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Palladium-Catalyzed α-Arylation of Tetramic Acids

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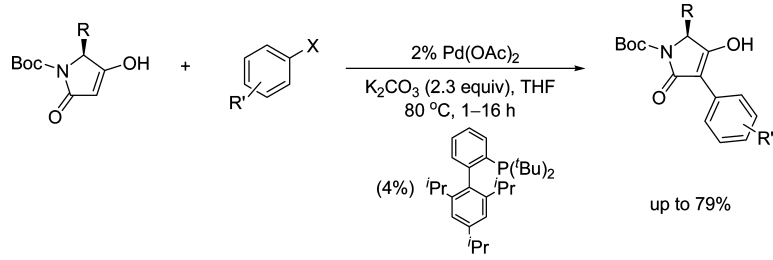
Received April 17, 2009



R = "Phe", "Tyr(ᵗBu)", "Lys(Cbz)", "Arg(Pbf)", "Thr(ᵗBu)", "Asp(ᵗBu)", "Gly"
R' = H, *meta*- or *para*-EDG or EWG
X = Cl, Br, OTf

A mild, racemization-free, palladium-catalyzed α-arylation of tetramic acids (2,4-pyrrolidinediones) has been developed. Various amino acid-derived tetramic acids were cleanly arylated by treatment with 2 mol % of $Pd(OAc)_2$, 4 mol % of a sterically demanding biaryl phosphine, 2.3 equiv of K_2CO_3 or K_3PO_4, and aryl chlorides, bromides, or triflates in THF. With conventional heating, conversions >95% could be attained after 1 h at 80 °C, whereas microwave-induced heating led to much shorter reaction times (5 min at 110 °C). The electron density of the aryl electrophile had no effect on their reactivity: both electron-rich and electron-poor aryl chlorides and bromides or triflates led to good yields. Ortho-substituted aryl halides and heteroaryl halides, however, did not undergo the title reaction.

Introduction

Tetramic acids are β-keto-γ-lactams which are slightly acidic ($pK_a \approx 6.4$).[1,2] Depending on solvent, concentration, and temperature, tetramic acids can exist as both an enol (4-hydroxy-3-pyrrolin-2-one) and a keto tautomer (2,4-pyrrolidindione) (see Figure 1).[1,3,4]

The structural unit of tetramic acids has been known for more than 100 years,[5] and it is found in many biologically active natural products,[3] typically either as 3-acyl or 4-*O*-alkyl derivatives, examples being althiomycin,[6a,b] dolastatin 15,[6c,d] and epicoccamide.[6e] Tetramic acids are important intermediates

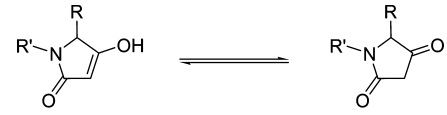


FIGURE 1. Tetramic acids can exist as both an enol and a keto tautomer.[1,3,4]

in the synthesis of statins,[7a,b] β-hydroxy γ-amino acids,[7c] and lactams[7d] which are inhibitors of renin. Renin is involved in the renin−angiotensin system (blood pressure and fluid regulating system in the body), hypertension, congestive heart failure, and development of HIV. Furthermore, tetramic acid derivatives have been reported as key intermediates for the synthesis of analogues of penicillins and cephalosporins[7e] and 4-substituted 3-hydroxy-1*H*-pyrrole-2,5-dione derivatives[7f] which are inhibitors of glycolic acid oxidase and thus potentially useful drugs for the treatment of calcium oxalate renal lithiasis (kidney stones) and primary hyperoxalurias, which is an inborn error of metabolism resulting in increased urinary excretion of oxalate. 2-Ethyl-4,6-dimethylphenyl-substituted tetramic acid derivatives have been described in the patent literature as novel pesticides

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10.1021/jo900799y CCC: $40.75
Published on Web 05/27/2009

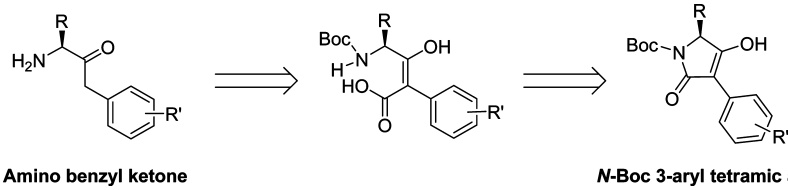
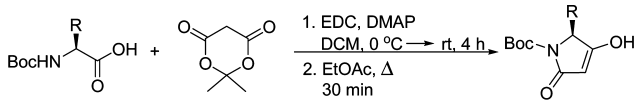


FIGURE 2. Retrosynthetic analysis of amino benzyl ketones.

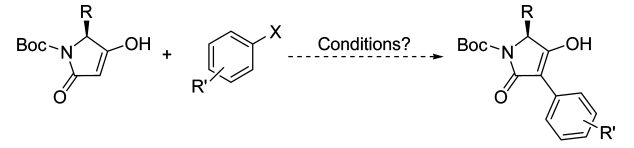
SCHEME 1. General Synthesis of *N*-Boc-Protected Amino Acid-Derived Tetramic Acids[8,9]



and herbicides.[7g] Recently, methods for incorporation of amino acid-derived tetramic acids into peptides have been developed,[8] giving rise to more stable tripeptides. Tetramic acids derived from amino acids are easily synthesized in good yield from commercially available *N*-Boc amino acids and Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) via DCC (*N*,*N*′-dicyclohexylcarbodiimide) or EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) activation (see Scheme 1).[8,9]

Only a few examples in the literature have described the 3-aryl tetramic acids,[10a,b] the most important being the use of 3-phenyl 5-olefinic tetramic acids as novel glycine site *N*-methyl-D-aspartate receptor antagonists, for the treatment of neurological diseases.[10c] The development of a solid-phase synthesis of substituted 3-aryl tetramic acids has also been described.[10d] However, none of these methods utilize the easy synthesis of *N*-Boc protected tetramic acids described above, and the methods are not general, requiring the use of strong base (e.g., KHMDS or NaOEt) and many synthetic steps. None of these methods make it easy to efficiently synthesize a broad range of 3-aryl-substituted amino acid-derived tetramic acids as potentially interesting biologically active compounds. We therefore wished to develop a useful method for the synthesis of 3-aryl tetramic acids from the readily available *N*-Boc amino acid-derived tetramic acids.

SCHEME 2. Proposed α-Arylation of Tetramic Acids with an Aryl Halide (X = Cl, Br, I)



Specifically, we want to use these compounds as building blocks for *C*-terminal modified peptides toward the preparation of peptidyl enzyme inhibitors. For example, ring-opening of the 3-aryl tetramic acids followed by decarboxylation would lead to a new type of amino benzyl ketones (see Figure 2), which subsequently can be coupled to the *C*-terminal of a peptide.

Traditionally, α-arylated ketones or carboxylic acid derivatives have been synthesized by nucleophilic aromatic substitution reactions (S_NAr) of aryls substituted with electron-withdrawing groups by reaction with stabilized enolates[11] or via copper-catalyzed enolate reaction with 2-bromobenzoic acid.[12] These methods all have drawbacks and are not very general. Usually, they require harsh reaction conditions, which are not suitable for protected, enantiomerically pure amino acid derivatives. Using a palladium-catalyzed α-arylation would be much more efficient since these reactions are typically more general, mild, and broad in substrate scope.

The literature reports a number of palladium-catalyzed α-arylation conditions for different substrates containing electron-withdrawing groups such as ketones,[13a] aldehydes,[13b] malonates,[13c] cyanoesters,[13c] sulfones,[13d] esters,[13e] amides,[13f] protected amino acids,[13g] piperidinones,[13h] and nitriles.[13i] Only a few examples of α-arylation of 1,3-dicarbonyls have been described, and most of them are nonchiral and synthetically undemanding compounds. Most of the examples have been reported by Buchwald and co-workers,[13a] using substrates such as diethyl malonate, 1,3-cyclohexanedione, and 1,3-cyclopentanedione. Very recently more functionalized substrates have been subjected to palladium-catalyzed arylation, e.g. the sp^2 arylation of azine *N*-oxides,[14] α-arylation of highly function-

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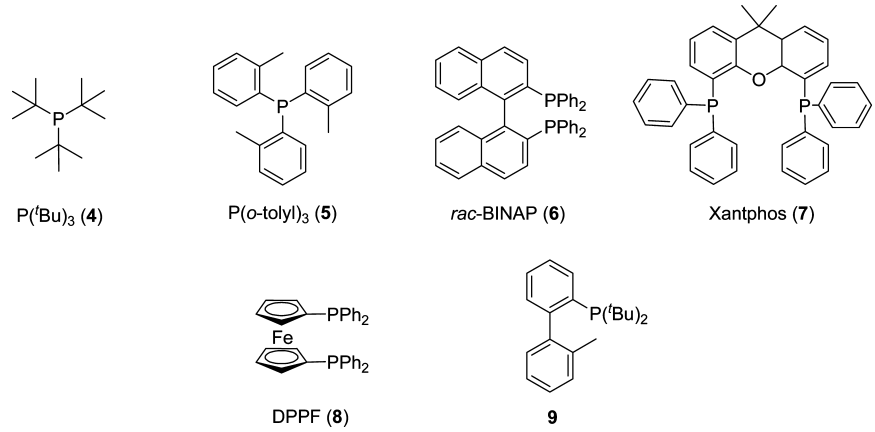
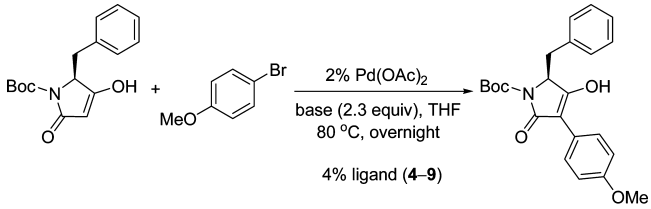


FIGURE 3. Ligands used in the initial screening experiments.

TABLE 1. Results from Initial Screening of Bases and Ligands

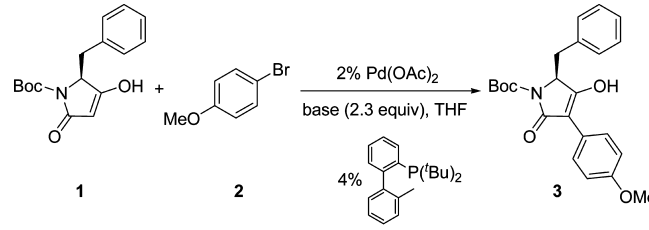


1 2 3

entry	ligand	base	conv (%)[a]
1	**4**−**8**[b]	all four[b]	<5
2	**9**	Cs_2CO_3	15
3	**9**	K_3PO_4	36
4	**9**	Na_2CO_3	−[c]
5	**9**	K_2CO_3	36

[a] Determined by ^{1}H NMR. [b] Ligands **4**−**8** tested with Cs_2CO_3, K_3PO_4, Na_2CO_3, and K_2CO_3, respectively, in 20 experiments. [c] No significant product formation determined by ^{1}H NMR or LC-MS.

TABLE 2. Increased Temperature and Prolonged Reaction Time



1 2 9 3

entry	base	temp (°C)	time (h)	conv (%)[a]
1	Cs_2CO_3	80	72	21
2	K_3PO_4	80	72	33
3	Na_2CO_3	80	72	<5
4	K_2CO_3	80	72	32
5	Cs_2CO_3	100	16	25
6	K_3PO_4	100	16	71
7	Na_2CO_3	100	16	<5
8	K_2CO_3	100	16	52

[a] Determined by ^{1}H NMR.

alized cyclohexanones,[15] and asymmetric intramolecular α-arylation of aldehydes.[16] However, to the best of our knowledge, tetramic acids have never before been subjected to this kind of transformation (see Scheme 2), and we set out to determine suitable reaction conditions.

Even though no general reaction conditions exist in the literature, it was possible to discern a general trend for the reaction of substrates similar to tetramic acids, e.g., 1,3-dicarbonyl compounds, cyclic substrates, and amino acids, from the literature. It was found that an α-arylation is usually conducted with either $Pd(OAc)_2$ or $Pd_2(dba)_3$ with use of an aryl bromide or iodide.[13] Aryl chlorides are often too unreactive for this type of chemistry. Many different solvents can be used, but THF, toluene, dioxane, MeCN, or DMF are the most common. The bases used can be divided into two groups: weak inorganic bases such as Cs_2CO_3, K_2CO_3, K_3PO_4, Na_3PO_4, or Na_2CO_3 and strong organic bases such as NaO^{t}Bu, KHMDS, NaHMDS, LDA, or $LiN(SiMe_2Ph)_2$. The choice of base is strongly dependent on the pK_a value of the substrate but, in general, strong bases can be used for most simple substrates. However, if base-sensitive functionalities are present in the molecule or deprotonation can cause racemization, strong bases may give problems. Sometimes strong bases even require a two-step procedure with addition of base at reduced temperature and then the actual arylation at elevated temperature.[13h] Buchwald and co-workers[13a] reported the first use of a weak inorganic base, K_3PO_4, in palladium-catalyzed α-arylations of ketones. Finally, a very important parameter is the choice of ligand. This can be difficult, since many different ligands have been reported to work in α-arylation of carbonyl substrates, with a broad variety of stereo- and electronic properties. In general the ligands are either mono- or bis-phosphines. With a rational selection of parameters it should be easier to find the optimal reaction conditions for the α-arylation of tetramic acids (see Scheme 2).

Results and Discussion

Initially, we tried to arylate Boc-*py*Phe-OH (**1**) (the prefix "*py*" is used to indicate that the amino acid is converted to a tetramic acid[8]) with 4-bromoanisole (**2**) in the presence of 2 mol % of $Pd(OAc)_2$ in THF at 80 °C overnight for the synthesis of the 3-aryl tetramic acid **3** (see Table 1). Four different weak inorganic bases were chosen: Cs_2CO_3, K_3PO_4, Na_2CO_3, and K_2CO_3, respectively, in 2.3 equiv inspired by results published by Buchwald and co-workers.[13a] We prioritized the screening of a variety of weak bases because they are much more compatible with functional groups, and because tetramic acids

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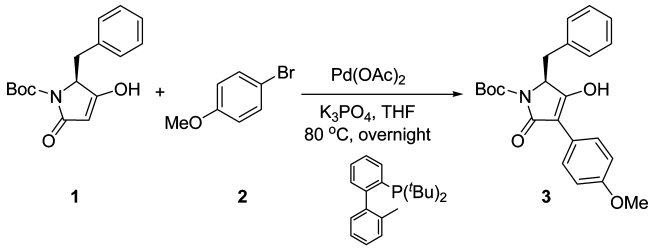
TABLE 3. Variation of Equivalents of Aryl Bromide 2, $Pd(OAc)_2$, Ligand 9, and K_3PO_4



1 2 9 3

entry	Ar−Br **2** (equiv)	$Pd(OAc)_2$ (mol %)	ligand **9** (mol %)	K_3PO_4 (equiv)	conv (%)[a]
1	2.0	2	4	2.3	43
2	1.0	2	4	5.0	15
3	1.0	4	8	2.3	>95
4	1.0	2	8	2.3	>95
5	1.0	4	4	2.3	79

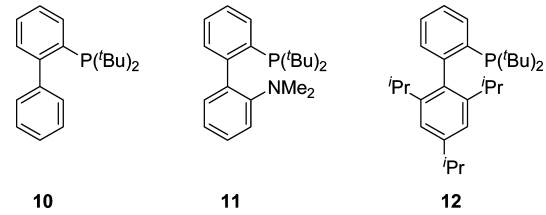
[a] Determined by ^1H NMR.

are slightly acidic. The phosphine ligands $P(^tBu)_3$ (**4**), $P(o\text{-tolyl})_3$ (**5**), *rac*-BINAP (**6**), Xantphos (**7**), and DPPF (**8**) (see Figure 3) were screened with the four bases in 20 initial experiments. Unfortunately, none of these conditions gave rise to any significant product formation (conv <5%) and only starting materials were isolated upon acidic workup (see Table 1, entry 1). However, to our gratification screening experiments with 4 mol % of biaryl phosphine ligand **9** gave promising results. Not surprisingly, a major difference among the bases was observed, K_3PO_4 and K_2CO_3 giving comparable results, 36% conversion (entries 3 and 5), whereas Na_2CO_3 did not give any product formation at all (entry 4). Cs_2CO_3 gave an intermediate result with a conversion of 15% (entry 2).

To further increase the conversion with 4 mol % of biaryl phosphine ligand **9** and 2.3 equiv of K_3PO_4, a series of experiments at elevated temperature (100 °C) and a series with prolonged reaction time (3 days) was conducted (see Table 2). No significant change in conversions was observed after 3 days (entries 1−4). On the other hand, the conversion was increased at 100 °C overnight, especially with K_3PO_4, which almost gave a 2-fold increase in conversion to 71% (entry 6). In both experimental series, the use of Na_2CO_3 still did not give any significant product formation (entries 3 and 7).

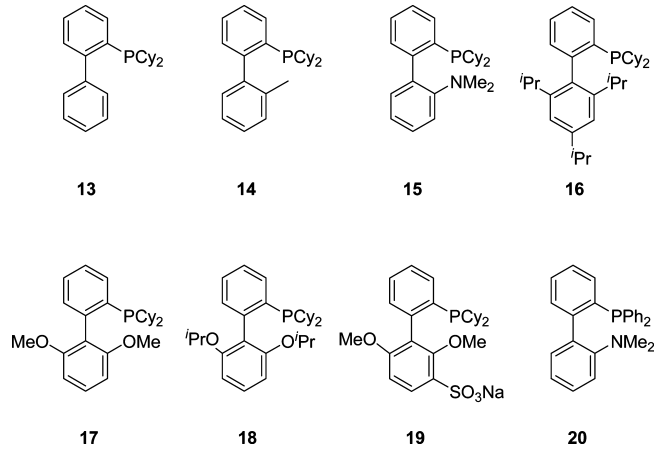
We reasoned that inefficient activation of the catalyst may cause the low to moderate conversions obtained so far. Therefore we tested the screening reaction at 80 °C with all four bases, respectively, with 2 mol % of $Pd_2(dba)_3$ as a direct source of Pd(0). However, we found that there was no improvement in conversion, and we therefore assumed that the problem with low conversion was not due to the nature of the palladium catalyst.

Having a set of reaction conditions giving a moderate conversion and a catalyst that presumably is sufficiently activated, we screened a set of different equivalents with regard to 4-bromoanisole (**2**), $Pd(OAc)_2$, biaryl phosphine ligand **9**, and K_3PO_4 (see Table 3). Increasing the equivalents of **2** from 1.0 to 2.0 only increased the conversion slightly (entry 1), whereas increasing the equivalents of K_3PO_4 to 5.0 gave a significant reduction in conversion (entry 2). Furthermore, we examined the effect of catalyst and ligand loading. Increasing the loading of both catalyst and ligand to 4 and 8 mol %, respectively, gave full conversion of the starting material to the desired product **3** (entry 3). The same was true with increased ligand loading only (entry 4). It was found that an excess of ligand was essential, since 4 mol % of $Pd(OAc)_2$ and 4 mol % of biaryl phosphine ligand **9** gave a conversion of 79% (entry 5).



10 11 12

FIGURE 4. Di-*tert*-butyl biaryl phosphine ligands.



13 14 15 16 17 18 19 20

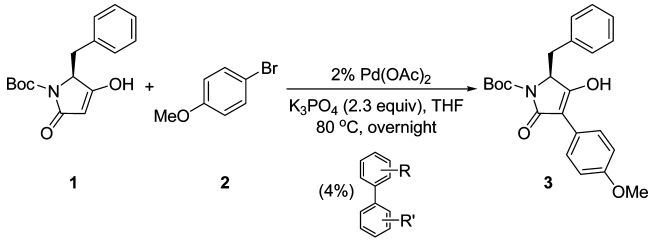
FIGURE 5. Dicyclohexyl (**13**−**19**) and diphenyl (**20**) biaryl phosphine ligands.

On the basis of these results, it seemed likely that screening other biaryl phosphine ligands might give full conversion without increased ligand loading. We therefore screened three classes of commercially available biaryl phosphine ligands: a series of di-*tert*-butyl biaryl phosphines **10**−**12** (see Figure 4), a series of dicyclohexyl biaryl phosphines **13**−**19**, and a single diphenyl biaryl phosphine **20** (see Figure 5). Only 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (**12**) gave full conversion with 4 mol % of ligand loading (see Table 4, entry 3), the two other di-*tert*-butyl biaryl phosphines (**10** and **11**) gave only poor conversion (entries 1 and 2). All dicyclohexyl biaryl phosphine ligands **13**−**19** and the diphenyl biaryl phosphine ligand **20** gave only traces of product. Apparently, this reaction requires a sterically hindered and electron-rich ligand and the di-*tert*-butyl substituents are essential for reactivity, which is demonstrated by the absence of reactivity with the analogous dicyclohexyl biaryl phosphine ligand **16**.

Before moving on with substrate scope and limitations, we analyzed the enantiomeric purity of the product **3**, by means of chiral HPLC. Fortunately, little racemization had occurred (ee 97%), which was expected due to the use of mild base.

Having arrived at these optimized reaction conditions we wished to examine the scope and limitations of the reaction by testing other different aryl coupling partners, namely aryl chlorides, iodides, tosylates, and triflates. For comparison reasons we chose to screen 4-methoxy derivates only (see Table 5). To our delight, 4-chloroanisole (**21**) reacted identically (entry 1) compared to 4-bromoanisole (**2**), as did aryl triflate **24** (entry 4). Use of aryl triflates expands the scope of the reaction further because it allows conversion of phenols into functional coupling partners very easily. Aryl iodide **22** and aryl tosylate **23** gave

TABLE 4. Screening of Different Biaryl Phosphine Ligands

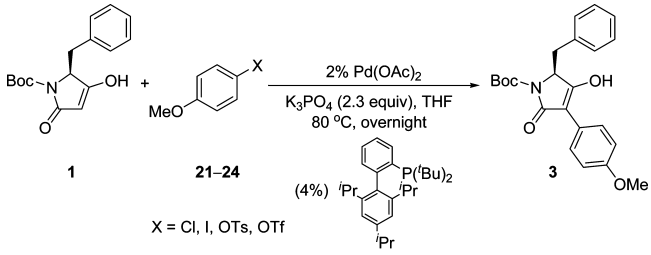


1 2 3 **10–20**

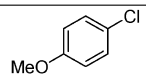
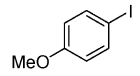
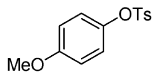
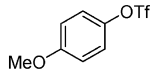
entry	ligand	conv (%)[a]
1	**10**	5
2	**11**	21
3	**12**	>95
4	**13**−**20**	<5

[a] Determined by ^{1}H NMR.

TABLE 5. Testing of Different Coupling Partners: Aryl Halides, Tosylate, and Triflate



1 **21–24** 3 **12**

entry	Ar-X	conv. %[a]
1	 **21**	>95
2	 **22**	<5
3	 **23**	8
4	 **24**	>95

[a] Determined by ^{1}H NMR.

only traces of the product **3** (entries 2 and 3). This observation is important because aryl chlorides are generally much cheaper than the corresponding iodides and a wider range of commercially available compounds exists.

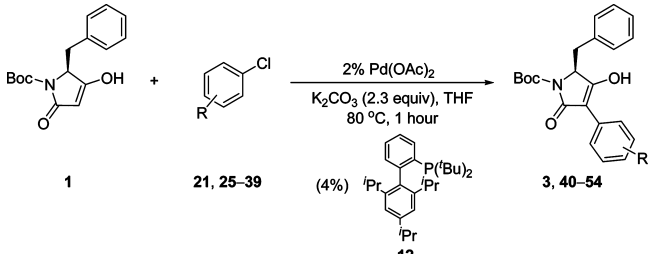
To fine-tune the chemistry, reaction time and temperature were taken into consideration again. It was found that the reaction is in fact complete in less than an hour at 80 °C with 4-chloroanisole (**21**) as the coupling partner. The product is stable under the reaction conditions and the reaction time can be extended to 16−20 h with no product decomposition. In addition, lower temperatures were also tested. At room temperature no reaction occurred and at 60 °C only 11% conversion was observed after 1 h. Therefore a temperature at 80 °C was chosen for further experiments.

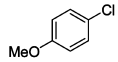
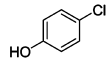
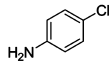
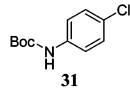
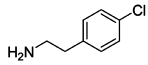
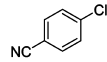
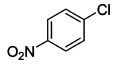
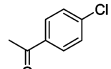
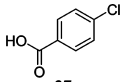
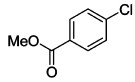
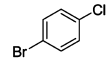
With these suitable reaction conditions in hand, we once again examined the catalyst loading. Reducing the loading of $Pd(OAc)_2$ to 1 mol % and ligand **12** to 2 mol %, only 35% conversion was achieved after 1 h. However, full conversion was achieved with overnight reaction times. As previously shown, K_3PO_4 and K_2CO_3 gave similar conversions. We chose to use K_2CO_3 exclusively because it is the most inexpensive. Control experiments with no palladium catalyst or ligand were performed, but no product was formed, as expected.

Using the optimized reaction conditions we tested a broad range of aryl chlorides with different substituents, electron-donating (EDG) as well as electron-withdrawing groups (EWG), and with different disubstitution patterns (see Table 6). Both meta- and para-disubstituted aryl chlorides reacted efficiently giving full conversion after 1 h for most of the substrates. Electron-donating groups such as ethers, alcohols, and amines (entries 3, 6, and 7) worked well and the same was true for a variety of electron-withdrawing groups like nitriles, nitro groups, ketones, and esters (entries 10, 12, 13, and 15). Chlorobenzene (**25**) itself also reacted smoothly giving full conversion after 1 h (entry 1). Coupling of 4-chlorophenol (**29**), 4-chloroaniline (**30**), and 4-chlorobenzoic acid (**37**) did not proceed to completion after 1 h (entries 6, 7, and 14), but full conversion was achieved overnight (16 h). Apparently, the unprotected functional groups slowed down the reaction. Protection of the aniline nitrogen as in (*N*-Boc)-4-chloroaniline (**31**) gave full conversion after 1 h (entry 8). In the case of a free aliphatic amine (entry 9), the unprotected nitrogen completely quenched the reaction. To synthesize a halogen-substituted product, we tested the chemistry with 1-bromo-4-chlorobenzene (**39**) (entry 16) and the 4-chloro product **54** was formed exclusively. This is reasonable because bromides react faster than chlorides. Finally, we examined a couple of similar ortho-substituted aryl chlorides, but none of them gave any significant product formation after 16 h (entries 4 and 11). For the case of 2-chloroanisole (**27**) we also tested 2-bromoanisole (**28**) to examine if the more reactive bromide would react, but that was not the case (entry 5). It is not surprising that ortho-substituted aryl halides did not react at all, since there is much more steric hindrance around the halogen. Use of less sterically demanding ligands did not solve this problem.

In all cases, the crude product was isolated as the enol tautomer upon acidic workup. However, during flash chromatography we discovered some degree of shifting in equilibrium toward the keto tautomer, which gives more complex NMR spectra. To shift back the equilibrium we found that suspension in EtOAc and treatment with 10% $KHSO_4$ was suitable, which eventually dissolved the compound completely as the solubilities of the keto and enol tautomers are quite different. An example of this equilibrium shifting is shown in Figure 6 with the 3-aryl tetramic acid **3**. To the left is shown the enol tautomer and the appurtenant ^{1}H NMR spectrum in DMSO-d_6 and to the right the two possible keto tautomers. The ^{1}H NMR spectrum of **3**-keto is more complex because of broad peaks which might be a result of the coexistence of both a cis and trans tautomer. For both the enol and the keto tautomers, LC-MS (5→95% MeCN in H_2O added 0.05% TFA) showed one peak with the same retention time. The acidic conditions apparently shift the equilibrium to one of the tautomers independent of the initial

TABLE 6. Substrate Scope with Different Substituted Aryl Chlorides



entry	Ar-Cl	time (h)	product	yield (%)[a]
1	 **25**	1	**40**	75
2	 **21**	1	**3**	79
3	 **26**	1	**41**	78
4	 **27**	16	**42**	–[b]
5	 **28**	1	**43**	–[b]
6	 **29**	16	**44**	72
7	 **30**	16	**45**	conv.: >95%[c]
8	 **31**	1	**46**	75
9	 **32**	1	**47**	–[b]
10	 **33**	1	**48**	74
11	 **34**	16	**49**	–[b]
12	 **35**	16	**50**	60
13	 **36**	1	**51**	74
14	 **37**	16	**52**	conv.: >95%[c]
15	 **38**	1	**53**	75
16	 **39**	1	**54**[d]	77

[a] Purified by flash chromatography. [b] No significant product formation determined by ^{1}H NMR or LC-MS. [c] Not purified by flash chromatography, but crude ^{1}H NMR is provided in the Supporting Information. [d] Only the 4-chlorobenzene product was observed determined by the isotope pattern of the molecular ion (LC-MS) of the product (see the Supporting Information).

equilibrium position. In the ^{1}H NMR spectra (see Figure 6) the chemical shift of H^5 is 4.71 ppm (dd) for the enol tautomer but 4.28 ppm (m) for the keto tautomers ($H^{5'}$). The coupling pattern of the H^6 diastereotopic protons also changes; for the enol-tautomer **3** the two protons are two well-resolved double doublets ($H^6{}_a + H^6{}_b$), whereas the keto tautomers (**3**-keto) show a multiplet in the region slightly upfield ($H^{6'}{}_a + H^{6'}{}_b$). On the basis of ^{1}H NMR it was not possible to determine the ratio between the cis/trans tautomers.

Besides the aryl chlorides we also examined the scope of the reaction with a series of chloro-substituted heterocycles (see Figure 7). Three different pyridines **55**−**57**, 2-chloropyrimidine (**58**), 5-chloro-1-methyl-1*H*-imidazole (**59**), two chloro thiophenes (**60** and **61**), and finally a bromo-substituted heterocycle, 3-bromothiophene (**62**), were tested. Unfortunately, none of them gave any significant formation of product after 16 h. It is plausible that the heteroatoms simply coordinate to palladium resulting in an unreactive complex.

The reaction between Boc-*py*Phe-OH (**1**) and 4-chloroanisole (**27**) was tested with microwave heating and it was found that full conversion (>95%) was achieved within only 5 min at 110 °C.

Finally, we wanted to expand the scope with other tetramic acids than Boc-*py*Phe-OH (**1**). A series of functionalized tetramic acids were chosen: Boc-*py*Tyr(*t*Bu)-OH (**63**), Boc-*py*Lys(Cbz)-OH (**64**), Boc-*py*Arg(Pbf)-OH (**65**), Boc-*py*Thr(O*t*Bu)-OH (**66**), Boc-*py*Asp(O*t*Bu)-OH (**67**), and the glycine-derived tetramic acid Boc-*py*Gly-OH (**68**). These were all subjected to the optimized reaction conditions with 4-chloroanisole (**21**) as the coupling partner (see Table 7). The chosen tetramic acids represent a broad variety of functional side chains and different protecting groups. Most of them gave similar yields compared to the previous results, but Boc-*py*Asp(*t*Bu)-OH (**67**) and especially Boc-*py*Gly-OH (**68**) gave much lower yield of the corresponding 3-aryl tetramic acids **73** and **74**, respectively (entries 5 and 6).

So far, all reactions were conducted in THF. We then revisited the initial reaction and tested some other solvents (see Table 8). Dioxane, MeCN, and DMF gave very low conversions (<5%) no matter which base was used (Cs_2CO_3, K_3PO_4, Na_2CO_3, and K_3CO_3, respectively) (entries 1−3). However, running the reaction in toluene gave a significantly different result (entries 4−7). First of all, conversions were all much higher than the equivalent experiments in THF (cf. Table 1, entries 2−5), even with Na_2CO_3 a conversion of 29% was achieved (see Table 8, entry 6). Full conversion was achieved with K_3PO_4, which gave only 36% conversion in THF with the very same ligand (**9**). Steric properties of the ligand are therefore not the only factor dependent on the efficiency of the catalytic system.

Surprisingly, the crude product isolated from the toluene/K_3PO_4 reaction was exclusively the keto tautomer (**3**-keto cis/trans, see Figure 6), whereas THF gave the enol tautomer **3** when the same acidic workup procedure was used. To investigate this point further, we tried to shift the equilibrium of the enol tautomer **3** by dissolving it in toluene, but nothing happened based on TLC analysis. When adding aqueous 10% $KHSO_4$ the enol tautomer was slowly shifted toward the keto tautomers (**3**-keto cis/trans), which have a significantly different R_f value. Isolation as the keto tautomers is unfortunately not always straightforward, and we discovered that it is easily shifted back to the enol tautomer. Formation of the less stable keto tautomers is not easy and it is rather unpredictable, probably because the

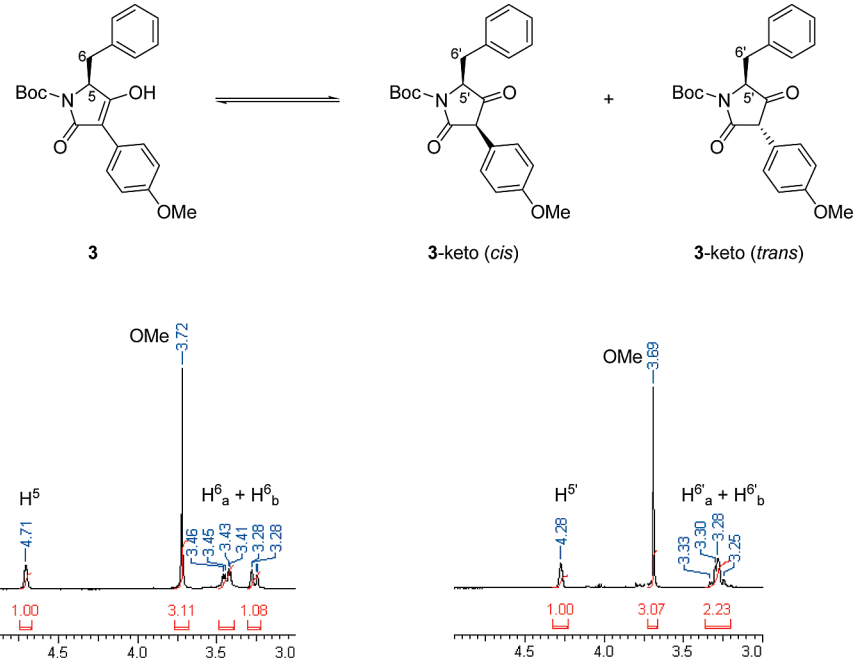
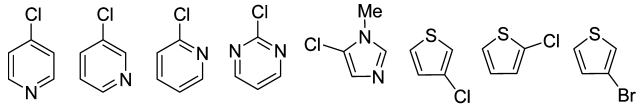


FIGURE 6. Observed tautomeric equilibrium and appurtenant ^{1}H NMR spectra (upfield region); the spectrum to the left belongs to the enol tautomer of **3** and the spectrum to the right to the keto tautomer (**3**-keto cis/trans).



55 **56** **57** **58** **59** **60** **61** **62**

FIGURE 7. Heteroaryl halides which did not undergo the title α-arylation.

equilibrium shifting is dependent on concentration, temperature, pH, and solvent. This is comparable with the literature regarding the keto−enol equilibrium of tetramic acids,[1,3,4] as previously described.

On the basis of the literature,[13a] we propose the following mechanism for the coupling reaction (see Figure 8). The catalytic cycle is assumed to be initiated by reduction of Pd(II) to the active Pd(0), which might happen by a homocoupling of the tetramic acids. Oxidation of phosphine ligands is another well-known pathway for generation of Pd(0). However, Barder and Buchwald reported recently that dialkylbiaryl phosphines are highly resistant toward oxidation by molecular oxygen.[17] Following reduction of Pd(II) to Pd(0), oxidative addition of the aryl halide **25** takes place, then transmetalation by the potassium enolate of the tetramic acid **1**. Upon reductive elimination the product is released and Pd(0) re-enters the catalytic cycle. The desired product **40** can be isolated by acidic workup.

In conclusion, we have developed a new, mild, and racemization-free palladium-catalyzed α-arylation of tetramic acids giving rise to 3-aryl amino acid-derived tetramic acids. Through optimization it was found that 2 mol % of $Pd(OAc)_2$ and 4 mol % of 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl (**12**) gave full conversion in THF at 80 °C after 1 h for most substrates. The two weak inorganic potassium bases, K_2CO_3 and K_3PO_4, worked equally well. The product could be isolated as either the enol or the keto tautomer depending on reaction solvent and the workup conditions, but shifted back to the enol tautomer upon EtOAc/10% $KHSO_4$ treatment. A variety of different substrates was tested and a range of functionalities are tolerated, e.g., Boc- or Cbz-protected amines, Pbf-protected guadinine groups, ethers, esters, ketones, alcohols, nitriles, and nitro groups. Heterocycles and unprotected amines are not compatible with this chemistry. Aryl chlorides, bromides, and triflates all coupled nicely, whereas aryl iodides and tosylates did not work. With respect to the substitution pattern of the aryl chloride, electron-withdrawing as well as electron-donating groups showed similar reactivity and meta- and para-substituted aryl chlorides reacted identically. Due to steric hindrance ortho-substituted aryl chlorides did not react. The title reaction can be facilitated by microwave heating with reaction time down to 5 min at 110 °C.

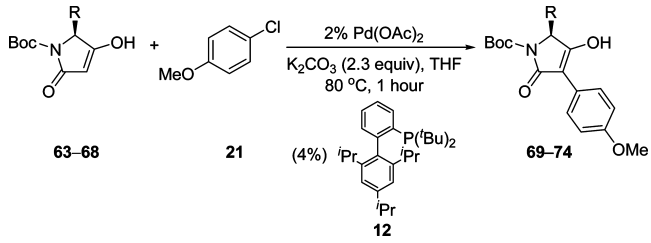
Synthesis of the previously mentioned amino benzyl ketones is currently under development in our laboratory. These building blocks will ultimately be used for the preparation of *C*-terminal modified peptidyl enzyme inhibitors.

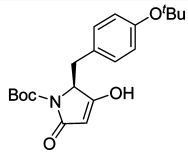
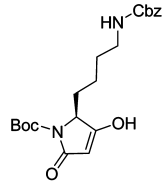
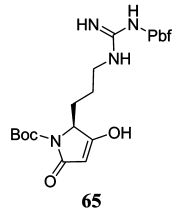
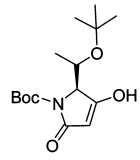
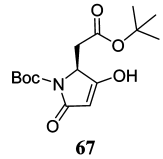
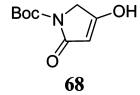
Experimental Section

General Arylation Procedure. A vial was charged with dry THF (3.0 mL), tetramic acid (1.00 mmol, 1.00 equiv), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (**12**) (17 mg, 0.04 mmol, 0.04 equiv), K_2CO_3 (318 mg, 2.30 mmol, 2.30 equiv), and an aryl chloride (1.00 mmol, 1.00 equiv). N_2 was bubbled through the reaction mixture and $Pd(OAc)_2$ (4 mg, 0.02 mmol, 0.02 equiv) was added, then the vial was filled with N_2, sealed with a screw cap, and placed in an aluminum heating block. The mixture was stirred vigorously at 80 °C for 1 h (or 16 h, cf. Tables 6 and 7). After being cooled to ambient temperature, the crude mixture was transferred to a separatory funnel with 10% aqueous $KHSO_4$ (10 mL) and extracted with EtOAc (30 mL + 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The yellow crude product was purified by flash chromatography (5→10% MeOH in EtOAc, in some cases up to 20% MeOH) affording the pure product typically as a keto/enol tautomer mixture. The product was subsequently suspended

(17) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.

TABLE 7. Substrate Scope with Different Tetramic Acids



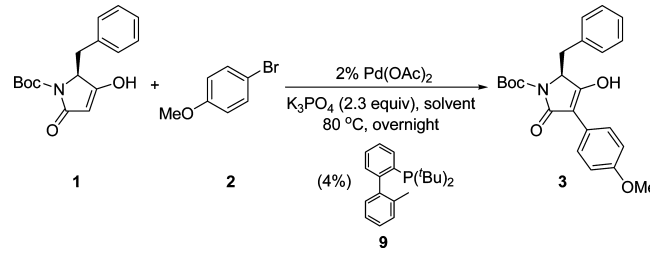
entry	tetramic acid	time (h)	product	yield (%)[a]
1	 **63**	1	**69**	69
2	 **64**	1	**70**	69
3	 **65**	16	**71**	67
4	 **66**	1	**72**	62
5	 **67**	16	**73**	45
6	 **68**	16	**74**	28[b]

[a] Purified by flash chromatography. [b] Flash chromatography did not successfully purify the product.

in EtOAc (50 mL). Ten percent aqueous $KHSO_4$ (50 mL) was added and the biphasic system was stirred vigorously at room temperature until complete dissolution of the compound. The mixture was transferred to a separatory funnel and the organic layer was separated. The aqueous layer was extracted with EtOAc (20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, evaporated in vacuo, and dried overnight in high vacuum, which afforded the pure product mostly as the enol tautomer.

(5*S*)-5-Benzyl-1-(*tert*-butyloxycarbonyl)-4-hydroxy-3-(4-methoxyphenyl)-1,5-dihydropyrrol-2-one (3). Following the general method for the arylation afforded 79% (313 mg) of the desired product as a pale brown solid. ^{1}H NMR (DMSO-d_6) δ 12.11 (br s, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.21−7.13 (m, 3H), 6.98 (d, J = 6.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.71 (dd, J = 4.3, 2.3 Hz, 1H), 3.72 (s, 3H), 3.44 (dd, J = 14.0, 4.9 Hz, 1H), 3.26 (dd, J = 13.8, 1.9 Hz, 1H), 1.53 (s, 9H). ^{13}C NMR (DMSO-d_6) δ 168.9, 167.6, 157.7, 149.0, 134.2, 129.5, 128.7, 127.9, 126.8, 122.9, 113.2,

TABLE 8. Initial Reaction Conducted in Toluene and Screened with Four Different Bases



entry	solvent	base	conv (%)[a]
1	dioxane	all four[b]	<5
2	MeCN	all four[b]	<5
3	DMF	all four[b]	<5
4	toluene	Cs_2CO_3	86
5	toluene	K_3PO_4	>95
6	toluene	Na_2CO_3	29
7	toluene	K_2CO_3	88

[a] Determined by ^{1}H NMR. [b] Tested with the four bases Cs_2CO_3, K_3PO_3, Na_2CO_3, and K_2CO_3, respectively.

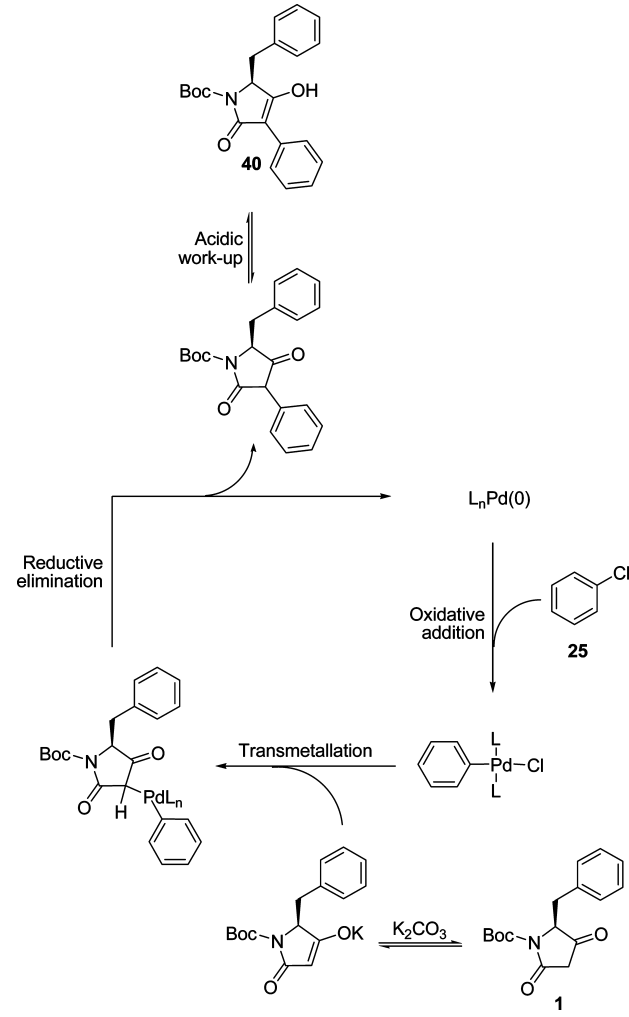


FIGURE 8. Proposed reaction mechanism for the α-arylation of tetramic acids.

105.1, 81.2, 57.9, 55.0, 34.6, 27.9. HRMS (*m*/*z*) calcd for $C_{46}H_{50}N_2O_{10}Na$ $[2M + Na]^+$ 813.3358, found 813.3367. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.84; H, 6.52; N, 3.49. Mp 142−145 °C. IR (neat) ν 2975, 2930, 1750 (strong), 1363, 1284, 1251, 1147, 1095, 833, 699 cm^{-1}. Chiral HPLC: 4.57 min (minor) and 5.78 min (major) gave an enantiomeric excess of 97%.

Microwave-Assisted Synthesis of (5*S*)-5-Benzyl-1-(*tert*-butyloxycarbonyl)-4-hydroxy-3-(4-methoxyphenyl)-1,5-dihydropyrrol-2-one (3). A microwave vial was charged with Boc-*py*Phe-OH (**1**) (289 mg, 1.00 mmol, 1.00 equiv), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (**12**) (17 mg, 0.04 mmol, 0.04 equiv), $Pd(OAc)_2$ (4 mg, 0.02 mmol, 0.02 equiv), and K_2CO_3 (318 mg, 2.30 mmol, 2.30 equiv). Dry THF (3.0 mL) was added and used to carefully rinse the inside of the vial (for safety reasons no solid may be stuck on the glass!). 4-Chloroanisole (**21**) (143 mg, 0.08 mL, 1.00 equiv) was added and N_2 was bubbled into the vial to secure an inert reaction atmosphere. The vial was capped, sealed, and heated to 110 °C in a microwave synthesizer for 5 min. After being cooled to ambient temperature, the crude product was neutralized with 10% $KHSO_4$ (10 mL) and EtOAc (30 + 20 mL) was added. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was analyzed by ^1H NMR in DMSO-d_6, which showed full conversion (>95%), and the spectrum was identical with that of the product obtained by conventional heating (80 °C, 1 h).

(5*S*)-5-Benzyl-1-(*tert*-butyloxycarbonyl)-4-hydroxy-3-phenyl-1,5-dihydropyrrol-2-one (40). Following the general method for the arylation afforded 75% (273 mg) of the desired product as a pale brown solid. ^1H NMR (DMSO-d_6) δ 12.30 (br s, 1H), 7.52 (dd, J = 8.3, 1.3 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.22−7.15 (m, 4H), 7.01−6.98 (m, 2H), 4.73 (dd, J = 4.8, 2.5 Hz, 1H), 3.45 (dd, J = 13.9, 4.8 Hz, 1H), 3.27 (dd, J = 14.0, 2.4 Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (DMSO-d_6) δ 170.2, 167.4, 149.0, 134.2, 130.5, 129.5, 127.9, 127.7, 127.5, 126.8, 126.3, 105.4, 81.2, 57.9, 34.6, 27.9. HRMS (*m*/*z*) calcd for $C_{44}H_{46}N_2O_8Na$ $[2M + Na]^+$ 753.3146, found 753.3153. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 71.97; H, 6.60; N, 3.96. Mp 86−88 °C. IR (neat) ν 3082, 3061, 2977, 2928, 1753, 1702, 1661, 1645 (strong), 1397, 1359, 1298, 1149, 694 cm^{-1}.

(5*S*)-5-(4-*tert*-Butoxybenzyl)-1-(*tert*-butyloxycarbonyl)-4-hydroxy-3-(4-methoxyphenyl)-1,5-dihydropyrrol-2-one (69). Following the general method for the arylation afforded 69% (324 mg) of the desired product as a pale brown solid. ^1H NMR (DMSO-d_6) δ 12.02 (s, 1H), 7.42 (d, J = 9.1 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 9.1 Hz, 2H), 6.77 (d, J = 8.6 Hz), 4.66 (dd, J = 4.6, 2.8 Hz, 1H), 3.71 (s, 3H), 3.39 (dd, J = 13.9, 4.6 Hz, 1H), 3.19 (dd, J = 13.9, 2.5 Hz, 1H), 1.53 (s, 9H), 1.16 (s, 9H). ^{13}C NMR (DMSO-d_6) δ 168.8, 167.6, 157.7, 153.7, 149.0, 130.0, 128.9, 128.7, 123.2, 122.8, 113.1, 105.4, 81.1, 77.7, 57.9, 55.0, 34.1, 28.4, 27.9. HRMS (*m*/*z*) calcd for $C_{54}H_{66}N_2O_{12}Na$ $[2M + Na]^+$ 957.4508, found 957.4516. Mp 147−153 °C. IR (neat) ν 2975, 2932, 1748, 1643, 1607, 1514, 1392, 1363, 1290, 1247, 1150 (strong), 1095, 894, 830 cm^{-1}.

Acknowledgment. Morten Storgaard thanks Novo Nordisk A/S, Corporate Research Affairs, and the Danish Ministry of Science, Technology and Innovation for financial support.

Supporting Information Available: Experimental procedures and characterization of all new compounds except those mentioned in the Experimental Section (compounds **3**, **40**, and **69**) and copies of ^1H and ^{13}C NMR spectra (including ^1H NMR spectra of compounds **45** and **52**), analytical HPLC chromatograms of compounds not provided with elemental analysis, chiral HPLC chromatogram of compound **3**, and MS (TOF ES+) of compound **54**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900799Y