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Synthesis of γ,δ-Unsaturated 6-Hydroxy Substituted α-Amino Acids by Palladium-Catalyzed Alkylation of Monoepoxydienes

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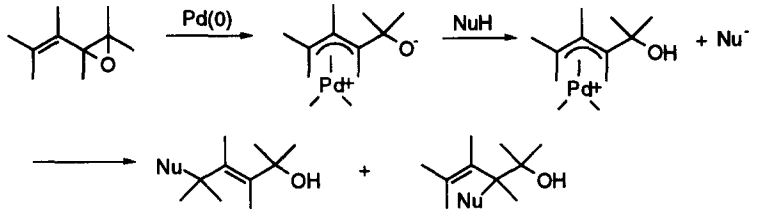
Abstract: Monoepoxydienes **1**, derived from acyclic and cyclic conjugated dienes, react under neutral conditions with the benzophenone imine of glycine nitrile **4** in the presence of a catalytic amount of $Pd(PPh_3)_4$ (5% mol) to afford the corresponding unsaturated 6-hydroxy substituted α-amino acids **5** in a regio (1,4-addition) and stereoselective manner. However, the benzophenone imine of glycine ethyl ester **2** only react with butadiene monoepoxide to furnish regio and stereoselectively ethyl (4*E*)-6-hydroxy-2-(diphenylmethylene)amino-4-hexenoate (**3**) a precursor of a bulgecinine diastereomer.

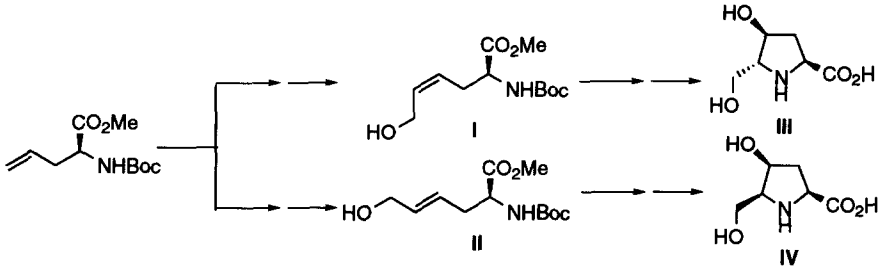
The inter[1] or intramolecular[2] palladium(0)-catalyzed addition of carbon and heteronucleophiles to vinyl epoxides can be carried out with a high degree of regioselectivity (Scheme 1). In macrocyclization reactions mainly 1,4-addition has been observed with different type of nucleophiles. Soft carbonucleophiles such as nitroalkanes, 1,3-dicarbonyl compounds, bis(arylsulfonyl)methane or α-(arylsulfonyl)acetates gave 1,4-adducts[1a,b,e,g,i,j] in intermolecular reactions. However, oxygenated[1f] and nitrogenated[1a,d,h] nucleophiles afforded 1,2- or 1,4-addition products depending on the reaction conditions and their acidity due to the hydrogen bonding between the heteronucleophile and the oxygen leaving group that increases 1,2-adduct formation.[1h] This methodology has been used for the synthesis of the alkaloid inandenin-12-one,[1c] (±)-aristeromycin,[1d] all-*trans*-geranylgeraniol[1g] and (*S*)-vinylglycinol.[1h]



Scheme 1.

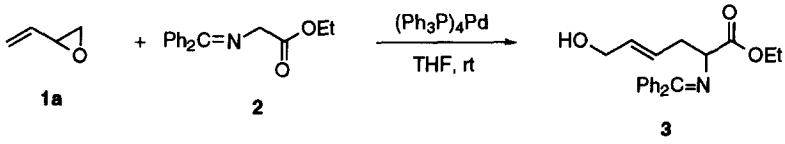
The ability of Schiff bases derived from glycine[3] to act as soft nucleophile in palladium mediated allylations under basic and neutral conditions with allyl esters, carbonates and halides has been applied to the synthesis of racemic and optically active α-amino acids.[4] Since vinyl epoxides are very reactive substrates in palladium-catalyzed reactions, imino glycinates should be appropriate soft carbonucleophiles for the neutral 1,4-addition to these electrophiles. This methodology should be a direct route to acyclic and cyclic γ,δ-unsaturated

6-hydroxy substituted α-amino acids. The corresponding acyclic derivatives **I** and **II** are precursors of the antibiotic (-)-bulgecinine **III**[5] and its epimer **IV**, respectively and has been prepared from protected allylglycine in a multi-step procedure[6] (Scheme 2). Compound **I** has been recently prepared by diastereoselective alkylation of the sultam-derived imino glycine with *O*-silylated (*Z*)-4-bromo-2-buten-1-ol.[7]



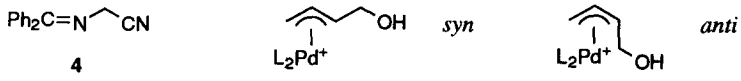
Scheme 2.

Initially we studied the reaction of butadiene monoepoxide (**1a**) with the benzophenone imine of glycine ethyl ester (**2**)[8] in the presence of tetrakis(triphenylphosphine)palladium(0) (5% mol) in THF at room temperature, which gave the expected ethyl (4*E*)-6-hydroxy- 2-(diphenylmethylene)amino-4-hexenoate (**3**) in 85% yield (Scheme 3). However, the reaction of this nucleophile **2** with other unsaturated epoxides derived from acyclic and cyclic dienes **1b-f**, failed.



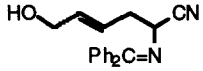
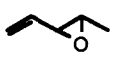
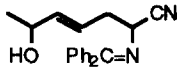
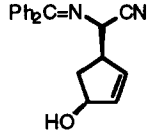
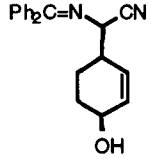
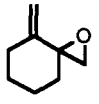
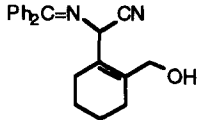
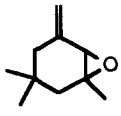
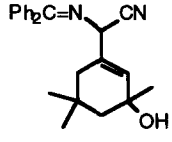
Scheme 3.

When the glycine benzophenone imino nitrile (**4**),[8] a less sterically demanding nucleophile and with similar nucleophilicity,[9] was allowed to react with different epoxides **1** under Pd(0) catalysis in THF at room temperature the corresponding 1,4-addtion products **5** were obtained (Table 1). Vinyloxirane **1a** furnished compound **5a** as a mixture 1/1 of *Z/E* diastereomers and in the presence of a ligand such as 1,2-bis(diphenylphosphino)ethane (dppe) **5a** was isolated with similar yield as a ratio 1/5:*Z/E* (Table 1, entries 1 and 2, respectively). It can be postulated that with a less stericaly demanding nucleophile competitive attack to both *syn* and *anti* (η^3-allyl)palladium intermediates[2c] is possible.



In the case of the epoxide derived from piperylene **1b** only the *E*-diastereomer was formed. Cyclic epoxides **1c** and **1d** gave *cis*-1,4-adducts **5c** and **5d**, respectively (Table 1, entries 4 and 5) according to the *anti* attack of the nucleophile to the *trans*-π-allylpalladium intermediates.[1b] The configuration of these products was deduced by studies of the coupling constants pattern as previously described for malonate derivatives[1b] and

Table 1. Alkylations of Epoxydienes with Imino Nitrile **4**

	epoxydiene		reaction	product[a]		
Entry	no.	structure	time (d)	no.	structure	yield (%)[b]
1	**1a**		1	**5a**		97[c]
2	**1a**		1	**5a**		90[d,e]
3	**1b**		1	**5b**		50[f,g]
4	**1c**[h]		1	**5c**		56[f]
5	**1d**[h]		3	**5d**		51[d]
6	**1e**[i]		1	**5e**		30
7	**1f**[j]		5	**5f**		81[f]

[a] All compounds were fully characterized by their spectroscopic data (IR, ^{1}H and ^{13}C NMR, and mass spectra). [b] Isolated yield after flash chromatography (neutral alumina) based on starting imino nitrile **4**. [c] 1/1 Mixture of *Z/E* diastereomers. [d] dppe (14% mol) was added. [e] 1/5 Mixture of *Z/E* diastereomers. [f] 1/1 Mixture of *erythro/threo* diastereomers. [g] *E*-diastereomer. [h] Prepared according to ref. 11. [i] Prepared according to ref. 12. [j] Prepared according to ref. 13.

by NOE experiments. Cyclohexane derived epoxides **1d** and **1f** reacted slugishly and **1e** with low yield. Compounds **5b-d** and **5f** were isolated as *ca.* 1/1 mixture of diastereomers (Table 1, entries 3-5 and 7). The derivative of cyclopentadiene monoepoxide **5c** can be used as starting material for the synthesis of biologically

important cyclopentanoids.

We conclude that this procedure represents a simple and direct way for the preparation of acyclic and cyclic γ,δ-unsaturated 6-hydroxy substituted α-amino acids. Efforts to extend this methodology to the asymmetric synthesis[14] of these type of α-amino acids are being pursued in these laboratories.

Synthesis of Compounds **3** *and* **5**. *Typical Procedure:* To a solution of imino ester **2**[8] or nitrile **4**[8] (1 mmol) and $(Ph_3P)_4Pd$ (58 mg, 0.05 mmol) in dry THF (5 ml) was added, under argon atmosphere, the epoxydiene **1** (0.6 mmol) and the solution was stirred at room temperature for the time indicated on Table 1. The reaction mixture was treated with water and extracted with ether. The organic layers were dried (Na_2SO_4), concentrated and the residue purified by column chromatography (neutral alumina) to afford compounds **3** and **5**.[18]

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