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

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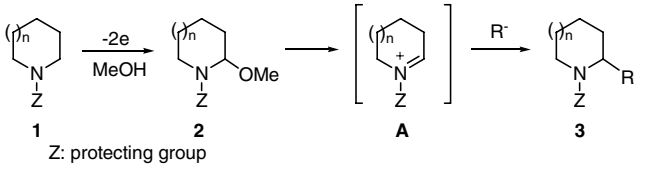
Abstract—Copper ion-catalyzed regioselective introduction of active methylene groups into the γ-position of piperidine skeleton was exploited. In the case of using chiral ligand as an additive, this reaction proceeded with moderate enantioselectivities. This method was applied to the synthesis of (−)-cincholoiponic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

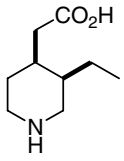
Carbon–carbon bond forming reactions at the α-position of cyclic amines **1** through iminium ion intermediates **A** to afford α-alkylated cyclic amines **3** have attracted a lot of interest (Eq. 1) since they provide one of the simplest routes for the formation of **3**, which are often found as an 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)

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.[4–6] 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]

This letter 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 the formation of undesired regioisomers **8** (Eq. 2)[9,10] and its asymmetric application leading to formal synthesis of optically active *cis*-**1** with moderate enantioselectivity. The key starting compounds **6a**,**b** (**a**;[11] R = H, **b**;[12] R = Et) in Eq. 2 are known to be prepared by electrochemical oxidation of



cis-**1**

Figure 1.

Keywords: Piperidine; Nucleophilic substitution; Copper; Regioselective; Asymmetric.
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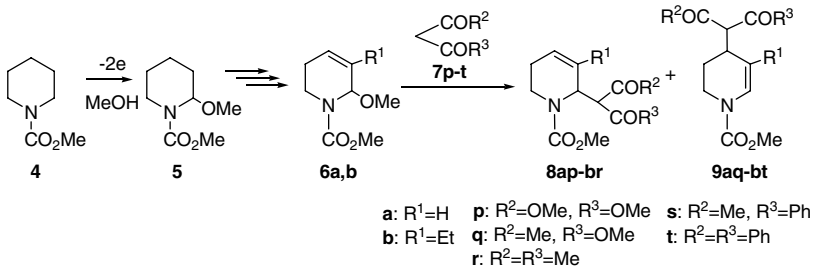
N-methoxycarbonylpiperidine (**4**) through α-methoxylated piperidine **5**.[13]

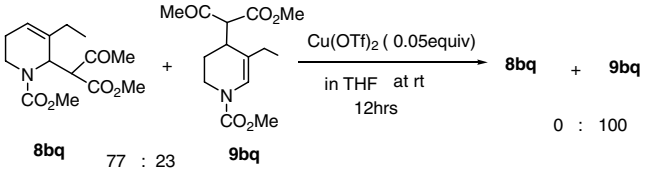


(2)

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 $Cu(OTf)_2$ (5 mol %) in THF at room temperature for 12 h 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.

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 the 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.

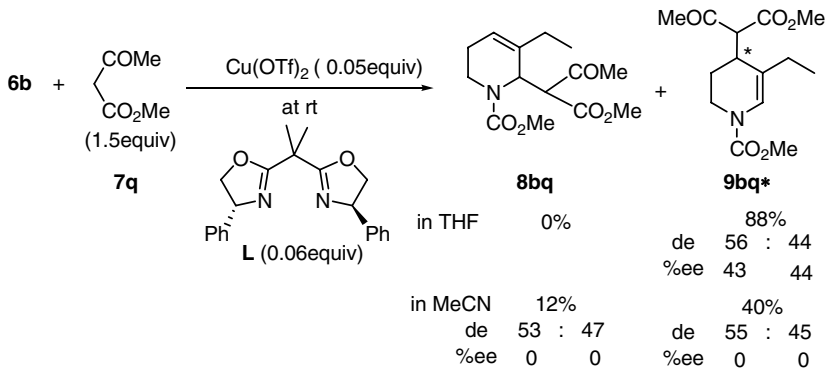
After finding the best conditions that γ-substituted piperidine **9bq** was selectively formed, we then tried asymmetric reaction of **6b** with **7q** in the presence of $Cu(OTf)_2$ and chiral bisoxazoline ligand **L**.[15] The result was interesting since a mixture of diastereomers **9bq*** was generated 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 (Eq. 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).

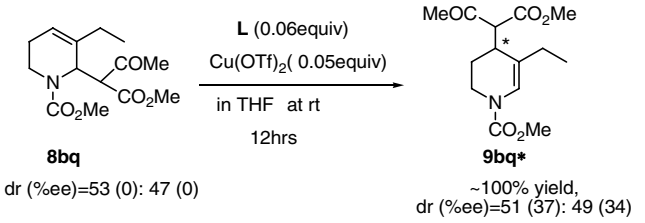
Table 1. The reaction of **6a**,**b** with various active methylene compounds **7p**–**t**[a]

Entry	Substrate		Active methylene compound			Product **8**,**9**				Ratio
	6a,**b**	R^1	**7p**–**t**	R^2	R^3	Yield (%)				**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** (0.5 mmol), **7p**–**t** (0.75 mmol), $Cu(OTf)_2$ (0.025 mmol) in THF (2 mL) at rt for 12 h.
[b] A mixture of diastereomers was obtained.
[c] At 0 °C.



(4)

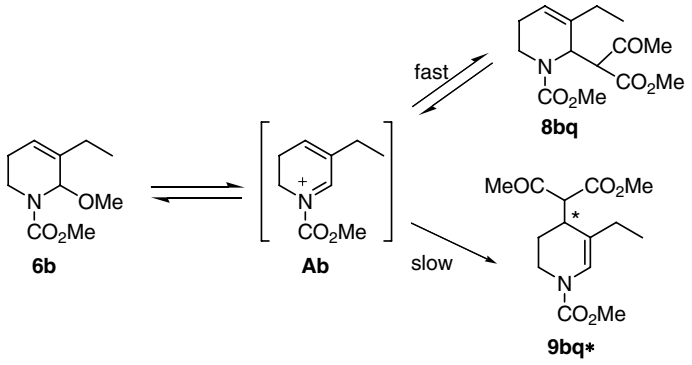


(5)

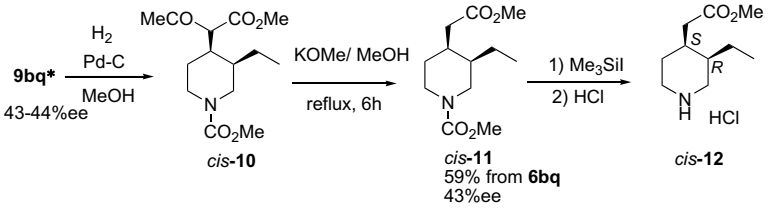
These results strongly suggest that **8bq** is a kinetically controlled product, while **9bq** is a thermodynamically stable product, and the rearrangement of **8bq** into **9bq**∗ proceeds through an iminium ion **Ab** with an intermolecular mechanism (Scheme 1). The observed regioselectivity may be 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.

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]

In summary, we present a facile method for selective introduction of active methylene groups into the γ-position of piperidine skeleton and its application to the formal synthesis of (−)-cincholoiponic acid (*cis*-**1**).



Scheme 1.



(6)

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

Acknowledgements

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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 (1 mL). After stirring for 12 h, 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): $[\alpha]_D^{29}$ −8.8 (*c* 2.5, MeOH) [lit.[7a] $[\alpha]_D^{29}$ −8.3 (*c* 1.0, MeOH)].