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Ligand-free iridium-catalyzed regioselective C–H borylation of indoles†

Zilong Pan,[abc] Luhua Liu,[bc] Senmiao Xu *[b] and Zhenlu Shen *[a]

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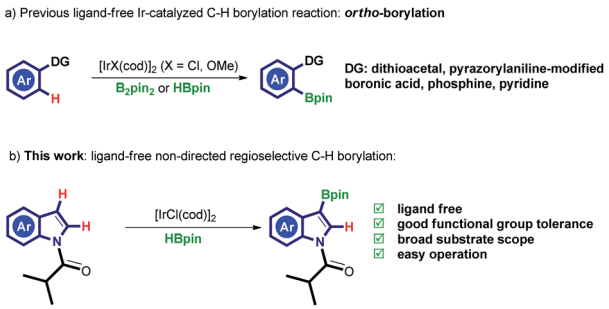
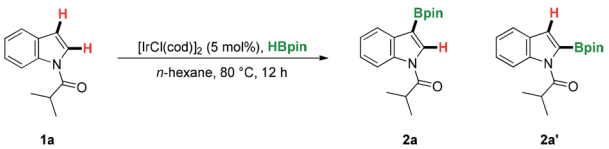
We herein report a ligand-free Ir-catalyzed C–H borylation of *N*-acyl protected indoles. This simple protocol could tolerate a variety of functional groups, affording C3 borylated indoles in good yields with excellent regioselectivities. We also demonstrated that the current method is amenable to gram-scale borylation and the C–B bonds could be easily converted to C–C and C-heteroatom bonds.

Indoles are not only widespread subunits but also useful building blocks in drug discovery and synthetic chemistry.[1] Thus, their functionalization and transformation have gained attention. In particular, borylated indoles are of significant importance because they can serve as useful synthons by converting C–B bonds into many other functionalities.[2] As a result, a number of regioselective C–H borylation methods have been developed. In this context, regioselective transition-metal-catalyzed C–H borylation has emerged as a powerful tool for preparing borylated indoles in an atom- and step-economic way under mild reaction condition.[3,4] Because the C–H borylation at the C2 positions of indoles are electronically more favorable,[4f–i] the reactions at the other positions are more challenging. In general, directing groups are usually required to realize regioselective C–H borylation reactions. For example, bulky directing groups at nitrogen atoms such as Boc and Si(i-Pr)$_3$ could result in C3-selective C–H borylation enabled by dtbpy/Ir catalysis (dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine).[5] The N-Bpin moiety could serve as a traceless directing group for the dtbpy/Ir- and Ni(IMes)$_2$-catalyzed C–H borylation at C3 positions.[6] The use of C2 substituted indoles enables nitrogen-directed dtbpy/Ir-catalyzed C7-selective C–H borylation.[7] Hartwig and co-workers used N–SiEt$_2$H as the directing group to achieve relay directed dtbpy/Ir-catalyzed C7-selective C–H borylation.[8] Another attractive and simple approach is the metal-free C–H borylation, which can regioselectively provide borylated indoles at C2, C3, C4, and C7 positions under mild reaction conditions.[9] Despite the fact, the compatibility of functional groups is still narrow and usually limited to halogens, alkyl, and alkoxy



Scheme 1 Ligand-free Ir-catalyzed C–H borylation of arenes.

Table 1 Optimization of reaction conditions for the Ir-catalyzed distal hydroboration of **1a**[a]



Entry	Variation from standard conditions	**2a**/**2a′**[b]	Yield of **2a**[c] (%)
1	None	97 : 3	79
2	5 mol% [Ir(OMe)(cod)]$_2$ *in lieu* of [IrCl(cod)]$_2$	97 : 3	43
3	5 mol% [IrCl(coe)]$_2$ *in lieu* of [IrCl(cod)]$_2$	95 : 5	65
4	10 mol% P(C$_6$F$_5$)$_3$	<1 : 99	—
5	THF *in lieu* of *n*-hexane	89 : 11	47
6	70 °C instead of 80 °C	95 : 5	73
7	60 °C instead of 80 °C	90 : 10	31

[a] Unless otherwise noted, all the reactions were carried out with **1a** (0.20 mmol), HBpin (0.30 mmol) in *n*-hexane (1.0 mL) at 80 °C for 12 h. [b] The ratio of **2a**/**2a′** was determined by GC analysis. [c] Isolated yield of **2a**.

[a]*College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014, China. E-mail: zhenlushen@zjut.edu.cn*

[b]*State Key Laboratory for Oxo Synthesis and Selective Oxidation, Center for Excellence in Molecular Science, Suzhou Research Institute, Lanzhou Institute of Chemical Physics, Chinese Academy of Science, Lanzhou 730000, China. E-mail: senmiaoxu@licp.cas.cn*

[c]*University of Chinese Academy of Sciences, Beijing 100049, China*

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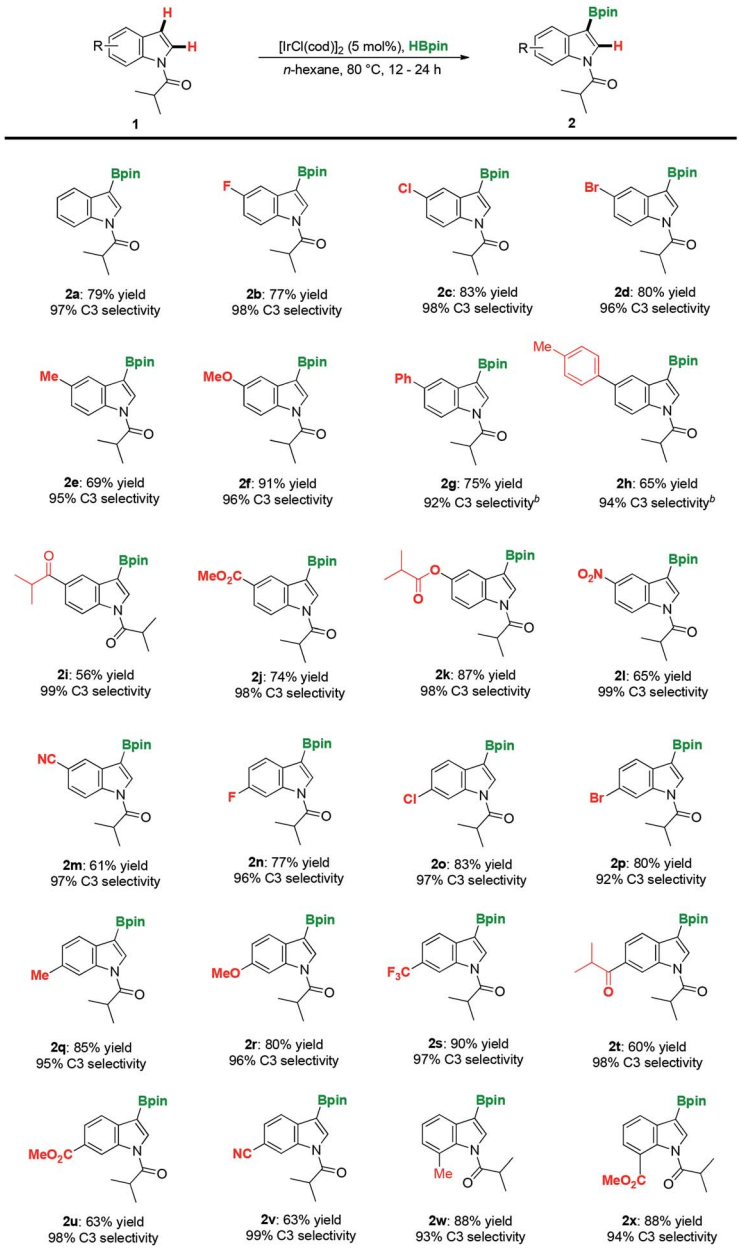
Table 2 Substrate scope[a]



[a] Unless otherwise noted, all the reactions were carried out with **1** (0.20 mmol), HBpin (0.30 mmol) in *n*-hexane (1.0 mL) at 80 °C for 12–24 h. The regioselectivity was determined by GC analysis. [b] The regioselectivity was determined by ^{1}H NMR of crude product.

substituted indoles. Thus, it is still appealing to develop complementary methods in this area.

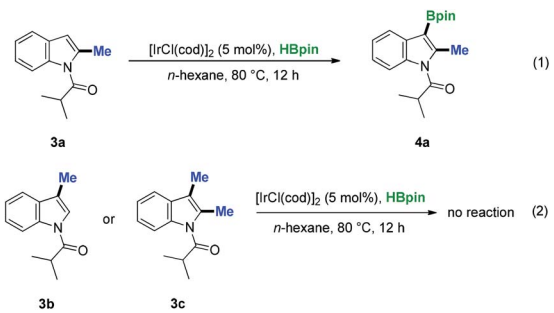
Ligand-free Ir-catalyzed regioselective C–H borylation of arenes have received growing interest. In this context, a judicious choice of directing group (DG) is crucial to promote the reaction. Usually, strong coordinating DGs are required. In this context, dithioacetal,[10] pyrazorylaniline-modified boronic acid,[11] phosphine,[12] pyridine[13] are commonly used for these transformations. It should be noted that all of the above-mentioned methods result in *ortho*-borylated products (Scheme 1A). In this work, we disclose the first example of ligand-free Ir-catalyzed C3-selective C–H borylation of *N*-acyl protected indoles. The current simple method could tolerate a variety of functionalities, including ester, ketone, nitro, and cyanide.

Our research commenced with the optimization of the reaction conditions. We chose *N*-isobutyryl indole **1a** as our pilot substrate.[14] The reaction **1a** (0.20 mmol) with 1.5 equivalents of HBpin (pinacolborane) in the presence of a catalytic amount of $[IrCl(cod)]_2$ (5.0 mol%) (cod: 1,5-cyclooctadiene) in *n*-hexane (1.0 mL) at 80 °C for 12 h affords C–H borylated product **2a** in 79% yield with 97% C3 selectivity (Table 1, entry 1). GC/MS analysis of crude reaction mixture revealed that cod was

reduced to cyclooctane, mono-borylated cyclooctane and mono-borylated cyclooctene.[15] Replacement of $[IrCl(cod)]_2$ to either $[Ir(OMe)(cod)]_2$ or $[IrCl(coe)_2]_2$ (coe: cyclooctene) results in significantly decreased yields (Table 1, entries 2 and 3). We then survey the ligand effect on the reaction. We then used $P(C_6F_5)_3$ (10 mol%) as the ligand which resulted in directed C2-borylated product **2a′** exclusively (Table 1, entry 4). The observed C2-selectivity is consistent with other C–H borylation using this ligand.[16] The solvent effect showed that the reaction in THF yield and regioselectivity (Table 1, entry 5), which might be caused by coordinating nature of THF. Further examination of the reaction temperature indicates that the 80 °C is optimal in terms of both reactivity and regioselectivity (Table 1, entry 1 *vs.* entries 6 and 7). The significant loss of reactivity in the presence of a droplet of mercury indicates that the current catalytic process is more likely nanoparticle catalysis.[17]

With optimized reaction conditions in hand (Table 1, entry 1), we then determined the additional substrate scope of the current ligand-free regioselective Ir-catalyzed of C–H borylation of indoles as shown in Table 2. Generally, all of the substrates underwent reactions smoothly, giving most of borylated indoles with greater than 95% C3 selectivity. The reactions of substrates with substituents including F, Cl, Br, Me, MeO, and CF_3, at C5, and C6 positions gave C3-selective borylated indoles **2b–f**, **2n–o**, **2p–s**, and **2w** in moderate to good isolated yields (65–91%) with constantly excellent regioselectivities (>95%). The C6-Br and C7-Me substituted indole **1p** and **1w** gave the C3-borylated product **2p** and **2w** in 80% and 88% yields with slightly diminished regioselectivities (92% and 93%, respectively) compared to their C5- and C6-counterparts. Substrates with Ar groups at C5 positions gave products **2g** and **2h** in 75% and 65% yields with 92% and 94% regioselectivities, respectively. Interestingly, the current method could also well tolerate a variety of sensitive substituents including ketone (**1i** and **1t**) ester (**1j**, **1k**, **1u**, and **1x**), and nitro (**1l**), cyanide (**1m** and **1v**) at indoles' C5, C6, and C7 positions, furnishing corresponding C3-borylated products **2i–m**, **2t–v**, and **2x** in moderate to good isolated yields (56–88%) with excellent regioselectivities (94–99%).

Interestingly, the reaction of C2-methyl substituted indole **3a** under standard conditions could give C3-borylated product **4a** exclusively, albeit with 40% isolated yield (eqn (1)). In contrast, no reaction was observed when C3-methyl or C2,C3-dimethyl substituted indoles **3b** and **3c** was employed (eqn (2)).



In order to demonstrate the synthetic utility of the current protocol, a gram-scale reaction of **1a** and several transformations of **2a** were conducted as shown in Fig. 1. The reaction of **1a** (1.00 g) with 2.5 mol% $[IrCl(cod)]_2$ for 24 h afforded **2a** in 79% isolated yield (1.32 g) with 97% C3 selectivity, which is almost identical with that obtained from the small-scale reaction. The C–B bond could be transferred to other functional groups bearing C–Br (**5**), C–I (**6**), C–CN (**8**), and C–Ph (**10**) bonds under various reaction conditions in good to excellent yields (70–90%).[18–21] Interestingly, prolonging the reaction time of iodination and cyanation could ultimately result in deacylation products **7** and **9** in both 80% yields.

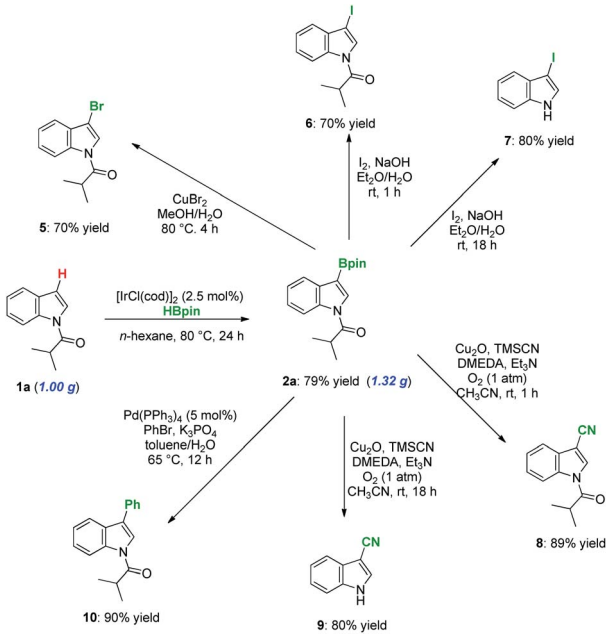


Fig. 1 Gram-scale C–H borylation of **1a** and synthetic application of borylated product **2a** (DEMEDA = *N*,*N*′-dimethylenediamine).

Conclusions

In conclusion, we have developed a ligand-free Ir-catalyzed C–H borylation under mild reactions for the first time. This easy-to-operate method could tolerate a variety of functional groups, affording C3 borylated products in good to excellent yields. We have also demonstrated that the obtained borylated product could be used in a series of C–C and C-heteroatom bond-forming reactions. Further exploration of ligand-free regioselective C–H borylation is currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) M. A. Corsello, J. Kim and N. K. Garg, *Chem. Sci.*, 2017, **8**, 5836; (*b*) J. Vaca, F. Salazar, A. Ortiz and E. Sansinenea, *J. Antibiot.*, 2020, **73**, 798; (*c*) A. Kumari and R. K. Singh, *Bioorg. Chem.*, 2019, **89**, 103021; (*d*) A. K. Clarke, H. E. Ho, J. A. Rossi-Ashton, R. J. K. Taylor and W. P. Unsworth, *Chem.–Asian J.*, 2019, **14**, 1900; (*e*) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, 2013, **18**, 6620.

2 (*a*) D. Leonori and V. K. Aggarwal, in *Synthesis and Application of Organoboron Compounds*, ed. E. Fernández and A. Whiting, Springer International Publishing, Cham, 2015, pp. 271–295; (*b*) H.-Y. Sun, and D. G. Hall, in *Synthesis and Application of Organoboron Compounds*, ed. E. Fernández and A. Whiting, Springer International, Cham, Switzerland, 2015, pp 221–242; (*c*) S. Panda and J. M. Ready, *J. Am. Chem. Soc.*, 2017, **139**, 6038.

3 (*a*) L. Xu, G. Wang, S. Zhang, H. Wang, L. Wang, L. Liu, J. Jiao and P. Li, *Tetrahedron*, 2017, **73**, 7123; (*b*) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890; (*c*) J. F. Hartwig, *Chem. Soc. Rev.*, 2011, **40**, 1992; (*d*) A. Ros, R. Fernández and J. M. Lassaletta, *Chem. Soc. Rev.*, 2014, **43**, 3229.

4 (*a*) Y. Pang, T. Ishiyama, K. Kubota and H. Ito, *Chem.–Eur. J.*, 2019, **25**, 4654; (*b*) S. Kawamorita, H. Ohmiya and M. Sawamura, *J. Org. Chem.*, 2010, **75**, 3855; (*c*) K. Mertins, A. Zapf and M. Beller, *J. Mol. Catal. A: Chem.*, 2004, **207**, 21; (*d*) P. Harrisson, J. Morris, T. B. Marder and P. G. Steel, *Org. Lett.*, 2009, **11**, 3586; (*e*) I. A. I. Mkhalid, D. N. Coventry, D. Albesa-Jove, A. S. Batsanov, J. A. K. Howard, R. N. Perutz and T. B. Marder, *Angew. Chem., Int. Ed.*, 2006, **45**, 489; (*f*) T. Ishiyama, J. Takagi, J. F. Hartwig and N. Miyaura, *Angew. Chem., Int. Ed.*, 2002, **41**, 3056; (*g*) T. Furukawa, M. Tobisu and N. Chatani, *Chem. Commun.*, 2015, **51**, 6508; (*h*) T. Furukawa, M. Tobisu and N. Chatani, *J. Am. Chem. Soc.*, 2015, **137**, 12211; (*i*) N. G. Léonard, M. J. Bezdek and P. J. Chirik, *Organometallics*, 2017, **36**, 142; (*j*) M. R. Smith, R. Bisht, C. Haldar, G. Pandey, J. E. Dannatt, B. Ghaffari, R. E. Maleczka and B. Chattopadhyay, *ACS Catal.*, 2018, **8**, 6216; (*k*) V. A. Kallepalli, K. A. Gore, F. Shi, L. Sanchez, G. A. Chotana, S. L. Miller, R. E. Maleczka and M. R. Smith, *J. Org. Chem.*, 2015, **80**, 8341; (*l*) H. Zhang, S. Hagihara and K. Itami, *Chem. Lett.*, 2015, **44**, 779; (*m*) A. Das, P. K. Hota and S. K. Mandal, *Organometallics*, 2019, **38**, 3286.

5 (*a*) J. Takagi, K. Sato, J. F. Hartwig, T. Ishiyama and N. Miyaura, *Tetrahedron Lett.*, 2002, **43**, 5649; (*b*) V. A. Kallepalli, F. Shi, S. Paul, E. N. Onyeozili, R. E. Maleczka and M. R. Smith, *J. Org. Chem.*, 2009, **74**, 9199.

6 (*a*) S. M. Preshlock, D. L. Plattner, P. E. Maligres, S. W. Krska, R. E. Maleczka and M. R. Smith, *Angew. Chem., Int. Ed.*, 2013, **52**, 12915; (*b*) Y.-M. Tian, X.-N. Guo, Z. Wu, A. Friedrich, S. A. Westcott, H. Braunschweig, U. Radius and T. B. Marder, *J. Am. Chem. Soc.*, 2020, **142**, 13136.

7 (*a*) S. Paul, G. A. Chotana, D. Holmes, R. C. Reichle, R. E. Maleczka and M. R. Smith, *J. Am. Chem. Soc.*, 2006, **128**, 15552; (*b*) F. Shen, S. Tyagarajan, D. Perera, S. W. Krska, P. E. Maligres, M. R. Smith and R. E. Maleczka, *Org. Lett.*, 2016, **18**, 1554; (*c*) W. F. Lo, H. M. Kaiser, A. Spannenberg, M. Beller and M. K. Tse, *Tetrahedron Lett.*, 2007, **48**, 371.

8 D. W. Robbins, T. A. Boebel and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 4068.

9 (*a*) V. Bagutski, A. D. Grosso, J. A. Carrillo, I. A. Cade, M. D. Helm, J. R. Lawson, P. J. Singleton, S. A. Solomon, T. Marcelli and M. J. Ingleson, *J. Am. Chem. Soc.*, 2013, **135**, 474; (*b*) T. Stahl, K. Müther, Y. Ohki, K. Tatsumi and M. Oestreich, *J. Am. Chem. Soc.*, 2013, **135**, 10978; (*c*) J. L. Lavergne, A. Jayaraman, L. C. M. Castro, É. Rochette and F.-G. Fontaine, *J. Am. Chem. Soc.*, 2017, **139**, 14714; (*d*) M.-A. Légaré, M.-A. Courtemanche, É. Rochette and F.-G. Fontaine, *Science*, 2015, **349**, 513; (*e*) S. Zhang, Y. Han, J. He and Y. Zhang, *J. Org. Chem.*, 2018, **83**, 1377; (*f*) Q. Zhong, S. Qin, Y. Yin, J. Hu and H. Zhang, *Angew. Chem., Int. Ed.*, 2018, **57**, 14891; (*g*) S. A. Iqbal, J. Cid, R. J. Procter, M. Uzelac, K. Yuan and M. J. Ingleson, *Angew. Chem., Int. Ed.*, 2019, **58**, 15381; (*h*) J. Lv, X. Chen, X.-S. Xue, B. Zhao, Y. Liang, M. Wang, L. Jin, Y. Yuan, Y. Han, Y. Zhao, Y. Lu, J. Zhao, W.-Y. Sun, K. N. Houk and Z. Shi, *Nature*, 2019, **575**, 336–340; (*i*) É. Rochette, V. Desrosiers, T. Soltani and F.-G. Fontaine, *J. Am. Chem. Soc.*, 2019, **141**, 12305.

10 L. Liu, G. Wang, J. Jiao and P. Li, *Org. Lett.*, 2017, **19**, 6132.

11 (*a*) T. Yamamoto, A. Ishibashi and M. Suginome, *M. Org. Lett.*, 2019, **21**, 6235; (*b*) T. Yamamoto, A. Ishibashi and M. Suginome, *Org. Lett.*, 2017, **19**, 886.

12 K. M. Crawford, T. R. Ramseyer, C. J. A. Daley and T. B. Clark, *Angew. Chem., Int. Ed.*, 2014, **53**, 7589.

13 Y. Yang, Q. Gao and S. Xu, *Adv. Synth. Catal.*, 2019, **361**, 858.

14 See the ESI Table S1† for more details.

15 (*a*) P. Nguyen, H. P. Blom, S. A. Westcott, N. J. Taylor and T. B. Marder, *J. Am. Chem. Soc.*, 1993, **115**, 9329; (*b*) T. Ishiyama, J. Takagi, K. Ishida and N. Miyaura, *J. Am. Chem. Soc.*, 2002, **124**, 390.

16 I. Sasaki, J. Taguchi, S. Hiraki, H. Ito and T. Ishiyama, *Chem.–Eur. J.*, 2015, **21**, 9236.

17 V. M. Chernshev, A. V. Astahov, I. E. Chikunov, R. V. Tyurin, D. B. Eremin, G. S. Ranny, V. N. Khrustalev and V. P. Ananikov, *ACS Catal.*, 2019, **9**, 2984.

18 H. L. Li, Y. Kuninobu and M. Kanai, *Angew. Chem., Int. Ed.*, 2017, **56**, 1495.

19 J. Szyling, A. Franczyk, P. Pawluć, B. Marciniec and J. Walkowiak, *Org. Biomol. Chem.*, 2017, **15**, 3207.

20 Y. Ye, Y. Wang, P. Liu and F. Han, *Chin. J. Chem.*, 2013, **31**, 27.

21 Y.-C. Hu, D.-W. Ji, C.-Y. Zhao, H. Zheng and Q.-A. Chen, *Angew. Chem., Int. Ed.*, 2019, **58**, 5438.