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Synthesis of Cyclic Peptidomimetics via a Pd-Catalyzed Macroamination Reaction

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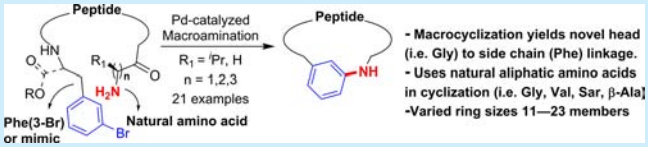
Supporting Information

ABSTRACT: A new method to access cyclic peptidomimetics via a Pd-catalyzed macroamination reaction is presented. Natural amino acid amines are revealed as proficient coupling partners in these transformations. With a commercially available CPhos G3 catalyst system and substrates bearing diverse amino acid and aryl halide backbones, the unique head to side-chain (or side-chain mimic) macrocycles are afforded with ring sizes from 11 to 23 members in yields up to 84%.



Peptide-based therapeutics are a major focus in drug discovery as these molecules can disrupt difficult targets with extended binding sites (e.g., protein−protein interactions) while maintaining good target specificity and low toxicity profiles.[1,2] However, many peptide therapeutics have certain limitations, notably poor cellular permeability, which often restricts many of these agents to extracellular target space.[2f] One way of improving the cellular permeability of peptide therapeutics (to allow their interaction with desired intracellular targets) is by constraining the amino acid sequence of interest via the synthesis of a cyclic peptide (CP) or cyclic peptidomimetic (CPM).[2] Along with enhanced cellular permeability, CPs and CPMs frequently possess other desired druglike properties such as improved enzymatic stability and target binding.[2a,3]

Because of the importance of CPs and CPMs, methods to access these molecules have been an area of extreme interest.[4] Traditionally, cyclizations to afford CPs and CPMs have been achieved via macrolactamization and macrolactonization reactions,[5] S_NAr,[6] and multicomponent reactions,[7] among others.[8,9] Lately, there has been an increased interest in using transition-metal-catalyzed reactions to access novel CPMs (Figure 1) including Suzuki−Miyaura couplings,[10] Cu-catalyzed "click" reactions,[11] and ring-closing metathesis,[12] to name a few.[13,14] However, none of the aforementioned transition-metal-catalyzed reactions utilize the natural amino acid amine in their respective cyclization steps (Scheme 1).[15]

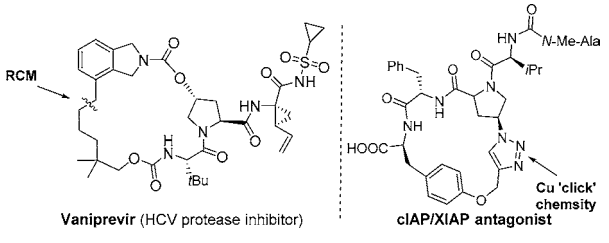
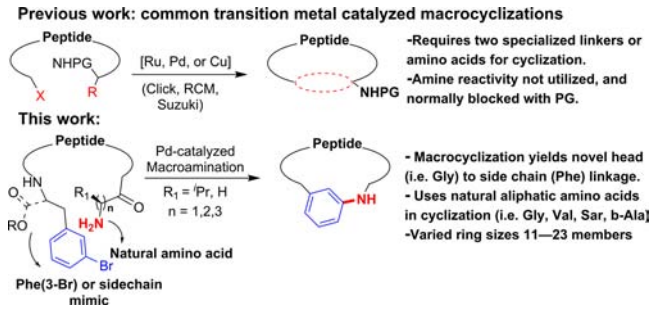


Figure 1. Biologically relevant CPMs.

Scheme 1. Summary of This Work



The Buchwald−Hartwig amination (BHA) is one of the most widely utilized reactions in medicinal chemistry.[16] This transformation has been the key step in a variety of reactions, including recent natural product applications and the synthesis of advanced pharmaceutical intermediates.[17] Despite this widespread utility, macrocyclizations of amino acid sequences via the BHA reaction have been limited to a single method that only uses aniline nucleophiles and one aryl bromide.[18] Even with a limited use for CPM synthesis, we were interested in the BHA reaction to access these molecules for two main reasons. First, using the natural aliphatic amino acid amine as the nucleophiles does not require special prefunctionalization. Also, the wide availability of aminoaryl halides would allow facile access to novel and diverse macrocyclic cores (Scheme 1).

For our initial experimentation, 3-bromophenethylamine was used as a direct surrogate for the side chain in the amino acid Phe and a weak base was used to limit epimerization concerns. Under these conditions, a variety of catalyst systems were tested for this macroamination reaction.[19] The use of the BINAP G3 precatalyst (P1) led to poor results with both **1a** and **1b**, affording small amounts of product along with substantial substrate reduction in the reaction with **1a** (entries

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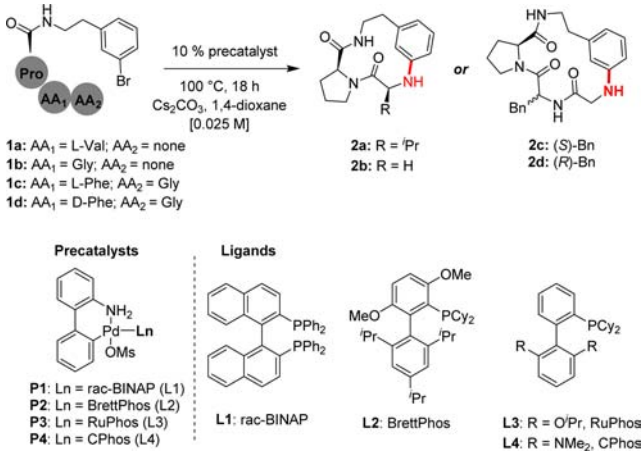
1 and 2).[20] Other commonly employed precatalyst systems (P2 and P3, entries 3–6) provided a good yield of either product **2a** or **2b** but were not general for both products. The CPhos G3 precatalyst (P4), which has been used in other hindered amine amination reactions, and has been shown to diminish substrate reduction,[21] afforded a good yield of both products **2a** and **2b** in our reaction (Table 1, entries 7 and 8).[21] This precatalyst

Table 1. Initial Screen[a]



entry	substrate	precatalyst	NMR yield[b] (%)	product
1	**1a**	P1	10 **2a**, reduced **1a**[c]	**2a**
2	**1b**	P1	trace[d]	**2b**
3	**1a**	P2	36	**2a**
4	**1b**	P2	65	**2b**
5	**1a**	P3	73	**2a**
6	**1b**	P3	43	**2b**
7	**1a**	**P4**	**72 (62)**	**2a**
8	**1b**	**P4**	**65 (60)**	**2b**
9	**1c**	**P4**	**88 (84)**	**2c**
10[e]	**1c**	P4 (5%)	55	**2c**
11	**1d**	**P4**	**77 (80)**	**2d**

[a]Conditions: 1.0 equiv of **1a–d**, 4 equiv of Cs_2CO_3, 10% precatalyst, 1,4-dioxane (0.025 M), 100 °C, 18 h. Reactions were conducted on a 0.05 mmol scale. [b]Yields were based on ^1H NMR with phenanthrene as an internal standard. Yields in parentheses refer to isolated yields. [c]Product **2a** was afforded along with 35% of **1a** and reduction of **1a**. [d]Mostly starting material. [e]5% of the CPhos ligand was used too.

also worked well with substrate **1c**, providing the 15-membered ring product **2c** in excellent yield (entry 9). Lowering the catalyst loading afforded product **2c** in a reduced yield (entry 10).

We wondered if epimerization was occurring in this reaction, since phenylalanine groups are particularly susceptible to epimerization.[22] Thus, we desired to see if the lowest energy conformation of (*S*,*S*)-**2c** correlated with its NMR data.[23] The lowest energy conformation of **2c** was generated with MOE 2015.10 using the Amber10:EHT force field,[24] which revealed hydrogens a and b to be in close proximity (only in the (*S*,*S*) diastereomer, Figure 2). Further analysis of product **2c** by ^1H–^1H ROESY NMR confirmed the spatial proximity of hydrogens a and b (structure II, Figure 2), showing that the stereochemistry was preserved.[24] We also synthesized the epimeric substrate **1d** (Table 1, entry 11), and it afforded product **2d** with no trace of **2c**. All of the above data suggest that no epimerization was occurring in our reaction.[25]

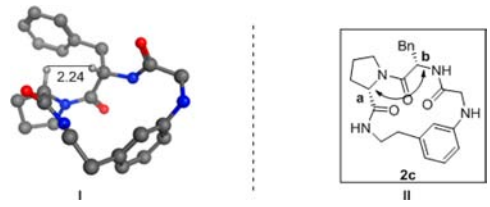
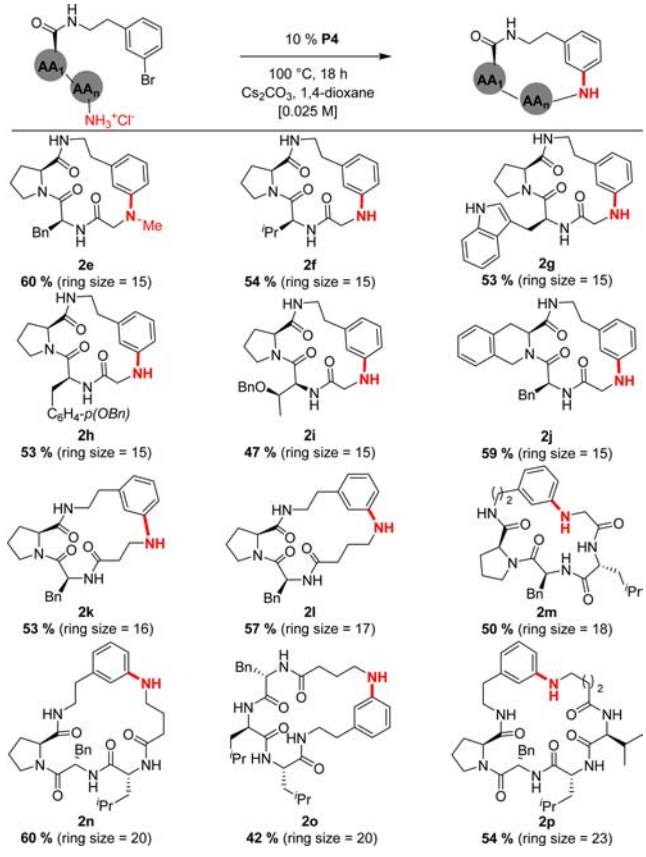


Figure 2. Epimerization study. (I) Lowest energy conformer of **2c** (*S*,*S*) displaying the close spatial proximity of hydrogens *a* and *b* (all hydrogens removed except the two of interest). (II) Diagram of key couplings from ROESY spectrum.

With the optimal conditions for cyclization in hand, we tested the scope of this head to side chain (Phe mimic) macroamination reaction. Cyclizing with an *N*-Me secondary amine, present in many biologically relevant molecules,[26] provided product **2e** in 60% yield (Scheme 2). Substitutions

Scheme 2. Substrate Scope[a]



[a]Conditions: 1.0 equiv of **1e–p**, 4 equiv of Cs_2CO_3, 10% **P4**, 1,4-dioxane (0.025 M), 100 °C, 18 h. Reactions were conducted on a 0.05 mmol scale. [b]A catalyst system composed of 10% BrettPhos G4 was used for **2m** and **2o**.

in the backbone for different amino acids and different cyclizing nitrogens were well tolerated (**2f–l**).[27] An unprotected heteroatom in the amino acid sequence was tolerated for the indole ring in tryptophan (**2g**), although the oxygens in tyrosine and threonine required protecting groups in this reaction (**2h** and **2i**). Extra amino acid residues in the backbone worked as well, and products **2m**, **2n**, and **2p** were afforded in good yields. Substrates without a heterocyclic amino acid were also synthesized. Under the reaction conditions, product **2o**

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(*S*,*R*,*S*) was afforded in 42% yield. However, the epimer with an (*S*,*S*,*S*) backbone was only observed in a trace amount.[5c,27]

The next aim was to expand the scope of the aryl bromide linker. To start, a change in the linker by simply moving the aryl bromide from the *meta* position to the *ortho* position was made. As shown in Figure 3, the 11-membered ring product **2q** and

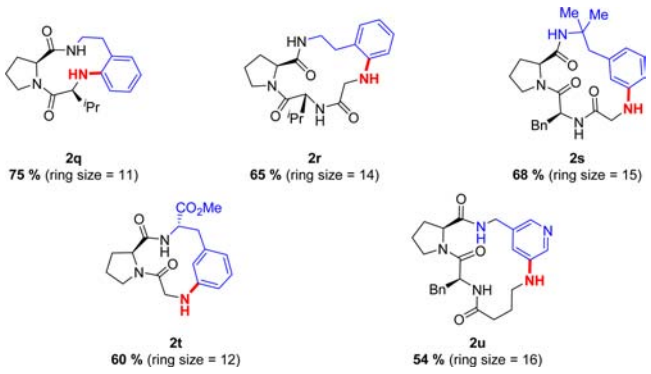

Figure 3. Linker changes. Conditions: 1.0 equiv of **1q**−**u**, 4 equiv of Cs_2CO_3, 10% **P4**, 1,4-dioxane (0.025 M), 100 °C, 18 h. Reactions were conducted on a 0.05 mmol scale. Blue indicates the change from the linker used in Scheme 2; red indicates the new bond formed.

the 14-membered ring product **2r** were afforded in 75% and 65% yields, respectively. A motif bearing a dimethyl-substituted linker yielded product **2s** in a 68% yield. A linker possessing a chiral methyl ester was also tolerated, and product **2t** was afforded in 60% yield. Furthermore, although Pd-catalyzed amination reactions with heterocycles are known to be difficult,[28] under these reaction conditions product **2u**, bearing a 3,5 disubstituted pyridine, was accessed in 54% yield.

In conclusion, a Pd-catalyzed macroamination reaction utilizing natural aliphatic amino acids as the nucleophiles has been shown to be a practical method for the synthesis of CPMs, forming 11−23 membered rings with a unique head to side chain linkage in yields up to 84%. This reaction works for a variety of amino acid backbones and aryl halide linkers, and the products show no sign of having epimerized, even at sensitive amino acids such as phenylalanine. Moreover, this new method allows for the formation of smaller 11−15-membered-ring peptidic macrocycles, which are notoriously difficult to construct. It is imagined that the simple mix and stir procedure, minimal solvent requirements, and use of commercially available linkers and catalyst systems will all aid in the adaptation of this methodology for the synthesis of novel CPMs for drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01961.

Experimental procedures, characterization data for all new compounds (starting material and final products), and ^1H and ^{13}C NMR spectra along with LCMS spectra (UV and TIC) for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) McCauley, J. A.; McIntyre, C. J.; Rudd, M. T.; Nguyen, K. T.; Romano, J. J.; Butcher, J. W.; Gilbert, K. R.; Bush, K. J.; Holloway, M. K.; Swestock, J.; Wan, B.-L.; Carroll, S. S.; DiMuzio, J. M.; Graham, D. J.; Ludmerer, S. W.; Mao, S.-S.; Stahlhut, M. W.; Fandozzi, C. M.; Trainor, N.; Olsen, D. B.; Vacca, J. P.; Liverton, N. J. *J. Med. Chem.* **2010**, *53*, 2443−2463. (b) Seigal, B. A.; Connors, W. H.; Fraley, A.; Borzilleri, R. M.; Carter, P. H.; Emanuel, S. L.; Fargnoli, J.; Kim, K.; Lei, M.; Naglich, J. G.; Pokross, M. E.; Posy, S. L.; Shen, H.; Surti, N.; Talbott, R.; Zhang, Y.; Terrett, N. K. *J. Med. Chem.* **2015**, *58*, 2855−2861.

(2) Reviews on macrocyclic peptide therapeutics: (a) Yudin, A. K. *Chem. Sci.* **2015**, *6*, 30−49. (b) Driggers, E.; Hale, S.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608−624. (c) Terrett, N. K. *Drug Discovery Today: Technol.* **2010**, *7*, e97−e104. (d) Marsault, E.; Peterson, M. L. *J. Med. Chem.* **2011**, *54*, 1961−2004. (e) Giordanetto, F.; Kihlberg, J. *J. Med. Chem.* **2014**, *57*, 278−295. (f) Tsomaia, N. *Eur. J. Med. Chem.* **2015**, *94*, 459−470.

(3) LaPlante, S. R.; Nar, H.; Lemke, C. T.; Jakalian, A.; Aubry, N.; Kawai, S. H. *J. Med. Chem.* **2014**, *57*, 1777−1789.

(4) Reviews on synthesis of macrocycles: (a) Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, S. V. *Chem. Rev.* **2015**, *115*, 8736−8834. (b) White, C. J.; Yudin, A. K. *Nat. Chem.* **2011**, *3*, 509−524.

(5) (a) Davies, J. S. *J. Pept. Sci.* **2003**, *9*, 471−501. (b) Song, Z. J.; Tellers, D. M.; Journet, M.; Kuethe, J. T.; Lieberman, D.; Humphrey, G.; Zhang, F.; Peng, Z.; Waters, M. S.; Zewge, D.; Nolting, A.; Zhao, D.; Reamer, R. A.; Dormer, P. G.; Belyk, K. M.; Davies, I. W.; Devine, P. N.; Tschaen, D. M. *J. Org. Chem.* **2011**, *76*, 7804−7815. (c) Marsault, E.; Hoveyda, H. R.; Gagnon, R.; Peterson, M. L.; Vézina, M.; Saint-Louis, C.; Landry, A.; Pinault, J.-F.; Ouellet, L.; Beauchemin, S.; Beaubien, S.; Mathieu, A.; Benakli, K.; Wang, Z.; Brassard, M.; Lonergan, D.; Bilodeau, F.; Ramaseshan, M.; Fortin, N.; Lan, R.; Li, S.; Galaud, F.; Plourde, V.; Champagne, M.; Doucet, A.; Bhérer, P.; Gauthier, M.; Olsen, G.; Villeneuve, G.; Bhat, S.; Foucher, L.; Fortin, D.; Peng, X.; Bernard, S.; Drouin, A.; Déziel, R.; Berthiaume, G.; Dory, Y. L.; Fraser, G. L.; Deslongchamps, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4731−4735. (d) Goodreid, J. D.; dos Santos, E. S.; Batey, R. A. *Org. Lett.* **2015**, *17*, 2182−2185.

(6) (a) Zou, Y.; Spokoyny, A. M.; Zhang, C.; Simon, M. D.; Yu, H.; Lin, Y.-S.; Pentelute, B. L. *Org. Biomol. Chem.* **2014**, *12*, 566−573. (b) Feng, Y.; Burgess, K. *Chem. - Eur. J.* **1999**, *5*, 3261−3272. (c) Fotsch, C.; Kumaravel, G.; Sharma, S. K.; Wu, A. D.; Gounarides, J. S.; Nirmala, N. R.; Petter, R. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2125−2130.

(7) (a) Vasco, A. V.; Pérez, C. S.; Morales, F. E.; Garay, H. E.; Vasilev, D.; Gavín, J. A.; Wessjohann, L. A.; Rivera, D. G. *J. Org. Chem.* **2015**, *80*, 6697−6707. (b) Hili, R.; Rai, V.; Yudin, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 2889−2891. (c) Roxin, A.; Chen, J.; Scully, C. C. G.; Rotstein, B. H.; Yudin, A. K.; Zheng, G. *Bioconjugate Chem.* **2012**, *23*, 1387−1395.

(8) (a) Jo, H.; Meinhardt, N.; Wu, Y.; Kulkarni, S.; Hu, X.; Low, K. E.; Davies, P. L.; DeGrado, W. F.; Greenbaum, D. C. *J. Am. Chem. Soc.*

DOI: 10.1021/acs.orglett.6b01961
Org. Lett. 2016, 18, 4072−4075

2012, *134*, 17704−17713. (b) Zhang, F.; Sadovski, O.; Xin, S. J.; Woolley, G. A. *J. Am. Chem. Soc.* **2007**, *129*, 14154−14155.
(9) Thiol−ene coupling: (a) Wang, Y.; Chou, D. H-C. *Angew. Chem., Int. Ed.* **2015**, *54*, 10931−10934. For a reaction using pyridine oxides, see: (b) Londregan, A. T.; Farley, K. A.; Limberakis, C.; Mullins, P. B.; Piotrowski, D. W. *Org. Lett.* **2012**, *14*, 2890−2893.
(10) (a) Meyer, F.-M.; Collins, J. C.; Borin, B.; Bradow, J.; Liras, S.; Limberakis, C.; Mathiowetz, A. M.; Philippe, L.; Price, D.; Song, K.; James, K. *J. Org. Chem.* **2012**, *77*, 3099−3114. (b) Afonso, A.; Cussó, O.; Feliu, L.; Planas, M. *Eur. J. Org. Chem.* **2012**, *2012*, 6204−6211.
(11) (a) Turner, R. A.; Oliver, A. G.; Lokey, R. S. *Org. Lett.* **2007**, *9*, 5011−5014. (b) Chouhan, G.; James, K. *Org. Lett.* **2011**, *13*, 2754−2757. (c) Chouhan, G.; James, K. *Org. Lett.* **2013**, *15*, 1206−1209.
(12) (a) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855−5856. (b) Kong, J.; Chen, C.; Balsells-Padros, J.; Cao, Y.; Dunn, R. F.; Dolman, S. J.; Janey, J.; Li, H.; Zacuto, M. J. *J. Org. Chem.* **2012**, *77*, 3820−3828.
(13) For C−H activation, see: (a) Dong, H.; Limberakis, C.; Liras, S.; Price, D.; James, K. *Chem. Commun.* **2012**, *48*, 11644−11646. (b) Mendive-Tapia, L.; Preciado, S.; García, J.; Ramón, R.; Kielland, N.; Albericio, F.; Lavilla, F. *Nat. Commun.* **2015**, *6*, 7160.
(14) For other Pd-catalyzed macrocyclizations, see the following. Tsuji−Trost reaction: (a) Lawson, K. V.; Rose, T. E.; Harran, P. G. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, E3753−E3760. Larock indole annulation: (b) Breazzano, S. P.; Poudel, Y. B.; Boger, D. L. *J. Am. Chem. Soc.* **2013**, *135*, 1600−1606. Heck reaction: (c) Hiroshige, M.; Hauske, J. R.; Zhou, P. *J. Am. Chem. Soc.* **1995**, *117*, 11590−11591.
(15) For an example of a reaction that uses glycine and other nonbranched amino acids amines in a Pd-carbonylative cyclization on resin, see: Kamioka, S.; Shimazu, S.; Doi, T.; Takahashi, T. *J. Comb. Chem.* **2008**, *10*, 681−690.
(16) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443−4458.
(17) For a review of N-arylation for biologically relevant molecules, see: (a) Fischer, C.; Koenig, B. *Beilstein J. Org. Chem.* **2011**, *7*, 59−74. For applications of BHA to APIs, see: (b) Hopkin, M. D.; Baxendale, I. R.; Ley, S. V. *Chem. Commun.* **2010**, *46*, 2450−2452. (c) Sperry, J. B.; Price Wiglesworth, K. E.; Edmonds, J.; Fiore, P.; Boyles, D. C.; Damon, D. B.; Dorow, R. L.; Piatnitski Chekler, E. L.; Langille, J.; Coe, J. W. *Org. Process Res. Dev.* **2014**, *18*, 1752−1758. For an application of BHA to natural product synthesis, see: (d) Mari, M.; Bartoccini, F.; Piersanti, G. *J. Org. Chem.* **2013**, *78*, 7727−7734.
(18) Balraju, V.; Iqbal, J. *J. Org. Chem.* **2006**, *71*, 8954−8956. Attempts to use this previous catalyst system for our desired products led to no reaction. See the Supporting Information. Also, other reactions such as macrolactamization for syntheis of **2c** afforded poor results; see the Supporting Information. It is known that macrolactamizations of smaller amino acid chains can be difficult; see: Thakkar, A.; Trinh, T. B.; Pei, D. *ACS Comb. Sci.* **2013**, *15*, 120−129.
(19) Other reaction conditions and other G3 catalyst such as APhos, NiXantPhos, Qphos, and P(^{t}-Bu)$_3$ led to no improvements for the reaction of **1a** either.
(20) See the Supporting Information for a crude LCMS trace comparing the BINAP reaction of substrate **1a** to the CPhos reaction.
(21) (a) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532−7533. (b) Park, N. H.; Vinogradova, E. V.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8259−8262.
(22) Ivkovic, J.; Lembacher-Fadum, C.; Breinbauer, R. *Org. Biomol. Chem.* **2015**, *13*, 10456−10460.
(23) Albadry, M. A.; Elokely, K. M.; Wang, B.; Bowling, J. J.; Abdelwahab, M. F.; Hossein, M. H.; Doerksen, R. J.; Hamann, M. T. *J. Nat. Prod.* **2013**, *76*, 178−185.
(24) The default parameters on MOE 2015.10 were used for the calculation with the Amber10:EHT forcefield. See the Supporting Information for a comparison between the (*S*,*S*)-**2c** and (*S*,*R*)-**2d** lowest energy conformations and ROESY NMRs.
(25) Under our conditions, both product **2c** and **2d** were always isolated as single and distinct diastereomers. However, strong base does induce epimerization; see the Supporting Information .
(26) (a) Köck, M.; Kessler, H.; Seebach, D.; Thaler, A. *J. Am. Chem. Soc.* **1992**, *114*, 2676−2686. (b) Rajeswaran, W. G.; Hocart, S. J.; Murphy, W. A.; Taylor, J. E.; Coy, D. H. *J. Med. Chem.* **2001**, *44*, 1416−1421. (c) Hewitt, W. H.; Leung, S. S. F.; Pye, C. R.; Ponkey, A. R.; Bednarek, M.; Jacobson, M. P.; Lokey, R. S. *J. Am. Chem. Soc.* **2015**, *137*, 715−721.
(27) For other amino acid backbones attempted, see the Supporting Information.
(28) Buitrago Santanilla, A.; Regalado, E. L.; Pereira, T.; Shevlin, M.; Bateman, K.; Campeau, L.-C.; Schneeweis, J.; Berritt, S.; Shi, Z.-C; Nantermet, P.; Liu, Y.; Helmy, R.; Welch, C. J.; Vachal, P.; Davies, I. W.; Cernak, T.; Dreher, S. D. *Science* **2015**, *347*, 49−53.

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