Palladium Catalysed Addition of Masked Formyl Cyanides $ROCH(CN)_2$ to Aldehydes

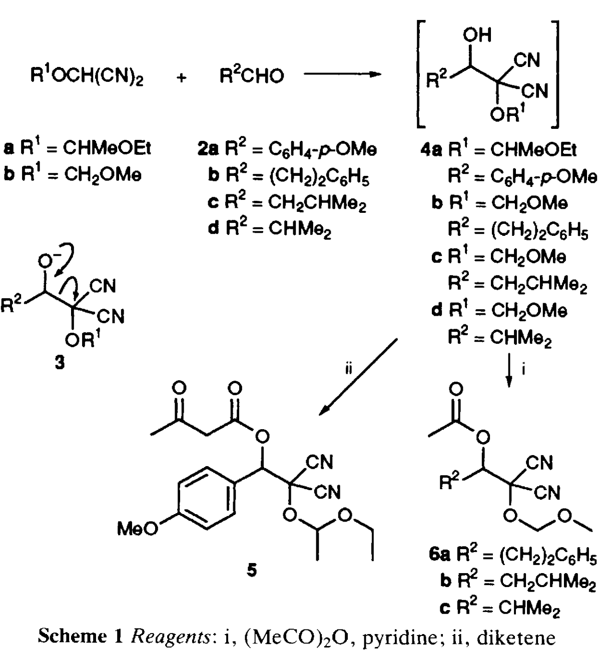
Hisao Nemoto,[a] Yasufumi Kubota[b] and Yoshinori Yamamoto*[b]

[a] *Department of Applied Molecular Science, Okazaki Institute for Molecular Science, Myodaiji 38, Okazaki 444, Japan*
[b] *Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980-77, Japan*

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 imines[1–3] and α,β-unsaturated carbonyl compounds[4] (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*-butyllithium, 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% $RuH_2(PPh_3)_3$ 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), $RuH_2(PPh_3)_3$ (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 $RuCl_2(PPh_3)_3$ 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), $Pd_2(dba)_3{\cdot}CHCl_3$ (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).

R^4CH_2CN

7

$R^2CH{=}CR^4CN$

8

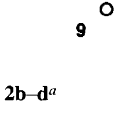


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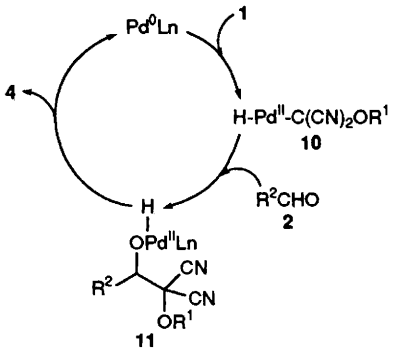
Table 1 Palladium catalysed addition of **1b** to **2b–d**[a]

Entry	Aldehyde **2**	Yield **6** (%)[b]
1	$C_6H_5(CH_2)_2CHO$ **2b**	**6a** ~ 100
2	$C_6H_5(CH_2)_2CHO$ **2b**[c]	**6a** 77
3	Me_2CHCH_2CHO **2c**	**6b** 74
4	Me_2CHCHO **2d**	**6c** 46

[a] A mixture of **2** (2 mmol), **1b** (1 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (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.



Scheme 2

A mechanistic rationale for the palladium catalysed addition of **1** to aldehydes is shown is Scheme 2. The oxidative insertion of Pd^0 into the activated C–H bond of **1** would give the palladium(II) intermediate **10**.[5,6] The addition of **10** to **2** would 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 compounds[4] 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 Bu^{t}Li 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.

References

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