This is the Pre-Published Version.

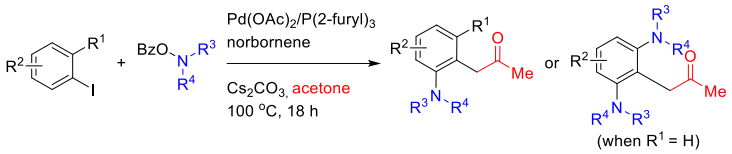
This document is the Accepted Manuscript version of a Published Work that appeared in final form in Organic Letters, copyright © American Chemical Society after peer review and technical editing by the publisher. To access the final edited and published work see https://doi.org/10.1021/acs.orglett.7b02023.

Cascade Amination and Acetone Monoarylation with Aryl Iodides by Palladium/Norbornene Cooperative Catalysis

Wai Chung Fu,[†,‡] Bin Zheng,[†] Qingyang Zhao,[†,‡] Wesley Ting Kwok Chan[†] and Fuk Yee Kwong*[,†,‡]

[†]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong

[‡]Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

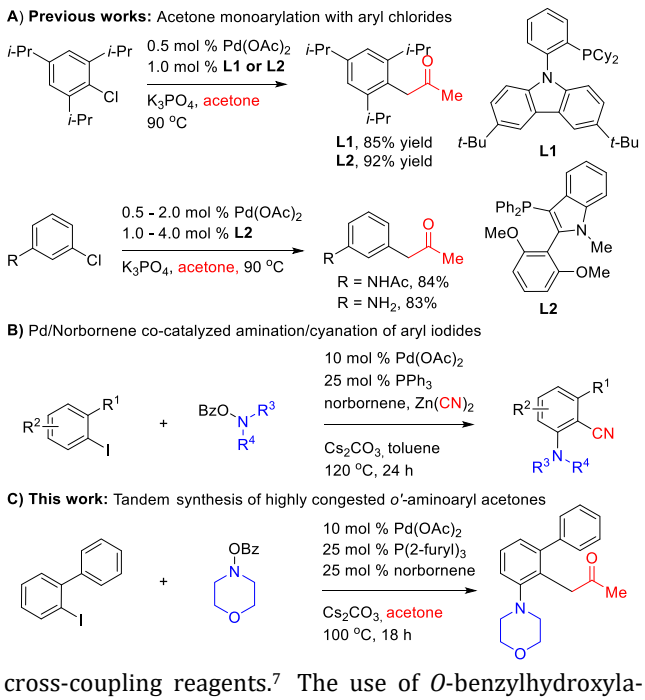


ABSTRACT: A palladium/norbornene co-catalyzed three-component reaction of aryl iodides, *O*-benzylhydroxylamines and acetone is reported. *o*'-Aminoaryl acetones or *o,o*'-diaminoaryl acetones are efficiently prepared via tandem *ortho*-C–H amination/*ipso*-C–I α-arylation sequence and the regiospecificity has been confirmed by X-ray analysis. The proposed method addresses the condensation/amination of free-*N*–H-bearing substrates in acetone monoarylations and the synthesis of extremely congested 2,6-disubstituted aryl acetones.

Acetone is an easily available three-carbon feedstock for the construction of C(sp^2)–C(sp^3) bonds via palladium-catalyzed α-arylation reaction.[1] Products from this process are indeed useful motifs and important intermediates in pharmaceutical syntheses and medicinal chemistry.[2] However, the monoarylation of acetone with highly sterically encumbered arenes is considered to be a difficult task.[3] Although we have previously achieved the cross-coupling of acetone with 2-chloro-1,3-diisopropylbenzene with a catalyst loading as low as 0.5 mol % Pd (Scheme 1A, **L1** and **L2**),[1a,1b] the reaction with sterically congested *o,o*'-disubstituted aryl halides bearing bulkier groups, such as six-membered phenyl rings, was not possible. Moreover, the α-arylation of ketones was not entirely feasible for arenes substituted with free *N*–H groups because of the inherent condensation of free amines with ketones to form enamines or imines which limits their utility and reaction scope, while possible amination would occur to afford aniline side products. The indolylphosphine ligand we previously developed (Scheme 1A, **L2**) enabled the α-arylation of ketones with chloroanilines but nonetheless, a small amount of self-condensation product was still observed and could not be completely separated either by column chromatography nor distillation.[4] With our continuing interest in the functionalization of ketones by palladium catalysis,[1a,1b,5] we sought to develop an efficient catalyst to tackle the aforementioned problems.

Tandem or domino palladium-catalyzed reactions are powerful tools for the construction of complicated molecules in an efficient one-pot manner by controlled-assembly of molecular fragments.[6] In this regard, the Pd/norbornene(NBE) catalysis is a versatile bisfunctionalization strategy for arenes and it enables sequential *ortho*-C–H functionalization with secondary electrophiles and *ipso*-C–I termination with formal

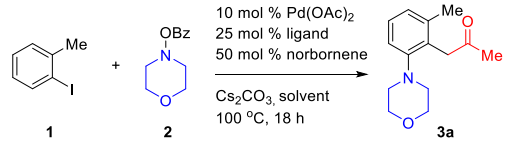
Scheme 1. Acetone Monoarylation and Pd/NBE Catalysis



cross-coupling reagents.[7] The use of *O*-benzylhydroxylamines in Pd/NBE-catalyzed *ortho*-amination of aryl iodides was reported in 2013,[8] and the scope of this reagent has been widened in the tandem synthesis of amino-substituted compounds such as vinyl anilines, α-alkynyl anilines and others.[9] Recently, Gao and Lautens reported a Pd-catalyzed

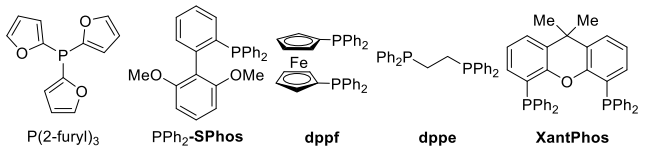
NBE-mediated tandem amination/cyanation reaction towards aminobenzonitriles (Scheme 1B).[10] Very recently, Zhou's group developed a Pd-catalyzed NBE-mediated synthesis of *o,o*'-disubstituted aryl ketones using ketone enolates as terminating reagents.[12] We recently started a research program in Pd/NBE catalysis,[11] and envisioned that the protected *O*-benzylhydroxylamines is a promising amination candidate, and more importantly the extremely congested aryl intermediates could be *in situ* assembled with the Pd/NBE-catalyzed pathway. Given the importance of aromatic amines in pharmaceuticals and natural products,[13] as well as the synthetic versatility of acetone as a three-carbon keto-feedstock, we herein report the development of a Pd/NBE co-catalyzed synthesis of sterically hindered *o*'-aminoaryl acetones and *o,o*'-diaminoaryl acetones.

Table 1. Reaction Development and Ligand Screening[a]



1 2 3a

entry	ligand	solvent	% yield[b]
1	$P(2\text{-}OMeC_6H_4)_3$	toluene	14[c]
2	$P(2\text{-}OMeC_6H_4)_3$	1,4-dioxane	17[c]
3	$P(2\text{-}OMeC_6H_4)_3$	acetone	65
4	PCy_3	acetone	10
5	$PCyPh_2$	acetone	77
6	PPh_3	acetone	35
7	$P(4\text{-}OMeC_6H_4)_3$	acetone	22
8	$P(2\text{-}MeC_6H_4)_3$	acetone	25
9	$P(2\text{-furyl})_3$	acetone	85
10	PPh_2-**SPhos**	acetone	37
11	**dppf**	acetone	54[d]
12	**dppe**	acetone	14[d]
13	**XantPhos**	acetone	5[d]

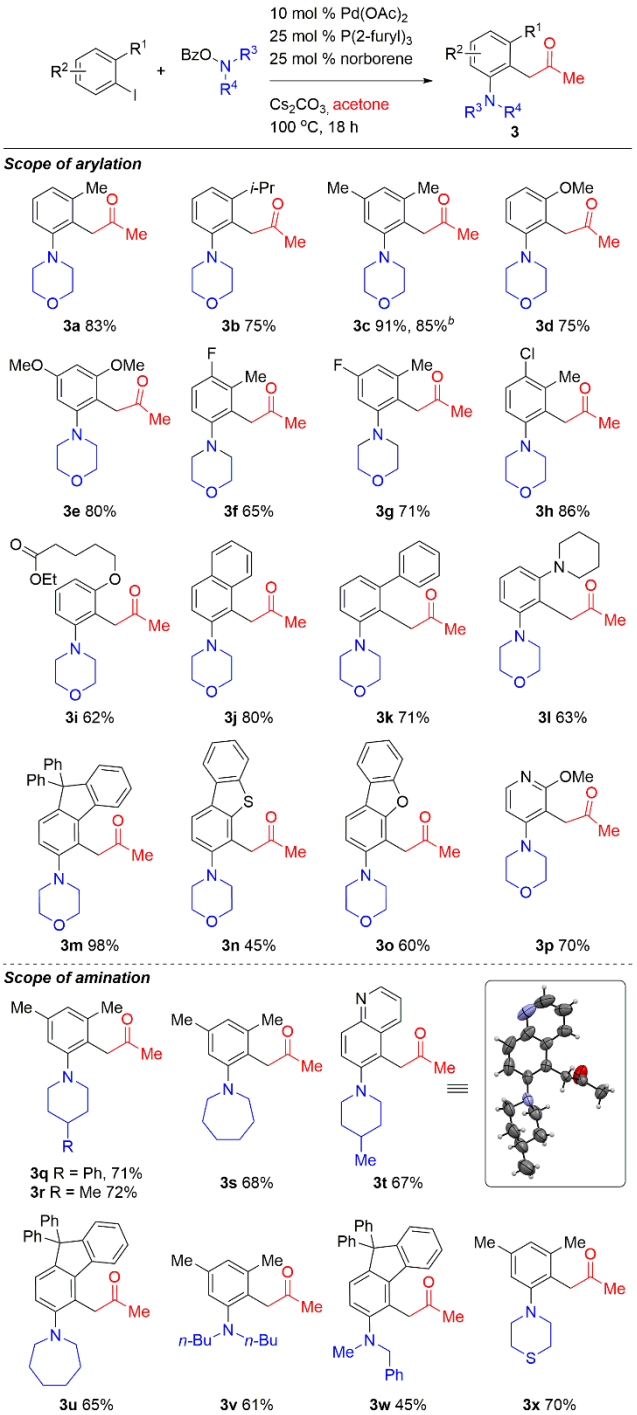


$P(2\text{-furyl})_3$ PPh_2-**SPhos** **dppf** **dppe** **XantPhos**

[a]Reaction conditions: $Pd(OAc)_2$ (10 mol %), ligand (25 mol %), norbornene (50 mol %), 2-iodotoluene (0.2 mmol), morpholino benzoate (0.24 mmol), Cs_2CO_3 (0.6 mmol), solvent (0.1 M, 2 mL) were stirred at 100 °C for 18 h under N_2. [b]Calibrated GC-FID yields were reported. [c]Acetone (0.26 mmol) was used. [d]12.5 mol % of ligand was used.

We initially attempted a reaction between 2-iodotoluene, morpholino benzoate and acetone as depicted in Table 1, but only 14-17% product yield was given in toluene and dioxane (Table 1, entries 1-2). Gratifyingly, using acetone directly as the solvent provided the desired product in 65% yield (Table 1, entry 3). To further improve the reaction efficacy, we tested an array of phosphine ligands with different electronic richness, steric hindrance and coordination number. $P(2\text{-furyl})_3$ (Table 1, entry 9) proved to be the best ligand and delivered the product in 85% yield. Either the highly electron-rich PCy_3 or bidentate ligands (Table 1, entries 4 and 11-13) were poor performers in this survey. Other reaction parameters were also investigated and the results were summarized in Table S1 (see Supporting Information). Only Cs_2CO_3 was able to promote the reactions while the other carbonate or phosphate bases were inapplicable. We found that the product yield experienced a slight increase when less norbornene was used while the stoichiometry of morpholino benzoate and Cs_2CO_3 have minimal effect on this catalysis. A palladium salts screening revealed that the economically attractive $Pd(OAc)_2$ was the optimal catalyst.

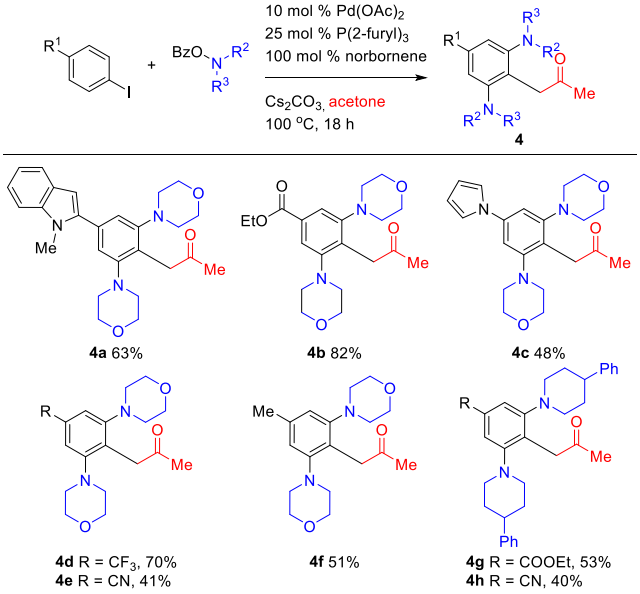
Scheme 2. Reaction Scope of α-Arylation and Amination[a]



[a]Reaction conditions: $Pd(OAc)_2$ (10 mol %), P(2-furyl)$_3$ (25 mol %), norbornene (25 mol %), aryl iodide (0.2 mmol), *O*-benzylhydroxylamines (0.24 mmol), Cs_2CO_3 (0.6 mmol), acetone (0.1 M, 2 mL) were stirred at 100 °C for 18 h under N_2. Isolated yields were reported. Reaction times were not optimized for each substrate. [b]Reaction in 1.5 mmol scale with respect to 4-iodo-*m*-xylene.

With the promising reaction conditions in hand, we next explored the substrate scope by first examining a series of aryl iodides (Scheme 2). In terms of electronic properties, electronically neutral arenes from **1a** to **1c** underwent the α-arylation/amination sequence smoothly to give regiospecific products in 75-91% yield and the electron-rich aryl iodides were feasible substrates (75-80% yield). Unfortunately, we found that *ortho*-substituted electron-deficient arenes (-CF_3, -Cl, -F) gave a low conversion of starting materials (ca. 5-20%). This phenomenon could presumably be due to the ineffective reductive elimination of electron-poor substrates with the acetone as reported in literature,[1a-1c] given that the oxidative addition of aryl iodides and subsequent insertion with norbornene is very facile.[11] Sterically congested *ortho*-substituted aryl iodides reacted smoothly to deliver **3i** to **3m** in good-to-excellent yields. Notably, aryl acetone with unsymmetrical *o*'-amino groups (Scheme 2, **3l**) could be prepared by using *ortho*-NR_2-substituted aryl iodides. Heterocyclic substrates (Scheme 2, **3n-3p, 3t**) were also tolerated and gave moderate-to-good product yields. To realize the generality of this method, the scope of amination was investigated using different *O*-benzylhydroxylamines. In general, six- or seven-membered cyclic amine and dialkyl amine derivatives underwent the cross coupling successfully, affording desired products in 45-72% yields (Scheme 2, **3q-3w**). Sulfur-containing thiomorpholine-derived substrate, which could cause catalyst poisoning, was well-tolerated and **3x** was obtained in 70% yield. However, *O*-benzoyl-*N,N*-dibenzylhydroxylamine was unreactive under standard conditions and *O*-benzoyl-*N,N*-diethylhydroxylamine gave only ca. 10% product yield as revealed by GC analysis. The regiospecificity of our reaction was confirmed by X-ray analysis of **3t**.[14] The single crystal of **3t** suitable for X-ray diffraction was grown by slow evaporation of $CDCl_3$ solution at room temperature. To realize the synthetic utility of our method, we performed the synthesis of **3c** in 1.5 mmol scale and 315 mg of desired product was successfully obtained (85% yield)

Scheme 3. Synthesis of *o,o*'-Diaminoaryl Acetones [a]



[a]Reaction conditions: $Pd(OAc)_2$ (10 mol %), P(2-furyl)$_3$ (25 mol %), norbornene (0.2 mmol), aryl iodides (0.2 mmol), *O*-benzylhydroxylamines (0.48 mmol), Cs_2CO_3 (1.0 mmol), acetone (0.1 M, 2 mL) were stirred at 100 °C for 18 h under N_2. Isolated yields were reported. Reaction times were not optimized for each substrate.

During the course of our study, we found that the reaction of aryl iodides without an *ortho*-substituent resulted in the formation of *o,o*'-diaminoaryl acetones. The identification of suitable reaction conditions was achieved with increased amounts of norbornene, base and *O*-

benzylhydroxylamines. Aryl iodides bearing electron-withdrawing groups (–CO_2Et, –CF_3, –CN) or electron-rich heterocycles (indole, pyrrole) were successfully transformed to the corresponding products in moderate-to-good yields through dual amination and C(sp^2)–C(sp^3) bond formation processes (Scheme 3, **4a-4h**). Single crystal of **4h** suitable for X-ray analysis was grown by slow evaporation of a hexane/ethyl acetate solution at room temperature (Figure 1).[14] Overall, a variety of functional groups were compatible in the proposed system including ester, nitrile, chloro, fluoro, trifluoromethyl and a wide range of heterocycles.

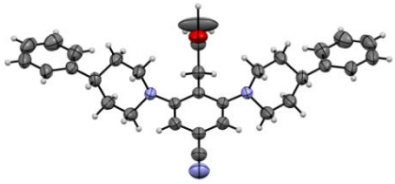
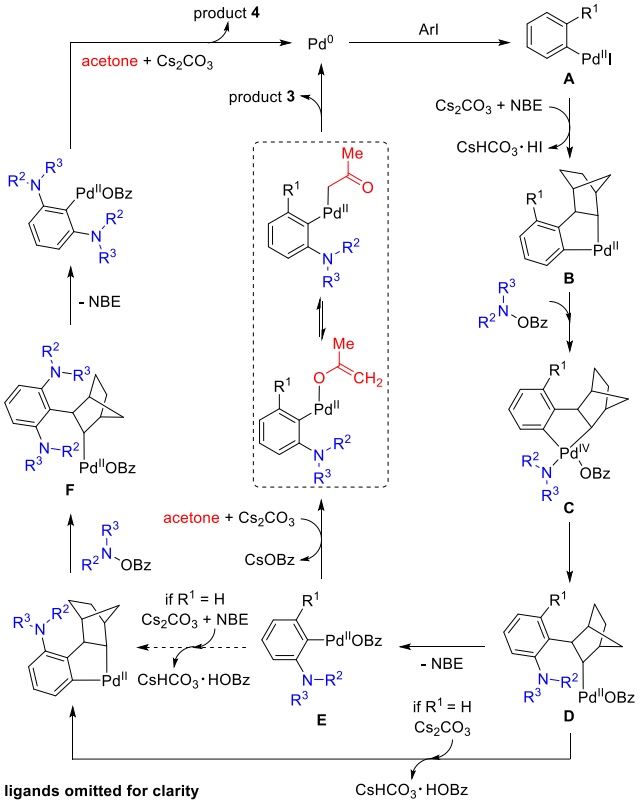


Figure 1. X-ray Crystal Structure of **4h**.

Scheme 4. Mechanistic Proposal



Base on the reported Pd/NBE-catalyzed cross-coupling reactions and our experimental observations,[7] we proposed a plausible mechanism to account for this catalysis (Scheme 4). The initial oxidative addition of aryl iodide to a palladium(0) species generates aryl palladium(II) iodide **A**, followed by insertion of norbornene and a Concerted Metalation–Deprotonation (CMD) for *ortho*-C–H activation to afford palladacycle **B**. *O*-benzylhydroxylamines may either be oxidatively added to **B** to give a Pd(IV) species **C** through N–O bond cleavage or undertake an electrophilic substitution with arylnorbornylpalladacycle **B** to directly give complex **D** with the amination intermediate.[15] Followed by the extrusion of norbornene from **D**, **E** reacts with acetone enolate to give an *o*'-aminoaryl acetone product and regenerates Pd(0) for the next catalytic cycle. For the formation of *o,o*'-diaminoaryl acetone, intermediate **D** undergoes a secondary *ortho*-C–H activation as well as amination with *O*-benzylhydroxylamines to form species **F** with a diaminated intermediate. Since stoichiometric amount of NBE needs to be used, the insertion of NBE and CMD process may be repeated starting from intermediate **E**. **F** then proceeds a similar pathway as arylnorbornylpalladium species **D** and affords the final *o,o*'-diaminoaryl acetone.

In conclusion, we have successfully developed a palladium/norbornene co-catalyzed three-component cross-coupling reaction towards the synthesis of *o'*-aminoaryl acetone and *o,o'*-diaminoaryl acetone. The proposed method addresses the imine/enamine formation of free-amino-bearing substrates during ketone α-arylations and allows the syntheses of extremely congested 2,6-disubstituted aryl acetones which are previously very difficult to prepare. Good functional group tolerance was demonstrated and substrates featuring six-membered rings next to the C–I bond can also be coupled to deliver good-to-excellent product yields. We believe this newly developed protocol will be a complementary method to provide access to valuable aromatic amines while the versatile three-carbon acetone feedstock can readily be derived into other useful functionalities.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures for catalytic studies; ^{1}H, ^{13}C spectra; and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail: fykwong@cuhk.edu.hk

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank RGC of Hong Kong (CRF: C5023-14G and PolyU11/CRF/13E) for financial and X-ray equipment support, respectively. National Natural Science Foundation of China (grant number 21602172) is acknowledged for financial support.

REFERENCES

(1) For our works on the monoarylation of acetone, see: (a) Fu, W. C.; So, C. M.; Chow, W. K.; Yuen, O. Y.; Kwong, F. Y. *Org. Lett.* **2015,** *17*, 4612. (b) Fu, W. C.; Zhou, Z; Kwong, F. Y. *Organometallics* **2016,** *35*, 1553. For other pioneering works and notable examples, see: (c) Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194. (d) Rotta-Loria, N. L.; Borzenko, A.; Alsabeh, P. G.; Lavery, C. B.; Stradiotto, M. *Adv. Synth. Catal*. **2015**, *357*, 100. (e) Li, P.; Lü, B.; Fu, C.; Ma, S. *Adv. Synth. Catal.* **2013**, *355*, 1255. (f) Gäbler, C.; Korb, M.; Schaarschmidt, D.; Hildebrandt, A.; Lang, H. *Adv. Synth. Catal.* **2014**, *356*, 2979. (g) Ackermann, L.; Mehta, V. P. *Chem. Eur. J.* **2012**, *18*, 10230. (h) MacQueen, P. M.; Chisholm, A. J.; Hargreaves, B. K. V.; Stradiotto, M. *Chem. Eur. J.* **2015**, *21*, 11006. For recent progress in new Pd-catalyzed direct α-arylation of carbonyl compounds: (i) Zheng, B; Jia, T; Walsh, P. J. *Adv. Synth.*

Catal. **2014,** *356*, 165. (j) Sha, S.-C.; Zhang, J.; Walsh, P. J. *Org. Lett.* **2015,** *17*, 410. (k) Zheng, B; Jia, T; Walsh, P. J. *Org. Lett.* **2015,** *15*, 4190.

(2) (a) Vitale, P.; Tacconelli, S.; Perrone, M. G.; Malerba, P.; Simone, L.; Scilimati, A.; Lavecchia, A.; Dovizio, M.; Marcantoni, E.; Bruno, A.; Patrignani, P. *J. Med. Chem.* **2013**, *56*, 4277. (b) N. J. Parry, J. C. O'Keeffe, C. F. Smith, WO 2014118240A1, 2014. (c) Singh, F. V., Parihar, A.; Chaurasia, S.; Singh, A. B.; Singh, S. P.; Tamrakar, A. K., Srivastava, A. K., Goel, A., *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2158. (d) Sivanandan, S. T.; Shaji, A.; Ibnusaud, I.; Seechurn, C. C. C. J.; Colacot, T. J. *Eur. J. Org. Chem.* **2015,** *2015*, 38. (e) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010,** *49*, 676.

(3) See ref 1f for the effect of steric hindrance of *ortho*-substituents to the α-arylation of acetone.

(4) See entry **2s** in Supporting Information of ref 1a.

(5) (a) Fu, W. C.; So, C. M.; Yuen, O. Y.; Lee, I. T. C.; Kwong, F. Y. *Org. Lett.* **2016,** *18*, 1872. (b) Fu, W. C.; Wu, Y.; So, C. M.; Wong, S. M.; Lei, A.; Kwong, F. Y. *Org. Lett.* **2016,** *18*, 5300. (c) Wu, Y.; Fu, W. C.; Chiang, C. W.; Choy, P. Y.; Kwong, F. Y.; Lei, A. *Chem. Commun.* **2017,** *53*, 952.

(6) For recent notable examples, see: (a) Kim, K.; Vasu, D.; Im, H.; Hong, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 8652. (b) Jia, T.; Bellomo, A.; Montel, S.; Zhang, M.; Baina, K. E.; Zheng, B.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 260. (c) Qureshi, Z.; Kim, J. Y.; Bruun, T.; Lam, H.; Lautens, M. *ACS Catal.* **2016,** *6*, 4946. (d) Yamamoto, K.; Bruun, T.; Kim, J. Y.; Zhang, L.; Lautens, M. *Org. Lett.* **2016**, *18*, 2644. (e) Zhang, L.; Qureshi, Z.; Sonaglia, L.; Lautens, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 13850.

(7) For reviews on Pd/NBE chemistry, see: (a) Ye, J.; Lautens, M. *Nat. Chem.* **2015**, *7*, 863. (b) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res*. **2008**, *41*, 1512. (c) Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem.* **2009,** *292*, 1. (d) Lautens, M.; Alberico, D.; Bressy, C.; Fang, Y.-Q.; Mariampillai, B.; Wilhelm, T. *Pure Appl. Chem.* **2006,** *78*, 351. (e) Ferraccioli, R. *Synthesis* **2013,** *45*, 581. (f) Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M.; *Acc. Chem. Res*. **2016**, *49*, 1389.

(8) Dong, Z.; Dong, G. *J. Am .Chem. Soc*. **2013,** *135*, 18350.

(9) (a) Majhi, B.; Ranu, B. C. *Org. Lett.* **2016,** *18*, 4162. (b) Sun, F.; Gu, Z. *Org. Lett.* **2015,** *17*, 2222. (c) Shi, H.; Babinski, D. J.; Ritter, T. *J. Am. Chem. Soc.* **2015,** *137*, 3775. (d) Wang, J.; Gu, Z. *Adv. Synth. Catal*. **2015,** *358*, 2990. (e) Chen, Z.-Y.; Ye, C.-Q.; Zhu, H.; Zeng, X.-P.; Yuan, J.-J. *Chem. Eur. J.* **2014,** *20*, 4237.

(10) Luo, B.; Gao, J.-M.; Lautens, M. *Org. Lett.* **2016,** *18*, 4166.

(11) Fu, W. C.; Wang, Z; Chan, W. T. K.; Lin, Z.; Kwong, F. Y. *Angew. Chem. Int. Ed.* **2017,** *56*, 7166.

(12) Lei, C.; Cao, J.; Zhou, J. *Org. Lett.* **2016,** *18*, 6120.

(13) (a) Kim, J.; Movassaghi, M. *Acc. Chem. Res.* **2015**, *48*, 1159. (b) Quintas-Cardama, A.; Cortes, J. *Clin. Cancer Res.* **2008**, *14*, 4392. (c) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(14) The X-ray crystallographic data for **3t** (CCDC 1556795) and **4h** (CCDC 1558942) are available free of charge on the The Cambridge Crystallographic Data Centre at: www.ccdc.cam.ac.uk/data_request/cif

(15) (a) Berman, A. M.; Johnson, J. S. *J. Am .Chem. Soc*. **2004**, *126*, 5680. (b) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521. (c) Berman, A. M.; Johnson, J. S. *Synlett.* **2005**, 1799. (d) Iwao, M.; Reed, J. N.; Snieckus, V. *J. Am .Chem. Soc.* **1982**, *104*, 5531.