

## Heck arylations of pent-4-enoates or allylmalonate using a palladium/tetraphosphine catalyst

Mhamed Lemhadri <sup>a</sup>, Ahmed Battace <sup>a</sup>, Touriya Zair <sup>b</sup>, Henri Doucet <sup>c,\*</sup>, Maurice Santelli <sup>a,\*</sup>

<sup>a</sup> *Laboratoire de Synthèse Organique associé au CNRS, Faculté des Sciences de Saint Jérôme, Université d'Aix-Marseille, Avenue Escadrille Normandie-Niemen, 13397 Marseille, France*

<sup>b</sup> *Laboratoire de Chimie Organique Appliquée, Faculté des Sciences, Université Moulay Ismail, BP 4010, Beni M'hammed, 50000 Meknes, Morocco*

<sup>c</sup> *Institut Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes "Catalyse et Organometalliques", Campus de Beaulieu, 35042 Rennes, France*

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### Abstract

The Heck reaction of aryl halides with functionalised alk-1-enes should be a powerful method for the synthesis of functionalised (*E*)-1-aryllalk-1-ene derivatives. The major problem of this reaction is the palladium-catalysed migration of the carbon–carbon double bond along the alkyl chain when there are no substituents on the C3 carbon of the alk-1-enes. We observed that for the arylation of ethyl pent-4-enoate, ethyl 2-methylpent-4-enoate or dimethyl allylmalonate this migration could be partially or completely controlled using appropriate reaction conditions. The ramification on the alkyl chain and the substituents on the aryl halide have also an important influence on this migration. Moreover, the *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane/1/2[PdCl(C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>] system catalyses this reaction with a wide range of aryl bromides using very high ratio substrate/catalyst in good yields.

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### 1. Introduction

The palladium-catalysed Heck vinylation is one of the most powerful methods for the formation of C–C bonds. The reactivity of alkenes such as acrylates with aryl halides has been studied in detail [1]. On the other hand, despite the rich chemistry of the other ester-containing alk-1-enes, these palladium-catalysed Heck vinylations have attracted much less attention. Substrates such as pent-4-enoates have long been known to give mixtures of regio- and stereoisomers due to the palladium-catalysed migration of the carbon–carbon double bond of the alkene, which often rendered these catalytic reactions quite ineffective. A few

examples of vinylations using pen-4-enoates have been described [2–6]. In most cases, Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> was used as catalyst. For example, the reaction of 4-bromobenzonitrile with pent-4-enoic acid using 3 mol% of Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> with a substoichiometric amount of tetrabutylammonium chloride gave quite selectively (*E*)-5-(4-cyanophenyl)-pent-4-enoic acid in 54% yield [2]. The vinylation of 4-fluoroiodobenzene with pent-4-enoic acid and tetrabutylammonium chloride as additive affords a 1/1 mixture of 4-(*E*)-pent-1-enoic acid and 3-(*E*)-pent-1-enoic acid. This mixture could be partially purified by recrystallisation, but was preferably used directly for the next step of the synthesis [3]. The reaction of an iodoanisole with methyl pen-4-enoate using the expensive base Ag<sub>2</sub>CO<sub>3</sub> gave an inseparable mixture of (*Z*)- and (*E*)-5-arylpent-4-enoates and several other isomers [4]. Using ethyl pent-4-enoate and aryl bromide with Pd(OAc)<sub>2</sub>/P(*o*-tol)<sub>3</sub> as catalyst a mixture of 51% of (*E*)-5-arylpent-4-enoate, 14% of (*E*)-5-arylpent-3-enoate, 9% of (*E*)-5-arylpent-2-enoate and

\* Corresponding authors. Tel.: +33 02 23 23 62 80; fax: +33 02 23 23 69 39 (H. Doucet); tel.: +33 04 91 28 88 25; fax: +33 04 91 98 91 12 (M. Santelli).

E-mail addresses: [henri.doucet@univ-rennes1.fr](mailto:henri.doucet@univ-rennes1.fr) (H. Doucet), [m.santelli@univ-cezanne.fr](mailto:m.santelli@univ-cezanne.fr) (M. Santelli).

24% of (*E*)-4-aryl-pent-4-enoate was obtained [5]. Iodophthalonitrile and benzyl pent-4-enoate were reacted using 5 mol% of Pd(OAc)<sub>2</sub> and tetrabutylammonium bromide to give a mixture of isomers which was directly hydrogenated on Pd/C [6]. A few examples of arylations using hex-5-enoate, oct-7-enoate or undec-10-enoate have also been reported [7–9]. The reactivity of allylmalonate has also been described. Balme et al. reported the reaction of allylmalonate with iodobenzene using Pd(dba)<sub>2</sub> and dppe as catalyst to give (*Z*)- and (*E*)-3-phenylallylmalonates and the branched isomer as a mixture in a 1/1/1 ratio and in 65% yield [10]. The use of 2-(hex-5-enyl)malonate gave (*E*)-2-(6-phenylhex-5-enyl)malonic acid dimethyl ester with a higher selectivity and a yield of 60% [8]. Finally, the reaction also proceeds with Pd(OAc)<sub>2</sub> without added ligand. Iodobenzene reacted with allylmalonate using N(*n*-Bu)<sub>3</sub> as base and 2 mol% Pd(OAc)<sub>2</sub> gave 90% of 3-phenylprop-2-en-1-yl propanedioate [11]. If monophosphine ligands have been successfully used for the reaction with pent-4-enoate or allylmalonate derivatives, to the best of our knowledge, the efficiency of polydentate ligands has not been demonstrated. Moreover, an effective and more regio- and stereoselective method for the arylation of these alkenes employing lower amounts of catalyst especially in the presence of aryl bromides is still subject to very significant improvements.

The nature of the phosphine ligand on complexes has an important influence on the stability of the catalysts, on the reaction rates, and also on the regio- and stereoselectivities of the reactions. In order to find more stable and more efficient palladium catalysts, we have prepared the tetrapodal phosphine ligand, *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl) cyclopentane or Tedicyp (Fig. 1) [12] in which the four diphenylphosphinoalkyl groups are stereospecifically bound to the same face of the cyclopentane ring. We have reported that the complex formed by association of Tedicyp with [PdCl(C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>] is an extremely efficient catalyst for allylic substitution [12], for the Suzuki cross-coupling, for the Sonogashira alkynylation [13], for Negishi reaction [14], and also for Heck vinylation [15]. Here, we wish to describe the results obtained with the functionalised alkenes: ethyl pent-4-enoate, ethyl 2-methyl-

pentenoate or dimethylallylmalonate with a variety of aryl halides using Tedicyp as ligand.

## 2. Experimental

### 2.1. General

All reactions under argon were run using vacuum lines in Schlenk tubes in oven-dried glassware. DMAc (99%) and DMF (99%) were not distilled before use. Some of the aryl halides were distilled before use. The reactions were followed by GC and NMR. <sup>1</sup>H (300 MHz) and <sup>13</sup>C (75 MHz) spectra were recorded in CDCl<sub>3</sub> solutions. Chemical shift (δ) are reported in ppm relative to CDCl<sub>3</sub>. Flash chromatography were performed on silica gel (230–400 mesh) eluting with ether/pentane mixtures.

### 2.2. Preparation of the Pd–Tedicyp catalyst [12]

An over-dried 40-mL Schlenk tube equipped with a magnetic stirring bar, under argon atmosphere, was charged with [Pd(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (4.2 mg, 11.6 μmol) and Tedicyp (20 mg, 23.2 μmol). 2.5 mL of anhydrous DMF were added, then the solution was stirred at room temperature for 10 min.

### 2.3. Catalytic procedure for Heck reactions

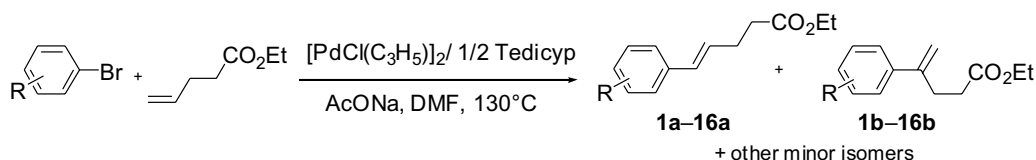
As a typical experiment, the reaction of aryl halide (1 mmol), alkene (2 mmol) and AcONa, NaHCO<sub>3</sub> or KF (2 mmol, see tables) at 130 °C during 20 h in DMF or DMAc (3 mL, see tables) in the presence of *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane/1/2[PdCl(C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>] complex under argon affords the products after addition of water, extraction with ether or dichloromethane, separation, drying (MgSO<sub>4</sub>), evaporation and chromatography on silica gel.

### 2.4. Vinylation products with ethyl pent-4-enoate (Table 1)

5-(4-Acetylphenyl)-pent-4-enoic acid ethyl ester (**1a**) (Table 1, entry 1), 4-bromoacetophenone (0.199 g, 1 mmol), Pd complex (1 μmol) and ethyl pent-4-enoate (0.256 g, 2 mmol). The residue was purified by column chromatography to give **1a** in 84% (0.207 g) isolated yield. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.86 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 6.44 (d, *J* = 15.8 Hz, 1H), 6.32 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 2.55 (s, 3H), 2.49 (m, 4H), 1.23 (t, *J* = 6.9 Hz, 3H). <sup>13</sup>C NMR



Fig. 1. Tedicyp ligand.



Scheme 1.

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