



## An economic and efficient tetrahydrofuranylation of alcohols, imines and alkynes

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### ABSTRACT

The tetrahydrofuranyl radical, generated by heating tetrahydrofuran in the presence of air and allyl or benzyl chloride, becomes a useful tool in order to transform the hydroxyl functions into ethers, or the C=N double bond into amine, or the C–C triple bond into vinyl derivatives. A radical mechanism is proposed followed by a nucleophilic substitution for the alcohol substrate and a radical addition for the iminic and the acetylenic reactants.

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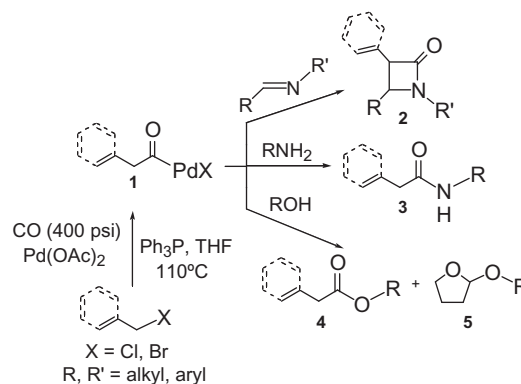
In the last few years our research group has been involved in the study of the Pd(0)-catalysed carbonylation reaction of allyl and benzyl halides. Through the generation of the palladium complex **1** (Scheme 1),  $\beta$ -lactam rings **2**, amides **3** and esters **4** could be prepared by reaction with imines,<sup>1–5</sup> amines<sup>6</sup> and alcohols,<sup>7</sup> respectively.

Moreover, the reaction with alcohols and phenols produced esters **4** (>90%) together with small amounts of tetrahydrofuranyl alkyl or aryl ethers **5** (1–5%), respectively.

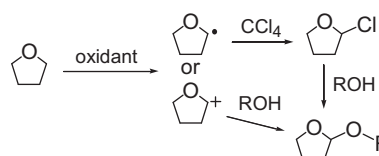
In the literature, reactions of tetrahydrofuranylation of alcoholic centres were recently reported to be based on the use of one-electron oxidants to activate the tetrahydrofuran (THF). Peroxydisulfates,<sup>8</sup> cerium(IV) reagents,<sup>9</sup> peroxy- $\lambda^3$ -iodane,<sup>10</sup> or alternatively, CrCl<sub>2</sub>,<sup>11</sup> Mn(0) powder<sup>12</sup> or VCl<sub>3</sub><sup>13</sup> in the presence of CCl<sub>4</sub> were reported as good reactants in the alcohol tetrahydrofuranylation. All the mentioned studies described a prior transformation of THF to 2-tetrahydrofuranyl radical or cation which then reacted by two different ways. The radical underwent firstly halogenation by CCl<sub>4</sub> and then a nucleophilic substitution by the alcohol, the cation linked directly the alcoholic moiety (Scheme 2).

In order to explore the mechanism of generation of compound **5**, occurring under experimental conditions (Scheme 1) completely different from those reported in the literature, several experiments were planned. In the first instance, benzyl alcohol (1.0 mmol) and THF (20 mL) were reacted in autoclave (110 °C) for 15 h. In order to find better experimental conditions for the best yields, the

operating parameters, including the presence of allyl chloride, CO, Pd(OAc)<sub>2</sub>, and PPh<sub>3</sub>, were modulated each time. The final results of this investigation are shown in Table 1.



Scheme 1. Pd(0)-catalysed carbonylation of allyl and benzyl halides.



Scheme 2. Tetrahydrofuranylation of alcoholic centres using one-electron oxidants to activate the THF unit.

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**Table 1**  
Reaction of benzyl alcohol with THF modulating the experimental conditions

Entry	RCl (mmol)	Gas (psi)	Pd(OAc) <sub>2</sub> (mmol)	PPh <sub>3</sub> (mmol)	T <sup>a</sup> (°C)	Yield <sup>b</sup> (%)	Products distribution <sup>c</sup> (%)	
							4a	5a
1	CH <sub>2</sub> =CHCH <sub>2</sub> - (1.2)	CO (400)	0.1	0.4	110	50	97	3
2	—	CO (400)	0.1	0.4	110	—	—	—
3	CH <sub>2</sub> =CHCH <sub>2</sub> - (1.2)	—	0.1	—	110	45	—	100
4	CH <sub>2</sub> =CHCH <sub>2</sub> - (1.2)	CO (400)	—	0.4	110	43	—	100
5	CH <sub>2</sub> =CHCH <sub>2</sub> - (1.2)	CO (400)	—	—	110	45	—	100
6	CH <sub>2</sub> =CHCH <sub>2</sub> - (1.2)	—	—	—	Reflux	60	—	100
7	CH <sub>2</sub> =CHCH <sub>2</sub> - (1.2)	N <sub>2</sub> (400)	—	—	110	—	—	—

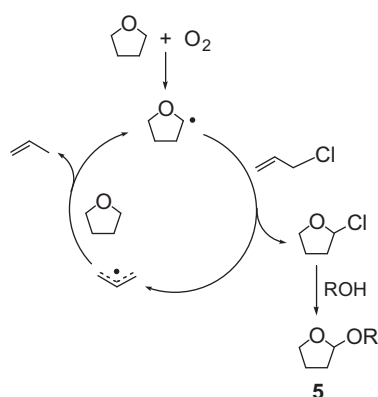
<sup>a</sup> The reactions at 110 °C were carried out in autoclave; all the reactions were carried out for 15 h.

<sup>b</sup> Transformation yield calculated by GC, no other products were formed and unreacted alcohols were recovered.

<sup>c</sup> Products distribution measured by GC.

The presence of allyl chloride, CO, Pd(OAc)<sub>2</sub>, and PPh<sub>3</sub> in THF afforded the butenyl-palladium-complex **1**, which, by reaction with the benzyl alcohol, gave mostly ester **4a** with a small amount of the tetrahydrofuranyl ether **5a** (entry 1, Table 1). In the absence of allyl chloride, the benzyl alcohol-THF mixture under CO pressure, with Pd(OAc)<sub>2</sub> and PPh<sub>3</sub>, did not afford any product (entry 2, Table 1). These preliminary results suggested the great importance of allyl chloride in the tetrahydrofuranylation reaction. Then, more reactions were performed using allyl chloride and benzyl alcohol in THF, but without Pd(OAc)<sub>2</sub> and/or PPh<sub>3</sub> and/or CO, with the aim of understanding a possible influence of the other reactants. Ether **5a** was obtained selectively in modest yields (entries 3–5, Table 1), excluding the Pd(II) and the Pd(0) as possible initiator of a supposed radical mechanism in these kind of reactions. Moreover, these results allowed us to deduce that the process did not need to be carried out under CO pressure. Thus, in order to find milder operating conditions, the reaction of allyl chloride and benzyl alcohol in THF was performed at reflux temperature, instead of 110 °C in autoclave (entry 6, Table 1). Ether **5a** was selectively obtained in a reasonable transformation yield of 60%, in the same reaction time, while a 40% of unreacted alcohol was recovered by chromatography. Finally, allyl chloride and benzyl alcohol in THF were reacted in autoclave under N<sub>2</sub> pressure, removing any O<sub>2</sub> traces. Ether **5a** was not observed (entry 7, Table 1); this result drove us to an important consideration: even in small amounts oxygen was necessary for the reaction to progress.

Therefore, all these results clearly highlight that the benzyl alcohol tetrahydrofuranylation is mostly dependent on the presence of the allyl chloride and on the O<sub>2</sub> traces.



**Scheme 3.** Proposed mechanism for tetrahydrofuranylation reaction of alcohol.

According to these results, obtained in the absence of any metal or peroxide catalyst, we suggest a radical mechanism initiated by the atmospheric oxygen, where the tetrahydrofuranyl radical is favored by slightly high temperature, and the allyl radical is a propagator of the radical chain (Scheme 3).

For better investigating this mechanism, we performed more experiments. Adding benzyl chloride (entry 2, Table 2), instead of allyl chloride (entry 1, Table 2), into benzyl alcohol and THF mixture at reflux temperature, compound **5a** was obtained in similar isolated yield (45%).

The presence of a primary halide such as the 1-Cl-hexane instead of the allyl or benzyl chloride did not afford any reaction product (entry 3, Table 2). Therefore, the allyl or benzyl chlorides are strategic for the reaction because of the easy formation and high stability of the corresponding radicals. The reaction performed with lower amount of allyl chloride gave ether **5a** in lower isolated yields (entry 4, Table 2). The same reaction carried out without allyl chloride produced **5a** in traces (entry 5, Table 2). The reaction performed with de-aerated THF did not give, in 15 h, any product (entry 6, Table 2). Thus, it is reasonable to conclude that the proposed mechanism needs oxygen as the initiator and the allyl chloride as the propagator of the radical chain (Scheme 3). These considerations were furthermore supported by more experiments:

**Table 2**  
Reaction of benzyl alcohol with RCl in THF at refluxing temperatures for 15 h

Entry	RCl	mmol	Yield <sup>a</sup> (%)
1	CH <sub>2</sub> =CHCH <sub>2</sub> -	(1.2)	57
2	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> -	(1.2)	45
3	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub> -	(1.2)	—
4	CH <sub>2</sub> =CHCH <sub>2</sub> -	(0.3)	5
5	—	—	Traces
6 <sup>b</sup>	CH <sub>2</sub> =CHCH <sub>2</sub> -	(1.2)	—
7 <sup>c</sup>	CH <sub>2</sub> =CHCH <sub>2</sub> -	(1.2)	—
8	CH <sub>2</sub> =CHCH <sub>2</sub> -	(3.0)	70

<sup>a</sup> Isolated yield.

<sup>b</sup> Reaction performed in de-aerated THF.

<sup>c</sup> Reaction carried out in the presence of 1.2 mmol of 2,2,6,6-tetramethyl-1-oxy-piperidine (TEMPO).

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