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2-AZA-π-ALLYLPALLADIUM COMPLEXES FOR THE SYNTHESIS OF β-CARBOXYASPARTIC ACID (ASA) DERIVATIVES[1]

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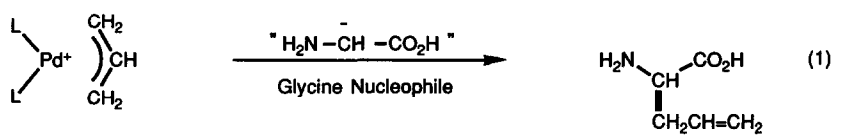
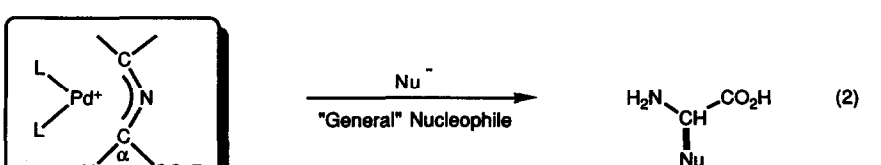
Reaction of malonate anions with Schiff base acetates (**3**) in the presence of a palladium catalyst yields protected derivatives of β-carboxyaspartic acid (**5**).

The rich chemistry of π-allylpalladium complexes has been utilized extensively in organic synthesis.[2] While the all-carbon allylic systems (**1**) have received considerable attention, examples of the synthetic utilization of heteroatom-substituted π-allyl systems are much rarer.[3,4] In conjunction with our program for the synthesis of α-amino acids from Schiff base protected derivatives of glycine and higher amino acids,[5] we were interested in exploring the 2-aza-π-allyl system (**2**) as a cationic glycine equivalent, which represents an "umpolung" of the method developed by Genet for the palladium catalyzed allylation of Schiff base esters (Eq. 1).[6] In principle, provided nucleophilic attacks occurs at the α-carbon of the palladium complex **2**, it should be possible to use a variety of nucleophilic reagents for reaction with **2** to prepare α-substituted amino acid derivatives (Eq. 2). We report here preliminary studies toward the realization of this goal.



1
Allylic Electrophile

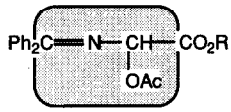
(1)



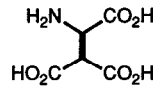
2
Glycine Electrophile

(2)

The Schiff base acetates (**3**), which are readily prepared and also commercially available,[7] have served as versatile cationic glycine equivalents. These multifunctional compounds can be reacted with nucleophiles by a number of different routes.[7a, 8] Consideration of the shaded structural subunit of (**3**) demonstrates the potential



3

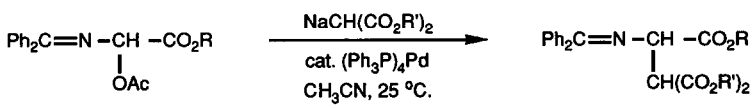


4

for using these compounds as *pseudo* allylic acetates in the context of palladium-catalyzed reactions. Thus, reaction of (**3**) with malonate anion followed by deprotection could lead to the interesting, recently discovered α-amino acid, β-carboxyaspartic acid (**4**) (ASA)[9] by construction of the indicated α,β carbon-carbon bond.

Indeed, reaction of acetate (**3**) (R=Et) with sodium dimethyl malonate overnight at room temperature in acetonitrile in the presence of 10% of commercial tetrakis(triphenylphosphine)palladium(0) gave, following purification, a 37% yield of the protected ASA derivative (**5**) (R=Et, R'=Me).[10] Both the reaction time as well as yield of purified product[11] were improved substantially by reacting the methyl ester of (**3**) and $NaCH(CO_2Me)_2$ with freshly prepared $(Ph_3P)_4Pd$[12,13] (Table 1, entry a). Further experiments have shown that it is also possible to use benzyl groups for protection of the carboxylic acid functionalities (Table 1, entry b) although the time of reaction is lengthened with a slight decrease in yield. Combinations of the methyl and benzyl ester protecting groups demonstrated that the key steric requirement is, as expected, in the 2-aza-π-allylic system (Table 1, entries c and d; 4 vs. 18 hours reaction time).[14]

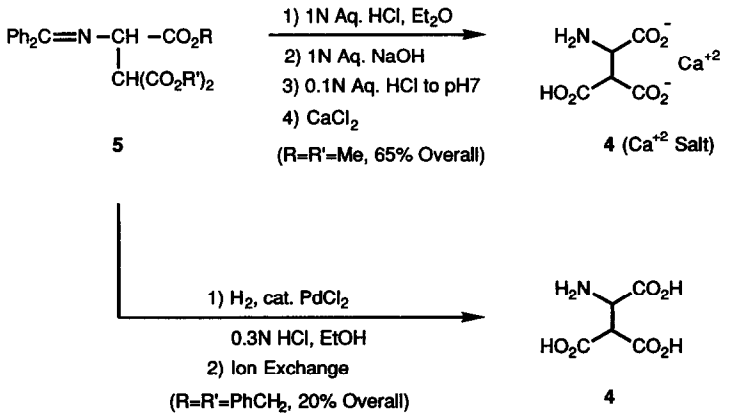
Table 1. Preparation of Protected ASA Derivatives **5**.[11]



3 **5**

Entry	R	R'	Time (hr)	Isolated Yield(%)
a	Me	Me	2	79
b	CH_2Ph	CH_2Ph	18	58
c	Me	CH_2Ph	4	50
d	CH_2Ph	Me	18	36

The protected derivatives (**5**) can be readily converted into ASA (**4**) by suitable variations in described procedures for the isolation of ASA.[9] Thus, mild acid hydrolysis of (**5a**) (to remove the imine) followed by mild saponification and isolation as the calcium salt led to (**4**) (Ca^{+2} salt). Hydrogenolysis of (**5b**) followed by workup yielded ASA directly, along with small amounts of the decarboxylated product, aspartic acid.



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10. Reaction in the absence of catalyst gave only recovered starting materials.
11. All new compounds (**3** and **5**) were characterized by analytical and spectral data.
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13. Typical Experimental Procedure (Synthesis of **5a**): Methyl N-(diphenylmethylene)-2-acetoxyglycinate (**3a**) (0.118 g, 0.379 mmol), tetrakis(triphenylphosphine)palladium(0) (0.044 g, 0.038 mmol) and dry CH_3CN (10 mL) were added under argon to a 50 mL three-necked round-bottomed flask equipped with a gas bubbler, magnetic stirring bar and septum. The mixture was cooled to -78 ^{0}C, then the apparatus was connected to an oil-pump vacuum line and was allowed to deoxygenate under reduced pressure at -78 ^{0}C. The apparatus was flushed with argon using a Firestone valve. After three such evacuations and inert gas-flushing cycles, the mixture was allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 60 minutes for Pd-complex formation and then this mixture was added dropwise to a solution of sodium dimethyl malonate (0.088 g, 0.571 mmol) in CH_3CN (10 mL) under argon at room temperature (this solution was first deoxygenated as above). The resulting mixture was stirred for 2 hours at room temperature,the reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL), and the organic solvent was evaporated *in vacuo*. The residue was dissolved in ether (20 mL) and washed with saturated $NaHCO_3$ solution (3x15 mL) and dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave crude product which was purified by Chromatotron (hexane/ether = 9/1) to yield 0.114 g of 1-N-(diphenylmethylene)-1,2,2,-tris(methoxycarbonyl)ethane **5a** (79%) as a colorless oil. Recrystalization from hexane/ether gave white crystals of **5a**. mp 79.5-80 ^{0}C. ^{1}H NMR δ: 3.7 (s, 9H); 4.35 (d, 1H); 4.85 (d, 1H); 7.2-7.5 (m, 10H). Anal. Calcd. for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 66.01; H, 5.45; N, 3.51.
14. The following control experiments substantiate the intermediacy of a 2-aza-π-allylpalladium intermediate rather than an oxa-π-allylpalladium intermediate[3] formed from the AcO-CH-C=O portion of **3**: reaction of $AcOCH_2CO_2Me$[15] with $NaCH(CO_2Me)_2$ under reaction conditions described above[13] both in the presence and absence of $(Ph_3P)_4Pd$ gave <1-2% of the expected product $(MeO_2C)_2CH\text{-}CH_2CO_2Me$.[16]
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