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Unexpected Synthesis of 5,6-Dihydropyridin-2(1*H*)-ones by a Domino Ugi/Aldol/Hydrolysis Reaction Starting from Baylis–Hillman Phosphonium Salts

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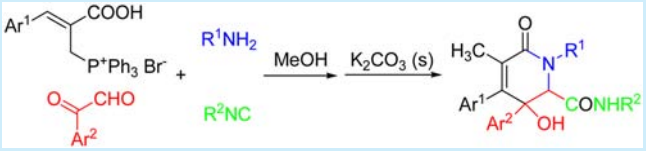
Supporting Information

ABSTRACT: A one-pot synthetic approach to 5,6-dihydropyridin-2(1*H*)-ones has been developed using a domino process involving Ugi, aldol, and hydrolysis reactions, starting with Baylis–Hillman phosphonium salts, primary amines, isocyanides, and arylglyoxals.



Multicomponent reactions (MCRs) have become useful tools for diversity-oriented and complexity-generating synthesis of natural products and druglike small molecules with novel properties.[1] The Ugi reaction is an effective and atom-economical multicomponent reaction which assembles aldehyde (or ketone), amine, isonitrile, and carboxylic acid to afford an α-acylamino-carboxamide adduct.[2] The sequences of Ugi multicomponent reactions, followed by various postcondensation transformations, constitute an extremely powerful synthetic method for heterocyclic compounds with elaborate substitution patterns.[3] For example, Balalaie et al. recently reported a metal-free sequential Ugi-4CR/cyclization reaction for the synthesis of various β-lactams and pyrrolidine-2,5-diones.[4] A domino Ugi/Buchwald–Hartwig/Michael reaction was successfully utilized to prepare functionalized spiro[indoline-3,2′-pyrrole]-2,5′-diones.[5] A facile one-pot synthesis of functionalized benzonaphthyridines was also described via a sequential Ugi/Heck reaction.[6] The sequential Ugi/aldol, Ugi/Bischlere Napieralski, and Ugi/Gold-catalyzed reactions were reported to produce pyrrolinones, imidazo[1′,5′:1,2]pyrido[3,4-*b*]indol-2-ium salts, and imidazo-[1,4]diazepin-7-ones in good to high yields.[7]

The derivatives containing a pyridinone moiety are of great importance because they have been proven to show significant antifungal,[8] antidiabetic,[9] and anti-HIV activities.[10] Recent synthetic methodology for the construction of the pyridinone scaffold has been focused primarily on the palladium-catalyzed oxidative reaction of acrylic amide with some alkynes,[11] ruthenium-catalyzed alkyne annulations,[12] and the cyclization reaction of 2-(phenylsulfinyl)acetamides.[13]

Intramolecular Wittig reaction has become an extremely powerful tool in the preparation of various heterocycles through intramolecular cyclization.[14] Thus, it is speculated that combining the efficiency of the Ugi condensation with a subsequent Wittig reaction would provide an efficient synthetic method for a series of biologically useful heterocycles. Indeed, some heterocycles such as butenolides, pyrrolidinones, and pyridones have been prepared successfully by the sequence of the Ugi/Horner or Passerini/Horner reaction.[15] In our previous work, the tandem Ugi/Wittig or Passerini/Wittig cyclization was also used to afford multisubstituted 2,3-dihydro-1*H*-2-benzazepin-1-ones and 3*H*-2-benzoxepin-1-ones starting from phosphonium salt precursors.[16] So we envisioned that if a suitable Baylis–Hillman phosphonium salt **1** was utilized as starting material, the tandem Ugi/Wittig cyclization would take place to produce pyridin-2(1*H*)-ones **7** (Scheme 1). By continuing our interest in the synthesis of various heterocycles via multicomponent reaction[17] or by using the Baylis–Hillman adducts as starting materials,[18] we wish to disclose herein an unexpected synthesis of 5,6-dihydropyridin-2(1*H*)-ones **8** instead of **7**, by a domino Ugi/aldol/hydrolysis reaction starting from Baylis–Hillman phosphonium salts **1** in a one-pot fashion.

We selected initially the Baylis–Hillman phosphonium salt **1a**, *n*-propylamine **2a**, 4-bromophenylglyoxal **3a**, and *tert*-butylisocyanide **4a** as the reactants (Scheme 2). When the Baylis–Hillman phosphonium salt **2a**, 4-bromophenylglyoxal **3a**, and *tert*-butylisocyanide **4a** was stirred in methanol at room temperature for 24 h, the Ugi adduct **5a** was produced and used directly in a further reaction without purification. As the crude **5a** was refluxed in toluene in the presence of solid K_2CO_3, the final major product was verified surprisingly to be 5,6-dihydropyridin-2(1*H*)-one **8a** (32%) and the expected pyridin-2(1*H*)-one **7a** was obtained in only 8% yield (Table 1, entry 1). When the reaction temperature was reduced to 60 °C, the yield of the product **8a** was promoted slightly (40%, Table 1, entry 2). However, the yield was diminished, as the reaction was carried out at room temperature (20%, Table 1, entry 3). There was no improvement as the base was changed from K_2CO_3 to Na_2CO_3, Cs_2CO_3, NaOH, or NEt_3 (Table 1, entries 4–8). The solvent used had a remarkable effect on this reaction. When MeOH, EtOH, or DMF was utilized as the solvent in the presence of

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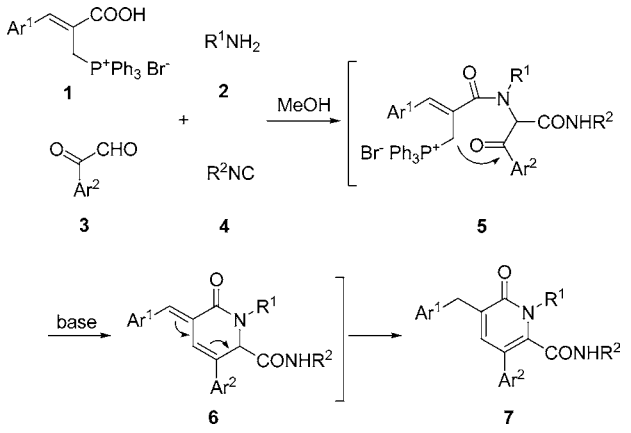
Scheme 1. Proposed Tandem Ugi 4CC/Wittig Cyclization



Scheme 2. Preparation of Compound 6a

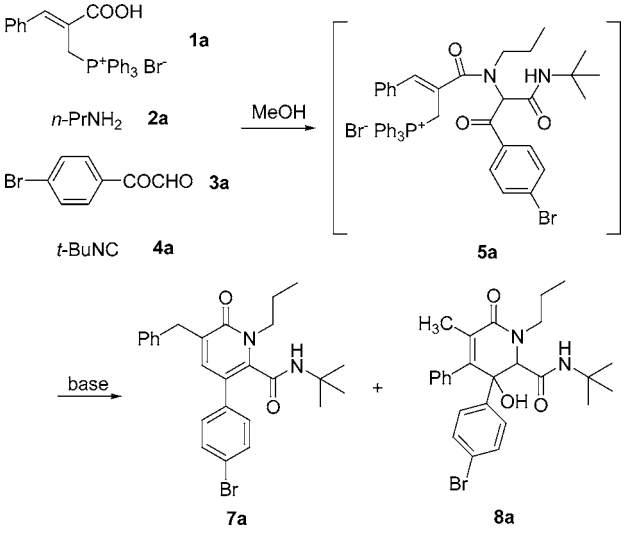


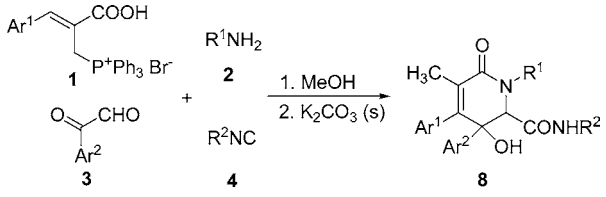
Table 1. Optimization of the Reaction Conditions

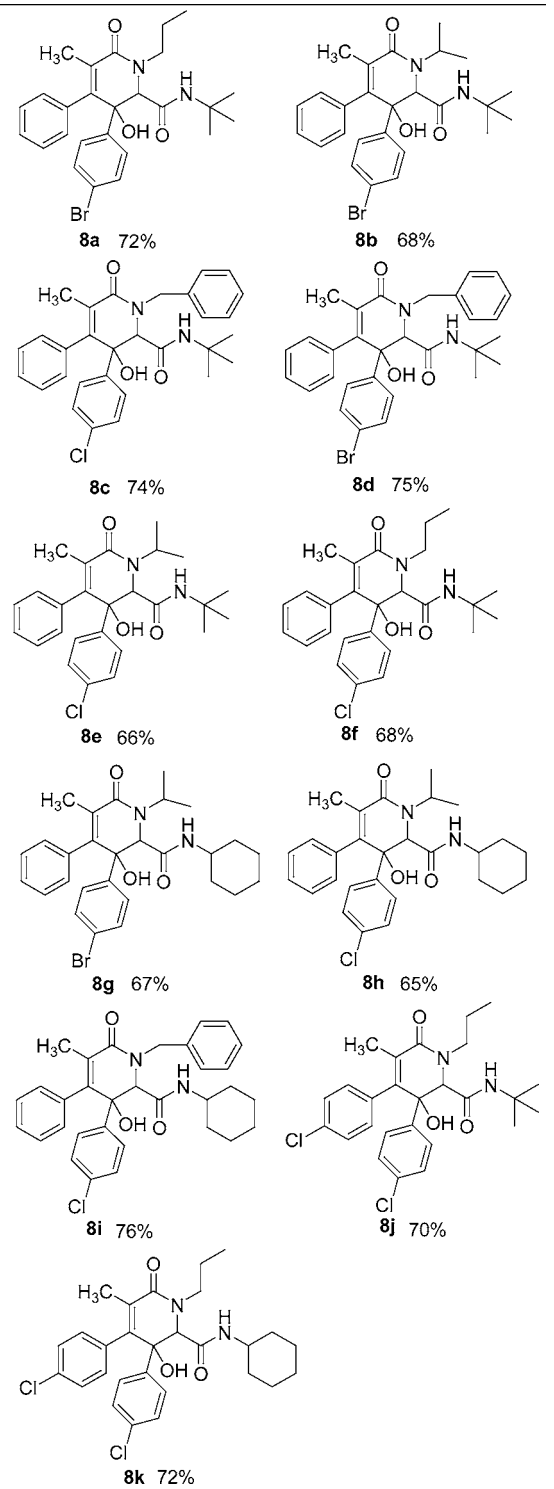
				yield (%)[a]	
entry	base	solvent	temp	7a	8a
1	K_2CO_3	toluene	110 °C	8	32
2	K_2CO_3	toluene	60 °C	10	40
3	K_2CO_3	toluene	rt	5	20
4	Na_2CO_3	toluene	60 °C	6	24
5	Cs_2CO_3	toluene	60 °C	6	23
6	NaOH	toluene	60 °C	5	20
8	NEt_3	toluene	60 °C	0	0
9	K_2CO_3	MeOH	60 °C	0	72
10	K_2CO_3	EtOH	60 °C	0	54
11	K_2CO_3	DMF	60 °C	0	41
12	K_2CO_3	EtOAc	60 °C	11	43
13	K_2CO_3	CH_3CN	60 °C	6	41

[a]Isolated yields based on phosphonium salt **1a**.

K_2CO_3, only 5,6-dihydropyridin-2(1*H*)-one **8a** was produced with no pyridin-2(1*H*)-one **7a** formation (Table 1, entries 9–11). The best result was obtained (72% yield of **8a**, Table 1, entry 9) as MeOH was used as the solvent. However, low yields of the products were reached as other solvents (EtOAc or CH_3CN) were utilized (Table 1, entries 12, 13).

Table 2. Preparation of Compounds 8a–8k





With the optimized conditions, a variety of Baylis–Hillman phosphonium salt **1**, amine **2**, arylglyoxal **3**, and isocyanide **4** were employed for the reaction. Most of the reactions proceeded

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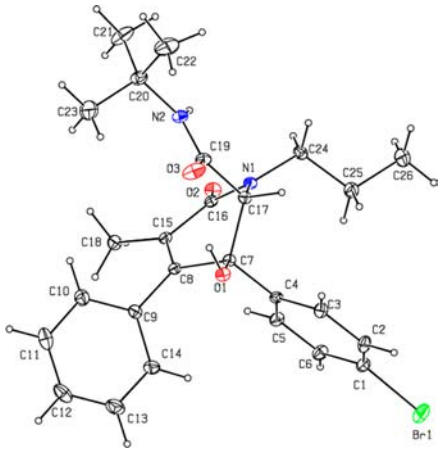
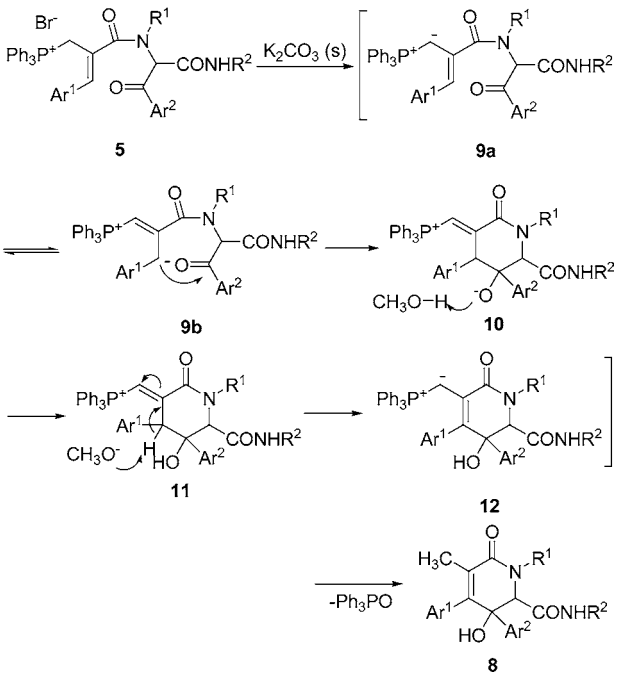


Figure 1. ORTEP drawing of **8a** with 50% probability thermal ellipsoids (with only one enantiomer shown).

Scheme 3. A Possible Mechanism for the Formation of 8



smoothly to give the corresponding 5,6-dihydropyridin-2(1*H*)-ones **8** (Table 2). As shown in Table 2, various aliphatic amines (R^1 = *n*-Pr, *i*-Pr, and benzyl) can be used in the above-mentioned one-pot cyclization to prepare 5,6-dihydropyridin-2(1*H*)-ones **8**. However, no products were obtained when aromatic amines (R^1 = Cl-C_6H_4, 4-MeC_6H_4, and Ph) were utilized. The electron-donating ability of the R^1 group might be an important influencing factor for the yields of the products.

The compounds **8a**–**k** were confirmed by their spectral data. For example, the ^{1}H NMR spectrum of **8a** shows a singlet at 6.41 ppm due to the CH of the 5,6-dihydropyridin-2(1*H*)-one ring. The signals of CONH and OH are found at 6.08 and 3.66 ppm as two singlets. The signals of NCH_2 appear at 3.42–3.37 and 2.81–2.76 ppm as two multiplets. The signals of CH_3 linking to the 5,6-dihydropyridin-2(1*H*)-one ring appears at 1.95 ppm as a singlet. The signals attributable to the Ar–Hs and other CH_2 and CH_3 are found at 7.51–6.93 ppm and 1.39–0.65 ppm, respectively. The ^{13}C NMR spectrum data in **8a** showed the signals of CON carbon at 171.0 and 165.6 ppm. The quaternary carbon of the 5,6-dihydropyridin-2(1*H*)-one ring absorbs at 76.6 ppm. The MS spectrum of **8a** shows M^+-CONHBu-*t* at *m*/*z* 398 with 47% abundance. Furthermore, a single crystal for **8a** was obtained from the CH_2Cl_2/ethanol solution of **8a**, and X-ray structure analysis verified the proposed structure (Figure 1).

The Ugi product **5** is an allylic phosphonium salt, which may be transformed into a ylide in the presence of a base to undertake a conjugate γ-addition reaction through ylide isomerization. On the basis of the results obtained and the related literature,[19] a possible mechanism for the formation of **8** can be proposed (Scheme 3). It presumably involves (i) transformation of phosphonium salt **5** into the ylide **9a** in the presence of solid K_2CO_3; (ii) isomerization of the ylide **9a** to **9b**; (iii) intramolecular aldol reaction of **9b** to give **10**; and (iv) solvent mediated proton transfer of **10** to produce ylide **12**, which undertakes ylide hydrolysis to give 5,6-dihydropyridin-2(1*H*)-ones **8**.

Reactions using ylide hydrolysis have occasionally appeared in the literature.[20] For example, Tang et al. recently reported highly selective access to dihydrobenzofurans via a tandem ylide initiated Michael addition–ylide hydrolysis reaction.[19] Herein we provided a new tandem ylide-initiated aldol-ylide hydrolysis reaction to prepare 5,6-dihydropyridin-2(1*H*)-ones.

In conclusion, we have developed a simple one-pot synthesis of 5,6-dihydropyridin-2(1*H*)-ones via an Ugi/aldol/hydrolysis reaction starting from Baylis–Hillman phosphonium salts. Due to the mild reaction conditions, good yields, and easily accessible starting material, we think that the new synthetic approach has potential in the synthesis of 5,6-dihydropyridin-2(1*H*)-ones, which are of considerable interest as potential biologically active compounds or pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **7a** and **8a**–**8k**, and the data for the X-ray structure of **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005. (b) Choudhury, L. H.; Parvin, T. *Tetrahedron* **2011**, *67*, 8213.

(2) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8.

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Org. Lett. 2015, 17, 2234–2237

(3) (a) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (c) Sadjadi, S.; Heravi, M. M. *Tetrahedron* **2011**, *67*, 2707. (d) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (e) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (f) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321. (g) Armstrong, W. A.; Brown, S. D.; Keating, T. A.; Tempest, P. A. In *Combinatorial Chemistry*; Wilson, S. R., Czarnik, A. W., Eds.: Wiley-VCH: Weinheim, Germany, 1997. (h) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935. (i) Hulme, C.; Morrissette, M. M.; Volz, F. A.; Burns, C. J. *Tetrahedron Lett.* **1998**, *39*, 1113.

(4) Ghabraie, E.; Balalaie, S.; Mehrparvar, S.; Rominger, F. *J. Org. Chem.* **2014**, *79*, 7926.

(5) Sharma, N.; Li, Z.; Sharma, U. K.; Van der Eycken, E. V. *Org. Lett.* **2014**, *16*, 3884.

(6) Asthana, M.; Sharma, N.; Singh, R. M. *Tetrahedron* **2014**, *70*, 7996.

(7) (a) Xu, Z.; De Moliner, F.; Cappelli, A. P.; Hulme, C. *Org. Lett.* **2013**, *15*, 2738. (b) Xu, Z.; De Moliner, F.; Cappelli, A. P.; Hulme, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8037. (c) Silvani, A.; Lesma, G.; Crippa, S.; Vece, V. *Tetrahedron* **2014**, *70*, 3994. (d) Kumar, A.; Li, Z.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. *Org. Lett.* **2013**, *15*, 1874.

(8) (a) Haga, A.; Tamoto, H.; Ishino, M.; Kimura, E.; Sugita, T.; Kinoshita, K.; Takahashi, K.; Shiro, M.; Koyama, K. *J. Nat. Prod.* **2013**, *76*, 750. (b) Xiao, J.; Zhang, Q.; Gao, Y.-Q.; Tang, J.-J.; Zhang, A.-L.; Gao, J.-M. *J. Agric. Food Chem.* **2014**, *62*, 3584.

(9) Wacker, D. A.; Wang, Y.; Broekema, M.; Rossi, K.; O'Connor, S.; Hong, Z.; Wu, G.; Malmstrom, S. E.; Hung, C.-P.; LaMarre, L.; Chimalakonda, A.; Zhang, L.; Xin, L.; Cai, H.; Chu, C.; Boehm, S.; Zalaznick, J.; Ponticiello, R.; Sereda, L.; Han, S.-P.; Zebo, R.; Zinker, B.; Luk, C. E.; Wong, R.; Everlof, G.; Li, Y.-X.; Wu, C. K.; Lee, M.; Griffen, S.; Miller, K. J.; Krupinski, J.; Robl, J. A. *J. Med. Chem.* **2014**, *57*, 7499.

(10) (a) Johns, B. A.; Kawasuji, T.; Weatherhead, J. G.; Taishi, T.; Temelkoff, D. P.; Yoshida, H.; Akiyama, T.; Taoda, Y.; Murai, H.; Kiyama, R.; Fuji, M.; Tanimoto, N.; Jeffrey, J.; Foster, S. A.; Yoshinaga, T.; Seki, T.; Kobayashi, M.; Sato, A.; Johnson, M. N.; Garvey, E. P.; Fujiwara, T. *J. Med. Chem.* **2013**, *56*, 5901. (b) Li, A.; Ouyang, Y.; Wang, Z.; Cao, Y.; Liu, X.; Ran, L.; Li, C.; Li, L.; Zhang, L.; Qiao, K.; Xu, W.; Huang, Y.; Zhang, Z.; Tian, C.; Liu, Z.; Jiang, S.; Shao, Y.; Du, Y.; Ma, L.; Wang, X.; Liu, J. *J. Med. Chem.* **2013**, *56*, 3593.

(11) Yu, Y.; Huang, L.; Wu, W.; Jiang, H. *Org. Lett.* **2014**, *16*, 2146.

(12) (a) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (b) Alvarez, S.; Medina, S.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* **2013**, *78*, 9995.

(13) Fujii, M.; Nishimura, T.; Koshiba, T.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2013**, *15*, 232.

(14) (a) Zhou, R.; Wang, J.; Yu, J.; He, Z. *J. Org. Chem.* **2013**, *78*, 10596. (b) Tsai, Y.-L.; Fan, Y.-S.; Lee, C.-J.; Huang, C.-H.; Das, U.; Lin, W. *Chem. Commun.* **2013**, *49*, 10266. (c) Lee, Y.-T.; Lee, Y.-T.; Lee, C.-J.; Sheu, C.-N.; Lin, B.-Y.; Wang, J.-H.; Lin, W. *Org. Biomol. Chem.* **2013**, *11*, 5156. (d) Syu, S.-E.; Lee, Y.-T.; Jang, Y.-J.; Lin, W. *Org. Lett.* **2011**, *13*, 2970. (e) Kao, T.-T.; Syu, S.-E.; Jhang, Y.-W.; Lin, W. *Org. Lett.* **2010**, *12*, 3066. (f) Matsuo, K.; Shindo, M. *Org. Lett.* **2010**, *12*, 5346. (g) Ghosh, S.; Das, J. *Tetrahedron Lett.* **2011**, *52*, 1112.

(15) (a) Beck, B.; Magnin-Lachaux, M.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2001**, *3*, 2875. (b) Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2004**, *6*, 39.

(16) Wang, L.; Ren, Z. L.; Ding, M. W. *J. Org. Chem.* **2015**, *80*, 641.

(17) (a) Wang, Y.; Chen, M.; Ding, M. W. *Tetrahedron* **2013**, *69*, 9056. (b) Wang, Y.; Xie, H.; Pan, Y. R.; Ding, M. W. *Synthesis* **2014**, *46*, 336. (c) Zeng, X. H.; Wang, H. M.; Yan, Y. M.; Wu, L.; Ding, M. W. *Tetrahedron* **2014**, *70*, 3647. (d) He, P.; Nie, Y. B.; Wu, J.; Ding, M. W. *Org. Biomol. Chem.* **2011**, *9*, 1429.

(18) (a) Yuan, D.; Kong, H. H.; Ding, M. W. *Tetrahedron* **2015**, *71*, 419. (b) Zeng, X. H.; Wang, H. M.; Wu, L.; Ding, M. W. *Tetrahedron* **2013**, *69*, 3823. (c) Zhong, Y.; Wu, L.; Ding, M. W. *Synthesis* **2012**, *44*, 3085.

(19) Zhu, J.-B.; Wang, P.; Liao, S.; Tang, Y. *Org. Lett.* **2013**, *15*, 3054.

(20) (a) Zaragoza, F. *J. Org. Chem.* **2002**, *67*, 4963. (b) Lee, K. Y.; Na, J. E.; Lee, M. J.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 5977. (c) Duvvuru, D.; Retailleau, P.; Betzer, J.-F.; Marinetti, A. *Eur. J. Org. Chem.* **2012**, 897. (d) Zhu, J.-B.; Wang, P.; Liao, S.; Tang, Y. *Chem. Commun.* **2013**, *49*, 4570.

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Org. Lett. 2015, 17, 2234−2237