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View Article Online
DOI: 10.1039/C8CC03195A

Journal Name

COMMUNICATION

Ligand-Promoted Ruthenium-Catalyzed Meta C-H Chlorination of Arenes Using *N*-Chloro-2,10-camphorsultam†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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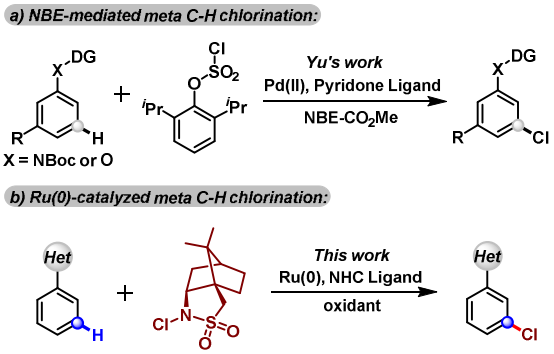
A practical meta C-H chlorination protocol is established via a Ru(0)-catalyzed ortho-metalation strategy. The use of *N*-chloro-2,10-camphorsultam as a new chlorinating agent is crucial for the success of the current reaction and the *N*-heterocyclic carbene (NHC) ligand could significantly enhance the reactivity of the catalytic transformation. The mechanistic studies reveal that an unusual ortho C-H ruthenation relay ortho chlorination of C-Ru bond process is probably involved.

Aryl chlorides constitute an ample source of chlorinated pharmaceuticals that are used for the treatment of multiple diseases, especially cardiovascular and central nervous disorders.[1] Meanwhile, they are also a class of versatile precursors for diverse cross-coupling reactions.[2] The conventional methods for aromatic chlorination include Sandmeyer reaction,[3] electrophilic aromatic chlorination[4] or stoichiometric ortho-metalation-chlorination sequence.[5] Despite these approaches have been frequently employed for the preparation of aryl chlorides, they have significant liabilities that limit their application involving tedious operation, poor ortho-/para-selectivity and harsh reaction conditions.

To overcome the limitations, transition metal-catalyzed ortho C-H activation/chlorination have been realized.[6] In stark contrast, there have been few studies on meta C-H chlorination. So far, only the Yu group recently revealed a modified norbornene-mediated meta C-H chlorination protocol, in which they used pyridone ligand to improve the efficiency of Pd(II) catalysis (Scheme 1a).[7] However, the transformation suffered from two major drawbacks: a) limited substrate scope of anilines and phenols and b) installation and removal of directing groups. As a consequence, establishment of the practical and complementary meta C-H chlorination method is still an impending demand.

Recently, the emerging ortho-ruthenation strategy is an useful tool for meta functionalization.[8,9] Pioneering works including meta sulfonation,[10] alkylation,[11] bromination,[12] nitration[13] and fluoromethylation[14] have been accomplished. To overcome the insufficiencies of previous meta C-H chlorination as well as identify new meta C-H functionalization approach under Ru catalysis, herein, we report a *N*-heterocyclic carbene(NHC)-promoted Ru(0)-catalyzed meta-selective C-H chlorination. This protocol contains several notable features, including: a) ample scope of heterocyclic substrates, b) the use of *N*-chloro-2,10-camphorsultam as a new chlorinating agent, c) employing a NHC ligand to enhance the reactivity, d) an ortho C-H ruthenation relay ortho chlorination process is involved and e) the practical utility for rapid synthesis and diversification of pharmaceutically useful benzodiazepines and fluorescent probe molecules (Scheme 1b).



Scheme 1 Different strategies enabled meta C-H chlorination of arenes.

We commenced the study with substrate **1a** and a variety of chlorinating agents under $Ru_3(CO)_{12}$/$PhI(TFA)_2$ catalytic system.[13b] To our delight, the chlorinating agent **[Cl]-1** gave the meta chlorination product **2a** in 15% yield. We subsequently screened various factors including solvent, temperature and

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Electronic Supplementary Information (ESI) available: experimental procedures, characterization data and X-ray for **4b**$_{mono}$ (CCDC 1587232), **6e** (CCDC 1586057), **B** (CCDC 1586058) and ^{1}H and ^{13}C NMR spectra for all of the new compounds. See DOI: 10.1039/x0xx00000x

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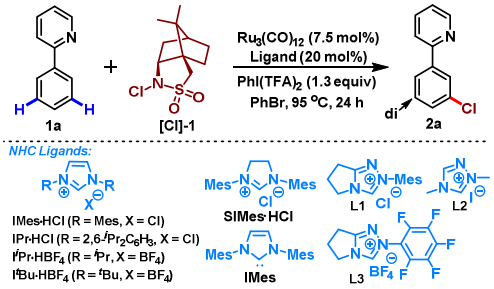
substrate concentration, however, the yield was only slightly increased to 25% (see the Supporting Information). Notably, the unusual PhBr is the best solvent for this transformation because of its excellent solubility. Considering ligand effect on ruthenium-catalyzed C-H activation,[14a] we next investigated a number of commonly used ligands. The significant improvement was observed in the presence of NHC ligands (entries 1-9, Table 1). 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl) was found as the optimal ligand to afford **2a** in 58% total yield (entry 2). Along with employing higher amount of ligand and prolonging the reaction time, the best result was obtained in 82% isolated yield and the ratio of mono-/di-chlorination products is 8:1. Therefore, entry 11 is chosen as the standard condition.

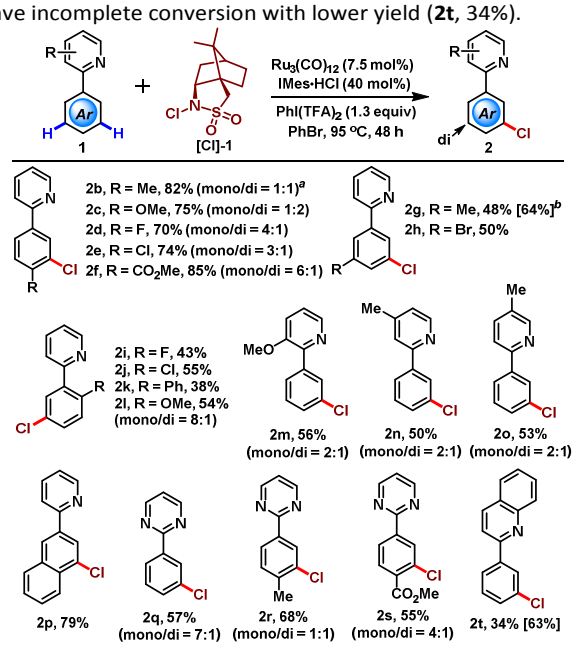
Table 1 Optimization of the reaction conditions[a]



Entry	Ligand	Total yield (mono+di)(%)[b]
1	IPr•HCl	47
2	IMes•HCl	58
3	SIMes•HCl	54
4	IMes	46
5	$I^iPr•HBF_4$	41
6	$I^tBu•HBF_4$	43
7	**L1**	52
8	**L2**	49
9	**L3**	37
10[c]	IMes•HCl	67[d]
11[c,e]	IMes•HCl	86(82)[d,f]

[a] Reaction conditions: **1a** (0.1 mmol), **[Cl]-1** (1.75 equiv), $Ru_3(CO)_{12}$ (7.5 mol%), ligand (20 mol%), $PhI(TFA)_2$ (1.3 equiv), PhBr (1 mL), air, 95 °C, 24 h. [b] Yields were determined by ^1H NMR analysis using CH_2Br_2 as an internal standard. Unless otherwise stated, mono/di > 20:1. [c] Using 40 mol% ligand. [d] mono/di = 8:1. [e] For 48 h. [f] Isolated yield.

With the optimized reaction conditions in hand, we probed the versatility of the meta C-H chlorination of 2-arylheterocycle scaffolds (Scheme 2). It was found that both the electron-rich and -deficient substituents on phenyl or pyridyl rings were widely tolerated and the desired products were obtained in moderate to excellent yields (**2b-o**). However, the lower selectivity of mono-/di-chlorination was received for the substrates bearing electron-rich substituents on the para position of phenyl rings. Unexpectedly, the preferable chlorination on the less steric meta position was observed in the cases of ortho-substituted arylpyridines as the substrates (**2i-l**). Due to the Ru-C bond owns the ortho/para-directing effect, we supposed that less ortho steric hinderance of complex and the smaller chlorine may cause the ortho chlorination of C-Ru bond. Besides, 2-(naphthalen-2-yl)pyridine was subjected to the meta chlorination reaction and afforded the selective mono-chlorination product **2p** in 79% yield. We also found that reactions with substituted 2-phenylpyrimidines proceeded smoothly under the standard conditions (**2q-s**). Regrettably, the bicycloheterocyles such as 2-phenylquinoline gave incomplete conversion with lower yield (**2t**, 34%).



Scheme 2 Meta C-H chlorination of 2-arylheterocycle scaffolds. [a] Ratio of isolated mono- *vs* di-chlorination products. [b] Yield based on recovered starting material.

We then examined the transformation of a wide range of purine bases under slightly modified meta C-H chlorination conditions (Scheme 3). Though the electronic property of the para or meta substituents has little influence on the reactivity, the selectivity of mono- or di-chlorination products was markedly relevant (**4a-j**). Notably, the substrate bearing 4-methoxyl substituent almost only afforded di-chlorination product **4e**. This approach was also applicable to naphthylpurine affording the corresponding product **4l** in moderate yield. In the cases of *N*-benzyl, -butyl, -methyl and -cyclopentyl purines, the desired products **4m-p** were obtained in moderate yields. More appealingly, the key synthetic intermediate for a p-38 kinase inhibitor[15] was also suitable for the protocol and the chlorinated product **4q** was obtained in 63% yield, which may provide a fast-track en route to various antineoplastic drugs.

Next, we turned our attention to benzodiazepine scaffolds that generally have sedative activities (Scheme 4).[16] The compatibility of substituents on the aromatic ring was investigated first (**6a-h**). Interestingly, only meta-selective mono-chlorination products were generated, among which the structure of **6e** was confirmed by the X-ray diffraction. The frontline antidepressant drug diazepam[13b,17] was subjected to the catalytic system as well and the desired product **6h** was obtained in 54% yield. Besides, diverse *N*-substituted benzodiazepines also participated in the reaction albeit with lower yields (**6i-k**). All these compounds built in a new library

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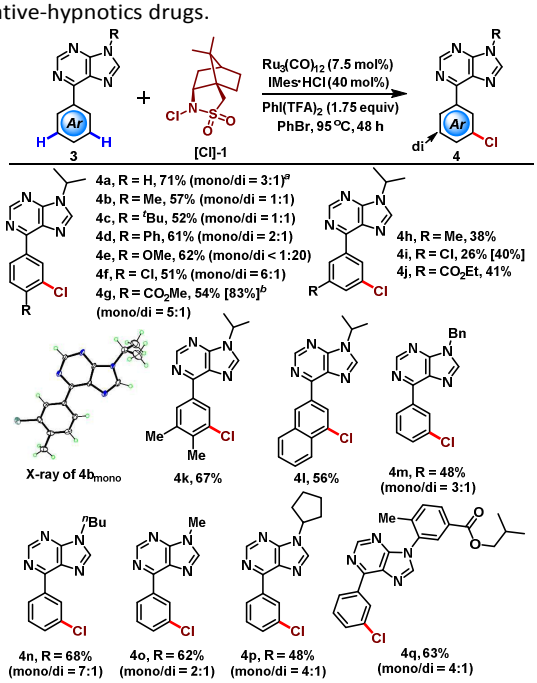
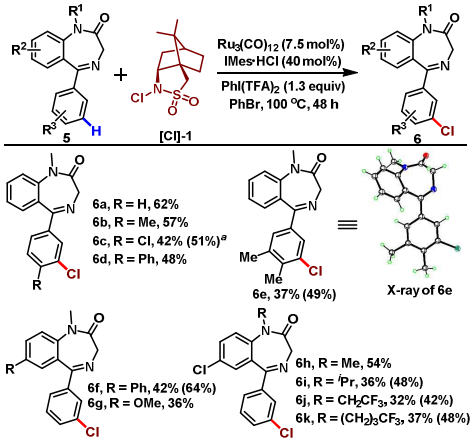
of chlorinated benzodiazepines that may help identifying new sedative-hypnotics drugs.



Scheme 3 Substrate scope with 6-arylpurines. [a] Ratio of isolated mono- *vs* di-chlorination products. [b] Yield based on recovered starting material.



Scheme 4 Meta chlorination of benzodiazepines. [a] Yields based on recovered starting material.

To further demonstrate the synthetic application of this methodology, we then proceeded the reduction of 2-(3-chlorophenyl)pyridine (**2a**) via a $B(C_6F_5)_3$-catalyzed cascade process,[18] leading to cyclopentylamine **7** in 82% yield, which can be used for further transformations (Fig. 1a). Meanwhile, palladium-catalyzed arylation,[19a] alkynylation,[7] amination,[19b] alkenylation[19c] and borylation[19d] of chloro-benzodiazepine **6a** with corresponding coupling partners were conducted under modified literature conditions yielding corresponding products **8-12** in high yields. The use of Cs_2CO_3 or K_2CO_3 as the base was found to be crucial for the success of these conversions (Fig. 1b). Moreover, a shortcut synthesis of benzodiazepine-containing fluorescent probe **13** was developed in 41% overall yield, starting from borylation product **12** through Suzuki-Miyaura cross-coupling following by reduction and cyclization (Fig. 1b).[20] The UV-Vis-NIR absorption spectrum of **13** in DMSO exhibited an absorption peak at 555 nm, whereas the fluorescence emission spectrum disclosed an emission peak centered at 654 nm (see the Supporting Information).

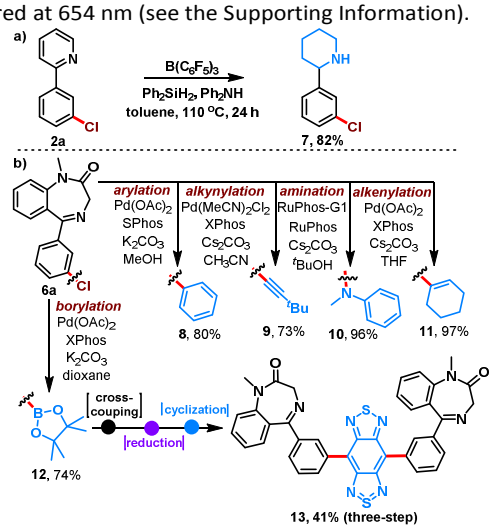


Fig. 1 a) Reductive transformation of pyridine. b) Diversified conversion and synthetic application of meta chlorinated benzodiazepines.

To get more insights on the details of reaction mechanism, we firstly captured the active dinuclear ruthenium complex **A**, the structure was inferred by X-ray analysis of its stable derivative **B** which was cordinated with MeCN. The successfully catalytic reaction and the significant ortho H/D exchange of **[D$_5$]-1a** using species **A** instead of $Ru_3(CO)_{12}$ imply that species **A** may be involved in the catalytic cycle. Subsequently, the use of radical scavengers was found to obviously suppress the meta chlorination, indicating that a single electron transfer (SET) process might be involved. Then, more than 50% ortho hydrogen atom was deuterated when **1a** was treated with or without **[Cl]-1** under the standard condition in the presence of 5 equivalent of D_2O, supporting that the initial ortho C-H ruthenation is reversible. Furthermore, the parallel kinetic isotope effect was measured and the value of k_H/k_D was 1.0, which reveals that the meta C–H cleavage doesn't occur at the rate-determining step. Eventually, the LC-MS study of the reaction mixture confirmed the formation of Mes ligand, release of **[N]-H** and the formation of ruthenacycle intermediate **II** (see the Supporting Information).

Taking into account these results and the reported literature precedents,[13b,21] we proposed the reaction mechanism as depicted in Scheme 5. Coordination of species **A** with the ligand gives the active catalyst **I**, which then initiates the ortho C-H bond activation of **1a** to afford the intermediate **II**. Subsequently, ortho SET chlorination of C-Ru bond occurs in the presence of chlorinating agent, which is different from the reported meta functionalization under ruthenium catalysis.[10-14] The reductive deprotonation of **III** leads to the intermediate **IV**. The ligand exchange of species **IV** with TFA delivers the desired

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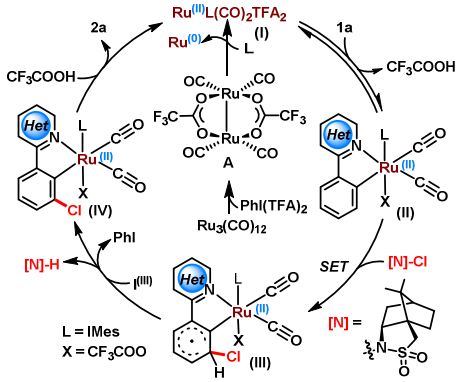
product **2a**. Meanwhile, the catalyst **I** is regenerated for the next cycle.



Scheme 5 Proposed mechanism.

In conclusion, we have developed a commercially available NHC ligand-accelerated meta C-H chlorination of arenes under ruthenium catalysis. In this protocol, the use of *N*-chloro-2,10-camphorsultam as a chlorinating agent is demonstrated for the first time. Further, the reaction is suitable for ample scope of heterocyclic substrates including arylpyridines, arylpyrimidines, purines and benzodiazepines. The mechanism studies disclose that the catalytic meta chlorination involves an ortho C-H ruthenation relay ortho chlorination of C-Ru bond. Synthetic application of this method is showcased through the late-stage diversified conversion of druglike benzodiazepines and the synthesis of potential fluorescent probes.

This work was supported by grants from Chinese NSF (81430080, 81773565). Supporting from the National Program on Key Basic Research Project of China (2015CB910603), the International Cooperative Program (GJHZ1622) and Key Program of the Frontier Science (QYZDJ-SSW-SMC002) of the Chinese Academy of Sciences, the Shanghai Commission of Science and Technology (16XD1404600) are also highly appreciated.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 B. R. Smith, C. M. Eastman and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 9764.
2 A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176.
3 H. H. Hodgson, *Chem. Rev.*, 1947, **40**, 251.
4 (a) A. M. Suess, M. Z. Ertem, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 9797; (b) R. A. Rodriguez, C.-M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 6908; (c) L. Zhang and X. Hu, *Chem. Sci.*, 2017, **8**, 7009.
5 (a) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879; (b) W. Lin, O. Baron and P. Knochel, *Org. Lett.*, 2006, **8**, 5673.
6 (a) K. J. Stowers and M. S. Sanford, *Org. Lett.*, 2009, **11**, 4584; (b) X. Sun, G. Shan, Y. Sun and Y. Rao, *Angew. Chem., Int. Ed.*, 2013, **52**, 4440; (c) X. Sun, Y. Sun, C. Zhang and Y. Rao, *Chem. Commun.*, 2014, **50**, 1262; (d) G. Zhang, S. Sun, F. Yang, Q. Zhang, J. Kang, Y. Wu and Y. Wu, *Adv. Synth. Catal.*, 2015, **357**, 443; (e) P. Zhang, L. Hong, G. Li and R. Wang, *Adv. Synth. Catal.*, 2015, **357**, 345; (f) D. A. Petrone, J. Ye and M. Lautens, *Chem. Rev.*, 2016, **116**, 8003; (g) F. Lied, A. Lerchen, T. Knecht, C. Mück-Lichtenfeld and F. Glorius, *ACS Catal.*, 2016, **6**, 7839; (h) B.-B. Zhan, Y.-H. Liu, F. Hu and B.-F. Shi, *Chem. Commun.*, 2016, **52**, 4934; (i) X.-H. Liu, H. Park, J.-H. Hu, Y. Hu, Q.-L. Zhang, B.-L. Wang, B. Sun, K.-S. Yeung, F.-L. Zhang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2017, **139**, 888; (j) G. Li, B. Zhu, X. Ma, C. Jia, X. Lv, J. Wang, F. Zhao, Y. Lv and S. Yang, *Org. Lett.*, 2017, **19**, 5166; (k) S. Kathiravan and I. A. Nicholls, *Chem. Eur. J.* , 2017, **23**, 7031.
7 (a) H. Shi, P. Wang, S. Suzuki, M. E. Farmer and J.-Q. Yu, *J. Am. Chem. Soc.*, 2016, **138**, 14876; (b) P. Wang, M. E. Farmer and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 5125.
8 (a) F. Juliá-Hernández, M. Simonetti and I. Larrosa, *Angew. Chem., Int. Ed.*, 2013, **52**, 11458; (b) C. G. Frost and A. J. Paterson, *ACS Cent. Sci.*, 2015, **1**, 418; (c) J. Li, S. De Sarkar and L. Ackermann, *Top. Organomet. Chem.*, 2015, **55**, 217; (d) R. Sharma, K. Thakur, R. Kumar, I. Kumar and U. Sharma, *Catal. Rev.: Sci. Eng.*, 2015, **57**, 345; (e) J. Yang, *Org. Biomol. Chem.*, 2015, **13**, 1930; (f) A. Dey, S. Agasti and D. Maiti, *Org. Biomol. Chem.*, 2016, **14**, 5440; (g) M. T. Mihai, G. R. Genov and R. J. Phipps, *Chem. Soc. Rev.*, 2018, **47**, 149.
9 J. A. Leitch and C. G. Frost, *Chem. Soc. Rev.*, 2017, **46**, 7145.
10 O. Saidi, J. Marafie, A. E. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc.*, 2011, **133**, 19298.
11 (a) N. Hofmann and L. Ackermann, *J. Am. Chem. Soc.*, 2013, **135**, 5877; (b) J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa and L. Ackermann, *J. Am. Chem. Soc.*, 2015, **137**, 13894; (c) A. J. Paterson, S. St. John-Campbell, M. F. Mahon, N. J. Press and C. G. Frost, *Chem. Commun.*, 2015, **51**, 12807; (d) J. Li, K. Korvorapun, S. De Sarkar, T. Rogge, D. J. Burns, S. Warratz and L. Ackermann, *Nat. Commun.*, 2017, **8**, 15430; (e) G. Li, D. Li, J. Zhang, D.-Q. Shi and Y. Zhao, *ACS Catal.*, 2017, **7**, 4138; (f) G. Li, X. Ma, C. Jia, Q. Han, Y. Wang, J. Wang, L. Yu and S. Yang, *Chem. Commun.*, 2017, **53**, 1261; (g) B. Li, S.-L. Fang, D.-Y. Huang and B.-F. Shi, *Org. Lett.*, 2017, **19**, 3950; (h) G. Li, P. Gao, X. Lv, C. Qu, Q. Yan, Y. Wang, S. Yang and J. Wang, *Org. Lett.*, 2017, **19**, 2682.
12 (a) C. J. Teskey, A. Y. W. Lui and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2015, **54**, 11677; (b) Q. Yu, L. Hu, Y. Wang, S. Zheng and J. Huang, *Angew. Chem., Int. Ed.*, 2015, **54**, 15284; (c) S. Warratz, D. J. Burns, C. Zhu, K. Korvorapun, T. Rogge, J. Scholz, C. Jooss, D. Gelman and L. Ackermann, *Angew. Chem., Int. Ed.*, 2017, **56**, 1557.
13 (a) Z. Fan, J. Ni and A. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 8470; (b) Z. Fan, J. Li, H. Lu, D.-Y. Wang, C. Wang, M. Uchiyama and A. Zhang, *Org. Lett.*, 2017, **19**, 3199.
14 (a) Z. Ruan, S.-K. Zhang, C. Zhu, P. N. Ruth, D. Stalke and L. Ackermann, *Angew. Chem., Int. Ed.*, 2017, **56**, 2045; (b) Z.-Y. Li, L. Li, Q.-L. Li, K. Jing, H. Xu and G.-W. Wang, *Chem. Eur. J.*, 2017, **23**, 3285.
15 Z. Fan, H. Lu and A. Zhang, *J. Org. Chem.*, 2018, **83**, 3245.
16 L. H. Sternbach, *J. Med. Chem.*, 1979, **22**, 1.
17 S. Shu, Z. Fan, Q. Yao and A. Zhang, *J. Org. Chem.*, 2016, **81**, 5263.
18 Z.-Y. Liu, Z.-H. Wen and X.-C. Wang, *Angew. Chem., Int. Ed.*, 2017, **56**, 5817.
19 (a) T. E. Barder and S. L. Buchwald, *Org. Lett.* , 2004, **6**, 2649; (b) D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 57; (c) T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685; (d) K. L. Billingsley, T. E. Barder and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2007, **46**, 5359.
20 C. Qin, Y. Fu, C.-H. Chui, C.-W. Kan, Z. Xie, L. Wang and W.-Y. Wong, *Macromol. Rapid Commun.*, 2011, **32**, 1472.
21 M. I. Bruce, M. L. Cole, R. S. C. Fung, C. M. Forsyth, M. Hilder, P. C. Junk and K. Konstas, *Dalton Trans.*, 2008, 4118.