Palladium Catalysed Addition of Masked Formyl Cyanides ROCH(CN)₂ to Aldehydes

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The palladium catalysed reactions of masked formyl cyanides 1 with aldehydes 2, followed by treatment with either diketene or acetic anhydride–pyridine, afford the addition products protected with acetylacetate 5 or acetyl group 6, respectively.

We have recently developed a new type of active methyne compound ROHC(CN)₂ 1 as a masked formyl cyanide.¹ The reaction of 1 with alkyl halides $(R'X)^1$ in the presence of base affords the substitution products ROCR'(CN)₂, and the base mediated reaction with activated imines¹⁻³ and α,β -unsaturated carbonyl compounds⁴ (X=Y) gives the addition products RO(CN)₂C-X-YH. However, reaction with aldehydes 2, highly reactive electrophiles, in the presence of bases such as LDA, potassium carbonate, triethylamine, and *tert*-butyl-lithium, did not proceed, perhaps because the initial adduct 3 can readily undergo C–C bond cleavage under the reaction conditions.[‡] It occurred to us that this back reaction would be reduced if a negative charge could not be generated in the course of the C–C bond formation.

We report that the palladium catalysed reaction of 1 with 2, followed by treatment with either diketene or acetic anhydride, gives the desired adduct 5 or 6, respectively, in good yields (Scheme 1). The success of this C-C bond formation is significantly due to the finding by Murahashi's group that the reaction of nitrile derivatives 7 with aldehydes 2 in the presence of ruthenium catalysts affords unsaturated nitriles 8.5 We first attempted the reaction of anisaldehyde 2a with 1a in the presence of 3 mol% RuH₂(PPh₃)₃ in THF at room temperature (under the Murahashi's conditions). NMR examination of the crude products revealed the formation of adduct 4a together with recovered starting materials. Isolation of 4a with silica gel and alumina column chromatography was attempted, but the backward reaction took place and the starting materials, 1a and 2a, were obtained. Accordingly, it is clear that the back reaction of 4a is slower than that of 3 bearing a negative charge on an oxygen atom, although 4a undergoes the C-C bond cleavage reaction upon chromatography.



Scheme 1 Reagents: i, (MeCO)₂O, pyridine; ii, diketene

Our goal is to prepare a synthetic equivalent of α -hydroxy acyl cyanides 9. Therefore, isolation of the adduct is essential.‡ This problem was solved by adding diketene to the reaction mixture; a mixture of 1a (1 mmol), 2a (2 mmol), RuH₂(PPh₃)₃ (0.03 mmol) in THF (1 ml) was stirred for 24 h at room temperature, diketene (4 mmol) was added, and the mixture was stirred for 3 h. Purification of the product by silica gel column chromatography gave 5 in 25% yield. The use of RuCl₂(PPh₃)₃ did not give the adduct 5: even formation of 4a was not observed in the NMR examination of the crude products. The use of $Pd(dppe)_2$ in THF as a catalyst gave 5 in 25% yield, and we finally found that the reaction in MeCN in the presence of $Pd(dppe)_2$ (0.03 mmol) afforded 5 in 52% yields. The complex Pd(dppe)₂ was prepared in situ from bis(dibenzylideneacetone)palladium and 1,2-bis(diphenylphosphino)ethane.

Further, we found that not only the diketene addition but also the treatment with acetic anhydride-pyridine was quite effective for isolation of the adduct.§ The results are summarized in Table 1. The reaction of 1b with 2 equiv. of 4-phenylbutanal 2b proceeded quite smoothly to give the adduct 6a, upon treatment with (MeCO)₂O-pyridine, in essentially quantitative yield (entry 1). The use of 1 equiv. of 2b gave 6a in 77% yield (entry 2). The reaction of 3-methylbutanal 2c afforded 6b in 74% yield (entry 3). However, the yield of 6 decreased in the case of sterically bulky aldehydes: 2-methylpropanal 2d gave 6c in 46% yield (entry 4) and pivalaldehyde did not afford the corresponding adduct.

The reaction of **1b** with isobutyraldehyde **2c** is representative. A mixture of **1b** (1 mmol), $Pd_2(dba)_3$ ·CHCl₃ (0.015 mmol) and dppe (0.03 mmol) in acetonitrile (0.5 ml) was stirred for 30 min at room temperature under an argon atmosphere. A solution of isobutyraldehyde **2c** (2 mmol) in acetonitrile (0.5 ml) was added and the mixture was stirred for 24 h. Acetic anhydride (5 mmol) and pyridine (1.2 mmol) were added, and the mixture was stirred for 3 h at room temperature. The resulting mixture was diluted with diethyl ether (10 ml) and filtered through florisil. The eluent was concentrated *in vacuo* and the residue was purified by silica gel column chromatography to give **6b** (0.74 mmol, 74% yield).



Table 1 Palladium catalysed addition of 1b to 2b-da

Entry	Aldehyde 2	Yield 6 (%) ^b
1	C ₆ H ₅ (CH ₂) ₂ CHO 2b	6a ~ 100
2	C ₆ H ₅ (CH ₂) ₂ CHO 2b ^c	6a 77
3	Me ₂ CHCH ₂ CHO 2c	6b 74
4	Me_2 CHCHO 2d	6c 46

^{*a*} A mixture of **2** (2 mmol), **1b** (1 mmol), Pd₂(dba)₃·CHCl₃ (0.015 mmol) and dppe (0.03 mmol) in acetonitrile (1 ml) was stirred for 24 h. ^{*b*} Isolated yield. ^{*c*} 1 mmol of the aldehyde was used.

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A mechanistic rationale for the palladium catalysed addition of 1 to aldehydes is shown is Scheme 2. The oxidative insertion of Pd⁰ into the activated C-H bond of 1 would give the palladium(II) intermediate 10.5.6 The addition of 10 to 2would afford the adduct 11, which give 4 and palladium(0) species via reductive elimination.

In conclusion, we have accomplished the addition of masked formyl cyanides 1 to aldehydes 2 with the aid of palladium catalyst. Although the adduct undergoes easily the C-C bond cleavage reaction (back reaction), it can be isolated as the derivatives protected with acetyl or acetylacetate group (5 and 6). Accordingly, we are now in a position to prepare a synthetic equivalent of α -hydroxy acyl cyanides 9.

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Footnotes

† In fact, we observed a retro-Michael reaction in the case of certain α,β -unsaturated carbonyl compounds⁴ and similar back reaction in the addition of certain activated imines.² Free negative charge shown in 3 is an extreme representation. The use of LDA or ButLi as a base produces a lithium-oxygen bond.

‡ Formation of α , β -unsaturated nitriles from 4, as was observed previously,⁵ is not desirable for our purpose. § The reaction of anisaldehyde **2a** with **1b**, followed by treatment with

diketene, gave also the corresponding adduct in good yield. However, acetyl protection of a hydroxy group using acetic anhydride did not give 9 in the case of anisaldehyde; presumably the back reaction would be very rapid.

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