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Concise synthesis of *trans*- and *cis*-3,4-disubstituted piperidines based on regio- and stereoselective allylation of cyclopentenyl esters

Junji Igarashi, Hiroyuki Ishiwata and Yuichi Kobayashi*

Department of Biomolecular Engineering, Tokyo Institute of Technology, 4259-B-52 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan

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Abstract—3,4-Disubstituted piperidines were synthesized through anti S_N2' allylation of 4-substituted 2-cyclopentenyl esters with reagents based on RMgX and CuX, thus allowing equal access to both *trans*- and *cis*-isomers. As an application, the paroxetine intermediate was synthesized efficiently. During the investigation, the $MeOCH_2CO_2$ group was found to show high reactivity in the pivotal anti S_N2' type reaction using the reagent derived from (*i*-PrO)Me_2SiCH_2MgCl and CuCN.

The 3,4-disubstituted piperidine framework is frequently seen in an important class of nitrogen-containing compounds such as those delineated in Figure 1. Due to their unique biological properties, the piperidines have been target molecules in organic synthesis.[1] A crucial step in most of the previous syntheses[2] is installation of the second substituent, and the step has been accomplished stereoselectively by taking advantage of the thermodynamic stability of the disubstituted product or of the kinetic approach of the reagent from a less hindered side of the monosubstituted piperidine. Consequently, these syntheses produce *trans* substituted piperidines efficiently, and application to *cis*-isomer synthesis suffers from low efficiency and/or lengthy sequence. Recently, new approaches to *trans* as well as *cis* disubstituted piperidines have been published by Beak and co-workers[3] and Amat et al.[4] Herein, we report another approach to these piperidines, which relies on allylic substitution reaction, for the first time.

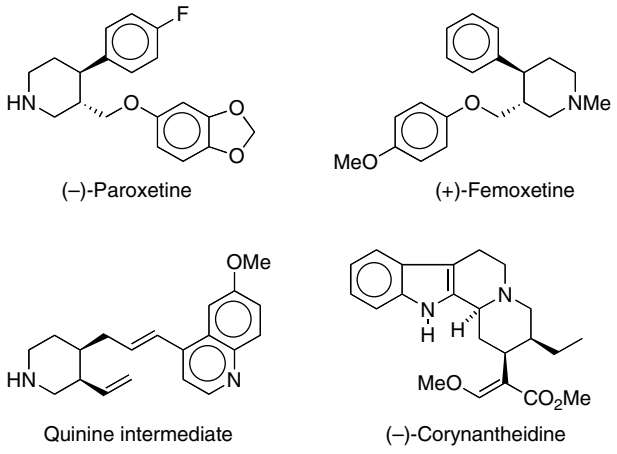

Figure 1. 3,4-Disubstituted piperidines.

Recently, we have reported several reagents for the S_N2 or S_N2' reaction of carbon nucleophiles to 4-cyclopentene-1,3-diol monoacetate (**1**)[5] and their application to cyclopentanoids synthesis.[6] The reagents and the solvent indicated in step 1 of Scheme 1 afford the S_N2 products **2** with *trans* stereochemistry. We also reported S_N2 or anti S_N2' butylation of *cis* and *trans* acetates derived from **2**.[7] The anti S_N2' butylation (step 2 of Scheme 1, R^2 = *n*-Bu) proceeds with reagents derived from BuMgX and CuCN in ratio of 1:1 or 2:1 in Et_2O. Although examination of other RMgX for step 2 was probably the next step of investigation before application, we started the investigation presented in Scheme 2 in expectation that the transformation would furnish *trans*- and *cis*-3,4-disubstituted piperidines in a stereoselective manner. This approach was indeed successful in several cases as

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* Corresponding author. Tel.: +81 45 924 5789; fax: +81 45 924 5789; e-mail: ykobayas@bio.titech.ac.jp

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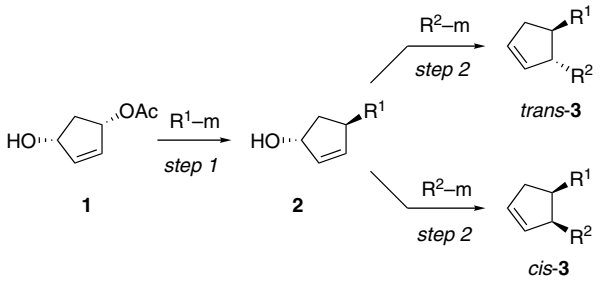
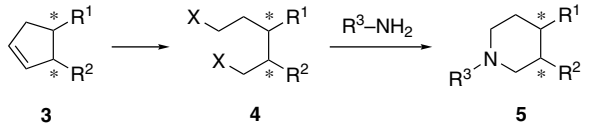


Scheme 1. Method for synthesis of *trans*- and *cis*-**3**: step 1, Li^+ [R^1-borate]$^-$/$NiCl_2$ $(PPh_3)_2$ (cat.) in THF or R^1MgCl/CuX (cat.) (X = CN, I) in THF; step 2, see the text. For the present study, the following compounds were synthesized from **2a** (R^1 = Ph) and **2b** (R^1 = *p*-F–C_6H_4): *trans*- and *cis*-**3a**, R^1 = Ph, R^2 = Bu; *trans*- and *cis*-**3b**, R^1 = Ph, R^2 = CH_2SiMe_2 (OPr-*i*); *trans*-**3c**, R^1 = *p*-F–C_6H_4, R^2 = CH_2SiMe_2 (OPr-*i*); *trans*-**3d**, R^1 = *p*-F–C_6H_4, R^2 = Bu.

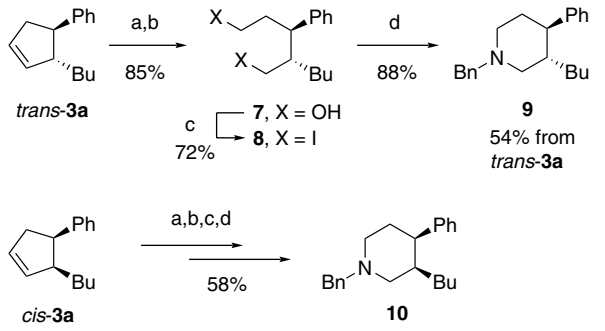


Scheme 2. An approach to 3,4-disubstituted piperidines.

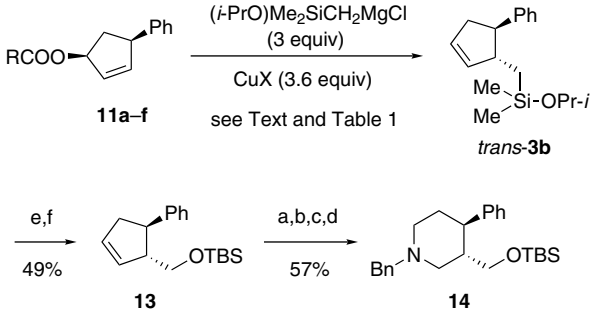
mentioned below. Moreover, we found a new leaving group to achieve step 2 of Scheme 1 efficiently.

Results of the preliminary study are summarized in Scheme 3, in which the starting cyclopentene, *trans*-**3a**, was prepared from monoacetate **1** by a sequence of reactions: (1) PhMgCl/CuCN (cat.) to produce **2a** (R^1 = Ph), 87%; (2) AcOH, DIAD, PPh_3, 90%; (3) BuCu(CN)MgBr in Et_2O, 90%. Ozonolysis proceeded well in *n*-PrOH to afford diol **7** in 85% yield after reductive workup with $NaBH_4$. Subsequently, diol **7** was converted into iodide **8**. Finally, reaction of **8** with $BnNH_2$ at 115 °C for 2 h in dioxane produced *trans* piperidine **9** in 54% overall yield from *trans*-**3a**. The corresponding tosylate derived from diol **7** was less reactive than iodide **8** for the piperidine ring formation.

The above transformation was applied to *cis*-**3a**, which was prepared from **2a** by acetylation (Ac_2O, pyridine,



Scheme 3. A simple case of the transformation: (a) O_3, −70 °C then Me_2S; (b) $NaBH_4$, 0 °C; (c) I_2, imidazole, PPh_3; (d) $BnNH_2$, dioxane, 115 °C.



Scheme 4. (a)–(d): See steps (a)–(d) in Scheme 3; (e) H_2O_2, KF, $KHCO_3$, 60–65 °C; (f) TBSCl, imidazole.

91%) followed by reaction with BuCu(CN)(MgBr) in Et_2O(91%). Transformation of *cis*-**3a** proceeded with similar efficiency to that of *trans*-**3a**, thus providing *cis* piperidine **10** in 58% overall yield.

Synthesis of piperidine with a CH_2OR group at the 3-position was next studied by using (*i*-PrO)Me_2SiCH_2MgCl as a source of the CH_2OR group,[8] which is a part of paroxetine and femoxetine[9] (Scheme 4). As mentioned above, butylation of acetate **11a** (R = Me) to *trans*-**3a** was best accomplished in Et_2O with the copper reagents derived from BuMgX (X = Br, Cl) and CuCN.[10] In the present case, THF was unfortunately the solvent for preparation of (*i*-PrO)Me_2SiCH_2MgCl. As expected from the butylation, **11a** with (*i*-PrO)Me_2-$SiCH_2Cu(CN)MgCl$ (**12a**) in THF proceeded little, and most of **11a** was recovered after the reaction.

We explored copper salts and leaving groups other than the AcO group. The reaction of **11a** (R = Me) with (*i*-PrO)$Me_2SiCH_2Cu{\cdot}MgICl$ (**12b**) prepared from (*i*-PrO)Me_2 $SiCH_2MgCl$ and CuI in place of CuCN proceeded at 15–20 °C regioselectively, but slowly, to provide *trans*-**3b** in 24% yield after 15 h (Table 1, entry 1). Due to the slow reaction, decomposition of **12b** and a nucleophilic reaction at the acetyl carbon competed with the desired reaction. We then investigated potency of an RCO_2 group as a leaving group of **11**.

Table 1. Reaction of **11**[a] with reagents **12a**[b] and **12b**[b] derived from (*i*-PrO)Me_2SiCH_2MgCl (3.0 equiv) and CuX (3.6 equiv)[c]

Entry	Substrate **11**		Reagent	Results (% obtained)[d]		
	No	R		*trans*-**3b**	Alcohol[e]	**11**
1	**11a**	Me	**12b**	24	13	63
2	**11b**	*t*-Bu	**12b**	<1	<1	99
3	**11c**	*p*-$NO_2C_6H_4$	**12b**	Mixture[f]		
4	**11d**	CH_2Cl	**12b**	76 (62)	24	<1
5	**11e**	$CHCl_2$	**12b**	67 (55)	33	<1
6	**11f**	CH_2OMe	**12b**	99 (97)	<1	<1
7	**11f**	CH_2OMe	**12a**	88	12	<1

[a] Prepared by Mitsunobu inversion of **2a** with RCO_2H in good yields.
[b] **12a**: (*i*-PrO)$Me_2SiCH_2Cu(CN)MgCl$; **12b**: (*i*-PrO)$Me_2SiCH_2Cu{\cdot}MgICl$.
[c] Reaction was carried out between 0 and 20 °C in THF for 2–15 h.
[d] Yields in parentheses are those isolated by chromatography.
[e] Produced by nucleophilic attack at the ester carbon of **11**.
[f] A mixture of unidentified products.

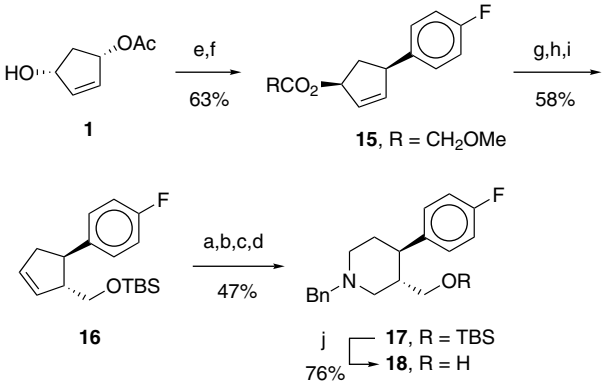
Among the RCO_2 groups indicated in entries 2–7 of Table 1, $ClCH_2CO_2$, Cl_2CHCO_2, and $MeOCH_2CO_2$ groups provided better yields of *trans*-**3b**. Inter alia, the $MeOCH_2CO_2$ group produced *trans*-**3b** as the sole product in 97% isolated yield without formation of the corresponding alcohol (entry 6).[11,12] In entry 7, the reagent based on CuCN (i.e., **12a**) was also examined to provide *trans*-**3b** in 10% lower yield and the alcohol in 12% yield, thus ensuring the excellent result of entry 6 with CuI-based reagent **12b**.

The product synthesized above (*trans*-**3b**) was converted into **13** by the Tamao reaction[8] (56%) followed by silylation of the resulting alcohol (87%). The transformation established for *trans*-**3a** (Scheme 3) was applied to **13** to produce piperidine **14** (**5** in Scheme 2 with R^1 = Ph, R^2 = CH_2OTBS, and R^3 = Bn) in 57% yield from **13**.

In a similar way, *cis*-isomer of *N*-benzyl 3-[(MOM-oxy)-methyl]-4-phenylpiperidine was synthesized as well.

The present transformation was highlighted by synthesis of the paroxetine intermediate **18**,[9j] which is summarized in Scheme 5. Reaction of monoacetate **1** with *p*-F–C_6H_4MgCl (3 equiv) in the presence of CuI (30 mol%) followed by Mitsunobu inversion with $MeOCH_2CO_2H$ afforded **15** in 63% yield from **1**. Reaction of **15** with (*i*-PrO)$Me_2SiCH_2Cu{\cdot}MgICl$ (**12b**) furnished 16 after Tamao oxidation and subsequent TBS protection. Transformation established for *trans*-**3a** to piperidine **9** (Scheme 3) was applied to **16** to produce piperidine **17** efficiently. During the transformation, little influence of the fluorine atom on the reactivity and the selectivity was observed. Finally, deprotection of **17** with Bu_4NF furnished **18** in 76% yield. The ^1H NMR and ^{13}C NMR spectra of **18** thus synthesized were consistent with the data reported.[9f]

In summary, an approach to 3,4-disubstituted piperidines was established. An advantage of the approach is the equal access to *trans* as well as *cis* piperidines. Moreover, the $MeOCH_2CO_2$ group was found to provide sufficient reactivity in reaction with (*i*-PrO)$Me_2SiCH_2Cu{\cdot}MgICl$ (**12b**). The generality of the ester group as a leaving group in allylation reaction is under investigation.[13]



Scheme 5. (a)–(d): See steps (a)–(d) in Scheme 3; (e) *p*-F–C_6H_4MgCl (3 equiv), CuI (0.3 equiv), THF; (f) $MeOCH_2CO_2H$, DIAD, PPh_3, −78 °C; (g) **12b** (3 equiv), THF, 2 h; (h) H_2O_2, KF, $KHCO_3$, 60–65 °C; (i) TBSCl, imidazole; (j) Bu_4NF.

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References and notes

1. For recent reviews: (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989; (b) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Curr. Org. Chem.* **2000**, *4*, 231–261; (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813; (d) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873; (e) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931–8952; (f) Fujii, T.; Ohba, M. *Heterocycles* **1998**, *47*, 525–539.
2. (a) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706–707; (b) Igarashi, J.; Katsukawa, M.; Wang, Y.-G.; Acharya, H. P.; Kobayashi, Y. *Tetrahedron Lett.* **2004**, *45*, 3783–3786; (c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204–11205; (d) Williams, J. T.; Bahia, P. S.; Snaith, J. S. *Org. Lett.* **2002**, *4*, 3727–3730; (e) Kozikowski, A. P.; Araldi, G. L.; Boja, J.; Meil, W. M.; Johnson, K. M.; Flippen-Anderson, J. L.; George, C.; Saiah, E. *J. Med. Chem.* **1998**, *41*, 1962–1969; (f) Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 517–524; (g) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1469–1476; (h) Fujii, T.; Ohba, M.; Sakaguchi, J. *Chem. Pharm. Bull.* **1987**, *35*, 3628–3640; (i) Funk, R. L.; Munger, J. D., Jr. *J. Org. Chem.* **1984**, *49*, 4319–4322; (j) Imanishi, T.; Inoue, M.; Wada, Y.; Hanaoka, M. *Chem. Pharm. Bull.* **1982**, *30*, 1925–1928; (k) Takano, S.; Takahashi, M.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1979**, 556–557; (l) Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571–576; (m) Stork, G.; McElvain, S. M. *J. Am. Chem. Soc.* **1946**, *68*, 1053–1057; (n) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860–874.
3. (a) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004–1005; (b) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689–11698.
4. (a) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335–338; (b) Amat, M.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2002**, *4*, 2787–2790; (c) Amat, M.; Pérez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611–614.
5. (a) Hattori, H.; Abbas, A. A.; Kobayashi, Y. *Chem. Commun.* **2004**, 884–885; (b) Ainai, T.; Ito, M.; Kobayashi, Y. *Tetrahedron Lett.* **2003**, *44*, 3983–3986; (c) Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110–7123; (d) Ito, M.; Matsuumi, M.; Murugesh, M. G.; Kobayashi, Y. *J. Org. Chem.* **2001**, *66*, 5881–5889; (e) Kobayashi, Y. *Curr. Org. Chem.* **2003**, *7*, 133–147.

6. (a) Acharya, H. P.; Kobayashi, Y. *Tetrahedron Lett.* **2004**, *45*, 1199–1202; (b) Ainai, T.; Wang, Y.-G.; Tokoro, Y.; Kobayashi, Y. *J. Org. Chem.* **2004**, *69*, 655–659; (c) Ainai, T.; Matsuumi, M.; Kobayashi, Y. *J. Org. Chem.* **2003**, *68*, 7825–7832.
7. Kobayashi, Y.; Ito, M.; Igarashi, J. *Tetrahedron Lett.* **2002**, *43*, 4829–4832.
8. Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4245–4248.
9. Recent syntheses: (a) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253–11258; (b) de Gonzalo, G.; Brieva, R.; Sánchez, V. M.; Bayod, M.; Gotor, V. *J. Org. Chem.* **2003**, *68*, 3333–3336; (c) Takasu, K.; Nishida, N.; Ihara, M. *Tetrahedron Lett.* **2003**, *44*, 7429–7432; (d) Murthy, K. S. K.; Rey, A. W.; Tjepkema, M. *Tetrahedron Lett.* **2003**, *44*, 5355–5358; (e) Greenhalgh, D. A.; Simpkins, N. S. *Synlett* **2002**, 2074–2076; (f) Cossy, J.; Mirguet, O.; Pardo, D. G.; Desmurs, J.-R. *Eur. J. Org. Chem.* **2002**, 3543–3551; (g) Cossy, J.; Mirguet, O.; Pardo, D. G.; Desmurs, J.-R. *Tetrahedron Lett.* **2001**, *42*, 7805–7807; (h) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852–6856; (i) Amat, M.; Bosch, J.; Hidalgo, J.; Cánto, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074–3084; (j) Yu, M. S.; Lantos, I.; Peng, Z.-Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647–5651.
10. In THF, the 1:1 or 2:1 reagents from BuMgX and CuCN were less reactive or less selective, providing ca. 30% yield of the butylation product or ca. 2:1 regioselection.
11. To an ice-cold mixture of CuI (224 mg, 1.18 mmol) and THF (1 mL) was added (*i*-PrO)Me_2SiCH_2MgCl (1.4 mL, 0.70 M in THF, 0.98 mmol) slowly. After 20 min of stirring at 0 °C, compound **11f** (76 mg, 0.327 mmol) in THF (0.7 mL) was added dropwise. The reaction was carried out at 15–20 °C for 2 h, and quenched by addition of saturated NH_4Cl and 28% NH_4OH to afford *trans*-**3b** (87 mg) in 97% yield after chromatography on silica gel.
12. Although results of entries 4 and 6 suggested use of the FCH_2CO_2 group, we did not examine it for reasons of toxicity.
13. Butylation of **15** afforded *trans*-**3d** (see Scheme 1 for the structure), which produced the corresponding piperidine as well.