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Synthesis of substituted azafluorenones from dihalogeno diaryl ketones by palladium-catalyzed auto-tandem processes†

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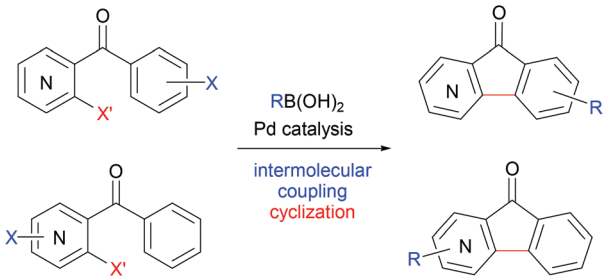
Substituted azafluorenones were synthesized from different dihalogeno diaryl ketones under palladium catalysis by combining either Suzuki or Heck coupling with direct cyclizing arylation. Conditions were identified to allow both auto-tandem processes to proceed successfully from 3-(bromobenzoyl)- or 3-benzoyl-4-bromo-2-chloropyridines, as well as 4-benzoyl-2,3- and 4-benzoyl-2,5-dichloropyridines.

Azafluorenones are compounds endowed with biological properties, for example in connection with their antifungal,[1] antimicrobial,[2] antimalarial,[2b,3] and cytotoxic[2b,4] activities, or else for their role in the treatment of neurodegenerative disorders.[5] Thus, many studies have been devoted to their synthesis. Among modern synthetic methods to access them, lithiations[6] and multicomponent reactions[2d,4a,7] can be cited.

In 2010, Kraus and Kempema developed an approach involving 2-bromoaryl 3-pyridyl ketones (prepared in two steps by reaction of 3-pyridyllithiums with 2-bromobenzaldehydes followed by oxidation) in intramolecular Heck cyclization reactions.[2c] In 2013, Ray and co-workers achieved the conversion within one step of α-aryl-α-(2-bromo-3-pyridyl)methanols to 4-azafluorenones, owing to facile oxidation of the alcohols.[8]

Recently, we developed an approach[9] to azafluorenones using diaryl ketones bearing a halogen at the 2 position of one of the aryl groups (prepared by deprotocupration–aroylation[10]) in intramolecular direct palladium-catalyzed arylation reactions.[11] We thus thought that the presence of an additional halogen on such diaryl ketones could permit tandem reactions. Combining cyclization with cross-couplings such as Suzuki reaction[12] could notably afford substituted azafluorenones (Scheme 1). We here describe the results of the study.



Scheme 1 Possible syntheses of substituted azafluorenones using palladium-catalyzed tandem reactions.

We first turned our attention to palladium-catalyzed Suzuki coupling-intramolecular arylation auto-tandem[13] reactions using 2-chloro-3-(halogenobenzoyl)pyridines in order to attain 4-azafluorenones functionalized on their phenyl ring. These conversions were attempted using a protocol optimized for the cyclization of 3-benzoyl-2-chloropyridine to 4-azafluorenone.[9] Inspired by conditions previously described for the cyclization of 2-chloro diaryl aniline to carbazole,[14] this protocol employed catalytic amounts of $Pd(OAc)_2$ as the transition metal source, electron-rich and bulky trialkyl phosphine Cy_3P (Cy = cyclohexyl) as a ligand, K_2CO_3 as a base, and DMF at 130 °C. Similar conditions being suitable for Suzuki coupling reactions,[12] we thus involved in the process 2-chloro-3-(4-halogenobenzoyl)pyridines together with 1 equiv. of different arylboronic acids (Scheme 2). Using phenylboronic acid with 3-(4-chlorobenzoyl)-2-chloropyridine (**1-Cl**)[10c] only led to a mixture in which the expected 6-phenyl-4-azafluorenone (**2a**) was identified (yield < 15%) from a mixture also containing 2-phenyl-3-(4-phenylbenzoyl)pyridine (bis-Suzuki coupling product, about 33% yield). In contrast, using the same boronic acid with 3-(4-bromobenzoyl)-2-chloropyridine (**1-Br**) afforded the functionalized tricycle **2a** (Fig. 1, left) in 91% yield. By extending the reaction involving **1-Br** to other arylboronic

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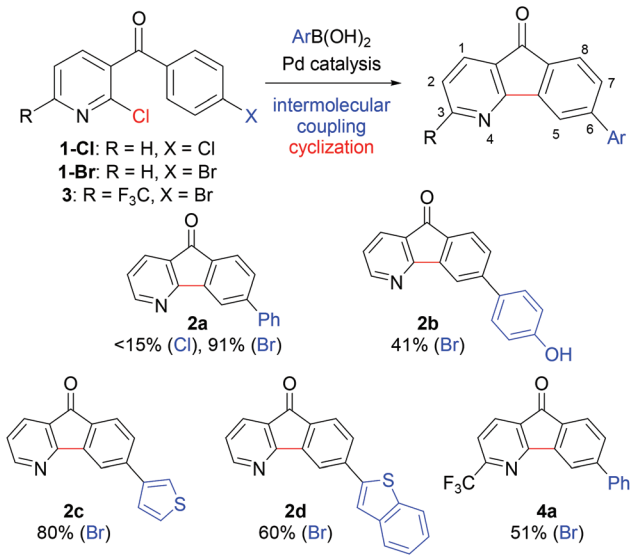
†Electronic supplementary information (ESI) available: General procedures, experimental procedures and compound characterizations, ^1H and ^{13}C NMR spectra of the new compounds, and X-ray crystallographic data. CCDC 1015380 (**2a**), 1015381 (**4a**), 1015382 (**6a**) and 1015383 (**9a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01629g



Scheme 2 Palladium-catalyzed Suzuki coupling-intramolecular arylation from the dihalides **1** and **3**. Reaction conditions: $Pd(OAc)_2$ (5 mol%), $Cy_3P{\cdot}HBF_4$ (10 mol%), K_2CO_3 (2 equiv.), DMF, 130 °C, 24 h.

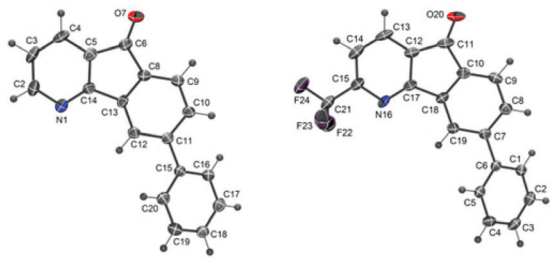


Fig. 1 ORTEP diagrams (50% probability) of **2a** and **4a**.

acids, 6-(4-hydroxyphenyl)-, 6-(3-thienyl)- and 6-(2-benzo[*b*]-thienyl)-4-azafluorenones (**2b–d**) were isolated in 41, 80 and 60% yield, respectively. GC analysis of the crude mixtures also showed the presence of diaryl ketones resulting from a Suzuki coupling on the phenyl ring (without cyclization).

Reacting with phenylboronic acid the 3-(4-bromobenzoyl)-2-chloropyridine **3**, substituted on its pyridine ring by a trifluoromethyl electron-withdrawing group, led to competitive cross-coupling on the pyridine ring. Indeed, the expected phenyl-substituted 4-azafluorenone **4a** (Fig. 1, right) was obtained in a medium 51% yield due to the competitive formation (17% yield) of uncyclized 2-phenyl-3-(4-phenylbenzoyl)-6-(trifluoromethyl)pyridine (bis-Suzuki coupling product). The formation of bis-Suzuki coupling product also happens from **1-Br** using the arylboronic acid in excess. These results suggest that Suzuki cross-coupling reactions are easier than the C–H arylation giving the azafluorenone.

By carrying out the reaction on 3-(3-bromobenzoyl)-2-chloropyridine (**5**) in the presence of phenylboronic acid, both 7-phenyl-4-azafluorenone (**6a**, Fig. 2, top, 30% yield) and 2-chloro-3-(3-phenylbenzoyl)pyridine (**7a**, 41% yield) were isolated, also suggesting a Suzuki coupling prior to cyclization.

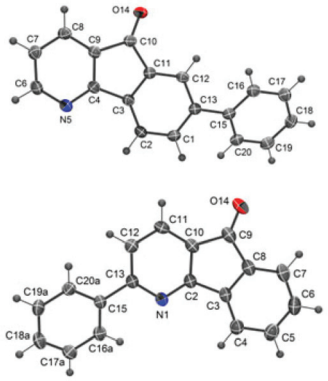
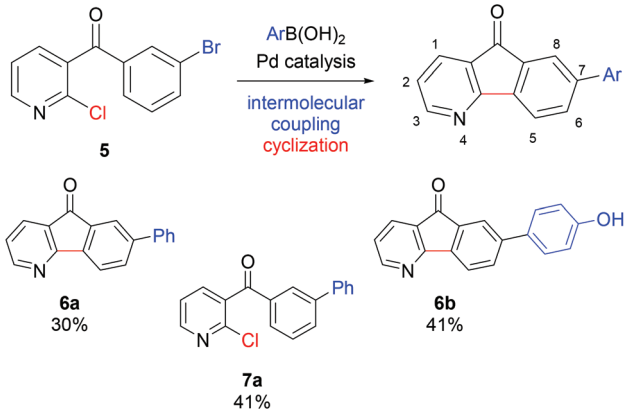


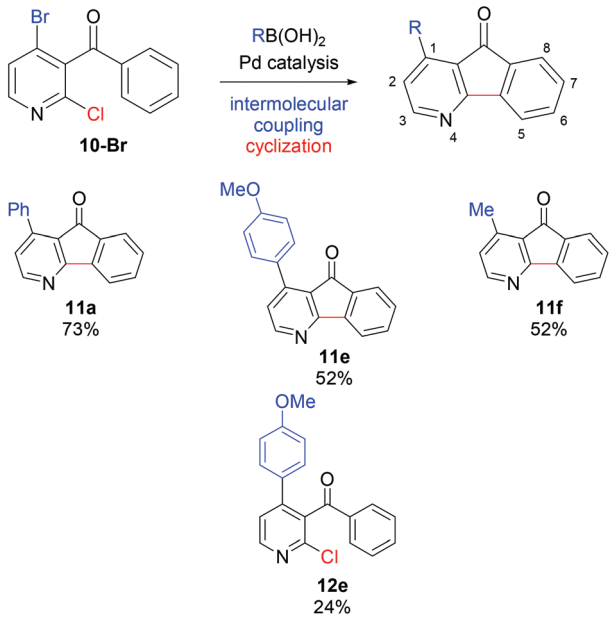
Fig. 2 ORTEP diagrams (50% probability) of **6a** and **9a**.



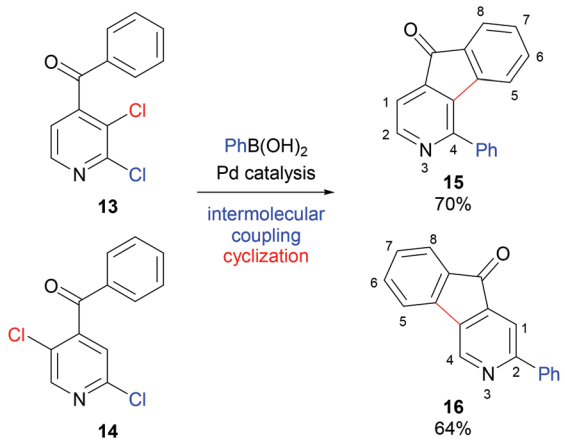
Scheme 3 Palladium-catalyzed Suzuki coupling-intramolecular arylation from the dihalide **6**. Reaction conditions: $Pd(OAc)_2$ (5 mol%), $Cy_3P{\cdot}HBF_4$ (10 mol%), K_2CO_3 (2 equiv.), DMF, 130 °C, 24 h.

Using 4-hydroxyphenylboronic acid similarly led to the azafluorenone **6b** in a moderate 41% yield due to competitive formation of 2-chloro-3-(3-(4-hydroxyphenyl)benzoyl)pyridine (Scheme 3).

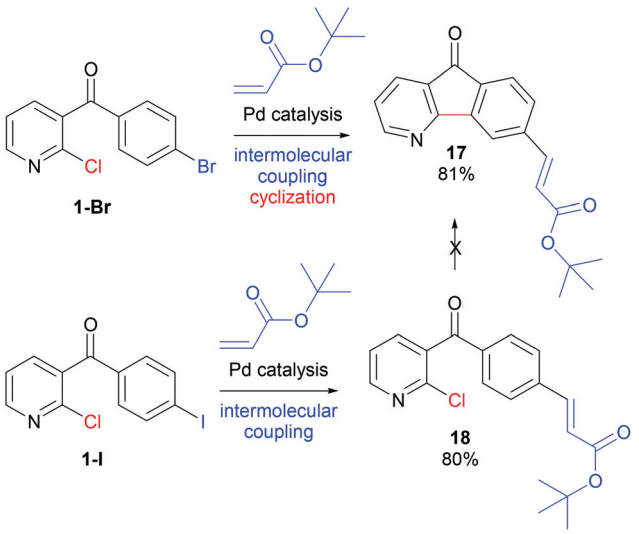
We next turned our attention to reactions using 2-chloro-3-benzoylpyridines bearing a second halogen on their pyridine ring in order to reach 4-azafluorenones differently functionalized. With 3-benzoyl-2,6-dichloropyridine (**8**),[10c] using phenylboronic acid showed a favored Suzuki coupling at the pyridine 6 position, furnishing 3-phenyl-4-azafluorenone (**9a**), which was identified by X-ray diffraction (Fig. 2, bottom). A moderate 38% yield was noted for the latter, due to competitive formation of 3-benzoyl-2,6-diphenylpyridine (bis-Suzuki coupling product). Using 3-benzoyl-2,4-dichloropyridine (**10-Cl**)[10c] led to a mixture in which 1-phenyl-2-azafluorenone was identified (11% yield). As expected,[15] Suzuki coupling at the pyridine 2 position was favored, but the formation of 3-benzoyl-4-chloro-2-phenylpyridine in 12% yield (together with 3-benzoyl-2,4-diphenylpyridine in 26% yield and 3-benzoyl-2-phenylpyridine in 3% yield) showed an intermediate coupled product reluctant to cyclizing C–H arylation.



Scheme 4 Palladium-catalyzed Suzuki coupling-intramolecular arylation from the dihalide **10-Br**. Reaction conditions: $Pd(OAc)_2$ (5 mol%), $Cy_3P{\cdot}HBF_4$ (10 mol%), K_2CO_3 (2 equiv.), DMF, 130 °C, 24 h.



Scheme 5 Palladium-catalyzed Suzuki coupling-intramolecular arylation from the dihalides **13** and **14**. Reaction conditions: $Pd(OAc)_2$ (5 mol%), $Cy_3P{\cdot}HBF_4$ (10 mol%), K_2CO_3 (2 equiv.), DMF, 130 °C, 24 h.



Scheme 6 Palladium-catalyzed Heck coupling-intramolecular arylation attempted from the dihalides **1-Br** and **1-I**. Reaction conditions: $Pd(OAc)_2$ (5 mol%), $Cy_3P{\cdot}HBF_4$ (10 mol%), K_2CO_3 (2 equiv.), DMF, 130 °C, 24 h.

Compared with 3-benzoyl-2,4-dichloropyridine (**10-Cl**), the reaction of 3-benzoyl-4-bromo-2-chloropyridine (**10-Br**) proved more promising, benefiting from a selective cross-coupling (at the brominated 4 position of the pyridine ring) (Scheme 4). By using phenylboronic acid as before, 1-phenyl-4-azafluorenone (**11a**) was obtained in 73% yield. Reacting **10-Br** with more electron-rich 4-methoxyphenylboronic acid gave 1-(4-methoxyphenyl)-4-azafluorenone (**11e**) in a moderate 52% yield; indeed, 3-benzoyl-2-chloro-4-(4-methoxyphenyl)pyridine (the coupled product **12e**) was also isolated in 24% yield. The use of methylboronic acid was attempted in order to reach the structure of onychine, an alkaloid endowed with anticandidal activity.[1a] Under the above conditions, the expected tricycle **11f** was isolated in 52% yield. The Suzuki-coupled uncyclized product and the Suzuki bis-coupled product were also detected (in 7 and 11% estimated yields, respectively).

Since 2,3- and 2,5-dichloropyridines generally react regioselectively in Suzuki cross-coupling reactions to afford the 2-functionalized derivatives,[16] we took the opportunity of involving such substrates in the sequence in order to reach 3-azafluorenones. From 4-benzoyl-2,3-dichloropyridine (**13**)[10c] and 4-benzoyl-2,5-dichloropyridine (**14**),[10c] the expected 4-phenyl- and 2-phenyl-3-azafluorenones **15** and **16** were respectively synthesized in 70 and 64% yield (Scheme 5).

Finally, we examined the behavior of both 3-(4-bromobenzoyl)-2-chloropyridine (**1-Br**) and 3-(4-iodobenzoyl)-2-chloropyridine (**1-I**) in palladium-catalyzed Heck coupling-intramolecular arylation auto-tandem[13] reactions. Reactions of this type were documented in 2006 by Fagnou and co-workers, but starting from dihalogenated benzyl phenyl ethers and amines.[17] By using *tert*-butyl acrylate under the conditions used before, which can also be suitable conditions for Heck coupling reactions,[18] the expected coupled azafluorenone **17** was obtained in 81% yield from **1-Br** whereas **1-I** led to the coupled non-cyclized product **18** (Scheme 6). It is true that an initial catalyst can be transformed after the first step of the tandem process,[17] thus becoming unsuitable for the second step, and this could explain why **1-I** cannot be converted to **17**. Nevertheless, applying the same reaction conditions to **18** did not furnish any cyclized product **17** (no conversion). Such a result suggests that from **1-Br** direct arylation could take place before Heck coupling.

In conclusion, we have developed palladium-catalyzed auto-tandem processes by which various substituted azafluorenones can be obtained from dihalogeno diaryl ketones. The results

presented here should be of interest for both medicinal and materials science.

Extended synthetic studies as well as evaluation of the biological properties of the new azafluorenones synthesized are in progress. Preliminary tests performed on the functionalized azafluorenone **17** showed a high antifungal activity against *Candida albicans* (higher than nystin) and a high antibacterial activity against *Staphylococcus aureus* (higher than ciprofloxacin).

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Notes and references

1 (*a*) C. D. Hufford, S. Liu, A. M. Clark and B. O. Oguntimein, *J. Nat. Prod.*, 1987, **50**, 961–964; (*b*) Y. C. Wu, *Heterocycles*, 1989, **29**, 463–475.

2 (*a*) J. Koyama, I. Morita, N. Kobayashi, T. Osakai, Y. Usuki and M. Taniguchi, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1079–1082; (*b*) S. Prachayasittikul, P. Manam, M. Chinworrungsee, C. Isarankura-Na-Ayudhya, S. Ruchirawat and V. Prachayasittikul, *Molecules*, 2009, **14**, 4414–4424; (*c*) G. A. Kraus and A. Kempema, *J. Nat. Prod.*, 2010, **73**, 1967–1968; (*d*) D. Addla, Bhima, B. Sridhar, A. Devi and S. Kantevari, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7475–7480.

3 D. Mueller, R. A. Davis, S. Duffy, V. M. Avery, D. Camp and R. J. Quinn, *J. Nat. Prod.*, 2009, **72**, 1538–1540.

4 (*a*) M. Manpadi, P. Y. Uglinskii, S. K. Rastogi, K. M. Cotter, Y.-S. C. Wong, L. A. Anderson, A. J. Ortega, S. Van Slambrouck, W. F. A. Steelant, S. Rogelj, P. Tongwa, M. Y. Antipin, I. V. Magedov and A. Kornienko, *Org. Biomol. Chem.*, 2007, **5**, 3865–3872; (*b*) K. Pumsalid, H. Thaisuchat, C. Loetchutinat, N. Nuntasaen, P. Meepowpan and W. Pompimon, *Nat. Prod. Commun.*, 2010, **5**, 1931–1934; (*c*) R. Banjerdpongchai, P. Khaw-On, C. Ristee and W. Pompimon, *Asian Pacific J. Cancer Prev.*, 2013, **14**, 2637–2641.

5 B. C. Shook, S. Rassnick, M. C. Osborne, S. Davis, L. Westover, J. Boulet, D. Hall, K. C. Rupert, G. R. Heintzelman, K. Hansen, D. Chakravarty, J. L. Bullington, R. Russell, S. Branum, K. M. Wells, S. Damon, S. Youells, X. Li, D. A. Beauchamp, D. Palmer, M. Reyes, K. Demarest, Y.-T. Tang, K. Rhodes and P. F. Jackson, *J. Med. Chem.*, 2010, **53**, 8104–8115.

6 (*a*) F. Bracher, *Synlett*, 1991, 95–96; (*b*) A.-S. Rebstock, F. Mongin, F. Trecourt and G. Queguiner, *Tetrahedron*, 2003, **59**, 4973–4977; (*c*) A.-S. Rebstock, F. Mongin, F. Trecourt and G. Queguiner, *Tetrahedron*, 2004, **60**, 2181–2186; (*d*) M. Alessi, A. L. Larkin, K. A. Ogilvie, L. A. Green, S. Lai, S. Lopez and V. Snieckus, *J. Org. Chem.*, 2007, **72**, 1588–1594.

7 (*a*) S. Tu, B. Jiang, R. Jia, J. Zhang and Y. Zhang, *Tetrahedron Lett.*, 2007, **48**, 1369–1374; (*b*) Y. Li, W. Fan, H.-W. Xu, B. Jiang, S.-L. Wang and S.-J. Tu, *Org. Biomol. Chem.*, 2013, **11**, 2417–2420.

8 S. Dhara, A. Ahmed, S. Nandi, S. Baitalik and J. K. Ray, *Tetrahedron Lett.*, 2013, **54**, 63–65.

9 (*a*) N. Marquise, P. J. Harford, F. Chevallier, T. Roisnel, A. E. H. Wheatley, P. C. Gros and F. Mongin, *Tetrahedron Lett.*, 2013, **54**, 3154–3157; (*b*) N. Marquise, P. J. Harford, F. Chevallier, T. Roisnel, V. Dorcet, A.-L. Gagez, S. Sablé, L. Picot, V. Thiéry, A. E. H. Wheatley, P. C. Gros and F. Mongin, *Tetrahedron*, 2013, **69**, 10123–10133.

10 (*a*) T. T. Nguyen, F. Chevallier, V. Jouikov and F. Mongin, *Tetrahedron Lett.*, 2009, **50**, 6787–6790; (*b*) T. T. Nguyen, N. Marquise, F. Chevallier and F. Mongin, *Chem. – Eur. J.*, 2011, **17**, 10405–10416; (*c*) K. Snégaroff, T. T. Nguyen, N. Marquise, Y. S. Halauko, P. J. Harford, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Chevallier, A. E. H. Wheatley, P. C. Gros and F. Mongin, *Chem. – Eur. J.*, 2011, **17**, 13284–13297. For a review, see: (*d*) P. J. Harford, A. J. Peel, F. Chevallier, R. Takita, F. Mongin, M. Uchiyama and A. E. H. Wheatley, *Dalton Trans.*, 2014, **43**, 14181–14203.

11 (*a*) L.-C. Campeau, M. Parisien, A. Jean and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 581–590; (*b*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (*c*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826.

12 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (*b*) S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633–9695.

13 Concerning auto-tandem reactions, see for example: (*a*) A. K. Yadav, S. Verbeeck, S. Hostyn, P. Franck, S. Sergeyev and B. U. W. Maes, *Org. Lett.*, 2013, **15**, 1060–1063, and references cited therein. For a review, see: (*b*) D. E. Fogg and E. N. dos Santos, *Coord. Chem. Rev.*, 2004, **248**, 2365–2379.

14 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295–4298.

15 X. Dai, Y. Chen, S. Garrell, H. Liu, L.-K. Zhang, A. Palani, G. Hughes and R. Nargund, *J. Org. Chem.*, 2013, **78**, 7758–7763.

16 (*a*) E. Maerten, M. Sauthier, A. Mortreux and Y. Castanet, *Tetrahedron*, 2006, **63**, 682–689; (*b*) S. Brumfield, J. J. Matasi, D. Tulshian, M. Czarniecki, W. Greenlee, C. Garlisi, H. Qiu, K. Devito, S.-C. Chen, Y. Sun, R. Bertorelli, J. Ansell, W. Geiss, V.-D. Le, G. S. Martin, S. A. Vellekoop, J. Haber and M. L. Allard, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 7287–7290.

17 J.-P. Leclerc, M. André and K. Fagnou, *J. Org. Chem.*, 2006, **71**, 1711–1714.

18 S. Bräse and A. de Meijere, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd edn, 2004, vol. 1, 217–315.

