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Selective arene functionalization through sequential oxidative and non-oxidative Heck reactions†

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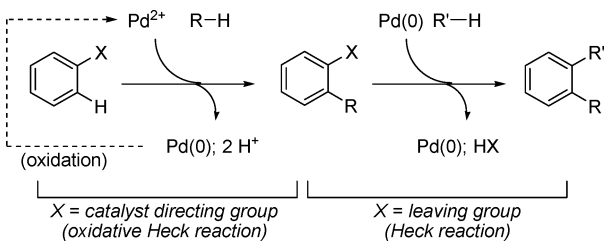
A sequence of acetamide directed oxidative Heck reaction and deacetylation–diazotation–Heck coupling allows the traceless removal of the acetamide group and its dual exploitation as a catalyst directing group and a leaving group.

The regioselective functionalization of arenes is an important issue in numerous syntheses of dyes, pharmaceuticals or crop protecting agents.[1] With electrophilic and nucleophilic substitution reactions still being the standard methods, Pd-catalysed coupling and cross coupling reactions, such as the Heck-,[2] Stille-, Suzuki-, Negishi- and Sonogashira coupling,[3] are becoming increasingly important alternatives. In contrast, reactions involving oxidative Pd-catalyzed C–H-activation steps, such as the Fujiwara–Moritani reaction,[4–9] have attracted considerably less attention in organic synthesis. These reactions proceed *via* electrophilic attack of Pd^{2+} at the arene moiety, preferably in the presence of an electron donating and catalyst directing group,[10–13] *e.g.* an amide, in the *ortho* position. This group not only activates the arene for electrophilic palladation, but is also required to ensure high regioselectivity.[14] From a synthetic point of view, the presence of a catalyst directing group is clearly a limitation of the method, unless either its traceless removal[15] or its subsequent exploitation as a leaving group in a conventional Pd-catalyzed coupling reaction is possible (Scheme 1).

Over the past few years, we investigated deacetylation–diazotation sequences that allow the conversion of acetanilides to isolable diazonium salts in an operationally simple one-flask procedure.[16,17] As arene diazonium salts are highly reactive reagents in numerous Pd-catalyzed coupling and cross coupling reactions,[18–20] we thought that this would open up an interesting opportunity to combine oxidative and non-oxidative Pd-catalyzed C–C-bond forming reactions in a sequential, highly regioselective synthesis of *ortho*-dialkenylated arenes. In a first step, we investigated the oxidative Pd-catalyzed coupling of acetanilide **1a** with methyl acrylate (Table 1).



Scheme 1 Sequential oxidative–non-oxidative Pd-catalyzed arene functionalization.

Originally, we planned to adapt the conditions previously described by van Leeuwen *et al.*, who described the oxidative coupling of butylacrylate with **1a** using benzoquinone (BQ) as an oxidant.[14] When we applied these conditions to our test reaction, a yield of 57% of methyl cinnamate **2a** was obtained.

Unfortunately, the separation of **2a** from unreacted benzoquinone turned out to be very difficult and required repeated chromatography. This prompted us to evaluate alternative oxidizing agents, such as *tert*-BuOOH and MnO_2 in combination with a co-catalytic system of $Pd(OAc)_2$ and benzoquinone, which had previously been applied to the oxidative coupling of benzene with various alkenes by Fujiwara *et al.*[21] While these protocols resulted in the formation of the desired coupling product **2a**, albeit in unsatisfactory rates of conversion (Table 1, entries 2 and 3), only trace amounts of **2a** were observed with AgOAc as an oxidant (entry 4).[21] A first breakthrough was achieved when we used $Na_2S_2O_8$ in trifluoroacetic acid (TFA) at elevated temperatures (entry 5). Under these conditions, inspired by a recently reported oxidative *ortho*-arylation of phenyl carbamates,[22] **2a** was conveniently isolated in 60% yield. Unfortunately, all attempts to reduce the catalyst loading and to further improve the yield by variation of the catalyst, the solvent and the additive failed (entries 6–24). While these optimization studies were in progress, Youn *et al.* disclosed conditions for the alkenylation of various acetanilides **1** with methyl acrylate, using $K_2S_2O_8$ as an oxidizing agent and a TFA–CH_2Cl_2 solvent mixture.[23] We then decided to test this protocol, and were pleased to find that **2a** can be obtained in 89% yield, without the workup problems encountered with benzoquinone as an oxidant (entry 25). We wondered if the success of Youn's protocol can be solely attributed to the special solvent mixture, or if the counterion of the persulfate, K^+ *vs.* Na^+, has a significant effect. Therefore, we repeated the reaction of **1a** with methyl acrylate using $Na_2S_2O_8$ as an oxidant, under otherwise identical conditions. Surprisingly, the yield of **2a** dropped to 31%, indicating a remarkable counterion effect which will be investigated in more detail in the future.

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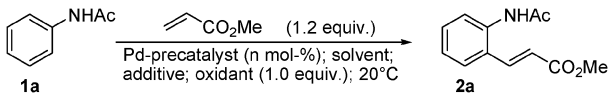
Table 1 Optimization of oxidative Heck coupling

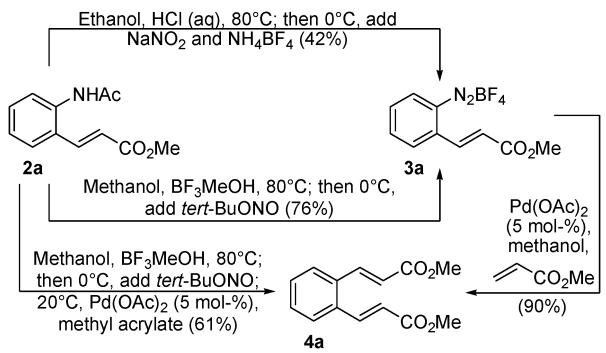


Entry	Catalyst/mol%	Solvent	Additive	Oxidant	Yield [%]
1	$Pd(OAc)_2$ (2)	HOAc/Toluol[a]	TsOH[b]	BQ	57
2	$Pd(OAc)_2$ (0.5)	HOAc/Ac_2O[c]	—	^tBuOOH/BQ[d]	20
3	$Pd(OAc)_2$ (1)	HOAc	—	MnO_2/BQ[e]	n.d.[f]
4	$Pd(OAc)_2$ (1)	HOAc	—	AgOAc[g]	Traces
5	$Pd(OAc)_2$ (10)	TFA	—	$Na_2S_2O_8$[h,i]	60
6	$Pd(OAc)_2$ (5)	TFA	—	$Na_2S_2O_8$[i]	52
7	$Pd(OAc)_2$ (2)	TFA	—	$Na_2S_2O_8$[i]	36
8	$Pd(OAc)_2$ (1)	TFA	—	$Na_2S_2O_8$[i]	21
9	$Pd(OAc)_2$ (10)	HOAc	—	$Na_2S_2O_8$[i]	43
10	$Pd(OAc)_2$ (10)	THF	—	$Na_2S_2O_8$[i]	28
11	$Pd(OAc)_2$ (10)	DMF	—	$Na_2S_2O_8$[i]	7[k]; 5[j,k]
12	$Pd(OAc)_2$ (10)	HBF_4	—	$Na_2S_2O_8$[i]	<5
13	$Pd(O_2CCF_3)_2$ (5)	TFA	—	$Na_2S_2O_8$[i]	21
14	$Pd(O_2CCF_3)_2$ (5)	HOAc	—	$Na_2S_2O_8$[i]	22
15	$Pd(dba)_2$ (5)	TFA	—	$Na_2S_2O_8$[i]	40
16	$[Pd(IMes)(NQ)]_2$ (5)	TFA	—	$Na_2S_2O_8$[i]	17
17	$PdCl_2$ (5)	TFA	—	$Na_2S_2O_8$[i]	15
18	$Pd(OAc)_2$ (5)	THF	HBF_4[m]	$Na_2S_2O_8$[i]	0[j]
19	$Pd(OAc)_2$ (5)	THF	TFA[m]	$Na_2S_2O_8$[i]	6[j]
20	$Pd(OAc)_2$ (5)	THF	TsOH[b]	$Na_2S_2O_8$[i]	7[j]
21	$Pd(OAc)_2$ (5)	Toluol	TsOH[b]	$Na_2S_2O_8$[i]	3[j]
22	$Pd(OAc)_2$ (5)	Toluol	TFA[m]	$Na_2S_2O_8$[i]	9[j]
23	$Pd(OAc)_2$ (5)	HOAc	TsOH[b]	$Na_2S_2O_8$[i]	37; 14[l]
24	$Pd(OAc)_2$ (5)	HOAc/Toluol[a]	TsOH[b]	$Na_2S_2O_8$[i]	22
25	$Pd(OAc)_2$ (5)	TFA/DCM[n]	—	$K_2S_2O_8$	89[o]
26	$Pd(OAc)_2$ (5)	TFA/DCM[n]	—	$Na_2S_2O_8$	31[o]

[a] Ratio 2 : 1 (v/v). [b] 0.5 equiv. [c] Ratio 3 : 1 (v/v). [d] 1.3 equiv. ^tBuOOH; 5 mol% BQ. [e] 1.2 equiv. MnO_2; 5 mol% BQ. [f] Not determined; ratio of **1a : 2a** = 3 : 1 (GC-MS). [g] 1.1 equiv. AgOAc. [h] 3.0 equiv. [i] Reaction temperature: 70 °C. [j] Reaction temperature: 160 °C. [k] Conversion (GC-MS). [l] Reaction temperature: 20 °C. [m] 1.0 equiv. HBF_4 or TFA. [n] Ratio 4 : 1 (v/v). [o] 2.0 equiv. of methyl acrylate.

In the following step the one-flask conversion of acetanilide **2a** to arene diazonium salt **3a** was investigated. Based on our previous results, we first tested a sequence of deacetylation in ethanol and hydrochloric acid, followed by diazotation with $NaNO_2$ and precipitation of the resulting diazonium salt as a tetrafluoroborate.[16] Separation of **3a** from inorganic byproducts required repeated washing with water, resulting in a moderate yield of 42%, presumably due to a rather high solubility of the diazonium salt in water. Therefore, the deacetylation–diazotation sequence was conducted in methanol, using the BF_3·MeOH complex as a Lewis acid for both the deacetylation and the subsequent diazotation[24] with *tert*-butyl nitrite.[16] Pure diazonium salt **3a** was obtained in 76% yield, simply by filtration of the precipitate formed upon diazotation. The subsequent Mizoroki–Heck-reaction of **3a** with methyl acrylate proceeded smoothly in methanol under base-free conditions with $Pd(OAc)_2$ as a catalyst, and the 1,2-dialkenylated benzene **4a** was isolated in 90% yield (Scheme 2).

As methanol is a suitable solvent for the deacetylation–diazotation sequence and for the subsequent Mizoroki–Heck-reaction, we thought that it might be possible to synthesize *ortho*-dialkenylated benzenes **4** in a one-flask sequence from acetanilides **2**, thereby avoiding the isolation of the diazonium salt. Thus, **2a** was converted in one flask to **4a** by conducting the deacetylation–diazotation as described above using BF_3·MeOH and *tert*-butyl nitrite, followed by addition of $Pd(OAc)_2$ and methyl acrylate after completion of the diazotation. This method turned out to be indeed a viable alternative to the two step synthesis,

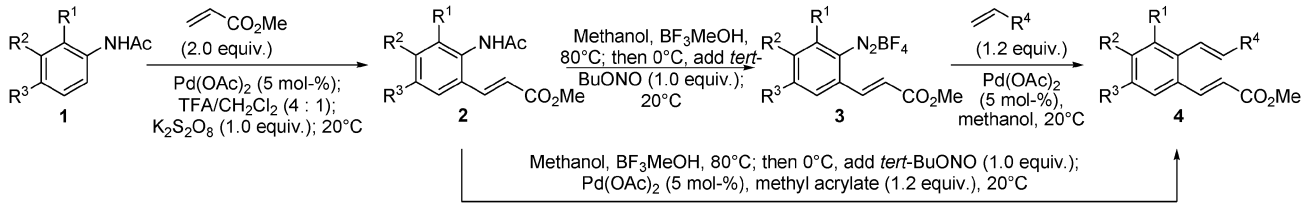


Scheme 2 Deacetylation–diazotation sequence for **2a** and subsequent Mizoroki–Heck-reaction of **3a**.

because **4a** could be isolated in a yield of 61% from **2a**. Notably, the Pd-catalyzed coupling proceeds heterogeneously and the diazonium salt slowly dissolves during the reaction (Scheme 2).

Ortho-dialkenylated benzenes **4** have previously been synthesized from 1,2-dibromobenzene and used as starting materials for stereoselective sequential Michael additions[25,26] and other cyclizative reactions.[27] The sequential oxidative–non-oxidative Pd-catalysed *ortho*-dialkenylation described above should be a useful alternative, and we were therefore interested to extend the scope of this sequence to other examples (Table 2). For example, diazonium salt **3a** reacts with styrene or *para*-nitrostyrene, to stilbenes **4ab** and **4ac** in 68% and 76% yield, respectively. While the one-flask route

Table 2 Scope of the sequential Pd-catalyzed oxidative–non-oxidative twofold alkenylation of acetanilides **1**



Entry	1	R^1	R^2	R^3	**2** (yield)	**3** (yield)	R^4	**4** (yield)[a]	**4** (yield)[b]
1	**1a**	–H	–H	–H	**2a** (89%)	**3a** (76%)	$-CO_2CH_3$	**4a** (90%)	**4a** (61%)
2							-*para*-C_6H_5	**4ab** (68%)	**4ab** (66%)
3							-*para*-$C_6H_4NO_2$	**4ac** (76%)	**4ac** (34%)
4	**1b**	–H	–H	–OMe	**2b** (85%)	**3b** (94%)	$-CO_2CH_3$	**4b** (quant.)	**4b** (40%)
5	**1c**	–OMe	–H	–H	**2c** (80%)	**3c** (65%)	$-CO_2CH_3$	**4c** (quant.)	**4c** (51%)
6	**1d**	–H	–H	–OH	**2d** (55%)[c]	**3d** (92%)	$-CO_2CH_3$	**4d** (quant.)	**4d** (43%)
7	**1e**	–H	–H	–Br	**2e** (49%)	**3e** (70%)	$-CO_2CH_3$	**4e** (quant.)	**4e** (49%)
8	**1f**	–H	–H	–Cl	**2f** (73%)	**3f** (43%)	$-CO_2CH_3$	**4f** (76%)	**4a** (49%)
9	**1g**	–Cl	–H	–H	**2g** (40%)	**3g** (50%)	$-CO_2CH_3$	**4g** (37%)	**4g** (14%)
10	**1h**	–H	$-CF_3$	–H	**2h** (72%)	**3h** (77%)	$-CO_2CH_3$	**4h** (quant.)	**4h** (56%)
11	**1i**	–H	–H	$-C_6H_5$	**2i** (60%)	**3i** (60%)[d]	$-CO_2CH_3$	**4i** (52%)	**4i** (57%)

[a] Yields of isolated products **4** obtained from diazonium salts **3**. [b] Yields of isolated products **4** obtained through one-flask sequence from acetanilides **2**. [c] *Reagents and conditions*: BQ (1.0 equiv.), *p*-TSA (0.5 equiv.), $Pd(OAc)_2$ (2.0 mol%), methyl acrylate (1.2 equiv.), acetic acid/toluene (2 : 1), 20 °C. [d] 2.0 equiv. of *tert*-BuONO were required.

gives an improved overall yield of **4ab**, the yield of **4ac** is somewhat lower (entries 2 and 3). As can be seen from entries 4 to 11, the oxidative–non-oxidative Heck coupling sequence can be realized for various substituted acetanilides **1b–i** in acceptable yields. A notable exception is *ortho*-chloro acetanilide **1g**. For this derivative only moderate yields of approximately 40% were obtained for each individual step, and a low yield of 14% of **4g** if the one-flask conditions were applied (entry 9). In the case of paracetamol (**1d**, entry 6) $K_2S_2O_8$ turned out to be an unsuitable oxidant for the oxidative Heck reaction, because **2d** was observed only in minor amounts, along with numerous unidentified byproducts. We assume that due to the *para*-OH group the aromatic core is easily oxidized, inducing various side reactions. Therefore, van Leeuwen's conditions were used for this particular example, providing **2d** in 55% yield. Diazonium salt formation and subsequent Heck reaction to **4d** worked very well for this derivative, without the necessity to protect the OH-group. Finally, we applied the sequence to biaryl **1i** (entry 11), which was synthesized from **1e** using a Suzuki–Miyaura coupling with phenyl boronic acid. The conversion of **2i** to **4i** was achieved in 57% yield. Thus, the triple substituted benzene **4i** was obtained from **1e** *via* three consecutive mechanistically distinct Pd-catalyzed C–C-bond forming reactions. In summary, we have shown that an acetamide group attached to an aromatic core may serve as a catalyst directing and leaving group, and that acetanilides can be converted by a sequence of mechanistically distinct Pd-catalyzed coupling reactions to dialkenylated arenes.

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