# Dehydrogenative Heck Reaction (Fujiwara–Moritani Reaction) of Unactivated Olefins with Simple Dihydropyrans under Aprotic Conditions

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**Abstract:** The dehydrogenative Heck coupling (Fujiwara–Moritani reaction) of unactivated olefins with 3,4-dihydro-2*H*-pyrans is described. The two main highlights of the work are the use of unconventional unactivated olefins as coupling partners in the palladium-catalyzed reaction and the use of aprotic conditions for the coupling reaction of the acid-labile dihydropyrans.

**Keywords:** alkenylation; C–H activation; dehydrogenative Heck reaction; dihydropyrans; Fujiwara– Moritani reaction

The palladium-catalyzed Fujiwara–Moritani reaction<sup>[1]</sup> or the dehydrogenative Heck reaction (DHR) has become one of the most popular transformations falling under the class of modern C–H functionalization reactions.<sup>[2,3]</sup> Several excellent reviews have covered the recent advances in this C–C bond forming reaction.<sup>[4]</sup> Not limited to just arenes or heteroarenes, in



Scheme 1. The Fujiwara-Moritani reaction.

Adv. Synth. Catal. 0000, 000, 0-0

the recent times, there have been reports of heteroatom-guided C-palladation either on non-aromatic heterocycles or heteroatom-substituted alkenes.<sup>[5–7]</sup> This process is followed by the standard carbopalladation with an olefin substrate and  $\beta$ -hydride elimination, resulting in overall alkenylation (Scheme 1).

Unactivated olefins are often quite unwilling coupling partners under the usual dehydrogenative Heck reaction conditions. Barring a few reports, most of the olefin substrates used for such reactions are activated ones  $(\alpha,\beta$ -unsaturated or styrene analogues)<sup>[6]</sup> and are often used in conjunction with standard protic conditions for C-H functionalization or with Lewis acidic salts. The reason is obvious, if the electronic nature of both coupling partners is the same, then the dehydrogenative coupling often results in reduced reactivity and more of homo-coupled products than cross-coupled ones. However, using activated olefins not only limits the scope of the reaction but also often hampers the synthetic utility by having an unwanted functionality in the reactant. It is therefore necessary to come up with efficient catalyst systems capable of effecting cross-couplings of olefins of similar electronic natures.

Functionalized pyrans and, in particular, dihydropyrans are ubiquitous building blocks in several natural products, including polyether compounds possessing important biological activities (Figure 1).<sup>[8]</sup> They are also important intermediates in several natural product syntheses.<sup>[9]</sup> Although several methods for the synthesis of 2-substituted pyrans are available, not many methods are available for the functionalization of the 3-position of pyrans.

Recently, Liu and co-workers reported a palladiumcatalyzed method for the alkenylation of glycals with activated alkenes.<sup>[5i]</sup> This method works very well with glycals, which are fairly stable molecules and activat-

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 $R^1$ 



Figure 1. Natural occurrence of the dihydropyran moiety.

ed olefins as coupling partners. To the best of our knowledge, there seems to be no literature report on the dehydrogenative Heck coupling of simple dihydropyrans and unactivated alkenes. We report herein a general method for the alkenylation of labile dihydropyrans with unactivated olefins under aprotic dehydrogenative Heck conditions. The reaction is fairly general and results in moderate yields with both unactivated as well as activated alkenes. Our efforts began with using simple 3,4-dihydro-2*H*-pyran, scanning several of the catalyst systems reported in the literature, which resulted in a mixed bag of results (Table 1).<sup>[10,11]</sup>

ĺ		Pd(II) (cat.), oxidant, additive/co-oxidant			
$\begin{array}{c c} R & & \\ \hline \\ \hline$					
Entry	Olefin	Conditions	Yield <sup>[a]</sup>		
1	styrene ( <b>2a</b> )	Pd(OAc) <sub>2</sub> (10 mol%)/Cu(OAc) <sub>2</sub> (2 equiv.)/THF/65 °C	25%		
2	styrene	Pd(OAc) <sub>2</sub> (10 mol%)/Cu(OAc) <sub>2</sub> (2 equiv.)/THF/65 °C	20%		
3	O_Ph	Pd(OAc) <sub>2</sub> (10 mol%)/Cu(OTf) <sub>2</sub> (1 equiv.) DMA-AcOH/O <sub>2</sub> / 70 °C	messy		
4	styrene	Pd(OAc) <sub>2</sub> (10 mol%)/Cu(OTf) <sub>2</sub> (1 equiv.) DMA-AcOH/O <sub>2</sub> / 70 °C	messy		
5	styrene	Pd(OAc) <sub>2</sub> (5 mol%)/AgOAc (2 equiv.) Cu(OAc) <sub>2</sub> (1 equiv.)/ THF/65 $^\circ\text{C}$	60%		
6	styrene	Pd(OAc) <sub>2</sub> (5 mol%)/AgOAc (2 equiv.) O <sub>2</sub> balloon/THF/65 $^\circ\text{C}$	40%		
7	styrene	Pd(OAc) <sub>2</sub> (5 mol%)/AgOAc (2 equiv.) Cu(OAc) <sub>2</sub> (1 equiv.), O <sub>2</sub> balloon/THF/65 °C	38%		
8	styrene	Pd(OAc) <sub>2</sub> (5 mol%)/AgOAc (2 equiv.) Cu(OAc) <sub>2</sub> (1 equiv.), air (1 atm)/THF/65 °C	42%		
9	styrene	Pd(OAc)_2 (5 mol%)/AgOAc (2 equiv.) BQ (1 equiv.)/THF/65 $^\circ\text{C}$	30%		
10	styrene	Pd(O <sub>2</sub> CCF <sub>3</sub> ) <sub>2</sub> (5 mol%)/AgOAc (2 equiv.)/THF/65 °C	20%		
11	styrene	PdCl <sub>2</sub> (MeCN) <sub>2</sub> (5 mol%)/AgOAc (2 equiv.)/THF/r.t.	35%		
12	styrene	[RuCl <sub>2</sub> ( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3 mol%)/Cu(OAc) <sub>2</sub> (1 equiv.)/THF/r.t.	NR <sup>[b]</sup>		
13	O_Ph	Pd(OAc) <sub>2</sub> (5 mol%)/AgOAc (2 equiv.) 1,10-phenanthroline (10 mol%)/THF/65 °C	NR		
14	O Bn O 2c	Pd(OAc) <sub>2</sub> (10 mol%)/Ag <sub>2</sub> CO <sub>3</sub> (3 equiv.) Cu(OAc) <sub>2</sub> (3 equiv.)/PivOH/100 °C	80%		
15	O Ph 2b	Pd(OAc) <sub>2</sub> (10 mol%)/Ag <sub>2</sub> CO <sub>3</sub> (3 equiv.) Cu(OAc) <sub>2</sub> (3 equiv.)/PivOH/100 °C	messy		
16	styrene	Pd(OAc) <sub>2</sub> (10 mol%)/Ag <sub>2</sub> CO <sub>3</sub> (3 equiv.) Cu(OAc) <sub>2</sub> (3 equiv.)/PivOH/100 °C	messy		

Table 1. Efforts in screening various catalyst systems.

<sup>[a]</sup> All yields are isolated yields.

<sup>[b]</sup> NR = no reaction.

2

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Table 2. Substrate scope with unactivated olefins.

<sup>[b]</sup> NR = no reaction.

Many of the catalyst systems indeed did result in alkenylation products with activated olefins but fared very poorly in the case of unactivated ones. Notable was the catalyst system using protic media (entries 14, 15 and 16, Table 1) which resulted in a very good isolated yield for benzyl acrylate but failed with O-allylphenol and styrene. To our delight, the best yields and cleanest reactions were obtained with Pd(OAc)<sub>2</sub>, using Cu(OAc)<sub>2</sub>/AgOAc as the oxidant combination in THF. Various combinations of the relative stoichiometries were attempted to improve the yield and minimize side-reactions. Copper and silver salts as terminal oxidants have been used by several research groups in the past, either individually or together. DeBoef and others have also suggested that, in some cases, the regioselectivity is oxidant controlled and is a consequence of the formation of polymetallic catalytically active clusters.<sup>[12]</sup> For this reason, several combinations of copper and silver salts as oxidants were tried, either individually or together, to check any effect on regioselectivity.<sup>[13]</sup> In the cases where the reaction worked, we obtained only the C-3 C–H functionalization product, the C-2 regioisomers were not obtained.

The substrate scope of the reaction with unactivated olefins is depicted in Table 2. In all cases, only the *E*-isomer was selectively obtained and the C–H functionalization was also highly regioselective. As expected, small amounts of self-coupling of the dihydropyran were observed in all reactions and the amount varied based upon the reactivity of the coupling partner (unactivated olefin) used. In some cases, upto 20% of homo-coupled olefin was also observed. In cases where there were multiple options for  $\beta$ -hydride elimination, the reaction expectedly afforded isomeric mixtures (Table 2).<sup>[14]</sup> In some cases coupling products

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3

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<sup>&</sup>lt;sup>[a]</sup> All yields are isolated yields.





<sup>[a]</sup> All yields are isolated yields.

arising out of regioisomeric carbopalladation (migratory insertion) were also observed (**3a**, **3gb**, Table 2). These could also arise *via* C–H activation of the olefin instead of the dihydropyran. The overall conversions in most cases were good (as indicated by GC-MS) but some products had low isolated yields due to problems in purification (**3h**, **3j**, Table 2).

The reaction worked decently well with terminal olefins but fared poorly with internal and 1,1'-disubstituted olefins (3m, Table 2). The reasons for this are not quite understood but in these cases it could be due to reduced reactivity more on account of both electronic and steric reasons. With electron-rich olefins, the reactions resulted in several side-products (3I, Table 2). In order to test the generality of the catalyst system, the reaction was attempted on activated olefins and gratifyingly found to be compatible to these systems too. Depicted in Table 3 is the scope of the reaction with electron-deficient olefins. Here too, 1,1'-disubstituted olefins did not result in the desired products (3q, Table 3), most probably due to steric reasons in this instance.

The reaction follows the plausible pathway for heteroatom-guided regioselective C–H functionalization (Scheme 2), starting with electrophilic palladation at the most nucleophilic position (C-3), followed by olefin coordination and carbopalladation.<sup>[4d]</sup> Subsequent  $\beta$ -hydride elimination leads to the coupled product. The oxidant system acts as a base as well as an oxidant to regenerate the Pd(II) species. Since the C-3 palladated species is not very stable, moderate yields are obtained with unactivated olefins.<sup>[5d]</sup>

In summary, we have developed a new catalyst system for the dehydrogenative alkenylation of labile dihydropyrans under aprotic conditions which results in moderate yields with unactivated olefins and good yields with activated olefins. This system works well where other catalyst combinations utilizing protic methods fail to afford the desired results. The reaction has a good substrate scope with a few exceptions. The additional advantage of using unactivated olefins is that various synthetically useful transformations like carbonyl insertions are also feasible, which enhances the scope and utility of the methodology. The resulting electron-rich dienes are potential partners in Diels–Alder cycloadditions,<sup>[15]</sup> which can give rise to interesting molecular frameworks and thereby are proposed as potential building blocks in many polyether-type natural products containing the pyran skeleton.

#### **Experimental Section**

#### General Procedure for Dehydrogenative Heck Coupling of Dihydropyrans with Alkenes

In a pressure tube equipped with a stir bar, the 3, 4-dihydro-2*H*-pyran (1.19 mmol) and olefin (2.38 mmol) in 3.5 mL dry THF were charged. Then  $Pd(OAc)_2$  (0.059 mmol), AgOAc (2.38 mmol), and  $Cu(OAc)_2$  (1.19 mmol) were added under an argon flow. The tube was fitted with Teflon screw cap and the reaction mixture was heated at 65 °C for 24 h. Upon cooling to room temperature, the reaction mixture was diluted with about 10 mL of diethyl ether or dichloromethane and the slurry was filtered through a pad of Celite; the filtrate was concentrated under reduced pressure. The crude product was purified by a basic alumina column chromatography (eluent: Petroleum ether:EtOAc).

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<sup>&</sup>lt;sup>[b]</sup> By GC-MS, product not isolated.



Scheme 2. Plausible reaction mechanism.

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5

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Dehydrogenative Heck Reaction (Fujiwara–Moritani Reaction) of Unactivated Olefins with Simple Dihydropyrans under Aprotic Conditions <i>Adv. Synth. Catal.</i> <b>2013</b> , <i>355</i> , 1–7	R <sup>1</sup> Pd(OAc) <sub>2</sub> (cat), Cu(OAc) <sub>2</sub> (1 equiv.) AgOAc (2 equiv.), THF, 65 °C, 24 h	7 R 0 R <sup>1</sup>
Govind Goroba Pawar, Gaurav Singh, Virendra Kumar Tiwari, Manmohan Kapur*	R = H, mesityl R <sup>1</sup> = alkyl, aryl	(14 examples, 30–64% yield)

7