Organic LETTERS

Letter

pubs.acs.org/OrgLett

Enantioselective Synthesis of *N*-PMP-1,2-dihydropyridines via Formal [4 + 2] Cycloaddition between Aqueous Glutaraldehyde and Imines

Panduga Ramaraju,[†] Nisar A. Mir,[†] Deepika Singh,[‡] Vivek K. Gupta,[§] Rajni Kant,[§] and Indresh Kumar*[,†]

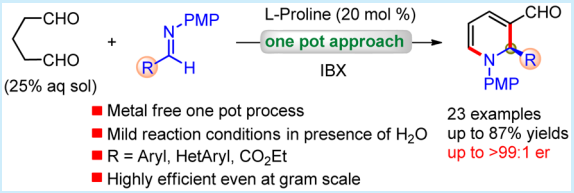
[†]Department of Chemistry, Birla Institute of Technology and Science, Pilani 333 031, Rajasthan India

[‡]Instrumentation Division, IIIM-CSIR Laboratory, Jammu 180 001, Jammu and Kashmir, India

[§]X-ray Crystallography Laboratory, Post-Graduate Department of Physics & Electronics, University of Jammu, Jammu 180 006, Jammu and Kashmir, India

Supporting Information

ABSTRACT: A simple and highly practical one-pot formal [4 + 2] cycloaddition approach for the enantioselective synthesis of *N*-PMP-1,2-dihydropyridines (DHPs) is described. This chemistry involves an amino-catalytic direct Mannich reaction/cyclization followed by IBX-mediated chemo- and regioselective oxidation sequence between readily available aqueous glutaraldehyde and imines under very mild conditions. A series of *N*-PMP-1,2-DHPs have been prepared in high yields and excellent enantioselectivity. This method also gives access to both enantiomers of 1,2-DHPs in surplus amount by shifting the catalyst configuration.



Dihydropyridines (DHPs) are frequently encountered in natural and synthetic compounds that possess many interesting biological activities.[1] In particular, 1,2-DHPs are important building blocks to synthesize a wide range of organic molecules, such as piperidines, pyridines, indolizidines, and quinolizidines.[2] This structural unit has also been considered as a suitable substrate to prepare isoquinuclidines,[3] an important structural motif for a variety of complex natural products.[4] Owing to the high synthetic and biological importance of 1,2-DHPs, a number of methods have been developed for their synthesis.[5] More strictly, these synthetic efforts can be broadly divided into two main categories: *(i) Nucleophilic addition to activated pyridines* (path 1, Figure 1),[6] and *(ii) 6π-electro-cyclization of 1-azatrienes* (path 2, Figure 1).[7] Alternatively, methods involving imines as suitable unsaturated partners to synthesize 1,2-DHPs have had some success.[8] Initially, the Ogoshi group developed a metal-catalyzed [2 + 2 + 2] cycloaddition reaction between alkynes and *N*-sulfonyl-[8a,b] or *N*-arylimines.[8c] A similar cycloaddition was independently explored by Yoshikai and co-workers using *N*-pyridylimines.[8d] These approaches were mainly restricted to produce racemic 1,2-DHPs (eq 1, Scheme 1). Recently, Gandon and co-workers developed the first asymmetric variant of this metal-catalyzed [2 + 2 + 2] cycloaddition between diynes and *N*-sulfonimines (eq 2, Scheme 1).[9] Previously, a very few graceful asymmetric syntheses for 1,2-DHPs were reported, although they possess experimental limitations like tedious preactivation.[10] Despite these efforts, the development of a simple and efficient enantioselective method to access 1,2-DHPs presents a difficult task and is still in high demand. Herein, we report a straightforward one-pot strategy for the enantioselective synthesis of *N*-PMP-1,2-DHPs (PMP = *p*-OMeC$_6$H$_4$) from inexpensive materials with high yields and enantioselectivity

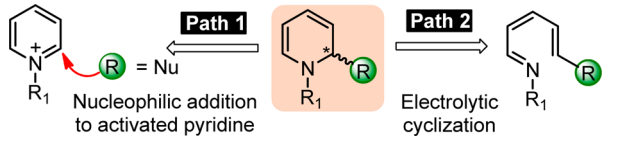
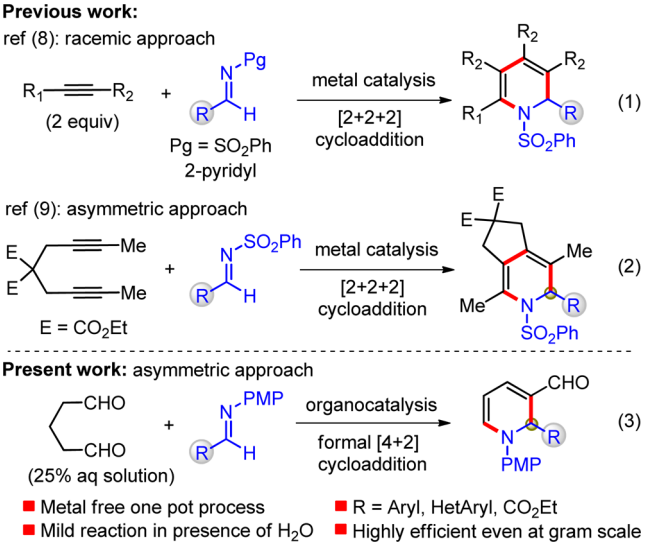


Figure 1. General routes to 1,2-dihydropyridines.

Scheme 1. Involvement of Imines in Cycloaddition Approaches to 1,2-DHPs



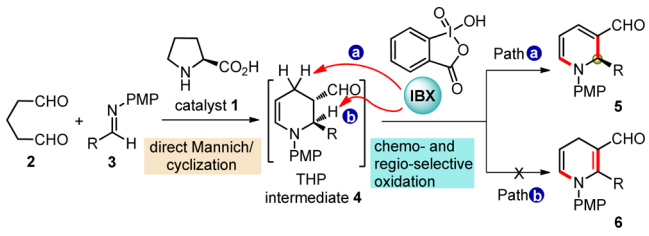
Received: September 22, 2015

DOI: 10.1021/acs.orglett.5b02744
Org. Lett. XXXX, XXX, XXX−XXX

under an organocatalytic system (eq 3, Scheme 1). To the best of our knowledge, there is no report on the organocatalytic approach for 1,2-DHPs in asymmetric fashion.

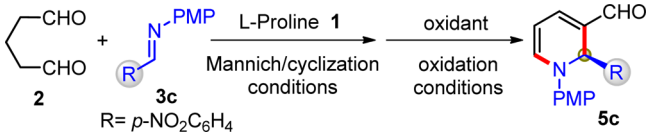
Conversely, organocatalysis is considered an important eco-friendly toolbox to develop several asymmetric, nonasymmetric transformations and also to contribute proficient one-pot cascade processes.[11] Recently, linear dialdehydes have been established as suitable bifunctionalized substrates for amino-catalyzed cascade transformations to synthesize important bioactive carbo- and heterocyclic compounds.[12] In this context, Xu and co-workers have utilized glutaraldehyde **2** and imines **3** for enantioselective tetrahydropyridines (THPs),[13] while chiral piperidines were synthesized through in situ reduction of THPs **4** by our group, independently.[14] We further envisioned that in situ site-selective oxidation of THP compound **4** could lead to the synthesis of DHPs (Scheme 2). Interestingly, the oxidation

Scheme 2. IBX-Mediated Chemo- and Regioselective Dehydrogenative Oxidation of THP 4



of **4** could occur at two different places, which could subsequently give 1,2-DHPs **5** (path a, Scheme 2) or 1,4-DHPs **6** (path b, Scheme 2). Keeping this idea in mind, we quickly established the reaction conditions for one-pot asymmetric synthesis of 1,2-DHPs as shown in Table 1.

Table 1. Optimization of Reaction Conditions



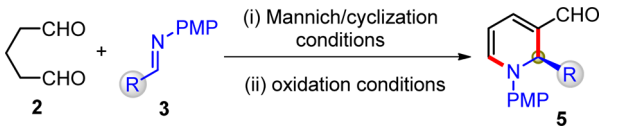
entry	conditions[a]	yield[b] (%)	er[c]
1	DMSO, rt, 5 h/DDQ, rt, 12 h		
2	DMSO, rt, 5 h/SeO_2, rt, 6 h		
3	DMSO, rt, 5 h/IBX, 70 °C, 3 h	76	88:12
4	DMSO, 10 °C, 6 h/IBX, 40 °C, 4 h	87	93:7
5	DMSO, 10 °C, 6 h/IBX, rt, 6 h	76	93:7
6	DMSO, 10 °C, 6 h/IBX, 10 °C, 9 h	65	93:7
7[d]	DMSO, 10 °C, 12 h/IBX, 40 °C, 4 h	58	93:7

[a]Unless otherwise indicated, the reaction was carried out with (i) **3c** (0.3 mmol), **2** (25% aqueous sol., 0.9 mmol), L-proline **1** (20 mol %), solvent (3.0 mL); (ii) oxidant (120 mol %). [b]Isolated yield of **5** refers to **3c**. [c]Determined using stationary chiral columns. [d]Catalyst **1** (10 mol %).

Our initial attempts failed to give any DHPs (**5** or **6**) through in situ oxidation of THP intermediate **4** in DMSO (entries 1 and 2, Table 1). Gratifyingly, *N*-PMP-1,2-DHP **5c** was obtained as the sole product with good yield (76%) and enantioselectivity (88:12 er) when IBX (2-Iodoxybenzoic acid) was used as oxidizing agent at 70 °C in the same flask (entry 3, Table 1). This one-pot transformation was made feasible by taking advantage of IBX solubility in DMSO as well as the ability to dehydrogenate carbonyls into the corresponding α,β-unsaturated carbonyls.[15] Here, the exclusive production of 1,2-DHPs **5** could be justified through chemo- and regioselective oxidation of intermediate **4** by using bulky IBX at a less substituted allylic position C4 (path a, Scheme 2). While oxidation at the more substituted position C2 (path b, Scheme 2) was not observed, enhancement in the yield (87%) and enantioselectivity (93:7 er) was observed when amino-catalyzed direct Mannich/cyclization sequence was carried out at 10 °C followed by in situ IBX oxidation at 40 °C. Further decreasing the reaction temperature during IBX oxidation (entry 5 and 6, Table 1) and catalyst loading (entry 7, Table 1) led to extended reaction time with reduced yields without variation in enantioselectivity. Thus, we preferred to perform this one-pot, two-step sequence to *N*-PMP-1,2-DHPs **5** with optimized conditions (entry 4, Table 1).

The scope of this method was then investigated to confirm its robustness with regard to a variety of preformed imines **3** under optimized conditions, and the results are summarized in Table 2. The reaction proceeded well with good yields and enantioselectivity in almost all cases when electron-withdrawing groups (EWG) (e.g., $-NO_2$, $-F$, $-Cl$, $-Br$, and $-CN$) were substituted at the ortho-, meta-, or para-positions on the arylimines (entries 1−16, Table 2). However, the reactions were rather slow in the case of arylimines substituted at the

Table 2. Substrate Scope for Formal [4 + 2] Cycloaddition



entry[a]	R	time[b] (h)	5	yield[c] (%)	er[d]
1	2-$NO_2C_6H_4$	9	**5a**	68	99:1
2	3-$NO_2C_6H_4$	8	**5b**	83	98:2
3	4-$NO_2C_6H_4$	6	**5c**	87	93:7
4	2-FC_6H_4	9	**5d**	69	96:4
5	3-FC_6H_4	8	**5e**	71	93:7
6	4-FC_6H_4	8	**5f**	77	88:12
7	2-ClC_6H_4	9	**5g**	68	96:4
8	3-ClC_6H_4	8	**5h**	70	95:5
9	4-ClC_6H_4	8	**5i**	73	90:10
10	2-BrC_6H_4	10	**5j**	68	98:2
11	3-BrC_6H_4	9	**5k**	74	93:7
12	4-BrC_6H_4	9	**5l**	79	91:9
13	3-Br-4-FC_6H_3	8	**5m**	72	95:5
14	3,4-$Cl_2C_6H_3$	8	**5n**	70	97:3
15	3-CNC_6H_4	9	**5o**	72	84:16
16	4-CNC_6H_4	9	**5p**	70	94:6
17	Ph	9	**5q**	66	88:12
18	2-pyridyl	8	**5r**	67	94:6
19	3-pyridyl	9	**5s**	71	84:16
20	4-pyridyl	8	**5t**	73	92:8
21	2-thiophene	9	**5u**	67	88:12
22	2-(5-NO_2)furan	8	**5v**	71	87:13
23[e]	CO_2Et	6	**5w**	87	>99:1
24	4-$OMeC_6H_4$	20	**5x**	nr	nd

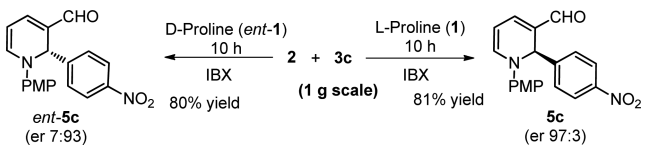
[a]Unless otherwise indicated, the reaction was carried out with (i) **3** (0.3 mmol), **2** (25% aqueous sol., 0.9 mmol), L-proline **1** (20 mol %), DMSO (3.0 mL); (ii) IBX (120 mol %), 40 °C, 4 h. [b]Time for direct Mannich/cyclization reaction. [c]Isolated yield. [d]Determined using stationary chiral columns. [e]Reaction was carried out without water.

DOI: 10.1021/acs.orglett.5b02744
Org. Lett. XXXX, XXX, XXX−XXX

ortho-position (entries 1, 4, 7, and 10, Table 2), possibly due to steric effects. A similar result was obtained when imine derived from benzaldehyde was employed (entry 17, Table 2). Pleasingly, heteroaromatic imines also gave the corresponding products **5r**–**v** in good yields and enantioselectivity (entries 18–22, Table 2) under these optimized conditions. A clean transformation to highly functionalized *N*-PMP-1,2-DHP **5w** was observed with high yields (90%) and excellent selectivities (>99:1 er) when activated imine **3w** was utilized without water (entry 23, Table 2). This reaction is limitated to electron-deficient imines as the reaction failed in the case of electronically rich arylimine (entry 24, Table 2).

Next, we decided to prepare *N*-PMP-1,2-DHPs in a reasonably good amount and in stable form. The presence of a −CHO group at C3 provides stabilization, as electron-withdrawing substituents stabilize DHPs. To fulfill the first objective and to demonstrate the practical utility of our protocol, we prepared both enantiomers of 1,2-DHP at gram scale by utilizing both L- and D-proline as catalysts. While a somewhat longer reaction time was required, **5c** and *ent*-**5c** were obtained without much reduction in yields and with the same selectivity from **3c** (1.0 g) as shown in Scheme 3. Easy

Scheme 3. Gram-Scale Synthesis of Both Enantiomers of *N*-PMP-1,2-DHP (5c and *ent*-5c)



availability of starting materials, glutaraldehyde **2**, and imines **3** and metal-free access to both enantiomers of *N*-PMP-1,2-DHP make this approach quite practical and attractive.

Single-crystal X-ray study of **5b** and **5w** further confirmed the stereochemical outcome at C2 (Figure 2), as expected through

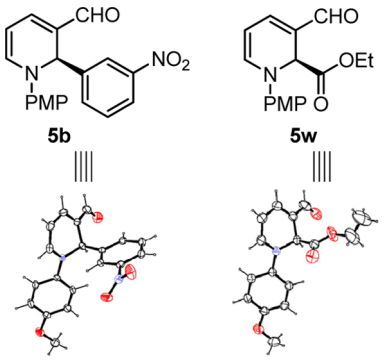
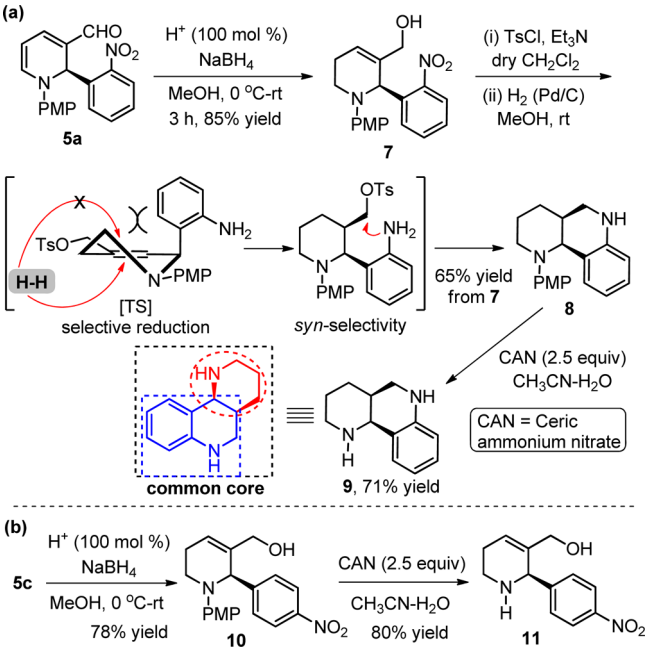


Figure 2. Single-crystal X-ray analysis of **5b** and **5w**.

L-proline **1** catalyzed *syn*-Mannich reaction[16]/intramolecular cyclization/oxidation sequence. The absolute stereochemistry of all other products was assigned through analogy. A complete plausible mechanism has been proposed to rationalize the high stereochemical outcome of this transformation, as shown in the Supporting Information.

In order to show the synthetic application of our strategy, we quickly converted compound **5a** into fused polycyclic compound **8** using the sequence of synthetic transformation as shown in Scheme 4 (a). Initially, **5a** was reduced to tetrahydropyridine (THP) **7** constituted with an allylic alcohol

Scheme 4. Synthetic Applications



group using acidic $NaBH_4$ in 85% yield. Next, the alcohol group was converted into −OTs under standard conditions, and catalytic hydrogenation using Pd/C and $(H_2)_{(g)}$ was performed with crude material without purification. The reduction of $-NO_2$ and alkene groups takes place under these conditions as expected. Interestingly, intramolecular cyclization of in situ generated amine furnished polycyclic alkaloid-type product **8** having *syn*-stereochemistry at two chiral centers in the same pot (see the SI). Our initial efforts to convert **5a** directly to **8** through one-pot reduction of all alkene bonds and a $-NO_2$ group, followed by reductive cyclization with aldehyde under different reaction conditions, failed. After PMP removal from **8**, a fused product **9** was obtained that contained tetrahydroquinoline and piperidines moieties. These units are key elements found in numerous biologically active natural products and synthetic pharmaceuticals.[17] *N*-PMP deprotection from 1,2-DHP **5** failed, while this deprotection was successfully demonstrated from *N*-PMP-tetrahydropyridine **10** to highly functionalized tetrahydropyridine **11** as shown in Scheme 4 (b). This compound can be further transformed to various piperidine derivatives.

In conclusion, we have developed an operationally simple, metal-free enantioselective synthesis of *N*-PMP-1,2-dihydropyridines via one-pot formal [4 + 2] cycloaddition between readily available aldimines and aqueous glutaraldehyde. This reaction proceeds through proline-catalyzed direct Mannich/cyclization, followed by an IBX-mediated site-selective dehydrogenative–oxidation sequence with high yields and selectivity. The viability of this method was established through (i) gram-scale synthesis of both enantiomers of *N*-PMP-1,2-DHPs and (ii) quick synthesis of fused chiral tetrahydroquinoline-based important alkaloid skeleton. This novel strategy sets the stage for the synthesis of chiral isoquinuclidines and their applications in natural product synthesis. Further study in this direction is in progress.

DOI: 10.1021/acs.orglett.5b02744
Org. Lett. XXXX, XXX, XXX–XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02744.

Experimental procedures, spectra, and X-ray data for obtained compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: indresh.chemistry@gmail.com, indresh.kumar@pilani.bits-pilani.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was made possible by support from DST−New Delhi and BITS Pilani. P.R. thanks UGC−New Delhi for a Senior Research Fellowship.

■ REFERENCES

(1) (a) Stout, D. M. *Chem. Rev.* **1982**, *82*, 223. (b) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141. (c) Edraki, N.; Mehdipour, A. R.; Khoshneviszadeh, M.; Miri, R. *Drug Discovery Today* **2009**, *14*, 1058.

(2) (a) Comins, D. L. *J. Heterocycl. Chem.* **1999**, *36*, 1491. (b) Joseph, S. P.; Comins, D. L. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 870. (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191. (d) Sales, M.; Charette, A. B. *Org. Lett.* **2005**, *7*, 5773. (e) Comins, D. L.; Kuethe, J. T.; Miller, T. M.; Février, F. C.; Brooks, C. A. *J. Org. Chem.* **2005**, *70*, 5221. (f) Duttwyler, S.; Chen, S.; Lu, C.; Mercado, B. Q.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 3877. (g) Pelletier, G.; Constantineau-Forget, L.; Charette, A. B. *Chem. Commun.* **2014**, *50*, 6883.

(3) For recent selected examples, see: (a) Krow, G. R.; Huang, Q.; Szczepanski, S. W.; Hausheer, F. H.; Carroll, P. J. *J. Org. Chem.* **2007**, *72*, 3458. (b) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2013**, *15*, 444. (c) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y. *Chem. Commun.* **2010**, *46*, 4827. (d) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734. (e) Sellstedt, M.; Dang, H. T.; Prasad, G. K.; Sauer, U.; Almqvist, F. *Eur. J. Org. Chem.* **2013**, *2013*, 7476.

(4) (a) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2013**, *6*, 57. (b) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532. (c) Khan, M. O. F.; Levi, M. S.; Clark, C. R.; Ablordeppey, S. Y.; Law, S.-L.; Wilson, N. H.; Borne, R. F. *Stud. Nat. Prod. Chem.* **2008**, *34*, 753. (d) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, *30*, 694. (e) Jana, G. K.; Paul, S.; Sinha, S. *Org. Prep. Proced. Int.* **2011**, *43*, 541. (f) Beatty, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2014**, *136*, 10270. (g) Moisan, L.; Thuéry, P.; Nicolas, M.; Doris, E.; Rousseau, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 5334.

(5) (a) Tanaka, K.; Fukase, K.; Katsumura, S. *Synlett* **2011**, *2011*, 2115. (b) Silva, E. M. P.; Varandas, P. A. M. M.; Silva, A. M. S. *Synthesis* **2013**, *45*, 3053.

(6) (a) Comins, D. L.; Mantlo, N. B. *J. Org. Chem.* **1986**, *51*, 5456. (b) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829. (c) Crotti, S.; Berti, F.; Pineschi, M. *Org. Lett.* **2011**, *13*, 5152. (d) Chau, S. T.; Lutz, J. P.; Wu, K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 9153. (e) For review, see: Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642.

(7) (a) Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763. (b) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099. (c) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, *2005*, 23. (d) Harschneck, T.; Kirsch, S. F. *J. Org. Chem.* **2011**, *76*, 2145. (e) Tejedor, D.; Méndez-Abt, G.; García-Tellado, F. *Chem. - Eur. J.* **2010**, *16*, 428. (f) Wei, H.; Wang, Y.; Yue, B.; Xu, P.-F. *Adv. Synth. Catal.* **2010**, *352*, 2450. (g) Yamakawa, T.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 196. (h) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (i) Trost, B. M.; Biannic, B. *Org. Lett.* **2015**, *17*, 1433.

(8) (a) Ogoshi, S.; Ikeda, H.; Kurosawa, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4930. (b) Ogoshi, S.; Ikeda, H.; Kurosawa, H. *Pure Appl. Chem.* **2008**, *80*, 1115. (c) Hoshimoto, Y.; Ohata, T.; Ohashi, M.; Ogoshi, S. *Chem. - Eur. J.* **2014**, *20*, 4105. (d) Adak, L.; Chan, W. C.; Yoshikai, N. *Chem. - Asian J.* **2011**, *6*, 359. (e) Brunner, B.; Stogaitis, N.; Lautens, M. *Org. Lett.* **2006**, *8*, 3473. (f) Zhao, G.-L.; Huang, J.-W.; Shi, M. *Org. Lett.* **2003**, *5*, 4737.

(9) Amatore, M.; Leboeuf, D.; Malacria, M.; Gandon, V.; Aubert, C. *J. Am. Chem. Soc.* **2013**, *135*, 4576.

(10) (a) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 11808. (b) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300. (c) Black, D. A.; Beveridge, R. E.; Arndtsen, B. A. J. *J. Org. Chem.* **2008**, *73*, 1906.

(11) For recent reviews, see: (a) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390. (b) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492. (c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (d) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. (e) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712. (f) Ramachary, D. B.; Jain, S. *Org. Biomol. Chem.* **2011**, *9*, 1277. (g) Ren, Q.; Wang, J. *Asian J. Org. Chem.* **2013**, *2*, 542. (h) Renzi, P.; Bella, M. *Chem. Commun.* **2012**, *48*, 6881.

(12) Kumar, I.; Ramaraju, P.; Mir, N. A.; Singh, A. *Org. Biomol. Chem.* **2015**, *13*, 1280.

(13) Han, R. G.; Wang, Y.; Li, Y. Y.; Xu, P. F. *Adv. Synth. Catal.* **2008**, *350*, 1474.

(14) Kumar, I.; Ramaraju, P.; Mir, N. A.; Singh, D.; Gupta, V. K.; Rajnikant. *Chem. Commun.* **2013**, *49*, 5645.

(15) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.

(16) (a) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677. (b) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III *J. Org. Chem.* **2003**, *68*, 9624. For a review on direct Mannich reaction, see: (c) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, *2007*, 5797.

(17) (a) Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem.* **1998**, *35*, 761. (b) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031. (c) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Tamiki, N.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, Y.; Nakamura, M. J. *J. Med. Chem.* **1994**, *37*, 3956. (d) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (e) Gigant, N.; Gillaizeau, I. *Org. Lett.* **2012**, *14*, 4622.

DOI: 10.1021/acs.orglett.5b02744
Org. Lett. XXXX, XXX, XXX−XXX