

Cite this: *Chem. Sci.*, 2019, 10, 788

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 6th September 2018

Accepted 29th October 2018

DOI: 10.1039/c8sc03967d

rsc.li/chemical-science

# Enantioselective synthesis of *gem*-disubstituted *N*-Boc diazaheterocycles via decarboxylative asymmetric allylic alkylation†

Alexander W. Sun,<sup>‡</sup> Stephan N. Hess<sup>‡</sup> and Brian M. Stoltz<sup>‡\*</sup>

An enantioselective synthesis of diverse *N*4-Boc-protected  $\alpha,\alpha$ -disubstituted piperazin-2-ones using the palladium-catalyzed decarboxylative allylic alkylation reaction has been achieved. Using a chiral Pd-catalyst derived from an electron deficient PHOX ligand, chiral piperazinones are synthesized in high yields and enantioselectivity. The chiral piperazinone products can be deprotected and reduced to valuable *gem*-disubstituted piperazines. This reaction is further extended to enable the enantioselective synthesis of  $\alpha,\alpha$ -disubstituted tetrahydropyrimidin-2-ones, which are hydrolyzed into corresponding chiral  $\beta^{2,2}$ -amino acids.

## Introduction

Nitrogen containing heterocycles are ubiquitous components of biologically active small molecules.<sup>1</sup> For instance, piperazine, a representative diazaheterocycle, is the third most prevalent heterocycle in small molecule pharmaceuticals<sup>1</sup> and can be found in bioactive molecules such as the antiviral natural product herquiline A,<sup>2</sup> the blockbuster psychiatric drug aripiprazole,<sup>3</sup> and the HIV integrase inhibitor dolutegravir<sup>4</sup> (as the oxidized counterpart, piperazin-2-one) (Fig. 1).

In the field of medicinal chemistry and fragment-based drug discovery, an emerging paradigm to enhance drug-like properties of small molecules involves reducing molecular flatness by incorporating chiral centers.<sup>5</sup> This method of increasing molecular complexity can enhance binding affinity and

specificity for a target, as receptor–ligand binding is often defined by three dimensional contacts.<sup>5b</sup> Furthermore, depending on the chemical composition of the chiral center, other properties such as metabolism, aqueous solubility, and cell-penetration may be optimized.<sup>5a</sup> The prevalence of piperazine in bioactive molecules makes it an excellent scaffold upon which to introduce chirality and increase molecular complexity. Chiral *gem*-disubstitution on any of four carbon atoms in the piperazine ring could dramatically alter physicochemical properties (Fig. 2). Despite this potential, there are no *gem*-disubstituted piperazines among the current 98 FDA approved piperazine-containing non-natural product derived drugs.<sup>6</sup> In contrast, a significant number contain mono-substituted piperazines, which can be prepared through a variety of strategies,<sup>7</sup> including cyclization of chiral precursors,<sup>7b–d</sup> enantioselective hydrogenation of pyrazines,<sup>7ef</sup> palladium-catalyzed cyclizations,<sup>7g–i</sup> or asymmetric lithiation.<sup>7j,k</sup>

The dearth of piperazine *gem*-disubstitution in the pharmacopoeia highlights the significant challenge of installing fully substituted chiral centers into diazaheterocycles.<sup>8</sup> The state of the art is perhaps best exemplified by the Bode laboratory's extensive development of tin (SnAP) and silicon (SLAP) coupling reagents to generate spiro-substituted piperazines (Scheme 1a).<sup>9</sup> However, this method is not yet enantioselective and involves potentially toxic tin reagents. Other non-enantioselective methods to synthesize *gem*-disubstituted piperazines include [4 + 2] cycloadditions of 1,2 diamines with

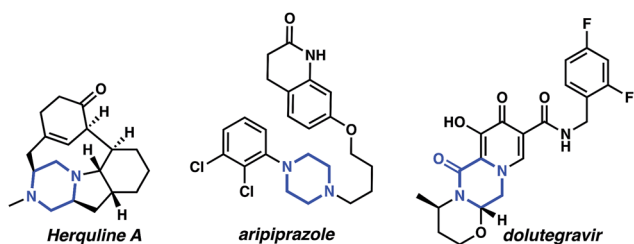


Fig. 1 Representative piperazine and piperazine-2-one pharmaceuticals and natural products.

Warren and Katherine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, USA. E-mail: stoltz@caltech.edu

† Electronic supplementary information (ESI) available: Experimental procedures, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and IR spectra. See DOI: 10.1039/c8sc03967d

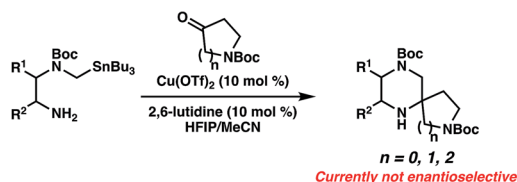
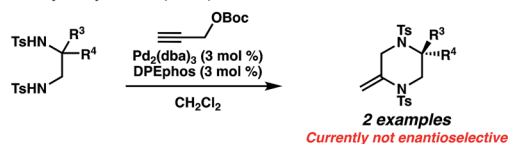
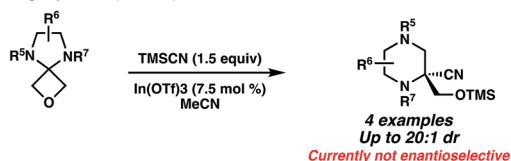
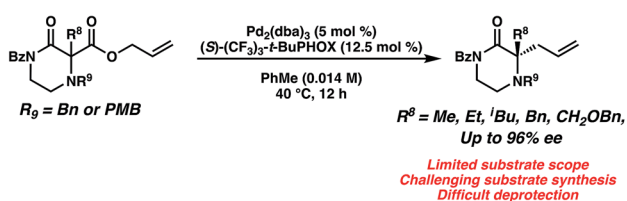
‡ These authors contributed equally.



*gem*-Disubstituted piperazine

Increased molecular complexity<sup>5c</sup>  
Augmented properties: specificity, metabolism, solubility, permeability  
Absent in all 98 FDA-approved piperazine containing drugs<sup>6</sup>

Fig. 2 Advantages of chiral *gem*-disubstituted piperazines.

a) Tin amine protocol (SnAP) coupling with ketones to form spiro-piperazines (Bode)<sup>9</sup>b) Palladium catalyzed cyclization (Rawal)<sup>7g</sup>c) Oxetane ring expansion (Carreira)<sup>10</sup>d) Decarboxylative Asymmetric Allylic Alkylation (Stoltz 2015)<sup>11</sup>Scheme 1 Existing approaches for *gem*-disubstituted piperazines and piperazinones.

propargyl alcohols developed by Rawal (Scheme 1b),<sup>7g</sup> and the ring expansion of oxetane spirocycles by Carreira (Scheme 1c).<sup>10</sup>

To our knowledge, the only method enabling the highly enantioselective synthesis of *gem*-disubstituted piperazines was published by our group in 2015.<sup>11</sup> We leveraged the palladium-catalyzed decarboxylative asymmetric allylic alkylation reaction to synthesize chiral  $\alpha,\alpha$ -disubstituted *N*4-benzylated piperazin-2-ones (Scheme 1d). These piperazin-2-ones could then be reduced into desirable chiral *gem*-disubstituted piperazines. However, we encountered two issues during the course of our attempts to utilize this method to synthesize disubstituted piperazines for medicinal chemistry purposes: first, the optimal nucleophilic benzyl-protected *N*4 significantly complicated substrate synthesis *via* nucleophilic side reactions, leading to low yields of products. As a result, we failed to synthesize many desired substrates *via* standard enolate functionalization of the dicarbonyl precursor. Instead, we resorted to a low-yielding 5-step convergent sequence beginning from an amino acid (Scheme 2a). As a result, our substrate scope displayed limited functional group diversity. Second, in the course of working with a *N*4-PMB-protected piperazin-2-one, we failed to remove the recalcitrant PMB group using a variety of common cleavage conditions that were orthogonal to the sensitive allyl functionality.

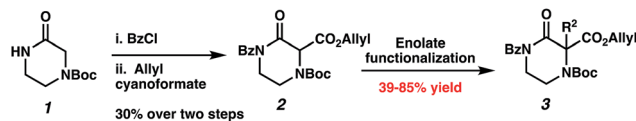
## Results and discussion

The substrate-dependent drawbacks of our approach leave room for an improved method to synthesize chiral disubstituted

## a) Previous route to allylic alkylation substrates (Stoltz 2015)



## b) Streamlined route to allylic alkylation substrates (This research)



Scheme 2 Comparison of routes to piperazin-2-one decarboxylative allylation substrates.

piperazines. In an effort to expand upon our group's long-standing interest in transition-metal catalyzed allylic alkylation, we sought to identify an alternative protecting group that could overcome the aforementioned limitations by enabling both facile substrate synthesis and protecting group cleavage. After extensive explorations directed toward this goal, we were pleased to discover that replacing the *N*4-benzyl protecting group with a simple Boc (*tert*-butoxycarbonyl) protecting group addressed the issue of difficult substrate synthesis. Presumably, the electron-withdrawing Boc group attenuates the nucleophilicity of *N*4, enabling divergent access to a wider array of substrates **3** *via* enolate functionalization of dicarbonyl compound **2**, which could be synthesized in only two steps from Boc-piperazinone **1** (Scheme 2b, see the ESI† for full synthetic details).

With a streamlined approach toward a wide range of decarboxylative alkylation substrates, we began optimizing the reaction conditions: with model substrate **3m**, conditions based on our previous report<sup>11</sup> using 10 mol% (*S*)-(CF<sub>3</sub>)<sub>3</sub>-*t*-BuPHOX ligand and 4 mol% Pd<sub>2</sub>(pmda)<sub>3</sub> in 0.014 M toluene gave the product **3m** in only 76% ee (Table 1, entry 1). Other commonly used allylic alkylation ligands such as (*S*)-*t*-BuPHOX (**L2**) and (*S,S*)-ANDEN-Ph Trost (**L3**) were tested, both giving suboptimal enantioselectivities (entries 2 and 3). We then examined the effect of solvent on the enantioselectivity (entries 4–6), ultimately finding that 2 : 1 hexanes–toluene provided high yield and ee.

Employing these satisfactory reaction conditions, we then explored the substrate scope of the decarboxylative alkylation of various *N*4-Boc protected piperazinones (Table 2). We first tested the  $\alpha$ -monosubstituted piperazinone **3a**, finding that typical conditions in a 0.033 M solution of toluene afforded the product **4a** in high yield and enantioselectivity. Another monosubstituted piperazinone **4b** with a *N*1-anisoyl protecting group, was also obtained in high yield and ee. Furthermore, replacement of the *N*4-Boc protecting group with Cbz (**3c**), and 2-chloro substitution of the allyl group (**3d**) similarly provided good results.

Next, we examined  $\alpha,\alpha$ -disubstituted substrates, finding that for the simple cases of methyl substitution (**3e**, **3f**), performing the reaction at 0.033 M concentration in toluene gave high yields and ee, with no improvement with the use of 2 : 1 hexanes–toluene at 0.014 M concentration. The exception was



Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Ligand	Solvent	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	L2	Tol	75	76
2	L2	Tol	70	1
3	L3	Tol	83	52
4	L1	THF	—	13
5	L1	MTBE	—	80
6	L1	2 : 1 Hex/Tol	93	93

(S)-L1

(S)-L2

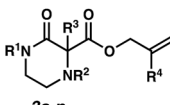
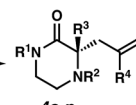

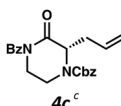
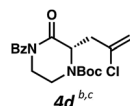
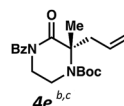
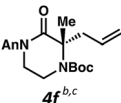
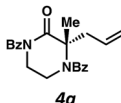
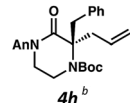
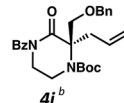
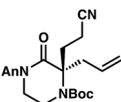
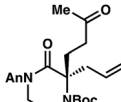
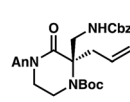
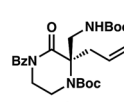
(S,S)-L3

<sup>a</sup> Screens performed on a 0.04 mmol scale. <sup>b</sup> All reported yields are for isolated products. <sup>c</sup> The ee values were determined by chiral SFC analysis. Bz = benzoyl, Boc = *tert*-butoxycarbonyl, pmdba = bis(4-methoxybenzylidene)acetone.

N4-benzoyl protected substrate **3g**, which in our previous work gave 52% ee in toluene;<sup>11</sup> under our optimized conditions in 2 : 1 hexanes–toluene, the substrate gave an improved albeit modest ee of 70%. Larger substituents such as  $\alpha$ -benzylated compound **3h** or benzyloxymethyl ether **3i** required the use of 2 : 1 hexanes–toluene to achieve high enantioselectivity. This unique mixed-solvent requirement was observed in all substituents other than methyl. A wide range of functional groups was tolerated: notably, the nitrile, ketone, and methylcarbamate substrates, which could not be accessed in our previously described efforts, gave high ee and yields (**3j–m**).

With the *N*-Boc piperazin-2-one substrates providing excellent results, we wondered whether an isomeric substrate class, the *N*-Boc tetrahydropyrimidin-2-ones (**5**), would perform similarly as well (Scheme 3C). The resulting  $\alpha,\alpha$ -disubstituted tetrahydropyrimidin-2-one products (**6**) are especially interesting as they may be hydrolyzed to afford valuable  $\beta^{2,2}$ -amino acids (**7**), which are used in peptidomimetic therapeutics and in the design of unnatural peptides and proteins with unique secondary and tertiary structures.<sup>12</sup> In fact, there is strong precedent for an allylic alkylation approach toward  $\beta^{2,2}$ -amino acids. In 2018 the Shibasaki group described the decarboxylative allylic alkylation of an N,O heterocycle to set the quaternary stereocenter, followed by N–O bond heterolysis to generate  $\beta^{2,2}$ -amino acids (Scheme 3A).<sup>13a</sup> Later in 2018, Cossy and co-workers described a similar approach involving intermolecular allylic alkylation (Scheme 3B).<sup>13b</sup> Notably, the substrate scope for these two examples is limited to mostly  $\alpha$ -benzylic and  $\alpha$ -aryl compounds. If decarboxylative alkylation could be achieved with the versatile tetrahydropyrimidin-2-one scaffold, a broader range of chiral  $\beta^{2,2}$ -amino acids might be

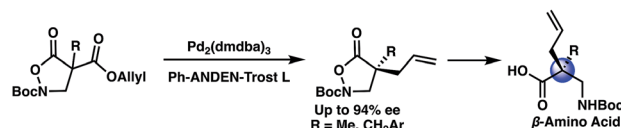
Table 2 Substrate scope exploration<sup>a</sup>

 <p><b>3a-n</b></p>	<p><math>\text{Pd}_2(\text{dba})_3</math> (4 mol %) (<i>S</i>)-(CF<sub>3</sub>)<sub>3</sub>-tBuPHOX (10 mol %) 2:1 hexanes-toluene 40 °C</p>	 <p><b>4a-n</b></p>	
 <p><b>4a</b><sup>c</sup>: R<sup>1</sup> = Bz, 90% yield, 92% ee</p>	 <p><b>4c</b><sup>c</sup> 75% yield 99% ee</p>	 <p><b>4d</b><sup>b,c</sup> 85% yield 98% ee</p>	 <p><b>4e</b><sup>b,c</sup> 90% yield 96% ee</p>
 <p><b>4f</b><sup>b,c</sup> 85% yield 96% ee</p>	 <p><b>4g</b> 80% yield 70% ee</p>	 <p><b>4h</b><sup>b</sup> 70% yield 96% ee</p>	 <p><b>4i</b><sup>b</sup> 87% yield 92% ee</p>
 <p><b>4j</b> 88% yield 97% ee</p>	 <p><b>4k</b> 73% yield 97% ee</p>	 <p><b>4l</b> 75% yield 92% ee</p>	 <p><b>4m</b><sup>b</sup> 93% yield 93% ee</p>

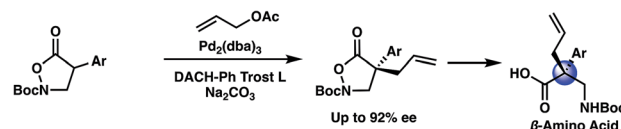
<sup>a</sup> Conditions: piperazin-2-one **3** (1.0 equiv.), Pd<sub>2</sub>(dba)<sub>3</sub> (4 mol%), (S)-(CF<sub>3</sub>)<sub>3</sub>-tBuPHOX (10 mol%), in 2 : 1 hexanes/toluene (0.014 M) at 40 °C for 12–24 h. <sup>b</sup> Pd<sub>2</sub>(pmdba)<sub>3</sub> (4 mol%) instead of Pd<sub>2</sub>(dba)<sub>3</sub>. <sup>c</sup> Toluene (0.033 M) instead of 2 : 1 hexanes/toluene. All reported yields are for isolated products. The ee values were determined by chiral SFC analysis. An = 4-methoxybenzyl, dba = dibenzylideneacetone.

accessible (Scheme 3C). Additionally, tetrahydropyrimidinones may be reductively transformed into hexahydropyrimidines, which are found in bioactive molecules such as the antibiotic hexetidine and the macrocyclic natural product verbamethine.<sup>14</sup>

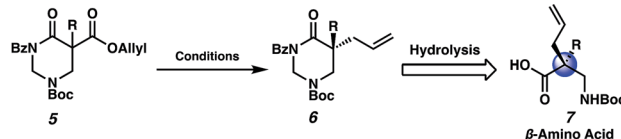
#### A. Decarboxylative allylation approach toward $\beta^{2,2}$ -amino acids (Shibasaki 2018)<sup>13a</sup>



#### B. Allylic alkylation approach toward $\beta^{2,2}$ -amino acids (Cossy 2018)<sup>13b</sup>



#### C. This Research: Decarboxylative allylation of tetrahydropyrimidin-2-ones

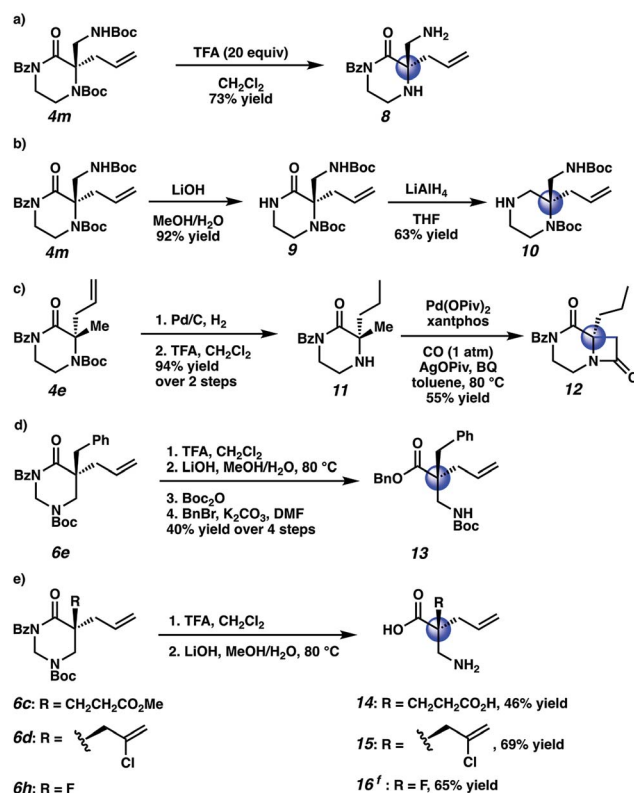


Scheme 3 Synthetic approaches toward  $\beta^{2,2}$ -amino acids using the allylic alkylation reaction.



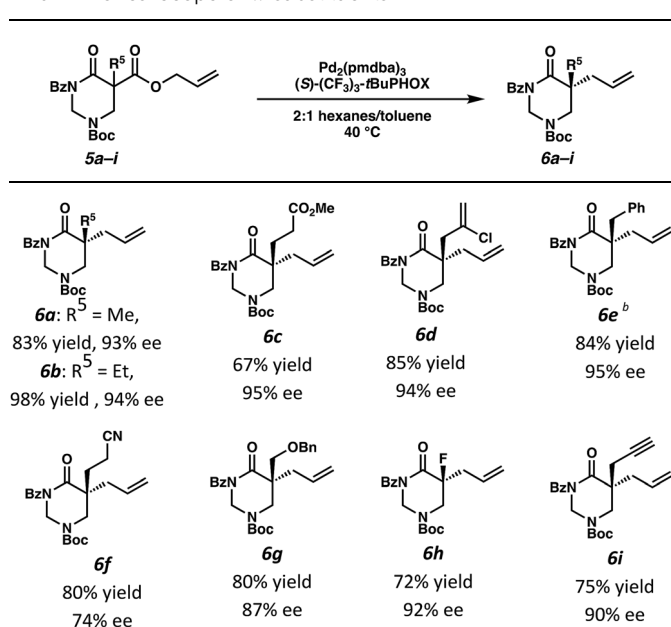
Beginning our investigations with methyl substrate **5a** (Table 3), we were pleased to find that our optimized conditions in 2 : 1 hexanes–toluene furnished the desired decarboxylative alkylation product **6a** in high yield and ee. The reaction proved amenable to a variety of  $\alpha$ -substituents, including ethyl (**6b**), methyl ester (**6c**), 2-chloroallyl (**6d**), and benzyl (**6e**). Furthermore, the reaction is scalable, with the benzyl substrate **5e** giving good results in a 1 gram reaction. In contrast, the nitrile and benzyloxymethyl ether products **6f** and **6g** were isolated with reduced enantioselectivities. Pleasingly, the fluorine and propargyl substrates **5h** and **5i** performed well, and may serve as a precursor to a novel fluorinated  $\beta^{2,2}$ -amino acid, or for bi-orthogonal click reactions, respectively.

Having demonstrated excellent results for the decarboxylative alkylation of piperazin-2-ones and tetrahydropyrimidin-2-ones, we began exploring their synthetic utility. In contrast to the relative difficulty of removing the *N*4-benzyl type protecting groups in our previous work, both Boc groups of **4m** were easily removed by treatment with excess TFA to give aminopiperazinone **8** (Scheme 4a). With LiOH, the benzoyl group could be orthogonally removed to provide the free amide **9** (Scheme 4b). The amide **9** could then be reduced with LiAlH<sub>4</sub> to the corresponding chiral aminopiperazine **10**. To further illustrate the synthetic versatility realized by Boc-deprotection of *N*4, we hydrogenated the allyl olefin of methyl piperazinone **4e** before cleaving the Boc group to obtain **11**. We then applied Gaunt's<sup>15</sup> method of C–H carbonylation on the aliphatic amine of **11** to forge the fused  $\beta$ -lactam **12**, which bears resemblance to the core of various  $\beta$ -lactam antibiotics and  $\beta$ -lactamase



**Scheme 4** Product derivatization: (a) Boc cleavage to the free amine. (b) Benzoyl cleavage and reduction to the piperazine. (c) Boc cleavage, allyl hydrogenation, and C–H carbonylation of the free amine. (d, e) hydrolysis and subsequent protection of the  $\beta^{2,2}$ -amino acid. <sup>f</sup>KOH, 1 : 1 MeOH/H<sub>2</sub>O, rt; then, HCl, MeOH, rt. BQ = benzoquinone. Piv = pivalate.

**Table 3** Pd-Catalyzed decarboxylative alkylation of tetrahydropyrimidin-2-ones. Scope of  $\alpha$ -substituents<sup>a</sup>



<sup>a</sup> Conditions: tetrahydropyrimidin-2-one **5** (1.0 equiv.), Pd<sub>2</sub>(pmdba)<sub>3</sub> (4 mol%), (S)-(CF<sub>3</sub>)<sub>3</sub>-tBuPHOX (10 mol%), in 2 : 1 hexanes/toluene (0.014 M) at 40 °C for 12–24 h. All reported yields are for isolated products. <sup>b</sup> Reaction performed with 1 gram of substrate **5e**. The ee values were determined by chiral SFC analysis.

inhibitors (Scheme 4c). Lastly, we transformed four tetrahydropyrimidinone substrates, **6c–e** and **6h**, into their corresponding acyclic forms (Scheme 4d, e). Using a two-step protocol involving TFA-mediated Boc cleavage followed by saponification with LiOH, we successfully obtained the crude  $\beta^{2,2}$ -amino acid (Scheme 4d); to facilitate silica gel chromatographic isolation, we chose to mask the free amine and carboxylic acid with Boc and benzyl groups, respectively, resulting in protected  $\beta^{2,2}$ -amino acid **13**. We note that in this four step sequence, we only performed one chromatographic separation to isolate the protected  $\beta$ -amino acid. In contrast, novel unprotected  $\beta^{2,2}$ -amino acids **14–16** bearing pendant carboxylic acid, chloroallyl, and fluorine atom functional groups could be obtained directly by purification with reverse phase preparatory HPLC following the two-step deprotection sequence (Scheme 4e).

## Conclusions

In summary, we have developed a decarboxylative asymmetric allylic alkylation reaction to synthesize unprecedented chiral  $\alpha,\alpha$ -disubstituted piperazin-2-ones and tetrahydropyrimidin-2-ones. This work represents a significant improvement upon existing technology, featuring ease of substrate synthesis, facile





N4-Boc deprotection, and broader substrate scope. The resulting piperazinones can be transformed into valuable chiral *gem*-disubstituted piperazines that are anticipated to provide stereodefined access to new chemical space in drug discovery. Similarly, the tetrahydropyrimidinone scaffold could be hydrolyzed to provide access to corresponding protected and free  $\beta^{2,2}$ -amino acids. We anticipate this decarboxylative allylic alkylation protocol will find utility in the field of medicinal chemistry as well as in natural products synthesis.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The NIH-NIGMS (R01GM080269) and Caltech are thanked for support of our research program. Additionally, 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). S. N. H. thanks the Bayer Foundation for an Otto Bayer Scholarship. Dr David VanderVelde is thanked for assistance with structural assignments *via* NMR analysis. Dr Scott Virgil, Dr Marchello Cavitt, Dr Brendan O'Boyle, Dr Justin Hilf, Dr Corey Reeves, and Kevin Yang are thanked for helpful discussions.

## Notes and references

- 1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
- 2 (a) S. Omura, A. Hirano, Y. Iwai and R. Masuma, *J. Antibiot.*, 1979, **32**, 786–790; (b) T. Chiba, Y. Asami, T. Suga, Y. Watanabe, T. Nagai, F. Momose, K. Nonaka, M. Iwatsuki, H. Yamada, S. Ōmura and K. Shiomi, *Biosci., Biotechnol., Biochem.*, 2017, **81**, 59–62; (c) X. Yu, F. Liu, Y. Zou, M.-C. Tang, L. Hang, K. N. Houk and Y. Tang, *J. Am. Chem. Soc.*, 2016, **138**, 13529–13532.
- 3 M. A. Grady, T. L. Gasperoni and P. Kirkpatrick, *Nat. Rev. Drug Discovery*, 2003, **2**, 427–428.
- 4 (a) H. Wang, M. D. Kowalski, A. S. Lakdawala, F. G. Vogt and L. Wu, *Org. Lett.*, 2015, **17**, 564–567; (b) R. E. Ziegler, B. K. Desai, J.-A. Jee, B. F. Gupton, T. D. Roper and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2018, **57**, 7181–7185.
- 5 (a) K. Hirata, M. Kotoku, N. Seki, T. Maeba, K. Maeda, S. Hirashima, T. Sakai, S. Obika, A. Hori, Y. Hase, *et al.*, *ACS Med. Chem. Lett.*, 2016, **7**, 23–27; (b) A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons and D. W. Young, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6799–6804; (c) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (d) F. Lovering, *Med. Chem. Commun.*, 2013, **4**, 515–519; (e) S. Monteleone, J. E. Fuchs and K. R. Liedl, *Front. Pharmacol.*, 2017, **8**, 552.
- 6 Using the drugbank.ca database, we curated a structure search of piperazine-containing small molecule drugs. Out of 98 drugs, none were *gem*-disubstituted on the piperazine ring.
- 7 For a review, see: (a) K. E. Gettys, Z. Ye and M. Dai, *Synthesis*, 2017, **49**, 2589–2604; (b) R. Holl, D. Schepmann and B. Wünsch, *Med. Chem. Commun.*, 2012, **3**, 673–679; (c) G. Sudhakar, S. Bayya, K. J. Reddy, B. Sridhar, K. Sharma and S. R. Bathula, *Eur. J. Org. Chem.*, 2014, 1253–1265; (d) S. Chamakuri, P. Jain, S. K. Reddy Guduru, J. W. Arney, K. R. MacKenzie, C. Santini and D. W. Young, *J. Org. Chem.*, 2018, **83**, 6541–6555; (e) R. Kuwano and Y. Ito, *J. Org. Chem.*, 1999, **64**, 1232–1237; (f) W.-X. Huang, L.-J. Liu, B. Wu, G.-S. Feng, B. Wang and Y.-G. Zhou, *Org. Lett.*, 2016, **18**, 3082–3085; (g) T. D. Montgomery and V. H. Rawal, *Org. Lett.*, 2016, **18**, 740–743; (h) J. S. Nakhla and J. P. Wolfe, *Org. Lett.*, 2007, **9**, 3279–3282; (i) B. M. Cochran and F. E. Michael, *Org. Lett.*, 2008, **10**, 329–332; (j) B. P. McDermott, A. D. Campbell and A. Ertan, *Synlett*, 2008, 875–879; (k) J. D. Firth, P. O'Brien and L. Ferris, *J. Am. Chem. Soc.*, 2016, **138**, 651–659.
- 8 (a) J. Meyers, M. Carter, N. Y. Mok and N. Brown, *Future Med. Chem.*, 2016, **8**, 1753–1767; (b) C. M. Marson, in *Advances in Heterocyclic Chemistry*, ed. E. F. V. Scriven and C. A. Ramsden, Academic Press, 2017, pp. 13–33; (c) C.-V. T. Vo and J. W. Bode, *J. Org. Chem.*, 2014, **79**, 2809–2815.
- 9 (a) W.-Y. Siau and J. W. Bode, *J. Am. Chem. Soc.*, 2014, **136**, 17726–17729; (b) K. Geoghegan and J. W. Bode, *Org. Lett.*, 2015, **17**, 1934–1937; (c) S.-Y. Hsieh and J. W. Bode, *Org. Lett.*, 2016, **18**, 2098–2101.
- 10 S. A. Ruider, S. Müller and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2013, **52**, 11908–11911.
- 11 K. M. Korch, C. Eidamshaus, D. C. Behenna, S. Nam, D. Horne and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2015, **54**, 179–183.
- 12 (a) B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656–1691; (b) D. L. Steer, R. A. Lew, P. Perlmutter, A. I. Smith and M.-I. Aguilar, *Curr. Med. Chem.*, 2002, **9**, 811–822; (c) D. Seebach, A. K. Beck and D. J. Bierbaum, *Chem. Biodiversity*, 2004, **1**, 1111–1239.
- 13 (a) J.-S. Yu, H. Noda and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2018, **57**, 818–822; (b) M. Nascimento de Oliveira, S. Arseniyadis and J. Cossy, *Chem.-Eur. J.*, 2018, **24**, 4810–4814.
- 14 (a) A. Guggisberg, K. Drandarov and M. Hesse, *Helv. Chim. Acta*, 2000, **83**, 3035–3042; (b) K. Drandarov, A. Guggisberg and M. Hesse, *Helv. Chim. Acta*, 2002, **85**, 979–989.
- 15 J. R. Cabrera-Pardo, A. Trowbridge, M. Nappi, K. Ozaki and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2017, **56**, 11958–11962.

