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Palladium-Catalyzed Chemoselective Cross-Coupling of Acyl Chlorides and Organostannanes

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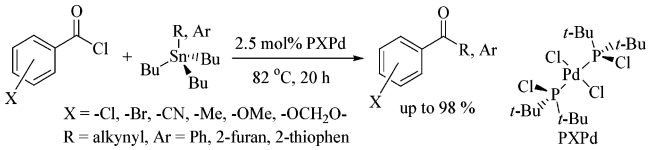

Chemoselective cross-coupling of aliphatic and aromatic acyl chlorides with aryl-, heteroaryl-, and alkynylstannanes proceeds in up to 98% yield using 2.5 mol % of bis(di-*tert*-butylchlorophosphine)palladium(II) dichloride as the precatalyst. Various functional groups including aryl chlorides and bromides that usually undergo oxidative addition to palladium complexes bearing phosphinous acid or dialkylchlorophosphine ligands are tolerated. This procedure allows convenient ketone formation and eliminates inherent limitations of Friedel−Crafts acylations such as substituent-directing effects and typical reactivity requirements of Lewis acid-catalyzed electrophilic aromatic substitutions.

Palladium-catalyzed cross-coupling reactions utilizing aryl halides and boronic acids (Suzuki), organostannanes (Stille), organosiloxanes (Hiyama), organozinc compounds (Negishi), Grignard reagents (Kumada coupling), alkynes (Sonogashira), or alkenes (Heck reaction) have found widespread popularity in synthetic chemistry during recent years.[1] The remarkable advance of organometallic C−C, C−N, C−O, and C−S bond-forming reactions has been possible through the development of effective and versatile palladium complexes bearing electron-rich and bulky ligands.[2] In particular, the introduction of 2-biphenyldicyclohexylphosphine ligands or tri-*tert*-butylphosphine and derivatives thereof in combination with $Pd_2(dba)_3$ and $Pd(OAc)_2$ by Nishiyama,[3] Hartwig,[4] Fu,[5] and Buchwald[6] proved to generate highly active catalyst species that readily undergo oxidative addition even with sterically hindered aryl chlorides. Noteworthy, Herrmann, Beller, Nolan, and others showed that palladium complexes exhibiting sterically demanding *N*-heterocyclic carbene ligands afford another class of catalysts providing excellent results in cross-coupling reactions.[7]

Numerous applications of Pd-catalyzed cross-coupling reactions with alkyl, alkenyl, and aryl halides or triflates have been developed in recent years. Interestingly, few examples of cross-coupling reactions with acyl chlorides can be found in the literature, although they are known to readily undergo oxidative addition to Pd(0) species. Stille et al. were first to employ acyl chlorides and organotin compounds in the Pd-catalyzed formation of unsymmetrical ketones.[8] They obtained good to excellent results using aryl-, alkenyl-, and alkynylstannanes although yields dropped when reactive aryl halide functionalities such as in 4-bromobenzoyl chloride were present. Apparently, competitive oxidative addition of Pd(0) complexes with aryl halides limits the versatility of this method. Neumann reported tin-mediated Friedel−Crafts acylations using aluminum trichloride to avoid the use of transition metals, but yields generally suffered from concomitant Fries rearrangements.[9] Since palladium/copper cocatalyzed cross-coupling reactions of acyl chlorides with α-amino- and α-alkoxystannanes were reported by Falck and co-workers,[10] acyl chlorides have been successfully employed in Sonogashira,[11] Suzuki,[12] Negishi,[13] and Stille-type couplings with α-sulfonami-

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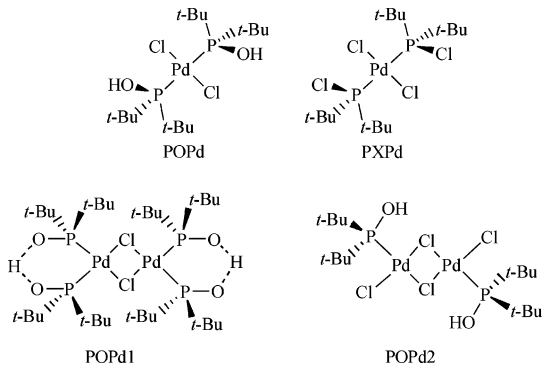
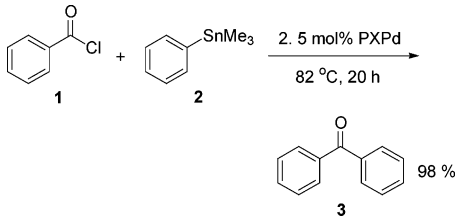


FIGURE 1. Structures of palladium−phosphinous acid complexes POPd, POPd1, and POPd2 and bis(di-*tert*-butylchlorophosphine)palladium(II) dichloride, PXPd.

doorgannostannanes[14] and vinylstannanes[15] and in multicomponent reactions involving vinylstannanes and imines.[16]

The use of palladium−phosphinous acid complexes such as $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ (POPd), $[[(t\text{-Bu})_2P(OH)(t\text{-Bu})_2PO)]PdCl]_2$ (POPd1), and $[(t\text{-Bu})_2P(OH)PdCl_2]_2$ (POPd2) for various cross-coupling reactions has recently been reported by us and others (Figure 1).[17] General features of palladium−phosphinous acid catalysts include simple preparation from readily available phosphine oxides, RR′P(O)H, and $Pd_2(dba)_3$, $Pd(cod)Cl_2$ or $Pd(OAc)_2$, stability to air, and high catalytic activity. The catalysts can be stored under air without loss in activity and can be directly employed in C−C, C−N, and C−S bond-forming reactions. Moreover, palladium−phosphinous acid-catalyzed coupling reactions do not have to be performed in anhydrous solvents and under inert atmosphere. The structure of bis(di-*tert*-butylchlorophosphine)palladium-(II) dichloride, PXPd, is similar to palladium-phosphinous acids POPd, POPd1, and POPd2. The latter are known to form negatively charged and thus strongly electron-donating phosphine ligands $(t\text{-Bu})_2PO^-$ that greatly facilitate oxidative addition of the corresponding Pd(0) species to aryl halides including aryl chlorides under basic conditions. Since the di-*tert*-butylphosphinous acid groups are replaced by less activating di-*tert*-butylchlorophosphine ligands, we rationalized that PXPd might be a useful catalyst for selective Stille-type cross-coupling reactions with acyl chlorides. Herein, we wish to report PXPd-catalyzed Stille cross-coupling reactions of aryl- and alkynylstannanes with acyl chlorides exhibiting various functional groups including aryl chlorides and bromides.

SCHEME 1. PXPd-Catalyzed Formation of Benzophenone, 3, from Benzoyl Chloride, 1, and Phenyltrimethyltin, 2



During our search for palladium−phosphinous acids and dialkylchlorophosphine analogues that would catalyze cross-coupling of acyl chlorides with organostannanes but not affect aryl halide bonds we found that ketone formation from benzoyl chloride, **1**, and 1.3 equiv of phenyltrimethyltin, **2**, proceeds in the presence of 5 mol % of PXPd after refluxing in acetonitrile for 20 h in 98% yield. Further studies revealed that benzophenone, **3**, can be obtained from **1** and 1.1 equiv of stannane **2** using 2.5 mol % of PXPd without compromising yields (Scheme 1). The reaction does not require any base or fluoride additives. Interestingly, slow *ipso*-substitution in the absence of the catalyst was also observed resulting in the formation of 10% of **3** under the same conditions. Based on our experience with Stille cross-couplings of aryl halides and organostannanes using palladium−phosphinous acid catalysts we anticipated that under these conditions PXPd might promote coupling with acyl chlorides but not with aryl halides thus extending selectivity and functional group tolerance of this method.[17d,g]

We were pleased to find that excellent coupling results can be obtained with a variety of acyl chlorides and organostannanes (Table 1). Coupling of **1** and tributyl(phenylethynyl)tin, **4**, gave the corresponding alkynone **5** in 93% yield (entry 2, Table 1). The reaction proceeds equally well with heteroaryltin compounds. For example, 2-(tributylstannyl)furan, **7**, affords ketones **8** and **10** in 92 and 96 yield, respectively, although coupling with 4-methoxybenzoyl chloride, **12**, provides ketone **13** in only 67% (entries 3, 4, and 6). Comparison of results obtained with substituted benzoyl chloride derivatives indicates that incorporation of electron-withdrawing groups increases yields (entries 2−6). PXPd-catalyzed cross-coupling of piperonyloyl chloride, **14**, with 2-(tributylstannyl)thiophene, **16**, or stannanes **4** and **7** gave ketones **15**, **17**, and **18** in 76−82% yield (entries 7−9). As expected, the method can also be used to produce ketones from aliphatic acyl chlorides. Employing **19** and **21** in the coupling reaction with stannanes **7** and **16** yielded ketones **20** and **22** in 78 and 85% (entries 10 and 11).

We then decided to screen *ortho*-, *meta*-, and *para*-halosubstituted benzoyl chlorides to evaluate competition between ketone formation via Stille-type coupling involving oxidative addition to an acyl chloride moiety and biaryl formation via cross-coupling utilizing an aryl halide functionality (Scheme 2). For example, 4-chlorobenzoyl chloride, **23**, can be expected to undergo Pd(0)-catalyzed reaction with stannane **7** toward ketone **24** followed by biaryl formation to give ketone **26**. Alternatively, oxidative addition of the palladium catalyst to the aryl halide bond could proceed first to yield acyl chloride

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TABLE 1. PXPd-Catalyzed Coupling of Acyl Chlorides and Organostannanes

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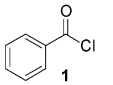
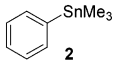
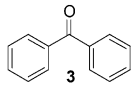
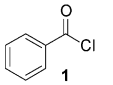
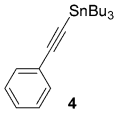
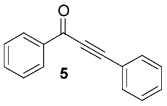
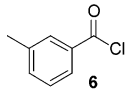
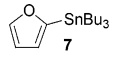
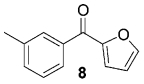
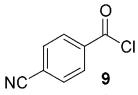
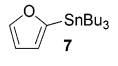
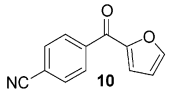
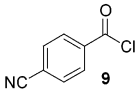
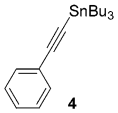
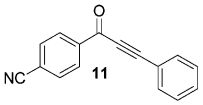
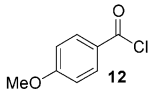
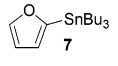
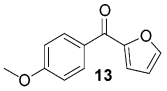
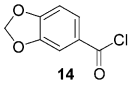
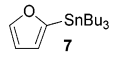
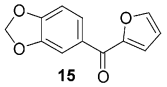
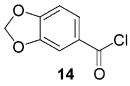
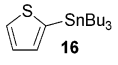
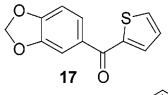
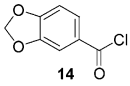
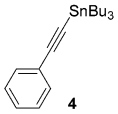
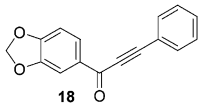
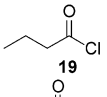
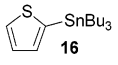
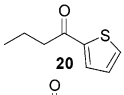
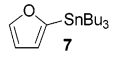
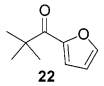
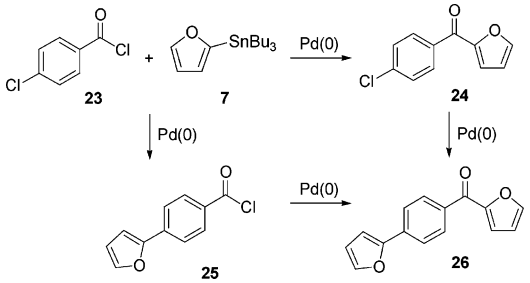
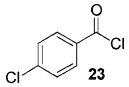
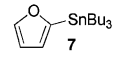
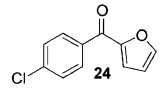
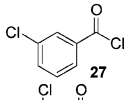
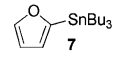
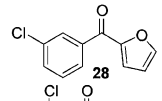
1	 1	 2	 3	98
2	 1	 4	 5	93
3	 6	 7	 8	92
4	 9	 7	 10	96
5	 9	 4	 11	98
6	 12	 7	 13	67
7	 14	 7	 15	82
8	 14	 16	 17	81
9	 14	 4	 18	76
10	 19	 16	 20	78
11	 21	 7	 22	85

SCHEME 2. Possible Cross-Coupling Pathways of Pd(0)-Catalyzed Cross-Couplings between 4-Chlorobenzoyl Chloride, 23, and Stannane 7



25 which may react further to ketone **26**. Although one might expect that oxidative addition of a Pd(0) species proceeds faster with acyl chlorides than with aryl chlorides or bromides, competition between these two processes could compromise overall yields of halo-substituted ketones such as **24** limiting the usefulness of this method. This problem becomes evident since it has been shown that palladium−phosphinous acids and dialkylchlorophosphine palladium catalysts promote cross-coupling

TABLE 2. PXPd-Catalyzed Ketone Formation Using Halobenzoyl Chlorides and Organostannanes

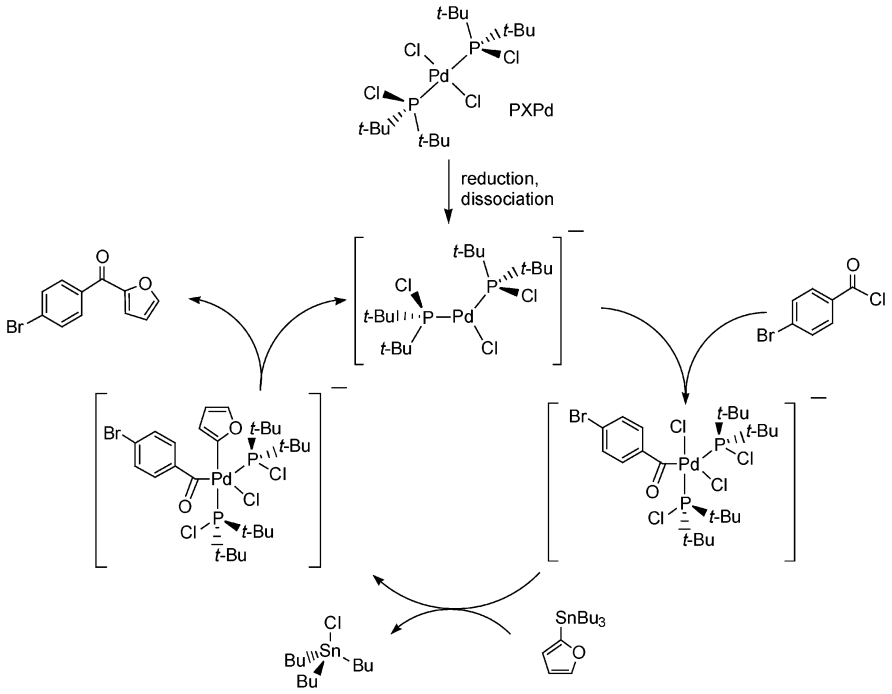
entry	acyl halide	organostannane	ketone	yield
1	 23	 7	 24	80
2	 27	 7	 28	80
3	29	7	30	87
4	23	4	31	67
5	23	16	32	72
6	27	16	33	72
7	34	7	35	85
8	36	7	37	62
9	38	7	39	57

reactions with chloro- and bromoaryl ketones such as **24** under the reaction conditions employed in this study.[17]

Employing the same reaction conditions as discussed above, we found that **23** undergoes PXPd-catalyzed ketone formation with stannane **7** to give 4-chlorophenyl-2-furan ketone, **24**, in 80% yield and chlorobenzoyl chlorides **27** and **29** produced ketones **28** and **30** in 80 and 87% yield, respectively (Table 2, entries 1−3). Similar results were obtained with stannanes **4** and **16** (entries 4−6). The coupling procedure also tolerates the presence of aryl bromides. In contrast to the results obtained with chlorosubstituted benzoyl chlorides **23**, **27**, and **29**, the highest yields were observed with 4-bromobenzoyl chloride providing 4-bromophenyl-2-furan ketone **35** in 85% yield while 2- and 3-bromobenzoyl chlorides **36** and **38** gave the corresponding ketones in only 57−62% (entries 7−9).

We assume that PXPd undergoes reduction and dissociation favored by the bulky di-*tert*-butylchlorophosphine ligands to generate a catalytically active Pd(0) species that readily reacts with acyl halides under the reaction conditions used in this study, Scheme 3. The previously reported high catalytic activity of palladium−phosphinous acids POPd, POPd1, and POPd2 under basic conditions has been attributed to formation of Pd(0) species bearing negatively charged and thus strongly electron-donating phosphine ligands $(t\text{-Bu})_2PO^-$ that greatly facilitate oxidative addition.[17] By contrast, the di-*tert*-butylchlorophosphine ligands of PXPd are less electron-donating and can therefore be used for chemoselective activation of the acyl halide moiety of halobenzoyl

SCHEME 3. Catalytic Cycle of PXPd-Promoted Stille-Type Coupling of Acyl Chlorides and Organostannanes



chlorides. Formation of an acyl Pd(II) complex by oxidative addition is then followed by transmetalation with an organostannane and reductive elimination to complete the catalytic cycle (Scheme 3).

We found that increasing the amount of stannane **7** employed in the reaction with 4-chlorobenzoyl chloride, **23**, from 1 to 2 equiv still affords ketone **24**. No sign of PXPd-catalyzed Stille coupling of the aryl chloride moiety of **23** and the additional equivalent of **7** was observed which proves the high chemoselectivity of the catalyst favoring ketone formation under the reaction conditions used. Accordingly, PXPd-catalyzed Stille coupling of stannane **7** and 4-chloroacetophenone, **40**, was found to be very sluggish providing 4-(2-furan)acetophenone, **41**, in only 15%. Employing 4-bromoacetophenone, **42**, and **7** in the same reaction gave the corresponding Stille cross-coupling product **41** in 85%. However, a competition experiment using equal amounts of stannane **7**, 4-bromoacetophenone **42**, and 4-bromobenzoyl chloride **34** gave acylation product **35** in 90% while unreacted **42** was recovered quantitatively. The observed chemoselectivity of the PXPd-catalyzed cross-coupling of stannanes and halogenated benzoyl chloride derivatives can thus be attributed to a fast acylation process that is favored over relatively slow or sluggish biaryl formation.[18]

In summary, we have shown that the selectivity of bis(di-*tert*-butylchlorophosphine)palladium(II) dichloride toward cross-coupling of acyl chlorides with organostannanes in refluxing acetonitrile provides a means to prepare aliphatic and aromatic ketones in good to high yields. Various functional groups including aryl chlorides and bromides that usually undergo oxidative addition to palladium complexes bearing phosphinous acid or dialkylchlorophosphine ligands are tolerated. This procedure allows convenient ketone formation and eliminates inherent limitations of Friedel−Crafts acylations such as substituent-directing effects and reactivity requirements of Lewis acid-catalyzed electrophilic aromatic substitutions.

Experimental Section

Representative Coupling Procedure. A mixture of 4-cyanobenzoyl chloride **9** (250 mg, 1.51 mmol), PXPd (20.3 mg, 2.5 mol %), 2-(tributylstannyl)furan **7** (571 mg, 1.60 mmol) in 5 mL of anhydrous acetonitrile was stirred under nitrogen at 82 °C for 20 h. The reaction mixture was allowed to cool to room temperature, quenched with water, and extracted with methylene chloride. The combined organic layers were washed withbrine and dried over $MgSO_4$, and the solvents were removed under vacuum. Purification by flash chromatography (1:1 diethyl ether/hexanes) gave 4-cyanophenyl 2-furan ketone **10** (286 mg, 1.45 mmol, 96%) as yellow crystals: mp 136−138 °C; ^{1}H NMR δ 6.67 (dd, J = 1.0 Hz, 3.4 Hz, 1H), 7.33 (d, J = 3.4 Hz, 1H), 7.76 (d, J = 1.0 Hz, 1H). 7.83 (d, J = 8.2 Hz, 2H), 8.10 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 113.0, 116.1, 118.2, 121.5, 130.0, 132.5, 140.8, 148.1, 152.1, 180.9. Anal. Calcd for $C_{12}H_7NO_2$: C, 73.09; H, 3.58; N, 7.10. Found: C, 73.19; H, 3.56; N, 6.91.

Acknowledgment. We thank Combiphos Catalysts, Inc., New Jersey (www.combiphos.com), for PXPd.

Supporting Information Available: Synthetic procedure, characterization data of all coupling products, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Attempts to apply the acylation procedure to the coupling of benzoyl chlorides and tetraalkylstannanes were not successful. Employing 4-cyanobenzoyl chloride **9** and tetrabutylstannane or tetramethylstannane in the PXPd-catalyzed coupling reaction did not result in the formation of the corresponding arylalkyl ketones and all starting materials were recovered.