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Controlling reactivity in the Fujiwara–Moritani reaction: Examining solvent effects and the addition of 1,3-dicarbonyl ligands on the oxidative coupling of electron rich arenes and acrylates

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ABSTRACT

A palladium-catalysed direct alkenation of electron rich arenes in the presence of $K_2S_2O_8$ with an acetic acid/1,4-dioxane solvent combination has been developed. The 1,4-dioxane co-solvent dramatically influences the rate of reaction, giving selectively disubstituted alkenes, while the addition of acetylacetone ligands was shown to increase site selectivity for the alkenation of monofunctionalized arenes. The participation of these carbonyl ligands has been confirmed by ESI-MS studies, with some key *in situ* intermediates in the catalytic cycle identified. A variety of electron rich arenes and olefinic substrates can be utilised in the direct oxidative coupling to give disubstituted alkenes in moderate to good yields.

In the case of alkene derivatization, the Fujiwara–Moritani (F-M), or dehydrogenative Heck reaction, has become a popular transformation in the modern class of C—H functionalization reactions [1]. First developed by Fujiwara and co-workers, this methodology showed both olefinic and aromatic bonds could be activated in acetic acid with a stoichiometric, and later, catalytic amount of palladium to give alkenylated aromatic compounds [2]. Although extensively explored for the conversion of monosubstituted alkenes, such as acrylates into disubstituted products [3], little study has been conducted on developing a general methodology for controlling "over reactivity". A typical reaction outcome observed in systems where both olefin and arene are electron rich. In this case, yields of the desired disubstituted products are reduced by the formation of trisubstituted alkenes; a competitive process typically controlled by reaction time, increased arene concentration, or directing groups [3b,3e,3–4].

Of late, our research focus has been the development of novel strategies for the synthesis of tri- and tetrasubstituted alkenes [5]. More recently we have developed a general and efficient F-M protocol for the direct arene-1,2-disubstituted alkene couplings to generate trisubstituted alkenes [6]. In this study the reaction solvent mixture (AcOH/MeCN) and the use of a relatively insoluble inorganic oxidant ($K_2S_2O_8$) were key to achieving positive reaction outcomes. In this report we have built upon our earlier findings and describe our effort toward a general set of reaction conditions, for the direct arylation of electron rich monosubstituted alkenes using a Pd-catalysed oxidative coupling approach.

It was considered that the problem of "over reactivity", so typically observed in the formation of electron rich disubstituted alkenes, could be controlled by the appropriate choice of solvent system. Computational studies of C—H activation reactions have shown that solvent molecules coordinating the active metal center can lower the energetics of key intermediates, control the speed of product release and directly affect the yield [7]. In our previous research [6] we demonstrated a dramatic accelerating or decelerating effect in the synthesis of trisubstituted alkenes with the addition of a co-solvent; MeCN or 1,4-dioxane. ESI-MS of *in situ* intermediates identified several key organopalladium species expected for a F-M catalytic cycle containing MeCN solvent molecules. With this in mind, our optimization strategy was to use previously developed conditions for the synthesis of tri-substituted alkenes; $Pd(OAc)_2$ as a palladium source, $K_2S_2O_8$ as an inexpensive and relatively insoluble inorganic oxidant and AcOH/MeCN (4:1) as a solvent system at 80 °C.

The coupling of ethylacrylate **1a** and 1,4-dimethoxybenzene **2a** were tested in a preliminary reaction utilizing 5 mol% of $Pd(OAc)_2$ and a 7.5-fold excess of arene in AcOH/MeCN (4:1) for 24 h at 80 °C (Table 1, entry 1) [8]. To our surprise, the sole reaction product was the undesired trisubstituted alkene **4a**, in 78% yield. In order to limit the unwanted 2nd arene addition, the reaction time was shortened to 1.5 h [9] giving the desired product **3a** in 37% yield (entry 2). Variation of the arene under these reaction conditions

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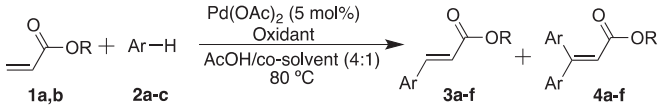
Table 1
Optimization of the reaction conditions.[a]



Entry	1	2	Co-solvent	R	Ar	Oxidant	Time (h)	3	Yield(%)[b]	4	Yield (%)[b]
1	**a**	**a**	MeCN	Et	1,4-$(MeO)_2C_6H_3$	$K_2S_2O_8$	24	**a**	–	**a**	78
2	**a**	**a**	MeCN	Et	1,4-$(MeO)_2C_6H_3$	$K_2S_2O_8$	1.5[d]	**a**	37	**a**	–
3	**a**	**b**	MeCN	Et	$MeOC_6H_4$	$K_2S_2O_8$	1.5[d]	**b**	43[c]	**b**	–
4	**a**	**c**	MeCN	Et	Ph	$K_2S_2O_8$	1.5[d]	**c**	21	**c**	–
5	**b**	**a**	MeCN	Bu	1,4-$(MeO)_2C_6H_3$	$K_2S_2O_8$	24	**d**	–	**d**	74
6	**b**	**a**	MeCN	Bu	1,4-$(MeO)_2C_6H_3$	$K_2S_2O_8$	3[d]	**d**	44	**d**	–
7	**b**	**b**	MeCN	Bu	$MeOC_6H_4$	$K_2S_2O_8$	3[d]	**e**	52[c]	**e**	–
8	**b**	**c**	MeCN	Bu	Ph	$K_2S_2O_8$	3[d]	**f**	32	**f**	–
9	**b**	**a**	1,4-Dioxane	Bu	1,4-$(MeO)_2C_6H_3$	$K_2S_2O_8$	24	**d**	71	**d**	–
10	**b**	**b**	1,4-Dioxane	Bu	$MeOC_6H_4$	$K_2S_2O_8$	24	**e**	63[c]	**e**	–
11	**b**	**c**	1,4-Dioxane	Bu	Ph	$K_2S_2O_8$	24	**f**	48	**f**	–
12	**b**	**a**	1,4-Dioxane	Bu	1,4-$(MeO)_2C_6H_3$	$(Bu_4N)_2S_2O_8$	24	**d**	<5	**d**	–
13	**b**	**a**	1,4-Dioxane	Bu	1,4-$(MeO)_2C_6H_3$	$(NH_2)_2S_2O_8$	24	**d**	<5	**d**	–

[a] Reagents and conditions: 2 mmol of alkene, 15 mmol of arene, 5 mol% $Pd(OAc)_2$, 4 mmol $K_2S_2O_8$, AcOH/co-solvent (4:1).
[b] Isolated yield after chromatography.
[c] Product isolated as a series of isomers, *o*:*m*:*p*.
[d] Longest possible reaction time before detection of the undesired trisubstituted alkene (as determined by GC) [9].

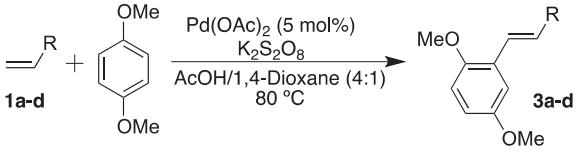
gave yields of 43% for **3b** and 21% for **3c** using anisole and benzene, respectively (entries 3, 4).

In order to minimize suspected alkene polymerization and increase the product yield, the more stable butylacrylate was trialled as a suitable alkene substrate. At 24 h (entry 5) the sole product, **4d** was isolated in 74% yield, comparable to that of **4a**. Shortened reaction times [9] gave the disubstituted alkenes **3d**, **3e** and **3f** in 44%, 52% and 32% yields, respectively (entries 6–8). The addition of 1,4-dioxane has previously been shown to dramatically slow the rate of alkene conversion and minimize palladium mediated alkene polymerization [6]. Computational studies of solvent effects in C—H activation reactions support this and show that dioxane can have a direct influence on reaction outcomes; by coordinating to the Pd metal center when required and helping the product separation from the Pd ligand field [7d]. In our case, use of 1,4-dioxane as a co-solvent (entries 9–11), indeed slowed the rate of alkene conversion and polymerization giving a 71% yield for **3d** with no diarylated product detected in 24 h. It was observed in successive experiments with anisole and benzene, comparable yields of the desired alkenes **3e** and **3f** could be achieved (63% and 48% respectively; entries 10 and 11), with no trisubstituted products detected. When the organic soluble oxidant variants tetrabutylammonium persulfate $(Bu_4N)_2S_2O_8$ and ammonium persulfate $(NH_4)_2S_2O_8$ were utilized (entries 12 and 13), the alkene was consumed but little to no coupling products were detected. This can be attributed to the competing oxidation of the starting material by the strong highly soluble oxidants.

Next, using 1,4-dimethoxybenzene as an electron rich arene, the four alkenes ethylacrylate, butylacrylate, phenylvinyl sulfone and acrylic acid (Table 2, entries 1–4), were examined for their ability to undergo F-M coupling under our developed conditions. In each case the reaction was successful, with disubstituted alkenes (**3a**, **d**, **g** and **h**) isolated in good to moderate yields of 65%, 71%, 61% and 51%, respectively. As expected, butylacrylate **1b** was the most reactive of the alkenes and acrylic acid **1d** the least. In all cases no doubly substituted product was observed in the 24 h reaction period.

It was hoped that our reaction conditions would be suitable for the introduction of 1,3-dicarbonyl compounds as ligands. Known for their use in Cu-catalyzed processes [10] and as metal stabilization reagents [11], they have had limited application in Pd-catalyzed transformations [12] and may act as alternatives for the typical pyridine [3b,3i,13] or amino acid based ligands [14] used in the F-M reaction. The reaction of butylacrylate **1b** and anisole **2d** in the developed conditions gave the coupling product **3e** in 63% yield with a *ortho*:*meta*:*para* ratio of 40:0:60 (Table 3, entry 1) using $Pd(OAc)_2$ as a catalyst.

Table 2
Alkene coupling with 1,4-dimethoxybenzene.[a]



Entry	1	Alkene (R)	Time (h)	3	Yield (%)[b]
1	**a**	C(=O)OEt	24	**a**	65
2	**b**	C(=O)OBu	24	**d**	71
3	**c**	SO_2Ph	24	**g**	61
4	**d**	C(=O)OH	24	**h**	51

[a] Reagents and conditions: 2 mmol of alkene, 15 mmol of **2a**, 5 mol% $Pd(OAc)_2$, 4 mmol $K_2S_2O_8$ AcOH/1,4-dioxane (4:1).
[b] Isolated yield after chromatography.

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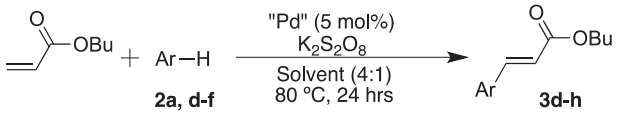
Table 3
Coupling of various acrylates and electron rich arenes using different catalysts and solvents to control the regioselectivity.[a]



2a, d-f **3d-h**

Entry	Solvent	Catalyst	2	Ar	Additive[b]	Selectivity[c]	Time (h)	3	Yield (%)[d]
1	AcOH/1,4-dioxane	$Pd(OAc)_2$	**d**	$MeOC_6H_4$	–	40, –, 60	24	**e**	63
2	AcOH/1,4-dioxane	$Pd(OAc)_2$	**d**	$MeOC_6H_4$	acac	19, 13, 68	24	**e**	55
3	AcOH/1,4-dioxane	$Pd(OAc)_2$	**d**	$MeOC_6H_4$	hfacac	50, –, 50	24	**e**	53
4	AcOH/1,4-dioxane	$Pd(OAc)_2$	**d**	$MeOC_6H_4$	^{t}Buacac	15, 22, 63	24	**e**	51
5	AcOH/1,4-dioxane	$Pd(acac)_2$	**d**	$MeOC_6H_4$	–	20, 12, 68	24	**e**	60
6	AcOH	$Pd(acac)_2$	**d**	$MeOC_6H_4$	–	19, 10, 71	24	**e**	33
7	AcOH/MeCN	$Pd(acac)_2$	**d**	$MeOC_6H_4$	–	44, –, 56	3	**e**	56[e]
8	AcOH/1,4-dioxane	$Pd(acac)_2$	**d**	$MeOC_6H_4$	120 °C	24, 21, 55	24	**e**	68
9	AcOH/1,4-dioxane	$Pd(acac)_2$	**d**	$MeOC_6H_4$	NaOAc	–	24	**e**	<5
10	AcOH	$Pd(OAc)_2$	**e**	$1,2\text{-}(MeO)_2C_6H_3$	–	14, 86	24	**i**	19
11	AcOH/MeCN	$Pd(OAc)_2$	**e**	$1,2\text{-}(MeO)_2C_6H_3$	–	10, 90	3	**i**	45[e]
12	AcOH/1,4-dioxane	$Pd(OAc)_2$	**e**	$1,2\text{-}(MeO)_2C_6H_3$	–	12, 88	24	**i**	50
13	AcOH/1,4-dioxane	$Pd(acac)_2$	**e**	$1,2\text{-}(MeO)_2C_6H_3$	–	5, 95	24	**i**	65
14	AcOH/1,4-dioxane	$Pd(acac)_2$	**f**	$1,3\text{-}(MeO)_2C_6H_3$	–	–	24	**j**	41

[a] Reagents and conditions: 2 mmol of alkene, 15 mmol of arene, 5 mol% $Pd(OAc)_2$, 4 mmol $K_2S_2O_8$, AcOH/co-solvent (4:1).
[b] 25 mol% of ligand were added per Pd. For entry 9, 10 mol% of NaOAc was added.
[c] *o:m:p* selectivity ratio determined from crude ^{1}H NMR and GC.
[d] Isolated yield after chromatography.
[e] Reaction time was shortened to 3 h, to eliminate the formation of trisubstituted alkene (as determined by GC) [9].

When the 1,3-dicarbonyl compounds, acetylacetone (acac), hexafluoroacetylacetone (hfacac) and 2,2,6,6-tetramethyl-3,5-heptanedione (^{t}Buacac) were utilized as ligands (entries 2–4) a shift in product selectivity was detected. In the case of acac and ^{t}Buacac a decrease in *ortho* and an increase in *meta* product formation was observed with comparable yields (55% and 51%, respectively). In the case of hfacac (entry 3), a 50:50 mix of *ortho*:*para* isomers in addition to palladium mirror formation (indicating catalyst degradation, not previously detected) was observed. When the preformed catalyst $Pd(acac)_2$ was added to the reaction (entry 5) a comparable yield and product selectivity was observed for **3e** indicating that the ligand coordinates to the Pd center and remains present throughout the reaction time period of 24 h. If the alternative solvent systems of AcOH and AcOH/MeCN are used with Pd $(acac)_2$ (entries 6, 7) a comparable selectivity is achieved with AcOH (with a lower yield for **3e**, 33%) but for the AcOH/MeCN solvent system a switch in selectivity of 44:56, *ortho*:*para* is detected. This indicates MeCN is a stronger ligand than acac and can outcompete when used as a solvent. If the reaction temperature is increased (entry 8), a slight increase in yield and formation of the *meta* isomer is achieved for **3e** when compared to entry 5. If NaOAc is added to increase the rate of product release from the Pd centre [15], little to no product is formed with large amounts of acrylate decomposition products detected (entry 9). In order to show that this shift in product regioselectivity was possible for another electron rich arene, the coupling of butylacrylate **1b** and 1,2-dimethoxybezene **2e** was examined (entries 10–13). In AcOH, $Pd(OAc)_2$ gave product **3i** in a very low yield of 19% with a regioselectivity of 14:86 *ortho*:*para* (entry 10). Using MeCN as a co-solvent with $Pd(OAc)_2$ (entry 11) **3i** was formed in 44% yield with an *ortho*:*para* selectivity of 10:90. Exchanging 1,4-dioxane for MeCN (entry 12) results in a comparable yield and selectivity of **3 g**. If $Pd(acac)_2$ is utilized as the catalyst (entry 13) a higher yield of **3i** can be obtained and a shift in isomer formation to 5:95 is detected giving the expected shift to the favoured *para* isomer as observed for anisole. In the case of **1b** and 1,3-dimethoxybenzene **2f** (entry 14) the desired compound **3j** was formed as one isomer in low yield (41%).

Electrospray ionization mass spectrometry (ESI-MS), is an invaluable tool for the detection of short-lived species during catalytic processes [16]. To elucidate the role of acac as a ligand under our reaction conditions, butylacrylate **1b** and 1,4-dimethoxybenzene **2a** were used as substrates and the reaction was monitored by MS. ESI(+)-MS analysis was carried out on two key reagent compositions: (i) $Pd(acac)_2$ in AcOH/1,4-dioxane and (ii) $Pd(acac)_2$ in AcOH/1,4-dioxane with **1b**, **2a** and $K_2S_2O_8$ under the standard reaction conditions. In each case the MS analysis showed intermediates consistent with acac having an active role in the F-M catalytic cycle (ESI, Figs. 1, 2).

Analysis of the composition (i) showed two main Pd isotopic clusters centered at *m*/*z* 327.2 and 632.8. The most abundant cluster centered at *m*/*z* 327.2 is consistent with a sodium adduct of acac bound monomeric palladium species $[Pd(acac)_2 + Na]^+$, while the mass at 632.8 being that of the palladium dimer, $[Pd_2(acac)_4 + Na]^+$. This gives evidence of the predominance of monomeric Pd $(acac)_2$ in the AcOH/1,4-dioxane solvent mixture unlike $Pd(OAc)_2$ which tends to exist as a trimer in acidic solvent mixtures without the presence of strongly coordinating solvent such as MeCN [6,17].

With a key monomeric palladium species identified, the MS analysis of mixture (ii) (generated following the addition of 1,4-dimethoxybenzene (**2a**) butyl acrylate (**1b**) and $K_2S_2O_8$ to a solution of AcOH/1,4-dioxane and subsequent heating at 80 °C for 1 h), gave rise to a series of identifiable species consistent with the C—H insertion step of the F-M reaction (Fig. 1). The most abundant new cluster was observed at *m*/*z* 342.9 and is consistent with **2a** C—H inserted into the Pd species $[Pd(acac)(C_8H_9O_2)]^+$ (Fig. 1(b)). Two more clusters of interest are observed at *m*/*z* 469.4 and 508.6. Provisionally, they can be attributed to the palladium/product complex, $[Pd(acac)(C_{15}H_{19}O_4)]^+$ (Fig. 1(a)) and the dimeric arene coupled dimer containing an acetic acid molecule, $[Pd_2(OAc)(acac)(C_8H_9O_2)]^+$. Overall this study confirms that when utilized, acac, not 1,4-dioxane, is acting as a ligand in our F-M reaction conditions.

In conclusion, we have developed an efficient protocol for the direct electron rich arylation of acrylates to generate electron rich disubstituted alkenes. The use of AcOH/1,4-dioxane and the

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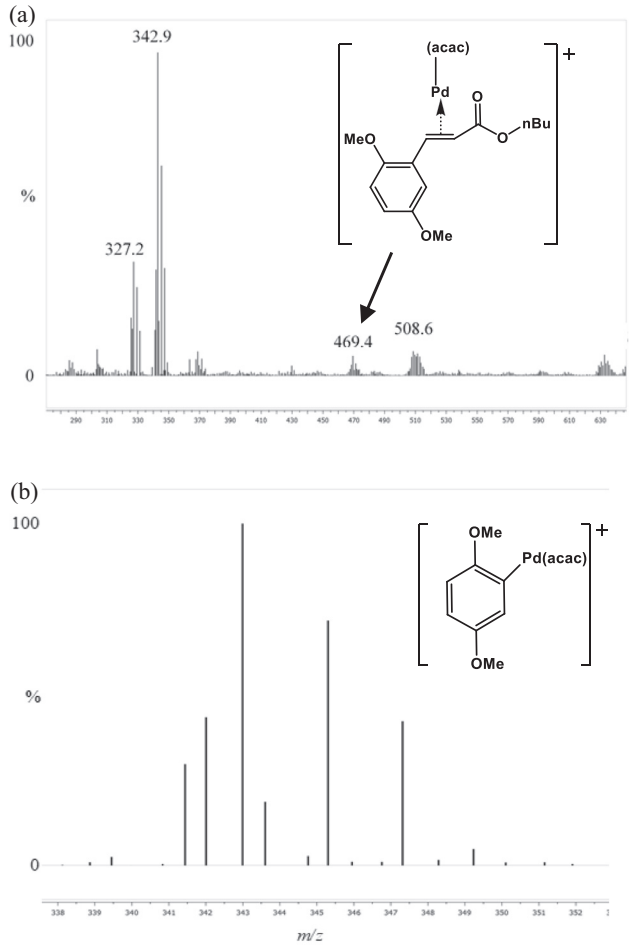

Fig. 1. (a) ESI(+)-MS of $Pd(acac)_2$, 1,4-dimethoxybenzene, butylacrylate and $K_2S_2O_8$, in AcOH/1,4-dioxane (4:1) after heating at 80 °C for 1 h. (a) MS in the range 250–640 *m*/*z*. Possible structural identity of peak 469.4 shown (inset). (b) Expansion of most abundant Pd cluster at *m*/*z* 342.9.

inorganic oxidant $K_2S_2O_8$ was key for achieving positive reaction outcomes, with 1,4-dioxane playing a significant role in decelerating the reaction to avoid undesired "over reactivity" to form trisubstituted alkenes. Acetylacetone has been shown to act as a new class of ligand in the F-M reaction of anisole and butylacrylate, altering the product selectivity to favour *meta* and *para* product formation. ESI-MS of *in situ* reaction intermediates helps confirm the role of acac and identifies several key reaction intermediates expected in an F-M catalytic cycle. Investigation of the application of 1,3-dicarbonyl compounds as ligands in the F-M reaction is ongoing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151471.

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specified). The reaction solution was then filtered, the solvent removed *in vacuo*, and the residue purified by column chromatography on silica gel.

[9] Reaction time was determined by GC reaction monitoring. During these studies, it was observed that the trisubstituted product would begin to form before full consumption of the acylate starting material (**1a** or **1b**); i.e. trisubstituted alkene formation would act as a competing process to the formation of the desired disubstituted alkene. Consequently, the reaction was stopped before any trisubstituted alkene was observed (i.e. double addition of the arene to the alkene).

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