Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 3, pp. 621-624, 1996

0957-4166/96 $15.00 + 0.00

S0957-4166(96)00048-1

Preparation of Optically Active β-Carboxyaspartic Acid Derivatives *via* Pd(0)-Catalyzed Asymmetric Substitution of Schiff Base Acetates

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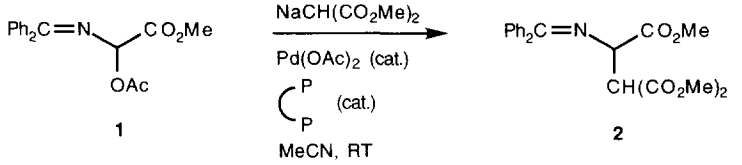
Abstract: Optically active β-carboxyaspartic acid derivative **6** (77% ee) was obtained in 48% total yield from the coupling of Schiff base acetate **3** with sodium dimethyl malonate in the presence of 5% $Pd(OAc)_2$-(*2S,4S*)-BPPM followed by a single recrystallization. Phase-transfer catalyzed alkylation of malonates **6** affords β-substituted ASA derivatives **7** in excellent yield without racemization at the α-carbon. Copyright © 1996 Elsevier Science Ltd

The combination of $Pd(OAc)_2$ and bis-phosphines was reported recently for effective catalysis of the coupling of sodium dimethyl malonate with the methyl ester Schiff base acetate **1** to afford the protected, racemic β-carboxyaspartic acid (ASA) derivative **2**.[1,2] It was shown that, in order to obtain good chemical yields and reasonable reaction rates, the bis-phosphine ligand should contain a flexible tether of at least four methylene

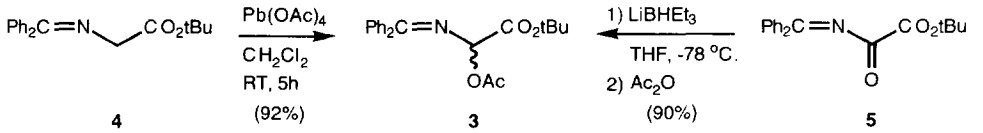


groups. Preliminary experiments demonstrated that optically active ASA derivatives could be prepared in high chemical yield by using chiral bis-phosphines such as BPPM (5-8% ee).[1]

We now report that the enantioselectivity is increased by using the *tert*-butyl ester acetate (**3**) rather than the methyl ester acetate (**1**) in conjunction with the BPPM ligand. This chiral bis-phosphine is of considerable practical interest because it is commercially available, it can be readily prepared in multigram scale from inexpensive *trans*-4-hydroxy-L-proline, and various derivatives of BPPM are easily synthesized.[3]

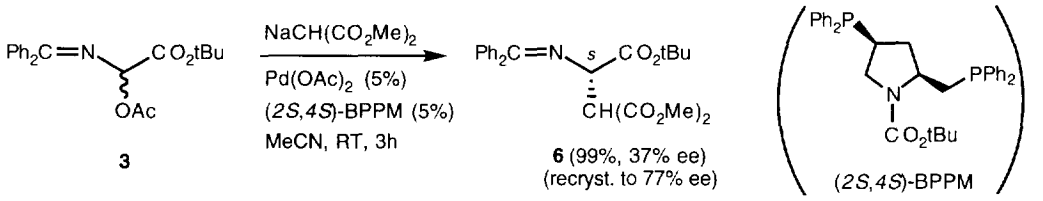
The starting Schiff base acetate **3** is prepared in high yield using either of two complementary routes (Scheme 1): $Pb(OAc)_4$ oxidation of the commercially available Schiff base *tert*-butyl ester **4**[4] or Super-Hydride® reduction of keto-ester **5**.[5,6] Both reactions can be scaled-up since the starting materials are easily prepared and the crude product can be purified by recrystallization.

Scheme 1. Preparation of Starting Schiff Base Acetate **3**.



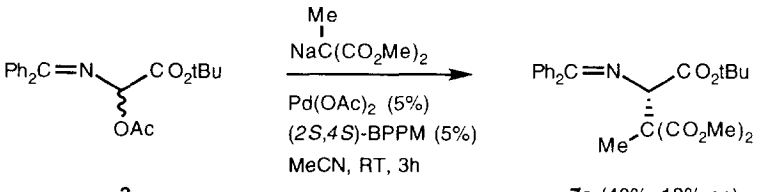
Reaction of acetate **3** with sodium dimethyl malonate was performed in the presence of $Pd(OAc)_2$ (5%) and (*2S,4S*)-BPPM (5%) in acetonitrile for 3 hours to afford **6** in quantitative yield and 37% ee (Scheme 2).[7] Even though the selectivity was only modest, the optical purity of product **6** was easily increased to a practical level by a single recrystallization from hexane/dichloromethane (77% ee, 48% overall from **3**, product in filtrate). The (*S*) absolute configuration of product **6** was established by hydrolysis and decarboxylation of this product to (*S*)-aspartic acid.[8]

Scheme 2. Asymmetric Coupling of Acetate **3** with Malonate Anion in the Presence of $Pd(OAc)_2$-BPPM.



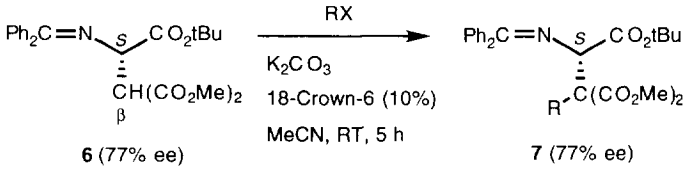
Direct extension of this methodology to the preparation of β-substituted derivatives of β-carboxyaspartic acid was problematic. When sodium dimethyl methylmalonate was used as the nucleophile for reaction with **3**, the product **7a** was obtained in 40% chemical yield and 18% ee (Scheme 3). Sodium dimethyl benzylmalonate, which is even more sterically demanding, gave poorer results (~20% conversion by TLC).

Scheme 3. Asymmetric Coupling of the Acetate **3** with Sodium Dimethyl Methylmalonate.



An alternative route to β-substituted ASA derivatives involves alkylation of the product **6** using phase transfer catalysis (PTC) (Scheme 4).[9] The alkylated products **7** were isolated in excellent yields by flash chromatography. As expected, due to the higher acidity of malonates compared with Schiff base esters,[10] alkylation using either PTC or classic anhydrous conditions (LDA/THF/-78 °C, RX, -78 °C to ambient temperature) occurred at the β-carbon rather than the α-carbon. Moreover, the product obtained from alkylation of **6** with MeI was identical with that obtained earlier from the coupling of **3** with sodium dimethyl methylmalonate. Finally, no racemization at the α-carbon was observed in the PTC alkylations as checked by chiral HPLC. The ready commercial and synthetic availability of a wide variety of alkyl halides makes this coupling/alkylation route particularly attractive for the preparation of various optically active β-carboxyaspartic acid derivatives.

Scheme 4. β-Alkylation of **6** under PTC conditions.



RX	Product	Yield
MeI	**7a**	90%
CH_2=$CHCH_2$Br	**7b**	97%
$PhCH_2$Br	**7c**	99%

In summary, a general method for the preparation of optically active β-carboxyaspartic acid derivatives has been developed. The starting substrate **3** is readily prepared either by known methodology or by the new reduction of the α-keto glycinate **5**. The synthetic potential of this methodology has been further demonstrated by the preparation of the unnatural β-substituted ASA derivatives **7** by phase-transfer alkylation of **6**.

Acknowledgement. We gratefully acknowledge the National Institutes of Health (GM28193) for support of this research and we thank Professor C. P. Kubiak for helpful discussions.

References and Notes

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3. (a) BPPM: (*2S,4S*)-1-*tert*-butoxycarbonyl-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine. (b) Achiwa, K. *J. Am. Chem. Soc.* **1976**, *98*, 8265; (c) Baker, G. L; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954; (d) Ojima, I.; Kogure, T.; Yoda, Y. *Organic Syntheses* **1984**, *63*, 18; (e) Leitner, W.; Brown, J. M.; Brunner, H. *J. Am. Chem. Soc.* **1993**, *115*, 152.
4. Preparation of *tert*-butyl (acetyloxy)[(diphenylmethylene)amino]acetate (**3**) from **4**. A mixture of *tert*-butyl *N*-(diphenylmethylene)glycinate (**4**) (14.7 g, 0.05 mol) and $Pb(OAc)_4$ (24.4 g, 0.055 mol) in dry CH_2Cl_2 (150 mL) was stirred at rt for 5 h. Water (200 mL) was added in one portion, the layers were separated, the organic layer was filtered through a pad of celite, dried over Na_2SO_4, and the solvent was evaporated. The

residue was recrystallized from hexane to give **3** as white crystals (16.2 g, 92 %). M.p. 105-106 °C. ^{1}H-NMR($CDCl_3$): 1.45 (s, 9H); 2.20 (s, 3H); 6.10 (s, 1H); 7.30-7.70 (m, 10 H). ^{13}C-NMR($CDCl_3$): 21.04, 27.88, 82.93, 84.68, 127-131 (m), 135.55, 138.74, 165.76, 169.90, 173.99. Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.41; H, 6.48; N, 3.99.

5. Preparation of *tert*-butyl (acetyloxy)[(diphenylmethylene)amino]acetate (**3**) from **5**. To a solution of freshly prepared *tert*-butyl [(diphenylmethylene)amino]oxoacetate (**5**)[6] (1.52 g, 5 mmol) in THF (10 mL) at -78 °C, a solution of Super Hydride® (1.0 M, 6 mL, 6 mmol) was added dropwise over 10 min. The mixture was stirred at -78 °C for 30 min, Ac_2O (0.45 g, 7.5 mmol) was added dropwise over 10 min, the mixture was stirred for 30 min at -78 °C and then at rt for 1 h. The THF was evaporated, the residue was dissolved in ether (20 mL), the organic phase was washed with H_2O, dried over Na_2SO_4, filtered, evaporated and then recrystallized from hexane to give **3** (1.58 g, 90%). M.p. 103-105 °C.
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7. Preparation of (*S*)-1-*tert*-butyl 2,2-dimethyl 1-[(diphenylmethylene)amino]-1,2,2-ethanetricarboxylate (**6**). A three-necked round-bottom flask (100 mL) containing (*2S,4S*)-BPPM[3a] (554 mg, 1.0 mmol) and NaH (65 % oil, 1.44 g, 36 mmol) was connected to a vacuum line, deoxygenated under reduced pressure and then flushed with argon using a Firestone valve. This operation was repeated three times. To the flask was added a solution of dimethyl malonate (8.0 g, 60 mmol) in MeCN (40 mL) in one portion and then a solution of $Pd(OAc)_2$ (224 mg, 1.0 mmol) in MeCN (20 mL) in one portion. The mixture was stirred for 15 min at rt. To this mixture was added a solution of Schiff base acetate **3** (7.06 g, 20 mmol) in MeCN (40 mL). The mixture was stirred at rt for 3 h and then poured into H_2O (200 mL). The aq. solution was extracted with EtOAc, the layers were separated, the organic phase was dried over Na_2SO_4, filtered and evaporated. The residue was subjected to flash chromatography (silica gel, hexane/EtOAc 4/1) to give **6** as a white solid (8.5 g, 100 %). This solid was dissolved in a minimum amount of CH_2Cl_2 and then diluted with hexane (50 mL). The resulting crystals (4.4 g, racemic **6** by chiral HPLC) were collected by vacuum filtration. The filtrate was evaporated and dried to afford optically active **6** as a white solid (4.05 g, 48 % yield, 77 % ee). HPLC (Chiralcel OD column, hexane/iPrOH: 100/1 v/v): 10.20 min (R), 20.81 min (S). M.p. 97-98 °C. $[\alpha]_D$ = -167.0 (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$): 1.44 (s, 9H); 3.69 (s, 3H); 3.71 (s, 3H); 4.33 (d, J = 8.4 Hz, 1H); 4.68 (d, J = 8.4 Hz, 1H): 7.20-7.60 (m, 10H). ^{13}C-NMR: 27.84, 52.49, 55.14, 65.81, 82.12, 127.94, 128.10, 128.25, 128.79, 129.01, 130.45, 135.78, 139.59, 167.64, 167.71, 168.29, 172.62. Anal. Calcd. for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.56; H, 6.33; N, 3.27.
8. Compound **6** (127 mg, 0.3 mmol, 77% ee) was stirred with 1N aq. HCl (5 mL) at rt for 5 h. Benzophenone was throughly extracted from the resulting aq. solution with hexane. The aq. solution was evaporated, the residue was refluxed with 37% aq. HCl (5 mL) for 35 h, evaporated and dried *in vacuo* (50 °C/0.5 mm. Hg) for 15 h. The resulting aspartic acid hydrochloride (white solid, 45 mg, 88%) was used directly for optical rotation and NMR determinations. $[\alpha]_D$ = +17.3 (5N aq. HCl, c = 1.56, 72% o.p.) [*S*-form from Aldrich: +24 (5N HCl, c = 1.56, determined in our laboratory)]. ^{1}H-NMR(D_2O): 2.97 (d, J = 3.6 Hz, 2H); 4.17 (m, 2H).
9. Preparation of (*S*)-1-*tert*-butyl 2,2-dimethyl 1-[(diphenylmethylene)amino]-1,2,2-pent-4-enetricarboxylate (**7b**) (typical procedure). A mixture of **6** (0.85 g, 2 mmol, 77% ee), allyl iodide (0.37 mL, 0.672 g, 4 mmol), 18-crown-6 (0.053 g, 0.2 mmol) and anhydrous K_2CO_3 (1.38 g, 10 mmol) in dry MeCN (10 mL) was stirred at rt for 5 h. The solid was discarded after filtration and washing. The filtrate was evaporated to remove MeCN. The residue was subjected to flash chromatography (silica gel, hexane/EtOAc 4/1) to give **7b** as a white solid (97%, 77% ee). HPLC (Chiralcel OD column, hexane/iPrOH: 100/1 v/v): 6.77 min (major), 8.67 min (minor). M.p. 118-119 °C. $[\alpha]_D$ = -97.0 (c=1.1, MeOH). ^{1}H-NMR ($CDCl_3$): 1.49 (s, 9H), 2.22 (q, 1H); 2.83 (q, 1H); 3.64 (s,3H); 3.83 (s, 3H); 4.33 (s, 1H); 4.99 (s, 1H); 5.03 (d, J = 2.6 Hz, 1H); 5.95 (m, 1H); 7.20-7.75 (m, 10H). Anal. Calcd. for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.71; H, 6.66; N, 3.04.
7a: Yield: 90% (77% ee). HPLC: 9.26 min (major); 12.77 min (minor). M.p. 102-103 °C. ^{1}H-NMR ($CDCl_3$): 1.41 (s, 9H); 1.62 (s, 3H); 3.66 (s, 3H); 3.76 (s, 3H); 4.58 (s,1H); 7.25-7.60 (m, 10H). Anal. Calcd. for $C_{25}H_{29}NO_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.22; H, 6.55; N, 3.19.
7c: Yield: 99% (77% ee). HPLC: 10.1 min (major); 11.5 min (minor). M.p. 134-135 °C. ^{1}H-NMR: 1.41(s, 9H); 2.81 (d, J = 6.0 Hz, 1H); 3.46 (s, 3H); 3.60 (d, J = 6.0 Hz, 1H); 3.77 (s, 3H); 4.52 (s, 1H); 7.20-7.70 (m, 15H). Anal. Calcd. for $C_{31}H_{33}NO_6$: C, 72.21; H, 6.45; N, 2.72. Found: C, 72.43; H, 6.43; N: 2.78.
10. The pKa (DMSO) of the α-proton in **6** is ~23 while the pKa of the β-proton in **6** is ~18 [Compound, pKa (DMSO): $Ph_2C{=}NCH(CH_2Ph)CO_2Et$, 23.2; $MeCH(CO_2Me)_2$, 18.0]. See: (a) O'Donnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8520; (b) Zhang, X. -M.; Bordwell, F. G. *J. Phys. Org. Chem.* **1994**, *7*, 751.

(*Received in USA* 11 *October* 1995; *accepted* 2 *January* 1996)