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Palladium-Catalyzed α-Arylation of Azlactones to Form Quaternary Amino Acid Derivatives

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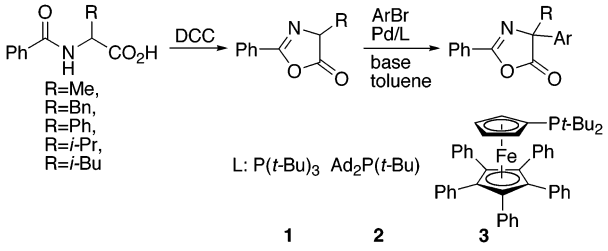
ABSTRACT



The synthesis of α-aryl-α-alkyl amino acid derivatives from α-amino acids by the arylation of azlactone derivatives is reported. Arylation of azlactones derived from alanine, valine, phenalanine, phenyl glycine, and leucine all provided good yields of the arylated product. Mechanistic studies of this reaction revealed that a stable complex containing a ligand formed by reaction of dba with the azlactone accounts for a new inhibiting effect of dba when reactions are initiated with $Pd(dba)_2$.

The coupling between an sp^2 carbon and an enolate has emerged as a useful synthetic method only recently.[1,2] Using sterically hindered electron-rich phosphines as ligands, we and others have developed efficient palladium-catalyzed methods for the α-arylation of ketones,[3,4] esters,[5−7] amides,[8,9] cyanoesters,[10,11] malonates,[3b,4b,11] and nitriles.[12]

Substitution at the α-carbon of α-amino acid derivatives introduces conformational constraints that can probe the molecular structure of receptors or enhance biological activity by helping to preorganize peptides for binding.[13,14] While a variety of methods for the synthesis of α,α-dialkyl glycine derivatives are available, methods for the synthesis of α-aryl-α-alkyl amino acids, particularly from natural amino acids, are more limited. For example, α-aryl-α-alkyl amino acids can be prepared from the Strecker synthesis, but the linkages between the α-carbon and the two side chains must be present in the ketone prior to the Strecker reaction. Hydrolysis of the cyano group also requires harsh conditions.

Palladium-catalyzed α-arylation of suitably protected amino acids could provide a general route to quaternary, α-aryl amino acids by formation of the C−C bond linking the aryl side chain to the α-carbon. We previously reported the arylation of glycine derivatives by palladium-catalyzed coupling of aryl bromides with diphenylmethylene-protected glycinates,[5] but no coupling with similarly protected α-substituted amino acids occurred. Intramolecular arylation of

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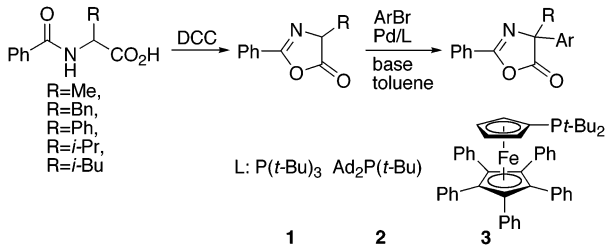
α-substituted amino acid derivatives[15] has been reported, but the more versatile intermolecular arylation of protected amino acids is unknown. Herein, we report the convenient synthesis of α-aryl-α-alkyl amino acid derivatives from α-substituted amino acids by the arylation of azlactone derivatives. Keys to the development of this new transformation were the use of an unexplored adamantyl phosphine and the discovery of a new means by which dibenzylidene acetone (dba) inhibits catalyst activity.

To develop the arylation of α-substituted amino acids, an amino acid derivative that is more reactive toward palladium coupling than benzophenone imine-protected amino acids was needed. We considered that azlactones may be more reactive because they are more acidic than imine-protected amino acids and are less hindered because of their cyclic structure. The sodium enolates of azlactones are stable for hours at elevated temperatures.[16] Indeed, Trost has recently reported azlactones as pronucleophiles for asymmetric allylic alkylation.[16−18] Scheme 1 includes the simple preparation of

Scheme 1



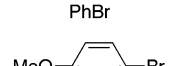
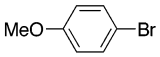
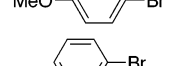
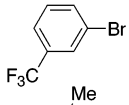
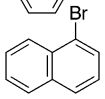
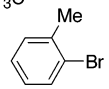
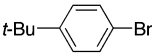
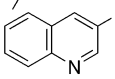
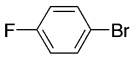
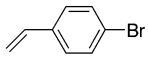
azlactones from standard amino acids.[13] The azlactone derived from alanine was selected for a model study.

Several ligands, solvents, and bases were evaluated for the reaction of PhBr with the azlactone derived from alanine. Reactions were conducted at 100 °C in toluene with a combination of $Pd(dba)_2$ and a phosphine ligand as the catalyst and K_3PO_4 as the base. Only reactions conducted with sterically hindered electron-rich phosphines such as P(*t*-Bu)$_3$ gave substantial amounts of product. BINAP, DPPF, and sterically hindered carbene ligands, which were effective in related α-arylation chemistry,[5,12] were ineffective in the arylation of the azlactone. Reactions with catalysts generated in situ from $Ad_2P(t\text{-Bu})$ (**2**) occurred in the highest yield and with the fastest rates. This ligand was prepared in 1994[19] but has not been exploited for catalysis previously.[10,20]

Reactions in aromatic solvents proceeded smoothly, but those in THF, CH_3CN, or DMF occurred in low yield. Reactions conducted with K_3PO_4 as a base occurred in good yield, but those conducted with Li_3PO_4 or Na_3PO_4 occurred to lower conversions. For reasons described in detail below, reactions initiated with $Pd(OAc)_2$ instead of $Pd(dba)_2$ or $Pd_2(dba)_3$ occurred under milder conditions and with a smaller excess of azlactone. Thus, reactions conducted with a combination of $Pd(OAc)_2$ and $Ad_2P(t\text{-Bu})$ as a catalyst with 1.5 equiv of azlactone and 3.3 equiv of K_3PO_4 generated the quaternary aryl amino acid derivatives in good yields at 80 °C in 14 h.

Reactions of the azlactone of alanine are summarized in Table 1. Reactions of electron−neutral aryl bromides (entries 1 and 8) occurred in 77 and 83% yield. Reaction of the electron-rich 4-bromoanisole (entry 3) gave 75% yield of coupled product. Reactions of aryl halides with electron-withdrawing trifluoromethyl, nitro, and cyano groups (entries 5, 10 and 11) also occurred, though the yields were slightly lower than those of electron-neutral substrates. 4-Bromostyrene (entry 15), which could undergo Heck coupling to deplete the aryl halide, formed the arylamino acid derivative in good yield. Even somewhat hindered aryl bromides with an *ortho* substituent such as 2-bromotoluene (entry 7) or 1-naphthyl bromide (entry 12) reacted to give 80 and 83% yield of coupled product.

Table 1. α-Arylation and Vinylation of the Alanine-Derived Azlactone

entry	substrate	condition	yield	entry	substrate	condition	yield
1	PhBr	A	77%				
2		B	85%	10		A	62%
3		A	75%				
4		B	85%	11		A	58%
5		A	66%				
6		B	75%	12		A	83%
7		A	80%	13		A	60%
8		A	83%	14		A	40%
9		A	75%	15		A	75%

[a] Procedures: (A) 5% $Pd(dba)_2$, 10% $Ad_2P(t\text{-Bu})$, 3.3 equiv of K_2CO_3 and 2 equiv of azlactone in toluene, 100 °C, 14−36 h. (B) 5% $Pd(OAc)_2$, 5% $Ad_2P(t\text{-Bu})$, 3.3 equiv of K_3PO_4, 1.5 equiv of azlactone in toluene, 80 °C, 14 h. [b] Isolated yields are averages of at least two runs on a 1 mmol scale.

Some related vinyl and heteroaryl bromides were also suitable substrates. For example, 1-bromo-2-methylpropene (entry 13) reacted in good yield. Substrates with a pyridyl nitrogen can deactivate palladium catalysts with monodentate ligands,[21] and 2-, 3-, and 4-bromopyridine did not react. However, 3-bromoquinoline (entry 14) gave the desired product in 40% yield.

To explore the steric sensitivity of the process toward branched α-substituents on the amino acid derivative, we explored the arylation of azlactones derived from phenyla-

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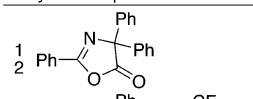
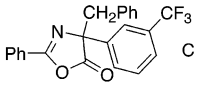
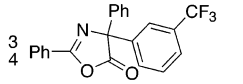
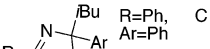
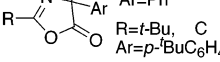
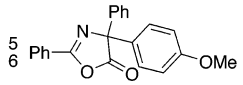
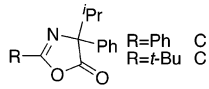
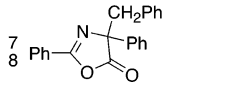
Table 2. Arylation of Azlactones

entry	product	method[a]	yield[b]	entry	product	method[a]	yield[b]
1		A	94%	9		C	74%
2		B	55%				
3		A	92%	10		C	47%[c]
4		B	55%	11		C	82%[d]
5		A	75%	12		C	29%[c]
6		B	30%	13		C	63%[d, e]
7		C	78%				
8		B	65%				

[a] Procedures: (A) 5% $Pd(OAc)_2$, 5% Q-phos **3**, 3.3 equiv of K_2CO_3, 1.5 equiv of azlactone in toluene, 80 °C, 14 h. (B) 5% $Pd(dba)_2$, 10% $Ad_2P(t\text{-Bu})$, 3.3 equiv of K_2CO_3 and 2 equiv of azlactone in toluene, 100 °C, 14 h. (C) 5% $Pd(OAc)_2$, 5% $Ad_2P(t\text{-Bu})$, 3.3 equiv of K_3PO_4, 1.5 equiv of azlactone in toluene, 80 °C, 14 h. [b] Isolated yields are averages of at least two runs on a 1 mmol scale. [c] $Ad_2P(t\text{-Bu})$ (10%), GC yield. [d] $Ad_2P(t\text{-Bu})$ (10%), 36 h. [e] Temperature = 100 °C.

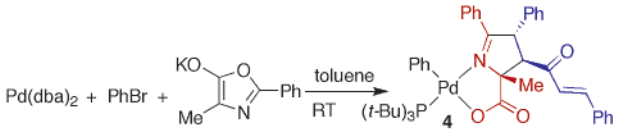
lanine, phenylglycine, leucine, and valine. As summarized in Table 2, these azlactones also reacted to give quaternary amino acid derivatives. The optimal catalyst for these substrates depended on the type of side chain, but general trends were observed. Reaction of the azlactone derived from the more acidic and more hindered phenylglycine was best conducted with Q-phos[22] as a ligand. The azlactone derived from phenylglycine reacted with electron-neutral, -poor, or -rich bromoarenes in the presence of $Pd(OAc)_2$ and Q-phos (entries 1, 3, and 5). As shown in entry 2, analogous reactions conducted with $Ad_2P(t\text{-Bu})$ as a ligand occurred in lower yields.

However, reactions of azlactones from naturally occurring alkyl- and benzyl-substituted amino acids occurred in higher yields with catalysts derived from $Ad_2P(t\text{-Bu})$. Thus, the azlactone derived from phenylalanine (entries 7 and 9) reacted with electron-neutral or electron-poor bromoarenes in good yields in the presence of $Pd(OAc)_2$ and $Ad_2P(t\text{-Bu})$. In some cases, the azlactone containing a 2-*tert*-butyl substituent instead of a 2-phenyl group reacted in higher yield. For example, the 2-phenyl azlactone derived from *N*-benzoyl leucine coupled in modest yields (entry 10), but reaction of the 2-*tert*-butyl azlactone derived from the pivaloyl amide of leucine gave 82% yield of the coupled product (entry 11). Steric protection of the imine nitrogen or electronic stabilization of the azlactone ring would account for the higher yields with the *tert*-butyl derivative. Reaction of the 2-*tert*-butyl azlactone derived from valine also occurred in a much higher 63% yield (entry 13) than reaction of the 2-phenyl azlactone from valine (29% yield, entry 12).

The arylation most likely occurs by oxidative addition,[23] transmetalation, and reductive elimination.[24] Though we have not prepared arylpalladium halide complexes containing $Ad_2P(t\text{-Bu})$ as a ligand, we have isolated $Pd[AdP(t\text{-Bu})_2](Ph)Br$ a related phenylpalladium bromide ligated by $AdP(t\text{-Bu})_2$.[23] Treatment of this complex with the potassium enolate of the azlactone derived from alanine generated the coupled product in 40% yield by GC. The lower yield relative to the catalytic reactions in Table 2 is due to the presence of $AdP(t\text{-Bu})_2$ instead of $Ad_2P(t\text{-Bu})$ on the palladium center. Thus, oxidative addition of aryl bromide to Pd(0) and reaction of the aryl palladium complex with the deprotonated azlactone most likely accounts for the formation of coupled product.

However, ^{31}P NMR spectroscopy of the reaction between the azlactone potassium enolate and phenyl bromide in the presence of $Pd(dba)_2$ and $P(t\text{-Bu})_3$ as catalysts showed a single resonance at 70.6 ppm. This resonance does *not* correspond to the Pd(0) species or the oxidative addition product. X-ray crystallography revealed this complex to be **4** in Scheme 2 containing palladium, phosphine, and a ligand

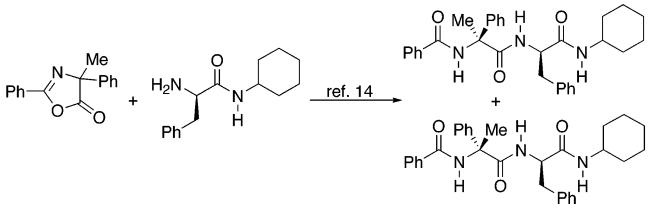
Scheme 2



generated from dba and the enolate of the azlactone. Complex **4** (5 mol %) catalyzed the reaction of PhBr with the azlactone of alanine at 100 °C to give 66% yield of coupled product by GC. However, complex **4** is more likely to be a precatalyst than a true catalytic intermediate.

If **4** is a catalytic precursor and not an intermediate, then the accumulation of **4** would siphon active catalyst from the cycle, and a metal−ligand combination that forms the active catalyst without formation of **4** would induce faster reactions. Indeed, the results in Table 1 show that reactions initiated with $Ad_2P(t\text{-Bu})$ and $Pd(OAc)_2$ instead of $Pd(dba)_2$ occurred at lower temperatures, in higher yields, with less catalyst, and with less of an excess of azlactone. Further consistent with a conventional mechanism involving oxidative addition of aryl halide to Pd(0), ^{31}P NMR spectroscopy of the reaction of the azlactone enolate and phenyl bromide initiated by the combination of $Pd(OAc)_2$ and $P(t\text{-Bu})_3$ contained $Pd[P(t\text{-Bu})_3]_2$ as the major palladium complex in solution. Finally, reactions catalyzed by isolated $Pd[P(t\text{-Bu})_3]_2$ occurred faster than those initiated with $P(t\text{-Bu})_3$ and $Pd(OAc)_2$ and occurred in 76% yield.

Scheme 3



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In summary, a new palladium-catalyzed method for the α-arylation of azlactones was developed. The products of these reactions can be hydrolyzed easily to generate α-aryl-α-substituted amino acid derivatives.[17] Moreover, resolution of the quaternary azlactones has been accomplished previously by Müller by reaction with optically active amine as shown in Scheme 3.[14] Enantioselective versions of the azlactone arylation are under investigation.

Acknowledgment. The authors thank the NIH (GM 58108) for funding.

Supporting Information Available: Procedures and spectral data of products of all catalytic reactions and X-ray data of complex **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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