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Copper ion-catalyzed asymmetric carbon–carbon bond-forming reaction at the 2-position of a piperidine skeleton

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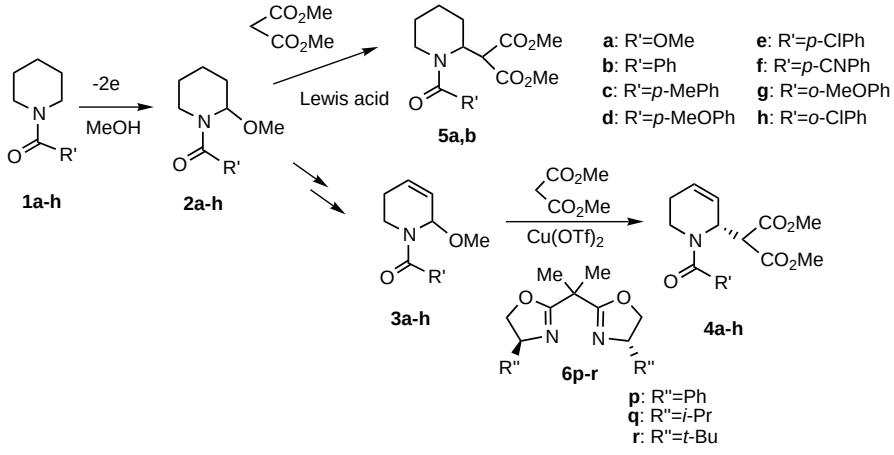
Abstract—An asymmetric carbon–carbon bond-forming reaction at the 2-position of a piperidine skeleton was exploited. This method consisted of a reaction between 1-benzoyl-3,4-didehydro-2-methoxypiperidines and dimethyl malonate catalyzed by Cu(II)-chiral 2,2′-isopropylidenebis(4-phenyl-2-oxazoline) to afford a 2-substituted piperidine skeleton with moderate enantioselectivity.

Piperidines **2** possessing substituents at the 2-position are useful synthetic intermediates for a variety of alkaloids and medicines. Optically active 2-substituted piperidines **2*** are particularly worthwhile.[1] The asymmetric introduction of a substituent R into the 2-position of simple piperidine **1** is the simplest and most promising method for the preparation of **2*** (path a in Scheme 1), although so far very few effective methods have been reported.[2]

We describe herein a new facile method for a copper ion-catalyzed asymmetric introduction of a bis(methoxycarbonyl)methyl group into the 2-position of **1** through 3,4-didehydro-2-methoxypiperidines **3**, which are easily prepared from **1**, with moderate enantioselectivity (path b in Scheme 1).

We have previously reported that $TiCl_4$ mediated a reaction of *N*,*O*-acetals **2a**[3] with dimethyl malonate to afford substituted products **5a** in high yields.[4] On the basis of this result, we first tried an asymmetric introduction of dimethyl malonate toward **2a**,**b** in the presence of metal ion catalysts, but the metal ions scarcely catalyzed the desired carbon–carbon bond-forming reaction.[5]



(1)

Keywords: acetals; asymmetric reactions; catalysis; piperidines.

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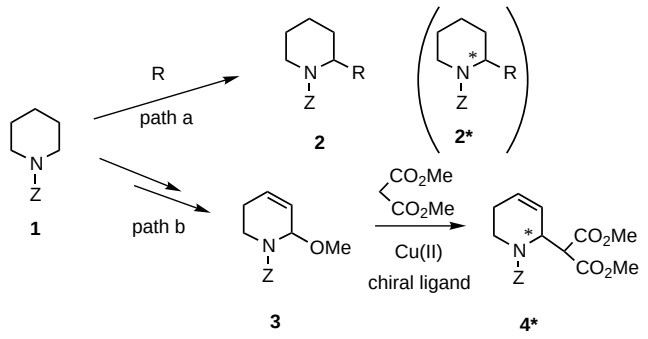
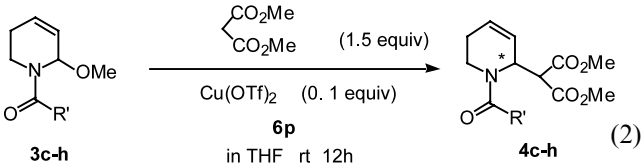


Scheme 1.

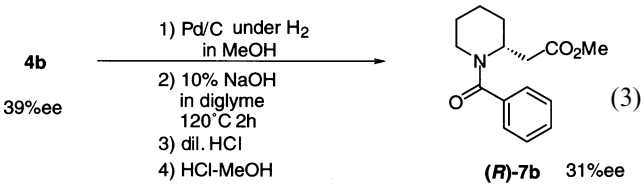
Next, we modified the structure of **2a**,**b** to search for substrates which could be easily activated by a Lewis acid catalyst. As a result, 3,4-didehydro-2-methoxylated piperidines **3a**,**b**, which were prepared in three steps from **1a**,**b**,[6] were found to be activated by a catalytic amount of $Cu(OTf)_2$ (0.1 equiv.) in THF[7] to afford 2-substituted piperidines **4a**,**b** (**4a**; 59% yield, **4b**; 36% yield) with a small amount of the corresponding 4-substituted ones (Eq. (1)).[8] Furthermore, we carried out the reaction in the presence of chiral 2,2′-isopropylidenebis(4-phenyl-2-oxazoline) **6p** (0.1 equiv.) as a ligand,[9] and observed formation of optically active **4b** (46% ee)[10] in the case of **3b**, while compound **4a** was obtained with lower optical purity (21% ee) (Eq. (1)).[11] The asymmetric reaction was also achieved by only 0.01 equiv. of $Cu(OTf)_2$ and **6p** (0.012 equiv.) to afford **4b** (45% yield, 47% ee) from **3b**.

In order to improve the selectivity, we examined other chiral ligands **6q**,**r**, but **6p** gave the best result (**6q**: **4a** (2% ee), **4b** (0% ee); **6r**: **4a** (13% ee), **4b** (41% ee)). Furthermore, we carried out the reaction of 1-benzoylated compounds **3c–h**, which were also prepared from **1c–h**,[6] with dimethyl malonate using **6p** with expecting an enhancement of ee by electronic and/or steric effect of *N*-substituents (Eq. (2)). The results together with those for **3b** are shown in Table 1. In the presence of chiral ligand **6p**, all 2-substituted products **4b–h** were obtained with moderate enantioselectivities. Definitive correlation between *N*-substituent and the ee was not observed.

The absolute stereoconfiguration of (*R*)-**4b** was determined as the assigned structure by converting obtained **4b** (39% ee) to **7b** with 31% ee (Eq. (3)) followed by comparison with the authentic sample.[12,13]

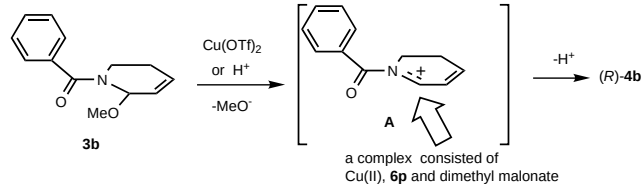


(2)



(3)

A plausible reaction mechanism is not clear yet, but we can tentatively suppose it is as follows (Scheme 2 represented by **3b**); Cu(II) ion may play a role of Lewis acid at the initiation step to generate acyl iminium ion **A** from **3b** with a loss of MeO^-. Then, **A** is attacked by dimethyl malonate to afford the product **4b** with formation of a proton. The generated proton or Cu(II) ion again attacks on **3b** to regenerate **A**.[14] Thus, a catalytic cycle for formation of **A** from **3b** is achieved. Formation of (*R*)-**4b** indicates a predominant attack of a complex consisted of Cu(II), **6p** and dimethyl malonate toward **A** from its *Re*-face (Scheme 2).[15]



Scheme 2. Plausible reaction mechanism.

Table 1. Copper ion-catalyzed bond-forming reaction for **3b–h**[a]

Entry	Compound	R′	**6p** (equiv.)	**4**	
				Yield (%)	% ee
1	**3b**	Ph	0	36	–
2	**3b**		0.1	36	46
3	**3c**	*p*-MePh	0	70	–
4	**3c**		0.1	57	43
5	**3d**	*p*-MeOPh	0	68	–
6	**3d**		0.1	78	41
7	**3e**	*p*-ClPh	0	53	–
8	**3e**		0.1	38	49
9	**3f**	*p*-CNPh	0	33	–
10	**3f**		0.1	39	53
11	**3g**	*o*-MeOPh	0	36	–
12	**3g**		0.1	67	44
13	**3h**	*o*-ClPh	0	42	–
14	**3h**		0.1	34	41

[a] 0.1 equiv. of $Cu(OTf)_2$ in THF was used.

In summary, we have presented a facile method for asymmetrically introducing a bis(methoxycarbonyl)methyl group into the 2-position of a piperidine skeleton with moderate enantioselectivities.

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

Acknowledgements

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5. Activities of $Cu(OTf)_2$, $Pd(PPh_3)_4$, Ag(OTf), and $Zn(OTf)_2$ as catalysts were tested.
6. Compounds **3a–h** were prepared by our previously reported method, see: Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. *Tetrahedron Lett*. **1987**, *28*, 4073–4074.
7. The yields of **4a** in other solvents than THF; in CH_2Cl_2: 13%; in AcOEt: 59%; in CH_3CN: 0%; in toluene: 14%; in Et_2O: 56%.
8. A reaction between saturated *N*,*O*-acetals **2a**,**b** and dimethyl malonate did not proceed at all by using $Cu(OTf)_2$ whether **6p** was present or not.
9. Johnson, J. S.; Evans, D. A. *Acc. Chem. Res*. **2000**, *33*, 325–335.
10. Daicel Chiralpak AS (4.6 mmϕ, 25 cm), *n*-hexane:2-propanol = 15:1, detected at 210 nm, flow rate: 1.0 mL min^{-1}, retention time: 25 min for (*S*)-isomer and 41 min for (*R*)-isomer.
11. A typical experimental procedure: Under a nitrogen atmosphere, a solution of dimethyl malonate (1.5 mmol), **3b** (1.0 mmol), $Cu(OTf)_2$ (0.1 mmol) and (*S*,*S*)-**6p** (0.1 mmol) in THF (4 mL) was stirred for 12 h at rt. The resulting mixture was poured into water (5 mL). The organic portion was extracted with AcOEt and concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane:AcOEt = 5:1) to afford **4b** in 36% yield with 46% ee.
12. Daicel Chiralpak OJ (4.6 mmϕ, 25 cm), *n*-hexane:ethanol = 20:1, detected at 210 nm, flow rate: 1.0 mL min^{-1}, retention time: 17 min for (*S*)-isomer and 27 min for (*R*)-isomer.
13. The authentic sample (*R*)-**7b** was prepared from (*R*)-2-piperidiylacetic acid.[2d]
14. Bisoxazoline ligand did not improved the yield of **4**, suggesting an important role of a proton than Cu(II) for the formation of **A** from **3b**.
15. The structure of the complex is not clear.