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AN EFFICIENT ROUTE FOR THE STEREOSELECTIVE CONVERSION OF KETONES INTO THREE-CARBONS HOMOLOGATED PRIMARY E-ALLYLAMINES: THE PALLADIUM-CATALYSED REACTION OF VINYL TRIFLATES WITH N,N-DI-TERT-BUTOXYCARBONYL-N-ALLYLAMINE.

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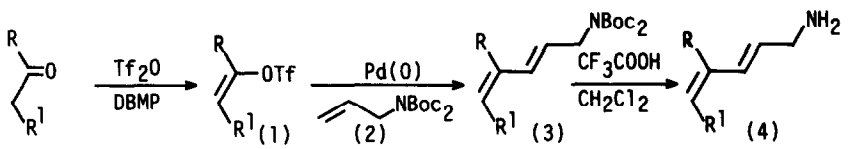
Summary - E-Allylamines N-protected with the easily removable tert-butoxycarbonyl group are stereoselectively prepared in good to high yield through the palladium-catalysed reaction of vinyl triflates with N,N-di-tert-butoxycarbonyl-N-allylamine in the presence of AcOK and n-Bu_4NCl. The reaction is very sensitive to the nature of the base. The use of bases other than AcOK has been examined and proved to be unsuccessful.

Primary allylamines are useful synthetic intermediates and, as a structural subunit, the allylaminic function is common to many natural products.[1] Because of these reasons, though several methodologies directed towards the synthesis of primary allylamines have been reported,[2] the development of new and more versatile synthetic methods is currently a target of great interest. Some of the procedures developed more recently are based on palladium chemistry. These syntheses rely upon formation of π-allylpalladium intermediates from allylacetates and chlorides followed by reaction with nitrogen nucleophiles such as 4,4'-dimethoxybenzhydrylamine,[3] di-tert-butyliminodicarbonate,[4] phthalimide,[5] sodium azide,[6] p-toluenesulfonamide[7] and oxidative addition of Pd(0) species to aryl halides followed by vinylic substitution reaction on N-allylphthalimide.[8]

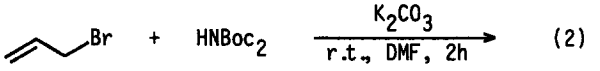
Owing to our interest in the synthesis of various antibiotics and as part of our ongoing studies on palladium-catalysed transformations of vinyl triflates,[9] we sought to develop a simple method for the conversion of ketones into three-carbons homologated primary allylamines (4) based on the vinylic substitution reaction of the easily available N,N-di-tert-butoxycarbonyl-N-allylamine (2) with vinyl triflates (1).



Boc = $-\overset{O}{\overset{\|}{C}}-OBu^t$; DBMP = 2,6-di-tert-butyl-4-methyl-pyridine

Scheme 1

Compound (2) was prepared in 86 % yield by reacting 1.5 eq of allyl bromide with commercially available di-tert-butyliminodicarbonate (5)[10] at room temperature in DMF in the presence of K_2CO_3.



Scheme 2

The use of tert-butoxycarbonyl as the protecting group represents an important feature of the overall procedure since it can be selectively removed under mild conditions.[4,11] For example, phthalimides are usually removed by hydrazine in refluxing ethanol.

As a model system, we have examined the reaction of 4-phenyl-cyclohex-1-en-1-yl triflate with (2) and found the reaction to be very sensitive to the nature of the base. Though vinyl triflates have been reported to give vinylic substitution products with alkenes in good yield under usual Heck conditions,[12] in the presence of n-Bu_3N the expected allylammine was isolated in only 36% yield (Table 1, entry a). The addition of LiCl, which sometimes increases the yields in palladium-catalysed transformations of vinyl triflates very likely through a ligand exchange mechanism,[9a,13] proved to be unsuccessfull (Table 1, entry b). Disappointing results were also obtained by using carbonate and bicarbonate bases in the presence of n-Bu_4NCl[14] (Table 1, entries c,d) as well as AcONa or AcOK (Table 1, entries e,g) and AcONa/n-Bu_4NCl (Table 1, entry f). This last combination was successfully used in the palladium-catalysed reaction of aryl iodides and bromides with β-substituted-α,β-enones and -enals.[15] Switching to AcOK/n-Bu_4NCl led to a remarkable improvement and the allylamine was isolated in 60 % yield (Table 1, entry h). Therefore, a variety of vinyl triflates was stereoselectively converted in good to high yield into the corresponding N-diprotected-E-allylamines in the presence of 0.05 eq of $Pd(OAc)_2$, 2.5 eq

Table 1 - Base, Salt, and Catalyst in the Reaction of 4-Phenyl-cyclohex-1-en-1-yl triflate with (2).[a]

Entry	Base (eq)	Salt (eq)	Catalyst (eq)	N-diprotected allylamine (% yield)[b,c]
a	n-Bu_3N (2.5)	-	$Pd(OAc)_2(PPh_3)_2$ (0.05)	36 (3)
b	n-Bu_3N (")	LiCl (3.0)	"	- (83)
c	K_2CO_3 (")	n-Bu_4NCl (1.0)	$Pd(OAc)_2$ (0.05)	- (83)[d]
d	$NaHCO_3$ (")	"	"	- (82)
e	AcONa (")	-	"	21 (73)
f	AcONa (")	n-Bu_4NCl (1.0)	"	6 (65)
g	AcOK (")	-	"	28 (50)
h	AcOK (")	n-Bu_4NCl (1.0)	"	60 (-)
i	AcOK (")	n-Bu_4NHSO_4 (1.0)	"	30 (58)

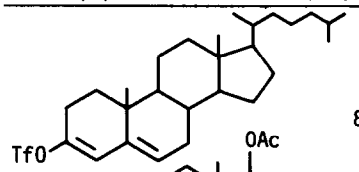
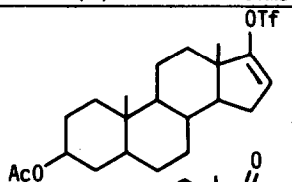
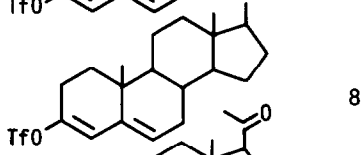
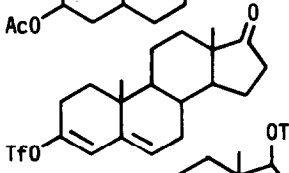
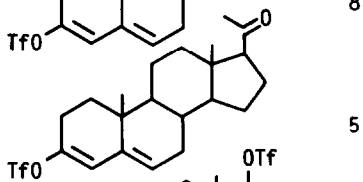
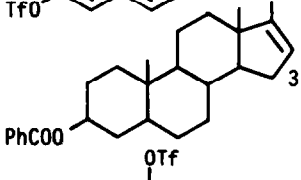
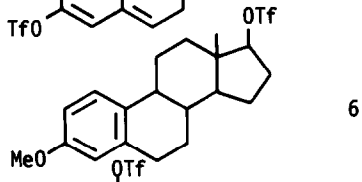
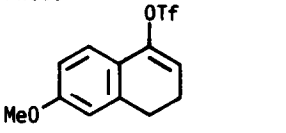
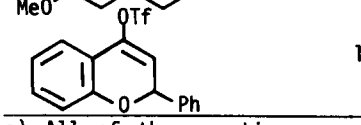
a) All of the reactions were carried out in DMF (3 ml) at 80°C for 5 h under an argon atmosphere on a 0.65 mmol scale by using the following molar ratio: 4-phenyl-cyclohex-1-en-1-yl triflate:(2) = 1:1.1. b) Yields refer to single runs and are given for pure, isolated products. c) Figures in parentheses refer to the recovered starting triflate. d) 48 h.

of AcOK, 1.0 eq. of n-Bu_4NCl, and 1.1 eq. of (2) (Table 2). It is worth noting that unsatisfactory results were obtained by using AcOK in the presence of n-Bu_4NHSO_4 (Table 1, entry i).

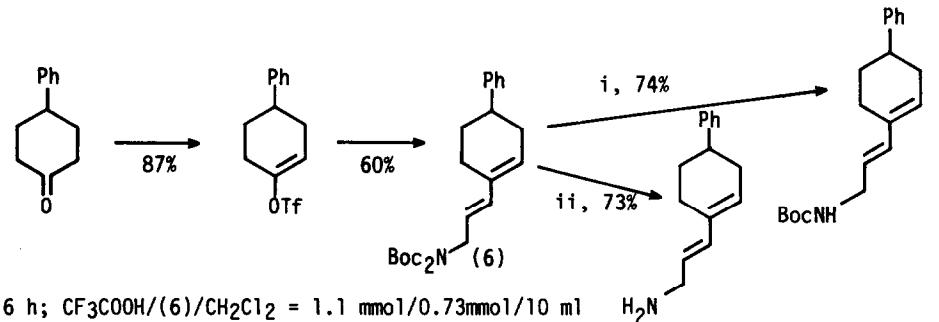
A typical procedure is as follows. 17β-Acetoxy-androst-3,5-dien-3-yl triflate (0.200 g, 0.433 mmol) was added to a mixture of (2) (0.122 g, 0.476 mmol), AcOK (0.106 g, 1.082 mmol), and n-Bu_4NCl (0.128 g, 0.433 mmol) in DMF (2 ml). Then $Pd(OAc)_2$ (0.005 g, 0.022 mmol) in DMF (1 ml), was added. The mixture was purged with argon and stirred at 80°C under an argon atmosphere for 5 h; diethyl ether and water were added, the organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. The residue, after filtration on a short silica gel column eluting with a n-hexane/AcOEt 70/30 (v/v) mixture, was purified by preparative HPLC on silica gel 20-45 μ (Amicon CO.). Elution with n-hexane/AcOEt 85/15 (v/v) gave the corresponding compound (3) (0.173 g, 70 % yield): mp 75-78°C; I.R. (KBr) 1737, 1688 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 6.23 (d, J= 16.1 Hz, 1H); 5.94 (bs, 1H); 5.67 (dt, J = 16.1 Hz, J = 6 Hz, 1H); 5.53 (m, 1H); 4.79-4.52 (m, 1H); 4.24 (d, J = 6 Hz, 2H); 2.03 (s, 3H); 1.48 (s, 18H); 0.93 (s, 3H); 0.83 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 171.21, 152.39, 142.28, 135.32, 132.59, 130.14, 124.53, 122.45.

As an example we also report the results obtained in the conversion of 4-phenyl--cyclohexan-1-one into the corresponding N-monoprotected and free allylamine (Scheme 2).

Table 2 - Palladium-Catalysed Reaction of Vinyl Triflates with (2).[a]

Vinyl triflate (1)	Reaction time (h)	Yield of (3) (%)[b,c]	Vinyl triflate (1)	Reaction time (h)	Yield of (3) (%)[b,c]
	8	61		8	75
	8	70		5	82
	5.5	74		3.5	61
	6	75		5	73
	1.5	48			

a) All of the reactions were carried out in DMF (2 ml-3ml) at 80°C under an argon atmosphere on a 0.39-0.65 mmol scale by using the following molar ratio: (1):(2):AcOK:n-Bu_4NCl:$Pd(OAc)_2$ = 1:1.1:2.5:1:0.05. b) Yields refer to single runs and are given for pure isolated products. c) All compounds had satisfactory elemental analysis and spectral data consistent with postulated structures.



i : r.t.; 6 h; $CF_3COOH/(6)/CH_2Cl_2$ = 1.1 mmol/0.73mmol/10 ml
ii: 0°C; 0.75 h; $CF_3COOH/(6)/CH_2Cl_2$ = 17 mmol/0.48 mmol/2 ml

Scheme 2

In summary, because of the easy and usually high yielding preparation of vinyl triflates, the facile synthesis of N,N-di-tert-butoxycarbonyl-N-allylamine, the gentle conditions, and the mildness of deprotection, the here reported procedure represents a very convenient route for converting ketones into primary allylic amines.

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