Empowering Cross-Coupling

Buchwald G1 to G6 Pre-Catalysts

Professor Stephen L. Buchwald,
Camille Dreyfus Professor of
Chemistry at MIT

Sigma-Aldrich®
Lab & Production Materials

Introduction

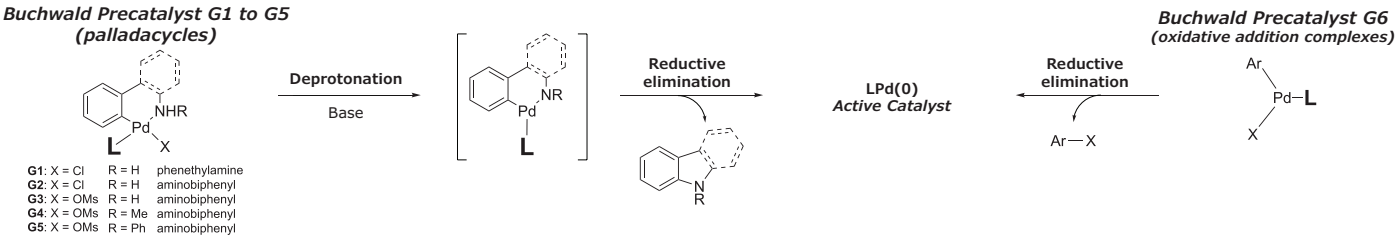
Efficient generation of the active catalyst is often pivotal to the success of a cross-coupling reaction. Traditional palladium sources, such as $Pd_n(dba)_m$ (n = 1 or 2, and m = 2 or 3, respectively),[1] Pd(II) salts,[2] and π-allyl Pd dimers,[3] can have varying degrees of efficacy in generating LPd(0) active catalyst species.

To help you achieve success in cross-coupling reactions – and the new chemistry you're engaged in – we offer a comprehensive range of G1 to G6 Buchwald pre-catalysts. The series consists of Pd(II) complexes comprised of highly active, versatile, and tunable biarylphosphine ligands, or other highly active phosphine ligands, capable of efficiently catalyzing C–C,[4] C–N,[5] C–O,[6] C–F,[7] C–CF_3,[8] C–S,[9] and other bond formations.[10]

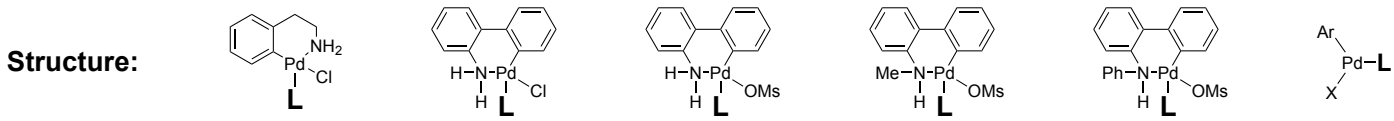
All Buchwald G1 to G6 pre-catalysts are air-, moisture-, and thermally-stable; display good solubility in common organic solvents; and support a wide array of phosphine ligands. In general, these robust pre-catalysts allow diverse reactivity, accurate control of the ligand-to-palladium ratio, efficient formation of LPd(0) species under mild conditions, low catalyst loadings, and short reaction times.

Discover our unparalleled Buchwald portfolio for your breakthrough ideas.

Activation of G1 to G5 Pre-Catalysts vs. G6 Pre-Catalysts



Generic Structures & Descriptions of G1 to G6 Pre-Catalysts



Generation:	Pd G1	Pd G2	Pd G3	Pd G4	Pd G5	Pd G6
Disclosure Year:	2008	2010	2013	2014	2014	2017

Pd G1

The first generation (G1) pre-catalysts[11] allow for easy generation of LPd(0) species, requiring merely a deprotonation with an amide base (below room temperature), an alkoxide base (at room temperature), or a carbonate base (at elevated temperature). The resulting catalytic species is very active, even at temperatures near -40 °C, and can be used in a variety of cross-coupling protocols.

Pd G2

The second generation (G2) pre-catalysts[12] contain an aminobiphenyl scaffold rather than the phenethylamine scaffold of G1 pre-catalysts. This change allows for the use of weak phosphate or carbonate bases to generate LPd(0) species from G2 pre-catalysts at room temperature. These catalysts prove remarkably adept at achieving a variety of cross-coupling reactions.

Pd G3

G1 and G2 pre-catalysts can suffer from limitations related to their syntheses and/or application scope. Replacing the chloride anion of the G2 pre-catalysts with a more electron-withdrawing, non-coordinating methanesulfonate anion provides the third generation (G3) pre-catalysts, which can accommodate very bulky ligands (e.g., t-BuBrettPhos).[13] In addition, these pre-catalysts show long life in solution and exhibit enhanced versatility, as they are highly soluble in a wide variety of common organic solvents.

Pd G4 and Pd G5

In rare cases, the carbazole leaving group generated from activation of G3 pre-catalysts can inhibit catalytic activity by consuming valuable reaction feedstock, and complicate workup/purification. To circumvent this issue, the Buchwald group prepared fourth generation (G4) and fifth generation (G5) pre-catalysts[14] by methylating and arylating the amino group on the aminobiphenyl scaffold, respectively. Compared to G3 pre-catalysts, G4 and G5 exhibit higher solubilities while maintaining excellent catalytic activity. However, G4 and G5 pre-catalysts of extremely bulky ligands (e.g., RockPhos and AlPhos) are only formed with great difficulty.

Pd G6

Overall, sixth generation (G6) pre-catalysts[15] are superior to earlier Buchwald pre-catalysts. First, G6 pre-catalysts are highly versatile, because each of the three ligands (anionic ligand **X**, phosphine ligand **L**, and aryl scaffold **Ar**) of the oxidative addition complexes (OACs) can be independently tuned to create a nearly endless number of pre-catalyst variations. Therefore, improved solubility, greater stability, increased reactivity, and/or easier purification can be achieved through careful design or selection of these three components. Second, G6 pre-catalysts are very reactive because these OACs are presumptive intermediates on the catalytic cycle for cross-coupling processes. In fact, unlike G1 through G5, the activation of G6 pre-catalysts to LPd(0) species does not require base. Third, G6 pre-catalysts are specifically superior to G3 pre-catalysts, since their activation only forms innocuous by-products. Fourth, G6 pre-catalysts are specifically superior to G4 and G5 pre-catalysts, as they can easily support extremely bulky ligands. Fifth, stability studies have indicated that G6 pre-catalysts are typically stable under air in a benchtop desiccator for over a year, and can be easily handled outside of a glovebox, like G1 through G5 pre-catalysts. Furthermore, several reports have directly compared the performance of G6 pre-catalysts against those of previous generations for a selection of cross-coupling reactions, and G6 pre-catalysts typically show superior reactivity, selectivity, reaction scope, and/or yields.[5,9,15]

References

1. Ueda, S.; Su, M.; Buchwald, S. L. J. Am. Chem. Soc. 2012, 132, 700.
2. Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. Org. Lett. 2008, 10, 3505.
3. Su, M.; Buchwald, S. L. Angew. Chem. Int. Ed. 2012, 51, 4710.
4. (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Chem. Sci. 2013, 4, 916. (b) Martin, R.; Buchwald, S. L. Acc. Chem. Res. 2008, 41, 1461.
5. (a) Dennis, J. M.; White, N. A.; Liu, R. Y.; Buchwald, S. L. J. Am. Chem. Soc. 2018, 140, 4721. (b) Ruiz-Castillo, P.; Buchwald, S. L. Chem. Rev. 2016, 116, 12564. (c) Surry, D. S.; Buchwald, S. L. Chem. Sci. 2011, 2, 27. (d) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. Tetrahedron 2019, 75, 4199.
6. (a) Zhang, H.; Ruiz-Castillo, P.; Buchwald, S. L. Org. Lett. 2018, 20, 1580. (b) Cheung, C. W.; Buchwald, S. L. J. Org. Chem. 2014, 79, 5351. (c) Cheung, C. W.; Buchwald, S. L. Org. Lett. 2013, 15, 3998. (d) Wu, X.; Fors, B. P.; Buchwald, S. L. Angew. Chem., Int. Ed. 2011, 50, 9943. (e) Zhang, H.; Ruiz-Castillo, P., Schuppe, A. W., and Buchwald, S. L. Org. Lett., 2020, 22, 5369.
7. (a) Sather, A. C.; Buchwald, S. L. Acc. Chem. Res. 2016, 49, 2146. (b) Watson, D. A.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. Science 2009, 325, 1661.
8. (a) Ferguson, D. M.; Bour, J. R.; Canty, A. J.; Kampf, J. W.; Sanford, M. S. J. Am. Chem. Soc. 2017, 139, 11662. (b) Cho, E. J.; Buchwald, S. L. Org. Lett. 2011, 13, 6552. (c) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. Science 2010, 328, 1679.
9. Xu, J.; Liu, R. Y.; Yeung, C. S.; Buchwald, S. L. ACS Catal. 2019, 9, 6461.
10. (a) Bruneau, A.; Roche, M.; Alami, M.; Messaoudi, S. ACS Catal. 2015, 5, 1386. (b) Palladacycles: Catalysis and Beyond by Anant Kapdi and Debabrata Maiti.
11. Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. J. Am. Chem. Soc. 2008, 130, 6686.
12. Kinzel, T.; Zhang, Y.; Buchwald, S. L. J. Am. Chem. Soc. 2010, 132, 14073.
13. (a) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Chem. Sci. 2013, 4, 916. (b) Bruno, N. C.; Buchwald, S. L. Org. Lett. 2013, 15, 2876.
14. Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. J. Org. Chem. 2014, 79, 4161.
15. Ingoglia, B. T.; Buchwald, S. L. Org. Lett. 2017, 19, 2853.

Product List

Ligand Name	Ligand No.	G1	G2	G3	G4	G6 Br	G6 OTf	G6 TES
SPhos	638072	704946	753009	776246	804282			
XPhos	638064	704954	741825	763381	804274			
RuPhos	663131	707589	753246	763403	804290			
t-BuXPhos	638080	708739		762229	804266*			
BrettPhos	718742	718750		761605	804355			
t-BuBrettPhos	730998			745979	807877*	912646		912883
AdBrettPhos	768154			776106		915378		
AdCyBrettPhos	900278					Pending		
CPhos	759171		763012	763004	900471			
(t-Bu)PhCPhos	900275			900534	900533			
RockPhos	791016			773905	900330*			
Me_4t-BuXPhos	675938			900620	900546*			
Me_3(OMe)t-BuXPhos	792470			804193	900547*			
DavePhos	638021		903728	804959	900702			
PhDavePhos	695882							
t-BuDavePhos	695874			903701	903663			
JohnPhos	638439							
CyJohnPhos	638099		747807	900621	900284			

Ligand Name	Ligand No.	G1	G2	G3	G4	G6 Br	G6 OTf	G6 TES
AdJohnPhos	767689			RNI00025*				
MePhos	695262							
t-BuMePhos	695211							
JackiePhos	731013			762830	900532*			
TrixiePhos	710342			796530	900548*			
VPhos	900331			901219	901218			
EPhos	901215				901220			
sSPhos	677280		763314					
RuPhos-JackiePhos hybrid	900268							
CPhos-JackiePhos hybrid	900277							
AlPhos	799718					915602	916455	
GPhos	918008			Pending	Pending			Pending
2′-Dicyclohexylphosphino-2-methoxy-1-phenylnaphthalene	761265*							
2′-Dicyclohexylphosphino-2,4,6-trimethoxybiphenyl	707430*							
XantPhos	526460		763047	763039	900329			
N-XantPhos	666564			794228	900455			
APhos (AmPhos)	677264		764299	764183	900608			
MorDalPhos	751618		792349	792357	900276			
meCgPPh	695459		761281	762822	900697			
JosiPhos SL-J009-1	88733			747130	900541*			
JosiPhos SL-J009-2	88734			RNI00044				
rac-BINAP	481084			804967	900340			
(R)-Tol-BINAP	693049			905607	900472			
cataCXium® A	671479		761311	761435	900349			
QPhos	675784			903027				
DPPF	177261			804983	900454			
DTBPF	695149			804975				
PCy_3	261971		756741	764175	900287			
Neopentyl$(tBu)_2P$	676187		794198	794201	900698			
$P(t\text{-}Bu)_3$	570958		756482	804851	900701			
$(t\text{-}Bu)_2PMe$	642629		RNI00183	901194	900700			
$(t\text{-}Bu)_2PPh$	682411			901197	900699			
PPh_3	T84409		752762					
$P(o\text{-}Tol)_3$	287822		759163	804835				

*Discontinued or pending discontinuation from catalog. Please inquire about remaining catalog stock and/or custom manufacturing of bulk quantities.

Useful Links

Buchwald Ligands and Complexes **SigmaAldrich.com/Buchwald**

2nd Generation Buchwald Precatalysts **SigmaAldrich.com/Buchwald2Gen**

G3 and G4 Buchwald Precatalysts **SigmaAldrich.com/Buchwald3-4Gen**

Buchwald G6 Precatalysts: **Oxidative Addition Complexes *Coming Soon*!**

To place an order or receive technical assistance in Europe, please call Customer Service:
France: 0825 045 645
Germany: 069 86798021
Italy: 848 845 645
Spain: 901 516 645 Option 1
Switzerland: 0848 645 645
United Kingdom: 0870 900 4645

For other countries across Europe, please call: +44 (0) 115 943 0840
Or visit: **SigmaAldrich.com/offices**
For Technical Service visit: **SigmaAldrich.com/techservice**
Development/Custom Manufacturing: **LSCBULK@Merckgroup.com**

Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt, Germany

MK_BR7091EN Ver. 1.0
33556
11/2020