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Synthesis, Characterization, and Reactivity of Arylpalladium Cyanoalkyl Complexes: Selection of Catalysts for the α-Arylation of Nitriles

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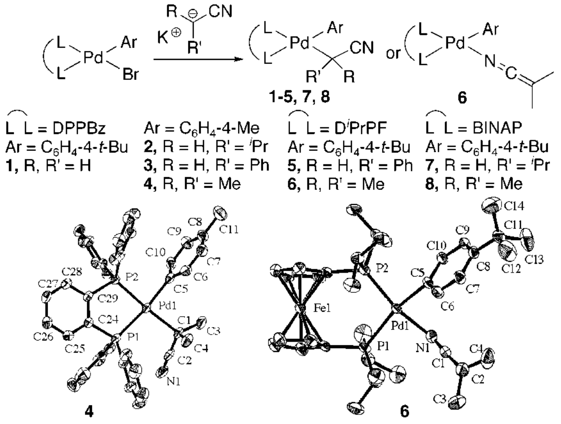
Cross-coupling reactions typically join an aryl or vinyl group with a second unsaturated moiety.[1] Recently our group and others have reported palladium-catalyzed methods for the direct coupling of aryl bromides with a variety of ketone enolates to form sp^2 to sp^3 C−C bonds.[2] After the development of improved catalyst systems, the reaction is now general for a wide range of carbonyl substrates[3] and has been developed as an enantioselective process.[4]

In principle, one could couple the anion of a nitrile with an aryl halide in the presence of a palladium catalyst to form products that are versatile intermediates and have biological activity.[5] A conventional mechanism would include reductive elimination of α-aryl nitrile from an arylpalladium cyanoalkyl intermediate. However, the chemistry of α-cyanoalkyl complexes is not well developed. Many bonding modes are available; anions of nitriles could coordinate to a single metal through the α-carbon[6] or the cyano-nitrogen[7] or bridge two metals in a μ^2-*C,N* fashion.[8] Moreover, the electronic effect of the cyano group on the rate of reductive elimination from even a simple cyanoalkyl complex is difficult to predict. Nitriles are less acidic than ketones, but a cyano group is more electron-withdrawing than an acyl group. To address these questions, we report the synthesis and characterization of a series of arylpalladium cyanoalkyl complexes, including examples of three distinct binding modes. These studies paved the way to catalysts for the coupling of nitriles with aryl halides, and initial results on this new coupling process are reported.

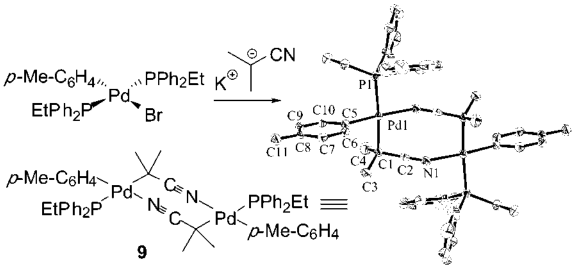
Arylpalladium cyanoalkyl complexes were prepared as analytically pure solids in 45−81% yield, as shown in Schemes 1 and 2. As expected for a soft, late metal, most of the arylpalladium cyanoalkyl complexes in Scheme 1 were C-bound (**1**−**5**, **7**, **8**). NMR and IR spectroscopic techniques, in combination with X-ray crystallography, revealed the coordination mode of the complexes. For example, complex **4**, ligated by 1,2-bis(diphenylphosphino)benzene (DPPBz), was shown to be C-bound by the typical nitrile ^{13}C NMR resonance at δ 125.8 and nitrile IR band at 2170 cm^{-1}. An X-ray structure of **4** confirmed this assignment; the C−N bond length is 1.16 Å.

However, other ancillary ligands induced unusual coordination modes. When the palladium was ligated by the larger, more donating 1,1′-bis(di-*i*-propylphosphino)ferrocene (D^{i}PrPF), the anion of isobutyronitrile coordinated to the metal through the nitrogen atom (**6**). This binding mode was deduced from the doublet ^{13}C NMR resonance at δ 175.5 ($J_{\mathrm{C-P}}$ = 8.2 Hz), which is far downfield of that observed for **4** and closer to the N═C resonance of ketenimines.[9] The two strong bands at 1997 and 2186 cm^{-1} in the IR spectrum also resemble those for ketenimines. X-ray crystallography secured the assignment of this rare binding mode, and the palladium-bound N═C distance of 1.21 Å and C═C distance of 1.35 Å are consistent with the proposed double bond character.

Scheme 1



Scheme 2



Spectral analysis of **9** suggested a dimeric structure with the nitrile bridging the metals by a μ^2-*C,N* coordination mode. The ^{1}H NMR spectrum showed only one phosphine per palladium-bound cyanoalkyl, and the nitrile resonance in the ^{13}C NMR spectrum was located at δ 138.8, which is only slightly downfield from the chemical shift of **4**. The IR spectrum displayed a broad absorption at 2195 cm^{-1}. The binuclear structure of **9** was decisively assigned by X-ray crystallography.

The three different binding modes observed for the anion of isobutyronitrile demonstrate that the nitrile anion prefers to coordinate to palladium through the carbon atom in the absence of steric effects. When a more sterically demanding ligand is bound to the metal, coordination through nitrogen is observed. When a labile phosphine is present, dissociation of ligand occurs, and the nitrogen of the α-cyanoalkyl displaces a phosphine donor to create a bridging cyanoalkyl complex.

Having established the distinct coordination modes, we explored the reactivity of these complexes. Thermolysis of **1**−**9** at 110 °C in the presence of added PPh$_3$ as a trap for the Pd(0) fragment induced the first reductive eliminations to form α-aryl nitriles. Reactions occurred in 40−99% yield by ^{1}H NMR spectroscopy with an internal standard (Table 1). Yet, yields of coupled product were notably lower and the rates of reductive elimination were signifi-

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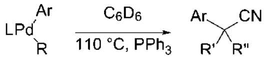
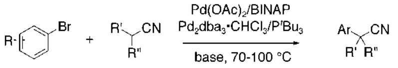
Table 1. Reductive Elimination from LPd(Ar)(R)[a]

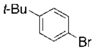
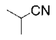
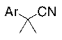
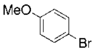
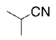
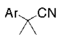
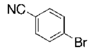
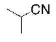
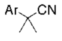
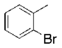
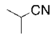
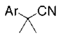
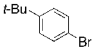
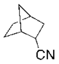
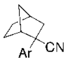
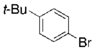
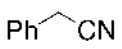
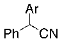
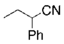
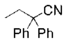
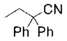
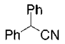
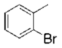
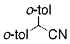


complex	L	Ar	R	time (h)	yield (%)
1	DPPBz	C_6H_4−4-*t*-Bu	CH_2CN	60	63
2	DPPBz	C_6H_4−4-Me	$CH(CHMe_2)CN$	60	57
3	DPPBz	C_6H_4−4-Me	CHPhCN	48	50
4	DPPBz	C_6H_4−4-Me	CMe_2CN	12	69
5	D^{i}PrPF	C_6H_4−4-*t*-Bu	CHPhCN	<1	73
6	D^{i}PrPF	C_6H_4−4-*t*-Bu	$N{=}C{=}CMe_2$	<1	40
7	BINAP	C_6H_4−4-*t*-Bu	$CH(CHMe_2)CN$	<1	99
8	BINAP	C_6H_4−4-*t*-Bu	CHPhCN	<1	98
9	PPh_2Et	C_6H_4−4-Me	CMe_2CN	<1	45

[a] Yields of nitrile were determined for reactions of 0.01 mmol of complex by ^1H NMR spectroscopy in C_6D_6 with an internal standard.

Table 2. Palladium-Catalyzed α-Arylation of Nitriles



Entry	ArX	nitrile	product	mol % Pd[a] /L	Conditions[b]	Yield[c]
1.				1 % A/ BINAP	100 °C 2 h	87 %
2.				1 % A/ BINAP	100 °C 8 h	83 %
3.				0.5 % A/ BINAP	100 °C 1 h	99 %
4.				1 % A/ BINAP	100 °C 6 h	70 %
5.				2 % A/ BINAP	100 °C 4 h	69 %[d]
6.				2 % A/ BINAP	100 °C 2 h[e]	95 %
7.	PhBr			1 % B/ P^{t}Bu$_3$	70 °C 3 h	89 %
8.	PhBr			1 % B/ P^{t}Bu$_3$	70 °C 6 h[f]	69 %
9.	PhBr	CH_3CN		5 % A/ BINAP	100 °C 16 h	62 %
10.		CH_3CN		5 % A/ BINAP	100 °C 16 h	60 %

[a] A = $Pd(OAc)_2$; B = $Pd_2dba_3{\cdot}CHCl_3$. [b] 1:1 ratio of Pd/L for reactions conducted with BINAP, 1.3 equiv of $NaN(SiMe_3)_2$; 1:2 ratio of Pd/L for reactions conducted with P^{t}Bu$_3$, 1.3 equiv of $LiN(SiMe_3)_2$; 1.2 equiv nitrile, toluene solvent. [c] Yields are an average of two runs on a 1 mmol scale. [d] 2:1 ratio of isomers. [e] Reaction conducted with 1.3 equiv of KO-t-Bu. [f] Reaction conducted with 2.2 equiv of $LiN(SiMe_3)_2$.

cantly slower than those observed for reductive elimination from similar arylpalladium enolates.[10] For instance, elimination of α-aryl nitriles from arylpalladium cyanoalkyls **1**−**4** occurred in only 50−69% yield and required up to 60 h, while analogous DPPBz-ligated arylpalladium enolate complexes formed α-aryl ketones in >90% yield in less than 3 h. Elimination from the dimeric **9** was complete within 1 h, but coupled product was formed in only 45% yield. In contrast, elimination from the more sterically crowded D^{i}PrPF- and BINAP-ligated complexes **5**−**8** generated the desired α-aryl nitrile in higher yields and shorter reaction times. These results suggested that *C*-coordination to a single metal center favors the desired reductive elimination and that BINAP-ligated palladium complexes could catalyze the arylation of nitriles.

The palladium-catalyzed arylation of nitriles is summarized in Table 2. After stirring in toluene for 10 min at 25 °C, nitrile and $NaN(SiMe_3)_2$ or $LiN(SiMe_3)_2$ were added to a solution of aryl halide, ligand, and $Pd(OAc)_2$ or $Pd_2dba_3{\cdot}CHCl_3$. The system was heated for 1−16 h at 70−100 °C. The arylation of nitriles occurred with aryl halides that possess a range of electronic properties; electron-rich (entry 2), electron-poor (entry 3), and sterically hindered (entries 4, 10) aryl bromides were all viable substrates. The reactions of secondary and benzyl nitriles occurred selectively to form the product of monoarylation in high yields. The arylation of 2-norbornanecarbonitrile formed a mixture of *endo* and *exo* adducts. Diarylation of butyronitrile (entry 8) and acetonitrile (entries 9, 10) occurred in preference to monoarylation, presumably because the monoarylated reaction product generates the required anion more readily and is unhindered enough to bind palladium. Reactions of 2-phenylbutyronitrile (entry 7) and butyronitrile (entry 8) conducted with tri-*tert*-butylphosphine and $Pd_2dba_3{\cdot}CHCl_3$ occurred in higher yields than those conducted with BINAP and $Pd(OAc)_2$.

Although the uncatalyzed reaction of aryl fluorides with anions of nitriles forms tertiary benzylic nitriles, the uncatalyzed reaction of aryl bromides and the uncatalyzed reaction of unactivated aryl fluorides with aceto, primary, or benzylic nitrile anions does not occur.[5] Only a single example of the palladium-catalyzed arylation of phenylacetonitrile, which occurred in moderate yield at high temperature, has been reported.[11] The synthesis of arylcyanoacetates via palladium catalysis has also been described.[12]

In summary, the effect of structure and electronic properties on the reactivity of arylpalladium cyanoalkyl complexes showed the potential for a new catalytic process. This new reaction provides a convenient route to α-aryl nitriles from readily available materials and commercially available catalysts and bases. Because these arylations occur to form quaternary centers in high yields, enantioselective couplings should be possible and will be the focus of future studies.

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Supporting Information Available: Experimental methods, spectral data, and X-ray diffraction data for palladium compounds and experimental procedures for catalytic studies (PDF). An X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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