New and Efficient Route to Pipecolic Acid Derivatives by Means of Rh-Catalyzed Intramolecular Cyclohydrocarbonylation

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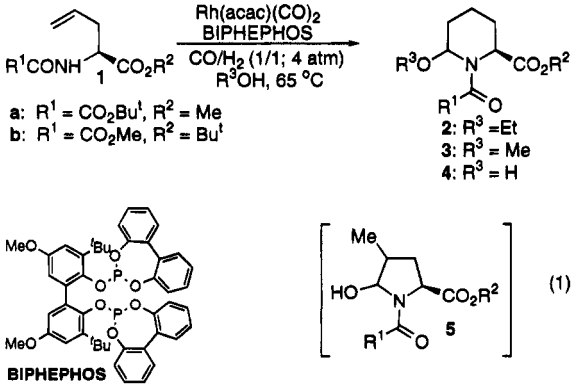
Recently, the syntheses of biologically active[1] 2,6-disubstituted piperidine alkaloids have attracted significant interest.[2] For the syntheses of these piperidine alkaloids, 6-alkoxypipecolates and 5,6-dehydropipecolates serve as versatile key intermediates and find a variety of applications in the syntheses of izidine alkaloids.[3] 6-Alkoxypipecolates can be synthesized through anodic oxidation[4] and 5,6-dehydropipecolates can be obtained from 2-alkoxypipecolates via dealkoxylation under acidic conditions.[5] We report here the new and convenient syntheses of 6-alkoxypipecolates, 5,6-didehydropipecolates, and their derivatives from allylglycinates through extremely regioselective intramolecular cyclohydrocarbonylation.[6]

The intramolecular cyclohydrocarbonylation of methyl 2-*t*-Boc-amino-4-pentenoate (**1a**) in the presence of Rh(acac)$(CO)_2$ (1.0 mol %) and BIPHEPHOS[7] (2 mol %) at 65 °C and 4 atm of CO/H_2 (1/1) for 16 h in ethanol gave 1-*t*-Boc-6-ethoxypipecolate (**2a**) in quantitative yield (eq 1). In the same manner, 1-*t*-Boc-6-methoxypipecolate (**3a**) and 1-(methoxycarbonyl)-6-methoxypipecolate (**3b**) were obtained in quantitative yield when the reactions were run in methanol. It is noteworthy that the reaction of **1** catalyzed by conventional hydroformylation catalysts, e.g., $HRh(CO)(PPh_3)_3$-20 PPh_3, Rh(acac)$(CO)_2$–PPh_3, and Rh(acac)$(CO)_2$–PCy_3, at 70 °C and 6–20 atm of CO/H_2 (1:1), gave a ca. 1:1 mixture of regioisomers, i.e., 6-hydroxypipecolate **4** and 4-methyl-5-hydroxyprolinate **5**.



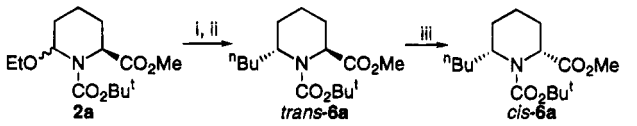
(1) (a) Jones, T. H.; Blum, M. S.; Robertson, H. G. *J. Nat. Prod.* **1990**, *53*, 429. (b) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, Chapter 6, pp 193-315 and referenced cited therein.

(2) (a) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 496 and references cited therein. (b) Pinder, A. R. *Nat. Prod. Rep.* **1990**, *7*, 448 and references cited therein.

(3) E.g., (a) Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118. (b) Izawa, K.; Nishi, S.; Asada, S. *J. Mol. Catal.* **1987**, *41*, 135. (c) Takahara, H.; Bandoh, H.; Momose, T. *Tetrahedron* **1993**, *49*, 11205.

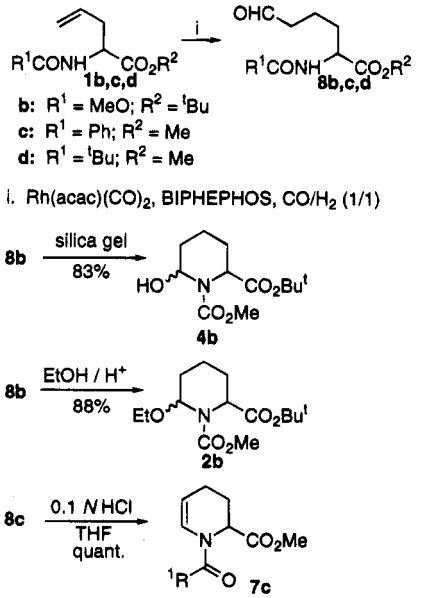
(4) Shono, T.; Matsumura Y.; Inoue, K. *J. Chem. Soc., Chem. Commun.* **1983**, 1169.

Scheme 1[a]



[a] (i) BuCu·BF_3, −78 °C to rt; (ii) NH_4Cl/NH_3 (2:1), rt, 1 h, 80% (>95% by NMR); (iii) LiHMDS, −20 °C → rt, 72% (>95% by NMR).

Scheme 2



The nucleophilic substitution of the ethoxy group at C-6 of **2a** with a *n*-BuCu–BF_3 complex[8] proceeded with excellent diastereoselectivity (>92% de), giving *trans*-1-*t*-Boc-6-*n*-butylpipecolate (*trans*-**6a**) in 80% isolated yield (100% de) after chromatography on silica gel (Scheme 1), viz., the nucleophilic attack on the acyliminium ion generated in situ takes place almost exclusively *anti* to the ester group at C-2. Because of $A^{1,3}$ strain, *trans*-**6** undergoes facile epimerization at C-2, giving the thermodynamically more favorable *cis*-**6** in 72% isolated yield (100% de) (>90% yield by NMR) upon reaction with LiHMDS in THF (Scheme 1).[3b] The cyclohydrocarbonylation of enantiopure (*S*)-**1a** followed by the reaction with *n*-BuCu–BF_3 complex gave enantiopure *trans*-**6a** and *cis*-**6a** with excellent diastereomeric purity. The enantiomeric integrity of the starting enantiopure (*S*)-**1a** has been maintained during the catalytic reaction (*vide infra*) as well as during the alkylation at C-6 on the basis of chiral HPLC analyses of racemic and enantiopure *trans*-**6a** and *cis*-**6a**.[9]

The cyclohydrocarbonylation of 2-(alkoxycarbonyl)-4-pentenoates **1** is very sensitive to the nature of solvent

(5) Driessens, F.; Hootelé, C. *Can. J. Chem.* **1991**, *69*, 211.

(6) (a) Eguchi, M.; Zeng, Q.; Korda, A.; Ojima, I. *Tetrahedron Lett.* **1993**, *34*, 915. (b) Ojima, I.; Donovan, R. J.; Eguchi, M.; Shay, W. R.; Ingallina, P.; Korda, A.; Zeng, Q. *Tetrahedron* **1993**, *49*, 5431. (c) Zhang, Z.; Ojima, I. *Organometallics* **1990**, *9*, 3122.

(7) (a) Billig, E.; Abatjoglou, A. G.; Bryant, D. R. U.S. Patent 4769 498, 1988. (b) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2066. (c) Cuny, G. D.; Buchwald, S. L. *Synlett* **1995**, *519*.

(8) (a) Wistrand, L.-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573. (b) Ludwig, C.; Wistrand, L.-G. *Acta Chem. Scand.* **1994**, *48*, 367.

(9) In addition, the *t*-Boc group of (−)-*trans*-**6a** was removed by treating with trifluoroacetic acid at 0 °C, and the resulting *N*-free piperidine was acylated with Mosher's chiral acid chloride, i.e., (*S*)-methoxy(phenyl)(trifluoromethyl)acetyl chloride,[12] in the presence of triethylamine in chloroform at 0–25 °C. The HPLC analysis of this Mosher amide (>99% de) also indicated that there was no loss of enantiopurity throughout this reaction sequence.

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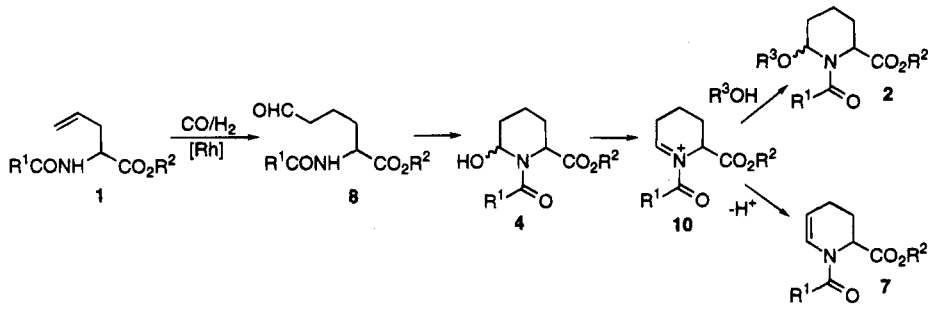
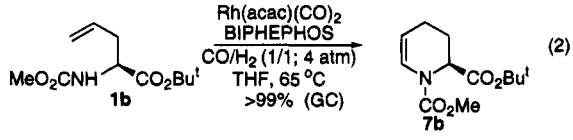
Scheme 3



used. For example, the use of *aprotic* solvents in this reaction led to the exclusive formation of 1-(alkoxycarbonyl)-5,6-didehydropipecolate **7** in excellent yield (eq 2), i.e., the formation of **2** or **3** was not observed at all. Polarity of the aprotic solvent, however, does not influence the course of the reaction since the reactions in toluene, hexane, methylene chloride, chloroform, tetrahydrofuran, and ethyl acetate all gave **7** exclusively with only minor differences in the yield. The reaction with enantiopure (*S*)-**1b** gave enantiopure **7b**, which was determined by chiral HPLC. Thus, it is proven that no racemization takes place during this catalytic process.



(2)

It has been shown that didehydropipecolates can be obtained by treatment of 1-(alkoxycarbonyl)-6-methoxypipecolates with *p*-toluenesulfonic acid.[10] In contrast with this, the present process gives didehydropipecolate **7** under neutral conditions. It is of interest to note that the direct formation of **7b** from **1b** is unique to BIPHEPHOS-Rh catalyst, and it does not occur on using Rh catalysts with phosphine ligands such as triphenylphosphine, tricyclohexylphosphine, and 1,4-bis(diphenylphosphino)butane, which give a mixture of **4b** and **5b**.

The reaction of **1b** in ethanol under the standard conditions, i.e., at 65 °C and 4 atm of CO/H_2 (1/1), is exceptional in that no cyclization took place, giving a simple hydroformylation product **8b** with 100% linear selectivity. The linear aldehyde **8b** was readily cyclized under weakly acidic conditions, i.e., 0.1 N hydrochloric acid in ethanol and silica gel column, affording **2b** and **4b**, respectively, in excellent yields (Scheme 2). The same reaction pattern was, however, observed when methyl 2-(benzoylamino)-4-pentenoate (**1c**)[11] and methyl 2-(pivaloylamino)-4-pentenoate (**1d**) were employed as substrates under the standard conditions in THF, which gave **8c** (87% yield) and **8d** (77% yield), respectively (Scheme 2). Treatment of **8c** with 0.1 N hydrochloric acid in THF gave **7c** in quantitative yields. Attempted transformation of **8c** and **8d** to **3c** (or **2c**) and **3d** (or **2d**), respectively, by treating with 0.1 N hydrochloric acid in methanol (or ethanol) resulted in the formation of the corresponding acetals, **9c** and **9d**.

On the basis of the observations described above, the most plausible mechanism for the intramolecular cyclohydrocarbonylation is proposed in Scheme 3. The reaction is believed to proceed via linear aldehyde **8** followed by cyclization to form **4**, which eliminates a hydroxyl group, generating an reactive acyliminium ion intermediate **10** (this is the only species not isolated), and **10** gives either 5,6-dehydropiperidine **7** or 6-alkoxylpipecolate **2**.

Further investigations on the applications of intramolecular cyclohydrocarbonylation processes are actively underway.

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Supporting Information Available: General experimental procedures for the extremely regioselective intramolecular cyclohydrocarbonylation of **1**, and the characterization data for new compounds **2**–**8** (5 pages).

JO951450Q

(10) Plehiers, M.; Hootelé, C. *Tetrahedron Lett.* **1993**, *47*, 7569.

(11) Easton, C. J.; Scharfbillig, I. M. *J. Org. Chem.* **1990**, *55*, 384.

(12) (a) Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1970**, *34*, 2543. (b) Yamaguchi, S.; Dale, J. A.; Mosher, H. S. *Ibid.* **1972**, *37*, 3174. (c) Yamaguchi, S.; Mosher, H. S. *Ibid.* **1973**, *38*, 1870.