



**HAL**  
open science

## Pd-Catalyzed direct C–H functionalization of imidazolones with aryl- and alkenyl halides

Mickaël Muselli, Christine Baudequin, Christophe Hoarau, Laurent Bischoff

► **To cite this version:**

Mickaël Muselli, Christine Baudequin, Christophe Hoarau, Laurent Bischoff. Pd-Catalyzed direct C–H functionalization of imidazolones with aryl- and alkenyl halides. *Chemical Communications*, 2015, 51 (4), pp.745-748. 10.1039/c4cc07917e . hal-01141471

**HAL Id: hal-01141471**

**<https://hal.science/hal-01141471v1>**

Submitted on 13 Apr 2015

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Cite this: *Chem. Commun.*, 2015, 51, 745

Received 7th October 2014,  
Accepted 20th November 2014

DOI: 10.1039/c4cc07917e

www.rsc.org/chemcomm

## Pd-Catalyzed direct C–H functionalization of imidazolones with aryl- and alkenyl halides†

Mickaël Muselli, Christine Baudequin, Christophe Hoarau\* and Laurent Bischoff\*

**Direct C–H arylation and alkenylation of 4,4'-dialkylimidazolones with a broad range of halides under palladium and copper catalysis have been developed. This methodology is applied to the preparation of recently discovered fatty acid synthetase (FAS) inhibitors.**

Imidazolone is a fundamental naturally-occurring non-aromatic heterocycle intensively used in the synthesis of functional materials and pharmaceuticals. Notably, due to both small size and attractive fluorescent properties, imidazolones mostly 4-arylidene and/or 2-aryl(alkynyl)ated constitute the main cores of numerous fluorescent probes for biological studies. Among the most-representative members of this family are the green-fluorescent proteins (GFP), the Kaede protein and BODIPY-like Burgess fluorophore (Fig. 1).<sup>1</sup> As recent remarkable applications in drug-design, 2-aryl(alkyl)ated imidazolones have been specifically selected for the treatment of obesity-related disorders<sup>2</sup> and hypertension.<sup>3</sup> They have also been found to display important biological activities<sup>4</sup> as fatty acid synthase (FAS) inhibitors (Fig. 1).<sup>5</sup>

Current synthetic methodologies towards highly functionalized imidazolones that allow challenging various substitutions at 2-position are mainly based upon a ring-closing condensation of  $\alpha$ -amidoamides (Scheme 1).<sup>6</sup> This synthetic route is fraught with the inherent difficulty in achieving highly electronically-different substrate scope so that notably, the 2-alkynylated imidazolones are mostly obtained *via* the 2-methyl imidazolones<sup>7</sup> or oxazolone intermediates (Scheme 1).<sup>8</sup> Innovative synthetic methods enabling a late-stage functionalization of simple imidazolones are thus actively needed. By contrast with the structurally-related aromatic imidazole, conventional transition-metal cross-coupling reactions are however poorly appropriated due to the hard access to required 2-metallated or 2-halogenated imidazolones. To our knowledge, only the cross-coupling of 2-methylthio-imidazolone has been reported.<sup>9</sup> In this

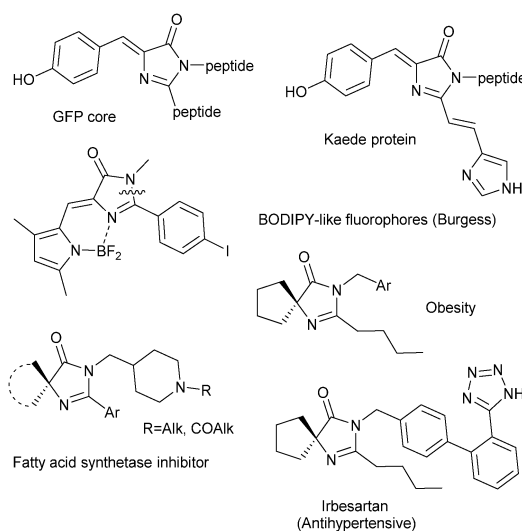
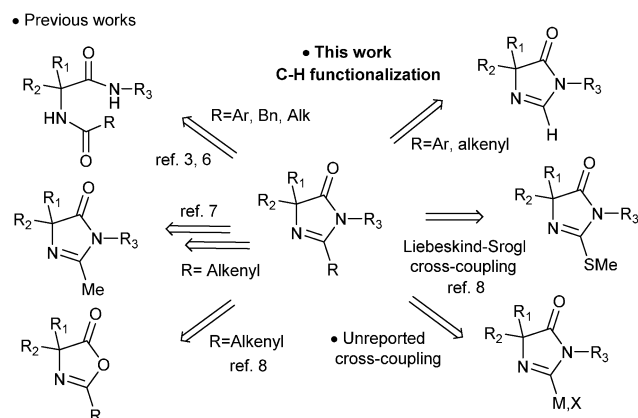


Fig. 1 Imidazolone framework in functional materials and pharmaceuticals.



Scheme 1 Previous and proposed access to 4-arylidene and 4,4'-dialkyl imidazolones.

context, the discovery of direct C–H functionalization of imidazolones methodologies<sup>10,11</sup> is particularly useful (Scheme 1). Herein, the first

Mickaël Muselli, Christine Baudequin, Christophe Hoarau, Laurent Bischoff  
Normandie Univ, COBRA, UMR 6014 et FR 3038, Univ Rouen, INSA Rouen, CNRS,  
IRCOF, 1 rue Tesnière, 76821 Mont Saint Aignan Cedex, France.

E-mail: christophe.hoarau@insa-rouen.fr, laurent.bischoff@insa-rouen.fr

† Electronic supplementary information (ESI) available: NMR spectra and data for all compounds. See DOI: 10.1039/c4cc07917e

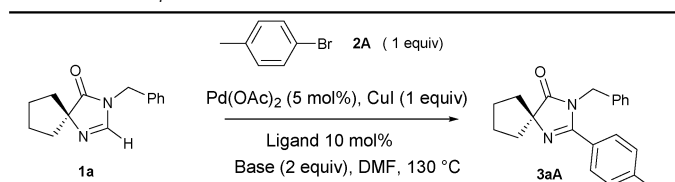
direct C–H arylation as well as alkenylation of 4,4'-dialkylimidazolones at 2-position with aryl- and alkenyl halides are reported under Pd<sup>(0)</sup>/Cu<sup>(I)</sup> bis-catalysis.

Importantly, the activation of the imidazolone ring by prior *N*-oxidation is not required. This work represents a rare use of the direct C–H functionalization methodology applied to non-aromatic heterocycles.<sup>12</sup>

We started to explore the direct C–H coupling of 4,4'-cyclopentylimidazolone **1a** with *p*-bromotoluene **2A**. Indeed, any reaction occurred under the strictly Bellina's conditions under Pd<sup>(0)</sup>/Cu<sup>(I)</sup> bis-catalysis without base and ligand assistance (Table 1, entry 1),<sup>13</sup> the use of potassium carbonate base led to the desired product in 63% isolated yield (Table 1, entry 2). The reaction became fairly effective by using DBU base and the full conversion of imidazolone **1a** was finally reached using PPh<sub>3</sub> ligand (Table 1, entry 5).<sup>14</sup> The reaction remained highly operative at a slightly lower 110 °C temperature, interestingly. We next investigated the generality of the optimized protocol using various arylhalides (Table 2). We found invariably that the electronic effect and the position of substituents on the aromatic unit of the halides slightly influenced the outcome of the reaction since various 2-arylated imidazolones **3aB–K** flanked with trifluoromethyl, cyano, fluoro and acetamido functions were isolated in good yields. Remarkably, the procedure remained successful with aryl iodides to produce imidazolones **3aA**, **3aG** and **3aK** in similar or better yields than those obtained using corresponding aryl bromides. Moreover, reaction of **1a** with *p*-iodobromobenzene **2K** proceeded highly selectively to afford the imidazolone **3aK** in good yield. The latter is useful to introduce further various substituents on the aromatic unit to design notably new precursors for biologically-active substances.

To extend the scope of this methodology, we focused on direct C–H alkenylation reaction with alkenylhalides. Interestingly, the direct C–H alkenylation of **1a** with 2-bromostyrene as its pure (*E*)-isomer was successfully achieved applying the above optimized C–H arylation protocol. However the 2-styrenylimidazolone **5aA** was isolated in poor 12% yield due to the low conversion of imidazolone **1a**.

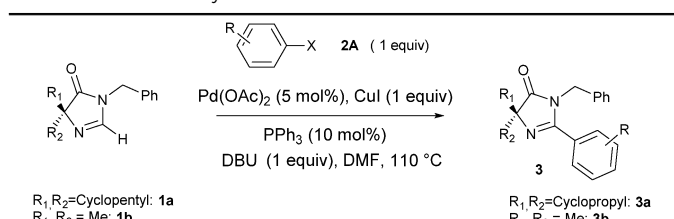
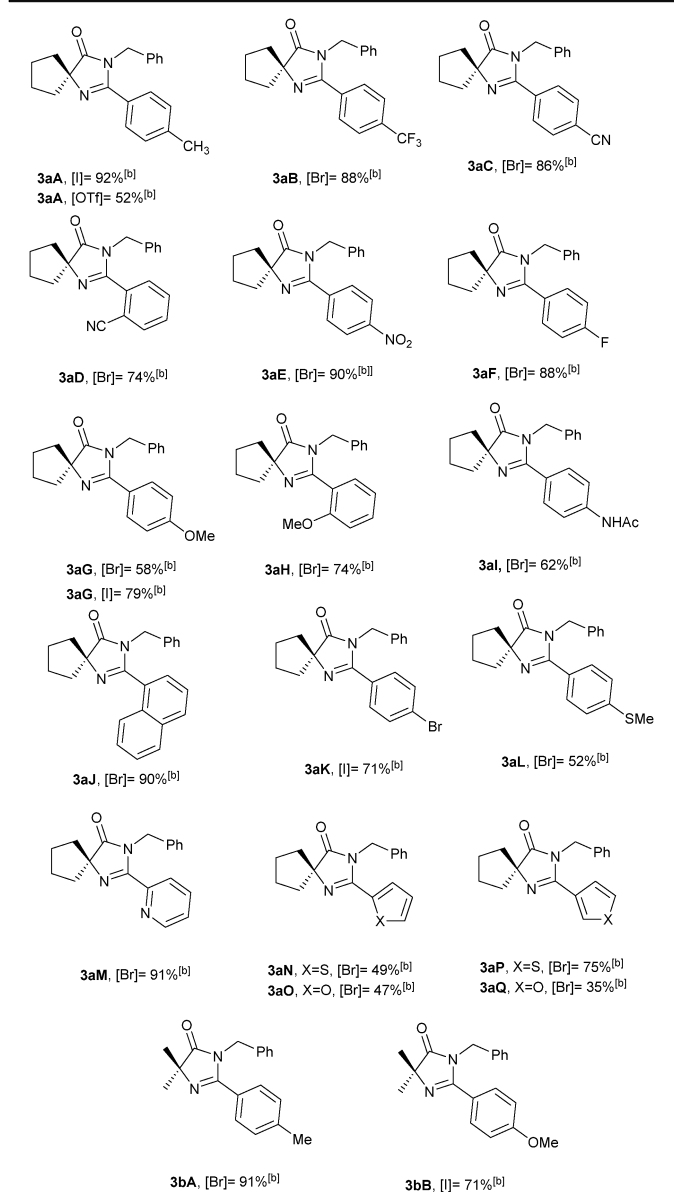
**Table 1** Pd-catalyzed C–H arylation of *N*-benzyl-4,4'-cyclopentylimidazolone **1a** with *p*-bromotoluene **2A**<sup>a</sup>



Entry	Ligand	Base	<i>T</i> (°C)	Yield <sup>b</sup> (%)
1	—	—	130	5
2	—	K <sub>2</sub> CO <sub>3</sub>	130	63
3	—	CS <sub>2</sub> CO <sub>3</sub>	130	45
4	—	DBU	130	65
5	PPh <sub>3</sub>	DBU	130	92
6	<b>PPh<sub>3</sub></b>	<b>DBU<sup>d</sup></b>	<b>110</b>	<b>92</b>
7	PPh <sub>3</sub>	DBU	90	64
8	PPh <sub>3</sub>	DBU <sup>d</sup>	110	92 <sup>c</sup>

<sup>a</sup> Pd(OAc)<sub>2</sub> (5 mol%), CuI (1 equiv.), ligand (10 mol%), base (2 equiv.), **1a** (1 equiv.), **2A** (1 mmol), DMF (0.35 M), 12 h. <sup>b</sup> Yield based on isolated product after flash chromatography. <sup>c</sup> Scale up on 2 mmol of halide under optimized conditions. <sup>d</sup> 1 equiv. of DBU used.

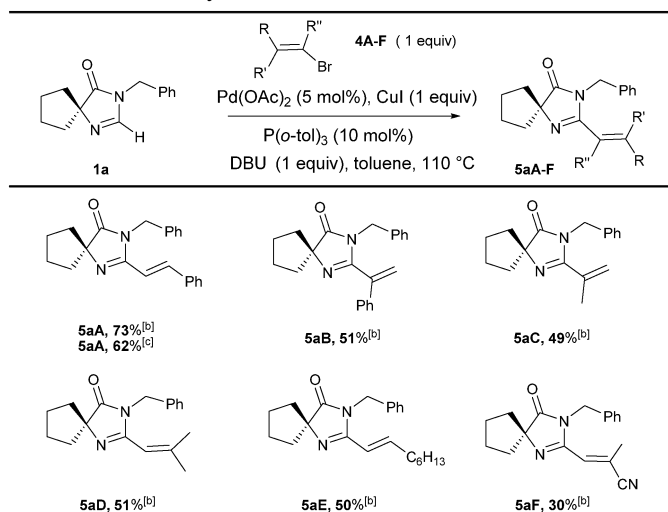
**Table 2** Pd-catalyzed direct C–H arylation of 4,4'-disubstituted imidazolones **1a–b** with aryl halides<sup>a</sup>

**3aA**, [I] = 92%<sup>[b]</sup>  
**3aA**, [OTf] = 52%<sup>[b]</sup>  
**3aB**, [Br] = 88%<sup>[b]</sup>  
**3aC**, [Br] = 86%<sup>[b]</sup>  
**3aD**, [Br] = 74%<sup>[b]</sup>  
**3aE**, [Br] = 90%<sup>[b]</sup>  
**3aF**, [Br] = 88%<sup>[b]</sup>  
**3aG**, [Br] = 58%<sup>[b]</sup>  
**3aG**, [I] = 79%<sup>[b]</sup>  
**3aH**, [Br] = 74%<sup>[b]</sup>  
**3aI**, [Br] = 62%<sup>[b]</sup>  
**3aJ**, [Br] = 90%<sup>[b]</sup>  
**3aK**, [I] = 71%<sup>[b]</sup>  
**3aL**, [Br] = 52%<sup>[b]</sup>  
**3aM**, [Br] = 91%<sup>[b]</sup>  
**3aN**, X=S, [Br] = 49%<sup>[b]</sup>  
**3aO**, X=O, [Br] = 47%<sup>[b]</sup>  
**3aP**, X=S, [Br] = 75%<sup>[b]</sup>  
**3aQ**, X=O, [Br] = 35%<sup>[b]</sup>  
**3aA**, [Br] = 91%<sup>[b]</sup>  
**3aB**, [I] = 71%<sup>[b]</sup>

<sup>a</sup> Pd(OAc)<sub>2</sub> (5 mol%), CuI (1 equiv.), PPh<sub>3</sub> (10 mol%), DBU (1 equiv.), **1a–b** (1 equiv.), HetAr-I or HetAr-Br (1 equiv.), DMF (0.35 M), 110 °C, 12 h. <sup>b</sup> Yield based on isolated product after flash chromatography.

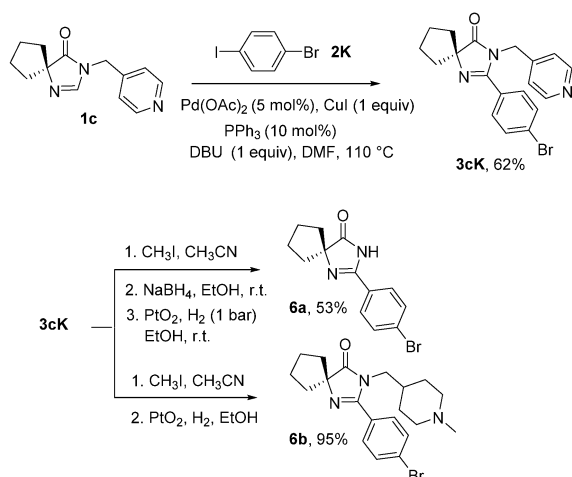
However, switching DMF solvent to toluene along with PPh<sub>3</sub> to P(*o*-Tol)<sub>3</sub> ligand afforded the expected cycloalkylimidazolone **5aA** in 73% yield in line to our previous observations in the oxazole series (Table 3).<sup>15</sup> A similar reactivity was observed using freshly prepared Hermann–Beller palladacycle precluding that the direct C–H

**Table 3** Pd-catalyzed direct C–H alkenylation of 4,4'-disubstituted imidazolone **1a** with alkenylbromides<sup>a</sup>

<sup>a</sup> Pd(OAc)<sub>2</sub> (5 mol%), CuI (1 equiv.), P(*o*-tol)<sub>3</sub> (10 mol%), DBU (1 equiv.), **1a** (1 equiv.), alkenyl-Br (1 equiv.), DMF (0.35 M), 110 °C, 12 h. <sup>b</sup> Yield based on isolated product after flash chromatography. <sup>c</sup> Hermann–Beller catalyst used.

alkenylation may proceed with this precatalyst readily formed by reacting Pd(OAc)<sub>2</sub> with P(*o*-tol)<sub>3</sub> in toluene at 80 °C.<sup>14</sup> Interestingly, the C–H alkenylation of **1a** remained effective under steric effect when 1-iodostyrene coupling partner was used. Several bromoalkenes **4C–E** were also successfully coupled with **1a** to afford 2-alkenylated **5C–E** in fair yields (Table 3). The scope was finally completed by the innovative production of the imidazolone **5aF** bearing an acrylamide function at 2-position giving novel opportunities in functional-diversity (Table 3). Notably the acrylamide may provide access to complex aminoalkyles through full or partial reduction of the nitrile in combination with prior Michael-type addition reaction to the acrylamide system (Scheme 2).

In the current context of intensive efforts in the discovery of therapeutics for the treatment of obesity-disorder, we directed the application towards an innovative synthesis of various *N*-alkylated

**Scheme 2** Innovative access to fatty acid synthase inhibitors.

2-aryl-4,4'-cycloalkylimidazolones claimed as fatty acid synthetase inhibitors (Scheme 1).<sup>4</sup> First, the *N*-isonicotinylimidazolone **1c** was successfully submitted to the optimized direct C–H arylation procedure to afford the imidazolone **3cK** in fair yield. Pleasingly, the subsequent methylation of **3cK** with iodomethane occurred only at the pyridine nitrogen. The pyridinium salt intermediate was subsequently cleanly reduced through the conventional double reduction with sodium borohydride and then dihydrogen under PtO<sub>2</sub> catalysis to provide the FAS inhibitor **6b** in 53% yield over a two-step synthesis. Furthermore interestingly, we found that the isonicotinyl protection could be fully removed. Indeed, the PtO<sub>2</sub>-catalyzed dihydrogen reduction of the pyridinium salt intermediate provided quantitatively the unprotected imidazolone **6a** previously used to prepare a wide variety of biologically active *N*-alkylated imidazolones.<sup>4,16</sup>

As summary, we have developed an innovative and efficient synthetic methodology for direct C–H arylation and alkenylation of 4,4'-dialkylimidazolones under Pd<sup>(0)</sup>/Cu<sup>(0)</sup> bis-catalysis. Several electronically-different aryl- and alkenyl halides proved to be efficient coupling partners enabling a wide range of 4,4'-dialkylated imidazolones to be prepared in moderate to good yields. This novel methodology is functional group-tolerant, step-economical and highly flexible. This work represents one of first investigations in challenging direct C–H functionalization of non-aromatic heterocycles. Remarkably, the standard activation *via* *N*-oxidation is not required. This methodology may find direct applications in pharmacological and material sciences. As demonstration in this communication, an innovative and neat preparation of a recently-discovered *N*-alkylated 4,4'-cycloalkylimidazolone-based fatty acid synthase (FAS) inhibitor is proposed.

This work has been partially supported by INSA Rouen, Rouen University, CNRS EFRD, CRUNCH network, Labex SynOrg (ANR-11-LABEX-0029).

## Notes and references

- (a) I. V. Yampolsky, A. A. Kislukhin, T. T. Amatov, D. Shcherbo, V. K. Potapov, S. Lukyanov and K. A. Lukyanov, *Bioorg. Chem.*, 2008, **36**, 96; (b) L. Wu and K. Burgess, *J. Am. Chem. Soc.*, 2008, **130**, 4089.
- (a) Y. Chen, S. J. O'Connor, D. Guan, J. Newcom, J. Chen, L. Yi, H. Zhang, L. M. Hunyadi and R. Natero, WO PCT 058727, 2004; (b) N. Murugesan, J. E. Tellew, J. E. Macor and Z. Gu, WO PCT 01389, 2000; (c) N. Murugesan, J. E. Tellew, J. E. Macor and Z. Gu, US PCT 0143024, 2002.
- P. Ye, K. Sargent, E. Stewart, J.-F. Liu, D. Yohannes and L. Yu, *J. Org. Chem.*, 2006, **71**, 3137.
- (a) M. S. Malamas, J. J. Erdei, W. F. Fobare, D. A. Quagliato, S. A. Antane and A. J. Robichaud, US PCT 0072925, 2007; (b) S. Berg, J. Holenz, K. Hoegdin, J. Kihlstrom, K. Kolmodin, J. Lindstrom, N. Plobeck, D. Rotticci, F. Sehgelmeble and M. Wirstam, WO PCT 145569 A1, 2007; (c) S. Berg, J. Hallberg, K. Hoegdin, S. Karlstrom, A. Kers, N. Plobeck and L. Rakos, WO PCT 076044A1, 2008.
- P. J. Connolly, T. L. Lu, M. H. Parker, D. Ludovici, C. Meyer, L. Meerpoel, K. Smans and C. Rocaboy, WO PCT 039769, 2014.
- For recent reviews or significant examples, see: (a) M. S. Baranov, K. A. Lukyanov and I. Yampolsky, *Russ. J. Bioorg. Chem.*, 2013, **39**, 223; (b) P. E. Ivashkin, I. V. Yampolsky and K. A. Lukyanov, *Russ. J. Bioorg. Chem.*, 2009, **35**, 652; (c) C.-Y. Lee, Y.-C. Chen, H.-C. Lin, Y. Jhong, C.-W. Chang, C.-H. Tsai, C.-L. Kao and T.-C. Chien, *Tetrahedron*, 2012, **68**, 5898; (d) P. E. Ivashkin, K. A. Lukyanov, S. Lukyanov and I. V. Yampolsky, *J. Org. Chem.*, 2011, **76**, 2782; (e) R. Bossio, S. Marcaccini, P. Paoli, S. Papaleo, R. Pepino and C. Polo, *Liebigs Ann. Chem.*, 1991, 843.

- 7 (a) B. K. Rajbongshi, N. N. Nair, M. Nethaji and G. Ramanathan, *Cryst. Growth Des.*, 2012, **12**, 1823; (b) W.-T. Chuang, B.-S. Chen, K.-Y. Chen, C.-C. Hsieh and P.-T. Chou, *Chem. Commun.*, 2009, 6982; (c) G. Bhattacharjya, S. S. Agasti and G. Ramanathan, *ARKIVOC*, 2006, **10**, 152; (d) M. Z. Badr, H. A. H. El-Sherief and M. E. Tadros, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2267.
- 8 (a) A. K. Mukerjee and P. Kumar, *Can. J. Chem.*, 1982, **60**, 317; (b) X. He, A. F. Bell and P. J. Tonge, *Org. Lett.*, 2002, **4**, 1523.
- 9 (a) S. Oumouch, M. Bourotte, M. Schmitt and J.-J. Bourguignon, *Synthesis*, 2005, 25; (b) S. Gosling, P. Rollin and A. Tatibouet, *Synthesis*, 2011, 3649.
- 10 For general reviews on direct C–H arylation of heterocycles, see: (a) R. Rossi, F. Bellina, M. Lessi and C. Manzini, *Adv. Synth. Catal.*, 2014, **356**, 17; (b) K. Hirano and M. Miura, *Synlett*, 2011, 294; (c) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (d) J. Roger, A. L. Gottumukkala and H. Doucet, *ChemCatChem*, 2010, **2**, 20; (e) F. Bellina and R. Rossi, *Adv. Synth. Catal.*, 2010, **352**, 1223; (f) F. Bellina and R. Rossi, *Tetrahedron*, 2009, **65**, 10269; (g) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174.
- 11 For general reviews on direct C–H alkenylation of heterocycles, see: (a) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74; (b) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886; (c) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (d) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (e) S. Messaoudi, J.-D. Brion and M. Alami, *Eur. J. Org. Chem.*, 2010, 6495.
- 12 For examples of direct Pd-catalyzed C–H functionalization of non-aromatic heterocycles, see: (a) E. Demory, D. Farran, B. Baptiste, P. Y. Chavant and V. Blandin, *J. Org. Chem.*, 2012, **77**, 7901; (b) H. Zhao, R. Wang, P. Chen, B. T. Gregg, M. M. Hsia and W. Zhang, *Org. Lett.*, 2012, **14**, 1872; (c) L. Ackermann, S. Barfusser, C. Kornhaass and A. R. Kapdi, *Org. Lett.*, 2011, **13**, 3082; (d) N. Gigant and I. Gillaizeau, *Org. Lett.*, 2012, **14**, 3304.
- 13 (a) F. Bellina, S. Cauteruccio and R. Rossi, *Eur. J. Org. Chem.*, 2006, 1379; (b) F. Bellina, C. Calandri, S. Cauteruccio and R. Rossi, *Tetrahedron*, 2007, **63**, 1970; (c) F. Bellina, S. Cauteruccio and R. Rossi, *J. Org. Chem.*, 2007, **72**, 8543.
- 14 See ESI† for all details.
- 15 C. Verrier, C. Hoarau and F. Marsais, *Org. Biomol. Chem.*, 2009, **7**, 647.
- 16 The unprotected imidazolone **6a** could not be produced alternatively from **3aK** following standard protocols for removing the benzyl group from amide function.