



Cite this: *Chem. Commun.*, 2020, 56, 1444

Received 13th November 2019,
Accepted 20th December 2019

DOI: 10.1039/c9cc08879b

rsc.li/chemcomm

Copper mediated C(sp²)–H amination and hydroxylation of phosphinamides†

Shang-Zheng Sun,^a Ming Shang,^{‡b} Hui Xu,^c Tai-Jin Cheng,^c Ming-Hong Li^c
and Hui-Xiong Dai^{†*c}

Copper mediated C(sp²)–H amination and hydroxylation of arylphosphinic acid are accomplished by adopting phosphinamide as the directing group. This method is distinguished by its wide substrate scope and excellent functional group tolerance, thus allowing for the rapid preparation of organophosphorus compounds in organic synthesis.

Organophosphorus compounds represent an important and fundamental class of molecules due to their extensive application in medicinal chemistry, organic materials and catalysis.¹ Traditionally, their preparation or modification needs tedious manipulation and usually suffers from a limited substrate scope.² In recent years, transition metal catalyzed C–H functionalization reactions have become a useful tool in organic synthesis.³ In this regard, a directing group (DG) is often required to locate the metal catalyst to proximate C–H bonds. To date, DGs based on the carbonyl group such as carboxylic acids, amides, and ketones have been frequently used in C–H functionalization reactions.⁴ However, examples employing P-containing functional groups as DGs are relatively rare, which extremely limits their utility in rapid preparation of important organophosphorus compounds.⁵ In 2013, Kim and co-worker introduced benzyl and phenoxy phosphonic acids as DGs for Pd-catalyzed oxidative Heck reaction.⁶ Since then, Pd, Rh, Ru, and Ir-catalyzed C–H transformations such as oxidative annulation, arylation, and amination in phosphorus compounds have been reported in succession (eqn (1), Scheme 1).⁷ However, the high price and toxicity of these precious metals limit their further industrial applications. Compared with

precious metals, the first-row transition metals such as Fe, Co, Ni, and Cu are earth abundant and low toxic.⁸ Recently, Daugulis and co-workers first employed arylphosphinic acid aminoquinoline amides as the substrates for cobalt catalyzed C–H annulation with alkynes and alkenes (eqn (2), Scheme 1).⁹ To the best of our knowledge, there are no examples of copper catalyzed C–H functionalization for arylphosphinic acid. Herein, we disclose a copper-mediated amination and hydroxylation of phosphinamide C(sp²)–H bonds (eqn (3), Scheme 1).

Recently, we developed an efficient amide-tethered oxazoline bidentate auxiliary for copper-mediated C–H amination, trifluoromethylation, alkynylation, hydroxylation, arylation, and thiolation of arenes and heteroarenes.¹⁰ Inspired by these results, we were curious whether the oxazoline-containing bidentate auxiliary could facilitate the C(sp²)–H functionalization of arylphosphinic amide. Though arylphosphinic amide containing oxazoline has a similar coordination model to its benzoic amide analogues, the relative acidity of the N–H bond and subtle changes of the molecular structure blurred this idea. Considering the importance of the N,P-bidentate ligand in homogenous catalysis,¹¹ we first chose Cu(OAc)₂-mediated ortho C–H amidation as our target reaction. Gratifyingly, amidation occurred smoothly on diphenylphosphinic

^a Department of Chemistry, Innovative Drug Research Center, Shanghai University, 99 Shangda Road, Shanghai, 200444, China

^b Department of Chemistry, The Scripps Research Institute, 10550N. Torrey Pines Road, La Jolla, California 92037, USA

^c Chinese Academy of Sciences Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai, 201203, China.
E-mail: hxdai@simm.ac.cn

† Electronic supplementary information (ESI) available: Data for new compounds and experimental procedures. See DOI: 10.1039/c9cc08879b

‡ These authors contributed equally to this work.



Scheme 1 C–H functionalization of organophosphorus compounds.

Table 1 Optimization of amination reaction conditions^a


Entry	Base	Solvent	Temp. (°C)	Yield ^b (%)
1	Na ₂ CO ₃	DMSO	90	69
2	K ₂ CO ₃	DMSO	90	66
3	Li ₂ CO ₃	DMSO	90	21
4	Cs ₂ CO ₃	DMSO	90	25
5	NaOAc	DMSO	90	41
6	KOAc	DMSO	90	54
7	Na ₂ CO ₃	DMF	90	15
8	Na ₂ CO ₃	DMA	90	10
9	Na ₂ CO ₃	NMP	90	20
10	Na ₂ CO ₃	MeCN	90	n.r.
11	Na ₂ CO ₃	DMSO	60	43
12	Na ₂ CO ₃	DMSO	80	66
13	Na ₂ CO ₃	DMSO	100	84
14	Na ₂ CO ₃	DMSO	110	82
15 ^c	Na ₂ CO ₃	DMSO	100	88 (76) ^d
16 ^c	Na ₂ CO ₃	DMSO	100	12 ^e , 30 ^f

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Cu(OAc)₂ (0.1 mmol), base (0.2 mmol), solvent (1.0 mL), temp., air, 6 h. ^b The yield was determined by ¹H NMR analysis of a crude reaction mixture using CH₂Br₂ as an internal standard. ^c Na₂CO₃ (0.25 mmol). ^d Isolated yield. ^e 20 mol% Cu(OAc)₂. ^f N₂ atmosphere.

amide **1a** with exclusive *ortho*-selectivity (Table 1, entry 1). Subsequently, we screened a variety of bases including K₂CO₃, Li₂CO₃, Cs₂CO₃, NaOAc, and KOAc, and found that Na₂CO₃ was the optimal choice (Table 1, entries 2–6). The yields dramatically decreased when DMSO was replaced with other polar solvents, such as DMF, DMA, NMP and MeCN (Table 1, entries 7–10). The yield could be improved to 84% by increasing the reaction temperature to 100 °C (Table 1, entries 11–14). Finally, a small improvement was observed by enhancing the loading of Na₂CO₃ to 2.5 equivalents, affording the amidated product in 88% yield (Table 1, entry 15). When we decreased the loading of Cu(OAc)₂ to 20 mol%, only 12% yield of product **3a** was obtained. The yield decreased to 30% when the reaction was carried out under a N₂ atmosphere, indicating that air was crucial for the reaction.

Having identified the optimal conditions for C–H amidation, we next explored the substrate scope (Table 2). To our delight, a variety of phosphinic amides with electron-donating methyl-, methoxy-, and *tert*-butyl substituents could be amidated smoothly, giving the corresponding products in moderate to good yields (**3a–3g**, 44–76%). To our surprise, only 21% yield of the amidation product was obtained when 8-aminoquinoline was used as the directing group (ESI[†]). Moreover, electron-deficient phosphinamide **1h** was also compatible with the reaction, providing the amidation product **3h** in 94% yield. For benzodioxole derived phosphinamide **1i**, two regioisomers were formed, with the less sterically hindered C6-position-amidated product as the major one (**3i**, 74%).

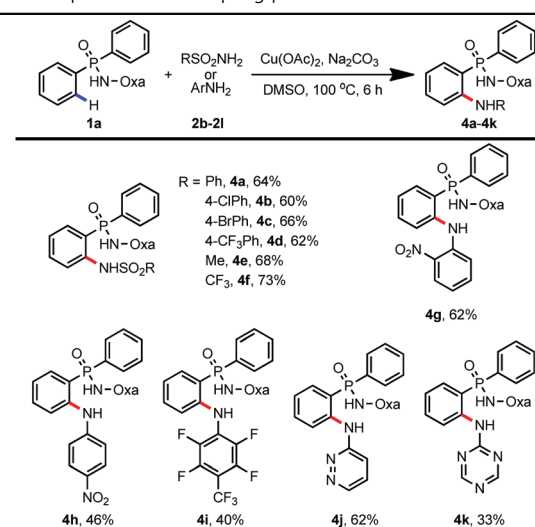
In addition to trifluoroacetamide, a wide range of sulfonamides and (hetero)anilines were also compatible with this transformation (Table 3). For example, amidation proceeded smoothly with sulfonamides bearing both electron-donating

Table 2 The scope of phosphinamides for C–H amination^{ab}

^a Reaction conditions: **1a–1i** (0.1 mmol), **2a** (0.2 mmol), Cu(OAc)₂ (0.1 mmol), Na₂CO₃ (0.25 mmol), DMSO (1 mL), 100 °C, air, 6 h. ^b Isolated yield.

and electron-withdrawing groups (**4a–4f**, 60–73%). To our surprise, electron-deficient anilines and heteroanilines could also serve as amine donors, providing a useful method for the preparation of organophosphorus compounds which have potential applications in homogenous catalysis and medicinal chemistry (**4g–4k**, 33–62%).^{11,12}

With the success of achieving C–H amidation and amination of phosphinamides, we wondered whether this protocol could be compatible with C–H hydroxylation reaction as well.¹³ To our delight, we could introduce a free hydroxyl group into a

Table 3 Scope of amine coupling partners^{ab}

^a Reaction conditions: **1a** (0.1 mmol), **2b–2l** (0.2 mmol), Cu(OAc)₂ (0.1 mmol), Na₂CO₃ (0.25 mmol), DMSO (1 mL), 100 °C, air, 6 h. ^b Isolated yield.

Table 4 Scope of phosphinamides for C–H hydroxylation^{a,b}

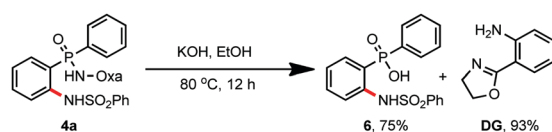
^a Reaction conditions: **1** (0.1 mmol), Cu(OAc)₂ (0.1 mmol), Na₂CO₃ (0.1 mmol), DMSO (1 mL), 80 °C, O₂, 6 h. ^b Isolated yield. ^c N₂ atmosphere.

variety of phosphinamides by adopting our previous reaction conditions.^{10f} As shown in Table 4, regardless of the electronic properties of the substituents, substrates bearing both electron-donating and electron-withdrawing groups were well tolerated, giving the desired hydroxylated products in moderate to good yields (**5a–5g**, 39–70%). In accordance with previous work, the yield of **5a** decreased to 22% when the reaction was carried out under a N₂ atmosphere.^{10f}

Finally, the removal of this amide-oxazoline directing group was demonstrated by treating product **4a** with 2 N KOH/EtOH at 80 °C, releasing the corresponding amino-phosphinic acid **6** in 75% yield with 93% recovery of the directing group (Scheme 2).

In conclusion, we developed a Cu-promoted C–H amination and hydroxylation for phosphinamide compounds. Unlike previously reported copper-catalyzed or copper-mediated C–H functionalization, in this study we developed phosphinamide as a new directing group. The technique showed a broad scope and excellent functional group tolerance, providing a new strategy for the preparation of various amino- and hydroxyl-containing arylphosphinic compounds in organic synthesis.

We gratefully acknowledge the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, NSFC (21772211), the Youth Innovation Promotion Association CAS (No. 2014229 and 2018293), the Institutes for Drug Discovery and Development, Chinese Academy of Sciences (No. CASIMM0120163006), the Science and Technology Commission of Shanghai Municipality (17JC1405000), the Program of Shanghai Academic Research Leader (19XD1424600), the National Science & Technology Major Project “Key New Drug Creation and Manufacturing Program”,



Scheme 2 Removal of the directing group.

China (2018ZX09711002-006), and the State Key Laboratory of Natural and Biomimetic Drugs for financial support.

Conflicts of interest

The authors declare no conflict of interest.

Notes and references

- (a) C. Dousson, D. Surleraux, J. Paparin, C. Pierra, J.-F. Grifffon, F. Leroy and D. Dukhan, WO2010101967 A2, 2010; (b) D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 6338–6361; (c) N. Deligonul, B. J. Laughlin, R. C. Smith, L. J. Higham and J. D. Protasiewicz, *Dalton Trans.*, 2012, **41**, 12016–12022; (d) *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*, ed. P. C. J. Kamer and P. W. N. M. van Leeuwen, Wiley-VCH, New York, 2012; (e) *Phosphorus: Chemistry, Biochemistry and Technology*, ed. D. E. C. Corbridge, CRC Press, Taylor & Francis Group, 6th edn, 2013.
- (a) O. I. Kolodiazhyi, *Russ. Chem. Rev.*, 2011, **80**, 883–910; (b) J. C. Tebbey, D. W. Allen, D. Loakes and R. Pajkert, *Organophosphorus Chemistry*, RSC, Cambridge, 2010, vol. 39; (c) R. Engel, *Handbook of Organophosphorus Chemistry*, New York, 1992; (d) L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley-VCH, New York, 2000; (e) J.-P. V. Majoral, *New Aspects in Phosphorus Chemistry*, Springer, 2004.
- For selected reviews on C–H functionalization using transition metals, see: (a) F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani and S. Murai, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 62–83; (b) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074–1086; (c) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (d) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272; (e) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (f) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624–655; (g) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4761; (h) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879–5918; (i) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295.
- (a) Z. Huang, H. N. Lim, F. Mo, M. C. Young and G. Dong, *Chem. Soc. Rev.*, 2015, **44**, 7764–7786; (b) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788–802; (c) R. Giri, N. L. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders and J.-Q. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3510–3511; (d) D.-H. Wang, M. Wasa, R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 7190–7191; (e) G. Li, L. Wan, G. Zhang, D. Lewo, J. Spangler and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 4391–4397.
- For transition-metal-catalyzed C–H functionalization of phosphorus-containing molecules, see: (a) Z. Zhang, P. H. Dixneuf and J.-F. Soule, *Chem. Commun.*, 2018, **54**, 7265–7280; (b) Y.-N. Ma, S.-X. Li and S.-D. Yang, *Acc. Chem. Res.*, 2017, **50**, 1480–1492.
- (a) L. Y. Chan, S. Kim, T. Ryu and P. H. Lee, *Chem. Commun.*, 2013, **49**, 4682–4684; (b) X. Meng and S. Kim, *Org. Lett.*, 2013, **15**, 1910–1913.
- (a) H.-L. Wang, R.-B. Hu, H. Zhang, A.-X. Zhou and S.-D. Yang, *Org. Lett.*, 2013, **15**, 5302–5305; (b) H.-Y. Zhang, H.-M. Yi, G.-W. Wang, B. Yang and S.-D. Yang, *Org. Lett.*, 2013, **15**, 6186–6189; (c) Y. Uoh, Y. Hashimoto, D. Takeda, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2013, **15**, 3258–3261; (d) D. Zhao, C. Nimphius, M. Lindale and F. Glorius, *Org. Lett.*, 2013, **15**, 4504–4507; (e) S. Park, B. Seo, S. Shin, J.-Y. Son and P. H. Lee, *Chem. Commun.*, 2013, **49**, 8671–8673; (f) M. Itoh, Y. Hashimoto, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2013, **78**, 8098–8104; (g) D. Gwon, D. Lee, J. Kim, S. Park and S. Chang, *Chem. – Eur. J.*, 2014, **20**, 12421–12425; (h) Y.-N. Ma, H.-Y. Zhang and S.-D. Yang, *Org. Lett.*, 2015, **17**, 2034–2037; (i) Z.-J. Du, J. Guan, G.-J. Wu, P. Xu, L.-X. Gao and F.-S. Han, *J. Am. Chem. Soc.*, 2015, **137**, 632–635; (j) S.-X. Li, Y.-N. Ma and S.-D. Yang, *Org. Lett.*, 2017, **19**, 1842–1845; (k) Y. Sun and N. Cramer, *Angew. Chem., Int. Ed.*, 2017, **56**, 364–367; (l) Y.-S. Jang, M. Dieckmann and N. Cramer, *Angew. Chem., Int. Ed.*, 2017, **56**, 15088–15092; (m) Y. Sun and N. Cramer, *Chem. Sci.*, 2018, **9**, 2981–2985.
- For reviews on inexpensive metal catalyzed C–H activation reactions, see: (a) B. Su, Z.-C. Cao and Z.-J. Shi, *Acc. Chem. Res.*, 2015, **48**, 886; (b) B. Zhan, B. Liu and B.-F. Shi, *Chin. Sci. Bull.*, 2015, **60**, 2907–2917;

- (c) M. Moselage, J. Li and L. Ackermann, *ACS Catal.*, 2016, **6**, 498–525; (d) G. Cera and L. Ackermann, *Top. Curr. Chem.*, 2016, **374**, 191–224; (e) J. Liu, G. Chen and Z. Tan, *Adv. Synth. Catal.*, 2016, **358**, 1174–1194; (f) W.-H. Rao and B.-F. Shi, *Org. Chem. Front.*, 2016, **3**, 1028–1047; (g) M. Shang, S.-Z. Sun, H.-L. Wang, M.-M. Wang and H.-X. Dai, *Synthesis*, 2016, 4381–4399; (h) A. Dey, N. Thrimurtulu and C. M. R. Volla, *Org. Lett.*, 2019, **21**, 3871–3875.
- 9 (a) T. T. Nguyen, L. Grigorjeva and O. Daugulis, *ACS Catal.*, 2016, **6**, 551–554; (b) X. Yao, L. Jin and Y. Rao, *Asian J. Org. Chem.*, 2017, **6**, 825–830.
- 10 (a) M. Shang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 3354–3357; (b) M. Shang, S.-Z. Sun, H.-L. Wang, B. N. Laforteza, H.-X. Dai and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2014, **53**, 10439–10442; (c) M. Shang, H.-L. Wang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2014, **136**, 11590–11593; (d) M. Shang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, *Org. Lett.*, 2014, **16**, 5666–5669; (e) H.-L. Wang, M. Shang, S.-Z. Sun, Z.-L. Zhou, B. N. Laforteza, H.-X. Dai and J.-Q. Yu, *Org. Lett.*, 2015, **17**, 1228–1231; (f) S.-Z. Sun, M. Shang, H.-L. Wang, H.-X. Lin, H.-X. Dai and J.-Q. Yu, *J. Org. Chem.*, 2015, **80**, 8843–8848; (g) M. Shang, M.-M. Wang, T. G. Saint-Denis, M.-H. Li, H.-X. Dai and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 5317–5321; (h) L.-L. Xu, X. Wang, B. Ma, M.-X. Yin, H.-X. Lin, H.-X. Dai and J.-Q. Yu, *Chem. Sci.*, 2018, **9**, 5160–5164; (i) X. Wang, X. Yi, H. Xu and H.-X. Dai, *Org. Lett.*, 2019, **21**, 5981–5985.
- 11 (a) T. Hayashi, M. Fukushima, M. Konishi and M. Kumada, *Tetrahedron Lett.*, 1980, **21**, 79–82; (b) T. Hayashi, M. Konishi, M. Fukushima, K. Kanehira, T. Hioki and M. Kumada, *J. Org. Chem.*, 1983, **48**, 2195–2202; (c) Y. Wang, D. Liu, Q. Meng and W. Zhang, *Tetrahedron: Asymmetry*, 2009, **20**, 2510–2512; (d) A. Lumbroso, N. R. Vautravers and B. Breit, *Org. Lett.*, 2010, **12**, 5498–5501; (e) P. J. Guiry and C. P. Saunders, *Adv. Synth. Catal.*, 2004, **346**, 497–537.
- 12 (a) W.-S. Huang, S. Liu, D. Zou, M. Thomas, Y. Wang, T. Zhou, J. Romero, A. Kohlmann, F. Li, J. Qi, L. Cai, T. A. Dwight, Y. Xu, R. Xu, R. Dodd, A. Toms, L. Parillon, X. Lu, R. Anjum, S. Zhang, F. Wang, J. Keats, S. D. Wardwell, Y. Ning, Q. Xu, L. E. Moran, Q. K. Mohemmad, H. G. Jang, T. Clackson, N. I. Narasimhan, V. M. Rivera, X. Zhu, D. Dalgarno and W. C. Shakespeare, *J. Med. Chem.*, 2016, **59**, 4948–4964; (b) Y. Chen, J. Wu, A. Wang, Z. Qi, T. Jiang, C. Chen, F. Zou, C. Hu, W. Wang, H. Wu, Z. Hu, W. Wang, B. Wang, L. Wang, T. Ren, S. Zhang, Q. Liu and J. Liu, *Eur. J. Med. Chem.*, 2017, **139**, 674–697; (c) J. Jang, J. B. Son, C. To, M. Bahcall, S. Y. Kim, S. Y. Kang, M. Mushajiang, Y. Lee, P. A. Jänne, H. G. Choi and N. S. Gray, *Eur. J. Med. Chem.*, 2017, **136**, 497–510; (d) C. Alonso, M. Fuertes, E. Martín-Encinas, A. Selas, G. Rubiales, C. Tesaro, B. K. Knudssen and F. Palacios, *Eur. J. Med. Chem.*, 2018, **149**, 225–237.
- 13 For selected examples of C–H hydroxylation, see: (a) T. Jintoku, K. Nishimura, K. Takaki and Y. Fujiwara, *Chem. Lett.*, 1990, 1687–1688; (b) Y.-H. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 14654–14655; (c) Y. Yan, P. Feng, Q.-Z. Zheng, Y.-F. Liang, J.-F. Lu, Y. Cui and N. Jiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 5827–5831; (d) Y. Yang, Y. Lin and Y. Rao, *Org. Lett.*, 2012, **14**, 2874–2877; (e) V. S. Thirunavukkarasu, J. Jonathan Hubrich and L. Ackermann, *Org. Lett.*, 2012, **14**, 4210–4213; (f) X. Yang, G. Shan and Y. Rao, *Org. Lett.*, 2013, **15**, 2334–2337; (g) W. Liu and L. Ackermann, *Org. Lett.*, 2013, **15**, 3484–3486; (h) F. Yang, K. Rauch, K. Kettelhoit and L. Ackermann, *Angew. Chem., Int. Ed.*, 2014, **53**, 11285–11288; (i) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790–6791; (j) X. Li, Y.-H. Liu, W.-J. Gu, B. Li, F.-J. Chen and B.-F. Shi, *Org. Lett.*, 2014, **16**, 3904–3907; (k) X.-Y. Chen, S. Ozturk and E. J. Sorensen, *Org. Lett.*, 2017, **19**, 6280–6283.