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Regioselective Palladium (0) Catalyzed Azidation and Amination of 1-Alkenylcyclopropyl Esters : A New Route to 2,3-Methanoamino Acids.

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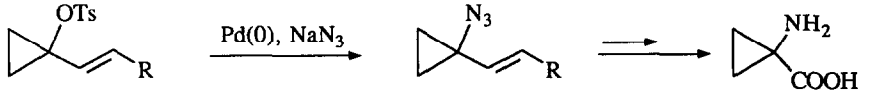
***Abstract** : Palladium (0) catalyzed azidation of 1-alkenylcyclopropyl esters provides regioselectively 1-azido-1-alkenyl cyclopropanes, convenient precursors of 2,3-methanoamino acids. On the other hand, amination occurred exclusively on the less substituted allylic end, providing strained 2-cyclopropylideneethylamine derivatives.*

Allyl esters (acetates, carbonates, phosphonates, ...) undergo efficient palladium (0) catalyzed azidation upon treatment with azide anion[1]. Generally a regioisomeric mixture of allyl azides is obtained at equilibrium because of rapid 1,3-rearrangement[2]. We have recently reported that 1-ethenylcyclopropyl esters underwent palladium (0) catalyzed nucleophilic substitution with complete retention of the three-membered ring. With stabilized nucleophiles, *i.e.*, enolates of malonic esters, β-dicarbonyl compounds, β-sulfonyl esters, Schiff bases, acetates, ... the substitution occurred at the vinyl end providing methylenecyclopropane derivatives, exclusively ; while tertiary substitution on the cyclopropane ring has been obtained with non-stabilized nucleophiles such as organometallic reagents or hydrides [3].

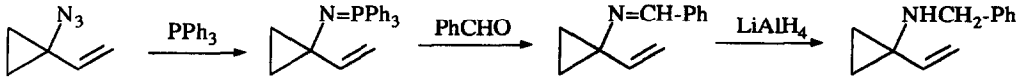


1a R = H
b C_6H_5

2a,b **3**

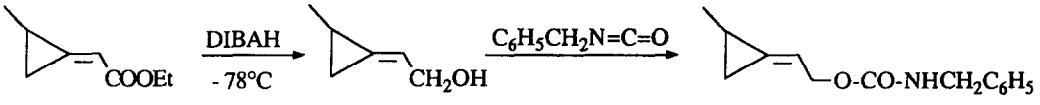
We have investigated the palladium (0) catalyzed azidation and amination of 1-alkenylcyclopropyl esters **1a,b**, in order to provide via the 1-alkenylcyclopropyl azides **2a,b** (or corresponding amines) a new and selective synthesis of the 2,3-methanoamino acid **3** (ACC) and derivatives, which due to their outstanding biological activities are currently attracting special attention[4]. Reaction of 3,3-dimethylallyl acetate **4** with sodium azide in the presence of $Pd(PPh_3)_4$ was reported to give through the allyl azide **5**, after successive treatment with triphenylphosphine and 2N sodium hydroxide at 50°C, the 3-methyl-2-butenylamine **6**, (see Table, entry 1)[1]. In the same way, azidation of 1-vinylcyclohexyl acetate **7** followed by one-pot reduction of **8** (PPh_3 and 2N NaOH), led to the 2-cyclohexylideneethylamine **9** (entry 2)[1]. On the other hand, reaction of 1-tosyloxy-1-vinylcyclopropane **1a**[3] with sodium azide (2 equiv) in the presence of palladium (0) ($Pd(dba)_2$, 2 PPh_3) (5-10%) and [15]-crown-5 ether (10%), offered in 80% yield the 1-azido-1-ethenylcyclopropane **2a**, exclusively (entry 3). Treatment of **2a** with 1,3-propanedithiol in methanol[5] or with triphenylphosphine in aqueous sodium hydroxide[1,6], gave in 40-60% yields the highly volatile 1-vinylcyclopropylamine **10** (entry 3). But successive treatment of **2a** with PPh_3 and benzaldehyde, in THF at reflux, provided through the

iminophosphorane **11** the N-benzylidene 1-amino-1-vinylcyclopropane **12**, almost quantitatively. Lithium aluminum hydride reduction of **12** in THF gave the N-benzyl 1-amino-1-vinylcyclopropane **13** in 85% yield.



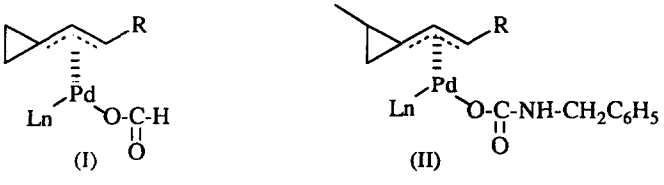
2a **11** **12** (100%) **13** (85%)

Comparatively, we have examined the Pd(0) catalyzed amination of these 1-alkenylcyclopropyl esters. Thus, reaction of **1a** with excess of benzylamine as nucleophile in the presence of $Pd(dba)_2$, $2PPh_3$ gave the bis(2-cyclopropylideneethyl)benzylamine **14** in 75% yield (entry 4), because the intermediate monoallylamine was more nucleophilic than benzylamine itself. Substitution of **1a** by dibenzylamine provided the N,N-dibenzyl (2-cyclopropylideneethyl)amine **15** in 85% yield, (entry 5). It has been reported that allylic amination occurred regioselectively on the more substituted end of π-allyl groups when using ferrocenylphosphine-palladium complexes[7] ; however, use of PPh_3 or bis (diphenylphosphino)ferrocene as ligand in the Pd(0) catalyzed amination of **1a** with dibenzylamine led exclusively to the product of amination at the primary vinylic end, *i.e.*, to allyl amine **15** (entry 5). Reaction of **1a** with benzophenone imine in the presence of Pd(0), provided the N-diphenylmethylene (2-cyclopropylideneethyl)amine **16** in 95% yield (entry 6). Contrary to the reduction of 1-alkenylcyclopropyl esters with sodium formate as hydride source[8] the regioselectivity of the amination was not depending on the bulkiness of the palladium phosphine : with dppe, PPh_3 and trimesitylphosphine as ligands, **16** was the single product of reaction with benzophenone imine (entry 6). Reaction of **1a** with O-benzyl hydroxylamine gave the N-benzyloxy (2-cyclopropylideneethyl)amine **17**, in 84% yield (entry 7).



18 **19** (89%) **20** (27%)

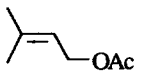
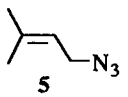
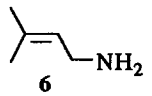
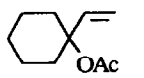
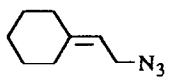
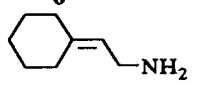
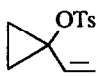
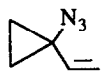
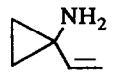
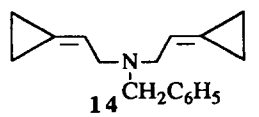
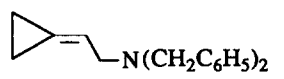
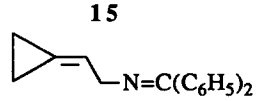
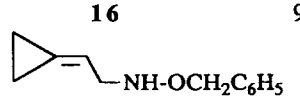
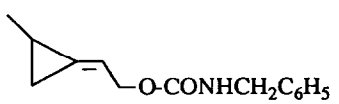
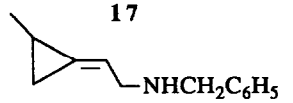
The ester **18** was prepared from the benzoic acid catalyzed Wittig reaction of 1-ethoxy-2-methylcyclopropanol[9] with ethoxycarbonylmethylenetriphenylphosphorane[10]; its reduction with diisobutylaluminum hydride gave the 2-(2-methylcyclopropylidene)ethanol **19** (89%), which was added to benzylisocyanate in THF at reflux for 48 h to yield the N-benzyl carbamate **20** (27%).



We have previously reported the regioselective transfer of the hydride moiety from the π 1,1-dimethyleneallyl palladium complex (I), formed by Pd(0) catalyzed reaction of 1-alkenylcyclopropyl esters with sodium formate, either on the three-membered ring or on the less substituted allylic site, depending on the phosphine ligand[8]. Formation of the palladium complex (II) could be expected upon treatment of the N-benzyl carbamate **20**, with Pd(0) ; however transfer of benzylamine was observed on the less substituted end, exclusively, whatever the ligand of Pd (0), *e.g.*, PPh_3 or PBu_3[11] (entry 8). Therefore it appeared that only

azidation of π 1,1-dimethyleneallyl palladium complexes can offer a convenient route to 2,3-methanoamino acid derivatives[12].

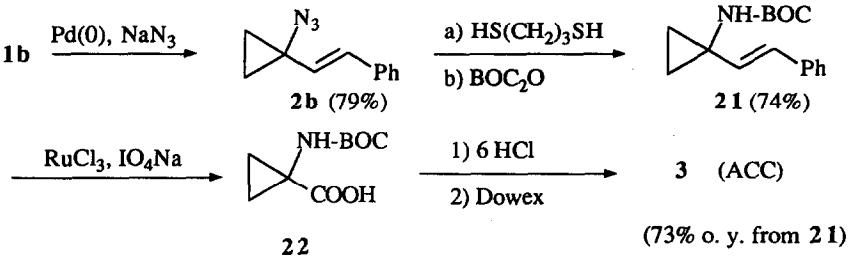
Table : Palladium (0) Catalyzed Azidation and Amination of Allyl Esters[a]

Entry	Allyl ester	Nu	Ln	Allyl azide	Allyl amine	y%
1	 **4**	NaN_3	4 PPh_3	 **5**	 **6**	61[b]
2	 **7**	NaN_3	4 PPh_3	 **8**	 **9**	80[b]
3	 **1a**	NaN_3	2 PPh_3	 **2a**	 **10**	60
4	**1a**	$C_6H_5CH_2NH_2$	2 PPh_3		 **14**	75
5	**1a**	$(C_6H_5CH_2)_2NH$	dppf		 **15**	85
6	**1a**	$HN{=}C(C_6H_5)_2$	2 PPh_3		 **16**	95
7	**1a**	$C_6H_5CH_2ONH_2$	2 PPh_3		 **17**	84
8	 **20**		2 PPh_3 2 PBu_3		 **21**	74

a) 5-10% of catalyst : $Pd(dba)_2$, PPh_3 (1:2) or $Pd(dba)_2$, dppf (1:1) were used at rt for about 12h; b) from ref. 1)

In order to overcome the problem of volatility observed with amine **10**, we have used the E 1-styryl-1-tosyloxycyclopropane **1b** (R = C_6H_5), which is readily available from the cyclopropanone hemiacetal [3,13]. Thus reaction of **1b** with sodium azide (NaN_3) in THF in the presence of $Pd(dba)_2$, 2 PPh_3 (5 mol. %) and [15]-crown-5 ether (10%), gave solely the 1-azido-1-styrylcyclopropane **2b**[14], in 79% yield. Reduction of this azide with 1,3-propanedithiol (5 equiv) in the presence of NEt_3 (5 equiv) in methanol[5], followed by one pot addition of di-t-butyl dicarbonate (BOC_2O) gave the desired N-BOC protected amine **21** in 74% yield,

which then underwent ruthenium trichloride catalyzed sodium periodate oxidation[15] to provide the N-BOC protected 2,3-methanoamino acid **22**.



Finally treatment with 6N HCl and ion-exchange (Dowex 50 WX 8.100) chromatography furnished the 1-aminocyclopropanecarboxylic acid (ACC) **3** in 73% overall yield from **21**[16]. Diastereoselective synthesis of substituted natural and non-natural ACC derivatives following this strategy are under current investigation and will be reported elsewhere.

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