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α-Arylation of Esters Catalyzed by the Pd(I) Dimer $\{[P(t\text{-}Bu)_3]PdBr\}_2$

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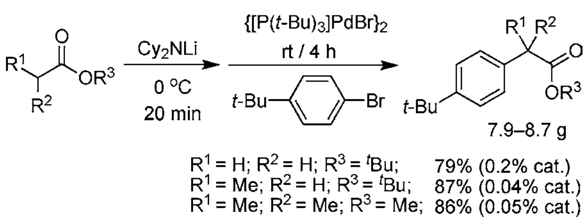
ABSTRACT



Conditions for the coupling of bromoarenes with esters using a single base and catalyst with improved turnover numbers are described. These general conditions were made possible by using the Pd(I) catalyst $\{[P(t\text{-}Bu)_3]PdBr\}_2$. Reactions of acetates, propionates, and isobutyrates are presented, and reactions of all three classes of esters on a 10 g scale are described.

The palladium-catalyzed α-arylation of carbonyl compounds provides a simple method to conduct formal aromatic substitution processes with alkali metal enolate nucleophiles.[1−6] These reactions have been reported with palladium catalysts containing hindered monodentate phosphines and *N*-heterocyclic carbenes. The coupling of each class of carbonyl compounds raises its own issues of selectivity, enolate stability, and enolate basicity. Moreover, the α-arylation of esters[7−10] is challenging because of the potential that Claisen condensation and decomposition of the ester enolates will occur faster than cross-coupling. Thus, catalysts that react rapidly under mild conditions are needed to create conditions in which the rate of coupling exceeds the rate of condensation and enolate decomposition. The need for fast rates places particularly high demands on the catalyst when low loadings of palladium are desired.

We recently reported a full account of the α-arylation of esters in the presence of alkali metal amide bases.[8] These reactions occurred between enolates derived from acetates, propionates and isobutyrates and a wide range of bromoarenes. However, the α-arylation of alkali metal enolates required different catalysts and different alkali metals, depending on the type of ester and the electronic property of the bromoarene. For example, the arylation of *tert*-butyl acetate and methyl isobutyrate occurred in high yields when using lithium bases and $P(t\text{-}Bu)_3$ as ligand, while the arylation of *tert*-butyl propionate occurred in the highest yields when using sodium bases and an *N*-heterocyclic carbene as ligand. Moreover, the reactions of *tert*-butyl propionate tended to occur in yields ranging from only 66% to 75% or with catalyst loadings that ranged from 1 to 5 mol % for most examples. The modest yields and high catalyst loadings for the couplings of aryl bromides at the methylene position of *tert*-butyl propionate were surprising because the yields, rates, and catalyst loadings for the coupling of aryl bromides at the methylene position of propiophenone are the most favorable of any coupling of ketone enolates studied thus far.[11−14]

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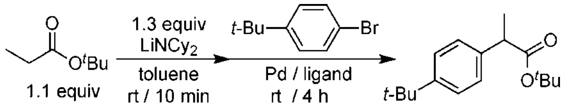
We report our studies on the use of $\{[P(t\text{-}Bu)_3]PdBr\}_2$[15,16−18] as catalyst for the α-arylation of esters. This catalyst couples bromoarenes with acetates, propionates, and isobutyrates in the presence of the same alkali metal amide base in each case. This Pd(I) complex $\{[P(t\text{-}Bu)_3]PdBr\}_2$[16,18,19] has been shown to be an exceptionally reactive catalyst or catalyst precursor for the amination of aryl bromides and chlorides,[18] for Suzuki couplings of aryl bromides,[18,20] and for the α-arylation of the zinc enolates of esters.[9,21] In addition to being highly reactive for cross-coupling, this complex is commercially available and is convenient to use because it is more stable to air than free $P(t\text{-}Bu_3)$. With this catalyst, the α-arylations of the alkali metal enolates of esters occur with turnover numbers that have been improved in many cases. Reactions of each class of ester have been conducted on a 10 gram scale.

Our initial studies to improve the α-arylation of esters focused on catalyst compositions derived from $P(t\text{-}Bu)_3$. We tested catalysts containing this ligand because they have been highly active for the α-arylation of the alkali metal enolates of ketones, amides, and several classes of esters[4,10] and because the ligand is available in large quantities.

Three different catalyst systems containing $P(t\text{-}Bu)_3$ as ligand have been typically used: the combination of $Pd(dba)_2$ or $Pd_2(dba)_3$ and $P(t\text{-}Bu)_3$, a combination of these Pd(0) precursors and $[HP(t\text{-}Bu)_3]BF_4$[22] instead of the free phosphine, and the Pd(I) dimer $\{[P(t\text{-}Bu)_3]PdBr\}_2$. To determine if the precursor affected the activity of the catalyst toward the α-arylation of *tert*-butyl propionate, we studied reactions of 4-bromo-*tert*-butylbenzene with the lithium enolate of *tert*-butyl propionate (generated from $LiNCy_2$) in the presence of these three catalyst systems.

The results of these experiments are summarized in Table 1. Reactions catalyzed by the combination of a 1:1 ratio of $Pd(dba)_2$ and free $P(t\text{-}Bu)_3$ occurred to about 75% conversion and 75% yield with 0.1 mol % of palladium catalyst (entry 1). The reactionconducted with 0.25% of the same components occurred to full conversion, and the coupled product was isolated in 91% yield (entry 2). Reactions conducted with the combination of $Pd(dba)_2$ and the air-stable $[HP(t\text{-}Bu)_3]BF_4$ also occurred with good mass balance of reactant and product, but the reaction did not occur to completion with 0.25% palladium (entry 3). Reactions catalyzed by the Pd(I) dimer occurred in 80% yield with about 20% unreacted starting material in the presence of only 0.05% of Pd(I) dimer (0.1% palladium) (entry 4). Considering the good reactivity and convenience of handling the Pd(I) catalyst precursor, we investigated additional α-arylations of esters with this system.

Table 1. Comparison of Palladium Catalysts Containing Tri-*tert*-Butylphosphine[a]

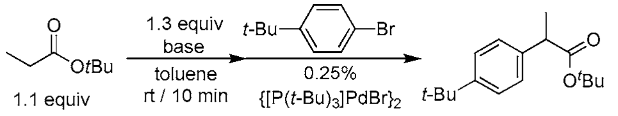


entry	Pd/ligand	yield[b] (%)
1	0.1% $Pd(dba)_2$/0.1% $P(t\text{-}Bu)_3$	75
2	0.25% $Pd(dba)_2$/0.25% $P(t\text{-}Bu)_3$	91[c]
3	0.25% $Pd(dba)_2$/0.25% $[HP(t\text{-}Bu)_3]BF_4$	60
4	0.05% $\{[P(t\text{-}Bu)_3]PdBr\}_2$	80

[a] Reactions conducted with 1 mmol of bromoarene in 3 mL of toluene. [b] Determined by GC-MS with dodecane as an internal standard. [c] Isolated yields (average of two runs).

To determine if $LiNCy_2$ or silylamide bases led to α-arylations of *tert*-butyl propionate in the highest yield, we compared reactions with lithium and sodium hexamethyldisilazide (HMDS) to those with $LiNCy_2$ as base. As shown in Scheme 1, the reaction with LiHMDS occurred in much lower yield than the reaction with $LiNCy_2$ under identical conditions. Either $LiNCy_2$ or NaHMDS appear to be suitable bases. In part because dicyclohexylamine is less expensive than hexamethyldisilazane ($4.5/mol vs $15/mol), further studies were conducted with commercial $LiNCy_2$ as base and reactions on larger scale were conducted with $LiNCy_2$ generated in situ from $HNCy_2$ and BuLi.

Scheme 1[a]



base	yield[b]
LiHMDS	20%
NaHMDS	100%
$LiNCy_2$	100%

[a] Reactions conducted with 1 mmol of bromoarene in 3 mL of toluene. [b] Yields determined by GC-MS with dodecane as an internal standard.

Table 2 summarizes the palladium-catalyzed coupling of the lithium enolate of *tert*-butyl propionate with aryl bromides in the presence of $\{[P(t\text{-}Bu)_3]PdBr\}_2$. The reaction

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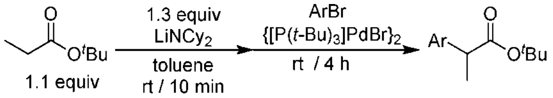
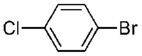
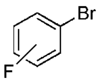
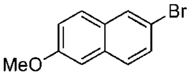
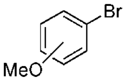
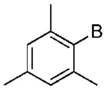
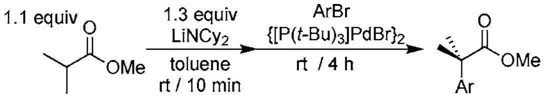
Table 2. Improved Conditions for Palladium-Catalyzed α-Arylation of *tert*-Butyl Propionate with Aryl Bromides

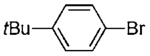
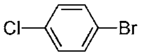
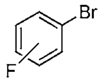
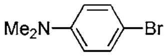
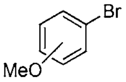
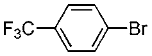
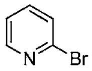
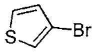


entry	ArBr		cat. loading	yield[a]
1			0.2%	83%
2		*p*-F	0.2%	88%
3		*m*-F	0.2%	90%
4			0.2%	75%
5		*p*-OMe	0.25%	87%
6		*m*-OMe	0.25%	84%
7		*o*-OMe	0.25%	87%
8			0.05%	72%

[a] Isolated yields (average of two runs) for reactions of 1 mmol of bromoarene in 3 mL of toluene.

Table 3. α-Arylation of Methyl Isobutyrate with Aryl Bromides in the Presence of {[P(*t*-Bu)$_3$]PdBr}$_2$



entry	ArBr		cat. loading	yield[a]
1			0.05%	72%
2			0.5%	89%
3		*p*-F	0.5%	85%
4		*m*-F	0.5%	72%
5			0.05%	88%
6		*p*-OMe	0.5%	85%
7		*m*-OMe	0.5%	88%
8			0.5%	60%
9			0.5%	71%
10			0.5%	75%

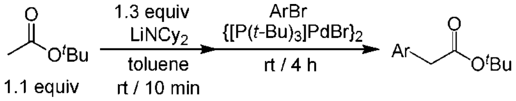
[a] Isolated yields (average of two runs) for reactions of 1 mmol of bromoarene in 3 mL of toluene.

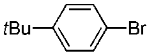
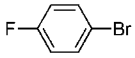
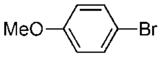
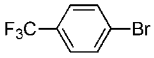
occurred with a variety of bromoarenes in high yields with only 0.05%−0.25% of Pd(I) dimer (0.1%−0.5% palladium). Entries 1−3 illustrate high yields for reactions of bromoarenes containing chloride and fluoride groups. Entry 4 shows that the precursor to Naproxen is generated in high yield with 0.2 mol % dimer (entry 4). Reactions of electron-rich *p*-bromoanisole occurred in high yields (entry 5). Even the reaction of the electron-rich and ortho-substituted 2-bromoanisole (entry 7) occurred in high yield. Most striking, the reaction of the sterically hindered bromomesitylene occurred in good yield with only 0.05 mol % {[P(*t*-Bu)$_3$]PdBr}$_2$ (0.1% palladium) (entry 8). In general, these yields and turnover numbers are significantly higher than those previously reported with the catalyst derived from an *N*-heterocyclic carbene or with the catalyst generated from Pd(dba)$_2$ and P(*t*-Bu)$_3$.[8]

Table 3 summarizes the coupling of aryl bromides with methyl isobutyrate catalyzed by {[P(*t*-Bu)$_3$]PdBr}$_2$. These reactions occurred with 0.05−0.5 mol % catalyst (0.1−1 mol % palladium). The reactions occurred in high yield with electron-neutral (entry 1) electron-poor (entries 2−4, 7, 8) and electron-rich (entries 5, 6) bromoarenes. Entry 2 illustrates the selectively at an aryl bromide over an aryl chloride. Reactions of these hindered enolates did not occur with ortho-substituted bromoarenes.

However, reactions of the lithium enolate of methyl isobutyrate did occur with certain heteroaryl bromides (entries 9, 10). For example, reactions with 2-bromopyridine occurred in 71% yields with 0.5 mol % {[P(*t*-Bu)$_3$]PdBr}$_2$ (entry 9), and the reaction of 3-bromothiophene occurred in 75% yield with the same amount of catalyst (entry 10). These reactions occur with much lower catalyst loading than was required for the reactions of these heteroaryl bromides with Pd(dba)$_2$ and P(*t*-Bu)$_3$ as catalyst.

Table 4. α-Arylation of *tert*-Butyl Acetate with Aryl Bromides in the Presence of {[P(*t*-Bu)$_3$]PdBr}$_2$



entry	ArBr	cat. loading	yield[a]
1		0.2%	83%
2		0.4%	82%
3		0.2%	86%
4		0.4%	73%

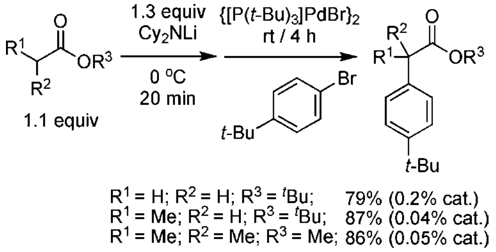
[a] Isolated yields (average of two runs) for reactions of 1 mmol of bromoarene in 3 mL of toluene.

The reactions of *tert*-butyl acetate also occurred in high yield with low loadings of the dimeric palladium(I) catalyst. These reactions are summarized in Table 4. The reaction of electron-neutral 4-bromo-*tert*-butylbenzene occurred in high yields in the presence of only 0.2% {[P(*t*-Bu)$_3$]PdBr}$_2$ (entry

1), and the reaction of 4-fluorobromobenzene occurred in good yield at the bromide with only 0.4 mol % catalyst (entry 2). In addition, the coupling of this enolate occurred in good yields with both electron-rich and electron-poor bromoarenes. Like the reactions of the enolate of *tert*-butyl propionate, the reaction of the lithium enolate of *tert*-butyl acetate with the electron-rich aryl bromide (entry 3) occurred with less catalyst than the reaction of the electron-poor aryl bromide (entry 4). These data are comparable to those reported previously with the combination of Pd(dba)$_2$ and P(*t*-Bu)$_3$ as catalyst.

With a particularly active catalyst for the α-arylation of esters, we sought to develop procedures to conduct this chemistry conveniently on a scale larger than the typical 1 mmol scale used to demonstrate reaction scope. To do so, reactions of *tert*-butyl acetate, *tert*-butyl propionate, and methyl isobutyrate were conducted with 40 mmol of bromoarene as limiting reagent in the presence of the catalyst generated from {[P(*t*-Bu)$_3$]PdBr}$_2$ (Scheme 2). Arylation of all three esters required less than 1% catalyst loading (0.4% palladium for arylation of the acetate, 0.08% palladium for arylation of the propionate, and 0.1% palladium for arylation of the isobutyrate).

Scheme 2



These reactions were conducted without the use of a drybox in toluene solvent at temperatures equal to or above 0 °C to generate the enolate. The enolate was generated in one reaction vessel at 0 °C by slow addition of the ester to LiNCy$_2$ in toluene solvent. A toluene solution of the bromoarene and catalyst was then added to this solution at room temperature. Stirring of this solution at room temperature for 4 h, followed by quenching, extraction, and distillation, led to the isolation of 7.9−8.6 g (79−86% yields) of the α-aryl esters.

Three aspects of the catalyst loading warrant comment. First, the amount of catalyst needed for the α-arylation of methyl isobutyrate is only 0.1 mol %, and the amount of palladium needed for reaction of the propionate is only 0.8 mol %. Second, the amount of ligand is equal to the amount of palladium and is easily removed. Third, less catalyst was required for the reactions on larger scale than was required for reactions on a 1 mmol scale. In particular, full conversion was observed for the arylation of *tert*-butyl propionate on a 10 g scale in the presence of 0.05% catalyst, but full conversion to the α-aryl ester was not observed with this amount of catalyst when conducting the reaction on a 1 mmol scale.

In summary, we have shown that the coupling of esters at methyl, methylene and methine positions occurs with a variety of bromoarenes with practical loadings of palladium and ligand when conducted with the dimeric Pd(I) species {[P(*t*-Bu)$_3$]PdBr}$_2$ as catalyst. The reactions occur under mild conditions and can be conducted easily without a drybox and on substantial scale.

Acknowledgment. We thank the NIH (GM-58108) for support of this work and Johnson-Matthey for palladium complexes. We thank Ryan DeLuca from the University of Illinois at Urbana-Illinois for checking experimental procedures and help with text editing.

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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