Carbonylative Cross-Electrophile Coupling Between Aryl Bromides and Aryl Triflates Enabled by Palladium and Rhodium Cooperative Catalysis

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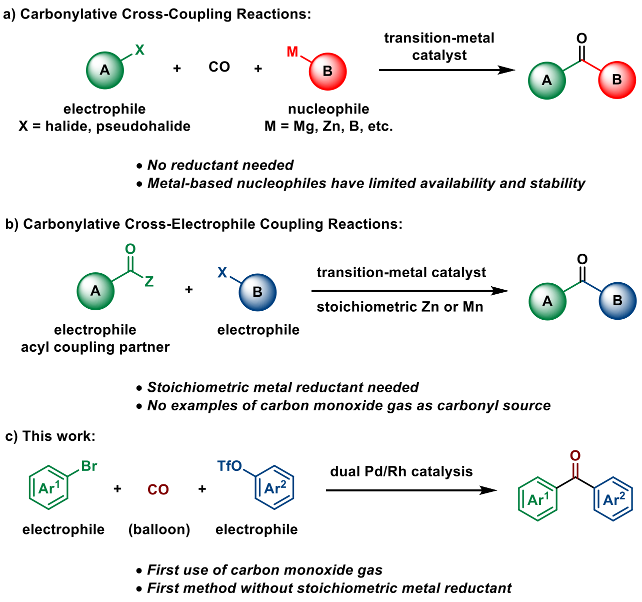
ABSTRACT: Ketones are among the most useful functional groups in organic synthesis. Here, we report the first carbonylative cross-electrophile coupling reaction that utilize carbon monoxide gas as the carbonyl source. The use of Pd/Rh cooperative catalysis enables the carbonylative coupling of easily accessible aryl triflates and aryl bromides. Unlike all previous carbonylative cross-electrophile coupling reactions, the method does not require addition of a stoichiometric metal reductant.

Ketones are among the most versatile functional groups in organic synthesis. Furthermore, they are part of the core skeleton in many natural products and pharmaceuticals.[1] The tremendous progress in transition-metal-catalyzed carbonylative cross-coupling reactions has made it a powerful strategy for accessing the ketone functionality (Scheme 1a).[2] These transition-metal-catalyzed reactions require the combination of an electrophilic coupling partner, typically aryl halides or pseudohalides, with a nucleophilic coupling partner, typically a metal-based reagent. Unfortunately, many of these metal-based nucleophiles have limited accessibility and stability, which can place restrictions on the substrate scope and affect the functional group tolerance for these normal cross-coupling reactions.

Due to the potential limitations with normal cross-coupling reactions, recently, significant efforts have been invested in the development of cross-coupling reactions between two electrophilic coupling partners.[3] Although these cross-electrophile coupling reactions require a stoichiometric reductant, typically Zn or Mn, it avoids the need for a nucleophilic coupling partner.[3-5] Nonetheless, achieving selective cross-coupling rather than homo-coupling between two electrophilic coupling partners is challenging. An elegant solution, pioneered by Weix, is the use of cooperative metal catalysis, where different metal catalysts are used to activate the two coupling partners.[6] In this approach, the two metal catalysts selectively undergo oxidative addition to each of the two different C-X bonds. Subsequent transmetallation between the two oxidative addition complexes followed by reductive elimination leads to the desired cross-coupling of the two electrophiles. Finally, the other metal catalyst is reduced back to its starting state by a stoichiometric metal reductant.

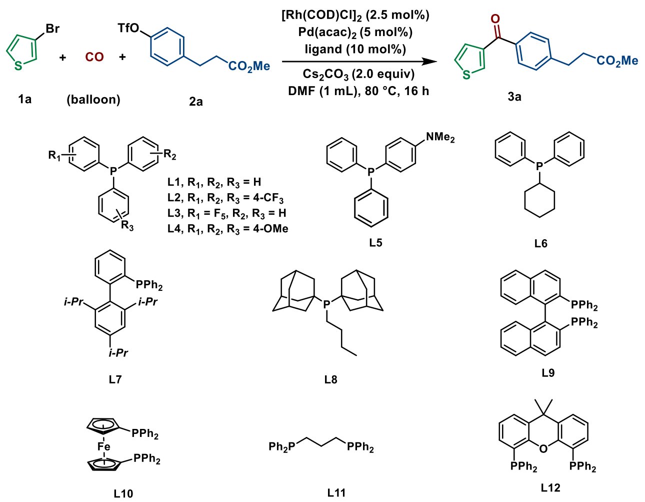
Recently, ketone synthesis using cross-electrophile coupling reactions has witnessed significant progress. However, essentially all the developed methods utilize an acyl coupling partner instead of carbon monoxide, and they all require stoichiometric amounts of a metal reductant such as Mn or Zn (Scheme 1b).[7-9] There are no reports of carbon monoxide gas as the carbonyl source despite that it is a widely available C1 building block.

Scheme 1. Comparison of Previous Work to This Work



Here, we report the first carbonylative cross-electrophile coupling method that use carbon monoxide as carbonyl source (Scheme 1c). Remarkably, unlike all previous carbonylative cross-electrophile coupling reactions, the method does not require a stoichiometric metal reductant. The developed methodology represents the first example of palladium/rhodium dual metal catalysis in carbonylative cross-electrophile coupling reactions.[10] Furthermore, the two electrophilic coupling partners used are aryl bro-

Table 1. Influence of Ligand on Reaction Outcome[a]



Entry	Ligand	Yield of **3a**[b]
1	**L1**	22%
2	**L2**	0%
3	**L3**	<1%
4	**L4**	22%
5	**L5**	24%
6	**L6**	19%
7	**L7-11**	0%
8	**L12**	19%

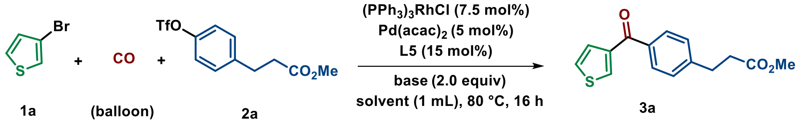
[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol, 1.0 equiv). [b] GC-yields.

mides and aryl triflates, which are easily accessible from phenols. Both aryl bromides and phenols are very abundant, thus enabling access to a broad range of products with the developed method.

We started the investigation of the carbonylative cross-electrophile coupling using 3-bromothiophene **1a** and aryl triflate **2a** as model substrates under a CO atmosphere (CO balloon). An initial reaction using $[Rh(COD)_2Cl]_2$ (2.5 mol%), $Pd(acac)_2$ (5 mol%), Cs_2CO_3 (2.0 equiv), and monodentate phosphine PPh_3 (10 mol%) in DMF confirmed the prospect of carbonylative coupling between the aryl bromide and aryl triflate (Table 1, entry 1). Encouraged by the initial result, PPh_3-derivatives bearing substituents with different electronic properties were examined. While electron-withdrawing substituents on the aryl moiety of the phosphine were detrimental for the reaction (**L2-3**), electron-donating substituents, such as OMe (**L4**) and NMe_2 (**L5**), led to comparable or slightly improved yields relative to PPh_3 (entries 2-5). The use of a more nucleophilic alkyl diaryl phosphine (**L6**) did not improve the yield further (entry 6). Other types of commonly used monodentate or bidentate phosphine ligands, such as XPhos (**L7**), *n*-$BuP(Ad)_2$ (**L8**), BINAP (**L9**), dppf (**L10**), and dppp (**L11**) did not afford the desired product (entry 7). Besides the PPh_3-based ligands, only Xantphos led to the desired product (entry 8). Overall, **L5** was identified as the most promising ligand.

Next, different Rh catalysts were examined. The commonly used $(PPh_3)_3RhCl$ showed better catalytic activity compared to $[Rh(COD)Cl]_2$ (Table 2, entries 1-2). Continuing with $(PPh_3)_3RhCl$, we found that increasing the amount of aryl triflate **2a** effectively reduced the formation of homocoupling product from **1a** thereby increasing the yield of the desired product (entry 3). Further improvement in yield was achieved by slightly increasing the loading of Rh catalysts and ligand **L5** (entry 4). The reaction outcome is highly base dependent (entries 4-7). Although Cs_2CO_3 afforded the highest yield, K_2CO_3 also led to significant product formation. Other bases, such as CH_3COOCs and CsF, led to poor yields. The solvent also had a large effect on the

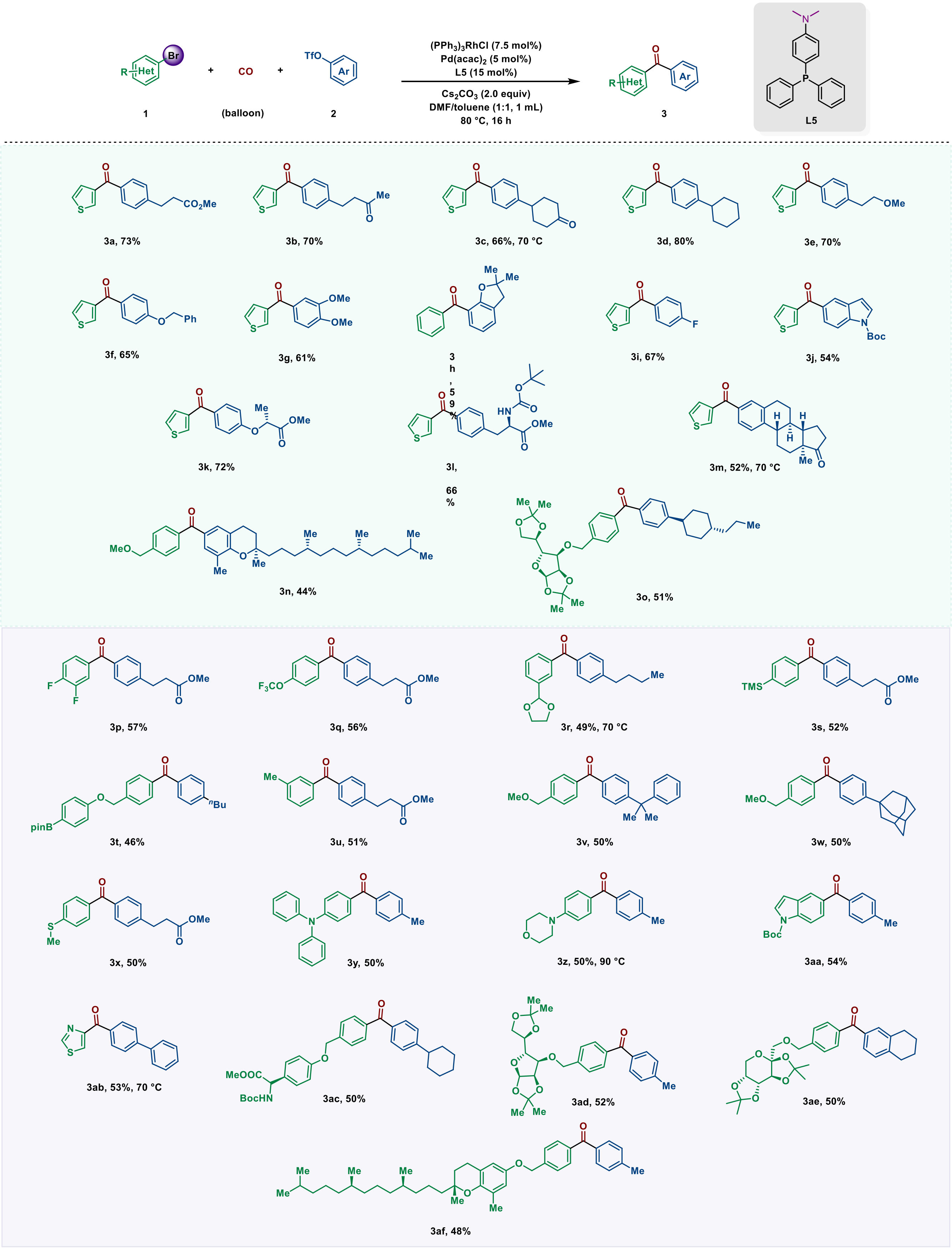
Table 2. Optimization of Reaction Conditions[a]



Entry	[Rh]	Base	Solvent	Yield of **3a**[b]
1[c]	$[Rh(COD)Cl]_2$	Cs_2CO_3	DMF	24%
2[c]	$(PPh_3)_3RhCl$	Cs_2CO_3	DMF	33%
3[d]	$(PPh_3)_3RhCl$	Cs_2CO_3	DMF	41%
4	$(PPh_3)_3RhCl$	Cs_2CO_3	DMF	58%
5	$(PPh_3)_3RhCl$	K_2CO_3	DMF	43%
6	$(PPh_3)_3RhCl$	CsF	DMF	12%
7	$(PPh_3)_3RhCl$	CH_3COOCs	DMF	0%
8	$(PPh_3)_3RhCl$	Cs_2CO_3	DMAc	16%
9	$(PPh_3)_3RhCl$	Cs_2CO_3	NMP	31%
10	$(PPh_3)_3RhCl$	Cs_2CO_3	DMSO	14%
11	$(PPh_3)_3RhCl$	Cs_2CO_3	toluene/DMF(1:1)	79% (73%)[e]
12	$(PPh_3)_3RhCl$	Cs_2CO_3	toluene/DMF(4:1)	50%
13	$(PPh_3)_3RhCl$	Cs_2CO_3	toluene/DMF(1:4)	71%

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.28 mmol, 1.4 equiv), [Rh] (7.5 mol%), **L5** (15 mol%). [b] GC-yields. [c] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol, 1.0 equiv), [Rh] (5 mol%), **L5** (10 mol%). [d] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.28 mmol, 1.4 equiv), [Rh] (5 mol%), **L5** (10 mol%). [e] Isolated yield in parenthesis.

Scheme 2. Substrate Scope for Aryl Triflates and Aryl Bromides[a]



[a] Reaction conditions from Table 2, entry 11, unless otherwise noted.

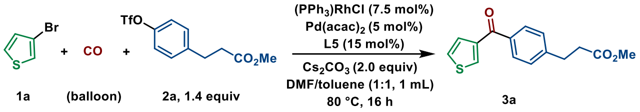
reaction outcome, but other pure solvents gave inferior results compared to DMF (entries 8-10). However, a 1:1 solvent mixture of DMF and toluene improved the yield leading to 73% isolated yield of the desired product (entry 11). Other toluene/DMF ratios gave lower yields (entries 12-13).

After having identified reactions conditions that produce the carbonylative cross-electrophile coupling product in a high yield, a variety of aryl triflates were examined as substrates for this transformation (Scheme 2). Aryl triflates bearing electron-withdrawing groups such as ketone and ester reacted smoothly with 3-bromothiophene **1a** delivering the corresponding diaryl ketones (**3a-c**) in good yields. A cyclohexyl-substituted aryl triflate provided 80% yield of the desired product **3d**. Aryl triflates bearing alkyl or aryl ether groups were also compatible with the transformation (**3e-g**). Even an *ortho*-substituted aryl triflate led to the desired ketone **3h** in 59% yield. Other functional groups such as fluoride and indole as well as a tyrosine-derived triflate were also tolerated, and the target products **3i-l** obtained in good yields. Encouraged by these results, we applied the carbonylative cross-electrophile coupling to more complex aryl triflates derived from estrone, δ-tocopherol, and allose. Pleasingly, they all provided the desired products (**3m-3o**).

To further explore the substrate scope, we investigated a series of aryl bromides (Scheme 2). In addition to 3-bromothiophene, bromobenzene derivatives are also suitable substrates for the carbonylative coupling process. A variety of functional groups are tolerated on the aryl bromide, such as fluoride, OCF_3, and an acetal (**3p-r**). Also, substrates bearing a trimethylsilyl group and a boronic ester are compatible with the transformation, thus providing useful handles for further functionalizations (**3s-t**). Substrates containing alkyl substituents, ether, or thioether groups afforded the desired products with no change in efficiency (**3u-x**). Amine functional groups are tolerated, although a slightly increased reaction temperature was necessary for the morpholine-substituted aryl bromide (**3y-z**). Pleasingly, the heterocyclic aryl bromides, 5-bromoindole and 4-bromothiazole, produced the corresponding products in 53-54% yield (**3aa-ab**). Notably, the carbonylative cross-electrophile coupling can also be performed on more complex aryl bromides such as derivatives of an amino acid, δ-tocopherol, a furanose, and a pyranose (**3ac-af**).

Control experiments showed that no carbonylative cross-coupling product **3a** was formed in the absence of either $Pd(acac)_2$ or $(PPh_3)_3RhCl$ (Table 3), In the absence of either $Pd(acac)_2$ or CO, no conversion of the starting materials **1a** and **2a** was observed. However, in the presence of $Pd(acac)_2$ and CO consumption of both aryl bromide and aryl triflate was observed although the desired product was not formed in the absence of $(PPh_3)_3RhCl$. Taken together these experiments could indicate that the palladium catalyst is responsible for activating both electrophiles, but that the presence of CO is required for the activation to take place.[11-13]

Table 3. Control Experiments



Entry	Change in Conditions	Conversion of **1a** and **2a**	Yield of **3a**
1	No change	Yes	73%
2	No $Pd(acac)_2$	No	0%
3	No $(PPh_3)_3RhCl$	Yes	0%
4	No CO (under argon)	No	0%

In summary, we have demonstrated the first method for carbonylative cross-electrophile coupling with carbon monoxide gas. The use of cooperative Pd/Rh catalysis enables carbonylative coupling between aryl bromides and aryl triflates, thereby avoiding the use of nucleophilic metal-based coupling partners with limited stability and accessibility. Both aryl bromides and the phenols used as precursors for aryl triflates are abundant compounds making them convenient coupling partners. Only a small excess of the aryl triflate is needed to achieve high selectivity for the carbonylative cross-coupling. Remarkably, unlike previous carbonylative cross-electrophile coupling reactions, the method does not require the addition of a stoichiometric metal reductant, possibly due to carbon monoxide gas serving as a reductant. The results presented here lays the foundation for future carbonylative cross-electrophile coupling reactions that avoids the formation of stoichiometric metal waste.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org. Experimental procedures along with characterization data and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF).

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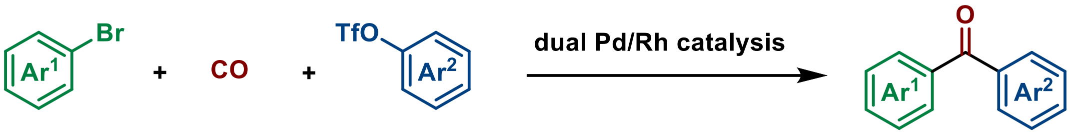
(11) The reductant for the catalytic process is not clear at this point. The need for CO to be present for conversion to take place indicates that CO could be the reductant for palladium, for example by reductive elimination of a phosgene equivalent (see reference 12). Alternatively, DMF can serve as reductant; however, catalytic turnover is also observed in other solvents (Table 2).

(12) (a) Baig, S.; Richard, B.; Serp, P.; Mijoule, C.; Hussein, K.; Guihéry, N.; Barthelat, J.-C.; Kalck, P., Synthesis and Theoretical Study of a Series of Dipalladium(I) Complexes Containing the Pd$_2$(μ-CO)$_2$ Core. *Inorg. Chem.* **2006**, *45*, 1935-1944; (b) Belli Dell'Amico, D.; Calderazzo, F.; Zandona, N., Formation of palladium(II) and palladium(I) carbonyl halo complexes. *Inorg. Chem.* **1984**, *23*, 137-140; (c) Levesque, T. M.; Kinney, R. G.; Arndtsen, B. A., A palladium-catalyzed C-H functionalization route to ketones via the oxidative coupling of arenes with carbon monoxide. *Chem. Sci.* **2020**, *11*, 3104-3109; (d) Ragaini, F.; Larici, H.; Rimoldi, M.; Caselli, A.; Ferretti, F.; Macchi, P.; Casati, N., Mapping Palladium Reduction by Carbon Monoxide in a Catalytically Relevant System. A Novel Palladium(I) Dimer. *Organometallics* **2011**, *30*, 2385-2393; (e) Stromnova, T. A.; Vargaftik, M. N.; Moiseev, II, Mechanism of reaction of palladium(II) carboxylates with carbon monoxide in nonaqueous media. *J. Organomet. Chem.* **1983**, *252*, 113-120.

(13) One example of an Fe/Co-catalyzed carbonylative homocoupling of aryl iodides without a metal reductant exists: Brunet, J. J.; Taillefer, M., Bimetallic catalysis: Synthesis of benzophenones through carbonylation of aryl iodides catalysed Fe(CO)$_5$-Co$_2$(CO)$_8$ Systems. *J. Organomet. Chem.* **1990**, *384*, 193-197.



- ***Carbon monoxide gas as carbonyl source***
- ***No stoichiometric metal reductant required***