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Palladium-catalyzed allylic alkylation of carbonucleophiles with allylic borates or allylic alcohols and boron oxide under neutral conditions

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Abstract

Under neutral conditions, $Pd(PPh_3)_4$ catalyzes the allylic alkylation of carbonucleophiles with allylic borates in high yields. Moreover, allylic borates are formed in situ from allylic alcohols with boron oxide, and the Pd-catalyzed allylic alkylation was achieved simply by the reaction of allylic alcohols with a nucleophile in the presence of boron oxide by a one-pot procedure. The mechanisms of these reactions are discussed.

Introduction

It is well known that a variety of allylic compounds, such as halides [1,2], esters [2,3], phenyl ethers [4], ammonium salts [5], phosphates [6] and sulfones [7] have been found to react with carbonucleophiles under palladium catalysis. Allylic acetates, in particular, have been most widely used in natural product synthesis [8,9], but generally a stoichiometric amount of base is necessary for the generation of the carbanions [1]. Only a few examples have been reported to carry out the palladium-catalyzed reactions under neutral conditions. They are those involving 1,3-diene monoepoxides [10,11], allylic carbonates [12], *O*-allyl isoureas [13], *O*-allyl imidates [14,15] as the alkylating agents. Allylic alcohols are also alkylating agents, but they are not so effective for synthetic purposes [12,16]. Our group has reported a palladium and arsenic oxide catalyzed allylic alkylation with allylic alcohols under neutral conditions, with the allylic arsenites being formed in situ from allylic alcohols and arsenic oxide, and the leaving group, arsenite anion, presumably being basic enough to abstract a proton from the active methylene group to generate the

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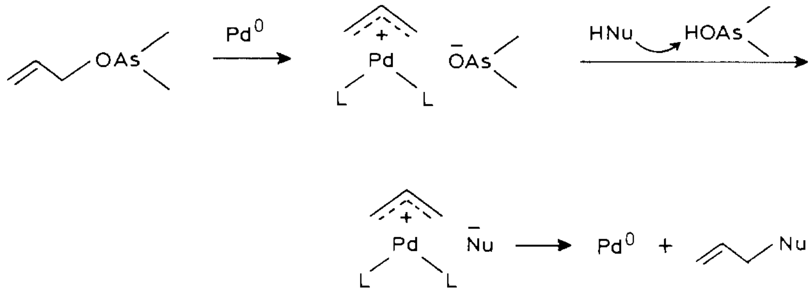
carbanions [17]:

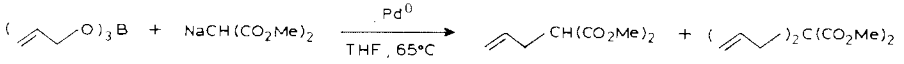


As boric acid is comparable with arsenous acid in acidity [18], its conjugated base, borate anion, should also show basicity which is similar to arsenite anion. Thus, as a result of the systematic study of the reaction of low valency transition metal complexes with compounds containing C–O–Z (Z = hetero atom) bonds [17,19–24], we report here on the palladium-catalyzed allylaton reaction of carbonucleophiles with allylic borates or allylic alcohols and boron oxide.

Results and discussion

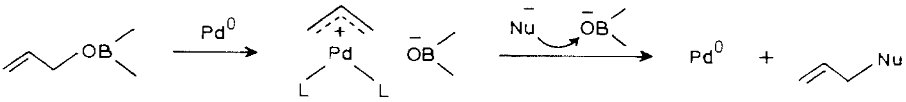
Allylic carbon–oxygen bond cleavage in allylic borates

Triallyl borate (**1**), when treated with sodium dimethyl malonate (**2**) in the presence of a catalytic amount of $Pd(PPh_3)_4$, gave the expected products **3** and **4**:



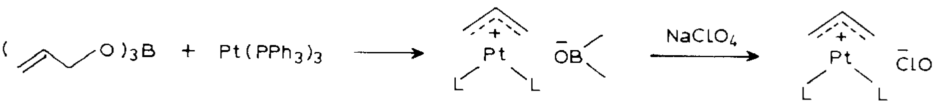
(1) (2) (3) (4)

The formation of the allylation products indicates that the allylic carbon–oxygen bond in triallyl borate was cleaved in the palladium-catalyzed reaction. In the absence of $Pd(PPh_3)_4$, no allylated products could be isolated. So this reaction probably proceeds by oxidative addition of palladium complex to the allylic carbon–oxygen bond first, followed by nucleophilic attack by the carbanion on the π-allylpalladium complex **5** to yield the allylated product:



(5)

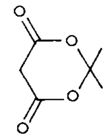
To verify the oxidative addition step in this case, π-allylplatinum complex **6** was obtained from the reaction of a stoichiometric amount of $Pt(PPh_3)_3$ with triallyl borate and subsequent anion exchange with $NaClO_4$:



(1) (L = PPh3) (6)

Table 1

Palladium-catalyzed allylation with triallyl borate [a]

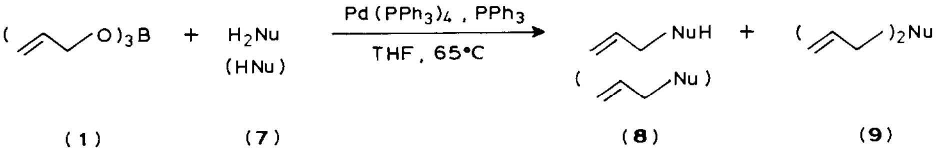
Nucleophile **7**	pK_a [26]	Time (h)	Yield [b] (%)	Product ratio **8**/ **9**
a 	5.2 [27]	5	83	0/100
b $CH_2(COMe)_2$	9	6	81	0/100
c $CH(COMe)(CO_2Et)_2$ [c]	6	5	87	100/0
d $CH_2(CN)CO_2Et$	9	5	97	0/100
e $CH_2(CN)_2$	9	4.5	83	0/100
f $CH_2(COMe)CO_2Me$	11	7	92	0/100
g $CH_2(COMe)CO_2Et$	11	7	91	0/100
h $CH_2(SO_2Ph)CO_2Me$	14 [28]	8	82	67/33
i $CHMe(COMe)_2$ [c]	11	14	79	100/0
j $CH_2(CO_2Me)_2$	13	24	71	75/25

[a] Mole ratio of **1**/**7** = 1.1/1; 5 mol% $Pd(PPh_3)_4$ and 20 mol% PPh_3 were used. [b] Isolated yield based on **7**. [c] Mole ratio of **1**/**7** = 1/1.

Complex **6** was identified by comparing the spectroscopic data (IR, ^1H NMR) and melting point with those of the authentic sample [25]. This palladium-catalyzed allylic carbon–oxygen bond cleavage in triallyl borate is yet another example of the low valency transition metal-catalyzed reactions of the series of allylic compounds under our scrutiny [17,19–24].

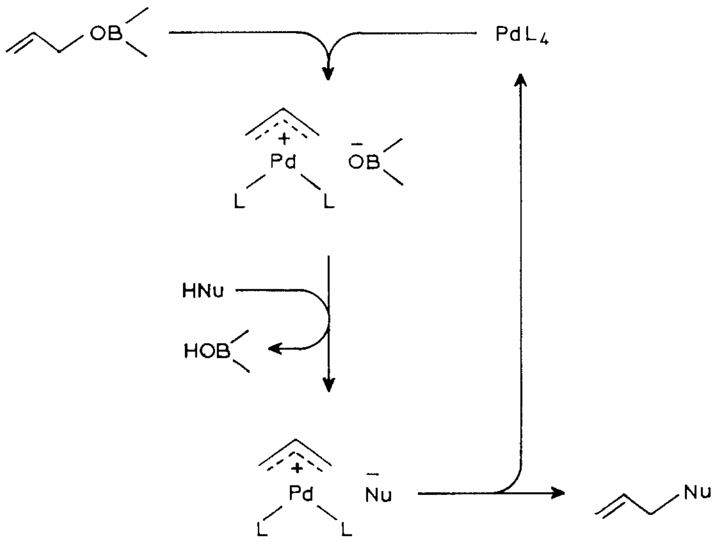
Allylic alkylation with allylic borates under neutral conditions

As shown in the above section, the leaving group borate anion is probably basic enough to abstract a proton from the active methylene group, thus implying that compounds containing active methylene group can be used directly as the carbonucleophiles in the palladium-catalyzed reactions. The results obtained are listed in Table 1.



Various compounds bearing active methylene group and having a wide range of pK_a values from 5 to 14 all function as excellent carbonucleophiles under neutral conditions. In contrast to Trost's result [29], the sodium salt of Meldrum's acid (**1a**) failed to react as a nucleophile due to its low nucleophilicity, but Meldrum's acid itself could react smoothly under our neutral conditions.

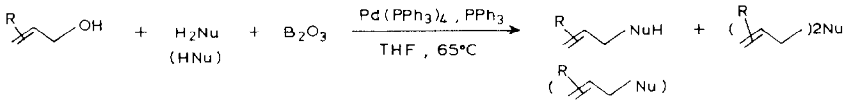
The mechanism of this neutral allylation with allylic borates may be accounted for by the fact that the borate anion, formed in situ from the oxidative addition reaction, acts as a base to abstract a proton from the active methylene group to produce a carbanion, which finally attacks the palladium intermediate to yield the products and to regenerate the palladium species:



The reaction proceeds at 65 °C in THF for several hours under palladium catalysis without the presence of base, and the boric acid is readily removed by washing the reaction mixture with water. Because the conditions are mild, the operations simple and the yields high, this reaction can be useful in organic synthesis.

Allylic alkylation with allylic alcohols under neutral conditions

In the reactions above, boric acid is formed in addition to the allylated products. However, allylic borates were originally prepared by the esterification of boric acid or boron oxide with allylic alcohols [30]. In order to make the allylation reaction even simpler and more convenient, we attempted to generate allylic borates in situ from allylic alcohols and boron oxide or boric acid during the reaction, this one-pot approach was successful (Table 2).



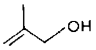
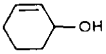
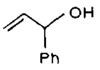
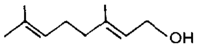
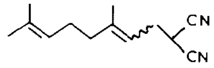
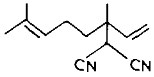
(7) (15) (8) (9)

The results obtained are the same as those for reaction with allylic borates as starting materials. The mechanism is probably the same as above, except for the in situ formation of allylic borates.

The overall outcome is that allylic alcohols are good allylating agents under neutral conditions. Hydroxyl group is a poor leaving group toward palladium-catalyzed reactions [12,20,31]. There is only one report, by Atkins et al. [16], that allyl alcohol can react under neutral conditions at elevated temperature with acetylacetone which is an active carbonucleophile, but it failed to react with a β-keto ester, a less active carbonucleophile, [12].

Table 2

Palladium-catalyzed allylation with allylic alcohols [a]

Allyl alcohol		Nucleophile 7	Time (h)	Yield [b] (%)	Product ratio **8**/ **9**
	(10)	**7a**	5	89	0/100
10		7e	4.5	80	0/100
10		**7f**	7	87	22/ 78 [c]
10		**7g**	7	93	22/ 78 [c]
10		**7j**	26	82	51/ 49 [c]
10		**7b**	36	88	0/100
	(11)	**7h**	22	65	100/ 0
11		$CH_2(SO_2Ph)CN$	6	93	41/ 59
	(12)	7e	5.5	58	100/ 0
	(13)	$CH_2(SO_2Ph)CN$	10.5	91	0/100 [d]
	(14)	7e	11	62	 (55) /  (45)

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[a] Mole ratio of alcohol 7/**15** = 2.1/1/1; 5 mol% $Pd(PPh_3)_4$ and 20 mol% PPh_3 were used. [b] Isolated yield based on 7. [c] Determined by ^1H NMR. [d] Only  was obtained.

Although allyl borate may be generated in situ by either boron oxide or boric acid with allylic alcohols, the oxide is the better choice. The amount of boron oxide is also important for this reaction. Attempts to make the reaction catalytic in boron oxide were not successful, which suggests that in addition to activation of the hydroxyl group, by transforming it into the borate moiety, boron oxide can be also regarded as the dehydrating agent thus serving to remove the water produced by the reaction.

Excess ligand is required to prevent the precipitation of palladium, and was found that PPh_3 is better than the bidentate ligand, 1,2-bis(diphenylphosphino)ethane (dppe). Selectivity to either mono- or diallylated product can be controlled by changing the ratio of starting materials, and the reaction time.

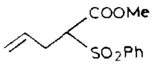
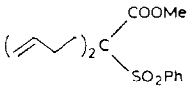
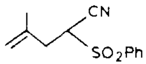
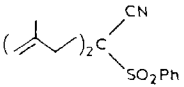
Further applications of this reaction in organic synthesis are being investigated in this laboratory.

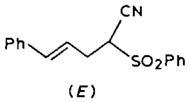
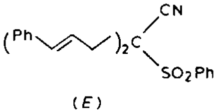
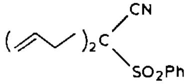
Experimental

All reactions were carried out under prepurified nitrogen using Schlenk techniques. THF was freshly distilled under nitrogen from sodium and benzophenone

Table 3

Spectral and analytical data for the new compounds

Compound	^{1}H NMR (CCl$_4$, 60 MHz) δ (ppm); *J* (Hz)	IR (KCl) ν (cm^{-1})	Molecular formula	MS (*m/e*)	B.p. (° C/torr) or m.p. (° C)	Analysis (Found (calc) (%))			
						C	H	N	S
	2.40–2.60(m,2H) 3.50(s,3H) 3.53–3.90(m,1H) 4.70–5.80(m,3H) 7.36–7.95(m,5H)	1745 [b] 1645 1330 1150	$C_{12}H_{14}O_4S$	256(M^+ +2) 255(M^+ +1) (254.23)	45.5–46.5	55.68 (56.68	5.63 5.55		12.64 12.16)
	2.71(d, *J* 7,4H) 3.56(s,3H) 4.90–6.15(m,6H) 7.45–7.95(m,5H)	1735 [b] 1640 1310 1150	$C_{15}H_{18}O_4S$ (294.29)	296(M^+ +2) 295(M^+ +1)	160/0.1	61.45 (61.21	5.99 6.16		10.88 10.89)
	1.79(s,3H) [a] 2.55(ddd, *J* 14,12, 1,1H) 2.92(dd, *J* 14,4, 1H) 4.04(dd, *J* 12, 4, (1H) 4.92(bs,1H) 5.01(bs,1H) 7.06–7.82(m,3H) 8.00–8.06(m,2H)	2250 1645 1330 1155	$C_{12}H_{13}O_2NS$	236(M^+ +1) (235.22)	77.5–78	61.26 (61.26	5.20 5.57	5.60 5.95	13.56 13.63)
	1.80(s,6H) 2.56(s,4H) 4.90(bs,4H) 7.43–7.70(m,3H) 7.86–8.10(m,2H)	2300 1645 1325 1155	$C_{16}H_{19}O_2NS$ (289.31)	290(M^+ +1)	62–63.5	66.66 (66.41	6.30 6.62	4.42 4.80	11.27 11.08)

	2.80(ddd, J 14.1, 10.5, 7.3, 1.3,1H) [a] 3.11(dddd, J 14.1, 7.3, 4.5, 1.0, 1H) 4.02(dd, J 10.5, 4.5,1H) 6.09(dt, J 15.7, 7.3,1H) 6.61(d, J 15.7, 1H) 7.24–7.35(m,5H) 7.60–7.80(m,3H) 8.01–8.06(m,2H)	2250 1330 1140 920	$C_{17}H_{15}O_2NS$ (297.29)	297(M^+)	72.5–73.5	68.67 (68.67	5.02 5.08	4.51 4.71	10.86 10.78)
	2.97(d, J 7.2,4H) [a] 6.30(dt, J 15.7, 7.2,2H) 6.53(d, J 15.7, 2H) 7.24–7.31(m,10H) 7.56–7.75(m,3H) 8.04–8.08(m,2H)	2255 1325 1150 970	$C_{26}H_{23}O_2NS$ (413.44)	414($M^+ + 1$)	111.5–112.5	75.40 (75.53	5.58 5.61	3.20 3.39	7.70 7.75)
	2.66(d, J 7,4H) 5.00–6.16(m,6H) 7.26–8.06(m,5H)	2255 1645 1335 1160	$C_{14}H_{15}O_2NS$ (261.26)	262($M^+ + 1$)	47.5–48.5	64.62 (64.35	5.49 5.79	5.00 5.26	12.14 12.27)

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[a] Determined in $CDCl_3$ on XL-200 (200 MHz) spectrometer. [b] Determined as liquid film.

immediately before use. All starting materials were purified by distillation under nitrogen or by recrystallization. Starting materials and products were characterized by comparing their boiling points or melting points, IR, ^{1}H NMR, and MS with literature data. ^{1}H NMR spectra were recorded on an EM-360A (60 MHz) or an XL-200 (200 MHz) spectrometer using CCl_4 or $CDCl_3$ solution containing tetramethylsilane as internal standard. Infrared spectra were taken as liquid films or KCl disc using a Shimadzu IR-440 spectrometer. Mass spectra were obtained on a Finnigan 4021 GC-MS instrument. GLC was carried out with a 2 m column (10% OV-101 supported on 102 silanized white support, 60–80 mesh).

The following reagents were prepared by standard procedures: Meldrum's acid (**7a**) [32], diethyl acetylmalonate (**7c**) [33], methyl 2-(phenylsulfonyl)acetate (**7h**) [34], 3-methyl-2,4-pentanedione (**7i**) [35], 2-(phenylsulfonyl)acetonitrile [36], tetrakis(triphenylphosphine)palladium [37], tris(triphenylphosphine)platinum [38] and triallyl borate [39].

Reaction of triallyl borate (1) with sodium dimethyl malonate (2) using $Pd(PPh_3)_4$ as catalyst

To a mixture of $Pd(PPh_3)_4$ (110 mg, 0.1 mmol), PPh_3 (104 mg, 0.4 mmol) and **1** (460 mg, 2.5 mmol) in THF (2 ml), was added by syringe sodium dimethyl malonate (**2**, 2.0 mmol, prepared by NaH in THF). The reaction mixture was refluxed, stirred and the products monitored by subjecting small samples to TLC (silica gel/petroleum ether/ethyl acetate = 8/1). After 19 h, the mixture was cooled to room temperature and concentrated under vacuum. Water (3 ml) was added to the residue and the mixture was extracted with ether (3 × 10 ml). The ether solution was dried with anhydrous magnesium sulfate and concentrated. The crude product was distilled in vacuum and purified by flash chromatography on silica gel, eluting with ethyl acetate : petroleum ether (5/95). A mixture of **3** and **4** was obtained in 40% yield. The ratio of **3** to **4** is 63/37.

Preparation of π-allyl platinum complex from triallyl borate

To a yellow solution of $Pt(PPh)_3$ (340 mg, 0.35 mmol) in dichloromethane (6 ml), was added by syringe a solution of triallyl borate (**1**, 270 mg, 1.48 mmol) in dichloromethane (3 ml) and the mixture was stirred at room temperature to give a colorless solution. Sodium perchlorate (100 mg, 0.8 mmol) was then added and the mixture was stirred at room temperature for 20 h. After the excess of sodium perchlorate had been removed by filtration, the solvent was removed in vacuum, and the solid residue was washed three times with hexane and three times with ethyl acetate. The solid was then recrystallized from dichloromethane to give white crystals (**6**), 160 mg, 53%, m.p. 254–260 °C (lit. [25]: 255–260 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): 3.05(dd, J 12.9, 8.0 Hz, 2H), 3.77(d, J 7.0 Hz, 2H), 5.57(m, 1H). IR (KCl, cm^{-1}): 1480m, 1440m, 1090s.

General procedure for the reaction of triallyl borate with nucleophiles

To a solution of $Pd(PPh_3)_4$ (0.1 mmol), PPh_3 (0.4 mmol) and **1** (2.2 mmol) in THF (5 ml) was added by syringe the carbonucleophile **7a–j** (2.0 mmol). The reaction mixture was refluxed, while monitoring by gas chromatography or TLC until the starting material had disappeared. After removal of solvent, water (3 ml) was added and the residue was extracted with ether (3 × 10 ml). The combined ether solution was dried over magnesium sulfate and concentrated. The crude product was purified either by distillation in vacuum followed by flash chromatography or by preparative TLC followed by crystallization (from ether/hexane). The products, **8** and **9**, were characterized by ^{1}H NMR, IR, and MS, and the new compounds gave satisfactory elemental analytical data.

General procedure for the reaction of allylic alcohols with nucleophiles

To a mixture of $Pd(PPh_3)_4$ (0.05 mmol), PPh_3 (0.2 mmol) and boron oxide (1.0 mmol) in THF (5 ml) were added successively allyl alcohol (2.1 mmol) by syringe, and carbonucleophile (2 mmol). The procedure and work-up then followed was the same as that in the general procedure for the reaction of triallyl borate with nucleophiles. Data for the new compounds are listed in Table 3.

Acknowledgement

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