Tetrahedron Letters, Vol.27, No.1, pp 83-86, 1986
Printed in Great Britain

0040-4039/86 $3.00 + .00

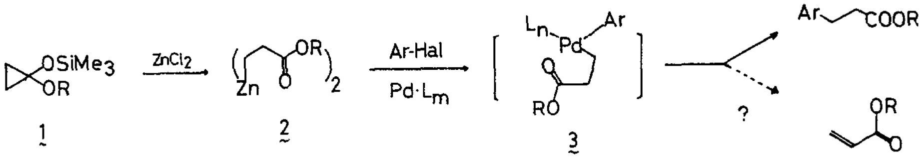
PALLADIUM CATALYZED REACTIONS OF PROPIONATE HOMOENOLATE. ARYLATION, VINYLATION, AND ACYLATION

Eiichi Nakamura* and Isao Kuwajima*

Department of Chemistry, Tokyo Institute of Technology
Meguro, Tokyo 152, Japan

Abstract: Zinc homoenolate of alkyl propionate undergoes clean C-C bond forming reactions with aryl, vinyl, and acid halides in the presence of a palladium catalyst.

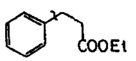
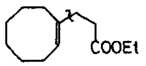
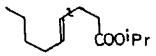
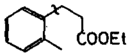
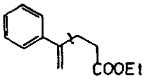
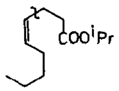
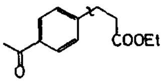
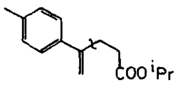
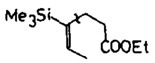
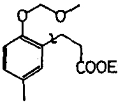
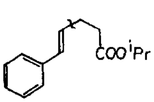
Recent progress in homoenolate chemistry[1] has made possible some C-C bond forming reactions via metal homoenolates.[2--6] However, most of these reactions are addition reactions, and there has been a conspicuous lack of precedents for the nucleophilic substitution reaction. Evidently, this has been caused by the absence of homoenolates with suitable reactivities. In this respect, we focused our attention upon Group 10 metals in conbination with the zinc homoenolate of propionate **2** (available from **1**).[7] Some recent reports have shown the viability of trans metallation from zinc to palladium.[8] We were well aware of the possibility that the intermediary palladium species **3** might break down to an acrylate ester rather to the desired coupling product. This side reaction, however, turned out to pose little problem. Herein is reported the coupling reaction of **2** with aryl and vinyl halides under palladium catalysis. A coupling reaction with acid chloride is also described.



Initial screening of the catalyst (5 mol%) performed on the reaction of **2** with bromobenzene in THF revealed the following order of the catalytic activity (yield of 3-phenylpropionate): $PdCl_2(\underline{o}\text{-}Tol_3P)_2$ (81%) > $NiCl_2(dppf)$ (76%) > $NiCl_2(Ph_3P)_2$ (57%) >

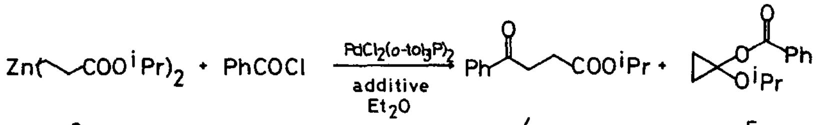
$NiCl_2(\underline{o}\text{-}Tol_3P)_2$ (15%) > $Ni(acac)_2$ (10%) > $PdCl_2(dppf)$ (3%). No significant side reactions occurred, and the material balance based on bromobenzene was excellent in all cases. The poor activity of $PdCl_2(dppf)$ was surprising, since this complex is the best catalyst for the reaction of simple zinc alkyls or Grignard reagents.[9] The (presumed) intermediate 3 must have suffered considerable perturbation due to the homoenolate structure. We currently ascribe this change to the internal coordination of the ester carbonyl oxygen.[7] One of the points in the reaction course under palladium catalysis where such a chelation would produce a deleterious effect is the reductive elimination stage which reportedly involve a dissociative mechanism.[10] The contrasting ligand effect seen in the nickel series (i.e., dppf > Ph_3P > $\underline{o}\text{-}Tol_3P$) suggests the advantage of chelation, which is in line with the associative mechanism proposed for the nickel catalysis.[11] Such chelation may also provide an understanding of the absence of β-elimination reaction, since the required proximity of the metal and the C-2 hydrogen cannot be attained in a five-membered chelate[7] (Cf. 3).

Table I. Arylation and Vinylation of Propionate Homoenolate

Entry Hal=	Product	%yield[b]	Entry Hal=	Product	%yield[b]	Entry Hal=	Product	%yield[b]
1 Br I		67 [81] 79 [91]	5 Br		79	9 I		90[d]
2 Br		83	6 Br		85	10 Br		76[e]
3 Br		49 (68)	7 Br		76	11 Br		87[f]
4 Br		73	8 Br		76[c]			

[a] The reaction was performed with ca. 1.5 equiv of $\underline{2}$ and 5 mol% of $PdCl_2(o\text{-}Tol_3P)_2$ in THF at room temperature, except in entry 2 where 2.5 equiv of $\underline{2}$ was used. [b] Isolated yield; ^1H NMR yield in parenthesis; GLC yield in bracket. [c] Starting halide, 90% E; product, 90% E. [d] Halide >97% E; product, 100% E. [e] Halide, 89% Z; product 86% Z. [f] Halide, >99% E; product 99% E.

THF is preferred to ether, but addition of hexamethylphosphoric triamide (HMPA) reduces the product yield. The presence of Me_3SiCl (due to 1) proved disadvantageous for less reactive substrates and should be removed before the reaction. About 5 mol% of $PdCl_2(\underline{o}\text{-}Tol_3P)_2$ was routinely used for the reaction, yet less than 1 mol % still works nicely. Table I summarizes the results with various halides. Not unexpectedly, iodides react much faster than bromides. For reactive iodobenzene, both of the propionate moieties in 2 is available for the reaction,[12] but excess reagent is required for less reactive substrates. The mild reaction conditions keep ketone and ester functionalities intact (entry 3). The vinylation reaction is stereospecific (entries 8--11). General synthetic utility of the present reaction is apparent from the structures of the compounds in Table I. Aryl chlorides, aryl and vinyl selenides, aryl sulfoxides, vinyl ethers, and enol silyl ethers were inert to the present conditions. N,N-Dimethyl-2-iodoaniline was reduced to the parent aniline. This is the only case where reduction of the substrate was noticed, and must be due to the base-acceleratead decomposition of a palladium intermediate.

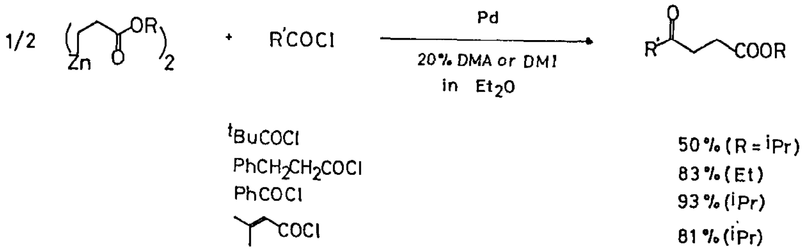


2 4 5

Table II. Benzoylation of Homoenolate under Palladium Catalysis

2	PhCOCl	Additive	% yield 4	% yield 5
1.0 eq	1 eq	–	75	11
0.5	1	–	42	36
0.5	1	1 eq $ZnCl_2$	13	33
0.5	1	20vol% DMA	93	0

Finally, we note that the palladium catalyst smoothly catalyzes the acylation[13] of the homoenolate. The reaction is much faster than the substitution reactions reported above. Both of the propionate moieties in 2 take part in the reaction. The reaction run in ether produces a considerable amount of O-acylation product 5 in addition to the desired product 4, and this side reaction becomes noticeable only after one of the propionate units is consumed. This was also supported by the dependence of the C/O-acylation ratio upon the reagent stoichiometry (Table II). Added $ZnCl_2$ further enhanced the O-acylation. Without the catalyst, virtually no reaction takes place.[5c,14] The formation of the O-acylation product poses an interesting mechanistic problem in that this product may be formed either from an intermediate related to 3 or more straightforwardly via 2 itself. At any event, the O-acylation was completely suppressed in the presence of a polar solvent such as dimethylacetamide (DMA, Table II), dimethylimidazolidinone (DMI), or HMPA. Examples for some representative acid chlorides are shown below.[15,16]



Phenylation of the Homoenolate 2. A solution of 2 in ether preparared from $ZnCl_2$ (1.42 g, 10.4 mmol) and 1 (3.48 g, 20 mmol)[7] was concentrated in vacuo at room temperature, and the residue was dissolved in 15 ml of THF under nitrogen. Iodobenzene (2.45 g, 12 mmol) and $PdCl_2$(*o*-$Tol_3P)_2$ (40 mg, 0.05 mmol) was added with exclusion of oxygen, and the yellowish suspension was stirred for 17 h at room temperature. Powdered KF (2.9 g) and water 1.2 ml was added with stirring, and the supernatant was filtered through a short column of silica gel. Distillation of the filtrate gave 1.68 g (79%) of ethyl 3-phenylpropionate.

References and Notes

1. (a) Nickon, A.; Lambert, J. L. J. Am. Chem. Soc. **1962**, 84, 4604. (b) Before ref 2a, homoenolates reacted with carbon electrophiles only on oxygen. Reviews: Werctiuk, N. H. Tetrahedron **1983**, 39, 205. Ryu, I.; Sonda, N. J. Syn. Org. Chem., Jpn. **1985**, 43, 112.
2. (a) Nakamura, E.; Kuwajima, I. J. Am. Chem. Soc. **1977**, 99, 7360. (b) Nakamura, E.; Kuwajima, I. J. Am. Chem. Soc. **1983**, 105, 651.
3. Caine, D.; Frobese, A. S. Tetrahedron Lett. **1978**, 883. Goswami, R. Corcoran, D. E. Tetrahedron Lett. **1982**, 23, 1463. Goswami, R. J. Am. Chem. Soc. **1980**, 102, 5973.
4. Giese, B.; Horler, H.; Zwick, W. Tetrahedron Lett. **1982**, 23, 931.
5. (a) Nakamura, E.; Kuwajima, I. J. Am. Chem. Soc. **1984**, 106, 3368. (b) Org. Synth. to be published. (c) Oshino, H.; Nakamura, E.; Kuwajima, I. J. Org. Chem. **1985**, 50, 2802.
6. Ryu, I.; Ando, M.; Ogawa, A.; Murai, S.; Sonoda, N. J. Am. Chem. Soc. **1983**, 105, 7192.
7. Nakamura, E.; Shimada, J.; Kuwajima, I. Organometallics **1985**, 4, 641.
8. Negishi, E.; Valente, L. F.; Kobayashi, M. J. Am. Chem. Soc. **1980**, 102, 3298.
9. Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. J. Am. Chem. Soc. **1984**, 106, 158.
10. Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. Bull. Chem. Soc. Jpn. **1981**, 54, 1868. Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. Ibid. **1981**, 54, 1857.
11. Tatsumi, K.; Nakamura, A.; Komiya, S.; Yamamoto, A.; Yamamoto, T. J. Am. Chem. Soc. **1984**, 106, 8181.
12. Ethereal solution of 2 has been standardized by iodine titration.
13. Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T. Tetrahedron Lett. **1983**, 24, 5181.
14. The uncatalyzed *o*-acylation of 2 proceeds only in halomethane.
15. The present acylation procedure is more practical than the two methods that we reported earlier (ref 5a,b).
16. All compounds were characterized by IR and ^1H NMR spectroscopy. For new compounds, adequate analytical and/or mass spectroscopic data have been obtained.

(Received in Japan 29 October 1985)