JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Phosphoric Acid-Catalyzed Asymmetric Classic Passerini Reaction

Jian Zhang,† Shao-Xia Lin,† Dao-Juan Cheng, Xin-Yuan Liu,* and Bin Tan*

Department of Chemistry, South University of Science and Technology of China, Shenzhen, 518055, China

Supporting Information

ABSTRACT: An efficient enantioselective classic three-component Passerini reaction with a broad substrate scope in the presence of a chiral phosphoric acid catalyst has been developed. This represents the general example for classic three-component Passerini reaction with good to excellent enantioselectivies involving aromatic aldehydes and the bulky pivalaldehyde under mild reaction conditions. The feature of this method is highlighted by using a chiral phosphoric acid to activate carboxylic acid, aldehyde, and isocyanide for the facile construction of widely useful complex compounds.

Multicomponent reactions (MCRs) represent a powerful chemical tool for the preparation of complex molecules due to the atom and step economy as well as high efficiency in generating complex molecules through structural modulations of each component.[1] The Passerini reaction, one of the oldest multicomponent reactions, has been found useful for the construction of multifunctional α-acyloxyamide in a practical process with the concurrent generation of a stereogenic center.[2] It is probably the best method for producing α-acyloxyamide in a highly convergent manner, and a large variety of biologically active substances can be accessed quickly.[2e] The mechanism, which has been widely studied, appears to involve activation of an aldehyde by the carboxylic acid, followed by addition of an isocyanide and trapping of the resulting nitrilium intermediate by the carboxylate to afford the final product by migration of the acyl group onto the oxygen atom derived from the aldehyde (Figure 1).[2,3]

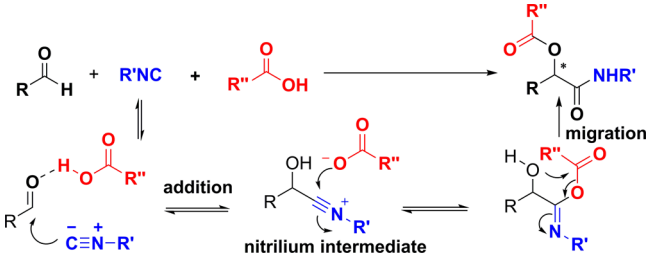


Figure 1. General mechanism for classic Passerini reaction.

Although great endeavors have been devoted to the asymmetric version of the Passerini-type reactions[4] via modification of the carboxylic acid or trapping the reactive nitrilium intermediate by intramolecular cyclization, only three examples succeeded in the development of enantioselective classic three-component Passerini reaction.[5] In 2003, Dömling et al. disclosed that a stoichiometric amount of a Ti-taddol complex promoted the Passerini reaction to afford α-acyloxyamides with moderate enantioselectivity by screening hundreds of metal–ligand combinations in a parallel fashion.[5a] Schreiber et al. demonstrated that a Cu-pybox complex was capable of catalyzing the Passerini reaction with good enantioselectivity only when chelating aldehydes were used as reaction partners.[5b] In 2008, Wang, Zhu et al. achieved a significant breakthrough by using chiral Al-salen complex as a catalyst to realize the enantioselective classic Passerini reaction in moderate to good enantiocontrol with a variety of simple aliphatic aldehydes.[5c] However, all these examples have encountered two major limitations (Figure 2): (1)

Research group	Catalyst system	Limitations
1. Dömling group (2003),	[Ti-taddol]	32-42% ee
2. Schreiber group (2004),	[Cu-pybox]	only good for chelating aldehydes
3. **Wang & Zhu group** (2008),	[Al-salen]	only for aliphatic aldehydes

Figure 2. Previous efforts for enantioselective classic three-component Passerini reaction.

Chiral metal–ligand complex is essential for the control of enantioselectivity; (2) only limited substrates were compatible with good results, and noteworthy is that aromatic aldehydes failed to participate in this classic reaction. Thus, the development of an asymmetric classic three-component Passerini reaction with wide substrate scope in enantioselective organocatalysis represents a significant challenge and is in great demand.

After careful consideration of the reaction mechanism and the previous metal-catalyzed examples, several challenges have to be encountered for achieving good results: (1) the competition of the uncatalyzed background reaction; (2) the difficulty of stereocontrol in the step of α-addition of an isocyanide to an aldehyde; (3) the complexity of the reaction mechanism; (4) the problem of catalyst turnover (catalyst acts as a reactive component or chelate with the resultant product). More recently, List et al. have elegantly demonstrated the use of chiral phosphoric acid to activate carboxylic acids via heterodimerization to realize a series of asymmetric reactions.[7] Based on this mode of activation, we envisioned that the use of chiral phosphoric acid as a catalyst could meet the challenges for the asymmetric classic three-component Passerini reaction as described above, since the formation of heterodimer via self-assembly between chiral phosphoric acid and carboxylic acid might increase the acidity of the phosphoric acid and further

Received: August 28, 2015
Published: October 21, 2015

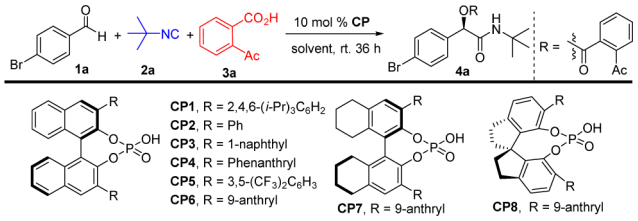
DOI: 10.1021/jacs.5b09117
J. Am. Chem. Soc. 2015, 137, 14039–14042

enhance the nucleophilicity of the carboxylic acid molecule.[7] With such results, the increased acidity of catalyst is important to improve the activation ability of the aldehyde with Brønsted acid organocatalysis, and the enhancement of the nucleophilicity of the carboxylic acid would also accelerate the carboxylate attack step of the resulting nitrilium intermediate during the course of cascade process. On the other hand, we further anticipated that chiral phosphoric acid might simultaneously activate the isocyanide via cooperative multiple hydrogen bonding to achieve hydrogen-bond-controlled stereoinduction.[8] To support our hypothesis, some control NMR experiments (Figure S1, see Supporting Information) were carried out and showed that the interactions of phosphoric acid with aldehyde, carboxylic acid, and isocyanide have been clearly displayed by using ^{31}P NMR spectrum. Noteworthy is that the interaction of phosphoric acid and carboxylic acid with isocyanide is particularly strong. As part of our continued interest for asymmetric multicomponent reactions[9] and phosphoric acid catalysis,[10] we herein describe the chiral phosphoric acid-catalyzed enantioselective classic three-component Passerini reaction with a broad substrate scope, including various aromatic and aliphatic aldehydes, aromatic and aliphatic carboxylic acids, and isocyanides.

On the basis of our hypothesis, our investigation commenced with the reaction by using 4-bromobenzaldehyde (**1a**), *tert*-butyl isocyanide (**2a**), and 2-acetyl benzoic acid (**3a**) as reactants and chiral phosphoric acid **CP1** as a catalyst in DCM at room temperature. To our delight, the reaction proceeded smoothly to afford the desired product in 49% ee (Table 1, entry 1). This result encouraged us to further investigate various chiral phosphoric acids in the reaction and found that the enantioselectivities varied significantly from 5% to 89% ee (Table 1, entries 2–6). Catalyst **CP6** with an anthryl group on the 3,3′-position was found to be the best considering the enantioselectivity and chemical yield (89% ee, 33% yield, entry 6). It should be noted that a lower ee of product **4a** was obtained with SPINOL- or $[H]_8$-BINOL-derived phosphoric acid (**CP7** and **CP8**) as the catalyst. Among the solvents screened (Table 1, entries 9–11), chloroform ($CHCl_3$) was found to be the most appropriate (entry 10). Further investigation revealed that molecular sieves (MS 5 Å) and drying reagent ($MgSO_4$) were useful in improving the chemical yield and asymmetric induction (entries 12, 13), and the best result with 66% yield and 94% ee was achieved when $MgSO_4$ was added into the reaction (entry 13). It was noteworthy that increase of the amount of catalyst loading or isocyanide had a negative influence on the results. Finally, the chemical yield was improved to 72% when more catalyst and isocyanide were further added to the reaction mixture after 12 h (Table 1, entry 16).[11]

With the optimal conditions in hand, we set out to explore the scope of generality using various aldehydes (Tables 2 and 3). Most reactions reached completion within 36 h and gave products in good to excellent enantioselectivities (85–99% ee). The reaction is applicable to a wide range of aromatic aldehydes. It was shown that the position and the electronic property of the substituents for aromatic rings have a very limited effect on the stereoselectivity of the process. For example, aromatic aldehydes bearing electron-withdrawing (R = F, Cl, Br, CN, NO_2, CF_3, **4a**–**4j**) or neutral (**4k**) or electron-donating (R = Me, **4m**) groups at the different positions of the phenyl ring reacted efficiently to afford the corresponding products **4a**–**4m** in 89–98% ee. It is revealed that with α,β-unsaturated aldehyde (**1l**) as the substrate the desired product **4l** was also obtained in 55% yield and 90% ee. Most importantly, the reaction is also suitable to general aliphatic

Table 1. Optimization of the Reaction Conditions[a]



Entry	CPA	Solvent	Additive	Yield (%)[b]	ee (%)[c]
1	**CP1**	DCM	-	22	49
2	**CP2**	DCM	-	13	8
3	**CP3**	DCM	-	15	9
4	**CP4**	DCM	-	14	47
5	**CP5**	DCM	-	7	5
6	**CP6**	**DCM**	**-**	**33**	**89**
7	**CP7**	DCM	-	26	50
8	**CP8**	DCM	-	17	44
9	**CP6**	DCE	-	27	84
10	**CP6**	**$CHCl_3$**	**-**	**53**	**92**
11	**CP6**	Toluene	-	34	78
12	**CP6**	$CHCl_3$	5Å MS	61	94
13	**CP6**	$CHCl_3$	$MgSO_4$	66	94
14[d]	**CP6**	$CHCl_3$	$MgSO_4$	62	94
15[e]	**CP6**	$CHCl_3$	$MgSO_4$	55	90
16[f]	**CP6**	**$CHCl_3$**	**$MgSO_4$**	**72**	**94**

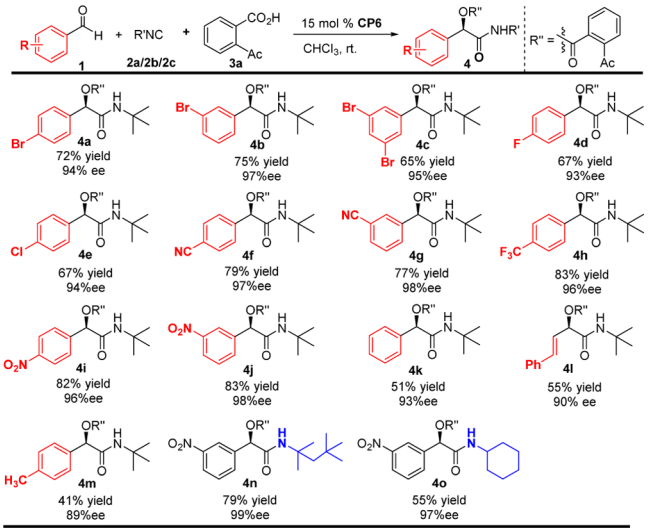
[a]Unless otherwise specified, the reaction of **1a** (0.1 mmol), **2a** (0.06 mmol), **3a** (0.05 mmol), and catalyst (10 mol %) was carried out for 36 h in 1 mL of solvent. [b]Isolated yield. [c]Determined by HPLC analysis. [d]15 mol % of catalyst was used. [e]15 mol % of catalyst and 2.3 equiv of *t*-BuNC were used. [f]Reaction conditions: **1a** (0.1 mmol), **2a** (0.06 mmol), **3a** (0.05 mmol), and catalyst (10 mol %) in 1 mL of solvent for 12 h under Ar, then catalyst (5 mol %) and **2a** (0.06 mmol) were further added and stirred for another 24 h.

aldehydes (Table 3) including linear aldehydes (**5a**–**5d**), α-branched isobutyraldehyde (**5e**), and cyclohexanecarbaldehyde (**5f**). The excellent yields (97–99%) and good to excellent enantioselectivities were attainable within 36 h. It should be noted that the highly hindered pivalaldehyde (**5g**) performed smoothly to produce the desired product in 78% yield with 92% ee. Furthermore, the *tert*-butyl isocyanide (**2a**) can be replaced by cyclohexyl isocyanide (**2b**) or 1,1,3,3-tetramethylbutyl isocyanide (**2c**), producing the corresponding products (**4n**, **4o**, **5h**) in good results. We would like to emphasize is that it is the first time, for classic three-component Passerini reaction, that good results are obtained involving aromatic aldehydes and the very bulky pivalaldehyde, thus clearly demonstrated that the chiral phosphoric acid is undoubtedly a robust organocatalyst to create a well-defined chiral pocket for the reaction.

We then evaluated the use of various carboxylic acids as the reactants. In this asymmetric chiral phosphoric acid-catalyzed Passerini reaction, a wide range of aromatic and aliphatic carboxylic acids were tolerated to provide the corresponding products (**6a**–**6k**) in high yields with good to excellent enantioselectivities (Table 4). In order to confirm the absolute

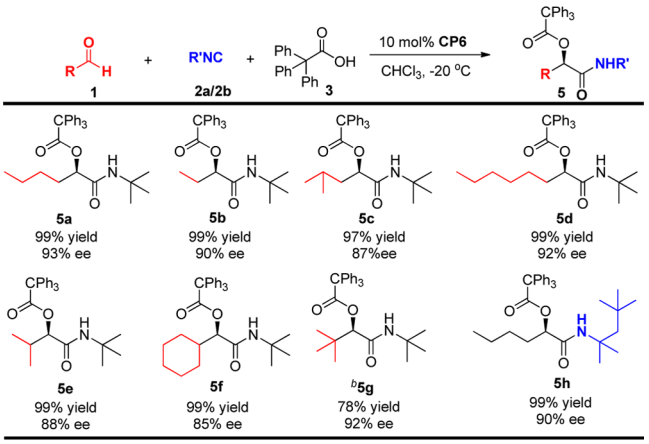
DOI: 10.1021/jacs.5b09117
J. Am. Chem. Soc. 2015, 137, 14039–14042

Table 2. Substrates Scope of Aromatic Aldehydes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.12 mmol), **3a** (0.1 mmol), and catalyst **CP6** (15 mol %) in 2 mL of $CHCl_3$ for 12 h under Ar, then catalyst (5 mol %) and **2** (0.12 mmol) were added and stirred for another 24 h.

Table 3. Substrates Scope of Aliphatic Aldehydes[a]



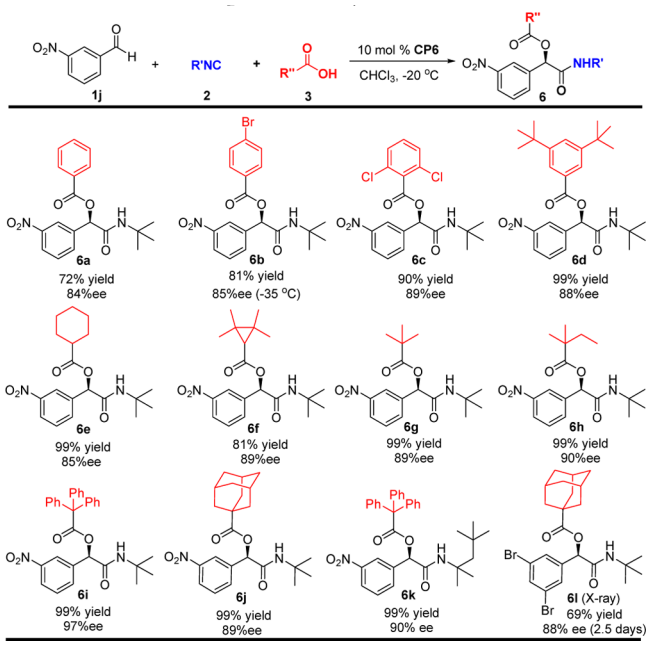
[a]Unless otherwise specified, the reaction of **1** (0.2 mmol), **2a** or **2b** (0.12 mmol), **3** (0.1 mmol), and catalyst **CP6** (10 mol %) was carried out for 36 h in $CHCl_3$ under Ar. [b]Reaction conditions: **1** (0.2 mmol), **2** (0.12 mmol), **3** (0.1 mmol), and catalyst **CP6** (10 mol %) in 3 mL solvent for 12 h under Ar at room temperature, then catalyst **CP6** (10 mol %) and **2** (0.12 mmol) were added and stirred for another 24 h at the same temperature.

configuration of the obtained product, we carried out a reaction involving 3,5-dibromobenzaldehyde, *tert*-butyl isocyanide, and adamantanecarboxylic acid to yield a solid product **6l**. The absolute configuration of **6l** was determined by X-ray crystallographic analysis (see Figure S2).

To further evaluate the practicality of this Passerini reaction, we carried out the reaction on a gram scale. As shown in Scheme 1, there was no change in reactivity and almost no influence on the chemical yield and enantioselectivity (80% yield with 98% ee), indicating this protocol should be potential for large-scale chemical production of α-acyloxyamide.

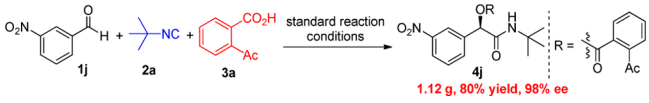
Based on our obtained results, NMR studies and List's investigations,[7a,b] a catalytic process can be proposed (Figure 3). Initially, a heterodimer between the phosphoric acid and

Table 4. Substrates Scope of Carboxylic Acids[a]



[a]Unless otherwise specified, the reaction of **1j** (0.2 mmol), **2** (0.12 mmol), **3** (0.1 mmol), and catalyst **CP6** (10 mol %) was carried out for 36 h in 2 mL of $CHCl_3$ under Ar.

Scheme 1. Gram-Scale Synthesis



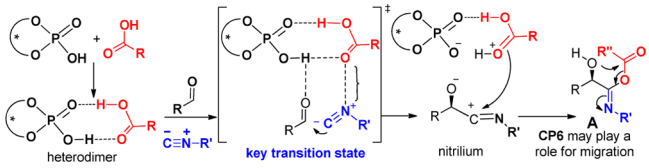


Figure 3. Proposed transition state and process.

carboxylic acid is formed after a fast equilibrium, which will be very useful for the activation of both aldehyde and isocyanide via hydrogen-bonding and ion pair interaction. Thus, the phosphoric acid may play an important role in creating an appropriate chiral environment for asymmetric induction during the key transition state. Furthermore, the enhancement of carboxylate nucleophilicity may perform an important role for the formation of the relatively active intermediate **A**. In addition, the chiral phosphoric acid may play an additional role to help the final migration step.

In summary, we have developed an efficient enantioselective classic three-component Passerini reaction with a broad substrate scope in the presence of a chiral phosphoric acid catalyst. For most of the cases, good to excellent enantioselectivies were achieved, which is the first time for classic three-component Passerini reaction to obtain such good results involving aromatic aldehydes and the very bulky pivalaldehyde. The important feature of this transformation is that a highly asymmetric induction was achieved by concurrent activation of aldehyde, carboxylic acid, and isocyanide by using a phosphoric acid catalyst under metal-free condition. Further investigation to

DOI: 10.1021/jacs.5b09117
J. Am. Chem. Soc. 2015, 137, 14039−14042

understand the reaction mechanism and the real role of the phosphoric acid and application of this catalytic system to the Ugi reaction[12] are current underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09117.

Experimental procedures, characterization of all new compounds, Figure S1 and S2 (PDF)
(CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*tanb@sustc.edu.cn
*liuxy3@sustc.edu.cn

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (nos. 21572095, 21572096), and South University of Science and Technology of China is greatly appreciated. B.T. thanks the Thousand Young Talents Program for financial support.

■ REFERENCES

(1) For recent leading reviews on multicomponent reactions (MCRs), see: (a) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (b) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. (c) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (d) Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948. (e) Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem.* **2014**, *16*, 2958. For a related book, see: (f) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH, Weinheim, 2005.

(2) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (c) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (d) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (e) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1. (f) Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. *Chem. Rev.* **2009**, *109*, 796.

(3) (a) Baker, R. H.; Stanonis, D. *J. Am. Chem. Soc.* **1951**, *73*, 699. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) Maeda, S.; Komagawa, S.; Uchiyama, M.; Morokuma, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 644. (d) Soeta, T.; Ukaji, Y. *Chem. Rec.* **2014**, *14*, 101.

(4) For the modified enantioselective Passerini-type reactions, see: (a) Denmark, S.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825. (b) Denmark, S.; Fan, Y. *J. Org. Chem.* **2005**, *70*, 9667. (c) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Eur. J. Org. Chem.* **2007**, *2007*, 4076. (d) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Org. Lett.* **2007**, *9*, 3615. (e) Yue, T.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 9454. (f) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 8396. (g) Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 8384. (h) Zeng, X.; Ye, K.; Lu, M.; Chua, P. J.; Tan, B.; Zhong, G. *Org. Lett.* **2010**, *12*, 2414.

(5) (a) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 4021. (b) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*, 4231. (c) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 388.

(6) For pioneering works on chiral phosphoric acid catalysis, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. For typical reviews, see: (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (d) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909. (e) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (f) Terada, M. *Chem. Commun.* **2008**, 4097. (g) Terada, M. *Synthesis* **2010**, *2010*, 1929. (h) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (i) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227. (j) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (k) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (l) Zhu, C.; Saito, K.; Yamanaka, M.; Akiyama, T. *Acc. Chem. Res.* **2015**, *48*, 388. For recent examples, see: (m) Huang, S.; Kötzner, L.; Kanta De, C.; List, B. *J. Am. Chem. Soc.* **2015**, *137*, 3446. (n) Kim, J. H.; Čorić, I.; Palumbo, C.; List, B. *J. Am. Chem. Soc.* **2015**, *137*, 1778. (o) Wang, S.-G.; Yin, Q.; Zhuo, C.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 647. (p) Wang, Z.; Sheong, F. K.; Sung, H. H. Y.; Williams, I. D.; Lin, Z.; Sun, J. *J. Am. Chem. Soc.* **2015**, *137*, 5895. (q) Yang, B.-M.; Cai, P.-J.; Tu, Y.-Q.; Yu, Z.-X.; Chen, Z.-M.; Wang, S.-H.; Wang, S.-H.; Zhang, F.-M. *J. Am. Chem. Soc.* **2015**, *137*, 8344. (r) Miles, D. H.; Guasch, J.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 7632. (s) Yang, X.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3205. (t) Hsiao, C.-C.; Raja, S.; Liao, H.-H.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 5762. (u) 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. (v) Gualtierotti, J.-B.; Pasche, D.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9926.

(7) For examples involving phosphoric acids activation of carboxylic acids: (a) Monaco, M. R.; Poladura, B.; Diaz de Los Bernardos, M.; Leutzsch, M.; Goddard, R.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7063. (b) Monaco, M. R.; Prévost, S.; List, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 8142. (c) Monaco, M. R.; Prévost, S.; List, B. *J. Am. Chem. Soc.* **2014**, *136*, 16982. (d) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2007**, *2007*, 1441. (e) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832. (f) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141.

(8) For phosphoric acid catalyzed reactions involving isocyanides: (a) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6717. (b) Su, Y.; Bouma, M. J.; Alcaraz, L.; Stocks, M.; Furber, M.; Masson, G.; Zhu, J. *Chem. - Eur. J.* **2012**, *18*, 12624.

(9) Wu, M.-Y.; He, W.-W.; Liu, X.-Y.; Tan, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 9409.

(10) (a) Cheng, D.-J.; Yan, L.; Tian, S.-K.; Wu, M.-Y.; Wang, L.-X.; Fan, Z.-L.; Zheng, S.-C.; Liu, X.-Y.; Tan, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 3684. (b) Yu, P.; Lin, J.-S.; Li, L.; Zheng, S.-C.; Xiong, Y.-P.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11890. (c) Lin, J.-S.; Yu, P.; Huang, L.; Zhang, P.; Tan, B.; Liu, X.-Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 7847.

(11) May be the competitive nucleophilic attack of phosphoric acid to nitrilium ion and consume the **CP6** (for detail, see Supporting Information).

(12) To date, no enantioselective classic Ugi reaction has been reported. For asymmetric Ugi-type reactions, see: (a) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 7279. (b) Zhao, W.; Huang, L.; Guan, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 3436.

DOI: 10.1021/jacs.5b09117
J. Am. Chem. Soc. 2015, 137, 14039−14042