EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

Title: Palladium-Catalyzed Reductive Carbonylation of (Hetero) Aryl halides and Triflates using Cobalt carbonyl as CO Source

Authors: Bhushanarao Dogga, C S Ananda Kumar, and Jayan T Joseph

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202001328

Link to VoR: https://doi.org/10.1002/ejoc.202001328

WILEY-VCH

Palladium-Catalyzed Reductive Carbonylation of (Hetero) Aryl halides and Triflates using Cobalt carbonyl as CO Source

Bhushanarao Dogga,[a,b] C S Ananda Kumar,[a] * Jayan T Joseph[b]*

[a] Bhushanarao Dogga, Dr. C S Ananda Kumar. Department of Nanotechnology, Visvesvaraya Technological University, CPGS Bangalore Region, Muddenahalli, Bangalore, 562101, India. e-mail: csanandakumar@gmail.com

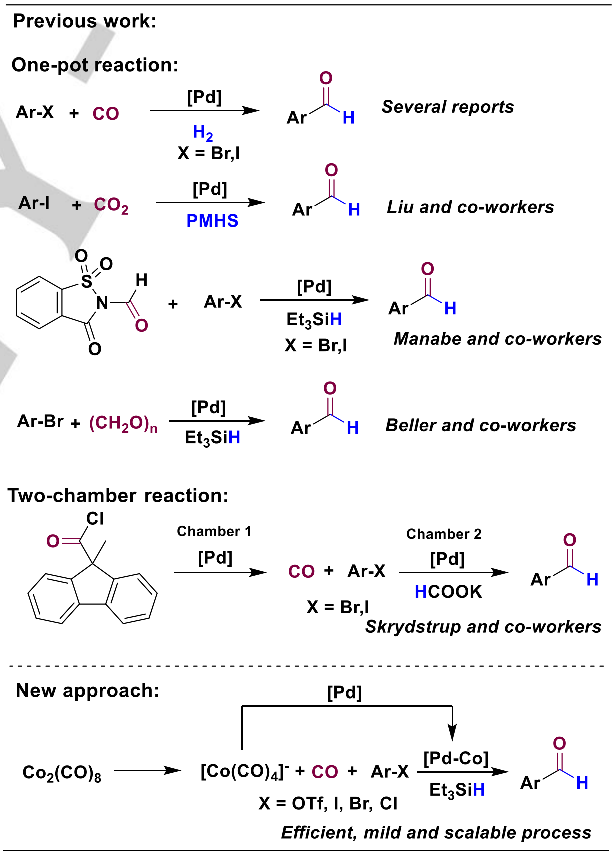
[b] Bhushanarao Dogga, Dr. Jayan T Joseph. Syngene International Ltd., Biocon Park, Bommasandra IV Phase, Jigani Link Road, Bangalore, 560099, India. Fax: (+91)-80-28082704; e-mail: jayan.joseph@syngeneintl.com.

Abstract: An efficient protocol for the reductive carbonylation of (hetero) aryl halides and triflates under CO gas free conditions using Pd/$Co_2(CO)_8$ and triethylsilane has been developed. The mild reaction conditions, enhanced chemoselectivity and, easy access to heterocyclic and vinyl carboxaldehydes highlights its importance in organic synthesis.

The generation of aldehyde, a key and reactive functional group for further transformations, by selective reactions from a choice of starting materials remains a topic of investigation for many research groups, both in the fine chemical and pharmaceutical industry. The commonly used methods are reduction of carboxylic acids or its activated ester derivatives, oxidation of alcohols, electrophilic formylation reactions, hydroformylation of alkenes, and others.[1] However, highly specific reaction parameters, multiple steps, and stoichiometric amounts of reagents used and waste generated limit these methodologies.[2] More importantly, the use of highly basic, acidic or reactive reagents, reduces the scope of functional groups which can be tolerated in these reactions. On the other hand, transition metal-catalyzed reductive carbonylations employing CO gas serves as an efficient and useful alternative for the aldehyde synthesis.[3] The high chemoselectivity and greater functional group tolerance make it superior to conventional strategies. Ever since its discovery by Heck and co-workers in 1974, metal-catalyzed reductive carbonylation using gaseous CO has evolved considerably, which is evident from the number of research articles published.[4]

Of late, gas-free carbonylation has been developed using a range of CO surrogates such as formates, formamides, formic acids, anhydrides, acid chlorides, silacarboxylic acids, metal carbonyls, and others.[5-11] The enhanced safety and automation readiness of this methodology allowed many researchers to use them routinely in natural products, medicinal chemistry as well as high throughput synthesis.

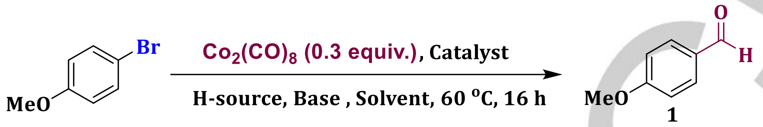
Recently, we have reported a mild protocol for the amino, alkoxy and hydroxy carbonylation of triflates and pentafluorobenzenesulfonates using cobalt carbonyl at room temperature.[12] The detailed mechanistic study revealed that supremacy of this methodology arises from 1) the use of metal carbonyl as solid, stoichiometric CO surrogate producing CO gas at room temperature and, 2) the augmented CO insertion facilitated by a bimetallic Pd-$Co(CO)_4$ catalyst generated *in situ* in the reaction mixture. Though there are many methods available for palladium-catalyzed hydroxy, alkoxy and aminocarbonylations of aryl/vinyl (pseudo)halides using CO surrogates, relatively lesser number of protocols are reported for demanding reductive carbonylation. In 2013, Skrydstrup and co-workers introduced a sealed, two-chamber system (COgen) for the *ex situ* generation of CO using solid CO surrogate and reported several efficient carbonylations.[13] They used potassium formate as the hydride source for the reductive carbonylation of aryl iodides and bromides, and also reported selective ^{13}C and deuterium labelling. In the same year, Manabe and co-workers reported another efficient palladium catalyzed reductive carbonylation of aryl bromides using *N*-formylsaccharin as CO source and Et_3SiH as reducing agent.[14]



Also, Beller's group has modified their previously reported reductive carbonylation protocol using syngas with readily available paraformaldehyde and Et_3SiH.[15] Liu and co-workers reported a direct formylation of aryl iodides using CO_2 and Et_3SiH.[16] Of late, Min Lie and Lihong Hu reported formylation of aryl iodides using HCOOH, serving as both CO and hydride source.[17] These encouraging results, together with our continuous interest in developing new carbonylation methodologies using cobalt carbonyl, prompted us to explore its potential in the challenging reductive carbonylation space. We envisioned that the easily accomplished acylpalladium complex through Pd-Co(CO)$_4$ bimetallic catalyst could be trapped efficiently using a hydride donor, producing aldehydes in good yield.

Our initial optimization study was focused on the reductive carbonylation of deactivated 4-Bromo anisole using cobalt carbonyl with different catalyst systems and silanes (Table 1). In agreement with our previous report on carbonylation, both Pd(OAc)$_2$/XantPhos and Pd(dppf)Cl$_2$.CH$_2$Cl$_2$ adduct displayed excellent catalytic activity when used in combination with Et$_3$SiH and KOAc in 1,4-dioxane at 60 °C (Table 1, entry 1 and 2).

Table 1. Optimization of the Reaction Conditions. [a]



Entry	Catalyst (mol %)	Ligand (mol %)	H-Source (equiv.)	Base (equiv.)	Solvent	Yield (%)
1	Pd(OAc)$_2$ (5)	XantPhos (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	70
2	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	76
3	Pd(OAc)$_2$ (5)	dppf (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	63
4	Pd(OAc)$_2$ (5)	dppe (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	44
5	Pd(OAc)$_2$ (5)	dppp (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	31
6	Pd(OAc)$_2$ (5)	dppb (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	27
7	Pd(OAc)$_2$ (5)	DPEPhos (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	46
8	Pd(OAc)$_2$ (5)	BINAP (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	52
9	Pd(OAc)$_2$ (5)	JosiPhos (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	33
10	Pd(OAc)$_2$ (5)	XPhos (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	8
11	Pd(OAc)$_2$ (5)	P(Cy)$_3$.HBF$_4$ (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	11
12	Pd(OAc)$_2$ (5)	P(t-Bu)$_3$ (5)	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	6
13	Pd(OAc)$_2$ (5)	-	Et$_3$SiH (2)	KOAc (3)	1,4-Dioxane	0
14	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	HCOONa (4)	-	1,4-Dioxane	0
15	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Oct$_3$SiH (2)	KOAc (3)	1,4-Dioxane	37
16	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Ph$_3$SiH (2)	KOAc (3)	1,4-Dioxane	14
17	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	i-Pr$_3$SiH (2)	KOAc (3)	1,4-Dioxane	0
18	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	PMHS (2)	KOAc (3)	1,4-Dioxane	46
19	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Et$_3$SiH (2)	NaOAc (3)	1,4-Dioxane	79
20	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Et$_3$SiH (2)	Na$_2$CO$_3$ (3)	1,4-Dioxane	12
21	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Et$_3$SiH (2)	Et$_3$N (3)	1,4-Dioxane	0
22	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Et$_3$SiH (2)	NaOAc (3)	DMF	74
23	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Et$_3$SiH (2)	NaOAc (3)	CH$_3$CN	82
24	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Et$_3$SiH (2)	NaOAc (3)	NMP	71
25	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Et$_3$SiH (2)	NaOAc (3)	THF	43
26	PdCl$_2$dppf.CH$_2$Cl$_2$ (5)	-	Et$_3$SiH (1.5)	NaOAc (2)	CH$_3$CN	84

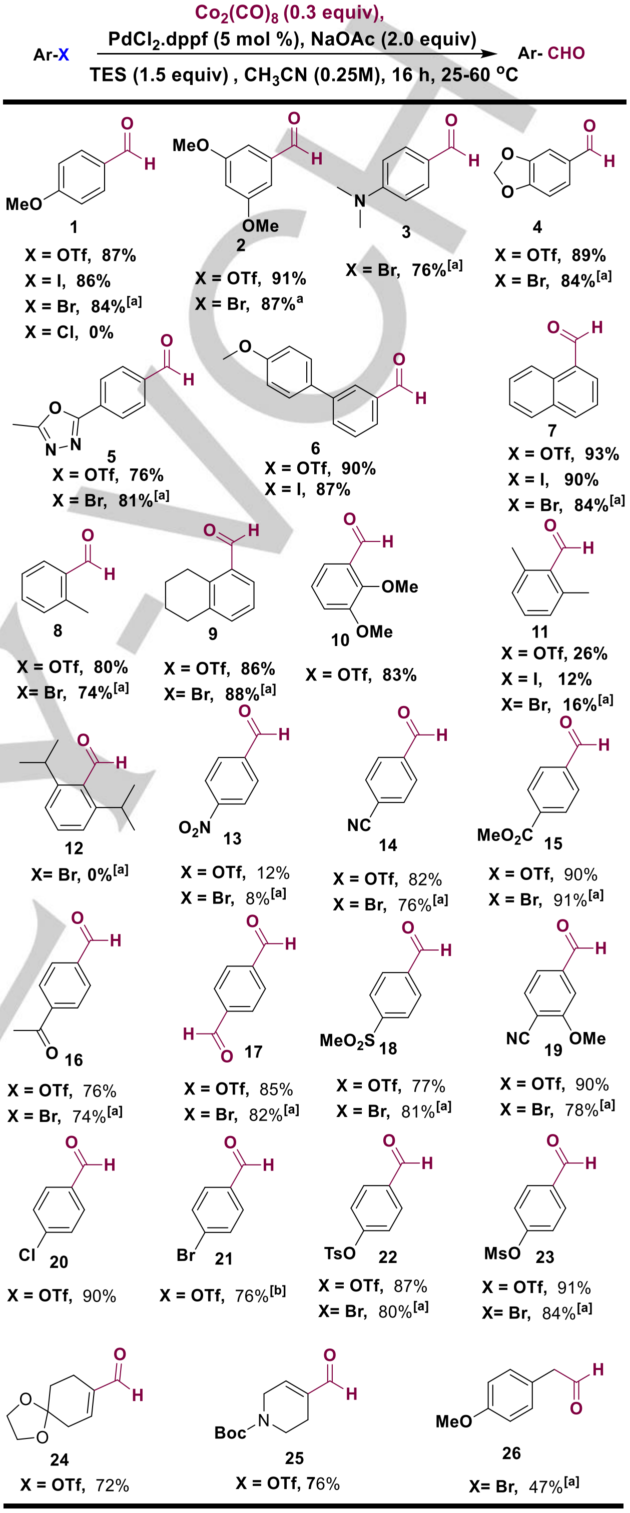
[a] Reaction condition: Ar-X (0.5 mmol), catalyst, base, solvent (0.25 M).

Next, a selection of commercially available mono and bidentate phosphines as well as Pd precursors were screened, but only with little success, highlighting the complex nature of reductive carbonylation (Table 1, entries 4-12). Among the silanes screened Et_3SiH gave the best result. The higher and branched ones (Oct_3SiH, Ph_3SiH, i-Pr_3SiH, and PMHS) resulted in lower yields underlining the steric dependence in the transmetallation step of catalytic cycle (Table 1, entries 15-18). Further, the effects of base and solvent were investigated using $Pd(dppf)Cl_2.CH_2Cl_2$ as the catalyst and Et_3SiH as the reductant. NaOAc turned out to be the best with 79% aldehyde yield (Table 1, entry 19). We also have observed that Na_2CO_3 and Et_3N, used extensively in reductive carbonylation, produce dehaloginated starting material as the major product (Table 1, entry 20 and 21). The optimal solvent was found to be CH_3CN, with slightly lower yields for 1,4-dioxane and DMF (Table 1, entries 22-25). Additional parameters such as catalyst loading, and reagents stoichiometry were explored to give the best result (See Table S1 in the supporting Information). The optimum catalyst loading was 5 mol%, and below this, a significant amount of unreacted starting material was recovered. Also, 2.0 and 1.5 equivalents of NaOAC and Et_3SiH, respectively, was found ideal (Table 1, entry 26).

With this optimized protocol in hand, we next explored the scope of this methodology using diverse substrates, as shown in Scheme 1. Our trials with different 4-methoxyphenyl (pseudo) halides revealed that triflate and iodide could effect this conversion even at 40 °C and with very good yield (1). Further, a set of electron-donating and neutral substrates were screened, and the reaction condition developed was found to be general for a variety of electronically diverse aryl halides and triflates (2-7). In activated systems, the carbonylation of triflate and iodide proceeded well at room temperature and the respective bromides at 60 °C (14-19). In agreement with many previous reports, 4-nitrobromobenzene continued to pose a problem,[3d,18] with undesired dehalogenation, and nitro group reduction dominated the reaction products (13).

Chemoselective synthesis of aldehydes from a choice of (pseudo) halides can be a powerful tool in advanced organic synthesis. With this mild protocol, selective formylation of triflates can be achieved in the presence of chloro, bromo and other pseudo halides (20-23). Also, the successful synthesis of vinyl and benzyl aldehydes in good yield (24-26) makes this methodology valuable for natural product synthesis. We next attempted the carbonylation of sterically hindered aryl halides. While *ortho*-substituted substrates worked well (7-10), the steric hindrance induced by 2,6-disubstitution decreased the reaction yield significantly (11 and 12).

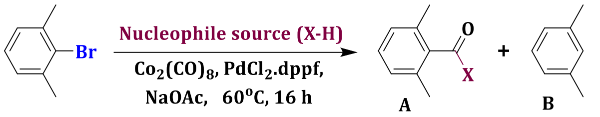
Further, to understand as well as to overcome the steric dependency of this protocol, we performed a set of experiments as in Table 2. We chose hindered 2,6-dimethyl bromobenzene as the substrate and, different catalyst systems and nucleophiles, in order to derive a correlation between their sizes and carbonylation efficiency. For alkoxycarbonylation, with the use of electron-rich, bulky JosiPhos ligand for enhanced oxidative addition, the yield of methyl ester could be increased significantly (Table 2, entry 2). But, with secondary and tertiary alcohols, dehaloginated starting material was recovered, confirming the steric dependency of acylpalladium complex in reductive elimination (Table 2, entries 3 and 4). We also observed that a similar trend holds good for the hydride transfer step of reductive carbonylation. While H_2 resulted in moderate conversion (Table 2, entry 7), silanes were not useful with bulky phosphine ligands, forcing us to speculate that the bulkiness of phosphine and hydride transfer reagent has to be balanced for a successful reductive carbonylation (Table 2, entries 6 and 8).



Reaction condition: Ar-X/OTf (1 mmol), catalyst, base, solvent (0.25 M).Yields represent isolated yields. [a] At 60 °C, 16 h. [b] 16% of dicarboxaldehyde.

Scheme 1. Reductive Carbonylation of Ar-X/OTf.

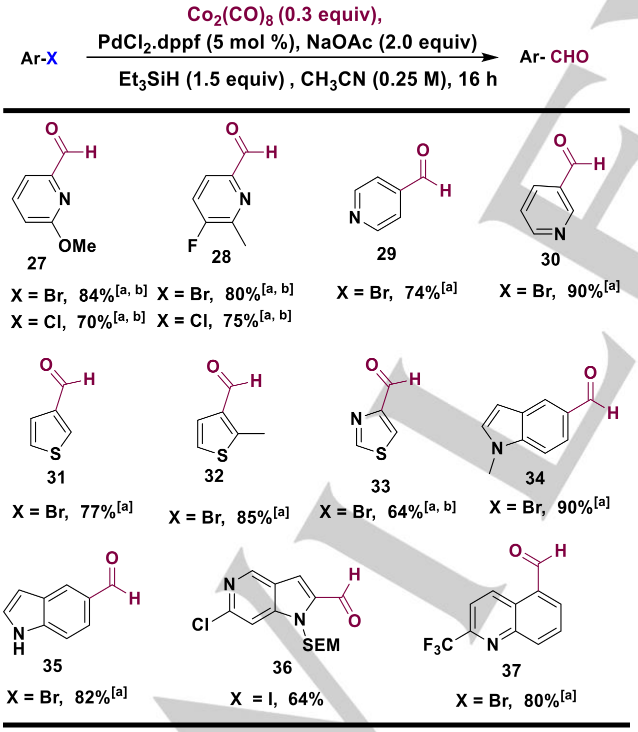
Table 2. Steric effects in Reductive Carbonylation. [a]



Entry	Catalyst / Ligand	Nucleophile source (X-H)	Yield (%)	A/B
1	$PdCl_2dppf.CH_2Cl_2$	MeOH	46/3	
2	$Pd(OAc)_2$ /JosiPhos	MeOH	78/16	
3	$Pd(OAc)_2$ /JosiPhos	i-PrOH	19/65	
4	$Pd(OAc)_2$ /JosiPhos	t-BuOH	0/88	
5	$PdCl_2dppf.CH_2Cl_2$	Et_3SiH	16/49	
6	$Pd(OAc)_2$ /JosiPhos	Et_3SiH	0/71	
7	$Pd(OAc)_2$ /JosiPhos	H_2	47/23	
8	$Pd(OAc)_2$ /JosiPhos	Ph_3SiH	0/78	

[a]Reaction condition: Ar-X (1 mmol), catalyst, base, CH_3CN (0.25 M).

Efficient and selective formylation of heteroaryl substrates is highly demanding as they constitute an integral part of many APIs and agrochemical syntheses. We next explored the efficacy of this new reductive carbonylation conditions with heteroaryl substrates (Scheme 2).

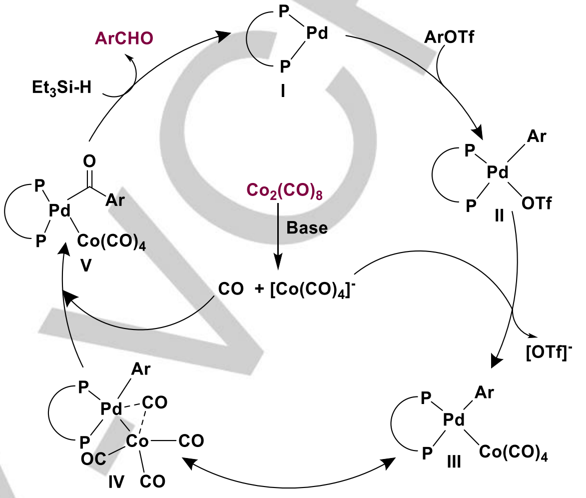


Reaction condition: Ar-X (1.0 mmol), catalyst, base, solvent (0.25 M). [a] At 60 °C, 16 h. [b] With 1.0 equiv. of TBAB.

Scheme 2. Reductive carbonylation of heteroaromatic halides.

This protocol now enables us to synthesize diverse five, six and fused ring heteroaryl carboxaldehydes with encouraging yields. Notably, indole with unprotected NH could be formylated without any side reactions (35). For 2-chloropyridine and thiazole substrates, the use of TBAB as additive enhanced the reaction yield considerably (27, 28 and 33). Also, to demonstrate the scalability of this reaction for industrial application we have successfully synthesized *N*-methylindole-5-carboxaldehyde (34) in 10 mmol scale using miniclave apparatus.

Based on the experimental results and our previous report on cobalt carbonyl mediated carbonylation featuring the mechanistic investigation,[12] a plausible reaction mechanism was proposed (Scheme 3).



Scheme 3. Mechanistic Proposal

Oxidative addition of activated catalyst species (**I**) into the carbon-(pseudo)halide bond leads to the cationic complex (**II**). In the next step, nucleophilic displacement (pseudo)halide by $[Co(CO)_4]^-$ occurs forming bimetallic catalytic species (**III**). Migration of bent, semi-bridging CO ligand from Co to Pd followed by its insertion into Ar-Pd bond results in the formation of acylpalladium complex (**V**). At this stage, the excess CO gas present in the reaction medium enters the catalytic cycle and regenerates the Pd-$Co(CO)_4$ intermediate. The acyl complex (**V**) then reacts with triethylsilane followed by reductive elimination to yield the aldehyde

In conclusion, we have developed a generalized protocol for the formylation of (pseudo)halides using Co2(CO)8 and triethyl silane. The method is tolerant to a range of functional groups on aromatic rings and for triflates and iodides the reaction works efficiently at room temperature. Additionally, the enhanced safety, high chemoselectivity and easy access to a number of heterocyclic and vinyl carboxaldehydes highlights its importance in routine organic synthesis. Further investigation on its application to less reactive aryl chlorides as well as C-H formylation is in progress at our laboratory.

Experimental Section

General Procedure for the Carbonylation Reaction

To a Schlenk tube equipped with a magnetic stirring bar and a Teflon septum was charged NaOAc (2.0 mmol, 2 equiv.), aryl halide or triflate (1.0 mmol, 1.0 equiv.) in acetonitrile (0.25 M) and $Pd(dppf)Cl_2.CH_2Cl_2$ (0.05 mmol, 5 mol%). The tube was then capped with a rubber septum, evacuated and backfilled with nitrogen and this cycle was repeated twice. Under an inert atmosphere triethylsilane (1.5 mmol, 1.5 equiv.) was added followed by $Co_2(CO)_8$ (0.3 mmol, 0.3 equiv.). The tube was immediately closed with a Teflon screw cap and this was sealed.

10.1002/ejoc.202001328

The Schlenk tube was stirred at room temperature in case of iodo and triflates, and at 60 °C for bromo derivatives. The reaction mixture was diluted with dichloromethane (5 mL) and filtered through celite® bed. The organic layer was concentrated under reduced pressure. The residue was purified through silica gel (230 - 400 mesh) column chromatography using ethyl acetate in petroleum ether.

Acknowledgements

The authors are thankful to Dr.Jeyaprakash and Dr. Sathya Shanker, Syngene Intl. Ltd. for their valuable suggestions and support during the course of this project.

Key Words: Reductive carbonylation; Cobalt carbonyl; Bimetallic catalyst; Formylation.

References

[1] a) L. S. Starkey, Ed. *Introduction to Strategies for Organic Synthesis*; John Wiley & Sons: Hoboken, NJ, **2012**; Chapter 3.9, pp 105−114. (b) B. M. Trost, Ed. *Comprehensive Organic Synthesis*; Pergamon: Oxford, **1991**; *Vol 8*, pp 259−305. (c) J. Pospech, I. Fleischer, R. Franke, S. Buchholz and M. Beller, *Angew. Chem., Int. Ed.,* **2013**, *52*, 2852; d) R. Franke, D. Selent and A. Börner, *Chem. Rev.,* **2012**, *112*, 5675; e) G. T. Whiteker and C. J. Cobley, Top. *Organomet. Chem*., **2012**, *42*, 35.

[2] a) F. Aldabbagh, *Compr. Org. Funct. Group Transform. II*, **2005**, *3*, 9; b) L. P. Crawford, S. K. Richardson, *Gen. Synth. Method,* **1994**, *16*, 37 – 91.

[3] a) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem., Int. Ed.*, **2009**, *48*, 4114; b) C. F. J. Barnard, *Organometallics*, **2008**, *27*, 5402; c) A. Brennfuhrer, H. Neumann, S. Klaus, T. Riermeier, J. Almena, M. Beller, *Tetrahedron*, **2007**, *63*, 6252; d) C. F. J. Barnard, *Org. Process Res. Dev*. **2007**, *11*, 39.

[4] a) A. Schoenberg, R. F. Heck, *J. Am. Chem. Soc*. **1974**, *96*, 7761; b) V. P. Baillargeon, J. K. Stille, *J. Am. Chem. Soc*. **1983**, *105*, 7175; c) V. P. Baillargeon, J. K. Stille, *J. Am. Chem. Soc*. **1986**, *108*, 452; c) W. J. Scott, G. T. Crisp, J. K. Stille, *J. Am. Chem. Soc*. **1984**, *106*, 4630; d) A. B. Smith III, Y. S. Cho, H. Ishiyama, *Org. Lett.* **2001**, *3*, 3971; e) I. Pri-Bar, O. Buchman, *J. Org. Chem*. **1984**, *49*, 4009; f) Y. Misumi, Y. Ishii, M. Hidai, *Organometallics.* **1995**, *14*, 1770; g) H. Kotsuki, P. K. Datta, H. Suenaga, *Synthesis*. **1996**, 470.

[5] a) For a review on carbonylation without CO gas, see: T. Morimoto, Kakiuchi, *Angew. Chem. Int. Ed*. **2004**, *43*, 5580; b) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Lett*. **2003**, *5*, 4269; c) G. Lesma, A. Sacchetti, A. Silvani, *Synthesis.* **2006**, 594.

[6] S. Ko, H. Han, S. Chang, *Org. Lett*. **2003**, *5*, 2687.

[7] a) J.-P. Simonato, T. Walter, P. Mtivier, *J. Mol. Catal. A*. **2001**, *171*, 91; b) J.-P. Simonato, *J. Mol. Catal. A*. **2003**, *197*, 61.

[8] S. D Friis, T. L. Andersen, T. Skrydstrup, *Org. Lett*. **2013**, *15*, 1378.

[9] a) P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, T. Skrydstrup, *J. Am. Chem. Soc*. **2011**, *133*, 6061; b) P. Hermange, T. M. Gøgsig, A. T. Lindhardt, R. H. Taaning, T. Skrydstrup, *Org. Lett*. **2011**, *13*, 2444; c) Z. Xin, T. M. Gøgsig, A. T. Lindhardt, T. Skrydstrup, *Org. Lett*. **2012**, *14*, 284.

[10] a) For a recent review on Mo(CO)$_6$, see: L. R. Odell, F. Russo, M. Larhed, *Synlett.* **2012**, 685; b) P. Baburajan, R. Senthilkumaran, K. P. Elango, *New J. Chem*. **2013**, *37*, 3050.

[11] a) S. N. Gockel, K. L. Hull, *Org. Lett*. **2015**, *17*, 3236; b) K. Fuji, T. Morimoto, K. Tsutsumi, K. Kaiuchi, *Angew. Chem. Int. Ed*. **2003**, *42*, 2409.

[12] J. T. Joseph, A. M. Sajith, R. C. Ningegowda, S. Shashikanth, *Adv. Synth. Catal*. **2017**, *359*, 419.

[13] S. Korsager, R. H. Taaning, A. T. Lindhardt, T. Skrydstrup, *J. Org. Chem*. **2013**, *78*, 6112.

[14] a) T. Ueda, H. Konishi, K. Manabe, *Angew. Chem*. **2013**, *125*, 8773; *Angew. Chem. Int. Ed*. **2013**, *52*, 8611; b) T. Ueda, H. Konishi, K. Manabe, *Org. Lett*. **2013**, *15*, 5370.

[15] K. Natte, A. Dumrath, H. Neumann, M. Beller, *Angew. Chem. Int. Ed*. **2014**, *53*, 10090.

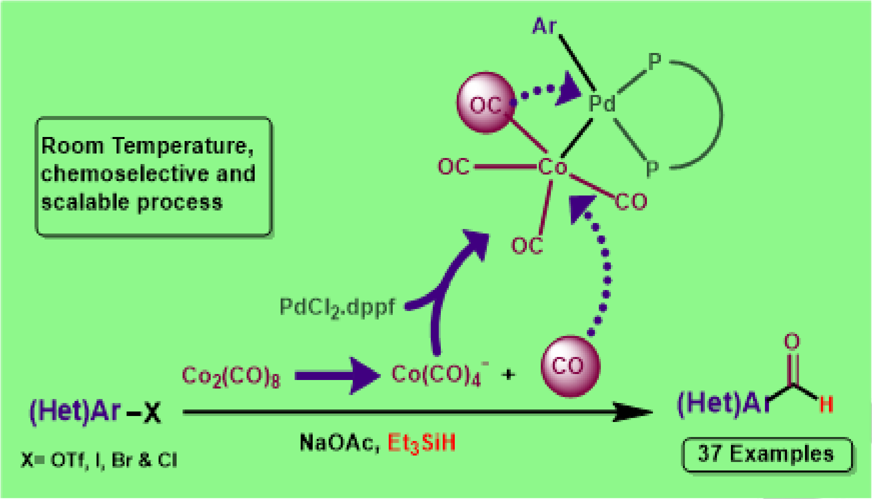
[16] B. Yu, Y. Zhao, H. Zhang, J. Xu, L. Hao, X. Gao, Z. Liu, *Chem. Commun*. **2014**, *50*, 2330.

[17] G. Sun, X. Lv, Y. Zhang, M. Lei, L. Hu, *Org. Lett*. **2017**, *19*, 4235.

[18] a) S. Klaus, H. Neumann, A. Zapf, D. Strubing, S. Huber, J. Almena, T. Riermeier, P. Gross, M. Sarich, W-R. Krahnert, K. Rossen, M. Beller, *Angew. Chem., Int. Ed*. **2006**, *45*, 154.

10.1002/ejoc.202001328

Entry for the Table of Contents



A generalized protocol for the reductive carbonylation of (hetero) aryl halides and triflates under CO gas-free conditions using Pd/$Co_2(CO)_8$ and triethylsilane has been developed. The mild reaction conditions, enhanced safety, and wide substrate scope highlights its importance in routine organic synthesis.