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Palladium(II) Acetate Catalyzed Reductive Heck Reaction of Enones; A Practical Approach

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A surprisingly practical Pd(OAc)₂ or Pd(TFA)₂-catalyzed reductive Heck reaction between aryl iodides and α,β -unsaturated ketones is described using *N,N*-diisopropylethylamine (DIPEA, Hünigs base) as the reductant. In general, 1 mol% of Pd(OAc)₂ is sufficient to afford good yields using electron-rich or halogen-substituted aryl iodides. Electron-deficient aryl iodides preferentially give homocoupling. Enones containing aryl or

bulky substituents on the β -carbon react smoothly, producing mainly reductive Heck product, whereas enones with alkyl substituents on the β -carbon afford a mixture of reductive Heck and Heck product. Deuterium labeling experiments show that the reaction is a bona fide reductive Heck reaction and exclude a Heck reaction-conjugate reduction cascade.

Introduction

Transition-metal catalyzed conjugate addition of organometallic reagents to enones, and other electron-deficient alkenes is an efficient method to form carbon-carbon bonds in organic synthesis.^[1] A variety of organometallic reagents, for example, organoboron, -zinc, -aluminum, -silicon, and -magnesium (Grignard) have been used with a plethora of Michael acceptors.^[2–6] Whereas the addition of alkyl, and to a lesser extent alkenyl and alkynyl, fragments is dominated by copper catalysis, the addition of aryl groups has been reported mainly using rhodium and palladium catalysis.

On the other hand, little effort has been devoted to value the conjugate addition of the corresponding aryl halides,^[7–11] although this pathway is often observed as a side reaction in the corresponding Mizoroki–Heck reaction.^[12] In this process, not the reagent but the catalyst is subjected to umpolung and, therefore, a stoichiometric reductant has to be added. Nevertheless, in particular from a practical point of view, this conjugate addition (also known as reductive Heck) reaction is much more convenient as it does not involve the use of stoi-

chiometric amounts of organometallic reagents and anhydrous conditions, but uses the parent aryl halides instead. Possibly because the reaction is reminiscent of the Heck reaction and more readily designed in an *intramolecular* fashion, most reports on the reductive Heck reaction concern the latter process, recently also with high enantioselectivity.^[13] We recently studied the intermolecular reductive Heck reaction with aryl halides and were able to dissect the different factors that lead to Heck reaction versus reductive Heck reaction.

Mechanistically both reactions proceed through a common aryl-Pd intermediate **A**, but to convert **A** into the reductive Heck product either protonation with subsequent reduction of Pd^{II} to Pd⁰ or formation of a hydrido-palladium-alkyl complex followed by a reductive elimination is necessary (Scheme 1). In 1983, Cacchi and coworkers reported the first example of palladium-catalyzed reductive Heck reaction of phenyl iodides to enones and enals in the presence of triethylamine, tetrabutylammonium iodide, and formic acid.^[10] In the absence of formic acid, the reaction still proceeded but much less efficient. We described the reductive Heck reaction of phenyl iodides to enones using an *N*-heterocyclic carbene (NHC) palladium complex as the catalyst in the presence of tributylamine as the reductant.^[11] This reaction is very effective, makes the addition of tetrabutylammonium iodide, and formic acid redundant and affords the reductive Heck products exclusively and in high yields. More recently, the groups of Deng^[14a,b] and Doucet^[14c] developed a desulfitative palladium-catalyzed conjugate addition reaction to enones. In the reaction, benzenesulfonyl chloride and arylsulfonyl hydrazides are used as the arylating agent to obtain selectively the conjugate addition product.

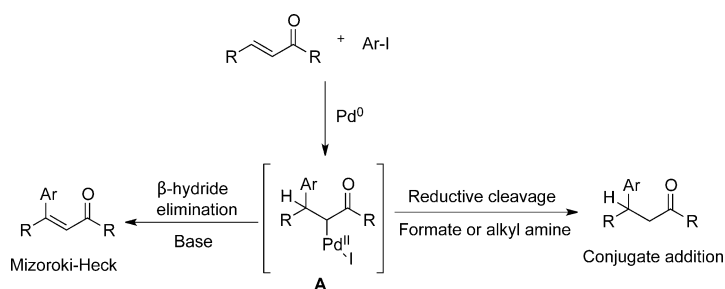
As our initially reported reaction^[11] was rather slow, we continued studying this reaction. This resulted in a novel catalytic system reported here, based on readily available Pd(OAc)₂ and Hünigs base (DIPEA) that is in several aspects as effective as the Pd-NHC catalyst system and considerably faster.^[19]

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Scheme 1. Mizoroki–Heck versus conjugate addition reaction.

Results and Discussion

As reported before, with the combination of 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphtho-quinone) palladium(0) dimer ($\text{Pd}^0\text{-NHC}$), Bu_3N and DMF as solvent, we observed the side products (*E*)-but-1-en-1-ylbenzene (**5**) and 1-phenylbutan-1-one (**6**) as a result of Heck reaction of 4-iodoanisole (**2a**) with the oxidized Bu_3N (Table 1). Moreover, the reaction is probably slowed down due to the immiscibility of Bu_3N and DMF, at least at room temperature. To overcome these downsides, we studied the reaction of benzalacetone (**1a**) and **2a** with various combinations of alkyl amines and solvents using $\text{Pd}^0\text{-NHC}$ as the catalyst. In the presence of tri-*n*-propylamine, triisobutylamine, and *N*-methylmorpholine, a low conversion of

1a, if any, was observed (entries 2, 3, and 5), indicating a remarkable effect of the precise nature of the amine (vide infra).^[19a] Already in an early stage of the research we noted a very low conversion with triethylamine. With DIPEA, **3a** was obtained in a much better yield (55%) (entry 4) along with a minor amount of Heck product **4a** and a large amount of homocoupling product **7**. Notably, however, side products originating from Heck reaction with oxidized DIPEA were not formed. Replacing DMF with NMP made the reaction medium homogeneous and afforded **3a** in 50% yield (entry 6). Use of other solvents including THF and acetonitrile gave **3a** in low yield (entries 7 and 8). A slight increase in the ratio of benzalacetone (**1a**) to 4-iodoanisole (**2a**) considerably improved the yield of **3a** (entry 9) in a shorter reaction time of 2 h, and suppressed formation of **7** to traces.

During this study, it was surprisingly found that $\text{Pd}(\text{OAc})_2$, in particular in combination with DIPEA, and NMP as the solvent, also catalyzes the reductive Heck reaction of **2a** to **1a** with similar reactivity as the $\text{Pd}^0\text{-NHC}$ system (entry 10). With 1 mol% of $\text{Pd}(\text{OAc})_2$, the reaction was completed in 6 h affording **3a** in 78% yield together with minor amounts of Heck product **4a** (<10%) (entry 12). It had been reported by Cacchi et al. that the same reaction with $\text{Pd}(\text{OAc})_2$ as catalyst and tributylamine as reductant in DMF, gave in low yield a mixture of reductive Heck and Heck product in a 4:1 ratio.^[10e]

The role of DIPEA is of particular note here, as this amine is crucial for a rapid reaction and high yield, especially in combination with NMP as the solvent that ensures a homogeneous reaction. As noted before, the enamine formed upon oxidation of tributylamine elicits a competing Heck reaction. This was not observed when DIPEA was applied. McAlees et al. compared the reaction of $\text{PdCl}_2 \cdot 2\text{PhCN}$ with Et_3N , Bu_3N , and DIPEA, and found that DIPEA reacts considerably faster, an observation that is congruent with our observations on the rate of the overall reaction with these amines.^[19a] In that reaction, DIPEA exclusively reacts at the ethyl substituent, as also observed in a mechanistic study by Peters et al.^[19b] who showed that selective oxidation of the ethyl substituent occurred when DIPEA was treated with a zwitterionic palladium complex. Iridium-catalyzed selective hydride elimination of the ethyl-substitu-

Table 1. Variation in the catalyst, the reductant and the solvent.^[a]

Entry	Catalyst	X [mol%]	Reductant	Solvent	t [h]	Yield [%] ^[c]	3a	4a ^[g]
1 ^[d]	$\text{Pd}^0\text{-NHC}$	1.5	Bu_3N	DMF	12	83 ^[b]	0	0
2 ^[d]	$\text{Pd}^0\text{-NHC}$	1.5	(<i>i</i> Bu) ₃ N	DMF	12	0	0	0
3 ^[d]	$\text{Pd}^0\text{-NHC}$	1.5	(<i>n</i> Pr) ₃ N	DMF	12	20	0	0
4 ^[d]	$\text{Pd}^0\text{-NHC}$	1.5	(<i>i</i> Pr) ₂ NEt	DMF	12	55	< 10	< 10
5 ^[d]	$\text{Pd}^0\text{-NHC}$	1.5	<i>N</i> -methylmorpholine	DMF	12	< 3	0	0
6	$\text{Pd}^0\text{-NHC}$	1.5	(<i>i</i> Pr) ₂ NEt	NMP	12	50	< 10	< 10
7	$\text{Pd}^0\text{-NHC}$	1.5	(<i>i</i> Pr) ₂ NEt	THF	12	22	< 10	< 10
8 ^[d]	$\text{Pd}^0\text{-NHC}$	1.5	(<i>i</i> Pr) ₂ NEt	CH ₃ CN	12	< 3	–	–
9 ^[e]	$\text{Pd}^0\text{-NHC}$	1.5	(<i>i</i> Pr) ₂ NEt	NMP	2	85 (81) ^[b]	10	10
10 ^[e]	$\text{Pd}(\text{OAc})_2$	3	(<i>i</i> Pr) ₂ NEt	NMP	3	73	9	9
11 ^[e]	$\text{Pd}(\text{OAc})_2$	3	Bu_3N	NMP	6	18	4	4
12 ^[f]	$\text{Pd}(\text{OAc})_2$	1	(<i>i</i> Pr) ₂ NEt	NMP	6	78 (75) ^[b]	7	7
13 ^[f]	$\text{Pd}(\text{OAc})_2$	0.5	(<i>i</i> Pr) ₂ NEt	NMP	12	61	10	10
14 ^[h]	$\text{Pd}(\text{OAc})_2$	1	(<i>i</i> Pr) ₂ NMe	NMP	9	60	24	24

[a] For the entries 1 to 8, reactions were carried out using **1a** (1.14 mmol), **2a** (2.72 mmol), catalyst (1.5–3.0 mol%), amine (4.5 equiv), 1.5 mL of solvent and decane as internal standard for 3–12 h. [b] Isolated yields. [c] GC yields. [d] Biphasic reaction medium. [e] For the entries 9 to 11, the reactions were carried out using **1a** (1.65 mmol), and **2a** (1.10 mmol). [f] For the entries 12 and 13, the reactions were carried out using **1a** (1.10 mmol), **2a** (1.32 mmol) and 5.0 equiv of DIPEA. [g] **4a** was obtained as an *E/Z* mixture. [h] The reaction was carried out using **1a** (1.10 mmol), **2a** (1.32 mmol) and 5.0 equiv of DIPMA (*N,N*-diisopropylmethylamine).

ent has been reported as well, producing bis-isopropylamino ethene.^[18a] Other reports propose^[19c-d] the requirement of water or hydroxide for the reduction of palladium in this way, however these studies focused on the reduction of Pd-phosphine complexes (and led to the oxidation of the phosphine). Upon performing the reaction with *N,N*-diisopropylmethylamine (DIPMA, Table 1, entry 14), a mixture of **3a** and **4a** in 60% and 24% yield, respectively, was obtained in an incomplete reaction after 9 h. This poor selectivity and moderate reaction rate further confirm that it is most probably the ethyl moiety in DIPEA that is oxidized, and that the bulky isopropyl groups apparently inhibit Heck reaction of the resulting bis-isopropylamino ethene. Thus, it was highly significant to explore the scope of the reaction using Pd(OAc)₂, a stable, an inexpensive palladium catalyst, in the reductive Heck reaction.

Initially, we studied the scope in aryl iodides using benzalacetone (**1a**) as the substrate (Table 2). In general, electron-rich

used for further transformations. Finally, the effect of a substituent at the different positions of the benzene ring was also examined. Thus, *m*-tolyl iodide (**2i**) gave **3i** in 82% yield whereas *o*-tolyl iodide (**2j**) afforded **3j** in only 32% yield, the latter due to incomplete conversion. The heteroaromatic iodides 3-iodothiophene (**2j**) and 5-iodoindole (**2k**) also furnished their corresponding reductive Heck products **3k** and **3l** in good yields.

Also the scope in terms of the Michael acceptor was studied using **2a** (Table 3). In addition to benzylidene acetone, also chalcone (**1b**) and the benzylidene derivatives **1c** and **1d** participated well in the reaction to give the reductive Heck products in good yields. The reaction with some of the β -alkyl substituted enones gave a low yield of reductive Heck product, however, due to formation of the Heck product in considerable amounts. The formation of the reductive Heck product increases upon the introduction of bulky substituents on the β -carbon of the enone. For example, in the series **3p**, **3q**, **3r**, yields increase from 32% to 60%.

Gratifyingly, also 2-cyclohexenone (**1h**) reacted smoothly, in this case with a catalytic amount of Pd(TFA)₂, giving **3s** in 74% yield. This is an improvement compared to the use of the Pd⁰-NHC/Bu₃N/DMF system (56% yield). The scope was extended to (*E*)-1-methoxy-4-(2-nitrovinyl)benzene, **1i**, which afforded solely the reductive Heck product **3t** in a moderate 33% yield. Unsaturated esters and nitriles did not give reductive Heck products but furnished solely the Heck products **4b** and **4c** in high yields. In general, for enones the selectivity of reductive Heck versus Heck product is 12:1 to 15:1, except for β -alkyl substituted enones. In comparison with our earlier reported palladium carbene catalyst system, the current yields are slightly lowered by 5 to 10%. However, for cyclohexenone and halo-substituted arenes, we observed higher yields.

Mechanistic studies by Friestad and Branchaud^[16] on the Cacchi system suggested that the absence of acid would result in the initial formation of the Mizoroki-Heck product **4a**, followed by its reduction to **3a** by accumulated Pd-H species formed from NBu₃. To study this hypothesis in our present catalyst system, we carried out a reaction with deuterated benzylidene acetone (**[D₁]-1a**) under the optimized reaction conditions (Scheme 2). Either the absence of deuterium or deuterium scrambling at the β -carbon of **3a**, will support the reaction pathway via Heck reaction followed by reduction. However, the reaction gave reductive Heck product **[D₁]-3a** in 80% yield with >97% remaining deuteration at the β -carbon. This rejects the hypothesis of Friestad and Branchaud and supports the pathway in which the Pd-alkyl complex **A** (Scheme 1) is reduced by DIPEA to a palladium hydride species followed by reductive elimination. Alternatively **A** tautomerizes to an O-bound palladium enolate that is subsequently reduced by DIPEA.^[20]

Table 2. The Pd(OAc)₂-catalyzed reductive Heck reaction of aryl iodides **2b-j** to benzalacetone **1a**.^[a,b,g]

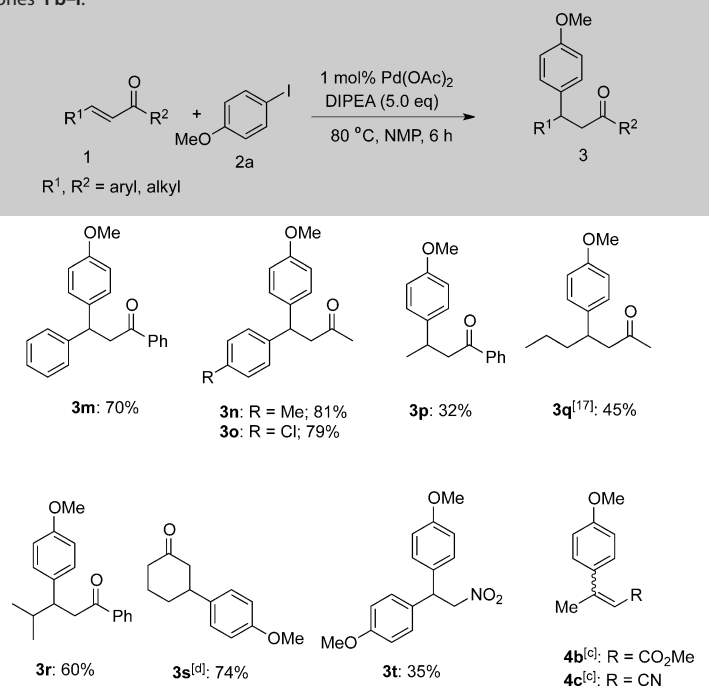
Reaction conditions: 1 mol% Pd(OAc)₂, DIPEA (5.0 eq), 80 °C, NMP, 6 h.

3a : 75%	3b : R = Me; 80%	3d ^[d] : R = CO ₂ Me; 15%	3f : X = F; 77%
	3c : R = H; 71%	3e ^[d] : R = NO ₂ ; 0%	3g ^[d] : X = Cl; 72%
			3h ^[e] : X = Br; 62%
3i : 3-Me; 82%	3k : 81%		3l : 73%
3j ^[f] : 2-Me; 35%			

[a] Unless otherwise mentioned, all reactions were carried out using **1a** (1.10 mmol), **2** (1.32 mmol), Pd(OAc)₂ (1.0 mol%) and 5 equiv of DIPEA in 1.5 mL of NMP. [b] Isolated yields. [c] homocoupling of **1** was found to be predominant. [d] 2.4 equiv of **2** was used. [e] 5.0 equiv of **2** was used. [f] The reaction was carried out for 24 h. [g] In all reactions, the selectivity of reductive Heck versus Heck product is > 11:1.

and electron neutral phenyl iodides participate well in the reaction and afford the product in good yields, whereas electron-deficient phenyl iodides preferentially give homocoupling. For instance, *p*-tolyl iodide (**2b**) and iodobenzene (**2c**) gave the reductive Heck products in good yields, but 4-iodo methylbenzoate (**2d**) afforded the product in low yield and the reaction with 4-iodonitrobenzene (**2e**) was completely ineffective. A separate class is formed by the halogen substituted phenyl iodides (**2f-h**) that furnish the desired products in good yields (62–77%). It is advantageous that bromo- and chloro substituents on the benzene ring remain unaffected, so these can be

Table 3. The Pd(OAc)₂-catalyzed reductive Heck reaction of *p*-iodo anisole (**2a**) to enones **1 b–i**.^[a,b]



[a] Unless otherwise mentioned, all reactions were carried out using **1a** (1.10 mmol), **2** (1.32 mmol), Pd(OAc)₂ (1.0 mol%) and 5 equiv of DIPEA in 1.5 mL of NMP. [b] Isolated yields. [c] 100% conversion of **2a** as determined by GC using *n*-decane as internal standard and **4** was obtained as an *E/Z* mixture [d] 1 mol% of Pd(TFA)₂ was used instead of Pd(OAc)₂.

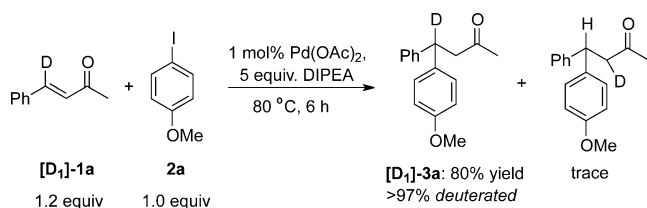
Experimental Section

General procedure for the conjugate addition of aryl iodides **1 to enones **2**:** An oven-dried Schlenk tube, equipped with stopper and stirrer bar, was placed under nitrogen, and charged with aryl iodide **2** (1.32 mmol), and alkene **1** (1.10 mmol), followed by Pd(OAc)₂ (1.0 mol%) as a stock solution (0.011 mmol in 0.5 mL NMP) using syringe. To this mixture, *N,N*-diisopropylethylamine (DIPEA) (5.5 mmol), and *N*-methylpyrrolidone (NMP, 1.0 mL) were added sequentially while stirring. The Schlenk tube was placed into a preheated oil bath at 80 °C. Upon completion (after 6 h, as judged by GC/MS), the reaction mixture was cooled down to RT, diluted with either diethyl ether or ethyl acetate, and filtered through a Celite and silica gel pad. The filtrate was concentrated and the residue was purified on silica gel chromatography to afford the desired product **3**.

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Keywords: alkenes • aryl iodides • conjugate addition • *N,N*-diisopropylethylamine • palladium



Scheme 2. Deuterium labeling discriminates between a bona fide conjugate addition reaction and a tandem Heck reaction–conjugate reduction.

Conclusions

The catalyst system Pd(OAc)₂/DIPEA/NMP is a straightforward and effective tool for the reductive Heck reaction of aryl iodides to enones. The system has a reasonable scope in both the aryl iodide and the enone. Also nitrostyrene is a suitable substrate, although the yield is moderate. Together with our previous report these are the first successful conjugate additions of aryl halides to unsaturated nitro compounds, whereas the Heck reaction on these substrates fails. An extension of this reaction to asymmetric synthesis is currently underway in our laboratory.

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