HHS Public Access

Author manuscript

Nat Chem. Author manuscript; available in PMC 2012 August 01.

Published in final edited form as:

Nat Chem. ; 4(2): 130–133. doi:10.1038/nchem.1222.

Enantioselective Construction of Quaternary *N*-Heterocycles by Palladium-Catalyzed Decarboxylative Allylic Alkylation of Lactams

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Abstract

The enantioselective synthesis of Nitrogen-containing heterocycles (*N*-heterocycles) represents a substantial chemical research effort and resonates across numerous disciplines including the total synthesis of natural products and medicinal chemistry. In this manuscript, we describe the highly enantioselective palladium-catalyzed decarboxylative allylic alkylation of readily available lactams to form 3,3,-disubstituted pyrrolidinones, piperidinones, caprolactams, and structurally related lactams. Given the prevalence of quaternary *N*-heterocycles in biologically active alkaloids and pharmaceutical agents, we envision that our method will provide a synthetic entry into the de novo asymmetric synthesis of such structures. As an entry for these investigations we demonstrate how the described catalysis affords enantiopure quaternary lactams that intercept synthetic intermediates previously employed in the synthesis of the *Aspidosperma* alkaloids quebrachamine and rhazinilam, but that were previously only available by chiral auxiliary approaches or as racemic mixtures.

Nitrogen-containing heterocycles are ubiquitous in natural products,[i] pharmaceuticals,[ii] and materials science.[iii,iv,v] Stereoselective methods for the synthesis of 3,3-disubstituted pyrrolidinones, piperidinones, and caprolactams, in addition to the corresponding amines, are valuable for the preparation of a wide array of important structures in these areas of research (Figure 1). Despite the prevalence of such architectures and the potential of lactam enolate alkylation as a direct method for their synthesis, a paucity of enantioselective lactam alkylations leading to C(α)-quaternary centers are known. While most methods rely on chiral auxiliary chemistry,[vi,vii,viii] the few catalytic examples that exist are specific to the

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Author contributions D.C.B., Y.L., T.Y., and J.K. planned and carried out the experimental work. D.C.B., T.Y., D.E.W. and S.C.V. took part in the initial reaction development and screening experiments. B.M.S. conceived of, initiated, and directed the project and wrote the manuscript. All authors commented on the manuscript.

The authors declare no competing financial interests.

Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry.

oxindole lactam nucleus[ix,x,xi,xii,xiii], α-carbonyl stabilized enolates,[xiv] or cyclic imides.[xv] Importantly, enolate stabilization is critical for success in both of these catalytic systems, thereby limiting the scope of each transformation. To the best of our knowledge, there are no examples of catalytic asymmetric alkylations of simple piperidinone, pyrrolidinone, and caprolactam scaffolds for the formation of C(α)-quaternary or C(α)-tetrasubstituted tertiary centers. Herein, we describe the stereoselective synthesis of a wide range of structurally-diverse, functionalized lactams by palladium-catalyzed enantioselective enolate alkylation. The importance of this chemistry to the synthesis of bioactive alkaloids is specifically demonstrated, and the potential utility of this transformation for the construction of novel building blocks for medicinal and polymer chemistry can be readily inferred.

Transition metal-catalyzed allylic alkylation is a key method for the enantioselective preparation of chiral substances and ranks among the best general techniques for the catalytic alkylation of prochiral enolates.[xvi,xvii,xviii,xix] We sought to develop a general method for catalytic asymmetric α-alkylation, given the importance of α-quaternary lactams (vide supra). Over the past seven years, our laboratory has reported an array of methods for the synthesis of α-quaternary ketones[xx,xxi,xxii,xxiii] and demonstrated the use of these methods in a number of complex molecule syntheses.[xxiv,xxv,xxvi,xxvii] Concurrent to our efforts, the Trost lab[xxviii,xxix,xxx,xxxi,xxxii] and others[xxxiii,xxxiv,xxxv,xxxvi] have developed a series or related allylic alkylation methods. In the course of our investigations of the ketone enolate allylic alkylation and other alkylation processes, we have often encountered interesting ligand electronic effects and, in certain cases, pronounced solvent effects.[xxxvii] In keeping with our ultimate goal of *N*-heterocycle alkylation, we set out to further probe these subtle effects by examining enolate reactivity in a lactam series that would be amenable to both steric and electronic fine-tuning.

Results and Discussion

We prepared a collection of racemic lactam substrates (i.e., **1a-h**) for palladium-catalyzed decarboxylative allylic alkylation and performed a reactivity and enantioselectivity screen across an array of solvents employing two chiral ligands, (*S*)-*t*-BuPHOX and (*S*)-$(CF_3)_3$-*t*-BuPHOX.[xxxviii,xxxix,xl] Preliminary data suggested that electron rich *N*-alkyl lactam derivatives were poor substrates for decarboxylative alkylation due to low reactivity. Thus, electron withdrawing *N*-protecting groups were chosen in our study. We screened these substrates across a series of four solvents (THF, MTBE, toluene, and 2:1 hexane–toluene) while employing two electronically distinct ligands on Pd. The results of this broad screen were highly encouraging (Figure 2, see also Supplementary Information). Reactivity across all substrates with either ligand was uniformly good, as all of the compounds were completely converted to the desired product. Strikingly, as the *N*-substituent group was changed from sulfonyl to carbamoyl to acyl functionalities, the enantioselectivity rose from nearly zero to nearly perfect. There was also a substantial difference between the two ligands, and electron poor (*S*)-$(CF_3)_3$-*t*-BuPHOX was clearly the superior choice. As the solvent system became less polar, a distinct increase in enantiomeric excess was observed, however, this effect was substantially less pronounced for reactions employing the electron poor ligand and for reactions varying the *N*-substituent. Ultimately, with the *N*-benzoyl

group (Bz) on the substrate (i.e., **1h**) and (*S*)-$(CF_3)_3$-*t*-BuPHOX as ligand, the reaction produced lactam **2h** in >96% ee in each of the four solvents.

With these stunning results in hand, we initiated efforts to investigate the reaction scope by exploring a range of substituted *N*-acyl lactam derivatives (Figure 3). Importantly, reproducing the screening reaction on preparative scale furnishes *N*-Bz piperidinone **2h** in 85% isolated yield and 99% ee (Figure 3b). Alteration of the C(α)-group to other alkyl and functionalized alkyl units (e.g., $–CH_2CH_3$ and $–CH_2Ph$), as well as to moieties possessing additional acidic protons (e.g., $–CH_2CH_2CO_2Me$ and $–CH_2CH_2CN$) leads to high yields of lactams **3–6** in uniformly excellent enantioenrichment (99% ee). Common silyl protecting groups are tolerated in the transformation and lactam **7** is furnished in 85% yield and 96% ee. Substituted allyl groups can be incorporated, however only at C(2), leading to products such as methallyl lactam **8** and chloroallyl lactam **9** in good yield and outstanding enantioselectivity (≥95% ee).

Beyond piperidinones, we have demonstrated that pyrrolidinones and caprolactams are also exceptional substrate classes, furnishing heterocycles **10–13** in excellent yield and ee (Figure 3c). Additionally, morpholine-derived product **14**, containing a C(α)-tetrasubstituted tertiary center, is produced in 91% yield and 99% ee. C(α)-Fluoro substitution is readily introduced into the 1,3-dicarbonyl starting material and is viable in the enantioselective reaction leading to fluoropyrrolidinone **12** (86% yield, 98% ee) and fluoropiperidinone **15** (89% yield, 99% ee). Moreover, *N*-Bz glutarimides serve as outstanding substrates smoothly reacting to provide cyclic imides **16** and **17** in high yield and enantioselectivity. Finally, alteration of the *N*-Bz group is possible (Figure 3d), giving lactams with an *N*-acetyl group (**18**), *N*-carbamates (**19** and **20**), and a variety of *N*-aroyl derivatives (**21–23**).

The enantioenriched lactam products formed by our catalytic asymmetric alkylation chemistry are envisioned to be of broad utility in synthetic chemistry. To illustrate this point, lactam **3** can be transformed into the *Aspidosperma* alkaloid (+)-quebrachamine by modification of a previous route that employed a chiral auxiliary.[viii] Additionally, cleavage of the *N*-Bz group of lactam **3** produces chiral lactam **24**, a compound previously used as a racemate in the synthesis of rhazinilam, a microtubule-disrupting agent that displays similar cellular characteristics to paclitaxel (Figure 4).[xli,xlii] Finally, reduction of lactam **24** produces the C(3)-quaternary piperidine (**25**) and demonstrates access to the corresponding amine building blocks.

In summary, we have reported the first method for catalytic enantioselective alkylation of monocyclic 5-, 6-, and 7-membered lactam enolate derivatives to form α-quaternary and α-tetrasubstituted tertiary lactams. The reaction discovery process was enabled by parallel screening of reaction parameters and led to the identification of a sterically and electronically tuned system for highly enantioselective alkylation. We have applied this method to the catalytic asymmetric synthesis of key intermediates previously employed for the construction of *Aspidosperma* alkaloids. Finally, the asymmetric products formed in this investigation are envisioned to be widely useful as building blocks for the preparation of range of nitrogen containing heterocycles in materials science, medicinal chemistry and natural products synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This publication is based on work supported by Award No. KUS-11-006-02, made by King Abdullah University of Science and Technology (KAUST). The authors wish to thank NIH-NIGMS (R01GM080269-01 and a postdoctoral fellowship to D.E.W.), the Gordon and Betty Moore Foundation, Amgen, Abbott, Boehringer Ingelheim, and Caltech for financial support. T.Y. acknowledges the Japan Society for the Promotion of Science for a predoctoral fellowship.

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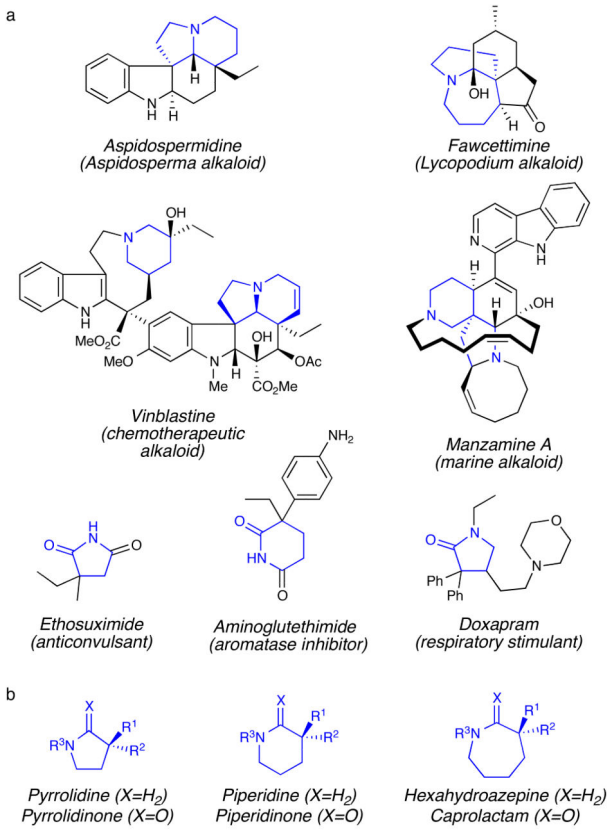

Figure 1. Natural Products and Pharmaceuticals Containing Chiral *N*-Heterocycles

a, An array of bioactive alkaloids and drug substances display the ubiquitous nature of quaternary carbon stereochemistry in these structures. **b**, The lactam and cyclic amine subtypes targeted in this study.

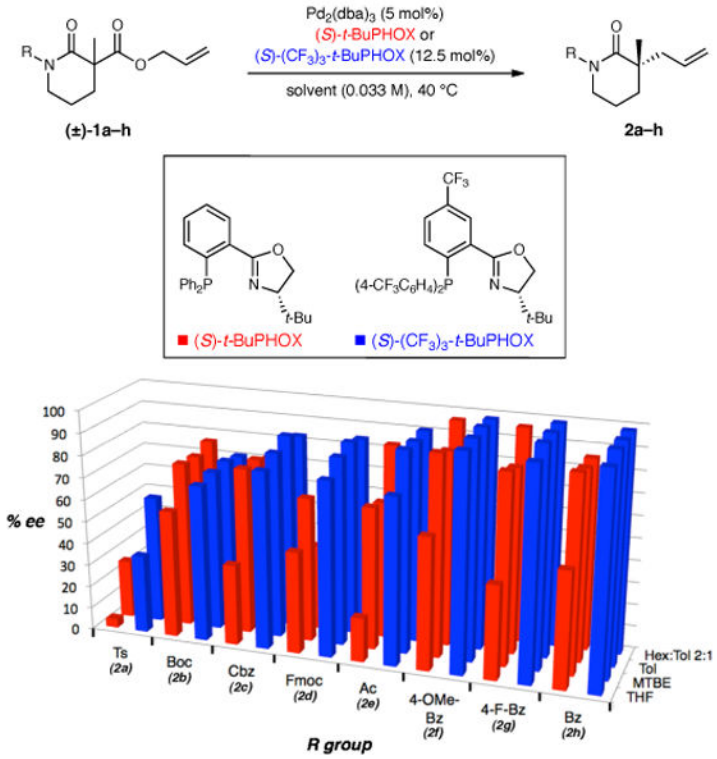

Figure 2. Solvent, *N*-substituent-Group, and Ligand Screen

Reactions were performed with lactam **1** (33.6 μmol), $Pd_2(dba)_3$ (5 mol%), and ligand (12.5 mol%) in solvent (1.0 mL) at 40 °C for 72 h (dba = dibenzylideneacetone). In all cases, complete consumption of starting material and product formation was observed by thin layer chromatography on silica gel. $Pd_2(pmdba)_3$ (5 mol%) was used for lactams **1a,b** at 50 °C (pmdba = bis(4-methoxybenzylidene)acetone). Enantiomeric excess (ee) was determined by chiral GC, SFC, or HPLC. See Supplementary Information for details.

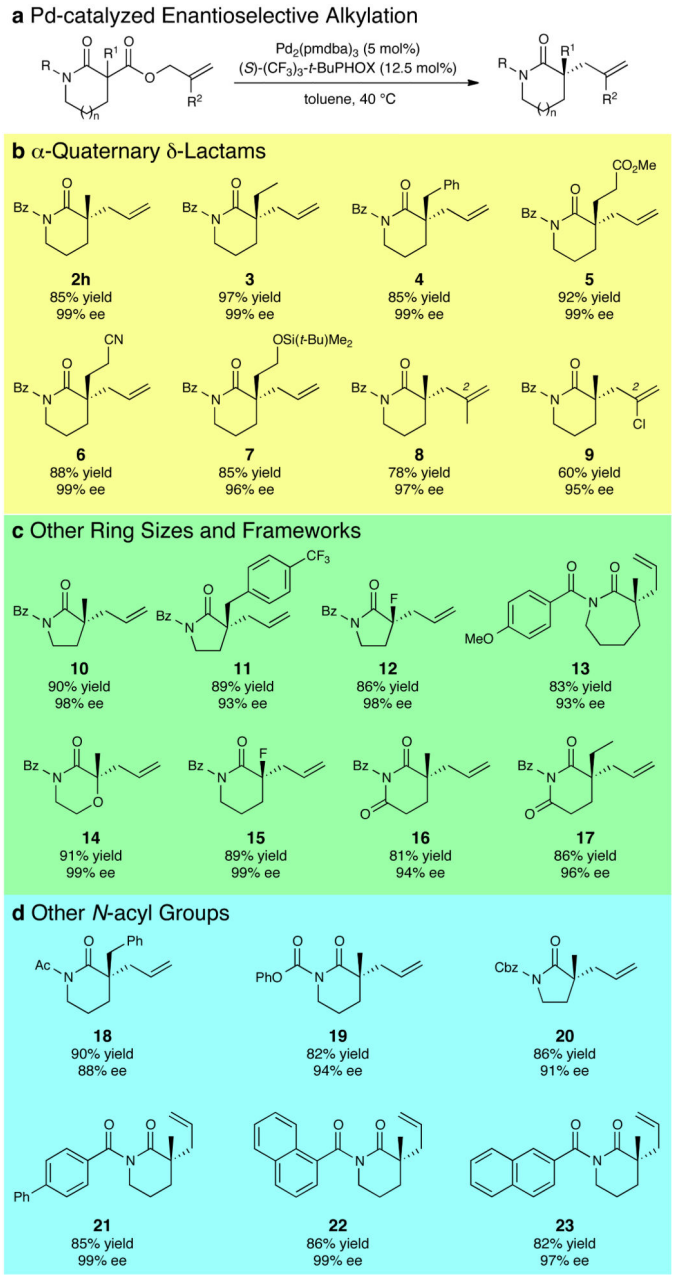

Figure 3. Scope of the Palladium-Catalyzed Decarboxylative Alkylation of Lactams

a, Palladium-catalyzed enantioselective decarboxylative lactam alkylation reactions were generally conducted by stirring of the corresponding lactam substrate (0.50 mmol), $Pd_2(pmdba)_3$ (5 mol%), and (*S*)-$(CF_3)_3$-*t*-BuPHOX (12.5 mol%) in toluene (15 mL) at 40 °C for 11–172 h. In all cases, complete consumption of starting material and product formation was observed by thin layer chromatography on silica gel. Isolated yields are reported. Enantiomeric excess (ee) was determined by chiral GC, SFC, or HPLC. See Supplementary Information for details and minor alterations to the conditions described above. **b**, α-Quaternary δ-lactams are accessed in excellent yield and with exceptional enantioselectivity. **c**, Alternative chiral lactams such as pyrrolidinone, caprolactam, and morpholinone, in

addition to glutarimides are accessed by the enantioselective alkylation method. **d**, A variety of *N*-acyl groups are also tolerated in the asymmetric reaction.

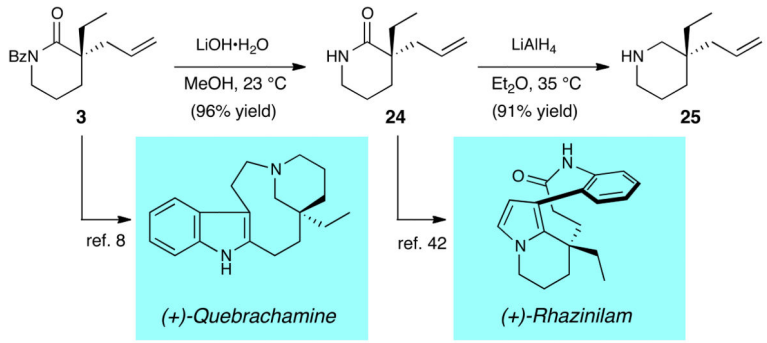

Figure 4. Utility of the lactam products

Conversion of *N*-Bz lactam **3** to lactam **24**, alkaloids quebrachamine and rhazinilam, and amine **25**.