A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201800958
Angew. Chem. 10.1002/ange.201800958

Link to VoR: http://dx.doi.org/10.1002/anie.201800958
http://dx.doi.org/10.1002/ange.201800958

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10.1002/anie.201800958

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Direct Palladium-Catalyzed *β*-Arylation of Lactams

Ming Chen[†], Feipeng Liu[†,‡] and Guangbin Dong*[†]

Abstract: A direct and catalytic method is reported here for β-arylation of *N*-protected lactams with simple aryl iodides. The transformation is enabled by merging soft enolization of lactams, Pd-catalyzed desaturation, Ar−X bond activation and aryl conjugate addition. The reaction is operated under mild conditions, scalable and chemoselective. Application of this method to concise syntheses of pharmaceutically relevant compounds is demonstrated.

Lactams with a β-aryl substituent are frequently found in drugs and pharmaceutical intermediates (Figure 1).[1] Conventionally, they are often prepared through conjugate addition of an aryl nucleophile to an α,β-unsaturated lactam.[2] This approach typically requires formation of an organometallic reagent from an aryl halide and oxidative dehydrogenation of a saturated lactam. Clearly, a more straightforward approach would be directly coupling of an aryl halide at the β-position of a saturated lactam, which remained an unmet challenge. Since the seminal work by Daugulis,[3] β-arylation of amides has been enabled using a directing group strategy (Scheme 1a).[4,5] Unfortunately, such a strategy is not applicable to lactams, and hence, the lack of chelation assistance in lactams calls for a different mode of activation for β-arylation. Herein, we describe the development of a Pd-catalyzed redox-cascade strategy for direct arylation at lactam β-positions with readily available aryl iodides (Scheme 1b). Compared with the conjugate addition approach, this method avoids preparing unsaturated lactams and aryl nucleophiles in advance.

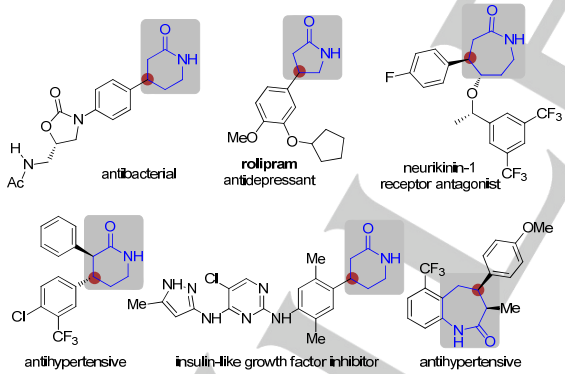
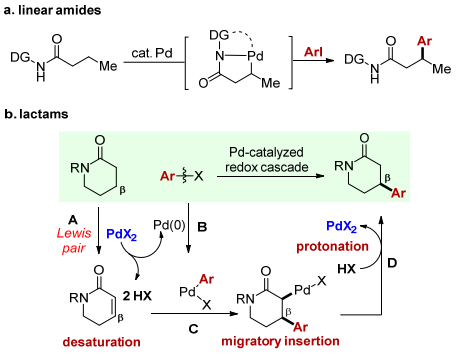


Figure 1. Bioactive lactams with β-aryl substituents

In 2013, we showed that direct β-arylation of ketones can be realized via a Pd-catalyzed redox cascade process (Scheme 1b), which involves Pd(II)-mediated ketone desaturation (step A), Pd(0)-mediated Ar−X oxidative addition (step B), Pd(II)-aryl conjugate addition (step C) and protonation of the resulting Pd(II)-enolate (step D).[6] However, direct implementation of this strategy for amide substrates is difficult, as amides do not easily undergo α,β-desaturation under such reaction conditions.[7] Recently, we developed a catalytic amide desaturation method assisted by soft enolization, in which a bulky benzoquinone serves as the optimal oxidant.[8] Despite the feasibility of desaturating lactams (step A) in the proposed redox cascade, *three concerns* remain to be addressed for successful β-arylation of lactams. *First*, it is uncertain if the Lewis pair used in the soft enolization would be compatible during the remaining catalytic cycle, particularly in the C−C bond forming step. *Second*, it is uncertain if aryl halides would substitute the bulky benzoquinone and serve as an effective oxidant for Pd(0), as electron-donating ligands cannot be used for lactam desaturation,[8,9] which increases difficulty for the oxidative addition step (step B). *Third*, the migratory insertion step (step C) needs to be fast enough; otherwise, α-arylation side reaction[10] would compete due to the presence of *highly nucleophilic* amide enolates (*vide infra*, Table 3).

Scheme 1. β-Arylation of Amides.



To examine the feasibility of the proposed strategy, our study began with valerolactam **1a** and 4-(CF_3)-iodobenzene **2v** as the model substrates. After careful optimization, the use of $Pd(TFA)_2$ as the pre-catalyst and AgTFA as the promoter ultimately afforded the desired β-arylation product **3v** in 73% yield at room temperature via a boron-enolate intermediate. (Table 1). The homo-coupling product **HC-2v** and the further oxidized product **DH-3v** were formed in 6% and 8% yields, respectively, and no desaturated **1a** (**DH-1a**) remained. To understand the role of each reactant, control experiments were conducted. Clearly, the palladium pre-catalyst, the silver salt and the Lewis pair are all critical for this transformation (entries 1-4). It was proposed that the silver salt promoted iodide-carboxylate exchange to regenerate the active Pd(II) catalyst. The Lewis acid/base pair plays a pivotal role in forming the boron-enolate intermediate.

[†]Department of Chemistry, University of Chicago, Chicago, Illinois, 60637, United States
[‡]Department of Applied Chemistry, China Agricultural University, 2 West Yuanmingyuan Road, Beijing 100193, China

* Correspondence: gbdong@uchicago.edu (G. D.)

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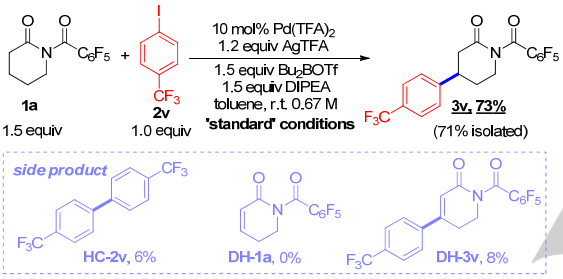
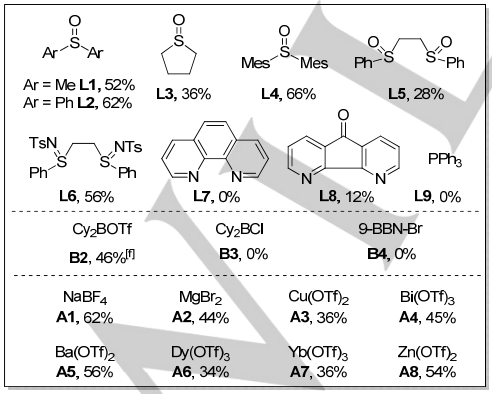
Notably, no additional ligand was used in this reaction. A range of phosphine, nitrogen and sulfur-based ligands have been examined (entry 5). Sulfoxide type ligands were previously found to be important in lactam dehydrogenation;[8] however, they led to decreased yields in this reaction. The use of pyridine or phosphine-based ligands dramatically shut down the reactivity. Using Cy_2BOTf instead of Bu_2BOTf gave a lower yield (46%), though formation of side products **HC-2v** and **DH-3v** also diminished (entry 6). Replacing the trifluoroacetate counterion of the palladium and the silver salt with OAc resulted in a decreased yield (entry 7), in which significant amounts of homo-coupling product **HC-2v** (17% yield) and desaturated lactam **DH-1a** (12% yield) were formed. This indicates that trifluoroacetate anion promotes the Pd-aryl species to undergo migratory insertion into **DH-1a**, rather than a self-coupling. Attempts of using Lewis acids to accelerate the protonation step (step D) were unfruitful (entry 8). A survey of different solvents suggests

Table 1. Selected Optimization Studies.[a]



Entry	Variations from the 'standard' conditions	Yield (%) of **3v**[b]
1	without **$Pd(TFA)_2$**	0
2	without **AgTFA**	0
3	without **Bu_2BOTf**	0
4	without **DIPEA**	0
5	**20 mol% L1-9 was used**	Listed below
6	**B2-B4** instead of **Bu_2BOTf**	Listed below
7	**$Pd(OAc)_2$ / AgOAc** instead of **$Pd(TFA)_2$ / AgTFA**	48[c]
8	5 mol% **Additive A1-A8** was used	Listed below
9	solvent = THF	0
10	solvent = 1,4-dioxane	60[d]
11	solvent = MeCN	0
12	solvent = PhF	75[e]



[a] Each reaction was run on a 0.1 mmol scale in a sealed 4 mL vial for 48 h. [b] Yields were determined by ^1H NMR using CH_2Br_2 as the internal standard. TFA = trifluoroacetate. [c] 17% yield of **HC-2v** and 12% yield of **DH-1a.** [d] 9% yield of **HC-2v** and 10% yield of **DH-3v**. [e] 5% yield of **HC-2v** and 8% yield of **DH-3v**. [f] 2% yield of **HC-2v** and 4% yield of **DH-3v.**

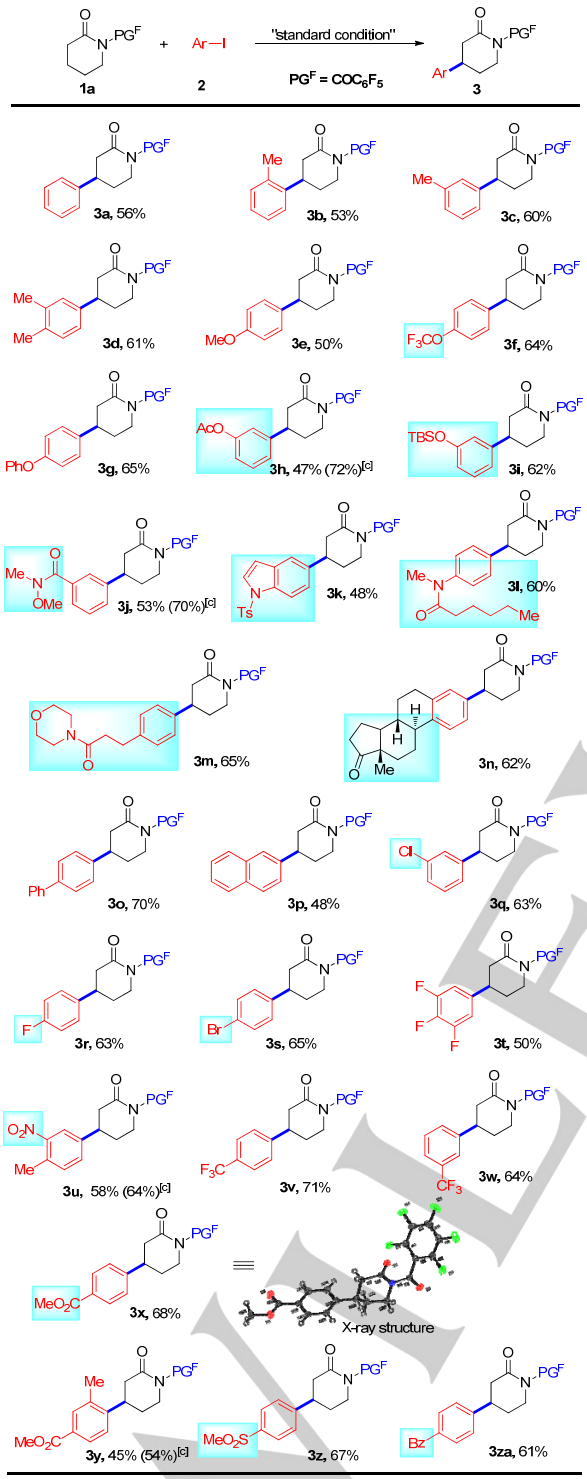
aromatic solvents, such as toluene and fluorobenzene, to be optimal (entries 9-12), though 1,4-dioxane also delivered the product in 60% yield; in contrast, more polar THF and CH_3CN gave no conversion of lactam **1a.**

Subsequently, the substrate scope of aryl iodides was investigated (Table 2). Aryl iodides bearing either electron-donating or -withdrawing groups all participated to give the corresponding β-arylated lactams in moderate to good yields. The corresponding aryl bromides are not reactive. In addition, substitutions at *ortho*, *meta*, or *para* positions all worked comparably well (**3a-d**). A range of functional groups are compatible, such as aryl esters (**3x,**[11] **3y**), Weinreb amides (**3j**), protected indoles (**3k**), amides (**3l, 3m**), ketones (**3n, 3za**) fluorides (**3r, 3t**), chlorides (**3q**), bromides (**3s**), nitro (**3u**), trifluoromethyl (**3v, 3w**), and sulfone moieties (**3z**). Acid sensitive groups, e.g. silyl-ether (**3i**), or base sensitive groups, e.g. phenolic ester (**3h**), are tolerated. When aryl iodides containing additional enolizable tertiary amides (**3l, 3m**) or ketone (**3n**) were employed, the β-arylation still occurred at the lactam moiety. One key for such chemoselectivity is the order of addition of the reagents: pre-mixing lactam substrates with Bu_2BOTf and DIPEA before adding aryl iodides allowed for selective enolization of the lactam moiety. In all these examples, the over-oxidation products were observed in 5-10% yields; no α-arylation products were found.

Lactams with different ring sizes were also examined as substrates (Table 3). 1,3-Difluorobenzene was found to be a better solvent for other lactams than **1a**. Surprisingly, the five-membered lactam only afforded the α-arylation product (**4a**) in 60% yield, and the seven-membered lactam gave a 1:1 mixture of the α- and β-arylation products (**4b**). We speculated that the α-arylation products might come from a direct enolate arylation pathway[12] as desaturation of five- and seven-membered lactams were found to be slower than the six-membered ones.[8] The benzofused six-membered lactams also only gave the α-arylation products (**4c, 4d**); however, the benzofused seven and eight-membered lactams all successfully delivered the desired β-arylation products (**4e-4l**). Interestingly, the substrate with a γ-substituent furnished product **4g** in an excellent diastereoselectivity favoring the *trans* product. In the presence of an enolizable ester group (**4h**), β-arylation still preferred to occur at the lactam. In addition, eight-membered lactams with aryl or cyclopropyl substituents (**4j, 4k**) are competent substrates.[13] The oxazocine derivative also gave the desired product (**4l**).

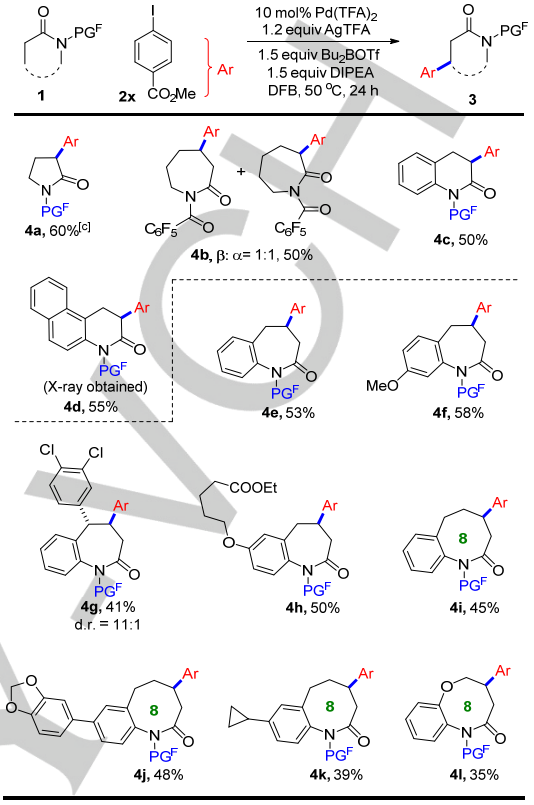
To understand why benzofused six-membered lactams preferred to give the α-arylation products, desaturation of benzofused six-eight membered lactams was carried out. The study showed that, while the seven- or eight-membered lactams worked normally and delivered the desired products in in good yields, the six-membered lactam surprisingly only gave the deprotected product **5a**. Due to the high aromaticity of **5a** aryl migratory insertion would be highly challenging. As a result, such substrates would be problematic to afford the β-arylation products; instead, the α-arylation pathway would then dominate.

Table 2. Substrate Scope with Aryl Iodides[a,b]



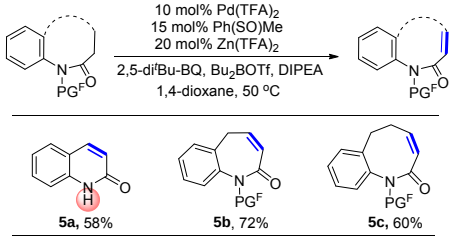
[a] Each reaction was run on a 0.2 mmol scale in a sealed 8 mL vial for 48 h. [b] Isolated yields. Numbers in parenthesis are yields based on recovered starting material. [c] 1.8 equiv **1a**, 1.8 equiv Bu_2BOTf and 1.8 equiv DIPEA was used.

Table 3. Substrate Scope with Lactams[a,b]

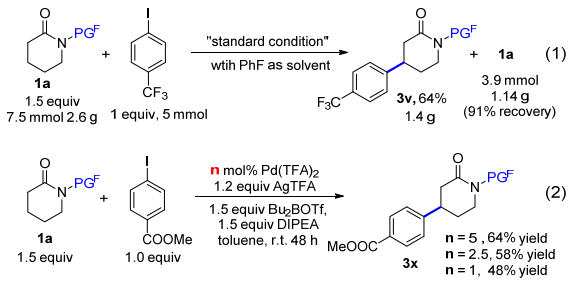


[a] Each reaction was run on a 0.2 mmol scale in a sealed 8 mL vial for 24 h. [b] Isolated yields. [c] 20 mol% $Pd(TFA)_2$ was used. DFB=1,3-difluorobenzene.

Scheme 2. Dehydrogenation of Benzofused-lactams

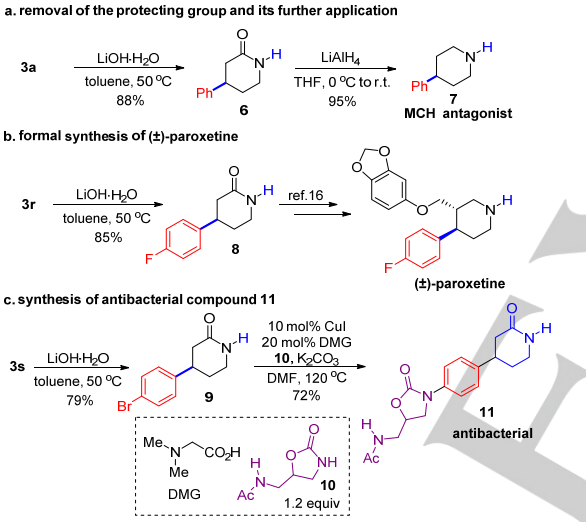


To test the practicality of this method, a gram-scale reaction was carried out, which gave 64% yield and high recovery of unreacted lactam **1a** (Eq 1). Moreover, when the palladium loading was reduced to 5, 2.5 and 1 mol%, though the conversion was lower, up to 48 turnovers were obtained (Eq 2).



To show the synthetic utility of this method, first, the acyl protecting group was easily removed to reveal free lactams under mild conditions (Scheme 3a).[14] Upon reduction with $LiAlH_4$, **6** was conveniently converted to γ-arylated piperidine **7** that is known to be a melanin-concentrating hormone (MCH) antagonist.[15] In addition, using this β-arylation method followed by deprotection, formal synthesis of paroxetine, an anti-depression drug, was realized in a concise fashion (Scheme 3b).[16] Furthermore, a streamlined synthesis of antibacterial compound **11** has been accomplished in a good overall yield (Scheme 3c). Given that arylbromide is tolerated under the β-arylation conditions, a highly chemoselective C−N coupling between the arylbromide (**9**) and the oxazolinone (**10**) moieties was enabled using copper catalysis.[17] Note that this antibacterial compound is now made in only four steps from inexpensive 2-pyrrolidinone; in contrast, the previous approach took seven steps.[1f]

Scheme 3. Synthetic Applications



In summary, an initial catalytic approach for direct β-arylation of lactams is developed. This method tolerates a wide range of functional groups, and shows promising scalability. It offers a unique strategy to access β-arylated lactams and γ-arylated piperidines, and streamlines synthesis of pharmaceutically important compounds. Future work will involve minimizing side-product formation through detailed mechanistic study as well as developing an enantioselective version of this transformation.

Acknowledgements

We thank University of Chicago for a startup fund. M.C. thanks Shanghai Institute of Organic Chemistry for a postdoc fellowship. F.L. is supported by a CSC fellowship. Mr. Chengpeng Wang is acknowledged for checking the experiments.

Keywords: β-arylation • lactam • palladium catalysis • soft enolization • C−C formation

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10.1002/anie.201800958

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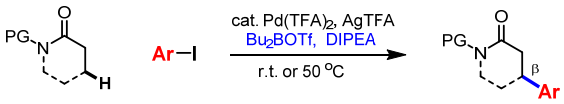

- *one-step operation and mild conditions*
- *direct functionalization of the β-C–H Bond*
- *scalable and high functional group compatibility*

36 examples

Ming Chen[†], Feipeng Liu[†,‡] and Guangbin Dong*[†]

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Direct Palladium-Catalyzed *β*-Arylation of Lactams

Direct β-arylation of *N*-protected lactams with simple aryl iodides is developed through merging soft enolization and Pd-catalyzed redox cascade. The reaction is operated under mild conditions, scalable and chemoselective.