Catalytic Enantioselective Reissert-Type Reaction: Development and Application to the Synthesis of a Potent NMDA Receptor Antagonist (−)-L-689,560 Using a Solid-Supported Catalyst

Masahiro Takamura, Ken Funabashi, Motomu Kanai, and Masakatsu Shibasaki*

Contribution from the Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received March 12, 2001

Abstract: Full details of the first catalytic enantioselective Reissert-type reaction are described. Utilizing the Lewis acid−Lewis base bifunctional catalyst **5** or **6** (9 mol %), the Reissert products were obtained in 57 to 99% yield with 54 to 96% ee. Electron-rich quinolines produced better yields and enantioselectivities than electron-deficient substrates. Kinetic studies indicated that the reaction should proceed via the rate-determining acyl quinolinium formation, followed by the attack of a cyanide. The catalyst does not facilitate the first rate-determining step; however, it strongly facilitates the second cyanation step. The reaction was successfully applied to an efficient catalytic asymmetric synthesis of a potent NMDA receptor antagonist (−)-L-689,560. A key step is the one-pot process using the Reissert-type reaction from quinoline **1f**, followed by stereoselective reduction of the resulting enamine **2f**. This step gave the key intermediate **20** in 91% yield with 93% ee, using 1 mol % of **6**. The enantiomerically pure target compound was obtained through 10 operations (including recrystallization) in total yield of 47%. Furthermore, **6** was immobilized to Jand*A*JEL, and the resulting solid-supported catalyst **11** afforded **20** in a comparable yield to the homogeneous **6**, but with slightly lower enantioselectivity.

Introduction

In 1905, Reissert reported the addition of KCN to quinoline in the presence of benzoyl chloride (Reissert reaction).[1] Since then, there have been many modifications and improvements of the Reissert reaction, such as employing other nucleophiles (Grignard reagents, allyltin reagents, enol trimethylsilyl ethers, and trimethylsilyl cyanide) and catalytic promotion by a Lewis acid.[2] To date, the Reissert-type reaction has been extremely useful for synthesis of a variety of pharmaceuticals and biologically active alkaloids.[3,4] The reaction is considered to proceed via two steps: the generation of an acyl quinolinium intermediate by a nucleophilic attack of quinoline to an acid chloride, followed by the addition of cyanide.[5]

A common approach for the enantiocontrol of the Reissert-type reaction is to use a stoichiometric amount of chiral acylating reagents.[6] Promotion and control of the reaction by a chiral catalyst should provide a synthetically significant advantage. Developing a catalytic asymmetric Reissert-type reaction, however, is a great challenge, due mainly to the following reasons. First, strong electrophiles such as an acid halide or TMSX (generated during the reaction) could decompose the catalyst by acylating and/or silylating the ligand. Second, the conformation (the *s*-trans/*s*-cis isomers of the amide bond, see **17** and **16**, Figure 2) of the reactive acyl quinolinium intermediate is rather dynamic. The two conformers produce opposing enantiomers even if a nucleophile attacks the reactive intermediate from a defined side. These two conformers should be strictly differentiated by the catalyst to realize high enantioselectivity.

We reported that the bifunctional catalyst **5** promotes the cyanosilylation of aldehydes and imines with high enantioselectivity and substrate generality.[7] The origin of the catalysis stems from the dual activation of the substrate and TMSCN at defined positions by the Lewis acid (aluminum metal) and the Lewis base (oxygen atom of the phosphine oxide) of the catalyst, respectively. Bifunctional catalysts should be advantageous for developing a catalytic asymmetric Reissert-type reaction of TMSCN. The catalyst was stable even in the presence of an electrophile (the acidic proton of alcohols and phenol).[8] In addition, the Lewis acid and the Lewis base of the catalyst could preorganize the acyl quinolinium and TMSCN. Thus, the reaction should proceed from a specific amide conformer. Herein we report a full account of the development of the first catalytic

(1) Reissert, A. *Chem. Ber*. **1905**, *38*, 1603.

(2) Ruchirawat, S.; Phadungkul, N.; Chuankamnerdkarn, M.; Thebtaranonth, C. *Heterocycles* **1977**, *6*, 43−46.

(3) (a) Popp, F. D. *Heterocycles* **1973**, *1*, 165−180. (b) McEwen, W. E.; Cobb, R. L. *Chem. Rev.* **1955**, *55*, 511−549.

(4) For selected recent examples, see: (a) Comins, D. L.; Huang, S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett*. **2001**, *3*, 467−471. (b) Shair, D. M.; Yoon, T.; Danishefsky, J. S. *J. Am. Chem. Soc*. **1996**, *118*, 9509−9525. (c) Itoh, T.; Nagata, K.; Miyazaki, M.; Osawa, A. *Synlett* **1999**, *7*, 1154−1156. (d) Tyrell, J. A., III; McEwen, W. E. *J. Org. Chem*. **1981**, *46*, 2476−2479.

(5) (a) Duarte, F. F.; Popp, F. D. *J. Heterocycl. Chem*. **1991**, *28*, 1801−1804. (b) Akiba, K.; Negishi, Y.; Inamoto, N. *Synthesis* **1979**, 55−57. (c) Abushanab, E.; Lee, D.-Y. *J. Org. Chem*. **1975**, *40*, 3376−3378.

(6) See refs 4a and 4c for representative examples.

(7) (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **1999**, *121*, 2641−2642. (b) Hamashima Y.; Sawada D.; Nogami H.; Kanai M.; Shibasaki M. *Tetrahedron* **2001**, *57*, 805−814. (c) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650−1652. (d) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Chem. Pharm. Bull*. **2000**, *48*, 1586−1592.

(8) The relative pK_a difference between the naphthol of the chiral ligand and the additive phenol or alcohol should be a reason for the stability of the catalyst. In addition, one of the two phosphine oxides of the ligand might perform a dative coordination to the aluminum metal, which should further stabilize the complex.

10.1021/ja010654n CCC: $20.00
Published on Web 06/19/2001

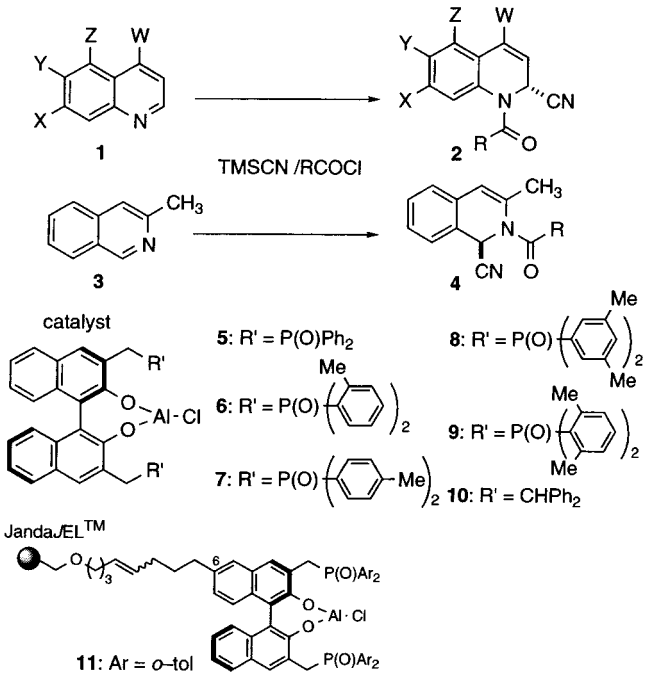


Figure 1. General scheme of the catalytic enantioselective Reissert-type reaction.

Table 1. Optimization of Catalytic Asymmetric Reissert-Type Reaction of **1a** with Various Acylating Reagents Using 9 mol % of **5**[a]

entry	R (RCOCl)	solvent	time/h	yield/%[b]	ee/%[c]
1	Ph	CH_2Cl_2	24	70	71
2	2-furyl	CH_2Cl_2	48	58	73
3	*o*-MeOPh	CH_2Cl_2	24	68	64
4	CH_3	CH_2Cl_2	24	42	58
5	PhCH=CH	CH_2Cl_2	24	52	54
6	1-naphthyl	CH_2Cl_2	24	63	46
7	Ph	CH_2Cl_2/toulene (1:1)	24	27	78
8	Ph	CH_2Cl_2/benzene (1:1)	24	25	78
9	Ph	CH_3CN	24	67	37

[a] The reaction was conducted at −40 °C using 2 equiv of TMSCN and 1.1 equiv of RCOCl. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

enantioselective Reissert-type reaction (Figure 1).[9] The reaction was further extended to an efficient catalytic asymmetric synthesis of a potent *N*-methyl-D-aspartate (NMDA) receptor antagonist, L-689,560. Moreover, a new solid-supported bifunctional catalyst was developed, and the easy separation of the catalyst facilitated the synthesis. The targeted compound is a promising drug candidate for Alzheimer's disease and for reducing ischemic brain damage.[10]

Results and Discussion

A. Optimization, Scope, and Limitations of Catalytic Enantioselective Reissert-Type Reaction. First, the effect of different acid chlorides (RCOCl) on the reaction was investigated using **5** (9 mol %) as a catalyst and quinoline (**1a**) as a substrate at −40 °C. As shown in Table 1 (entries 1−6), benzoyl chloride (entry 1) and 2-furoyl chloride (entry 2) afforded higher enantiomeric excesses than the aliphatic or substituted aromatic acid chlorides. 2-Furoyl chloride, which is more electron-rich and therefore less reactive than benzoyl chloride, gave slightly better enantioselectivity. No acylation or silylation of the chiral ligand was observed by TLC analysis. Thus, the catalyst seemed to be compatible with the strong electrophiles, although partial inactivation of the catalyst by TMSCl might compromise yield and enantiomeric excess of the product (vide infra).[11] Next, the solvent effect was investigated by using the more reactive benzoyl chloride as an acylating reagent. The ee increased from 71% to 78% when the solvent polarity was decreased, such as with toluene or benzene (entry 7 or 8), although the yield was much lower. In contrast, the ee was decreased to 37% when the more polar acetonitrile was used as solvent (entry 9). These results suggested the presence of a spontaneous reaction pathway independent of the catalyst that gives the racemic product. The acyl quinolinium intermediate derived from 2-furoyl chloride or an electron-rich aromatic acid chloride should be less reactive than the one derived from an aliphatic or reactive aromatic acid chloride. Therefore, the reaction would be mediated by the catalyst, using 2-furoyl chloride or an electron-rich aromatic acid chloride.[12] Using a reactive acid chloride, however, the acyl quinolinium intermediate should have a higher reactivity, and the reaction would proceed to some extent via the racemic pathway independent of the catalyst. The Lewis acid activation by the catalyst might be slightly lower in a polar solvent and therefore the racemic reaction should increase.[13] As expected, the spontaneous Reissert-type reaction of quinoline under these conditions proceeded in the absence of catalyst, giving the corresponding products in low yield. The corresponding Reissert compound was obtained in 5% yield in CH_2Cl_2 at −40 °C for 24 h when the more reactive acetyl chloride was used as an acylating reagent (reaction conditions corresponding to Table 1, entry 4). When 2-furoyl chloride was used as an acylating reagent in CH_2Cl_2−toluene (1:1) mixed solvent in the absence of the catalyst (optimized reaction conditions corresponding to Table 3, entry 1), however, only 1% yield of the corresponding Reissert compound was obtained (−40 °C for 64 h). Therefore, using the optimized reaction conditions (an electron-rich aromatic acid chloride and a less polar solvent), the spontaneous racemic reaction pathway could be almost completely suppressed. Thus, we have been able to significantly differentiate the reaction rate mediated by the catalyst from that of the spontaneous racemic reaction.

To improve the reaction by developing a more reactive catalyst, and avoid the contribution of the racemic pathway as much as possible, we designed a new catalyst that would facilitate the attack of TMSCN on the acyl quinolinium ion by favoring the catalyst conformer in which the Lewis acid and the Lewis base moieties are optimally positioned.[14] Molecular

(9) For the preliminary results, see: Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327−6328.

(10) (a) Leeson, P. D.; Carling, R. W.; Moore, K. W.; Moseley, A. M.; Smith, J. D.; Stevenson, G.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Hoogsteen, K. *J. Med. Chem.* **1992**, *35*, 1954−1968. (b) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Smith, J. D.; Saywell, K.; Tricklebank, M. D.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 65−70.

(11) Longer reaction time did not improve the chemical yield. As discussed in the Mechanistic Studies section, the inactivation of the catalyst was not caused by a silylation of the naphthol oxygen by TMSCl.

(12) Consistently, 4-methoxybenzoyl chloride gave the product with high ee (71%) under similar conditions of Table 1, entry 1, however, in only 28% yield. The low yield was attributed to the stability of the product, which was prone to retro-Reissert-type reaction.

(13) In a preliminary communication, we attributed the lower enantioselectivity using the reactive acid chloride and polar solvent to the generation of a larger amount of the acyl quinolinium intermediate. Because the acyl quinolinium intermediate was below the detection limit of ^1H NMR under any conditions of Table 1, however, the alternative explanation described in this full account seems to be more convincing.

(14) For the strategy to restrict the conformation of the ligand for the dual activation pathway, see: Kanai, M.; Hamashima, Y.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 2405−2409.

Table 2. Optimization of Catalyst Structure on the Reaction of **1a**[a]

entry	catalyst	R (RCOCl)	solvent	time/ h	yield/ %[b]	ee/ %[c]	*S*/*R*
1	**5**	Ph	CH_2Cl_2	24	70	71	*R*
2	**5**	Ph	CH_2Cl_2/toluene[d]	48	27	78	*R*
3	**6**	Ph	CH_2Cl_2	24	82	75	*R*
4	**6**	Ph	CH_2Cl_2/toluene[d]	24	49	83	*R*
5[e]	**6**	2-furyl	CH_2Cl_2/toluene[d]	64	91	85	*R*
6	**7**	Ph	CH_2Cl_2	24	44	50	*R*
7	**8**	Ph	CH_2Cl_2	24	33	2	*S*
8	**9**	Ph	CH_2Cl_2	24	61	38	*S*
9	**10**	Ph	CH_2Cl_2	24	78	24	*S*

[a] The reaction was conducted at −40 °C using 9 mol % of a catalyst, 2 equiv of TMSCN, and 1.1 equiv of RCOCl, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 1:1. [e] 4 equiv of TMSCN and RCOCl were used.

modeling studies suggested that if the steric bulkiness of the phosphine oxide's aryl groups is increased, the Lewis-basic oxygen atom would be positioned close to the acyl quinolinium ion activated by the Lewis acid. Thus, we synthesized new catalysts **6** through **9** containing more bulky phosphine oxides. Because these catalysts should also have higher Lewis basicity than the original catalyst **5**, higher reactivity as well as higher enantioselectivity should be realized. The results using these catalysts on the reaction of quinoline are summarized in Table 2. Although catalysts **7** through **9** gave disappointing results (entries 6−8), catalyst **6** containing di-*o*-methylphenylphosphine oxide afforded improved chemical yield and ee (entries 3 and 4 vs entries 1 and 2). Furthermore, using 4 equiv of TMSCN and 2-furoyl chloride, the Reissert product was obtained in 91% yield with 85% ee (entry 5). The inferior results by **7** and **8** might be explained as follows. One of the phosphine oxides of **7** and **8** could coordinate more strongly to the internal aluminum than in the case of **5**, due to the higher electron density (tolyl and xylyl vs phenyl), thereby diminishing the Lewis acidity of the catalyst, which should decrease the activity of **7** and **8** relative to **5**. Because of the presence of a spontaneous reaction pathway independent of the chiral catalyst, the reaction mediated by the less reactive catalyst should result in the lower enantioselectivity. Although catalyst **6** contains a more electron rich tolyl phosphine oxide, ortho substitution could hinder the internal coordination to the aluminum. Therefore, the Lewis acidity of **6** was maintained high enough, relative to **7** or **8**. On the other hand, catalyst **9** containing di-*o*,*o*′-dimethylphenylphosphine oxide afforded the opposite enantiomer (*S*) (entry 8). The reversal of the direction of enantioselectivity might be important from a mechanistic point of view. In the case of **9**, the Lewis basic phosphine oxide may be too sterically hindered and should not activate TMSCN, and only act to produce steric hindrance. Consistent with this, catalyst **10** containing the diphenylmethyl group gave the *S*-enantiomer (Table 2, entry 9). It is possible that TMSCN attacks the activated acyl quinolinium intermediate coordinating the Lewis acid from the less hindered side opposite the di-*o*,*o*′-dimethylphenylphosphine oxide or diphenylmethyl group. If so, in the case of **5** and **6**, TMSCN attacks the acyl quinolinium from the side of the phosphine oxide, supporting the bifunctional catalysis of **5** and **6**.

Using the optimized catalyst **6**, Reissert compounds were obtained in up to 96% ee in the case of the reactive, electron-rich quinolines **1a** through **1f** (Table 3, entries 1−6). The less reactive substrates **1h** and **1i** gave less satisfactory results, although they still yielded the products in 67% ee (entries 8 and 9). The absolute configuration of **2a** was determined as follows (Scheme 1). Hydrogenation of **2a** (R = Ph) catalyzed by rhodium on carbon, followed by successive hydrolysis and methylation, gave methyl tetrahydroquinoline-2-carboxylate (**13**) without any epimerization. The absolute configuration of **13** was determined from the optical rotation.[15,16] Optically active **13** has been used as a key intermediate for the synthesis of a potent NMDA receptor antagonist.[17,18] It was synthesized, however, via resolution of a racemic mixture.

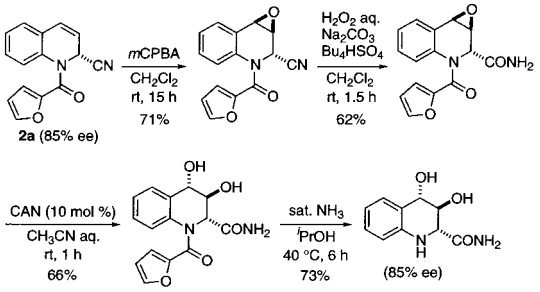
When this reaction was applied to the isomeric substrate, isoquinoline, however, the product was obtained in 75% yield with only 3% ee at −40 °C for 7.5 h, using benzoyl chloride and **5** (9 mol %). We attributed this discrepancy to the difficulty in controlling the amide conformer. From molecular modeling studies, there seems to be no significant preference between the two transition states involving either the *s*-cis or *s*-trans acyl isoquinolinium intermediate, at least sterically. Consequently, the reaction could proceed via both of these conformers. To overcome this, 3-methylisoquinoline (**3**) was used as the substrate (Figure 1). The methyl group at the 3-position should destabilize the transition state in which the 3-methyl group is oriented to the catalyst (*s*-cis, corresponding to **16**), thus favoring the *s*-trans conformer corresponding to **17**. As expected, **3** afforded the product **4** (R = Ph) in 97% yield with 68% ee at −40 °C for 15 h, using **5** as a catalyst and benzoyl chloride as an acylating reagent.[19] The enantioselectivity was further improved when the reaction was performed at −78 °C using acetyl chloride, giving **4** (R = CH_3) in 73% yield with 75% ee (Table 3, entry 10).[20] Although the selectivity and the generality of the reaction with isoquinoline derivatives were still unsatisfactory, these results indicated that differentiation between the catalyzed and uncatalyzed reaction rates, as well as between the two reactive conformers (*s*-trans against *s*-cis), is important for high enantioselection.

(15) Paradisi, M. P.; Romeo, A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 596−600.

(16) The absolute configuration of **2i** (R = 2-furyl) was determined converting to **12** (R = 2-furyl) via the following two steps: (1) saturation of the olefin by hydrogenation catalyzed by rhodium on carbon in MeOH and (2) debromination by hydrogenolysis catalyzed by palladium on carbon in MeOH. Unfortunately, partial epimerization (starting from **2i** (R = 2-furyl) with 67% ee to obtain **12** (R = 2-furyl) with 26% ee) occurred during these steps.

(17) (a) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Nishimura, T.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, Y.; Nakamura, M. *J. Med. Chem*. **1994**, *37*, 3956−3968. (b) Nagata, R.; Tanno, N. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 1527−1532. (c) Katayama, S.; Ae, N.; Nagata, R. *Tetrahedron: Asymmetry* **1998**, *9*, 4295−4299.

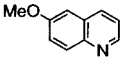
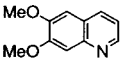
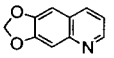
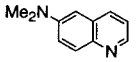
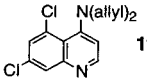
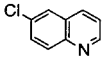
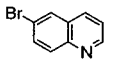
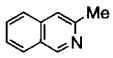
(18) Other interesting stereoselective functionalizations of the Reissert compound were conducted using optically active **2a** (85% ee) without any epimerization, following the reported procedures (Hiessböck, R.; Kratzel, M. *Heterocycles* **1996**, *43*, 873−882).



(19) Catalyst **6** gave less satisfactory results (32% ee, 99% yield). Molecular modeling studies indicated that the steric repulsion between the isoquinoline ring and the bulkier phosphine oxide destabilized the desired transition state corresponding to **17**.

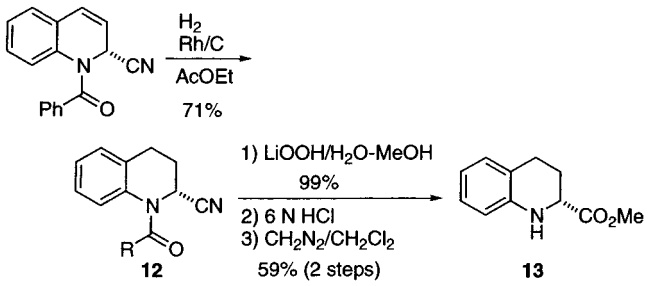
(20) In the case of **3**, acetyl chloride gave the better enantioselectivity because the reaction could be performed at lower temperature. Furthermore, the desired transition state (corresponding to **17**) should be more stable using a smaller R group in RCOCl that positions cis to the 3-methyl group.

Table 3. Scope and Limitations[a]

entry	substrate		solvent	h	yield (%)[b]	ee (%)[c]
1[d]		**1a**	CH_2Cl_2-toluene (1:1)	64	91	85[h]
2		**1b**	CH_2Cl_2-toluene (1:1)	40	74	89
3[e]		**1c**	CH_2Cl_2-toluene (1:1)	40	99	91
4[e]		**1d**	CH_2Cl_2-toluene (1:1)	64	77	83
5[e]		**1e**	CH_2Cl_2-toluene (1:5)	40	72	89
6[g]		**1f**	CH_2Cl_2	40	80	96[h]
7		**1g**	CH_2Cl_2-toluene (1:1)	40	71	54
8[d]		**1h**	CH_2Cl_2	64	57	67
9[d]		**1i**	CH_2Cl_2	112	63	67[h]
10[f]		**3**	CH_2Cl_2	24	73	75

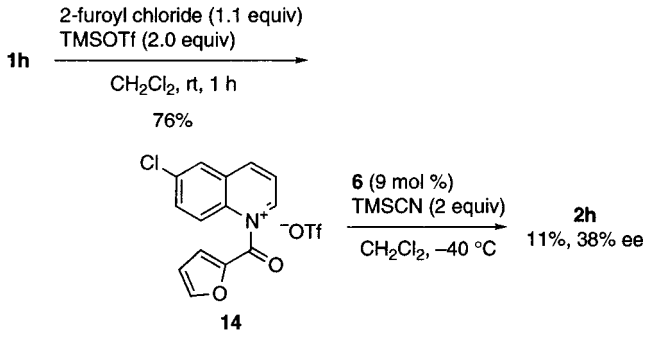
[a] The reaction was conducted at −40 °C using 9 mol % of **6**, 2 equiv of TMSCN, and 2 equiv of 2-furoyl chloride, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 4 equiv of TMSCN and 4 equiv of 2-furoyl chloride were used. [e] TMSCN was added slowly over 12 h. [f] The reaction was conducted at −78 °C using 9 mol % of **5**, 2 equiv of TMSCN, and 1.1 equiv of acetyl chloride. [g] The product was isolated after reduction of the enamine. See the text for details. [h] Absolute configurations were determined to be *R*. Absolute configurations of other products were temporarily assigned.

Scheme 1. Conversion to Methyl Tetrahydroquinoline-2-carboxylate



B. Mechanistic Studies. To confirm that the Reissert-type reaction proceeds via the acyl quinolinium intermediate, we performed the following studies. First, formation of the acyl quinolinium ion was observed using ^{1}H NMR, when quinoline (**1a**) was mixed with acetyl bromide in CD_3CN or CD_2Cl_2. This step was an equilibrium process and the ratio of quinoline and acyl quinolinium ion was dependent on the temperature (1:1 at −40 °C and 1:4 at 0 °C in CD_3CN). When catalyst **6** and TMSCN were added to the acyl quinolinium in CD_2Cl_2 at 0 °C, peaks corresponding to the acyl quinolinium disappeared and formation of the Reissert compound **2a** was confirmed.[21] Moreover, we performed the reaction using isolated *N*-(2-furoyl)-6-chloroquinolinium triflate (**14**), prepared following the reported procedure (Scheme 2).[22] As a result, the Reissert

Scheme 2. Catalytic Enantioselective Reissert-Type Reaction with the Isolated Acyl Quinolinium



product **2h** was obtained from **14** in 11% yield with 38% ee (vs 57% yield and 67% ee under the best reaction conditions, see Table 3, entry 8). Although the yield and ee using isolated **14** were not fully comparable with those under the best reaction conditions, these results provide support that the catalytic enantioselective Reissert-type reaction proceeds via the acyl quinolinium intermediate. The insolubility of **14** in CH_2Cl_2 and/or the different counteranion (triflate) might compromise the yield and ee in the case of **14**. Finally, the alternative reaction mechanism involving the direct attack of a cyanide to activated quinoline could be excluded because we did not observe any ^{1}H NMR peaks corresponding to the adduct of TMSCN to quinoline in the absence of an acid chloride, even in the presence of stoichiometric **6**. These results, together with the reported

(21) Even if the reaction was conducted in the presence of catalyst **6**, only racemic **2a** was obtained using acetyl bromide as an acylating reagent and CH_3CN or CH_2Cl_2 as a solvent.

(22) Pabel, J.; Hösl, C. E.; Maurus, M.; Ege, M.; Wanner, K. T. *J. Org. Chem.* **2000**, *65*, 9272−9275.

reaction mechanism of Reissert-type reactions,[5] led to the conclusion that the reaction proceeds via the formation of the acyl quinolinium intermediate as the first step, followed by the addition of cyanide as the second step.

When the Reissert-type reaction of quinoline using acetyl bromide was traced by ^{1}H NMR in CD_2Cl_2, interesting phenomena were observed. After adding TMSCN to the solution of the acetyl quinolinium intermediate in the presence of catalyst **6**, the peaks corresponding to the intermediate disappeared in 10 min at −40 °C and the product peaks started to emerge. After the disappearance of the intermediate, peaks corresponding only to quinoline and the Reissert product **2a** were observed. These observations indicated that cyanation is not the rate-determining step in the presence of the catalyst. In the absence of the catalyst, however, all the peaks corresponding to quinoline, acetyl quinolinium intermediate, and product **2a** were observed during the reaction. Therefore, in the absence of the catalyst, the cyanation is slow. Thus, the catalyst facilitates the cyanation step, and as a result, the first step (acyl quinolinium formation) becomes the rate-determining step.

Further insight into the reaction mechanism was obtained from kinetic studies. Utilizing concentration ranges of the reagents and the catalyst relevant to the actual reaction conditions, the initial reaction rate of **2a** formation in CH_2Cl_2−toluene (1:1) at −40 °C was 1.2, 0.15, and 0 order with respect to 2-furoyl chloride, TMSCN, and catalyst **6**, respectively.[23] These data indicate that the first step (acyl quinolinium formation) is the major rate-determining step, because the first step involves 2-furoyl chloride, which affected the reaction rate with higher order. Furthermore, 0 order dependence of the reaction rate on the catalyst indicates that the catalyst is not involved in the rate-determining step. From these studies, we postulate the reaction mechanism shown in Figure 2. The first step is a spontaneous and reversible addition of quinoline to the acid chloride, which is the rate-determining step and independent of the catalyst. When a small amount of the acyl quinolinium intermediate **15** is formed, the addition of TMSCN occurs immediately with the assistance of the catalyst in the second step. The enantioselective second step should proceed via dual activation: TMSCN activated by the phosphine oxide of the catalyst attacks an activated acyl quinolinium ion by the Lewis acid (aluminum metal). The two conformers of the amide bond **16** and **17** would exist in equilibrium. In the case of **16**, the distance between the activated TMSCN and the electrophilic carbon would be too remote for catalysis, in addition to a steric repulsion between the phosphine oxide moiety of the catalyst and the substrate. The transition state model **17** presents the *R* configuration of the major product. Based on this mechanism, if the TMSCN attack on the acyl quinolinium intermediate proceeds completely mediated by the catalyst, the order of TMSCN would be the same as that of the catalyst. The different rate orders of TMSCN and **6** indicate a very minor contribution of the spontaneous catalyst-independent reaction. This racemic reaction pathway should possess a higher order with respect to TMSCN, because the contribution of the second step to the total reaction rate would be more significant in the racemic pathway.

We also investigated the reason for moderate yields with electron deficient quinolines such as **1h** and **1i**. Tracing the reaction of **1h** using ^{1}H NMR at ambient temperature, the reaction proceeded during the initial 90 min to an approximately 70% yield of **2h**. The reaction slowed considerably, however, after that point (Figure 3, ■). We speculated that this feature of the reaction was caused by interference of the reaction by

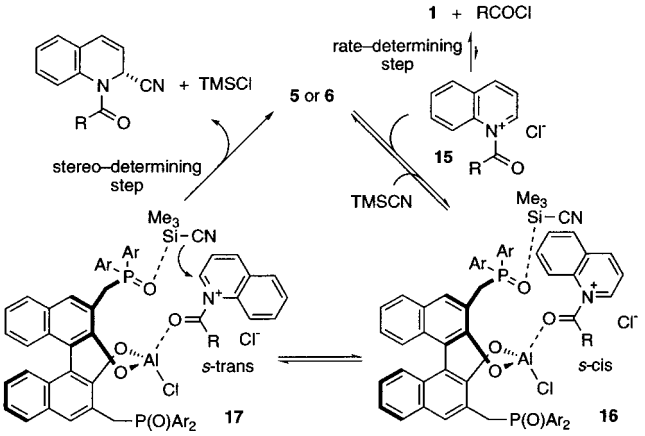


Figure 2. Postulated reaction mechanism.

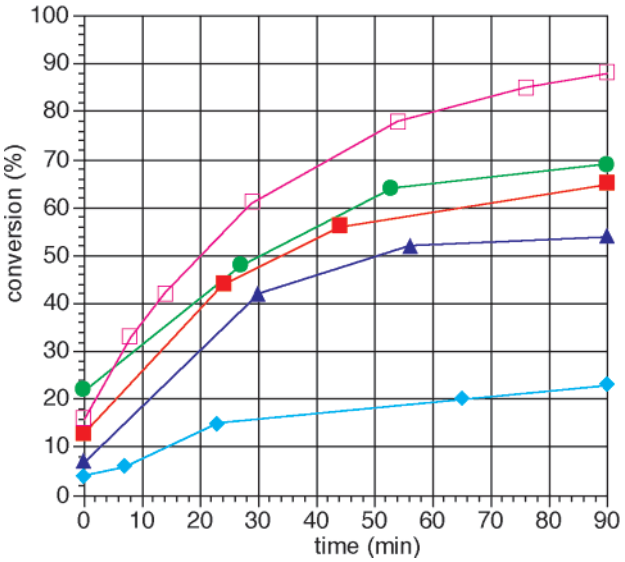
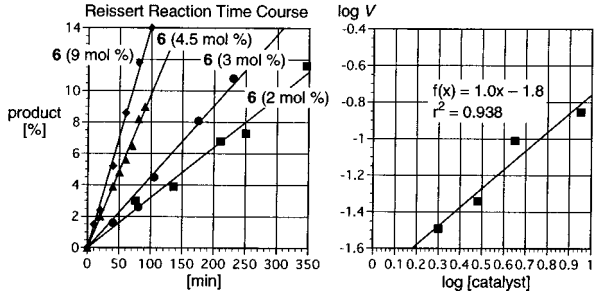


Figure 3. Reaction profiles of **1h** at ambient temperature in CH_2Cl_2 in the presence of TMSCN (4 equiv) and 2-furoyl chloride (4 equiv): ■, standard conditions (9 mol % of **6**); ●, 9 mol % of **6** premixed with Reissert product **2h**; ▲, 9 mol % of **6** premixed with TMSCl just before use; ◆, 9 mol % of **6** premixed with TMSCl for 1.5 h; and □, 9 mol % of Et_2AlCl.

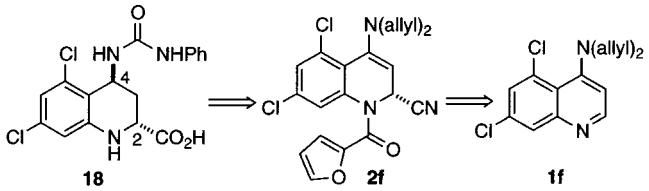
(23) To get further information on the cyanation step, we conducted kinetic studies using TBDMSCN, expecting the cyanation step to become the rate-determining step. In this case, the reaction was found to be first order in both TBDMSCN and catalyst **6** (left graph: initial reaction profiles varying catalyst concentrations; right graph: log−log plot to determine the order with respect to the catalyst), which is consistent with the proposed transition state of the cyanation containing one TMSCN and one catalyst, as shown in Figure 2. The Reissert-type reaction of **1a** using TBDMSCN (4 equiv) and 2-furoyl chloride (4 equiv) catalyzed by **6** (9 mol %) at −20 °C for 48 h afforded *R*-**2a** in 91% yield with 78% ee, which indicates a similar transition state to that with TMSCN. See Supporting Information for more details.



theproducts generated during the reaction (**2h** or TMSCl). On the basis of this assumption, the reaction was performed in the presence of 1 equiv of **2h**. The time course of the reaction, however, did not change much (Figure 3, ●). On the other hand, when the catalyst (9 mol %) was first premixed with 1 equiv of TMSCl, the time course of the reaction changed significantly. The degree of the interference seemed dependent on the premixing period (Figure 3, premixing period = 0 min (▲) and 1.5 h (◆)). Therefore, we concluded that TMSCl inhibited the reaction.[24] Because this interference did not occur when Et_2-AlCl was used as the catalyst (Figure 3, □), we assume that the inactivated species is an ate-complex, in which the phosphine oxide is silylated and two chlorides are bound to the aluminum binaphthoxide. Deactivation of the catalyst by silylation of the naphthoxide oxygen could be excluded, because we could not detect any O-silylated ligand using TLC and ^{1}H NMR. Preliminary attempts to reduce the concentration of TMSCl by converting TMSCl to TMSCN in situ using KCN or Bu_4NCN have not been successful.

C. Catalytic Enantioselective Synthesis of L-689,560. Overactivation of the NMDA subtype of excitatory amino acid receptors is implicated in several neurodegenerative disorders including epilepsy, stroke, and Alzheimer's disease.[25] As a result, NMDA antagonists might have therapeutic benefit, because these compounds are neuroprotective and anticonvulsant in a variety of animal models. L-689,560 (Scheme 3, **18**) is a strong NMDA receptor antagonist identified by the Merck group.[10] This tetrahydroquinoline-2-carboxylic acid derivative contains two chiral centers in a trans relationship. The (−)-enantiomer (2*R*,4*S*) is 540 times more potent than the (+)-enantiomer (2*S*,4*R*).[10a] Chiral tetrahydroquinoline-2-carboxylic acid, which should be useful for the synthesis of L-689,540, has only been available by resolution of the racemic compound.[10a] Our synthetic plan (Scheme 3) is to construct the chirality at the 2-position by the catalytic enantioselective Reissert-type reaction of **1f**,[26] followed by a stereoselective reduction of the resulting enamine to the amine with the desired configuration.

Scheme 3. Synthetic Plan for L-689,560



First, the optimized reaction conditions (2 equiv of TMSCN and furoyl chloride in CH_2Cl_2 at −40 °C for 40 h) were applied to the quinoline derivative **1f**.[27] The Reissert product **2f** was obtained in 29% yield with 91% ee, together with the hydrolyzed enamine **19** (13%, 90% ee) after the usual workup. When the reaction was quenched with AcOH to hydrolyze the enamine completely, **19** was obtained in 80% yield with 90% ee. Encouraged by these results, we tried a one-pot Reissert-type reaction-reduction process. After the Reissert-type reaction was completed, $NaBH_3CN$, AcOH, and MeOH were directly added to the reaction mixture. The reduction occurred with very high selectivity (>20:1) to give the desired trans isomer as the major product.[28] This stereoselectivity can be explained by the equatorial attack of the hydride to the iminium in the most stable chairlike conformation. The 0 order dependence of the Reissert-type reaction on the catalyst indicated that the overall reaction rate should not change very much even if the catalyst amount was reduced. Consistent with this expectation, the reaction proceeded smoothly to produce an 83% yield with 93% ee after reduction, even when using 1 mol % of the catalyst **6**. When 0.5 mol % of catalyst was used, however, ee was lower (87% ee, 74% yield). Thus, at present, the recommended catalyst loading of the Reissert-type reaction is 1 mol %. The reaction is possible on at least the 1-g scale.

Total synthesis of L-689,560 was completed from the key intermediate **20** as follows (Scheme 4). **20** was converted to the methyl ester **21** under acidic conditions. The furoyl group was hydrolyzed, and the resulting carboxylic acid was esterified to give **22** in 94% yield. At this stage, enantiomerically pure **22** was obtained by recrystallization from hexane (81% yield after recrystallization). The allyl groups were removed and the product was isolated as the hydrochloride salt **23**. The urea formation, followed by the hydrolysis of the ester, gave enantiomerically pure L-689,560 in 47% overall yield through 10 operations (including recrystallization) from quinoline **1f**. This clearly demonstrates that the catalytic enantioselective Reissert-type reaction offers an efficient and practical synthetic route for producing the target compound.

The development of an immobilized asymmetric catalysts is very important for easy separation of the product and potential to reuse the catalyst. Solid-supported catalysts have many advantages over homogeneous catalysts, especially in high throughput organic chemistry.[29] On the basis of the studies of the catalytic enantioselective Strecker-type reaction by immobilized **5**,[30] we designed a solid-supported catalyst **11**. The chiral ligand **6** was connected to Janda*J*EL[31] through the C-8 linker at the 6-position of the binaphthol core, following a similar synthetic route to immobilized **5**. The loading of the ligand on the polymer was determined to be 0.32−0.44 mmol/g, based on the loading of Cl on the commercially available Janda*J*EL.[32]

Using 3 mol % of **11**, 4 equiv of 2-furoyl chloride, and 4 equiv of TMSCN, the Reissert-type reaction of **1f** proceeded at a comparable rate as the homogeneous catalyst **6**, giving **20** in 92% yield with 86% ee (Table 4). The second cycle gave the product in comparable yield and ee. After the third cycle, however, the ee of the product was lower. These results indicated that the amount of the effective enantioselective catalyst was significantly reduced by repeated use under the reaction conditions. This might be caused by either a physical modification

(24) The inhibition by TMSCl should increase in the case of less reactive electron-deficient substrates. Because inactivation of the catalyst by TMSCl is a time-dependent process, the slower reaction should be influenced more. To exclude this deactivation process, we tried to use benzoyl fluoride or acetic anhydride. Reactions using these acylating reagents produce TMSF or TMSOAc, which should not react with aluminum. However, the reaction did not proceed at all with these reagents.

(25) Parsons, C. G.; Danysz, W.; Quack, G. *Drug News & Perspect.* **1998**, *11*, 523−569 and references cited in ref 10a.

(26) For the synthesis of **1f**, see Supporting Information.

(27) No reaction took place from the electron-deficient 5,7-dichloroquinoline.

(28) The relative configuration was defined by NOE observations, and also by converting **20** to L-689,560. To explain this excellent diastereoselectivity, we searched the most stable conformation of the iminium by the Monte Carlo method and found the chairlike conformation with equatorial cyanide to be the energy minimum. The peri-repulsion between the diallylimino group and the 5-Cl group might make the chairlike conformer more favored.

(29) Review: Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035−1074.

(30) Nogami, H.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 279−283.

(31) (a) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329−6332. (b) Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 6929−6934.

(32) For the synthesis of **11**, see Supporting Information.

Scheme 4. Catalytic Asymmetric Synthesis of L-689,560

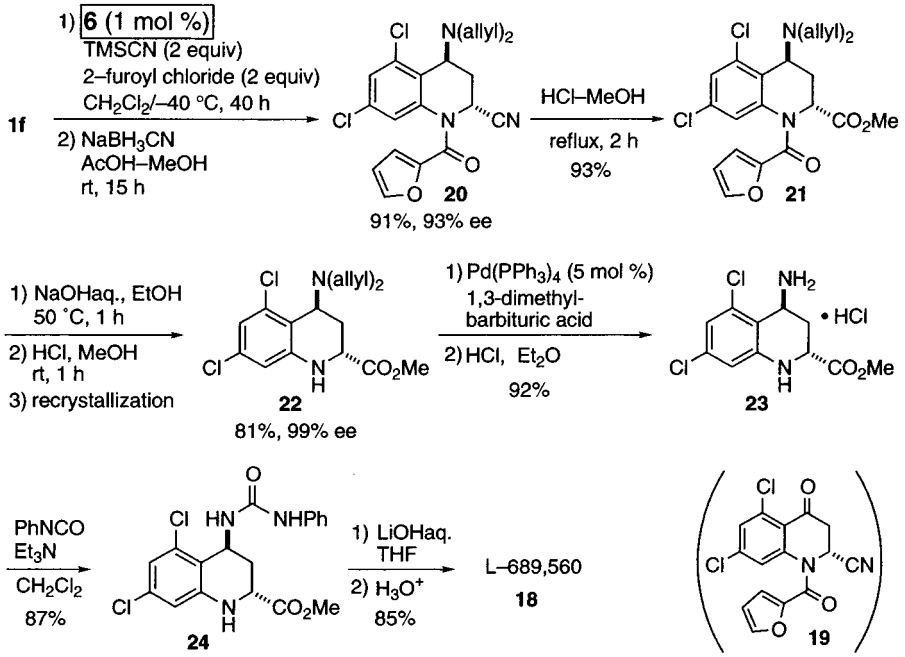


Table 4. Catalytic Enantioselective Reissert-Type Reaction of **1f** Using the Solid-Supported Catalyst[a]

cycle	yield/%	ee/%
1	92	86
2	93	84
3	93	79
4	92	64

[a] The reaction was performed using 3 mol % of **11**, 4 equiv of 2-furoyl chloride, and 4 equiv of TMSCN at −40 °C for 40 h in CH_2Cl_2.

of the polymer structure under the reaction conditions or a generation of a nonenantioselective catalyst. Although improvement is needed in terms of reusability, the polymer-supported catalyst **11** has promising utility. It should be applicable in a combinatorial synthesis of chiral quinoline derivatives.

Conclusion

We developed the first catalytic enantioselective Reissert-type reaction using bifunctional catalysts **5** and **6**. Although there was a competing racemic reaction pathway, the reaction proceeded mainly via the pathway mediated by the catalyst after optimization of the reaction conditions (acid chlorides, solvents, and ligands). Kinetic studies indicated that the reaction should proceed via two steps: the rate-determining acyl quinolinium formation followed by the attack of a cyanide. The catalyst strongly facilitates the second cyanation step. The reaction was successfully applied to the efficient catalytic asymmetric synthesis of a potent NMDA receptor antagonist (−)-L-689,-560. A key step was the one-pot process using the Reissert-type reaction from quinoline **1f**, followed by a stereoselective reduction of the resulting enamine **2f**. This step gave the key intermediate **20** in 91% yield with 93% ee, using 1 mol % of **6**. The enantiomerically pure target compound was obtained after 10 operations (including recrystallization) in a total yield of 47%. Furthermore, we immobilized **6** to Janda*J*EL, and the resulting solid-supported catalyst **11** afforded **20** in a comparable yield to the homogeneous **6**, but with slightly lower enantioselectivity.

Experimental Section

A Representative Procedure for the Catalytic Asymmetric Reissert-Type Reaction of Quinolines (Table 3, entry 3). Et_2AlCl (30 μL, 0.029 mmol in hexane) was added at ambient temperature to a solution of the ligand **6-L** (22 mg, 0.029 mmol) in CH_2Cl_2 (2.5 mL) and the resulting solution was stirred for 1 h. This catalyst solution of **6** was cooled to −40 °C, and a solution of **1c** (60.5 mg, 0.32 mmol) in CH_2Cl_2 (0.5 mL) was added, followed by the addition of 2-furoyl chloride (63 μL, 0.64 mmol). After adding toluene (2.5 mL), TMSCN (85 μL, 0.64 mmol) in toluene (0.5 mL) was added slowly over 24 h at −40 °C. A saturated aqueous solution of $NaHCO_3$ was added after 40 h and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated NaCl and dried over $NaSO_4$. Evaporation of the solvent and purification of the resulting crude product by silica gel column chromatography (eluent: AcOEt/hexane = 1/4) gave the pure product.

***trans*-*N*-(2-Furoyl)-2-cyano-4-diallylamino-5,7-dichloro-1,2,3,4-tetrahydroquinoline (20) (Procedure for One-Pot Synthesis of 20 Using 1 mol % Catalyst)**. Et_2AlCl (34 μL, 0.032 mmol in hexane) was added at ambient temperature to a solution of the ligand **6-L** (24.7 mg, 0.032 mmol) in CH_2Cl_2 (3 mL), and the resulting solution was stirred for 1 h. A solution of **1f** (940 mg, 3.20 mmol) in CH_2Cl_2 (2 mL), 2-furoyl chloride (630 μL, 6.40 mmol), and TMSCN (850 μL, 6.40 mmol) was added at −40 °C to the resulting catalyst solution of **6**. The mixure was diluted with MeOH (10 mL) after 40 h followed by the addition of $NaBH_3CN$ (402 mg, 6.4 mmol) and acetic acid (200 μL, 3.4 mmol). The whole mixture was allowed to warm to room temperature, and after 15 h was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O (50 mL, ×2). The combined organic layer was washed with brine (50 mL ×2) and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash column chromatography on SiO_2 (5∼20% ethyl acetate/hexane) to afford **20** (1.2 g, 91%, 93% ee).

Procedure for the Reissert-Type Reaction Using Polymer-Supported Catalyst 11. Et_2AlCl (31.0 μL of a 0.93 M hexane solution, 28.8 μmol) was added to the immobilized ligand (87 mg, loading = 0.32 mmol/g resin, 38 μmol) swelled in CH_2Cl_2 (4.0 mL), and the mixture was stirred for 1 h at room temperature. After the mixture was cooled to −40 °C, substrate **1f** (281 mg, 0.96 mmol) in CH_2Cl_2 (2.0 mL) and TMSCN (513 μL, 3.84 mmol) were added successively, and after further addition of 2-furoyl chloride (378 μL, 3.84 mmol), the mixture was stirred for 40 h at the same temperature. Dry Et_2O (3 times the volume of CH_2Cl_2) was added, and then the reaction mixture

was maintained for 1 h at −78 °C. The supernatant containing the enamine **2f** was removed by a syringe and the resin was washed with dry Et_2O twice under an inert atmosphere. The combined organic layer was concentrated in vacuo, diluted with MeOH (4.0 mL), and allowed to undergo reduction with $NaBH_3CN$ (60 mg, 0.96 mmol) and acetic acid (20 μL) at room temperature for 15 h. After the catalyst was dried under reduced pressure for 1 h, CH_2Cl_2 solvent, **1f**, TMSCN, and 2-furoyl chloride were added at −40 °C to start a new cycle.

Acknowledgment. Financial support was provided by CREST, The Japan Science and Technology Corporation (JST), and RFTF of Japan Society for the Promotion of Science.

Supporting Information Available: Experimental procedures and characterization of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA010654N