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Iridium-catalysed C–H borylation of β-aryl-aminopropionic acids†

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Iridium-catalysed catalytic, regioselective C–H borylation of β-aryl-aminopropionic acid derivatives gives access to 3,5-functionalised protected β-aryl-aminopropionic acid boronates. The synthetic versatility of these new boronates is demonstrated through sequential one-pot functionalisation reactions to give diverse building blocks for medicinal chemistry. The C–H borylation is also effective for dipeptide substrates. We have exemplified this methodology in the synthesis of a pan α_v integrin antagonist.

Introduction

Natural and non-natural amino acids are widespread and have been extensively exploited in the synthesis of therapeutic molecules.[1] As a result, there is a continued need to develop novel strategies for the synthesis of these fundamentally important building blocks. Of particular importance in the context of medicinal chemistry is the development of methods for the construction of structurally diverse β-aryl-aminopropionic acids. This motif is present in biologically active molecules with activity against Chagas disease,[2] breast cancer,[3] and in α_v integrin antagonists as potential treatments for osteoporosis,[4] melanoma[5] and idiopathic pulmonary fibrosis.[6] Additionally, β-phenyl-aminopropionic acid is an intermediate in the synthesis of Maraviroc,[7] a CCR-5 receptor antagonist used for the treatment and prevention of HIV. Therefore, a unified strategy to the synthesis of functionalised β-aryl-aminopropionic acid would be of significant value.

Three general strategies have been developed for the synthesis of β-aryl-aminopropionic acids to date (Scheme 1). The Rodionov reaction (Scheme 1A) represents the simplest option and involves the multicomponent coupling of an aldehyde, malonic acid and ammonium acetate to generate racemic β-aryl-aminopropionic acids.[8–10] A second protocol involves diastereoselective Reformatsky reactions of sulfinimines (Scheme 1B).[11] An alternative auxiliary-based approach is depicted in Scheme 1C and involves the addition of chiral lithium amides to cinnamic acid derivatives (Scheme 1C).[12–14] These strategies for the synthesis of β-aryl-aminopropionic acids are dependent on the availability of highly functionalised starting aldehydes (Scheme 1A and B) or aryl bromides (Scheme 1C). While some of these are commercially available, they are available in limited supply and, since the diversity is introduced in the first step, a multistep synthesis is required for each different β-aryl-aminopropionic acid. This makes the exploration of structure–activity relationships around the aryl ring time and resource consuming.

As part of our research into novel biologically active peptidomimetics for therapeutic application we sought to incorporate β-aryl-aminopropionic acids with diverse substituents in the 3- and 5-positions. Given that existing methods, require a bespoke aldehyde or aryl bromide for every new compound and we designed an alternative method based on a late-stage functionalisation approach. Specifically, we envisioned that an appropriately pre-functionalised 3-substituted β-aryl-aminopropionic acid derivative, accessed *via* a Rodionov multicomponent reaction from more widely available 3-substituted aldehyde, could undergo a C–H functionalisation reactions (Scheme 2) providing a platform for further chemistry.

In the past decade C–H activation chemistry emerged into the forefront of modern organic chemistry. The innovative work of Hartwig and Miyaura,[15] and Smith and Maleczka[16] in iridium-catalysed aromatic C–H borylation offers a potentially powerful method for functionalisation given that the synthetic versatility of boronate groups is ever increasing.[17–19]

Encouraged by previous examples of C–H borylation on simple phenylalanine[20] and tryptophan[21] derivatives we now report the substrate directed iridium borylation of β-3-aryl-aminopropionic acid precursors together with examples of "one-pot" transformations to diversely functionalised 3,5-substi-

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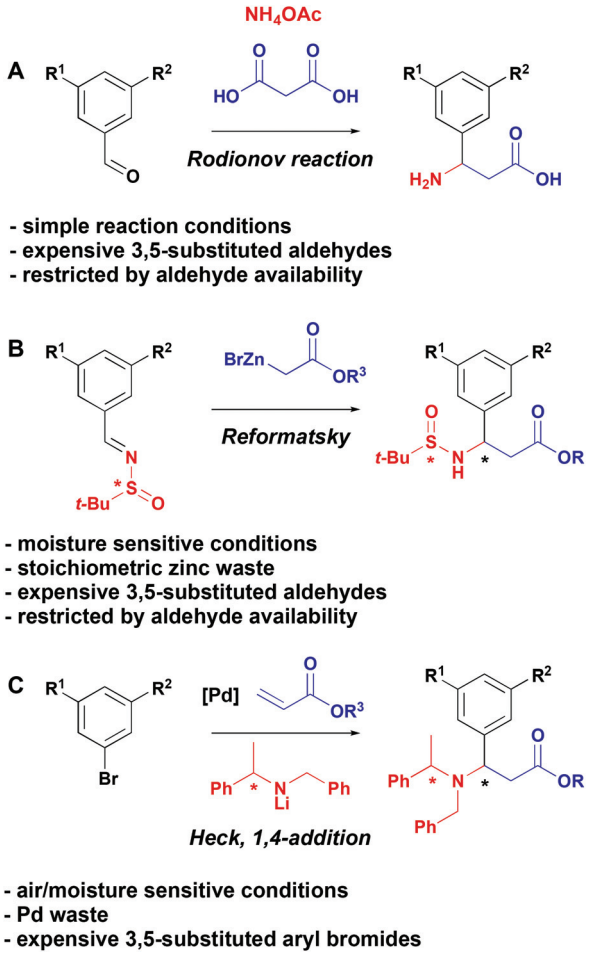
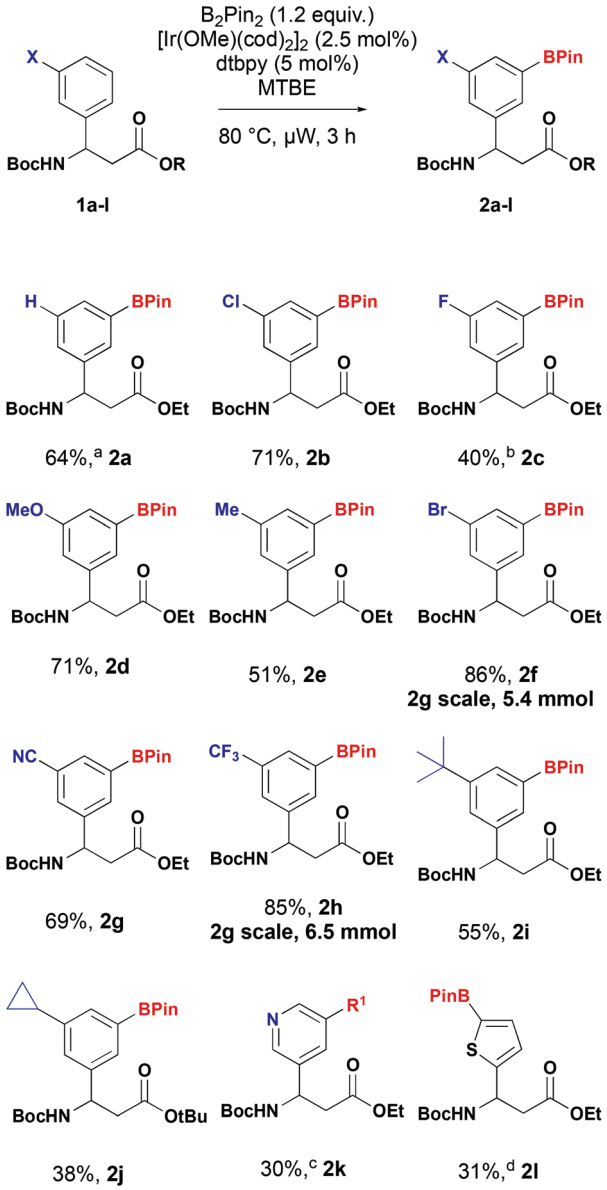


Scheme 1 Common approaches to β-aryl-aminopropionic acids.

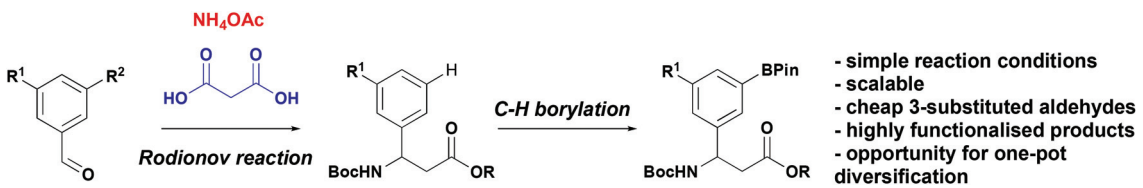
tuted products and implementation of this methodology in the preparation of an integrin antagonist bearing a β-3,5-aryl-aminopropionic acid motif.

Results and discussion

A series of 3-substituted β-aryl-aminopropionic acid derivatives were prepared by Rodionov multicomponent reaction or addition of the bromozincacetate to the corresponding sulfinimine followed by suitable protection as the *N*-Boc esters. Using **1d** as a model substrate we performed a brief screen of previously reported ligands and solvents to determine the



Scheme 3 Substrate scope of iridium-catalysed C–H borylation of β-aryl-aminopropionic acids. [a] 1:1 : 3 mixture of regioisomers (**2a**: 4-substitued:3,5-substituted), [b] 2:1 mixture of regioisomers (**2c**: 3,4-substituted), [c] borylated product (R^1 = Bpin) unstable to column chromatography; yield over two steps following Suzuki coupling with *p*-nitroiodobenzene to yield product **2k** (R^1 = *p*-nitrophenyl), [d] reaction conducted at room temperature.



Scheme 2 C–H functionalisation to diverse β-aryl-aminopropionic acids.

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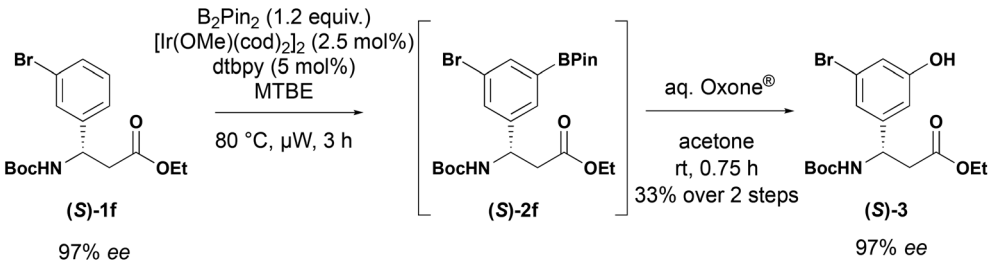
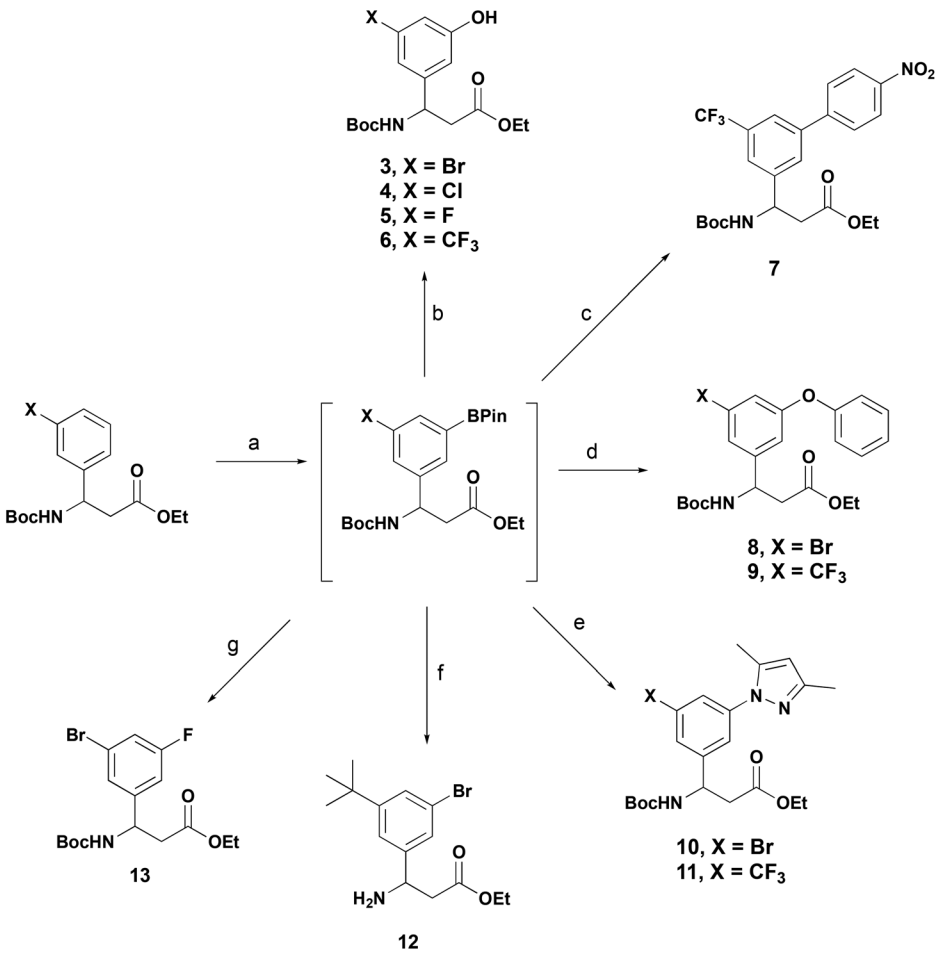
optimum conditions.[22] Methoxy(cyclooctadiene)iridium(I) dimer ($[Ir(OCH_3)(COD)]_2$) was chosen as the catalyst with *bis* (pinacolato)diboron (B_2pin_2) as the boron source. We evaluated three solvents (MTBE, THF and *i*PrNEt$_2$) with two ligands – 4-4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) and 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen). The reactions were heated at 80 °C for 24 h and a qualitative assessment of conversion determined by LCMS. The reaction did not reach completion when *i*PrNEt$_2$ was used a solvent. Conversion was comparable for both ligands and when ether solvents were used. Under standard heating conditions, shortening the reaction time from 24 h reduced the conversion, but complete conversion could be achieved using microwave irradiation in three hours. Based on this screen we selected MTBE and dtbpy to



Scheme 4 Iridium-catalysed C–H borylation of enantiopure β-aryl-aminopropionic acids.



Scheme 5 One-pot functionalisation of BPin-β-aryl-aminopropionic acids. Reagents and conditions: (a) Standard conditions Scheme 2; (b) Oxone®, aq. acetone, r.t., 0.75 h, **3** = 52%, **4** = 77%, **5** = 33%, **6** = 92% over two steps; (c) 1-iodo-4-nitrobenzene, Pd(dppf)·CH_2Cl_2, K_3PO_4, 1,2-DME : H_2O, 70 °C, 4.5 h, 93% over two steps; (d) phenol, $CuOAc_2$, $B(OH)_3$, 4 Å molecular sieves, 70 °C, 16 h, **8** = 36%, **9** = 34% over two steps; (e) 1,4-dimethylpyrazole, $Cu(OAc)_2$, $B(OH)_3$, 4 Å molecular sieves, 80 °C, 16 h, **10** = 74%, **11** = 68% over two steps; (f) $CuBr_2$, MeOH : H_2O (2 : 1), 70 °C, 16 h, 39%; (g) i. AgOTf, NaOH, MeOH, 0 °C, 0.5 h; ii. Selectfluor®, 3 Å MS, acetone, r.t., 3 h, 59%.

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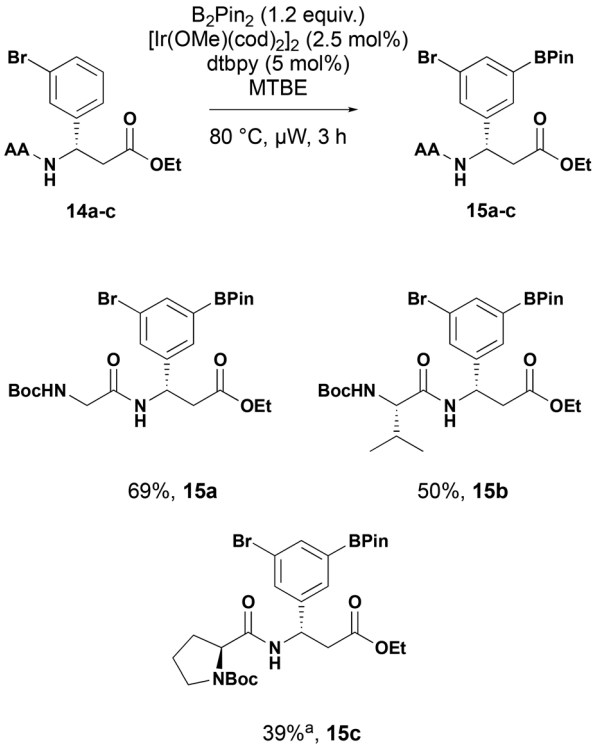
pair with ([Ir(OCH$_3$)(COD)]$_2$) and B_2Pin_2. MTBE was selected over THF. Under these conditions a range of β-aryl-aminopropionic acid derivatives were converted into the corresponding borylated derivatives (Scheme 3). As predicted, the reaction predominantly or exclusively yielded the 3,5-substituted products, in accordance with the reported directing regiochemistry of iridium-catalysed borylation reactions.[23]

The reaction of unsubstituted β-aryl-aminopropionic acid derivative (X = H) yielded a mixture of 3- and 4-isomers along with and 3,5-diborylated product in a ratio of 1 : 1 : 3, as determined by ^{1}H NMR. 3-Substituted substrates were readily tolerated in the reaction delivering the corresponding 3,5-substituted products in 38–86% yield (Scheme 3). 3-Fluorosubstituted substrate **1c** yielded a 2 : 1 mixture of 3,5 (**2c**) and 3,4-isomers that were inseparable by column chromatography. This is consistent with observations by other workers.[20,24] The borylated products were stable and could be readily purified by column chromatography to isolate them. Furthermore, the 3-trifluoromethyl **2f** and 3-bromo **2h** derivatives could be prepared on multigram scale with improved isolated yields. Under the standard borylation conditions, 2-thienyl derivative **1l** yielded exclusively the 3,5-diborylated product. The 5-borylated product **2l** was produced exclusively by conducting the reaction at room temperature. C–H borylation of the 3-pyridyl derivative **1k** yielded the desired product, however, attempts to purify the compound by chromatography resulted in protodeborylation and recovery of starting material **1k**. The yield reported is for the two-step procedure, involving Suzuki–Miyaura coupling of the unstable boronate ester with 4-nitroiodobenzene (R^1 = 4-nitrophenyl). When the enantioenriched substrate (*S*)-**1f** was subjected to C–H borylation followed by oxidation, phenol (*S*)-**3** was obtained with an 97% ee indicating no racemisation occurs in the borylation process (Scheme 4).

To demonstrate the versatility of these β-aryl-aminopropionic acid boronate derivatives in synthesis we have exemplified their applicability in typical reactions used in the synthesis of biologically active molecules (Scheme 5). In each example, the 3-substituted β-aryl-aminopropionic acid derivative was borylated under the previously described conditions and then telescoped into functionalisation without purification of the boronate. Oxidation of the boronate with aqueous Oxone® provided the phenols **3–6**.[16] 3-Trifluoromethyl derivative **1h** was borylated and transformed into biaryl ether **7** under standard Suzuki–Miyaura conditions. Attempts to alkylate the phenols under standard conditions (RBr, Cs_2CO_3) were unsuccessful, resulting in ester hydrolysis and transesterification only. To circumvent this and access ether containing products we utilised the Chan–Lam coupling to provide phenyl ethers **8** and **9**.[25] The Chan–Lam coupling was also an effective methodology to access *N*-linked heteraraomatic β-aryl-aminopropionic acid derivatives, the 1,3-dimethylpyrazole derivates **10** and **11** were accessed in 74 and 68% yield respectively over two steps.[26] These transformations are further examples of the Chan–Lam coupling as a viable sustainable alternative to Pd-catalysed etherification and amination and are compatible with tandem iridium borylation. Bromination of **2i** with $CuBr_2$ provided the 3-bromo-5-*tert*-butyl derivative **12**, this motif is featured in recently reported selective integrin antagonists.[27,28] 3-Bromo-5-fluoroderivative **13** was prepared *via* metallation of the intermediate boronate to the organosilver reagent and reaction with Selectfluor®.[29]

While *tert*-butoxycarbonyl groups present a robust, stable protecting group for the substrates, further *N*-functionalisation requires deprotection before further reaction. To demonstrate the utility of the C–H borylation in peptidomimetics, we replaced the *tert*-butoxycarbonyl group with an α-amino acid (Scheme 6). Under the established C–H borylation conditions the amino acid derived substrates **14a–c** were converted to the corresponding dipeptide boronates **15a–c** in good yield showing the tolerance of the conditions to more complex conditions with additional hydrogen bond donors.

Finally, we used this C–H borylation strategy to prepare a reported selective integrin antagonist.[27,28] Utilising the C–H borylation strategy to prepare 3-bromo-5-*tert*-butyl derivative **12** (Scheme 5) we converted this through to dipeptide **16** by amide coupling with Boc-glycine in 50% yield (Scheme 7). Further acidic deprotection and coupling with 3-guanidinobenzoic acid and final ester hydrolysis provided the integrin antagonist **17**. While comparable in step count to the reported, this approach allows installation of the stereocenter by Reformatsky addition of ethyl bromozincacetate to the chiral sulfinamide, obviating a chiral HPLC separation as previously reported. The reported synthetic procedures for similar com-



Scheme 6 Iridium-catalysed C–H borylation of β-aryl-aminopropionic dipeptides. AA = amino acid. [a] Extended reaction time of 6 h.

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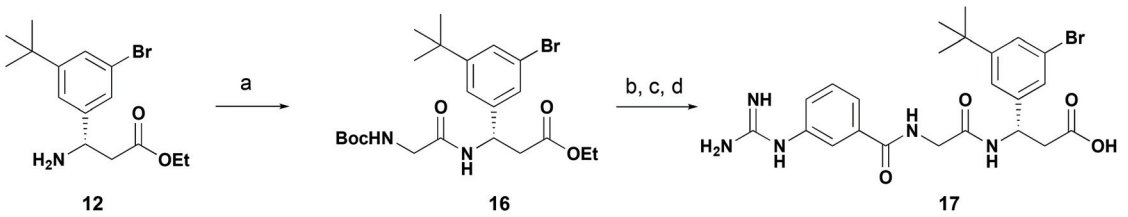

Scheme 7 Application of C–H borylation chemistry in the synthesis of an integrin antagonist. Reagents and conditions: (a) Boc-glycine, HATU, iPr$_2$EtN, MeCN, 0 °C to r.t., 16 h, 50%; (b) 4 M HCl in dioxane, 5 h; (c) 3-guanidinobenzoic acid, diisopropylcarbodiimide, HOBt, CH_2Cl_2 : DMF (1 : 1), r. t., 64 h; (c) 1 M aq. LiOH, THF, r.t., 64 h, 52% over three steps.

pounds require a bespoke aldehyde synthesis for each target compound, whereas a C–H borylation strategy allows a more sustainable synthesis of similar analogs by functionalising a common intermediate.

In conclusion, we have developed an efficient iridium-catalysed C–H borylation procedure of β-aryl- and heteroaryl-aminopropionic acids and explored the scope of the procedure with respect to functional group tolerance and retention of enantiointegrity. We have further explored the C–H borylation procedure in dipeptide substrates further demonstrating its synthetic utility. By applying telescoped "one-pot" reaction conditions we have shown that the C–H borylation approach allows an effective route to diversely functionalised β-aryl-aminopropionic acids across chemical space relevant to medicinal chemistry.

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Conflicts of interest

The authors declare no competing financial interest.

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References

1 M. A. T. Blaskovich, *J. Med. Chem.*, 2016, **59**, 10807–10836.
2 M. Kashif, K. F. Chacón-Vargas, J. C. López-Cedillo, B. Nogueda-Torres, A. D. Paz-González, E. Ramírez-Moreno, R. Agusti, M. L. Uhrig, A. Reyes-Arellano, J. Peralta-Cruz, M. Ashfaq and G. Rivera, *Eur. J. Med. Chem.*, 2018, **156**, 252–268.
3 Y. Guo, Y. Zhao, G. Wang, Y. Chen, Y. Jiang, L. Ouyang and B. Liu, *Eur. J. Med. Chem.*, 2018, **143**, 402–418.
4 J. H. Hutchinson, W. Halczenko, K. M. Brashear, M. J. Breslin, P. J. Coleman, L. T. Duong, C. Fernandez-Metzler, M. A. Gentile, J. E. Fisher, G. D. Hartman, J. R. Huff, D. B. Kimmel, C.-T. Leu, R. S. Meissner, K. Merkle, R. Nagy, B. Pennypacker, J. J. Perkins, T. Prueksaritanont, G. A. Rodan, S. L. Varga, G. A. Wesolowski, A. E. Zartman, S. B. Rodan and M. E. Duggan, *J. Med. Chem.*, 2003, **46**, 4790–4798.
5 A. Trabocchi, G. Menchi, N. Cini, F. Bianchini, S. Raspanti, A. Bottoncetti, A. Pupi, L. Calorini and A. Guarna, *J. Med. Chem.*, 2010, **53**, 7119–7128.
6 J. Adams, E. C. Anderson, E. E. Blackham, Y. W. R. Chiu, T. Clarke, N. Eccles, L. A. Gill, J. J. Haye, H. T. Haywood, C. R. Hoenig, M. Kausas, J. Le, H. L. Russell, C. Smedley, W. J. Tipping, T. Tongue, C. C. Wood, J. Yeung, J. E. Rowedder, M. J. Fray, T. McInally and S. J. F. Macdonald, *ACS Med. Chem. Lett.*, 2014, **5**, 1207–1212.
7 S. J. Haycock-Lewandowski, A. Wilder and J. Åhman, *Org. Process Res. Dev.*, 2008, **12**, 1094–1103.
8 W. M. Rodionow, *J. Am. Chem. Soc.*, 1929, **51**, 847–852.
9 W. M. Rodionow and E. A. Postovskaja, *J. Am. Chem. Soc.*, 1929, **51**, 841–847.
10 C. Y. K. Tan and D. F. Weaver, *Tetrahedron*, 2002, **58**, 7449–7461.
11 K. Brinner, B. Doughan and D. J. Poon, *Synlett*, 2009, 991–993.
12 S. G. Davies, A. D. Smith and P. D. Price, *Tetrahedron: Asymmetry*, 2005, **16**, 2833–2891.
13 S. G. Davies, A. M. Fletcher, P. M. Roberts and J. E. Thomson, *Tetrahedron: Asymmetry*, 2012, **23**, 1111–1153.
14 S. G. Davies, A. M. Fletcher, P. M. Roberts and J. E. Thomson, *Tetrahedron: Asymmetry*, 2017, **28**, 1842–1868.
15 T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 390–391.
16 R. E. Maleczka, F. Shi, D. Holmes and M. R. Smith, *J. Am. Chem. Soc.*, 2003, **125**, 7792–7793.
17 C. Sandford and V. K. Aggarwal, *Chem. Commun.*, 2017, **53**, 5481–5494.
18 J. W. B. Fyfe and A. J. B. Watson, *Chem*, 2017, **3**, 31–55.

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19 S. M. Nicolle, A. Nortcliffe, H. E. Bartrum, W. Lewis, C. J. Hayes and C. J. Moody, *Chem. – Eur. J.*, 2017, 13623–13627.
20 F.-M. Meyer, S. Liras, A. Guzman-Perez, C. Perreault, J. Bian and K. James, *Org. Lett.*, 2010, **12**, 3870–3873.
21 V. A. Kallepalli, F. Shi, S. Paul, E. N. Onyeozili, R. E. Maleczka and M. R. Smith, *J. Org. Chem.*, 2009, **74**, 9199–9201.
22 S. M. Preshlock, B. Ghaffari, P. E. Maligres, S. W. Krska, R. E. Maleczka and M. R. Smith, *J. Am. Chem. Soc.*, 2013, **135**, 7572–7582.
23 T. Ishiyama, Y. Nobuta, J. F. Hartwig and N. Miyaura, *Chem. Commun.*, 2003, 2924–2925.
24 T. E. Hurst, T. K. Macklin, M. Becker, E. Hartmann, W. Kügel, J.-C. Parisienne-La Salle, A. S. Batsanov, T. B. Marder and V. Snieckus, *Chem. – Eur. J.*, 2010, **16**, 8155–8161.
25 J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules and A. J. B. Watson, *J. Am. Chem. Soc.*, 2017, **139**, 4769–4779.
26 H. Robinson, S. A. Oatley, J. E. Rowedder, P. Slade, S. J. F. Macdonald, S. P. Argent, J. D. Hirst, T. McInally and C. J. Moody, *Chem. – Eur. J.*, 2020, **26**, 7678–7684.
27 P. G. Ruminski and D. W. Griggs, WO2017117538, 2009.
28 P. G. Ruminski and D. W. Griggs, WO2014015054, 2014.
29 T. Furuya and T. Ritter, *Org. Lett.*, 2009, **11**, 2860–2863.