C−C Bond-Forming Reductive Elimination of Ketones, Esters, and Amides from Isolated Arylpalladium(II) Enolates

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Received February 28, 2001
Revised Manuscript Received April 20, 2001

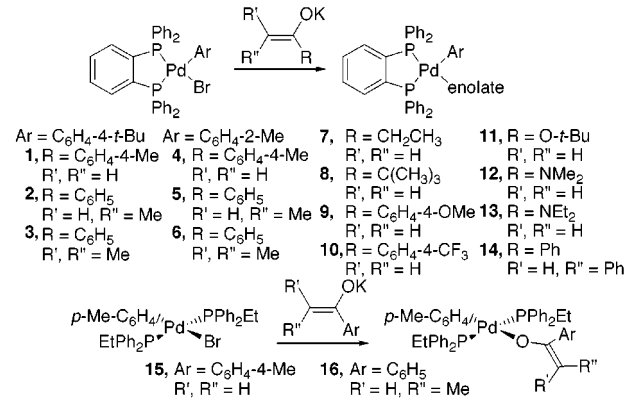
Metal enolates provide the foundation for many synthetic methods. We and others have recently developed a palladium-catalyzed process for the direct arylation of ketone enolates.[1] The reaction displays a high degree of regioselectivity and functional group tolerance. It now encompasses reactions of amides,[2] malonates,[3] and diketones[3b] with both bromo- and chloroarene[3a,b] electrophiles and has been conducted enantioselectively.[4]

The key step of this reaction is a C−C bond-forming reductive elimination from an arylpalladium enolate. On the surface, this reaction resembles C−C reductive eliminations of palladium dimethyl or arylpalladium methyl complexes that occur with nonpolar transition states.[5] However, the pK_b values of the enolates[6] are more similar to those of amides than of alkyls. Thus, C−C reductive elimination from enolate complexes may more closely resemble C−N bond-forming reductive eliminations of amines,[7] which show rates that depend strongly on the electronic properties of the amide. The effect of carbon-bound ligand properties on reductive elimination has been evaluated theoretically,[8] but rarely experimentally.[9]

We report the first examples of arylpalladium enolates that are sufficiently stable to isolate in pure form, but sufficiently reactive to undergo reductive elimination of α-aryl carbonyl compounds in high yields. Using these complexes, we have evaluated the effect of enolate steric and electronic properties on geometry, thermodynamic stability, and reductive elimination rates.

Previously, we generated arylpalladium enolate complexes at −78 °C[3a] and as mixtures with Pd(0),[1a] but modification of these systems to generate stable arylpalladium enolates that underwent reductive elimination was not straightforward. Experiments involving a series of arylpalladium enolate complexes with different ligands showed that 1,2-bis(diphenylphosphino)benzene (DPPBz) provided the appropriate balance of small bite angle, backbone stability, and modest electron donation to create a spectrum of isolable enolate complexes that undergo reductive elimination upon heating. Diphenylethylphosphine complexes also showed suitable stability and reactivity.

Scheme 1



DPPBz- and PPh_2Et-ligated arylpalladium enolate complexes were prepared as analytically pure solids in 44−81% yield, as shown in Scheme 1. Several coordination modes are possible for isolated palladium enolate complexes,[10] and both the enolate and phosphine structure affected the connectivity in **1**−**16**. With the exception of benzyl phenyl ketone enolate **14**, enolate complexes from ketones with α-methyl or methylene protons and DPPBz as phosphine were C-bound. The enolate of 2-butanone was bound solely through the former methyl, instead of ethyl, group. However, enolate complexes from ketones with α-methine protons were O-bound, and **14** was a mixture of C- and O-bound isomers. Complexes with PPh_2Et as ligand displayed a trans geometry and showed significantly greater preference for the O-bound form. Complex **16** was exclusively O-bound, while **15** was a mixture of O- and C-bound isomers in a 17:1 ratio.

The enolate connectivity was determined by NMR spectroscopic methods. For example, C-bound **1** displayed a single methylene ^{1}H NMR signal at δ 3.88, which was split by the two inequivalent phosphine ligands (J_{H-P} = 10.3, 6.9 Hz). In addition, the ^{13}C NMR spectrum displayed a doublet of doublets for the palladium-bound methylene carbon and a triplet at δ 202.7 (J_{H-P} = 4.1 Hz) for the carbonyl. In contrast, the ^{1}H NMR spectrum for O-bound **15** displayed two singlets at δ 4.90 and 4.99, and the ^{13}C NMR spectrum contained a singlet vinyl C−O resonance at δ 168.9 and a second vinyl resonance at δ 77.9. The connectivities of C-bound **4** and O-bound **16** were confirmed by X-ray analysis.

Thus, the C-bound isomer is favored electronically in these systems if the enolate is located trans to a phosphine, but the

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10.1021/ja015732l CCC: $20.00
Published on Web 05/25/2001

Scheme 2

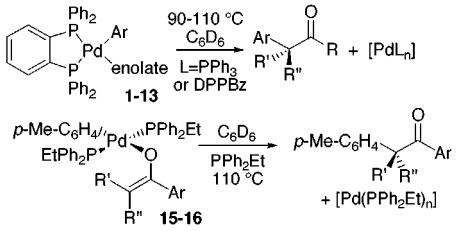


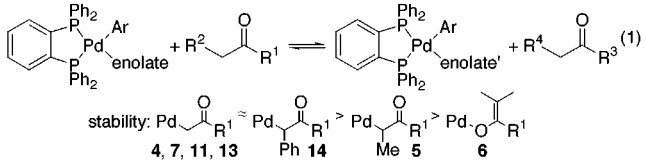
Table 1. Rates and Yields of Reductive Elimination for C- and O-Bound Enolates of [Pd(DPPBz)(Ar)(R)] at 90 °C

complex	Ar	R	$k_{obs} \times 10^4$ [a]	yield[b]
1	C_6H_4-4-*t*-Bu	$CH_2C(O)C_6H_4$-4-Me	3.0 ± 0.2	87
2	C_6H_4-4-*t*-Bu	$CHCH_3C(O)C_6H_5$	6.5 ± 0.4	57
3	C_6H_4-4-*t*-Bu	$OC(=CMe_2)C_6H_5$		82
4	C_6H_4-2-Me	$CH_2C(O)C_6H_4$-4-Me	3.7 ± 0.4	99
5	C_6H_4-2-Me	$CHCH_3C(O)C_6H_5$	5.8 ± 0.4	98
6	C_6H_4-2-Me	$OC(=CMe_2)C_6H_5$		<10

[a] Units: s^{-1}; reactions conducted with added DPPBz; [b] Units: %; reactions conducted with added PPh_3.

O-bound form is favored if located trans to an aryl group. However, a C-bound enolate complex that would possess a quaternary carbon bound to the metal is less stable in all cases than its O-bound tautomer for steric reasons.

In addition to geometry, we determined the thermodynamic stability of the enolate complexes relative to the corresponding ketone, ester, or amide, as shown in eq 1. In some cases, catalytic



amounts of potassium enolates were added to promote the rate of equilibration. The relative stabilities were the following: **4**, **7**, **11**, **13** ≈ **14** > **5** > **6** (see eq 1). Therefore, the stability was controlled by the number of substituents at the α-carbon and not by the pK_a of the carbonyl compound, except when an aryl group was directly bound to the α position (**14** vs **4** and **5**).

Thermolysis of **1**−**13** at 110 °C in the presence of added PPh_3 to bind the released Pd(0) fragment induced reductive elimination of the corresponding α-aryl carbonyl compound. Except for **6**, they formed product in 57−99% yield by ^{1}H NMR spectroscopy with an internal standard (Scheme 2). Similar thermolysis of PPh_2Et-complexes **15** and **16** in the presence of PPh_2Et generated α-aryl ketones in 70 and 45% yield.

To determine if coordination mode controlled reaction rates, we measured k_{obs} values for reductive elimination from both O- and C-bound DPPBz-ligated enolates (Table 1). Instead of a simple reductive elimination, coupling could occur by migratory insertion of the C=C unit of the O-bound enolate into the Pd−Ar bond, by a pathway related to that for the Heck reaction.[11] In addition, isomerization of a C-bound enolate to its enol tautomer, followed by favorable $C(sp^2)-C(sp^2)$ coupling, could occur. In the first case, O-bound enolates should react faster, and in the second, isobutyrophenone enolates should not couple. The low yield observed from O-bound **6** vs the high yields from **4** and **5** disfavors the first path, and the high yield from **3** argues against a palladaenol intermediate. Simple reductive elimination occurs.

Values of k_{obs} (Table 2) were measured at 90 °C by UV−vis spectroscopy for reductive elimination from enolate complexes derived from carbonyl compounds with pK_a values ranging from 23 to 34 in DMSO. These values are essentially identical to those

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Table 2. Rates and Yields of Reductive Elimination for [Pd(DPPBz)(C_6H_4-2-Me)(R)] at 90 °C

complex	R	pK_a[a]	$k_{obs} \times 10^4$ [b]	yield[c]
7	$CH_2C(O)CH_2CH_3$	24.4	2.7 ± 0.1	96
8	$CH_2C(O)C(CH_3)_3$	27.7	4.5 ± 0.2	96
9	$CH_2C(O)C_6H_4$-4-OMe	25.7	3.0 ± 0.2	95
10	$CH_2C(O)C_6H_4$-4-CF_3	22.7	3.6 ± 0.4	85
11	$CH_2C(O)OC(CH_3)_3$	ca. 31	2.6 ± 0.1	93
12	$CH_2C(O)NMe_2$	34−35	3.7 ± 0.3	98
13	$CH_2C(O)NEt_2$	34−35	6.3 ± 0.1	96
18	Me	56	>20	96

[a] Values are from ref 6 in DMSO solvent. [b] Units: s^{-1}; reactions conducted with added DPPBz. [c] Units: %; reactions conducted with added PPh_3.

of diarylamines, anilines, and alkylamines. For a set of arylpalladium amido complexes derived from these amines, reductive elimination occurred at 65 °C for diarylamides and below room temperature for alkylamides.[7] In contrast, the reductive elimination of enolates **7**−**13** showed little difference in rate constant as a function of enolate electronic properties. These complexes reacted with rate constants that varied by less than a factor of 3 and without any correlation with pK_a, as shown most dramatically by comparing k_{obs} values for **10** and **12**.

It is well established that reductive elimination can occur from both three- and four-coordinate palladium complexes.[7,8] Although elimination after partial dissociation of the rigid DPPBz is unlikely, rate-limiting dechelation is consistent with the small electronic effect. Thus, we evaluated reductive elimination from [(DPPE)Pd(*o*-Tol)($CH_2C(O)(C_6H_4$-4-Me)] (**17**), which is identical to **4** except for containing the more flexible bis(diphenylphosphino)ethane ligand. This complex reacted roughly 2-fold slower ($k_{obs} = (1.6 \pm 0.1) \times 10^{-4}$ s^{-1}) than did **4**, implying that reductive elimination occurs directly from the four-coordinate DPPBz complex.

In fact, the rates for C−C bond-forming reductive elimination from the DPPBz complexes were not independent of electronics in all cases: arylpalladium methyl (DPPBz)Pd(Me)(*o*-tolyl) (**18**) underwent reductive elimination at 90 °C with a half-life of less than 5 min ($k_{obs} > 20 \times 10^{-4}$ s^{-1}), and a DPPBz-ligated arylpalladium complex of a malonate anion did not produce any arylmalonate product upon thermolysis.

The steric properties of the enolate influenced reaction rates in a systematic fashion, but the magnitudes of the differences were small. Reductive eliminations from the more crowded arylpalladium propiophenone enolates **2** and **5** were faster than those from the corresponding acetophenone enolates **1** and **4** (6.5×10^{-4} and 5.8×10^{-4} s^{-1} vs 3.0×10^{-4} and 3.7×10^{-4} s^{-1}). Likewise, diethylacetamide enolate **13** reacted faster than did dimethylacetamide **12** (6.3×10^{-4} s^{-1} vs 3.7×10^{-4} s^{-1}), and pinacolone enolate **8** reacted faster than did 2-butanone enolate **7** (4.5×10^{-4} s^{-1} vs 2.7×10^{-4} s^{-1}). These results demonstrate that arylation of the less hindered carbon of a dialkyl ketone occurs with high selectivity in the catalytic arylation of ketone enolates because the less hindered enolate complex is the major tautomer, not because of a large difference in rates for reductive elimination.

In summary, C−C bond-forming reductive elimination is less sensitive to electronic perturbations than analogous C−N bond formation, but is sensitive to large changes in electronics. We will investigate carbon-bound ligands that possess other functional groups in the α position to understand further the effect of electronics on this fundamental reaction.

Acknowledgment. We thank the National Institutes of Health (R01GM58108-02-04) for support of this work.

Supporting Information Available: Experimental procedures for compound preparation and kinetic analysis (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA015732L