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Efficient Synthesis of α-Aryl Esters by Room-Temperature Palladium-Catalyzed Coupling of Aryl Halides with Ester Enolates

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Abstract: A catalytic amount of $Pd(dba)_2$ ligated by either carbene precursor *N,N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium (**1**) or P(*t*-Bu)$_3$ mediated the coupling of aryl halides and ester enolates to produce α-aryl esters in high yields at room temperature. The reaction was highly tolerant of functionalities and substitution patterns on the aryl halide. Improved protocols for the selective monoarylation of *tert*-butyl acetate and the efficient arylation of α,α-disubstituted esters were developed with $LiNCy_2$ as base and P(*t*-Bu)$_3$ as ligand. In addition, *tert*-butyl esters, such as those of Naproxen and Flurbiprofen, were prepared from *tert*-butyl propionate and aryl bromides in high yields in the presence of $Pd(dba)_2$ and the hindered, saturated heterocyclic carbene ligand precursor.

Introduction

A classic method to construct C−C bonds involves deprotonation α to a carbonyl group and addition of the resulting nucleophile to electrophiles such as aldehydes, ketones, Michael acceptors, and alkyl halides.[1] Methods to attach enolate nucleophiles to an aromatic ring, however, are more limited.[2,3] Ketone enolates have been coupled with aryl radicals under thermal[4] and photolytic[5] conditions. Aryllead(IV) species have been coupled to cyanoacetates, malononitriles,[6] β-keto esters,[7] and malonates[8] to give the α-arylated products, but stoichiometric amounts of lead are undesirable for most applications. Barton used bismuth reagents to arylate ketones, diketones, and β-keto esters,[9] but only one of the three aryl groups is transferred, and few of these reagents are commercially available. Cyanoacetates and malonates have also been arylated in the presence of manganese,[10,11] copper,[12] and cerium[13] salts, but these procedures were limited to aryl iodides and they gave moderate yields of regioisomeric products.

Metal-catalyzed cross-coupling reactions have been used widely to connect two sp^2 carbon centers.[14−17] The formation of sp^3-sp^2 C−C bonds is less common, and high-yield examples with reagents that display functional group tolerance are generally limited to terminal or cyclic alkylboranes[18,19] and -zinc reagents.[20,21] The coupling of iodo- and bromobenzene, as well as vinyl bromides, with *tert*-butyl acetate in the presence of stoichiometric $NiBr_2$ and 25 mol % BuLi was reported a number of years ago.[22] Moreover, electrochemical, metal-mediated enolate coupling reactions have been reported.[23,24] These results suggested that a metal-catalyzed route could be developed for the arylation of ester enolates. Palladium-catalyzed coupling of Reformatsky reagents[25] and tin enolates[26] was reported about 15 years ago, while a protocol involving a combination of copper fluoride and silylketene acetal[27] was developed more recently.

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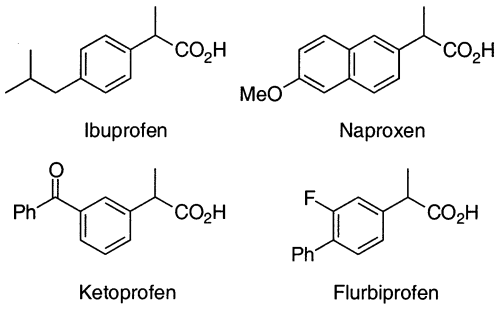
However, the scope of these reactions was narrow, the yields were variable, and the procedures involved separate preparation of zinc enolates, tin enolates, or silylketene acetals prior to the arylation reaction in all three cases. The coupling of aryl boronic acids with α-bromo acetates under Suzuki−Miyaura conditions was reported recently by Goossen.[28]

Over the past few years, we and others have developed palladium-catalyzed procedures for the α-arylation of ketones,[29−38] malonates,[31,34,39] and cyanoacetates,[39] as well as the preparation of oxindoles by an intramolecular amide α-arylation.[40,41] The coupling of aryl halides with ester enolates would provide easy access to α-aryl esters, including precursors to α-aryl propionic acids such as Ibuprofen, Ketoprofen, Naproxen, and Flurbiprofen, which are used extensively in the treatment of inflammatory diseases and for the relief of pain.[42,43]



We showed recently that the rates and yields for reductive elimination from arylpalladium enolate complexes were similar for complexes of enolates derived from ketones, esters, or amides.[44] Because the coupling step occurred from complexes of ketone and ester enolates with similar rates and yields and α-arylations of ketones occurred in a general fashion,[29−33,35−38] it seemed that a general coupling of ester enolates would occur if the palladium enolate could be generated in high yield. Rathke showed many years ago that *tert*-butyl esters generate more stable enolates than less hindered alkyl esters.[45,46] Thus, we initiated our studies with *tert*-butyl acetate and propionate as substrate. Effective arylation would require that the catalytic coupling occur faster than any decomposition or condensation of the alkali metal enolate. As a result, the recently developed, highly efficient catalysts for coupling reactions proved critical to the development of clean arylation of esters.

The palladium-catalyzed α-arylation of esters[47] was reported independently by Buchwald[48] with biphenylphosphines and by our group[49] with both carbene and trialkylphosphine ligands. Miura earlier reported three reactions of phenyl iodide or bromide with methyl phenylacetate in low to modest yield with PPh_3-ligated palladium or ligandless palladium.[36] Buchwald's procedure required 2 equiv of ester relative to the aryl halide, and the coupling was conducted at elevated temperatures with relatively high catalyst loadings (3 mol %, 70 °C). Miura's reactions were conducted at an even higher 100−130 °C. We found that reactions with only a slight excess of ester occurred at room temperature in the presence of 2 mol % $Pd(dba)_2$ and heterocyclic carbene precursor *N*,*N*′-bis(2,6-diisopropylphenyl)4,5-dihydroimidazolium (**1**) or P(*t*-Bu)$_3$, but an excess of ester and base was required for the arylation of α,α-disubstituted esters. We now present a full account of the arylations of esters with carbene precursor **1** and P(*t*-Bu)$_3$. These studies produced improved protocols that increased the scope and efficiency of the arylation of *tert*-butyl acetate and α,α-disubstituted esters and addressed mechanistic issues about the origin of the high selectivity from the arylation of *tert*-butyl acetate.

Results and Discussion

1.1. Conditions for the α-Arylation of *tert*-Butyl Acetate and Scope of the Coupling. Successful arylation of acetates required careful selection of ester, solvent, base, and ligand.[50] Because most acetate enolates are unstable, we focused our effort on reactions of *tert*-butyl acetate that forms an enolate that is stable in solution for several hours at room temperature.[45,46] We initially tested a variety of ligands for the reaction of this ester with 4-*tert*-butylbromobenzene in the presence of alkali metal *tert*-butoxide and hexamethyldisilylamide bases, which had been used previously for the arylation of ketones and amides. Screening of the ligands was conducted with 2.3 equiv of base to ensure that the base or starting enolate would not be fully quenched by the more acidic product during the reaction. Reactions catalyzed by $Pd(dba)_2$ and carbene ligand precursor **1** occurred in quantitative yields without formation of the diarylation product when this excess quantity of lithium hexamethyldisilazide was used as base. These couplings occurred in the highest yields in aromatic solvents. No product was formed in ether solvents.

A few of the biaryldialkylphosphines developed by Buchwald gave yields above 90% under similar conditions, but none we tested were as effective as the carbene generated from **1**. Complexes of PCy(*t*-Bu)$_2$, PCy$_2$(*t*-Bu), and PAd$_2$(*n*-Bu)[51,52] catalyzed the coupling in slightly lower yields that ranged from 80 to 88%, while reactions catalyzed by complexes of P(*t*-Bu)$_3$[53,54] or several of the adamantyl ligands were less selective for formation of the monoarylation product when this base was used.[55,56] Reactions attempted with carbene precursor **1** and *tert*-

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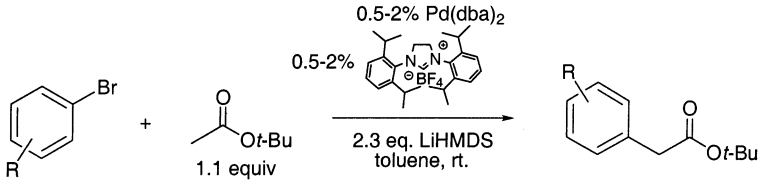
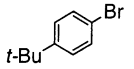
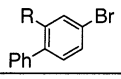
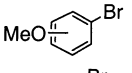
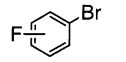
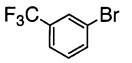
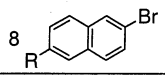
Table 1. Arylation of *tert*-Butyl Acetate Catalyzed by $Pd(dba)_2$ and Carbene Precursor **1**



Entry	Substrate		Cat. loading	Time	Isolated yield
1			0.5%	12h	92%
2	PhBr		1.0%	12h	87%
3			0.5%	12h	98%[a]
4		R=H R=F	0.5% 1.0%	15h 12h	93% 80%
5		*o* *m* *p*	2.0% 0.5% 1.0%	12h 12h 12h	87% 88% 85%
6		*m* *p*	1.0% 1.0%	12h 12h	91% 90%
7			1.0%	12h	88%
8		R=H R=OMe	0.5% 1.0%	12h 12h	90% 60%

[a] $P(t\text{-Bu})_3$ was used as a ligand.

butoxide bases did not occur, and those conducted with NaHMDS or KHMDS gave lower yields because of competing diarylation (NaHMDS) and hydrodehalogenation (KHMDS). Reactions conducted with dialkylamide bases and palladium ligated by the carbene generated from **1** also occurred in low yield.

The scope of the coupling of *tert*-butyl acetate with aryl bromides in the presence of $Pd(dba)_2$ and carbene precursor **1** as catalyst and HMDS as base is shown in Table 1. Reactions of this ester with alkyl- and aryl-substituted aryl bromides occurred in high yields (entries 1−4). Electron-rich *o*- and *p*-bromoanisoles, as well as the less electron-rich *m*-bromoanisole, reacted with *tert*-butyl acetate to give the coupled product in high yield under these conditions (entry 5). Electron-withdrawing fluoro- and trifluoromethyl groups on the aryl bromide were also tolerated (entries 6 and 7). The reaction occurred in high yield with bromonaphthalenes, as shown in entry 8. The most hindered aryl halides reacted in higher yields with a catalyst bearing $P(t\text{-Bu})_3$. For example, bromomesitylene reacted with *tert*-butyl acetate in higher yield in the presence of this catalyst than in the presence of catalysts bearing the carbene from 1 (entry 3). *tert*-Butyl acetate did not couple with pyridyl halides in the presence of this combination of base and catalyst.

1.2. Improved Conditions for the α-Arylation of *tert*-Butyl Acetate. During our studies described below on ester arylations that form fully substituted carbon centers, we uncovered a protocol that improved significantly the α-arylation of *tert*-butyl acetate. Reactions of aryl halides with the lithium enolate of *tert*-butyl acetate generated prior to addition of the palladium catalyst and aryl halide occurred with high selectivity for monoarylation of *tert*-butyl acetate and with less catalyst, ester, and base. However, these improved reactions also required careful selection of ligand and base. It was critical to generate the enolate with $LiNCy_2$ as base and to conduct the coupling process with $P(t\text{-Bu})_3$ as ligand to observe high yields when using preformed enolate. Lower yields and lower selectivity for the monoarylation product were observed from reactions conducted by mixing the hexamethyldisilazide bases with ester prior to addition of the same catalyst and aryl halide. Reaction of the enolate from *tert*-butyl acetate and $LiNCy_2$ in the presence of catalysts generated from carbene precursor **1** or other ligands tested originally with lithium hexamethyldisilazide base occurred in significantly lower yield. Moreover, reactions of the enolate generated from other alkylamide bases also occurred in lower yields.

Table 2 summarizes the yields of reactions catalyzed by a combination of $Pd(dba)_2$ and $P(t\text{-Bu})_3$ in the presence of $LiNCy_2$ as base. Reaction of 1.1 equiv of *tert*-butyl acetate with $LiNCy_2$ at room temperature in toluene solvent, followed by addition of a solution of this preformed enolate to the aryl bromide and catalyst, generated the coupled product in high yield. In many cases, consumption of the aryl bromide was complete within minutes (vide infra), although the products were generally isolated after 8−24 h. By this procedure, reactions in the presence of 0.2−1.0 mol % of $Pd(dba)_2$ and $P(t\text{-Bu})_3$ formed the monoarylated product selectively at room temperature in isolated yields that were generally higher than they were under the conditions of reactions summarized in Table 1. Electron-rich (entry 4) and electron-poor (entry 6) aryl halides generated the products in high yields. In addition, fluorinated aryl bromides gave the products in high yields (entry 5). These reactions did not occur with pyridyl halides.

2. Arylation of *tert*-Butyl Propionate. The α-arylation of *tert*-butyl propionate proceeded smoothly in the presence of the catalyst generated from $Pd(dba)_2$ and carbene precursor **1**. Results of the α-arylation of *tert*-butyl propionate are shown in Table 3. Reactions in the presence of NaHMDS as base occurred in higher yields than did those containing LiHMDS. In general, reactions of the enolate of *tert*-butyl propionate formed from $LiNCy_2$ prior to addition of catalyst and aryl halide formed the desired product in lower yields than did reactions of the ester in the presence of hexamethyldisilazide base. However, certain reactions did occur in higher yields when the preformed enolate of *tert*-butyl propionate was used. For example, the reaction of *tert*-butyl propionate with *p*-(trifluoromethyl)bromobenzene pro-

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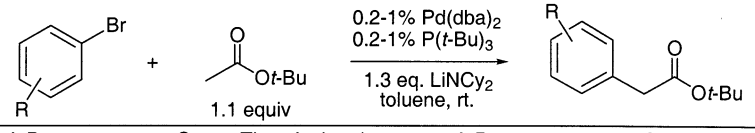
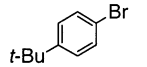
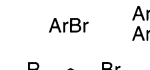
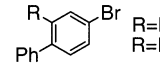
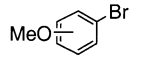
Table 2. Arylation of the Enolate of *tert*-Butyl Acetate Formed from $LiNCy_2$ in the Presence of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ as Ligand



Entry	ArBr		Cat. loading	Time	Isolated yield
1			0.5%	8h	87%
2		Ar=Ph	0.2%	24h	92%
		Ar=mes	0.2%	10h	97%
3		R=H	0.5%	15h	96%
		R=F	1.0%	15h	93%
4		*m*	0.5%	24h	94%
		p	0.5%	24h	95%

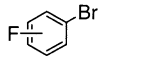
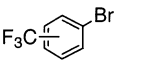
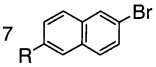
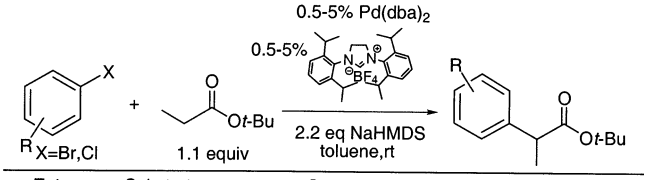
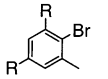
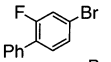
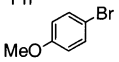
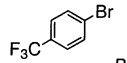
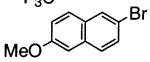
Entry	ArBr		Cat. loading	Time	Isolated yield
5		*o*	1.0%	15h	88%
		m	1.0%	15h	95%
		p	1.0%	15h	95%
6		*o*	1.0%	15h	82%
		m	0.5%	24h	85%
		p	1.0%	10h	94%
7		R=H	0.2%	15h	93%
		R=OMe	0.5%	15h	96%

Table 3. Arylation of *tert*-Butyl Propionate Catalyzed by $Pd(dba)_2$ and Carbene Precursor



Entry	Substrate		Cat. loading	Time	Isolated yield
1	PhX	X=Br	0.5%	12h	75%
		X=Cl	1.0%	12h	71%
2		R=H	0.5%	12h	88%
		R=Me	1.0%	12h	74%
3			2.0%	12h	66%
4			1.0%	12h	82%
5[a]			5%	12h	74%
6			1.0%	12h	83%

[a] 1.3 equiv of preformed enolate from reaction with $LiNCy_2$ was used.

ceeded in high yield when the lithium enolate was formed from $LiNCy_2$ prior to addition of aryl halide and catalyst. In contrast, no reaction occurred between *tert*-butyl propionate and this aryl halide in the presence of NaHMDS as base and even 5 mol % catalyst. Moreover, no reaction occurred with the sodium enolate generated from $NaNCy_2$ prior to addition of aryl halide and catalyst.

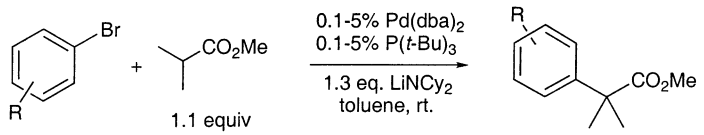
3.1. Development of Reaction Conditions for the Arylation of α,α-Disubstituted Esters. A match of the steric bulk of the substrate with that of the ligand allowed for our initial formation of quaternary carbons by ester arylation, and the use of $LiNCy_2$ as base produced our most efficient arylations of α,α-disubstituted esters. Reactions of *tert*-butyl isobutyrate in the presence of LiHMDS generated a mixture of products that included those formed from coupling of the silylamide with the aryl halide,[57] but reactions of methyl isobutyrate occurred to form the α-arylated material as the major product. With 1−2 equiv of base, however, the reaction of methyl isobutyrate with 4-*tert*-butylbromobenzene produced, as a side product, the silylamine from C−N coupling. The reaction even produced this product when the more hindered $LiN(SiMePh_2)_2$ and $LiN(SiMe_2Ph)_2$ were used as base.[40] Wide ranges of solvents and ligands were tested, but the C−N coupling of this base[57] was suppressed effectively only when 2.0 equiv of the ester and 3.0 equiv of base were used in toluene solvent and the combination of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ was used as catalyst. Reactions of enolates generated from sodium and potassium hydride, alkoxide, or amide bases generally occurred with low conversions, except for those generated from NaHMDS. Reactions in the presence of this base gave mainly arene.

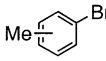
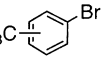
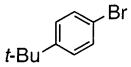
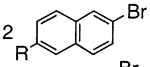
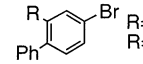
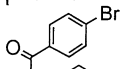
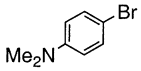
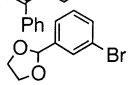
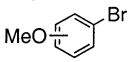
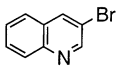
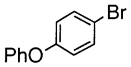
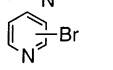
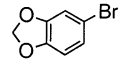
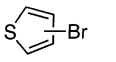
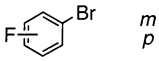
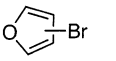
The use of specific lithium amide bases allowed for the arylation of α,α-disubstituted esters to be conducted without competing C−N coupling and without excess of ester or base. A series of lithium amides were tested for the reaction of methyl isobutyrate with 4-*tert*-butylbromobenzene because LiN(*i*-Pr)-Cy is effective at generating isolable ester enolates.[45,46] Lithium amides had not been useful bases for previous couplings of enolates with aryl halides. Yet, the coupling occurred rapidly when LDA was used to generate the enolate and formed 76% yield of coupled product, although the reaction proceeded to only 90% conversion in the presence of 1 mol % catalyst. Arene was formed in 14% yield. Reactions in the presence of LiN(*i*-Pr)Cy were less selective and also did not proceed to completion. Reactions in the presence of 2,2,6,6-tetramethylpiperazide occurred to full completion, but only 71% yield of product was formed. Finally, reactions of the enolate of methyl isobutyrate generated from $LiNCy_2$ completely consumed the aryl halide and formed the arylated ester in an excellent 93% yield with only 7% arene. This reaction occurred most readily in arene solvents. Reactions in pentane and cyclohexane did not proceed to completion, and arene was the major product from reactions in ether solvent. No reaction occurred in Et_3N.

Thus, we tested a wide range of ligands for the reaction of isobutyrate with 4-*tert*-butylbromobenzene in the presence of $LiNCy_2$ base in toluene solvent. The highest yields of the desired product were obtained when employing bulky trialkylphosphine ligands such as $P(t\text{-}Bu)_3$, 1-adamantyldi-*tert*-butylphosphine ((1-Ad)$P(t\text{-}Bu)_2$), $(1\text{-Ad})_2P(t\text{-Bu})$, or ferrocenyldi-*tert*-butylphosphines. Poor yields and conversions were observed when the less bulky PCy_3, $PCy(t\text{-Bu})_2$, $PCy_2(t\text{-Bu})$, and $P(2\text{-Ad})(t\text{-Bu})_2$ were used. The carbene precursors that we tested generated poor

(57) Lee, S.; Jørgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729.

Table 4. Scope of the Arylation of Methyl Isobutyrate



Entry	Substrate		Cat. loading	Time	Isolated yield	Entry	Substrate		Cat. loading	Time	Isolated yield
1			0.1%	18h	87%	10		*m* *p*	0.1% 0.1%	12h 14h	71% 72%
2		*m* *p*	0.1% 0.1%	24h 24h	97% 90%	11		*m* *p*	0.1% 0.1%	24h 24h	89% 86%
3			0.1%	12h	91%	12		R=H R=OMe	0.1% 0.2%	8h 24h	94% 93%
4		R=H R=F	0.05% 0.2%	18h 14h	96% 91%	13			3.0%	16h	73%
5			0.05%	18h	88%	14			2.0%	16h	77%
6		*m* *p*	0.1% 0.1%	24h 24h	97% 90%	15			5.0%	12h	70%
7			0.1%	12h	95%	16		2-Br 3-Br 4-Br[a]	5.0% 5.0% 5.0%	7h 12h 16h	94% 80% 51%
8			0.1%	20h	95%	17		2-Br[b] 3-Br	5.0% 5.0%	9h 9h	91% 71%
9		*m* *p*	0.1% 0.1%	16h 16h	93% 90%	18		2-Br 3-Br	5.0% 5.0%	7h 9h	72% 71%

[a] This aryl halide was used as the HCl salt. A 2.3 equiv amount of $LiNCy_2$ was used. [b] 2:1 ratio of products from α- and β-arylation of the ester; 48% yield of pure α-isomer was isolated.

yields of the α-arylation of methyl isobutyrate. The most convenient and effective combination of palladium and ligand was $Pd(dba)_2$ and $P(t\text{-}Bu)_3$.[53,57,58] The yield was independent of the ratio of ligand to palladium (ranging from 0.33:1 to 3:1), and the rate was similarly fast when an excess or an equimolar amount of ligand relative to $Pd(dba)_2$ was used.

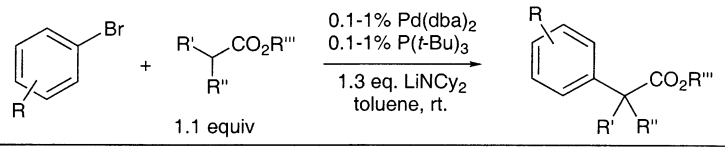
3.2. Scope of the Arylation of α,α-Disubstituted Esters. Methyl isobutyrate was chosen as the benchmark substrate to examine the scope of the reaction with a wide range of aryl bromides. These results are summarized in Table 4. Because competing decomposition of the ester enolates could control the amount of required catalyst, we evaluated the minimum amount that would give suitably fast reactions. A wide range of electron-neutral and electron-donating substituents were tolerated on the aryl bromide (entries 1−3, 5−8). The biphenyl and naphthyl bromides that would generate protected Flurbiprofen and Naproxen analogues gave high yields of the coupled product (entries 4 and 16). In addition, biologically attractive amino, dioxolane, and fluoro functionalities were tolerated. Although dibromoarenes could not be selectively monofunctionalized, chlorobromoarenes generated the monofunctionalized chloro-substituted product in high yield (entries 9 and 10). Although (trifluoromethyl)arenes were suitable substrates, bromobenzaldehydes, methyl or *tert*-butyl bromobenzoates, and bromobenzonitrile generated product mixtures. Bromobenzophenone and the ethylene glycol acetal of bromobenzaldehydes, however, reacted in good yields (entries 13 and 14).

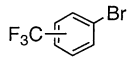
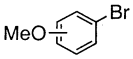
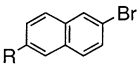
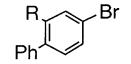
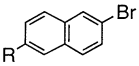
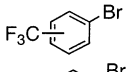
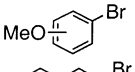
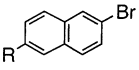
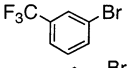
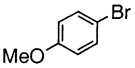
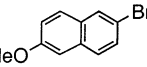
In contrast to reactions of *tert*-butyl acetate and propionate, reactions of methyl isobutyrate occurred with heterocyclic aryl bromides such as bromoquinoline and bromopyridines, -thiophenes, and -furans (entries 15−18), although more catalyst was required than for reactions of bromoarenes. The reactions of all the heterocyclic aryl bromides gave a single product, except for the reaction of methyl isobutyrate with 2-bromothiophene. In this case, products from coupling of the heteroaryl bromide to the α- and β-positions of the ester were observed in a 2:1 ratio. The latter product probably forms by rearrangement of the hindered palladium enolate to a less hindered homoenolate, followed by reductive elimination. This migration could occur by β-hydrogen elimination and reinsertion of the olefin into the metal hydride to form a primary alkyl. We suggest that this sequence is observed only during reaction of bromothiophene because reductive elimination of coupled product from the electron-rich thiophenylpalladium enolate intermediate is slower than it is from the analogous intermediates formed from aryl or other heteroaryl bromides.

Reactions of several other esters were studied to evaluate the scope of the ester component (Table 5). The slightly more hindered methyl 2-methylbutyrate was as reactive as methyl isobutyrate. The isolated yields were high in all cases, and the amount of catalyst required for full conversion of the aryl bromide was lower than 0.5 mol %. Reactions of the more hindered, but more acidic, methyl 2-phenylpropionate also occurred in good yields by the standard protocol. A slightly higher catalyst loading of 1 mol % was required, but the coupled product was formed in good to excellent yields with various

(58) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.

Table 5. Scope of the Coupling of α,α-Disubstituted Methyl and Benzyl Esters



Entry	Substrate		Cat. loading	Time	Isolated yield	Entry	Substrate		Cat. loading	Time	Isolated yield
R'=Me, R''=Et, R'''=Me											
1		*m*	0.1%	18h	87%	4		*m*	0.1%	10h	76%
		p	0.1%	14h	81%			*p*	0.1%	10h	83%
2		R=H	0.1%	10h	78%	5		*m*	0.1%	16h	96%
		R=F	0.1%	10h	83%			*p*	0.2%	10h	99%
3		*m*	0.2%	12h	91%	6		R=H	0.1%	12h	88%
		p	0.2%	12h	90%			R=OMe	0.2%	10h	99%
R'=Me, R''=Ph, R'''=Me											
7		*m*	0.5%	8h	89%	9		R=H	0.5%	15h	93%
		p	0.5%	8h	87%			R=F	1.0%	15h	97%
8		*m*	1.0%	15h	82%	10		R=H	0.5%	15h	78%
		p	1.0%	15h	84%			R=OMe	1.0%	15h	82%
R',R''=-(CH2)5-, R'''=Me											
11		*m*	0.2%	24h	92%	14		*m*	0.5%	8h	90%
		p	0.2%	24h	95%			*p*	0.5%	10h	78%
12		R=H	0.5%	18h	86%	15		*m*	0.1%	20h	94%
		R=F	0.5%	18h	90%			*p*	0.2%	12h	94%
13		*m*	0.1%	24h	94%	16		R=H	0.1%	18h	91%
		p	0.1%	24h	82%			R=OMe	0.1%	10h	97%
R'=Me, R''=Me, R'''=Bn[a]											
17		*m*	1.0%	12h	93%	20			1.0%	12h	80%
		p	1.0%	12h	90%						
18			1.0%	12h	90%	21			1.0%	12h	83%
19			1.0%	12h	82%	22			1.0%	12h	88%

[a] 1.5 equiv of ester and 1.8 equiv of $LiNCy_2$ were employed.

aryl bromides. Cyclic esters such as methyl cyclohexylcarboxylate reacted similarly to acyclic systems. Again, a slightly higher catalyst loading of 0.5−1.0 mol % was required, but electron-neutral, -rich, and -poor aryl bromides, as well as biphenyl bromides and bromonaphthalenes, reacted with this ester in high yields in all cases.

Because benzyl esters are more conveniently converted to carboxylic acids than methyl esters, we evaluated reactions of benzyl isobutyrate (entries 17−22 of Table 5). In contrast to the 1.1 equiv of methyl isobutyrate, 1.5 equiv of the benzyl esters was required to obtain good yields; reactions containing less ester occurred in lower yields or with incomplete conversion of the aryl halide. Yet, the palladium-catalyzed arylation of these benzyl esters afforded the desired product in high yields when 1.5 equiv of ester and 1 mol % catalyst were used. The slightly lower reactivity of this benzyl ester is consistent with a deceleration of the reaction as the size of the substituent on the oxygen of an α,α-disubstituted ester is increased.

4. Conditions for Convenient Use of P(*t*-Bu)$_3$ as Ligand. Conditions were developed for convenient arylation of esters in the presence of catalysts generated from the air-sensitive P(*t*-Bu)$_3$. First, 1 mol % of the catalyst was generated by adding P(*t*-Bu)$_3$ by syringe from a commercially available stock solution in toluene. This procedure generated a catalyst that induced formation of the coupled product in high yield in just 10 min at room temperature when the enolate was generated from 1.1 equiv of methyl isobutyrate and 1.3 equiv of $LiNCy_2$ in toluene. Presumably, similar results would be observed from reactions initiated with the air stable HBF_4 salt of P(*t*-Bu)$_3$, which is now commercially available.[59] A 1:1 ratio of the commercially available and air-stable Pd[P(*t*-Bu)$_3$]$_2$ and Pd(dba)$_2$[60] and the air stable palladium(I) species [PdBrP(*t*-Bu)$_3$]$_2$[61,62] also generated active catalysts. Reactions catalyzed by these two systems were approximately four times slower, but the reaction yields were similar. Reactions catalyzed by Pd[P(*t*-Bu)$_3$]$_2$ alone formed the coupled product, but the selectivity was lower and the reaction required a longer time of 2 h.

5.1. Comments on the Relationship between pK_a of the Base and Selectivity. Dialkylation of alkali metal enolates is commonly observed,[63] but diarylation of the alkali metal enolates from the palladium-catalyzed coupling occurs for different reasons. The enolate of the coupling product is more

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stable than the starting enolate. Moreover, the palladium enolate intermediates are less aggregated than the alkali metal enolates[64] and are most likely monomeric. The palladium-catalyzed coupling of acetate enolates involves multiple equilibria. The ratio of the two enolates generated from the starting and product esters is substantially different at different stages of the reaction and can be substantially different when bases are used that have conjugate acids with different pK_a values.

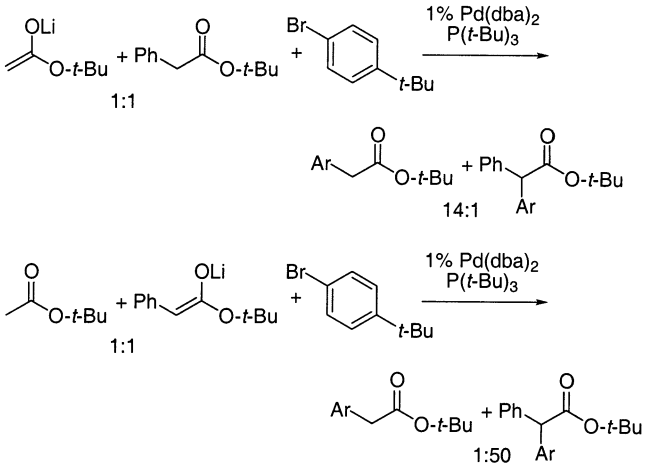
The pK_a data that are relevant to the equilibria of enolates in the coupling process are available in THF[65] and DMSO.[66,67] Values for the same substrate in THF and DMSO are often within 2−3 pK_a units of each other, with the value in THF generally the higher of the two. Our catalytic reactions were conducted in the less polar solvent toluene in which pK_a values will be even higher and ion pairs will not be solvent separated. Thus, the literature pK_a values can help interpret results but do not provide quantitative predictions on the population of species in the reaction solutions.

The pK_a of hexamethyldisilazane in THF is 25.8.[65] The pK_a of *tert*-butyl acetate in DMSO is 30.3, and the pK_a of *tert*-butyl phenylacetate in DMSO is 23.6.[67] Thus, it is likely that reactions conducted with 1 equiv of LiHMDS base will be initiated with only small concentrations of the acetate enolate, and the silylamide base will be quenched by the coupled product in toluene solvent. These data suggest that 1 equiv of base to starting ester will be consumed at 50% conversion and that the product will be the dominant enolate in solution after 33% conversion. If an excess of base is used, then some starting enolate will be present throughout the reaction and the major product is formed from this more basic, less hindered enolate. We do not have a detailed explanation for the higher selectivity observed from reactions conducted with lithium hexamethyldisilazide versus those conducted with sodium hexamethyldisilazide.

Dialkylamines have pK_a values in DMSO that exceed 40.[66] Thus, mixing of *tert*-butyl acetate and this base will generate the enolate quantitatively. This complete formation of enolate contrasts with the partial formation of enolate from the silylamide bases and *tert*-butyl acetate. We were surprised to find that 1.2 equiv of the enolate provided the product from monoarylation with high selectively. If proton exchange is faster than the palladium-catalyzed chemistry, then reaction with 1 equiv of enolate would consume the starting enolate at 50% conversion. Thus, the difference in pK_a values requires that the acetate enolate be roughly 10^8 times more reactive than the phenylacetate enolate or that proton transfer between esters be slower than the coupling process.

More substituted arylpalladium enolates undergo faster reductive elimination.[44] Thus, a greater population of palladium acetate enolate or faster formation of this intermediate must account for the difference in reactivity if equilibration of the alkali metal enolates has occurred. Although this trend in stability has been observed,[44] the stabilities of primary and secondary alkyls have been measured previously,[68] and the magnitude of the difference in stability of the palladium enolates

Scheme 1



required by the conditions of enolate equilibration is too large. Thus, the high selectivity must arise from different rates for transmetalation of the *tert*-butyl acetate vs *tert*-butyl phenylacetate enolates if the proton transfer equilibrium is fully established. We tested these relative rates by studying a single turnover. Reaction of [(1-Ad)P(*t*-Bu)$_2$]Pd(Ph)(Br)[69] with a 1:1 mixture of the enolates gave a 5:1 ratio of products instead of the 18:1 ratio observed from the catalytic reactions conducted with this ligand. Moreover, reactions of [(1-Ad)P(*t*-Bu)$_2$]Pd(Ph)(Br) with the lithium enolate of *tert*-butyl acetate and with the enolate of *tert*-butyl phenylacetate both gave the coupled product essentially instantaneously.

Thus, we tested the alternative hypothesis that the catalytic reaction is faster than proton transfer. The proton transfer between the enolate of *tert*-butyl acetate generated from LiNCy$_2$ and *tert*-butyl phenylacetate required hours. The half-life of this process was on the order of 0.5−1 h. In contrast, the catalytic coupling was shown to be complete within 15 min when the reaction progress was checked by GC. We confirmed these relative rates by conducting reactions with one ester and the enolate of a second ester together (Scheme 1). The catalytic reaction of the enolate of *tert*-butyl acetate with 4-bromo-*tert*-butylbenzene in the presence of 1 equiv of added *tert*-butyl phenylacetate occurred with 14:1 selectivity for reaction with the acetate enolate. In contrast, reaction of the enolate of *tert*-butyl phenylacetate with 4-bromo-*tert*-butylbenzene in the presence of *tert*-butyl acetate occurred with 50:1 selectivity for reaction with the phenylacetate enolate. These data confirm that the product is generated from the starting enolate and that the palladium-catalyzed coupling process is faster than proton transfer between the enolates.

5.2. Effect of Amine on the Arylation of Esters. The difference between the reactivity of enolates formed from LiNCy$_2$ and LDA in the α-arylation of methyl isobutyrate was unexpected because a similar enolate would be formed.[70] Yet, ligands affect the solvation[71] and the mechanism by which LiHMDS participates in acid−base reactions.[72] Thus, a brief set of experiments was conducted to investigate the potential effect of the neutral amine on the reactivity of the ester enolate.

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Deprotonation of the ester with lithium tetramethylpiperazide (LiTMP), followed by addition of diisopropylamine, dicyclohexylamine, or *N*-isopropylcyclohexylamine, generates the same enolate aggregates as when the enolate is generated from LDA, $LiNCy_2$, or LiN(*i*-Pr)Cy alone because of the hindrance of LiTMP. The enolates generated from addition of LiTMP, followed by $HNCy_2$ or $HN(i\text{-Pr})_2$, reacted in yields more similar to those observed from reactions of the enolates generated from $LiNCy_2$ or $LiN(i\text{-Pr})_2$ than from reactions of the enolates generated from LiTMP alone. These results suggested that the presence of the amine in the enolate aggregate influenced the palladium chemistry. However, reaction of the enolate formed from LiTMP and Cy(*i*-Pr)NH occurred in higher yields than those of the enolate generated from LiN(*i*-Pr)Cy alone. Perhaps, an impurity present in the noncrystalline LiN(*i*-Pr)Cy influenced the reaction when this base was used alone to form the enolate.[73,74]

5.3. Comments on Ligand Effects. The high activity of palladium catalysts generated from strongly electron-donating trialkylphosphines or *N*-heterocyclic carbenes toward C−C and C−N bond-forming reactions stems, in part, from the ability of these ligands to stabilize the zerovalent palladium species and to promote oxidative addition.[75−77] In many cases high yields also rely on the ability of these ligands to promote reductive elimination.[78−80] Both the high overall activity and the high selectivity for reductive elimination over β-hydrogen elimination are important for successful coupling of ester enolates. Although we cannot explain the influence on activity of subtle steric differences among related ligands, it is clear that less active catalysts generated the product in lower yield even at long reaction times. Fast rates for the coupling are crucial for the arylation of esters because the catalytic process must occur faster than competing decomposition of the ester enolate. In addition, most of the enolate intermediates can undergo β-hydrogen elimination. Complexes of several ligands simply catalyzed the reduction of aryl halides in the presence of the enolate. Thus, the sterically hindered ligands that create catalysts for coupling with broad scope must be efficient at promoting reductive elimination at the expense of β-hydrogen elimination, even when the enolate is similar in structure to a tertiary alkyl. Tertiary alkyls have generally undergone homolysis or β-hydrogen elimination more often than they have undergone productive processes such as reductive elimination.[81]

Conclusion

Two sets of conditions that allow for the effective coupling of ester enolates and aryl halides in the presence of palladium catalysis have been uncovered. Reactions of acetates and propionates occurred when protected as the *tert*-butyl esters because this hindered group suppresses competing decomposition and Claisen condensations of the ester enolate. A catalyst generated from $Pd(dba)_2$ and the *N*-heterocyclic carbene precursor **1** in the presence of LiHMDS mediated the coupling of *tert*-butyl acetate, and the same catalyst in the presence of NaHMDS mediated the coupling of *tert*-butyl propionate. However, we found that enolates of *tert*-butyl acetate and α,α-disubstituted esters formed from lithium dicyclohexylamide prior to addition of catalyst and aryl halide reacted in higher yields to form aryl acetic acid esters and products with quaternary carbons. In these cases catalysts generated from $Pd(dba)_2$ and $P(t\text{-Bu})_3$ were most active.

Experimental Section

General Methods. Reactions were conducted using standard drybox techniques. However, $P(t\text{-Bu})_3$ is available as a solution in toluene or as an air-stable HBF_4 salt (Strem), lithium hexamethyldisilazide is available as a solution in hexanes, sodium hexamethyldisilazide is available as a solution in toluene (Aldrich), and $Pd(dba)_2$ can be weighed in air without decomposition. Thus, addition of these reagents to a degassed solution of toluene and aryl halide using standard syringe techniques provides an alternative procedure to those described below. When tested, equivalent yields by GC were obtained without use of the drybox. ^1H and ^{13}C NMR spectra were recorded at 400 MHz with tetramethylsilane or residual protiated solvent used as a reference, and coupling constants are reported in Hertz (Hz). Chromatographic purifications were performed by flash chromatography on 200−400 mesh silica gel. Yields for final products in all tables refer to isolated yields and are the average of at least two runs. Spectroscopic data and combustion analyses are reported for all new compounds. Previously reported products were isolated in greater than 95% purity as determined by ^1H NMR and capillary gas chromatography (GC). All ^{13}C NMR spectra were proton decoupled. GC analyses were performed with a DB-1301 narrow-bore column and 120 °C/min temperature ramps. GCMS spectra were obtained using an HP-1 methyl silicone column. All reagents and bases were purchased from Aldrich and used without further purification. $Pd(dba)_2$[82] and $NaNCy_2$[83] were prepared according to literature procedures. Toluene was distilled from sodium and benzophenone and stored in a drybox.

General Procedure for the Arylation of Esters in the Presence of LiHMDS or NaHMDS. To a screw-capped vial containing carbene precursor **1** or $P(t\text{-Bu})_3$ (0.0050 mmol), $Pd(dba)_2$ (0.0050 mmol), and LiHMDS (2.3 mmol, for *tert*-butyl acetate) or NaHMDS (2.3 mmol, for *tert*-butyl propionate) were added aryl halide (1.0 mmol) and ester (1.1 mmol) followed by toluene (2.5 mL). The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The heterogeneous reaction mixture was stirred at room temperature and monitored by GC. Upon consumption of aryl halide, the crude reaction was diluted with Et_2O and was quenched with aqueous NH_4Cl. The organic phase was washed with a saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The organic solution was concentrated in vacuo. The residue was then purified by chromatography on silica gel using 5% ethyl acetate in hexanes, unless otherwise stated.

General Procedure for the Arylation of Esters in the Presence of $LiNCy_2$. A solution of the ester (1.1 mmol, 1.5 mmol for benzyl esters) in toluene (2 mL) was added to a vial containing 1.3 equiv (1.8 equiv for benzyl esters) of $LiNCy_2$ (1.3 mmol). The solution was stirred for 10 min before it was transferred to a screw-capped vial containing a catalytic amount of $Pd(dba)_2$ and the aryl or heteroaryl halide (1.0

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mmol). Finally, P(*t*-Bu)$_3$ was added from a 0.5 M toluene stock solution. The vial was fitted with a PFTE septum and removed from the drybox. The reaction mixture was stirred at room temperature. The solvent was evaporated under vacuum, and the crude product mixture was purified over silica gel using 5% ethyl acetate in hexanes as the eluent. Alternatively, the crude product mixture was extracted with dichloromethane (10 mL) and 5% aqueous hydrochloric acid (10 mL). The precipitate was removed by filtration, and the organic layer was extracted with 5% aqueous hydrochloric acid (10 mL) and water (10 mL) before it was dried over $MgSO_4$ and concentrated. The residue was filtered through a plug of silica gel, and eluted with 5% ethyl acetate in hexane unless otherwise stated.

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Supporting Information Available: Tables of data from varying reaction parameters, conditions for isolation, spectral and analytical data, and literature references for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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