Synthesis of Tricyclic Nitrogen Heterocycles by a Sequence of Palladium-Catalyzed N—H and C(sp³)—H Arylations

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A range of tricyclic nitrogen heterocycles were synthesized in a straightforward and efficient manner via a sequence involving palladiumcatalyzed *N*-arylation and $C(sp^3)$ —H arylation as the key steps. Whereas the $C(sp^3)$ —H arylation furnished fused 6,5,6-membered ring systems efficiently, the formation of the more strained 6,5,5-membered systems proved to be more challenging and required a subtle adjustment of the reaction conditions.

In recent years, transition-metal-catalyzed C–H bond functionalization has emerged as a powerful tool to transform otherwise unreactive C–H bonds into carbon– carbon or carbon–heteroatom bonds.^{1,2} In particular, this approach has been utilized to construct³ and functionalize⁴ heterocyclic systems, which have broad interest for the synthesis of bioactive molecules and organic materials. Most existing C–H functionalization methods employed to assemble heterocycles involve the cleavage of $C(sp^2)$ –H bonds, and in comparison much less effort has been devoted to methods involving the somewhat more challenging

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activation of nonacidic $C(sp^3)$ -H bonds.^{5–7} Inspired by former work on the synthesis of indolines by palladium(0)-catalyzed $C(sp^3)$ -H arylation,^{6f,k} we envisioned that a similar strategy could be utilized to access fused tricyclic

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 γ - and δ -lactams **1** (Z = CH₂) and analogues from aryl bromides **2** (Scheme 1). An efficient synthesis of these rather unique heterocycles⁸ should streamline access to bioactive alkaloids such as mangochinine (**5**)⁹ and glionitrin **B** (**6**).¹⁰ In turn, aryl bromides **2** would be obtained by a Buchwald–Hartwig *N*-arylation/electrophilic bromination sequence, thereby securing a straightforward and modular synthesis of target lactams **1**.





We began our study with the exploration of the first key N-arylation step (Scheme 2). The Pd-catalyzed N-arylation of γ -lactams has been reported to occur with high yields.¹¹ In line with these data, N-arylated γ -lactams 7a-f bearing electron-withdrawing substituents on the benzene ring were obtained in good-to-excellent yield (68-99%) by using Pd(OAc)₂/Xantphos as the catalyst.¹² Similarly to γ -lactams, analogous oxazolidinone (Z = O) and imidazolidinone (Z = NCy) also underwent N-arylation efficiently (7g,h), in line with literature precedents.¹³ In contrast, δ -lactams have been shown to be less reactive than γ -lactams, and as a consequence the Pd-catalyzed *N*-arylation of the former has been much less developed.^{11a} Nevertheless, the above reaction conditions were found to be also applicable to δ -lactams (7i–o) as well as analogous 6-membered cyclic carbamate (7p), urea (7q), and diketopiperazine (7r). Indeed, high yields of the corresponding

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(12) Aryl substituents R^1 , R^2 were chosen for their ability to direct bromination in *ortho* position to the lactam during the next step.

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Following *N*-arylation, the regioselective bromination of compounds 7a-r was performed, giving rise to the corresponding aryl bromides 2a-r in 73-97% yield by using either Br₂/AgNO₃ or *N*-bromosuccinimide (see the Supporting Information for details). Next, the second key $C(sp^3)$ -H arylation step was investigated. We first applied conditions initially reported by Fagnou et al.^{6d} and then successfully transposed to other heterocyclic systems^{6f,j-1} to aryl bromide 2f (Table 1, entry 1). Thus, with Pd(OAc)₂/ PCy₃ as the catalyst and cesium carbonate/pivalic acid as the base/additive in mesitylene at 140 °C, protodebromination product 7f was formed with complete conversion. This failure can be ascribed to the excessive strain of the target tricyclic ring system, as compared to previously successful bi- and tricyclic systems.^{6f} Changing the base to potassium carbonate (entry 2) or the solvent to DMF (entry 3) failed to provide any observable trace of desired product 1f. Interestingly, compound 1f was formed in small amounts with toluene as the solvent (entry 4). A reexamination of different carbonates with this solvent

⁽¹⁴⁾ For instance, N-arylation failed with $Z = CH_2$ and $R^1 = R^2 = OMe$.

(entries 5–8) led to an optimal result with potassium carbonate (entry 6). Moreover, by combining K_2CO_3 with various amounts of Na₂CO₃ (entries 9–12), we found that the selectivity of **1f** vs **7f** could be reversed, with **1f** becoming the major product.



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entry	base(s) (equiv)	solvent	$\operatorname{conversion}^{a}\left(\%\right)$	$\mathbf{1f}:\mathbf{7f}^{a}$
1	$Cs_2CO_3(2.0)$	mesitylene	>99	<1:99
2	$K_{2}CO_{3}\left(2.0\right)$	mesitylene	>99	<1:99
3	$Cs_{2}CO_{3}\left(2.0\right)$	DMF	>99	<1:99
4	$Cs_{2}CO_{3}\left(2.0\right)$	toluene	>99	1:49
5	$Rb_2CO_3\left(2.0 ight)$	toluene	>99	1:11
6	$K_{2}CO_{3}(2.0)$	toluene	>99	1:1.6
$\overline{7}$	$Na_2CO_3\left(2.0 ight)$	toluene	4	1:1
8	$Li_{2}CO_{3}(2.0)$	toluene	14	<1:99
9	$K_{2}CO_{3}(1.3)$	toluene	>99	1:2
10	$K_{2}CO_{3}(1.3)$	toluene	>99	3:1
	$Na_2CO_3\left(1.3 ight)$			
11	$K_{2}CO_{3}(1.3)$	toluene	>99	2.8:1
	$Na_2CO_3\left(0.9 ight)$			
12	$K_{2}CO_{3}(1.3)$	toluene	>99	2.7:1
	$Na_2CO_3\left(0.3 ight)$			
13	K ₂ CO ₃ (1.3)	toluene	>99	3:1 (86%) ^b
	Na_2CO_3 (0.3)			

^{*a*} Conversion of **2f** and ratio of **1f**:**7f** determined by ¹H NMR and GCMS analysis of the crude mixture. ^{*b*} Pd(PCy₃)₂ was used instead of the Pd(OAc)₂/PCy₃·HBF₄ mixture. Yield of the isolated mixture in parentheses.

In related reactions, the $C(sp^3)$ –H activation step was shown to occur through the base-induced, concerted metalation–deprotonation (CMD) mechanism.^{6d,j,k,15} The beneficial effect of the combination of K₂CO₃ and Na₂CO₃ highlights the impact of the base countercation, lying in the second coordination sphere of Pd, in such mechanism. Finally, more reproducible results were obtained when the well-defined Pd(PCy₃)₂ complex was employed instead of the in situ mixture of Pd(OAc)₂ and phosphine ligand (entry 13). Under these conditions, an inseparable mixture of **1f**:**7f** (3:1) was isolated in 86% combined yield. The above results show that, for difficult cases of $C(sp^3)$ –H arylation, subtle adjustments of the solvent and base must be performed to form the desired product at the expense of the competitive protodebromination product.





^a Yield of the isolated products in parentheses.

 $^{b}\,\mathrm{Yield}$ and ratio of the mixture of desired:protodebromination products.

 $^{c}\operatorname{Protodebromination}$ and degradation were observed by GCMS analysis.

^d 85% of the starting material was recovered after 48 h.

The optimized conditions were then applied to various aryl bromides obtained by the *N*-arylation/electrophilic bromination sequence (Scheme 3). In line with the above results, fused γ -lactams **1a**-**f** were obtained in moderateto-good yields together with the corresponding protodebromination products, that could be separated in most instances (**1b**-**e**). Unfortunately, the more rigid oxazolidinone **2g** and imidazolidinone **2h** failed to undergo intramolecular C(sp³)-H arylation under the same conditions. In contrast, the reaction of the less rigid δ -lactams **2i**-**o**, oxazinanone **2p** and tetrahydropyrimidone **2q** provided the corresponding tricyclic products **1i**-**q** in good-to-excellent yields. In addition, original fused diketopiperazine **1r** was also obtained efficiently by this method.^{10,16}

The X-ray crystal structures of representative target molecules **1m** and **1r** were elucidated (Figure 1), showing that these compounds exhibit a relatively similar rigid tricyclic scaffold.

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Figure 1. X-ray crystal structure of compounds **1m** (top) and **1r** (bottom) (30% probability ellipsoids plot).

In conclusion, we have described a straightforward strategy to synthesize original fused tricyclic nitrogen

heterocycles by using Pd-catalyzed *N*-arylation and C (sp^3) -H arylation as the key steps. This work further illustrates the impact of emerging C-H functionalization methods on the synthesis of new interesting molecular scaffolds.

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Supporting Information Available. Full characterization of all new compounds, detailed experimental procedures, copies of NMR spectra for target molecules, and X-ray crystal structure data (CIF) for compounds **1m** and **1r**. This material is available free of charge via the Internet at http://pubs.acs.org.