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Exploiting Aryl Mesylates and Tosylates in Catalytic Mono-α-arylation of Aryl- and Heteroarylketones

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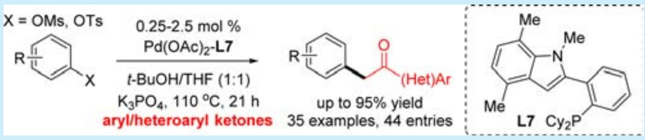
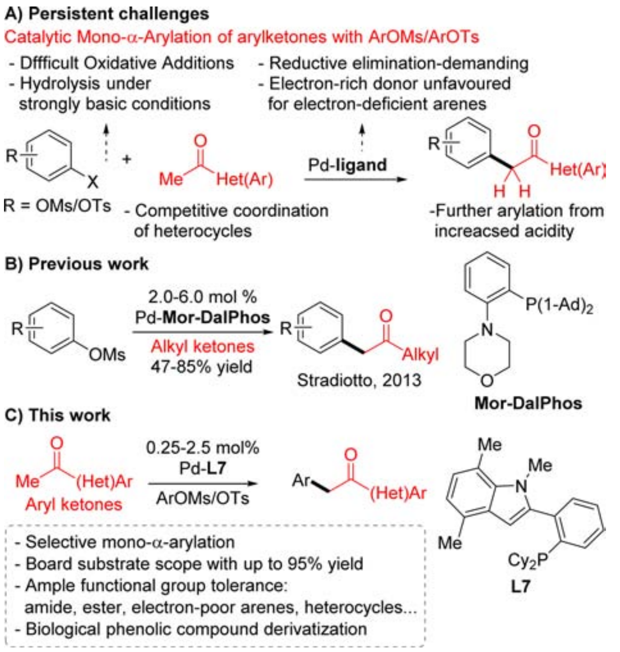
S *Supporting Information*

ABSTRACT: The first general palladium catalyst for the catalytic mono-α-arylation of aryl- and heteroarylketones with aryl mesylates and tosylates is described. The newly developed indolyl-derived phosphine ligand **L7** has been identified to promote this reaction efficiently. The key to success is attributed to the enhanced steric congestion of the catalyst and effective oxidative addition of the $C_{(Ar)}$−OMs bond. In the presence of $Pd(OAc)_2$ (0.25−2.5 mol %) and **L7**, selective monoarylations are achieved with ample reaction scope and product yields up to 95%. Importantly, we demonstrated the applicability of this protocol with the modification of biological phenolic compounds, rendering it amenable for functionalization of phenolic (pro)drugs.



Palladium-catalyzed α-arylation of carbonyl compounds has been well documented as versatile approaches to construct $C(sp^3)-C(sp^2)$ bonds.[1] These approaches opened up new possibilities to access key structures present in numerous pharmaceutical intermediates and natural products.[2] Since the pioneering works by Buchwald,[3] Hartwig,[4] and Miura[5] on the direct α-arylation of ketones, tremendous advancements in this field have been made.[6] However, several challenges persist in this catalysis (Scheme 1). For instance, selective mono-α-arylation of ketone is, in general, recognized to be difficult due to the increased acidity of the remaining α-C−H bonds after the first arylation process, rendering facile formation of ketone enloates and giving undesirable α,α-diarylated products. Moreover, the reductive elimination process is sensitive to the catalyst characteristics in terms of electron richness and steric bulkiness; minor adjustments between these two factors will lead to a completely different outcome.[7]

Scheme 1. Palladium-Catalyzed Mono-α-arylations



Despite the fact that aryl halides were commonly employed as electophiles in the α-arylation of ketones due to its facile oxidative addition by palladium and copper catalysts, halogenated compounds are not common in view of medicinal chemistry. The halogenation of specific sites in natural products or pharmacophores would be undesirable due to lengthy synthetic pathways and functional group manipulations. However, biologically active compounds with phenolic moieties are common and a general while effective method for direct functionalization of these sites would be highly desirable. In this regard, aryl sulfonates such as aryl mesylate and tosylate are indeed more attractive alternatives owing to their cost-effectiveness over other sulfonating agents,[8] as well as their high stability and environmental friendliness.[9] There is room for development of a general and active catalyst system for accessing these attractive aryl sulfonates, which are useful complements to aryl halides. However, the highly demanding oxidative addition by a palladium species accompanied by the inherent chemical stability of these aryl sulfonates is still problematic, and a suitable ligand candidate is needed to tackle these concerns. Thus, a very limited number of phosphine ligands were known to promote such difficult oxidative additions, including BrettPhos,[10] Mor-dalPhos,[11] CM-Phos,[12] and a few others.[13] Unfortunately, the

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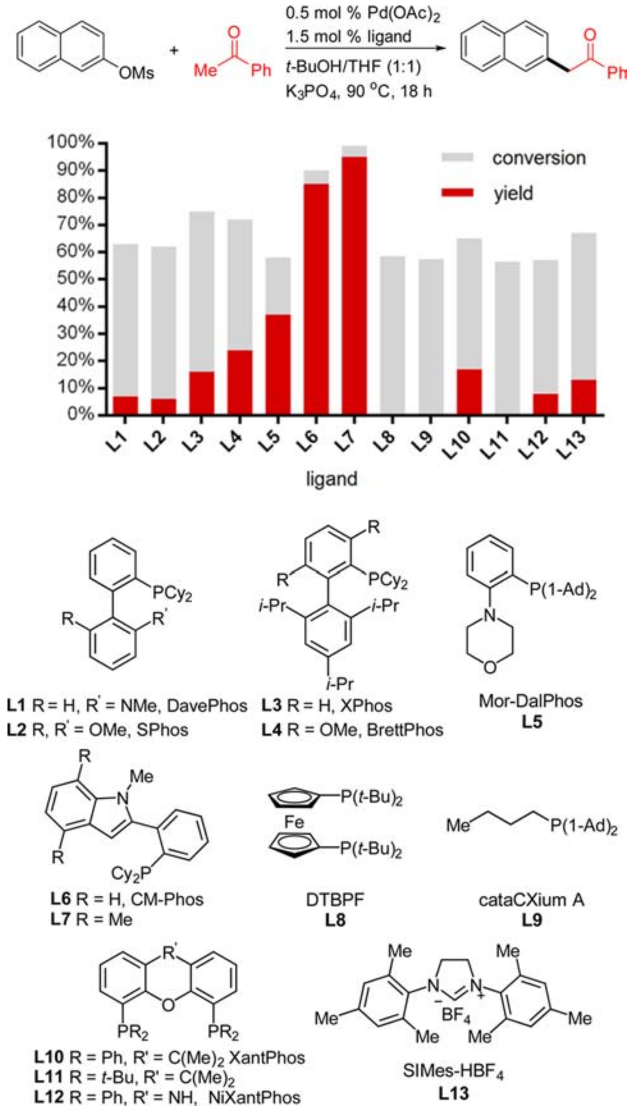
high electron-richness embedded with these ligands may result in the inefficacy against electron-deficient arene substrates in ketone arylation reactions, as reported in literatures.[14,15] In terms of aryl mesylates specifically, only one report by Stradiotto and co-workers detailed the α-arylation of strictly alkylketones with aryl mesylates using a $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst.[6w] Taking the aforementioned points into account, the identification of a general palladium catalyst system for the monoarylation of arylketones with aryl mesylates is deemed a challenge. Herein, we describe the first general palladium catalyst for mono-α-arylation of arylmethylketones with aryl mesylates and tosylates. Under mildly basic conditions, excellent functional group tolerance was achieved with a modest catalyst loading (0.25−2.5 mol %) and no diarylated products were detected.

During the initial investigations, we surveyed an array of state-of-the-art ligand candidates which are effective in aryl sulfonate cross-couplings or ketone arylations (Scheme 2). Preliminary screening employing Buchwald's biaryl[10,13a,b] or Stradiotto's *P,N*-type phosphine ligands[11] resulted in modest product yields (6−37% yield), but they demonstrated the importance of the steric bulkiness of ligands with an increasing trend of yields (from **L1** to **L5**). With our previous experience in aryl mesylate cross-couplings,[12] we then chose the CM-Phos-type ligands (**L6** and **L7**) in our ligand library for evaluation in this model reaction. We found that these ligands were able to give the monoarylated product in excellent yields while the new **L7** was even more promising (95% yield). We attribute the superior performance of **L7** over **L6** to the enhanced steric congestion provided by the indolyl scaffold. These results complied with previous findings regarding the importance of steric bulkiness in reductive elimination of ketone arylation reactions.[6v,q,w] Other mono-/bidentate phosphine and N-heterocyclic carbene ligands were shown to be ineffective (**L8** to **L13**).[16]

Scheme 2. Ancillary Ligand Screen[a]



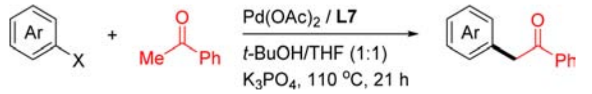
[a]Reaction conditions: $Pd(OAc)_2$ (0.5 mol %), ligand (1.5 mol %), 2-naphthyl mesylate (0.5 mmol), acetophenone (2.0 mmol), K_3PO_4 (1.0 mmol), *t*-BuOH/THF (1:1, 4.0 mL) at 90 °C under N_2 for 18 h, calibrated GC-FID yields were reported.

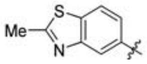
To improve the effectiveness of the Pd/**L7** catalyst system, we further investigated the reaction conditions with various Pd sources, bases, and solvents (Table S1, Supporting Information). We found that using neat *t*-BuOH as solvent led to an unstirrable reaction mixture, rendering unstable results (Table S1, entry 1). Various solvents were used in an attempt to dilute the mixture, and THF was found to be the best counterpart in a 1:1 ratio with *t*-BuOH (Table S1, entries 2−5 vs 6). Yet, the use of neat THF provided an inferior result (Table S1, entry 6 vs 7). Lowering the ketone equivalents to 4 equiv was found to preserve the catalytic performance of the system (Table S1, entry 9 vs 8 and 10−11). It is worth noting that 5−10 equiv of ketones were required for the cross-coupling with aryl mesylates in a previous report (Scheme 1, B) .[6w] The best metal-to-ligand ratio was found to be 1:3 (Table S1, entry 9 vs 12). The effect of water equivalents in $K_3PO_4{\cdot}H_2O$ was minimal (Table S1, entry 13 vs 14). Replacing K_3PO_4 with either Na_3PO_4 or Cs_2CO_3 resulted in a significant drop in product yields (Table S1, entry 13 vs 15−16). The source of palladium has a minimal effect on the reaction; $Pd(OAc)_2$ was shown to have comparable performance to $[Pd(cinnamyl)Cl]_2$ (Table S1, entry 17 vs 13 and 18−20). This relatively more cost-effective $Pd(OAc)_2$ was then chosen for further study.

Having identified the best reaction conditions, we next investigated the functional group tolerance of our system by examining a wide range of aryl mesylates and tosylates. In general, 1.0 to 2.0 mol % of Pd completed the cross-couplings of acetophenone enolate with no diarylated product formation (Table 1). Electron-neutral and -rich arenes were converted to the corresponding products in good-to-excellent yields (Table 1, entries 1−6). Sterically hindered substrates were also applicable in our system (Table 1, entries 7−8). Notably, electron-deficient arenes, which proved to be difficult substrates in ketone arylations,[15] gave moderate-to-good product yields (Table 1, entries 9−10). An enolizable amide group was well-tolerated and gave chemoselective ketone α-arylation products (Table 1, entries 11−12). An ester and a variety of heterocyclics such as benzodioxole, pyrrolylarene, quinoline, and benzothiazole were compatible (Table 1, entries 13−20).

To demonstrate the applicability of our system in a wider scope, we synthesized a diverse library of mono-α-arylated arylketones. Electron-neutral (Scheme 3, **1a**−**1d**, **1h**), -rich (Scheme 3, **1e**−**1g**), and -poor (Scheme 3, **1j**) arylmethylketones were suitable counterparts and afforded the corresponding products in good-to-excellent yields (65−94% yield). While achieving mono-α-arylations with arylketones, our system is capable of handling highly sterically hindered α-substituted arylketones such as α-tetralone and deoxybenzoin with good

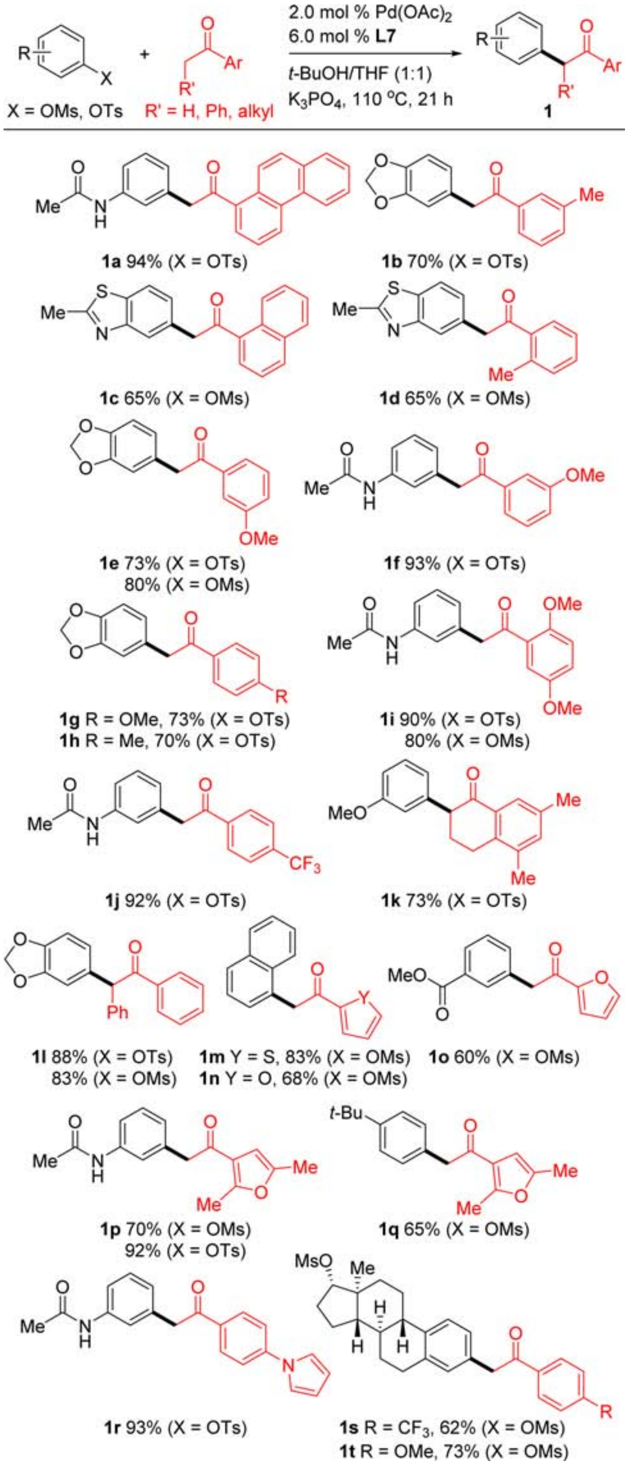
Table 1. Pd-Catalyzed Selective Mono-α-arylation of Acetophenone Enolate with Aryl Mesylates and Tosylates[a]



entry	X	Ar	Pd (mol %)	% yield
1	OMs	2-Naphthyl	0.25	76
2	OMs	3,5-MeC$_6$H$_4$	1.5	85
3	OMs	4-*t*-BuC$_6$H$_4$	2.0	89
4	OMs	4-OMeC$_6$H$_4$	2.5	71
5	OTs	4-OMeC$_6$H$_4$	2.0	72
6	OTs	3-OMeC$_6$H$_4$	1.5	83
7	OMs	1-Naphthyl	1.0	83
8	OTs	2,4-MeC$_6$H$_4$	2.0	80
9	OTs	4-FC$_6$H$_4$	1.0	83
10	OMs	3-CF$_3$C$_6$H$_4$	2.0	65
11	OMs	3-NHCOCH$_3$C$_6$H$_4$	2.0	71
12	OTs	3-NHCOCH$_3$C$_6$H$_4$	2.0	95
13	OMs	3-COOEtC$_6$H$_4$	2.0	61
14	OTs	3-COOEtC$_6$H$_4$	2.0	68
15	OMs	3,4-OCH$_2$O-C$_6$H$_3$	1.5	81
16	OTs	3,4-OCH$_2$O-C$_6$H$_3$	1.5	90
17	OTs	3-PyrrolylC$_6$H$_4$	2.0	78
18	OMs	6-Quinolyl	2.0	53
19	OTs	6-Quinolyl	2.0	67
20	OMs		2.0	71

[a] Reaction conditions: Pd(OAc)$_2$/**L7** = 1:3 (mol % as indicated), ArOMs or ArOTs (0.3 mmol), acetophenone (1.2 mmol), K$_3$PO$_4$ (0.6 mmol), *t*-BuOH/THF (1:1, 2.4 mL) at 110 °C under N$_2$ for 21 h. Reaction time was not optimized for each substrate. Isolated yields were reported.

Scheme 3. A Library of Mono-α-arylated Arylketones Synthesized Using Pd(OAc)$_2$/L7 Catalyst[a]



[a] Reaction conditions: Pd(OAc)$_2$/**L7** = 1:3, ArOMs or ArOTs (0.30 mmol), arylketone (1.2 mmol), K$_3$PO$_4$ (0.6 mmol), *t*-BuOH/THF (1:1, 2.4 mL) at 110 °C under N$_2$ for 21 h. Catalyst loading and reaction time were not optimized for each substrate. Isolated yields were reported.

reactivity (Scheme 3, **1k**–**1l**). Previously, there were very few successful attempts with the mono-α-arylations of heteroarylketones, even with the use of aryl halides.[17] With our system, various acetyl furans, thiophene, and pyrrole-embedded arylketone were successfully monoarylated (Scheme 3, **1m**–**1r**). Additionally, our protocol allowed for modification of a human sex hormone 17β-estradiol. The mesyated 17β-estradiol was coupled smoothly with arylmethylketones to furnish **1s** and **1t** (Scheme 3). The aliphatic mesylate on the ketone products remained intact during the course of the reaction, thus allowing for further functionalization with other common organic syntheses. We anticipate our system will be useful in the modification of various phenolic (pro)drugs.[18]

In summary, we have developed a general and efficient Pd catalyst for the mono-α-arylation of arylmethylketones with aryl mesylates and tosylates. The new **L7**–Pd system exhibited good compatibility to a wide range of functional groups and heterocyclics within the aryl mesylates and tosylates. Excellent chemo- and monoselectivity at a modest catalyst loading (0.25–2.5 mol %) were attained. Heteroarylketones were smoothly monoarylated, and heteroaromatic substituents were well-tolerated. Furthermore, this protocol provided a straightforward modification of biologically active phenolic compounds. We believe this newly developed palladium catalyst would be useful in the synthesis of a drug library for lead optimizations and fine-tuning the biological properties of phenolic drugs. Further investigations in the exceptional reactivity of phosphine ligand

L7 for aryl mesylate cross-couplings are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00643.

Detailed experimental procedures; ^{1}H, ^{13}C, ^{31}P NMR spectra; and characterization data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on Pd-catalyzed α-arylation of carbonyl compounds, see: (a) Sivanandan, S. T.; Shaji, A.; Ibnusaud, I.; Seechurn, C. C. C. J.; Colacot, T. J. *Eur. J. Org. Chem.* **2015**, *2015*, 38. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (d) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (e) Novak, P.; Martin, R. *Curr. Org. Chem.* **2011**, *15*, 3233.

(2) (a) Li, H. Q.; Luo, Y.; Song, R.; Li, Z. L.; Yan, T.; Zhu, H. L. *ChemMedChem* **2010**, *5*, 1117. (b) Venkatesan, H.; Davis, M. C.; Altas, Y.; Snyder, J. P.; Liotta, D. C. *J. Org. Chem.* **2001**, *66*, 3653. (c) Vontzalidou, A.; Zoidis, G.; Chaita, E.; Makropoulou, M.; Aligiannis, N.; Lambrinidis, G.; Mikros, E.; Skaltsounis, A.-L. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5523. (d) Kim, Y. W.; Hackett, J. C.; Brueggemeier, R. W. *J. Med. Chem.* **2004**, *47*, 4032. (e) Kanagalakshmi, K.; Premanathan, M.; Priyanka, R.; Hemalatha, B.; Vanangamudi, A. *Eur. J. Med. Chem.* **2010**, *45*, 2447.

(3) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

(4) (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382. (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

(5) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740.

(6) For recent reviews on Pd-catalyzed α-arylation of carbonyl compounds, see: Reference 1. For notable examples of Pd-catalyzed α-arylation of ketones, see: (a) Lundgren, R. J.; Stradiotto, M. *Chem. - Eur. J.* **2012**, *18*, 9758. (b) Gildner, P. G.; Colacot, T. J. *Organometallics* **2015**, *34*, 5497. (c) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053. (d) Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2007**, *9*, 5489. (e) Grasa, G. A.; Colacot, T. J. *Org. Process Res. Dev.* **2008**, *12*, 522. (f) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (g) Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168. (h) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (i) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195. (j) Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082. (k) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398. (l) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209. (m) Marelli, E.; Corpet, M.; Davies, S. R.; Nolan, S. P. *Chem. - Eur. J.* **2014**, *20*, 17272. (n) Biscoe, M. R.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 1773. (o) Crawford, S. M.; Alsabeh, P. G.; Stradiotto, M. *Eur. J. Org. Chem.* **2012**, *2012*, 6042. (p) Ackermann, L.; Mehta, V. P. *Chem. - Eur. J.* **2012**, *18*, 10230. (q) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194. (r) Li, P.; Lü, B.; Fu, C.; Ma, S. *Adv. Synth. Catal.* **2013**, *355*, 1255. (s) Gäbler, C.; Korb, M.; Schaarschmidt, D.; Hildebrandt, A.; Lang, H. *Adv. Synth. Catal.* **2014**, *356*, 2979. (t) MacQueen, P. M.; Chisholm, A. J.; Hargreaves, B. K.; Stradiotto, M. *Chem. - Eur. J.* **2015**, *21*, 11006. (u) Rotta-Loria, N. L.; Borzenko, A.; Alsabeh, P. G.; Lavery, C. B.; Stradiotto, M. *Adv. Synth. Catal.* **2015**, *357*, 100. (v) Fu, W. C.; So, C. M.; Chow, W. K.; Yuen, O. Y.; Kwong, F. Y. *Org. Lett.* **2015**, *17*, 4612. (w) Alsabeh, P. G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7242. (x) Xu, Y.; Su, T.; Huang, Z.; Dong, G. *Angew. Chem., Int. Ed.* **2016**, *55*, 1. (y) Fu, W. C.; Zhou, Z.; Kwong, F. Y. *Organometallics* **2016**, *in press*, doi:10.1021/acs.organomet.6b00154.

(7) Our previous work demostrated the introduction of one or two methoxy groups in the lower aryl ring will greatly increase the product yield; see ref 6v. See also ref 6k for a detailed investigation into these factors by Hartwig and co-workers.

(8) According to Aldrich catalog 2014: mesyl chloride ($168/1 L), tosyl chloride ($91.1/1 kg), and triflic anhydride ($1690/1 kg).

(9) (a) Kozhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. *Catal. Sci. Technol.* **2013**, *3*, 562. (b) Wilkinson, M. C. *Org. Lett.* **2011**, *13*, 2232.

(10) For the use of BrettPhos in Pd-catalyzed cross-couplings of aryl mesylates, see: Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552.

(11) For the use of Mor-Dal Phos in cross-coupling reactions of aryl mesylates, see: Reference 6w and (a) Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8686.

(12) (a) So, C. M.; Kwong, F. Y. *Chem. Soc. Rev.* **2011**, *40*, 4963. (b) So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem. - Eur. J.* **2011**, *17*, 761. (c) Fu, W. C.; So, C. M.; Kwong, F. Y. *Org. Lett.* **2015**, *17*, 5906. (d) Yeung, P. Y.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 8918. (e) Choy, P. Y.; Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem. - Eur. J.* **2010**, *16*, 9982. (f) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059.

(13) For the use of DCPP, SPhos, and XPhos in Pd-catalyzed cross-couplings of aryl mesylates, see: (a) Choy, P. Y.; Luk, K. C.; Wu, Y.; So, C. M.; Wang, L.-l.; Kwong, F. Y. *J. Org. Chem.* **2015**, *80*, 1457. (b) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430. (c) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754.

(14) For the effect of electon-rich phosphine ligands on electron-deficient substrates in ketone arylation reactions, see: Reference 1c, 6q, and w.

(15) We have recently designed an indolylphosphine ligand which is capable of handling electron-deficient arenes in acetone arylation; see ref 6v.

(16) For the use of **L8** and **L9** in Pd-catalyzed α-arylation of ketones, see ref 6d, m. For the use of **L10**−**L12** in a cross-coupling reaction of aryl sulfonates and other challenging catalysis, see: (a) Zhang, J.; Bellomo, A.; Creamer, A. D.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 13765. (b) Sha, S.-C.; Zhang, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2013**, *135*, 17602. For a recent review on the use of N-heterocyclic carbene ligands in Pd catalysis, see: (c) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314.

(17) For a few successful attempts in mono-α-arylation of heteroaryl ketone, see: References 4a, 6m−o, and t.

(18) For selected examples of modifying phenolic sites to improve pharmacological properties, see: (a) Hoffman, W. F.; Woltersdorf, O. W.; Novello, F. C.; Cragoe, E. J.; Springer, J. P.; Watson, L. S.; Fanelli, G. M. *J. Med. Chem.* **1981**, *24*, 865. (b) Lee, J.; Lee, J.; Kang, M.-S.; Kim, K.-P.; Chung, S.-J.; Blumberg, P. M.; Yi, J.-B.; Park, Y. H. *Bioorg. Med. Chem.* **2002**, *10*, 1171. (c) Thomas, J. D.; Majumdar, S.; Sloan, K. B. *Molecules* **2009**, *14*, 4231. (d) Latham, K. R. WO2013010102 A2, 2013.