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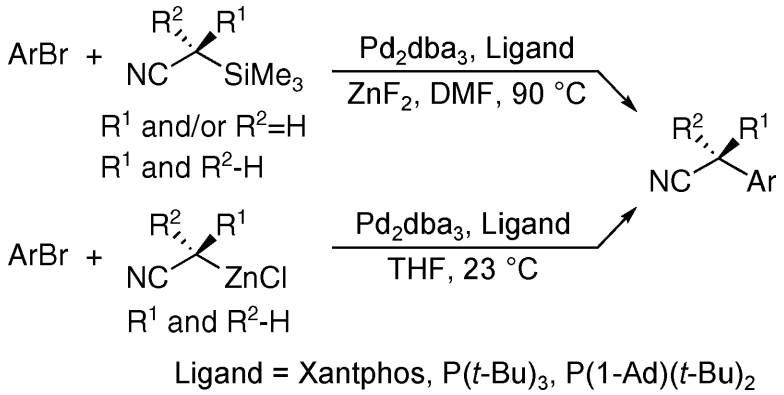

Ligand = Xantphos, P(*t*-Bu)$_3$, P(1-Ad)(*t*-Bu)$_2$

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Mild Palladium-Catalyzed Selective Monoarylation of Nitriles

Lingyun Wu and John F. Hartwig*

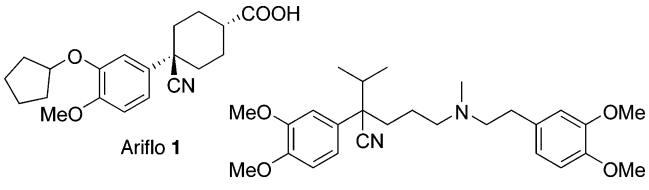
Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06510

Received May 9, 2005; E-mail: john.hartwig@yale.edu

Abstract: Two new palladium-catalyzed procedures for the arylation of nitriles under less basic conditions than previously reported have been developed. The selective monoarylation of acetonitrile and primary nitriles has been achieved using α-silyl nitriles in the presence of ZnF_2. This procedure is compatible with a variety of functional groups, including cyano, keto, nitro, and ester groups, on the aryl bromide. The arylation of secondary nitriles occurred in high yield by conducting reactions with zinc cyanoalkyl reagents. These reaction conditions tolerated base-sensitive functional groups, such as ketones and esters. The combination of these two methods, one with α-silyl nitriles and one with zinc cyanoalkyl reagents, provides a catalytic route to a variety of benzylic nitriles, which have not only biological significance but utility as synthetic intermediates. The utility of these new coupling reactions has been demonstrated by a synthesis of verapamil, a clinically used drug for the treatment of heart disease, by a three-step route from commercial materials that allows convenient variation of the aryl group.

Introduction

α-Aryl nitriles can possess biological activity and are useful synthetic intermediates. For example, ariflo (cilomilast) **1**[1] and verapamil **2**[2] are used in the clinic for chronic obstructive pulmonary disease (COPD) and hypertension. α-Aryl nitriles lead to α-aryl amides and carboxylic acids by hydrolysis, and this hydrolysis is part of a commercial route to Ibuprofen.[3] They can also generate β-arylamines by reduction[4,5] and can serve as precursors to ketones by addition of Grignard reagents and hydrolysis of the resulting imine.[6] α-Arylnitriles are also useful in the synthesis of heterocycles, such as thiozoles, oxazolines, tetrazoles, imidazoles, and triazoles.[7]



Ariflo **1**

Verapamil **2**

α-Aryl nitriles are traditionally prepared by cyanation of a benzylic halide,[8] Friedel−Crafts reactions,[9] or dehydration of amides.[10] However, selective halogenation to form the benzylic halide is challenging in many cases, and the use of cyanide can be undesirable in some settings. Friedel−Crafts reactions have limited functional group tolerance, and the use of amides diverts the synthetic problem to the synthesis of α-aryl amides. Thus, alternative routes to α-aryl nitriles have been sought,[11−16] and a general, catalytic coupling of cyanoalkyl anions with aryl halides would be a valuable method.

Although palladium-catalyzed α-arylation of carbonyl compounds has been established as a general method for the synthesis of α-aryl ketones[17−19] and α-aryl esters,[20−24] the coupling of nitriles has only been partially addressed.[21,25−29] The coupling of nitriles with aryl halides has proven to be challenging for several reasons. First, nitriles are only weakly acidic. Therefore, strong bases must be used to generate the cyanoalkyl anions, and the resulting anions may react faster with

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auxiliary functionality than they react in the catalytic process. Thus, the current procedures involving the reactions of nitriles with strong base limit the functional group tolerance, and products from the arylation that contain an α-proton undergo racemization under the strongly basic reaction conditions. This racemization would prevent any future development of enantioselective couplings to form secondary nitriles.

Second, nitriles are Lewis bases and can form insoluble oligomeric compounds when combined with main group reagents. This property limits the use of some less basic main group reagents of nitriles. Third, complexes of nitrile anions undergo slower reductive elimination than complexes of enolates. The strong inductive effect of the cyano substituent retards reductive elimination, and the nitrile anion can bind to the transition metal through nitrogen, through carbon, or in a bridging mode to form stable dinuclear structures. The slow reductive elimination allows side reactions to compete with the desired coupling. Fourth, reactions of acetonitrile and primary nitriles generate products from diarylation. These products are observed because the pK_a values of benzylic nitriles are closer to the range that leads to full deprotonation in the presence of bases that are compatible with the palladium catalyst. Thus, the α-arylation of nitriles from a catalytic reaction of aryl halide, nitrile, and base can be conducted, but the reactions have limited scope and poor selectivity for the monoarylation product.[21,25−29]

Perhaps for these reasons, studies on the scope of the coupling of main group reagents with aryl halides, such as Negishi,[30−32] Suzuki−Miyaura,[33] Stille,[34] and Hiyama coupling,[35] have not addressed the problem of coupling aryl halides at the position α to a nitrile. Based on our recent success in broadening the scope of coupling processes with main group enolates[36,37] and a desire to avoid organostannanes reagents for reasons of toxicity, we sought to develop the coupling of aryl halides with zinc and silicon cyanoalkyl reagents. These reagents are less basic than alkali metal cyanoalkyl reagents, and this lower basicity should lead to greater functional group tolerance.

We report the α-arylation of nitriles with two new methods, the combination of which leads to mild reactions that encompass the coupling of aceto, primary, and secondary nitriles with aryl halides. By one process, the coupling of α-silyl nitriles occurs with added zinc fluoride and selectively generates the products from monoarylation of aceto and primary nitriles. By a second process, zinc cyanoalkyl reagents generated from secondary nitriles react with a substrate scope that is broad and encompasses reactions of zinc reagents generated from hindered secondary nitriles. As one demonstration of the utility of this coupling, the arylation of a hindered primary nitrile by this latter method creates a short, flexible synthesis of Verapamil.

Results and Discussion

A. Coupling of α-Silyl Nitriles. 1. Coupling of Aryl Halides with Silyl Acetonitrile Derivatives. Our initial studies of the coupling of aryl halides with main group cyanoalkyl reagents focused on reactions of commercially available trimethylsilylacetonitrile **3**. With this reagent, we sought to conduct the monoarylation of acetonitrile. Such a monoarylation reaction would contrast with the less desirable diarylation of acetonitrile that formed from palladium-catalyzed reactions of aryl halides with the combination of acetonitrile and base. We evaluated the coupling of **3** with para-*tert*-butylbromobenzene in a variety of solvents and with a variety of metal fluoride additives. We conducted these reactions in the presence of catalytic amounts of the combination of Pd_2dba_3 (dba = dibenzylideneacetone) and P(*t*Bu)$_3$, which we have shown to catalyze the α-arylation of ketones,[18] esters,[22] and silyl ketene acetals.[36]

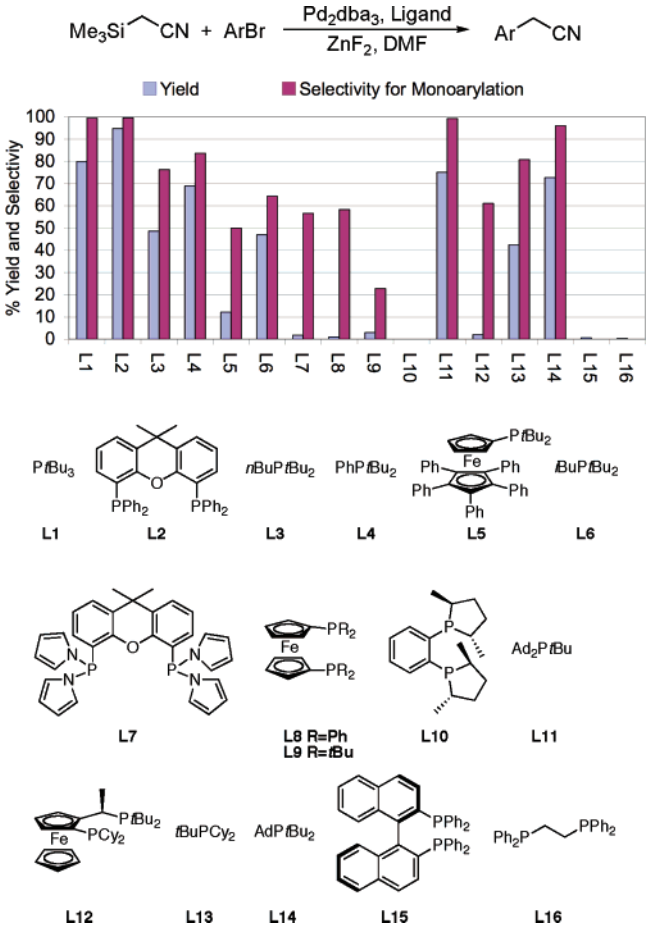

Figure 1. Yields and selectivities for monoarylation from the coupling of trimethylsilyl-acetonitrile with bromobenzene catalyzed by $Pd_2(dba)_3$ and a series of phosphine ligands.

The reaction of trimethylsilylacetonitrile with 4-*tert*-butyl bromobenzene in the presence of Pd_2dba_3 and P(*t*Bu)$_3$ as catalyst and zinc fluoride as additive generated the monoarylation product in 80% yield. No reaction between trimethylsilylacetonitrile and 4-*tert*-butyl bromobenzene with Pd_2dba_3 and P(*t*Bu)$_3$ as catalyst was observed without any Lewis basic additive, and the same reaction conducted with more basic fluorides, such as CsF or KF, formed exclusively the product from diarylation. We presume that the diarylation products were formed when reactions were run with these additives because the alkali metal cyanoalkyl reagent is generated from the silylacetonitrile in the presence of the strongly basic fluorides (vide infra). Reactions conducted with added CuF_2, which has been used for the coupling of silyl enol ethers,[38] did not lead to the formation of any coupled product. Thus, the zinc fluoride appears to be strong

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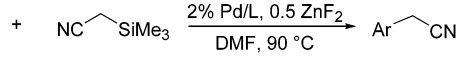
Table 1. Palladium-Catalyzed Coupling of Trimethylsilylacetonitrile[a]



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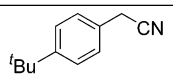
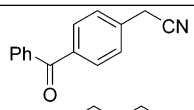
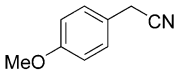
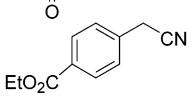
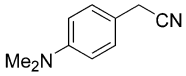
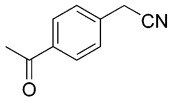
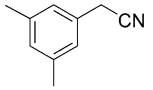
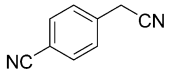
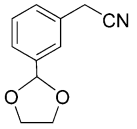
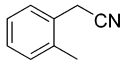
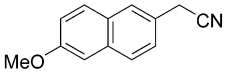
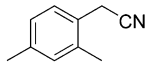
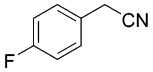
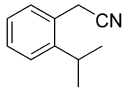
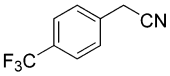
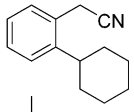
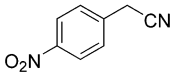
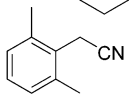
1		A	18	87	10		A	8	92
2		A	18	64	11		A	8	84
3		C	18	83	12		A	8	78
4		A	18	74	13		A	8	81
5		A	18	78	14		B	24	83
6		A	18	87	15		B	24	78
7		A	18	79	16		B	24	69
8		A	18	78	17		B	24	71
9		A	8	68	18		B	24	84

[a] Conditions A: 2 mol % Pd_2dba_3, 2 mol % Xantphos, 0.5 equiv of ZnF_2, DMF, 90 °C. B: 2 mol % Pd_2dba_3, 4 mol % P(*t*-Bu)$_3$, 0.5 equiv of ZnF_2, DMF, 90 °C. C: 2 mol % Pd_2dba_3, 4 mol % PhP(*t*-Bu)$_2$, 0.5 equiv of ZnF_2, DMF, 90 °C.

enough to generate a hypervalent silicon species that is activated for transmetalation, but it is not so strong that it prematurely cleaves the Si−C bond or deprotonates the monoarylated product. Stoichiometric amounts of fluoride were essential for this reaction. Reactions with 0.25 equiv of ZnF_2 occurred in only 61% yield, but reaction with 0.5 equiv of ZnF_2 occurred in 88% yield. A polar solvent was also needed to observe high yields. The coupling of nitrile **3** occurred in the highest yields in DMF and NMP, and no product was formed in nonpolar solvents, such as ether and toluene.

Although our initial experiments to develop reaction conditions were conducted with P(*t*Bu)$_3$ as ligand, palladium complexes ligated by both monodentate and bidentate ligands catalyzed the coupling of aryl halides with the combination of nitrile **3** and ZnF_2. A variety of monodentate and bidentate ligands were tested for this coupling process, and the results of these experiments are displayed in Figure 1. Although complexes of most bidentate ligands did not catalyze the reaction, high yields were observed from reactions catalyzed by complexes of Xantphos, which contains a large bite angle. The ratio of palladium to ligand did not significantly affect yield or selectivity. Changing the metal-to-ligand ratio from 1:2 to 1:1 increased the yield only slightly.

The scope of the coupling of aryl bromides with trimethylsilylacetonitrile is summarized in Table 1. Three ligands were used in combination with $Pd_2(dba)_3$ in the reactions reported in this table. Reactions of the unhindered aryl halides were conducted with Xantphos as ligand; reactions of *ortho*-substituted aryl halides were conducted with P(*t*Bu)$_3$ as ligand, and one example of the most electron-rich aryl halide was most successfully conducted with PhP(*t*Bu)$_2$. Both electron-rich (entries 1−6) and electron-poor aryl bromides (entries 7−13) participated in this reaction. The aryl bromides with electron-withdrawing substituents were somewhat more reactive than the aryl bromides with electron-donating substituents. The coupling reactions with electron poor substrates occurred to completion and in high yield in 8 h, whereas reactions of electron-rich aryl halides were complete after 18 h.

This reaction occurred successfully in the presence of a variety of functional groups. For example, the reaction of the aryl halide in entry 9, which contains a nitro group, the reaction

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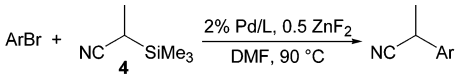
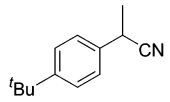
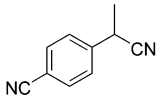
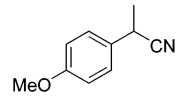
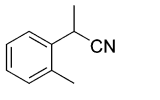
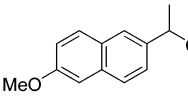
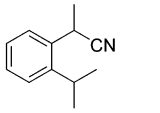
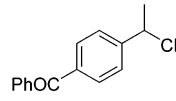
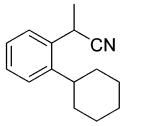
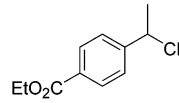
Table 2. Palladium-Catalyzed Coupling of α-Trimethylsilylpropionitrile[a]



Entry	Product	Condition	Time (h)	Yield (%)	Entry	Product	Condition	Time (h)	Yield (%)
1		A	18	77	6		A	8	82
2		A	18	71	7		B	24	71
3		A	18	98	8		B	24	60
4		A	8	87	9		B	24	64
5		A	8	84					

[a] Conditions A: 2 mol % Pd_2dba_3, 2 mol % Xantphos, 0.5 equiv of ZnF_2, DMF, 90 °C. B: 2 mol % Pd_2dba_3, 4 mol % P(*t*-Bu)$_3$, 0.5 equiv of ZnF_2, DMF, 90 °C.

of the aryl bromide in entry 10, which contains a keto group, and the reaction of the aryl bromide in entry 11, which contains ester functionality, all gave the desired products in high yields. Moreover, the reaction of the aryl bromide in entry 12, which contains enolizable hydrogens, afforded the coupled product in 78% yield.

The reaction also occurred with aryl halides bearing ortho substituents. In this case, the coupling reaction with the catalyst generated from P(*t*-Bu)$_3$ was faster than that from Xantphos. The reactions of *ortho*-substituted aryl halides occurred to completion in 24 h in the presence of catalysts generated from P(*t*-Bu)$_3$, whereas the reactions of these substrates were sluggish in the presence of catalysts generated from Xantphos, and low conversions were observed even after 2 d.

2. Coupling of Aryl Halides with Silyl Derivatives of Primary Nitriles. Having developed procedures to conduct the monoarylation of acetonitrile, we sought conditions for the monoarylation of primary nitriles. The α-silyl propionitrile derivatives that would be required to conduct reactions analogous to those with silylacetonitrile **3** were prepared by several methods. The α-silyl propionitrile was synthesized in 60−70% by the reaction of the nitrile Reformasky reagent with chlorotrimethylsilane.[39] The nitrile Reformatsy reagent was prepared by known procedures[39] from the α-chloronitrile and commercially available granular zinc. Alternatively, the α-silyl propionitriles were prepared by the hydrosilylation of acrylonitrile with Wilkinson's catalyst.[40] Dimethylethylsilyl propionitrile and diphenylmethylsilyl propionitrile analogues were prepared by this hydrosilylation in 68% and 73% yield. These nitrile derivatives have also been prepared in the past by Michael addition of an alkylzinc reagent to an α,β-unsaturated nitrile in the presence of trimethylsilyl chloride.[30]

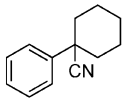
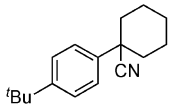
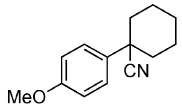
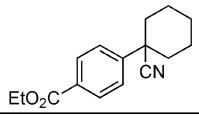
The reaction conditions developed for the arylation of acetonitrile were extended successfully to the coupling of the α-silyl derivatives of priopionitrile. These results are summarized in Table 2. Like the reaction of silylacetonitrile **3**, the reaction of silylpropionitrile **4** occurred with electron-rich (entries 1−3) and electron-poor aryl halides (entries 4−6). Further, this reaction tolerated functionality that reacts with the alkali metal cyanoalkyl reagents derived from propionitrile. For example, aryl halides containing a ketone (entry 4), ester (entry 5), and cyano (entry 6) functionality coupled with the silyl reagent to give the arylated nitriles in 87%, 84%, and 82% yields, respectively. The coupling of the α-silyl propionitrile also occurred with an aryl halide containing an ortho methyl group, although less readily than did the coupling of trimethylsilylacetonitrile **3**. The reaction of α-silyl propionitrile **4** with aryl halides containing more sterically demanding ortho isopropyl and ortho cyclohexyl substituents also afforded the products, albeit in moderate yields (entries 8 and 9).

Nitriles that contained other silyl substituents, such as ethyldimethylsilylacetonitrile and diphenylmethylsilylacetonitrile, were less reactive in this coupling process. The coupling of 4-*tert*-butyl bromobenzene with ethyldimethylsilyl propionitrile was much slower than the analogous reactions with the trimethylsilyl reagent. Further, coupling with diphenylmethylsilyl-priopionitrile did not occur under the conditions that led to selective reactions of trimethylsilyl-acetonitrile.

3. Coupling of Aryl Halides with Silyl Derivatives of Secondary Nitriles. The conditions for the coupling of aryl bromides with the combination of ZnF_2 and α-silyl nitriles did not extend to the coupling of aryl halides with hindered

(39) Constantieux, T.; Picard, J. P. *Synth. Commun.* **1997**, *27*, 3895.
(40) Ojima, I.; Kumagai, M.; Nagai, Y. *Tetrahedron Lett.* **1974**, *46*, 4005.

Table 3. Palladium-Catalyzed Coupling of α-Trimethylsilylcyclohexanecarbonitrile[a]

Entry	Product	Time (h)	Yields (%)
1		24h	68
2		24h	62
3		24h	77
4		24h	84

[a] Conditions: 2 mol % Pd_2dba_3, 2 mol % Xantphos, 1.0 equiv of KF, DMF, 90 °C.

secondary nitriles. Presumably, the more hindered pentacoordinate silyl species is not reactive enough to undergo transmetalation or is not present in high enough concentration. To overcome this problem, we first conducted reactions with the stronger Lewis base KF.

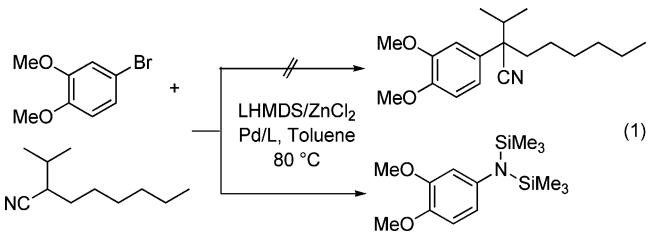
In the presence of this stronger base, α-silyl cyclohexylcarbonitrile **5** reacted with aryl bromides to form the α-aryl nitriles. These results are summarized in Table 3. For example, the coupling with electron-poor aryl halides, such as the ester in entry 4, occurred in a high 84% yield. However, these reactions were more limited in scope than reactions of the α-silyl derivatives of aceto and primary nitriles, and the reactions with electron−neutral and electron-rich aryl halides occurred in somewhat lower yields than reactions with electron-poor aryl halides. For example, reaction with 4-bromo-*tert*-butylbenzene formed the coupled product in 62% yield, and the reactions of the more electron-rich 4-bromoveratrole generated a mixture of products from which the desired product was isolated in low yield (<10%). The reaction of the α-silyl derivative of the secondary nitrile was also severely limited by steric effects. The coupling of ortho-substituted aryl bromides with the combination of KF and silylnitrile **5** did not occur. Thus, the reactions of silyl derivatives of acetonitrile and primary nitriles provide a mild, general method to prepare α-aryl nitriles, but the analogous reactions of α-silyl secondary nitriles are useful only in specific cases.

B. Coupling of Zinc Cyanoalkyl Reagents. To address the limited scope of the coupling of silyl reagents of secondary nitriles, we investigated the coupling of zinc reagents. The zinc reagents of the anion of acetonitrile were insoluble in most solvents. Further, their reactions with aryl bromides only afforded diarylated products, and these diarylated products were formed in low yields (<50%). However, we observed that the zinc reagents of secondary nitriles are more soluble than that of acetonitrile, and we considered that this greater solubility could give rise to faster reactions with the zinc reagents of secondary nitriles than were observed with the zinc reagent of acetonitrile. In addition, diarylation cannot occur with the zinc reagent of a secondary nitrile.

The zinc reagents of secondary nitriles can be prepared by two methods. They can be prepared by generating a Reformatsky-type reagent from the corresponding 2-bromonitrile[41,42] or by quenching an alkali metal cyanoalkyl anion with zinc halide. We investigated reactions of the zinc reagents generated by quenching of alkali metal cyanoalkyls in situ because this procedure would provide a synthetic method that would be more convenient than one starting with the α-bromonitrile.

To avoid formation of any product from C−N bond formation (vide infra), LDA was used to generate the lithium reagent. The diisopropylamine product from the deprotonation was removed under vacuum, and 1 equiv of zinc chloride was added to the system to generate the zinc cyanoalkyl halide reagent. Reaction of the resulting zinc reagent with the aryl bromide in the presence of the combination of P(*t*Bu)$_3$ and Pd(OAc)$_2$ as catalyst then generated the product from α-arylation of the nitrile in good yield.

Reactions in which we attempted to generate the zinc reagent by treatment of the nitrile with lithium hexamethyldisilyl azide (LiHMDS) followed by quenching with zinc halide generated, in the presence of 2% Pd(OAc)$_2$ and P(*t*-Bu)$_3$ as catalyst, the products from coupling of the aryl bromide with LiHMDS instead of the nitrile (eq 1). Thus, the reaction is best conducted with a hindered dialkylamide base. However, the amine should be removed prior to the coupling chemistry. Reactions with $LiNCy_2$ as base gave the coupled product, along with *N*-aryl dicyclohexylamine products.[43] Because of these observations, we used the lithium amide of a volatile amine and evaporated the amine prior to conducting the coupling of the zinc reagent.



(1)

An evaluation of several reaction parameters showed that the solvent is important for the success of this coupling reaction, but the identity of the zinc halide was less important. Reactions in THF and dioxane occurred in higher yields than reactions in hydrocarbon solvents. Reactions conducted with both zinc bromide and zinc chloride occurred, even at room temperature.

Results from reactions with a variety of monophosphine and bisphosphine ligands are illustrated in Figure 2. Among the ligands tested for this reaction, those that are monodentate, bulky, and electron rich generated the most active catalysts. For example, the reaction of 4-bromoveratrole with nitrile **6** gave the coupled product in 70−88% yield with catalysts derived from $Pd_2(dba)_3$, and either P*t*Bu$_3$, AdP*t*Bu$_2$, or Ad$_2$P*t*Bu. Reactions conducted with the less sterically bulky *i*BuP*t*Bu$_2$ occurred

(41) Goasdoue, N.; Gaudemar, M. *J. Organomet. Chem.* **1972**, *39*, 17.
(42) Fleming, F. F.; Zhang, Z.; Knochel, P. *Org. Lett.* **2004**, *6*, 501.
(43) This product more likely forms from addition of the amine to a benzyne intermediate than by palladium-catalyzed coupling.

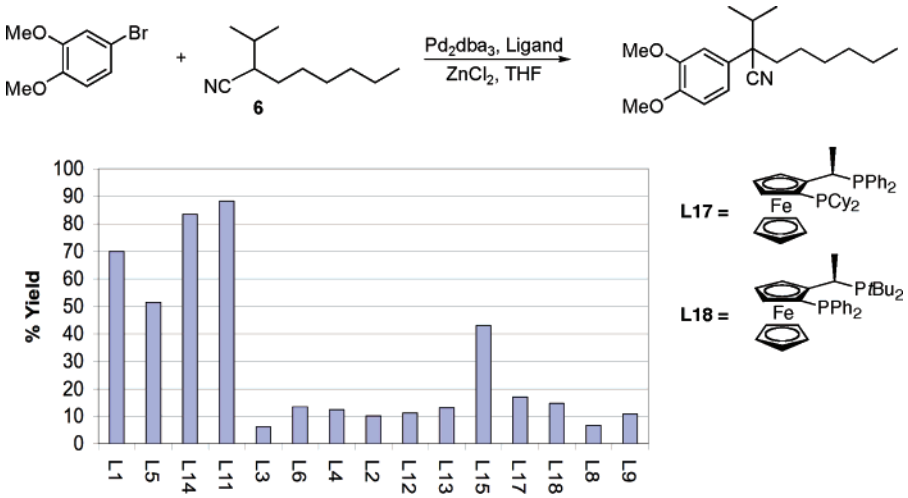


Figure 2. Yields from coupling of 4-bromoveratrole with nitrile **6**. For structures of the ligands, see Figure 1.

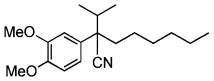
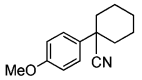
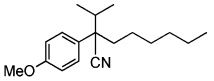
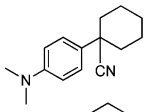
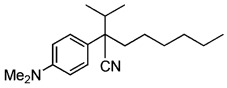
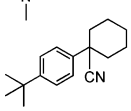
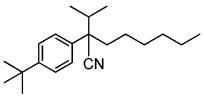
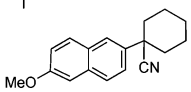
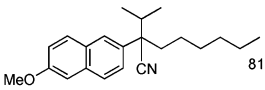
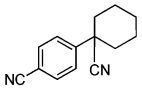
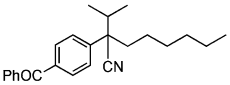
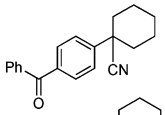
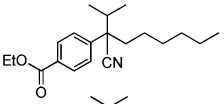
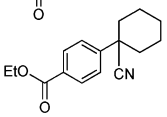
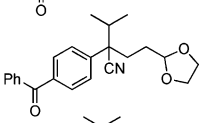
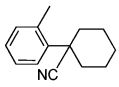
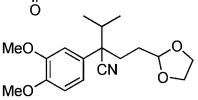
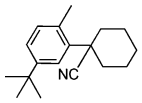
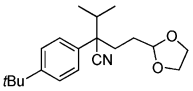
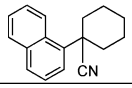
in a yield of only 15%. Similar trends were observed for the reactions of *p*-Bu^{t}C$_6$H$_4$Br, *p*-PhC(O)C$_6$H$_4$Br, and *p*-EtCO$_2$C$_6$H$_4$Br.

The scope of the coupling of the zinc reagents of secondary nitriles in the presence of palladium and P(*t*-Bu)$_3$ was evaluated, and the results are shown in Table 4. Unlike the coupling of the α-silyl secondary nitrile, which was limited to reactions of electron-poor aryl bromides, the scope of the reactions of the zinc cyanoalkyl reagents from secondary nitriles encompassed reactions of both electron-rich (entries 1−5) and electron-poor (entries 6 and 7) aryl bromides. In addition, the conditions for coupling of these zinc reagents were compatible with various functional groups. For example, reactions of the zinc reagent derived from acyclic nitrile **6** occurred with aryl halides bearing alkoxo (entries 1 and 2), dialkylamino (entry 3), phenacyl (entry 5), and ester groups (entry 6). In contrast, reactions of this zinc reagent with aryl halides containing ketones with enolizable hydrogens or free protic functionality did not occur, and the reaction with 4-bromobenzonitrile occurred in a yield of only about 20%.

The reaction was also tested with cyclic secondary nitriles. The reactions of aryl bromides with the zinc reagent generated in situ from cyclohexanecarbonitrile occurred at room temperature with both electron-rich (entries 11−14) and electron-poor (entries 15−17) aryl halides. This reaction even occurred with aryl halides bearing ortho substituents (entries 18−20). Again, this reaction also occurred with aryl halides bearing alkoxo (entry 11), dialkylamino (entry 12), phenacyl (entry 16), and ester groups (entry 17). It also occurred with an aryl halide containing a cyano substituent (entry 15).

C. Application of the α-Arylation to the Synthesis of Verapamil. Considering the clinical use of racemic Verapamil for hypertension,[2] we sought to investigate the α-arylation of the nitrile by a route that would provide a short synthesis that installs the aryl group from a simple aryl halide reagent after generation of the core nitrile. This route would provide a versatile synthesis for studies of structure reactivity relationships because the aryl group could be drawn from many of the commercially available aryl halides. A more conventional synthesis would begin with the benzylic nitrile. Because more aryl halides are commercially available than benzylic nitriles and because the aryl group is introduced in the second step instead of the first, the route involving α-arylation is more convenient for the synthesis of derivatives with varied aryl substituents.

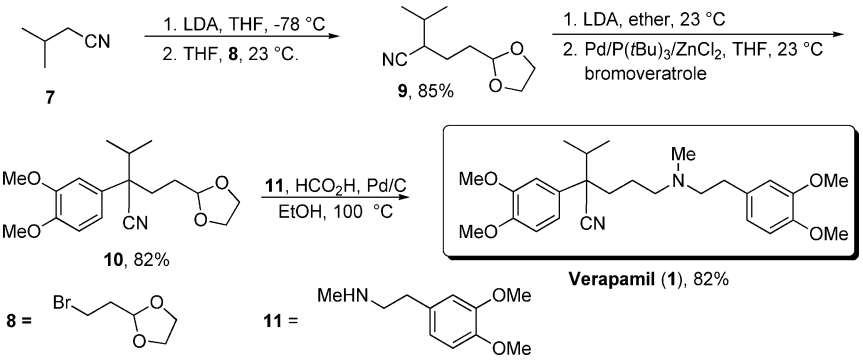
Table 4. Palladium-Catalyzed Coupling of Zinc Cyanoalkyl Reagents of Secondary Nitriles[a]

Entry	Product	yield (%)[b]	Entry	Product	yield (%)
1		68 (72)	11		72
2		72	12		82
3		69	13		85
4		85	14		81
5		81	15		71
6		78	16		75
7		47 (55)	17		63
8		86 (77)	18		87
9		82	19		91
10		76 (80)	20		91

[a] Pd(OAc)$_2$ (2 mol %), P*t*Bu$_3$ (4 mol %), ZnCl$_2$ (1.2 equiv), THF as solvent, room temperature. [b] Yields in brackets represent the isolated yields of reactions with Pd(OAc)$_2$ (2 mol %) and AdP*t*Bu$_2$ (4 mol %) as catalyst.

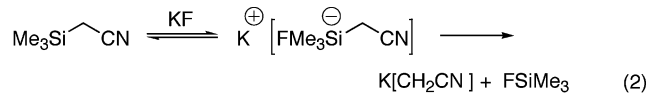
This short synthesis is shown in Scheme 1. From the commercially available nitrile **7** and alkyl halide **8**, the secondary

Scheme 1



nitrile **9** was prepared. The development of the coupling of a hindered zinc cyanoalkyl group with electron-rich aryl bromides allowed the coupling of nitrile **9** with bromoveratrol to generate the tertiary nitrile **10**. Simultaneous conversion of the acetal to the aldehyde and reductive amination by conducting the reduction with formic acid and palladium on carbon led to the Verapamil **1** in 57% overall yield.

D. Mechanistic Studies of the Reactions of Trimethylsilylnitriles. 1. Studies of the Reactions of Silylnitriles with Fluoride Additives. To begin to understand the role of fluoride in the coupling process, we investigated the reactions of KF and ZnF_2 with the silyl nitriles. The diarylation of trimethylsilylacetonitrile with aryl halides and KF implied that KF cleaved this silyl nitrile to form the potassium cyanoalkyl derivative. However, the successful couplings of aryl halides bearing base-sensitive functionality with the combination of the secondary nitrile and KF implied that the combination of secondary nitrile and KF did not cleave the C−Si bond of the secondary α-silyl nitrile. To evaluate these hypotheses, we heated the acetonitrile and secondary alkyl nitrile derivatives in DMF-d_7 at the temperatures and times of the catalytic process. Consistent with cleavage of the silylacetonitrile reagent by the most basic fluoride additives, heating of KF with trimethylsilylacetonitrile in DMF-d_7 at 90 °C for 18 h completely consumed the silylnitrile, as determined by ^{1}H NMR spectroscopy (eq 2). In contrast, heating of a mixture of the α-silyl derivative of cyclohexanecarbonitrile for the same time at the same temperature did not lead to any change in the ^{1}H NMR spectrum (eq 3).



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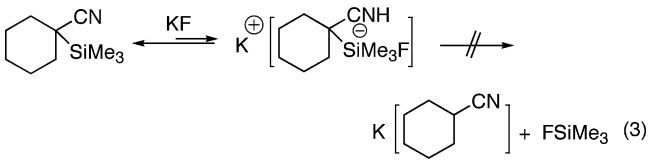
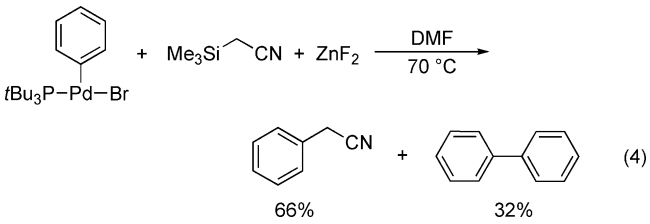


(3)

We also evaluated whether the reaction between zinc fluoride and either trimethylsilylacetonitrile or the secondary carbonitrile led to transmetalation from silicon to zinc. Heating of the mixture of ZnF_2 and trimethylsilylacetonitrile in DMF-d_7 at 90 °C for 18 h did not lead to any change in the ^{1}H NMR spectrum. Although this experiment does not rule out an equilibrium that generates only small quantities of the zinc cyanoalkyl derivative, it does argue strongly against complete transfer of the nitrile anion from silicon to zinc in the catalytic reaction.

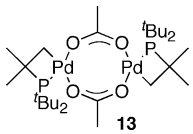
2. Reactions of the Silylnitriles and Fluoride Additives with Isolated Palladium Complexes. To begin to identify the palladium species that undergoes transmetalation with the α-silylnitrile reagents, we conducted stoichiometric reactions of the silylnitriles with isolated arylpalladium halide complexes ligated by P(*t*-Bu)$_3$ in the presence of zinc fluoride. The phenylpalladium halide complex Pd[P(*t*-Bu)$_3$](Ph)(Br)] (**12**), containing a single P*t*Bu$_3$ ligand, was synthesized by previously published methods.[44] This complex was allowed to react with 20 equiv of trimethylsilylacetonitrile in the presence of 20 equiv of zinc fluoride at 70 °C (eq 4). The reaction was complete in about 60 min (determined by ^{31}P NMR spectroscopy) and gave the coupled product in 66% yield (determined by GC), along with some biphenyl (32%).



(4)

Because the arylpalladium bromide complexes ligated by P(*t*-Bu)$_3$ are somewhat unstable, decomposition of this complex occurs in parallel with the reactions with the silylnitrile. Heating of **12** in DMF at 70 °C in the absence of any reagents generated about 55% biphenyl after 1.5 h. Thus, the yield of coupled product from reaction of **12** with the silylnitrile and zinc fluoride is similar to that of the catalytic process (85%) with the same reagents, but is slightly lower because of parallel decomposition of **12**.

Because the formation of biphenyl must be bimolecular, we suggest that the slightly higher yield of coupled product from the catalytic process is observed because the concentration of the arylpalladium halide complex in the catalytic system is low (vide infra). Differences in the amounts of coupled product from reactions with different concentrations of the palladium complex **12** were consistent with this hypothesis, although the differences were small. Reaction of the silylnitrile and zinc fluoride with a 5-fold lower concentration of **1** gave the coupled product in 73 ± 4% yield, instead of 66 ± 1% yield. Thus, the good yield of α-silyl nitrile from reaction of **12** with the combination of the α-silylnitrile and zinc fluoride, with consideration of the side reactions, suggests that the catalytic reaction occurs through this



13

Figure 3. The major complex present in reactions initiated with $Pd(OAc)_2$ and $P(t\text{Bu})_3$.

arylpalladium halide complex. At the same time, further studies are required to cement this conclusion and to provide a detailed picture of how the transmetalation process occurs.

3. Identification of the Palladium Complexes in the Catalytic System. The catalytic reaction was also monitored by ^{31}P NMR spectroscopy to determine the major palladium complexes in the catalytic system. The reaction catalyzed by the combination of Pd_2dba_3 and $Pt\text{Bu}_3$ contained several phosphine-ligated palladium species, and a single major species was not present. However, the reactions catalyzed by the combination of $Pd(OAc)_2$ and $P(t\text{Bu})_3$ contained one major complex. This complex resonated in the upfield region of the ^{31}P NMR spectrum at -7.8 and is the cyclometalated complex **13** in Figure 3. This complex has been disclosed in the patent literature.[45] The reactivity of isolated and purified **13** as a catalyst for the arylation of the α-silyl nitrile was tested. The reaction of *p-tert*-butylbromobenzene with trimethylsilylacetonitrile in the presence of 2 mol % of complex **13** was much slower than the reaction initiated with $Pd(OAc)_2$ and $Pt\text{Bu}_3$ in a 1:2 ratio. However, the same reaction catalyzed by complex **13** with 1 equiv of added $Pt\text{Bu}_3$ per palladium occurred with rates and yields that were similar to those of reactions initiated with the combination of $Pd(OAc)_2$ and $Pt\text{Bu}_3$. Because palladacycles such as **13** are typically catalyst precursors,[46,47] because an additional ligand is needed to observe high activity, and because the arylpalladium halide complex **12** with a κ^1-$P(t\text{Bu})_3$ ligand reacts with the silylacetonitrile reagent to give the coupled product, we suggest that the catalytic process occurs with a small fraction of the palladium present in the system in the form of the active catalyst and occurs by a conventional sequence of oxidative addition, transmetalation, and reductive elimination.

Conclusions

Two new procedures for the coupling of nitriles with aryl halides in the presence of palladium catalysis under conditions that are only mildly basic have been uncovered. Unlike reactions of aryl halides with alkali metal cyanoalkyl reagents, the coupling of aryl halides with α-silyl nitriles in the presence of ZnF_2 selectively generated products from monoarylation. This procedure is compatible with various functional groups, such as cyano, keto, nitro, and ester substituents, on the aryl bromide that would react with the alkali metal cyanoalkyl reagents that have been used for this chemistry in the past. In addition, a new protocol for the arylation of secondary nitriles at room temperature has been developed with zinc cyanoalkyl reagents. These reagents were simply generated by quenching the alkali metal cyanoalkyl with zinc halide. Like the reactions of the silylnitriles, the coupling of the zinc reagents also tolerated many base-sensitive functional groups. The combination of two new methods provides a catalytic route to a variety of benzylic nitriles that are not only biologically significant but serve as important synthetic intermediates. As one example, a three-step synthesis of Verapamil was developed in which the aryl group is installed by the α-arylation of the zinc derivative of a hindered secondary nitrile with commercially available aryl halides. Further mechanistic studies are needed to understand the factors that control the rate of transmetalation, but cleavage of the silylnitriles with a strongly basic fluoride reagent erodes the selectivity for monoarylation. Finally, the amount of active catalyst in this system is small, and efforts to develop catalysts that are present in higher concentrations in an active form will create even milder reactions.

Experimental Section

General Methods. Reactions were conducted using standard drybox techniques. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 400 or 500 MHz spectrometer with tetramethylsilane or residual protiated solvent used as a reference and coupling constants reported in hertz (Hz). Chromatographic purifications were performed by flash chromatography using silica gel (200−400 mesh) or an automated chromatography system. The yields of the coupled products included in all tables refer to isolated yields and are the average of two runs. Products that had been reported previously were isolated in greater than 95% purity, as determined by ^1H NMR and capillary gas chromatography (GC). All ^{13}C NMR spectra were proton decoupled. GC analyses were obtained with a DB-1301 narrow bore column suitable for use with a fast temperature ramp (max 120 °C/min).

Representative Procedure for the Arylation of Trimethylsilylacetonitrile. 4-*tert*-Butylbenzylnitrile (Table 1, Entry 1). To a screw-capped vial containing Xantphos (11.6 mg, 0.0200 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.010 mmol), and 4-bromo-*tert*-butylbenzene (213 mg, 1.00 mmol) in DMF (1.0 mL) were added trimethylsilylacetonitrile (136 mg, 1.20 mmol), followed by ZnF_2 (62.0 mg, 0.600 mmol). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The heterogeneous reaction mixture was stirred at 90 °C for 18 h. The crude reaction was then allowed to cool to room temperature and was diluted with Et_2O (50 mL). The resulting solution was washed with H_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The residue was then purified by chromatography on silica gel, eluting with hexane/ethyl acetate (95:5) to provide the title compound (150 mg) in 87% yield. ^1H NMR ($CDCl_3$): δ 7.39 (d, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 3.70 (s, 2H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 151.17, 127.73, 127.02, 126.12, 118.17, 34.62, 31.35, 23.14.

Representative Procedure for the α-Arylation of Nitrile 7. 2-(3,4-Dimethoxyphenyl)-2-isopropyl Octanenitrile (Table 4, Entry 1). To a screw-capped vial containing $HNi\text{Pr}_2$ (141 mg, 1.40 mmol) in ether (1.0 mL) was added *n*-BuLi (0.62 mL, 1.4 mmol). The reaction mixture was allowed to stir at room temperature for 10 min, at which time nitrile **7** (234 mg, 1.40 mmol) in ether (1.0 mL) was added. After the mixture was stirred at room temperature for 2 h, the volatile materials were removed under vacuum (0.1 Torr). The residue was redissolved in THF (0.5 mL), and the solution was added to another screw-capped vial containing $Pt\text{Bu}_3$ (8.0 mg, 0.040 mmol), $Pd_2(dba)_3$ (9.1 mg, 0.010 mmol), $ZnCl_2$ (191 mg, 1.40 mmol), and 4-bromoveratrole (217 mg, 1.00 mmol) in THF (0.5 mL). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred at 23 °C for 12 h. The crude reaction was then allowed to cool to room temperature and was diluted with Et_2O (50 mL). The resulting solution was washed with H_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated at reduced pressure. The residue was then purified by chromatography on silica gel, eluting with hexane/ethyl acetate (95:5) to provide the title compound (203 mg) in 68% yield. ^1H NMR ($CDCl_3$): δ 6.90 (dd, $J = 9.0$ Hz, 2.5 Hz, 1H), 6.84

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(d, $J = 9.0$ Hz, 1H), 6.83 (d, $J = 2.5$ Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.11−2.00 (m, 2H), 1.79−1.71 (m, 1H), 1.39−1.13 (m, 10H), 0.99−0.88 (m, 1H), 0.82 (t, $J = 7.0$ Hz, 3H), 0.78 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 148.92, 148.17, 130.85, 121.59, 118.73, 111.00, 109.62, 55.99, 55.86, 53.43, 37.86 (big peak with two $-CH_3$ on isopropyl), 31.47, 29.22, 25.48, 22.51, 18.93, 18.58, 13.99. Anal. Calcd for $C_{19}H_{29}NO_2$: C, 75.21; H, 9.63; N, 4.62. Found: C, 75.16; H, 9.78; N, 4.63.

Representative Procedure for the Stoichiometric Reactions of the Silylnitriles with Isolated Arylpalladium Halide Complexes. To a screw-capped vial were added palladium complex **12**[44] (4.6 mg, 0.010 mmol), trimethylsilylacetonitrile (23.0 mg, 0.200 mmol, 20 equiv), ZnF_2 (21.0 mg, 0.200 mmol, 20 equiv), and dodecane (10 mg) followed by DMF (0.2 mL). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred at 90 °C for 0.5 h. The mixture was then cooled to room temperature. The sample was analyzed via ^{31}P NMR spectroscopy and GC.

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Supporting Information Available: Detailed experimental procedures and full characterization of all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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