

Catalytic Direct C2-Alkenylation of Oxazoles at Parts per Million Levels of Palladium/PhMezole-Phos Complex

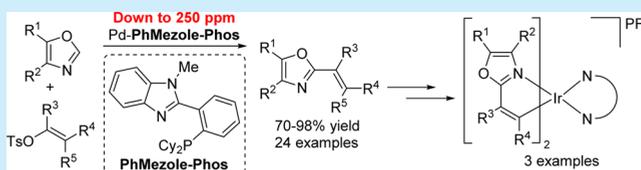
Wai Chung Fu,^{†,§} Yong Wu,^{‡,§} Chau Ming So,[†] Shun Man Wong,[†] Aiwen Lei,^{*,‡} and Fuk Yee Kwong^{*,†}

[†]State Key Laboratory of Chirosciences and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon 852, Hong Kong

[‡]College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, Hubei, P.R. China

S Supporting Information

ABSTRACT: General direct C2-alkenylation of oxazoles is reported using alkenyl tosylates at parts per million levels of palladium catalyst. From a series of ligands screened, PhMezole-Phos emerged as the promising ligand candidate to facilitate this reaction. Significantly, the method is scalable and exhibits excellent substrate tolerance. Highly sterically hindered substrates and small vinyl tosylate can be coupled successfully. Moreover, our method enables a rapid diversification of oxazole-based C^N ligands which can be readily derived into new group 9 organometallic compounds.

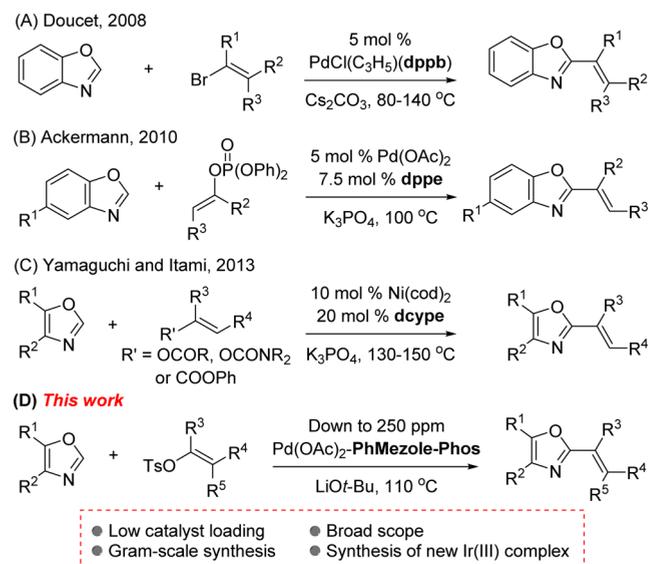


of oxazole-based C^N ligands which can be readily derived

C2-Alkenylated oxazole and benzoxazole derivatives are essential motifs in pharmaceuticals and medicinal chemistry, while alkenylazoles play important roles in the construction of organic materials.¹ However, traditional organic syntheses leading to these compounds often require harsh reaction conditions and prefunctionalization of reagents.² On the other hand, emerging transition-metal-catalyzed reactions allow the rapid and concise functionalization of heterocyclic C–H bonds and synthesis of heteroarenes.³ The research for metal-catalyzed direct functionalization of azoles has been intensive, and notably, direct C2-alkenylations with alkenyl electrophiles have received significant attention.⁴ Other catalytic approaches include cross-dehydrogenative coupling⁵ (C–H/C–H coupling) and addition of alkynes to transition-metal complexes to form heteroarenes.⁶

In view of the C–X/C–H direct alkenylation of benzoxazoles, the first method employing alkenyl bromides was pioneered by Doucet and co-workers using a PdCl(C₃H₅)-(dppb) catalyst (Scheme 1A).^{4a} Later, the group of Piguel reported copper^{4b} and palladium catalysts,^{4c} respectively, for the alkenylation of oxazoles, and a few isolated examples of Pd catalysts also showed fair efficacy in these reactions.^{4d,e} In addition to alkenyl halides, ketone derivatives were demonstrated as applicable electrophilic coupling partners by Ackermann (Scheme 1B).^{4f} Very recently, the work of Yamaguchi and Itami detailed a nickel catalyst for the alkenylation of oxazoles with enols and esters (Scheme 1C).^{4g} The aforementioned methods often employed high catalyst loadings (5–10 mol %), and the scope might be impaired by the unavailability of particular substrates. Although nickel sources are economically attractive, the cost of ancillary ligands and efforts in removal of high loading of nickel salt after the reaction may offset this factor. As part of our laboratory's interest in developing cross-coupling of alkenyl electrophiles⁷

Scheme 1. Direct C2-Alkenylation of (Benz)oxazoles^{4a}



^adppb = 1,4-bis(diphenylphosphino)butane, dppe = 1,2-bis(diphenylphosphino)ethane, dcype = 1,2-bis(dicyclohexylphosphino)ethane.

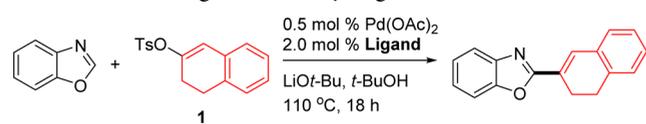
and direct functionalization of C–H bonds,⁸ we decided to address these difficulties. Herein we report the first general, direct C2-alkenylation of (benz)oxazoles using alkenyl tosylates with ample reaction scope and substrate compatibility. Remarkably, the catalyst loading can reach up to 250 ppm (0.025 mol %). We also demonstrated the scalability and

Received: September 1, 2016

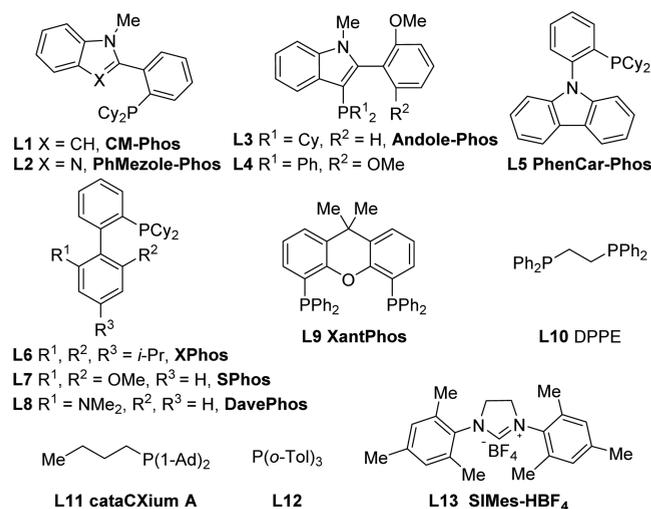
further practicality of our method by utilizing the newly synthesized alkenyloxazoles in the preparation of new group 9 organometallic compounds.

Alkenyl halides are not generally available. However, the pseudohalide complements, alkenyl tosylates, can be readily prepared from easily available ketones with diverse substitution patterns that are not accessible within their halide counterparts. In addition to the advantages of substitution pattern and availability, their cost-effectiveness and higher stability are desirable from a synthetic perspective.⁹ Nonetheless, the oxidative addition of alkenyl tosylates to Pd(0) is more demanding than those of alkenyl halides. We anticipated that the main challenge was the identification of a suitable ancillary ligand for overcoming this energy barrier. To address this, we investigated the catalytic efficacy of a library of electronically and sterically diverse ligands using a model reaction between benzoxazole and **1** (Table 1). Commercially available ligands as

Table 1. Screening of Ancillary Ligands^a



entry	L	% yield	entry	L	% yield
1	L1	79	8	L8	74
2	L2	99, 94 ^b	9	L9	31
3	L3	91	10	L10	42
4	L4	86	11	L11	92
5	L5	86	12	L12	56
6	L6	65	13	L13	73
7	L7	73			



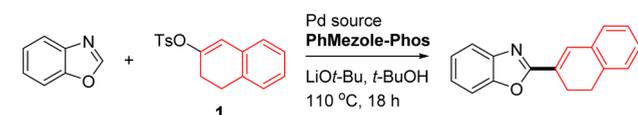
^aReaction conditions: **1** (0.3 mmol), LiO-*t*-Bu (0.6 mmol), benzoxazole (0.45 mmol), *t*-BuOH (0.3 M), Pd(OAc)₂/ligand under nitrogen at 110 °C for 18 h under N₂; calibrated GC-FID yields are reported. ^bPd(OAc)₂ loading = 500 ppm.

well as customized ligands¹⁰ used in our previous works were screened. In general, we found that monodentate phosphines were superior to bidentate phosphines (Table 1, entries 1–8, 11 vs 9–10), while PhMezole-Phos¹¹ (L2) was outstanding in this survey. Triarylphosphine L12 was inferior to the aforementioned electron-rich and bulky ligands (Table 1, entry 12). *N*-Heterocyclic carbenes ligand such as L13

promoted the reaction but gave a lower product yield (Table 1, entry 13).

Encouraged by the initial ligand screening results, we next studied other reaction parameters (Table 2). We found that

Table 2. Reaction Condition Optimization^a

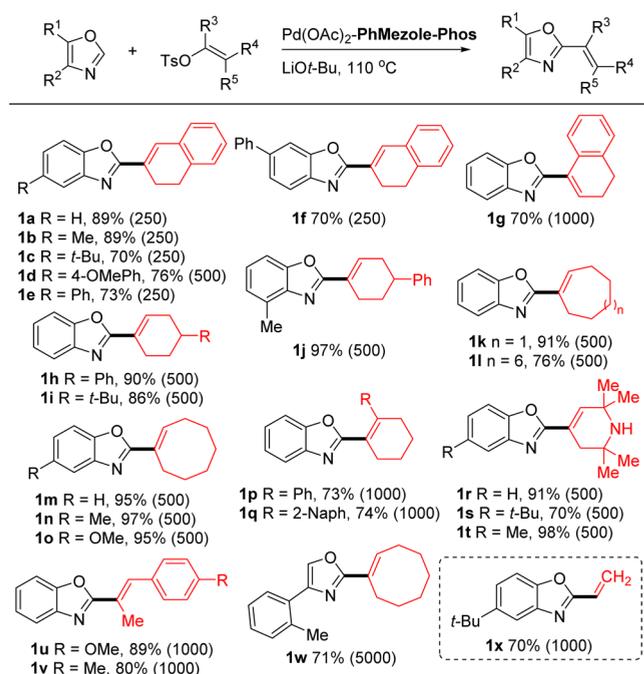


entry	base	Pd source	ppm ^b	solvent	% yield
1	LiO- <i>t</i> -Bu	Pd(OAc) ₂	500	<i>t</i> -BuOH	94
2	NaO- <i>t</i> -Bu	Pd(OAc) ₂	500	<i>t</i> -BuOH	17
3	KO- <i>t</i> -Bu	Pd(OAc) ₂	500	<i>t</i> -BuOH	trace
4	Li ₂ CO ₃	Pd(OAc) ₂	500	<i>t</i> -BuOH	0
5	LiOH	Pd(OAc) ₂	500	<i>t</i> -BuOH	0
6	LiO- <i>t</i> -Bu	Pd(OAc) ₂	500	toluene	74
7	LiO- <i>t</i> -Bu	Pd(OAc) ₂	500	dioxane	75
8	LiO- <i>t</i> -Bu	Pd(OAc) ₂	500	THF	71
9	LiO- <i>t</i> -Bu	Pd(OAc) ₂	500	DMA	trace
10	LiO- <i>t</i> -Bu	Pd(OAc) ₂	100	<i>t</i> -BuOH	66
11	LiO- <i>t</i> -Bu	Pd(TFA) ₂	100	<i>t</i> -BuOH	41
12	LiO- <i>t</i> -Bu	PdCl ₂ (ACN) ₂	100	<i>t</i> -BuOH	57
13	LiO- <i>t</i> -Bu	Pd ₂ (dba) ₃	100	<i>t</i> -BuOH	30
14	LiO- <i>t</i> -Bu	Pd(dba) ₂	100	<i>t</i> -BuOH	54
15	LiO- <i>t</i> -Bu	Pd(OAc) ₂	100	<i>t</i> -BuOH	55 ^c
16	LiO- <i>t</i> -Bu	Pd(OAc) ₂	100	<i>t</i> -BuOH	60 ^d

^aReaction conditions: **1** (0.3 mmol), base (0.6 mmol), benzoxazole (0.45 mmol), solvent (0.3 M), Pd source (500 ppm), Pd/PhMezole-Phos = 1:4, under nitrogen at 110 °C for 18 h under N₂, calibrated GC-FID yields were reported. ^bLoading of the Pd monomer with respect to **1**. ^cPd/PhMezole-Phos = 1:3. ^dPd/PhMezole-Phos = 1:2.

only LiO-*t*-Bu was able to promote the reaction, while lithium hydroxide and lithium carbonate were inapplicable (Table 2, entries 1 vs 2–5). Toluene and etheral solvents reduced the yield to 71–75%, and DMA gave no product yields (Table 2, entries 1 vs 6–9). The less expensive Pd(OAc)₂ was shown to be the optimal palladium catalyst among the other Pd(II) and Pd(0) sources surveyed (Table 2, entries 10 vs 11–14). Another crucial reaction parameter was the metal-to-ligand ratio, and 1:4 was found to be the best, as a lower ligand ratio led to a drop in product yields (Table 2, entries 10 vs 15–16).

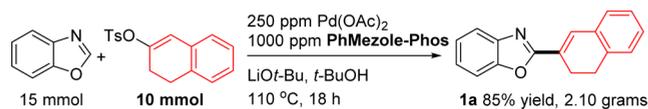
Having confirmed the optimal reaction conditions, we next examined the substrate scope of our catalyst system (Scheme 2). We first evaluated a series of fundamentally different alkenyl tosylates in terms of conjugation, electron-richness, and steric profile. Tetralone- (Scheme 2, 1a–g) and cycloalkanone-derived enol tosylates (Scheme 2, 1h–o) were successfully converted to the corresponding products in good-to-excellent yields, whereas alkyl rings as large as 12 carbons (Scheme 2, 1l) were also applicable. The reaction with highly congested *o*-aryl-substituted enol tosylates gave the desired product in 73 and 74% yields (Scheme 2, 1p,q). Substrates featuring an unprotected N–H site were tolerated and afforded up to 98% yield (Scheme 2, 1r–t). Arylacetone-derived substrates also reacted under these reaction conditions and gave **1u** and **1v** in 89% and 80% product yield, respectively. It is particularly noteworthy that the coupling product **1x** with unprecedented vinyl tosylate was successfully obtained, while other catalytic approaches such as CDC (cross-dehydrogenative coupling) sometimes required the use of ethylene gas. For the scope of

Scheme 2. Pd/PhMezole-Phos-Catalyzed Direct C2-Alkenylation of (Benz)oxazoles^a

^aReaction conditions: Alkenyl tosylate (0.3 mmol), LiOt-Bu (0.6 mmol), oxazoles (0.45 mmol), *t*-BuOH (0.3 M), $\text{Pd}(\text{OAc})_2$ /PhMezole-Phos = 1:4 under nitrogen at $110\text{ }^\circ\text{C}$ for 18 h under N_2 , isolated yields were reported. Catalyst loading is reported in parentheses as ppm of Pd with respect to alkenyl tosylate. Reaction times were not optimized for each substrate.

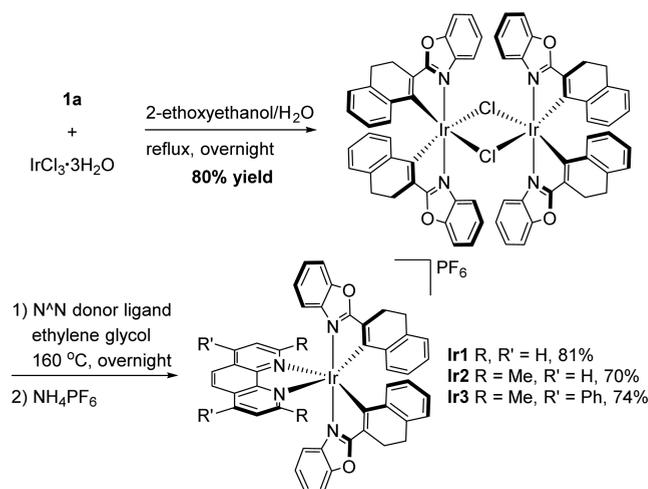
oxazoles, 4-, 5-, or 6-substituted benzoxazoles as well as oxazole derivative (Scheme 2, 1w) were found to be suitable in this catalysis. To realize the synthetic utility of our method, we carried out the gram-scale synthesis of 1a without any alternation of reaction conditions, and 2.1 g of product was successfully afforded (85% yield, Scheme 3).

Scheme 3. Gram-Scale Synthesis of 1a



In light of the remarkable catalytic efficiency of our system, we envisioned our method could be employed for the rapid and efficient assembly of potential C[^]N donor ligands for cyclometalated group 9 organometallic complexes. Group 9 organometallic compounds such as Ir(III) and Rh(III) complexes have been well-documented to be utilized as molecular therapeutics, cell-imaging agents, optoelectronics, and luminescent molecular probes for biomolecules or metal ions due to their highly environmentally sensitive emissive behavior.¹² Here, we prepared a new class of Ir(III) complexes using 1a (Scheme 4). On the basis of reported synthetic procedures,¹³ 1a was successfully coupled with iridium(III) chloride and afforded the dichlorobridged iridium dimer complex. The dimer was subsequently treated with a series of N[^]N donor ligands to afford the corresponding mononuclear Ir(III) complexes in good yields (Scheme 4, Ir1–Ir3). We anticipated that the adjustable alkyl extension of the alkenyl

Scheme 4. Application to the Synthesis of Cyclometalated Ir(III) Complexes Using 1a



motifs would provide a more flexible fit to certain protein binding pockets in comparison with the existing planar aromatic C[^]N ligands used.

In conclusion, we have demonstrated the first example of high-yielding and scalable direct C2-alkenylation of oxazoles using alkenyl tosylates with only parts per million levels of palladium catalyst. Our method enables a facile access to a wide range of substitution patterns via alkenyl tosylates that can be easily derived from readily available ketones. Highly sterically hindered *ortho*-substituted alkenyl tosylates and small vinyl tosylate were successfully coupled. We envisioned that the use of Pd catalyst at parts per million levels minimizes the residual Pd in products, which is highly important for pharmaceutical syntheses. New cyclometalated Ir(III) complexes were synthesized employing the C2-alkenyl oxazoles to demonstrate the applicability of our method. We believe our method could allow the rapid diversification of group 9 organometallic compounds for high-throughput screening techniques. Future efforts will be focused on the extension of reaction scope to other azole compounds.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02619.

Detailed experimental procedures for catalytic studies and metal complexes syntheses; ¹H, ¹³C spectra; characterization data of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: aiwenlei@whu.edu.cn.

*E-mail: fuk-yee.kwong@polyu.edu.hk.

Author Contributions

§W.C.F. and Y.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Research Grants Council of Hong Kong (CRF: C5023-14G), General Research Fund (PolyU 153034/15P), and State Key Laboratory of Chirosciences for financial support.

REFERENCES

- (1) (a) Siddiqui, M. A.; Mansoor, U. F.; Reddy, P. A.; Madison, V. S. Compounds for the treatment of inflammatory disorders and microbial diseases. WO Patent 2007064732 A1, Jun 7, 2007. (b) Kuroyanagi, J.-i.; Kanai, K.; Sugimoto, Y.; Horiuchi, T.; Achiwa, I.; Takeshita, H.; Kawakami, K. *Bioorg. Med. Chem.* **2010**, *18*, 7593. (c) Fuwa, H.; Noguchi, T.; Kawakami, M.; Sasaki, M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2415. (d) Ge, J.; Normant, E.; Porter, J. R.; Ali, J. A.; Dembski, M. S.; Gao, Y.; Georges, A. T.; Grenier, L.; Pak, R. H.; Patterson, J.; Sydor, J. R.; Tibbitts, T. T.; Tong, J. K.; Adams, J.; Palombella, V. J. *J. Med. Chem.* **2006**, *49*, 4606. (e) Matsumura, K.; Ono, M.; Kitada, A.; Watanabe, H.; Yoshimura, M.; Iikuni, S.; Kimura, H.; Okamoto, Y.; Ihara, M.; Saji, H. *J. Med. Chem.* **2015**, *58*, 7241. (f) Kovalska, V. B.; Kryvorotenko, D. V.; Balanda, A. O.; Losytskyy, M. Y.; Tokar, V. P.; Yarmoluk, S. M. *Dyes Pigment.* **2005**, *67*, 47. (g) Xue, P.; Yao, B.; Sun, J.; Zhang, Z.; Li, K.; Liu, B.; Lu, R. *Dyes Pigment.* **2015**, *112*, 255. (h) Zhang, G.; Wu, F.-I.; Jiang, X.; Sun, P.; Cheng, C.-H. *Synth. Met.* **2010**, *160*, 1906. (i) Mahuteau-Betzer, F.; Piguel, S. *Tetrahedron Lett.* **2013**, *54*, 3188.
- (2) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389.
- (3) (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (d) Yamamoto, Y. *Chem. Soc. Rev.* **2014**, *43*, 1575. (e) Yuan, K.; Soulé, J.-F.; Doucet, H. *ACS Catal.* **2015**, *5*, 978. (f) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610. (g) Yamada, S.; Murakami, K.; Itami, K. *Org. Lett.* **2016**, *18*, 2415. (h) Gao, F.; Kim, B.-S.; Walsh, P. J. *Chem. Commun.* **2014**, *50*, 10661.
- (4) (a) Gottumukkala, A. L.; Derridj, F.; Djebbar, S.; Doucet, H. *Tetrahedron Lett.* **2008**, *49*, 2926. (b) Besselièvre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. S. *Org. Lett.* **2008**, *10*, 4029. (c) Besselièvre, F.; Lebrequier, S.; Mahuteau-Betzer, F.; Piguel, S. *Synthesis* **2009**, 2009, 3511. (d) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 2010, 6097. (e) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. (f) Ackermann, L.; Barfüsser, S.; Pospech, J. *Org. Lett.* **2010**, *12*, 724. (g) Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048. (h) Vabre, R.; Chevot, F.; Legraverend, M.; Piguel, S. *J. Org. Chem.* **2011**, *76*, 9542. (i) Muto, K.; Hatakeyama, T.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2015**, *6*, 6792.
- (5) For selected recent examples, see: (a) Lee, W.-C.; Wang, T.-H.; Ong, T.-G. *Chem. Commun.* **2014**, *50*, 3671. (b) Miyasaka, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 5421. (c) Liu, W.; Yu, X.; Kuang, C. *Org. Lett.* **2014**, *16*, 1798.
- (6) For selected recent examples, see: (a) Ding, Z.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4698. (b) Suarez, L. L.; Greaney, M. F. *Chem. Commun.* **2011**, *47*, 7992. (c) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146. (d) Ding, Z.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180. (e) Huang, J.-R.; Zhang, Q.-R.; Qu, C.-H.; Sun, X.-H.; Dong, L.; Chen, Y.-C. *Org. Lett.* **2013**, *15*, 1878.
- (7) Wong, P. Y.; Chow, W. K.; Chung, K. H.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem. Commun.* **2011**, *47*, 8328.
- (8) (a) Yuen, O. Y.; Charoensak, M.; So, C. M.; Kuhakarn, C.; Kwong, F. Y. *Chem. - Asian J.* **2015**, *10*, 857. (b) Choy, P. Y.; Luk, K. C.; Wu, Y.; So, C. M.; Wang, L.-L.; Kwong, F. Y. *J. Org. Chem.* **2015**, *80*, 1457. (c) Yang, Q.; Choy, P. Y.; Fu, W. C.; Fan, B.; Kwong, F. Y. *J. Org. Chem.* **2015**, *80*, 11193. (d) Yang, Q.; Choy, P. Y.; Wu, Y.; Fan, B.; Kwong, F. Y. *Org. Biomol. Chem.* **2016**, *14*, 2608. (e) Fu, W. C.; So, C. M.; Chow, W. K.; Yuen, O. Y.; Kwong, F. Y. *Org. Lett.* **2015**, *17*, 4612. (f) Fu, W. C.; So, C. M.; Yuen, O. Y.; Lee, I. T. C.; Kwong, F. Y. *Org. Lett.* **2016**, *18*, 1872. (g) Fu, W. C.; Zhou, Z.; Kwong, F. Y. *Organometallics* **2016**, *35*, 1553.
- (9) For recent reviews, see: (a) Kozhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. *Catal. Sci. Technol.* **2013**, *3*, 562. (b) So, C. M.; Kwong, F. Y. *Chem. Soc. Rev.* **2011**, *40*, 4963. (c) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486. (d) Tobisu, M.; Chatani, N. *Top. Curr. Chem.* **2016**, *374*, 41.
- (10) For a review on the development of indolylphosphine ligands by our group, see: (a) Wong, S. M.; Yuen, O. Y.; Choy, P. Y.; Kwong, F. Y. *Coord. Chem. Rev.* **2015**, 293–294, 158. For our development of PhMezole-Phos, see: (b) Chung, K. H.; So, C. M.; Wong, S. M.; Luk, C. H.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Chem. Commun.* **2012**, *48*, 1967. (c) Wong, S. M.; So, C. M.; Chung, K. H.; Lau, C. P.; Kwong, F. Y. *Eur. J. Org. Chem.* **2012**, 2012, 4172. (d) Chung, K. H.; So, C. M.; Wong, S. M.; Luk, C. H.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Synlett* **2012**, 23, 1181. (e) Wong, S. M.; So, C. M.; Chung, K. H.; Luk, C. H.; Lau, C. P.; Kwong, F. Y. *Tetrahedron Lett.* **2012**, *53*, 3754. For the use of Andole-Phos on Pd-catalyzed reactions, see: (f) Yuen, O. Y.; So, C. M.; Man, H. W.; Kwong, F. Y. *Chem. - Eur. J.* **2016**, *22*, 6471. (g) Chow, W. K.; Yuen, O. Y.; So, C. M.; Wong, W. T.; Kwong, F. Y. *J. Org. Chem.* **2012**, *77*, 3543. For our recent developments on PhenCar-Phos, see: ref 8g. (h) Chun To, S. C.; Yee Kwong, F. Y. *Chem. Commun.* **2011**, *47*, 5079. (i) Fu, W. C.; Zhou, Z.; Kwong, F. Y. *Org. Chem. Front.* **2016**, *3*, 273. For other relevant ligands, see: (j) Chen, G.; Lam, W. H.; Fok, W. S.; Lee, H. W.; Kwong, F. Y. *Chem. - Asian J.* **2007**, *2*, 306. (k) Kwong, F. Y.; Chan, K. S. *Chem. Commun.* **2000**, 1069. (l) Kwong, F. Y.; Chan, K. S. *Organometallics* **2001**, *20*, 2570.
- (11) For pioneering works of our group on the PhMezole-Phos ligand motif, see ref 10b–e. It was later independently reported by the group of Goossen; see: Song, B.; Knauber, T.; Goossen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2954.
- (12) (a) Ma, D.-L.; Chan, D. S.-H.; Leung, C.-H. *Acc. Chem. Res.* **2014**, *47*, 3614. (b) Ying, L.; Ho, C.-L.; Wu, H.; Cao, Y.; Wong, W.-Y. *Adv. Mater.* **2014**, *26*, 2459. (c) Ma, D.-L.; He, H.-Z.; Leung, K.-H.; Chan, D. S.-H.; Leung, C.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7666. (d) Ma, D.-L.; Zhong, H.-J.; Fu, W.-C.; Chan, D. S.-H.; Kwan, H.-Y.; Fong, W.-F.; Chung, L.-H.; Wong, C.-Y.; Leung, C.-H. *PLoS One* **2013**, *8*, e55751.
- (13) Zhang, K. Y.; Li, S. P.-Y.; Zhu, N.; Or, I. W.-S.; Cheung, M. S.-H.; Lam, Y.-W.; Lo, K. K.-W. *Inorg. Chem.* **2010**, *49*, 2530.