

# Rapid Pd - Catalyzed Synthesis of Protected $\alpha,\beta$ -Unsaturated Methyl Ketones and Alkoxy Dienes under Microwave Irradiation

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## Introduction

Dioxolanation is one of the most widely used protective techniques for carbonyl compounds. Many synthetic methods are available, but methodologies for chemoselective ketalization are rare (Path 1).

In addition, alkoxy dienes have found numerous applications in the synthesis of functionalized cyclohexene derivatives by cycloaddition reactions (Path 2).

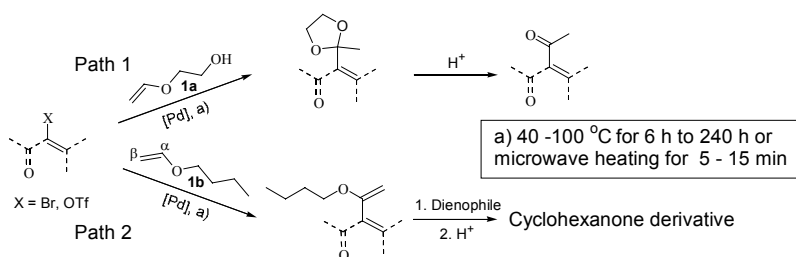


Table 1. Synthesis of 2-Alkene-2-Methyl-1,3-Dioxolanes and alkoxy dienes via internal vinylation of 2-Hydroxyethyl vinyl ether or butyl vinyl ether

Entry	Vinyl Triflate or Vinyl Bromide	Vinyl Ether	Additive	Time (h)	Temperature (°C)	Product	Isolated Yield (%)	Method
1		1a	-	18	40		68	A
2		1b <sup>a</sup>	-	18	40		86	A
3		1a	-	22	40		51	A
4		1b	-	22	60		73	B
5		1a	-	18	40		69	A
6		1b	-	18	40		87	A
7		1a	TIOAc	68	60		67	A
8		1b	TIOAc	29	40		55	B
9		1a	TIOAc	22	60		56	A
10		1b	TIOAc	168	60		10	A
11		1a	TIOAc	240	100		72 <sup>b</sup>	A
12		1b	TIOAc	144	80		28	B
13		1a	-	18	40		59	A
14		1b	-	6	60		79	A

Reaction conditions: Method A: 2.0 equiv vinyl ether, 3 mol% Pd(OAc)<sub>2</sub>, 6 mol% DPPP, 1.5 equiv Et<sub>3</sub>N, mol sieves (4Å) in DMSO under N<sub>2</sub>. Method B: 5.0 equiv vinyl ether, 3 mol% Pd(OAc)<sub>2</sub>, 6 mol% tol-BINAP, 1.5 equiv K<sub>2</sub>CO<sub>3</sub>, mol sieves (4Å) in DMSO under N<sub>2</sub>. <sup>a</sup>5.0 equiv vinyl ether, <sup>b</sup>GC/MS yield

## Results

**Ketal synthesis:** A new tandem Heck-coupling cyclization reaction is described<sup>1</sup> (Table 1). The reaction proceeds via an internal vinylation to give an intermediate hydroxy alkyl vinyl ether, which subsequently cyclizes into a ketal. The procedure allows for the formation of a blocked  $\alpha,\beta$ -unsaturated methyl ketone in the presence of a free aldehyde or ketone (entry 9, 11 and 13).

**Alkoxy diene synthesis:** In order to improve the regioselectivity in the Heck-reaction with alkyl vinyl ethers and vinyl halides or vinyl triflates the coupling is performed under "cationic" conditions<sup>2,3</sup> (Table 1). The regioselectivity for internal  $\alpha$ -vinylation employing bidentate ligands is found to be high ( $\alpha/\beta > 98/2$ ), and the products can be isolated in synthetically useful yields.

Table 2. Microwave induced synthesis of 3 and 4

Entry	Vinyl Triflate or Vinyl Bromide	Vinyl Ether	Product	Power (W)	Time (min)	Yield (%)	Selectivity $\alpha/\beta$
1	2a	1a	3a	10	5	95 <sup>b</sup>	99/1
2	2a	1b	4a	10	5	99 <sup>b</sup>	90/10
3	2c	1a	3c	5	5	73 <sup>a</sup> 93 <sup>b</sup>	99/1
4	2c	1b	4c	5	5	89 <sup>b</sup>	98/2
5	2f	1a	3f	20	5	46 <sup>a</sup> 70 <sup>b</sup>	99/1
6	2f	1b	4f	25	5	57 <sup>a</sup> 82 <sup>b</sup>	80/20
7	2g	1a	3g	10	7	53 <sup>a</sup> 90 <sup>b</sup>	99/1
8	2g	1b	4g	10	5	64 <sup>a</sup>	98/2

Reaction conditions: 2.0 equiv vinyl ether, 3 mol% Pd(OAc)<sub>2</sub>, 6 mol% DPPP, 1.5 equiv Et<sub>3</sub>N, mol sieves (4Å) in DMSO under N<sub>2</sub>. Continuous irradiation (2450 MHz, Microwell 10). <sup>a</sup>Isolated yield <sup>b</sup>GC/MS yield

**Microwave:** The use of microwave flash-heating to promote Heck vinylation reactions results in reduction of the reaction time from hours to a few minutes<sup>4</sup> (Table 2). The reaction can be accomplished in fair yields, but an inferior regioselectivity is encountered in entries 2 and 6.

## Conclusion

We herein report:

⇒ A rapid method for chemoselective synthesis of protected methyl ketones.

⇒ A highly regioselective procedure for internal vinylation of alkyl vinyl ethers.

⇒ Dramatic accelerations of Heck vinylation reactions under microwave irradiation.

## REFERENS

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