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# Pd-Catalysed Coupling Reactions: (*Z*)-Vinyl (*N,N*-Diisopropyl)Carbamate Group as an Efficient Precursor of a (*Z*)-Vinyl triflate Function

François-Hugues Porée, Julien Barbion, Sylvie Dhulut, Jean-François Betzer,\* Ange Pancrazi, Janick Ardisson

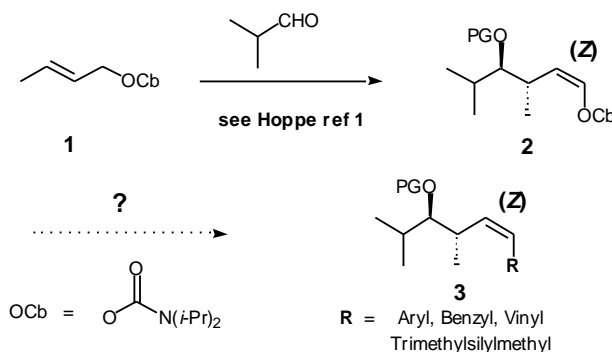
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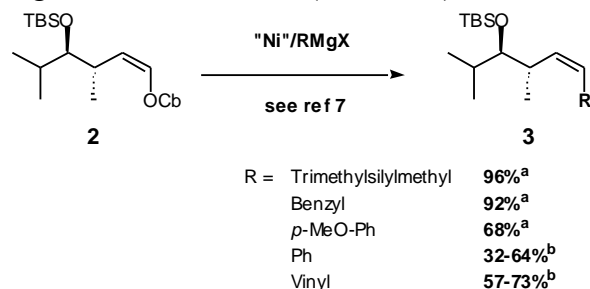
As part of an ongoing project directed toward total synthesis, we focused on an efficient aldehyde allylation reaction described by Hoppe,<sup>1</sup> which corresponded to the preparation of the (*Z*)-*anti* homoallylic alcohol **2**, from crotyl (diisopropyl)carbamate **1**, in an enantioselective way *via* a second order asymmetric induction (Scheme 1). Application of this method was advantageously used in total synthesis <sup>2</sup> for an enantioselective introduction of two *anti*-asymmetric centers.

For synthetic aspects, our goal was to access (*Z*)-substituted alkenes **3** from the (*Z*)-vinyl carbamate **2** (Scheme 1).



## Scheme 1

Several reports about transformation of the vinyl carbamate function into lactol,<sup>2d,3</sup> acetylenic,<sup>2b,2c</sup> aldehyde <sup>1,2</sup> and more recently into cyclopropylaldehyde **4** have appeared. However, only few reports described preparation of a (*Z*)-or (*E*)-alkyl compound,<sup>5a-c</sup> or enyne,<sup>5d</sup> in application of the Wenkert' method,<sup>6</sup> which involves a Ni-catalysed coupling reaction. In an earlier paper,<sup>7</sup> we described the use of Ni-catalysts in Et<sub>2</sub>O at 0 °C,<sup>8a</sup> or in boiling toluene or benzene,<sup>8b</sup> using an excess of the Grignard reagent. Under these conditions, it was shown that (*Z*)-vinyl carbamate **2** afforded the corresponding (*Z*)-coupled products **3** in good yields and high stereoselectivities (Scheme 2).



**a)** Isolated yield. **b)** Isolated yield but together with the (*E*) and/or homocoupled and/or reduced products.

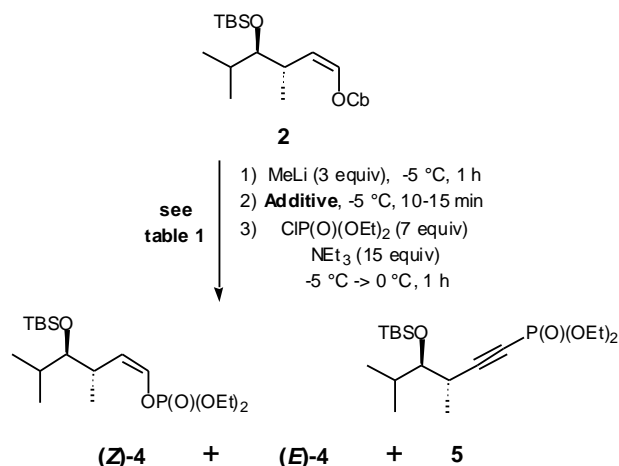
## Scheme 2

This reaction gave good results with trimethylsilylmethyl-, benzyl- and *p*-OMe-phenyl Grignard reagents to conduct to the corresponding (*Z*)-alkenyl derivatives **3**. However employing vinylmagnesium bromide, to a large extent, and phenylmagnesium bromide, this coupling reaction was not totally satisfying, due to the production of homocoupled and reduced derivatives. So we turned our efforts to an indirect way for the conversion of **2** into **3**.

Interestingly transformation of a (*Z*)-vinyl carbamate into the corresponding (*Z*)-*tert*-butyldimethylsilyl enol ether in 84% yield was earlier described,<sup>9</sup> by reaction with 3 equivalents of MeLi and quenching the intermediate lithium enolate with *tert*-butyldimethylsilylchloride.

Considering the lithium enolate intermediate stable enough at 0 °C, other trapping agents could be envisaged as phosphate or triflate; the remaining and important question was to preserve the (*Z*)-stereochemistry of the double bond.

Thus, carbamate **2**<sup>10</sup> was treated with 3 equivalents of MeLi at -5 °C, in THF or Et<sub>2</sub>O, in presence of TMEDA (10 equiv). After quenching with diethyl chlorophosphate (7 equiv) and NEt<sub>3</sub> (15 equiv), reaction led to the (*E*)-vinyl phosphate (**E**)-**4** in 37% or 14% yield (Scheme 3, table 1, entries 1,2).



## Scheme 3

Table 1: Results using diethyl chlorophosphate as trapping agent

Entry	Solvent	Additive	Yields <sup>a</sup>	( <i>Z</i> )- <b>4</b> /( <i>E</i> )- <b>4</b> / <b>5</b> <sup>b</sup>
1	THF	TMEDA <sup>c</sup>	37	0:100:0
2	Et <sub>2</sub> O	TMEDA <sup>c</sup>	14	0:100:0
3	Et <sub>2</sub> O	none	79	80:0:20
4	Et <sub>2</sub> O	none <sup>d</sup>	25	70:0:30
5	Et <sub>2</sub> O	DMPU <sup>e</sup>	79	100:0:0
6	Et <sub>2</sub> O	HMPA <sup>e</sup>	94	100:0:0

**a)** Isolated yields. **b)** GC/MS analysis. **c)** 10 equiv of TMEDA were used. **d)** Only 2 equiv of ClP(O)(OEt)<sub>2</sub> were used. **e)** DMPU or HMPA was added for a 3:1 final ratio of Et<sub>2</sub>O/DMPU or Et<sub>2</sub>O/HMPA.

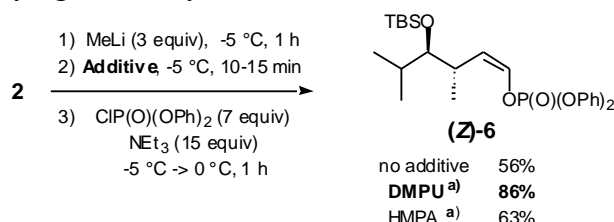
When the reaction was carried out in Et<sub>2</sub>O, without addition of TMEDA formation of the (*E*)-vinyl phosphate (**E**)-**4** was prevented, and the expected (*Z*)-**4** isomer was produced together with the acetylenic byproduct **9** in 79% yield and an 80:20 ratio (entry 3).

The trapping agent must be used in an excess (7 equiv): when only 2 equivalents were employed, yield decreased to 25% (entry 4).

In another experiment, addition of DMPU in place of TMEDA,<sup>11</sup> resulted in the formation of the pure isomer (**Z**)-**4** in 79% yield (entry 5), the acetylenic and isomeric products **5** and (**E**)-**4** not being isolated under these conditions.

When using HMPA under the same conditions yield increased to 94% to deliver the pure isomer (**Z**)-**4** (entry 6).

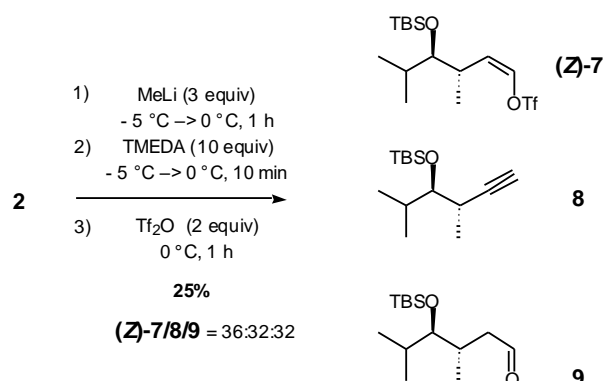
Changing the diethyl chlorophosphate into the diphenyl chlorophosphate, as the trapping agent, reaction conducted to the (**Z**)-vinyl phosphate **6** in 56% yield (Scheme 4), and in a better yield (86%) when DMPU was used. Surprisingly employing HMPA, yield decreased to 63%.



#### Scheme 4

In spite of this good result and due to the restrictive scope of vinyl phosphates to undergo metal-catalysed reactions,<sup>12</sup> we turned our efforts to the preparation of a (**Z**)-vinyl triflate compound. However, vinyl triflate formation was reported in literature in most cases for cyclic ketones.<sup>13</sup> From aliphatic ketone (more often β-keto-ester) or aldehyde, only few and non-general preparations of stereodefined derivatives were described,<sup>14,15</sup> and the construction of a pure (**Z**)-vinyl triflate remained an interesting and important challenge.

When the vinyl carbamate **2** was treated under the same conditions used before, MeLi (3 equiv)/THF/TMEDA/0 °C, followed by a triflic anhydride trap<sup>16</sup> (2 equiv), the expected (**Z**)-vinyl triflate **7** was produced together with the acetylenic and aldehyde derivatives **8** and **9** in 25% overall yield (Scheme 5).

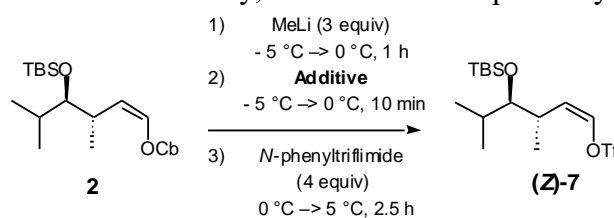


#### Scheme 5

Using *N*-phenyltriflimide,<sup>17,13a</sup> as the quenching agent (4 equiv), and TMEDA, yield rose to 43% and the (**Z**)-vinyl triflate **7** was obtained together with the acetylenic compound **8** in a 60:40 mixture (Scheme 6, Table 2, entry 1). As an unexpected result, using only 2 equivalents of PhNTf<sub>2</sub>, compounds (**Z**)-**7** and **8** were obtained in a same yield (43%) but with an increasing ratio **7/8** = 90:10 (Table 2, entry 2). Changing THF with diethyl ether, in presence of 2 equivalents of *N*-phenyltriflimide, reaction smoothly delivered the vinyl triflate (**Z**)-**7** in 74% yield together with an amount of the acetylenic derivative **8** in a 92:8 ratio (Table 2, entry 3).

In the last experiments, carried out in Et<sub>2</sub>O, the enolate was trapped by addition of a solution *N*-

phenyltriflimide in DMPU or HMPA. This change let us to obtain in comparable yields (76% and 74% respectively) the (*Z*)-7 triflate in better selectivity, 96:4 and 98:2 respectively.



## Scheme 6

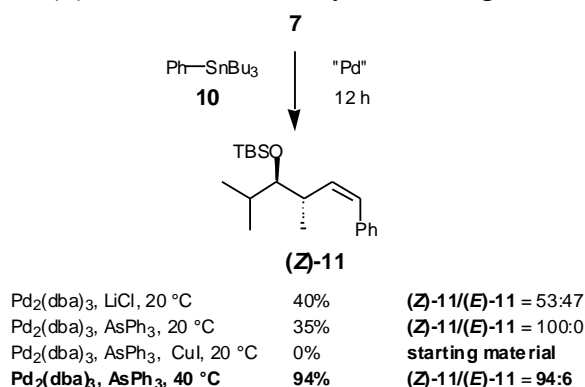
**Table 2: Results using *N*-phenyltrifluoromethanesulfonimide as trapping agent**

Entry	Solvent	Additive	Yields <sup>a</sup>	( <i>Z</i> )-7/8 <sup>b</sup>
1	THF	TMEDA <sup>c</sup>	43	60:40
2	THF	TMEDA <sup>c,d</sup>	43	90:10
3	Et <sub>2</sub> O	TMEDA <sup>c,d</sup>	74	92:8
4	Et <sub>2</sub> O	DMPU <sup>e</sup>	74	96:4
5	Et <sub>2</sub> O	HMPA <sup>e</sup>	76	98:2

**a)** Isolated yields. **b)** GC/MS analysis. **c)** 10 equiv of TMEDA were used. **d)** Only 2 equiv of PhNTf<sub>2</sub> were used. **e)** DMPU or HMPA was added for a 3:1 final ratio of Et<sub>2</sub>O/DMPU or Et<sub>2</sub>O/HMPA.

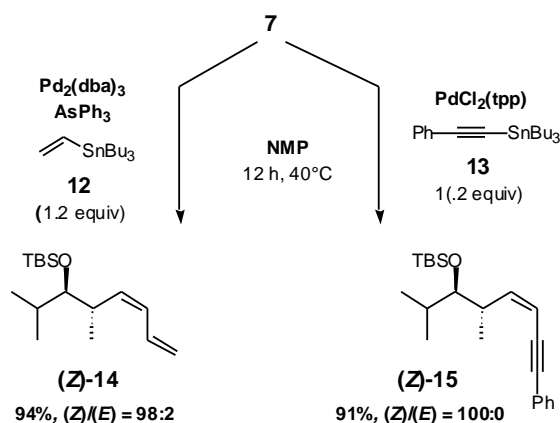
As the preparation of the pure vinyl triflate (*Z*)-7 was achieved in good yield and total stereoselectivity, the second goal was to realize Pd-catalysed coupling reactions in respect with the (*Z*)-geometry of the double bond.

Reaction of (*Z*)-7 with phenyltributyltin **10** and Pd<sub>2</sub>(dba)<sub>3</sub>/LiCl (Ligandless), in NMP <sup>18</sup> at 20 °C for 12 h, led to a 53:47 mixture of coupled products (*Z*)-11 and (*E*)-11 in 40% yield (Scheme 7). When triphenylarsine (AsPh<sub>3</sub>) was used as ligand,<sup>19</sup> the pure (*Z*)-11 derivative was formed, the yield remaining low (35%). Surprisingly, addition of CuI (catalytic or stoichiometric) <sup>14,20</sup> and AsPh<sub>3</sub> did not produce any coupling reaction. Optimization of this reaction was attained under [Pd<sub>2</sub>(dba)<sub>3</sub>/AsPh<sub>3</sub>/NMP, 40 °C, 12 h] conditions to furnish the expected (*Z*)-11 adduct in 94% yield and a good selectivity [(*Z*)/(*E*) = 94:6].



## Scheme 7

Applying these conditions, Pd-catalysed coupling reactions of (*Z*)-7 with tributyl(vinyl)tin **12** and (phenylethynyl)tributyltin **13** (Scheme 8) delivered the corresponding diene (*Z*)-14 <sup>7</sup> and enyne (*Z*)-15 in 94% and 91% yield respectively and high (*Z*)/(*E*) selectivity (98:2 and 100:0 respectively).



### Scheme 8

In this paper, it was shown that a vinyl carbamate group <sup>21</sup> could be transformed in one step to the corresponding (*Z*)-vinyl phosphate or (*Z*)-vinyl triflate function in good yield and high selectivity. It was also demonstrated that a (*Z*)-vinyl triflate derivative could be engaged in Pd-catalysed coupling reactions with tin derivatives, without loss of the (*Z*)-geometry of the double bond, leading to an efficient preparation of (*Z*)-substituted vinyl derivatives.

Application of this sequence, following a Hoppe aldehyde allylation reaction, should be considered as a useful tool in total synthesis.

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