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# Synthesis of 3-aminoaspartic acid derivatives from glycine precursors

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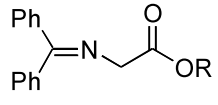
**Abstract**—3-Aminoaspartic acid derivatives **3** have been synthesized via stereoselective alkylation of α-acetyloxyglycine Schiff base **2** with the enolate of glycine anion equivalent **1** as a carbon nucleophile in the presence of $Pd(OAc)_2$ and BINAP at room temperature. High chemical yields and moderate stereoselectivities were observed. The enantiomeric excess of the *dl* diastereomer can be increased to 95% after a single recrystallization from isopropanol and hexanes. 

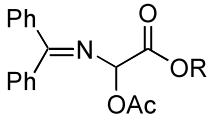
The synthesis of natural and unnatural α-amino acids as building blocks towards compounds with therapeutic properties has attracted considerable attention.[1] Among them, α,β-diamino acids are components of several peptidic antibiotics and other biologically interesting targets.[2] The development of new methods for asymmetric synthesis of α,β-diamino acid derivatives with $C_2$ symmetry is also of interest for the preparation of new analogs of *cis*-platin, as well as new ligands for asymmetric catalysis.[2a] In particular, 3-aminoaspartic acid derivatives are important intermediates for the synthesis of other biologically active molecules, such as biotin, 3-fluoroaspartic acid and 5-fluorouracil.[3] Several synthetic methods for the preparation of 3-aminoaspartic acid derivatives were reported so far in both racemic and in asymmetric forms.[2a,c,3]

In the course of our studies in the synthesis of amino acids and related compounds, we decided to explore new methods for the preparation of 3-amino aspartic acids and their derivatives. The results of these investigations are presented in this letter.

The benzophenone-based imines of glycine alkyl esters **1** have been widely used as glycine anion equivalents for asymmetric synthesis of α-amino acids.[4] The complementary electrophilic glycine cation equivalent **2** can be prepared from **1** in one step and was reported as an alternative precursor in the synthesis of α-amino acids.




**1**




**2**

Various nucleophilic reagents, such as neutral heteroatom nucleophiles,[5] carbanions,[6] organoboranes[7] and neutral carbon nucleophiles[8] react with **2** to regioselectively displace the acetate moiety at the α-carbon. This provides a complementary route to several types of amino acid derivatives that cannot be directly prepared from **1**. Recently, **1** was reported as a nucleophile in palladium-catalyzed asymmetric allylic alkylation reactions to afford the corresponding alkylated amino acids.[9] The derivative **2** was also reported by O'Donnell and co-workers as a substrate in the palladium-catalyzed π-azaallylic substitution reaction, which resulted in the formation of β-carboxyaspartic acid derivatives.[10] However, to the best of our knowledge, using the glycine anion equivalent **1** as the carbon nucleophile to replace the acetate in the glycine cation equivalent **2** has not yet been attempted.

Herein we report a method for the synthesis of alkyl-3-amino-*N*,*N*′-bis(diphenylmethylene)aspartate **3**, using the enolate of glycine anion equivalent **1** as a carbon nucleophile. The latter replaces the acetate of the glycine cation equivalent **2** through palladium-catalyzed π-azaallylic substitution reaction in high chemical yields and moderate stereoselectivity. Optical purity of the products can be dramatically increased after a simple recrystallization.

Both the benzophenone glycine Schiff base and its α-acetyloxy derivatives were prepared according to the

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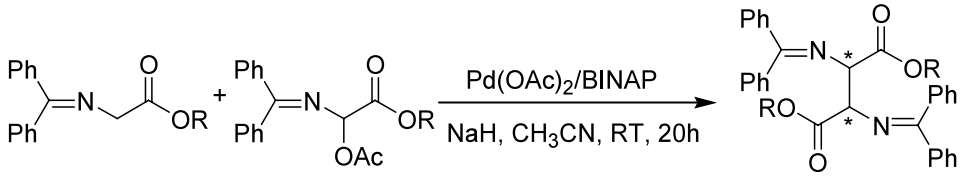
literature.[4] The benzophenone glycine Schiff base was first deprotonated by sodium hydride, then added dropwise to the mixture containing $Pd(OAc)_2$, ligand, and **2** through a cannula. It should be noted that the background reaction proceeds in the presence of 10 mol% $Pd(OAc)_2$ giving product **3c** in 66% yield with a *dl*/*meso* ratio as 36/64 after 20 h (entry 13 in Table 2). Nonetheless, we decided to explore the possibility of a ligand-controlled pathway. As reported in the literature, the size of the ester group has an effect on the enantioselectivity of the coupling reaction.[10a,11] In our case, increasing the size of the ester group from methyl to ethyl led to an increase of the % ee value from 3% (entry 1 in Table 1) to 10% (entry 3 in Table 1). The % ee was further increased to 36% when the bulkier *tert*-butyl ester was introduced (entry 5 in Table 1). The ratio of the *dl*/*meso* diastereomers changed from 45:55 to 56:44 and 67:33, respectively. We have observed a small solvent effect on the stereoselectivity. In acetonitrile, the highest ee was obtained (36%), with the *dl*/*meso* ratio of 67:33 (entry 4 in Table 2). However, in toluene, only 9% ee was obtained and the ratio of *dl*/*meso* diastereomers was 43:57 (entry 9 in Table 2). In THF, the % ee was further decreased to 4% with the ratio of *dl*/*meso* as 24:76, though the chemical yield still remanined high (89%) (entry 1 in Table 2). Another type of bidentate chiral phosphine ligand, (*R*)-(−)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldiphenylphosphine, was used together with allylpalladium chloride dimer as the catalyst precursor instead of the combination of palladium acetate and BINAP. The % ee was found to be 15% in toluene (entry 8 in Table 2) and 1% in acetonitrile (entry 7 in Table 2) with the ratio of *dl*/*meso* of 52:48 and 57:43, respectively. In both cases only moderate chemical yields (52% and 57%) were obtained. The bidentate chiral *P*,*N*-ligand (*R*)-(+)-2-[2-(diphenylphosphino)phenyl]-4-(1-methylethyl)-4,5-dihydrooxazole was then tested in $CH_3CN$. 11% ee was observed with 71% yield and *dl*/*meso* ratio as 47/53 (entry 10 in Table 2). Our attention was then focused on the tetradentate Trost ligands, (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl) and (1*S*,2*S*)-(−)-1,2-diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphino-1-naphthoyl). To our disappointment, neither of them showed efficient enantioselectivity in this case (9% ee with the former and 7% ee with the latter) (entries 11 and 12 in Table 2). In another attempt to control the nature of the enolate of benzophenone glycine Schiff base **1**,[12] we used LiHMDS and (−)-sparteine as a chiral auxiliary, but the observed ee's were still low (17% ((*S*)-BINAP) and 15% ((*R*)-BINAP) in THF, 3% in $CH_3CN$, entries 2, 3 and 5 in Table 2). Both cinchoninium and cinchonidinium derivatives were reported as efficient chiral phase-transfer catalysts in controlling the geometry of the enolate of **1**. The reaction conditions described by Corey[12a] and Takemoto[9a] were introduced to our reaction system. Unfortunately, the α-acetyloxy benzophenone glycine Schiff base **2** decomposed under PTC conditions after 3 h and no product was observed. When the reaction was run at −25°C in $CH_3CN$, the enantioselectivity was increased to 47% and the *dl*/*meso* ratio changed to 48:52 (entry 6 in Table 2) with a slightly lower yield (77%). We were pleased to find that the *dl*/*meso* diastereomers can be easily separated by recrystallization from acetonitrile. The *meso* diastereomer crystallized as white crystals while the *dl* diastereomer remained in the mother liquor. Furthermore, the % ee value of the *dl* diastereomer can be increased up to 95% after further recrystallization from hexanes/isopropanol.[13]

**Table 1.** Palladium-catalyzed π-azaallylic alkylation between **1** and **2** (Eq. (1))



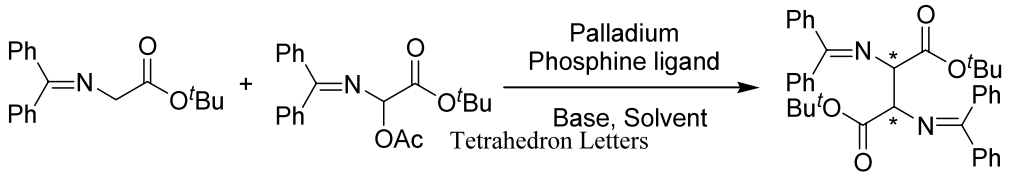

(1)

**1a-3a**, R=$CH_3$
**1b-3b,** R=Et
**1c-3c**, R=$^t$Bu

| Entry | Ligand | Product | Yield (%)[a] | *dl*/*meso*[b] | ee of *dl* (%)[c,d] |
|---|---|---|---|---|---|
| 1 | (*R*)-BINAP | **3a** | 75 | 45/55 | 3 (*S*,*S*) |
| 2 | (*S*)-BINAP | **3a** | 79 | 44/56 | 4 (*R*,*R*) |
| 3 | (*R*)-BINAP | **3b** | 81 | 56/44 | 10 (*S*,*S*) |
| 4 | (*S*)-BINAP | **3b** | 83 | 57/43 | 13 (*R*,*R*) |
| 5 | (*R*)-BINAP | **3c** | 84 | 67/33 | 36 (*S*,*S*) |
| 6 | (*S*)-BINAP | **3c** | 86 | 67/33 | 35 (*R*,*R*) |

[a] Combined isolated yields of *meso* and *dl* compounds.
[b] The ratio of *dl*/*meso* was measured by $^1$H NMR.
[c] The % ee of compounds **3a** and **3b** was measured on Chiralcel OD column with 99/1 hexanes/*i*PrOH as mobile phase; the % ee of compound **3c** was measured on Chiralcel AD column with 99/1 hexanes/*i*PrOH as mobile phase.
[d] The absolute configurations were determined by comparing the sign of optical rotation with the literature.[2a,14]

**Table 2.** Palladium-catalyzed π-azaallylic alkylation between **1c** and **2c**: the effects of solvents and catalysts (Eq. (2))




(2)

| Entry[a] | Pd source | Phosphine ligand | Solvent | Base | Time (h) | Yield (%)[d] | *dl*/*meso* | ee of *dl* (%)[e,f] |
|---|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | (*R*)-BINAP | THF | NaHMDS | 20 | 89 | 24/76 | 4 (*S*,*S*) |
| 2[g] | $Pd(OAc)_2$ | (*S*)-BINAP | THF | LiHMDS | 18 | 91 | 62/38 | 17 (*R*,*R*) |
| 3[g] | $Pd(OAc)_2$ | (*R*)-BINAP | THF | LiHMDS | 18 | 83 | 63/37 | 15 (*S*,*S*) |
| 4 | $Pd(OAc)_2$ | (*R*)-BINAP | $CH_3CN$ | NaH(60%) | 20 | 84 | 67/33 | 36 (*S*,*S*) |
| 5[g] | $Pd(OAc)_2$ | (*S*)-BINAP | $CH_3CN$ | LiHMDS | 20 | 68 | 44/56 | 3 (*R*,*R*) |
| 6[b] | $Pd(OAc)_2$ | (*R*)-BINAP | $CH_3CN$ | NaH(60%) | 24 | 77 | 48/52 | 47 (*S*,*S*) |
| 7 | $[Pd(allyl)Cl]_2$ | Ligand[c] | $CH_3CN$ | NaH(60%) | 20 | 57 | 57/43 | 1 (*R*,*R*) |
| 8 | $[Pd(allyl)Cl]_2$ | Ligand[c] | $PhCH_3$ | NaHMDS | 30 | 52 | 52/48 | 15 (*R*,*R*) |
| 9 | $Pd(OAc)_2$ | (*R*)-BINAP | $PhCH_3$ | NaHMDS | 30 | 87 | 43/57 | 9 (*S*,*S*) |
| 10 | $Pd(OAc)_2$ | Ligand[h] | $CH_3CN$ | NaH(60%) | 20 | 71 | 47/53 | 11 (*S*,*S*) |
| 11 | $Pd(OAc)_2$ | Ligand[i] | $CH_3CN$ | NaH(60%) | 20 | 82 | 22/78 | 9 (*S*,*S*) |
| 12 | $Pd(OAc)_2$ | Ligand[j] | $CH_3CN$ | NaH(60%) | 20 | 69 | 20/80 | 7 (*S*,*S*) |
| 13 | $Pd(OAc)_2$ | – | $CH_3CN$ | NaH(60%) | 20 | 66 | 36/64 | – |

[a] The reactions were run at room temperature except for entry 6.
[b] The reaction was run at −25°C.
[c] (*R*)-(−)-1-[(*S*)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldiphenylphosphine was used as the ligand.
[d] Combined isolated yields of *meso* and *dl* compounds.
[e] % ee was detected by Chiralcel AD column, using 99/1 hexanes/*i*PrOH as mobile phase, 1 ml/min.
[f] The absolute configuration was determined by comparing the sign of optical rotation with the literature.[2a,14]
[g] 1 equiv. (−)-sparteine was added.
[h] (*R*)-(+)-2-[2-(Diphenylphosphino)phenyl]-4-(1-methylethyl)-4,5-dihydrooxazole was used as ligand.
[i] (1*R*,2*R*)-(+)-1,2-Diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl) was used as ligand.
[j] (1*S*,2*S*)-(−)-1,2-Diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphino-1-naphthoyl) was used as ligand

In conclusion, 3-aminoaspartate derivatives were prepared via the palladium-catalyzed π-azaallylic substitution reaction, using the anion equivalent of the benzophenone Schiff base as the carbon nucleophile. Good yields and moderate stereoselectivities were obtained. The optical purity of the *dl* diastereomer can be increased to 95% by a simple recrystallization. This reaction can be used for the synthesis of 1,2-diamine compounds of biological interest. Further investigation of increasing the steoreoselectivity and the construction of the quaternary stereocenters of this series of compounds is currently underway.

## Acknowledgements

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## References

1. For selected recent reviews on the synthesis of α-amino acids, see: (a) Abellam, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Najera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, 2689; (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (c) Williams, R. M. *Synthesis of Optically Active a-Amino Acid*; Pergamon: Oxford, 1989; (d) Hanessian, S.; Mcnaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789; (d) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.
2. (a) Alvarez-Ibarra, C.; Csaky, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478; (b) Dunn, P. J.; Haner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017 and references cited therein; (c) Fernandez-Megia, E.; Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1994**, *59*, 7643 and references cited therein.
3. Ozaki, Y.; Iwasaki, T.; Miyoshi, M.; Matsumoto, K. *J. Org. Chem.* **1979**, *44*, 1714 and references cited therein.
4. O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3.
5. O'Donnell, M. J.; Benner, W. D.; Polt, R. L. *Tetrahedron Lett.* **1985**, *26*, 695.
6. O'Donnell, M. J.; Falmagne, J. B. *Tetrahedron Lett.* **1985**, *26*, 699.
7. (a) O'Donnell, M. J.; Falmagne, J. B. *Chem. Commun.* **1985**, 1168; (b) O'Donnell, M. J.; Drew, M. D.; Cooper, J. T.; Delgado, F.; Zhou, C. Y. *J. Am. Chem. Soc.* **2002**, *124*, 9348.
8. O'Donnell, M. J.; Benner, W. D. *Tetrahedron* **1988**, *44*, 5389.

9. (a) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329; (b) Chen, G.; Deng, Y.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1567; (c) You, S. L.; Dai, L. X.; Cao, B. X.; Sun, J. *Chem. Commun.* **2000**, 1933.
10. (a) O'Donnell, M. J.; Chen, N.; Zhou, C.; Murray, A. *J. Org. Chem.* **1997**, *62*, 3962; (b) O'Donnell, M. J.; Zhou, C.; Chen, N. *Tetrahedron: Asymmetry*. **1996**, *7*, 621; (c) O'Donnell, M. J.; Yang, X. B.; Li, M. *Tetrahedron Lett.* **1990**, *31*, 5135.
11. Yamaguchi, M.; Ohba, K.; Tomonaga, H.; Yamagishi, T. *J. Mol. Catal. A: Chem.* **1999**, *140*, 255.
12. For selected examples, see: (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414; (b) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519; (c) MacMillan, J. B.; Molinski, T. F. *Org. Lett.* **2002**, *4*, 1883.
13. *General procedure for the asymmetric coupling reaction using Pd catalysis*: *tert*-Butyl-3-amino-*N*,*N*′-bis(diphenylmethylene)aspartate (**3c**). To a 10 ml flame dried Schlenk flask (flask A) equipped with a magnetic stirring bar was added palladium acetate (4.5 mg, 0.02 mmol) and (*S*)-BINAP (12.5 mg, 0.02 mmol) under an argon atmosphere. NaH (60% dispersion in mineral oil) (20 mg, 0.5 mmol) and *tert*-butyl-*N*-(diphenylmethylene)glycine ester **1c** (59 mg, 0.2 mmol) were added to a similar flask (flask B, 10 ml) under an argon atmosphere. Acetonitrile (2 ml) was added to both flasks. The mixtures were stirred for 5 min at room temperature. Then *tert*-butyl-acetyloxy-diphenylmethyleneaminoacetate **2c** (71 mg, 0.2 mmol) was added to flask A under argon an atmosphere and the reaction mixture was stirred for an additional 5 min. The yellow solution in flask B was transferred dropwise by a cannula to flask A over 10 min. The entire mixture was stirred at room temperature for 20 h. The reaction mixture was then quenched with saturated sodium bicarbonate aqueous solution (10 ml) and extracted with diethyl ether (3×5 ml). The organic phase was dried with $MgSO_4$, filtered and concentrated in vacuo to give a red oil. The crude product was purified by flash chromatography on silica gel eluting with 9/1 hexanes/EtOAc to yield the product (*meso*+*dl*) (101 mg, 86%). The *meso* diastereomer was recrystallized from acetonitrile as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.37 (18H, s), 4.59 (2H, s), 7.16–7.63 (20H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 28.3, 69.7, 81.3, 128.0, 128.3, 128.5, 128.7, 129.3, 130.4, 136.8, 140.0, 169.3, 171.5; MS (M+1) calcd: 589.3066; found: 589.3048. The *dl* diastereomer was purified by prep. HPLC (65/35 $CH_3CN/H_2O$ as mobile phase) and analyzed by chiral HPLC (chiralcel AD column, hexanes/*i*PrOH 99/1, 1 ml/min, $\lambda = 254$ nm, retention times: (*R*,*R*) (major) 4.5 min; (*S*,*S*) (minor) 5.2 min) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.38 (18H, s), 4.74 (2H, s), 7.21–7.60 (20H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 28.2, 68.9, 81.3, 128.0, 128.3, 128.6, 128.8, 129.3, 130.3, 136.4, 139.7, 169.5, 171.3; MS (*m*/*z*) calcd: 588.2988; found: 588.2990.
Methyl - 3 - amino - *N*,*N*′ - bis(diphenylmethylene)aspartate (**3a**): The same conditions as **3c**, except that 8/2 hexanes/EtOAc as eluent. Yield: (*meso*+*dl*), 79%. The *meso* diastereomer was recrystallized from acetonitrile as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.67 (6H, s), 4.80 (2H, s), 7.15–7.59 (10H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 52.4, 69.0, 128.2, 128.2, 129.0, 129.0, 129.3, 130.6, 136.3, 139.8, 170.6, 172.5. MS (*m*/*z*) calcd: 504.2049; found: 504.2053.
The *dl* diastereomer was purified by prep. HPLC (65/35 $CH_3CN/H_2O$ as mobile phase) and analyzed by chiral HPLC (chiralcel OD column, hexanes/*i*PrOH 99/1, 1 ml/min, $\lambda = 254$ nm, retention times: (*S*,*S*) (minor) 10.8 min; (*R*,*R*) (major) 17.4 min) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.66 (6H, s), 4.95 (2H, s), 7.23–7.57 (20H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 52.4, 68.0, 128.1, 128.5, 128.7, 128.9, 129.3, 130.6, 136.0, 139.5, 170.8, 172.2; MS (M+1) calcd: 505.2127; found: 505.2143.
Ethyl - 3 - amino - *N*,*N*′ - bis(diphenylmethylene)aspartate (**3b**): The same conditions as **3a**. Yield: (*meso*+*dl*) 83%.
The *meso* diastereomer was recrystallized from acetonitrile as a white solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.18 (6H, t), 4.12 (4H, m), 4.78 (2H, s), 7.16–7.61 (20H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.3, 61.1, 69.1, 128.1, 128.2, 128.6, 128.8, 129.3, 130.5, 136.5, 139.8, 170.2, 172.2; MS (M+1) calcd: 533.2440; found: 533.2444.
The *dl* diastereomer was purified by prep. HPLC (65/35 $CH_3CN/H_2O$ as mobile phase) and analyzed by chiral HPLC (chiralcel OD column, hexanes/*i*PrOH 99/1, 1 ml/min, $\lambda = 254$ nm, retention times: (*S*,*S*) (minor) 9.0 min; (*R*,*R*) (major) 15.2 min) $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.19 (6H, t), 4.10 (4H, m), 4.93 (2H, s), 7.23–7.58 (20H, m); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.2, 61.2, 68.0, 128.0, 128.4, 128.7, 128.8, 129.2, 130.5, 136.1, 139.5, 170.2, 172.0; MS (M+1) calcd: 533.2440; found: 533.2456.
14. Hochstein, F. A. *J. Org. Chem.* **1959**, *24*, 679.