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Allylation of Active Methylene Compounds with Allyl Oxime Carbonates Catalyzed by Pd(0)

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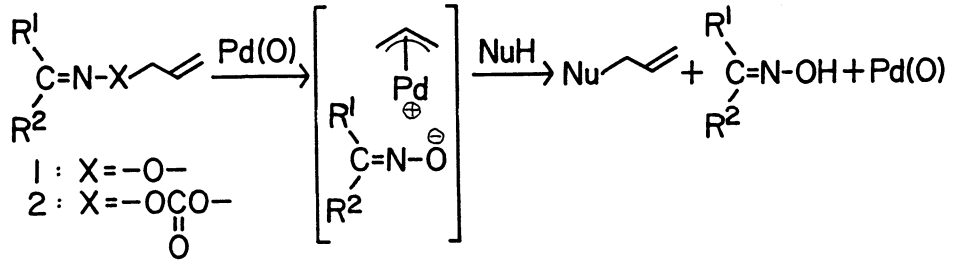
Allylation of active methylene compounds catalyzed by a palladium(0)-phosphine system took place highly stereoselectively by employing allyl oxime carbonates as the allylating reagent.

Palladium catalyzed allylation of carbanions is a useful method for carbon-carbon bond formation.[1,2] Allylic acetates are commonly used as precursors of π-allylpalladium intermediate. In this reaction, generally a stoichiometric amount of bases such as NaH is used for carbanion generation. Although the allylation is a very useful reaction, it would be much more valuable if it can be carried out under neutral conditions. Allylation using allyl carbonates,[3] 1,3-diene monoepoxides[4] and O-allylisoureas[5] without any added bases has been reported. But stereoselective allylation has not been achieved.

Now we wish to report a new system for allylation toward active methylene compounds under neutral conditions using allyl oxime ethers[6] or allyl oxime carbonates with high stereoselectivity. In this system oxime anion acts as an internal base (Scheme 1).

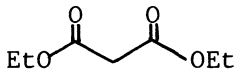
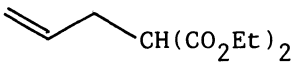
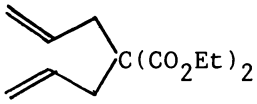
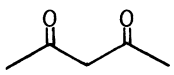
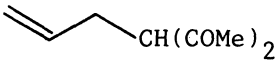
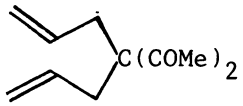
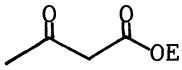
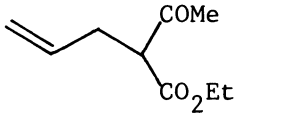
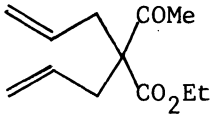
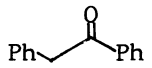
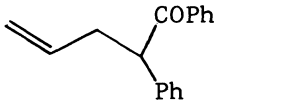
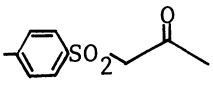
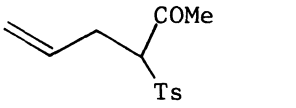
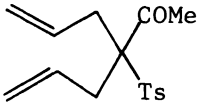
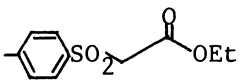
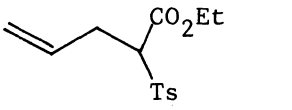
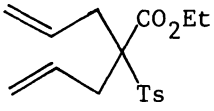
In a typical example, a solution of $Pd(dba)_2$ (5 mg, 8×10^{-3} mmol) (dba = dibenzylideneacetone), dppe (diphenylphosphinoethane) (4 mg, 8×10^{-3} mmol), an active methylene compound (0.4 mmol) and allyl oxime carbonate 2 (0.4 mmol) in dry THF (10 cm^3) was stirred at room temperature under nitrogen. The allylated product was isolated by the usual work up and column chromatography. Results are shown in Table 1.

When allyl oxime ethers 1 were employed, a catalytic amount of base was needed to initiate the allylation (runs 1, 2), but allyl oxime carbonates 2 needed no base.



Scheme 1.

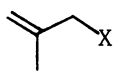
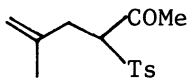
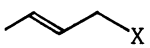
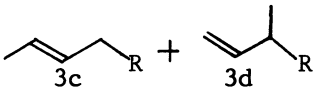
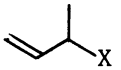
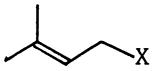
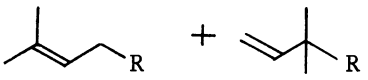
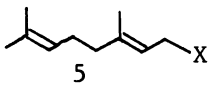
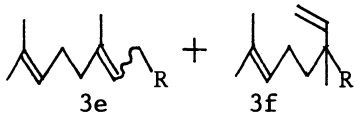
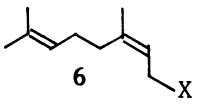
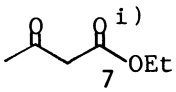
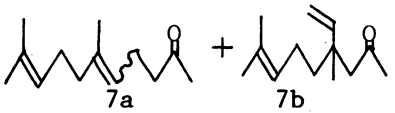
Table 1. Allylation of active methylene compounds using allyl oxime ether 1 or allyl oxime carbonate 2[a)]

Run	Oxime		NuH	Time/h	Products (Yield/%)[b)]			
	R^1	R^2						
1	1 Ph	H		24[c)]				
			3		3a	(50)	3b	(23)
2	1 p-$NO_2C_6H_4$	H	3	24[c)]	3a	(67)	—	
3	2 Ph	H	3	2.5	3a	(47)	3b	(8)
4	2 Ph	Me	3	1.5	3a	(75)	3b	(14)
5	2 Ph	Ph	3	3	3a	(54)	—	
6	2 $-(CH_2)_5-$		3	3	3a	(69)	3b	(2)
7	2 Me	Me	3	1	3a	(75)	3b	(3)
8	2 Me	Me		2				
						(26)		(55)
9	2 Me	Me		2				
						(39)		(41)
10	2 Me	Me		18				
						(79)		
11	2 Me	Me		1.5				
			4		4a	(51)	4b	(26)
12	2 Me	Me	4[d)]	1.5	4a	(80)	4b	(6)
13	2 Me	Me		2				
						(70)		(18)

a) $Pd(dba)_2$ and dppe (2 mol% each) were used as a catalyst and a ligand in THF at room temperature. b) Isolated yield. c) Reaction was carried out in N,N-dimethylformamide at 100 °C and $NaCH(CO_2Et)_2$ (2 mol%) was added. d) Two equiv. of the sulfone was used.

p-Nitrophenylaldoxime and benzophenone oxime induced only mono-allylation toward diethyl malonate (runs 2, 5). Various kinds of oxime carbonates were effective in the reaction.

Table 2. Allylation of active methylene compounds using substituted allyl oxime carbonates[a)]

Run	Oxime carbonate	NuH	Time/h	Products	Ratio[b)] prim:tert(sec)	E:Z	Yield/%[c)]
1[d)]		4	20		—	—	67
2[d)]		3	23	 3c + 3d	64:36	—	23
3[e)]		3	3.5	3c + 3d	63:37	—	70
4		3[f)]	16		75:25	—	35
5	 5	3[g)]	24	 3e + 3f	93:7	96:4	62
6	 6	3[g)]	24	3e + 3f	89:11	11:89	54
7[h)]	6	3[g)]	20	3e + 3f	43:57	3:97	60
8	5	 7 i)	18	 7a + 7b j)	100:0	100:0	50
9	6	7[i)]	18	7a + 7b	88:12	0:100	42

a) X = $-OCO_2N{=}CMe_2$, R = $-CH(CO_2Et)_2$; a combination of $Pd(dba)_2$ and dppe (2 mol% each) was used as a catalyst in dimethyl sulfoxide at 100 °C unless otherwise noted. b) Ratio was determined by GLC analysis. c) Isolated yield. d) In THF at reflux temperature. e) In THF at room temperature. f) $NaCH(CO_2Et)_2$ (2 mol%) was added. g) Diethyl malonate (2 equiv.) and $NaCH(CO_2Et)_2$ (2 mol%) were used. h) PPh_3 (30 mol%) was added (as a ligand) instead of dppe. i) Ethyl acetoacetate (2 equiv.) and $NaCH(CO_2Et)_2$ (2 mol%) were used. j) After decarboxylation.

Allylation toward acetylacetone (pKa = 9, run 8), ethyl acetoacetate (pKa = 11, run 9), diethyl malonate (pKa = 13, run 7) afforded mono- and di-allylated compounds and the ratio of di-allylation to mono-allylation decreased with a decrease in the acidity of active methylene compounds. In case of benzyl phenyl ketone (pKa = 16, run 10), no di-allylated product was detected. The formation of di-allylated product could be suppressed by employing 2 equiv. of active

methylene compound (run 12).

The present system of allylation is successfully applicable to substituted allyl oxime carbonates as shown in Table 2.

It is noteworthy that no more di-allylated products were given when substituted allyl oxime carbonates were used. Allylation of diethyl malonate (3) with crotyl oxime carbonate afforded a mixture of regioisomers, i.e., (E)-crotyl derivative **3c** and α-methallyl one **3d** (run 2). Quite similar results were obtained on α-methallyl oxime carbonate and prenyl oxime carbonate (runs 3, 4), allylation at the primary carbon being predominant in every case.

The stereoselectivity in the case of geranyl and neryl oxime carbonate was fairly high compared with the reported case of methyl carbonate.[3] This is probably due to the coordinating effect of the nitrogen atom of oximes. The yields of allylated products were improved by the use of 2 equiv. of active methylene compound and addition of 2 mol% of sodio diethyl malonate (runs 5-9; c.f. 49% yield when 1 equiv. of **3** to **5** was used). In these cases regio- and stereoselectivity was not affected. It is noteworthy that higher stereoselectivity was obtained by using triphenylphosphine as an additive ligand, although regioselectivity was lowered (run 7).

Application of this reaction to syntheses of more complex natural products are under active investigation.

References

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