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Palladium-Catalyzed Enantioselective Relay Heck Arylation of Enelactams: Accessing α,β-Unsaturated δ-Lactams

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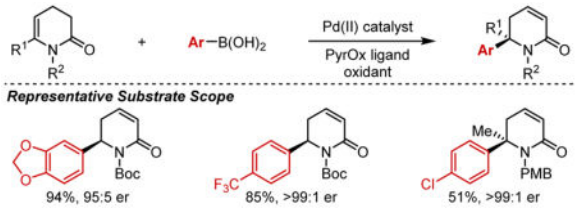
Abstract

In this report, we describe the construction of chiral α,β-unsaturated δ-lactams, a widely used pharmacophore, in high yields and excellent enantioselectivities using an oxidative relay Heck arylation reaction. This strategy also allows facile access to 7-substituted α,β-unsaturated ε-lactam products and δ-lactams containing a tetrasubstituted nitrogen-bearing stereocenter.

Graphical Abstract



Chiral lactams are a ubiquitous pharmacophore as they are found in a wide-range biologically active compounds and natural products.[1] As an example, lactam **A** is an antagonist of the CGRP receptor, which is applicable to the treatment or prevention of migraines (Scheme 1A).[2] Similarly, lactam **B** is an NK1 antagonist used to treat nausea and vomiting associated with chemotherapy.[3] Accordingly, various methodologies have been developed for the enantioselective synthesis of δ-lactam precursors to such targets.[4] These are highlighted by Cu-catalyzed aza-Diels-Alder reactions,[5] *N*-heterocyclic carbene-catalyzed cyclizations of α,β-unsaturated carbonyl compounds with sulfonylimines,[6] and transition-metal catalyzed asymmetric hydrogenation of *N*-arylimines or *N*-(*tert*-butylsulfinyl)iminosters.[7] Given the importance of this molecular substructure, we postulated that expanding our recently disclosed enantioselective relay Heck chemistry may provide a rapid entry to access highly enantioenriched substituted lactams through a site and enantioselective oxidative Heck reaction of arylboronic acids with readily accessible enelactams.

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Notes

The authors declare no competing financial interests.

Supporting Information

Experimental procedures, compound characterization, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

Traditional Heck reactions on enelactam substrates are reported to afford over-arylated products in a non-enantioselective fashion.[8] However, we postulated a relay Heck strategy could be applied to this cyclic system (**1**, Scheme 1B) to promote enantioselective monoarylation. In 2015, our lab published an enantioselective relay Heck arylation using acyclic alkenyl carbonyl derivatives to access α,β-unsaturated compounds bearing a remote stereocenter.[9] In this report, the carbonyl moiety was crucial to obtain a single monoarylated product due to the propensity of the palladium catalyst to migrate toward the carbonyl yielding the thermodynamically more stable α,β-unsaturated compound. It is important to note that diarylated products are not observed using this method, which can be ascribed to the catalyst not engaging with electron deficient alkenes (i.e., the conjugated alkene in the product).

In contrast to our previous work, the enelactam presents a polarized alkene, which should preclude issues associated with site selective addition (which does occur with other cyclic substrates). Therefore, regioselective arylation of cyclic enelactam **1** should afford intermediate **C** with subsequent β-hydride elimination to yield **D.** From this intermediate, it was unclear if the Pd-hydride would dissociate to deliver the corresponding alkene, similar to traditional Heck reactions (which could ultimately lead to diarylated products), or reinsert to give Pd-alkyl intermediate **E**. Finally, from this intermediate, it was hypothesized that β-hydride elimination of H_b would occur selectively to produce the thermodynamically more stable α,β-unsaturated δ-lactam product (**2**). It should be noted that our catalytic system has not been utilized using such alkene type substrates previously.

Based on our previous reports,[10] $Pd(CH_3CN)_2(OTs)_2$ and a pyridine oxazoline (PyrOx) ligand were evaluated under oxidative Heck relay conditions for the reaction of Boc-protected lactam **1a** (Table 1). Promisingly, product **2a** was obtained in 50% yield and 98:2 er when 1 equivalent of phenylboronic acid was used (entry 1). The yield of product **2a** was increased to 78% and >99:1 er when 2 equivalents of phenylboronic acid were employed (entry 2). No significant increase in yield was observed when phenylboronic acid was increased to 3 equivalents (entry 3). Increasing the catalyst loading to 10 mol % resulted in 81% yield of desired product **2a** (entry 4). Additionally, product **2a** was isolated in 67% yield when $Cu(OTf)_2$ was omitted from the reaction conditions. Using the conditions shown in entry 2, a variety of other nitrogen protecting groups on the enelactam were evaluated. Tosyl-protected lactam **1b** delivered product **2b** in 56% yield, while Bn and PMB-protected substrates (**1c**, **1d**) furnished the corresponding products in 92% and 91% yield, respectively. In addition, an unprotected lactam (**1e**) gave product **2e** in 60% yield, while the methylated substrate (**1f**) produced product **2f** in 68% yield. In all instances, the enantioselectivity remained relatively high although the combination of yield and er was considered to be optimal with the easy to manipulate Boc-protected lactam.

With the optimal reaction conditions in hand, the scope of compatible arylboronic acids was examined to form various arylated α,β-unsaturated δ-lactam products (**2**, Table 2). Alkyl-substituted boronic acids furnished the desired products in high yields and enantioselectivities (**2g**–**2j**). Interestingly, methyl substitution at the *ortho* position on the boronic acid resulted in the formation of desired product **2k** in 88% yield, albeit in diminished enantioselectivity (87:13 er). The transformation also performs well with an

electron-donating 4-methoxy group on the boronic acid to give product **2l** in 84% yield and 93.5:6.5 er. A variety of electron-withdrawing groups were well-tolerated under the reaction conditions including: fluoro, chloro, bromo, and trifluoromethyl (**2m**–**2t**). An electron-withdrawing methyl ester at the 4-position of the boronic acid delivered the corresponding product (**2u**) in 74% yield and 98.5:1.5 er. A benzodioxole boronic acid produced the desired α,β-unsaturated δ-lactam (**2v**) in 94% yield and 95:5 er. Additionally, 2-naphthaleneboronic acid afforded product **2w** in 93% yield with 97.5:2.5 er. A variety of heteroaromatic moieties were also successfully incorporated including: fluoropyridyl, *N*-methylindole, Boc-protected pyrrole, and furan (**2x**–**2aa**) although more Lewis basic examples did not lead to the desired product.[11] While the enantioselectivity is generally high, diminished er is correlated with the use of electron rich boronic acid coupling partners (e.g., **2l**, **2y**, **2z**, **2aa**).

In an effort to expand this strategy beyond formation of unsatu-rated δ-lactam products, ε-lactam **3a** (Table 3) was evaluated with several arylboronic acids to produce enantiomerically-enriched 7-substituted α,β-unsaturated ε-lactam products (**4**). Although chiral 7-substituted ε-lactams are present in biologically active molecules,[12] few methods are reported for their syntheses.[7b, 13] Compared with the 6-membered enelactam, diminished reactivity of the analogous seven-membered substrate was observed in this reaction wherein generally lower yields were obtained. To address this issue, the catalyst loading was increased to 10 mol % and the arylboronic acid was added in two batches (the second equivalent was added after 24 h). As a result, phenylboronic acid afforded product **4a** in 45% yield and >99:1 er. Electron-rich 4-methoxyphenylboronic acid gave product **4b** in 55% yield and 96:4 er, while the electron-poor 4-chlorophenylboronic acid delivered product **4c** in 47% yield and >99:1 er.

This method also enables the construction of δ-lactams containing a tetrasubsituted nitrogen-bearing stereocenter from trisubstituted enelactam **5a** (Table 4).[14] For this substrate class, we were cognizant that migratory insertion with a sterically encumbered trisubstituted enelactam would be more challenging and may lead to substantial homocoupling byproducts.[15] Under slightly modified reaction conditions, addition of phenylboronic acid to trisubstituted enlactam **5a** delivered the desired product **6a** in 59% yield and >99:1 er. Electron rich 4-methylphenylboronic acid furnished the corresponding product (**6b**) in 50% yield and 99:1 er. Electron deficient 4-chlorophenylboronic acid gave product **6c** in 51% yield and >99:1 er, demonstrating electronic variation on the boronic acid has a minimal effect on this trisubstituted enelactam. It should be noted that the reaction of 6-ethyl and 6-phenyl unsaturated δ-lactams resulted in the formation of no desired arylated product (see SI for more details).

The relay Heck arylation reaction can be performed on gram-scale, providing desired product **2d** in 93% yield without any erosion in enantioselectivity (Scheme 2A). The enantiomerically enriched 6-substituted δ-lactams can be easily derivatized to a variety of synthetically useful heterocyclic building blocks. For example, PMB-protected lactam **2d** can be converted into piperdine **7** via a two-step reduction sequence (hydrogenation followed by $LiAlH_4$, Scheme 2B). Alternatively, a diastereoselective Rh-catalyzed conjugate addition[16] using phenylboronic acid can be employed to convert enelactam **2d** to product **8**

in 86% yield and 14:1 dr. Additionally, **2a** was converted to the free lactam **10** in 90% yield over two steps without any reduction in the enantiomeric ratio. Lactam **10** is a reported chiral building block that can be converted into compounds **A** and **F**, an antagonist of CGRP receptor[2] and a modulator of the signaling of TNFα[1h] respectively. It is important to note the enantiomeric ratio was effectively preserved in all functional group transformations that were performed. The absolute configuration of product **10** was determined to be (*R*) by comparing the optical rotation value with previously reported data.[17] The remainder of the products was assigned by analogy to product **10**.

As discussed in the introduction, a key mechanistic question is whether the Pd chain-walks to yield the observed product or do alkene isomers form, which undergo non-specific isomerization to form the α,β-unsaturated δ-lactams. Circumstantially, our previous mechanistic experiments on acyclic systems and the observation that the seven-membered ring only yields the conjugated product is suggestive of Pd chain-walking.[10c] In order to further address the mechanism, a putative alkene intermediate (**11**, Scheme 3) was submitted to the reaction conditions.[18] Two Heck products, **12** and **13**, were observed in 34% and 25% yield, respectively (as well as 34% recovered starting material), which were not identified using enelactam substrates. Of more importance, the α,β-unsaturated δ-lactam product (**2c**) was not observed. Taken together, these results suggest that **2c** is not formed under the reaction conditions and that a chain-walking mechanism is likely responsible for the isomerization process.

In summary, we have successfully developed a method to synthesize enantiomerically enriched 6-arylated α,β-unsaturated δ-lactams, an important nitrogen-containing heterocycle, in good yields (up to 94% yield) and excellent enantiomeric ratios (up to >99:1 er) using a relay Heck reaction strategy. This process utilizes readily accessible enelactams and commercial available arylboronic acids and is performed under mild reaction conditions. Excellent enantiomeric ratios were also obtained when using 7-membered enelactams and 6-methyl γ,δ-unsaturated δ-lactams as substrates to provide chiral 7-arylated α,β-unsaturated ε-lactams and α,β-unsaturated δ-lactams containing a tetrasubsituted nitrogen-bearing stereocenter, respectively. Future work is aimed at accessing chiral building blocks bearing heteroatoms using relay Heck approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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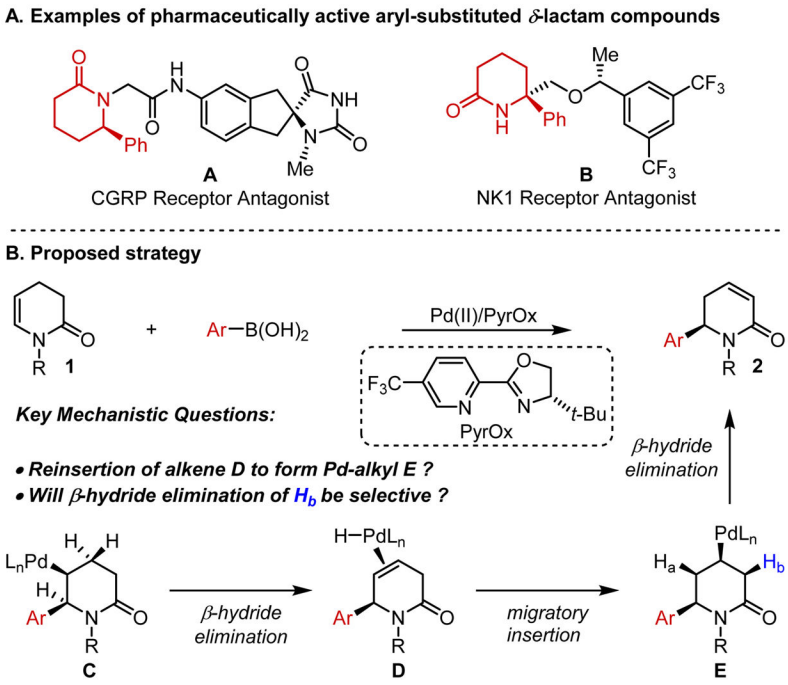
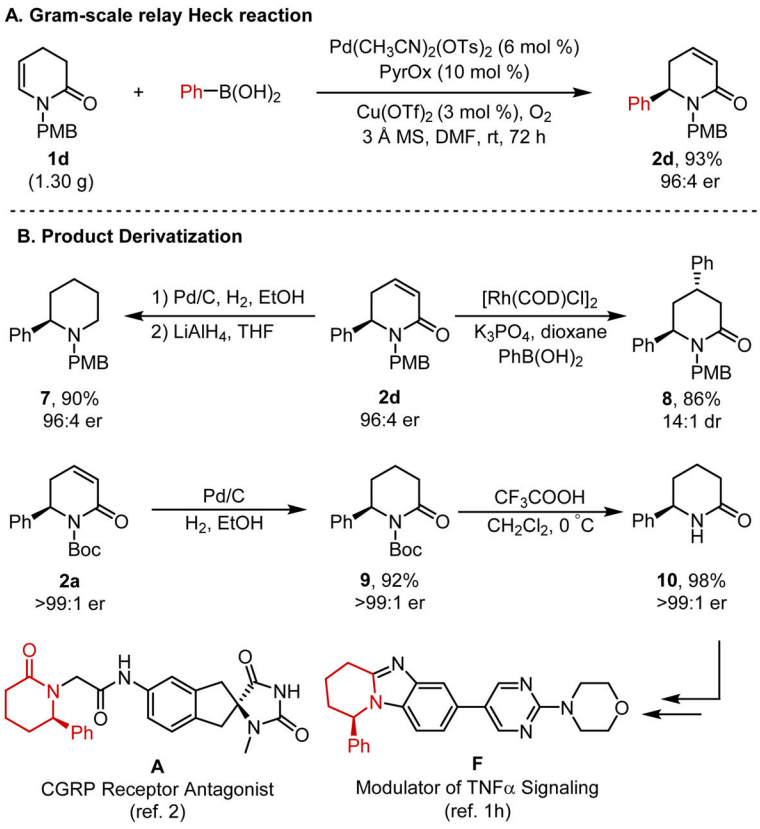
17. **10** {$[\alpha]_D^{20} = +60.0$ (*c* 1.0, $CHCl_3$)}; Lit.[4c] {$[\alpha]_D^{20} = +58.5$ (*c* 1.0, $CHCl_3$)}.
18. For details and additional control experiments see Supporting Information.

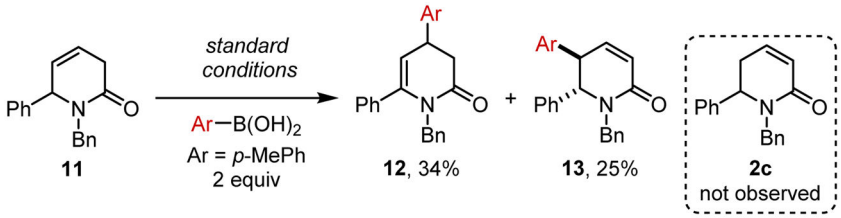


Scheme 1.

Proposed Method to Access Aryl-Substituted δ-Lactams



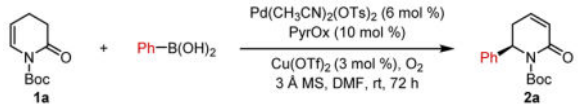
Scheme 2.
Gram-Scale Reaction and Derivatization



Scheme 3.
Mechanistic Analysis

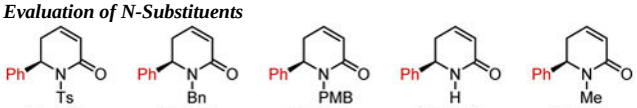
Table 1

Reaction Optimization and Evaluation of *N*-Substituents[a]



entry	phenylboronic acid	yield (%)	er
1	1 equiv	50	98:2
2	**2 equiv**	**78**	**>99:1**
3	3 equiv	80	98.5:1.5
4[b]	2 equiv	81	99:1
5[c]	2 equiv	67	97.5:2.5

Evaluation of N-Substituents



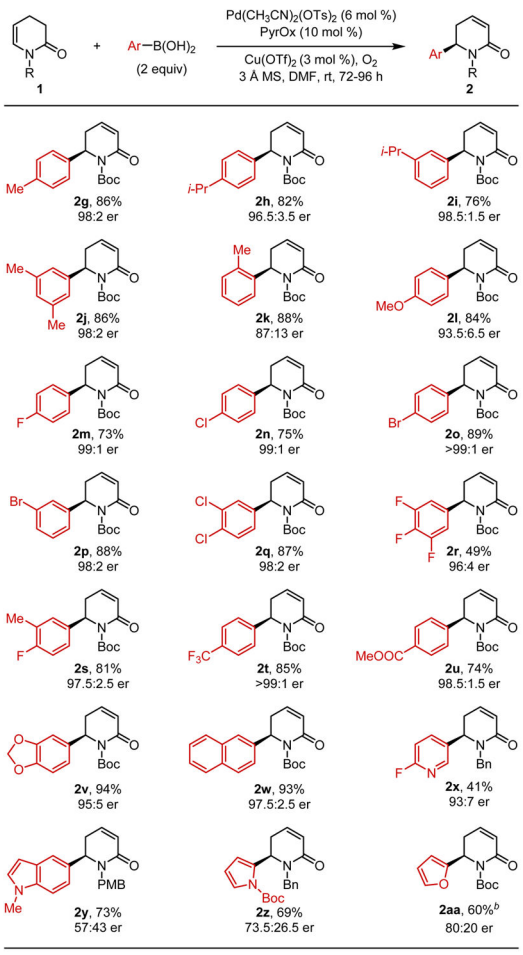
[a] Each entry represents the isolated yield on 0.2 mmol scale. The er values were determined by SFC.

[b] Pd/PyrOx/Cu loading was increased to 10/15/4 (mol %).

[c] $Cu(OTf)_2$ was omitted.

Table 2

Substrate Scope[a]

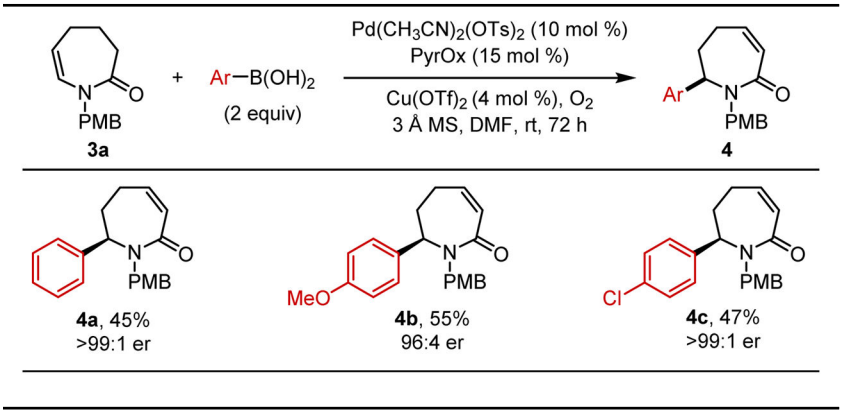


[a]Each entry represents the isolated yield on 0.2 mmol scale. The er values were determined by SFC.

[b]$Pd(CH_3CN)_2(OTs)_2$ (10 mol %), PyrOx (15 mol %), $Cu(OTf)_2$ (4 mol %) and 2-furanboronic acid (3 equiv) were used.

Table 3

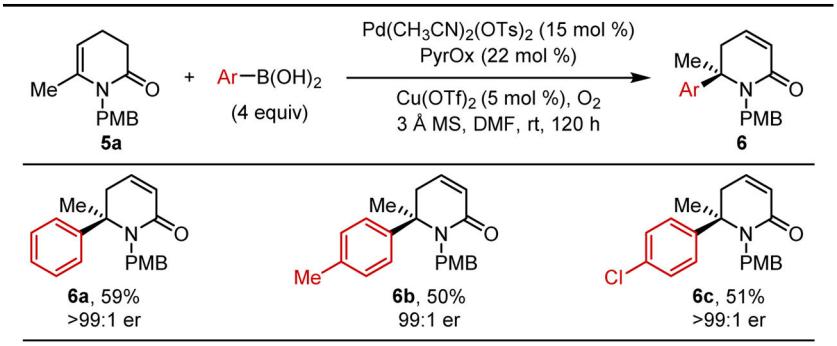
Evaluation of a Seven-Membered Enelactam[a]



[a]Each entry represents the isolated yield on 0.2 mmol scale. The arylboronic acid was added in two batches (0.2 mmol + 0.2 mmol). The er values were determined by SFC.

Table 4

Evaluation of a Trisubstituted Enelactam[a]



[a]Each entry represents the isolated yield on 0.2 mmol scale. The arylboronic acid was added in two batches (0.4 mmol + 0.4 mmol). The er values were determined by SFC.