Chinese Chemical Letters 33 (2022) 2005–2008

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Metal-free directed C–H borylation of 2-(*N*-methylanilino)-5-fluoropyridines and 2-benzyl-5-fluoropyridines

Gaorong Wu[a], Xiaobo Xu[a], Shuai Wang[a], Lu Chen[a], Binghan Pang[a], Tao Ma[b,*], Yafei Ji[a,*]

[a] *Engineering Research Center of Pharmaceutical Process Chemistry, Ministry of Education; School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China*
[b] *School of Chinese Materia Medica, Beijing University of Chinese Medicine, Liangxiang Campus, Beijing 102488, China*

ARTICLE INFO

Article history:
Received 1 September 2021
Revised 22 September 2021
Accepted 24 September 2021
Available online 30 September 2021

Keywords:
Metal-free
C–H borylation
2-(*N*-Methylanilino)-5-fluoropyridines
2-Benzyl-5-fluoropyridines
BBr3

ABSTRACT

A novel method for metal-free C–H borylation of 2-(*N*-methylanilino)-5-fluoropyridines and 2-benzyl-5-fluoropyridines has been reported. The 5-fluoropyridine directed borylation reaction exhibited high efficiency and site exclusivity. The useful protocol could be executed on a gram-scale easily and the borylated products showed good derivatization applications. Moreover, the practicality of the strategy was expanded by the fact that the directing group could be removed in an acceptable yield.

Organoborons play a major role in organic synthesis as their power in the conversion of functional groups coupled with the low toxicity and ease of handling. Among various C–H borylation strategies, one of the commonly known strategies is a metal-catalyzed directed approach [1–3]. Owing to the extensive range of applications in natural products and drugs, the development of protocols for the functionalization of *N*-methylanilines has attracted more attention in recent years. Traditional methods used for the borylation of *N*-methylanilines were focused on noble transition-metal-catalyzed, such as Ir and Pd (Scheme 1a) [4–6]. However, these works usually need ligands and harsh reaction conditions. From an economic and environmental perspective, the ability to achieve C–H borylation of *N*-methylanilines under mild conditions by using cheaper boron reagents and avoiding the use of transition metals would be very significant.

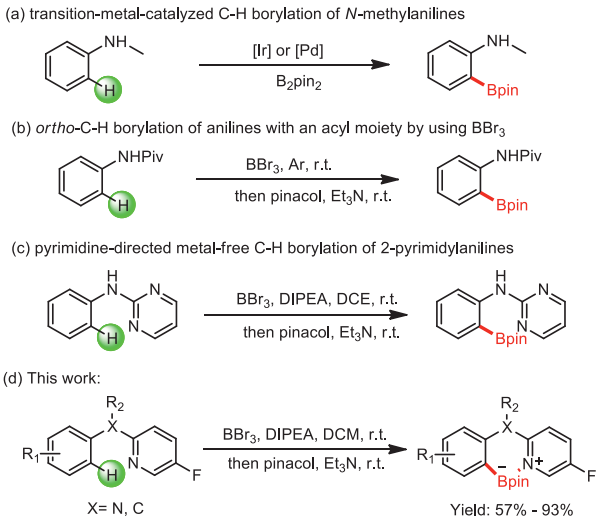
At present, the use of strong Lewis acids such as $B(C_6F_5)_3$ or BX_3 (X = Cl, Br) for the $C(sp^2)$–H bond borylation is considered to be a very effective method [7–25]. Among these, BBr_3 is particularly prominent because of its strong reactivity, low cost and easy availability. In 2010, Murakami developed a seminal method to borylate 2-aryl-pyridines using BBr_3 [26]. Two years later, Fu's group had successfully developed an efficient metal-free *ortho* C–H borylation *via* sequential borylation of substituted 2-phenoxypyridines with BBr_3 following esterification with pinacol [27]. After that, other N-directing groups such as pyrazoles, pyrazines, pyrimidines, pyridines, imidazolones, imidazoles and quinolines were developed [28–36]. In 2019, Shi group and Ingleson group described the *ortho*-C–H borylation of aniline derivatives with an acyl moiety by using BBr_3 (Scheme 1b) [37,38]. More recently, Chatani and co-workers reported the pyrimidine-directed metal-free C–H borylation of 2-pyrimidylanilines (Scheme 1c) [39]. These researches provided outstanding strategies for the borylation of anilines. Although substantial progress has been made in the development of metal-free directed C–H borylation reactions with BBr_3, the borylation of *N*-methylanilines directed by pyridine under metal-free conditions has never been reported.

Inspired by these achievements and given the importance of *N*-methylaniline derivatives, we hope to develop a new pyridine directing group to obtain *N*-methylanilines borates. Herein, we reported a novel route for directed C–H borylation of 2-(*N*-methylanilino)-5-fluoropyridines using BBr_3. The reaction was also applicable to 2-benzyl-5-fluoropyridine derivatives as a substrate (Scheme 1d). Moreover, the obtained boronic esters exhibited good derivatization applications and the directing group could be removed in an acceptable yield, which provided a practical, efficient and simple pathway for synthesizing structurally diversified *N*-methylaniline and 2-benzyl-5-fluoropyridine derivatives.

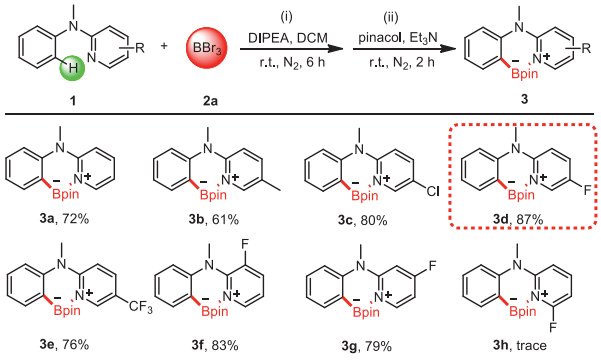
Our initial study focused on screening the directing groups (Scheme 2). First, a solution of **1a**, DIPEA (*N,N*-diisopropylethylamine) (1.0 equiv.) and **2a** (2.0 equiv.) in dried

* Corresponding authors.
E-mail addresses: 201701033@bucm.edu.cn (T. Ma), jyf@ecust.edu.cn (Y. Ji).

https://doi.org/10.1016/j.cclet.2021.09.081
1001-8417/



Scheme 1. Borylation of anilines and *N*-methylanilines.

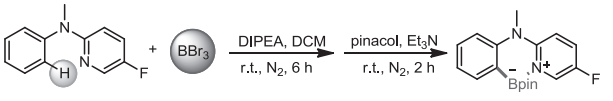


Scheme 2. Screening of directing groups. Reaction conditions: (i) **1** (0.2 mmol), **2a** (0.4 mL, 1 mol/L in DCM), DIPEA (0.2 mmol), DCM (1.5 mL), N_2, 6 h; (ii) pinacol (0.4 mmol, dissolved in 1 mL dry DCM), Et_3N (2.0 mmol), r.t., N_2, 2 h. Isolated yields.

DCM was stirred at room temperature under a N_2 atmosphere for 6 h, and then pinacol (2.0 equiv.) and Et_3N (10.0 equiv.) were added and the mixture was stirred for another 2 h offering the desired compound **3a** in 72% yield. Then we performed a brief survey of the electronic effects on pyridine ring. The results showed that, compared to **1a**, 5-CH_3 substituted substrate decreased the yield, but 5-Cl substituted substrate increased the yield, indicating that electron-withdrawing group on pyridine ring was beneficial to the reaction. Inspired by this result, stronger electron-withdrawing group 5-F and 5-CF_3 were conducted. To our surprise, **3d** was obtained in excellent yield (87%), but the yield of **3e** was decreased, revealing the importance of proper electronic effects on pyridine ring. Finally, we investigated the influence of the position of the fluorine atom on the pyridine. 3-F and 4-F substituted substrates lowered the borylation efficiency compare to 5-F. Besides, only a trace amount of **3h** was obtained when the fluorine atom at the 6-position, possibly due to the steric hindrance that prevented the formation of N–B bond [40]. Given that the fluorine atom played a crucial role in drugs and this reaction, 5-fluoropyridine was identified as the optimal directing group for further surveys.

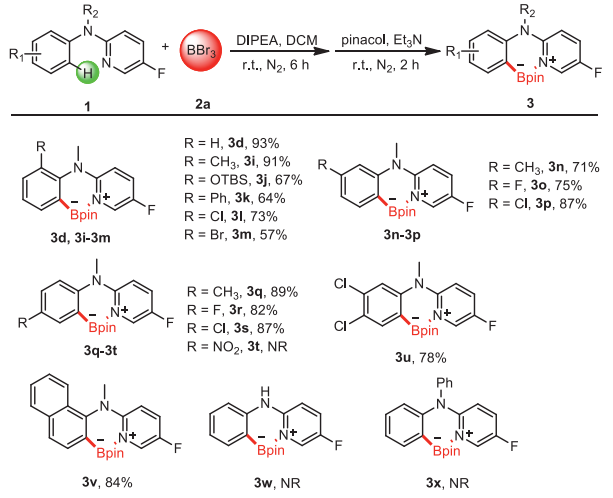
Next, we evaluated the main parameters to optimize reaction conditions (Table 1). When the boron source was BCl_3 and ClBcat, no target product was obtained (entries 2 and 3). To our delight, increasing the amount of **2a** to 3.0 equiv., the yield of **3d** was as high as 93% (entry 4). However, further increasing **2a** did not give a higher yield (entry 5). Among various bases, DIPEA functioned as the best one (entries 6–8). Regrettably, we found that other

Table 1
Optimization of the reaction conditions.[a]



Entry	Deviation from the "primary conditions"	Yield (%)[b]
1	None	87
2	BCl_3 instead of BBr_3	0
3	ClBcat instead of BBr_3	0
4	**2a** (3.0 equiv.)	93
5	**2a** (4.0 equiv.)	88
6	DBU instead of DIPEA	34
7	DABCO instead of DIPEA	25
8	K_2CO_3 instead of DIPEA	17
9	NPG instead of pinacol	0
10	MPD instead of pinacol	0
11	DCE instead of DCM	21
12	CFC-113a instead of DCM	83
13	THF instead of DCM	0

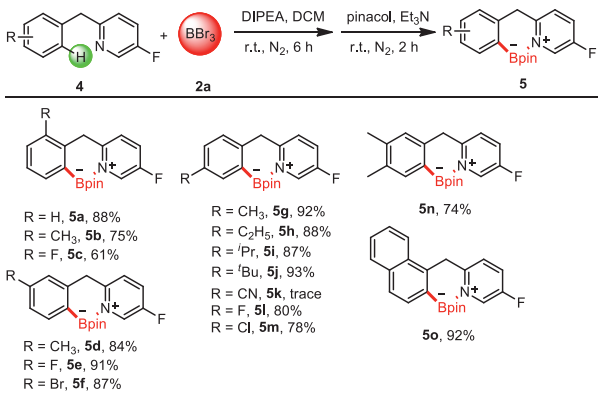
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DABCO = 1,4-diaza[2.2.2]bicyclooctane; NPG = 2,2-dimethyl-1,3-propanediol; MPD = hexylene glycol.
[a] Reaction conditions: **1d** (0.2 mmol), **2a** (0.6 mL, 1 mol/L in DCM), DIPEA (0.2 mmol), DCM (1.5 mL), N_2, 6 h; then pinacol (0.6 mmol, dissolved in 1 mL dry DCM), Et_3N (2.0 mmol), r.t., N_2, 2 h.
[b] Isolated yields.



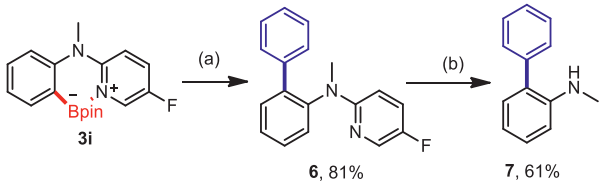
Scheme 3. Substrate scope of 2-(*N*-methylanilino)-5-fluoropyridines. Reaction conditions: **1d, 1i**–**1x** (0.2 mmol), **2a** (0.6 mL, 1 mol/L in DCM), DIPEA (0.2 mmol), DCM (1.5 mL), N_2, 6 h; then pinacol (0.6 mmol, dissolved in 1 mL dry DCM), Et_3N (2.0 mmol), r.t., N_2, 2 h, isolated yields.

boronate esters could not be accessed when different diols were used instead of pinacol (entries 9 and 10). Changing the solvent to DCE and CFC-113a (1,1,1-trichlorotrifluoroethane) provided 21% and 83% yields of **3d**, respectively. But the use of Lewis basic solvent THF was inefficient (entries 11–13).

With the optimized reaction conditions in hand, the scope of 2-(*N*-methylanilino)-5-fluoropyridines was examined as shown in Scheme 3. To our delight, amines bearing electron-donating (Me, OTBS and Ph) or -withdrawing (F, Cl and Br) groups at the *ortho*-, *meta*- and *para*-positions afforded the corresponding borylation products in 57%–93% yields (**3d, 3i**–**3v**). Generally, the yields of the *ortho*-substitution substrates were lower than the *meta* and *para* ones. The large steric hindrance group OTBS (**3j**) at the *ortho* position of the amine was also suitable to C–H borylation. In comparison with **3n**–**3p**, amines containing CH_3, F and Cl groups at *para*-position (**3q**–**3s**) delivered relatively better yields. But stronger electron-withdrawing group NO_2 was not suitable for



Scheme 4. Substrate scope of 2-benzyl-5-fluoropyridines. Reaction conditions: **4a**–**4o** (0.2 mmol), **2a** (0.6 mL, 1 mol/L in DCM), DIPEA (0.2 mmol), DCM (1.5 mL), N_2, 6 h; then pinacol (0.6 mmol, dissolved in 1 mL dry DCM), Et_3N (2.0 mmol), r.t., N_2, 2 h. Isolated yields.

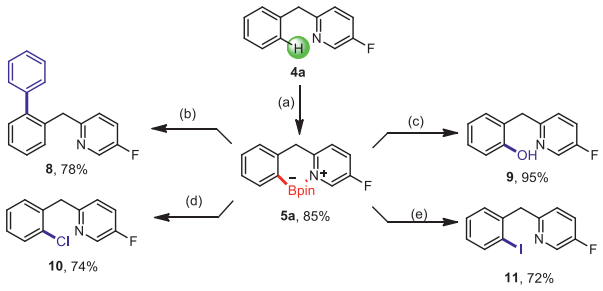


Scheme 5. Synthetic application of product **3i** and removal of the directing group. Reaction conditions: (a) **3i** (0.2 mmol), PhI (0.24 mmol), $Pd(PPh_3)_4$ (0.01 mmol), Na_2CO_3 (0.6 mmol, 2 mol/L in H_2O), PhMe (1.5 mL), reflux, N_2, 12 h. (b) **6** (0.2 mmol), MeOTf (0.4 mmol), DCM (1.0 mL), r.t., N_2, 24 h; then $NaBH_4$ (1.2 mmol), MeOH (1.5 mL), r.t., air, 6 h. Isolated yields.

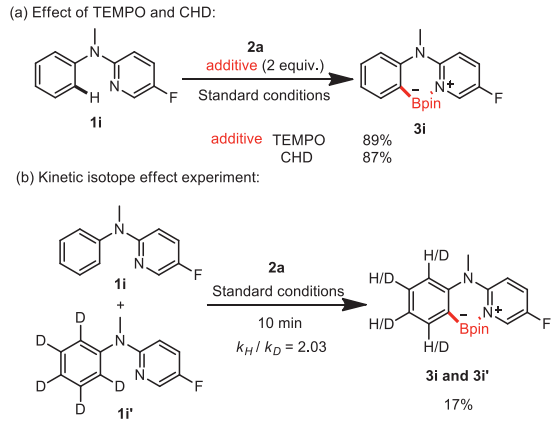
this reaction. Notably, 3,4-dichloro substituted amine **1u** worked well, affording the desired products in 78% yield. Moreover, treatment of 1-naphthyl-substituted substrate **1v** could afford **3v** in an excellent yield under the standard reaction conditions. However, no desired products were obtained with almost all starting materials intact when amines containing N-H or N-Ph substituents instead of N-Me, indicating that the great importance of the Me group.

The strategy was not restricted to 2-(*N*-methylanilino)-5-fluoropyridines; 2-benzyl-5-fluoropyridines were also viable substrates for the reaction. The scope was investigated under the developed reaction conditions (Scheme 4). Most substrates exhibited high borate activity, especially **4e, 4g, 4j** and **4o**, and the yield of the corresponding products all exceeded 90%. In general, the compounds bearing electron-donating groups such as Me, C_2H_5, ^{i}Pr and ^{t}Bu gave the target products in higher yields than electron-withdrawing ones (such as F, Cl, Br, CN), indicating that the electron-donating groups were beneficial to the electrophilic borylation reaction by increasing the electron cloud density of the aromatic ring [41]. Similarly, among the *ortho*-, *meta*-, and *para*-positions substituted substrates, the borylated yields of the *ortho*-position substrates were relatively lower. However, the borylation of **4k** became sluggish, in which the strong electronegativity affected the formation of C–B bond, thus leading to poor conversion. Subjecting compound **4n** containing two methyl groups at the C3 and C4 positions could undergo C–H borylation. Besides, 1-naphthyl-substituted substrate **4o** generated **5o** in an excellent yield (92%).

To certify the potential utility of this method, we realized the arylation of **3i** *via* Suzuki–Miyaura coupling in 81% yield. Subsequent MeOTf-driven reductive removal of the pyridine directing group provided the *N*-methyl-[1,1′-biphenyl]-2-amine in an acceptable yield (Scheme 5) [42,43]. Importantly, this convenient, easily handled, synthetically useful protocol could be executed on a



Scheme 6. Gram-scale reaction and synthetic application of product **5a**. Reaction conditions: (a) **4a** (6.0 mmol), **2a** (18.0 mL, 1 mol/L in DCM), DIPEA (6.0 mmol), DCM (15.0 mL), N_2, 6 h; then pinacol (18.0 mmol, dissolved in 10 mL dry DCM), Et_3N (60.0 mmol), r.t., N_2, 2 h. (b) **5a** (0.2 mmol), PhI (0.24 mmol), $Pd(PPh_3)_4$ (0.01 mmol), Na_2CO_3 (0.6 mmol, 2 mol/L in H_2O), PhMe (1.5 mL), reflux, N_2, 12 h. (c) **5a** (0.2 mmol), $NaBO_3{\cdot}4H_2O$ (0.8 mmol), THF (1.0 mL), H_2O (1.0 mL), r.t., 12 h. (d) **5a** (0.2 mmol), $CuCl_2$ (0.6 mmol), MeOH (1.0 mL), H_2O (1.0 mL), 90 °C, 24 h. (e) **5a** (0.2 mmol), NaI (1.0 mmol), Cu_2O (0.02 mmol), $NH_3{\cdot}H_2O$ (0.5 mmol), EtOH, r.t., air, 20 h. Isolated yields.

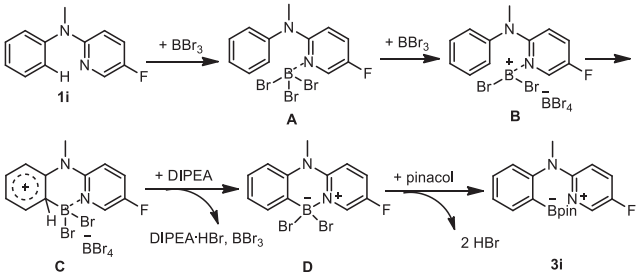


Scheme 7. Effect of TEMPO and CHD and kinetic isotope effect experiments.

gram-scale without any difficulties. The borylated compound **5a** could be transformed into a number of important compounds *via* a Suzuki–Miyaura coupling (**8**) and oxidation with $NaBO_3{\cdot}4H_2O$ (**9**) in good to excellent yields [42, 44]. Moreover, the synthesis of 2-(2-chlorobenzyl)-5-fluoropyridine (**10**) and 2-(2-iodobenzyl)-5-fluoropyridine (**11**) could be achieved by deborylative chlorination and iodination (Scheme 6) [27].

To elucidate the mechanism of this reaction, a control experiment was performed. Radical scavengers TEMPO and CHD were added into the reaction of **1i** and **2a**, respectively. As a result, the yield of **3i** was almost unaffected, thus precluding the radical pathway (Scheme 7a) [45]. Subsequently, the kinetic isotope effect experiment between equivalent **1i** and **1i'** with **2a** under the standard conditions for 10 min was conducted (Scheme 7b) and gave a KIE value of 2.03 by ^{1}H NMR spectroscopic analysis (Supporting information). This result indicated that the cleavage of C(sp^2)–H bond might be related to the rate-determining step [46].

On the basis of experimental investigations and literature precedents [9,10,14,24-26,39]. We depicted a plausible mechanism in Scheme 8. First, a Lewis acid–base adduct was initially formed between BBr_3 and the N atom of 5-fluoropyridine group in **1i**. Then Br transferred from **A** to another BBr_3 and generated a borenium species **B**. An electrophilic aromatic substitution proceeded readily to offer a Wheland intermediate **C**, because of the strong electrophilic nature of the *N*-methylaniline ring in **B**. Subsequently, proton abstraction by DIPEA gave the dibromoboron complex **D**. Finally, under the protection of pinacol, compound **3i** was obtained.



Scheme 8. Proposed mechanism.

In summary, we firstly reported the method for C–H borylation of 2-(*N*-methylanilino)-5-fluoropyridines and 2-benzyl-5-fluoropyridines under metal-free conditions. The obtained borylated products could be converted to various useful intermediates through common synthetic methods. Importantly, the directing group could be removed to enrich synthetic applications. Considering its simplicity and versatility, we expect that this novel borylation approach could show great promise in the screening of potential pharmaceuticals of 2-(*N*-methylanilino)-5-fluoropyridines and 2-benzyl-5-fluoropyridines.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

We gratefully thank the National Natural Science Foundation of China (No. 21676088) for financial support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.09.081.

References

[1] M.Y. Liu, S.B. Hong, W. Zhang, W. Deng, Chin. Chem. Lett. 26 (2015) 373–376.
[2] A.K. Cook, S.D. Schimler, A.J. Matzger, M.S. Sanford, Science 351 (2016) 1421–1424.
[3] T.J. Gong, Y.Y. Jiang, Y. Fu, Chin. Chem. Lett. 25 (2014) 397–400.
[4] M.E. Hoque, M.M.M. Hassan, B. Chattopadhyay, J. Am. Chem. Soc. 143 (2021) 5022–5037.
[5] M.R. Smith, R. Bisht, C. Haldar, et al., ACS Catal. 8 (2018) 6216–6223.
[6] T.A. Boebel, J.F. Hartwig, J. Am. Chem. Soc. 130 (2008) 7534–7535.
[7] Y.L. Liu, G. Kehr, C.G. Daniliuc, G. Erker, Chem. Eur. J. 23 (2017) 12141–12144.
[8] V. Bagutski, A. Del Grosso, J.A. Carrillo, et al., J. Am. Chem. Soc. 135 (2013) 474–487.
[9] J. Lv, B. Zhao, Y. Yuan, Y. Han, Z. Shi, Nat. Commun. 11 (2020) 1316.
[10] G. Wu, X. Fu, Y. Wang, et al., Org. Lett. 22 (2020) 7003–7007.
[11] F. Focante, I. Camurati, D. Nanni, R. Leardini, L. Resconi, Organometallics 23 (2004) 5135–5141.
[12] Z.J. Wang, X. Chen, L. Wu, et al., Angew. Chem. Int. Ed. 60 (2021) 8500–8504.
[13] V. Iashin, D. Berta, K. Chernichenko, et al., Chem. Eur. J. 26 (2020) 13873–13879.
[14] S. Rej, N. Chatani, J. Am. Chem. Soc. 143 (2021) 2920–2929.
[15] F.A. Davis, M.J.S. Dewar, J. Am. Chem. Soc. 90 (1968) 3511–3515.
[16] C. Cazorla, T.S. De Vries, E. Vedejs, Org. Lett. 15 (2013) 984–987.
[17] Z. Zhao, Z. Chang, B. He, et al., Chem. Eur. J. 19 (2013) 11512–11517.
[18] J. Chen, R.A. Lalancette, F. Jäkle, Organometallics 32 (2013) 5843–5851.
[19] D.L. Crossley, I.A. Cade, E.R. Clark, et al., Chem. Sci. 6 (2015) 5144–5151.
[20] A.C. Shaikh, D.S. Ranade, S. Thorat, et al., Chem. Commun. 51 (2015) 16115–16118.
[21] M. Yusuf, K. Liu, F. Guo, R.A. Lalancette, F. Jäkle, Dalton Trans 45 (2016) 4580–4587.
[22] D.L. Crossley, I. Vitorica-Yrezabal, M.J. Humphries, M.L. Turner, M.J. Ingleson, Chem. Eur. J. 22 (2016) 12439–12448.
[23] K. Liu, R.A. Lalancette, F. Jäkle, J. Am. Chem. Soc. 139 (2017) 18170–18173.
[24] S.A. Iqbal, K. Yuan, J. Cid, J. Pahl, M.J. Ingleson, Org. Biomol. Chem. 19 (2021) 2949–2958.
[25] J. Lv, B. Zhao, Y. Han, Y. Yuan, Z. Shi, Chin. Chem. Lett. 32 (2021) 691–694.
[26] N. Ishida, T. Moriya, T. Goya, M. Murakami, J. Org. Chem. 75 (2010) 8709–8712.
[27] L. Niu, H. Yang, R. Wang, H. Fu, Org. Lett. 14 (2012) 2618–2621.
[28] V. Mukundam, S. Sa, A. Kumari, R. Das, K. Venkatasubbaiah, J. Mater. Chem. C 7 (2019) 12725–12737.
[29] C. Zhu, Z.H. Guo, A.U. Mu, et al., J. Org. Chem. 81 (2016) 4347–4352.
[30] S. Tanaka, Y. Saito, T. Yamamoto, T. Hattori, Org. Lett. 20 (2018) 1828–1831.
[31] Y. Li, B. Pang, H. Meng, et al., Tetrahedron Lett. 60 (2019) 151286.
[32] Y. Li, H. Meng, T. Liu, et al., Adv. Mater. 31 (2019) 1904585.
[33] C.R. Opie, H. Noda, M. Shibasaki, N. Kumagai, Chem. Eur. J. 25 (2019) 4648–4653.
[34] S. Olsen, M.S. Baranov, N.S. Baleeva, et al., PCCP 18 (2016) 26703–26711.
[35] M.S. Baranov, K.M. Solntsev, N.S. Baleeva, et al., Chem. Eur. J. 20 (2014) 13234–13241.
[36] K. Dhanunjayarao, S. Sa, B.P.R. Aradhyula, K. Venkatasubbaiah, Tetrahedron 74 (2018) 5819–5825.
[37] J. Lv, X. Chen, X.S. Xue, et al., Nature 575 (2019) 336–340.
[38] S.A. Iqbal, J. Cid, R.J. Procter, et al., Angew. Chem. Int. Ed. 58 (2019) 15381–15385.
[39] S. Rej, A. Das, N. Chatani, Chem. Sci. 12 (2021) 11447–11454.
[40] S.A. Iqbal, J. Pahl, K. Yuan, M.J. Ingleson, Chem. Soc. Rev. 49 (2020) 4564–4591.
[41] F.G. Oliveira, F.L. Rodrigues, A.V.B. de Oliveira, D.V.L.M. Marçal, P.M. Esteves, Struct. Chem. 28 (2017) 545–553.
[42] M. Alessi, A.L. Larkin, K.A. Ogilvie, et al., J. Org. Chem. 72 (2007) 1588–1594.
[43] W. Miura, K. Hirano, M. Miura, Org. Lett. 18 (2016) 3742–3745.
[44] X. Zou, H. Zhao, Y. Li, et al., J. Am. Chem. Soc. 141 (2019) 5334–5342.
[45] F. Michailidou, N. Klöcker, N.V. Cornelissen, et al., Angew. Chem. Int. Ed. 60 (2021) 480–485.
[46] J.Y. Zhou, J.B. Wang, Sci. China Chem. 46 (2016) 573–578.