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Synthesis of chiral *N*-aryl pyrrolidinones via a palladium-catalyzed cross-coupling reaction

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Abstract—The direct synthesis of non-racemic *N*-aryl pyrrolidinones through the application of the Buchwald/Hartwig aryl amination reaction is reported. These reactions proceed in generally good yield, with a variety of electron deficient aryl bromides and with retention of stereochemical purity.

The *Martinella* alkaloids, **1** and **2** have attracted considerable attention from the synthetic community over the past few years.[1,2] This interest is due in large part to their unique structure and the unusual presence of three guanidino groups in a natural product. Our own efforts have centered on exploring the utility of an intramolecular azomethine ylide-alkene [3+2] cycloaddition.[3] Initial studies in this area employed C2-truncated models to establish the viability of the approach, and more recently, approaches to the construction of cyclization precursors containing the complete carbon side-chain have been investigated. As the retrosynthetic analysis in Fig. 1 indicates, we had hoped to employ a Buchwald/Hartwig aryl amination reaction with an appropriate aryl halide and a differentially protected amine derived from *S*-glutamic acid **6**.[4] Unfortunately, despite considerable effort, we were unable to effect this transformation. However, a report by Shakespeare appeared which suggested an alternate approach.[5,6] This report demonstrated that lactams, including pyrrolidinone, would effectively participate in cross-coupling reactions with aryl bromides, which in turn led us to investigate

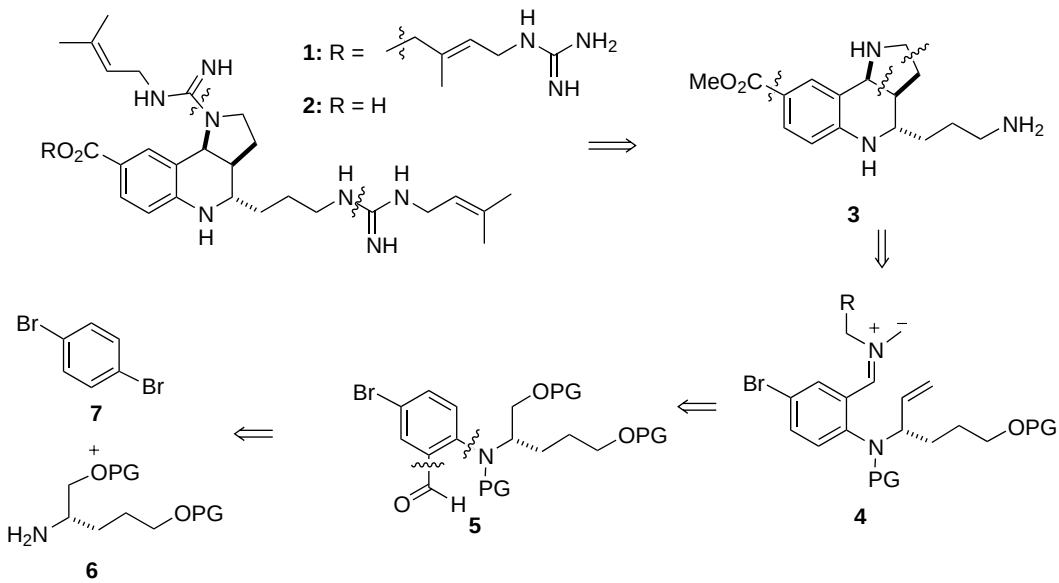

Figure 1. Retrosynthetic analysis of the *Martinella* alkaloids.

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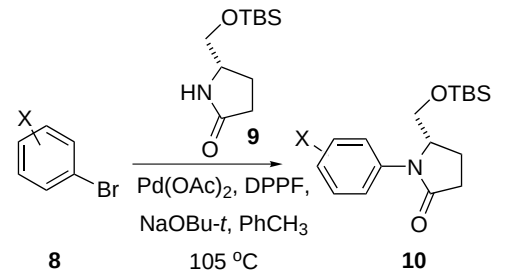
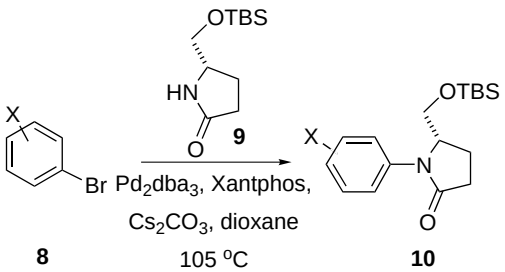
the possibility of utilizing pyroglutamate dervatives (Scheme 1). If this approach were successful, the somewhat lengthy preparation of the differentially protected glutamic acid derivative would be circumvented and a readily available, internally protected congener could be employed en route to martinelline. Although other approaches to related *N*-aryl lactams have been reported previously, they typically involve more steps or require harsher reaction conditions.[7,8] At the outset of this project there was concern that the introduction of the protected hydroxymethyl group might cause the cross-coupling to be sluggish. Also, of issue was the potential for racemization of the chiral center, which has been shown to be ligand dependent.[9] In the event, both of these concerns proved to be unfounded.

Initial experiments utilized conditions analogous to those employed in the Shakespeare report, i.e. 5 mol% $Pd(OAc)_2$, 6 mol% DPPF, *t*-BuONa, an aryl bromide **8** and the silylated lactam **9** (Scheme 1).[5,10] Under these conditions, only low yields of the cross-coupled product **10** were obtained. Optimization of this reaction was attempted and it did prove possible to obtain reasonable yields (ca. 70%) of *N*-aryl pyrrolidinones with highly electron deficient aryl bromides (*p*-CN or *p*-NO_2). Unfortunately, to obtain these yields, high catalyst loadings ($Pd(OAc)_2$-15 mol%, DPPF-30 mol%) were required. Further, the substrate scope was essentially limited to these two electron deficient systems.[11] During the course of these experiments, the Buchwald group disclosed that both inter- and intramolecular cross-couplings of amides (cyclic and acyclic) and aryl bromides would proceed efficiently with the appropriate choice of ligand.[12,13]



Scheme 1.



Scheme 2.

When the conditions developed by Buchwald for the intermolecular cross-coupling were applied to the pyrroglutamate derivative **9** with *p*-bromobenzonitrile, we were delighted to find that a smooth cross-coupling reaction had taken place to provide **10a** in 95% yield (Scheme 2). Given that this reaction had worked so efficiently, it was then applied to a variety of *p*-substituted aryl bromides. As can be seen in the Table 1, this coupling reaction proceeds effectively with all of the electron deficient systems, providing the aryl lactams in 62–95% yields. Interestingly, and in complete contrast with the Shakespeare conditions, some *o*-substituted bromobenzenes underwent cross-coupling to provide the *N*-aryl lactams in moderate to good yield (Table 1, entries 10 and 11, X = *o*-CN and *o*-NO_2). As expected, with larger *ortho* substituents the reaction was poor or failed altogether (X = *o*-CO_2Me and *o*-CHO). Interestingly, simple bromobenzene did not participate efficiently in this reaction in contrast with both Shakespeare's and Buchwald's results with the corresponding unsubstituted lactam.[5,12] An experiment with 4-iodobromobenzene illustrated that reaction occurs chemoselectively with the iodide.

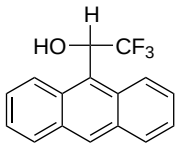
One of the remaining questions regarding these cross-coupling reactions was whether the stereochemical integrity of the chiral center was compromised. In order

Table 1. Yields for the *N*-arylation of aryl bromides[16]

Entry	R	**10**	Time (h)	Yield (%)	$[\alpha]_D$ (*c*)[a]
1	*p*-CN	**a**	3.5	95	−11.4 (0.5)
2	*p*-NO_2	**b**	3.5	91	+22.2 (0.5)
3	*p*-CO_2Et	**c**	8	91	+15.0 (2.0)
4	*p*-CF_3	**d**	3.5	95	−33.6 (0.3)
5	*p*-COPh	**e**	5.5	75	+41.8 (0.5)
6	*p*-Br	**f**	18	62	−31.2 (0.5)
7	*p*-Br[b]	**f**	18	63	−30.8 (0.5)
8	H	**g**	24	15	−12.4 (2.0)
9	*m*-OMe	**h**	6	86	−41.8 (0.5)
10	*o*-CN	**i**	48	74	−50.8 (0.5)
11	*o*-NO_2	**j**	48	52	−171.2 (0.5)
12	*o*-CO_2Me	**k**	48	5	Nd
13	*o*-CHO	**l**	48	0	Nd

[a] The optical rotations were recorded as solutions in $CHCl_3$ at 25°C (*c* = g/100 mL).
[b] In this case X = I and the reaction occurred with displacement of the iodide substituent.

to establish this unequivocally, the corresponding racemic lactams (from aryl bromides **8a**–**j** and (±)-**9**)[14] were prepared and then both racemic and non-racemic lactams were investigated by ^{1}H NMR spectroscopy in the presence of Pirkle's chiral solvating agent **11**.[15] These experiments demonstrated without a doubt that these transformations proceeded with retention of stereochemical integrity. When 4 equiv. of **11** were added to a $CDCl_3$ solution of the racemic *N*-aryl lactams, the *t*-butyl signals were well resolved. Under identical conditions, only one *t*-butyl signal was observed from the coupling products derived from the *S*-lactam. Doping experiments indicated that >2% of the other enantiomer would have been detected under the conditions employed to determine the optical purity and therefore these products are obtained in >95% ee.



11

In summary, non-racemic *N*-aryl lactams can be prepared from a variety of aryl bromides with retention of stereochemical integrity by application of the Buchwald/Hartwig reaction in excellent to moderate yield by employing xantphos as a ligand. The elaboration of these adducts into the *Martinella* and other alkaloids is currently under investigation and the results of these studies will be reported in due course.

Acknowledgements

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16. General procedure: A 10 mL Schlenk tube containing lactam **9** (278 mg, 1.2 mmol), Cs_2CO_3 (456 mg, 1.4 mmol), xantphos (44 mg, 7.5 μmol), and Pd_2dba_3 (23 mg, 2.5 μmol) was alternately evacuated and backfilled with nitrogen. Dioxane (1 mL) and the aryl bromide (1.0 mmol) were introduced and then the mixture was heated at 105°C until the reaction was complete. The mixture was cooled, diluted with CH_2Cl_2 and then filtered through Celite. After concentration, the residue was purified by flash chromatography (SiO_2, hexane/EtOAc) to provide the *N*-aryl pyrrolidinone.