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Palladium Catalyzed C-Arylation of Amino Acid Derived Hydantoins

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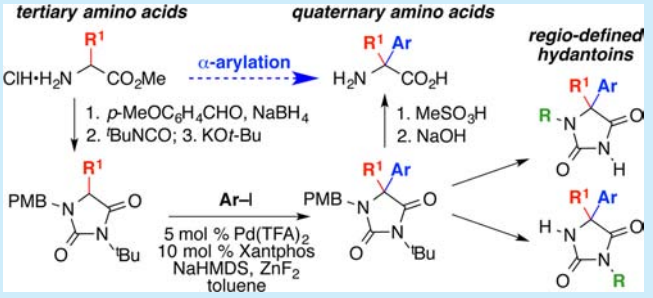
Supporting Information

ABSTRACT: Palladium(II) trifluoroacetate (5 mol %) catalyzes the C-arylation of *N,N*-disubstituted hydantoins by aryl iodides in good yield. The reaction proceeds through base-promoted enolization of the amino acid derived hydantoins, and the resulting 5,5-disubstituted hydantoins may be deprotected at one or both N atoms to yield biologically active structures or alternatively hydrolyzed to the parent α-aryl α-amino acids. The reaction is successful with a variety of parent amino acids and a range of electron-rich and electron-poor aryl iodides.

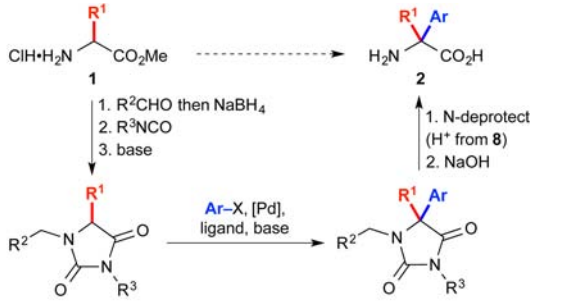


The hydantoin motif is found in numerous drugs and bioactive natural products.[1,2] Its value in organic chemistry is further enhanced by its utility as an intermediate in the synthesis of natural and unnatural α-amino acids,[3] particularly by Bucherer–Bergs chemistry.[4] Of the many possible nonproteinogenic α-amino acids, α,α-disubstituted quaternary amino acids are of particular importance in both medicinal and structural biological chemistry.[5,6] Many methods exist for the α-alkylation of α-amino acids, but α-arylation remains challenging.

Because of the specific challenges of reactivity evident in the coupling of an enolate nucleophile with an aryl electrophile, the α-arylation of carbonyl compounds in general is an important transformation that has received considerable attention in recent years.[7] Arylation of amino acid enolates may be achieved using rearrangement chemistry,[8] but the direct C-arylation of a tertiary amino acid would constitute a particularly efficient method for the preparation of α-arylated quaternary amino acids. The use of a transition metal catalyst[9] has led to a small selection of methods allowing the coupling of an sp^2 carbon with an amino acid derived enolate, but to date these are far from general with regard to amino acid and aryl coupling partners.[10] α-Arylations have been carried out with a limited number of amino acids using palladium[11] or iron[12] catalysis, and with stoichiometric amounts of aryl metal[13] or diaryliodonium[14] species, or with more toxic arenechromium tricarbonyl complexes.[15]

In this work we show that direct α-arylation of the hydantoin derivatives of readily available amino acids provides a short, general route to 5,5-disubstituted hydantoins, and hence also to quaternary α-aryl amino acids in racemic form. Our general synthetic approach to the quaternary amino acids is detailed in Scheme 1 and entails the construction of hydantoins **5** carrying suitable base-stable N-protecting groups from amino esters **1** by reductive amination with *p*-anisaldehyde,[16] urea formation with *tert*-butyl isocyanate, and base-promoted ring closure.[17] C-Arylation of hydantoins **5** yields **8**, from which acid-catalyzed deprotection and base-catalyzed ring cleavage provide the quaternary amino acids **2**.

Scheme 1. General Approach to Quaternary 5-Arylated Hydantoins and Quaternary α-Aryl α-Amino Acids



3 R^1 = Me; R^2 = 2,4-$(MeO)_2C_6H_3$; R^3 = Et
4 R^1 = Me; R^2 = 4-ClC_6H_4; R^3 = Et
5 R^2 = 4-$MeOC_6H_4$; R^3 = ^{t}Bu

6 R^1 = Me; R^2 = 2,4-$(MeO)_2C_6H_3$; R^3 = Et
7 R^1 = Me; R^2 = 4-ClC_6H_4; R^3 = Et
8 R^2 = 4-$MeOC_6H_4$; R^3 = ^{t}Bu

Hartwig had previously reported the arylation in moderate to good yield of azlactone derivatives of unfunctionalized/branched amino acids,[11b] but we were first alerted to the susceptibility of hydantoins to C-arylation during the attempted N-arylation of urea **9** during a related project (Scheme 2).[8a,b] Rather than the desired *N*-pyridyl urea **10**, the C-arylated hydantoin **11a** was formed. Stepwise arylation, under similar conditions, of the hydantoin **12** (presumably an intermediate in the formation of **11a**) with bromobenzene gave a good yield of **11b**.

Trial couplings of related alanine-derived hydantoins **3** and **4** (Scheme 1) with bromobenzene gave the products **6** (Ar = Ph) in 65% yield and **7** (Ar = Ph) in 80% yield, suggesting the

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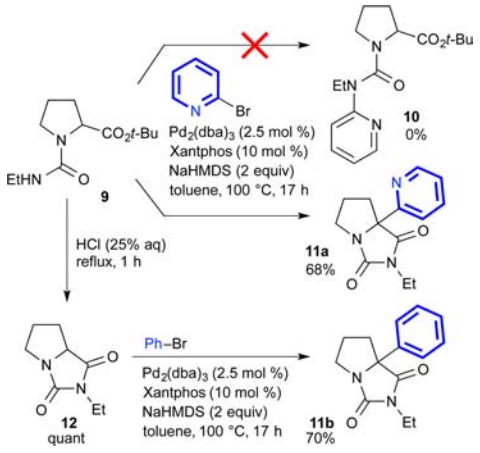
Scheme 2. A Hydantoin Arylation

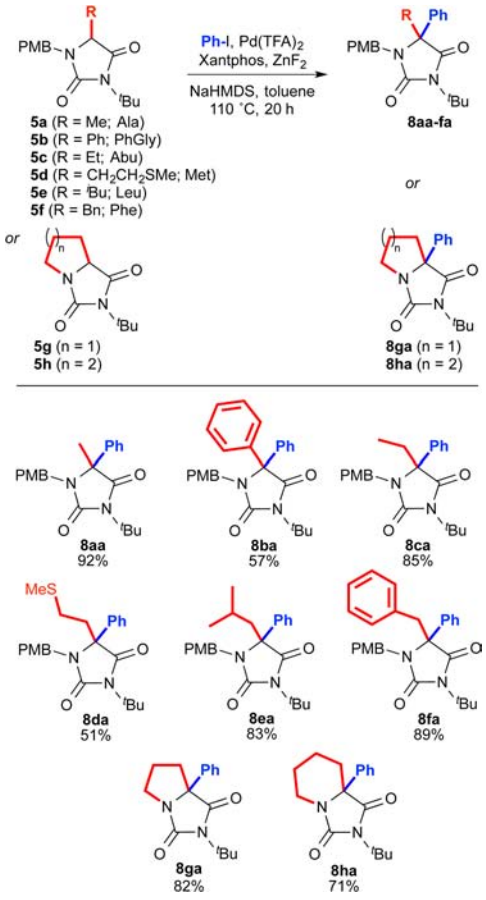


hydantoin arylation might turn out to be a general method for quaternary amino acid synthesis.

Encouraged by this preliminary work, we proceeded to develop a more versatile approach to both hydantoins and quaternary amino acids, by replacing the various less easily removable N-substituents of **3**, **4**, and **12** by the simple acid-labile protecting groups of **5** (Scheme 1). Initial explorations of the α-arylation of the enolate derivatives of hydantoins **5** were carried out using the alanine-derived substrate **5a** (R^1 = Me) in the presence of halobenzenes and a palladium catalyst. A range of conditions were screened, as shown in Table 1.

Initially, several bases were tested (Table 1, entries 1−6), and under typical enolate arylation conditions,[11] using Xantphos as a ligand, only NaHMDS or KHMDS gave the desired arylated hydantoin **8a**, in moderate yield. Aiming to improve upon these results, we next screened a range of palladium catalysts, maintaining NaHMDS as the base (entries 7−10). We found that the yield was increased markedly, to 82%, with $Pd(TFA)_2$ as the source of Pd(II). No benefit was obtained either by changing to KHMDS (entry 11) or by varying the bulky phosphine ligand (entries 12, 13). Using bromobenzene as an arylating agent still gave product, but in lower yield (entry 14). Other solvents (1,4-dioxane and DMF) were as effective as toluene (entries 15, 16), but the best results were obtained by adding 1.5 equiv of ZnF_2 to

Scheme 3. Arylation of α-Amino Acid Derived Hydantoins[a]



[a]Reactions were conducted with PhI (1.5 equiv), $Pd(TFA)_2$ (5 mol %), Xantphos (10 mol %), ZnF_2 (1.5 equiv), NaHMDS (2 equiv).

Table 1. Optimization of Reaction Conditions for the Arylation of 5a[a]

entry	base	[Pd]	L[b]	solvent	Ar−X	yield **8a**/%[c]
1	K_3PO_4	$Pd_2(dba)_3$	**L1**	toluene	Ph−I	–[d]
2	NaO^{t}Bu	$Pd_2(dba)_3$	**L1**	toluene	Ph−I	–[d]
3	LDA	$Pd_2(dba)_3$	**L1**	toluene	Ph−I	–[d]
4	LiHMDS	$Pd_2(dba)_3$	**L1**	toluene	Ph−I	–[d]
5	KHMDS	$Pd_2(dba)_3$	**L1**	toluene	Ph−I	38
6	NaHMDS	$Pd_2(dba)_3$	**L1**	toluene	Ph−I	52
7	NaHMDS	$Pd(acac)_2$	**L1**	toluene	Ph−I	25
8	NaHMDS	$Pd(hacac)_2$	**L1**	toluene	Ph−I	32
9	NaHMDS	$Pd(OAc)_2$	**L1**	toluene	Ph−I	48
10	NaHMDS	$Pd(TFA)_2$	**L1**	toluene	Ph−I	84
11	KHMDS	$Pd(TFA)_2$	**L1**	toluene	Ph−I	61
12	NaHMDS	$Pd(TFA)_2$	**L2**	toluene	Ph−I	–[d,e]
13	NaHMDS	$Pd(TFA)_2$	**L3**	toluene	Ph−I	–[d]
14	NaHMDS	$Pd(TFA)_2$	**L1**	toluene	Ph−Br	37[e]
15	NaHMDS	$Pd(TFA)_2$	**L1**	1,4-dioxane	Ph−I	81
16	NaHMDS	$Pd(TFA)_2$	**L1**	DMF	Ph−I	86
17	NaHMDS	$Pd(TFA)_2$	**L1**	toluene + Ph−I of ZnF_2	Ph−I	92

[a]Reactions were conducted with [Pd] (5 mol %), **L** (10 mol %), base (200 mol %), and Ph−X (150 mol %). [b]Ligand **L1**, Xantphos; **L2**, NiXantphos; **L3**, P(^{t}Bu)$_3$. [c]Isolated yield. [d]**5a** recovered unchanged. [e]No reaction with chlorobenzene.

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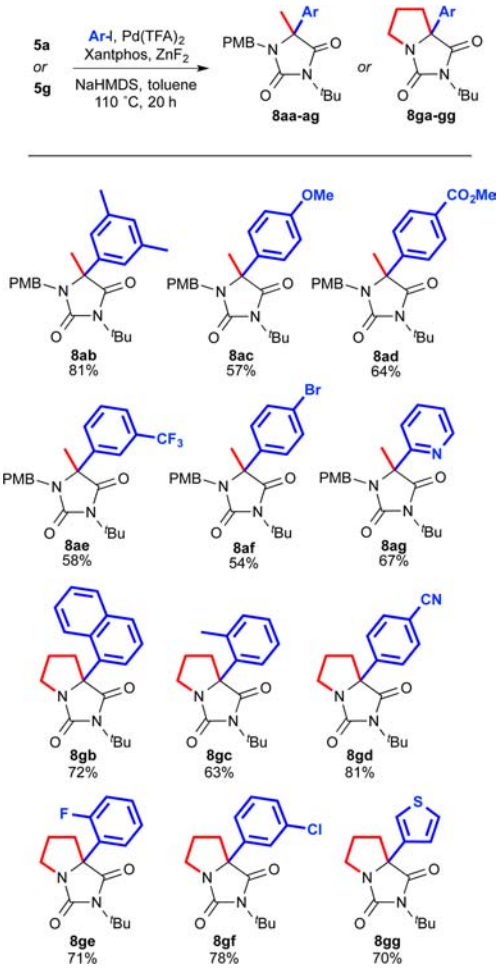
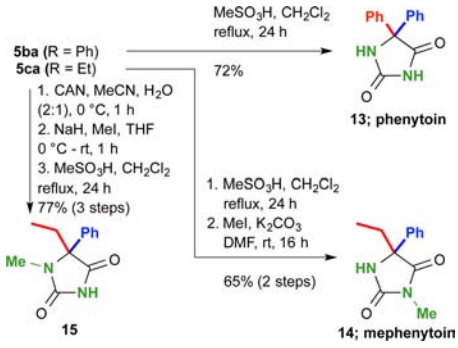
Scheme 4. Scope of the Aryl Coupling Partner[a]



[a]Reactions were conducted with Ar−I (1.5 equiv), $Pd(TFA)_2$ (5 mol %), Xantphos (10 mol %), ZnF_2 (1.5 equiv), NaHMDS (2 equiv).

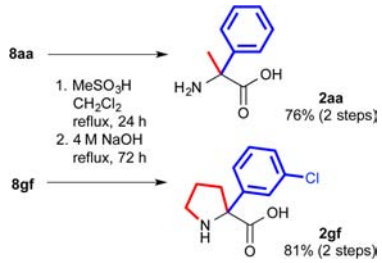
Scheme 5. Synthesis of Pharmaceutically Active Hydantoins



the reaction mixture[18] (entry 17) to act as a Lewis acid and possibly to transmetallate to a zinc enolate.

Using these optimized conditions, α-phenylation was successful with substrates carrying a range of different side chains (Scheme 3). For example, phenylglycine-derived hydantoin **5b** gave 5,5-diphenyl hydantoin **8ba**, and amino acids with linear alkyl substituents, namely 2-aminobutyric acid (butyrine) and methionine, led to 5-phenylated hydantoins **8ca** and **8da** in 85% and 51% yield, respectively. The reaction was also successful with bulkier aliphatic and aromatic side chains: leucine and phenylalanine-derived hydantoins giving phenylated

Scheme 6. Cleavage to Quaternary α-Aryl Amino Acids



products **8ea** and **8fa**. Proline and pipecolic acid provided the quaternary bicyclic compounds **8ga** and **8ha** also in remarkably good yield. All chiral products formed from the couplings were racemic.

The coupling partner was also varied, with a number of different iodoarenes carrying electron-rich and electron-poor groups in different positions on the aromatic ring screened for successful coupling with acyclic (Ala) and cyclic (Pro) amino acid derived hydantoins **5a** and **5g** (Scheme 4).

Iodoarenes bearing electron-donating (methyl, methoxy) substituents in *ortho*, *meta*, and *para* positions all coupled reasonably well, providing the corresponding quaternary hydantoins **8ab**, **8ac**, and **8gc** in moderate yields. Rings carrying electron-withdrawing groups such as a methyl ester, a trifluoromethyl group, and a nitrile also proved to be compatible with the reaction conditions, affording **8ad**, **8ae**, and **8gd** in good yields. A 2-naphthyl group was coupled successfully to give the hindered product **8gb** in good yield. Halogen atoms in different positions, namely *ortho*-F, *meta*-Cl, and *para*-Br, were tolerated, providing the hydantoins **8ge**, **8gf**, and **8af** respectively. Even the electron-deficient and electron-rich heteroaryl iodides 2-iodopyridine and 3-iodothiophene produced satisfactory results (**8ag**, **8gg**) in a similar yield.

The products **8** are *N*-protected analogues of some important biologically active hydantoins.[19] Both the *p*-methoxybenzyl and *tert*-butyl protecting groups could be removed simultaneously by treatment with methanesulfonic acid in refluxing dichloromethane.[20] As shown in Scheme 5, this allowed us to make the anticonvulsant agents phenytoin **13** and, after selective methylation of the more acidic 3-position, mephenytoin **14**. On the other hand, selective orthogonal cleavage of the PMB group from the 1-position with ceric ammonium nitrate revealed an N3-protected hydantoin that could be methylated at N1. Acidic cleavage of the *tert*-butyl group resulted in compound **15**, a regioisomeric analogue of mephenytoin.

Further base-promoted hydrolysis of the fully deprotected hydantoins led to the quaternary α-aryl amino acids **2** in racemic form, as illustrated for two examples, α-phenylalanine and α-(3-chlorophenyl)proline in Scheme 6.[21] The route from **1** to **2**, via **5** and **8** (illustrated in Scheme 1), thus constitutes a divergent method for the racemic α-arylation of natural and unnatural amino acids.

In summary, intermolecular palladium-catalyzed α-arylation of the enolates of amino acid derived N-protected hydantoins has been achieved for the first time, using readily available starting materials. The optimized protocol provides a valuable tool for the synthesis of 5-aryl hydantoins (including biologically active compounds such as phenytoin or mephenytoin) and, after deprotection and hydrolysis, α-arylated quaternary amino acids. Previous methods for the direct intermolecular α-arylation of amino acid derivatives required either electron-deficient aryl

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partners[10d,e] or stoichiometric reagents,[13−15] or were limited to unfunctionalized and acyclic amino acids.[12] Current work seeks to develop an enantioselective version of this metal-catalyzed arylation.[22]

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01803.

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Notes

The authors declare no competing financial interest.

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(17) Experimental details for each step are included in the Supporting Information.

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(22) We recently reported a pseudoephedrine-directed intramolecular asymmetric amino acid arylation that yields related hydantoins: see ref 8b.

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