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Palladium/di-1-adamantyl-*n*-butylphosphine-catalyzed reductive carbonylation of aryl and vinyl halides

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Abstract—A general and efficient palladium-catalyzed reductive carbonylation with low catalyst loadings (0.5 mol % Pd or below) has been developed. The formylation of aryl and heteroaryl bromides proceeds smoothly in the presence of palladium/di-1-adamantyl-*n*-butylphosphine at ambient pressure of synthesis gas to afford the corresponding aromatic aldehydes in good yields and excellent selectivity. In addition, vinyl halides react under similar conditions to form α,β-unsaturated aldehydes in good yield.

1. Introduction

The palladium-catalyzed carbonylation of aryl and heteroaryl halides is a versatile reaction and easily provides access to aromatic ketones,[1] carboxylic acids,[2] esters,[3] amides,[4] and the corresponding α-*oxo*-derivatives.[5] With respect to the different variants of carbonylations aromatic aldehydes are probably the most useful class of products, as the highly reactive aldehyde group can be easily employed in numerous C–C- and C–N-coupling reactions, reductions as well as other transformations (Scheme 1). Obviously, the resulting substituted benzaldehydes are important substrates for the preparation of numerous biologically active molecules and their intermediates. Although the first palladium-catalyzed formylation was reported by Heck et al. already in 1974,[6] still this method had several limitations until very recently. In the past, often the use of expensive reduction reagents such as silicon[7] and tin[8] hydrides was necessary to achieve the formylation at lower pressures of CO. A more economical method to perform palladium-catalyzed reductive carbonylations is based on the use of readily available formate salts[9] or acetic formic anhydride.[10] However, also these formylation procedures require the use of high catalyst loadings.

In addition, most palladium-catalyzed formylations are accompanied by side reactions, especially the reductive dehalogenation of the aryl halide. In order to overcome the limitations of known procedures, we started a joint program between industry and academia to explore the potential of various palladium catalysts and ligands. After an initial communication,[11] here we describe a full account of our investigations, which led to the most general, active, and productive palladium catalyst known to date for reductive carbonylations of aryl and vinyl halides.

2. Results and discussion

Based on our experience in palladium-catalyzed coupling[12] and carbonylation reactions,[13] the formylation of 4-bromoanisole with synthesis gas to give 4-methoxybenzaldehyde was tested in the presence of 20 different phosphine ligands. Selected results are shown in Table 1. Apart from standard phosphines, ligands developed in our group such as di-1-adamantylalkylphosphines[14] and *N*-arylated heteroaryldialkylphosphines[15] were compared under identical conditions (100 °C; 5 bar CO/H_2). In order to ensure a more rapid testing all experiments were carried out in a modified sixfold parallel autoclave (reaction volume 4 mL). To our surprise under these conditions only one ligand (di-1-adamantyl-*n*-butylphosphine; cata*CX*ium® A) permits efficient formylation of the model substrate (92%, Table 1, entry 10). Typical bidentate ligands such as 1,3-bis(diphenylphosphino)-propane (dppp), 1,4-bis(diphenylphosphino)butane (dppb) or 1,1′-bis(diphenylphosphino)ferrocene (dppf) did not lead to significant conversion and 4-methoxybenzaldehyde formation (Table 1, entries 1–4). Triarylphosphines and dialkylheteroarylphosphines were less active or nearly inactive (Table 1, entries 5 and 6, entries 13–19). The electron rich and sterically bulky ligands such as

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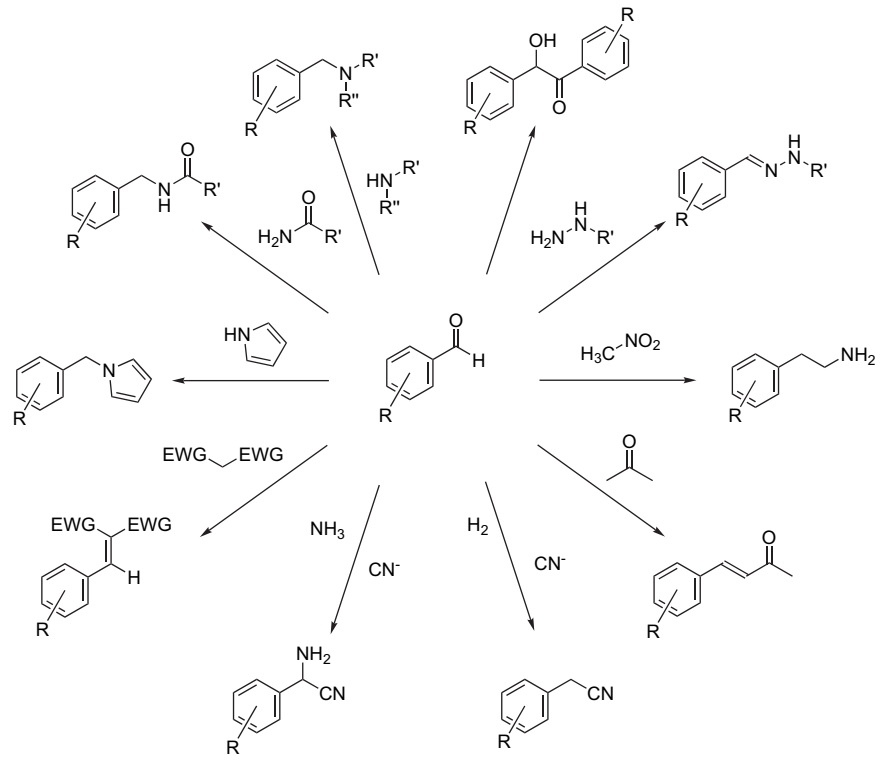
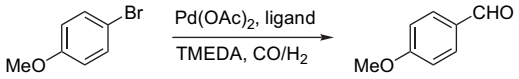
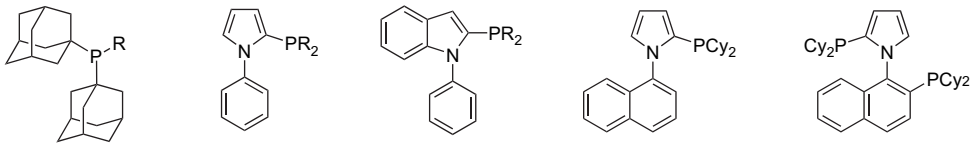


Scheme 1. Synthetic application of aromatic aldehydes.

Table 1. Effect of ligands on the formylation of 4-methoxybromobenzene





1a, R=*n*-Bu
1b, R=Bn
1c, R=H

2a, R=Cy
2b, R=*t*-Bu
2c, R=Ad

3a, R=Cy
3b, R=*t*-Bu

4

5

Entry	Ligand	Ligand [mol %]	Conversion[a] [%]	Yield[a] [%]	Selectivity[a] [%]
1	dppp	0.75	3	0	0
2	dppp	0.375	2	1	50
3	dppb	0.75	9	7	78
4	dppf	0.375	6	3	50
5	PPh_3	0.75	2	0	0
6	P(*o*-Tol)$_3$	0.75	1	0	0
7	P(*n*-Bu)$_3$	0.75	1	0	0
8	P(*t*-Bu)$_3$	0.75	22	18	82
9	PCy_3	0.75	13	11	85
10	**1a**	0.75	97	92	95
11	**1b**	0.75	26	19	73
12	**1c**	0.75	7	4	57
13	**2a**	0.75	9	6	67
14	**2b**	0.75	2	0	0
15	**2c**	0.75	2	1	50
16	**3a**	0.75	4	2	50
17	**3b**	0.75	1	0	0
18	**4**	0.75	13	9	69
19	**5**	0.375	3	0	0

Reaction conditions: 2 mmol 4-bromoanisole, 0.25 mol % $Pd(OAc)_2$, 0.75 equiv TMEDA, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 5 bar CO/H_2 (1:1), 100 °C, 16 h.

[a] Determined by gas chromatography.

di-1-adamantylbenzylphosphane (**1b**) and P(*t*-Bu)$_3$, which can be compared to cata*CX*ium® A, also gave only low yields of the desired product (<20%, Table 1, entries 8 and 11).

Next to the ligand screening, we studied the influence of different solvents, pressure, and bases. In general, *N*-methylpyrrolidinone (NMP), 1,2-dimethoxyethane, and acetonitrile were less suitable compared to toluene. It is important to note that a low synthesis gas pressure (<5 bar) is necessary in order to achieve complete conversion. Obviously, a higher CO concentration leads to deactivation of the catalyst system. In Figure 1, the influence of carbon monoxide pressure on the yield of 4-methoxybenzaldehyde is shown in detail for seven different bases. For all tested bases the maximum yield of 4-methoxybenzaldehyde is achieved at a total pressure of about 5 bar (CO/H_2=1:1). Due to the low solubility and competing formation of 4-methoxybenzoic acid, inorganic bases, for example, K_2HPO_4, were less effective compared to organic nitrogen bases such as DABCO, TMEDA, NEt_3, and N(*n*-Bu)$_3$. Notably, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) has been rarely used as a base for palladium-catalyzed coupling reactions, but is the most active base for our model substrate.

Among the different palladium sources tested, $Pd(OAc)_2$ proved to be the best since it is better soluble in toluene than, for example, $PdBr_2$ or $Pd_2(dba)_3$. With respect to minimization of the catalyst loading, one should note that high conversion and good yield of 4-methoxybenzaldehyde are already obtained at a palladium concentration of 0.25 mol % (Fig. 2).

To prevent the formation of palladium carbonyl clusters and to stabilize the palladium catalyst, a threefold excess of the ligand (P/Pd=3:1) is necessary. The amount of palladium can be reduced at constant ligand concentration by raising the temperature from 100 °C to >120 °C. Typically a higher reaction temperature increased the conversion, but sometimes diminished the chemoselectivity of the reaction, since reductive dehalogenation of the aryl bromide becomes faster. On the other hand, decreasing the temperature retarded the conversion but increased the chemoselectivity.

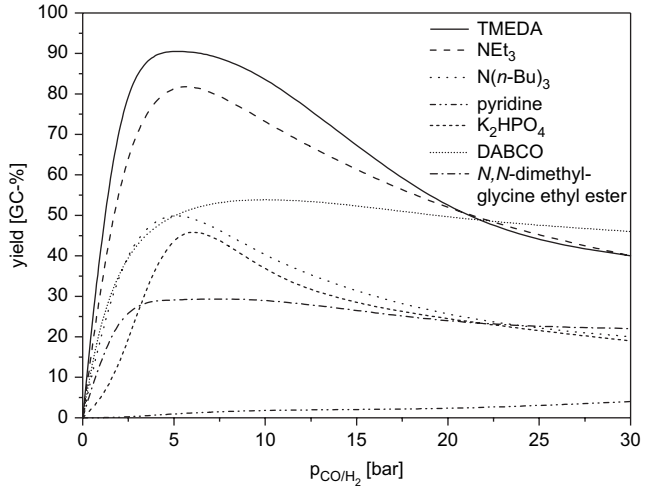


Figure 1. Influence of base and carbon monoxide pressure on the yield of 4-methoxybenzaldehyde. Reaction conditions: 2 mmol 4-bromoanisole, 0.33 mol % $Pd(OAc)_2$, 1 mol % cata*CX*ium® A, 1.5 equiv base, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 100 °C, 16 h.

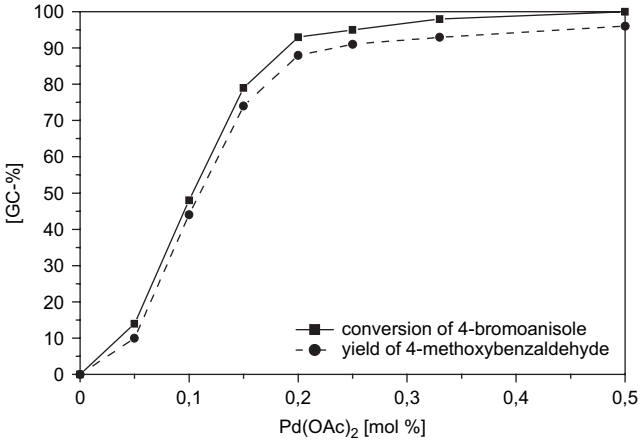


Figure 2. Influence of catalyst concentration on conversion and yield of the model reaction. Reaction conditions: 2 mmol 4-bromoanisole, $Pd(OAc)_2$/cata*CX*ium® A=1:3, 0.75 equiv TMEDA, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 5 bar CO/H_2 (1:1), 100 °C, 16 h.

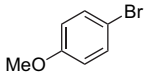
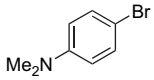
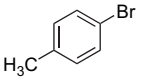
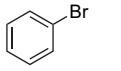
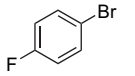
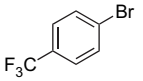
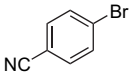
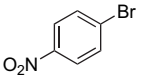
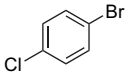
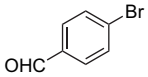
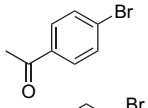
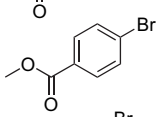
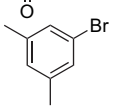
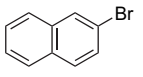
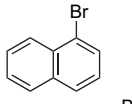
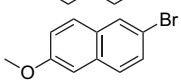
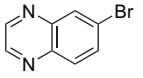
The promising results obtained with di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) encouraged us to study the general scope and limitations of this catalyst system for the formylation of different aryl and heteroaryl bromides (Table 2).

High conversion and excellent selectivity (>90%) are observed for the formylation of various monosubstituted aryl bromides such as 4-bromoanisole, 4-bromofluorobenzene, 4-bromobenzonitrile, 4-(dimethylamino)bromobenzene, methyl 4-bromobenzoate, 4-bromoacetophenone, and 4-bromochlorobenzene (Table 2, entries 1, 5, 7, 2, 14, 13, and 9). Problematic is the carbonylation of 4-bromonitrobenzene due to deactivation of the catalyst. The formylation protocol works well also with 1-bromo-3,5-xylene, different bromonaphthalenes (Table 2, entries 15–18), and heteroaryl halides such as 3-bromothiophene and 3-bromopyridine (Table 2, entries 11 and 12). This is of special importance since heteroaromatic aldehydes are particularly useful intermediates for the synthesis of a number of biologically active molecules.[16] In case of 2-bromopyridine the catalyst seems to be deactivated by the formation of inactive dimers after the oxidative addition step.

Since all experiments shown in Table 2 were performed under similar conditions no significant difference in the rate of electron-rich substrates (e.g., 4-bromoanisole, 4-(dimethylamino)bromobenzene) and electron-deficient educts (e.g., 4-bromobenzonitrile, 4-bromoacetophenone) was observed. Thus, we conducted competition experiments in order to investigate the effect of electron-withdrawing and electron-donating substituents. Equimolar amounts of bromobenzene and the corresponding *para*-substituted derivatives were reacted with synthesis gas for 2 h. For data interpretation, we employed the Hammett equation

$$\log\frac{k}{k_0} = \sigma\rho$$

Table 2. Scope and limitations of the $Pd(OAc)_2$/di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) catalyst system

Entry	(Hetero)aryl bromide	Conversion[a] [%]	Yield[a] [%]	Selectivity[a] [%]
1		98	94	95
2		99	98	99
3		74	71	96
4		95	95	99
5		98	89	91
6		100	84	84
7		99	74	75
8		8	0	0
9		100	89	89
10		100	87	87
11		97	82	85
12		97	77	79
13		100	88	88
14		100	91	91
15		85	85	>99
16		100	92	92
17		100	86	86
18		100	99	99
19		100	85	85

Reaction conditions: 2 mmol (hetero)aryl bromide, 0.25 mol % $Pd(OAc)_2$, 0.75 mol % cata*CX*ium® A, 0.75 equiv TMEDA, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 5 bar CO/H_2 (1:1), 100 °C, 16 h.
[a] Determined by gas chromatography.

where k is the rate constant of the reaction of the substituted compound, k_0 is the value for bromobenzene, σ is a constant characteristic of the substituent, and ρ is the specific reaction constant. For six different substituents the Hammett σ-values were linearly correlated with the change in relative rate constants.[17]

As shown in Figure 3, the reaction mechanism is consistent for the different substituted bromoarenes. The relative rate constant increases with increasing σ, reflecting a reaction rate that is enhanced by a decreased electron density of the aromatic ring. As a result it is likely that the oxidative addition of the active palladium species to the aryl halide constitutes the rate-determining step.

Next, we studied the reductive carbonylation of vinyl halides in the presence of different catalyst systems. Here, the formylation of (*E*)-2-bromo-2-butene was investigated as a model system in the presence of six different phosphines (Table 3, entry 1, entries 7–11).

In agreement with the results obtained for aryl bromides only cata*CX*ium® A permitted an efficient formylation of our model system (yield: 98%; Table 3, entry 1). Triphenylphosphine, the standard bidentate ligand 1,4-bis(diphenylphosphino)butane, and P(*t*-Bu)$_3$ gave only low yields of *trans*-2-methyl-2-butenal (1–12%) (Table 3, entries 7, 8, 11). On the other hand, PCy_3 and 1,1′-bis(diphenylphosphino)ferrocene (dppf) gave slightly higher, but no sufficient yields (22–30%) of the desired product (Table 3, entries 9–10).

After the ligand screening, the influence of different solvents, pressure, and bases (Table 3, entries 1–6) has also been studied. In general, we obtained similar trends as for the formylation of (hetero)aryl bromides. Toluene and THF gave better results than the more polar solvents DMF, *N*,*N*-dimethylacetamide, and NMP. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) is again the most active base

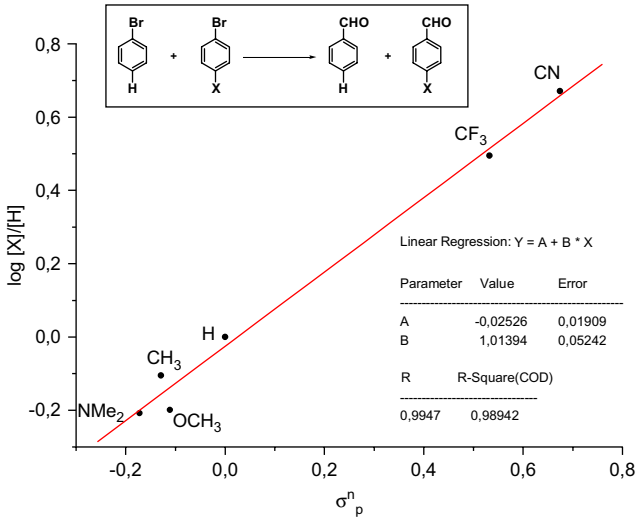
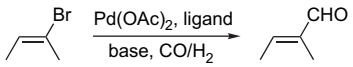


Figure 3. Relationship between rate constant and Hammett σ-values for *para*-substituents. Reaction conditions: 1 mmol bromobenzene, 1 mmol *para*-substituted bromobenzene, 0.25 mol % $Pd(OAc)_2$, 0.75 mol % cata*CX*ium® A, 0.75 equiv TMEDA, 0.2 equiv hexadecane (internal standard), 2 mL toluene, 5 bar CO/H_2 (1:1), 100 °C, 2 h.

Table 3. Palladium-catalyzed formylation of (*E*)-2-bromo-2-butene



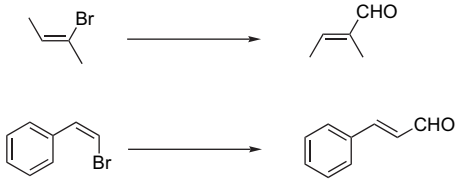
Entry	Ligand	Base	CO/H_2 [bar]	*T* [°C]	Conversion[a] [%]	Yield[a] [%]	Selectivity[a] [%]
1	cata*CX*ium® A	TMEDA	7.5	100	100	98	98
2		NEt_3	7.5	100	88	48	54
3		DABCO	7.5	100	88	50	56
4		$(CH_3)_2NCH_2COOC_2H_5$	7.5	100	89	19	22
5		K_2CO_3	7.5	100	99	46	46
6		K_2HPO_4	7.5	100	52	1	1
7	PPh_3	TMEDA	7.5	100	86	1	1
8	P(*t*-Bu)$_3$	TMEDA	7.5	100	40	12	30
9	PCy_3	TMEDA	7.5	100	51	22	44
10	dppf	TMEDA	7.5	100	98	30	31
11	dppb	TMEDA	7.5	100	46	9	19

Reaction conditions: 2 mmol (*E*)-2-bromo-2-butene, 0.5 mol % $Pd(OAc)_2$, 1.5 mol % cata*CX*ium®A, 0.75 equiv TMEDA, 0.2 equiv dodecane (internal standard), 2 mL toluene, 16 h.
[a] Determined by gas chromatography.

for the model substrate. Complete conversion and excellent yield (>98%) are obtained at a synthesis gas pressure of 7.5 bar.

Finally, the scope of the optimized catalyst system for the reductive carbonylation of vinyl halides was tested with eight different substrates (Table 4). In addition to 2-bromo-2-butene, 1-chloro-1-cyclopentene, 1-bromostyrene, and 2-bromo-3-methyl-2-butene yielded the corresponding α,β-unsaturated aldehydes in mediocre to very good yield (41–98%). Unfortunately, no desired reaction is observed applying 1-bromo-1-propene and methyl 2-bromoacrylate as substrates. Noteworthy, the formylation of (*Z*)-2-bromo-2-butene and *cis*-β-bromo-styrene[18] gave selectively the corresponding *trans*-aldehydes (Scheme 2).

Apparently, the initially generated oxidative addition product is not stable under these conditions and rearranges to the thermodynamically more stable *trans*-product. This is in contrast with other palladium-catalyzed coupling reactions of vinyl halides.[19]

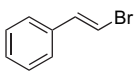
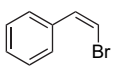


Scheme 2. Reductive carbonylation leading to α,β-unsaturated *trans*-aldehydes.

3. Conclusion

In conclusion, we presented a general reductive carbonylation procedure for the synthesis of aromatic and heteroaromatic aldehydes, as well as α,β-unsaturated aldehydes.

Table 4. Reductive carbonylation of different vinyl halides

Entry	Vinyl halide	$Pd(OAc)_2$ [mol %]	cata*CX*ium® A [mol %]	Conversion[a] [%]	Yield[a] [%]	Selectivity[a] [%]
1		0.5	1.5	100	98	98
2[b]		0.5	1.5	92	76	82
3		0.5	1.5	96	87	91
4		0.5	1.5	100	59	59
5[c]		0.5	1.5	100	51	51
6		0.5	1.5	64	41	59

Reaction conditions: 2 mmol vinyl halide, 0.75 equiv TMEDA, 0.2 equiv dodecane (internal standard), 2 mL toluene, 7.5 bar CO/H_2 (1:1), 100 °C, 16 h.
[a] Determined by gas chromatography.
[b] As product only *trans*-2-methyl-2-butenal is formed.
[c] Only *trans*-cinnamaldehyde is observed.

Advantageously, the most simple and environmentally benign formylation source synthesis gas can be used at ambient pressure and low catalyst concentration. The ligand di-1-adamantyl-*n*-butylphosphine (cata*CX*ium® A) leads to a highly active catalyst species, but is comparably stable to air and moisture, and thus easy to handle. Due to its superior performance compared with other palladium catalysts, this system is employed for the industrial production of a drug intermediate on multi-1000 kg scale.

4. Experimental section

4.1. General remarks

All reactions were performed using standard Schlenk techniques (argon). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 spectrometer. Chemical shifts (δ) are given in ppm and refer to the residual solvent as the internal standard ($CDCl_3$: 7.26/77.0). Gas chromatography was performed on a Hewlett Packard HP 6890 chromatograph with a HP1 column. Chemicals were purchased from Fluka, Aldrich, and Strem, and used as received. The cata*CX*ium® A ligand is available from Strem or directly from Degussa. Solvents were distilled from sodium and benzophenone.

4.2. General procedure for the formylation of (hetero)-aryl bromides and vinyl halides

A 50 mL Schlenk flask was charged with $Pd(OAc)_2$ (11.2 mg, 0.25 mol %), cata*CX*ium® A (53.8 mg, 0.75 mol %), and toluene (20 mL). Subsequently, hexadecane (1.17 mL, internal GC standard) and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) (2.25 mL, 15 mmol) were added. About 2.34 mL of this clear yellow stock solution was transferred to six vials (4 mL reaction volume) equipped with a septum, a small cannula, a stirring bar, and 2 mmol of the corresponding (hetero)aryl bromide. The vials were placed in an alloy plate, which was transferred to a 300 mL autoclave of the 4560 series from Parr Instruments® under argon atmosphere. After flushing the autoclave three times with CO/H_2 (1:1), the appropriate synthesis gas pressure was adjusted to ambient temperature and the reaction was performed for 16 h at 100 °C. Before and after the reaction an aliquot of the reaction mixture was subjected to GC analysis for determination of yield and conversion.

4.2.1. Quinoxaline-6-carbaldehyde. R_f (SiO_2, *n*-heptane/EtOAc=3:1): 0.1. Yield: 85%. Yellow solid, mp 130–131 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ=10.28 (s, 1H, CHO), 9.09 (m, 2H, NCH=CHN), 8.71 (s, 1H, OHCCC*H*CN), 8.22 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=192.8 (C=O), 148.0 (CH), 147.1 (CH), 145.0, 141.9, 136.8, 134.5 (CH), 130.4 (CH), 126.6 (CH). MS (EI, 70 eV): *m*/*z* (%)=158 (100) M^+, 129 (49) $[M-CHO]^+$, 103 (32), 75 (23), 50 (13). IR (KBr): 1697 (vs) [C=O], 1353 (s), 1226 (m), 1142 (m), 1118 (s), 1024 (s), 960 (s), 914 (s), 880 (m), 832 (m), 774 (s), 760 (m) cm^{-1}. HR-MS (EI): calcd for $C_9H_6N_2O$: 158.0475; found: 158.04706 $[M]^+$.

4.2.2. 1-Cyclopentene-1-carbaldehyde. Yield: 87%. Colorless liquid, bp 47–48 °C (14 Torr).[20] ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.78 (s, 1H, CHO), 6.87 (m, 1H, C*H*=CCHO), 2.60 (m, 2H, CH_2), 2.51 (m, 2H, CH_2), 1.99 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.9 (C=O), 153.2 (CH), 147.9, 33.7 (CH_2), 28.3 (CH_2), 22.9 (CH_2). MS (EI, 70 eV): *m*/*z* (%)=96 (62) M^+, 67 (100) $[M-CHO]^+$, 41 (29), 39 (30). IR (capillary): 2957 (m), 2714 (w), 1679 (vs) [C=O], 1615 (m) cm^{-1}. HR-MS (EI): calcd for C_6H_8O: 96.0570; found: 96.0571 $[M]^+$.

4.2.3. 2,3-Dimethyl-2-butenal. Yield: 41%. Colorless liquid, bp 57 °C (20 Torr).[21] ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.12 (s, 1H, CHO), 2.19 (m, 3H, CH_3), 1.96 (m, 3H, CH_3), 1.74 (m, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=191.2 (C=O), 155.0, 132.6, 23.8 (CH_3), 19.4 (CH_3), 11.0 (CH_3). MS (EI, 70 eV): *m*/*z* (%)=98 (100) M^+, 69 (45) $[M-CHO]^+$, 55 (45), 41 (79), 39 (30). IR (capillary): 1671 (vs) [C=O], 1635 (s) [C=C] cm^{-1}. HR-MS (EI): calcd for $C_6H_{10}O$: 98.0726; found: 98.0720 $[M]^+$.

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References and notes

1. (a) Kikukowa, K.; Kono, K.; Wada, F.; Matsuda, T. *Chem. Lett.* **1982**, 35–36; (b) Kobayashi, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1981**, 333–334; (c) Tanaka, M. *Tetrahedron Lett.* **1979**, *20*, 2601–2602.
2. Cassar, L.; Foa, M.; Gardano, A. *J. Organomet. Chem.* **1976**, *121*, C55–C56.
3. (a) El-ghayoury, A.; Ziessel, R. *J. Org. Chem.* **2000**, *65*, 7757–7763; (b) Martin, L. D.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 3630–3633; (c) Murray, T. F.; Samsel, E. G.; Varma, V.; Norton, J. R. *J. Am. Chem. Soc.* **1981**, *103*, 7520–7528; (d) Tanaka, M.; Koyanagi, M.; Kobayashi, T. *Tetrahedron Lett.* **1981**, *22*, 3875–3878; (e) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193–4198; (f) Ito, T.; Mori, K.; Mizoroki, T.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2091–2094; (g) Hidai, M.; Hikita, T.; Wada, Y.; Fujikura, Y.; Uchida, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2075–2077; (h) Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 532–534; (i) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318–3326.
4. (a) Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* **2002**, *4*, 2849–2851; (b) Etridge, S. K.; Hayes, J. F.; Walsgrove, T. C.; Wells, A. S. *Org. Process Res. Dev.* **1999**, *3*, 60–63; (c) Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 433–446; (d) Kondo, T.; Sone, Y.; Tsuji, Y.; Watanabe, Y. *J. Organomet. Chem.* **1994**, *473*, 163–173; (e) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1982**, *231*, C12–C14; (f) Ozawa, F.; Soyama, H.; Yamamoto, T.; Yamamoto, A. M. *Tetrahedron Lett.* **1982**, *23*, 3383–3386; (g) Ishikura, M.; Mori, M.; Terashima, M.; Ban, Y.

J. Chem. Soc., Chem. Commun. **1982**, 741–742; (h) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.

5. For α-oxo-amides, see: (a) Ozawa, F.; Soyama, H.; Yanagihara, H.; Aoyama, I.; Takino, H.; Izawa, K.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235–3245; (b) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1982**, *233*, C64–C66; for α-oxo-esters, see: (c) Morin, B.; Hirschauer, A.; Hugues, F.; Commereuc, D.; Chauvin, Y. *J. Mol. Catal.* **1986**, *34*, 317–319; (d) Tanaka, M.; Kobayashi, T. A.; Skakura, F.; Itatani, N.; Danno, S.; Zushi, K. *J. Mol. Catal.* **1985**, *32*, 115–118; for α-oxo-acids, see: (e) Tanaka, M.; Kobayashi, T. A.; Sakakura, T. *J. Chem. Soc., Chem. Commun.* **1985**, 837–838.
6. Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761–7764.
7. (a) Kikukawa, K.; Totoki, T.; Wada, F.; Matsuda, T. *J. Organomet. Chem.* **1984**, *207*, 283–287; (b) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1984**, *49*, 4009–4011.
8. (a) Baillardgeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452–461; (b) Baillardgeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175–7176.
9. (a) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1989**, 1816–1817; (b) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1988**, *53*, 624–626; (c) Okano, T.; Harada, N.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2329–2332; (d) Cai, M. Z.; Zhao, H.; Zhou, J.; Song, C.-S. *Synth. Commun.* **2002**, *32*, 923–926.
10. Cacchi, S.; Fabrizi, G.; Goggiamani, A. *J. Comb. Chem.* **2004**, *6*, 692–694.
11. Klaus, S.; Neumann, H.; Zapf, A.; Strübing, D.; Hübner, S.; Almena, J.; Riermeier, T.; Groß, P.; Sarich, M.; Krahnert, W.-R.; Rossen, K.; Beller, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 154–156.
12. For a personal account, see: Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431–440.
13. (a) Mägerlein, W.; Indolese, A. F.; Beller, M. *J. Organomet. Chem.* **2002**, *641*, 30–40; (b) Beller, M.; Indolese, A. F. *Chimia* **2001**, *55*, 684–687; (c) Schnyder, A.; Beller, M.; Mehltretter, G.; Indolese, A. F.; Nsenda, T.; Studer, M. *J. Org. Chem.* **2001**, *66*, 4311–4315; (d) Mägerlein, W.; Indolese, A. F.; Beller, M. *Angew. Chem.* **2001**, *113*, 2940–2943; *Angew. Chem., Int. Ed.* **2001**, *40*, 2856–2859; (e) Mägerlein, W.; Indolese, A. F.; Beller, M. *J. Mol. Catal. A: Chem.* **2000**, *156*, 213–221.
14. These ligands are commercially available on industrial-scale under the trade name cata*CX*ium® A. For catalytic applications of adamantylphosphines, see: (a) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, 1589–1592; (b) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem.* **2000**, *112*, 4315–4317; *Angew. Chem., Int. Ed.* **2000**, *39*, 4153–4155; (c) Ehrentraut, A.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 515–523; (d) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209–217; (e) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Synthesis* **2004**, 935–941; (f) Frisch, A.; Shaik, N.; Zapf, A.; Beller, M.; Briel, O.; Kayser, B. *J. Mol. Catal.* **2004**, *214*, 231–239; (g) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Tetrahedron* **2005**, *61*, 9705–9709; (h) Neumann, H.; Brennführer, A.; Groß, P.; Riermeier, T.; Almena, J.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 1255–1261; (i) Tillack, A.; Hollmann, D.; Michalik, D.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8881–8885; (j) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087–1090.
15. These ligands are commercially available up to multi-kg-scale under the trade name cata*CX*ium® P. For catalytic applications, see: (a) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38–39; (b) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 2983–2990; (c) Beller, M.; Zapf, A.; Riermeier, T. H. *Chem. Oggi* **2004**, *11–12*, 16–20 (Supplement Chiral Catalysis); (d) Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T. H.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742–1748; (e) Harkal, S.; Kumar, K.; Michalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 3237–3240.
16. For the importance of heteroaromatic derivatives in agrochemicals, see: Stetter, J.; Lieb, F. *Angew. Chem.* **2000**, *112*, 1793–1812; *Angew. Chem., Int. Ed.* **2000**, *39*, 1724–1744.
17. The σ^n-values were derived by van Bekkum, Verkade, and Wepster, see: van Bekkum, H.; Verkade, P. E.; Wepster, B. M. *Rec. Trav. Chim.* **1959**, *78*, 815–850.
18. For the synthesis of *cis*-β-bromo-styrene, see: Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron Lett.* **2001**, *42*, 3893–3896.
19. (a) Lee, P. H.; Seomonn, D.; Lee, K. *Org. Lett.* **2005**, *7*, 343–345; (b) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950–3956; (c) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* **2002**, *67*, 8450–8456; (d) Lu, L.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 7673–7676; (e) Jiang, B.; Xu, Y. *Tetrahedron Lett.* **1992**, *33*, 511–514; (f) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813–817; (g) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *36*, 3437–3440; (h) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729–6731.
20. For comparison, see: Maitte, P. *Bull. Soc. Chim. Fr.* **1959**, 499–504.
21. For comparison, see: Blanco, L.; Amice, P.; Conia, J.-M. *Synthesis* **1981**, *4*, 291–293.