Palladium-Catalyzed α-Arylation of Esters and Protected Amino Acids

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α-Aryl carboxylic acids and α-aryl amino acids are among the most important carbonyl compounds. These molecules include the profen family of drugs,[1] as well as α-aryl amino acid and acetic acid building blocks.[2,3] Naproxen and ibuprofen are prepared by multistep syntheses.[1] α-Aryl amino acids are generally prepared by Strecker chemistry, which forms the linkage between the α carbon and the final carboxylic acid unit.[4] α-Aryl acetic acids are generally formed from one of several classical reactions that lack functional group tolerance or regiospecificity.

The direct α-arylation of esters and protected amino acids could provide a short, general route to these molecules. One paper 25 years ago described catalytic (20 mol %) coupling of *tert*-butyl acetate with phenyl iodide using BuLi and $NiBr_2$;[5] others describe coupling of Reformatsky reagents[6] or copper enolates,[7] which were generated in two steps from the ester. Although the palladium-catalyzed, direct α-arylation of carbonyl compounds now encompasses many substrates,[8−18] the intermolecular α-arylation of monocarbonyl compounds at the carboxylic acid oxidation level has not been conducted in a general fashion.[10]

We report a set of α-arylations of esters and protected amino acids that reveals both important concepts for direct arylation of carbonyl compounds and useful catalytic systems. First, we show by the choice of ester and base that the formation of the palladium enolate complexes controls the reaction scope as much as the chemistry of the palladium enolate, and second we show that glycinates are activated for direct coupling by unsaturated amine protective groups. Using this information, we uncovered two readily available catalyst systems that provide a general, palladium-catalyzed reaction of esters with aryl halides to form *tert*-butyl- or methyl-protected α-aryl carboxylic acids, and a general, palladium-catalyzed reaction of imine-protected glycinates with aryl halides to form protected, α-aryl amino acids (Scheme 1).

Recently, we showed that the rates for reductive elimination from arylpalladium ketone, ester, and amide enolate complexes were nearly identical.[19] These results implied that the arylation of esters was deterred by the instability of the alkali metal enolate and slow formation of the palladium enolate complex, not by unfavorable reductive elimination. Thus, reactions should occur using more stable ester enolates and a strong enough base to generate the alkali metal and subsequent palladium enolate efficiently. Therefore, we focused initially on reactions of *tert*-butyl esters. We evaluated reactions using *tert*-butoxide and ultimately hexamethyldisilazide (HMDS) bases, which we had shown previously to induce some successful arylation of amides.[10] Neither base can reduce the palladium by β-hydrogen elimination.

Scheme 1

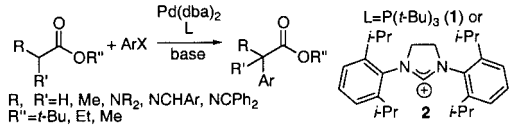

Table 1. Palladium-Catalyzed α-Arylation of Esters[a]

Entry	ArX	% Pd	L	Yield
	Ester= O-*t*-Bu			
1	4-*t*-Bu-C6H4-Br	0.5%	**2**	92%
2	C6H5-Br	1%	**2**	87%
3	2-Me-C6H4-Br	0.5	**2**	98%
4	2-Ph-C6H4-Br	0.5%	**2**	92%
5	2-MeO-C6H4-Br	0.5%	**2**	88%
6	2-MeO-C6H4-Br	2%	**2**	87%
7	1-Br-naphthalene	0.5%	**2**	90%
8	3-MeO-C6H4-Br	1%	**2**	85%
	Ester= O-*t*-Bu			
9	4-X-C6H4-Br, X=Br	0.5%	**2**	75%
10	4-X-C6H4-Br, X=Cl	1%	**2**	71%
11	3-Me-C6H4-Br	0.5%	**2**	88%
12	2-Me-C6H4-Br	1%	**1**	74%
13	2-MeO-C6H4-Br	1%	**2**	83%
Entry	Ester			
	ArX= *p*-*t*-BuC6H4Br			
14	OEt	5%	**2**	95%
15	OMe	5%	**2**	98%
16	N(Me)-CH2-C(=O)OEt	2%	**1**	84%[b]
17	OMe	0.5%	**1**	92%[c]

[a] Reactions were conducted for 12 h at room temperature on a 1 mmol scale using 1.1 equiv of ester and 2.3 equiv of Li− (entries 1−8 and 17) or $NaN(SiMe_3)_2$ (entries 9−15) as base. The catalyst consisted of a 1:1 mixture of $Pd(dba)_2$ and ligand. Yields are for isolated material of >95% purity by GC or combustion analysis. [b] Reaction conducted with K_3PO_4 as base at 100 °C. [c] Two equiv of ester.

Table 1 summarizes our results from reactions of esters. An evaluation of several simple and inexpensive ligands showed that a combination of $Pd(dba)_2$[24] and tri-*tert*-butylphosphine (**1**) or the hindered carbene precursor **2** (Scheme 1)[21−23] generated catalysts that couple esters with aryl halides. Although *tert*-butoxide was a strong enough base to couple ketones with aryl halides, low conversions of aryl halide were observed from reactions of esters. Instead, HMDS bases were more effective and led to reactions of aryl bromides at room temperature. The use of lithium HMDS

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Table 2. Palladium-Catalyzed Arylation of Protected Amino Acids[a]

Entry	Ar	Yield(%)	Entry	Ar	Yield(%)
ester = Ph_2CN–CH_2–CO_2Et			19		87
1	C_6H_5Br	88	20	3-Bromopyridine	85
2	C_6H_5Cl	82	21	3-Chloropyridine	80
3	C_6H_5Br	90[b]	22	2-$MeOC_6H_4Br$	89
4	2-MeC_6H_4Br	84	ester = ArHCN–CH_2–CO_2Et, Ar = *p*-$MeOC_6H_4$		
5	2-MeC_6H_4Cl	81			
6	4-$MeOC_6H_4Br$	85	23	C_6H_5Br	75
7	4-$MeOC_6H_4Cl$	83	24	C_6H_5Cl	67
8	4-FC_6H_4Br	86	25	4-$MeOC_6H_4Br$	71
9	4-FC_6H_4Cl	83	26	2-MeC_6H_4Br	72
10	4-NCC_6H_4Br	89	27		71
11	4-NCC_6H_4Cl	85			
12	4-$MeO_2CC_6H_4Br$	89	28	1-Bromonaphthalene	74
13	4-$F_3CC_6H_4Br$	86	29	2-Bromonaphthalene	74
14	4-$F_3CC_6H_4Cl$	84	30	4-bromobiphenyl	80
15	4-bromobiphenyl	92	31	4-$F_3CC_6H_4Br$	73
16	1-Bromonaphthalene	87	32	4-$F_3CC_6H_4Cl$	67
17	2-Bromonaphthalene	89	33	4-FC_6H_4Br	67
18	4-Bromodiphenyl ether	90			

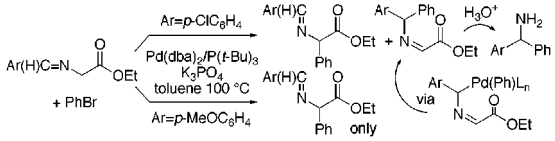
[a] For entries 23−33 the free, neutral α-aryl glycinate was isolated. Yields are for reactions conducted on a 1 mmol scale using 2 mol % $Pd(dba)_2$, 4 mol % P(*t*-Bu)$_3$, 3 equiv of K_3PO_4 in 2 mL of toluene. Reactions of aryl bromides were conducted at 100 °C for 20 h and of aryl chlorides at 120 °C. [b] *tert*-Butyl diphenylmethyleneglycinate used as protected amino acid.

led to fast reactions and high selectivity for monoarylations of *tert*-butyl acetate; the use of the sodium salt led to high yields for reactions of *tert*-butyl propionate. Potassium HMDS was ineffective for either ester. Reaction of *tert*-butyl acetate with the unhindered aryl halides in entries 1, 2, 4, and 7 occurred without competing diarylation when using LiHMDS. Only bromoanisole showed any diarylation product by GC, and this side product was formed in <2% yield. The selectivity for monoarylation was achieved, as it was for reactions of methyl ketones,[9] by using 2 equiv of base. This ratio of base to substrate encourages deprotonation of both product *and* reactant and, therefore, discourages quenching of the starting ester enolate by the more acidic product. Reactions of sterically hindered substrates gave high selectivity for monoarylation with either Li or NaHMDS.

Complexes of ligand **2** also catalyzed reactions of *tert*-butyl propionate with aryl halides under appropriate conditions. Reactions of this ester with aryl bromides (entries 9, 11−13) and even chlorobenzene (entry 10) occurred in high yields at room temperature, but this time using excess NaHMDS. Hydrodehalogenation of the haloarene was the major competing reaction when using other ligands for reactions of this ester. Reaction of the most hindered bromide in entry 12 occurred in higher yield when using P(*t*-Bu)$_3$. Coupling of esters with branching at the *β*-position (entries 14−16) was accomplished using ethyl or methyl esters. For example, essentially quantitative yields were obtained from reaction of ethyl 3-methylbutyrate and methyl cyclohexyl acetate with a representative aryl bromide. The sterically similar ethyl *N*,*N*-dimethylglycinate also gave the α-arylation product in high yield, even when using K_3PO_4 as base. Finally, the use of P(*t*-Bu)$_3$ instead of carbene precursor **2** as ligand led to construction of quaternary carbons, for example by reaction of 4-bromo-*t*-butylbenzene with methyl isobutyrate in the presence of LiHMDS (entry 17).

The reaction of *N*,*N*-dimethylglycinate led us to evaluate the α-arylation of amino acids with more convenient nitrogen protection.[25] We focused our studies on *N*-(diphenylmethylene)-glycinate and *N*-benzylideneglycinate. These materials are convenient to prepare, and the imine unit can modulate the acidity of the α C−H bond.[20] The results from these reactions are shown in Table 2. High yields of coupled product were obtained using P(*t*-Bu)$_3$ as ligand and K_3PO_4 as base. The weaker base may be

Scheme 2



effective because of the lower pK_a. Alternatively, coordination of the substrate nitrogen may assist formation of the enolate, as suggested by the coupling of ethyl *N*,*N*-dimethylglycinate, but not other esters when using K_3PO_4. Electron-rich, ortho-substituted, and sterically unhindered aryl halides all reacted in high yields with benzophenone ethyl or *tert*-butyl glycinate. In addition, reactions of pyridyl halides and aryl chlorides provided good yields of isolated product.

Because benzophenone imine is more expensive than aromatic aldehydes, we investigated the α-arylation of ethyl *N*-benzylidene glycinates. Reaction of phenyl bromide with the conveniently crystalline[26] ethyl *N*-(*p*-chlorobenzylidene) glycinate (Scheme 2) gave two products: one the desired product from α-arylation and the other from coupling at the imine carbon. The latter product formed the corresponding diarylmethylamine upon hydrolysis.

We reasoned that the undesired product was formed by reductive elimination from the iminobenzylic tautomer of the expected palladium enolate (Scheme 2). To disfavor this undesired tautomer, we conducted the reaction with a more electron-rich aldimine. By increasing the electron density of the aryl group, the iminobenzylic anion would be less stable, and the α-imino ester enolate would be more favored. As shown in entries 23−33 of Table 2, this strategy was effective. Reactions of aryl bromides with the *p*-methoxy aldimine of ethyl glycinate formed the free, neutral α-aryl glycinate upon workup. Reactions of this substrate with aryl chlorides were less favorable than reactions of benzophenone ethyl glycinate, but they did occur to give substantial yields of the coupled products (entries 24 and 32). Thus far, reactions to form quaternary amino acids have not occurred.

The α-arylations described here most likely occur by oxidative addition of aryl halide, formation of arylpalladium enolate complexes, and reductive elimination. As mentioned in the introductory paragraphs, the reductive elimination rate is relatively insensitive to enolate electronic properties.[19] Thus, the yields are most dependent on the stability of alkali ester enolates and the formation of palladium ester enolates.

The turnover-limiting step of coupling reactions involving chloro- and bromoarenes is often oxidative addition. Indeed, the reactions of protected amino acids with bromo or chloroarenes catalyzed by palladium complexes of P(*t*-Bu)$_3$ showed Pd[P(*t*-Bu)$_3$]$_2$ as the major phosphine complex in solution during the reaction. In most cases, these data would imply that oxidative addition is turnover-limiting. Yet, these reactions are much slower than those of the simple esters or of other nucleophiles when the same catalyst and aryl halide are used. Reversible oxidative addition and turnover-limiting formation of the palladium enolate could account for these observations. Alternatively, oxidative addition could occur to an anionic palladium enolate complex. These mechanistic issues will be the subject of future studies.

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Supporting Information Available: Reaction procedures and spectral and analytical data for reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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