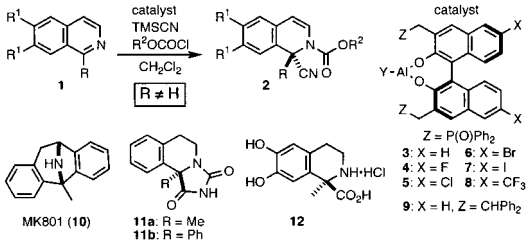
Enantioselective Construction of Quaternary Stereocenter through a Reissert-Type Reaction Catalyzed by an Electronically Tuned Bifunctional Catalyst: Efficient Synthesis of Various Biologically Significant Compounds

Ken Funabashi, Hassen Ratni, Motomu Kanai, and Masakatsu Shibasaki*

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

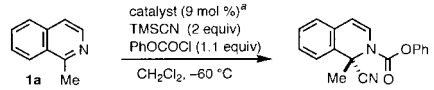
Received August 25, 2001

Catalytic enantioselective construction of chiral quaternary stereocenters is a formidable challenge.[1] For this type of reaction to proceed successfully, catalysts must differentiate between the subtle sterical differences of substituents on a *pro*-chiral carbon that lacks the remarkably small hydrogen. In addition, catalysts must activate substrates more strongly than in cases of chiral tertiary stereocenter construction, due to higher steric repulsion during bond-formation. Chiral quaternary centers are quite often essential for the activity of biologically active natural products and pharmaceuticals. Therefore, development of enantioselective catalysts that can promote chiral fully substituted carbon formation is extremely important. In this communication, we describe the first example of a catalytic enantioselective Reissert-type reaction in which chiral quaternary stereocenters can be constructed. This new reaction was successfully applied to an efficient catalytic enantioselective synthesis of several biologically significant compounds (**10**−**12**), such as the potent anticonvulsant MK801 (dizocilpine, **10**).[2]



We developed the first catalytic enantioselective Reissert-type reaction with quinolines using a bifunctional catalyst (such as **3**, Y = Cl), giving products containing chiral trisubstituted carbons.[3] The quaternary stereocenter-constructing reaction did not proceed, however, when the optimized reaction conditions (9 mol % of catalyst, 1.1 equiv of 2-furoyl chloride as an acylating reagent, and 2 equiv of TMSCN) were applied to 2-methylquinoline as a substrate. On the other hand, the more reactive substrate, 1-methylisoquinoline (**1a**), gave the corresponding Reissert product in 60% yield with 38% ee at −40 °C for 48 h.[4] Preliminary screening of acylating reagents revealed that chloroformates produced better chemical yields and enantioselectivity than acid chlorides.[5] Thus, PhOCOCl gave the corresponding product from **1a** in 72% yield with 56% ee at −60 °C (Table 1, entry 1).

Table 1. Ligand Effect on Catalytic Enantioselective Reissert-Type Reaction



entry	catalyst	time (h)	yield (%)[b]	ee (%)[c]
1	**3** (X = H)	48	72	56
2	**4** (X = F)	48	74	71
3	**5** (X = Cl)	48	88	81
4	**6** (X = Br)	48	91	84
5[d]	**6** (X = Br)	48	93	88
6	**7** (X = I)	60	85	81
7	**8** (X = CF_3)	60	68	48

[a] Y (counterion of aluminum) = Cl. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Vinyl chloroformate (1.2 equiv) was used instead of phenyl chloroformate.

The bifunctional catalyst was then electronically tuned to further improve its efficiency. The Lewis acidity and/or Lewis basicity were increased by substitution on the naphthyl or phenyl groups. Although the catalyst containing a more electron-rich di-*p*-methoxyphenylphosphine oxide gave poorer results (29% yield and 40% ee), the strategy to increase the Lewis acidity by introducing an electron-withdrawing group at the 6,6′-positions of the BINOL (X) was successful. Thus, as shown in Table 1, entries 2−4 and 6, catalysts derived from the 6,6′-dihalogen substituted BINOL had improved activity and enantioselectivity.[6] Among them, the 6,6′-dibromo-substituted catalyst **6** (Y = Cl) had the best results and the product was obtained in 91% yield with 84% ee (entry 4). Use of vinyl chloroformate improved yield (93%) and ee (88%) (entry 5).

These initial promising results led us to apply this reaction to a catalytic enantioselective synthesis of a pharmaceutically important agent, MK801 (**10**).[7] MK801 is a very potent noncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) subclass of receptors for the excitatory amino acid L-glutamate in brain tissue, and might therefore be clinically useful as an anticonvulsant and neuroprotective drug. The (5*S*,10*R*)-(+) isomer is seven times more potent than the (5*R*,10*S*)-(−) isomer; however, there are no reports of an enantioselective synthesis.[8] We expected that Reissert compound **2h** would be directly converted to the 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine core structure of MK801 by regioselective radical cyclization.

Thus, we attempted a Reissert-type reaction of 1-*o*-bromophenylisoquinoline (**1h**) at −40 °C in the presence of 9 mol % of **6** (Y = Cl), and product **2h** was obtained in 53% yield with 73% ee (Table 2, entry 1). To improve the yield and enantioselectivity, we further increased the Lewis acidity of the catalyst by tuning the counterion (Y) of the aluminum.[9] As shown in Table 2, when an aluminum triflate (Y = OTf) was used as the Lewis acid, product **2h** was obtained in higher yield (63%) with 98% ee (entry 3). These improvements were not attributed to the formation of

(1) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(2) Thompson, W. J.; Anderson, P. S.; Britcher, S. F.; Lyle, T. A.; Thies, J. E.; Magill, C. A.; Varga, S. L.; Schwering, J. E.; Lyle, P. A.; Christy, M. E.; Evans, B. E.; Colton, D.; Holloway, M. K.; Springer, J. P.; Hirshfield, J. M.; Ball, R. G.; Amato, J. S.; Larsen, R. D.; Wong, E. H. F.; Kemp, J. A.; Tricklebank, M. D.; Singh, L.; Oles, R.; Priestly, T.; Marshall, G. R.; Knight, A. R.; Middlemiss, D. N.; Woodruff, G. N.; Iversen, L. L. *J. Med. Chem.* **1990**, *33*, 789−808.

(3) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801−6808.

(4) For racemic Reissert-type reaction with 1-substituted isoquinolines, see: Berg, M. A.; Gibson, H. W. *J. Org. Chem.* **1992**, *57*, 748−750.

(5) Benzyl chloroformate and methyl chloroformate gave the corresponding Reissert products at −40 °C in 57% yield with 52% ee and 64% yield with 48% ee, respectively.

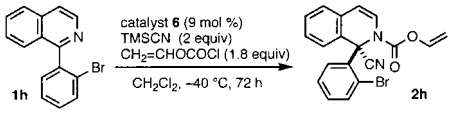
(6) There was a good correlation between ee values and Hammet constants for para substitutions: F (0.06), Cl (0.22), Br (0.23), I (0.18), CF_3 (0.53) (Pine, S. H.; Hendrickson, J. B.; Cram, D. J.; Hammond, G. S. *Organic Chemistry*, 4th ed.; McGraw-Hill: New York, 1980).

(7) For a review on target-oriented catalytic enantioselective reactions, see: Hoveyda, A. H. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, Germany, 2000; p 145.

(8) Enantiomerically pure **10** was obtained by resolution. For racemic synthesis of **10**, see: (a) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1999**, *64*, 6515−6517. (b) Christy, M. E.; Anderson, P. S.; Britcher, S. F.; Colton, C. D.; Evans, B. E.; Remy, D. C.; Engelhardt, E. L. *J. Org. Chem.* **1979**, *44*, 3117. (c) Evans, B. E.; Anderson, P. S.; Christy, M. E.; Colton, C. D.; Remy, D. C.; Rittle, K. E.; Engelhardt, E. L. *J. Org. Chem.* **1979**, *44*, 3127.

10.1021/ja016935c CCC: $20.00
Published on Web 10/09/2001

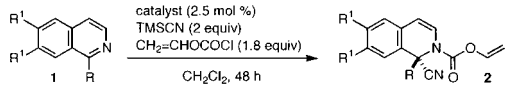
Table 2. Counterion Effect on Catalytic Enantioselective Reissert-Type Reaction

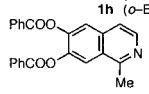


entry	catalyst	yield (%)[a]	ee (%)[b]
1	**6** (Y = Cl)	53	73
2	**6** (Y = CN)	73	65
3	**6** (Y = OTf)	63	98
4	**6** (Y = NTf_2)	55	88
5	**6** (Y = BF_4)	58	31

[a] Isolated yield. [b] Determined by HPLC analysis.

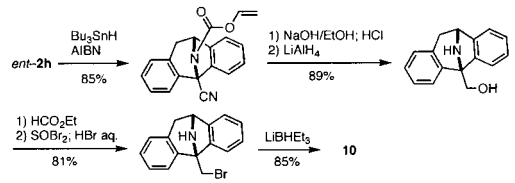
Table 3. Catalytic Enantioselective Quaternary Stereocenter-Forming Reissert-Type Reaction[a]



entry	1 (R)	catalyst 6 Y	temp (°C)	yield[b] (%)	ee[c] (%)
1	**1a** (Me)	OTf	–60	88	89
2	**1b** (Et)	OTf	–60	98	88
3	**1c** (CH_2Ph)	OTf	–60	95	92
4	**1d** (CH_2OCH_3)	OTf	–60	84	73
5	**1e** ($CH{=}CH_2$)	OTf	–60	80	84
6	**1f** ((*E*)–CH=$CHCH_3$)	OTf	–60	88	87
7	**1g** (Ph)	OTf	–40	95	95
8[e]	**1g** (Ph)	OTf	–50	88	95
9[f]	**1h** (*o*–Br–C_6H_4)	OTf	–40	62	95[d]
10[e,f]	**1h** (*o*–Br–C_6H_4)	OTf	–40	59	93[d]
11	 **1i**	Cl	–60	94	94[d]

[a] For the representative procedure, see ref 12. [b] Isolated yield. [c] Determined by chiral HPLC (see Supporting Information). [d] Absolute configurations were determined as shown (see Supporting Information). [e] 1 mol % of catalyst was used. [f] The reaction time was 72 h.

Scheme 1. Application of the Catalytic Enantioselective Reissert-Type Reaction to the Synthesis of MK801



an aluminum cyanide (Y = CN) by anion exchange, because the aluminum cyanide catalyst gave significantly lower ee (entry 2), albeit in higher yield. On the other hand, when more electron-withdrawing counterions (Y = NTf_2[10] or BF_4) than triflate were used (entries 4 and 5), enantioselectivity decreased, possibly due to a partial contribution of a racemic pathway promoted by a Lewis acidic silicon. These results indicated that there was almost no anion exchange on the aluminum, when weakly coordinating triflate was used as a counterion.

Having optimized the reaction conditions, substrate scope was investigated. As shown in Table 3, using 2.5 mol % of **6**, a quaternary stereocenter forming Reissert-type reaction proceeded with a broad range of 1-substituted isoquinolines to give the products in excellent yield and enantioselectivity. The reaction is not very sensitive to the steric bulkiness of the substituent at the 1-position (R). In some cases, catalyst loading could be reduced to 1 mol % (entries 8 and 10).[11,12]

The utility of this reaction was clearly demonstrated by an efficient catalytic enantioselective synthesis of several biologically significant compounds. First, MK801 (**10**) was synthesized in six steps from the Reissert product *ent*-**2h**, using radical cyclization as a key step (Scheme 1). Second, anticonvulsant phenytoin analogues[13] **11a** and **11b** were synthesized in high yield from

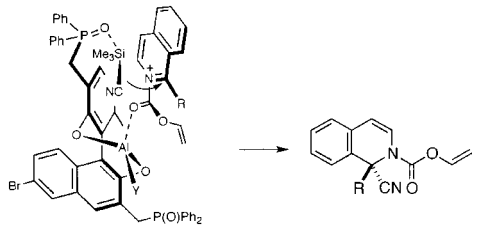


Figure 1. Working model.

ent-**2a** or *ent*-**2g**.[14] To our knowledge, this is the first example of an asymmetric synthesis of these three compounds. Similarly, an enantioselective synthesis of **12**, a biosynthetic intermediate of a dopamine-derived alkaloid salsolinol,[15] was achieved in three steps from *ent*-**2i**.[14]

Although the complete reaction mechanism is not clear at the moment, the absolute configuration of the products and results with use of control catalyst **9** supports the idea that the reaction proceeds via dual activation of the acyl isoquinolinium and TMSCN by the Lewis acid and the Lewis base of the catalyst, as depicted in Figure 1. Thus, with 2.5 mol % of **9** (Y = Cl), (*R*)-**2a** (the opposite configuration) was obtained in 36% yield with 12% ee. Similarly, **9** (Y = OTf) gave (*R*)-**2g** in 95% yield with 4% ee. These control experiments indicated that, in the case of bifunctional catalyst **6**, the cyanide attacked the activated acyl isoquinolinium from the side of the phosphine oxide.

In summary, we report the first example of a catalytic enantioselective quaternary stereocenter construction through a Reissert-type reaction. This new reaction should allow for the efficient synthesis of many useful compounds, and several examples are described in this paper. Further extension of this reaction to other substrates such as quinolines and pyridines is now in progress.

Acknowledgment. Financial support was provided by RFTF of the Japan Society for the Promotion of Science. We thank Dr. M. Takamura and Dr. G. Manickam for their contribution in the ligand synthesis. H.R. thanks the "Roche Research Foundation" for a fellowship.

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.

JA016935C

(9) A major concern of this approach using a hard aluminum metal and a silylated nucleophile was that an extremely Lewis acidic silicon (such as TMSOTf) would be generated via anion exchange. This strong Lewis acid could promote a racemic reaction. Therefore, chiral cationic complexes of hard metals have been used only for reactions with nonsilylated reagents. For examples, see: (a) Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884−1888 (aldol-type reaction with aluminum). (b) Odenkirk, W.; Bosnich, B. *Chem. Commun*. **1995**, 1181 (Diels−Alder reaction with titanium). (c) Mikami, K.; Terada, M.; Sawa, E.; Nakai, T. *Tetrahedron Lett*. **1991**, *32*, 6571 (carbonyl-ene reaction with titanium). Indeed, a Reissert-type reaction proceeded using TMSOTf (2.5 mol %) as catalyst, giving **2g** in 38% yield at −40 °C for 48 h. For a discussion of a racemic reaction pathway mediated by silicon, see: Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol.3, Chapter 29.1.

(10) Marx, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 178−181.

(11) When a strongly Lewis acidic catalyst **6** (Y = OTf) was used in the case of **1i**, product **2i** was obtained in 58% yield with 90% ee. The lower yield may be attributed to the deprotonation of the terminal methyl group.

(12) A representative procedure (Table 3, entry 8): To a solution of **6** (13.1 mg, 0.015 mmol) in CH_2Cl_2 (3 mL) and Me_3Al (15.3 μL of a 0.98 M solution in hexane, 0.015 mmol) was added at ambient temperature and the resulting solution was stirred for 1 h. TfOH (freshly distilled, 250 μL of a 0.0585 M solution in CH_2Cl_2, 0.146 mmol, 97.5 mol % to Me_3Al) was then added and the mixture was stirred for 30 min. To the catalyst solution (or suspension) was added a solution of **1g** (308 mg, 1.5 mmol) in CH_2Cl_2 (2.5 mL) at −50 °C, followed by TMSCN (400 μL, 3.0 mmol) and vinyl chloroformate (230 μL, 2.7 mmol) to start the reaction.

(13) (a) Brouillette, W. J.; Brown, G. B.; DeLorey, T. M.; Liang, G. *J. Pharm. Sci*. **1990**, *79*, 871−874. (b) Zaugg, H. E.; Arendsen D. L. *J. Heterocycl. Chem.* **1974**, *11*, 803−806.

(14) See Supporting Information.

(15) Dostert, P.; Varasi, M.; Della Torre, A.; Monti, C.; Rizzo, V. *Eur. J. Med. Chem.* **1992**, *27*, 57−59.