Organic LETTERS
Letter
pubs.acs.org/OrgLett

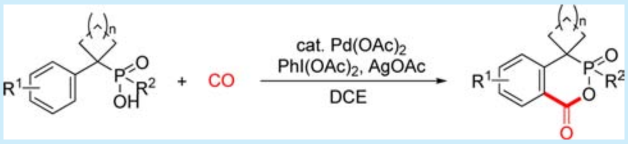
Phosphaannulation by Palladium-Catalyzed Carbonylation of C−H Bonds of Phosphonic and Phosphinic Acids

Seohyun Shin,[†] Yeonseok Jeong,[†] Woo Hyung Jeon, and Phil Ho Lee*

Department of Chemistry, Kangwon National University, Chuncheon 200-701, Republic of Korea

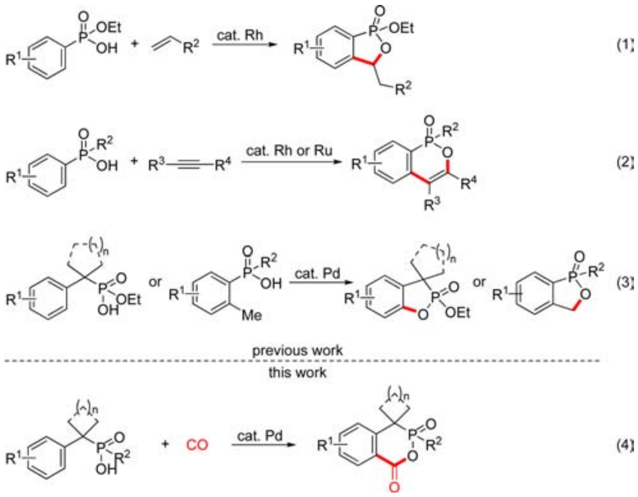
S Supporting Information

ABSTRACT: An efficient phosphaannulation by Pd-catalyzed carbonylation of C−H bonds of phosphonic and phosphinic acids for the synthesis of oxaphosphorinanone oxides is reported. These compounds are novel phosphorus heterocyclic scaffolds, thus opening a new avenue to sequential C−C/C−O bond formation in one pot.



Because inhibition of β-lactamases remains a practical method to maintaining the efficacy of β-lactam antibiotics, the investigation for inhibitors of these enzymes has continued during the past 80 years.[1] Since the cyclic phosphonates have been known to be reversible covalent inhibitors of the P99 β-lactamase, a new synthetic approach to these compounds was required.[2] In this context, we recently developed a wide range of synthetic methods of cyclic phosphonates through phosphoryl group-directed C−H bond activation: Rh-catalyzed oxidative alkenylation/Michael reaction (eq 1),[3] Rh- or Ru-catalyzed C−H activation/cyclization (eq 2),[4] and Pd-catalyzed C−H activation/C−O bond formation (eq 3, Scheme 1).[5]

Scheme 1. Phosphaannulation through Phosphoryl Group-Directed C−H Activation



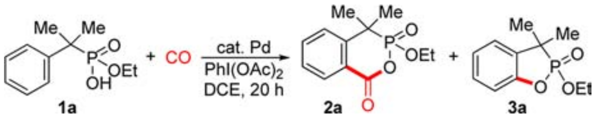
Next, we envisioned that transition-metal-catalyzed carbonylation of phosphonic and phosphinic acids would be a highly desirable synthetic method to access cyclic phosphonates because carbon monoxide is regarded as an economical and atom-efficient C1 feed stock.[6] Although a multitude of transition-metal-catalyzed chelation-assisted carbonylation of C−H bonds were demonstrated for the synthesis of acids, esters, amides, and ketones,[7] there is no synthetic method for C−H bond carbonylation to prepare oxaphosphorinanone oxide,[8] which can be considered as an inhibitor of β-lactamase and a bioisoster of acid anhydride. Therefore, C(sp^2)−H bond activation of phosphonic and phosphinic acids followed by carbonylation has been an irresistible synthetic challenge. In our continuing efforts to develop efficient C−H activation,[9] we report herein an efficient phosphaannulation by Pd-catalyzed carbonylation of C−H bonds of phosphonic and phosphinic acids, producing oxaphosphorinanone oxides, which are novel phosphorus heterocyclic scaffolds (eq 4).

Initially, Pd-catalyzed carbonylation of C−H bonds was examined with ethyl hydrogen dimethylbenzylphosphonate (**1a**) (Table 1). First, we employed the optimum reaction conditions[5] of C(sp^2)−H activation/C−O cyclization to Pd-catalyzed carbonylation of **1a** under CO atmosphere, thus producing delightedly the desired carbonylated product **2a** (63%) together with **3a** (37%) (entry 1). Although electron-deficient palladium catalysts such as Pd(TFA)$_2$ and Pd(OTf)$_2$·2H$_2$O were used, the formation of **3a** was still inevitable (entries 2 and 3). However, when this transformation was conducted at 60 °C, the carbonylated product **2a** was selectively obtained in 66% yield without the contamination of **3a** (entry 4). The present reaction at 40 °C did not complete, but there was the selective formation of **2a** (entry 5). Thus, the carbonylation at 60 °C was employed to conduct a selective formation of **2a**. Gratifyingly, when Pd(OAc)$_2$ loading was lowered from 10 to 5 mol %, the carbonylation still proceeded well and gave the similar yield (67%) of **2a** (entry 6). Increasing the amount (1.5 equiv) of NaOAc failed to improve the yield (entry 7). AgOAc gave the best result among the bases such as NaOAc, LiOAc, KOAc, CsOAc, K$_2$HPO$_4$, Li$_3$PO$_4$, NaHCO$_3$, NaHPO$_4$, and Na$_2$CO$_3$ (see the Supporting Information). The best reaction conditions could be obtained with AgOAc (1.5 equiv) and PhI(OAc)$_2$ (1.5 equiv) in the

Received: April 12, 2014
Published: May 23, 2014

dx.doi.org/10.1021/ol501066k | *Org. Lett.* 2014, 16, 2930−2933

Table 1. Optimization of Carbonylation Reaction[a]

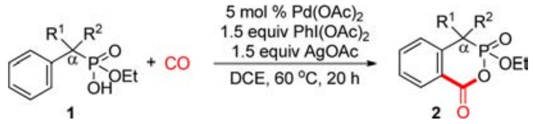


entry	Pd (mol %)	base (equiv)	temp (°C)	yield^b (%)
1	$Pd(OAc)_2$ (10)	NaOAc (1)	80	63 (37)
2	$Pd(TFA)_2$ (10)	NaOAc (1)	80	52 (48)
3	$Pd(OTf)_2 \cdot 2H_2O$ (10)	NaOAc (1)	80	38 (62)
4	$Pd(OAc)_2$ (10)	NaOAc (1)	60	66
5	$Pd(OAc)_2$ (10)	NaOAc (1)	40	18
6	$Pd(OAc)_2$ (5)	NaOAc (1)	60	67
7	$Pd(OAc)_2$ (5)	NaOAc (1.5)	60	61
8	$Pd(OAc)_2$ (5)	AgOAc (1)	60	70
9	**$Pd(OAc)_2$ (5)**	**AgOAc (1.5)**	**60**	**90 (85)**^{c}

[a] Reaction conditions: **1a** (0.2 mmol, 1 equiv), $PhI(OAc)_2$ (1.5 equiv), and DCE (2.0 mL) under CO atmosphere. [b] ^1H NMR yields of **2a** using CH_2Br_2 as an internal standard. Numbers in parentheses indicate ^1H NMR yields of **3a**. [c] Isolated yield of **2a**.

presence of $Pd(OAc)_2$ (5 mol %) and selectively provided **2a** in 90% yield (isolated yield 85%) in DCE at 60 °C for 20 h under CO atmosphere (entry 9).

Table 2. Effect of Substituents at the α-Position on Pd-Catalyzed Carbonylation[a]

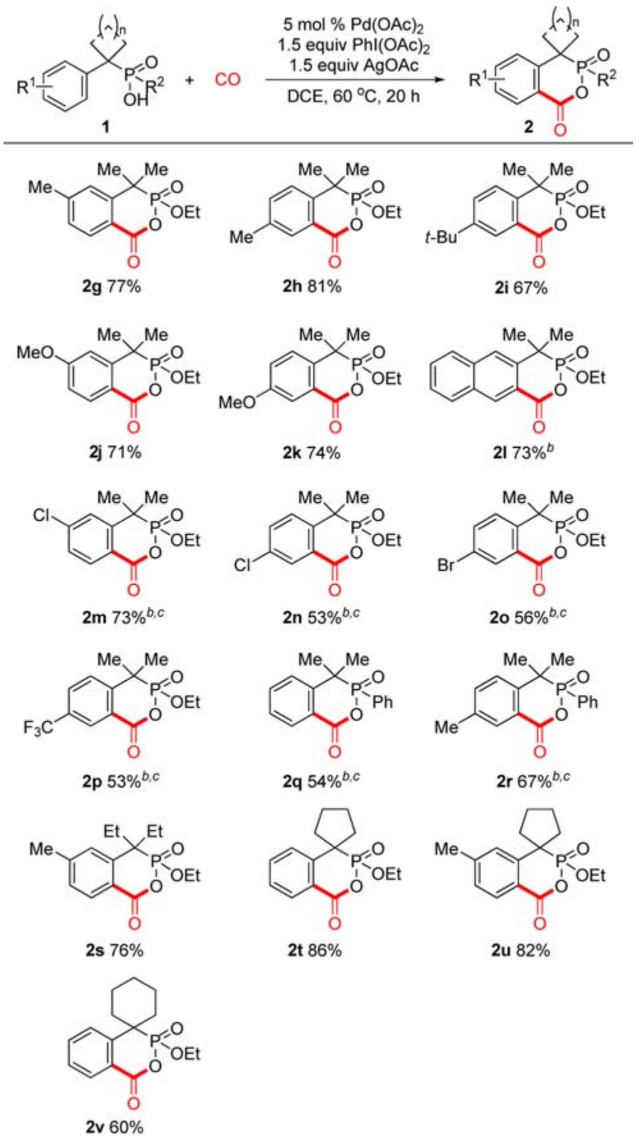


entry	R^1	R^2	1	2	yield^b (%)
1	H	H	**1b**	**2b**	NR
2	H	Me	**1c**	**2c**	NR
3	Me	Me	**1a**	**2a**	85
4	Et	Et	**1d**	**2d**	75
5	*n*-Pr	*n*-Pr	**1e**	**2e**	63
6	Me	Et	**1f**	**2f**	74^c

[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (5 mol %), $PhI(OAc)_2$ (0.3 mmol), and AgOAc (0.3 mmol), 60 °C, 20 h, DCE (2.0 mL) under CO atmosphere. [b] Isolated yield. [c] Diastereomeric ratio = 2.0:1.

Next, the effect of substituents at the α-position in Pd-catalyzed carbonylation was examined (Table 2). Introduction of a variety of substituents at the α-positions of ethyl hydrogen benzylphosphonates **1** obviously influenced the effectiveness of Pd-catalyzed carbonylation. Pd-catalyzed carbonylations of ethyl hydrogen benzylphosphonate **1b** and methyl-substituted phosphonate **1c** were totally ineffective (entries 1 and 2). These results indicate that introduction of two substituents at the α-position is essential for successful carbonylation. However, introduction of more sterically hindered ethyl and propyl groups rather than methyl at the α-position lowered slightly yields of carbonylation and produced **2d** and **2e** in 75% and 63% yields, respectively (entries 4 and 5). These results are evidently in contrast to Pd-catalyzed C(sp^2)−H activation/C−O cyclization,[5] suggesting that ring size affects oppositely the effectivness of cyclization in the carbonylation and C−O bond formation. Ethyl hydrogen benzylphosphonate **1f** having both methyl and ethyl substituents at the α-position afforded the carbonylated product **2f** in 74% (dr = 2.0:1) yield (entry 6).

Scheme 2. Scope of Benzyl Phosphonic and Phosphinic Acids[a]



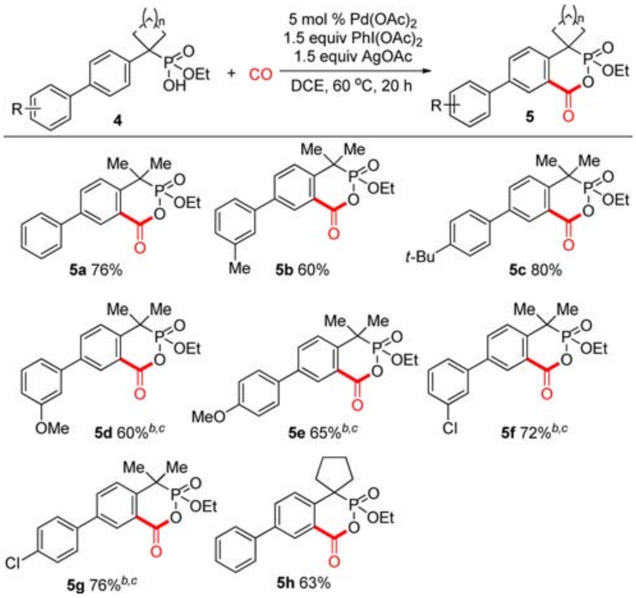
[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), $PhI(OAc)_2$ (0.3 mmol), and AgOAc (0.3 mmol), 60 °C, 20 h, and DCE (2.0 mL) under CO atmosphere. [b] Reaction time 36 h.

To demonstrate the scope of this transformation, a myriad of benzylphosphonic and phosphinic acid derivatives were examined under the optimized reaction conditions (Scheme 2). Benzylphosphonic acid **1g** having a 3-methyl group on the phenyl ring was subjected to Pd-catalyzed carbonylation regioselectively at the sterically less hindered position to provide the desired oxaphosphorinanone oxide **2g** in 77% yield. Benzylphosphonic acids **1h** and **1i** possessing 4-methyl and 4-*tert*-butyl groups on the phenyl ring were smoothly transformed to the desired carbonylated products **2h** and **2i** in 81% and 67% yields, respectively. Substrates **1j** and **1k** having an electron-donating methoxy group were cyclized to oxaphosphorinanone oxides **2j** and **2k** in good yields. 2-Naphthalenyl-substituted phosphonic acid **1l** was also converted to the cyclized product

2l in 73% yield. Phosphonic acids **1m**, **1n**, and **1o** having electron-withdrawing chloro and bromo groups on the phenyl ring underwent Pd-catalyzed carbonylation with $PhI(OAc)_2$ (2 equiv) to deliver the desired products **2m**, **2n**, and **2o** in yields ranging from 53% to 73%. The tolerance of chloro and bromo groups is meaningful because of the possibility of a following catalytic cross-coupling reaction. To our delight, the present carbonylation proceeded despite the presence of a trifluoromethyl group on the phenyl ring and gave **2p** in acceptable yield. Interestingly, when phenyl dimethylbenzylphosphinic acid **1q** was used, the carbonylation reaction proceeded with $PhI(OAc)_2$ (2 equiv) after 36 h, affording oxaphosphorinanone oxide **2q** in 54% yield. Also, phenylphosphinic acid **1r** bearing a 4-methyl group on the phenyl ring was transformed to the desired carbonylated product **2r** in 67% yield. Substrate **1s** having two ethyl groups at the α-position afforded the carbonylated product **2s** in 76% yield. Phosphonic acids **1t**, **1u**, and **1v** having five- and six-membered rings of spiro type at the α-position are also excellent substrates for the C−H carbonylation, producing the desired oxaphosphorinanone oxides in high yields ranging from 60% to 86%.

Next, this transformation was employed to a cascade of phosphonic acids **4** possessing biaryl moieties (Scheme 3). The present carbonylation worked equally well with biaryl phosphonic acid **4a**, resulting in the production of **5a** in 76% yield. For biaryl substrates (**4b** and **4c**) having 3-methyl and 4-*tert*-butyl groups, the corresponding oxaphosphorinanone oxides (**5b** and **5c**) were obtained in 60% and 80% yields, respectively. Biaryl phosphonic acid (**4d** and **4e**) having the strong electron-donating methoxy group turned out to be compatible with the reaction conditions. An electron-withdrawing chloro group was tolerated on the substituted aryl ring, thus allowing an opportunity for further functionalization. We were pleased to obtain **5h** from substrate **4h** possessing a five-membered ring of spiro type at the α-position.

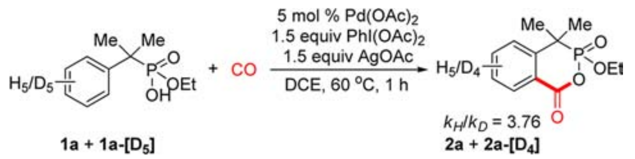
Scheme 3. Scope of Biaryl Phosphonic Acids



[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), $PhI(OAc)_2$ (0.3 mmol), and AgOAc (0.3 mmol), 60 °C, 20 h, DCE (2.0 mL) under CO atmosphere. [b]Reaction time 36 h. [c]$PhI(OAc)_2$ (0.4 mmol) was used.

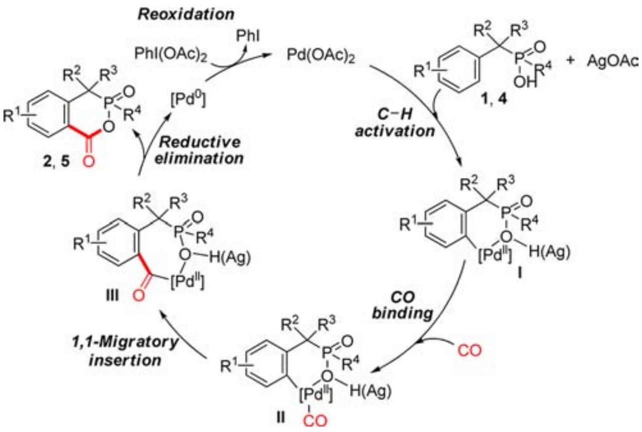
We carried out kinetic isotope effect (KIE) studies to prove the reaction mechanism (Scheme 4). In the case of intermolecular competition reaction using **1a** and **1a**-$[D_5]$, a KIE was detected (k_H/k_D = 3.76). These results indicate that the C−H cleavage at the *ortho*-position of benzylphosphonic acids is most likely involved with the rate-limiting step.

Scheme 4. KIE Experiments with Isotopically Labeled Compounds



A plausible mechanism for this catalytic carbonylation is described in Scheme 5. The proposed catalytic cycle commences by coordination of the OH group in the phosphonic and phosphinic acids **1** and **4** to Pd(II) catalyst to provide palladium(II) phosphonate and phosphinate, respectively. Subsequent *ortho*-metalation to provide palladacycle intermediate **I**, CO binding, 1,1-migratory insertion, and reductive elimination affords the corresponding carbonylated products, oxaphosphorinanone oxides **2** and **5**. However, the possibility of a mechanism of carbonylation via a Pd(II)/Pd(IV) process cannot be ruled out.

Scheme 5. Proposed Mechanism of Carbonylation



In conclusion, we have developed an efficient phosphaannulation by Pd-catalyzed carbonylation of C−H bonds of phosphonic and phosphinic acids, leading to the construction of oxaphosphorinanone oxides, which are novel phosphorus heterocyclic privileged structures. Thus, this transformation opens a new avenue to sequential C−C/C−O bond formation in one pot because carbon monoxide represents an economical and atom-efficient C1 building block.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: phlee@kangwon.ac.kr.

Author Contributions

†These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (2014001403). This paper is dedicated to Professor Sunggak Kim (Nangyang Technological University) on the occasion of his honorable retirement.

REFERENCES

(1) (a) Pratt, R. F. In *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman & Hall: London, 1992; pp 229−271. (b) Pratt, R. F. *Science* **1989**, *246*, 917. (c) Medeiros, A. A. *Clin. Infect. Dis.* **1997**, *24* (Suppl. 1), 519. (d) Miller, L. A.; Ratnam, K.; Payne, D. J. *Curr. Opin. Pharmacol.* **2001**, *1*, 451.

(2) (a) Kaur, K.; Lan, M. J. K.; Pratt, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 10436. (b) Kaur, K.; Adediran, S. A.; Lan, M. J. K.; Pratt, R. F. *Biochemistry* **2003**, *42*, 1529. (c) Silvaggi, N. R.; Kaur, K.; Adediran, S. A.; Pratt, R. F.; Kelly, J. A. *Biochemistry* **2004**, *43*, 7046.

(3) Ryu, T.; Kim, J.; Park, Y.; Kim, S.; Lee, P. H. *Org. Lett.* **2013**, *15*, 3986.

(4) (a) Seo, J.; Park, Y.; Jeon, I.; Ryu, T.; Park, S.; Lee, P. H. *Org. Lett.* **2013**, *15*, 3358. (b) Park, Y.; Seo, J.; Park, S.; Yoo, E. J.; Lee, P. H. *Chem.—Eur. J.* **2013**, *19*, 16461. (c) Park, Y.; Jeon, I.; Shin, S.; Min, J.; Lee, P. H. *J. Org. Chem.* **2013**, *78*, 10209.

(5) Eom, D.; Jeong, Y.; Kim, Y. R.; Lee, E.; Choi, W.; Lee, P. H. *Org. Lett.* **2013**, *15*, 5210.

(6) (a) Schoenberg, A.; Bartoleti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327. (c) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (d) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (e) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686. (f) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 5326. (g) Lu, Y.; Leow, D.; Wang, X.; Engle, K. M.; Yu, J.-Q. *Chem. Sci.* **2011**, *2*, 967. (h) Haffemayer, B.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312.

(7) (a) Chatani, N.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 493. (b) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522. (c) Chatani, N.; Yorimitsu, S.; Asaumi, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7557. (d) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (e) Asaumi, T.; Matsuo, T.; Fukuyama, T.; Ie, Y.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 4433. (f) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830. (g) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898. (h) Guan, Z.-H.; Ren, Z.-H.; Spinella, S. M.; Yu, S.; Liang, Y.-M.; Zhang, X. *J. Am. Chem. Soc.* **2009**, *131*, 729. (i) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7316. (j) Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312. (k) Lang, R.; Wu, J.; Shi, L.; Xia, C.; Li, F. *Chem. Commun.* **2011**, *47*, 12553. (l) López, B.; Rodriguez, A.; Santos, D.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J. *Chem. Commun.* **2011**, *47*, 1054. (m) Du, Y.; Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 12074. (n) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070. (o) Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 5326. (p) Zhang, H.; Liu, D.; Chen, C.; Liu, C.; Lei, A. *Chem.—Eur. J.* **2011**, *17*, 9581. (q) Chen, H.; Cai, C.; Liu, X.; Li, X.; Jiang, H. *Chem. Commun.* **2011**, *47*, 12224. (r) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902. (s) Guan, Z.-H.; Chen, M.; Ren, Z.-H. *J. Am. Chem. Soc.* **2012**, *134*, 17490. (t) Lang, R.; Shi, L.; Li, D.; Xia, C.; Li, F. *Org. Lett.* **2012**, *14*, 4130. (u) Zhang, H.; Shi, R.; Gan, P.; Liu, C.; Ding, A.; Wang, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5204.

(8) Miles, J. A.; Street, R. W. *J. Org. Chem.* **1978**, *43*, 4668.

(9) (a) Chary, B. C.; Kim, S.; Park, Y.; Kim, J.; Lee, P. H. *Org. Lett.* **2013**, *15*, 2692. (b) Chan, L. Y.; Kim, S.; Ryu, T.; Lee, P. H. *Chem. Commun.* **2013**, *49*, 4682. (c) Park, S.; Seo, B.; Shin, S.; Son, J.-Y.; Lee, P. H. *Chem. Commun.* **2013**, *49*, 8671. (d) Mo, J.; Lim, S.; Ryu, T.; Kim, S.; Lee, P. H. *RSC Adv.* **2013**, *3*, 18296. (e) Kang, D.; Cho, J.; Lee, P. H. *Chem. Commun.* **2013**, *49*, 10501. (f) Kim, J.; Kang, D.; Yoo, E. J.; Lee, P. H. *Eur. J. Org. Chem.* **2013**, 7902. (g) Ryu, T.; Min, J.; Choi, W.; Jeon, W. H.; Lee, P. H. *Org. Lett.* **2014**, DOI: 10.1021/ol501250t. (h) Kim, Y.; Cho, S.; Lee, P. H. *Org. Lett.* **2014**, DOI: 10.1021/ol501207w. (i) Shin, S.; Kang, D.; Jeon, W. H.; Lee, P. H. *Beilstein J. Org. Chem.* **2014**, *10*, in press.