

Catalyst Controlled Divergent C4/C8 Site-Selective C–H Arylation of Isoquinolones

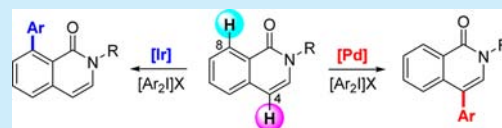
Soyoung Lee,^{†,‡} Shinmee Mah,^{†,‡} and Sungwoo Hong^{*,†,‡}

[†]Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 305-701, Korea

[‡]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-701, Korea

S Supporting Information

ABSTRACT: The catalyst-controlled C4/C8 site-selective C–H arylation of isoquinolones using arylodonium salts as the coupling partners was developed. The C4-selective arylation was successfully achieved via an electrophilic palladation pathway. A completely different selectivity pattern was observed using an Ir(III) catalytic system, which resulted in C–C bond formation exclusively at the C8 position. The isoquinolone scaffold can be conveniently equipped with various aryl substituents at either the C4 or C8 position.



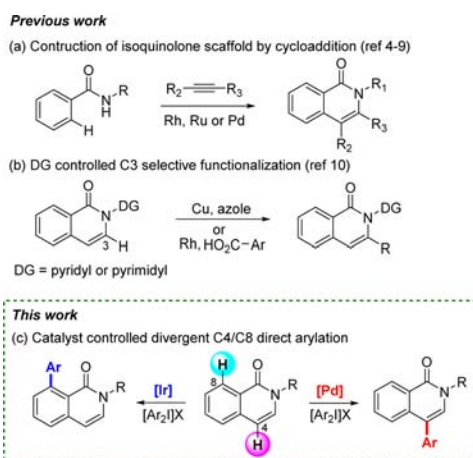
Transition-metal-catalyzed direct and regioselective C–H bond functionalization is a rapidly evolving research field that is useful in organic synthesis and total synthesis.¹ Multisite-selective C–H functionalization has received considerable attention because this approach provides strategically attractive synthetic routes for the rapid derivatization of medicinally important privileged scaffolds and ultimately streamlines late-stage drug modification. The isoquinolone scaffold is a prominent structural motif present in a variety of natural and bioactive compounds.^{2,3} Many elegant examples of the construction of the isoquinolone framework via annulative couplings of benzamides with alkynes have been reported using various catalytic systems (Scheme 1a).^{4–9} However, there remain distinct challenges to regio- and chemoselective C–H functionalization for the introduction of aryl groups into the isoquinolone core due to difficulties associated with controlling the C–H bond at precise locations in the presence of electronically or sterically similar C–H bonds. Recently, catalytic

methods for C–H functionalization at the C3 position were achieved by installation of suitable directors, such as *N*-pyridyl or *N*-pyrimidyl groups on the nitrogen atom of isoquinolones (Scheme 1b).¹⁰

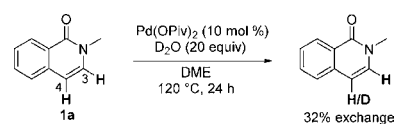
Driven by the need for a more efficient synthetic route, we were particularly interested in investigating catalytic systems that would enable modulating the site selectivity on unfunctionalized isoquinolone substrates. We envisioned that C8-regiocontrol could be achieved in isoquinolone arylation guided by coordination of the carbonyl group to the transition-metal catalyst. We also hypothesized that the bias of isoquinolone to undergo C8–H functionalization might be overridden by taking advantage of the inherent nucleophilic characteristics of isoquinolones upon treatment with an electrophilic metal catalyst to promote the reaction at the C4 position.¹¹ During our studies, an unprecedented and remarkable switch in the site selectivity was observed by the action of the catalytic system, which enabled facile installation of aryl groups in a highly selective and efficient fashion. Herein, we report the catalyst-controlled divergent C4/C8 site-selective C–H arylation of isoquinolones without recourse to extra directing groups (Scheme 1c).

The interaction of Pd(II) with isoquinolone **1a** was initially investigated using H/D exchange experiments (Scheme 2).¹² A significant level of deuterium incorporation (after 24 h, 32% D) was observed at the C4 position as shown in Scheme 2 (see the Supporting Information). It is conceivable that the C4–

Scheme 1. Synthetic Strategies for Arylated Isoquinolones



Scheme 2. Pd(II)-Catalyzed H/D Exchange Study



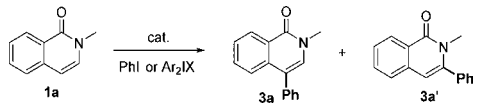
Received: June 26, 2015

Published: July 28, 2015

deuterated product may arise from an electrophilic palladation pathway.

This result prompted us to explore the feasibility of an expeditious synthetic approach for the installation of an aryl group at the C4 position of isoquinolones via the presumed electrophilic palladation pathway. Our efforts began by examining a possible collection of C–H arylation conditions using the Pd-catalytic system and iodobenzene as a coupling partner (Table 1). The use of Pd catalysts initiated arylation to

Table 1. Optimization of C4-Selective Arylation of Isoquinolone^a



entry	cat. (10 mol %)	aryl source (1.2 equiv)	additive	solvent	yield (%)	
					3a	3a'
1 ^b	Pd(PPh ₃) ₄	PhI		DMF	17	21
2 ^b	Pd(OAc) ₂	PhI		DMF	5	8
3	Pd(OAc) ₂	PhB(OH) ₂	Cs ₂ CO ₃	DMF/H ₂ O		
4	Pd(OAc) ₂	Ph ₂ IBF ₄		hexanes	51	2
5	Pd(OPiv) ₂	Ph ₂ IBF ₄		hexanes	69	2
6	Pd(OPiv) ₂	Ph ₂ IPF ₆		DME	55	2
7	Pd(OPiv) ₂	Ph ₂ IBF ₄		DME	78	1
8	Pd(TFA) ₂	Ph ₂ IBF ₄		DME	23	1
9	Pd(OPiv) ₂	Ph ₂ IBF ₄	PivOH	DME	25	8
10	Cu(OTf) ₂	Ph ₂ IBF ₄		DME		

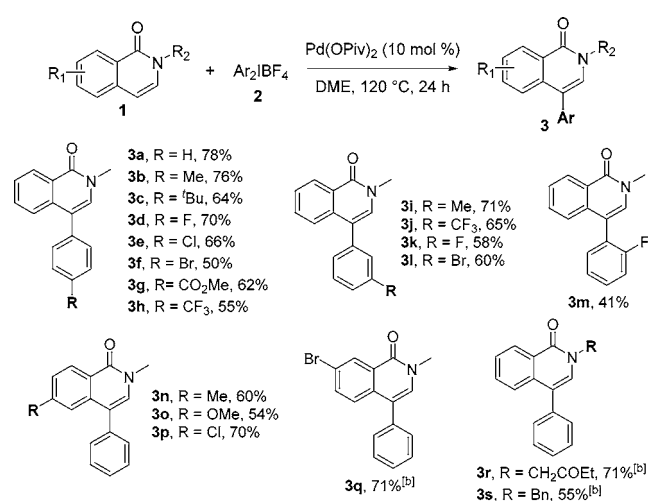
^a1a, iodonium salt (1.2 equiv), and catalyst (0.1 equiv) in solvent (0.1 M) at 120 °C; yields were determined by ¹H NMR. ^b1a, iodobenzene (2 equiv), Pd (0.1 equiv), Ag₂CO₃ (3 equiv), and CsOPiv (3 equiv) in DMF (0.1 M) at 120 °C.

some extent. However, mixtures of the coupling products (3a and 3a') were obtained (entries 1 and 2). The low level of C3/C4 regioselectivity for arylation can be attributed to the Pd^{0/II} mechanisms, which may follow two feasible pathways: (1) an electrophilic palladation pathway leading to C4-arylation or (2) a carbopalladation process generating a Heck-type product (C3-arylation).¹³ We reasoned that both the selectivity and reactivity may be enhanced by promoting the electrophilic palladation pathway and preventing the carbopalladation process. Therefore, we investigated the Pd^{II/IV} catalytic cycle, and a breakthrough was observed with arylidonium salts.¹⁴ By systematic optimization of the reaction conditions, it was found out that [Ph₂I]BF₄ not only increased the yield of 3a but also promoted a nearly exclusive reaction at the C4-position of isoquinolone. Altering the iodonium salt counterion demonstrated that anion –BF₄ was optimal for the reaction efficiency and regioselectivity. Among the Pd species screened, Pd(OPiv)₂ was the most effective for promoting the reactivity (see the Supporting Information). A survey of solvents revealed that DME provided the highest yield and the best regioselectivity. With the aim of tuning the electrophilicity of Pd(II), the ligand effect was investigated, but the addition of phosphine ligands or acid additives led to lower yields under the reaction conditions. The optimized catalytic conditions allowed for the direct installation of phenyl group using Pd(OPiv)₂ (10 mol %) and Ph₂IBF₄ (1.2 equiv) in DME to afford 3a in 78% yield. In considering C–H functionalization examples involving a highly electrophilic aryl–Cu(III) inter-

mediate, Cu catalytic systems were also screened but no desired product was obtained.¹⁴

The scope of both the arylidonium salts and isoquinolone substrates was next investigated to extend the utility of this methodology. Consistent with the previous observation, the C4-arylation process occurred almost exclusively at the C4 position and could tolerate the presence of a variety of functional groups from electron-donating (alkyl and methoxy) to electron-withdrawing (ester, halides, and trifluoromethyl) groups (Scheme 3). The reaction scope was extended to the

Scheme 3. Reaction Scope for C4 Arylation of Isoquinolone^a



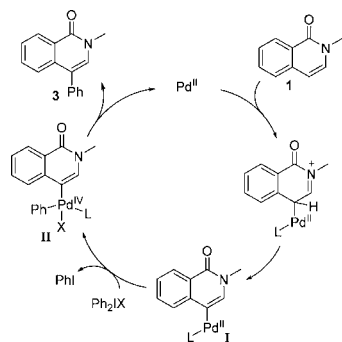
^aIsoquinolone, arylidonium salts (1.2 equiv) and Pd(OPiv)₂ (10 mol %) in DME (0.1 M) at 120 °C for 24 h; isolated yields. ^bReaction was conducted with Ph₂IPF₆ (1.2 equiv) in benzene (0.1 M).

arylidonium salt bearing an *ortho*-substituted aryl group, but the product was obtained in a modest yield (3m, 41%), which may due to steric factors. The bromo group was well tolerated to afford the synthetically versatile 3f, 3l, and 3q, thereby providing an opportunity for streamlining late-stage synthetic routes. The resilience of the bromo group indicates that reactive Pd(0) species is not likely to be formed under the reaction conditions. In addition, the *N*-substituents of isoquinolone tolerated the inclusion of benzyl and 2-oxobutyl groups (3r and 3s).

No obvious effects on the reaction were observed upon addition of galvinoxyl or TEMPO, which suggests that a radical mechanism is unlikely to be operative.^{14,15} On the basis of the experimental results and previous studies, the aforementioned electrophilic palladation pathway involving a Pd^{II/IV} catalytic cycle most likely accounts for the observed C4-regioselectivity (Scheme 4).¹⁴ The initial addition of Pd(II) to isoquinolone would be prone to proceed via electrophilic palladation, followed by deprotonation by the pivalate ligand to afford the C4-palladated species I. The oxidation of the Pd(II) complex to a Pd(IV) intermediate is readily promoted by arylidonium salt, and the subsequent reductive elimination of II delivered the C4-arylated isoquinolone 3.

Next, we speculated that C8-regiocontrol could be achieved using a coordinating amide moiety as a directing group, and this prediction was tested with a range of transition-metal catalysts (Table 2). Our initial attempts at C–H arylation were not successful with aryl iodide. Intriguingly, when the arylation was carried out using arylidonium salts in the presence of Ru(II) catalyst, a completely different selectivity pattern was observed

Scheme 4. Plausible Mechanism for C4 Arylation

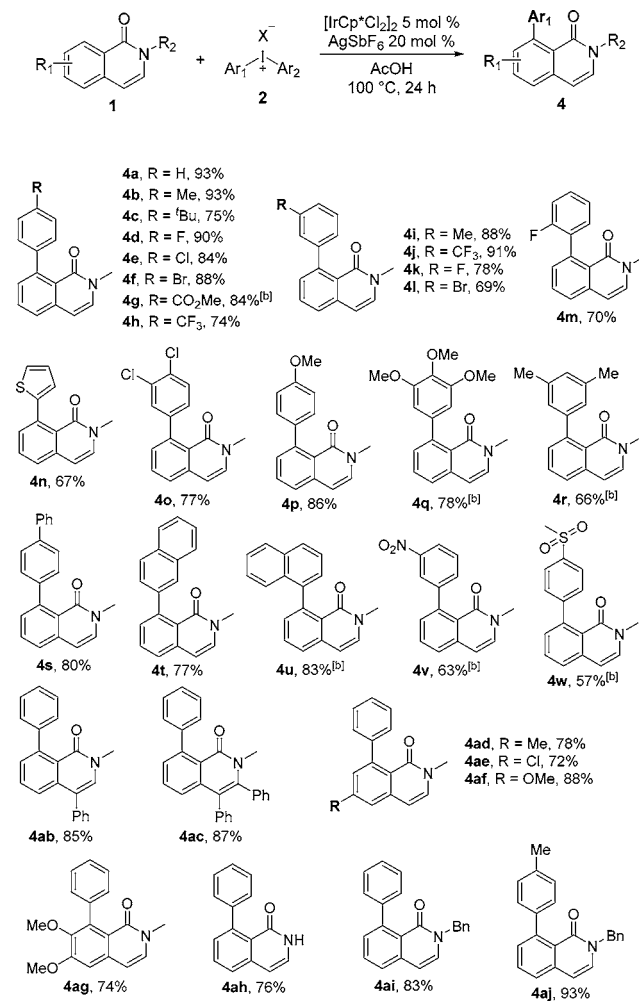
Table 2. Optimization Conditions for Arylation at the C8 Position of Isoquinolone^a

entry	cat.	ligand	additive	solvent	4a (%)
1	(CO) Ru(PPh ₃) ₃ H ₂	AgSbF ₆		hexanes	37
2	[RuCl ₂ (<i>p</i> - cymene)] ₂			hexanes	5
3	[Rh(1,5-COD) Cl] ₂	AgSbF ₆		hexanes	3
4	[RhCp*Cl ₂] ₂	AgSbF ₆		hexanes	18
5	[IrCp*Cl ₂] ₂	AgSbF ₆		hexanes	44
6	[IrCp*Cl ₂] ₂	AgNTf ₂		hexanes	28
7	[IrCp*Cl ₂] ₂	AgSbF ₆		PivOH	71
8	[IrCp*Cl ₂] ₂	AgSbF ₆		AcOH	93
9 ^b	[IrCp*Cl ₂] ₂	AgSbF ₆	Cu(OAc) ₂ · H ₂ O	AcOH	30
10 ^b	[IrCp*Cl ₂] ₂	AgSbF ₆	CsOAc	AcOH	24
11 ^c	[IrCp*Cl ₂] ₂	AgSbF ₆		AcOH	trace

^a1a, Ph₂IPF₆ (1.2 equiv), cat. (5 mol %), and AgSbF₆ (20 mol %) in solvent (0.1 M) at 100 °C for 24 h; yields were determined by ¹H NMR. ^bAdditive (3 equiv) was added. ^cIodobenzene was used.

that successfully resulted in C–C bond formation exclusively at the C8 position. Promising results were obtained using the Ir(III) complex, which exclusively afforded a C8-arylated product, which highlights the favorable coordination effect of the carbonyl group on the Ir catalyst. It is worth noting that the Ir(III)-catalyzed reaction with diaryliodonium salts is unprecedented. [IrCp*Cl₂]₂ was determined to be the most effective catalyst for promoting the C8-arylation reaction. The use of AcOH as the solvent was necessary to achieve a higher conversion. Anion –BF₄ was also optimal for the reaction efficiency. A systematic investigation of the catalytic systems resulted in optimized conditions involving the treatment of [IrCp*Cl₂]₂ (5 mol %) and AgSbF₆ (20 mol %) in AcOH with an excellent yield of 93%.

Next, studies of the C8 arylation reactions were extended to include various functionalized aryliodonium salts and isoquinolone substrates (Scheme 5). In general, variation in both the aryliodonium salts and isoquinolone substrates did not significantly affect the reaction efficiency, permitting the construction of a series of C8-arylated isoquinolones with complete site selectivity. For example, alkyl, phenyl, fluoride, bromide, chloride, ester, trifluoromethyl, methoxy, nitro, and sulfone groups were all viable under the reaction conditions, and yielded the C8-arylated isoquinolones. In some cases, the use of

Scheme 5. Arylation Reaction of C8 of Isoquinolone^a

^a1, aryliodonium salt (1.2 equiv), [IrCp*Cl₂]₂ (5 mol %), and AgSbF₆ (20 mol %) in AcOH (0.1 M) at 100 °C for 24 h; isolated yields. ^bAryliodonium salt (3 equiv), [IrCp*Cl₂]₂ (10 mol %), and AgSbF₆ (40 mol %) were used.

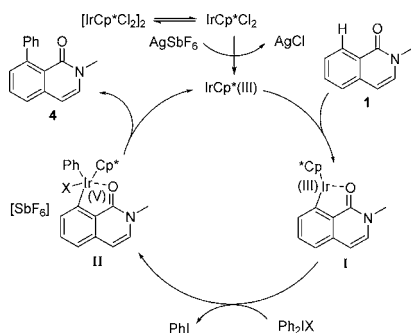
the arylmesityliodonium salts improved the product yields. Thiophene could also be efficiently installed at the C8 position with similar efficiency to afford the desired product 4n.

Nearly complete conversion was observed when H/D exchange experiments were carried out with the Ir catalytic system, indicating a reversible and fast C–H cleavage step (Scheme S1 in the SI). The C8–H coupling reaction appears to be initiated by chelate-directed C–H bond activation of the substrate, leading to iridacycle complex I (Scheme 6).¹⁶ Iridacycle I would be oxidized by the aryliodonium salt to afford arylrhodium complex II. Subsequent reductive elimination in II affords the arylated product 4 with the regeneration of the active Ir(III) species.

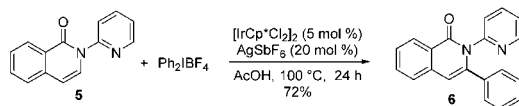
For broad utility, we preliminarily explored the possibility of extending this catalytic system to C3 arylation by investigating the influence of *N*-directing groups on the reaction sites. Indeed, the arylation of an isoquinolone substrate containing an *N*-pyridyl directing group proceeded smoothly using the iridium catalytic system, which resulted in the exclusive formation of the C3-arylated product (Scheme 7).

In summary, we developed the catalyst-controlled site-selective C–H arylation of isoquinolone using aryliodonium

Scheme 6. Plausible Reaction Pathway of C8 Arylation



Scheme 7. Preliminary Study of C3 Arylation Reaction



salts as the coupling partners. This strategy has been verified in divergent C4/C8 arylation, which can be broadly applied for the rapid derivatization of isoquinolones of high synthetic utility. The Pd(II)-catalyzed C4-selective arylation was successfully realized via an electrophilic palladation pathway. The use of the Ir(III) catalytic system enables catalytic cross-coupling at the C8 position.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.5b01840](https://doi.org/10.1021/acs.orglett.5b01840).

Experimental procedure and characterization of new compounds (^1H and ^{13}C NMR spectra) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hongorg@kaist.ac.kr

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported financially by the Institute for Basic Science (IBS-R010-G1) and the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2010-0022179 and 2011-0020322).

■ REFERENCES

- (1) For selected examples, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958. (c) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (d) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (e) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (f) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (g) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (h) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (i) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (j) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (k) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (l) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084.

(2) Pettit, G. R.; Ducki, S.; Eastham, S. A.; Melody, N. J. *J. Nat. Prod.* **2009**, *72*, 1279.

(3) Kaila, N.; Follows, B.; Leung, L.; Thomason, J.; Huang, A.; Moretto, A.; Janz, K.; Lowe, M.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. *J. Med. Chem.* **2014**, *57*, 1299.

(4) For Pd catalysis, see: (a) Zhong, H.; Yang, D.; Wang, S.; Huang, J. *Chem. Commun.* **2012**, *48*, 3236. (b) Zheng, Z.; Alper, H. *Org. Lett.* **2008**, *10*, 4903. (c) Batchu, V. R.; Barange, D. K.; Kumar, D.; Sreekanth, B. R.; Vyas, K.; Reddy, E. A.; Pal, M. *Chem. Commun.* **2007**, *19*, 1966.

(5) For Rh catalysis, see: (a) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592. (b) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (c) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744. (d) Yu, D. G.; de Azambuja, F.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 2754.

(6) For Ru catalysis, see: (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (b) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (c) Reddy, M. C.; Manikandan, R.; Jegannathan, M. *Chem. Commun.* **2013**, *49*, 6060.

(7) For Co catalysis, see: Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209.

(8) For Cu catalysis, see: (a) Lu, J.; Gong, X.; Yang, H.; Fu, H. *Chem. Commun.* **2010**, *46*, 4172. (b) Wang, F.; Liu, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2009**, *11*, 2469. (c) Too, P. C.; Chiba, S. *Chem. Commun.* **2012**, *48*, 7634. (d) Zhu, W.; Zhang, D.; Yang, N.; Liu, H. *Chem. Commun.* **2014**, *50*, 10634.

(9) For Ni catalysis, see: (a) Liu, C. C.; Parthasarathy, K.; Cheng, C. H. *Org. Lett.* **2010**, *12*, 3518. (b) Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (c) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085.

(10) (a) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10784. (b) Kwon, S.; Kang, D.; Hong, S. *Eur. J. Org. Chem.* **2015**, *7*, 1584.

(11) (a) Zhao, P.; Niu, R.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 4166. (b) Wang, F.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5430.

(12) Min, M.; Kim, Y.; Hong, S. *Chem. Commun.* **2013**, *49*, 196.

(13) (a) Yu, Y. Y.; Bi, L.; Georg, G. I. *J. Org. Chem.* **2013**, *78*, 6163.

(b) Liu, Y.; Li, D.; Park, C.-M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10784. (c) Moon, Y.; Kwon, D.; Hong, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11333.

(14) For selected examples of C–H arylation using arylidonium salt, see: (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. (c) Tang, D. T.; Collins, K. D.; Ernst, J. B.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 1809. (d) Topczewski, J. J.; Sanford, M. S. *Chem. Sci.* **2015**, *6*, 70. (e) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (f) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778. (g) Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8851.

(15) Neufeldt, S. R.; Sanford, M. S. *Adv. Synth. Catal.* **2012**, *354*, 3517.

(16) Kim, J.; Chang, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 2203.