Asymmetric Reissert-type Reaction Promoted by Bifunctional Catalyst

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

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

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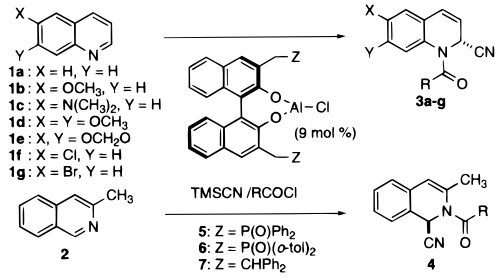
The addition of cyanide to quinoline or isoquinoline derivatives (the Reissert-type reaction[1]) has been widely used as a key step for the synthesis of various heterocyclic compounds, especially for the synthesis of biologically important alkaloids.[2] Moreover, the Reissert reaction has been applied to solid-phase synthesis, opening the way to utilize this reaction for synthesizing heterocyclic compounds by a combinatorial strategy.[3] It is also specifically noteworthy that Reissert compounds could offer direct entries for synthesizing the chiral tetrahydroquinoline-2-carboxylate (**9**) derivative, which has been recently identified as a pharmacophore of the glycine-site antagonist of a *N*-methyl-D-aspartate (NMDA) receptor on neurons.[4,5] Despite the importance of Reissert compounds as a versatile chiral building block, no asymmetric Reissert-type reaction of cyanide has been reported so far, even by using a stoichiometric amount of a chiral promoter.[6] Developing a catalytic asymmetric Reissert-type reaction is a great challenge, mainly due to the following two reasons. First, strong electrophiles such as an acid halide or TMSCl (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 **11** and **12**) of the reactive acyl quinolinium or isoquinolinium ion[7,8] is rather flexible. The two conformers would produce opposing enantiomers even if TMSCN attacks the reactive intermediate from a defined side. So, these two conformers should be strictly differentiated by the catalyst. Despite these formidable difficulties, we expected that using the bifunctional catalyst[9] **5**, **6** should be advantageous for developing a catalytic asymmetric Reissert-type reaction. The bifunctional catalyst has been reported to promote the cyanosilylation reaction of aldehydes and imines with high enantioselectivity, simultaneously activating both the substrate and TMSCN by the Lewis acid and the Lewis base moieties of the catalyst. In this paper, we disclose the first catalytic asymmetric Reissert-type reaction promoted by the Lewis acid−Lewis base bifunctional catalyst.



We started the project by investigating the effect of different acid chlorides (RCOCl) on the reaction, using **5** (9 mol %) as the catalyst and quinoline **1a** as the substrate at −40 °C. The substituent (R) should have the predominant effect in controlling the distribution of *s*-trans/*s*-cis amide conformers of the acyl quinolinium intermediate. As shown in Table 1 (entries 1−6), it was found that benzoyl chloride (entry 1) and 2-furoyl chloride (entry 2) afforded higher enantiomeric excesses than aliphatic or substituted aromatic acid chlorides.[10] The more electron-rich and

Table 1. Catalytic Asymmetric Reissert-type Reaction[a]

entry	substrate	catalyst	solvent	R[b]	h	yield/%[c]	ee/%[d]
1	**1a**	**5**	CH_2Cl_2	Ph	24	70	71[i]
2	**1a**	**5**	CH_2Cl_2	2-furyl	48	58	73[i]
3	**1a**	**5**	CH_2Cl_2	*o*-MeOPh	24	68	64
4	**1a**	**5**	CH_2Cl_2	CH_3	24	42	58
5	**1a**	**5**	CH_2Cl_2	PhCH=CH	24	52	54
6	**1a**	**5**	CH_2Cl_2	1-naphthyl	24	63	46
7	**1a**	**5**	CH_2Cl_2/toluene[g]	Ph	24	27	78[i]
8	**1a**	**5**	CH_2Cl_2/pentane[g]	Ph	24	21	72[i]
9	**1a**	**5**	CH_3CN	Ph	24	67	37[i]
10	**1a**	**6**	CH_2Cl_2/toluene[g]	Ph	24	49	83[i]
11	**1a**	**6**	CH_2Cl_2/toluene[g]	2-furyl	64	91	85[i]
12	**1b**	**6**	CH_2Cl_2/toluene[g]	2-furyl	40	74	89
13[e]	**1c**	**6**	CH_2Cl_2/toluene[h]	2-furyl	40	72	89
14[e]	**1d**	**6**	CH_2Cl_2/toluene[g]	2-furyl	40	99	91
15[e]	**1e**	**6**	CH_2Cl_2/toluene[g]	2-furyl	60	77	83
16	**1f**	**6**	CH_2Cl_2	2-furyl	64	57	67
17	**1g**	**6**	CH_2Cl_2	2-furyl	112	63	67[i]
18[f]	**2**	**5**	CH_2Cl_2	CH_3	15	99	71

[a] For the representative procedure, see ref 14. [b] For entries 1−10 and 18, 1.1 equiv of acid chlorides and 2 equiv of TMSCN were used. For entries 12−15, 2 equiv of 2-furoyl chloride and TMSCN were used. For entries 11, 16 and 17, 4 equiv of 2-furoyl chloride and TMSCN were used. [c] Isolated yield. [d] Determined by chiral HPLC analyses (see Supporting Information). [e] TMSCN was added slowly over 12 h. [f] −60 °C. [g] 1:1. [h] 1:5. [i] Absolute configurations were determined to be *R* (see Supporting Information).

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

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(4) (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) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Tamiki, N.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, Y.; Nakamura, M. *J. Med. Chem*. **1994**, *37*, 3956−3968.

(5) Chiral tetrahydroquinoline-2-carboxylate **9** has only been available by the resolution of the racemic compound: (a) Paradisi, M. P.; Romeo, A. *J. Chem. Soc. Perkin Trans I* **1976**, 596−600. (b) Katayama, S.; Ae, N.; Nagata, R. *Tetrahedron: Asymmetry* **1998**, *9*, 4295−4299.

(6) To the best of our knowledge, even diastereoselective reactions using chiral acid chlorides have not been reported.

(7) For determination of the reactive acyl quinolinium ion intermediate of a Reissert-type reaction, see: (a) Duarte, F. F.; Popp, F. D. *J. Heterocycl. Chem*. **1991**, *28*, 1801−1804. (b) Abushanab, E.; Lee, D.-Y. *J. Org. Chem*. **1975**, *40*, 3376−3378. (c) Akiba, K.; Negishi, Y.; Inamoto, N. *Synthesis* **1979**, 55−57.

(8) To exclude that the reaction mechanism involves the direct attack of the cyanide to the activated quinoline coordinated to Al, followed by the trap with an acid halide, we performed the following studies. No peaks corresponding to the acyl quinolinium ion **10** were observed in ^{1}H NMR by mixing acid chlorides (PhCOCl and AcCl) and **1a** in CH_3CN, even in the presence of the catalyst **5** or Et_2AlCl from −50 °C to rt. Using AcBr, however, we could confirm the generation of **10** (R = CH_3) by observing new peaks at 9.9 ppm (C-2 proton) and 3.1 ppm (CH_3) (see also ref 7c). The ratio of **10** to **1a** depended on temperature (1: 1 at −40 °C and 1: 4 at 0 °C), indicating the equilibrium between **10** and **1a**. By adding only TMSCN to this equilibrium mixture at 0 °C, peaks corresponding to **10** disappeared, and formation of the Reissert compound was confirmed. The catalytic asymmetric Reissert reaction mediated by **5** using AcBr gave **3a** in 49% yield with 40% ee in CH_2Cl_2. Furthermore, even in the presence of stoichiometric **5** or Et_2AlCl, peaks corresponding to the adduct of TMSCN to **1a** were not observed in the absence of acid halides. In addition, as will be mentioned in ref 13, addition of TMSCN is not the major rate-determining step, which may not be consistent with the mechanism involving the direct attack of cyanide to quinoline. Consequently, it appears, at the moment, that the reaction would proceed via an acyl quinolinium intermediate.

(9) (a) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **1999**, *121*, 2641−2642. (b) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650−1652.

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therefore less reactive 2-furoyl chloride gave slightly better enantioselectivity than benzoyl chloride. Next, we investigated the effect of solvent by using the more reactive benzoyl chloride as the acylating reagent. It was found that, when the polarity of the solvent was decreased by adding a less polar solvent such as toluene (entry 7) or pentane (entry 8), the ee increased to 78% from 71%, although the yield of the product became much lower.[11] In contrast, the ee decreased to 37% when the more polar acetonitrile was used as solvent (entry 9). These experiments suggested that lowering the concentration of the reactive acyl quinolinium intermediate (by using 2-furoyl chloride or less polar solvent) would give better enantioselectivity, although the chemical yield would be lower. This tendency may arise because the spontaneous reaction (independent of the catalyst) of the acyl quinolinium ion with TMSCN that gives the racemic product could proceed with only a slightly slower rate than mediated by the chiral catalyst. The spontaneous reaction could become less negligible if the concentration of the acyl quinolinium becomes high.

Thus, we planned to improve the reaction by developing a more reactive catalyst. Our design for the new catalyst 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 to assist the reaction.[12] By facilitating this step,[13] the reaction rate should be increased with the concentration of the reactive acyl quinolinium ion maintained sufficiently low. Molecular modeling studies suggested that if the steric bulkiness of the phosphine oxide's aryl groups is increased, the Lewis-basic oxygen atom would be put into a position close to the acyl quinolinium ion activated by the Lewis acid. On the basis of this idea, we synthesized a new catalyst **6** containing di-*o*-tolylphosphine oxide. Because catalyst **6** should also have higher Lewis basicity than the original catalyst **5**, we expected that **6** would show higher reactivity as well as higher enantioselectivity. Gratifyingly, by using **6** as the catalyst, both the chemical yield and ee were improved to 49 and 83% (entry 10), respectively, from 27 and 78% (entry 7). Furthermore, using 4 equiv of TMSCN and 2-furoyl chloride, **3a** was obtained in 91% yield with 85% ee (entry 11). For other reactive quinolines, 2 equiv of TMSCN and 2-furoyl chloride were used. By using the optimized conditions, Reissert compounds were obtained in up to 91% ee and 99% yield in the case of the reactive, electron-rich quinolines **1b**−**1e** (entries 12−15).[14] The less reactive substrates **1f** and **1g** gave less satisfactory results, although still yielding the products in 67% ee (entries 16, 17). It is also important that this reaction could be applied to the isoquinoline derivative **2** (entry 18), giving the product **4** with 71% ee in 99% yield by using **5** as the catalyst and acetyl chloride as the acylating reagent.[15]

The Reissert product was successfully converted to the tetrahydroquinoline-2-carboxylate **9** without any loss of enantiomeric purity (Scheme 1). By comparison of the optical rotation of **9** with the literature value,[5] the absolute configuration of the Reissert compounds was determined to be *R*.

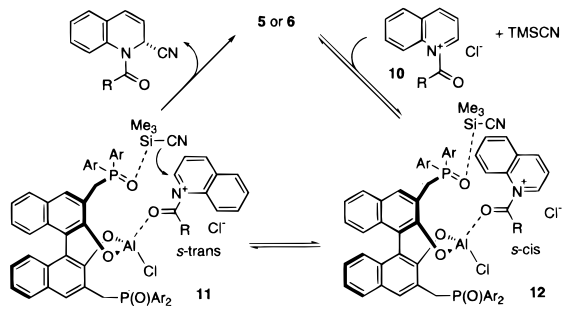
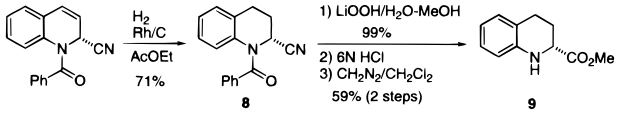


Figure 1. Working model for the catalytic cycle.

Scheme 1. Conversion to Tetrahydroquinoline-2-carboxylate



Although a detailed reaction mechanism is still not clear at this moment, the reaction should be promoted by the dual activation of the acyl quinolinium or isoquinolinium ion and TMSCN by the Lewis acid (Al) and the Lewis base (oxygen atom of the phosphine oxide) moieties of the catalyst, respectively. The results using the control catalyst **7** implied the dual activation mechanism by **5** and **6**. **7** contained diphenylmethyl groups providing only steric bulkiness without Lewis basicity. Thus, catalyst **7** afforded **3a** (R = Ph, 24% ee in 73% yield) and **3d** (R = 2-furyl, 46% ee in 95% yield) with the opposite configuration (*S*). These results suggest that, in the case of **5** and **6**, TMSCN appears to attack the acyl quinolinium intermediate from the phosphine oxide's side. Therefore, we postulated the working model for the catalytic cycle depicted in Figure 1. The first step should be the formation of the reactive acyl quinolinium intermediate **10** by the reaction of quinoline with the acid chloride.[7,8] The acyl quinolinium ion should be activated by complexation of the amide oxygen to the Lewis acid (Al). The two conformers of the amide bond **11** and **12** would exist in equilibrium. However, when TMSCN is activated by the Lewis-base moiety of the catalyst, the reaction via **11** would be more favorable than via **12**. In the case of **12**, the distance between the activated TMSCN and the electrophilic carbon would be too far for catalysis. The hypothetical transition state **11** could explain the absolute configuration of the product was *R*.

In summary, the first catalytic asymmetric Reissert-type reaction of quinoline and isoquinoline derivatives has been achieved by using a Lewis acid−Lewis base bifunctional catalyst. When quinoline derivatives were used as the substrates, the new catalyst **6**, containing di-*o*-tolylphosphine oxide, was found to be a better catalyst than the original catalyst **5**, in terms of activity as well as enantioselectivity. The Reissert compound was successfully converted to tetrahydroquinoline-2-carboxylate (**9**), without any loss of enantiomeric purity. Further investigations to increase the generality of substrates and to clarify the precise reaction mechanism, as well as applications to the catalytic asymmetric total synthesis of biologically active natural products, are currently in progress.

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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.

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(10) No acylated or silylated ligand was observed by TLC analysis.

(11) Longer reaction time did not improve the chemical yield.

(12) 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.

(13) The major rate-determining step would be the formation of the acyl quinolinium ion. However, the cyanation step was found to have some contribution to the reaction rate. Kinetic studies indicated that the total reaction rate was 0.2 order with respect to TMSCN. See Supporting Information.

(14) A representative procedure: To the solution of the ligand (22 mg, 0.029 mmol) in CH_2Cl_2 (2.5 mL), Et_2AlCl (30 μL, 0.029 mmol in hexane) was added at ambient temperature, and the resulting solution was stirred for 1 h. This catalyst solution of **6** was cooled to −40 °C, and a solution of **1d** (60.5 mg, 0.32 mmol) in CH_2Cl_2 (0.5 mL) was added, followed by 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. After 40 h, saturated aqueous solution of $NaHCO_3$ was added. Usual workup and purification by silica gel column chromatography (AcOEt/hexane, 3/7) gave the product in 99% yield. The ee was determined to be 91% by chiral HPLC analysis (DAICEL CHRALPAK AS, ^{i}PrOH/hexane, 3/7, flow = 1.0 mL/min, retention time, 15.7 min (major), 20.8 min (minor)).

(15) The absolute configuration was tentatively assigned. Using catalyst **6** with benzoyl chloride, 2-furoyl chloride or CH_2Cl_2−toluene mixed solvent with **5** gave less satisfactory results (32, 48, and 59% ee's, respectively).