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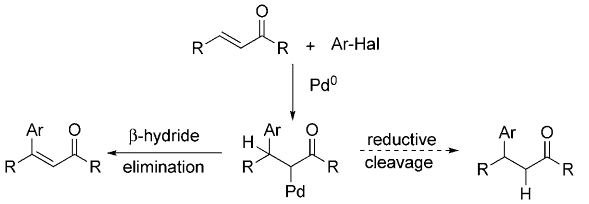
Pd–NHC Catalyzed Conjugate Addition versus the Mizoroki–Heck Reaction

Aditya L. Gottumukkala,[a] Johannes G. de Vries,*[a, b] and Adriaan J. Minnaard*[a]

The transition-metal-catalyzed conjugate addition of aryl organometallic reagents constitutes a cornerstone in organic chemistry.[1] The use of copper has been very successful for the conjugate addition of hard organometallics like Grignard reagents.[2] However, rhodium-[3] and palladium-catalyzed[4] conjugate additions of soft organometallics are becoming increasingly popular due to their broad functional group tolerance, mild reaction conditions, and wide scope. Irrespective of the catalysis, the required organometallic reagents, like Grignards,[5] organozincs,[6] and boronic acids[7] or their derivatives, are nearly invariably synthesized from the corresponding aryl halides. It is therefore remarkable that little attention has been given to the direct use of aryl halides in metal-catalyzed conjugate addition reactions; all the more so because the closely related Mizoroki–Heck[8] reaction has been studied and applied extensively. Thus, it would be a significant advance if, as in the latter reaction, the umpolung of the aryl halide would take place by the transition-metal catalyst. For the result to be a conjugate addition, a reductive cleavage would be necessary, as opposed to the β-hydride elimination that takes place during the Mizoroki–Heck reaction (Scheme 1).



Scheme 1. Reductive cleavage affords the conjugate addition product, whereas β-hydride elimination leads to the Mizoroki–Heck product.

The conjugate addition product in palladium-catalyzed Mizoroki–Heck reactions is in fact regularly observed as a side product,[9,10] and this derailing, sometimes referred to as the "reductive Heck reaction", has been partially appreciated in the literature in inter-[11] and intramolecular[12] cases. However, it remains unclear whether this involves a *bona fide* conjugate addition, or a Mizoroki–Heck reaction followed by reduction, the latter also being commonly observed.[13] Surprisingly, only the group of Cacchi[11b,d,14] has studied the conjugate addition of aryl halides in some detail for the addition of 4-iodoanisole to benzalacetone (**1**).

Herein, we report an efficient catalyst system that, under mild conditions, allows the reaction to be steered completely either to conjugate addition or to Mizoroki–Heck reaction solely by the base used. Our results indicate that in the conjugate addition, the Pd–alkyl complex is reduced by the Bu_3N via a β-hydride elimination reductive–elimination sequence.

Building upon the reaction conditions described by Cacchi et al. (Table 1, entry 1), we scrutinized both the product composition and the reaction parameters. In addition to the expected conjugate addition product **3a** (62 % yield), the Mizoroki–Heck product **3b**, and 4,4′-dimethoxybiphenyl (**3c**) were also obtained (Scheme 2). Careful analysis revealed that varying amounts of 4-methoxybutyrophenone

Table 1. Pd-catalyzed conjugate addition to benzalacetone.[a]

Entry	Pd source	mol %	Ligand	mol %	**3a**[b]
1[c]	$Pd(OAc)_2$	10	PPh_3	24	62
2	$Pd(OAc)_2$	5	PPh_3	11	60
3[d]	$Pd(OAc)_2$	5	PPh_3	11	54
4	$[Pd_2(dba)_3]\cdot CHCl_3$	2.5	PPh_3	11	62
5[e]	$[Pd_2(dba)_3]\cdot CHCl_3$	2.5	PPh_3	11	nd[f]
6[e]	$[Pd_2(dba)_3]\cdot CHCl_3$	2.5	Tol-BINAP[g]	10	58
7[e]	$[Pd_2(dba)_3]\cdot CHCl_3$	2.5	*rac*-BINAP	10	64
8[e]	PEPPSI-IPr[h]	5	–	–	nd
9[e,i]	Pd^{II}–NHC[j]	3	–	–	74
10[e]	Pd^0–NHC	1.5	–	–	82
11[e]	Pd^0–NHC[k]	0.2	–	–	58
12[e]	Pd^0–NHC[l]	0.02	–	–	54

[a] Reaction conditions: **1** (1.14 mmol), **2** (2.7 mmol), Bu_3N (5.1 mmol.), CF_3COOH (3 mmol), Bu_4NI (0.11 mmol), 80 °C, DMF, N_2, 18 h. [b] Yield of isolated product. [c] Reaction completed in 12 h. [d] 1.4 mmol of **2** used. [e] CF_3COOH and Bu_4NI omitted. [f] Incomplete conversion after 18 h; significant amounts of Mizoroki–Heck product observed; nd = not determined. [g] BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. [h] PEPPSI-Ipr, see reference [21]. [i] KOtBu (10 mol %) added, with 2-propanol as a solvent.[15] [j] NHC=N-heterocyclic carbene. [k] 100 °C. [l] 120 °C.

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[a] A. L. Gottumukkala, Prof. Dr. J. G. de Vries, Prof. Dr. A. J. Minnaard
Stratingh Institute for Chemistry, University of Groningen
Nijenborgh 4, 9747 AG, Groningen (The Netherlands)
Fax: (+31) 50-363-429
E-mail: A.J.Minnaard@rug.nl

[b] Prof. Dr. J. G. de Vries
DSM Innovative Synthesis BV, P.O. Box 18, 6160 MD
Geleen (The Netherlands)
E-mail: Hans-JG.Vries-de@dsm.com

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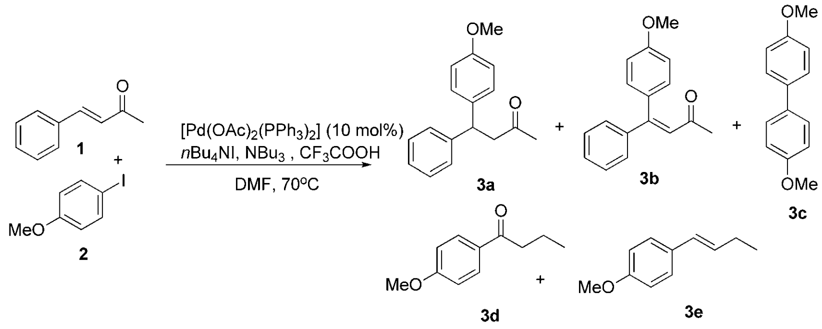
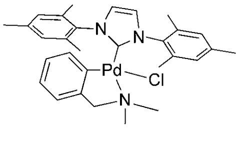


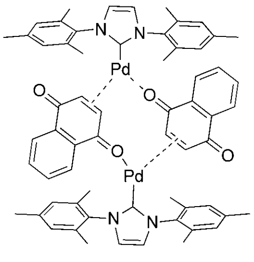
Scheme 2. Distribution of products, using the conditions in reference [14c].

(**3d**)[16] and 1-butenyl-4-methoxybenzene (**3e**)[17] were also formed, resulting from the oxidation of tributylamine. Lowering the catalyst loading led to only a slightly increased reaction time (Table 1, entry 2), whereas using either a Pd^0 precursor or bisphosphines instead of PPh$_3$ did not improve the outcome (Table 1, entries 3–7). Experiments performed in the absence of Pd or Bu$_3$N led to full recovery of the starting material. Taken together, this strongly suggests that the colloidal Pd particles[18] are the catalytically active species. To find a well-defined catalyst that would also be directly relevant for enantioselective conjugate addition, we next turned our attention to carbene ligands.

The use of Pd^{II}–NHC[19] resulted in an increase in yield compared to the other palladium catalysts (Table 1, entry 9 vs. entries 1–7). However, the use of Pd^0–NHC, as reported by Beller et al.,[20] enabled **3a** to be isolated in a higher yield (82 %, Table 1, entry 10), with no formation of **3b** observed. The comparatively lower activity of Pd^{II}–NHC could result from the fact that it needs to be reduced to Pd^0 prior to catalysis. Using PEPPSI–Ipr,[21] also a Pd^{II}–N-heterocyclic carbene catalyst, resulted in a similar outcome (Table 1, entry 8).



Pd^{II}-NHC



Pd^0-NHC

Surprisingly, it was found that this reaction gives the same outcome without the addition of trifluoroacetic acid and tetrabutylammonium iodide; this result greatly simplifies the catalytic system (Table 1, entries 5–10). Lowering the catalyst loading 10-fold (0.2 mol %, Table 1, entry 11) or 100-fold (0.02 mol %, entry 12) still resulted in significant yields, albeit at higher temperatures. The decrease in the yield of isolated product is probably caused by decomposition of the substrate at a higher temperature.

Although these findings indicate that protonolysis of the intermediate alkyl–Pd does not take place (as the reaction also occurs in the absence of an acid), mechanistic studies by Friestad and Branchaud[22] on the Cacchi system suggested that the absence of acid would result in the initial formation of the Mizoroki–Heck product **3b**, followed by its reduction to **3a** by an accumulation of the Pd–H species formed from NBu$_3$. With our system however, no formation of **3b** was observed during the entire course of the reaction.[23] In addition, when 0.5 mmol of **4b** was added to the reaction mixture, it could be recovered completely without the formation of **4a**, thus indicating that there is no accumulation of the Pd–H species. These observations convincingly suggest that **3a** is formed by arylation, followed by reduction of the palladium. The role of Bu$_3$N in this reaction, in addition to being the reductant, could be to keep the alkyl palladium species coordinatively saturated thereby avoiding β-hydride elimination from the substrate, yet facilitating β-hydride elimination from the NBu$_3$. Varying the electron density on the aryl halide (Table 2) showed that electron-poor aryl iodides also perform reasonably in the reaction. Replacement of iodides with aryl bromides or chlorides under the reaction conditions, only led to recovery of the starting materials.

Table 2. Substituted aryl iodides RC$_6$H$_4$I in the conjugate addition reaction. See Supporting Information for details.

Entry	R	Product	Yield[a] [%]
1	4-MeO	**3a**	82
2	H	**3f**	83
3	3-Cl	**3g**	52
4	3-Br	**3h**	56
5	4-Cl	**3i**	58
6	4-Br	**3j**	63

[a] Yield of the isolated product.

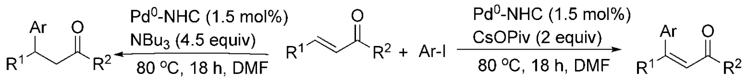
After having achieved selective conjugate addition, we aimed for selective formation of the Mizoroki–Heck product additionally, by choosing bases that are incapable of reducing Pd through hydride donation. Among the bases studied, cesium pivalate proved to be very efficient, perhaps due to its solubility in organic solvents. In short, complete reversal of selectivity to the Mizoroki–Heck product was achieved, proving that the base is key in tuning the selectivity.

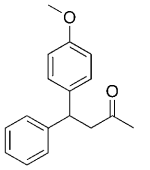
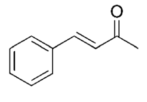
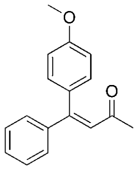
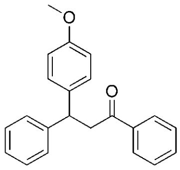
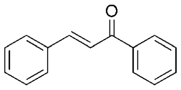
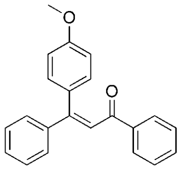
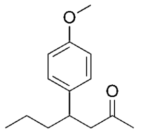
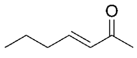
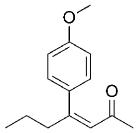
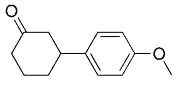
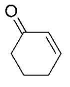
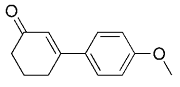
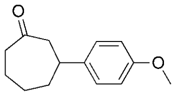
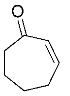
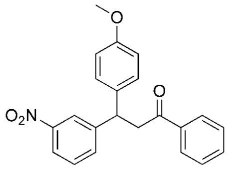
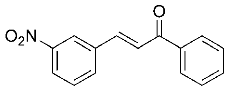
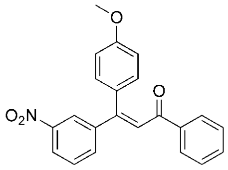
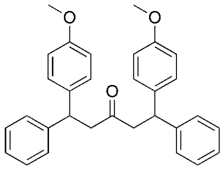
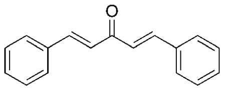
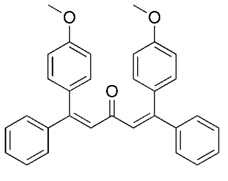
As is invariably found with Heck reactions to β-substituted enones, a mixture of double-bond isomers was obtained,[24] which is a strong indication for a fast palladium Cbound-to-O-bound equilibrium. At present, it is unclear whether in the conjugate addition the reduction takes place from the C- or O-bound palladium species. To complete our studies on benzalacetone, the reaction was performed under microwave irradiation, which enabled complete conversion and selectivity in the conjugate addition and the Mizoroki–Heck product in 30 min, with yields identical to those obtained with conventional heating.

Subsequently, the scope of this switchable catalyst system was explored (Table 3). Both linear and cyclic enones could be converted selectively into either the conjugate addition or the Mizoroki–Heck product depending on the base. The selective conjugate addition to cyclohexenone and cycloheptenone is noteworthy, especially since the Mizoroki–Heck reaction on cycloheptenone with aryl halides has not been reported to date (and did not take place in our hands, despite several attempts). In addition, the *trans,trans*-dibenzylideneacetone smoothly undergoes bis-conjugate addition to **9a** in 74 % yield and Mizoroki–Heck reaction to **9b** in an excellent 92 % yield. When D-mannitol-derived **10**[25] was employed, a diastereoselective conjugate addition took place affording a 5:1 mixture in favor of the *anti* product (Scheme 3). In contrast, α,β-unsaturated esters, amides, and nitriles yielded only their corresponding Mizoroki–Heck products, regardless of the base used.

To stretch the utility of the approach, we studied the β-nitrostyrenes (Table 4); a substrate class that until now has failed to undergo the Mizoroki–Heck reaction.[26] Intriguingly, although the attempted Mizoroki–Heck reaction led to recovered starting materials, the conjugate addition reaction readily took place when Bu_3N was used as the base (Table 4). This questions the current opinion[26] that lack of substrate coordination or sequestration of Pd by the nitro group are the reasons for the failure of these substrates in the Mizoroki–Heck reaction. The yield is strongly dependent on the electronic properties of the substrate; for example, 2,3-dimethoxy-β-nitrostyrene provided **13a** in 64 % yield, whereas 1-nitro-1-cyclohexene did not react and was recovered (Table 4, entry 3 vs. entry 6).

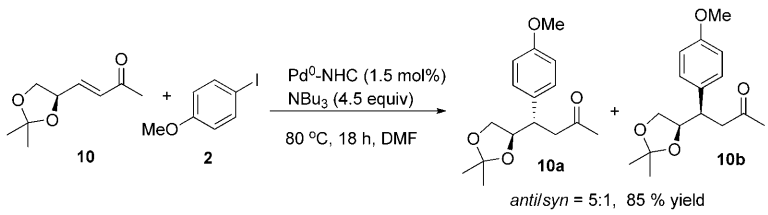
Table 3. Selectivity governed by base.



Conjugate addition product[a]		Yield [%]	Substrate	Mizoroki–Heck product[a,b]		Yield [%]
	**3a**	82			**3b**	83
	**4a**	73			**4b**	80
	**5a**	63			**5b**	84
	**6a**	56			**6b**	64
	**7a**	69		–	–	–
	**8a**	92			**8b**	71
	**9a**	74			**9b**	92

[a] Yield of isolated product. [b] Obtained as a mixture of *E*/*Z* isomers. nd = not determined.

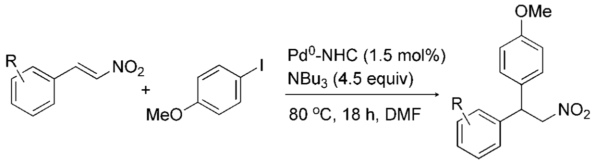
In summary, a catalytic system has been developed, which, by choice of the base, selectively switches between conjugate addition and Mizoroki–Heck reaction of aryl halides and Michael acceptors. For conjugate addition reactions, this avoids the preparation and use of organometallics, rendering the reaction easier to operate. Reductive cleavage of Pd, instead of protonolysis, is proposed to release the product. For the first time, the reaction is extended to β-nitrostyrenes; a class of substrates unamenable to the corresponding Mizoroki–Heck reaction. The reaction is completed in 30 min under microwave irradiation, and can be performed with

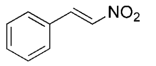
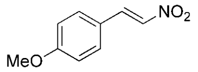
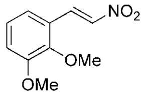
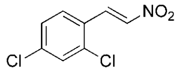
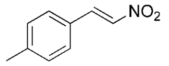
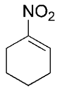


anti/*syn* = 5:1, 85 % yield

Scheme 3. Diastereoselective conjugate addition.

Table 4. Conjugate addition to β-nitrostyrenes.



Entry	Substrate	Product	Yield [%][b]
1		**11a**	28
2		**12a**	54
3		**13a**	64
4		**14a**	21
5		**15a**	38
6		–	–

[a] Yield of isolated product.

good diastereoselectivity. This conjugate addition reaction has considerable scope, including cases where the Mizoroki–Heck reaction fails. This reaction awaits its enantioselective version, which is a challenge we are currently working on. The results presented here are an excellent prelude to such a development.

Experimental Section

General procedure for conjugate addition: A flame-dried Schlenk tube, equipped with screw cap and stirrer bar, was placed under nitrogen, and charged with aryl iodide (2.72 mmol), enone (1.14 mmol), followed by Pd^0–NHC catalyst (1.5 mol%) as a stock solution (0.017 mmol in 1 mL DMF), and *n*-tributylamine (5.1 mmol) by using a syringe. The Schlenk tube was then alternated through three cycles of vacuum and nitrogen, and placed into a preheated oil bath at 80°C. Upon completion (as judged by GC/MS and/or TLC) the reaction mixture was cooled to room temperature and poured into HCl (v/v) solution (10%, 10 mL) and extracted with diethyl ether (3×25 mL). The organic extracts were combined, dried over anhydrous MgSO$_4$, and concentrated in vacuo. The concentrate was loaded directly or adsorbed onto silica prior to loading onto a silica gel column and eluted.

General procedure for the Mizoroki–Heck reaction: A flame-dried Schlenk tube, equipped with screwcap and stirrer bar, was placed under nitrogen, and charged with aryl iodide (1 mmol), enone (1.5 mmol), cesium pivalate (2 mmol) followed by Pd^0–NHC catalyst (1.5 mol%) as a stock solution (0.017 mmol in 1 mL DMF). The Schlenk tube was then alternated through three cycles of vacuum and nitrogen, and placed into a preheated oil bath at 80°C. Upon completion (as judged by GC/MS and/or TLC) the reaction mixture was cooled to room temperature and poured into HCl (v/v) solution (10%, 10 mL) and extracted with diethyl ether (3×25 mL). The organic extracts were combined, dried over anhydrous MgSO$_4$, and concentrated in vacuo. The concentrate was loaded directly, or adsorbed onto silica, before loading onto a silica gel column.

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Keywords: base • conjugate addition • carbenes. • elimination • palladium

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