OL Organic Letters

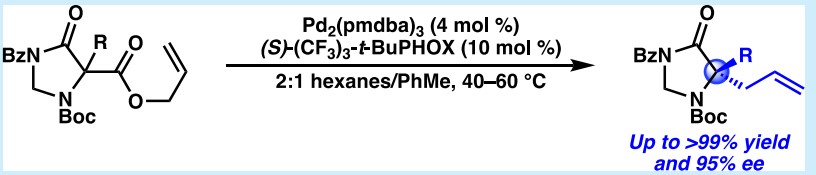
pubs.acs.org/OrgLett Letter

Synthesis of Enantioenriched *gem*-Disubstituted 4-Imidazolidinones by Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation

Zachary P. Sercel, Alexander W. Sun, and Brian M. Stoltz*

Cite This: https://doi.org/10.1021/acs.orglett.1c02134 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A variety of enantioenriched *gem*-disubstituted 4-imidazolidinones were prepared in up to >99% yield and 95% ee by the Pd-catalyzed decarboxylative asymmetric allylic alkylation of imidazolidinone-derived β-amidoesters. In the process of preparing these substrates, a rapid synthetic route to 4-imidazolidinone derivatives was developed, beginning from 2-thiohydantoin. The orthogonality of the benzoyl imide and *tert*-butyl carbamate groups used to protect these nitrogen-rich products was demonstrated, enabling potential applications in drug design.

Nearly 75% of small-molecule drugs contain at least one nitrogen heterocycle.[1] However, despite a significant correlation between the Csp^3 complexity of a drug and its clinical success,[2] most of the heterocycles found in marketed drugs lack stereochemical complexity. This phenomenon can largely be attributed to a lack of synthetic methods for the efficient incorporation of chiral centers into medicinally relevant heterocycles.

4-Imidazolidinones are a class of nitrogen-rich saturated lactams that have found applications in medicinal chemistry (Scheme 1a). Our attention was drawn to the fully substituted (albeit achiral) tertiary carbon atom at the 5-position of several of the drugs and drug candidates bearing this heterocyclic moiety, such as the spirocyclic drug spiperone. Given the prevalence of this substitution pattern, we reasoned that drug design would potentially benefit from a methodology for the asymmetric construction of chiral 4-imidazolidinones bearing fully substituted tertiary stereocenters. 4-Imidazolidinones have also been used as chiral auxiliaries in the preparation of artificial amino acids[3] and have found applications in popular organic catalysts,[4] but to our knowledge, preparation of these species has been largely restricted to processes involving the use of chiral pool materials or kinetic resolution.

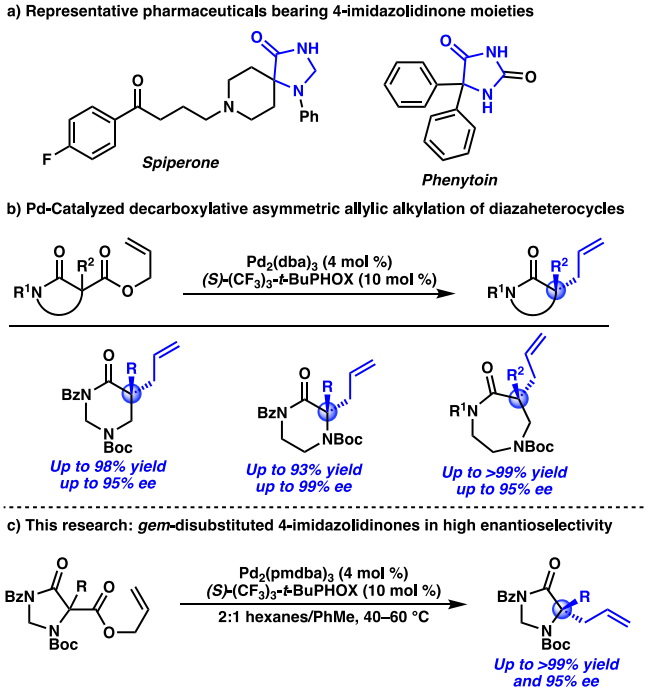
Our group and others have reported extensively on the palladium-catalyzed decarboxylative asymmetric allylic alkylation reaction,[5] including several recent publications detailing the use of these methods for the preparation of 6- and 7-membered *gem*-disubstituted diazaheterocycles.[6] *gem*-Disubstituted tetrahydropyrimidin-4-ones, piperazin-2-ones,[6b] and 1,4-diazepan-5-ones[6c] are all available in high yield and enantioselectivity via our group's allylic alkylation chemistry (Scheme 1b). We report our efforts to extend this methodology to the 5-membered imidazolidinone substrate class, enabling rapid access to stereochemically complex imidazolidinones suitable for further functionalization (Scheme 1c).

We began by developing a rapid and scalable synthetic route to imidazolidinone allylic alkylation substrates **7**, which proved to be a considerable challenge. We anticipated that the use of a Boc protecting group at the 4-position would be essential for high enantioselectivity by analogy to other substrate classes.[6b] Several routes to unsubstituted or carbamate-protected 4-imidazolidinones have been reported, but none of these routes were conducive to reliable material throughput in our hands.[7] Nevertheless, we were able to develop a rapid synthesis of **7** from 2-thiohydantoin (**1**) (Scheme 2).

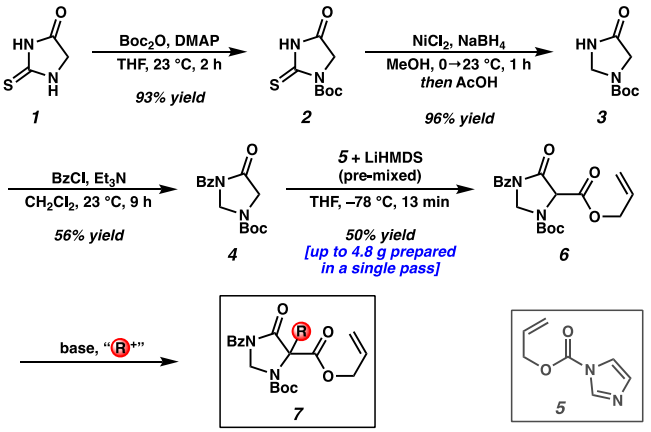
2-Thiohydantoin (**1**) was subjected to precedented Boc protection to provide carbamate **2**,[8] followed by nickel boride mediated reductive desulfurization to produce Boc-protected 4-imidazolidinone **3** in high yield.[9,10] Subsequent benzoylation furnished doubly protected imidazolidinone derivative **4**. Acylation of **4** proved challenging due to the extremely rapid reactivity of the corresponding enolate toward starting material even at −108 °C, but the use of acylimidazole electrophile **5**[11] and the precombination of **5** with LiHMDS prior to starting

Received: June 25, 2021

Scheme 1. *gem*-Disubstituted Diazaheterocycles by Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation



Scheme 2. Synthesis of Allylic Alkylation Substrates 7

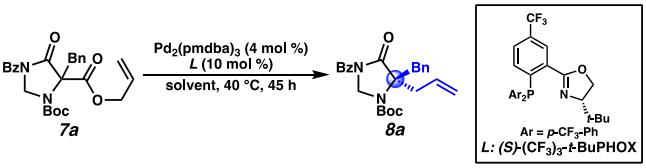


material addition allowed desired 1,3-dicarbonyl **6** to be prepared in 50% yield on a multigram scale. To our delight, treatment of **6** with base and various electrophiles allowed for the rapid preparation of multiple allylic alkylation substrates **7**.[12]

With model substrate **7a** in hand, beginning with the conditions for our group's prior allylic alkylation of *N*-Boc piperazinones,[6b] a brief solvent screen was conducted for the optimization of enantioselectivity (Table 1). In line with previously observed trends, ethereal solvents provided the product **8a** in only modest enantioselectivity. Less polar solvents such as benzene and toluene resulted in promising levels of enantioselectivity, but the use of a nonpolar hexanes/toluene mixture led to an ee of 91%.

Using this optimized solvent system, we examined the palladium-catalyzed decarboxylative asymmetric allylic alkylation of 4-imidazolidinone substrates **7a–k** (Scheme 3). Various nonpolar side chains proved to be well-tolerated,

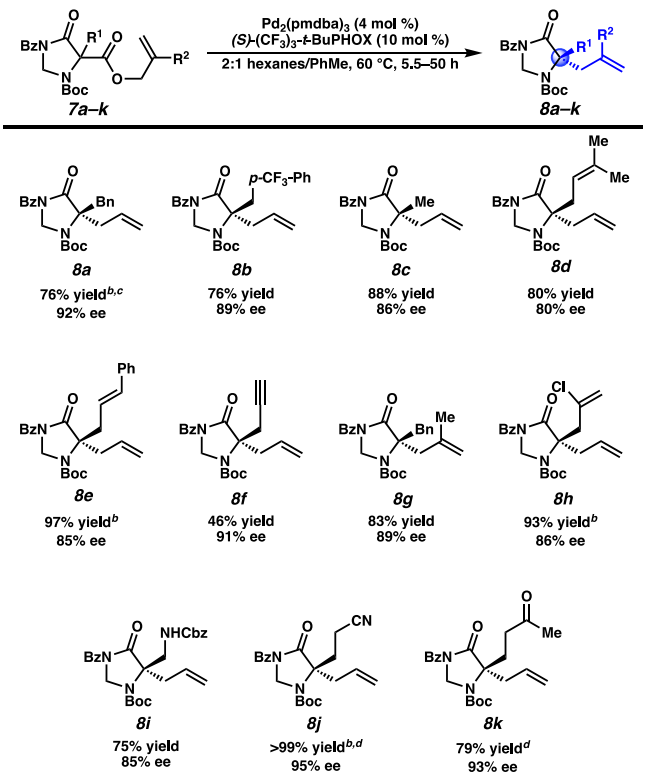
Table 1. Solvent Screen[a]



entry	solvent	ee[b] (%)
1	THF[c]	51
2	1,4-dioxane	68
3	benzene	89
4	PhMe	87
5	2:1 hexanes/PhMe	91

[a]Screening was performed on a 0.01 mmol scale at 0.014 M concentration. Reactions proceeded to completion unless otherwise noted. For additional experimentation, see the SI. [b]Values determined by chiral SFC analysis. [c]Reaction incomplete after 45 h.

Scheme 3. Substrate Scope[a]



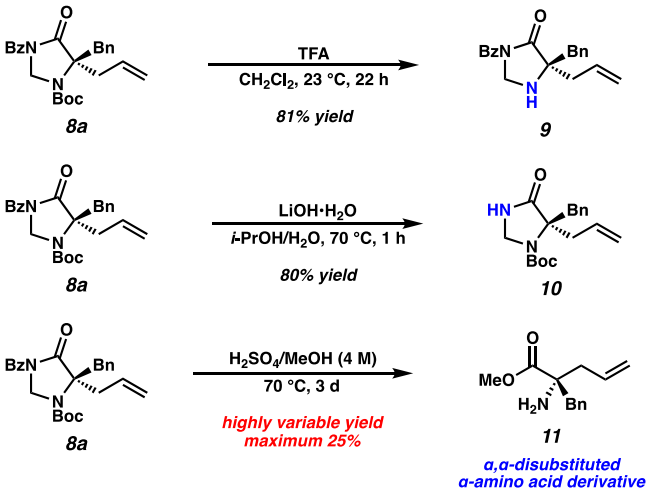
[a]Reactions were performed on a 0.1 mmol scale at 0.014 M concentration. ee values were determined by chiral SFC analysis. [b]Conducted at 40 °C. [c]1.86 mmol scale: 86% yield, 95% ee. [d]$Pd_2(dba)_3$ was used instead of $Pd_2(pmdba)_3$ to facilitate product purification.

such as benzyl (**8a**), *p*-trifluoromethylbenzyl (**8b**), methyl (**8c**), prenyl (**8d**), and cinnamyl (**8e**) groups. A propargyl group was also tolerated with high enantioselectivity (**8f**), albeit with a reduction in yield. We were pleased to observe that the reaction proceeded smoothly with a methyl group at the 2-position of the allyl fragment (**8g**). Lastly, several polar functional groups were also well-tolerated in the allylic alkylation (**8h–k**), including an alkenyl chloride and a carbamate. In particular, nitrile substrate **8j** was obtained in quantitative yield and an excellent 95% ee.

https://doi.org/10.1021/acs.orglett.1c02134
Org. Lett. XXXX, XXX, XXX–XXX

Having demonstrated the broad functional group tolerance of the reported method, we sought to explore the feasibility of further functionalization of the 4-imidazolidinone products (Scheme 4). The selective removal of either protecting group would likely prove essential for applications in medicinal chemistry. Toward this end, treatment of chiral benzyl imidazolidinone **8a** with TFA led to facile Boc cleavage, affording free secondary amine **9**. Similarly, treatment of **8a** with lithium hydroxide readily affected benzoyl group removal, providing free lactam **10**.

Scheme 4. Product Transformations



At the outset of this research, we had planned to explore the conversion of 4-imidazolidinone allylic alkylation products **8a**–**k** to synthetically useful derivatives of biologically relevant and synthetically challenging α,α-disubstituted α-amino acids.[13] Imidazolidinones were envisioned as surrogates for these desirable compounds based on prior examples of imidazolidinone chiral auxiliary-based strategies to access α,α-disubstituted α-amino acids,[3] as well as our own group's preparation of quaternary substituted β-amino acids from the analogous tetrahydropyrimidinones.[6b] Unfortunately, the presence of olefinic functionality hampered the feasibility of converting **8a**–**k** into amino acid derivatives due to the harsh conditions required for ring opening. Despite extensive experimentation, the highest yielding conditions identified for the conversion of imidazolidinone **8a** to amino ester **11** (H_2SO_4/MeOH) provided highly variable results, with the maximum observed yield of **11** being only 25%.

This research represents the first direct catalytic asymmetric synthesis of *gem*-disubstituted 4-imidazolidinones. Applying palladium-catalyzed decarboxylative asymmetric allylic alkylation to this nitrogen-rich substrate class enabled access to enantioenriched imidazolidinones bearing diverse functional groups in high yield and enantioselectivity. This methodology, in combination with the demonstrated orthogonality of the protecting groups of the products, could enable access to a novel class of medicinally relevant compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02134.

Experimental procedures, characterization data for all new compounds, and NMR and IR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Brian M. Stoltz − *Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States;* orcid.org/0000-0001-9837-1528; Email: stoltz@caltech.edu

Authors

Zachary P. Sercel − *Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Alexander W. Sun − *Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02134

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The NIH-NIGMS (R01GM080269) and Caltech are thanked for financial support. Z.P.S. thanks the Rose Hills Foundation for support via a Rose Hills Foundation Graduate Fellowship and the National Science Foundation for a predoctoral fellowship. A.W.S. thanks the NIH-NIGMS for a predoctoral fellowship (Ruth L. Kirschstein Institutional National Research Service Award F30GM120836) and a UCLA-Caltech Medical Scientist Training Program Fellowship (T32GM008042). We thank Dr. Scott Virgil (Caltech) for instrumentation and helpful discussions, Dr. David VanderVelde (Caltech) for NMR expertise, and Dr. Mona Shahgoli (Caltech) for mass spectrometry assistance.

■ REFERENCES

(1) (a) Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K. K.; Jonnalagadda, S. B. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules* **2020**, *25*, 1909. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(2) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52*, 6752−6756. (b) Lovering, F. Escape from Flatland 2: complexity and promiscuity. *MedChemComm* **2013**, *4*, 515−519.

(3) Representative publications: (a) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. Addition of Chiral Glycine, Methionine, and Vinylglycine Enolate Derivatives to Aldehydes and Ketones in the Preparation of Enantiomerically Pure α-Amino-β-hydroxy Acids. *Helv. Chim. Acta* **1987**, *70*, 237−261. (b) Wang, X.; Frutos, R. P.; Zhang, L.; Sun, X.; Xu, Y.; Wirth, T.; Nicola, T.; Nummy, L. J.; Krishnamurthy, D.; Busacca, C. A.; Yee, N.; Senanayake, C. H. Asymmetric Synthesis of LFA-1 Inhibitor BIRT2584 on Metric Ton Scale. *Org. Process Res. Dev.* **2011**, *15*, 1185−1191. (c) Leonard, D. J.;

Ward, J. W.; Clayden, J. Asymmetric α-arylation of amino acids. *Nature* **2018**, *562*, 105−109. (d) Abas, H.; Mas-Roselló, J.; Amer, M. M.; Durand, D. J.; Groleau, R. R.; Fey, N.; Clayden, J. Asymmetric and Geometry-Selective α-Alkenylation of α-Amino Acids. *Angew. Chem., Int. Ed.* **2019**, *58*, 2418−2422.

(4) Cozzi, P. G.; Gualandi, A.; Mengozzi, L.; Wilson, C. M. Imidazolidinones as Asymmetric Organocatalysts. In *Sustainable Catalysis: Without Metals or Other Endangered Elements, Part 2*; North, M., Ed.; Royal Society of Chemistry: Cambridge, 2016; pp 164−195.

(5) (a) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. Deracemization of Quaternary Stereocenters by Pd-Catalyzed Enantioconvergent Decarboxylative Allylation of Racemic β-Ketoesters. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924−6927. (b) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. Enantioselective construction of quaternary N-heterocycles by palladium-catalysed decarboxylative allylic alkylation of lactams. *Nat. Chem.* **2012**, *4*, 130−133. (c) Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, W.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. Expanding Insight into Asymmetric Palladium-Catalyzed Allylic Alkylation of N-Heterocyclic Molecules and Cyclic Ketones. *Chem. - Eur. J.* **2013**, *19*, 4414−4418. (d) James, J.; Jackson, M.; Guiry, P. J. Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation: Development, Mechanistic Understanding and Recent Advances. *Adv. Synth. Catal.* **2019**, *361*, 3016−3049.

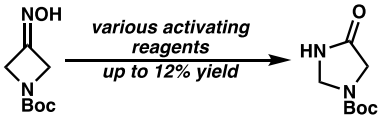
(6) (a) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. Enantioselective Synthesis of α-Secondary and α-Tertiary Piperazin-2-ones and Piperazines by Catalytic Asymmetric Allylic Alkylation. *Angew. Chem., Int. Ed.* **2015**, *54*, 179−183. (b) Sun, A. W.; Hess, S. N.; Stoltz, B. M. Enantioselective synthesis of gem-disubstituted N-Boc diazaheterocycles via decarboxylative asymmetric allylic alkylation. *Chem. Sci.* **2019**, *10*, 788−792. (c) Sercel, Z. P.; Sun, A. W.; Stoltz, B. M. Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of 1,4-Diazepan-5-ones. *Org. Lett.* **2019**, *21*, 9158−9161.

(7) (a) Freter, K.; Rabinowitz, J. C.; Witkop, B. Labile Stoffwechselprodukte V. Zur Biogenese Des Formiminoglycins Aus 4(5H)-Imidazolon. *Liebigs Ann. Chem.* **1957**, *607*, 174−187. (b) Nitta, Y.; Yamaguchi, T.; Tanaka, T. First Synthesis of 4-Imidazolidinone. *Heterocycles* **1986**, *24*, 25−28. (c) Pfeiffer, U.; Riccaboni, M. T.; Erba, R.; Pinza, M. A short synthesis of 4-imidazolidinone. *Liebigs Ann. Chem.* **1988**, *1988*, 993−995.

(8) Gosling, S.; Rollin, P.; Tatibouët, A. Thiohydantoins: Selective N- and S-Functionalization for Liebeskind−Srogl Reaction Study. *Synthesis* **2011**, *2011*, 3649−3660.

(9) A similar strategy has been employed for the preparation of 4-imidazolidinones bearing aryl groups: Khurana, J. M.; Agrawal, A.; Bansal, G. *J. Heterocycl. Chem.* **2009**, *46*, 1007−1010.

(10) Despite extensive efforts, a strategy utilizing the Beckmann rearrangement for the preparation of **3**, by analogy to the approach of Nitta and co-workers,[7b] led to consistently low yields:



3

(11) Acylimidazole electrophiles have previously been employed in the C-acylation of lactams by Trost and co-workers: Trost, B. M.; Nagaraju, A.; Wang, F.; Zuo, Z.; Xu, J.; Hull, K. L. Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Dihydroquinolinones. *Org. Lett.* **2019**, *21*, 1784−1788.

(12) Substrate **7g** was prepared from the methallyl analogue of **6**.

(13) Recent reviews: (a) Vogt, H.; Bräse, S. Recent approaches towards the asymmetric synthesis of α,α-disubstituted α-amino acids. *Org. Biomol. Chem.* **2007**, *5*, 406−430. (b) Bera, K.; Namboothiri, I. N. N. Asymmetric Synthesis of Quaternary α-Amino Acids and Their Phosphonate Analogues. *Asian J. Org. Chem.* **2014**, *3*, 1234−1260. (c) Metz, A. E.; Kozlowski, M. C. Recent Advances in Asymmetric Catalytic Methods for the Formation of Acyclic α,α-Disubstituted α-Amino Acids. *J. Org. Chem.* **2015**, *80*, 1−7. (d) Cativiela, C.; Ordóñez, M.; Viveros-Ceballos, J. L. Stereoselective synthesis of acyclic α,α-disubstituted α-amino acids derivatives from amino acids templates. *Tetrahedron* **2020**, *76*, 130875.

https://doi.org/10.1021/acs.orglett.1c02134
Org. Lett. XXXX, XXX, XXX−XXX