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A new synthesis of cyclic α-amino acid derivatives by the intramolecular reaction of magnesium carbenoid with *N*-magnesio arylamine as the key reaction

Tohru Ohbayashi, Shintaro Mitsunaga and Tsuyoshi Satoh*

Department of Chemistry, Faculty of Science, Tokyo University of Science, Ichigaya-funagawara-machi 12, Shinjuku-ku, Tokyo 162-0826, Japan

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Abstract—A new synthesis of pipecolic acid and homopipecolic acid derivative was accomplished from 1-chloroalkyl *p*-tolyl sulfoxides having a 2-aminophenyl group at the ω-position by treatment with *i*-PrMgCl via the intramolecular reaction of magnesium carbenoid with *N*-magnesio arylamine. In a similar way, proline and pipecolic acid derivatives were synthesized from 1-chloroalkyl *p*-tolyl sulfoxides having an arylamino group at the ω-position.

α-Amino acids are the fundamental building blocks of peptides, proteins, and many natural products and play essential roles in living organisms. Because of the physiological importance of α-amino acids, innumerable studies regarding their chemistry and synthesis have been published.[1] Recently, cyclic α-amino acids and their derivatives have received considerable attention. Of particular importance are cyclic α-quaternary α-amino acids, which are conformationally constrained, and used in controlling peptide secondary structures and in medicinal chemistry. The synthesis and chemistries of cyclic α-amino acids have attracted much attention.[2]

As our contribution to the synthesis of α-amino acid derivatives, we recently reported a novel synthesis of α-amino acid derivatives **4** based on the reaction of magnesium carbenoid **2**, which was derived from 1-chloroalkyl *p*-tolyl sulfoxide **1** with *i*-PrMgCl, with *N*-lithio arylamines via *N*-α-magnesioalkyl arylamine **3** (Scheme 1).[3] In continuation of our interest in the synthesis of α-amino acids by this method, we recently investigated an intramolecular version of the reaction of magnesium carbenoids with arylamines. The essence of this study is shown in Scheme 1. Thus, treatment of 1-chloroalkyl *p*-tolyl sulfoxide having a 2-aminophenyl group at the ω-position (**5**) with *i*-PrMgCl followed by ethyl chloroformate gave cyclic α-amino acid derivative **7** through α-amino-substituted alkylmagnesium intermediate **6**. On the other hand, treatment of 1-chloroalkyl *p*-tolyl sulfoxide having an arylamino group at the ω-position (**8**) with *i*-PrMgCl followed by ethyl chloroformate gave proline derivative **10** through α-amino-substituted alkylmagnesium intermediate **9** (Scheme 1). Preliminary results of this study are reported hereinafter.

In order to confirm the feasibility of the intramolecular reaction, we first synthesized 1-chloropropyl *p*-tolyl sulfoxide having a 2-aminophenyl group at the 3-position (**5a**) from 3,4-dihydro-2-(1*H*)-quinolinone **11** (Scheme 2). Thus, quinolinone **11** was treated with MOMCl followed by $NaBH_4$ to afford amino alcohol **12** in high yield.[4] The amino group of **12** was protected with Boc group and the hydroxyl group was converted to a sulfide group to give **13**. The sulfur was oxidized with *m*CPBA and the resultant sulfoxide was chlorinated with NCS to afford **14**. Finally, the Boc protecting group was removed with TFA to afford the desired compound, 1-chloro-3-(2-methylaminophenyl)propyl *p*-tolyl sulfoxide **5a**, in 71% overall yield from **11**.

Next, conditions for the intramolecular reaction of **5a** were investigated and the results are summarized in

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* Corresponding author. Tel.: +81 3 5228 8272; fax: +81 3 5261 4631; e-mail: tsatoh@rs.kagu.tus.ac.jp

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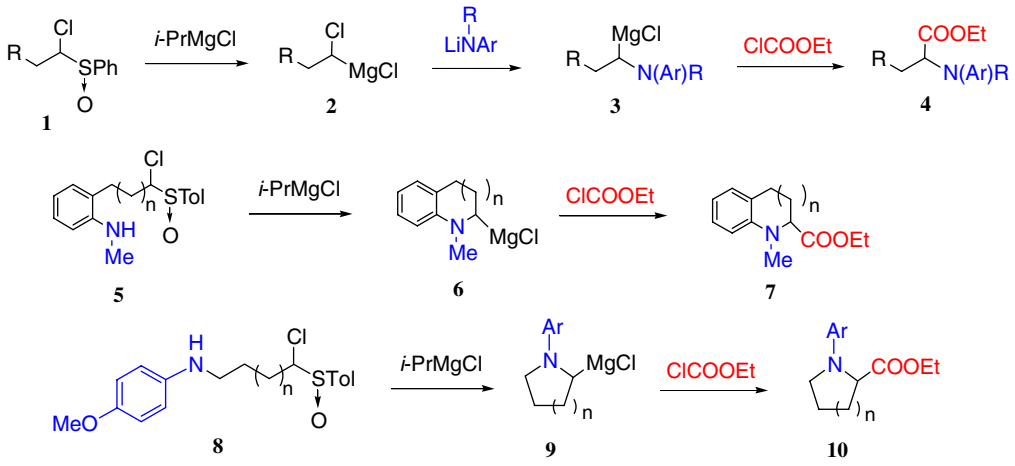
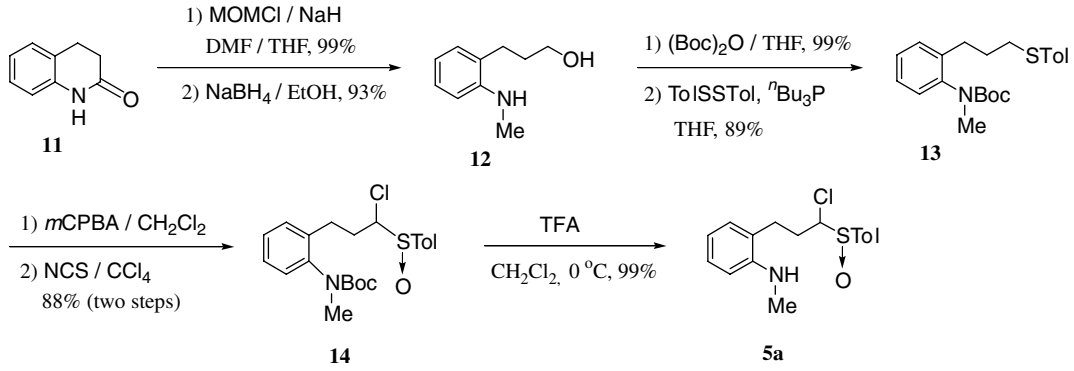


Scheme 1.



Scheme 2.

Table 1. Based on our previous study,[3] the hydrogen on the nitrogen of **5a** was replaced by MgCl (*t*-BuMgCl, 1.3 equiv) in THF at −78 °C in 5 min to give **15**. To this reaction mixture was added *i*-PrMgCl (2.5 equiv) and, after 5 min, the reaction was quenched with CH_3OD (entry 1). The desired *N*-methyltetrahydroquinoline **17**, which was deuteriated at the α-position, was obtained, albeit the yield was not satisfactory. In this reaction, α-deuteriated chloroalkane **16a** (see the footnote in Table 1) was obtained in 32% yield. From this result, it was implied that the sulfoxide–magnesium exchange reaction took place rapidly at −78 °C; however, the intramolecular reaction was slow at −78 °C (entry 1).

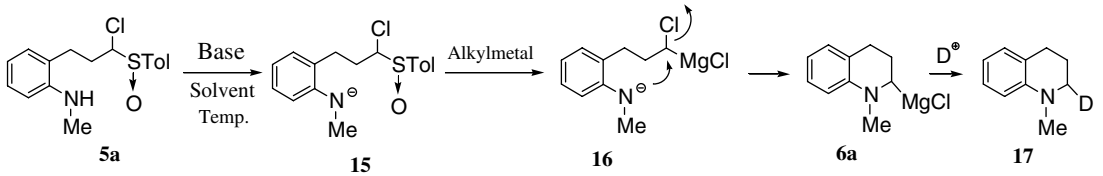
In fact, when the reaction was conducted in THF at −40 °C, the yield of the desired **17** was increased to 68% (entry 2). When this reaction was conducted in diethyl ether, the yield was decreased to 46% (entry 3). When toluene was used as the solvent, the yield increased to 88%; we selected the conditions in entry 4 as the optimized conditions. Combination of LDA and *i*-PrMgCl as well as using only *n*-BuLi or *i*-PrMgCl were found to be ineffective (entries 5–7).

The synthesis of cyclic α-amino acid using the above-mentioned conditions was investigated next (Scheme 3). Sulfoxide **5a** was treated with *t*-BuMgCl followed by *i*-PrMgCl in toluene at −40 °C and, after 5 min, 5 equiv of ethyl chloroformate was added to the reaction mixture. The desired pipecolic acid derivative **7a** was obtained in 66% yield from **5a** via the α-amino carbanion intermediate **6a**.[5]

The scope and limitations of this reaction were investigated using one- and two-carbon homologated sulfoxides (**5b** and **5c**) and nor-compound **5d** as shown in Scheme 3. The same treatment of **5b** with *i*-PrMgCl followed by CH_3OD gave seven-membered cyclic amine **19**, which was deuteriated at the α-position in good yield. When intermediate **18** was treated with ethyl chloroformate, the desired homopipecolic acid derivative **7b** was obtained in 68% yield. Although the synthesis of six- and seven-membered cyclic α-amino acid derivatives were successful, attempts to synthesize eight- and five-membered cyclic α-amino acid derivatives from **5c** and **5d** were unsuccessful. The treatment of **5c** and **5d** with *i*-PrMgCl followed by ethyl chloroformate under the conditions described above afforded only olefins **20** and **21**, respectively.

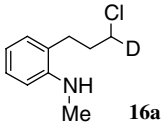
We next investigated the intramolecular reaction of magnesium carbenoid with *N*-magnesio arylamines derived from 1-chloroalkyl *p*-tolyl sulfoxide having an arylamino group at the ω-position (**8**). Starting material

Table 1. Synthesis of *N*-methyltetrahydroquinoline **17** from **5a** by the intramolecular nucleophilic reaction of the nitrogen to the magnesium carbenoid carbon



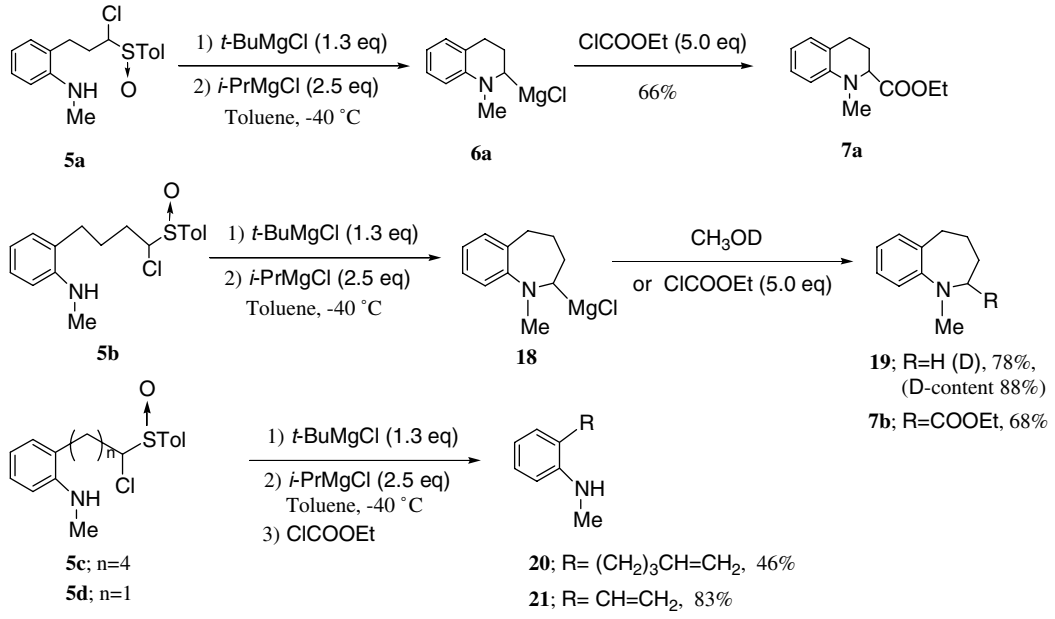
Entry	Base (equiv)	Alkylmetal (equiv)	Solvent	Temp (°C)	17	
					Yield (%)	D-Content[a] (%)
1	*t*-BuMgCl (1.3)	*i*-PrMgCl (2.5)	THF	−78	32[b]	98
2	*t*-BuMgCl (1.3)	*i*-PrMgCl (2.5)	THF	−40	68	81
3	*t*-BuMgCl (1.3)	*i*-PrMgCl (2.5)	Et_2O	−40	46	89
4	*t*-BuMgCl (1.3)	*i*-PrMgCl (2.5)	Toluene	−40	88	78
5	LDA (1.2)	*i*-PrMgCl (2.5)	Toluene	−40	Trace	—
6		*n*-BuLi (3.5)	Toluene	−40	Trace	—
7		*i*-PrMgCl (3.5)	Toluene	−40	22[c]	87

[a] The reaction was quenched with CH_3OD and the deuterium content was measured by ^1H NMR.
[b] 1-Deuteriated chloroalkane **16a** (deuterium content 89%) was obtained in 32% yield.



16a

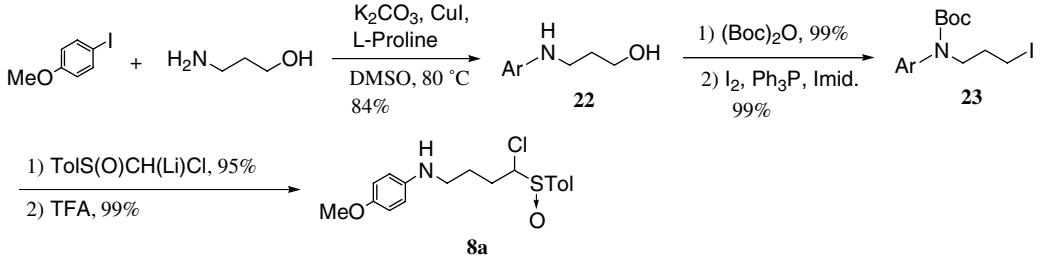
[c] Starting material **5a** was recovered in 62% yield.



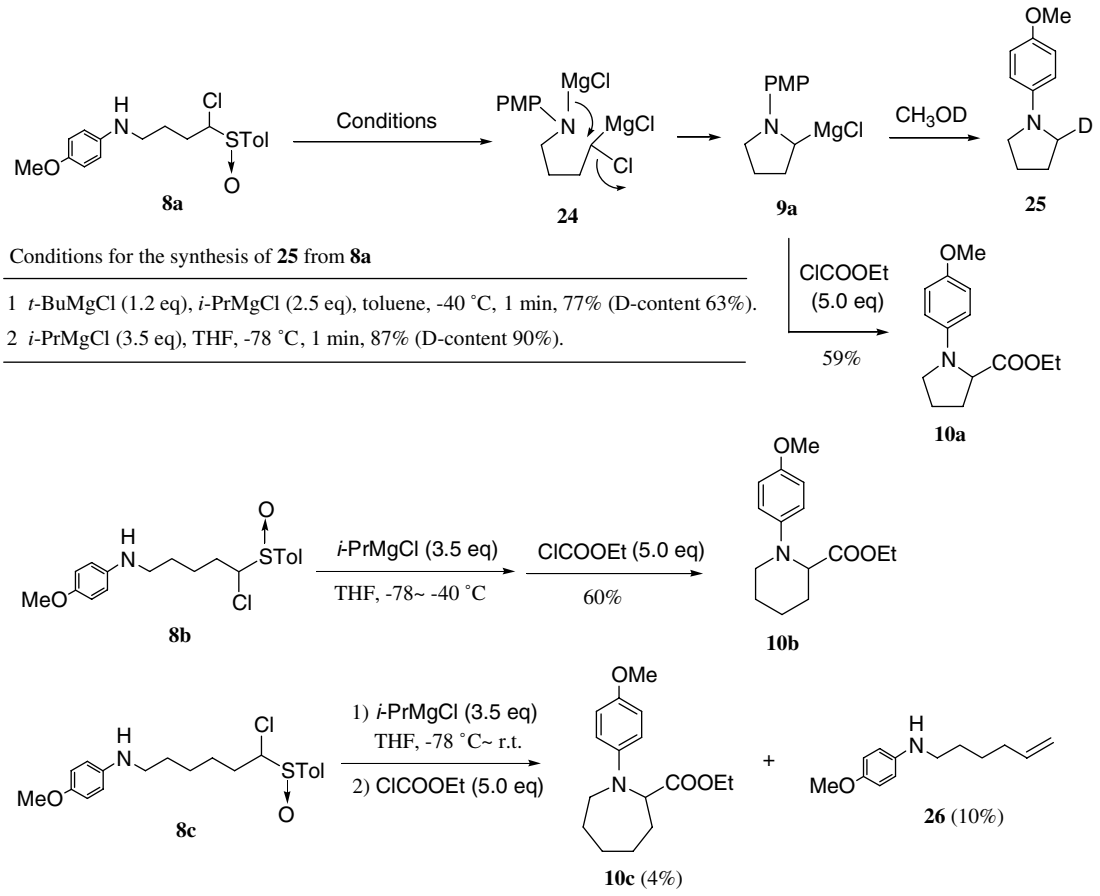
Scheme 3.

8a was synthesized as shown in Scheme 4. Thus, coupling of 4-iodoanisole and 3-aminopropanol promoted by L-proline gave aminoalcohol **22**.[6] The nitrogen of **22** was protected and the hydroxyl group was converted to iodide to give **23** in quantitative yield. Alkylation of the lithium α-sulfinyl carbanion of chloromethyl *p*-tolyl sulfoxide[7] with **23** followed by deprotection of the Boc protecting group afforded the desired **8a** in 77% overall yield from 3-aminopropanol.

Treatment of **8a** with the Grignard reagents as described above (Scheme 5, condition 1) gave deuteriated *N*-(4-methoxyphenyl)pyrrolidine **25** in 77% yield via the intramolecular reaction of magnesium carbenoid **24** and α-aminoalkylmagnesium intermediate **9a**. The yield of **25** was acceptable; however, the deuterium content was only 63%. We reinvestigated this reaction and found that simple addition of 3.5 equiv of *i*-PrMgCl to a solution of **8a** in THF at −78 °C was the conditions of choice (Scheme 5, condition 2). Generation of α-aminoalkylmagnesium intermediate **9a** using this protocol followed by treatment with ethyl chloroformate gave the desired *N*-arylproline **10a** in 59% yield from **8a**.[8]



Scheme 4.



Scheme 5.

Homo- and bishomo-sulfoxides **8b** and **8c** were synthesized in order to investigate the scope and limitations of this reaction and the results are shown in Scheme 5. Treatment of **8b** with *i*-PrMgCl followed by ethyl chloroformate afforded the desired *N*-arylpipecolic acid ethyl ester **10b** in 60% yield. Unfortunately, a similar treatment of the one-carbon homologated sulfoxide **8c** gave a rather complex mixture from which the desired **10c** (in only 4% yield) and 10% of olefin **26** were obtained as the isolable products.

In conclusion, a novel synthesis of cyclic α-amino acid derivatives (proline, pipecolic acid,[9] and homopipecolic acid derivatives) was achieved on the bases of the intramolecular reaction of a magnesium carbenoid and an *N*-magnesio arylamine. The results described in this paper contribute further development of the synthesis of cyclic α-amino acid derivatives and also the chemistry of magnesium carbenoids.

Acknowledgment

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References and notes

1. (a) *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; (b) Williams, R. M. *Synthesis of Optically Active α-Amino*

Acids; Pergamon Press: Oxford, 1989; (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (d) Beller, M.; Eckert, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1011; (e) Sano, S.; Nagao, Y. *J. Syn. Org. Chem. Jpn.* **2000**, *58*, 756; (f) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290; (g) Groger, H. *Chem. Rev.* **2003**, *103*, 2795.

2. Some recent reviews concerning chemistry and synthesis of cyclic α-amino acids. (a) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629; (b) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342; (c) Belvisi, L.; Colombo, L.; Manzoni, L.; Potenza, D.; Scolastico, C. *Synlett* **2004**, 1449; (d) Lasa, M.; Cativiela, C. *Synlett* **2006**, 2517.
3. Satoh, T.; Osawa, A.; Ohbayashi, T.; Kondo, A. *Tetrahedron* **2006**, *62*, 7892.
4. Wang, J.-J.; Hu, W.-P. *J. Org. Chem.* **1999**, *64*, 5725.
5. *1-Methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid ethyl ester* (**7a**). To a solution of **5a** (20 mg; 0.062 mmol) in 3 mL of dry toluene in a flame-dried flask at −40 °C under argon atmosphere was added a solution of *t*-BuMgCl (1.0 M solution in THF, 0.08 mL; 0.08 mmol) dropwise with stirring. After 5 min, a solution of *i*-PrMgCl (2.0 M solution in Et_2O, 0.078 mL; 0.155 mmol) was added to the reaction mixture dropwise with stirring. After 5 min, to a solution of α-aminoalkylmagnesium intermediate **6a** was added ethyl chloroformate (0.03 mL; 0.311 mmol) dropwise at −40 °C with stirring. After 10 min, the reaction was quenched with satd aq NH_4Cl. The whole was extracted with CH_2Cl_2. The organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **7a** (9 mg; 66%) as colorless oil; IR (neat) 2935, 1740 (CO), 1604, 1502, 1374, 1336, 1185, 1102, 1038, 746 cm^{-1}. ^1H NMR δ 1.24 (3H, t, $J = 7.1$ Hz), 2.07–2.16 (1H, m), 2.26–2.32 (1H, m), 2.68–2.72 (2H, m), 2.95 (3H, s), 4.01 (1H, t, $J = 4.7$ Hz), 4.10–4.24 (2H, m), 6.60–6.66 (2H, m), 6.93 (1H, d, $J = 7.6$ Hz), 7.10 (1H, t, $J = 7.8$ Hz). Ms *m*/*z* (%) 219 (M^+, 20), 146 (100), 130 (10). Calcd for $C_{13}H_{17}NO_2$: M, 219.1259; Found *m*/*z*, 219.1261.
6. Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.
7. (a) More, K. M.; Wemple, J. *J. Org. Chem.* **1978**, *43*, 2713; (b) Satoh, T.; Kaneko, Y.; Izawa, T.; Sakata, K.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1983.
8. *1-(4-Methoxyphenyl)pyrrolidine-2-carboxylic acid ethyl ester* (**10a**). To a solution of **8a** (43 mg; 0.12 mmol) in 6 mL of dry THF in a flame-dried flask at −78 °C under argon atmosphere was added a solution of *i*-PrMgCl (2.0 M solution in THF, 0.213 mL; 0.43 mmol) in THF dropwise with stirring. After 1 min, to a solution of α-aminoalkylmagnesium intermediate **9a** was added ethyl chloroformate (0.058 mL; 0.61 mmol) dropwise at −78 °C with stirring. After 10 min, the reaction was quenched with satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The organic layer was washed with satd aq NH_4Cl and dried over $MgSO_4$. The product was purified by silica gel column chromatography to afford **10a** (18 mg; 59%) as colorless oil; IR (neat) 2978, 2833, 1746 (CO), 1621, 1515, 1464, 1367, 1242, 1178, 1094, 1039, 978, 813 cm^{-1}. ^1H NMR δ 1.24 (3H, t, $J = 7.1$ Hz), 2.02–2.30 (4H, m), 3.31 (1H, q, $J = 5.7$ Hz), 3.52–3.57 (1H, m), 3.74 (3H, s), 4.10–4.23 (3H, m), 6.51 (2H, d, $J = 9.1$ Hz), 6.82 (2H, d, $J = 9.1$ Hz). Ms *m*/*z* (%) 249 (M^+, 20), 176 (100). Calcd for $C_{14}H_{19}NO_3$: M, 249.1363; Found *m*/*z*, 249.1361.
9. Some selected recent papers for synthesis of pipecolic acid derivatives. (a) Varray, S.; Gauzy, C.; Lamaty, F.; Lazaro, R.; Martinez, J. *J. Org. Chem.* **2000**, *65*, 6787; (b) Cossy, J.; Belotti, D. *Tetrahedron Lett.* **2001**, *42*, 2119; (c) Seitz, T.; Baudoux, J.; Bekolo, H.; Cahard, D.; Plaquevent, J.-C.; Lasne, M.-C.; Rouden, J. *Tetrahedron* **2006**, *62*, 6155; (d) Jung, J.-C.; Avery, M. A. *Tetrahedron: Asymmetry* **2006**, *17*, 2479.