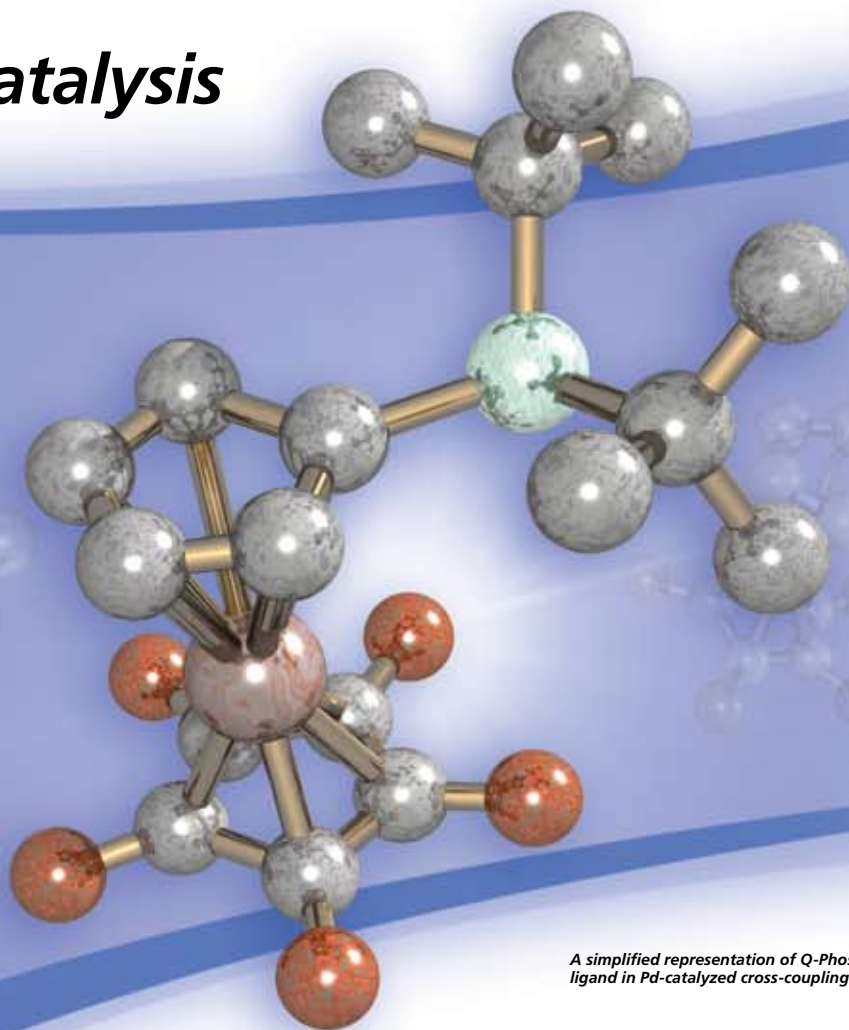


## Catalysis



*A simplified representation of Q-Phos: a potent ligand in Pd-catalyzed cross-coupling reactions.*

CATALYSTS FOR  
CARBONYLATION

PALLADACYCLE  
COUPLING CATALYSTS

NON-PROPRIETARY  
PHOSPHINE LIGANDS

Q-PHOS

NANOPARTICULATE  
Rh AND Pd CATALYSTS

## Introduction

Transition metal-mediated catalysis plays a vital role in the industrial production of bulk chemicals. As a result, there will continue to be a desire for innovative, chemically robust, and affordable catalysts and ligands emerging from the chemist's need to efficiently synthesize molecules. Sigma-Aldrich is proud to provide cutting-edge products for the rapid and successful construction of complex chemical architectures. The Bedford palladacyclic catalysts effect Suzuki-type couplings at very low catalyst loadings. The palladium complexes of BippyPhos, TrippyPhos, and A-<sup>18</sup>Phos each address gaps in the current C–C and C–N bond-forming methodologies. Hartwig's Q-Phos is a robust ligand capable of effecting various coupling reactions. This edition of *ChemFiles* describes applications of these and other exciting new additions to our catalysis portfolio.

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### About Our Cover

The cover graphic represents the three-dimensional structure of sterically encumbered Q-Phos. Phenyl rings are represented by orange spheres and hydrogen atoms have been omitted for clarity. Q-Phos is a powerful ligand in catalysis, participating in C–O, C–N, and C–C bond-forming reactions.

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## Catalysts for Carbonylation

Professor Geoffrey Coates and co-workers at Cornell University have reported the preparation and use of catalysts composed of an oxophilic Lewis acid and a cobalt tetracarbonyl anion (**1–3**, **Figure 1**) for the ring expansive carbonylation of epoxides to  $\beta$ -lactones and  $\beta$ -lactones to succinic anhydrides (**Scheme 1**).<sup>1,2</sup> Catalyst **3** provides access to succinic anhydrides directly from epoxides via a one-pot double carbonylation.<sup>3</sup> The catalysts are prepared from readily available ligand metal chlorides ( $[L_nM]Cl$ ) and  $NaCo(CO)_4$ .<sup>1,2</sup>

A generalized catalytic cycle for  $\beta$ -lactone formation (**Figure 2**) involves initial replacement of a THF ligand at the metal center by the epoxide oxygen followed by nucleophilic ring opening at the less substituted carbon by the cobalt tetracarbonyl anion. Insertion of CO then proceeds rapidly followed by ring closure and regeneration of the catalyst.<sup>4</sup> Consistent with this mechanism is the observed regioselectivity, retention of stereochemistry at the substituted epoxide carbon and inversion of stereochemistry at the  $\beta$ -carbon of the lactone (Figure 2, path A). A side reaction, observed at low CO pressure, is ketone formation resulting from elimination of  $HCo(CO)_4$  (path B). The ring expansion of  $\beta$ -lactone to succinic anhydride occurs via a similar catalytic cycle. A more detailed discussion of the two catalytic mechanisms has been published.<sup>3,5</sup>

These single-stage carbonylations proceed quickly in the absence of solvent or in polar, non-donating solvents such as ethers (e.g., DME). Catalyst loadings are typically 0.5–2 mol %. The reactions provide high yields of essentially pure products under CO

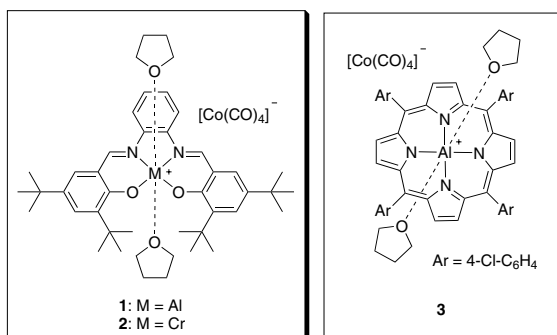
pressures of 200 psi or higher. Use of catalyst **2** enables the ring expansions to be run at lower CO pressures, even as low as one atmosphere.<sup>6</sup> However, at 1 atm CO, small amounts of ketone are formed (path B). The reactions are tolerant of functionality in the alkyl substituent such as silyl ethers, olefins, and esters (**Table 1** and **Table 2**).<sup>2,6</sup>

The double carbonylation process catalyzed by **3** proceeds in stages with  $\beta$ -lactone carbonylation occurring only on completion of the epoxide carbonylation. The solvent of choice is 1,4-dioxane. The reactions proceed with CO pressures as low as 100 psi. However, for the purposes of this study, the carbonylations were run at 850 psi. At lower pressures, or in the absence of CO, the epoxide rearranges to ketone. Without solvent small amounts of polyesters are formed. The double carbonylation process provides high yields of products requiring little, if any, purification and is tolerant of functional groups such as alkyl, aryl, olefins, ethers, silyl ethers, esters, amides, and nitriles (**Table 3**).<sup>3</sup>

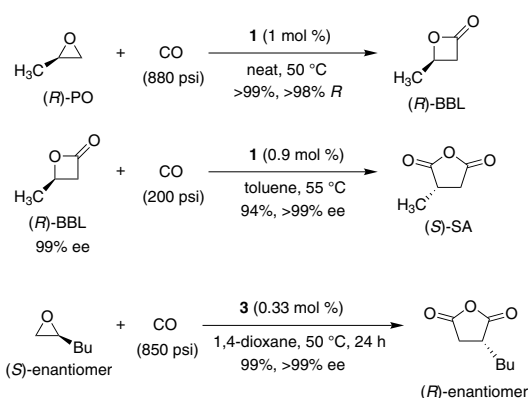
Oxetane<sup>2</sup> and *N*-tosyl aziridine **4**<sup>7</sup> have also been reported to undergo carbonylative ring expansion (**Scheme 2**).

Sigma-Aldrich is pleased to offer these carbonylation catalysts to researchers worldwide.

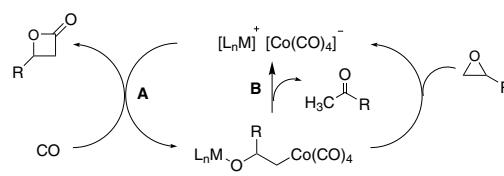
**References:** (1) Getzler, Y. D. Y. L. et al. *J. Am. Chem. Soc.* **2002**, *124*, 1174. (2) Getzler, Y. D. Y. L. et al. *J. Am. Chem. Soc.* **2004**, *126*, 6842. (3) Rowley, J. M. et al. *J. Am. Chem. Soc.* **2007**, *129*, 4948. (4) Schmidt, J. A. R. et al. *Org. Lett.* **2004**, *6*, 373. (5) Church, T. L. et al. *J. Am. Chem. Soc.* **2006**, *128*, 10125. (6) Kramer, J. W. et al. *Org. Lett.* **2006**, *8*, 3709. (7) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2006**, *41*, 2781.



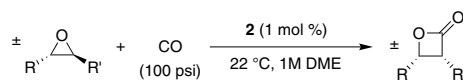
**Figure 1**



**Scheme 1**

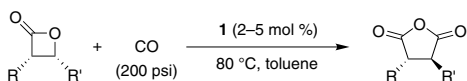


**Figure 2**



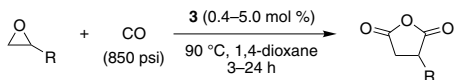
Entry	R	R'	Yield (%)
1	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	H	>98
2	CH <sub>2</sub> OCH <sub>2</sub> CH=CH <sub>2</sub>	H	>98
3	CH <sub>2</sub> OTBS	H	>98
4	CH <sub>2</sub> OC(O)Ph	H	>98

**Table 1**



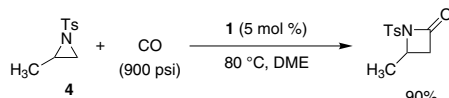
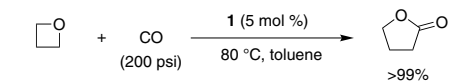
Entry	R	R'	Yield (%)
1	H	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	>99
2	H	CH <sub>2</sub> OTBS	97
3	H	(CH <sub>2</sub> ) <sub>2</sub> CH=CH <sub>2</sub>	90

Table 2



Entry	R	Yield (%)
1	Cy	97
2	CH <sub>2</sub> OTBS	98
3	(CH <sub>2</sub> ) <sub>3</sub> CN	99
4	(CH <sub>2</sub> ) <sub>6</sub> C(O)N(CH <sub>2</sub> ) <sub>2</sub>	98

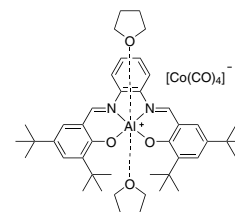
Table 3



Scheme 2

**[N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-phenylene-diamino-aluminum-di-THF]tetracarbonylcobaltate** NEW

C<sub>48</sub>H<sub>62</sub>AlCoN<sub>2</sub>O<sub>8</sub>  
FW: 880.93



674699-250MG

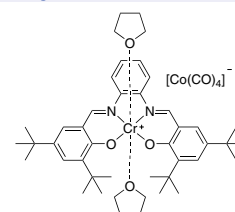
250 mg

674699-1G

1 g

**[N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-phenylene-diamino-chromium-di-THF]tetracarbonylcobaltate** NEW

C<sub>48</sub>H<sub>62</sub>CoCrN<sub>2</sub>O<sub>8</sub>  
FW: 905.94



674680-250MG

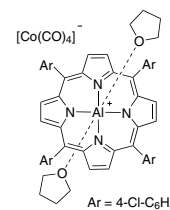
250 mg

674680-1G

1 g

**Tetrakis(4-chlorophenyl)porphinebis-(tetrahydrofuran)aluminum tetracarbonylcobaltate** NEW

C<sub>56</sub>H<sub>40</sub>AlCl<sub>4</sub>CoN<sub>4</sub>O<sub>6</sub>  
FW: 1092.67



681474-250MG

250 mg

681474-1G

1 g

**Jørgensen Organocatalyst for Asymmetric Catalysis**

Recently, the Jørgensen group communicated the use of the prolinol-based silyl ether **1** as an effective organocatalyst for the epoxidation of  $\alpha,\beta$ -unsaturated aldehydes in ethanol and aqueous solutions.<sup>1</sup> Hydrogen peroxide was used as the oxidant, and the reactions proceed in moderate to good yields with ee's up to 96%.

**(R)- $\alpha,\alpha$ -Bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether** NEW
C<sub>24</sub>H<sub>23</sub>F<sub>12</sub>NOSi

677213-1G

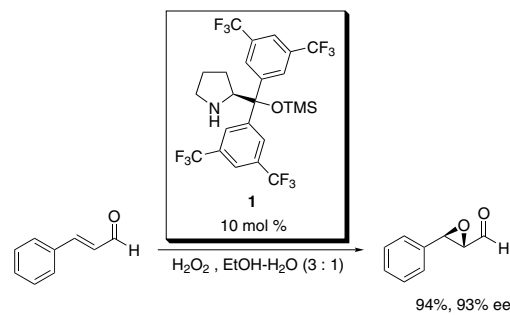
1 g

**(S)- $\alpha,\alpha$ -Bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether** NEW
C<sub>24</sub>H<sub>23</sub>F<sub>12</sub>NOSi

[848821-61-4]

677019-1G

1 g

(1) Zhuang, W. et al. *Org. Biomol. Chem.* **2005**, *3*, 3883.

## Palladacycle Coupling Catalysts

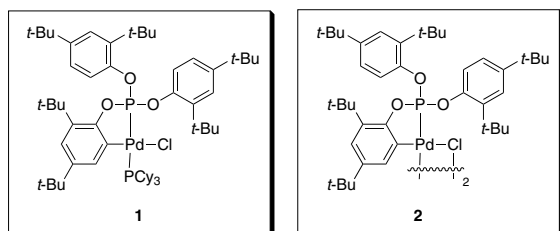
### Bedford Catalysts

Palladacyclic catalysts developed by the Bedford group are examples of a select group of catalysts capable of effecting a variety of coupling reactions using difficult-to-activate aryl chlorides at very low catalyst loadings (**Figure 1**).<sup>1</sup> For example, monomeric complex **1**, either as an isolated species or from the in situ treatment of **2** with PCy<sub>3</sub>, exhibits high catalytic activity in the Suzuki coupling reaction of arylboronic acids and aryl chlorides, with turnover numbers (TONs) exceeding 1,000,000.

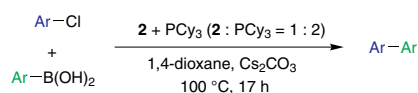
As shown in **Table 1**, both electronically activated and non-activated aryl chlorides couple with simple boronic acids at catalyst loadings as low as 0.00005%. The optimized protocol calls for two equivalents of phosphine ligand relative to **2** and the use of Cs<sub>2</sub>CO<sub>3</sub> as a base.

Reaction conditions nearly identical to those applied to Suzuki coupling of aryl chlorides can also be applied to Stille coupling of aryl- or vinyltin reagents with aryl chlorides to give functionalized biaryls or styrene derivatives (**Scheme 1**).<sup>2</sup>

Lastly, the treatment precatalyst **2** with P(*t*-Bu)<sub>3</sub> generates a catalyst system that is highly active in the amination of aryl chlorides with diarylamines, alkylarylamines, and dialkylamines (**Scheme 2**).<sup>3</sup> Yields typically exceed 80%, and as in other coupling reactions, catalyst loadings are low relative to more commonly used amination protocols.

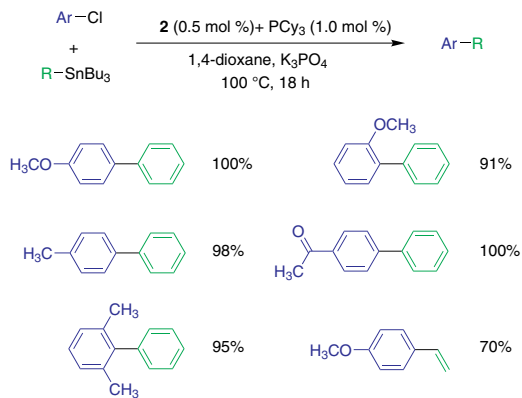


**Figure 1**

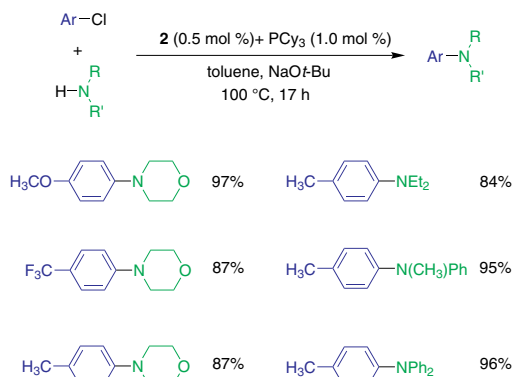


Entry	Product	Pd loading (%)	Conversion (%)	TON
1		0.005	100	10000
2		0.0005	82	82000
3		0.00005	88	880000
4		0.00005	92	920000
5		0.00005	100	1000000

**Table 1**



**Scheme 1**

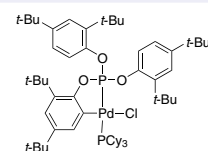


**Scheme 2**

### Chloro(η<sup>2</sup>-P,C-tris(2,4-di-*tert*-butylphenyl)phosphite)-(tricyclohexylphosphine)palladium(II)

NEW

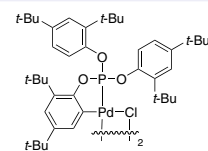
SamCat  
C<sub>60</sub>H<sub>95</sub>ClO<sub>3</sub>P<sub>2</sub>Pd  
FW: 1068.22



667315-250MG	250 mg
667315-1G	1 g
667315-5G	5 g

### 2-[Bis(2,4-di-*tert*-butyl-phenoxy)phosphinoxy]-3,5-di(*tert*-butyl)phenyl-palladium(II) chloride dimer, purum, ~12% as Pd

Bedford's Catalyst  
C<sub>84</sub>H<sub>124</sub>Cl<sub>2</sub>O<sub>6</sub>P<sub>2</sub>Pd<sub>2</sub>  
FW: 1575.57  
[217189-40-7]



94905-1G-F	1 g
------------	-----

## Nájera Catalysts

Oxime-derived palladacycles **3** and **4** (Figure 2) introduced by Professor Carmen Nájera and co-workers at the Universidad de Alicante (Alicante, Spain) are very efficient phosphine-free precatalysts for a variety of C–C bond-forming processes.<sup>4</sup> They are thermally robust and insensitive to both oxygen and moisture, slowly forming nanoparticulate palladium under the reaction conditions.<sup>5</sup>

These palladacycles are readily available from the corresponding benzophenone and acetophenone oximes via metallation of the aromatic moiety with lithium tetrachloropalladate (Scheme 3).<sup>4</sup>

Catalyst **3** provided the highest activities in these bond-forming processes carried out in organic solvents, while catalyst **4** proved to be more active in water or aqueous solvents.<sup>4</sup> Examples of the bond-forming processes mediated by these palladacycles include the Heck-Mizoroki,<sup>6</sup> Suzuki-Miyaura,<sup>7,8</sup> Sonogashira,<sup>9</sup> Sila-Sonogashira,<sup>9</sup> Ullmann,<sup>4</sup> and Stille<sup>10</sup> coupling reactions, examples of which are shown in Scheme 4.

Palladacycle **4** is an efficient precatalyst for mono- and  $\beta,\beta$ -diarylation of electron-deficient olefins (Scheme 5),<sup>5</sup> while **3** effectively catalyzes the homocoupling of terminal acetylenes in a direct synthesis of conjugated diynes (Scheme 6).<sup>9</sup>

Palladacycle **3** also promotes the copper-free synthesis of ynones<sup>11</sup> and the direct synthesis of 2,3-disubstituted indoles<sup>6</sup> from terminal and internal acetylenes (Scheme 7).

**References:** (1) (a) Bedford, R. B. et al. *Chem. Commun.* **2002**, 2610. (b) Bedford, R. B. et al. *Angew Chem., Int. Ed.* **2002**, *41*, 4120. (2) Bedford, R. B. et al. *Chem. Commun.* **2002**, 2608. (3) Bedford, R. B.; Blake, M. E. *Adv. Synth. Catal.* **2003**, *345*, 1107. (4) Alonso, D. A. et al. *Synthesis* **2004**, 1713. (5) Botella, L.; Nájera, C. *J. Org. Chem.* **2005**, *70*, 4360. (6) Alonso, D. A. et al. *Adv. Synth. Catal.* **2002**, *344*, 172. (7) Alonso, D. A. et al. *J. Org. Chem.* **2002**, *67*, 5588. (8) Botella, L.; Nájera, C. *J. Organomet. Chem.* **2002**, *663*, 46. (9) Alonso, D. A. et al. *Adv. Synth. Catal.* **2003**, *345*, 1146. (10) Alonso, D. A. et al. *Org. Lett.* **2000**, *2*, 1823. (11) Alonso, D. A. et al. *J. Org. Chem.* **2004**, *69*, 1615.

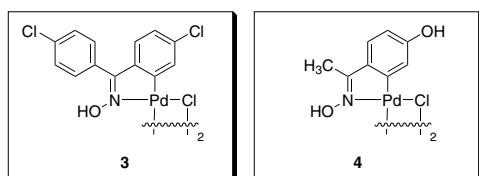
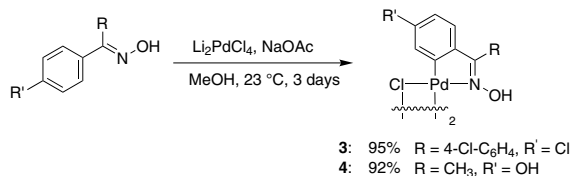
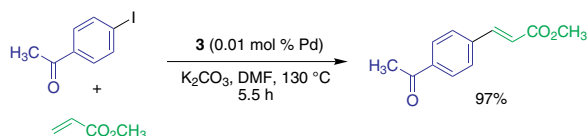


Figure 2

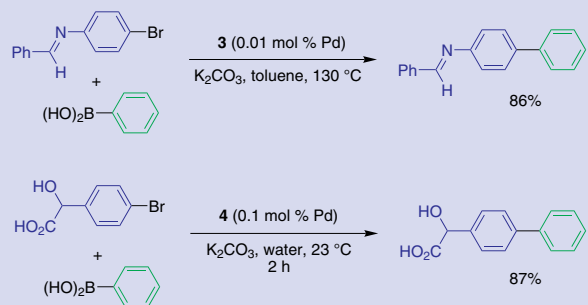


Scheme 3

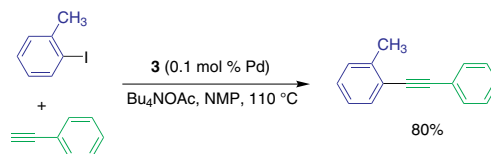
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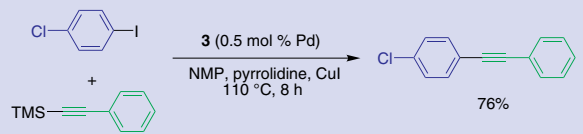
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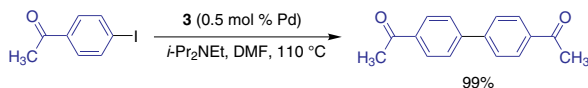
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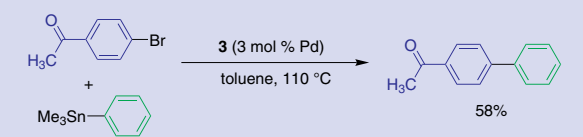
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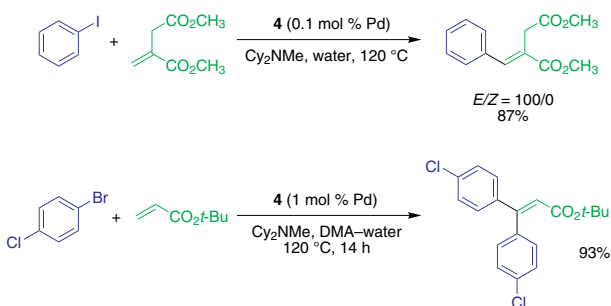
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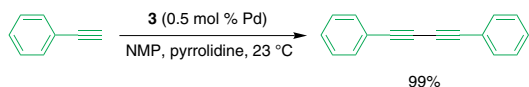
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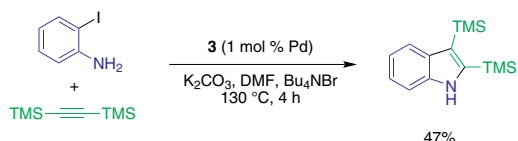
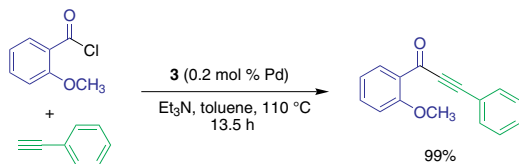
Scheme 4



Scheme 5



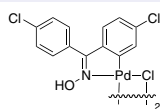
Scheme 6



Scheme 7

**Di- $\mu$ -chlorobis[5-chloro-2-[(4-chlorophenyl)-(hydroxyimino- $\kappa$ -N)methyl]phenyl- $\kappa$ -C]palladium dimer, 97%** NEW

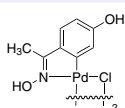
Nájera Catalyst I  
C<sub>26</sub>H<sub>16</sub>Cl<sub>6</sub>N<sub>2</sub>O<sub>2</sub>Pd<sub>2</sub>  
FW: 813.98  
[287410-78-0]



668923-250MG 250 mg  
668923-1G 1 g

**Di- $\mu$ -chlorobis[5-hydroxy-2-[1-(hydroxyimino- $\kappa$ -N)ethyl]phenyl- $\kappa$ -C]palladium(II) dimer, 98%** NEW

Nájera Catalyst II  
C<sub>16</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>Pd<sub>2</sub>  
FW: 584.06  
[419581-64-9]

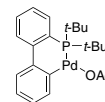


668532-250MG 250 mg  
668532-1G 1 g

## Other Palladacycles

**2-(2'-Di-*tert*-butylphosphine)biphenylpalladium(II) acetate, 97%** NEW

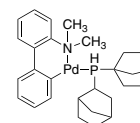
C<sub>22</sub>H<sub>29</sub>O<sub>2</sub>Pd  
FW: 462.86  
[577971-19-8]



655414-250MG 250 mg  
655414-1G 1 g

**2'-(Dimethylamino)-2-biphenyl-palladium(II) chloride dinorbonylphosphine complex, puriss.,  $\geq$ 99.0%** NEW

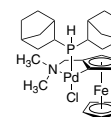
C<sub>28</sub>H<sub>37</sub>CINPPd  
FW: 560.45  
[359803-53-5]



36037-250MG-F 250 mg  
36037-1G-F 1 g  
36037-5G-F 5 g

**2-(Dimethylaminomethyl)ferrocen-1-yl-palladium(II) chloride dinorbonylphosphine complex, purum,  $\geq$ 97.0%** NEW

C<sub>27</sub>H<sub>39</sub>ClFeNPPd  
FW: 606.30  
[614753-51-4]



44696-250MG-F 250 mg  
44696-1G-F 1 g



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## Non-Proprietary Phosphine Ligands

In the pharmaceutical industry, Pd-catalyzed processes have frequently been relied on for carrying out key bond formations. While there are many ligands available that efficiently mediate C–C and C–N bond formations, there is still a need for ligands that address the gaps in the current methodologies. To this end, recent work has been reported by several pharmaceutical companies that details the application of non-proprietary ligands in key C–C and C–N bond-forming reactions.

The Singer group at Pfizer Inc. reported ligands that are efficient in mediating Pd-catalyzed aminations of aryl halides (**Table 1**).<sup>1</sup> Phenylpyrazole ligand **1**, TrippyPhos, has a fairly broad substrate scope for both amines and aryl halides and is effective in many cases with catalyst loadings down to 1 mol %.

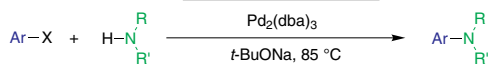
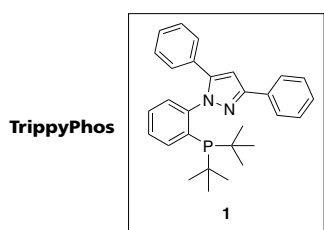
More recent work by the Singer group<sup>1b</sup> produced the triphenyl-bipyrazole ligand **2**, BippyPhos, which displayed even greater scope than TrippyPhos (**Table 2**). The BippyPhos system was particularly effective with primary amines, which are often susceptible to  $\beta$ -hydride elimination. Table 2 shows several of the aryl halides and amines tested. Pd<sub>2</sub>(dba)<sub>3</sub> was typically used for the palladium source in the amination reaction, as the use of Pd(OAc)<sub>2</sub> did not lead to product formation with primary amines. Increasing

the catalyst loading to 2 mol % Pd allowed for good conversions with 2-chloropyridine, although this was not attainable at lower Pd loadings.

The Suzuki-Miyaura cross-coupling reaction of heteroaryl halides is of particular interest to the pharmaceutical industry since many biologically active compounds are accessed through this methodology. Currently, there exists a need for efficient coupling of five-membered heteroaryl halides or six-membered heteroaryl chlorides bearing heteroatom substituents with boronic acids. Catalysts are thought to form inactive complexes with many of these types of substrates, and thus, they typically require high catalyst loadings in order to achieve good yields.

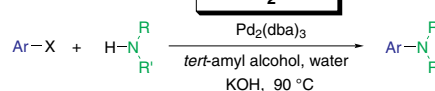
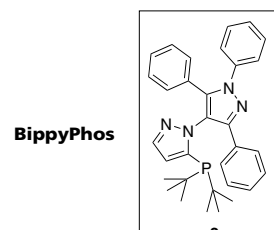
The Guram group at Amgen Inc. recently communicated the development of the air-stable palladium complex **3**, (A-<sup>10</sup>Phos)<sub>2</sub>PdCl<sub>2</sub>, for Suzuki-Miyaura cross-coupling reactions (**Table 3**).<sup>2</sup> The catalyst was very effective at coupling a wide variety of substrates with arylboronic acids, including amino-substituted 2-chloropyridines and five-membered heteroaryl halides. High product yields and turnover numbers (up to 10,000 TON) are typically observed.

**References:** (1) (a) Singer, R. A. et al. *Tetrahedron Lett.* **2006**, *47*, 3727. (b) Singer, R. A. et al. *Synthesis* **2003**, 1727. (2) Guram, A. S. et al. *Org. Lett.* **2006**, *8*, 1787.



Entry	X	Product	Yield (%)
1	Br		93
2	Cl		90
3	Br		99
4	Br		90
5	Br		88
6	Br		68
7	Br		99
8	Br		87
9	Br		95
10	Br		90
11	Br		89

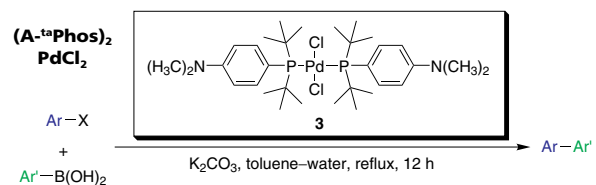
**Table 1**



Amine/Aryl Halide (% Yield)				
	99	99	97	99
	99	94	93	99
	86	88	60	<5
	95	98	95	99
	84	79	93	95
	96	98	87	93
	95	99	92	98

**Table 2**

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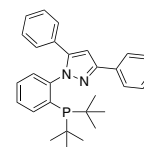
Entry	X	Product	Yield (%)
1	Cl		93
2	Cl		92
3	Cl		93
4	Cl		98
5	Cl		95
6	Cl		94
7	Cl		99
8	Cl		98
9	Cl		97
10	Cl		96
11	Br		93
12	Br		95

Table 3

### 1-[2-[Bis(*tert*-butyl)phosphino]phenyl]-3,5-diphenyl-1*H*-pyrazole, 96%

NEW

BippyPhos  
C<sub>29</sub>H<sub>33</sub>N<sub>2</sub>P  
FW: 440.56

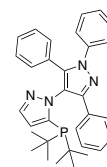


681555-1G	1 g
681555-5G	5 g

### 5-(Di-*tert*-butylphosphino)-1',3',5'-triphenyl-1'*H*-[1,4']bipyrazole, 97%

NEW

TrippyPhos  
C<sub>32</sub>H<sub>35</sub>N<sub>4</sub>P  
FW: 506.62

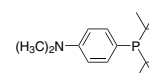


676632-250MG	250 mg
676632-1G	1 g

### (4-(*N,N*-Dimethylamino)phenyl)di-*tert*-butylphosphine, 95%

NEW

A-<sup>tert</sup>Phos  
C<sub>16</sub>H<sub>28</sub>NP  
FW: 265.37

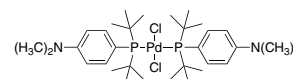


677264-1G	1 g
-----------	-----

### Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)-dichloropalladium(II)

NEW

(A-<sup>tert</sup>Phos)<sub>2</sub>PdCl<sub>2</sub>  
C<sub>32</sub>H<sub>56</sub>Cl<sub>2</sub>N<sub>2</sub>P<sub>2</sub>Pd  
FW: 634.64  
[887919-35-9]



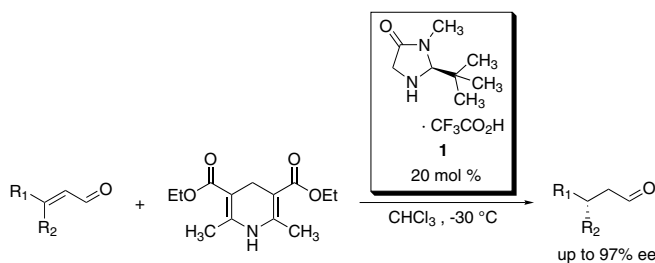
678740-1G	1 g
678740-5G	5 g

## Mac-H: Asymmetric Hydrogenation in a Bottle

MacMillan and co-workers have reported the combination of MacMillan Imidazolidinone OrganoCatalysts™ and Hantzsch esters to facilitate the first enantioselective organocatalytic hydride reduction of  $\alpha,\beta$ -unsaturated aldehydes.<sup>1</sup> Interestingly, isomerically pure *E*- and *Z*-olefin substrates will be reduced to the same enantiomer, allowing the researcher to use geometrically impure enals while maintaining excellent enantioselectivity. (*S*)-Mac-H is a convenient 6:1 formulation of the ethyl Hantzsch ester and OrganoCatalyst **1** for asymmetric reductions.

(1) Ouellet, S. G. et al. *J. Am. Chem. Soc.*, **2005**, *127*, 32.

MacMillan Imidazolidinone OrganoCatalysts are a trademark of Materia, Inc.



#### (*R*)-Mac-H

NEW

685429-1G 1 g

#### (*S*)-Mac-H

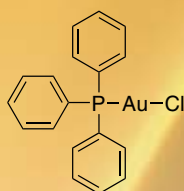
NEW

683558-1G 1 g

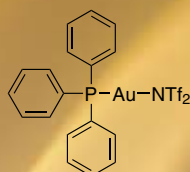
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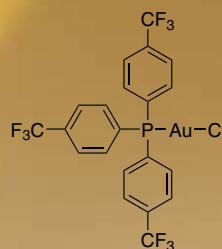


254037

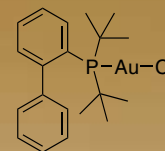


•0.5 CH<sub>3</sub>C<sub>6</sub>H<sub>5</sub>

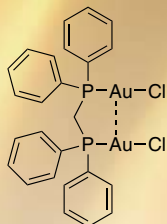
677922 **NEW**



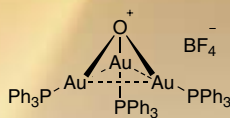
665177 **NEW**



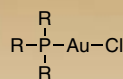
679771 **NEW**



665185 **NEW**

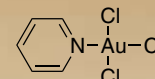


665142 **NEW**



404217 (R = Me)

288225 (R = Et)



677876 **NEW**

## Other Gold Complexes

AuCl	481130
AuCl <sub>3</sub>	379948
AuI	398411
KAuCl <sub>4</sub>	450235
NaAuCl <sub>4</sub> •2H <sub>2</sub> O	298174

## Silver Activators

AgNTf <sub>2</sub>	<b>NEW</b> 668001
AgOTf	176435
AgBF <sub>4</sub>	208361
AgPF <sub>6</sub>	227722
AgSbF <sub>6</sub>	227730

For detailed application information and additional references, please visit [sigma-aldrich.com/gold](http://sigma-aldrich.com/gold).

## References

- (1) For recent examples see: (a) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (d) Zhang, L. et al. *Adv. Synth. Catal.* **2006**, *348*, 2271. (e) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555.

## Q-Phos

The use of electron-rich, sterically congested monodentate phosphine ligands, in conjunction with a metal precursor, has become a common paradigm in transition-metal-catalyzed coupling reactions. Developed by the Hartwig group, pentaphenyl(di-*tert*-butylphosphino)ferrocene (Q-Phos, **Figure 1**) has emerged to be a premier ligand in coupling reactions because of its remarkably broad utility in a variety of C–N, C–O, and C–C bond-forming reactions. Additionally, the pure ligand is exceedingly robust, being stable in open air and in solution.

### Amination

In combination with common Pd precursors, Q-Phos has proven to be an excellent ligand for amination of aryl chlorides and aryl bromides of varying electronic character with both primary and secondary amines.<sup>1</sup> Typically, the amination reactions reach completion in less than 24 hours at temperatures of  $\leq 100$  °C, and in certain cases, the reaction proceeds rapidly at room temperature. In most instances, only small amounts of hydrodehalogenated byproducts are observed. The reaction protocol is straightforward and general, relying on either Pd(dba)<sub>2</sub> or Pd(OAc)<sub>2</sub> as a palladium source, and a base/solvent system of either NaOt-Bu/toluene or K<sub>3</sub>PO<sub>4</sub>/DME. As illustrated in **Table 1**, diarylamines rapidly couple with aryl bromides at room temperature (entry 1). Less expensive aryl chlorides also couple in high yield, although higher temperatures are required (entry 2). Similarly, alkylarylamines, dialkylamines, and anilines are viable nucleophiles for the coupling reaction (entries 3–7). In the case of primary aliphatic and benzylic amines, the amination was remarkably selective for the monoarylated product (entries 8 and 9). Finally, for some substrates, it is possible to conduct the amination at low catalyst loadings (e.g., entry 10).

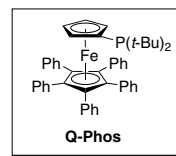
### Etherification

Until recently, mild aromatic C–O bond formation was exceedingly difficult to achieve. Palladium complexes of Q-Phos catalyze the mild etherification reaction of aryl halides with alkoxide, siloxide, and phenoxide partners (**Table 2**).<sup>1,2</sup> Reactions with aryl bromides, or electron-poor aryl chlorides, typically proceed at room temperature. The catalyst system was also successful in the synthesis of coumarans, via intramolecular etherification.

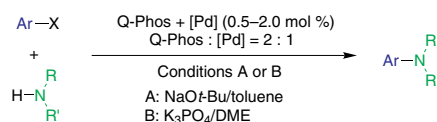
### Suzuki-Miyaura Coupling and $\alpha$ -Arylation

Suzuki-Miyaura coupling reactions using a Pd catalyst derived from Q-Phos are highly successful for both electron-poor and electron-rich aryl bromides and chlorides (**Table 3**).<sup>1</sup> As expected, aryl bromides are more reactive, and typically Suzuki couplings with arylboronic acids proceed at ambient temperature (entry 3). While reactions of aryl chlorides with aryl boronic acids typically require heating for extended periods, yields are generally quite high (>90%). Additionally, alkylboronic acids couple easily with aryl bromides and chlorides, without the aid of thallium or silver salts (entries 4 and 5).

As illustrated in **Scheme 1**, Q-Phos is an effective ligand for the palladium-catalyzed  $\alpha$ -arylation of either diethyl malonate or ethyl cyanoacetate.<sup>3</sup> Decarboxylation of the malonate products provides arylacetic acid derivatives that are synthetically useful intermediates. Alternatively, alkylation followed by decarboxylation provides  $\alpha$ -arylcarboxylic acid derivatives that are also highly valued synthons. Arylations of diethyl malonate with chloroarene electrophiles proceed smoothly in the presence of Pd(dba)<sub>2</sub> and Q-Phos, while reactions of chloro- or bromoarenes with ethyl cyanoacetate require Pd(dba)<sub>2</sub> or [Pd(allyl)Cl]<sub>2</sub> as Pd precursors, depending on the identity of the substrates. Simpler phosphines (such as P(*t*-Bu)<sub>3</sub>) may be used for the arylation of other alkyl malonates or alkyl cyanoacetates.

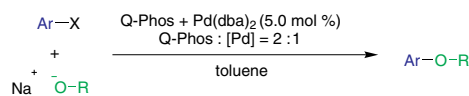


**Figure 1**



Entry	X	Product	Conditions	[Pd]	Time (h)	Temp (°C)	Yield (%)
1	Br		A	Pd(dba) <sub>2</sub>	1	23	99
2	Cl		A	Pd(dba) <sub>2</sub>	21	100	98
3	Br		A	Pd(OAc) <sub>2</sub>	25	100	93
4	Cl		A	Pd(dba) <sub>2</sub>	27	45	82
5	Br		A	Pd(dba) <sub>2</sub>	17	23	99
6	Cl		B	Pd(dba) <sub>2</sub>	15	100	97
7	Cl		B	Pd(dba) <sub>2</sub>	20	100	95
8	Br		A	Pd(dba) <sub>2</sub>	4	100	96
9	Cl		A	Pd(dba) <sub>2</sub>	16	100	94
10	Br		A	Pd(dba) <sub>2</sub> (0.05%)	19	100	99

**Table 1**



Entry	X	Product	Time (h)	Temp (°C)	Yield (%)
1	Br		17	23	96
2	Br		70	23	99
3	Br		12	80	79
4	Cl		12	80	78
5	Br		9	23	98
6	Cl		5	23	93

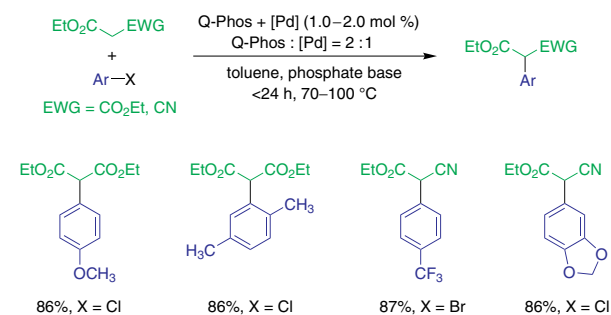
**Table 2**

More recently, the Hartwig group demonstrated the first general method for the  $\alpha$ -arylation of amides, via their zinc enolates.<sup>4</sup> While zinc amide enolates are not common intermediates, they are easily generated by reaction of an alkali enolate with  $\text{ZnCl}_2$ . Alternatively, they can also be generated via the reaction of activated Rieke<sup>®</sup> zinc with the requisite  $\alpha$ -bromoamide, although this approach is limited to those bromoamides that are readily available. The use of zinc amide enolates instead of alkali metal enolates is preferred because the former exhibit greater functional group tolerance in coupling reactions.

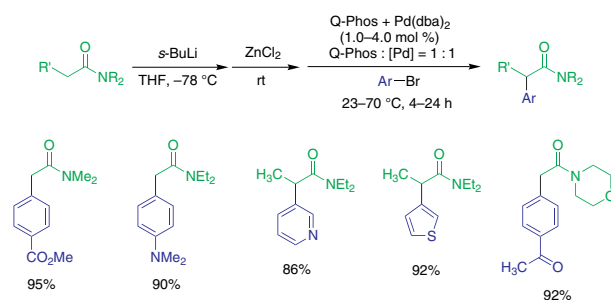
As shown in **Scheme 2**, treatment of dialkyl acetamides or dialkyl propionamides with *s*-BuLi, followed by transmetalation with  $\text{ZnCl}_2$ , generates an intermediate organozinc halide, which readily couples with aryl bromides in the presence of Q-Phos and  $\text{Pd}(\text{dba})_2$  to give the  $\alpha$ -arylamide. Electron-rich or electron-poor bromoarenes, vinyl bromides, and heteroaryl bromides are all reactive in the C–C bond-forming reaction. Finally, morpholine amides, which can behave similarly to Weinreb amides in their functional group manipulations,<sup>5</sup> also undergo arylation.

We are pleased to add this versatile ligand to our growing portfolio of electron-rich phosphine ligands for cross-coupling reactions.

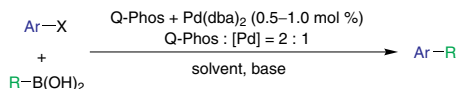
**References:** (1) Kataoka, N. et al. *J. Org. Chem.* **2002**, *67*, 5553. (2) Shelby, Q. et al. *J. Am. Chem. Soc.* **2000**, *122*, 10718. (3) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541. (4) (a) Hama, T. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11176. (b) Hama, T. et al. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (5) (a) Kurosu, M.; Kishi, Y. *Tetrahedron Lett.* **1998**, *39*, 4793. (b) Badioli, M. et al. *J. Org. Chem.* **2002**, *67*, 8938. (c) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652.



Scheme 1



Scheme 2



Entry	X	Product	Solvent	Base	Time (h)	Temp (°C)	Yield (%)
1	Br		THF	KF	5	23	99
2	Br		toluene	KF	3	23	99
3	Cl		THF	KF	4	100	89
4	Br		toluene	$\text{K}_3\text{PO}_4$	30	100	83*
5	Cl		toluene	$\text{K}_3\text{PO}_4$	12	100	97*

\*Q-Phos : [Pd] = 1 : 1

Table 3

### 1,2,3,4,5-Pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene

NEW

Q-Phos  
 $\text{C}_{48}\text{H}_{47}\text{FeP}$   
 FW: 710.71  
 [312959-24-3]



675784-100MG

100 mg

675784-500MG

500 mg

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## Nanoparticulate Rh and Pd Catalysts

The mild hydrogenation of a variety of arenes—such as benzene, mono- and disubstituted benzenes, naphthalene, and quinoline—has been achieved by using rhodium nanoparticles entrapped in a highly porous and fibrous boehmite (Al(O)OH) matrix (**Table 1**).<sup>1</sup> The Rh/boehmite system has performed very favorably when compared to other commonly used hydrogenation catalysts such as Rh/Al<sub>2</sub>O<sub>3</sub>, with reductions occurring rapidly at room temperature under H<sub>2</sub> at atmospheric pressure. It also offers the added advantages of an effortless catalyst recovery by simple filtration after the hydrogenation is completed and the ability to perform the reaction without added solvent. The recovered catalyst has been reused ten times without a noticeable loss of activity.

Aluminum hydroxide entrapped palladium nanoparticles (Pd/Al(O)OH) serve as a versatile heterogeneous catalyst that can be applied to a variety of reaction paradigms with low catalyst loadings. The easily recyclable catalyst is active in many organic solvents as well as in water.

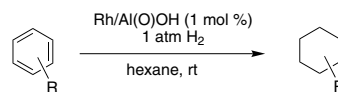
As shown in **Table 2**, palladium-catalyzed aerobic oxidation of a variety of aryl- and alkylcarbinols using Pd/Al(O)OH occurs at high yields to give ketones or aldehydes, often with superior results relative to existing heterogeneous catalysts (e.g., Pd/C, Pd/Al<sub>2</sub>O<sub>3</sub>).<sup>2</sup> Diols are also viable substrates for the oxidation, leading to lactone products.

Moreover, the catalyst is also effective in alkene hydrogenation, with reactions proceeding rapidly at room temperature. As illustrated in **Scheme 1**, both processes, catalytic oxidation and catalytic reduction, were employed in the one-pot conversion of cholesterol to cholestan-3-one using the same Pd catalyst.

This catalyst demonstrates enormous promise in the selective  $\alpha$ -alkylation of ketones with primary alcohols (**Scheme 2**).<sup>3</sup> Reactions performed in the presence of oxygen provide conjugated enone adducts, while anaerobic conditions result in the preferential formation of ketones. Importantly, since no additives (e.g., strong bases) are required to achieve the alkylation, there are no salt byproducts to remove after reaction work-up and the catalyst can be recycled by a simple filtration of the reaction mixture.

Finally, the catalyst, in conjunction with lipase, has been applied to the dynamic kinetic resolution (DKR) of primary amines to give acylated amines with excellent yields and selectivities (**Scheme 3**).<sup>4</sup> DKR is a powerful method for converting a racemic mixture into a single enantiomer. Racemic benzylic amines undergo DKR with a low Pd catalyst loading (1 mol %), and either ethyl acetate or ethyl methoxyacetate can function as acyl donors with similar yields. The latter donor allows for a reduced enzyme loading. Aliphatic amines can also participate in a high-yielding, highly selective DKR at increased Pd loadings.

**References:** (1) Park, I. S. et al. *Chem. Commun.* **2005**, 5667. (2) Kwon, M. S. et al. *Org. Lett.* **2006**, 7, 1077. (3) Kwon, M. S. et al. *Angew. Chem., Int. Ed.* **2005**, 44, 6913. (4) Kim, M.-J. et al. *Org. Lett.* **2007**, 9, 1157.



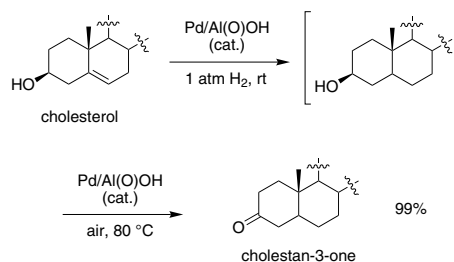
Entry	Substrate	Product	Time (h)	Yield (%)	TOF	cis : trans
1			0.5	100	600	–
2			1	100	300	–
3			2.3	100	130	82 : 18
4			3	97	65	–
5			10	100	50	88 : 12
6			6	94*	9	–

\*5 mol % of catalyst used.

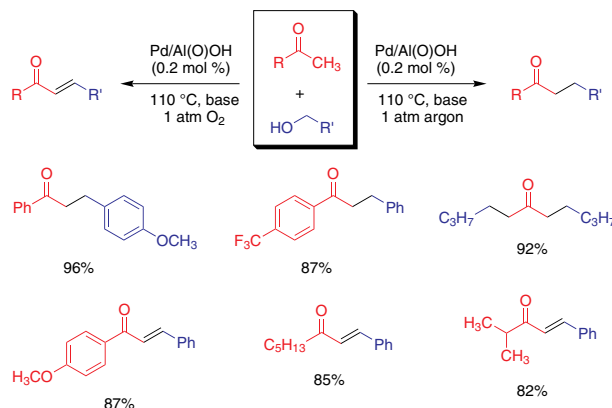
**Table 1**

Entry	Substrate	Product	Temp (°C)	Loading (%)	Yield (%)
1			80	0.20	>99
2			70	0.5	>99
3			100	5.0	92
4			100	1.0	94
5			110	2.0	99

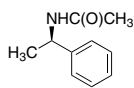
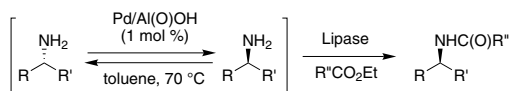
**Table 2**



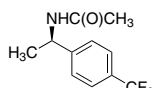
**Scheme 1**



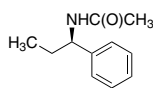
**Scheme 2**



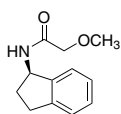
91%, 97% ee



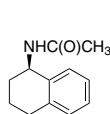
95%, 98% ee



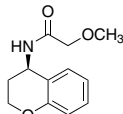
90%, 98% ee



87%, 97% ee



86%, 97% ee



92%, 99% ee

Scheme 3

**Rhodium nanoparticles entrapped in aluminum hydroxide matrix, extent of labeling: 5 wt. % loading**

NEW

Rh/AI(OH)<sub>3</sub>

679488-1G

1 g

PCT WO 2006/070964 and related patents apply.

**Palladium nanoparticles entrapped in aluminum hydroxide matrix, extent of labeling: 0.5 wt. % loading**

NEW

Pd/AI(OH)<sub>3</sub>

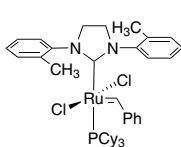
674133-10G

10 g

PCT WO 2006/070964 and related patents apply.

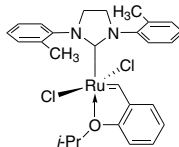
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Olefin metathesis has led scientists to discover new disconnections in organic synthesis, paving the way for new advances in polymer chemistry, drug discovery, and natural product synthesis. Sigma-Aldrich is proud to be the exclusive provider of Materia's ruthenium-based metathesis catalysts for research scale.



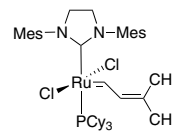
682284 NEW

Highly efficient catalyst for the preparation of tetrasubstituted olefins by RCM or CM of sterically hindered olefins.



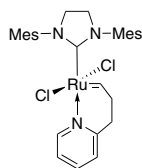
682373 NEW

Hoveyda-Grubbs analog of 682284 with similar reactivity profile. Depending on substrate and reaction conditions, may prove more efficient than 682284.



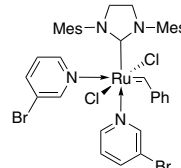
682365 NEW

Slower to initiate than Grubbs 2nd generation catalyst, thus potentially useful in exothermic ROMP applications. Typically, reaction temperatures of 50 to 60 °C are employed.



682381 NEW

Latent initiator that possesses the high activity of 2nd generation catalysts once initiated. Useful in ROMP applications where longer monomer/catalyst resin handling times are desired.



682330 NEW

Faster initiator than Grubbs 2nd generation catalyst; can be used at low temperatures (~0 °C, depending on reaction conditions). Less soluble than Grubbs 2nd generation catalyst in nonpolar solvents. Has been employed in polymer synthesis.

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
TO ORDER: Contact your local Sigma-Aldrich office (see back cover), or visit [sigma-aldrich.com/chemicalsynthesis](http://sigma-aldrich.com/chemicalsynthesis).

# New Catalysts and Ligands from Sigma-Aldrich

## Copper

### Copper(I) thiophene-2-carboxylate NEW

$C_5H_3CuO_2S$   
FW: 190.69  
[68986-76-5]



682500-1G 1 g

### Tetrakis(acetonitrile)copper(I) tetrafluoroborate, 97% NEW

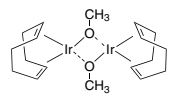
$C_4H_{12}BCuF_4N_4$   
FW: 314.56  
[(CH<sub>3</sub>CN)<sub>4</sub>Cu]BF<sub>4</sub>

677892-1G 1 g  
677892-5G 5 g

## Iridium

### Methoxy(cyclooctadiene)-iridium(I) dimer NEW

$C_{18}H_{30}Ir_2O_2$   
FW: 662.86



677930-250MG 250 mg  
677930-1G 1 g

## Palladium

### Bromo(tri-tert-butylphosphine)-palladium(I) dimer NEW

$C_{24}H_{54}Br_2P_2Pd_2$   
FW: 777.28  
[185812-86-6]



677728-1G 1 g

### Bis(tri-tert-butylphosphine)-palladium(0) NEW


$C_{24}H_{54}P_2Pd$   
FW: 511.05  
[(t-Bu)<sub>3</sub>P-Pd-(t-Bu)<sub>3</sub>]

676578-1G 1 g

## Rhenium

### Trioxo(triphenylsilyloxy)rhenium(VII) NEW

$C_{18}H_{15}O_4ReSi$   
FW: 509.60



674192-250MG 250 mg  
674192-1G 1 g

## Rhodium

### Rhodium on carbon NEW

Rh Rh/C  
FW: 102.91

680710-1G 1 g  
680710-5G 5 g

### Bis(norbornadiene)rhodium(I) tetrafluoroborate NEW

$C_{14}H_{16}BF_4Rh$   
FW: 373.99  
[36620-11-8]

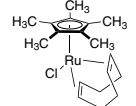


676195-1G 1 g

## Ruthenium

### Chloro(pentamethylcyclopentadienyl)-(cyclooctadiene)ruthenium(II) NEW

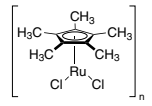
$C_{18}H_{27}ClRu$   
FW: 379.93



667234-250MG 250 mg  
667234-1G 1 g

### Dichloro(pentamethylcyclopentadienyl)ruthenium(III) polymer NEW

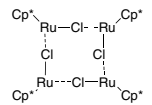
[(C<sub>10</sub>H<sub>15</sub>)RuCl<sub>2</sub>]<sub>n</sub>  
[96503-27-4]



676497-1G 1 g  
676497-5G 5 g

### Chloro(pentamethylcyclopentadienyl)-ruthenium(II) tetramer NEW

$C_{40}H_{60}Ru_4Cl_4$   
FW: 1087.00  
[113860-07-4]



676500-500MG 500 mg  
676500-2G 2 g

### Bis(2-methylallyl)(1,5-cyclooctadiene)-ruthenium(II) NEW

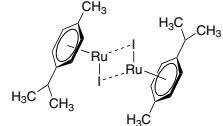
$C_{16}H_{26}Ru$   
FW: 319.45  
[12289-94-0]



676209-1G 1 g

### Diiodo(p-cymene)ruthenium(II) dimer NEW

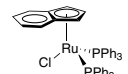
$C_{20}H_{28}I_2Ru_2$   
FW: 978.19  
[90614-07-6]



676241-1G 1 g

### Chloro(indenyl)bis-(triphenylphosphine)ruthenium(II) NEW

$C_{45}H_{37}ClP_2Ru$   
FW: 776.25  
[99897-61-7]

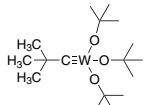


667242-1G 1 g  
667242-5G 5 g

## Tungsten

### Tris(tert-butoxy)-(2,2-dimethylpropylidene)tungsten(VI) NEW

$C_{17}H_{36}O_3W$   
FW: 472.31  
[78234-36-3]




666440-250MG 250 mg  
666440-1G 1 g

## Phosphorus

### Phenylphosphine, ca. 10 wt. % in hexanes NEW

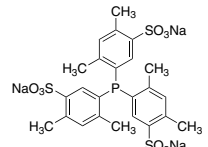
$C_6H_7P$   
FW: 110.09  
[638-21-1]



674389-50ML 50 mL

### Tris(2,4-dimethyl-5-sulfophenyl)-phosphine trisodium salt, 95% NEW


$C_{24}H_{24}Na_3O_3P_3S_3$   
FW: 652.58  
[443150-11-6]



667382-500MG 500 mg  
667382-1G 1 g

### tert-Butyldimethylphosphine borane, 97% NEW

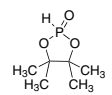
$C_6H_{18}BP$   
FW: 131.99



677647-2G 2 g

### 4,4,5,5-Tetramethyl-1,3,2-dioxaphospholane 2-oxide NEW

$C_6H_{13}O_3P$   
FW: 164.14



686344-1G 1 g

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