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# Stereocontrolled synthesis of 3-hydroxy-2-piperidinone carboxamides by catalytic ring-opening aminolysis of bridged $\delta$ -lactam- $\gamma$ -lactones†

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The  $\alpha$ -hydroxy- $\delta$ -valerolactam, 3-hydroxypiperidine, and piperidine-3-carboxamide topologies are resident in several natural products and pharmaceuticals, including anticonvulsant and antithrombotic agents. A modular and stereocontrolled strategy that merges these privileged scaffolds into one motif could facilitate the discovery of more small molecules with medicinal value. Here, we demonstrate that bridged valerolactam-butyrolactones can be skeletally remodelled to highly decorated 3-hydroxy-2-piperidinone carboxamides by catalytic and site-selective deconstructive aminolysis with primary and secondary amines. The products are obtained in a stereocontrolled manner following oxidative addition and concomitant trapping with the amine. The scaffold hopping proceeds with exclusive acyl C–O bond cleavage under palladium catalysis and represents the first catalytic method for activating the acyl C–O bonds of  $\gamma$ -lactones.

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## Introduction

The 3-hydroxy-2-piperidinone topology is resident in natural products and pharmaceuticals, including anticonvulsant **A**, natural alkaloids **B** and **C**, as well as (+)-awajanomycin (Fig. 1).<sup>1</sup> Additionally, polysubstituted saturated piperidines bearing the  $\beta$ -hydroxypiperidine substructure constitute the core of several natural products and pharmaceuticals, including deoxocassine, spectaline, azimic acid, and afegostat.<sup>2,3</sup> These  $\beta$ -hydroxypiperidines also serve as cyclic choline analogs.<sup>4</sup> Meanwhile, the piperidine-3-carboxamide scaffold is prevalent in antithrombotic agents<sup>5</sup> and is known to induce senescence-like phenotypic changes in human melanoma A375 cells<sup>6</sup> (see **D** and **E**, Fig. 1).

We surmised that a strategy that merges these pharmaceutically pertinent topologies into one motif (Fig. 1, bottom) would likely expand the 3D-chemical space for the discovery of more small molecules with medicinal value. Although the literature is replete with several approaches to 3-hydroxy-2-piperidinones,<sup>7</sup>  $\beta$ -hydroxypiperidines,<sup>8</sup> and piperidine-3-carboxamides,<sup>5,6</sup> we are not aware of any report on the stereocontrolled and the catalytic construction of the 3-hydroxy-2-piperidinone carboxamide scaffold.

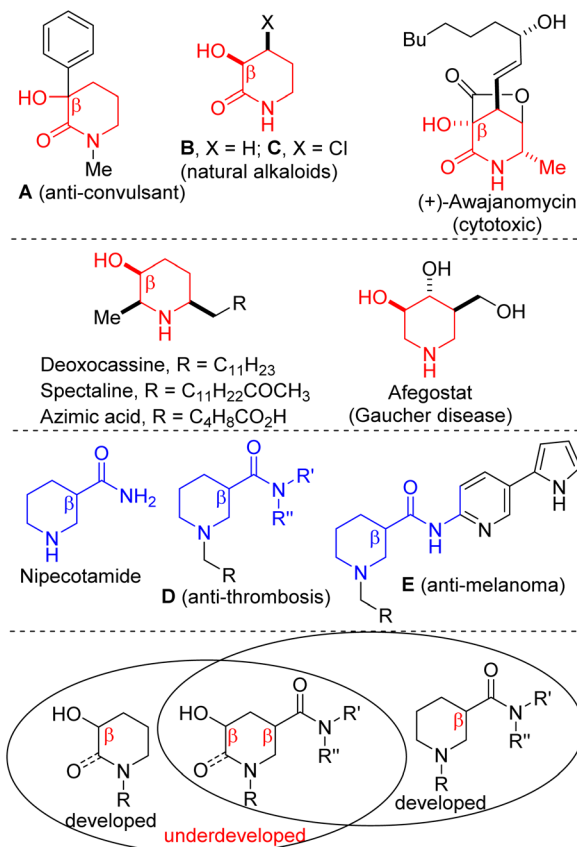


Fig. 1 Examples of bioactive 3-hydroxy-2-piperidinones,  $\beta$ -hydroxypiperidines, and piperidine-3-carboxamides.

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As part of a program aimed at leveraging the synthetic versatility of lactam acids of type **1** (Fig. 2A),<sup>9</sup> our group has identified catalytic and stereocontrolled sp<sup>3</sup> C–H lactonization as a means to access conformationally restricted bicyclic lactam-lactones (see 2).<sup>9k</sup> Organic synthesis strategies that seek to achieve flexible peripheral editing of heterocycles as well as skeletal editing are becoming increasingly popular in medicinal chemistry programs. Within this context and with **2** in hand, we next sought to explore its amenability to skeletal diversification by means of catalytic deconstructive functionalization, in view of assembling highly decorated 3-hydroxy-2-piperidinone carboxamides. We hypothesized that **2** could undergo site-selective and stereocontrolled ring-opening with amine nucleophiles under transition metal catalysis.

As depicted in Fig. 2B, a major challenge associated with the transition metal (TM)-catalyzed ring-opening of conformationally restricted lactones such as **2** is the possibility of formation of two constitutionally isomeric products due to competing acyl C–O bond cleavage (pathway A) and alkyl C–O bond cleavage (pathway B).<sup>10</sup> Some reports exist on the alkyl C–O bond

activation of 4-membered ring lactones.<sup>11</sup> However, TM-catalyzed ring opening of esters,<sup>12</sup> especially lactones, at the acyl C–O bond, is still at the incipient stages. Another challenge that needs to be addressed is that of diastereoselectivity (Fig. 2C). One of the most important aspects for the reaction to proceed in high diastereoselectivity is for the OH-bearing stereocenter in the opened chain to retain the same configuration as the original stereocenter in the lactone (stereoretentive ring-opening aminolysis, see 7) or for the OH-bearing stereocenter to have the opposite configuration (stereoinvertive ring-opening aminolysis, see 8). Inspired by the only existing report on the transition metal-catalyzed deconstructive functionalization of a strained  $\beta$ -lactone with amines (Fig. 2D),<sup>13</sup> we herein describe efforts toward the elicitation of our ideals. We find that the ring-opening with amines proceeds with exclusive site-selective acyl C–O bond activation and complete stereoretention at the OH-bearing stereocenter.

## Results and discussion

As articulated previously, the development of practical and stereocontrolled synthesis strategies for the construction of the carboxamide motif is a responsibility entrusted on the organic synthesis community given that it is commonly found in peptides, natural products, pharmaceuticals, and active ingredients in crop protection.<sup>14</sup> The sustainable construction of the amide scaffold has been highlighted by the American Chemical Society (ACS) Green Chemistry Institute as one of the top impactful areas.<sup>15</sup> Within this context, the catalytic ring-opening aminolysis of a cyclic ester is a highly desirable transformation given that it obviates the need for stoichiometric activation and side-steps the undesirable ester hydrolysis step. We commenced these studies by benchmarking our optimization efforts toward the synthesis of  $\alpha$ -hydroxy- $\delta$ -valerolactam-carboxamides with the reaction conditions described in Table 1. In the event, using acid **2a** as a model substrate, 2-methyl-tetrahydrofuran (2-MeTHF) emerged as the solvent of choice (entries 1–9). Of note, ethyl acetate, itself an ester, performs satisfactorily as a solvent in this reaction (entry 9). Pd(TFA)<sub>2</sub> and PPh<sub>3</sub> emerged as the most effective catalyst system (entries 10–21). No background ring-opening aminolysis is observed in the absence of Pd(TFA)<sub>2</sub> (entry 10) or in the absence of the phosphine ligand (entry 11). Therefore, these results support the notion that palladium catalysis is indeed operative in the lactone acyl C–O bond-cleavage process. Increasing the Pd(TFA)<sub>2</sub> loading to 5 mol% only leads to a marginal increase in the yield of **7a** (entry 18). However, lowering the loading to 1 mol% has a deleterious effect on the efficiency of the transformation (entry 19). Other catalytic aminolysis conditions that were developed primarily for methyl-bearing noncyclic esters have been surveyed and none of them promoted ring-opening aminolysis of **2a** to **7a** (entries 22–24). Base-mediated aminolysis of **2a** with isopropylamine using conventional bases such as Cs<sub>2</sub>CO<sub>3</sub> (entry 25), K<sub>2</sub>CO<sub>3</sub>, and CsF led to complete epimerization at the OH-bearing stereocenter. These results further highlight the merit of our newly developed protocol from both the standpoints of regioselectivity and

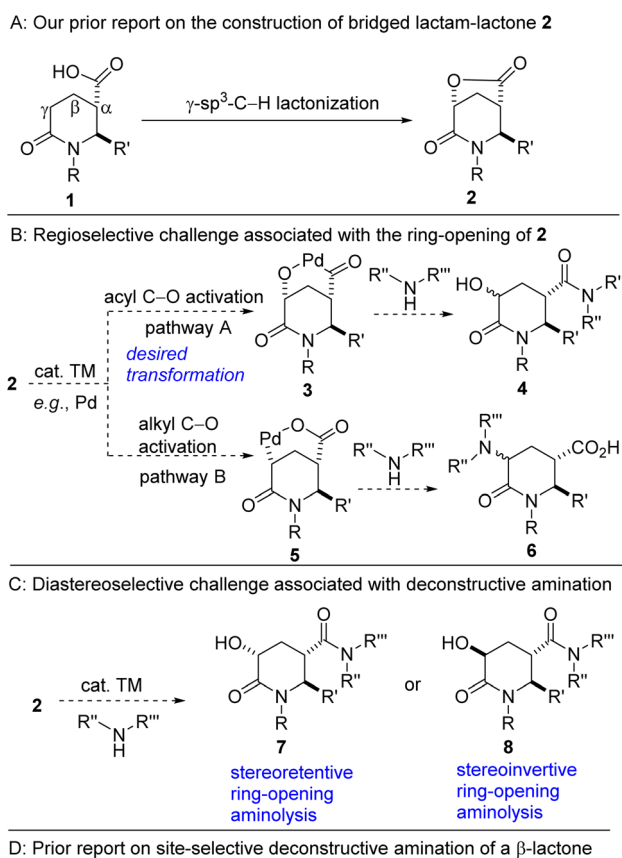
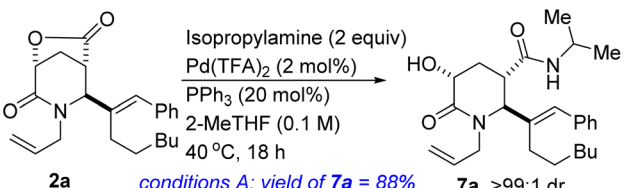


Fig. 2 (A) Our prior efforts to prepare lactam-lactone **2**, (B and C) our designed plan for accessing 3-hydroxy-2-piperidinone carboxamides from **2**, (D) existing report on Pd-catalyzed ring-opening of methylene- $\beta$ -lactones.



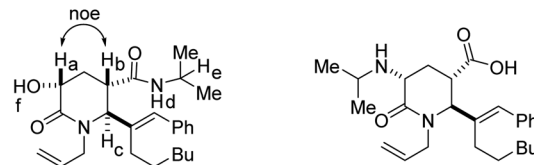
**Table 1** Optimization of the deconstructive amination of bridged lactam-lactone **2a**


Entry	Deviation from conditions A	%Yield <b>7a</b>
1	Tetrahydrofuran (THF) as solvent	76
2	2,2,5,5-Tetramethyloxolane (TMO) as solvent	70
3	Acetonitrile (MeCN) as solvent	52
4	<i>N,N</i> -Dimethylformamide (DMF) as solvent	39
5	<i>N,N</i> -Dimethylacetamide (DMA) as solvent	22
6	<i>N,N</i> -Dimethylsulfoxide (DMSO) as solvent	13
7	Dichloromethane (DCM) as solvent	65
8	Dichloroethane (DCE) as solvent	60
9	Ethyl acetate (EtOAc) as solvent	71
10	No Pd(TFA) <sub>2</sub>	0
11	No PPh <sub>3</sub>	0
12	Pd(OAc) <sub>2</sub> in place of Pd(TFA) <sub>2</sub>	82
13	Pd <sub>2</sub> (dba) <sub>3</sub> in place of Pd(TFA) <sub>2</sub>	58
14	Pd(PPh) <sub>3</sub> in place of Pd(TFA) <sub>2</sub>	41
15	Pd[(allyl)Cl] <sub>2</sub> in place of Pd(TFA) <sub>2</sub>	67
16	Pd(MeCN) <sub>2</sub> Cl <sub>2</sub> in place of Pd(TFA) <sub>2</sub>	0
17	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub> in place of Pd(TFA) <sub>2</sub>	0
18	Using 5 mol% Pd(TFA) <sub>2</sub>	90
19	Using 1 mol% Pd(TFA) <sub>2</sub>	70
20	P(OEt) <sub>3</sub> in place of PPh <sub>3</sub>	0
21	PCl <sub>3</sub> in place of PPh <sub>3</sub>	45
22	Conditions B in place of conditions A	0
23	Conditions C in place of conditions A	0
24	Conditions D in place of conditions A	0
25	Conditions E in place of conditions A	34(1 : 1 dr)

<b>conditions B</b>	<b>conditions D</b>
Pd(IPr)(allyl)Cl (20 mol%)	Ni(cod) <sub>2</sub> (10 mol%)
K <sub>3</sub> PO <sub>4</sub> (3 equiv)	IPr (20 mol%),
PhMe, 110 °C, 22 h	PhMe, 110 °C, 22 h
<b>conditions C</b>	<b>conditions E</b>
Ni(cod) <sub>2</sub> (15 mol%)	Cs <sub>2</sub> CO <sub>3</sub> (50 mol%)
SIPr (30 mol%)	DMF:MeCN (1:3)
Al(OtBu) <sub>3</sub> (1.3 equiv)	23 °C, 22 h
PhMe, 80 °C, 22 h	

SIPr = 1,3-Bis(2,6-diisopropylphenyl)imidazolidin



- **7a** (exclusive product) confirmed by HMBC analysis.
  - <sup>1</sup>H NMR spectrum shows that the NH proton (H<sub>d</sub>) is highly deshielded (6.17 ppm (d, J = 5.2 Hz, 1H), consistent with the amide resonance.
  - Unusual doublet for H<sub>d</sub> is due to coupling across nitrogen to H<sub>e</sub>.
  - NOESY shows that H<sub>a</sub> and H<sub>b</sub> are on the same side.
  - OH stretching frequency on IR spectrum is ~3200 cm<sup>-1</sup>, consistent with that of alcohol functionality.
- **6a** (not observed)
  - No carboxylic acid resonance on <sup>1</sup>H NMR spectrum.
  - OH stretching frequency on IR spectrum ~3200 cm<sup>-1</sup>, and does not go below 3000 cm<sup>-1</sup>, which is inconsistent with that of the carboxylic acid functionality.
  - The IR spectrum of **1**, which bears the CO<sub>2</sub>H functionality is provided in the ESI for comparison.

**Fig. 3** Spectroscopic evidence for the exclusive formation of **7a** by regioselective acyl C–O bond cleavage.

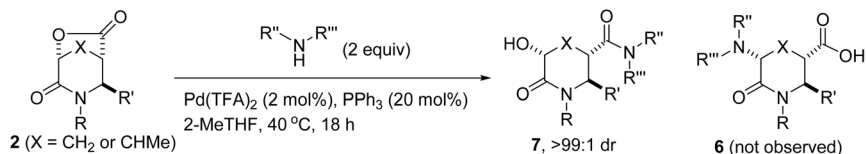
restricted bridged lactam-lactones into 3-hydroxy-2-piperidinone carboxamides.

Using the optimized conditions, the scope of the catalytic and site-selective ring-opening aminolysis protocol was explored. We began by surveying various diversely substituted bridged lactam-lactones using isopropylamine as the nucleophile. In the event, the differentially substituted hydroxypiperidinone carboxamides depicted in Scheme 1 were obtained (see **7a–s**). The functional group tolerance exhibited by the transformation is impressive given that alkenes, allyl ethers, tertiary anilines, anisoles, thioethers, and thiophenes are well tolerated in this transformation. As a testament to the mildness of these reaction conditions, ring-opening of methylbenzoate-bearing substrates occurs exclusively on the lactone moiety (see **7j** and **7p**). Such chemoselectivity is noteworthy and speaks to the enhanced reactivity of the inherently strained bridged lactam-lactone scaffold. We envision that this would pave the way for orthogonal aminolysis given that amide formation at the methyl ester terminus should be achievable using the well established Ni-catalyzed conditions.<sup>12a–f</sup> Piperidinone carboxamides bearing four contiguous stereocenters have been prepared in a stereocontrolled manner (see **7l/m**). Our studies have revealed that other primary alkyl amines undergo excellent deconstructive aminolysis without complications arising from epimerization at the OH-bearing stereocenter (see **7t–7z2**). In the field of organic synthesis, alkynes have become a staple given that they are often employed as synthons and as catalysts in enantioselective studies.<sup>16</sup> We were therefore pleased to find that the ring-opening aminolysis with propargyl amine proceeds uneventfully leading to products such as **7x/y**. An inherently less nucleophilic primary aryl amine afforded the product in high yield and diastereoselectivity (see **7z3**). When both enantiomers of  $\alpha$ -methyl benzylamine are employed in this transformation, the optically active 3-hydroxy-2-piperidinone carboxamides are obtained in high stereochemical fidelity. These results indicate that epimerization at the methyl-bearing stereocenter did not

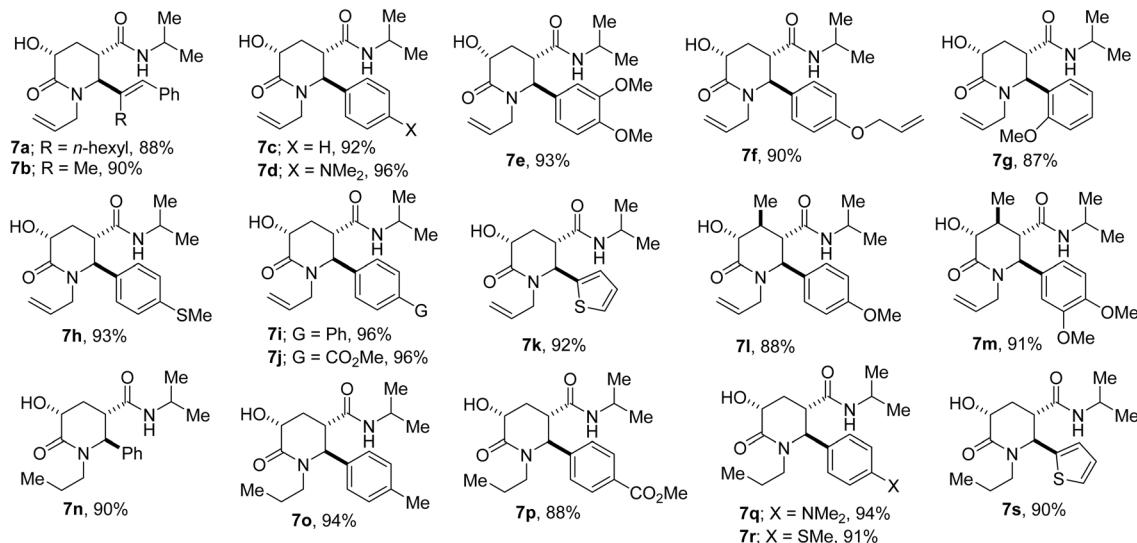
diastereoselectivity. The atom efficiency of this transformation is commendable given that all atoms originating from the bicyclic lactam-lactone and the amine are incorporated into the product structure.

The exclusive formation of **7a** and the failure to observe side products of type **6** are a testament to the fact that alkyl C–O bond activation (see pathway B, Fig. 2) is not operative. Support for this assertion comes from spectroscopic data (see Fig. 3). Representative COSY, HSQC, HMBC, NOESY, and IR spectra for **7a** and several other compounds depicted in Scheme 1 are provided in the (ESI<sup>†</sup>). Decarbonylation was also not observed in this palladium-catalyzed conversion of conformationally

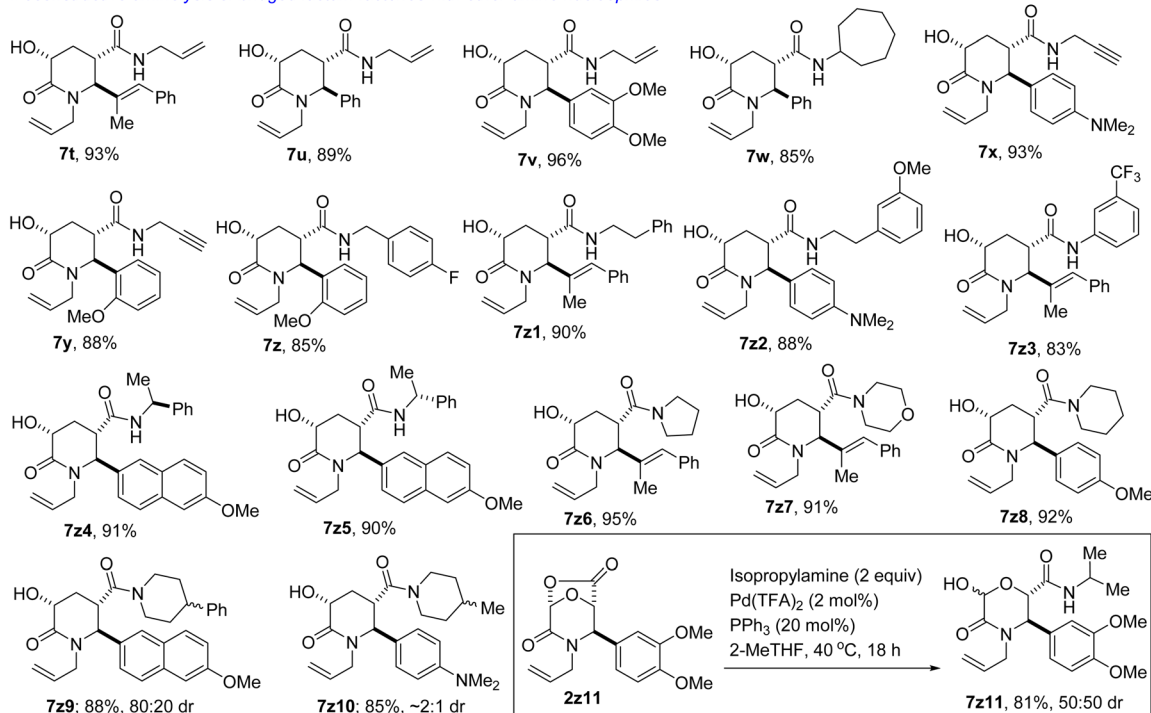




## Deconstructive aminolysis of bridged lactam-lactones with isopropylamine



## Deconstructive aminolysis of bridged lactam-lactones with other amine nucleophiles



Isolated yields are reported in all cases. Performed on 1.0 mmol scale using 5 mL 2-MeTHF. Reaction times ranged from 12 to 32 h. Diastereomeric ratios were determined by GC-MS and <sup>1</sup>H NMR analyses of the crude lactam carboxamide. Relative configurations were established through coupling constant and NOE analyses. The correct regioisomer (*i.e.* 7 vs 6) was identified using IR-, 1D-, and 2D-NMR analyses.

**Scheme 1** Construction of  $\alpha$ -hydroxy- $\delta$ -valerolactam carboxamides by catalytic deconstructive functionalization of [3-2-1] bicyclic lactam-lactones with primary and secondary amines.

occur in either case. Ring-opening aminolysis with sterically challenged secondary amines proceeds satisfactorily (see **7z6**–**7z8**). When 4-substituted piperidines are employed as the

amine nucleophile, the lactam carboxamides are obtained in variable diastereoselectivities (see **7z9** and **7z10**) as judged by GC-MS and <sup>1</sup>H NMR of the crude reaction mixture. In both



cases, the diastereomeric mixture was inseparable in our hands. Unsurprisingly, when inherently less nucleophilic tertiary amines such as *N*-methylpiperidine and triethylamine were employed, no ring-opening aminolysis occurred even at elevated temperatures (80 °C, for 18 h). In these cases, the mass balance was mostly accounted for by the recovered bridged lactam-lactone precursor. The addition of fluorine-containing scaffold to standard organic frameworks tends to enhance properties such as metabolic stability and dissolution, which justifies why ~25% of current preclinical medicines harbor one or more fluorine atoms.<sup>17</sup> For instance, the well-heralded trifluoromethyl (CF<sub>3</sub>) group facilitates drug metabolism.<sup>18</sup> We were therefore thrilled to see that compounds **7z** and **7z3** were produced in high efficiencies and selectivities. The synthesis of compounds capable of serving as drug candidates in a scalable manner is an important objective as it makes it relatively easier for clinical tests to be performed. Fittingly, we have synthesized compounds such as **7a** and **7z4** in gram-scale quantities (starting with as much as 5 mmol of **2**), with little to no compromise in efficiency and diastereoselectivity. When morpholinone-bridged lactone **2z11** was engaged in this ring-opening aminolysis protocol, complete epimerization at the OH-bearing stereocenter was observed as cyclic hemiacetal **7z11** was obtained in 1 : 1 dr. The diastereomeric mixture was inseparable in our hands. These results further exemplify why efforts to extend reactivity trends from one class of a nitrogen heterocycle to another can sometimes seem like a wild goose chase.

## Conclusions

In summary, the stereocontrolled deconstructive amination of bridged  $\delta$ -lactam- $\gamma$ -lactones has been accomplished under palladium catalysis, leading to the synthesis of 3-hydroxy-2-piperidinone carboxamides. The approach enables a formal  $\alpha$ -hydroxylation of inherently inert lactams in a way that is modular and amenable to rapid diversity incorporation. The target compounds are obtained in high yields and diastereoselectivities. Primary and secondary amines are suitable reactive partners. This skeletal diversification of strained lactones bridged to lactams proceeds with exclusive acyl C–O bond scission and stereoretentive ring-opening aminolysis is implicated. We anticipate that the epimerization-free nature of the reaction conditions would endear this approach to the synthesis and medicinal chemistry communities. Detailed mechanistic studies as well as the development of an enantioselective variant of the transformation are underway and the results will be disclosed in due course.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Author contributions

T. K. B. – conceptualized, administered, and supervised the project. Also carried our exploration, data analysis, and

optimization studies. Wrote the original draft manuscript and acquired internal funds. K. C., A. G., K. Y., and S. E. carried our investigation, data curation, and exploration of the scope of the reaction. K. C., A. G., K. Y., and S. E. contributed equally.

## Conflicts of interest

There are no conflicts of interest to declare.

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## Notes and references

- (a) I. Choudhury-Mukherjee, H. A. Schenck, S. Cechova, T. N. Pajewski, J. Kapur, J. Ellena, D. S. Cafiso and M. L. Brown, *J. Med. Chem.*, 2003, **46**, 2494–2501; (b) I. Krasteva, V. Bratkov, F. Bucar, O. Kunert, M. Kollroser, M. KondevaBurdina and I. Ionkova, *J. Nat. Prod.*, 2015, **78**, 2565–2571; (c) J. Masschelein, M. Jenner and G. L. Challis, *Nat. Prod. Rep.*, 2017, **34**, 712–783; (d) G. J. Patrick, L. Fang, J. Schaefer, S. Singh, G. R. Bowman and T. A. Wenczewicz, *Biochemistry*, 2018, **57**, 117–135; (e) K. E. Harding and M. W. Jones, *Heterocycles*, 1989, 663–668.
- (a) A. Grauer and B. König, *Eur. J. Org. Chem.*, 2009, **30**, 5099–5111; (b) S. Hanessian, G. McNaughton-Smith, H.-G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, **53**, 12789–12854.
- (a) M. C. Maillard, F. A. Brookfield, S. M. Courtney, F. M. Eustache, M. J. Gemkow, R. K. Handel, L. C. Johnson, P. D. Johnson, M. A. Kerry, F. Krieger, M. Meniconi, I. Munoz-Sanjuán, J. J. Palfrey, H. Park, S. Schaertl, M. G. Taylor, D. Weddell and C. Dominguez, *Bioorg. Med. Chem.*, 2011, **19**, 5833–5851; (b) M. Quibell, A. Benn, N. Flinn, T. Monk, M. Ramjee, Y. Wang and J. Watts, *Bioorg. Med. Chem.*, 2004, **12**, 5689–5710.
- M. Bollenbach, M. Ortega, M. Orman, C. L. Drennan and E. P. Balskus, *ACS Med. Chem. Lett.*, 2020, **11**, 1980–1985.
- (a) A. Lasslo, E. O. Dillingham, J. C. McCastlain, G. Carter-Burks, R. P. Quintana, R. W. Johnson and J. N. Naylor, *Med. Prog. Technol.*, 1986, **11**, 109; (b) R. Gollamudi, E. O. Dillingham and S. E. Bond, *Thromb. Haemost.*, 1993, **69**, 1322; (c) A. Lasslo, R. P. Quintana, D. Crisan, R. E. Baier, A. E. Meyer and M. S. Fornalik, *Med. Prog. Technol.*, 1984, **10**, 71–78; (d) W. H. Lawrence, R. D. Howell and R. Gollamudi, *J. Pharm. Sci.*, 1994, **83**, 222; (e) Z. Guo, X. Zheng, W. Thompson, M. Dugdale and R. Gollamudi, *Bioorg. Med. Chem.*, 2000, **8**, 1041–1058; (f) K. S. Anil



- Kumar, A. Misra, T. I. Siddiqi, S. Srivastava, M. Jain, R. S. Bhatta, M. Barthwal, M. Dikshit and D. K. Dikshit, *Eur. J. Med. Chem.*, 2014, **81**, 456–472.
- 6 S. Oh, D. Y. Kwon, I. Choi, Y. M. Kim, J. Y. Lee, J. Ryu, H. Jeong, M. J. Kim and R. Song, *ACS Med. Chem. Lett.*, 2021, **12**, 563–571.
- 7 (a) P. R. Krishna, P. V. A. Kumar, V. S. Mallula and K. V. S. Ramakrishna, *Tetrahedron*, 2013, **69**, 2319; (b) A. Kamal, K. V. Ramana, A. V. Ramana and A. H. Babu, *Tetrahedron Asymmetry*, 2003, **14**, 2587; (c) J. Romero-Ibanez, S. Cruz-Gregorio, L. Quintero and F. Sartillo-Piscil, *Synthesis*, 2018, **50**, 2878–2886.
- 8 J.-D. Ha, D. Lee and J.-K. Cha, *J. Org. Chem.*, 1997, **62**, 455024551.
- 9 (a) H. Braunstein, S. Langevin, M. Khim, J. Adamson, K. Hovenkotter, L. Kotlarz, B. Mansker and T. K. Beng, *Org. Biomol. Chem.*, 2016, **14**, 8864–8872; (b) T. K. Beng and A. Moreno, *New J. Chem.*, 2020, **44**, 4257–4261; (c) T. K. Beng, M. Bauder, M. J. Rodriguez and A. Moreno, *New J. Chem.*, 2018, **42**, 16451–16455; (d) K. Hovenkotter, H. Braunstein, S. Langevin and T. K. Beng, *Org. Biomol. Chem.*, 2017, **15**, 1217–1221; (e) T. K. Beng and A. Moreno, *RSC Adv.*, 2020, **10**, 8805–8809; (f) J. Garcia, J. Eichwald, J. Zesiger and T. K. Beng, *RSC Adv.*, 2022, **12**, 309–318; (g) T. K. Beng, J. Garcia, J. Eichwald and C. Borg, *RSC Adv.*, 2023, **13**, 14355–14360; (h) T. K. Beng, J. Eichwald, J. Fessenden, K. Quigley, S. Sharaf, N. Jeon and M. Do, *RSC Adv.*, 2023, **13**, 21250–21258; (i) T. K. Beng, M. Rodriguez and C. Borg, *RSC Adv.*, 2022, **12**, 17617–17620; (j) T. K. Beng, C. Borg and M. Rodriguez, *RSC Adv.*, 2022, **12**, 28685–28691; (k) T. K. Beng, V. Shearer and A. O. Farah, *J. Am. Chem. Soc.*, 2025, under review.
- 10 (a) S. G. Nelson, R. D. Dura and T. J. Peelen, *Org. React.*, 2013, **82**, 471; (b) E. H. Wiedemann, F. A. Mandl, I. D. Blank, C. Ochsenfeld, A. R. Ofial and S. A. Sieber, *ChemPlusChem*, 2015, **80**, 1673; (c) A. Noel, B. Delpech and D. Crich, *Org. Biomol. Chem.*, 2012, **10**, 6480; (d) M. A. Calter and X. Guo, *J. Org. Chem.*, 1998, **63**, 5308; (e) E. S. Ratemi and J. C. Vederas, *Tetrahedron Lett.*, 1994, **35**, 7605; (f) A. Griesbeck and D. Seebach, *Helv. Chim. Acta*, 1987, **70**, 1326; (g) L. D. Arnold, T. H. Kalantar and J. C. Vederas, *J. Am. Chem. Soc.*, 1985, **107**, 7105.
- 11 (a) K. T. Aye, D. Colpitts, G. Ferguson and R. J. Puddephatt, *Organometallics*, 1988, **7**, 1454; (b) A. F. Noels, J. J. Herman and P. Teyssie, *J. Org. Chem.*, 1976, **41**, 2527; (c) T. Hattori, Y. Suzuki, O. Uesugi, S. Oi and S. Miyano, *Chem. Commun.*, 2000, **1**, 73–74; (d) T. Hattori, Y. Suzuki, Y. Ito, D. Hotta and S. Miyano, *Tetrahedron*, 2002, **58**, 5215.
- 12 (a) L. Hie, N. F. Fine Nathel, X. Hong, Y.-F. Yang, K. N. Houk and N. K. Garg, *Angew. Chem., Int. Ed.*, 2016, **55**, 2810–2814; (b) L. Hie, N. F. Fine Nathel, X. Hong, Y.-F. Yang, K. N. Houk and N. K. Garg, *Angew. Chem.*, 2016, **128**, 2860–2864; (c) T. Ben Halima, J. Masson-Makdissi and S. G. Newman, *Angew. Chem., Int. Ed.*, 2018, **57**, 12915–12929; (d) T. Ben Halima, J. Masson-Makdissi and S. G. Newman, *Angew. Chem.*, 2018, **130**, 13107–13111; (e) Y.-L. Zheng and S. G. Newman, *ACS Catal.*, 2019, **9**, 4426–4433; (f) T. Ben Halima, J. K. Vandavasi, M. Shkoor and S. G. Newman, *ACS Catal.*, 2017, **7**, 2176–2180; (g) W. Zhang, J. Smilovich and V. Albert, *Tetrahedron*, 2022, **114**, 154242; (h) Z. Fu, X. Wang, S. Tao, Q. Bu, D. Wei and N. Liu, *J. Org. Chem.*, 2021, **86**, 2339–2358; (i) A. Mondal, M. Subaramanian, A. Nandakumar and E. Balaraman, *Org. Lett.*, 2018, **20**, 3381–3384; (j) S. Sultan, M. Kumar, S. Devari, D. Mukherjee and B. A. Shah, *ChemCatChem*, 2016, **8**, 703–707.
- 13 C. A. Malapit, D. R. Caldwell, N. Sassu, S. Milbin and A. R. Howell, *Org. Lett.*, 2018, **19**, 1966–1969.
- 14 (a) H. Charville, D. Jackson, G. Hodges and A. Whiting, *Chem. Commun.*, 2010, **46**, 1813–1823; (b) L. J. Goossen, D. M. Ohlmann and P. P. Lange, *Synthesis*, 2009, **209**, 160–164; (c) B. S. Jursic and Z. Zdravkovski, *Synth. Commun.*, 1993, **23**, 2761–2770; (d) L. Zhang, X. J. Wang, J. Wang, N. Grinberg, D. Krishnamurthy and C. H. Senanayake, *Tetrahedron Lett.*, 2009, **50**, 2964–2966; (e) N. Goyal, *Synlett*, 2010, **20**, 335–336; (f) J. W. Bode and L. J. Goossen, *Top. Organomet. Chem.*, 2012, **44**, 13–33; (g) H. Lundberg, F. Tinnis, N. Selander and H. Adolfsson, *Chem. Soc. Rev.*, 2014, **43**, 714–2742; (h) F. Ye, Y. Ge, A. Spannenberg, H. Neumann and M. Beller, *Nat. Commun.*, 2020, **11**, 5383; (i) D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443–4458; (j) R. W. Dugger, J. A. Ragan and D. H. B. Ripin, *Org. Process Res. Dev.*, 2005, **9**, 253–258; (k) J. Magano, *Org. Process Res. Dev.*, 2022, **26**, 1562–1589; (l) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405–3415; (m) R. M. De Figueiredo, J.-S. Suppo and J.-M. Campagne, *Chem. Rev.*, 2016, **116**, 12029–12122; (n) E. Massolo, M. Pirola and M. Benaglia, *Eur. J. Org. Chem.*, 2020, **30**, 4641–4651; (o) J. R. Dunetz, J. Magano and G. A. Weisenburger, *Org. Process Res. Dev.*, 2016, **20**, 140–177; (p) W. Muramatsu, T. Hattori and H. Yamamoto, *J. Am. Chem. Soc.*, 2019, **141**, 12288–12295; (q) D. T. Nguyen, D. C. Lenstra and J. Mecinović, *RSC Adv.*, 2015, **5**, 77658–77661; (r) M. A. Ali, S. M. A. H. Siddiki, K. Kon and K.-I. Shimizu, *ChemCatChem*, 2015, **7**, 2705–2710; (s) H. Morimoto, R. Fujiwara, Y. Shimizu, K. Morisaki and T. Ohshima, *Org. Lett.*, 2014, **16**, 2018–2021; (t) D. C. Lenstra, D. T. Nguyen and J. Mecinović, *Tetrahedron*, 2015, **71**, 5547–5553; (u) M. N. Rashed, K. Masuda, T. Ichitsuka, N. Koumura, K. Sato and S. Kobayashi, *Adv. Synth. Catal.*, 2021, **363**, 2529–2535; (v) B. D. Mkhonazi, M. Shandu, R. Tshinavhe, S. B. Simelane and P. T. Moshapo, *Molecules*, 2020, **25**, 1040–1048; (w) H. Tsuji and H. Yamamoto, *J. Am. Chem. Soc.*, 2016, **138**, 14218–14221.
- 15 (a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411–420; (b) M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven and F. J. Weiberth, *Green Chem.*, 2018, **20**, 5082–5103.



- 16 (a) H. Ehrhorn and M. Tamm, *Chem.–Eur. J.*, 2019, **25**, 3190; (b) U. H. F. Bunz, *Chem. Rev.*, 2000, **100**, 1605; (c) U. H. F. Bunz, K. Seehafer, M. Bender and M. Porz, *Chem. Soc. Rev.*, 2015, **44**, 4322; (d) R. Chinchilla and C. Najera, *Chem. Rev.*, 2014, **114**, 1783; (e) X. Ren, G. Li, S. Wei and H. Du, *Org. Lett.*, 2015, **17**, 990; (f) A. Ahlers, T. de Haro, B. Gabor and A. Furstner, *Angew. Chem., Int. Ed.*, 2016, **55**, 1406; (g) P. M. Cromm, S. Schaubach, J. Spiegel, A. Furstner, T. N. Grossmann and H. Waldmann, *Nat. Commun.*, 2016, **7**, 11300.
- 17 T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264.
- 18 K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.

