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Synthesis of Protected Allylic Amines via Palladium(0)-Catalyzed Amination of Allylic Acetates#

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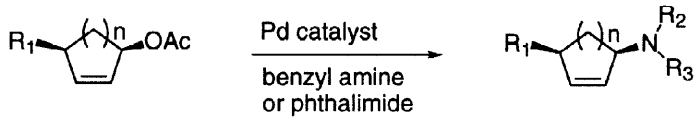
Abstract: Synthesis of potential antiparisitic 5'-aminonucloesides such as **10** could not be accomplished using standard amination procedures. Palladium(0)-catalyzed amination of cyclic allylic acetates with benzylamine or phthalimide gave the corresponding protected amines. This method was then extended to the synthesis of target analogue **10**.

Palladium-catalyzed amination reactions of allylic substrates have received considerable attention in recent years.[1] Primary and secondary amines have been successfully used as nucleophiles in these reactions.[2] Because ammonia can not be used as a nucleophile, several ammonia equivalents have emerged. Trost and Keinen[3] used 4,4'-dimethoxybenzhydrylamine while Bäckvall[4] used *p*-toluenesulfonamide to overcome this problem. Recently Brüning used lithium and potassium bis(trimethylsilyl)amide as nitrogen sources in catalytic amination of allylic chlorides.[5] Our interest in the synthesis of *N*-(5'-deoxy-5'-adenosyl)-*cis*-1-ammonio-4-methylamino-2-cyclopentene (NAM) analogues led us to investigate stereospecific methods to produce a series of protected 1,4-diaminocycloalkenes such as those shown in Table 1 (**4a** and **b**, **6a** and **b**, **8a** and **b**). In our hands, numerous attempts to produce these compounds using nucleophilic substitution or Mitsunobu strategies were unsuccessful.[6] Pi-allylpalladium chemistry has been successfully employed to introduce nitrogen equivelents using trimethylsilyl azide[7] and sodium azide.[8] For our purposes, the palladium(0)-catalyzed introduction of phthalimide or benzylamine nucleophiles in these amination reactions was more suitable as an alternate strategy to introduce a nitrogen equivalent. In this communication, we report that these nitrogen nucleophiles can be readily used to generate protected allylic amine intermediates which can be later manipulated and/or readily deprotected.[9] Treatment of the appropriate allylic acetate with two equivalents of phthalimide or benzyl amine in the presence of a catalytic amount of $Pd_2(dba)_3$ and bis-1,4-(diphenylphospino)butane (dppb) in THF (Scheme 1) afforded the corresponding allylic amine/amide in good to excellent yield, as outlined in Table 1. In all cases, the reaction time was less than 1 h at 75° C.



Scheme 1

#This publication is dedicated to Professor Carl R. Johnson of the Department of Chemistry, Wayne State University, on the occasion of his 60th birthday.

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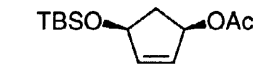
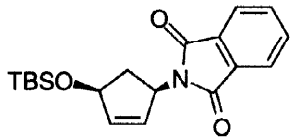
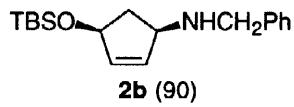
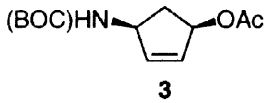
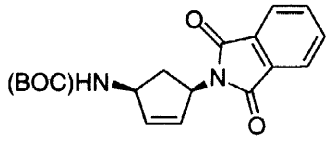
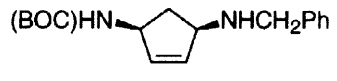
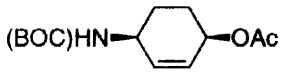
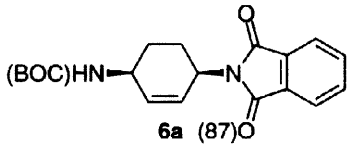
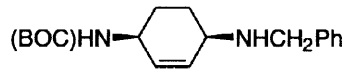
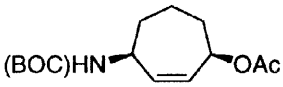
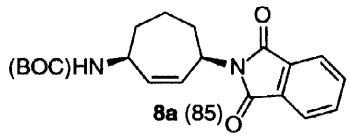
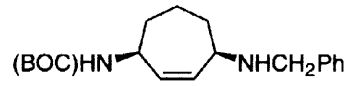
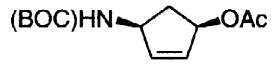
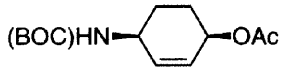
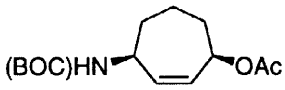
Table 1. Palladium catalyzed phthalimidation/amination of allylic acetates[a]

allylic acetate	product (% yield)[b]	
 **1**	 **2a** (85)	 **2b** (90)
 **3**	 **4a** (80)	 **4b** (84)
 **5**	 **6a** (87)	 **6b** (80)
 **7**	 **8a** (85)	 **8b** (89)

[a]All reactions were performed in THF with 5 mol% of $Pd_2(dba)_2$, 10 mol% dppb and 2.1 equivalents of nucleophile under argon atmosphere at 75 °C. [b]Crude reaction mixture was concentrated and purified by column chromatography on silica gel.

The general protocol prescribed above was modified by using either aqueous Na_2CO_3 or solid K_2HPO_4 as base, which allowed the use of one equivalent of nucleophile (Table 2).

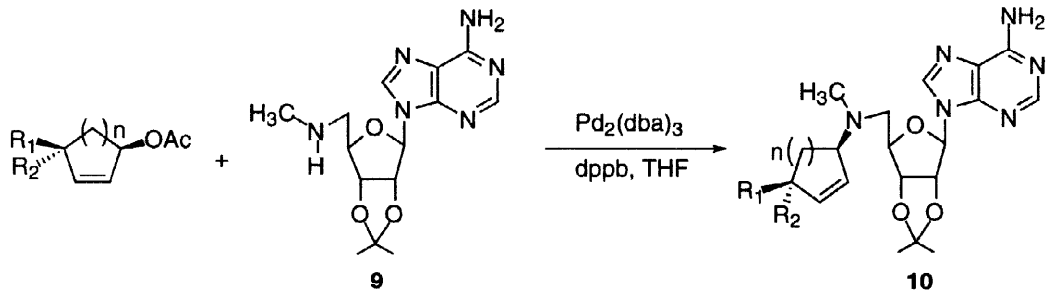
Table 2. Allylic phthalimidation using inorganic bases[a]

allylic acetate	Base, % yield	
	Na_2CO_3[b]	K_2HPO_4[c]
 **3**	87	99
 **5**	80	87
 **7**	98	99

[a]Exact reaction conditions as described in Table 1 were used except 1.1 equivalents of phthalimide. [b]1 M Aqueous Na_2CO_3 1.1 equivalents. [c]Solid K_2HPO_4 1.1 equivalents.

It has been reported that palladium(0)-mediated allylic substitution proceeds with overall retention of configuration. The generally accepted mechanism for this transformation involves oxidative addition of allylic acetate to the palladium(0) catalyst, generating (π-allyl)palladium intermediate with inversion of configuration, which is then exposed to the second phase of the catalytic cycle, attack by the nitrogen nucleophile opposite to the metal (second inversion), leading to the product with overall retention.[10]

This methodology was further elaborated by the preparation of *N*-AdoMac (NAM or *N*-(5′-deoxy-5′-adenosyl)-*cis*-1-ammonio-4-methylamino-2-cyclopentene) analogues.[11] Allylic amination of series of a acetates was carried out using the secondary amine **9** as nucleophile (Table 3). It seems that **9** is temperature sensitive and at lower temperature yields increased considerably. With respect to our first report on the synthesis and biological evaluation of several conformationally restricted *S*-AdoMet (SAM) analogues,[12] the present communication describes the second generation of these analogues.[13]



Scheme 2

Table 3. Preparation of analogues of **10**

R_1	R_2	n	method[a]	product (% yield)
TBSO	H	1	A	**10a** (93)[b]
H	(BOC)NH	1	A	**10b** (64)
(BOC)NH	H	3	A	**10c** (58)
(BOC)NH	H	1	A	**10d** (69)
(BOC)NH	H	1	B	**10d** (65)
(BOC)NH	H	2	B	**10e** (78)[b]
(BOC)NH	H	3	B	**10c** (76)[b]

[a]Method A: as described in Table 1, method B: as described in Table 2 using aqueous. Na_2CO_3. [b]Reaction temperature was 50 °C.

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12. Wu, Y. Q.; Woster, P. M. *Bio. Med. Chem.* **1993**, *1*, 349.
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Gatti, R. G. P.; Larsson, A. L. E.; Bäckvall, Jan-E. *J. Chem. Soc. Perkin Trans.* 1, **1997**, 577.

NMR data for selected compounds:

2a ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 0.11 (s, 3H), 0.92 (s, 9H), 2.13 (m, 1H), 2.74 (dt, J_1 = 7.5 Hz, J_2 = 12.0 Hz, 1H), 4.87 (m, 1H), 5.14 (m, 1H), 5.89 (m, 1H), 6.00 (m, 1H), 7.73 (m, 2H), 7.84 (m, 2H). ^{13}C-NMR δ ($CDCl_3$, 75 MHz): -4.6, 18.2, 25.9, 39.9, 53.4, 75.5, 123.1, 130.7, 131.9, 133.9, 136.9, 168.0.

4a ^{1}H-NMR δ ($CDCl_3$/CD_3OD, 300 MHz): 1.35 (s, 9H), 1.75 (dt, J_1 = 3.0 Hz, J_2 = 14.7 Hz, 1H), 2.79 (dt, J_1 = 9.0 Hz, J_2 = 14.4 Hz, 1H), 4.74 (m, 1H), 5.13 (m, 1H), 5.60 (m, 1H), 5.89 (m, 2H), 7.62 (m, 2H), 7.71 (m, 2H). ^{13}C-NMR δ ($CDCl_3$/CD_3OD, 75 MHz): 28.1, 35.6, 53.3, 54.8, 79.3, 123.1, 131.4, 132.6, 133.9, 134.0, 155.5, 168.1.

8a ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 1.45 (s, 9H), 1.53 (m, 1H), 1.69 (m, 1H), 1.81 (m, 1H), 1.92 (m, 1H), 2.01 (m, 1H), 2.25 (m, 1H), 4.36 (m, 1H), 4.81 (m, 1H), 4.95 (m, 1H), 5.65 (dt, J_1 = 2.7 Hz, J_2 = 12.0 Hz, 1H), 5.72 (m, 1H), 7.7 (m, 2H), 8.84 (m, 2H). ^{13}C-NMR δ ($CDCl_3$, 75 MHz): 26.5, 28.4, 32.5, 33.8, 51.1, 51.9, 79.1, 123.2, 123.5, 131.8, 133.9, 134.3, 155.0, 167.7.

10a ^{1}H-NMR δ ($CDCl_3$, 300 MHz): 0.00 (s, 6H), 0.81 (s, 9H), 1.34 (s, 3H), 1.42 (m, 1H), 1.57 (s, 3H), 2.15 (m, 1H), 2.22 (s, 3H), 2.59 (m, 2H), 3.67 (t, J = 6.3 Hz, 1H), 4.32 (m, 1H), 4.61 (m, 1H), 4.87 (dd, J_1 = 3.6 Hz, J_2 = 6.6 Hz, 1H), 5.38 (dd, J_1 = 2.4 Hz, J_2 = 6.6 Hz, 1H), 5.77 (s, 2H, D_2O), 6.03 (d, J = 2.4 Hz, 1H), 6.20 (s, 2H), 7.92 (s, 1H), 8.30 (s, 1H). ^{13}C-NMR δ ($CDCl_3$, 75 MHz): -4.7, 18.0, 25.3, 25.8, 27.1, 34.1, 38.9, 55.4, 68.9, 75.2, 83.0, 83.9, 85.3, 90.5, 114.4, 120.1, 133.6, 136.2, 139.6, 149.2, 153.0, 155.6.