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Catalytically Enantioselective Synthesis of Acyclic α-Tertiary Amines through Desymmetrization of 2-Substituted 2-Nitro-1,3-diols

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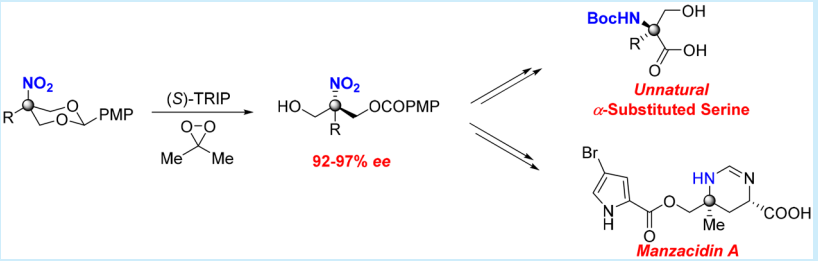
Supporting Information

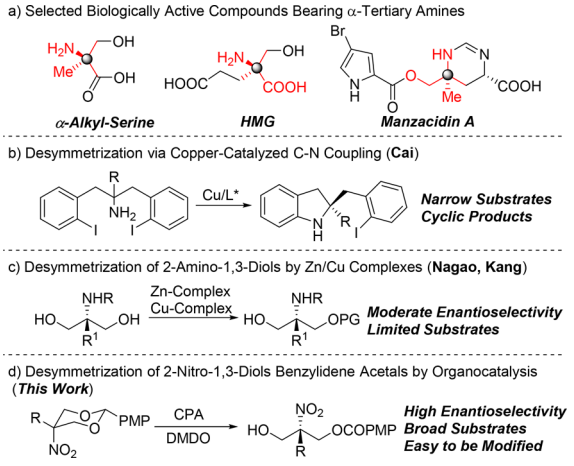


ABSTRACT: Highly enantioselective synthesis of acyclic α-tertiary amines through asymmetric desymmetrization is reported. This approach is based on chiral phosphoric acid mediated, enantioselective, oxidative desymmetrization of 2-substituted 2-nitro-1,3-diolbenzylidine acetals in the presence of DMDO as an oxidant. The method allows for the formation of a wide variety of chiral 2-nitro-1,3-diols in high enantioselectivity, which could be transformed into optically pure, unnatural α-alkyl series. The synthetic utility of this method has been further demonstrated by the expedient construction of the core structure of natural products manzacidins enantioselectively.

Optically active amines are highly important structural motifs that are widely found in natural products as well as medicinal compounds.[1] Among them, α-tertiary amines have attracted considerable interest due to their unique properties.[2] For instance, chiral α-substituted nonproteinogenic serines[3] are used in peptide chemistry and (*S*)-α-(hydroxymethyl)glutamic acid (HMG)[4] was found to be a potent a potent mGluR3 agonist. However, catalytic enantioselective synthesis of those moieties has met with limited success.[5] A typical strategy is the addition of organometallic reagent to ketimines in the presence of chiral organocatalyst or transition-metal complex.[5−7] The reaction scope, however, is relatively limited probably because of the electronic and steric factors (for example, low reactivity and the *E*/*Z* isomer of ketimines).[6] Other methods, including rearrangement,[8] asymmetric amination/alkylation[9] and allylic amination,[10] have been developed to address this challenging issue. Despite remarkable progress, accessing optically pure acyclic aliphatic group substituted α-tertiary amines in a catalytic enantioselective version remains a daunting task.[5]

Enantioselective desymmetrization is one of the most powerful strategies to afford the chiral compounds.[11] Although there are many elegant examples of asymmetric desymmetrization, highly catalytically enantioselective desymmetrization method to tackle on synthesis of α-tertiary amines remains largely unexplored (Scheme 1). In this respect, Cai and coworkers recently reported the first highly enantioselective intramolecular Ullmann reactions in the presence of copper catalyst to afford products bearing N-substituted quaternary stereocenter.[12] However, the substrates are limited and products are usually indolines. Alternatively, Nagao's group[13] and Kang's group[14] independently reported enantioselective acylation of 2-substituted 2-amino-1,3-diols employing chiral Zn and Cu complexes, respectively; however, the enantioselectivity is moderate to good or removal of the protecting group on the nitrogen requires harsh conditions.[14]

Scheme 1. Accessing Chiral α-Tertiary Amines through Enantioselective Desymmetrization



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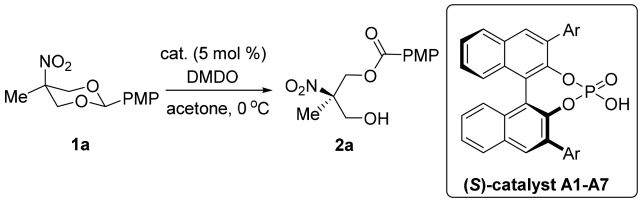
Based on our previous success with a chiral phosphoric acid[16,17] mediated enantioselective desymmetrization of 2-aryl-1,3-diols,[15] we hypothesized that in the presence of suitable catalyst and proper protection group on the nitrogen asymmetric desymmetrization of 2-substituted 2-amino-1,3-diols would be feasible. Thus, 2-methyl-2-amino-1,3-diols with different protecting groups on the nitrogen were tested. To our disappointment, all failed because of the difficulty in preparation of acetals or the oxidative problem of nitrogen. We then turned to the nitro compound because reduction of nitro group to amine is one of the most reliable protocols to obtain amine,[18] and nitro is a robust functional group which could tolerate many harsh conditions without extra protection as well.[18] 2-Methyl-2-nitro-1,3-diol was easily to be synthesized through nucleophilic addition of nitromethane to formaldehyde.[13] To the best of our knowledge, there are no example of nonenzymatic catalytic enantioselective desymmetrization of 2-substituted 2-nitro-1,3-diols.[19] Therefore, we evaluated the reaction conditions reported previously for oxidative desymmetrization of PMP-protected 2-methyl-2-nitro-1,3-diol (**1a**) and fortunately found the desired product **2a** was obtained in excellent yield (88% yield) and enantioselectivity (95% ee) (Table 1, entry 1). Next, an

Table 1. Survey of Chiral Phosphoric Acids[a]



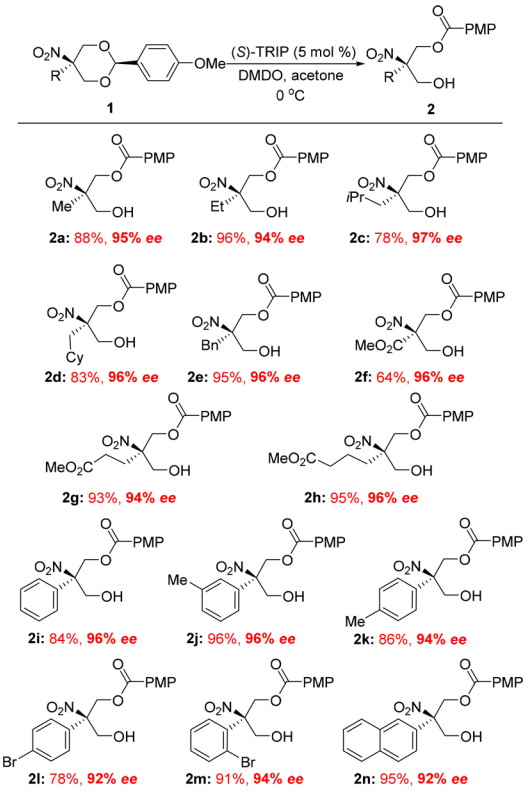
entry	catalyst, Ar	yield (%)[b]	ee (%)[c]
1	**(*S*)-catalyst A1, 2,4,6-(*i*Pr)$_3$C$_6$H$_2$, (*S*)-TRIP**	**88**	**95**
2	(*S*)-catalyst **A2**, 1-naphthyl	88	75
3	(*S*)-catalyst **A3**, 9-anthryl	95	50
4	(*S*)-catalyst **A4**, 3,5-(CF$_3$)$_2$C$_6$H$_3$	91	29
5	(*S*)-catalyst **A5**, SiPh$_3$	44	50
6	(*S*)-catalyst **A6**, 4-MeO-C$_6$H$_4$	89	64
7	(*S*)-catalyst **A7**, 4-Ph-C$_6$H$_4$	72	66

[a]Reaction conditions: **1** (0.1 mmol), cat. (5 mol %), and DMDO (5 mL) at 0 °C. [b]Isolated yield. [c]Enantiomeric excess determined by chiral HPLC analysis.

evaluation of potential chiral phosphoric acids was carried out (Table 1, entries 2−7). Although most of the reactions proceeded well in the presence of chiral phosphoric acids, poor or moderate enantioselectivity was achieved. In addition, further screening of the temperature and solvents did not give better results according to yield and ee.

Under the optimal reaction conditions, a variety of 2-substituted 2-nitro-1,3-diol benzylidene acetals were examined (Scheme 2). Generally, chiral phosphoric acid promoted oxidative desymmetrization can be effectively with a wide

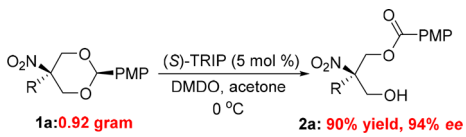
Scheme 2. Reaction Scope of Nitro-Substituted Substrates



range of substrates, thus delivering the 2-substituted 2-nitro-1,3-propanediol in high yield and excellent enantioselectivity. A series of substrates bearing different hindered alkyl chains underwent desymmetrization in excellent yields and enantioselectivity, giving the product in excellent yield and around 95% ee (**2a**−**e**). Ester group are compatible to afford the corresponding products in high enantioselectivity, while the distance of the chain does not have a significant effect on enantiocontrol (**2f**−**h**). Different electronic and steric aryl-substituted substrates were also tolerated, giving the expected products (**2i**−**n**) in excellent yield and high enantioselectivity (92−97% ee). The absolute configuration of **2a** was determined to be *R* compared with the optical rotation of known compound after several transformations (see the Supporting Information).

In order to further demonstrate the synthetic utility of this protocol, a large-scale reaction of **1a** was carried out (Scheme 3). Under the optimal conditions, the reaction proceeded well, delivering product **2a** in good yield and excellent enantioselectivity, without notable erosion of yield and ee.

Scheme 3. Large-Scale Reactions



The optically enriched amino alcohol or unnatural amino acid are both biologically and synthetically valuable due to their wide presence in natural products and medicinal chemistry. We considered that our catalytic enantioselective desymmetrization might provide a convenient entry to those important chiral building blocks. Hence, we set to investigate the transformations

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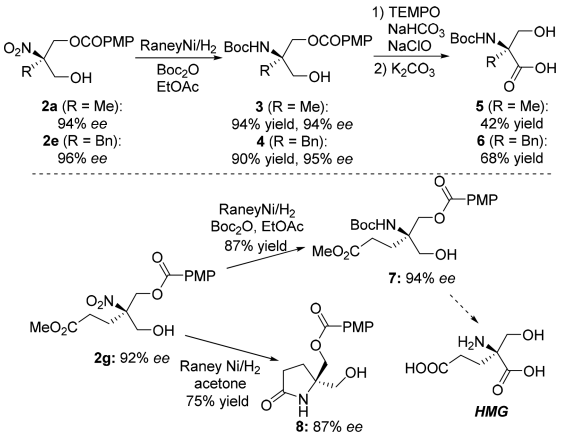
of optically active 2-substituted 2-nitro-1,3-diols. As illustrated in Scheme 4, reduction of nitro in **2a** and **2e** through Raney Ni/H_2

Scheme 4. Divergent Transformations of the Products



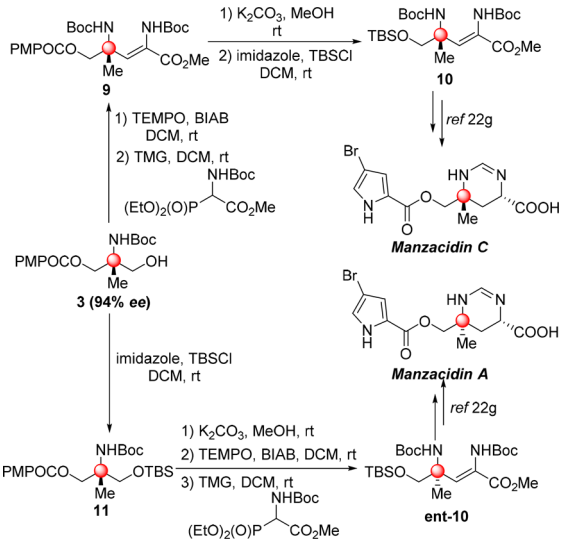
and then immediately protected with Boc anhydride afforded chiral 2-amino alcohol **3** and **4** in excellent yield, while the ee was maintained. The hydroxyl group was subsequently oxidized with TEMPO/NaClO under basic conditions to afford the corresponding acid,[20] and PMP ester was removed with K_2CO_3 to afford α-Me serine **5**[3b] and α-Bn serine **6**,[3c] which are one class of important unnatural amino acids in medicinal chemistry, without loss of ee (see the SI). More interestingly, chiral product **2g** bearing an ester group in the alkyl chain was converted into **7** under hydrogenation conditions, which could be further transformed to optically hydroxymethyl glutamic acid (HMG),[4] a potent mGluR3 agonist and a weak mGluR2 antagonist. Notably, **2g** was reduced and subsequently cyclized to afford product **8**, which is an important synthetic precursor of the natural product salinosporamide.[21]

Manzacidins were isolated from sponges, a family of bromopyrrole alkaloids.[22] Their structures are unique, and at the same time they have some interesting pharmacological activities, which inspired synthetic chemists to consider them as suitable targets for total synthesis.[22] The key challenge is the construction of chiral N-substituted quaternary stereocenter. Ohfune and co-workers synthesized intermediate **10** and converted it to natural product manzacidins A and C.[22g] To further evaluate the synthetic utility of this new process, efforts have been taken toward the formal synthesis of manzacidins A and C.

As shown in Scheme 5, the synthesis commenced with **3**, followed by oxidation of alcohol, and HWE reaction to furnish **9** in excellent yield. Subsequently, removal of the protecting group and reprotection with TBSCl afforded Ohfune's intermediate **10**, the precursor of manzacidin C, and the spectra data were in good agreement with those reported.[22g] Again, beginning with intermediate **3**, protection with TBSCl, removal of PMP ester, oxidation, and HWE reaction gave the Ohfune's intermediate **ent-10**, which is the precursor of manzacidin A. The optical rotation of **14** and **ent-14** is in agreement with that in literature.[22g]

In summary, we have developed a general and facile enantioselective oxidative desymmetrization of 2-substituted 2-nitro-1,3-diols mediated by chiral phosphoric acid. This protocol was shown to be effective with a broad substrate scope, including alkyl- and aryl-substituted 2-nitro-1,3-diols. The new approach

Scheme 5. Formal Synthesis of Manzacidins A and C



provides access to a variety of chiral valuable building blocks. The robustness and practicality were demonstrated by a variety of transformations and large-scale reactions. The synthetic utility was further demonstrated by the formal synthesis of manzacidins A and C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03581.

Experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Chiral Amine Synthesis*; Nugent, T. C., Ed.; Wiley-VCH: New York, 2008.

(2) (a) Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537. (b) Dake, G. *Tetrahedron* **2006**, *62*, 3467. (c) Hager, A.; Vrielink, N.; Hager, D.; Lefranc, J.; Trauner, D. *Nat. Prod. Rep.* **2016**, *33*, 491. (d) Mailyan, A. K.; Eickhoff, J. A.; Minakova, A. S.; Gu, Z.; Lu, P.; Zakarian, A. *Chem. Rev.* **2016**, *116*, 4441.

(3) (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569. (b) Smith, N. D.; Goodman, M. *Org. Lett.* **2003**, *5*, 1035. (c) Lempicka, E.; Slaninova, J.; Olma, A.; Lammek, B. *J. Pept. Res.* **1999**, *53*, 554.

(4) Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Org. Chem.* **2001**, *66*, 7555.

DOI: 10.1021/acs.orglett.7b03581
Org. Lett. XXXX, XXX, XXX−XXX

(5) (a) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
(6) (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (b) Connon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176. (c) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1997**, *62*, 5537. (d) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268.
(7) (a) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530. (b) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168. (c) Tan, C.; Liu, X.; Wang, L.; Wang, J.; Feng, X. *Org. Lett.* **2008**, *10*, 5305. (d) Trost, B. M.; Silverman, S. M. *J. Am. Chem. Soc.* **2010**, *132*, 8238. (e) Lauzon, C.; Charette, A. *Org. Lett.* **2006**, *8*, 2743. (f) Wang, H.; Jiang, T.; Xu, M.-H. *J. Am. Chem. Soc.* **2013**, *135*, 971. (g) Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11098. (h) Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309. (i) Yang, G.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 7540.
(8) Clayden, J.; Donnard, M.; Lefranc, J.; Tetlow, D. J. *Chem. Commun.* **2011**, *47*, 4624.
(9) (a) Wu, Y.; Hu, L.; Li, Z.; Deng, L. *Nature* **2015**, *523*, 445. (b) Yang, X.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3205.
(10) (a) Arnold, J. S.; Nguyen, H. M. *J. Am. Chem. Soc.* **2012**, *134*, 8380. (b) Cai, A.; Guo, W.; Martínez-Rodríguez, L.; Kleij, A. W. *J. Am. Chem. Soc.* **2016**, *138*, 14194. (c) Guo, W.; Cai, A.; Xie, J.; Kleij, A. W. *Angew. Chem., Int. Ed.* **2017**, *56*, 11797.
(11) For general reviews on desymmetrization, see: (a) Schneider. *Synthesis* **2006**, *2006*, 3919. (b) Pineschi, M. *Eur. J. Org. Chem.* **2006**, *2006*, 4979. (c) Díaz-de-Villegas, M. D.; Gálvaz, J. A.; Etayo, P.; Badorrey, R.; López-Ram-de-Víu, M. P. *Chem. Soc. Rev.* **2011**, *40*, 5564.
(12) Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, Q. *J. Am. Chem. Soc.* **2012**, *134*, 14326.
(13) Honjo, T.; Nakao, M.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y.; Nagao, Y. *Org. Lett.* **2007**, *9*, 509.
(14) (a) Hong, M. S.; Kim, T. W.; Jung, B.; Kang, S. H. *Chem. - Eur. J.* **2008**, *14*, 3290. (b) You, Y. S.; Kim, T. W.; Kang, S. H. *Chem. Commun.* **2013**, *49*, 9669. (c) Lee, W.; Youn, J.-H.; Kang, S. H. *Chem. Commun.* **2013**, *49*, 5231.
(15) Meng, S.-S.; Liang, Y.; Cao, K.-S.; Zou, L.; Lin, X.-B.; Yang, H.; Houk, K. N.; Zheng, W.-H. *J. Am. Chem. Soc.* **2014**, *136*, 12249.
(16) Selected reviews on chiral phosphoric acid catalysis: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Chem. Commun.* **2008**, 4097. (c) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2009**, *291*, 395. (d) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (e) Yu, J.; Shi, F.; Gong, L. *Acc. Chem. Res.* **2011**, *44*, 1156.
(17) For selected recent examples on CPA catalytic desymmetrization or kinetic resolution of alcohols, see: (a) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074. (b) Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3964. (c) Mensah, E.; Camasso, N.; Kaplan, W.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 12932. (d) Gualtierotti, J.-B.; Pasche, D.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9926. (e) Yamanaka, T.; Kondoh, A.; Terada, M. *J. Am. Chem. Soc.* **2015**, *137*, 1048. (f) Kim, J. H.; Čorić, I.; Palumbo, C.; List, B. *J. Am. Chem. Soc.* **2015**, *137*, 1778.
(18) *The Nitro Group in Organic Synthesis*; Ono, N., Ed.; Wiley-VCH: New York, 2001.
(19) For enzyme catalytic desymmetrization of 2-substituted-2-nitro-1,3-diols, see: Tian, P.; Xu, M.-H.; Wang, Z.-Q.; Li, Z.-Y.; Lin, G.-Q. *Synlett* **2006**, *2006*, 1201.
(20) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.
(21) (a) Reddy, L. R.; Saravanan, R. P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230. (b) Endo, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 8298. (c) Satoh, N.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 3028.
(22) (a) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708. (b) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950. (c) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (d) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174. (e) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553. (f) Tran, K.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2008**, *10*, 3165. (g) Oe, K.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2008**, *49*, 7426. (h) Ichikawa, Y.; Okumura, K.; Matsuda, Y.; Hasegawa, T.; Nakamura, M.; Fujimoto, A.; Masuda, T.; Nakano, K.; Kotsuki, H. *Org. Biomol. Chem.* **2012**, *10*, 614. (i) Yoshimura, T.; Kinoshita, T.; Yoshioka, H.; Kawabata, T. *Org. Lett.* **2013**, *15*, 864.

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Org. Lett. XXXX, XXX, XXX−XXX