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Enantioselective Hydrophosphonylation of *in Situ* Generated *N*-Acyl Ketimines Catalyzed by BINOL-Derived Phosphoric Acid

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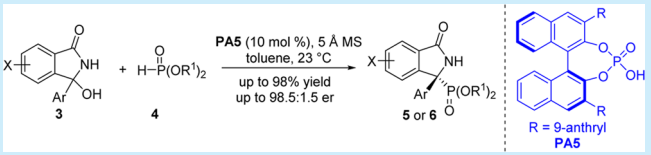
Supporting Information

ABSTRACT: An efficient route to pharmacologically interesting isoindolinone-based α-amino phosphonates is described via asymmetric hydrophosphonylation of *in situ* generated ketimines catalyzed by BINOL-derived phosphoric acid. The reaction proceeds smoothly at ambient temperature affording a variety of α-amino phosphonates with a quaternary stereogenic center embedded in isoindolinone motif in high yields with excellent enantiomeric ratios (up to 98.5:1.5 er). Several interesting transformations of the products into valuable synthetic intermediates are also depicted.



Enantiomerically enriched α-amino phosphonates, and phosphonic acids are considered as important surrogates for α-amino acids with an impressive diversity of biological activities.[1] Their intriguing biological potential is evident from observed anti-HIV,[2] antibacterial,[3] antitumor,[4] and antifungal[5] activities as well as inhibitors of protease,[6] and phosphatase activity.[7] Among various nonracemic derivatives, alafosfalin (**1b**) is reported as an antibacterial agent,[4] and K-26 (**1c**) as a natural product,[8] having an angiotensin converting enzyme inhibitory activity (Figure 1; **1a**–**c**).

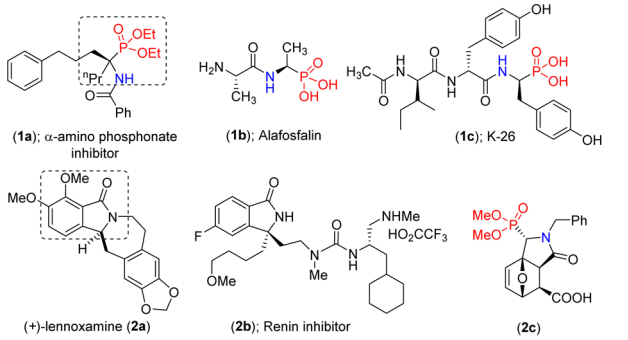


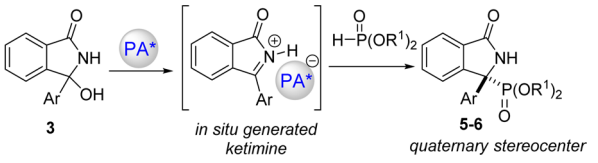
Figure 1. Representative examples of α-amino phosphonates and isoindolinones.

On the other hand, isoindolinones are important structural scaffolds from a synthetic perspective. Substituted isoindolinones are advanced intermediates in the synthesis of various drug molecules[9a−e] and complex natural products[9f,g] (Figure 1; **2a**–**c**). Therefore, stereoselective synthesis of α-amino phosphonate embedded with isoindolinone motif would be challenging in the context of drug discovery.[9b]

Prominent asymmetric approaches toward α-amino phosphonates include resolution,[10] chiral auxiliary-based processes,[10] and various enantioselective approaches.[11] The most direct and easy strategy is the enantioselective addition of phosphite to aldimines (commonly known as aza-Pudovik reaction).[12,13] Another attractive approach for the construction of the C−P bond is the direct catalytic asymmetric Kabachnik−Fields reaction.[14] In contrast, enantioselective synthesis of quaternary derivatives via functionalized ketimines remains elusive, due to their lower reactivity than aldimines and difficulty in enantiofacial discrimination.[15] Although few elegant approaches to these targets have been reported in the literature,[16a,b] access to configurationally and conformationally rigid quaternary α-amino phosphonates is still challenging. Recently, our research group has developed an expeditious approach to access enantioenriched isoindolinones via a Domino Cu(I)-catalyzed one-pot three-component alkynylation−lactamization strategy.[17] Herein, we envision a practical approach to enantioenriched isoindolinone-based α-amino phosphonates **5**−**6** bearing a C-3 quaternary stereogenic center via phosphoric acid catalyzed hydrophosphonylation of *in situ* generated ketimines of 3-hydroxyisoindolinone **3** (Scheme 1).

Initially, a model reaction comprising 3-hydroxy-3-phenylisoindolin-1-one **3a** and diphenyl phosphite **4a** was carried out using (*S*)-BINOL-derived phosphoric acid **PA1** (10 mol %) in dichloromethane (CH_2Cl_2) at 23 °C. We realized that the reaction was sluggish and isoindolinone-based α-amino

Scheme 1. Working Hypothesis (PA*: Chiral Phosphoric Acid)



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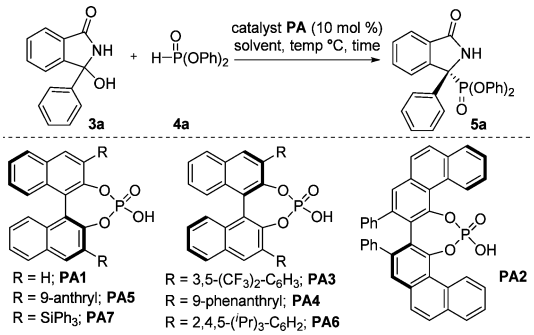
phosphonate **5a** was obtained in moderate yield (entry 1, Table 1). To our delight, the reaction could be expedited in better yield by proceeding in a closed vessel at 40 °C, affording **5a** in 69% yield with a 56:44 er after 30 h (entry 2).

Table 1. Selected Optimization Studies[a,g]



entry	PA	solvent	temp (°C)	time (h)	5a (%)[b,c]	er[d]
1	**1**	CH_2Cl_2	23	96	52	57:43
2	**1**	CH_2Cl_2	40	30	69	56:44
3	**2**	CH_2Cl_2	40	28	72	58:42
4	**3**	CH_2Cl_2	40	28	67	50:50
5	**4**	CH_2Cl_2	40	28	80	66:34
6	**5**	CH_2Cl_2	40	28	84	79:21
7	**6**	CH_2Cl_2	40	28	74	52:48
8	**7**	CH_2Cl_2	40	28	79	50:50
9[e]	**5**	CH_2Cl_2	40	16	90	85:15
10[e]	**5**	CH_2Cl_2	23	18	88	87:13
11[e]	**5**	$CHCl_3$	23	18	74	86:14
12[e]	**5**	*p*-xylene	23	14	90	88:12
13[e]	**5**	CH_3CN	23	32	32	72:28
14[e]	**5**	Et_2O	23	28	72	78:22
15[e]	**5**	$PhCH_3$	23	14	92	89:11
16[f]	**5**	$PhCH_3$	23	14	95	91:9
17[g]	**5**	$PhCH_3$	23	16	91	90:10

[a]Reactions were carried out with 0.05 mmol of **3a** and 0.065 mmol of **4a** in the presence of catalyst **PA** (10 mol %) at indicated temperature. [b]Isolated yields after column purification. [c]Decomposition of the rest of the mass balance. [d]Enantiomeric ratio (er) was determined by chiral HPLC. [e]4 Å MS (35 mg). [f]5 Å MS (35 mg). [g]3 Å MS (35 mg). MS denotes molecular sieves.

Encouraged by the preliminary outcome, various chiral phosphoric acids **PA2**−**PA7** were examined with the model substrate (entry 3−8). Among them, **PA5** was found to be the best Brønsted acid[18] catalyst to afford **5a** with very good chemical yield (84%) and optical yield (79:21 er). However, further improvement of yield and enantioselectivity was realized with the use of 4 Å molecular sieves (MS) to afford **5a** at room temperature with CH_2Cl_2 as a solvent. Afterward, screening of various solvents, including $CHCl_3$, *p*-xylene, CH_3CN, Et_2O, and toluene, revealed that toluene was the most suitable solvent of choice for the reaction. It was observed that 5 Å MS was the best choice as a water scavenger for the reaction. However, there was no significant change on the enantioselectivity of the reaction when different pore sizes of the MS were used (see Supporting Information (SI) for more details). Therefore, based on our extensive optimization, the substrate scope was explored using 10 mol % of **PA5** in toluene with 5 Å MS (35 mg) at room temperature.

Initially, a series of 3-hydroxy-3-arylisoindolin-1-ones **3** were subjected to the optimized reaction conditions and afforded the corresponding products **5** in synthetically viable yields as shown in Figure 2. Notably, substrates **3b**−**f** having an electron-rich

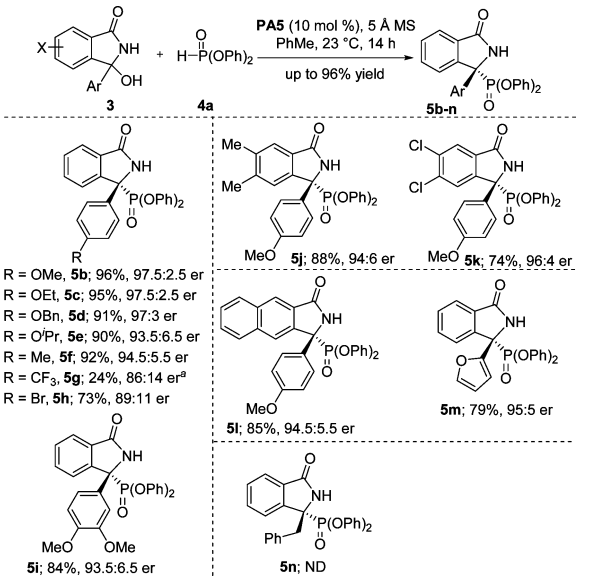


Figure 2. Scope of reaction with 3-hydroxyisoindolinones.[24] [a]22 h.

aryl group at the C-3 position reacted smoothly and afforded **5b**−**f** in synthetically viable yields with excellent enantiomeric ratios (er) of up to 97.5:2.5. Additionally, the substrates **3g**−**h** having electron-withdrawing functionalities (such as $-CF_3$, −Br) furnished **5g** (24% yield) and **5h** (73% yield) with selectivities of up to 89:11 er, indicating that electronic factors play a pivotal role in the hydrophosphonylation process.

Gratifyingly, our optimized conditions work fine with a variety of substrates **3i**−**l**, which afforded products **5i**−**l** with excellent selectivities of up to 96:4 er. Moreover, substrate **3m** having a furan moiety at C-3 furnished product **5m** in 79% yield and 95:5 er. Under the reaction conditions, **3n** having an alkyl group at the C-3 position failed to react with **4a** even at 40 °C. However, this led to the undesired 3-alkylidene isoindolinones.[19]

Next, a variety of dialkyl phosphites **4b**−**d** having different electronic properties were tested for the hydrophosphonylation reaction with diversely substituted 3-hydroxyisoindolinones **3** (Figure 3). Interestingly, dimethyl and diethyl phosphite **4b**−**c** furnished isoindolinone-based α-amino phosphonates **6a**−**b** in moderate yields with excellent selectivities of up to 97:3 er, when the reaction was conducted at 40 °C. We speculate that the low reactivity of dialkyl phosphites **4b**−**c** toward ketimines could be due to higher pK_a values[11d,20] of the P−H bond, leading to inefficient phosphonate-phosphite tautomerism.[12c] In contrast, bis(2,2,2-trifluoroethyl) phosphite **4d**, having comparatively a lower pK_a value than **4c**, was found to be a potent nucleophile and afforded **6c**−**e** in synthetically viable yields with excellent enantioselectivities (up to 98.5:1.5 er) at room temperature.

Substrates **3** consisting of a sterically demanding *o*-methoxyphenyl and β-naphthyl group at the C-3 position furnished **6f** with a moderate selectivity of 87:13 er and **6g** in 28% yield with 93:7 er (Figure 3). It probably indicates that steric hindrance at the *ortho* position plays a significant role in the enantioselectivity of the product formation. It was also observed that substrate **3** having −F and −CN functionality afforded **6h**−**i** with excellent selectivities (up to 97:3 er). To

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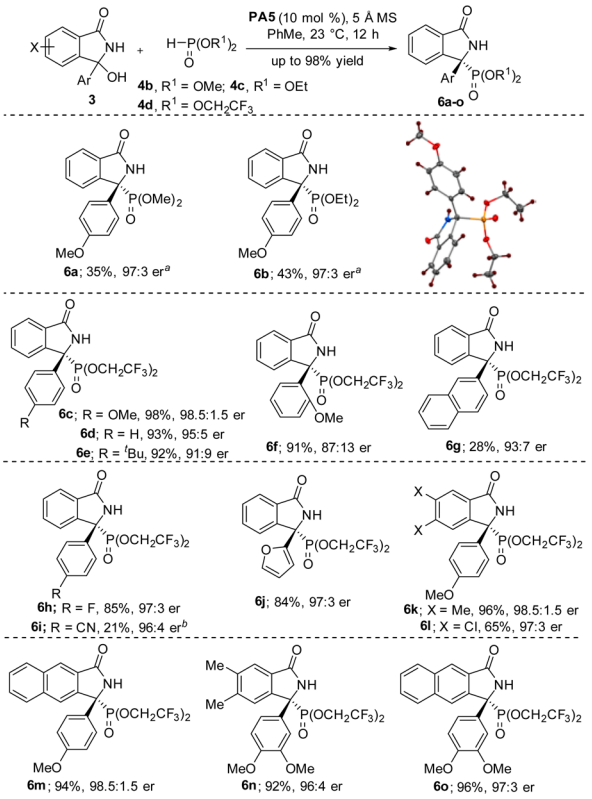


Figure 3. Scope of the reaction with dialkyl phosphites.[24] [a] 20 h at 40 °C. [b] 22 h at 23 °C.

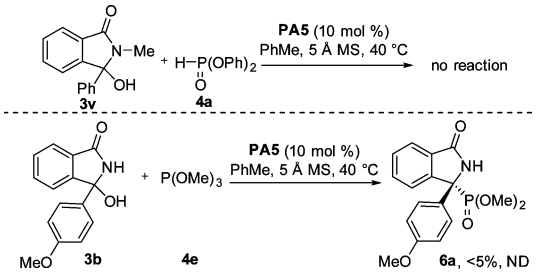
our delight, heteroaromatic substrate **3m** having a furan moiety afforded product **6j** with high yield and excellent 97:3 er. Rewardingly, a variety of substrates **3** having both electron-donating and -withdrawing substitution reacted with **4d** to afford products **6k–o** in synthetically viable yields with an excellent level of enantioselectivities (up to 98.5:1.5 er) (Figure 3).

The X-ray structure analysis of the isoindolinone-based α-amino phosphonate **6b** (CCDC 1516982) confirmed the absolute stereochemistry to be (*R*) (Figure 3). The absolute configuration of the other products within this series were assigned by analogy. In order to show the practical efficacy of the methodology, a hydrophosphonylation reaction was carried out on a 1.0 mmol scale using catalyst **PA5** (5 mol %), affording compound **6c** with excellent yield and enantioselectivity (91%, 98:2 er) (see SI for details).

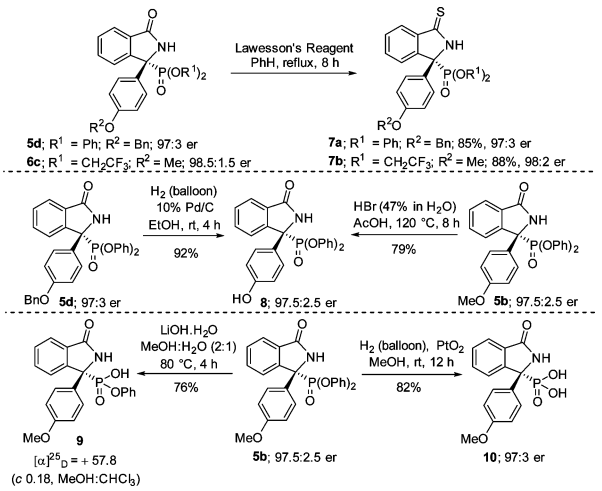
To gain some insight into the reaction mechanism, a control experiment was performed. Under the optimized conditions, *N*-methyl protected **3v** failed to react with **4a**, which indicates the requirement of a free N–H group is essential for the successful activation and preorganization of an acyliminium ion intermediate.[19] Furthermore, in the case of trimethyl phosphite **4e** as a nucleophile, the reaction led to formation of a trace amount of **6a** (Scheme 2). This probably suggests that the OH group of the dialkyl phosphite is essential for obtaining the high yields and enantioselectivity.[13b,21]

Finally, to illustrate the synthetic viability of our methodology, we converted the isoindolinones **5d** and **6c** into sulfur analogues **7a** and **7b**, respectively, by treatment with Lawesson's reagent (Scheme 3). The latter could be used for the synthesis of thioisomünchnone salts which act as a dipole for 1,3-dipolar cycloaddition reaction.[22] In another sequence, *O*-

Scheme 2. Control Experiments



Scheme 3. Synthetic Elaborations to Important Intermediates



deprotected isoindolinone **8** was obtained, either by debenzylation or by demethylation reaction in synthetically viable yields without any loss of enantiopurity. Eventually, hydrolysis of the phosphonate diester **5b** could be achieved easily by using LiOH·H_2O to obtain the α-amino phosphonate monoester **9** in 76% yield, which could serve as an important synthon for the phosphono-peptides inhibitors of β-lactamases.[23] Furthermore, complete hydrogenolysis of **5b** was carried out in the presence of a PtO_2 catalyst to afford enantiomerically enriched α-amino phosphonic acid **10** in 82% yield and 97:3 er (see SI for details).

In summary, we have reported the chiral phosphoric acid catalyzed hydrophosphonylation of *in situ* generated ketimines under ambient conditions for the first time, to the best of our knowledge. A variety of dialkyl and diphenyl phosphites were utilized to access biologically interesting isoindolinone-based α-amino phosphonates comprising a quaternary stereogenic center with remarkably high enantioselectivities (up to 98.5:1.5 er). The usefulness of this protocol has also been demonstrated by the synthesis of optically active α-amino phosphonic acid, α-amino phosphonate monoester, and other valuable synthetic intermediates. Further application of this strategy is under active investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and analytical data (^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra, HPLC traces, and HRMS) for all new compounds (PDF)
X-ray data for **6b** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Hiratake, J.; Oda, J. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 211. (b) *Aminophosphonic and Aminophosphinic Acids*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons: New York, 2000.

(2) Alonso, E.; Solis, A.; del Pozo, C. *Synlett* **2000**, 698.

(3) (a) Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56. (b) Pratt, R. F. *Science* **1989**, *246*, 917.

(4) (a) Gu, L.; Jin, C. *Org. Biomol. Chem.* **2012**, *10*, 7098. (b) Huang, X.-C.; Wang, M.; Pan, Y.-M.; Tian, X.-Y.; Wang, H.-S.; Zhang, Y. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5283.

(5) Maier, L.; Diel, P. J. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *57*, 57.

(6) Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234.

(7) Beers, S. A.; Schwender, C. F.; Loughney, D. A.; Malloy, E.; Demarest, K.; Jordan, J. *Bioorg. Med. Chem.* **1996**, *4*, 1693.

(8) Ntai, I.; Manier, M. L.; Hachey, D. L.; Bachmann, B. O. *Org. Lett.* **2005**, *7*, 2763.

(9) (a) Kanamitsu, N.; Osaki, T.; Itsuji, Y.; Yoshimura, M.; Tsujimoto, H.; Soga, M. *Chem. Pharm. Bull.* **2007**, *55*, 1682. (b) Kachkovskyi, G. O.; Kolodiazhnyi, O. I. *Tetrahedron* **2007**, *63*, 12576. (c) Yang, G.; Shen, C.; Zhang, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9141. (d) Dhanasekaran, S.; Suneja, A.; Bisai, V.; Singh, V. K. *Org. Lett.* **2016**, *18*, 634. (e) Suneja, A.; Bisai, V.; Singh, V. K. *J. Org. Chem.* **2016**, *81*, 4779. (f) Dhanasekaran, S.; Bisai, V.; Unhale, R. A.; Suneja, A.; Singh, V. K. *Org. Lett.* **2014**, *16*, 6068. (g) Dhanasekaran, S.; Kayet, A.; Suneja, A.; Bisai, V.; Singh, V. K. *Org. Lett.* **2015**, *17*, 2780.

(10) (a) Smith, A. B., III; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879. (b) Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757. (c) Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410.

(11) (a) Merino, P.; Marqués-López, E.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195. (b) Ordóñez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17. (c) Albrecht, Ł.; Albrecht, A.; Krawczyk, H.; Jørgensen, K. A. *Chem. - Eur. J.* **2010**, *16*, 28. (d) Zhao, D.; Wang, R. *Chem. Soc. Rev.* **2012**, *41*, 2095 and references cited therein.

(12) (a) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656. (b) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (c) Schlemminger, I.; Saida, Y.; Gröger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem.* **2000**, *65*, 4818. (d) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978. (e) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 10521. (f) Ingle, G. K.; Liang, Y.; Mormino, M. G.; Li, G.; Fronczek, F. R.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2054.

(13) (a) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (b) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (c) Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 6269. (d) Nakamura, S.; Nakashima, H.; Yamamura, A.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1209. (e) Fini, F.; Micheletti, G.; Bernardi, L.; Pettersen, D.; Fochi, M.; Ricci, A. *Chem. Commun.* **2008**, 4345. (g) Zhao, Y.; Li, X.; Mo, F.; Li, L.; Lin, X. *RSC Adv.* **2013**, *3*, 11895. (h) Cheng, M.-X.; Ma, R.-S.; Yang, Q.; Yang, S.-D. *Org. Lett.* **2016**, *18*, 3262.

(14) (a) Cheng, X.; Goddard, R.; Buth, G.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5079. (b) Zhou, X.; Shang, D.; Zhang, Q.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2009**, *11*, 1401. (c) Ohara, M.; Nakamura, S.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 3285. (d) Reddy, P. S.; Reddy, M. V. K.; Reddy, P. V. G. *Chin. Chem. Lett.* **2016**, *27*, 943.

(15) (a) Bella, M.; Gasperi, T. *Synthesis* **2009**, *2009*, 1583. (b) Denmark, S. E.; Wilson, T. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9980. (c) Bera, K.; Namboothiri, I. N. N. *Asian J. Org. Chem.* **2014**, *3*, 1234.

(16) (a) Nakamura, S.; Hayashi, M.; Hiramatsu, Y.; Shibata, N.; Funahashi, Y.; Toru, T. *J. Am. Chem. Soc.* **2009**, *131*, 18240. (b) Yin, L.; Bao, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2013**, *135*, 10338. (c) Bera, K.; Namboothiri, I. N. N. *Org. Lett.* **2012**, *14*, 980. (d) Kumar, A.; Sharma, V.; Kaur, J.; Kumar, V.; Mahajan, S.; Kumar, N.; Chimni, S. S. *Tetrahedron* **2014**, *70*, 7044. (e) Nazish, M.; Jakhar, A.; Khan, N. H.; Verma, S.; Kureshy, R. I.; Abdi, S. H. R.; Bajaj, H. C. *Appl. Catal., A* **2016**, *515*, 116. (f) Yan, Z.; Wu, B.; Gao, X.; Zhou, Y.-G. *Chem. Commun.* **2016**, *52*, 10882.

(17) (a) Bisai, V.; Suneja, A.; Singh, V. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 10737.

(18) (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (c) Zhang, H.; Wen, X.; Gan, L.; Peng, Y. *Org. Lett.* **2012**, *14*, 2126. (d) Ingle, G. K.; Mormino, M. G.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4822. (e) Desai, A. A.; Huang, L.; Wulff, W. D.; Rowland, G. B.; Antilla, J. C. *Synthesis* **2010**, 2106. (f) Desai, A. A.; Wulff, W. D. *Synthesis* **2010**, 3670.

(19) Chen, M.-W.; Chen, Q.-A.; Duan, Y.; Ye, Z.-S.; Zhou, Y.-G. *Chem. Commun.* **2012**, *48*, 1698.

(20) (a) Li, J.-N.; Liu, L.; Fu, Y.; Guo, Q.-X. *Tetrahedron* **2006**, *62*, 4453. (b) Gavara, L.; Petit, C.; Montchamp, J.-L. *Tetrahedron Lett.* **2012**, *53*, 5000. (c) Janesko, B. G.; Fisher, H. C.; Bridle, M. J.; Montchamp, J.-L. *J. Org. Chem.* **2015**, *80*, 10025.

(21) (a) Yamanaka, M.; Hirata, T. *J. Org. Chem.* **2009**, *74*, 3266. (b) Akiyama, T.; Morita, H.; Bachu, P.; Mori, K.; Yamanaka, M. *Tetrahedron* **2009**, *65*, 4950.

(22) Hamid, A.; Oulyadi, H.; Daïch, A. *Tetrahedron* **2006**, *62*, 6398.

(23) (a) Rahil, J.; Pratt, R. F. *Biochem. J.* **1991**, *275*, 793. (b) Staake, M.; Chauhan, J.; Zhou, D.; Shanker, A.; Chatterjee, A. D.; Das, S.; Patterson, S. E. *Org. Lett.* **2010**, *12*, 4596.

(24) The reactions were carried out with 0.1 mmol of **3** and 0.13 mmol of **4** in the presence of catalyst **PA5** (10 mol %) in toluene (1.0 mL) with 5 Å MS (35 mg).

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