# Palladium-Catalyzed α-Arylation of Esters with Chloroarenes
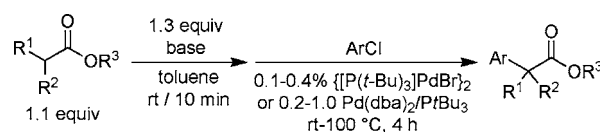
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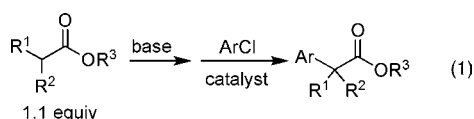Box 58-6, Urbana, Illinois 61801*

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**ABSTRACT**



Palladium-catalyzed α-arylations of esters with chloroarenes are reported. The reactions of chloroarenes with the sodium enolates of *tert*-butyl propionate and methyl isobutyrate occur in high yields with 0.2–1 mol % of {[P(*t*-Bu)₃]PdBr}₂ or the combination of Pd(dba)₂ and P(*t*-Bu)₃ as catalyst. The reactions of chloroarenes with the Reformatsky reagent of *tert*-butyl acetate were most challenging but occurred in high yields for chlorobenzene and electron-poor chloroarenes catalyzed by 1 mol % of Pd(dba)₂ and pentaphenylferrocenyl di-*tert*-butylphosphine (Q-phos).

The palladium-catalyzed α-arylation of esters (eq 1) has become a convenient route to form benzylic esters.[1–4] Such reactions between bromoarenes and the enolates of esters occur in high yields in the presence of palladium catalysts bearing sterically hindered, electron-rich phosphine or carbene ligands. The accompanying paper[14] reports reactions of bromoarenes in the presence of a dimeric palladium(I) catalyst that form α-aryl esters in high yields with good substrate scope with low loadings of palladium. However, few reactions between chloroarenes and the enolates of esters have been reported.[5,6]



$$ (1) $$

Buchwald and Moradi reported four arylations of esters with chloroarenes. These were conducted with *tert*-butyl propionate and ethyl phenylacetate as the ester and chloro-

toluene, chloroanisole, and 4-chlorodiphenyl ether as the haloarene using 2.3 equiv of lithium enolate and 3 mol % of palladium at 80 °C.[5] No examples of reactions of chloroarenes that could form benzyne intermediates or that contained functional groups that could interfere with the coupling process were reported.

The authors' laboratory reported the reactions of chloroarenes with the sodium enolate of *tert*-butyl propionate in the presence of 1 mol % palladium catalyst containing a hindered *N*-heterocyclic ligand.[6] This reaction required only a slight excess of the enolate and was conducted at room temperature, but only reactions of chlorobenzene were studied.

Thus, reactions of chloroarenes with the enolates of isobutyrates and acetates are not known, and reactions of chloroarenes possessing varied electronic properties and pendant functional groups are limited. The coupling of chloroarenes with the enolates of esters is challenging because of the combination of higher temperatures required for coupling of chloroarenes and low stability of the enolates of esters at elevated temperatures. To address this problem, catalysts with high reactivity are needed.

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Recently, we showed that the Pd(I) complex {[P(t-Bu)₃]-PdBr}₂[7] is highly active for cross-coupling.[8] Although this complex contains unusual Pd(I) centers, this complex appears to be readily reduced to form the key Pd(PtBu₃) intermediate. We also showed that the palladium catalyst containing pentaphenylferrocenyl di-tert-butylphosphine (Q-phos)[9,10] is highly active toward the α-arylation of esters with bromo-arenes.[11]

Here, we report that reactions of chloroarenes with the alkali metal enolates of esters catalyzed by {[P(t-Bu)₃]PdBr}₂ or the combination of Pd(dba)₂ and P(t-Bu)₃ occur in high yield with a range of esters and chloroarenes and that reactions of chloroarenes with Reformatsky reagents occurs when catalyzed by Pd(dba)₂ and P(t-Bu)₃. These results illustrate that practical couplings of these chloroarenes can be conducted with ester enolates.

Conditions for the palladium-catalyzed reactions of *tert*-butyl propionate were investigated first. These studies focused initially on the reaction of this enolate with chloro-benzene in toluene in the presence of the Pd(I) complex {[P(t-Bu)₃]PdBr}₂. Two different types of alkali metal enolates were evaluated: the lithium enolate generated from LiNCy₂, which formed high yields of α-aryl esters from reactions of bromoarenes, and the sodium enolate generated from NaHMDS, which one might expect to be more reactive than the lithium enolate. As shown in eq 2, the reaction of chlorobenzene with the sodium enolate of *tert*-butyl propi-onate in the presence of only 0.2 mol % {[P(t-Bu)₃]PdBr}₂ at room temperature occurred to form the α-aryl ester product in quantitative yield.

| base | yield[a] |
|---|---|
| LiNCy₂ | 60% |
| NaHMDS | 100% |
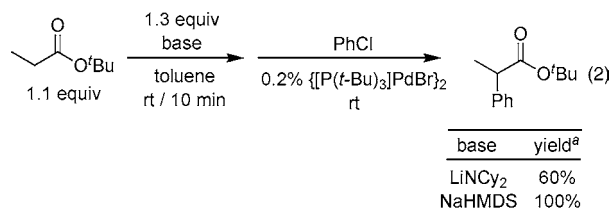
[a] Yields for comparative purposes were estimated by GC-MS with dodecane as an internal standard.

Table 1 summarizes reactions between chloroarenes and the sodium enolate of *tert*-butyl propionate. Reactions were conducted using two different catalyst systems bearing P(t-Bu)₃. One system was generated by mixing Pd(dba)₂ and P(t-Bu)₃. The other system was generated from the Pd(I) precatalyst {[P(t-Bu)₃]PdBr}₂. These reactions occurred in good yields at room temperature or 60 °C. Products from diarylation of the ester were not observed.

Reactions of the sodium enolate of *tert*-butyl propionate with chlorobenzene occurred in high yields with only 0.4

**Table 1.** Arylation of Sodium Enolate of *tert*-Butyl Propionate with Chloroarenes

| entry | ArCl | Pd / ligand | temp | yield[a] |
|---|---|---|---|---|
| 1 | PhCl | 0.4% Pd(dba)₂ / 0.4% P(t-Bu)₃ | rt | 91% |
| 2 | | 0.2% {[P(t-Bu)₃]PdBr}₂ | rt | 94% |
| 3 | p-OMe | 1% Pd(dba)₂ / 1% P(t-Bu)₃ | rt | 69% |
| 4 | | 0.4% {[P(t-Bu)₃]PdBr}₂ | rt | 88% |
| 5 | o-OMe | 1% Pd(dba)₂ / 1% P(t-Bu)₃ | rt | 62% |
| 6 | | 0.4% {[P(t-Bu)₃]PdBr}₂ | rt | 77% |
| 7 | m-OMe | 1% Pd(dba)₂ / 1% P(t-Bu)₃ | rt | 41% |
| 8 | | 0.4% {[P(t-Bu)₃]PdBr}₂ | rt | 75% |
| 9 | | 0.4% Pd(dba)₂ / 0.4% P(t-Bu)₃ | 60 °C | 42% |
| 10 | | 0.2% {[P(t-Bu)₃]PdBr}₂ | 60 °C | 81% |
| 11 | | 0.15% {[P(t-Bu)₃]PdBr}₂ | 60 °C | 73% |
| 12 | | 0.3% Pd(dba)₂ / 0.3% P(t-Bu)₃ | 60 °C | 84%[b] |
| 13 | | 0.15% {[P(t-Bu)₃]PdBr}₂ | 60 °C | 81%[b] |

[a] Isolated yields (average of two runs) for reactions of 1 mmol of chloroarene in 3 mL of toluene. [b] Product from reaction with aryl bromide.

mol % of palladium using either catalyst system (entries 1 and 2). Reactions of the more electron-rich 2- and 4-chloro-anisole were conducted using the catalyst generated from 1 mol % Pd(dba)₂ and 1 mol % P(t-Bu)₃ or 0.4 mol % {[P(t-Bu)₃]PdBr}₂ (0.8 mol % palladium) (entries 3, 4, 5, and 6). Entries 3 and 4 show that the reactions of 4-chloroanisole occur in higher yield when conducted with {[P(t-Bu)₃]PdBr}₂ as precatalyst.[5] These conditions required only 1.2 equiv of the enolate and occurred at room temper-ature with only 0.8−1 mol % palladium. Entries 5 and 6 illustrate that the same trend in catalyst activity was observed for reactions of the ortho-substituted, electron-rich 2-chloro-anisole. Finally, reactions of the more electron-poor *m*-chloroanisole (entries 7 and 8) occurred in only 41% yield in the presence of the catalyst generated from 1 mol % Pd-(dba)₂ and 1 mol % P(t-Bu)₃, but in a higher 75% yield with only 0.4 mol % of the Pd(I) precatalyst {[P(t-Bu)₃]PdBr}₂.

Entries 9−13 illustrate reactions conducted at the mildly elevated temperature of 60 °C. Again, yields were higher for reactions conducted with the Pd(I) precatalyst {[P(t-Bu)₃]-PdBr}₂. No diarylation was observed even at 60 °C. In contrast to the reactions of the chloroanisoles, these reactions occurred to about 80−90% conversion with 0.15−0.2 mol % of {[P(t-Bu)₃]PdBr}₂, and some *N*-aryl disilylamine was observed as a side product. Nevertheless, the isolated yields of α-aryl ester were high in most cases.

Reactions of the hindered 2-chloro-*m*-xylene occurred at 60 °C with 0.4 mol % palladium (entries 9 and 10). When conducted with 0.4 mol % Pd(dba)₂ and 0.4 mol % P(t-Bu)₃, this reaction occurred in only 42% yield (entry 9), but when conducted with the same loading of {[P(t-Bu)₃]PdBr}₂ as catalyst, it occurred in 81% yield (entry 10). Chloroarenes containing fluoride substituents also underwent arylation in good yield, in this case using only 0.15 mol % {[P(t-Bu)₃]-

(7) Vilar, R.; Mingos, D. M. P.; Cardin, C. J. *J. Chem. Soc., Dalton Trans.* **1996**, 4313.
(8) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746.
(9) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718.
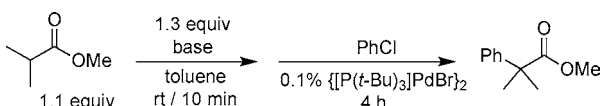(10) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.
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PdBr}$_2$ at 60 °C (entry 11). The reation of 4-chlorobromobenzene occurred in high yield at the bromide (entries 12 and 13).

Reactions of electron-poor chloroarenes presented the greatest limitation. For example, reactions of the electron-poor 4-chloro-trifluoromethylbenzene in the presence of 0.2 mol % Pd(I) dimer or 0.4 mol % Pd(dba)$_2$ and P($t$-Bu)$_3$ as catalyst at room temperature did not give detectable amounts of the coupled product, and only 30% of coupled product from the reaction at 60 °C was observed by GC-MS. Reactions with higher loadings of palladium were not studied. The lower conversions for reactions of electron-poor aryl chlorides are in contrast with typical trends for palladium-catalyzed processes. We do not have a clear explanation for the lower reactivity of these arenes toward the α-arylation of esters.

We were also able to develop conditions for the coupling of the enolate of methyl isobutyrate with chloroarenes. Initially, reactions of chlorobenzene with enolates generated from several alkali metal amide bases were evaluated in the presence of 0.1 mol % of the Pd(I) precatalyst {[P($t$-Bu)$_3$]-PdBr}$_2$ in toluene solvent (Table 2). No conversion of

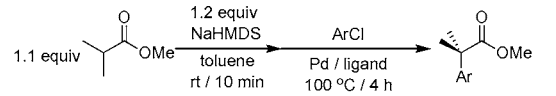**Table 2.** Optimized Conditions for Reactions of Methyl Isobutyrate and Chlorobenzene



| entry | base | $T$ (°C) | yield$^a$ (%) |
|-------|------|----------|---------------|
| 1 | LiNCy$_2$ | rt | 0 |
| 2 | NaHMDS | rt | 0 |
| 3 | NaHMDS | 60 | trace |
| 4 | LiNCy$_2$ | 100 | trace |
| 5 | NaHMDS | 100 | 90 |

$^a$ Determined by GC-MS with dodecane as an internal standard.

chlorobenzene was observed from reaction of either the lithium or sodium enolates at room temperature (entries 1 and 2), and low conversions were observed at 60 °C (entries 3 and 4). However, the reaction of the sodium enolate at 100 °C occurred in high yields (entry 5), even with only 0.1 mol % of the Pd(I) dimer.

Reactions of the sodium enolate of methyl isobutyrate with chloroarenes in the presence of the combination of Pd(dba)$_2$ and P($t$-Bu)$_3$ or {[P($t$-Bu)$_3$]PdBr}$_2$ as catalyst are summarized in Table 3. These reactions were conducted at 100 °C with only 0.2−0.4 mol % of palladium. In general, reactions with the Pd(I) dimer occurred in higher yields than those with Pd(dba)$_2$ and P($t$-Bu)$_3$, but the difference in yield was smaller than the difference in yields of the reactions of *tert*-butyl propionate using the two catalysts. The major side product of these reactions was the *N*-aryl bis-trimethylsilylamime from the known[12] palladium-catalyzed reaction of the base with the chloroarene.

**Table 3.** Arylation of Sodium Enolate of Methyl Isobutyrate with Chloroarenes



| entry | ArCl | | Pd / ligand | yield$^a$ |
|-------|------|--|-------------|-----------|
| 1 | PhCl | | 0.2% Pd(dba)$_2$ / 0.2% P($t$-Bu)$_3$ | 89% |
| 2 | | | 0.1% {[P($t$-Bu)$_3$]PdBr}$_2$ | 92% |
| 3 | | | 0.4% Pd(dba)$_2$ / 0.4% P($t$-Bu)$_3$ | 79% |
| 4 | | | 0.2% {[P($t$-Bu)$_3$]PdBr}$_2$ | 84% |
| 5 | | $p$-F | 0.4% Pd(dba)$_2$ / 0.4% P($t$-Bu)$_3$ | 90% |
| 6 | | | 0.2% {[P($t$-Bu)$_3$]PdBr}$_2$ | 87% |
| 7 | | $m$-F | 0.4% Pd(dba)$_2$ / 0.4% P($t$-Bu)$_3$ | 77% |
| 8 | | | 0.2% {[P($t$-Bu)$_3$]PdBr}$_2$ | 81% |
| 9 | | $p$-OMe | 0.4% Pd(dba)$_2$ / 0.4% P($t$-Bu)$_3$ | 69% |
| 10 | | | 0.2% {[P($t$-Bu)$_3$]PdBr}$_2$ | 73% |
| 11 | | $m$-OMe | 0.4% Pd(dba)$_2$ / 0.4% P($t$-Bu)$_3$ | 77% |
| 12 | | | 0.2% {[P($t$-Bu)$_3$]PdBr}$_2$ | 74% |
| 13 | | $p$-CF$_3$ | 0.4% Pd(dba)$_2$ / 0.4% P($t$-Bu)$_3$ | 67% |
| 14 | | | 0.2% {[P($t$-Bu)$_3$]PdBr}$_2$ | 71% |
| 15 | | $m$-CF$_3$ | 0.4% Pd(dba)$_2$ / 0.4% P($t$-Bu)$_3$ | 81% |
| 16 | | | 0.2% {[P($t$-Bu)$_3$]PdBr}$_2$ | 75% |
| 17 | | | 0.4% Pd(dba)$_2$ / 0.4% P($t$-Bu)$_3$ | 66% |
| 18 | | | 0.2% {[P($t$-Bu)$_3$]PdBr}$_2$ | 71% |
| 19 | | | 0.4% Pd(dba)$_2$ / 0.4% P($t$-Bu)$_3$ | 69%$^b$ |
| 20 | | | 0.2% {[P($t$-Bu)$_3$]PdBr}$_2$ | 82%$^b$ |

$^a$ Isolated yields (average of two runs) for reactions of 1 mmol of chloroarene in 3 mL of toluene. $^b$ Product from reactions of aryl bromide.

The examples in Table 3 encompass reactions of electron-neutral, electron-rich, and electron-poor chloroarenes. Reactions of the sodium enolate of methyl isobutyrate with chlorobenzene occurred in high yield with 0.2 mol % of palladium (entries 1 and 2). The reaction of 4-chlorotoluene occurred in good yield in the presence of 0.4 mol % Pd-(dba)$_2$ and 0.4 mol % P($t$-Bu)$_3$ (entry 3) or 0.2 mol % of the Pd(I) dimer (0.4 mol % palladium, entry 4). Reactions of 4- and 3-chlorofluorobenzene also occurred in high yields with 0.4 mol % palladium (entries 5−8). Reactions of the electron-rich 4-chloroanisole occurred in 69 and 73% yield with the two catalyst systems (entries 9 and 10), and reaction of the less electron rich 3-chloroanisole occurred in a somewhat higher 77% and 74% yield with the two catalysts (entries 11 and 12). No coupled product was observed from reactions of this hindered enolate with *o*-chloroanisole in the presence of either of these catalyst systems.

Reactions of electron-poor chloroarenes also occurred using both catalysts. The reaction of this enolate with 4-chloro benzotrifluoride occurred in acceptable yield when catalyzed by either 0.4 mol % Pd(dba)$_2$ and 0.4 mol % P($t$-Bu)$_3$ (entry 13) or 0.2 mol % {[P($t$-Bu)$_3$]PdBr}$_2$ (entry 14). Reactions of 3-trifluoromethyl chlorobenzene occurred in high yields with both catalysts (entries 15 and 16).

Like the sodium enolate of *tert*-butyl propionate, the enolate of methyl isobutyrate reacted selectively with the bromide of bromo chlorobenzene (entries 19 and 20). Unlike

(12) Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729.
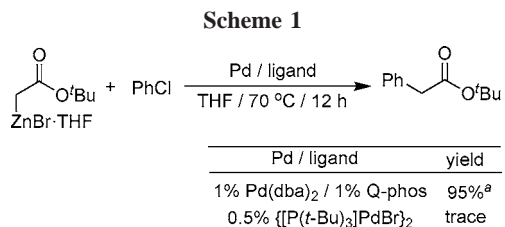
the reactions of the propionate enolate at 60 °C, some side product (ca. 10−15%) was observed from the reaction of the aryl bromide with excess amide base. No product from the reaction of both the bromide and chloride was observed.

Reactions of heteroaryl chlorides were also evaluated briefly. The reaction of the sodium enolate of methyl isobutyrate with 2-chloropyridine formed the coupled product in 66% yield when the catalyst was generated from 0.4 mol % Pd(dba)$_2$ and 0.4 mol % P($t$-Bu)$_3$ (entry 17) and in a slightly higher 71% yield when catalyzed by 0.2 mol % ({[P($t$-Bu)$_3$]PdBr}$_2$ entry 18). The same reactions with 3-chloropyridine occurred to low conversion.

The reations of chloroarenes with the alkali metal enolates of $tert$-butyl acetate were more challenging to develop than the reactions of the propionates and isobutyrates, and we have not developed conditions that produced more than 10% of the coupled product from reactions of chloroarenes with the alkali metal enolates of this ester. We presume this difficulty results from the low stability of the acetate enolate, relative to that of the more substituted propionate and isobutyrate enolates.

To overcome this problem, we studied reactions of chloroarenes with zinc enolates of acetates.[13] Because the catalyst system generated from Pd(dba)$_2$ and Q-phos was the most general for the coupling of zinc enolates of esters with bromoarenes,[13] reactions of chlorobenzene with this enolate were conducted in the presence of this catalyst. Even with 3 mol % of palladium and a reaction temperature of 70 °C, no coupled product was generated from the reactions of zinc enolates generated by quenching the sodium or lithium enolate of $tert$-butyl acetate with zinc chloride.

However, the coupling of the Reformatsky reagent of $tert$-butyl acetate generated from the α-bromo acetate occurred in high yield. As shown in Scheme 1, reactions of chlo-

**Scheme 1**

| Pd / ligand | yield |
|---|---|
| 1% Pd(dba)$_2$ / 1% Q-phos | 95%$^a$ |
| 0.5% {[P($t$-Bu)$_3$]PdBr}$_2$ | trace |

$^a$ Isolated yield (average of two runs) for reactions of 0.5 mmol of chlorobenzene in 2 mL of THF.

robenzene with the Reformatsky reagent of $tert$-butyl acetate occurred in the presence of the catalyst generated from Pd-(dba)$_2$ and Q-phos but did not occur in substantial yield in the presence of the Pd(I) complex {[P($t$-Bu)$_3$]PdBr}$_2$.

Table 4 summarizes the reactions of chloroarenes with this zinc enolate catalyzed by Pd(dba)$_2$ and Q-phos. The scope

**Table 4.** α-Arylation of Isolated Reformatsky Reagent of $tert$-Butyl Acetate with Chloroarenes

| entry | ArCl | yield$^a$ | entry | ArCl | yield$^a$ |
|---|---|---|---|---|---|
| 1 | PhCl | 95% | 3 | MeO$_2$C—⟨⟩—Cl | 85% |
| 2 | NC—⟨⟩—Cl | 86% | 4 | O$_2$N—⟨⟩—Cl | 83% |

$^a$ Isolated yield (average of two runs) for reactions of 0.5 mmol of chloroarene in 2 mL of THF.

of these reactions was narrower than of the reactions of chloroarenes with the alkali metal enolates of propionates and isobutyrates, but several examples of this process with electron-neutral and electron-poor chloroarenes occurred in high yield. For example, the reaction of chlorobenzene occurred in 95% yield (entry 1), and the reactions of electron-poor chloroarenes containing reactive functional groups (entries 2−4) occurred in high yields. No side products were observed for these reactions.

Unfortunately, reactions of electron-rich chloroarenes, such as 4-chloroanisole, reactions of ortho-substituted chloroarenes, such as 2-chloroanisole or 2-chloro-$m$-xylene, and reactions of heteroaryl chlorides, such as 2-chloropyridine and 3-chloropyridine, occurred in less than 50% yields. Future studies are needed to address the scope of the coupling of the enolates of $tert$-butyl acetate with chloroarenes.

In summary, the use of highly active catalysts and reaction conditions involving the sodium enolates has extended the α-arylation of esters to reactions with chloroarenes. The reactions of chloroarenes with the sodium enolates of $tert$-butyl propionate and $tert$-butyl isobutyrate occurred in high yields in the presence of palladium catalysts bearing P($t$-Bu)$_3$. Although reactions of the sodium enolates of $tert$-butyl acetate with chloroarenes did not occur, reactions of the Reformatsky reagent of $tert$-butyl acetate with electron-netural and electron-poor chloroarenes occurred. The reactions of chloroarenes with the propionate and isobutyrate enolates occurred in the highest yields in the presence of the Pd(I) dimer as precatalyst, and the turnover numbers for these processes are high for this type of coupling.

**Supporting Information Available:** Experimental procedures and characterization of reaction products. This information is available free of charge via the Internet at http://pubs.acs.org.

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(14) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1545.