

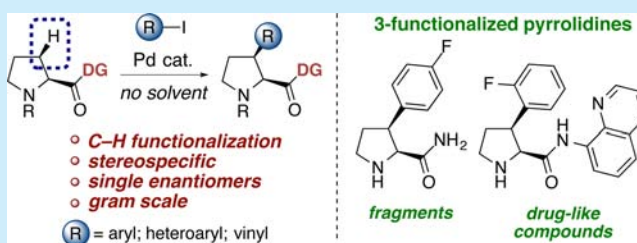
# Regio- and Stereospecific Synthesis of C-3 Functionalized Proline Derivatives by Palladium Catalyzed Directed C(sp<sup>3</sup>)-H Arylation

Dominic P. Affron, Owen A. Davis, and James A. Bull\*

Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, United Kingdom

## Supporting Information

**ABSTRACT:** Functionalization of C(sp<sup>3</sup>)-H bonds at the unactivated 3-position of proline derivatives has been achieved using aryl iodides and palladium catalysis. This directly affords *cis*-2,3-disubstituted pyrrolidines as single stereoisomers. 3-Arylation occurs in high yield under solvent-free conditions with aminoquinoline and methoxyaminoquinoline directing groups. The latter was readily removed to give primary amide derivatives with physicochemical properties appropriate for use as fragments in drug discovery.



Saturated heterocycles are central to life, biology, and medicine. The pyrrolidine ring is of particular interest due to its presence in cyclic amino acid proline, which has a pivotal role in protein secondary structure.<sup>1</sup> Pyrrolidines feature heavily in alkaloid natural products that display a wide variety of biological activity (Figure 1)<sup>2</sup> and are prevalent in active

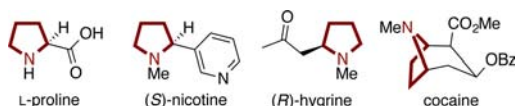


Figure 1. Pyrrolidine containing natural products.

pharmaceutical ingredients.<sup>3</sup> Furthermore, proline derivatives provide privileged catalysts for stereoselective synthesis.<sup>4</sup> Consequently, tremendous effort has been expended to develop synthetic routes to novel pyrrolidine derivatives.<sup>5–10</sup>

Functionalization of pyrrolidines at C-2 has received particular attention.<sup>6–9</sup> The activated C(2)-H bonds of *N*-Boc pyrrolidines allow enantioselective  $\alpha$ -lithiation and trapping with electrophiles<sup>7</sup> or Negishi cross-coupling (Figure 2A).<sup>7d</sup> Catalytic C-H functionalization of pyrrolidines at C-2 with both aryl and alkyl groups has been achieved using Ru-catalysis, utilizing 1-pyrroline<sup>8</sup> or 2-pyridyl<sup>9</sup> *N*-directing groups. On the other hand, there are markedly fewer methods for the functionalization of

pyrrolidines at C-3.<sup>10</sup> Moreover, there are no methods to functionalize the unactivated pyrrolidine C(3)-H bond.

Recently in drug discovery there has been considerable interest in incorporating more sp<sup>3</sup>-rich heterocycles,<sup>11</sup> and in the development of synthetic methods that can afford heterocyclic derivatives with desirable physicochemical properties and reliable stereocontrol.<sup>12</sup> As part of our program of fragment-oriented synthesis,<sup>13</sup> we considered that iterative functionalization at the pyrrolidine C-3 position would provide interesting fragments<sup>14</sup> in new and biologically relevant chemical space.<sup>15</sup> Here we report the synthesis of 2,3-difunctionalized pyrrolidines as single stereoisomers via directed C-H functionalization at the 3-position of proline derivatives (Figure 2B). Functionalized and heterocyclic aryl iodides are employed with minimal excess, and the resulting 3-(hetero)aryl pyrrolidines are transformed to compounds that comply with desirable criteria for drug discovery.

Catalytic direct functionalization of unactivated sp<sup>3</sup> C-H bonds has taken enormous strides in the past few years.<sup>16–22</sup> Unactivated primary and secondary alkyl C-H bonds undergo Pd-catalyzed arylation,<sup>17,18</sup> facilitated by the incorporation of removable directing groups to orient and stabilize palladacycle intermediates.<sup>16</sup> Daugulis' seminal report on the arylation of alkyl C-H bonds by a Pd<sup>II</sup>/Pd<sup>IV</sup> redox cycle used amide linked 8-aminoquinoline (AQ) as a directing group, with Pd(OAc)<sub>2</sub> and excess aryl iodide.<sup>17a</sup> Directed C(sp<sup>3</sup>)-H arylations have been extended to cyclopropanes,<sup>19</sup> cyclobutanes,<sup>20</sup> and acyclic amino acids.<sup>21,22</sup> However, to date there are only very limited applications of Pd-catalyzed functionalization to the unactivated C(sp<sup>3</sup>)-H bonds of heterocycles.<sup>23</sup>

Our study commenced from *N*-protected L-proline, from which we prepared amides **1** to **5** using EDC (*N*-(3-(dimethylamino)propyl)-*N'*-ethylcarbodiimide), to examine

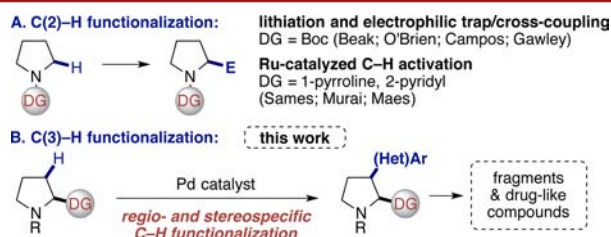


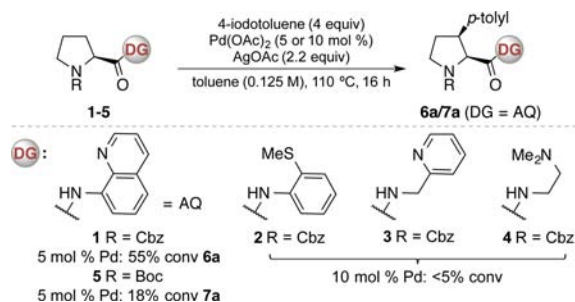
Figure 2. Pyrrolidine C-H functionalization approaches.

Received: August 26, 2014

Published: September 5, 2014

potential amide directing groups (Scheme 1).<sup>24</sup> We proposed that with carbamate *N*-protecting groups, the desired regio- and

### Scheme 1. Initial Optimization Varying Amide Auxiliary and *N*-Protecting Group



stereochemical outcome of the reaction would be facilitated by the amide adopting the pseudoaxial conformation to orient the directing group toward the *cis*-C(3)–H.

For initial investigation we selected conditions using 4-iodotoluene (4 equiv), Pd(OAc)<sub>2</sub> (5 or 10 mol %), and AgOAc as base. The reaction of amide **1** (R = Cbz) bearing the AQ auxiliary afforded an encouraging 55% conversion with a 5 mol % Pd loading. The reaction was stereospecific, affording 2,3-disubstituted pyrrolidine **6a** as the *cis*-diastereoisomer (*J* = 8.5 Hz, TolCH–CHN). Other directing groups examined gave <5% conversion even at 10 mol % Pd loading, and no conversion was observed with the *N*-Cbz acid. Reduced conversion (18%) was obtained for the *N*-Boc amide **5**.

Optimization of this transformation continued with *N*-Cbz AQ amide **1**. We aimed to maximize the yield of **6a**, but minimize loadings of aryl iodide and other reagents employed. Initial screening examined various Pd and Ni sources, with Pd(OAc)<sub>2</sub> giving the best yield.<sup>24</sup> The most suitable base was AgOAc from the range of bases investigated, with or without added pivalic acid, and toluene was the optimal solvent (Table 1, entry 1).<sup>24</sup> The concentration of the reaction had a major effect on the

**Table 1. Selected Optimization: Arylation of *N*-Cbz Proline AQ Amide **1****

entry	mmol of <b>1</b>	equiv of AgOAc	equiv of Tol-I	solvent (concn, M)	time (h)	yield <sup>a</sup> (%)
1	0.2	2.2	4.0	toluene (0.125)	15	55
2	0.2	2.2	4.0	toluene (0.5)	15	86
3	0.2	2.2	4.0	toluene (1.0)	15	97
4	0.2	1.8	1.8	toluene (1.0)	15	91
5	0.9	1.8	1.8	toluene (1.0)	20	64
6	0.9	1.8	1.8	toluene (2.0)	20	83
7	0.9	1.8	1.8	toluene (4.0)	20	86
8	0.9	1.8	1.8	– <sup>b</sup>	20	99 (91) <sup>c</sup>
9 <sup>d</sup>	0.9	1.8	1.8	– <sup>b</sup>	20	94
10	4.0	1.8	1.8	– <sup>b</sup>	36	(85) <sup>c</sup>
11 <sup>e</sup>	0.2	2.2	4.0	– <sup>b</sup>	20	33

<sup>a</sup>Yields calculated by <sup>1</sup>H NMR spectroscopy with respect to 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup>Reaction performed without solvent. <sup>c</sup>Isolated yield. <sup>d</sup>Reaction performed under air rather than argon. <sup>e</sup>Reaction performed with Tol-Br in place of Tol-I.

reaction yield (entries 1–3); increasing the concentration to 1.0 M raised the yield to 97%. The loading of iodotoluene and of AgOAc could both be reduced to 1.8 equiv with little compromise in yield (entry 4). However, on scaling up the reaction to 0.9 mmol the yield dropped to 64% (entry 5). Increasing the concentration further, to 2.0 and 4.0 M (entries 6–7), increased the yield to 83% and 86%, respectively. Finally, running the reaction in the absence of solvent increased the conversion to 99% (entry 8), which corresponded to a 91% isolated yield. Importantly the product was isolated as a single stereoisomer (>98% *ee*).<sup>24</sup> The reaction was operative under an air atmosphere (entry 9) and was also successful on a larger scale, affording 1.6 g of **6a** in 85% yield (entry 10). With tolyl bromide as the coupling partner the reaction was also successful, affording a 33% yield (entry 11).

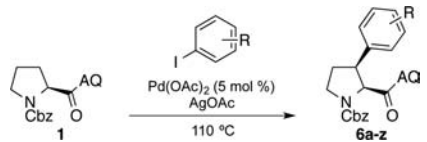
Using the optimized reaction conditions (Table 1, entry 8) we next examined an extensive range of aryl iodides to access 2-amido-3-aryl-pyrrolidines (Table 2). Phenyl and *m*- and *p*-alkyl substituted phenyl derivatives were successful (entries 1–3). 2-Methyliodobenzene was not compatible, presumably due to the increased steric congestion around palladacyclic intermediates, preventing oxidative addition or reductive elimination steps. An unfavorable steric effect was also apparent in 3,5-disubstituted examples though to a lesser extent. 4-Fluoroiodobenzene gave a high yield (entry 4), whereas the 2-fluoro analogue gave a 21% yield under standard conditions, which was increased to 44% upon heating for 60 h (entry 5). The 4-chloro-, 4-bromo-, and 4-iodo-aryl derivatives were successful, providing handles for potential further functionalization (entries 7–9). With both 4-bromoiodobenzene and 1,4-diiodobenzene, the bis-pyrrolidine aryl derivative was also isolated (9% and 33%, respectively).<sup>24</sup> The installation of highly electron-rich (entries 10–11) and electron-withdrawing (entries 12–18) aromatic groups was possible in similarly high yields; (4-MeO)C<sub>6</sub>H<sub>4</sub> was installed in 85% yield, and (4-CO<sub>2</sub>Et)C<sub>6</sub>H<sub>4</sub> was installed in 90% yield. Trifluoromethyl, ethyl ester, nitrile, and nitro functional groups were all tolerated (entries 14–18). An aromatic group bearing a methyl ketone gave a good yield (entry 19). Aromatics with pendant aldehyde and hydroxymethyl groups were also compatible though in reduced yields (entries 20–21).

Following this, the nature of the aromatic ring was varied. 2-Iodonaphthalene required the addition of solvent (toluene, 2.0 M) for the reaction to proceed, affording a 73% yield of **6v** (entry 22). 2-Iodothiophene afforded **6w** in 87% yield (entry 23), and pyridine derivatives substituted at the 2-, 3-, and 5-positions could also be successfully installed (entries 24–26). Finally, *E*-β-styryl iodide gave a 51% yield of the vinylylated product **8** (entry 27).

Having accessed a wide range of 3-substituted derivatives, we next examined removal of the protecting group and auxiliary to access compounds of interest for screening in biological programs. Deprotection of the Cbz group from a selection of the 3-arylated compounds occurred readily in high yield (Scheme 2), providing interesting drug-like structures.<sup>24</sup>

To access the targeted 3-aryl pyrrolidine fragments, removal of the directing group was required to afford appropriate MW and cLogP values. However, with both *N*-Cbz and *N*-H derivatives (**6a** and **9a**) the AQ group proved highly resistant to a wide variety of reagents. Therefore, we examined the use of 5-methoxy-8-aminoquinoline, recently reported by Chen as a directing group for C–H activations, which can be cleaved under mild oxidative conditions.<sup>22a</sup> We prepared amide **10** (Scheme 3) and found C–H arylation to be similarly successful under our

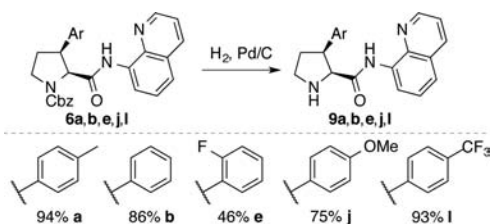
Table 2. Scope of the Aryl Iodides in the C–H Arylation of of *N*-Cbz Proline AQ Amide 1



entry	Arl	yield (%)	entry	Arl	yield (%)
1 <sup>a</sup>		a 91	14		n 90
2		b 86	15		o 83
3		c 45	16		p 59
4		d 88	17		q 74
5 <sup>b</sup>		e 44	18		r 70
6		f 60	19		s 74
7		g 78	20		t 29
8		h 68 <sup>c</sup>	21		u 22
9		i 64 <sup>d</sup>	22 <sup>c</sup>		v 73
10		j 85	23		w 87
11		k 34	24		x 34
12		l 84	25		y 28
13		m 76	26		z 54
			27		8 51 <sup>f</sup>

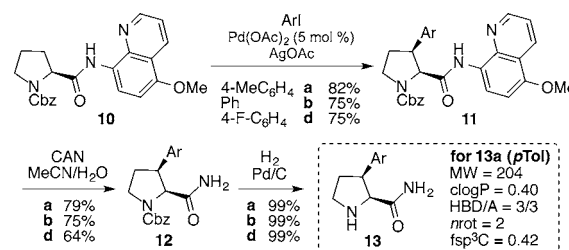
<sup>a</sup>ent-1 Afforded ent-6a in 80% yield. <sup>b</sup>60 h reaction time. <sup>c</sup>Bis-pyrrolidine: 9% yield. <sup>d</sup>Bis-pyrrolidine: 33% yield. <sup>e</sup>Modification to conditions: ArI (3 equiv), AgOAc (2.2 equiv), toluene (2.0 M). <sup>f</sup>E/Z = 95:5.

Scheme 2. Cbz Deprotection Affording Compounds with Drug-like Characteristics



optimal reaction conditions to afford compounds 11a,b,d. Pleasingly, oxidative deprotection with ceric(IV) ammonium nitrate (CAN) now proceeded readily to give the corresponding primary amides in high yields. Finally, removal of the Cbz group by hydrogenolysis was facile, affording *N*-H 2-amido-3-aryl pyrrolidines 13a,b,d exclusively as the *cis*-isomers, with attractive physicochemical properties, and functional groups, for fragment screening.

Scheme 3. Removal of Auxiliary and Cbz Groups To Afford Enantiopure Primary Amide “Fragments”



In conclusion, Pd-catalyzed C–H functionalization stereospecifically installs (hetero)aryl and vinyl substituents at the unactivated 3-position of proline derivatives that would otherwise require lengthy synthetic sequences and/or resolution. This enables the efficient preparation of small yet complex enantiopure *cis*-2,3-disubstituted pyrrolidines in fragment and drug-like chemical space. Efforts to extend this approach to other heterocyclic systems are currently underway in our lab.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra; details of reaction optimization; proposed catalytic cycle and calculated molecular properties for pyrrolidines 9 and 13. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [j.bull@imperial.ac.uk](mailto:j.bull@imperial.ac.uk)

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

For financial support we gratefully acknowledge the EPSRC (Career Acceleration Fellowship to J.A.B.; EP/J001538/1) and Imperial College London. Thanks are extended to Prof. Alan Armstrong (Imperial College London) for generous support and to Mr. Peter Haycock (Imperial College London) for NMR services. We thank the EPSRC National Mass Spectrometry Facility, Swansea.

## ■ REFERENCES

- (a) MacArthur, M. W.; Thornton, J. M. *J. Mol. Biol.* **1991**, *218*, 397.
- (b) Williamson, M. P. *Biochem. J.* **1994**, *297*, 249.
- (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Felpin, F.-X.; Lebretton, J. *Eur. J. Org. Chem.* **2003**, 3693.
- (c) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (d) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.
- (3) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845.

- (4) (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Panday, S. K. *Tetrahedron: Asymmetry* **2011**, *22*, 1817.
- (5) (a) Vo, C. T.; Bode, J. W. *J. Org. Chem.* **2014**, *79*, 2809. (b) Han, M.; Jia, J.; Wang, W. *Tetrahedron Lett.* **2014**, *55*, 784. (c) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (d) Gotoh, H.; Okamura, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 4056. (e) Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.* **1990**, *55*, 270.
- (6) Selected references: (a) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2012**, *18*, 10092. (b) Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 5257. (c) Zuo, Z.; Ahneman, D.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. (d) Haldar, S.; Mahato, S.; Jana, C. K. *Asian J. Org. Chem.* **2014**, *3*, 44. (e) Ma, L.; Chen, W.; Seidel, D. *J. Am. Chem. Soc.* **2012**, *134*, 15305. (f) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792. (g) Gribkov, D. V.; Pastine, S. J.; Schnürch, M.; Sames, D. *J. Am. Chem. Soc.* **2007**, *129*, 11750. (h) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114. (i) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568.
- (7) (a) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. (b) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870. (c) Beng, T. K.; Woo, J. S.; Gawley, R. E. *J. Am. Chem. Soc.* **2012**, *134*, 14764. (d) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538.
- (8) (a) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (b) Prokopcová, H.; Bergman, S. D.; Aelvoet, K.; Smout, V.; Herrebout, W.; Van der Veken, B.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2010**, *16*, 13063.
- (9) (a) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882. (b) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (c) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. *Org. Lett.* **2014**, *16*, 1876.
- (10) For recent examples: (a) Allwood, D. M.; Blakemore, D. C.; Brown, A. D.; Ley, S. V. *J. Org. Chem.* **2014**, *79*, 328. (b) Molander, G. A.; Traister, K. M.; O'Neill, B. T. *J. Org. Chem.* **2014**, *79*, 5771.
- (11) (a) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. *Drug Discovery Today* **2011**, *16*, 164. (b) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (c) Lovering, F. *Med. Chem. Commun.* **2013**, *4*, 515.
- (12) (a) Hung, A. W.; Ramek, A.; Wang, Y.; Kaya, T.; Wilson, J. A.; Clemons, P. A.; Young, D. W. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6799. (b) Nadin, A.; Hattotuagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114. (c) Doveston, R.; Marsden, S.; Nelson, A. *Drug Discovery Today* **2014**, *19*, 813.
- (13) (a) Morgan, K. F.; Hollingsworth, I. A.; Bull, J. A. *Chem. Commun.* **2014**, *50*, 5203. (b) Davis, O. A.; Hughes, M.; Bull, J. A. *J. Org. Chem.* **2013**, *78*, 3470.
- (14) Fragments targeted to comply with a modified 'rule-of-3': MW <300, cLogP <3; HBD ≤3; HBA ≤6. See: (a) Congreve, M.; Carr, R.; Murray, C.; Jhoti, H. *Drug Discovery Today* **2003**, *8*, 876. (b) Köster, H.; Craan, T.; Brass, S.; Herhaus, C.; Zentgraf, M.; Neumann, L.; Heine, A.; Klebe, G. *J. Med. Chem.* **2011**, *54*, 7784. (c) Murray, C. W.; Rees, D. C. *Nat. Chem.* **2009**, *1*, 187.
- (15) (a) Mok, N. Y.; Brenk, R.; Brown, N. *J. Chem. Inf. Model.* **2014**, *54*, 79. (b) Over, B.; Wetzel, S.; Grütter, C.; Nakai, Y.; Renner, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2013**, *5*, 21.
- (16) (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (c) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.
- (17) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689.
- (18) For recent examples of complementary ligand enabled Pd<sup>0</sup>/Pd<sup>II</sup> C–H arylation, see: (a) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216. (b) Li, S.; Chen, G.; Feng, C.-G.; Gong, W.; Yu, J. *J. Am. Chem. Soc.* **2014**, *136*, 5267. (c) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. *Nat. Chem.* **2014**, *6*, 146. (d) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138.
- (19) (a) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394. (b) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *Org. Lett.* **2013**, *15*, 3238.
- (20) (a) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076. (b) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7507. (c) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem.* **2013**, *78*, 11911.
- (21) (a) Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. Á.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175. (b) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. (c) Fan, M.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12152.
- (22) Also see: (a) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124. (b) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (c) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (d) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. For Ni catalysis, see: (e) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898. (f) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789.
- (23) (a) Wu reported C–H amination at C-3 of a proline derivative: Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett.* **2014**, *16*, 480. (b) Chen has shown one example of C–H alkylation on a piperidine derivative. See ref 22c. (c) For alkynylation on a tetrahydropyran derivative, see: He, J.; Wasa, M.; Chan, K. S. L.; Yu, J. *J. Am. Chem. Soc.* **2013**, *135*, 3387. (d) For arylation of a tetrahydropyran derivative: Wasa, M.; Chan, K. S. L.; Zhang, X.; He, J.; Miura, M.; Yu, J. *J. Am. Chem. Soc.* **2012**, *134*, 18570.
- (24) See Supporting Information for further details.