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Stereospecific Palladium-Catalyzed C−H Arylation of Pyroglutamic Acid Derivatives at the C3 Position Enabled by 8-Aminoquinoline as a Directing Group

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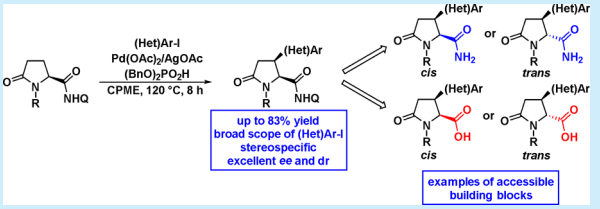
Supporting Information

ABSTRACT: An efficient and stereospecific Pd-catalyzed protocol for the C−H arylation of pyroglutamic acid derivatives that uses 8-aminoquinoline as a directing group is described. The reaction was shown to proceed efficiently with a variety of aryl and heteroaryl iodides bearing different functional groups, giving C3-arylated *cis* products in good to high yields. Removal of the 8-aminoquinoline unit from these C−H arylation products enables access to synthetically useful *cis* and *trans* pyroglutamic acid-based building blocks.



Pyroglutamic acid derivatives are an important class of molecules in organic and medicinal chemistry given their prevalence as intermediates or targets in the synthesis of bioactive compounds (Figure 1).[1] An appealing feature of the pyroglutamic

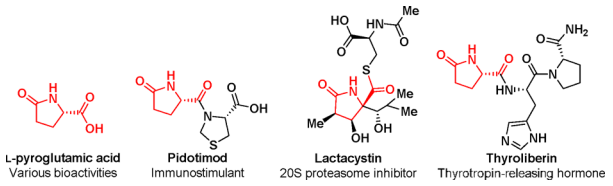


Figure 1. L-Pyroglutamic acid and its derivatives exhibit a wide range of bioactivities.

acid scaffold, particularly for applications in asymmetric synthesis, is that it presents an inexpensive source of chirality that can be conveniently accessed from glutamic acid. Most synthetic manipulations that have been conducted on pyroglutamic acid derivatives take advantage of the difference in stereoelectronic influence of the two carbonyl moieties, which have allowed for regioselective α-functionalization of either the C2 or C4 position.[1b] In contrast, functionalization of the C3 position of these compounds constitutes a significant challenge, particularly when attempted in the presence of other functional groups. Inspired by modern C−H functionalization methods that allow for more direct ways to form C−C and C−heteroatom bonds,[2] we identified an opportunity to functionalize the C3 position selectively using the carboxylic acid group as a handle for a directing group. Such a synthetic approach would enable straightforward access to a variety of C3-arylated pyroglutamic acid derivatives, which could comprise interesting entries in screening collections given the range of bioactivities exhibited by this family of compounds.[1]

Since the pioneering work of Daugulis and coworkers in 2005,[3] the combination of transition metal catalysis and directing group chemistry has emerged as a powerful technique to promote direct functionalization of a variety of unactivated primary and secondary alkyl C−H bonds.[2,4] This approach has proved particularly useful for a number of cycloaliphatic or heterocyclic substrates, as demonstrated by the recent protocols for the C(sp^3)−H arylation of benzodioxanes,[5] cyclopropanes,[6] cyclobutanes,[6d,7] pyrrolidines,[8] piperidines,[8a,9] and cyclic ethers.[5,6d,8a] For cyclic substrates, an attractive feature of these types of reactions is that the arylation proceeds *cis* with respect to the directing group, allowing for complete control of the stereochemistry. Despite the remarkable progress within the field of C−H functionalization in recent years, there exists, to the best of our knowledge, no report of a method for the Pd-catalyzed C−H arylation of pyroglutamic acid derivatives.

Our group recently developed a protocol for the Pd-catalyzed C−H arylation of azetidine derivatives utilizing 8-aminoquinoline (8-AQ) as the directing group, which facilitated the synthesis of a potent antimalarial compound.[10] Initial trials with model substrate **1** indicated that $Pd(OAc)_2$ and AgOAc with the 8-AQ auxiliary was an efficient combination for promoting C−H arylation at the C3 position of the pyroglutamic acid scaffold in a *cis* fashion. Further optimization efforts focused on the effects of additives, solvent, reaction concentration, and temperature on the C−H arylation of **1** (Table 1).[11] The first set of reactions was performed on a 0.1 mmol scale using $Pd(OAc)_2$ (5 mol %), AgOAc (1.5 equiv), and 4-iodotoluene (3 equiv) as the aryl source in DCE at 110 °C for 8 h (Table 1, entries 1−3). As observed in previous C−H functionalization studies,[8b,10,12] the addition of

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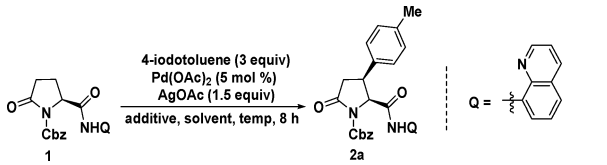
Table 1. Selected Entries from the Optimization of the Pd-Catalyzed C−H Arylation of Model Substrate 1[a]



entry	additive (equiv)	solvent (M)	temp (°C)	yield (%)[b]
1		DCE (0.5)	110	9
2	PivOH (0.2)	DCE (0.5)	110	8
3	$(BnO)_2PO_2H$ (0.2)	DCE (0.5)	110	65
4	$(BnO)_2PO_2H$ (0.2)	*i*-PrOH (0.5)	110	16
5	$(BnO)_2PO_2H$ (0.2)	toluene (0.5)	110	57
6	$(BnO)_2PO_2H$ (0.2)	1,4-dioxane (0.5)	110	60
7	$(BnO)_2PO_2H$ (0.2)	*t*-BuOAc (0.5)	110	65
8	$(BnO)_2PO_2H$ (0.2)	MeCN (0.5)	110	60
9	$(BnO)_2PO_2H$ (0.2)	CPME (0.5)	110	68
10	$(BnO)_2PO_2H$ (0.2)	CPME (1.0)	110	71
11	$(BnO)_2PO_2H$ (0.5)	CPME (1.0)	110	73
12	$(BnO)_2PO_2H$ (1.0)	CPME (1.0)	110	62
13	**$(BnO)_2PO_2H$ (0.2)**	**CPME (1.0)**	**120**	**80**
14[c]	$(BnO)_2PO_2H$ (0.2)	CPME (1.0)	120	nd
15[d]	$(BnO)_2PO_2H$ (0.2)	CPME (1.0)	120	<5

[a]Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (5 mol %), $Ag(OAc)_2$ (1.5 equiv), additive, and 4-iodotoluene (3 equiv) were dissolved in solvent and heated at the given temperature under N_2 atm for 8 h. [b]Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]Performed without $Pd(OAc)_2$; nd = not detected. [d]Performed with 4-bromotoluene (3 equiv) instead of 4-iodotoluene.

dibenzyl phosphate had a positive impact on the performance of this reaction, allowing for arylated product **2a** to be obtained in 65% yield (vs 9% without). Pivalic acid (PivOH), a common acidic additive in transition-metal-catalyzed C−H activation reactions,[13] was not found to have the same beneficial effect, and **2a** was observed in only 8% yield. The reaction displayed a broad tolerance for solvents, giving moderate to good yields in toluene, 1,4-dioxane, *t*-BuOAc, MeCN, and cyclopentyl methyl ether (CPME) (entries 5−8). The reactions were generally highly selective: only the desired *cis* product **2a**[14] and starting material **1** were observed by ^1H NMR of the crude reaction mixture. However, when *i*-PrOH was used as the solvent, the reaction appeared to be less selective and only 16% yield of **2a** was obtained (entry 4). Among the evaluated solvents, CPME was selected for further experiments as it allowed for a high yield of **2a** and possessed a number of favorable, practical properties over the other solvents, such as having a higher boiling point and good safety profile.[15] The reaction also worked well when the concentration was increased, as demonstrated by the entry performed at a 1 M concentration, which gave 71% yield (entry 10).

Although dibenzyl phosphate had a clear positive effect on the performance of the reaction, no improvements in terms of yields were seen when the stoichiometry of this additive was increased beyond 0.2 equiv (Table 1, entries 11 and 12). Instead, the reaction benefitted from being run at 1 M concentration and 120 °C, affording **2a** in 80% yield (entry 13). Further efforts to optimize the reaction by extending the reaction time had minimal influence on the yield, which suggested that the catalytic system becomes substantially deactivated after 8 h. As expected, a control experiment without any Pd catalyst did not form any of the anticipated product (entry 14). The protocol proved ineffective when 4-bromotoluene was employed as an aryl source (entry 15) or when the C−H arylation was conducted on the corresponding substrate with either a free lactam N−H or a Boc protecting group (entries not shown).

With optimized conditions in hand, we next explored the scope of aryl iodides that could be used for the C−H arylation of **1** (Figure 2). The developed protocol was applicable to a wide

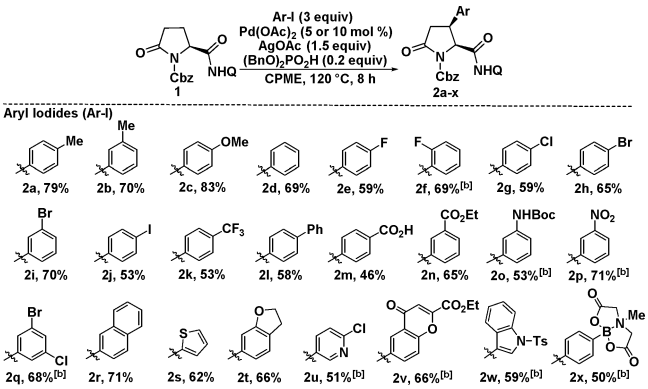


Figure 2. Scope of the Pd-catalyzed C−H arylation of pyroglutamic acid derivative **1**. Reaction conditions: substrate **1** (0.1 mmol, >99% ee), $Pd(OAc)_2$ (5 mol %), AgOAc (1.5 equiv), $(BnO)_2PO_2H$ (0.2 equiv), and aryl iodide (3 equiv) dissolved in CPME (0.2 mL) and heated at 120 °C under N_2 atm for 8 h. All yields refer to isolated yields following silica gel chromatography. [b]10 mol % of $Pd(OAc)_2$ was used.

variety of aryl and heteroaryl iodides, furnishing the corresponding C3-arylated lactam products in good to high yields with either 5 or 10 mol % of $Pd(OAc)_2$. C−H arylation reactions proceeded most efficiently with aryl iodides bearing electron-donating groups in the *para* position, as shown by reactions forming **2a** and **2c**. For aryl iodides containing electron-deficient groups or *meta* substituents, reactions were less efficient, but the desired arylated lactam products could still be isolated in satisfactory yields. Notably, the protocol also allowed aryl iodides containing chloro- and bromo-substituents to be used (**2g−2i**, **2q**) without giving rise to any side products originating from couplings over the C−Cl or C−Br bonds. Interestingly, when 1,4-diiodobenzene was used for the arylation, it was possible to obtain **2j** in 53% yield. The lower yield of this reaction was primarily due to a lower conversion of **1**, as only trace amounts were detected of the dimer product arising from arylation of another equivalent of **1** by **2j**. The developed protocol was used for installment of other synthetically useful functionalities such as carboxylic acid, ester and nitro groups, and Boc-protected amine (**2m−2p**), though these reactions typically proceeded in lower yields and required increased catalyst loadings. Successful C−H arylation was achieved with a number of different aryl and heteroaryl groups, including naphthyl **2r**, thiophene **2s**, dihydrobenzofuran **2t**, N-tosylated indole **2w**, and the more elaborately functionalized pyridine **2u** and chromene **2v**. The described protocol was also applied for synthesis of lactam **2x** bearing a MIDA boronate substituent in 50% yield, which is useful for further structural elaborations through cross-coupling chemistry.[16] Unfortunately, the C−H arylation was less efficient for incorporation of *ortho*-substituted aryl groups. With 10 mol % of Pd, we could prepare *ortho*-fluoro-substituted lactam **2f** in 69% yield; however, when arylation was attempted with 2-iodotoluene instead, only trace amounts of corresponding C3-arylated lactam was acquired (not shown). Importantly, reactions were fully stereospecific and

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proceeded without erosion of the stereochemistry when enantiomerically pure **1** (>99% ee; used in all reactions in Figure 2) was used.[17]

Next, we examined if the C−H arylation could be conducted on a broader scope of pyroglutamic acid derivatives, so we prepared **3a−c** bearing *N*-aryl substituents of varying electronic nature. These substrates were conveniently synthesized from enantiopure L-pyroglutamic acid in two steps via Cu-catalyzed Chan-Lam-type *N*-arylation[18] followed by installation of the 8-AQ directing group (see Supporting Information (SI)).

For this study, a small set of aryl iodides was chosen, comprising one electron-rich, one electron-deficient, and one heteroaromatic example (Figure 3). *N*-Arylated substrates **3a−c** were less reactive

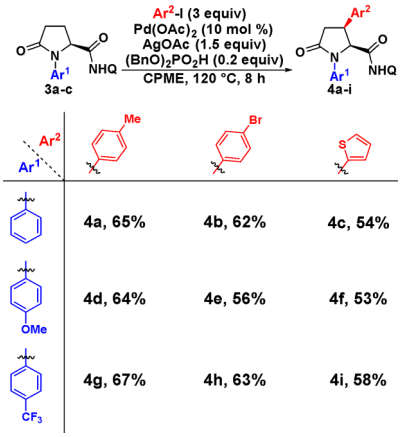


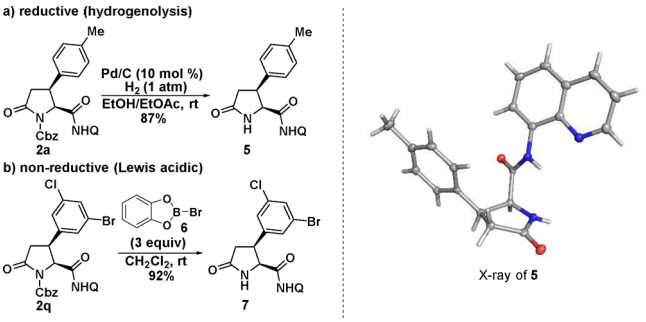
Figure 3. Pd-catalyzed C−H arylation of *N*-arylated pyroglutamic acid derivatives **3a−c**. Reaction conditions: substrate **3a−c** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (1.5 equiv), $(BnO)_2PO_2H$ (0.2 equiv) and aryl iodide (3 equiv) dissolved in CPME (0.2 mL) and heated at 120 °C under N_2 atm for 8 h. All yields refer to isolated yields following silica gel chromatography.

than **1**, calling for the use of higher catalyst loadings: with 10 mol % $Pd(OAc)_2$, the nine *N*-arylated lactam products **4a−i** were obtained in 53−67% yield with excellent control of stereochemistry.[19] The trend observed in aryl iodide reactivity in the reactions involving substrates **3a−c** were consistent with that observed for substrate **1**, where the highest yields were obtained with 4-iodotoluene. Although C−H arylation seemed to benefit slightly from electron-deficient *N*-aryl substituents, there was a very marginal difference in reactivity between **3a−c**.

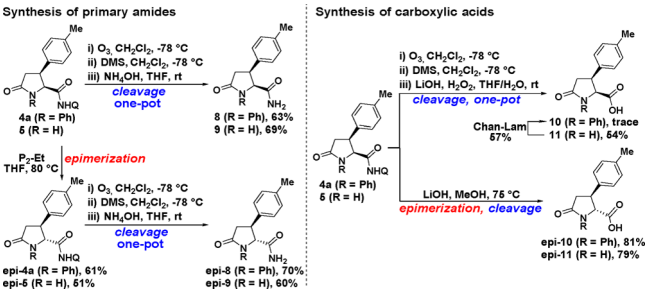
Having prepared a variety of C3-arylated pyroglutamic acid derivatives, we next evaluated their synthetic utility. For example, the Cbz-group of **2a** was conveniently removed by Pd/C-catalyzed hydrogenolysis to furnish unprotected lactam **5** in 87% yield (Scheme 1a), with both relative and absolute stereochemistry confirmed by X-ray crystallography. Although hydrogenolysis constitutes an operationally simple way of removing the Cbz group, it is incompatible with substrates containing reducible substituents. For the dihalogenated lactam **2q**, 3 equiv of catecholborane bromide **6**[20] can be used to remove the Cbz group, giving **7** in 92% yield (Scheme 1b).

To establish the synthetic utility of our method more completely, we focused on the cleavage of the 8-AQ directing group (Scheme 2). Using an operationally simple single-flask procedure,[21] we removed the 8-AQ directing group effectively from **4a** and **5** to form primary amides **8** and **9**, respectively. It was also possible to epimerize **4a** and **5** through the use of the phosphazene-type superbase P_2-Et[22] to give the *trans*-configured

Scheme 1. Reductive and Nonreductive Conditions for Removal of the Cbz Protecting Group from 2a and 2q



Scheme 2. Removal of the 8-AQ Directing Group from 4a and 5



products *epi*-**4a** and *epi*-**5** in 61 and 51% yield, respectively. With P_2-Et, complete epimerization was achieved after 24 h at 80 °C; the isolated yield of the epimeric products was typically moderate due to concomitant decomposition processes. For comparison, the same epimerization reaction was very inefficient with conventional bases, such as LiO^{t}Bu, DBU, and Et_3N. In an analogous manner, applying the ozonolytic directing group cleavage method on *epi*-**4a** and *epi*-**5** allowed access to *trans*-configured primary amides *epi*-**8** and *epi*-**9** in 70 and 60% yield, respectively.

Alternatively, the 8-AQ group can be cleaved to generate the free carboxylic acid building blocks. Using the ozonolytic conditions and cleaving the corresponding imide intermediate of **5** with $LiOH/H_2O_2$ at rt, it was possible to generate the *cis*-configured acid **11** in 54% yield. We observed significant amounts of *cis*-amide **9** in this reaction because of moderate regioselectivity in hydrolysis of the imide intermediate (Scheme S1). In the cleavage of **4a**, this side reaction was even more pronounced, and *cis*-amide **8** was formed almost exclusively over *cis*-acid **10**. Instead of optimizing this hydrolysis reaction, we prepared **10** from **11** by the same Chan-Lam method used previously for the synthesis of the *N*-arylated substrates **3a−c**. This reaction allowed us to obtain *cis*-acid **10** in 57% yield, which shows that **11** could be used as a potential building block for generating a diverse set of analogues through Cu-catalyzed *N*-arylation. The *trans*-configured acid products *epi*-**10** and *epi*-**11** were accessed in high yields by treating lactams **4a** and **5** with LiOH at 75 °C, which effectively cleaved the 8-AQ moiety with concomitant epimerization.

In summary, a new Pd-catalyzed protocol employing 8-AQ as the directing group was developed that allows for the stereospecific arylation of the C3 position of different pyroglutamic acid derivatives in good to high yields. Importantly, this C−H arylation proceeds efficiently with a diverse set of aryl and heteroaryl iodides containing a variety of functional groups. The obtained C3-arylated products were highly useful for a number of subsequent chemical transformations, which highlights the

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potential of this methodology to generate pyroglutamic acid derived analogues for small-molecule screening.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01776.

Experimental procedures, compound characterization data, and NMR spectra (PDF)
X-ray data for **5** (CIF)

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Notes

The authors declare no competing financial interest.

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