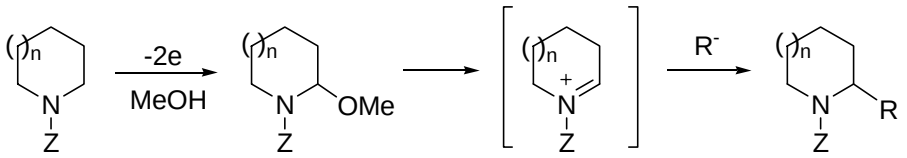
Copper ion-catalyzed regioselective introduction of active methylene groups into the γ-position of piperidine skeleton and its application to synthesis of (-)-cincholoiponic acid

Daishirou Minato, Mieko Imai, Yasuhisa Kanda, Osamu Onomura, and Yoshihiro Matsumura*

Department of Pharmaceutical Sciences, Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

Abstracts: Copper ion-catalyzed regioselective introduction of active methylene groups into the γ-position of piperidine skeleton was exploited. In the case of using chiral ligand as an additive, this reaction proceeded with moderate enantioselectivities. This method was applied to synthesis of (-)-cincholoiponic acid from *N*-methoxycarbonylpiperidine.

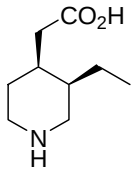
Carbon-carbon bond forming reactions at the α-position of cyclic amines **1** through iminium ion intermediates **A** to afford α-alkylated cyclic amines **3** have attracted a lot of interest (Eq. (1)) since it provides one of the simplest routes for formation of **3** which are often found as important moiety of naturally occurring nitrogen heterocycles.[1] We have already exploited electrochemical oxidation method through α-methoxylated piperidine **2** for the route.[2]



1 **2** **A** **3** (1)

Z: protecting group

On the other hand, there have been only two methods for carbon-carbon bond forming reaction at the γ-position of **1**, though γ-substituted piperidines are also worthwhile as synthetic intermediates for a variety of natural products and drug candidates.[3] One is conjugate addition of some aryl groups to β,γ-didehydro-α-oxopiperidines,[3e,g,i] and the other is introduction of some nucleophiles to pyridinium salts.[4,5,6] These methods however, are not applicable to piperidine derivatives possessing functionalized alkyl group at the γ-position, such as (-)-cincholoiponic acid (*cis*-**1**), (Fig. 1),[7] which is a structural moiety in a variety of alkaloids, and any asymmetric alkylation has not been reported.[8]



cis-**1**

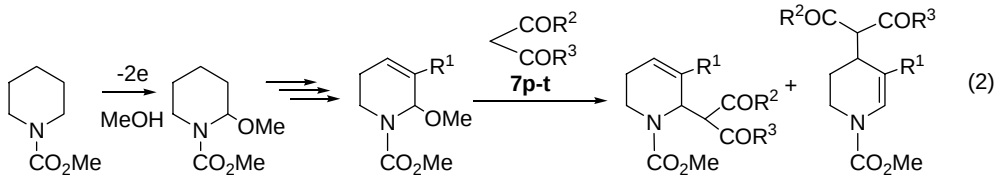
Figure 1

This paper presents copper ion-catalyzed coupling reaction of α-methoxylated β,γ-didehydropiperidines **6** with active methylene compounds **7** to afford γ-substituted piperidines **9** without formation of undesired regioisomers **8** (Eq. (2))[9,10] and its asymmetric application leading to formal synthesis of optically active *cis*-**1** with

Key words: piperidine, nucleophlic substitution, copper, regioselective, asymmetric

*Corresponding author, Tel +81-95-819-2429, Fax +81-95-819-2476, E-mail matumura@net.nagasaki-u.ac.jp (Y. Matsumura).

moderate enantioselectivity. The key starting compounds **6a,b** (**a**[11];R=H, **b**[12];R=Et) are known to be prepared by electrochemical oxidation of *N*-methoxycarbonylpiperidine (**4**) through α-methoxylated piperidine **5**.[13]



(2)

a: R^1=H **b**: R^1=Et **p**: R^2=OMe, R^3=OMe **q**: R^2=Me, R^3=OMe **r**: R^2=R^3=Me **s**: R^2=Me, R^3=Ph **t**: R^2=R^3=Ph

With **6a,b**, we first tried the coupling reaction of **6a,b** with dimethyl malonate (**7p**), methyl acetoacetate (**7q**), and 1,3-diketones **7r-t** and found that the coupling reaction proceeded in the presence of $Cu(OTf)_2$ (5mol%) in THF at room temperature for 12hrs to afford α-substituted piperidines **8ap-br** and/or selectively γ-substituted piperidines **9aq-bt**, the ratio being dependent on the structures of **6** and of nucleophiles **7**. The results are shown in Table 1.

Table 1. The reaction of **6a,b** with various active methylene compounds **7p-t**[a]

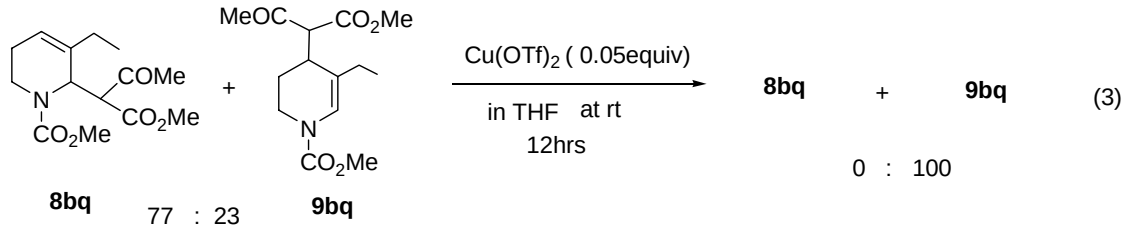
entry	substrate **6a,b**	R^1	active methylene compound **7p-t**	R^2	R^3	product **8,9**	yield (%)		yield (%)	ratio **8 /9**
1	**6a**	H	**7p**	OMe	OMe	**8ap**	68	**9ap**	0	100 / 0
2	**6b**	Et	**7p**	OMe	OMe	**8bp**	70	**9bp**	11	89 / 11
3	**6a**		**7q**	Me	OMe	**8aq**[b]	41	**9aq**[b]	21	66 / 34
4	**6b**		**7q**	Me	OMe	**8bq**	0	**9bq**[b]	85	0 / 100
5	**6b**		**7r**	Me	Me	**8br**	12	**9br**	37	25 / 75
6	**6b**		**7s**	Me	Ph	**8bs**	0	**9bs**[b]	55	0 / 100
7	**6b**		**7t**	Ph	Ph	**8bt**	0	**9bt**	48	0 / 100
8[c]	**6b**		**7q**	Me	OMe	**8bq**[b]	22	**9bq**[b]	6	77 / 23

[a] **6a,b** (0.5mmol), **7p-t** (0.75mmol), $Cu(OTf)_2$ (0.025mmol) in THF (2mL) at rt for 12hrs. [b] A mixture of diastereomers was obtained. [c] at 0℃.

The observed regioselectivity (**8**/**9**) was noticeable. Dimethyl malonate (**7p**) as a nucleophile afforded α-substituted piperidines (**8ap** and **8bp**) exclusively for **6a** (entry 1) and mainly for **6b** (entry 2), whereas the use of methyl acetoacetate (**7q**) decreased the ratio of **8**/**9** for **6a** (entry 3) and eventually resulted in formation of only **9bq** for **6b** (entry 4). Also a predominant formation of **9br-bt** was observed in the reaction of **6b** with 1,3-diketones **7r-t** (entries 5-7), though the yields of the products were in general lower than those in cases using malonates and acetoacetates.[14]

In order to elucidate the mechanism for the high regioselectivity observed in the reaction of **6b** and

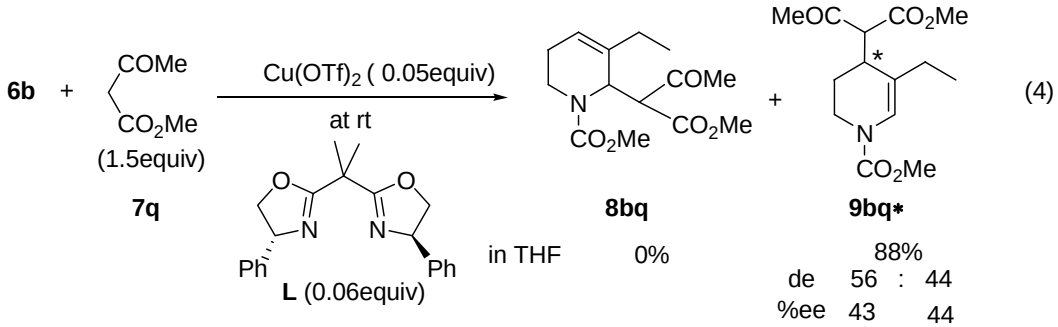
7q (entry 4), the reaction was carried out at 0°C to afford a mixture of **8bq** and **9bq** with a ratio of 77/23 in low yield (entry 8), whereas the treatment of a mixture of **8bq** and **9bq** (**8bq**/**9bq**=77/23) with $Cu(OTf)_2$ in THF at room temperature resulted in an exclusive formation of **9bq** (Eq. (3)).



(3)

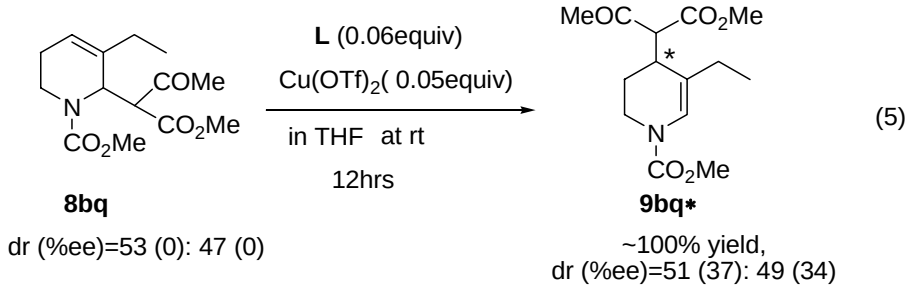
The selectivity can be explained in terms of the steric factor of both substrates and active methylene compounds as described later.

After finding the best conditions that γ-substituted piperidine **9bq** was selectively formed, we then tried asymmetric reaction of **6b** with **7q** in the presence of $Cu(OTf)_2$ and chiral bisoxazoline ligand **L**.[15] The result was interesting since a mixture of diastereomers **9bq*** was generated in a ratio of 56/44, each of which had modest optical purity (43~44%ee) (Eq. (4)). However, asymmetric reaction was not observed in MeCN in place of THF as a solvent.



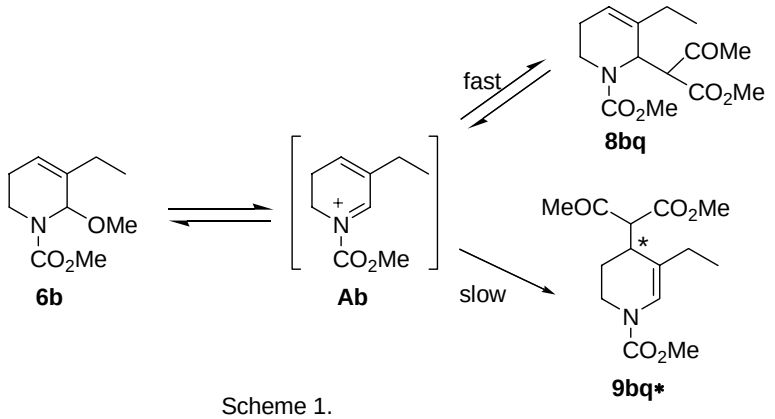
(4)

Further information to support the reaction mechanism was obtained when *racemic* α-substituted piperidine **8bq** was treated with $Cu(OTf)_2$ in the presence of chiral ligand **L** in THF at room temperature. The product was **9bq*** in a quantitative yield, and each of the diastereomers was optically active (Eq. (5)).



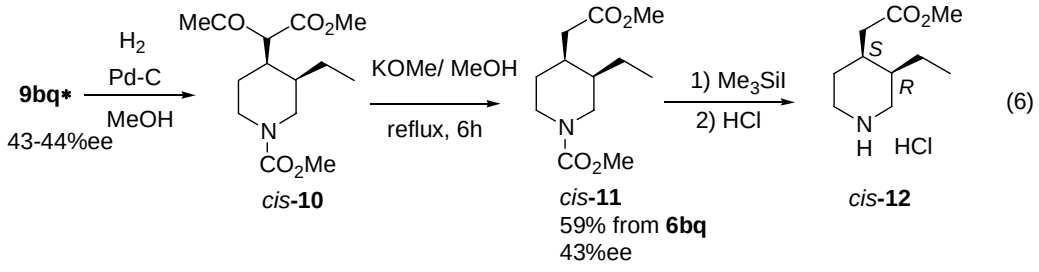
(5)

These results strongly suggest that **8bq** is a kinetically controlled product, while **9bq** is a thermodynamically stable product, and the rearrangement of **8bq** into **9bq*** proceeds through an iminium ion **Ab** with an intermolecular mechanism (Scheme 1). The observed regioselectivity may be determined by the steric factor of both β-ethyl substituent of **6b** and nucleophiles **7p-t,** though the effect of the reactivity of nucleophiles on the regioselectivity is not ruled out.



Scheme 1.

Finally, transformation of optically active **9bq*** into cincholoiponic acid methyl ester HCl salt (*cis*-**12**)[16] was achieved by the method described in Eq. (6), and the absolute configuration at the γ-position of *cis*-**12**, that is, the γ-position of **9bq***, was determined to be *S* by the comparison of the product *cis*-**12** with the authentic sample.[7a] It is known that the *cis*-**12** is easily transformed into (-)-cincholoiponic acid (*cis*-**1**).[7a]



(6)

In into the γ-position of piperidine skeleton and its application to the formal synthesis of (-)-cincholoiponic acid (*cis*-**1**).

Further studies on mechanistic aspects and the improvement of %ee are currently underway.

Acknowledgement

This study was supported by a Grant-in-Aid for Scientific Research on Priority Areas, (No. 420: Reaction Control of Dynamic Complexes) from the Ministry of Education, Science, Sports and Culture, Japan and by a Grant-in-Aid for Scientific Research (C) (No. 15550094) from Japan Society for the Promotion of Science.

References and Notes

1. a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817-3856. b) Loh, T.-P.; Lye,

P.-K.; Wang, R.-B.; Sim, K.-Y. *Tetrahedron Lett.* **2000**, *41*, 7779-7783. c) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809-823. d) Albrecht, U.; Armbrust, H.; Langer, P. *Synlett* **2004**, 143-145.

2. a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.*,**1981**, *103*, 1172-1176. b) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1984**, *63*, 206-213; **1990,** *Coll. Vol. VII*, 307-312. c) Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Org. Lett.* **1999**, *1*, 175-178. d) Onomura, O.; Ikeda, T.; Matsumura, Y. *Heterocycles* **2005**, *66*, 81-86. e) Matsumura, Y.; Ikeda, T.; Onomura, O. *Heterocycles* **2006**, *67*, 113-117.
3. For recent examples, see: a) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679-3681. b) Bowley, M.; Hallett, D. J.; Goodacre, S.; Moyes, C.; Crawforth, J.; Sparey, T. J.; Patel, S.; Marwood, R.; Patel, S.; Thomas, S.; Hitzel, L.; O'Connor, D.; Szeto, N.; Castro, J. L.; Hutson, P. H.; MacLeod A. M. *J. Med. Chem.* **2001**, *44*, 1603-1614. c) Thomas, J. B.; Atkinson, R. N.; Rothman, R. B.; Fix, S. E.; Mascarella, S. W.; Vinson, N. A.; Xu, H.; Dersch, C. M.; Lu, Y. –F.; Cantrell, B. E.; Zimmerman, D. M.; Carrol, F. I. *J. Med. Chem.* **2001**, *44*, 2687-2690. d) Agami, C.; Bisaro, F.; Comesse, S.; Guesné, S.; Kadouri-Puchot, C.; Morgentin, R. *Eur. J. Org. Chem.* **2001**, 2385-2389. e) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852-6856. f) Reilly, M.; Anthony, D. R.; Gallagher, C. *Tetrahedron Lett.* **2003**, *44*, 2927-2930. g) Murthy, K. S. K.; Rey, A. W.; Tjepkema, M. *Tetrahedron Lett.* **2003**, *44*, 5355-5358. h) Gill, C. D.; Greenhalgh, D. A.; Simpkins, N. S. *Tetrahedron* **2003**, *59*, 9213-9230. i) Ecija, M.; Diez, A.; Rubiralta, M.; Casamitjana, N.; Kogan, M. J.; Giralt, E. *J. Org. Chem.* **2003**, *68*, 9541-9553. j) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706-707. k) Tanaka, K.; Kobayashi, T.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 5906-5925. l) Mi, Y.; Corey, E. J. *Tetrahedron Lett.* **2006**, *47*, 2515-2516. m) Solares, L. F.; Lavandera, I.; Gotor-Fernández, V.; Brieva, R.; Gotor, V. *Tetrahedron* **2006**, *66*, 3284-3291.
4. Addition to pyridinium salts, see: a) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645-3655. b) Alvarez, M.; Lavilla, R.; Bosch, J. *Tetrahedron Lett.* **1987**, *28*, 4457-4460.
5. Addition to *N*-acyl pyridinium salts, see: a) Akiba, K.; Matsuda, H.; Wada, M. *Tetrahedron Lett.* **1981**, *22*, 4093-4096. b) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315-4319. c) Yamaguchi, R.; Nakazono, Y.; Kawanishi, M. *Tetrahedron Lett.* **1983**, *24*, 1801-1804. d) Wang, X.; Kauppi, A. M.; Olsson, R.; Almqvist, F. *Eur. J. Org. Chem.* **2003**, 4586-4592.
6. Addition to 5,6-dihydropyridinium salts, see: a) Grierson, D. S.; Harris, M.; Husson, H. P. *Tetrahedron* **1983**, *39*, 3683-3694. Allylation, see: b) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10972-10974.
7. a) Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571-576. b) Brown, R. T.; Leonard, J. *Tetrahedron Lett.* **1978**, 1605-1608. c) Fujii, T.; Ohba, M. *Chem. Pharm. Bull.* **1985**, *33*, 583-590. d) Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 517-524. e) Ihara, M.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 365-369. f) Amat, M.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4*, 2787-2790.
8. Catalytic asymmetric alkylation at the 2-position of piperidine skeleton have been already reported by us, see: a) Onomura, O.; Kanda, Y.; Nakamura, Y.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2002**, *43*, 3229-3231. b) Kanda, Y.; Onomura, O.; Maki, T.; Matsumura, Y. *Chirality* **2003**, *15*, 89-94. c) Onomura, O.; Kanda, Y.; Imai, M.; Matsumura, Y. *Electrochimica Acta* **2005**, *50*, 4926-4935.
9. Copper ion-catalyzed alkylation and phenylation, see: Shono, T.; Terauchi, J.; Ohki, Y.;

Matsumura, Y. *Tetrahedron Lett*. **1990**, *31*, 6385-6386.
10. Titanium-catalyzed diastereoselective introduction of sterically hindered active methylene groups, see: Matsumura, Y.; Yoshimoto, Y.; Horikawa, C.; Maki, T.; Watanabe, M. *Tetrahedron Lett*. **1996**, *37*, 5715-5718.
11. a) Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. *Tetrahedron Lett*. **1987**, *28*, 4073-4074. b) Matsumura, Y.; Onomura, O.; Suzuki, H.; Furukubo, S.; Maki, T.; Li, C.-J. *Tetrahedron Lett*. **2003**, *44*, 5519-5522.
12. Shono, T.; Matsumura, Y.; Ogaki, M.; Onomura, O. *Chem. Lett*. **1987**, 1447-1450.
13. Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc*. **1975**, *97*, 4264-4268.
14. Table 1 shows only the yields of major products.
15. A typical experimental procedure: A solution of methyl acetoaceate (**7q)** (0.75 mmol), $Cu(OTf)_2$ (0.025 mmol) and chiral ligand **L** (0.03 mmol) in THF (1 mL) was stirred for 5 min at room temperature under a nitrogen atmosphere. Into the solution was added a solution of **6b** (0.5 mmol) in THF (1mL). After stirring for 12 hrs, the resulting mixture was poured into aqueous $NaHCO_3$ (5 mL). The organic portion was extracted with AcOEt (10 mL × 3) and dried over $MgSO_4$. The resulting solution was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/AcOEt = 5/1) to afford **9bq*** (88% yield, diastereomer ratio = 56 (43%ee): 44 (44%ee)).
16. *cis*-**12** (recrystallization from MeOH-Acetone): $[\alpha]^{29}_D$ -8.8 (c 2.5, MeOH) [lit.[7a] $[\alpha]^{29}_D$ -8.3 (c 1.0, MeOH)].