bis[(*R*)-1-(1-naphthyl)ethyl]-*N*′-(2-pentenoyl)urea (1h)**: 81% yield; IR (KBr) 3430, 3050, 1705, 1665, 1625, 1520, 1375, 1220, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.7 Hz, 3H), 1.49 (d, *J* = 7.7 Hz, 3H), 1.83 (d, *J* = 7.7 Hz, 3H), 2.16 (dqd, *J* = 7.7, 7.7, 1.9 Hz, 2H), 5.62 (dq, *J* = 7.7, 7.7 Hz, 1H), 6.13 (dt, *J* = 15.4, 1.9 Hz, 1H), 6.40 (m, 1H), 6.55 (q, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.99 (dt, *J* = 15.4, 7.7 Hz, 1H), 6.95–7.05 (m, 1H), 7.15–7.35 (m, 2H), 7.40–7.55 (m, 5H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.85–7.93 (m, 3H), H); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 12.05 (q), 18.08 (q), 21.06 (q), 25.27 (t), 46.15 (d), 49.43 (d), 121.42 (d), 121.78 (d), 122.83 (d), 124.68 (d), 125.15 (d), 125.45 (d), 125.57 (d), 126.26 (d), 126.68 (d), 127.87 (d), 128.41 (d), 128.79 (d), 130.38 (s), 131.09 (s), 133.51 (s), 133.72 (s), 134.97 (s), 137.78 (s), 149.35

(6) (a) Kishikawa, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1988**, 351. (b) Kishikawa, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1988**, 1623. (c) Kishikawa, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1989**, 789. (d) Kishikawa, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *J. Org. Chem.* **1989**, *54*, 2428. (e) Kishikawa, K.; Horie, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1990**, 1009. (f) Kasimura, H.; Kishikawa, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Anal. Chim. Acta* **1990**, *239*, 297.

Scheme II. Transition States of the Hydrochlorination of 1g



(d), 153.89 (s), 166.65 (s); HRMS (FAB) (*m/z*) found $(MH)^+$ 451.2387, calcd for $C_{30}H_{31}N_2O_2$ (MH) 451.2385.

***N,N'*-[(*R*)-1-(1-naphthyl)ethyl]-*N*-(2-hexenoyl)-urea (1i)**: 79% yield; IR (KBr) 3480, 2930, 1705, 1665, 1630, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.7 Hz, 3H), 1.40 (tq, J = 7.7, 7.7 Hz, 2H), 1.49 (d, J = 7.7 Hz, 3H), 1.82 (d, J = 7.7 Hz, 3H), 2.09 (qd, J = 7.7, 1.4 Hz, 2H), 5.62 (dq, J = 7.7, 7.7 Hz, 1H), 6.13 (dt, J = 15.4, 1.4 Hz, 1H), 6.53 (q, J = 7.7 Hz, 1H), 6.98 (dt, J = 15.4, 7.7 Hz, 1H), 6.95–7.05 (m, 2H), 7.19–7.38 (m, 3H), 7.40–7.59 (m, 6H), 7.70–7.90 (m, 6H); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 13.69 (q), 18.17 (q), 21.15 (q), 21.27 (t), 34.37 (t), 46.24 (d), 49.58 (d), 121.87 (d), 122.47 (d), 122.98 (d), 124.77 (d), 125.24 (d), 125.66 (d), 125.72 (d), 126.38 (d), 126.77 (d), 127.96 (d), 128.53 (d), 128.73 (d), 128.89 (d), 130.46 (s), 131.18 (s), 133.60 (s), 133.81 (s), 135.03 (s), 137.57 (s), 148.13 (d), 153.97 (s), 166.74 (s); HRMS (FAB) (*m/z*) found $(MH)^+$ 465.2547, calcd for $C_{31}H_{32}N_2O_2$ (MH), 465.2552.

***N,N'*-Bis[(*S*)-1-(1-naphthyl)ethyl]-*N*-(3-chlorobutanoyl)-urea (2g)**: 54% yield. Major: IR (KBr) 3450, 3070, 2930, 1710, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (d, J = 7.7 Hz, 3H), 1.45 (d, J = 7.7 Hz, 3H), 1.75 (d, J = 7.7 Hz, 3H), 2.69 (dd, J = 15.4, 5.8 Hz, 1H), 3.03 (dd, J = 15.4, 7.7 Hz, 1H), 4.55 (dqd, J = 7.7, 7.7, 5.8 Hz, 1H), 5.60 (dq, J = 7.7, 7.7 Hz, 1H), 5.63 (br d, J = 7.7 Hz, 1H), 6.52 (q, J = 7.7 Hz, 1H), 6.89 (m, 2H), 7.16 (m, 1H), 7.30 (m, 1H), 7.40 (m, 5H), 7.69–7.81 (m, 3H), 7.81–8.00 (m, 3H); HRMS (FAB) (*m/z*) found (MH^+) 473.1996, calcd for $C_{29}H_{30}N_2O_2Cl$ (MH) 473.1996.

Minor: IR (KBr) 3420, 3050, 2970, 1710, 1665, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 7.7 Hz, 3H), 1.62 (d, J = 7.7 Hz, 3H), 1.76 (d, J = 7.7 Hz, 3H), 2.90 (dd, J = 9.1, 2.0 Hz, 1H), 2.96 (dd, J = 9.1, 3.3 Hz, 1H), 4.80 (qdd, J = 7.7, 3.3, 2.0 Hz, 1H), 5.20 (br d, J = 7.7 Hz, 1H), 5.43 (dq, J = 7.7, 7.7 Hz, 1H), 6.30 (d, J = 6.9 Hz, 1H), 6.46 (q, J = 7.7 Hz, 1H), 6.75 (dd, J = 6.9, 6.9 Hz, 1H), 7.08–7.20 (m, 2H), 7.30–7.62 (m, 5H), 7.70–7.90 (m, 5H); HRMS (FAB) (*m/z*) found (MH^+) 473.2000, calcd for $C_{29}H_{30}N_2O_2Cl$ (MH), 473.1996.

***N,N'*-Bis[(*R*)-1-(1-naphthyl)ethyl]-*N*-(3-chlorohexanoyl)-urea (2h)**: 50% yield. Major: IR (KBr) 3420, 1705, 1665, 1515, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, J = 7.7 Hz, 3H), 1.42 (d, J = 7.7 Hz, 3H), 1.60–1.70 (m, 2H), 1.75 (d, J = 7.7 Hz, 3H), 2.70 (dd, J = 18.4, 6.0 Hz, 1H), 2.98 (dd, J = 18.4, 6.7 Hz, 1Hz), 4.35 (m, 1H), 5.60 (dq, J = 7.7, 7.7 Hz, 1H), 5.80 (br, 1H), 6.52 (q, J = 7.7 Hz, 1H), 6.85–6.93 (m, 2H), 7.18 (m, 2H), 7.40–7.50 (m, 5H), 7.70–7.98 (m, 5H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 10.87 (q), 17.94 (q), 20.80 (q), 30.98 (t), 44.31 (t), 46.17 (d), 49.22 (d), 60.46 (d), 122.22 (d), 123.00 (d), 123.16 (d), 124.73 (d), 125.29 (d), 125.34 (d), 125.51 (d), 125.91 (d), 126.59 (d), 126.90 (d), 128.32 (d), 128.74 (d), 128.80 (d), 128.90 (d), 130.62 (s), 131.03 (s), 133.58 (s), 133.92 (s), 137.12 (s), 153.39 (s), 170.08 (s); HRMS (FAB) (*m/z*) found (MH^+) 487.2158, calcd for $C_{30}H_{32}N_2O_2Cl$ (MH) 487.2153.

Minor: IR (KBr) 3420, 3050, 2970, 1705, 1510, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, J = 7.7 Hz, 3H), 1.42 (d, J = 7.7 Hz, 3H), 1.60–1.70 (m, 2H), 1.75 (d, J = 7.7 Hz, 3H), 2.93 (dd, J = 9.0, 2.3 Hz, 1H), 2.95 (dd, J = 9.0, 3.3 Hz, 1H), 4.65 (m, 1H), 5.20 (br s, 1H), 5.40 (dq, J = 7.7, 7.7 Hz, 1H), 6.20 (d, J = 7.7 Hz, 1H), 6.50 (q, J = 7.7 Hz, 1H), 6.78 (dd, J = 7.7, 7.7 Hz, 1H), 7.00–7.15 (m, 2H), 7.25–7.60 (m, 5H), 7.68–7.95 (m, 5H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 10.89 (q), 17.46 (q), 21.04 (q), 31.53 (t), 43.80 (t), 46.19 (d), 49.04 (d), 61.81 (d), 122.75 (d), 123.02 (d), 123.14 (d), 124.64 (d), 125.30 (d), 125.36 (d), 125.60 (d), 126.70 (d), 126.39 (d), 127.07 (d), 127.91 (d), 128.64 (d), 128.71 (d), 128.76 (d), 130.11 (s), 131.09 (s), 133.27 (s), 133.51 (s), 133.77 (s), 136.84 (s), 166.48 (s), 168.41 (s); HRMS (FAB) (*m/z*) found (MH^+) 487.2151, calcd for $C_{30}H_{32}N_2O_2Cl$ (MH) 487.2153.

***N,N'*-Bis[(*R*)-1-(1-naphthyl)ethyl]-*N*-(3-chloropentanoyl)urea (2i)**: 29% yield. Major: IR (KBr) 3420, 2960, 1705, 1665, 1510, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.7 Hz, 3H), 1.40 (tq, J = 7.7, 7.7 Hz, 2H), 1.49 (d, J = 7.7 Hz, 2H), 1.82 (d, J = 7.7 Hz, 3H), 2.00 (m, 2H), 2.65 (dd, J = 15.7, 5.8 Hz, 1H), 2.90 (dd, J = 15.7, 7.5 Hz, 1H), 4.40 (m, 1H), 5.60 (dq, J = 7.7, 7.7 Hz, 1H), 5.80 (br, 1H), 6.50 (q, J = 7.7 Hz, 1H), 6.85–6.90 (m, 2H), 7.20–7.36 (m, 2H), 7.20–7.36 (m, 2H), 7.40–7.55 (m, 5H), 7.72–8.00 (m, 5H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 13.45 (q), 17.91 (q), 19.57 (t), 20.76 (q), 39.82 (t), 44.64 (t), 46.16 (d), 49.18 (d), 58.72 (d), 122.18 (d), 122.97 (d), 123.12 (d), 124.71 (d), 125.29 (d), 125.47 (d), 125.84 (d), 125.87 (d), 126.56 (d), 126.86 (d), 128.30 (d), 128.74 (d), 128.86 (d), 128.90 (d), 130.61 (s), 131.02 (s), 133.55 (s), 133.90 (s), 134.74 (s), 137.07 (s), 153.35 (s), 170.03 (s); HRMS (FAB) (*m/z*) found (MH^+) 501.2310, calcd for $C_{31}H_{34}N_2O_2Cl$ (MH) 501.2309.

Minor: IR (KBr) 3420, 2960, 1705, 1665, 1515, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.7 Hz, 3H), 1.40 (tq, J = 7.71, 7.71 Hz, 2H), 1.49 (d, J = 7.7 Hz, 2H), 1.82 (d, J = 7.7 Hz, 3H), 2.00 (m, 2H), 2.88 (dd, J = 6.2, 2.0 Hz, 1H), 2.96 (dd, H = 6.2, 2.0 Hz, 1H), 4.75 (m, 1H), 5.20 (br, 1H), 5.35 (dq, J = 7.7, 7.7 Hz, 1H), 6.20 (d, J = 7.7 Hz, 1H), 6.55 (q, J = 7.7 Hz, 1H), 6.80–6.95 (m, 1H), 7.00–7.20 (m, 2H), 7.35–7.60 (m, 5H), 7.68–7.95 (m, 5H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 13.45 (q), 17.45 (q), 19.62 (t), 21.05 (q), 40.38 (t), 44.22 (t), 46.21 (d), 48.99 (d), 60.00 (d), 121.67 (d), 122.76 (d), 123.16 (d), 124.61 (d), 125.33 125.57 (d), 125.70 (d), 125.74 (d), 126.39 (d), 127.07 (d), 127.89 (d), 128.68 (d), 128.71 (d), 128.76 (d), 130.13 (s), 131.10 (s), 133.27 (s), 133.51 (s), 133.77 (s), 136.84 (s), 153.11 (s), 168.41 (s); HRMS (FAB) (*m/z*) found (MH^+) 501.2300, calcd for $C_{31}H_{34}N_2O_2Cl$ (MH) 501.2308.

Supplementary Material Available: Copies of ^1H NMR spectra of compounds found in Experimental Section; ^1H chemical shifts of **2d–i** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.