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Palladium-Catalyzed α-Arylation of Carbonyl Compounds and Nitriles

DARCY A. CULKIN AND JOHN F. HARTWIG*
Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

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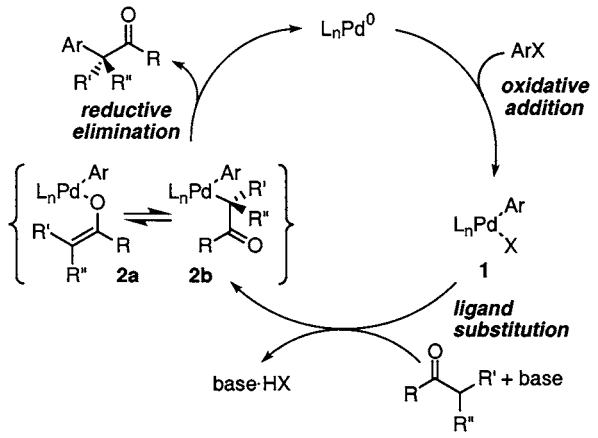
ABSTRACT
The palladium-catalyzed α-arylation of ketones has become a useful and general synthetic method. In this process, an enolate is generated from a ketone and base in the presence of an aryl halide, and a palladium catalyst couples this enolate with the aryl halide. With the advent of new catalysts composed of sterically hindered, electron-rich alkylphosphine and *N*-heterocyclic carbene ligands, this process now encompasses a broad range of enolates and related anions, including those derived from amides, esters, aldehydes, nitriles, malonates, cyanoesters, nitroalkanes, sulfones, and lactones. In the proposed mechanism for this reaction, the carbon−carbon bond of the product is formed by reductive elimination from an arylpalladium enolate intermediate. The structures and reactions of arylpalladium complexes of enolate, cyanoalkyl, and malonate ions have been studied to determine how the binding mode and electronic and steric parameters influence the rate and mechanism of reductive elimination.

I. Introduction

The deprotonation of ketones and addition of the resulting enolate nucleophile to alkyl halide electrophiles is presented in every introductory organic chemistry course. Reactions of aromatic compounds, including aryl halides, are also presented, but these reactions occur predominantly between aromatic compounds and electrophiles, not nucleophiles.[1] Enolate nucleophiles and aromatic halides are rarely reaction partners, even though many natural products, pharmaceutical candidates, synthetic intermediates, and precursors to emissive polymers possess an aromatic unit attached at the α-position of a ketone, ester, or amide.

Transition metal-catalyzed cross-coupling has become a common method to add a variety of main-group carbon nucleophiles, such as Grignard reagents, tin reagents, or boronic acids, to aryl halides.[2] However, catalysts for these reactions generally failed to induce reactions of enolates with aryl and vinyl halides or did so with narrow scope.

Scheme 1



The few palladium-catalyzed couplings of enolates with aryl or vinyl halides known in 1997 usually required preformed zinc[3] or tin enolates[4−7] and encompassed only acetates or methyl ketones. Success with metal-mediated coupling of enolates had been achieved initially with stoichiometric quantities of nickel complexes. Semmelhack et al. reported the nickel-mediated intramolecular arylation of an ester,[8] and Millard and Rathke discovered the nickel-mediated intermolecular arylation of lithium enolates.[9] Later, Fauvarque and Jutand reported the nickel-catalyzed coupling of a few aryl halides with a Reformatsky reagent, but the scope of the reaction was narrow.

A plausible catalytic cycle for the palladium-catalyzed addition of enolates to aryl halides is shown in Scheme 1. Oxidative addition of an aryl halide to a Pd(0) complex would form an arylpalladium(II) halide complex (**1**). Substitution of the coordinated halide by an enolate nucleophile and reductive elimination from the resulting palladium enolate complex (**2a** or **2b**) would form the α-aryl ketone, ester, or amide and regenerate the Pd(0) complex that started the cycle.

To develop the coupling of enolates with aryl halides by this mechanism, one must confront several challenges. For instance, the pK_a values of mono- and dicarbonyl compounds in organic solvents vary from 12 to 35.[10] Thus, electronic effects could have a large influence on the reaction chemistry. Moreover, alkali metal enolates are typically generated and allowed to react at low temperatures, but cross-coupling is usually conducted at elevated temperatures. Thus, uncatalyzed condensation chemistry of the enolate could occur before the desired catalytic coupling. Furthermore, C-bound enolates of transition metals, other than those from methyl carbonyl compounds, bear β-hydrogens. β-Hydrogen elimination could, therefore, compete with reductive elimination to form the desired coupled product.

The structures of the arylpalladium enolates could also vary from substrate to substrate. The structures of transition metal enolates include C-bound[11−14] and O-bound[15−17] enolates of monocarbonyl compounds, as well as η^1-C- and η^2-O,O-bound anions of β-dicarbonyl compounds.[18]

Darcy Culkin received a B.A. from Northwestern University, where she worked in the laboratory of Professor Duward F. Shriver. She is currently a graduate student in the Hartwig group at Yale University, where she is studying the reductive elimination of enolate complexes and developing the arylation of nitriles.

John Hartwig received his A.B. from Princeton University and received his Ph.D. with Profs. Bob Bergman and Dick Andersen at University of California, Berkeley. He was an American Cancer Society postdoctoral fellow in Prof. Steve Lippard's laboratory. In 1992, he began his independent career at Yale University, where he is now Professor of Chemistry. He has developed palladium-catalyzed couplings of amines, alkoxides, and enolates, a catalytic, regiospecific functionalization of alkanes with borane reagents, and hydroaminations of vinylarenes and dienes.

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These structures may all interconvert and allow access to the one that undergoes reductive elimination, but some structures could be too stable (or unstable) to undergo the desired reaction.

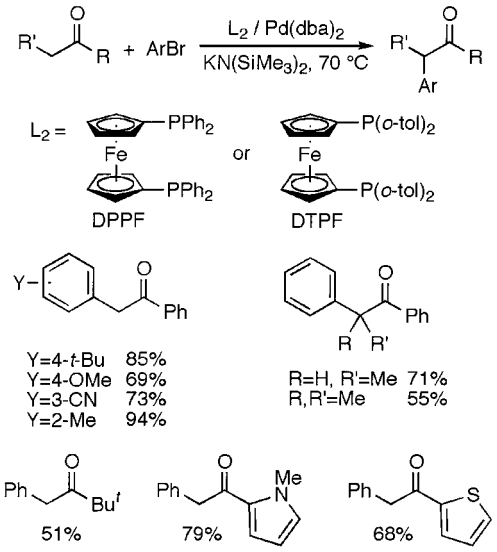
Despite these hurdles, the palladium-catalyzed arylation of carbonyl compounds has become a useful and general synthetic method. In 1997, our group[19] and those of Buchwald[20] and Miura[21] reported concurrently the palladium-catalyzed direct coupling of ketones with aryl bromides. This method displayed a high degree of regioselectivity and functional group tolerance. Improved catalysts have allowed this reaction to encompass ketones,[22−27] diketones,[24] amides,[28,29] esters,[30−33] aldehydes,[34] nitriles,[35,36] malonates,[22,24,37,38] cyanoesters,[38,39] nitroalkanes,[40,41] sulfones,[42] and lactones[43] and have allowed for enantioselective α-arylation.[29,43−45] This Account concentrates on the contributions from our laboratory toward the discovery of palladium catalysts for the α-arylation of carbonyl compounds[46] and the development of a mechanistic understanding of the product-forming reductive elimination step.

II. Palladium-Catalyzed Arylation of Ketone Enolates

A. Initial Discovery. The discovery of the palladium-catalyzed α-arylation of carbonyl compounds in our laboratory occurred during studies of the palladium-catalyzed amination of aryl halides.[47] While evaluating reactions of amines with phenyl bromide in acetone solvent, we observed phenylacetone as a reaction product. This experiment prompted us to appreciate that the similar pK_a values of arylamines and ketones[10] could allow for the coupling of aryl halides with enolates in the presence of base and palladium catalyst. Indeed, we found that the combination of $Pd(dba)_2$ and certain phosphine ligands catalyzed the coupling of aryl bromides and iodides with ketones in the presence of base.[19] Related arylations of ketones were reported concurrently by Palucki and Buchwald with BINAP-ligated palladium and by Miura et al. with ligandless palladium dichloride.[21]

As illustrated in Scheme 2, the palladium-catalyzed arylation of ketones showed promise as a general method for obtaining α-aryl ketones. Secondary, tertiary, and quaternary carbon centers were formed, and the reaction displayed high selectivity for monoarylation of substrates that could undergo diarylation. The reaction encompassed electron-rich, electron-poor, and sterically hindered or unhindered aryl bromides. Most surprising, a high yield of coupled product was observed from reactions of enolates that would possess β-hydrogens when bound to the metal through the α-carbon. Higher yields were observed with some dialkyl ketones when BINAP-ligated palladium catalysts were used,[20] and ligandless catalysts are advantageous for large-scale processes.[21] However, reactions catalyzed by any of the palladium complexes of the initial studies required high catalyst loadings, gave modest yields in several cases, and were conducted at elevated temperatures.

Scheme 2



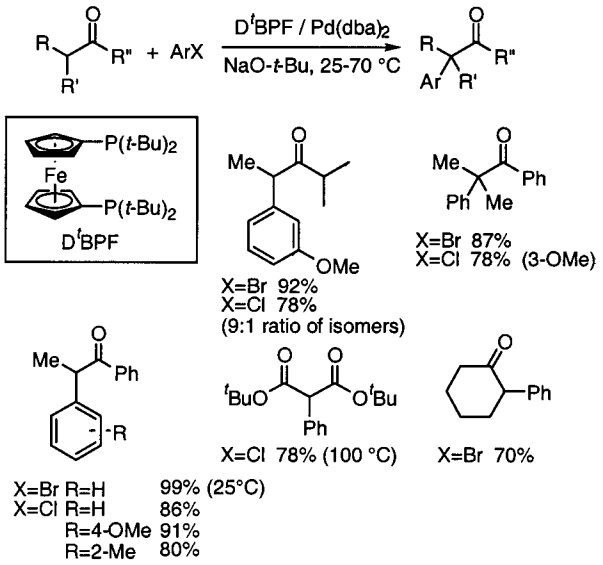
B. Catalyst Improvement. We initially employed palladium complexes of bis(diphenylphosphino)ferrocene (DPPF) as catalyst because we expected that chelating ligands would inhibit β-hydrogen elimination of the aryl-palladium enolates by rendering the intermediate palladium complex four-coordinate and preventing the generation of open coordination sites necessary for β-hydrogen elimination.[48] Reactions catalyzed by complexes of a hindered analogue of DPPF, 1,1′-bis(di-*o*-tolylphosphino)-ferrocene (DTPF), were more efficient than those catalyzed by complexes of DPPF.[19] Because the oxidative addition of aryl halides and reductive elimination of product both involve a low-coordinate Pd(0) intermediate, we reasoned that increased steric properties of the ligand should increase the energy of the stable, higher-coordinate species. This increased energy of the ground state would decrease the relative energy of the reactive intermediate and, most likely, increase the reaction rate. We also postulated that alkyl substituents at phosphorus would promote oxidative addition by making the metal more electron-rich and would increase catalyst lifetime by disfavoring cleavage of the ligand P−C bonds.

As shown in Scheme 3, a palladium catalyst containing the hindered alkyl bisphosphine 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D^{t}BPF)[22] provided fast rates for the cross-coupling of aryl halides with ketones. In some cases, turnover numbers reached 20 000 in a few hours at only 70 °C, and many reactions occurred at room temperature. In addition, this catalyst coupled ketone enolates with unactivated chloroarenes and, for the first time, coupled a malonate with an unactivated chloroarene.

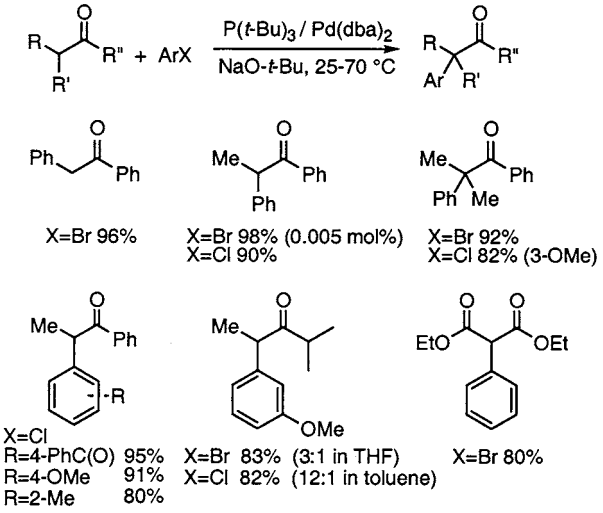
Although it contains two phosphorus donors, D^{t}BPF was ligated to the metal in an η^1-fashion in the aryl-palladium enolate intermediates.[22] This finding cast doubt upon our postulate that chelation was needed to observe reductive elimination instead of β-hydrogen elimination.

Indeed, palladium complexes of simple, sterically hindered monophosphines, such as tri(*tert*-butyl)phosphine (P(*t*-Bu)$_3$), catalyzed reactions of ketones with aryl halides

Scheme 3



Scheme 4

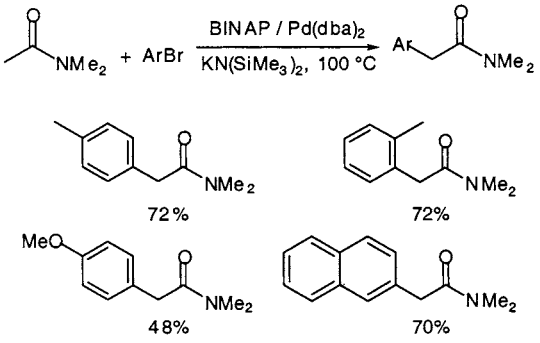


in high yields with high turnover numbers (Scheme 4).[22] Reactions of methyl aryl ketones occurred selectively to form the product from monoarylation when 2 equiv of base was used to ensure that the ketone reagent and the monoarylated product, which is more acidic, both existed in their enolate form. Ketones with two enolizable positions were preferentially arylated at the least hindered site. Buchwald and co-workers have prepared sterically hindered, electron-rich *o*-biphenyl monophosphines that also generate highly active palladium catalysts for the α-arylation of ketones and provide high selectivity for reaction at the less hindered position of dialkyl ketones.[24] Beller et al. have reported that palladium complexes of *n*-butyldi(1-adamantyl)phosphine are highly efficient for the arylation of acetophenones with aryl chlorides.[26]

III. Palladium-Catalyzed Arylation of Carboxylic Acid Derivatives

A. Amides. Although extension of the methods for the palladium-catalyzed arylation of ketones to the arylation

Scheme 5



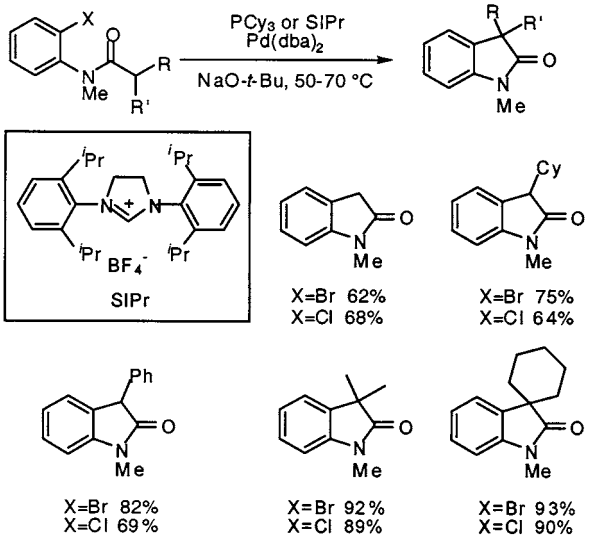
of amides appeared conceptually simple, and reactions of carboxylic acid derivatives present fewer regiochemical challenges, the higher pK_a's of amides[10] detracted from the intermolecular reaction. Reactions of amides with aryl halides catalyzed by complexes of DTPF or P(t-Bu)$_3$ occurred in low yields. However, palladium complexes of DPPF or BINAP did catalyze the arylation of selected amides (Scheme 5).[28] Coupling of unfunctionalized and electron-rich aryl bromides with *N*,*N*-dimethylacetamide afforded α-aryl amides in moderate to good yields when conducted with at least 2 equiv of KN(SiMe$_3$)$_2$ base. Products from diarylation of acetamides formed more readily than did those of methyl ketones, most likely because the pK_a of the starting amide is higher and the pK_a of the product is lower than that of the base. Hydrodehalogenation of the aryl halide also limited the intermolecular arylation of amides: aryl bromides with *N*,*N*-dimethylpropionamide formed arene as the major product.

In contrast, the intramolecular palladium-catalyzed α-arylation of amides to form oxindoles tolerated a range of steric and electronic properties of the aryl halide substituent.[28,29] The intramolecular arylation catalyzed by Pd(dba)$_2$, BINAP, and sodium *tert*-butoxide formed oxindoles in moderate to good yields during initial studies,[28] but sterically hindered alkylphosphines generated more active catalysts. Complexes of PCy$_3$ or the sterically hindered carbene precursor, *N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium (SIPr),[49] catalyzed the formation of oxindoles at lower temperatures and catalyst loadings than did complexes of BINAP (Scheme 6).[29] A less hindered phosphine than P(t-Bu)$_3$ may be preferable in this case because the substrates for the intramolecular arylation of amides are highly hindered.

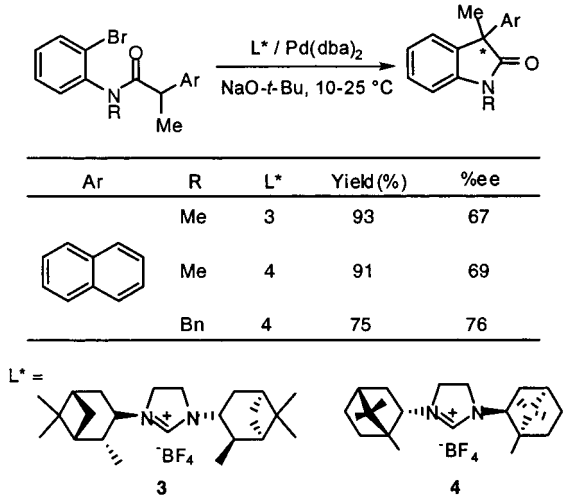
Catalysts ligated by PCy$_3$ or SIPr formed the quaternary carbon in α,α-disubstituted oxindoles in high yields. Consequently, we sought to develop an asymmetric variant of this process. Reactions conducted with commercial, optically active mono- or bisphosphines occurred with low enantioselectivity. Thus, we prepared new carbene ligands derived from (−)-isopinocampheylamine (**3**) and (+)-bornylamine (**4**), which bear chiral substituents at the nitrogen. Complexes of these ligands catalyzed the cyclizations with enantioselectivities up to 76% (Scheme 7).[29]

B. Esters. The arylation of esters could be more general than the arylation of amides because esters are more

Scheme 6



Scheme 7



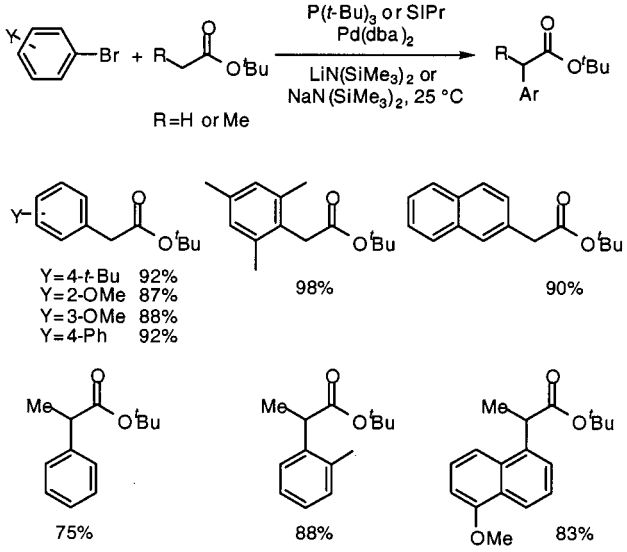
Ar	R	L*	Yield (%)	%ee
	Me	3	93	67
	Me	4	91	69
	Bn	4	75	76

acidic. However, the process could be less general because ester enolates undergo faster condensations and eliminations than ketone or amide enolates. If the coupling of ester enolates is to occur in high yield, the catalytic process must be faster than uncatalyzed condensations and thermal decomposition. Thus, the development of highly active catalysts comprised of bulky, electron-rich ligands provided the opportunity to conduct efficient couplings of these enolates.

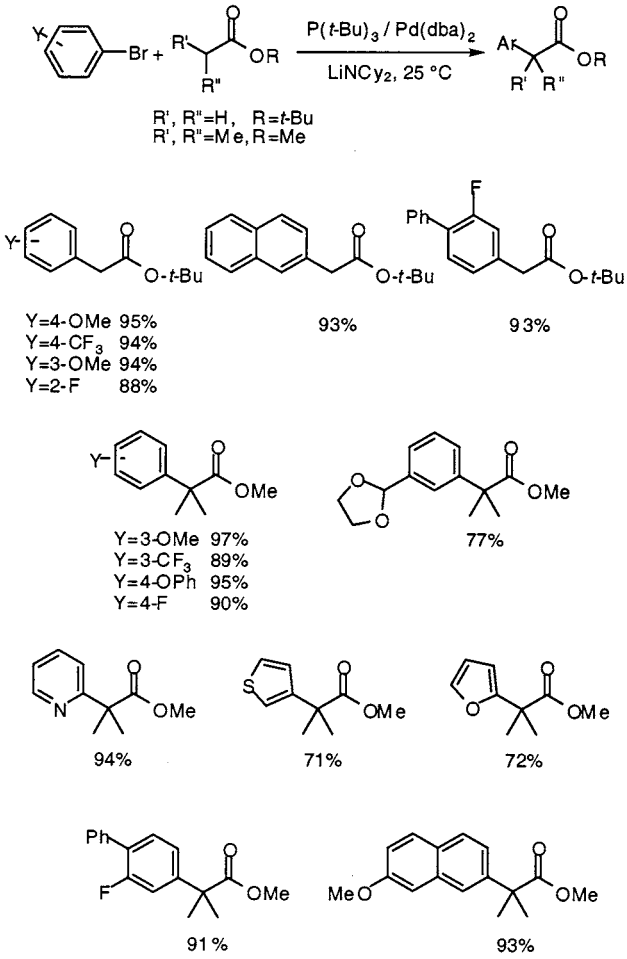
Palladium complexes ligated by P(*t*-Bu)$_3$ or the hindered carbene precursor, SIPr, in the presence of 2 equiv of either LiN(SiMe$_3$)$_2$ or NaN(SiMe$_3$)$_2$, generated catalysts that coupled esters with aryl halides (Scheme 8).[30] Reactions of *tert*-butyl acetate or *tert*-butyl propionate with a range of aryl bromides proceeded at room temperature with fast rates and high selectivity for monoarylation.

However, use of the stronger, hindered amide base, LiNCy$_2$ and generation of the enolate prior to addition of the palladium catalyst and aryl halide provided the most efficient couplings of *tert*-butyl acetate and of α,α-disubstituted esters (Scheme 9).[33] Lower catalyst loadings and only a slight excess of ester and base were

Scheme 8

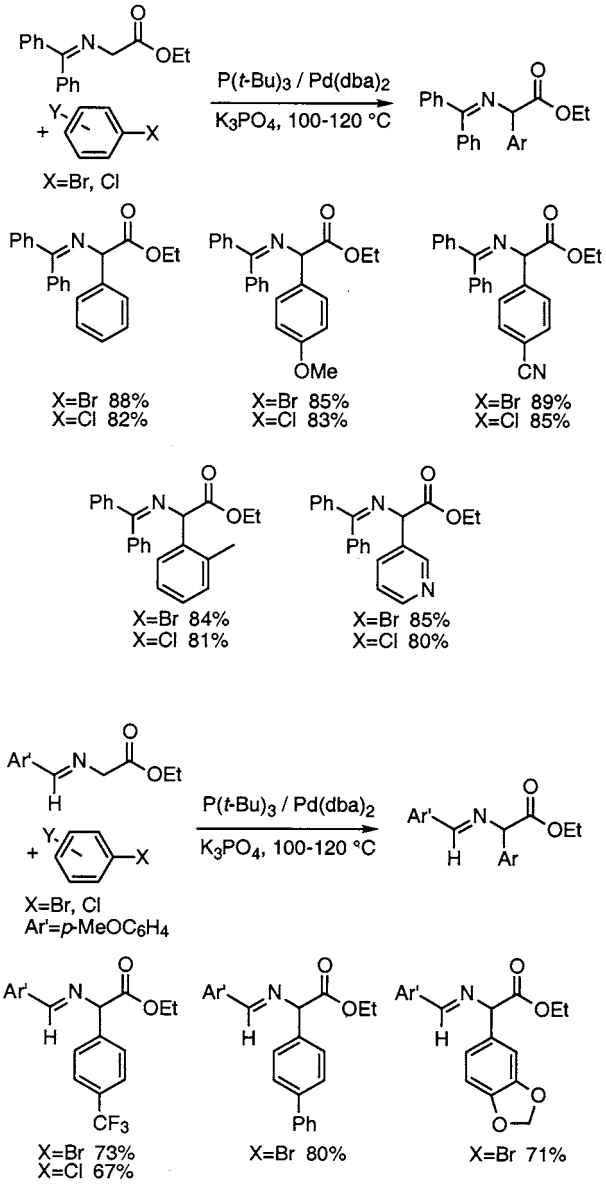


Scheme 9



required. Palladium catalysts ligated by P(*t*-Bu)$_3$ formed the monoarylated product of *tert*-butyl acetate or methyl isobutyrate in high yield at room temperature. In addition, this system catalyzed reactions of aryl halides with methyl 2-methylbutyrate, methyl 2-phenylpropionate, methyl cyclohexylcarboxylate, and benzyl isobutyrate to generate products with fully substituted carbon centers.

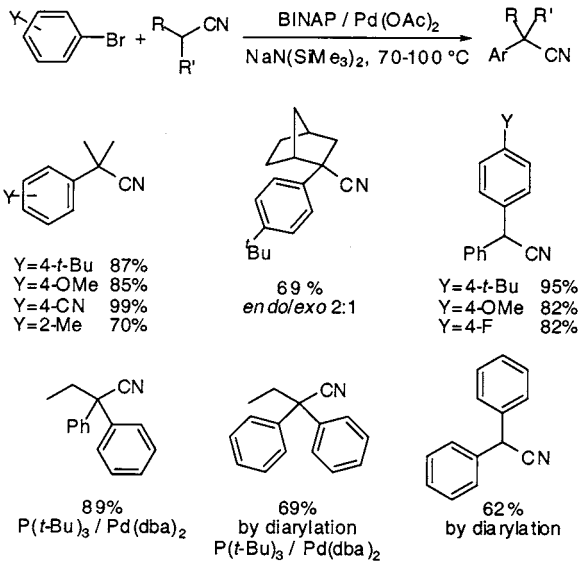
Scheme 10



Reactions of various heterocyclic bromides occurred with methyl isobutyrate, but reactions of pyridyl halides have not occurred thus far with *tert*-butyl acetate or *tert*-butyl propionate. Moradi and Buchwald have reported the α-arylation of esters with catalysts bearing *o*-biphenyl ligands, but 2 equiv of ester, higher catalyst loadings, and elevated temperatures were required. Moreover, reactions of α,α-disubstituted esters occurred in modest yields.[31]

C. Protected Amino Acids. The direct α-arylation of protected amino acids could provide a short, general route to α-aryl amino acids. During our studies of esters, we found that palladium complexes of P(*t*-Bu)$_3$ catalyzed the coupling between 4-bromo-*tert*-butylbenzene and ethyl *N*,*N*-dimethylglycinate in high yield. This reaction led us to evaluate the α-arylation of nitrogen-protected amino acids. P(*t*-Bu)$_3$-ligated complexes catalyzed the coupling of ethyl *N*-(diphenylmethylene)glycinate or the *p*-methoxybenzaldimine of ethyl glycinate with a variety of aryl halides in good yields at 100−120 °C in the presence of

Scheme 11



K_3PO_4 base (Scheme 10).[30] The weaker base may be effective because of the lower pK_a of the imino esters,[50] or coordination of the substrate nitrogen may assist deprotonation. Gaertzen and Buchwald reported recently the intramolecular arylation of amino acid esters.[32]

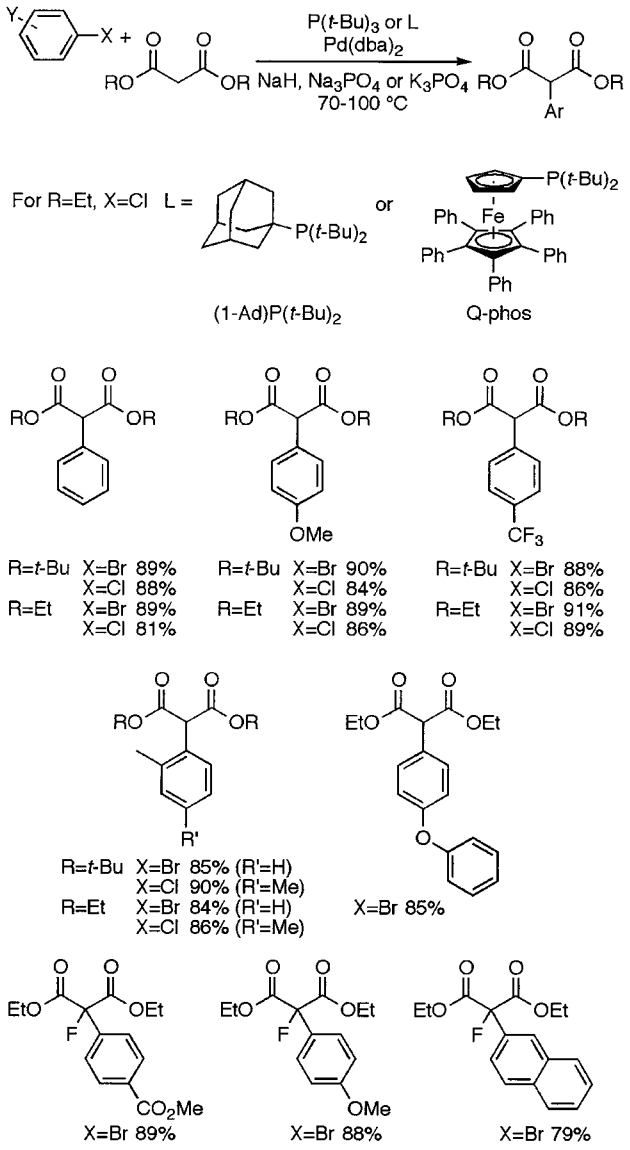
D. Nitriles. Alkyl nitriles are less acidic than ketones, but a cyano group is more electron-withdrawing than an acyl group. This high pK_a mandates the use of a strong base, and the strongly electron-withdrawing cyano group could make reductive elimination slow. Miura and coworkers reported the palladium-catalyzed arylation of phenylacetonitrile, but the electronic properties of this substrate are similar to those of ketones; no reactions of alkyl nitriles were reported.[35]

In our work, reactions of 2-phenylbutyronitrile and butyronitrile conducted with P(*t*-Bu)$_3$-ligated catalysts occurred in good yields, but palladium complexes of sterically hindered alkylphosphines did not generate efficient catalysts for the α-arylation of other nitriles. Instead, BINAP-ligated palladium was effective for the monoarylation of secondary and benzyl nitriles (Scheme 11).[36] Acetonitrile and unhindered primary nitriles, such as butyronitrile, underwent diarylation, presumably because the monoarylation product is readily deprotonated and is unhindered enough to bind palladium.

E. Malonates. Because of their multiple functional groups and their role as classic nucleophiles, we sought the arylation of malonates. The low pK_a of malonates allows a mild base to be used, but the stabilizing effect of the two carbonyl groups could make reductive elimination slow. Moreover, an η^2-O,O-bound complex of a malonate anion could be too stable to participate in catalytic chemistry.

Although matching the base with the substrate remains empirical, P(*t*-Bu)$_3$-ligated palladium complexes catalyzed the coupling of aryl bromides and chlorides with anions of di-*tert*-butyl malonate and diethyl malonate in excellent yields with high turnover numbers (Scheme 12).[38] Diethyl 2-fluoromalonate also reacted under similar conditions to

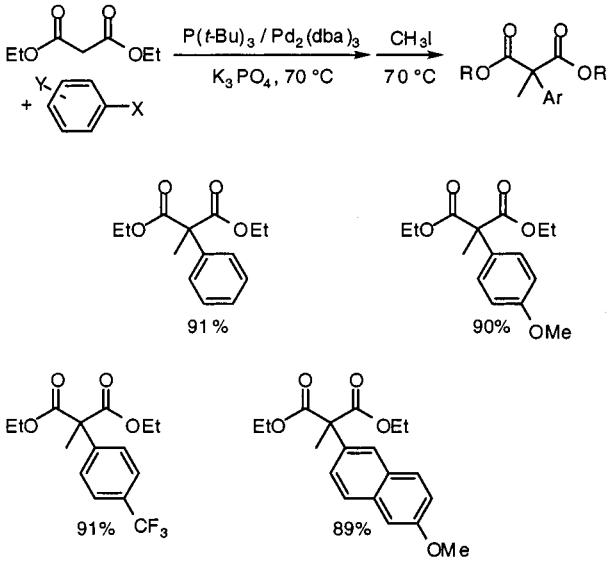
Scheme 12



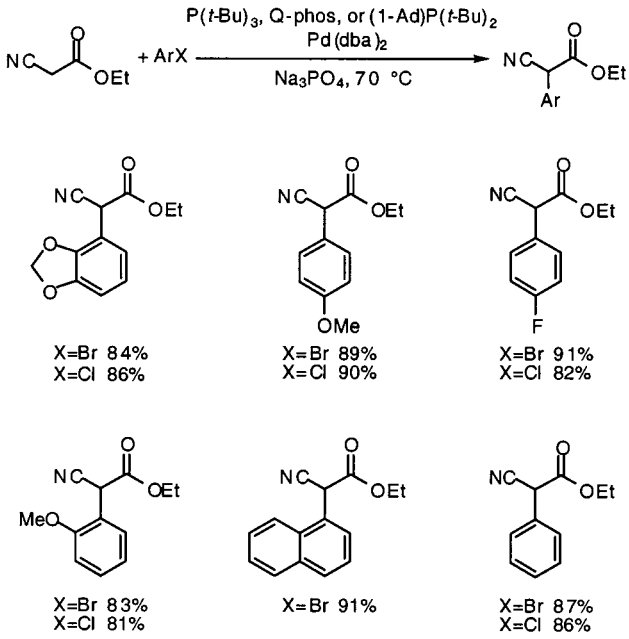
form products with fluorine-substituted, quaternary centers. The coupling of di-*tert*-butyl malonate with aryl chlorides occurred in high yields in the presence of P(*t*-Bu)$_3$-ligated catalysts, but the coupling of diethyl malonate with aryl chlorides in the presence of this catalyst generated significant amounts of arene from hydrodehalogenation. This limitation was overcome by use of catalysts containing the pentaphenylferrocenyl phosphine (Ph_5C_5)-Fe(C_5H_4)P(*t*-Bu)$_2$ (Q-phos)[51] or the adamantyl phosphine (1-Ad)P(*t*-Bu)$_2$.[52] Alkylmalonates did not react with aryl halides under any reaction conditions we tested, but diethyl alkylarylmalonates were formed in high yield by a sequence of palladium-catalyzed coupling of diethyl malonate with an aryl halide in the presence of excess base and treatment of the product in situ with an alkyl halide (Scheme 13). Di-*tert*-butyl malonate and diethyl malonate did not react with pyridyl halides or halobenzonitriles in the presence of these catalysts.

F. Cyanoesters. Because diethyl malonate and ethyl cyanoacetate have similar pK_a values, we expected that the palladium-catalyzed arylation of malonates could be

Scheme 13



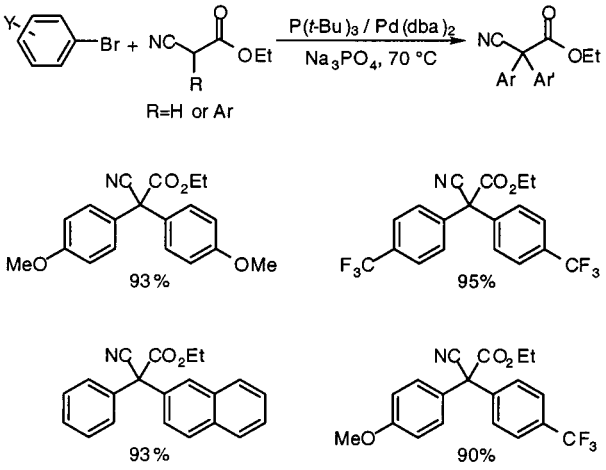
Scheme 14



extended to cyanoesters. Indeed, complexes generated from P(*t*-Bu)$_3$ or (1-Ad)P(*t*-Bu)$_2$ catalyzed reactions of electron-neutral, electron-rich, and ortho-substituted aryl halides with ethyl cyanoacetate (Scheme 14).[38,39] Reactions of electron-poor aryl halides with ethyl cyanoacetate in the presence of catalysts ligated by P(*t*-Bu)$_3$ generated the diarylated product in competition with the more abundant monoarylation product, but complexes of Q-phos formed the monoarylation product exclusively.

This formation of diaryl cyanoesters as side product suggested that the arylation of cyanoesters could be developed into a process that generates diaryl cyanoacetates. Indeed, reaction of 2 equiv of aryl halide and ethyl cyanoacetate produced symmetrical diaryl cyanoacetates, while reaction of monoaryl cyanoacetates with 1 equiv of a second aryl halide generated unsymmetrical diaryl cyanoacetates (Scheme 15). Ethyl alkyl cyano-

Scheme 15



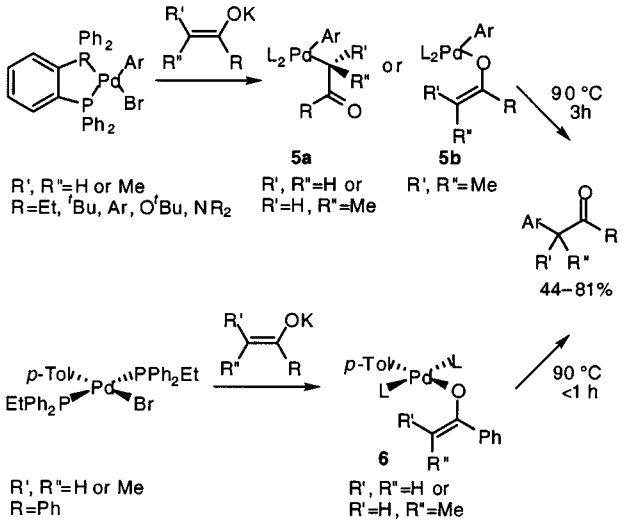
acetates did not react with aryl halides in the presence of these catalysts, but the desired product, most likely, can be obtained using the same sequence of palladium-catalyzed arylation and subsequent alkylation that we followed with malonates. As observed for malonate substrates, cyanoacetates did not couple with pyridyl halides or halobenzonitriles.

IV. Mechanism of C−C Bond-Forming Reductive Elimination from Arylpalladium Complexes of Enolate, Cyanoalkyl, and Malonate Anions

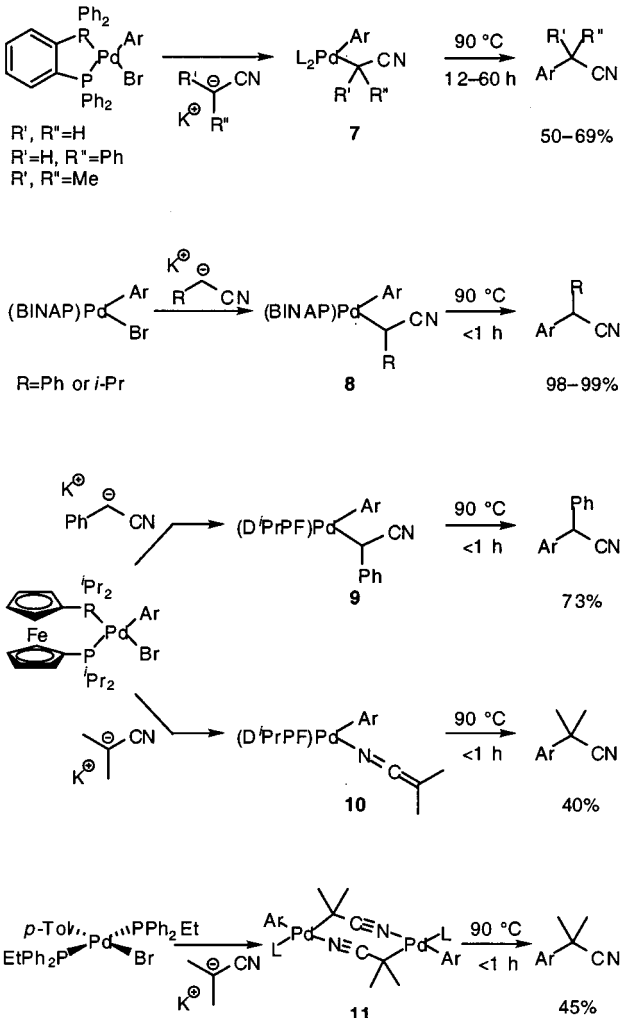
Concurrent with our investigation of the catalytic α-arylation of carbonyl compounds, we evaluated the structures and reactions of the enolate intermediates that undergo reductive elimination to form the carbon−carbon bond of the product. C−C bond-forming reductive eliminations from isolated transition metal enolate complexes are rare.[53] We felt that a better knowledge of how enolate binding modes and electronic and steric parameters influenced the rate and mechanism of reductive elimination would help to explain the scope of the catalytic chemistry, to design improved catalysts, and to provide fundamental information about reductive elimination.

A. Synthesis. The synthesis and reactivity of arylpalladium complexes of enolate, cyanoalkyl, and malonate anions are shown in Schemes 16−18. Although it was difficult to prepare enolate complexes that were sufficiently stable to isolate but sufficiently reactive to undergo reductive elimination, we ultimately found that complexes bearing 1,2-bis(diphenylphosphino)benzene (DPPBz), which possesses a balance of small bite angle, backbone stability, and modest electron donation, exhibited the required stability and reactivity (Scheme 16).[54] Ethyldiphenylphosphine ($EtPh_2P$) complexes of enolates also showed suitable stability and reactivity (Scheme 16).[54] We prepared arylpalladium cyanoalkyl complexes ligated by DPPBz and $EtPh_2P$, as well as cyanoalkyl complexes ligated by 1,1′-bis(diisopropylphosphino)ferrocene (D^iPrPF) and BINAP (Scheme 17).[36] Arylpalladium complexes of malonate ions ligated by aromatic phosphines were too stable to undergo reductive elimination, but analogous

Scheme 16



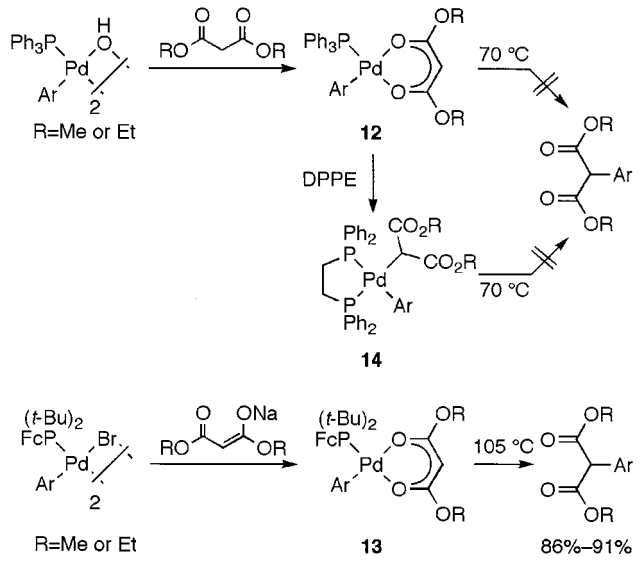
Scheme 17



complexes ligated by the bulky, electron-rich di-*tert*-butylferrocenyl phosphine ($FcP(t\text{-}Bu)_2$) did undergo reductive elimination (Scheme 18).[55]

B. Structure and Thermodynamic Stability. Transition metal complexes of enolate, cyanoalkyl, and malonate anions can display several coordination modes, and both

Scheme 18

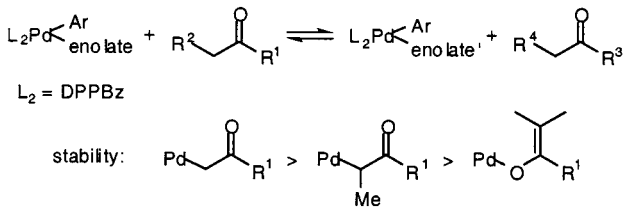


the anion and phosphine influenced the connectivity. DPPBz-ligated palladium complexes of enolates derived from ketones with α-methyl or methylene protons were C-bound (**5a**), except for the enolate of benzyl phenyl ketone, which was a mixture of O- and C-bound forms.[54] Enolate complexes from ketones with α-methine protons, such as **5b**, were O-bound to avoid a structure with a tertiary alkyl bound to palladium. Complexes such as **6**, bearing $EtPh_2P$ as ligand, displayed a trans geometry and showed significantly greater preference for the O-bound form.[54] A comparison of the coordination modes of the DPPBz- and $EtPh_2P$-ligated complexes suggests that the C-bound isomer is favored electronically if the enolate is located trans to a phosphine, but the O-bound form is favored if the enolate is located trans to an aryl group. A C-bound enolate complex that would possess a quaternary carbon with the metal as one substituent was less stable than its O-bound tautomer, regardless of the phosphine.

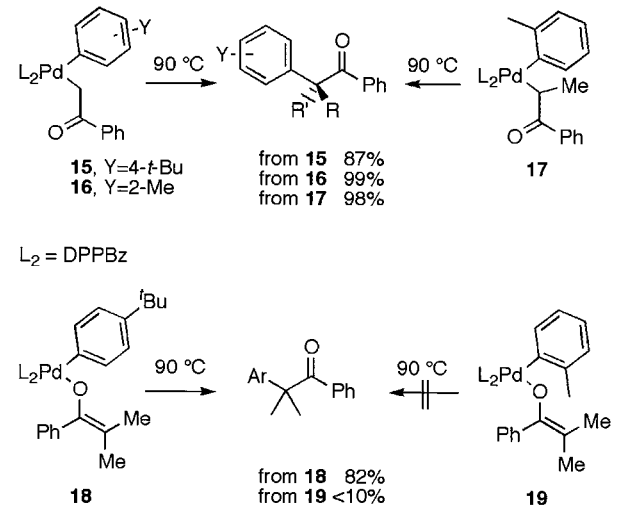
Nitrile anions can coordinate to a single transition metal center through the α-carbon[56−58] or the nitrogen,[59−62] or they can bridge two metals in a μ^2-C,N fashion.[63] Consistent with coordination of the softer carbon atom to the late, soft palladium metal, arylpalladium cyanoalkyl complexes of aceto and primary nitriles, as well as the DPPBz-ligated arylpalladium complex of the anion of isobutyronitrile, were C-bound (**7**−**9**).[36] However, complexes bearing other ancillary ligands displayed unusual coordination modes. When the larger, more donating D^{i}PrPF bound the metal, the anion of isobutyronitrile coordinated through the nitrogen atom (**10**).[36] When a labile phosphine, such as $EtPh_2P$, bound the metal, one of the phosphines dissociated, and the complex of the isobutyronitrile anion adopted the dimeric μ^2-C,N structure **11**.[36]

The anion of a β-dicarbonyl compound can coordinate to a transition metal through the central carbon or through the two oxygens.[18] Complexes containing monophosphines, such as PPh_3 or $FcP(t\text{-}Bu)_2$, bound the malonate in the η^2-O,O-bound form of **12** and **13**, even in

Scheme 19



Scheme 20

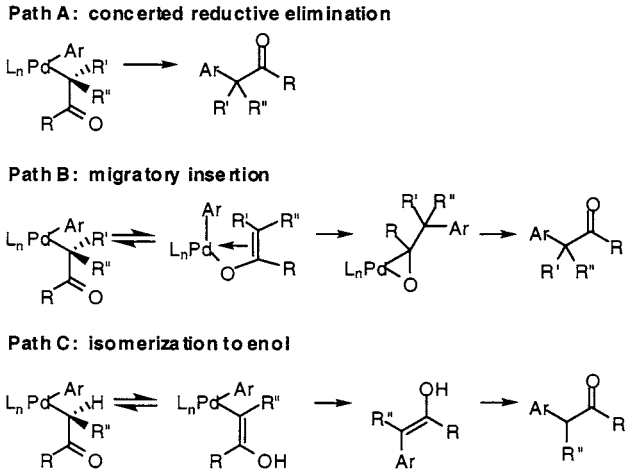


the presence of additional phosphine (Scheme 18).[55] Arylpalladium η^2-malonate complexes bound by chelating ligands would be five-coordinate. Thus, arylpalladium malonate complexes containing a chelating phosphine bound the malonate anion in an η^1-C-bound form, as in DPPE-ligated **14**.[55]

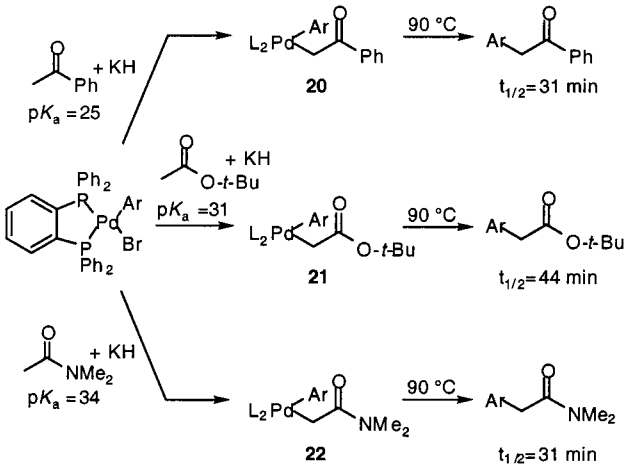
We also investigated the influence of steric and electronic properties on the thermodynamic stability of palladium enolates of ketones, esters, and amides. We determined the stability of the enolate complexes, relative to the corresponding carbonyl compound, by adding one carbonyl compound to the palladium enolate complex of another.[54] As illustrated in Scheme 19, stability was controlled by the number of substituents at the α-carbon, rather than by the pK_a of the carbonyl compound. Arylpalladium enolate complexes of ketones, esters, and amides with similar substitution at the α-carbon were similar in stability.

C. Reductive Elimination from Arylpalladium Complexes of Enolate, Cyanoalkyl, and Malonate Anions. 1. Scope of the Reductive Elimination. We observed reductive elimination from both C- and O-bound DPPBz-ligated arylpalladium enolates (Scheme 16).[54] C-bound enolates underwent reductive elimination to form the α-aryl ketone, ester, or amide product in 57%-99% yield at 90 °C. As illustrated in Scheme 20, yields of α-aryl ketone were high for reactions of C-bound palladium enolates with sterically unhindered (**15**) or hindered (**16**, **17**) palladium-bound aryl groups. The O-bound palladium enolate **18**, with a sterically unhindered palladium-bound aryl group, also underwent reductive elimination to form α-aryl ketone in a high 82% yield. However, the O-bound

Scheme 21



Scheme 22



palladium enolate **19** with a sterically hindered palladium-bound aryl group generated less than 10% of aryl ketone upon thermolysis. Presumably, the hindered aryl group inhibits rearrangement of the enolate to the more crowded C-bound form.

One could argue that α-aryl carbonyl compounds are formed from arylpalladium enolates by a mechanism other than concerted C−C reductive elimination (path A in Scheme 21). Coupling could occur by migratory insertion of the C=C unit of an O-bound enolate into a Pd−aryl bond (path B) or by isomerization of a C-bound enolate to its enol tautomer, followed by favorable C(sp^2)−C(sp^2) reductive elimination (path C). If path B operated, O-bound enolates should react faster. If path C operated, isobutyrophenone enolates should not couple. As illustrated in Scheme 20, the low yield observed from O-bound **19**, compared to the high yields from **16** and **17**, disfavors path B, and the high yield from **18** argues against the palladaenol intermediate in path C. The products do appear to form by the simple reductive elimination in path A.

Complexes of both C- and N-bound cyanoalkyls also underwent reductive elimination at elevated temperatures to form α-aryl nitriles (Scheme 17).[36] The yields of coupled product from reductive elimination from DPPBz-ligated arylpalladium cyanoalkyls **7** were lower than those observed for reductive elimination from similar arylpalladium enolates **5a**. However, elimination from the more sterically crowded BINAP- and D^{i}PrPF-ligated arylpalladium cyanoalkyls **8** and **9** generated the desired α-aryl nitrile in higher yields and shorter reaction times. Yields of aryl nitrile were higher for reductive elimination from C-bound cyanoalkyl complexes than from the N-bound complex **10** or the C,N-bridged dimer **11**. These data suggest that structures with the α-carbon bound to a single metal center favor the desired reductive elimination.

Heating PPh_3- and DPPE-ligated arylpalladium malonate complexes **12** and **14** did not generate any arylmalonate from reductive elimination (Scheme 18).[55] In contrast, FcP(*t*-Bu)$_2$-ligated arylmalonate complexes **13** underwent reductive elimination of the corresponding arylmalonates in high yields at 105 °C. The increased steric hindrance of FcP(*t*-Bu)$_2$, relative to that of PPh_3, apparently promotes reductive elimination from these typically stable complexes of 1,3-dicarbonyl anions. The η^2-O,O-binding mode of FcP(*t*-Bu)$_2$-ligated **13** is most stable; presumably, rearrangement to the reactive η^1-C-bound form occurs under mild conditions.

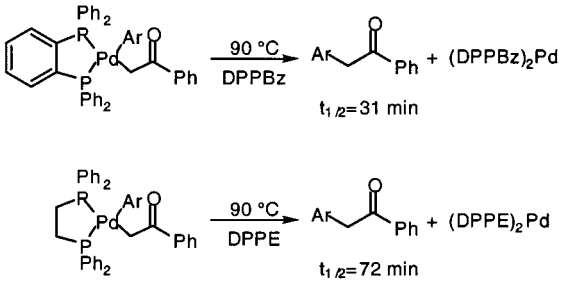
2. Electronic Effects on Reductive Elimination. At the outset of this work, it was unclear how the electronic properties of the enolate would affect the rate of reductive elimination. Although many cross-couplings have been performed over the years, only a subset of these form sp^2−sp^3 bonds, and even fewer possess functionality near the point of reaction on the alkyl group. Because the rates of reductive elimination from arylpalladium complexes of amides are significantly affected by electronic factors,[64] one might expect the rates of reductive elimination from arylpalladium complexes of the similarly basic enolate ligands to correlate with basicity.

However, arylpalladium complexes of ketone, ester, and amide enolates, which are derived from carbonyl compounds with pK_a values ranging from 25 to 34 in DMSO,[10] underwent reductive elimination with rate constants that varied by less than a factor of 3 and without any correlation with pK_a (see for example, **20**−**22** in Scheme 22).[54] These data show that the differences in the rates and yields for the catalytic formation of aryl ketones, amides, and esters result from the stability of the alkali enolate and the rate of formation of the palladium enolate, not from the rates and yields of reductive elimination.

Rate-limiting dechelation does not account for the absence of a measurable electronic effect within this set of complexes. Arylpalladium enolates with chelating phosphines that have similar bite angles, but different flexibility in the backbone, underwent reductive elimination with similar rates (Scheme 23). Complexes of C-bound ketone, ester, and amide enolates most likely undergo reductive elimination at similar rates because the M−C bond is predominantly covalent, and the different carbonyl groups impart similar electronic effects on the α-carbon in this covalent bond.

The electronic properties of the functionalized alkyl groups did significantly influence the rate of reductive

Scheme 23



elimination when electronic differences were larger than those between ketone, ester, and amide enolates. This conclusion was supported by studies on complexes of alkyl groups that are unsubstituted in the α-position and that possess one or two functional groups in the α-position. For example, reductive elimination from DPPBz-ligated *o*-tolylpalladium methyl, which lacks any electron-withdrawing group on the α-carbon, occurred much faster than elimination from complexes of C-bound enolates. This complex formed *o*-xylene by reductive elimination in <5 min.[54] Reductive eliminations from arylpalladium cyanoalkyls were significantly slower than those from analogous arylpalladium enolates.[36] A cyano group is more electron-withdrawing than an acyl or carboxyl group, according to its Taft parameter.[65] Elimination of α-aryl nitriles from DPPBz-ligated arylpalladium cyanoalkyls required up to 60 h, while elimination of α-aryl ketones from analogous arylpalladium enolates occurred in less than 3 h.[54] Further consistent with slower reductive elimination from complexes of alkyl groups containing strong electron-withdrawing groups on the α-carbon, η_1-C-bound DPPBz-ligated arylpalladium complexes of malonate anions, which possess two electron-withdrawing groups on the α-carbon, did not undergo reductive elimination at any temperature or time.[55]

Fortunately, the ancillary ligands can be altered to induce reductive elimination from complexes bearing these strongly electron-withdrawing groups. As described above, reductive elimination of arylmalonates occurred only from complexes of bulky phosphines, such as FcP(*t*-Bu)$_2$-ligated **13**. Moreover, we have been unable to isolate arylpalladium enolate complexes bearing *tert*-butylphosphine ligands because they eliminate too rapidly.

tert-Butyl-substituted phosphines could accelerate or decelerate reductive elimination, depending on whether the steric or electronic properties of these ligands dominate. The strong electron-donating property of alkylphosphines should disfavor reductive elimination, but the steric effect of the *tert*-butyl substituents should encourage reductive elimination. Apparently, the steric properties of the phosphine dominate. The rates for reductive elimination of enolate complexes containing these ligands are faster and the scope of many couplings catalyzed by complexes of these ligands is broader than reductive elimination from enolate complexes containing aromatic phosphines.

V. Summary

The observation of phenylacetone as a side product of an aryl halide amination in acetone solvent inspired the development of a practical synthetic method for the α-arylation of a variety of ketones and carboxylic acid derivatives. The design and use of electron-rich and sterically hindered alkylphosphines and *N*-heterocyclic carbenes has been essential to achieve the high selectivity and efficiency of these transformations. The steric and electronic properties of these ligands promote both oxidative addition and reductive elimination. The beginning of a mechanistic understanding of the catalytic process has emerged, and these studies have revealed the influence of both phosphine steric properties and enolate electronic properties on the rates of reductive elimination of α-aryl carbonyl compounds. A full investigation of the mechanism of the reaction, including studies on the oxidative addition of aryl halides in the presence of enolates and on the mechanism of enolate formation, will provide information to develop even more efficient catalysts and to increase the scope of substrates that undergo this process. In particular, a broader scope for reactions of amides, improved selectivity for monoarylation of nitriles, improved arylation of aldehydes,[34] improved scope for the arylation of α-substituted amino acids, and the development of asymmetric arylations that occur with broad scope are needed.

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