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PALLADIUM-CATALYZED REACTION OF ALLYL CARBAMATES; ALLYLATION OF CARBONUCLEOPHILES, AND PROTECTION-DEPROTECTION OF AMINES

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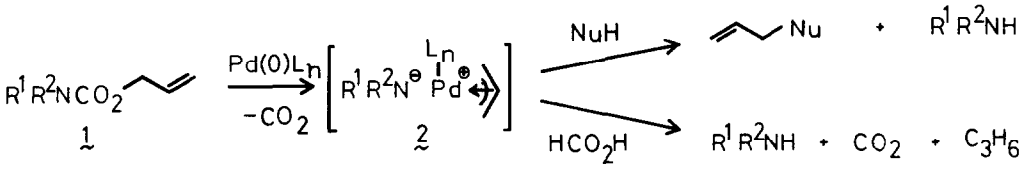
Abstract; Allylation of carbonucleophiles with allylic carbamates under neutral conditions has been studied. The C-allylation of carbonucleophile is competitive with the N-allylation of amines, and the structure of amines is crucial for the selectivity. Bulky secondary amines gave the best results. Also a new method of protection-deprotection of amines as carbamates has been developed. Smooth deprotection is possible by the palladium-catalyzed reaction of allyl carbamates with formic acid. This method is particulary useful for primary amines, including optically active amino acids.

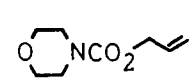
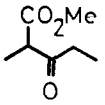
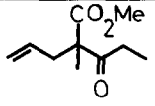
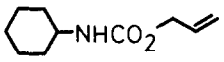
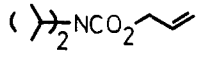
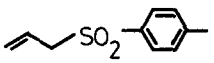
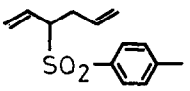
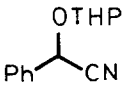
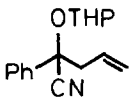
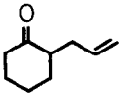
Palladium-catalyzed allylation of nucleophiles is a well-established synthetic method.[1] We have recently reported an improved method using allyl carbonates.[2] The allylation proceeds under neutral conditions due to the in situ formation of alkoxide anion by decarboxylation of carbonates. Based on this result, we speculated that allyl carbamates **1** should be better alllyating agents than carbonates, because amide anions **2** formed by decarboxylation of carbamates is stronger bases than alkoxides. We observed smooth allylation with allyl carbamates **1**. Furthermore, we have developed a new method of deprotection of allyloxycarbonyl group from allyl carbamates. In this paper, we wish to report following palladium-catalyzed reactions of allyl carbamates.



Results of the allylation of carbonucleophiles with allyl carbamates **3**, **6**, and **7** are shown in <Table 1>. Allylation of amines is competitive with allylation of carbonucleophiles, and the structure of amines is crucial for the selectivity. The reaction of **3** proceeded smoothly, but the major product was

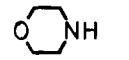
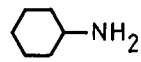
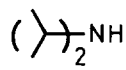
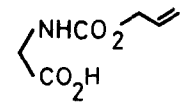
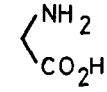
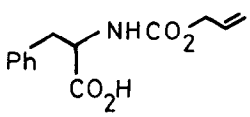
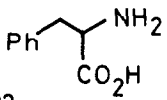
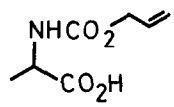
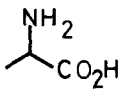
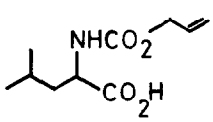
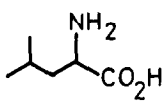
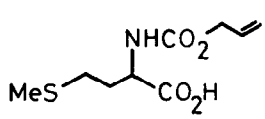
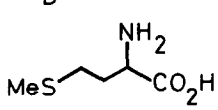
N-allylmorpholine rather than C-allylation product **5**. The reaction of carbamate of primary amine **6** proceeded at room temperature, and the desired **5** was obtained in 81% yield. The best results were obtained with **7**. The chemoselective C-allylation proceeded rapidly in high yields. Reaction of **7** with allyl sulfone gave only the mono-allylated product without forming the diallylated product.[2] Also, the protected cyanohydrin was allylated. But no reaction was observed with simple ketones.[3] Roughly speaking, observed reactivity of **7** with carbonucleophiles is similar to that of allyl carbonates.[2]

<Table 1> Allylation of carbonucleophiles with allyl carbamates[a]

RUN	ALLYL CARBAMATE	NUCLEOPHILE	TEMP.(°C)	TIME(h)	PRODUCT	YIELD(%)[b]
1	 **3**	 **4**	20-25	1	 **5**	(43)[c]
2	 **6**	**4**	20-25	1	**5**	(81)[d]
3	 **7**	**4**	20-25	0.2	5	(100)
4[e]	7	**4**	20-25	1	5	(93)
5	7		65	4		62
6	7		65	6		80
7	7		65	5		(2)

a) Procedure; A solution of allyl carbamate (2 mmol), nucleophile (1 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.05 mmol), and PPh_3 (0.2 mmol) in dry THF (5 mL) was stirred under argon. In runs 4-6, diphenylphosphinoethane (0.1 mmol) was used instead of PPh_3. b) GLC yields in parentheses. c) N-Allylmorpholine was obtained (c.a. 60% based on **3**). d) Unreacted **4** was recovered (c.a. 10%). e) Reaction was carried out using 1 mmol of **7** and 1 mmol of **4**.

<Table 2> Deprotection of allyloxycarbonyl group with formic acid[a)]

RUN	ALLYL CARBAMATE	TIME(h)	PRODUCT	YIELD(%)[b)]
1	**3**	3		(16)[c)]
2	**6**	3		(100)[d)]
3	**7**	1		(97)[d)]
4		**8** 1		90
5		**9** 2	 **10** $[\alpha]_D^{23} = -33.9^\circ$ (c=1, H_2O)	76
6[e)]		**11** 4	 **12** $[\alpha]_D^{20} = +14.5^\circ$ (c=10, 6N HCl)	85
7		**13** 3	 **14** $[\alpha]_D^{23} = +14.9^\circ$ (c=2, 6N HCl)	86
8		**15** 3	 **16** $[\alpha]_D^{25} = +25.3^\circ$ (c=3, 1N HCl)	74

a) Procedure; A solution of carbamate (1 mmol), formic acid (3-4 mmol), PPh_3 (0.2 mmol), and $Pd_2(dba)_3$ $CHCl_3$ (0.05 mmol) in THF (5 mL) was stirred at 30°C under argon. In runs 4-8, amino acids were isolated by the following work-up. After the reaction was complete (TLC analysis), the solvent and excess formic acid were evaporated in vacuo to give pale yellow solid, which was washed with THF (2 mL X 2) and ether (2 mL X 3), and dried to give nearly pure free amino acids. Instrumental analyses (NMR and IR spectra, and specific rotation) were performed without further purification. b) GLC yields in parentheses. c) N-Allylmorpholine was obtained (84%). d) No allylamine was detected by GLC. e) The reaction was carried out with 1 mol% of Pd catalyst.

Allyl carbamates as a protecting group of amines has been reportd.[4-7] The deprotection is carried out by the palladium-catalyzed allyl transfer to potassium 2-ethylhexanoate, 2-ethylhexenoic acid[4] and dimedone.[5] Also $Ni(CO)_4$ is used for deprotection.[6] The allylation with **6** without N-allylation suggests us a simpler method of deprotection of amines. However, careful analysis by GLC showed the formation of mono- and diallylamines in some extent (5-10%). To achieve clean deprotection, we applied the formate reduction of allyl compounds, which we have developed.[8] Results are shown in <Table 2>. To our surprize, N-allylation was observed with **3** even in the presence of formic acid. With this exception, clean deprotection proceeded smoothly in high yields with primary amines and bulky secondary amines in the presence of excess formic acid. The utility of this deprotection was examined in the reaction of N-protected optically active amino acids. N-protected amino acids **8, 9, 11, 13,** and **15** were prepared by the known procedure,[5,7] and they were deprotected without racemization. Comparing the specific rotations of the deprotected products **10, 12, 14** and **16** with those of starting materials, we found in all cases that the reactions (protection and deprotection) proceeded with >98% retention of optical purity. Further application of this deprotection of allyloxycarbonyl group in peptide synthesis is now in progress.

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