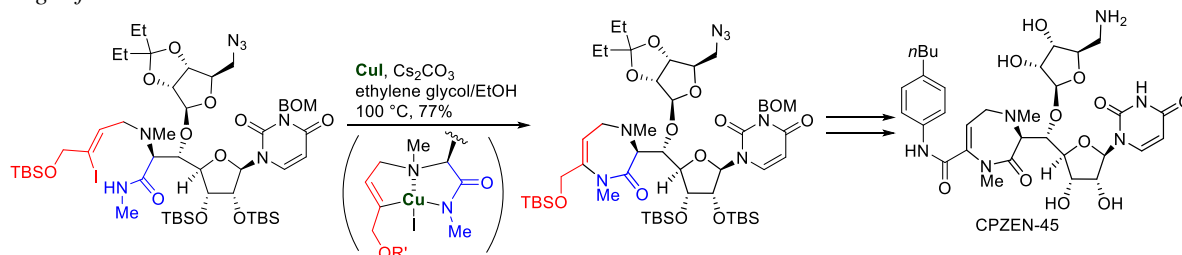


Synthesis of CPZEN-45: Construction of the 1,4-Diazepin-2-one Core by the Cu-catalyzed Intramolecular Amidation of a Vinyl Iodide

Hugh Nakamura,[†] Takuma Yoshida,[†] Chihiro Tsukano and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Supporting Information Placeholder



ABSTRACT: CPZEN-45 was developed as an antibiotic against *Mycobacterium tuberculosis* by the chemical modification of caprazamycins. CPZEN-45 has been synthesized in this study by the Cu-catalyzed intramolecular amidation of a complex vinyl iodide precursor bearing uridine and sugar moieties with a secondary amide, allowing for the construction of its 1,4-diazepin-2-one core.

CPZEN-45 (**1**) was developed as an antibiotic for the treatment of tuberculosis (TB),¹ which is one of the world's most common infectious diseases (Figure 1).² Notably, CPZEN-45 exhibits potent antibacterial activity against several multidrug-resistant strains of *Mycobacterium tuberculosis*, including extensively multidrug-resistant TB. CPZEN-45 was developed from the caprazamycins, which are natural products isolated from *Streptomyces sp.* MK730-62F2. Although caprazamycins inhibit the activity of the peptidoglycan biosynthetic enzyme MraY,³ CPZEN-45 inhibits WecA, which is an enzyme involved in the biosynthesis of mycolyl arabinogalactan.⁴ Structurally, CPZEN-45 and caprazamycins are both based on a seven-membered ring containing two nitrogen atoms, with both compounds bearing identical amino ribose and uridine moieties. In contrast to the caprazamycins, CPZEN-45 has an α,β -unsaturated amide instead of a fatty-acid side chain.

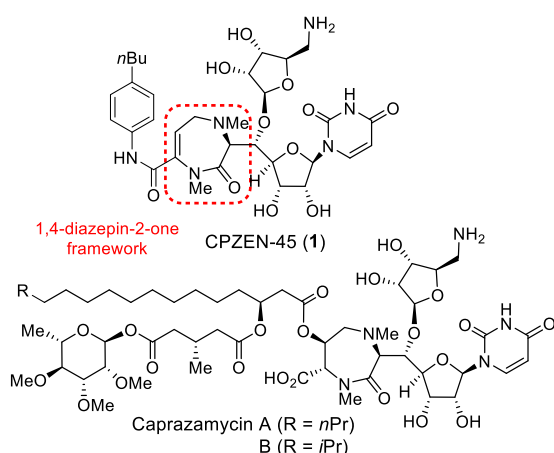


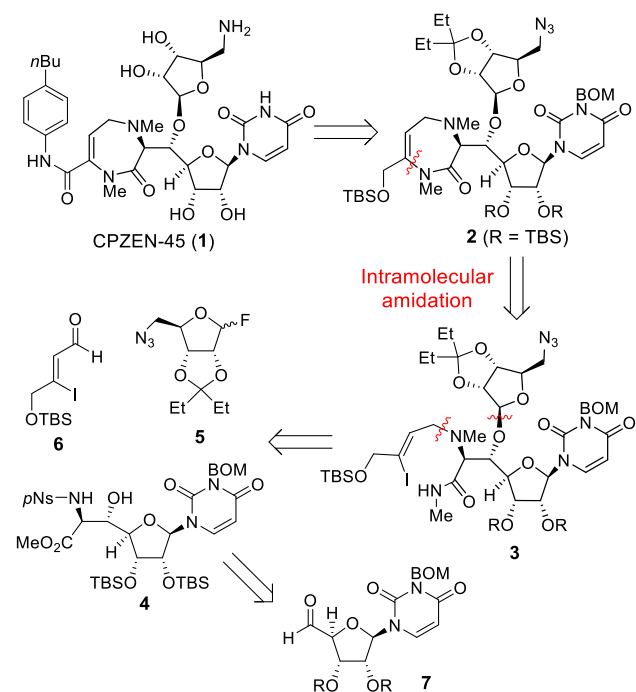
Figure 1. Structures of CPZEN-45 and caprazamycins A and B.

Several liponucleoside antibiotics, including caprazamycins, have been reported to show potent biological activities, which has prompted many groups to engage in synthetic studies towards these compounds.⁵ In 2015, we reported the first total synthesis of caprazamycin A.⁶ Furthermore, Shibasaki et al. recently reported a convergent total synthesis of caprazamycin B.⁷ As part of our ongoing synthetic studies,⁶ we recently established a stereoselective route for the synthesis of β -hydroxyamino acid derivatives. It was envisaged that this synthetic method could be applied to the synthesis of CPZEN-45, although a new method would be required for the construction of the 1,4-diazepin-2-one core. Herein, we report our recent work towards the synthesis of CPZEN-45 based on a Cu-catalyzed intramolecular amidation.

While the 1,4-diazepin-2-one core could be accessed by the formation of a saturated 1,4-diazepan-2-one followed by the dehydration of a hydroxyl group, the development of a new route providing direct access to this structure would be much more favorable. We previously reported the Pt-catalyzed 7-*endo* cyclization of alkynyl amides for the synthesis of this structure.⁸ However, substrates bearing a sugar moiety failed to provide the desired cyclization products under these conditions, presumably because of the unfavorable chelation of the oxygen atoms of the sugar to the metal center.⁹ With this in mind, we focused our efforts on the use of an intramolecular amidation¹⁰ as an alternative strategy for the synthesis of CPZEN-45 (**1**). According to this strategy, the cyclization of vinyl iodide **3** would give the 1,4-diazepin-2-one **2**, which would be converted to **1** by sequential oxidation and amidation reactions (Scheme 1). Although the cyclization of a secondary amide with a trisubstituted vinyl halide is rare, we hypothesized that this reaction would be promoted by the addition of a diamine ligand.¹¹ In this way, it was envisaged that the ligand would coordinate to the copper and prevent it from binding to the oxygen atoms of the substrate. The cyclization precursor **3** could be prepared by the coupling of the β -hydroxyamino acid

derivative **4** with fluoride **5** and the α,β -unsaturated aldehyde **6**. Lastly, the synthesis of compound **7** has been reported previously starting from an oxazolidinone.^{6,12} Shibasaki and Watanabe's synthesis^{7b} revealed that the nature of the protecting group on the secondary alcohols of the uridine derivative was important for the diastereoselectivity of their isocyanate aldol reaction. With this in mind, we planned to improve the diastereoselectivity of the synthesis of the oxazolidinone precursor by changing the protecting group used on aldehyde **7**.

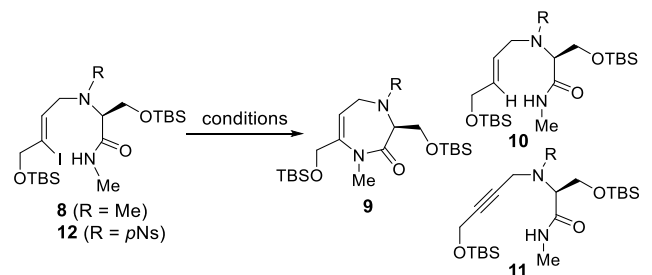
Scheme 1. Retrosynthesis of CPZEN-45.



We initially investigated the Pd- and Cu-catalyzed intramolecular amidation of compound **8**¹³ as a model substrate, under a variety of conditions previously reported to be successful for secondary amides and lactams (Table 1). Following Mori's procedure,¹⁴ the treatment of **8** with DPEphos and Cs₂CO₃, in the presence of a catalytic amount of Pd(OAc)₂, in toluene at 80 to 100 °C, gave the desired 1,4-diazepin-2-one **9**, along with the *des*-iodo compound **10** in 31% and 26% yields, respectively (Table 1, entry 1). Although the combination of CuI with *N,N*-dimethyl ethylenediamine¹⁵ (DMEDA) was found to be ineffective, the use of Cu(MeCN)₄PF₆ with 1,10-phenanthroline¹⁶ gave 1,4-diazepin-2-one **9** along with a considerable amount of alkyne **11** (Table 1, entries 2 and 3). These results indicated that the reduction of the vinyl iodide competed with the desired cyclization pathway after the oxidative addition step. Spring and co-workers recently reported the development of a Cu-catalyzed amination reaction for the synthesis of *N*-linked biaryl medium ring systems that involved the internal coordination of Cu to a nitrogen atom.^{17,18} Inspired by this work, we investigated the possibility of using the two nitrogen atoms in our substrate as an internal ligand to stabilize the intermediate and avoid these undesired side reactions (Scheme 2). As reported by Spring, the use of CuI with ethylene glycol in EtOH led to a dramatic improvement in the yield of the desired product by suppressing the production of

the unwanted alkyne **11**. However, the reaction gave a mixture of **9** and **11** when it was conducted in DMF with ethylene glycol (Table 1, entries 4–6). In the absence of ethylene glycol, the reaction also gave **9** in 70% yield (Table 1, entry 7). Interestingly, the reaction of vinyl iodide **12**, bearing a *p*-nosyl protecting group rather than a methyl group,¹⁹ failed completely (Table 1, entry 8).

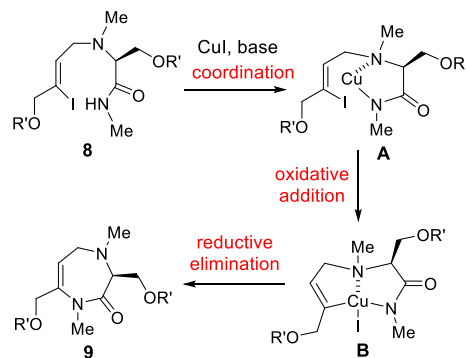
Table 1. Pd- or Cu-catalyzed amidation of vinyl iodide **8**.



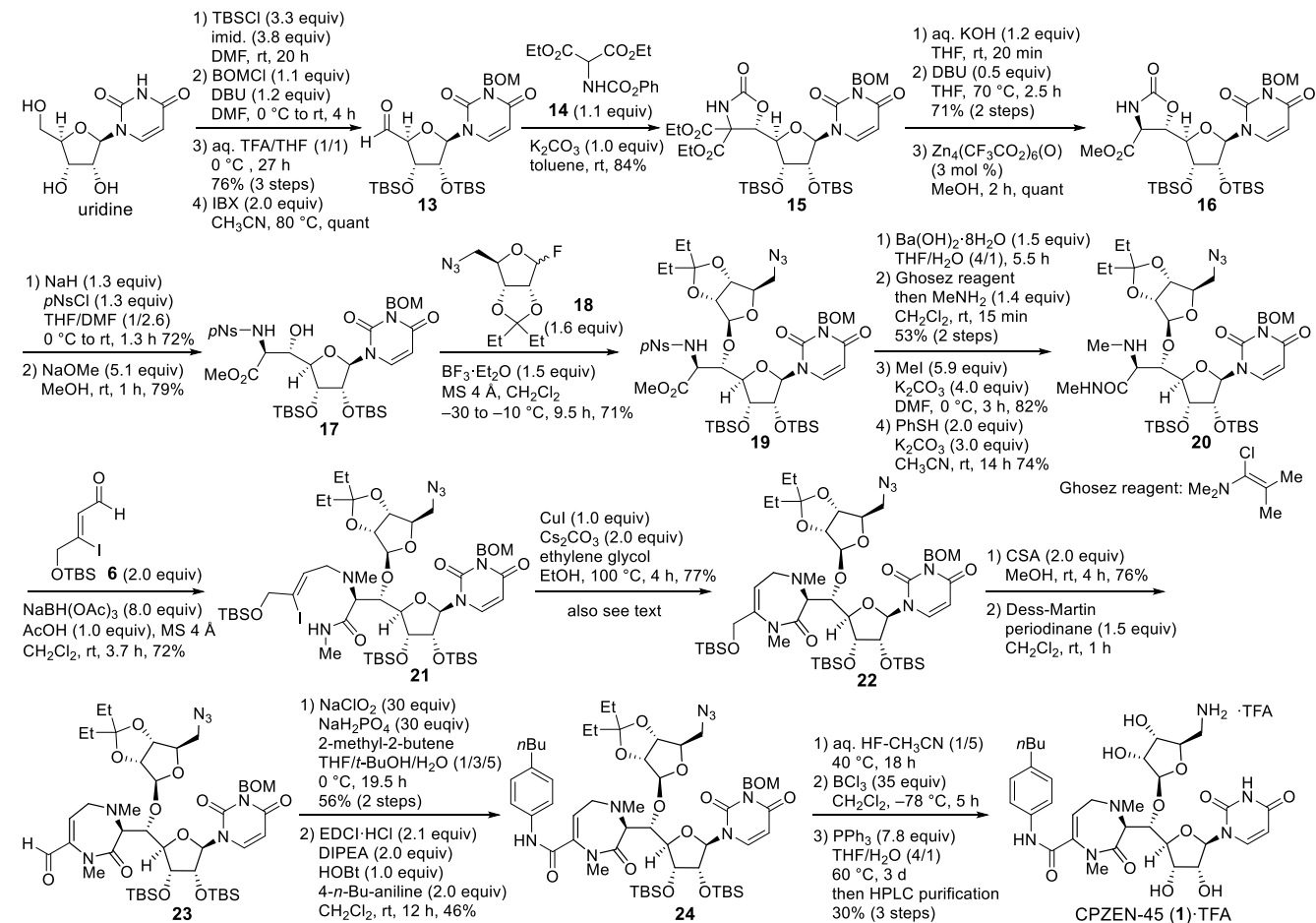
Entry	R	Conditions	Yield (%)		
			9	10	11
1	Me	Pd(OAc) ₂ , DPEphos, Cs ₂ CO ₃ , toluene, 80 to 100 °C	31	26	0
2	Me	CuI, Cs ₂ CO ₃ , DMEDA, toluene, 40 to 80 °C	0 ^a	0	0
3	Me	Cu(MeCN) ₄ PF ₆ , 1,10-phen, Rb ₂ CO ₃ , DMA, 40 to 80 °C	28	0	31
4	Me	CuI, Cs ₂ CO ₃ , ethylene glycol, DMF, 40 °C	32	0	61
5	Me	CuI, Cs ₂ CO ₃ , ethylene glycol, EtOH, 40 °C	57	0	0
6	Me	CuI, Cs ₂ CO ₃ , ethylene glycol, 40 °C	61	0	0
7	Me	CuI, Cs ₂ CO ₃ , EtOH, 40 °C	70	0	0
8	<i>p</i> Ns	CuI, Cs ₂ CO ₃ , ethylene glycol, 40 °C	0 ^b	0	0

^a The starting material was recovered in 67% yield. ^b No reaction. DPEphos = 2,2'-Bis(diphenylphosphino)diphenyl Ether, DMEDA = *N,N*-dimethylethylenediamine.

Scheme 2. The thinking behind the Cu-catalyzed amidation reaction.



Scheme 3. Synthesis of CPZEN-45.



Having successfully established good intramolecular amidation conditions for the construction of 1,4-diazepin-2-ones, we turned our attention to the synthesis of CPZEN-45. Our synthesis started with the aim of improving the diastereoselective synthesis of oxazolidinone **15** from aldehyde **7**. After screening an extensive series of bases, protecting groups for the secondary alcohol, and nucleophiles, we found that the aldol reaction of the known aldehyde **13**, which was prepared from uridine in four steps,²⁰ with diethyl 2-((phenoxycarbonyl)amino)malonate (**14**) proceeded smoothly to give the oxazolidinone **15** as a single isomer (Scheme 3).⁹ In addition to the excellent selectivity, it is noteworthy that this reaction only required (i) a simple base (i.e., K₂CO₃) and (ii) a stable nucleophile, **14**, rather than diethyl isocyanomalonate. The oxazolidinone **15** was converted into the β-hydroxy amino acid derivative **17** via the *trans*-oxazolidinone **16** through sequential decarboxylation, transesterification²¹ and oxazolidinone ring-opening reactions. Notably, this synthetic route was robust enough for a 10-gram scale synthesis.

The cyclization precursor **22** was prepared by the glycosylation of the β-hydroxy amino acid derivatives **17** with **18** using Ichikawa and Matsuda's procedure.^{5m,p} The resulting compound **19** was subsequently converted to a secondary amine via the formation of an amide using Ghosez's reagent,²² followed by *N*-methylation and the removal of the *p*-nosyl group.

The reductive amination of the secondary amine **20** with α,β-unsaturated aldehyde **6**²³ using NaBH(OAc)₃ and AcOH in the presence of 4 Å MS gave the cyclization precursor **21** in 72% yield. Notably, the addition of 4 Å MS led to an improvement in the yield of this reaction.

Following on from these model studies, we reacted vinyl iodide **21** with CuI (1.0 equiv.) and ethylene glycol in ethanol at 80 °C.²⁴ However, this reaction only resulted in a low yield of the desired cyclized product **23** (24% yield), with a significant amount of the starting material **21** being recovered unchanged. We also investigated the possibility of using a mixed solvent system composed of ethylene glycol and EtOH to increase the reaction temperature.²⁵ When this solvent system was used at 80 °C, the reaction did not reach completion (product **22**: 35%, starting material **21**: 36%). Pleasingly, however, the yield of **22** increased significantly to 77% when the reaction was conducted at 100 °C, with all of the starting material being consumed. Notably, the use of catalytic quantities of CuI (0.2 equiv.) and ethylene glycol (0.2 equiv.) at 100 °C only resulted in a minor decrease in the yield (63%).

For the final stage of the synthesis, the selective removal of the TBS group, followed by a stepwise oxidation and a condensation with 4-*n*-butylaniline gave protected CPZEN-45 (**24**). After an extensive investigation, we established that the treatment of **24** with aq. HF followed by BCl₃²⁶ allowed a successful removal of the TBS, BOM and acetal protecting

groups. Subsequent reduction of the azide with PPH₃ completed our synthesis of CPZEN-45. After HPLC purification,²⁷ the spectroscopic (¹H and ¹³C NMR, [α]_D) and high-resolution mass spectrometry data for our synthetic sample were found to be identical to those reported for CPZEN-45 TFA salt.¹

In summary, we have developed a Cu-catalyzed reaction for the construction of 1,4-diazepin-2-ones by the intramolecular amidation of a vinyl iodide with a secondary amide. The tertiary amine of the substrate was found to be essential for the cyclization. This method was also used for the synthesis of CPZEN-45 by the Cu-catalyzed intramolecular amidation to a complex vinyl iodide bearing uridine and sugar moieties. The robust nature of this synthesis means that it could be used to prepare other analogues of CPZEN-45 that would be otherwise impossible to access from caprazamycins.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectra data for all new compounds (¹H and ¹³C NMR, IR, and HRMS) (PDF)

AUTHOR INFORMATION

Corresponding Author

* E-mail: takemoto@pharm.kyoto-u.ac.jp

Author Contributions

†These authors contributed equally to this manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully thank Dr. Y. Takahashi (BIKAKEN) for providing the ¹H and ¹³C NMR spectra. We also thank Associate Prof. M. Hoshino (Kyoto Univ.) for measuring the ¹³C NMR spectra of CPZEN-45. This work was financially supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT (Y.T.), a Grant-in-Aid for JSPS fellows (H.N.) and Meiji Seika Pharma Award in Synthetic Organic Chemistry (Japan) (C.T.).

REFERENCES and FOOTNOTES

- (1) Takahashi, Y.; Igarashi, M.; Miyake, T.; Soutome, H.; Ishikawa, K.; Komatsuki, Y.; Koyama, Y.; Nakagawa, N.; Hattori, S.; Inoue, K.; Doi, N.; Akamatsu, Y. *J. Antibiot.* **2013**, *66*, 171.
- (2) WHO, Global tuberculosis report 2015.
- (3) (a) Igarashi, M.; Nakagawa, N.; Doi, N.; Hattori, S.; Naganawa, H.; Hamada, M. *J. Antibiot.* **2003**, *56*, 580. (b) Igarashi, M.; Takahashi, Y.; Shitara, T.; Nakamura, H.; Naganawa, H.; Miyake, T.; Akamatsu, Y. *J. Antibiot.* **2005**, *58*, 327.
- (4) Ishizaki, Y.; Hayashi, C.; Inoue, K.; Igarashi, M.; Takahashi, Y.; Pujari, V.; Crick, D. C.; Brennan, P. J.; Nomoto, A. *J. Biol. Chem.* **2013**, *288*, 30309.
- (5) (a) Fer, M. J.; Bouhss, A.; Patrão, M.; Corre, L. L.; Pietrancosta, N.; Amoroso, A.; Joris, B.; Mengin-Lecreulx, D.; Calvet-Vitale, S.; Gravier-Pelletier, C. *Org. Biomol. Chem.* **2015**, *13*, 7193. (b) Ichikawa, S.; Yamaguchi, M.; Hsuan, L. S.; Kato, Y.; Matsuda, A. *ACS Infect. Dis.* **2015**, *1*, 151. (c) Spork, A. P.; Büschleb, M.; Ries, O.; Wiegmann, D.; Boettcher, S.; Mihalyi, A.; Bugg, T. D. H.; Ducho, C. *Chem. Eur. J.* **2014**, *20*, 15292. (d) Fer, M. J.; Doan, P.; Prangé, T.; Calvet-Vitale, S.; Gravier-Pelletier, C. *J. Org. Chem.* **2014**, *79*, 7758. (e) Miyaoka, H.; Wada, J.; Kawashima, E. *Heterocycles* **2014**, *88*,

719. (f) Sarabia, F.; Vivar-García, C.; García-Ruiz, C.; Martín-Ortiz, L.; Romero-Carrasco, A. *J. Org. Chem.* **2012**, *77*, 1328. (g) Ii, K.; Ichikawa, S.; Al-Dabbagh, B.; Bouhss, A.; Matsuda, A. *J. Med. Chem.* **2010**, *53*, 3793. (h) Spork, A. P.; Koppermann, S.; Dittrich, B.; Herbst-Irmer, R.; Ducho, C. *Tetrahedron: Asymmetry* **2010**, *21*, 763. (i) Monasson, O.; Ginisty, M.; Mravljak, J.; Bertho, G.; Gravier-Pelletier, C.; Merrer, Y. L. *Tetrahedron: Asymmetry* **2009**, *20*, 2320. (j) Ichikawa, S. *Chem. Pharm. Bull.* **2008**, *56*, 1059. (k) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 569. (l) Xu, X. H.; Trunkfield, A. E.; Bugg, T. D. H.; Qing, F. L. *Org. Biomol. Chem.* **2008**, *6*, 157. (m) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2007**, *72*, 9936. (n) Monasson, O.; Ginisty, M.; Bertho, G.; Gravier-Pelletier, C.; Merrer, Y. L. *Tetrahedron Lett.* **2007**, *48*, 8149. (o) Fukunishi, S.; Ubukata, M.; Nakajima, N. *Heterocycles* **2007**, *73*, 627. (p) Hirano, S.; Ichikawa, S.; Matsuda, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1854. (q) Sarabia, F.; Martín-Ortiz, L.; Lopez-Herrera, F. J. *Org. Lett.* **2003**, *5*, 3927. (r) Yamashita, A.; Norton, E. B.; Williamson, R. T.; Ho, D. M.; Simishtaj, S.; Mansour, T. S. *Org. Lett.* **2003**, *5*, 3305. (s) Drouillat, B.; Poupardin, O.; Bourdreux, Y.; Greck, C. *Tetrahedron Lett.* **2003**, *31*, 2781. (t) Knapp, S.; Morriello, G. J.; Doss, G. A. *Org. Lett.* **2002**, *4*, 603. (u) Gravier-Pelletier, C.; Milla, M.; Merrer, Y. L.; Depezay, J. C. *Eur. J. Org. Chem.* **2001**, 3089. (v) Knapp, S.; Morriello, G. J.; Nandan, S. R.; Emge, T. J.; Doss, G. A.; Mosley, R. T.; Chen, L. *J. Org. Chem.* **2001**, *66*, 5822. (w) Kim, K. S.; Ahn, Y. H. *Tetrahedron: Asymmetry* **1998**, *9*, 3601. (x) Merrer, Y. L.; Gravier-Pelletier, C.; Gerrouache, M.; Depezay, J. C. *Tetrahedron Lett.* **1998**, *39*, 385. (y) Kim, K. S.; Cho, I. H.; Ahn, Y. H.; Park, J. I. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1783. (z) Knapp, S.; Nandan, S.; Resnick, L. *Tetrahedron Lett.* **1992**, *33*, 5485.
- (6) Nakamura, H.; Tsukano, C.; Yasui, M.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 3136.
- (7) (a) Gopinath, P.; Watanabe, T.; Shibasaki, M. *J. Org. Chem.* **2012**, *77*, 9260. (b) Gopinath, P.; Wang, L.; Abe, H.; Ravi, G.; Masuda, T.; Watanabe, T.; Shibasaki, M. *Org. Lett.* **2014**, *16*, 3364. (c) Abe, H.; Gopinath, P.; Ravi, G.; Wang, L.; Watanabe, T.; Shibasaki, M. *Tetrahedron Lett.* **2015**, *56*, 3782.
- (8) (a) Tsukano, C.; Yokouchi, S.; Girard, A. L.; Kuribayashi, T.; Sakamoto, S.; Enomoto, T.; Takemoto, Y. *Org. Biomol. Chem.* **2012**, *10*, 6074. (b) Girard, A. L.; Enomoto, T.; Yokouchi, S.; Tsukano, C.; Takemoto, Y. *Chem. Asian J.* **2011**, *6*, 1321.
- (9) The details of this experiment will be reported in due course.
- (10) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405.
- (11) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13.
- (12) Sakamoto, S.; Kazumi, N.; Kobayashi, Y.; Tsukano, C.; Takemoto, Y. *Org. Lett.* **2014**, *16*, 4758.
- (13) Compound **8** was prepared from L-serine. Also see Supporting Information.
- (14) Kozawa, Y.; Mori, M. *J. Org. Chem.* **2003**, *68*, 3064.
- (15) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. *Org. Lett.* **2003**, *5*, 3667.
- (16) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27.
- (17) Kenwright, J. L.; Galloway, W. R. J. D.; Blackwell, D. T.; Isidro-Llobet, A.; Hodgkinson, J.; Wortmann, L.; Bowden, S. D.; Welch, M.; Spring, D. R. *Chem. Eur. J.* **2011**, *17*, 2981.
- (18) The related reaction was also reported by Zhu et al: Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475.
- (19) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.
- (20) Spork, A. P.; Wiegmann, D.; Granitzka, M.; Stalke, D.; Ducho, C. *J. Org. Chem.* **2011**, *76*, 10083.
- (21) Ohshima, T.; Iwasaki, T.; Maegawa, Y.; Yoshiyama, A.; Mashima, K. *J. Am. Chem. Soc.* **2008**, *130*, 2944.
- (22) Devos, A.; Remion, J.; Frisque-Hesbain, A. -M.; Colens, A.; Ghosez, L. *J. Chem. Soc. Chem. Commun.* **1979**, 1180.
- (23) Li, H.; Morin, C. *Tetrahedron Lett.* **2004**, *45*, 5673.
- (24) A stoichiometric charge of CuI was added to the small scale reactions to ensure a sufficient charge of this reagent.
- (25) Compound **22** was not dissolved in ethylene glycol.
- (26) Babu, B. R.; Raunak; Poopeiko, N. E.; Juhl, M.; Bond, A. D.; Parmar, V. S.; Wengel, J. *Eur. J. Org. Chem.* **2005**, 2297.
- (27) Open column chromatography using silica gel was not suitable for its purification due to high polarity of the product.