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A New Synthesis of Polyunsaturated Allenic Carbonyls

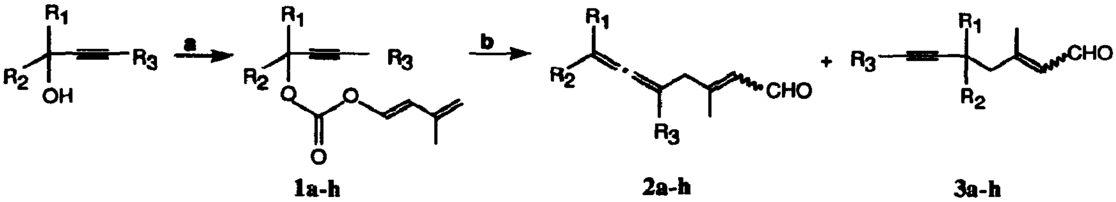
Hugues Bienaymé

Rhône-Poulenc Ind., CRIT-Carrières, BP 62, 69192 Saint-Fons, France

Key Words : Palladium, Allenes, Propargylic Carbonates.

Abstract : *Palladium-catalysed transformation of readily available mixed carbonates 1a-l gives rise to a variety of allenic polyunsaturated aldehydes and ketones 2a-l. These carbonyls were sometimes contaminated with minor amounts of the undesired acetylenic regioisomers 3, and could be purified by silicagel chromatography.*

In the preceeding letter, we described a new prenylation method which enabled us to efficiently prepare dehydrocitral and retinal starting from readily available propargylic alcohols. The mildness and experimental simplicity of the palladium-catalyzed key transformation **1** → **2** were believed to be major assets for rapid constuction of complex and/or sensitive polyunsaturated molecules, and encouraged us to evaluate this reaction for other than terpenic substrates.



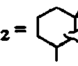
Following the standard two-step protocol, several propargylic alcohols were prenylated in fair to good yields (see table 1).

As already observed, varying ratios of regioisomers **2a-h**/**3a-h** were formed, and in one case the regioselectivity was univocal for the undesired alkynyl enal (**3b**, entry 2). On the whole, several comments could be made :

- Palladium tetrakis triphenylphosphine was chosen as the common catalyst for consistency in our study, though it is not necessarily the best one for a given edduct.
- The allenyl enals **2** are predominantly, if not exclusively, formed.

- Regioselectivity for **2** (vs **3**) is apparently favored for bulky propargylic substituents (R_1, R_2 ; see entries, 1, 2, and 3), but an opposite trend is observed for acetylenic substitution. A silyl, or even better an alkyl or aryl R_3 substituent, is strongly "allene-directing" (compare entries 1 and 6, 7, 8).
- No ligand (or catalyst) optimization was carried out, although it could have a spectacular result on the regioisomeric outcome of this reaction, even in the worst cases (see previous letter).

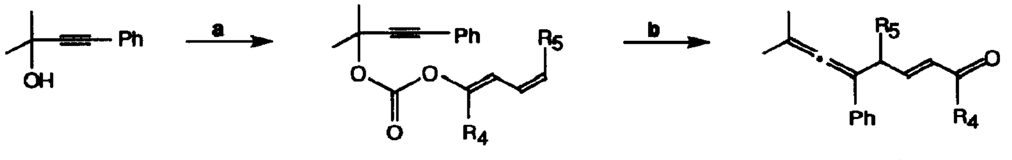
In all examples examined so far, regioisomerically pure aldehydes **2a-h** could be obtained by careful silica gel chromatographic separation.

Entry	Substrate	Yield (step a) %	Yield (step b) %	Selectivity (2 / 3)
1	**1a** ; $R_1 = R_2 = CH_3$, $R_3 = H$	65	59	36/64
2	**1b** ; $R_1 = R_2 = R_3 = H$	51	64	0/100
3	**1c** ; R_1, R_2 = , $R_3 = H$	31	69	100/0
4	**1d** ; $R_1 = Ph$, $R_2 = CH_3$, $R_3 = H$	78	35	66/33
5	**1e** ; R_1, = , $R_2 = CH_3$, $R_3 = H$	71	51	90/10
6	**1f** ; $R_1 = R_2 = CH_3$, $R_3 = TMS$	82	30	63/37
7	**1g** ; $R_1 = R_2 = CH_3$, R_3 = 	73	51	100/0
8	**1h** ; $R_1 = R_2 = CH_3$, $R_3 = Ph$	90	90	100/0

Conditions : a) BuLi (1 eq.), THF-hexane, -20°C then $COCl_2$ (1 eq.), toluene, -20°C then trimethyl siloxyisoprene (1.2 eq.), MeLi (1.1 eq.), THF-ether, -40°C → RT. **b)** Pd $(PPh_3)_4$ (0.05 eq.), THF, 60°C, unoptimized yields.

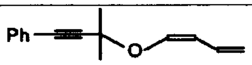
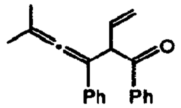
Table 1

As shown in table in Table 2, this reaction is not limited to the synthesis of allenic isoprenoid aldehydes, and other polyunsaturated aldehydes and ketones (cyclic or linear) can be prepared equally well. For the α-β unsubstituted enal **2i** and enone **2j**, a single stereoisomer (E) was formed[1].



1i-k

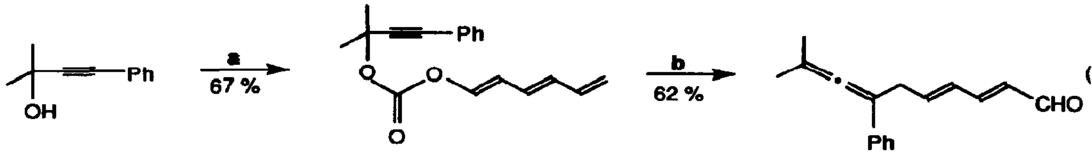
2i-k

Entry	Substrate	Yield (step a)	Yield (step b)	Other products (yield)
1	**1i** ; $R_4 = R_5 = H$	87%	54%	 (Z isomer, 37 %)
2	**1j** ; $R_4 = Ph$, $R_5 = H$	48%	50%	 (37 %)
3	**1k** ; R_4, $R_5 = CH_2\text{-}CH_2$	60%	82%	

Conditions : a) BuLi (1 eq.), THF-hexane, -20°C then $COCl_2$ (1 eq.), toluene, -20°C then silyl enol ether (1.2 eq.), MeLi (1.1 eq.), TMEDA (1.1 eq), THF, - 40°C. **b)** Pd $(PPh_3)_4$ (0.05 eq.); THF, 60°C.

Table 2

Taking advantage of the fact that once the η^3-π-allyl complex is formed, the metal nucleus can migrate along the polyolefinic carbon chain (through π-σ-π equilibriums), the tetraunsaturated aldehyde **2l** was prepared in only two steps from 3-methyl-1-phenyl-butynol (eq 1.) : In this case, for regioselectivity reasons, nickel (0) catalysis was found to be superior to the previously used palladium (0) catalysis. Again a single (E-E) stereoisomer was observed for **2l**.

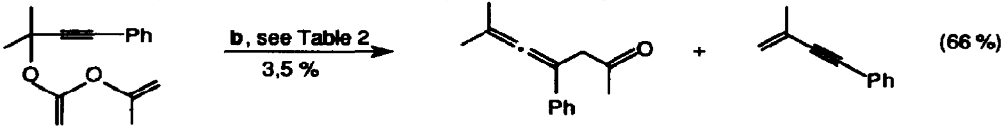


1l **2l**

(eq. 1)

Conditions : a) see Table 2 **b)** Ni(COD)$_2$ (0.20 eq.), PPh$_3$ (0.40 eq.), THF, 25°C, only E-E isomer observed.

One of the limitations of this methodology is in the preparation of β-γ, γ-δ unsaturated ketones, such as **2m**, from simple enol carbonates (although these ketones could easily be prepared by direct acetylenic Claisen rearrangement of the corresponding alcohols[2]) (eq 2.).



1m **2m**

(eq. 2)

A plausible mechanism for this new allene synthesis which accounts for some of the observed results is presented in scheme 1.

Oxidative insertion of a palladium (0) complex with carbonates **1a-j** generates, after CO$_2$ loss, a variety of equilibrated species (**A** - **E**) which reductively eliminates to afford the observed products. The relative concentrations of intermediates (**A** - **E**) as well as their respective rates of reductive elimination dictate the regioisomer proportion and/or product distribution[3]. These parameters being highly substituent and catalyst - dependant (and somewhat unpredictible), *a-priori* determination of a result is not easy. Nevertheless, several observations are worth considering :

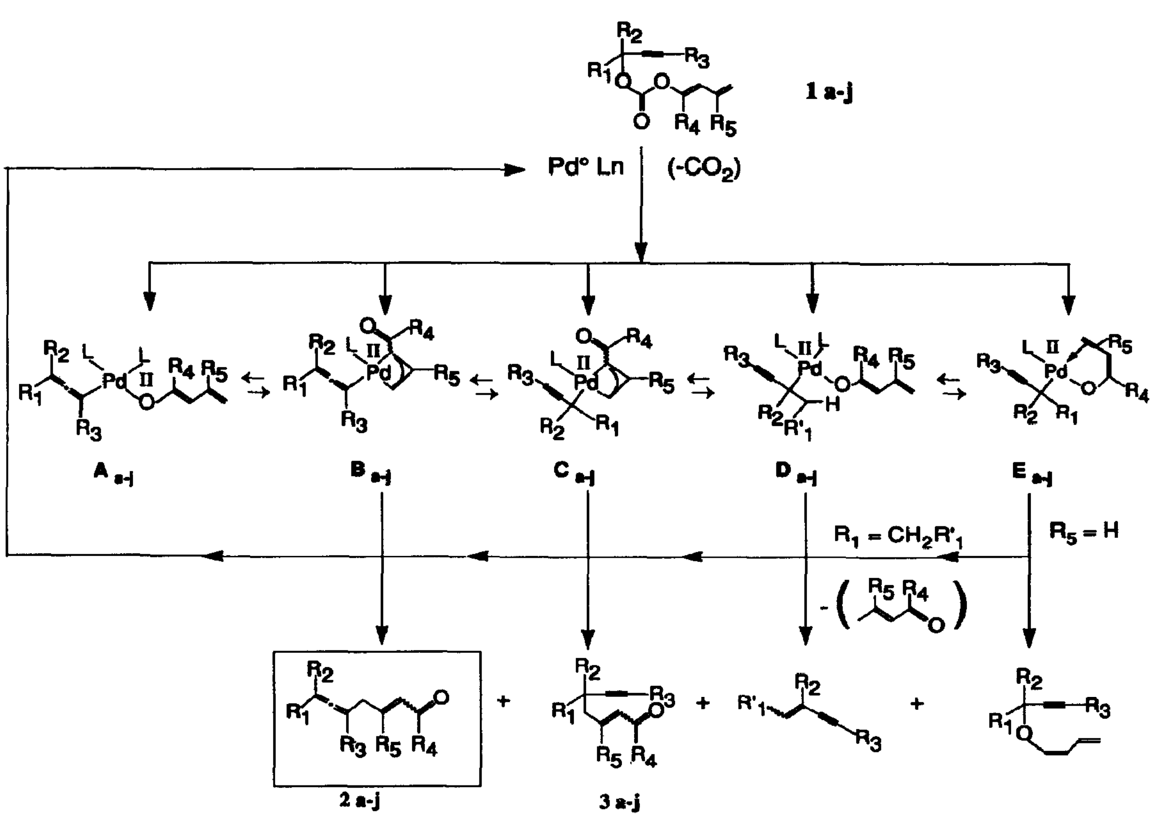
Although no extensive studies have been made, it has been shown that the **2a/3a** ratio is greatly increased when sterically demanding phosphines are used (see Table 1, previous Letter). This could be rationalized if one considers that the propargyl appendage in complex **C$_a$** is slightly larger (a metal-bound quaternary carbon, $R_1 = R_2 = CH_3$) than its allenyl counterpart in **B$_a$** ($R_3 = H$), and hence the **B$_a$** / **C$_a$** equilibrium is shifted towards **B$_a$** for bulky ligands L (See scheme I).

A similar reasoning[3] could be made to explain the R_1 and R_2 influence on the regioisomeric outcome of the reaction for a given phosphine (see Table 1). However, a purely steric model is obviously very limited, and for instance, fails to explain the dramatic role of the acetylenic R_3 substituent.

Two other pathways to unwanted by-products have been identified. The first involves a β-hybride elimination from intermediate **D$_{a\text{-}j}$** to generate the corresponding eneyne. Formation of this compound becomes predominant when the equilibrium C-bonded Pd-enolate $\rightleftharpoons$ O-bonded Pd- enolate is shifted to the right, as it is probably the case for carbonate **1m** (eq. 2), which upon oxidative insertion of Pd(0).cannot form a stabilized η^3-π-allyl complex.

Finally, a dienol ether was also observed (Table 2, entry 1), resulting from reductive elimination at the oxygen atom[4]. Stereochemistry of this product (Z) indicates that internal olefin coordination to palladium occurs (complex **E$_i$**). This probably results from the superior coordinating ability of the butadienyl moiety ($R_4 = R_5 = H$) as compared to the isoprenyloxy one ($R_4 = H$, $R_5 = Me$). An olefin trans effect might be responsible for a faster rate of reductive elimination (vs β-hydride elimination) in that case.

Thus, palladium (0)-catalyzed rearrangement of carbonates **1a-j** was found to be an expeditive and efficient method for the preparation of allenic unsaturated carbonyls. These allenes could be either reconjugated or used as carbon frameworks in the synthesis of complex molecules. Because of its mildness and intramolecular nature, optically active allenes[5] should be easily obtained through C-O → C-C chirality transfer, a goal which is actively pursued in our laboratories.



scheme 1

Acknowledgments

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References and Notes

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4. We checked that in the reaction conditions, this compound is not an intermediate in the formation of 2i from 1i.
5. See for instance : Elsevier, C. J. ; Mooiweer, H. H. ; Kleijn, H. Vermeer, P. *Tetrahedron Lett.* **1984**, *25*, 5571-72. Elsevier, C. J. ; Stehouwer, P. M. ; Westmijze, H. ; Vermeer, P. *J. Org. Chem.* **1983**, 48, 1103-05. Reviews : Taylor, D. R. *Chem. Rev.* **1966**, 317-359. Brandsma, L. ; Verkruijsee, H. D. Synthesis of acetylenes, Allenes, and Cumulenes. Elsevier, *New-York*, **1980**. Hopf, H. The *Chemistry of Ketenes, Allenes and Related Compounds* (Ed. S. Patai), 2, Chap 20, Wiley, *New-York*, **1980**. Pasto, D. *J. Tetrahedron*, **1984**, *40*, 2805-27.

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