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Highly Selective Palladium-Catalyzed Arene C−H Acyloxylation with Benzothiadiazole as a Modifiable Directing Group

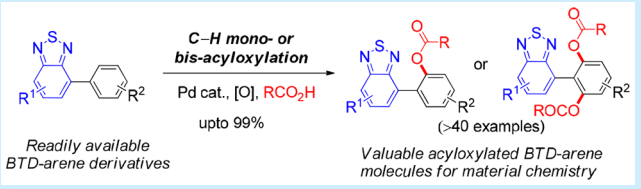
Jie Guo,[†] Hui He,[†] Zenghui Ye,[†] Kai Zhu,[†] Yanqi Wu,[‡] and Fengzhi Zhang*[,†]

[†]College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, P. R. China

[‡]Institute of Information Resource, Zhejiang University of Technology, Hangzhou 310014, P. R. China

Supporting Information

ABSTRACT: An efficient protocol for the palladium-catalyzed direct arene C−H acyloxylation of benzothiadiazole−arene derivatives is reported for the first time. The key strategy is the employment of benzothiadiazole as a modifiable directing group. The highly selective mono- or bis-acyloxylation can be achieved by tuning the reaction conditions, affording various acyloxylated benzothiadiazole derivatives, which could offer a rational tailoring of their electronic properties and be applied in organic electronic and optoelectronic materials. Finally, by diversity-oriented modification of the benzothiadiazole directing group, the acyloxylated products can be readily converted into various valuable functionalized (hetero)biaryls.



Heteroaromatic moties are found throughout many organic materials for organic electronics and optoelectronics, such as donor (D)/acceptor (A) polymers used in bulk heterojunction solar cells,[1] D−A compounds for dye-sensitized solar cells (DSC),[2] D−A second-order nonlinear optical chromophores,[3] A−D−A two-photon absorption (2PA) dyes,[4] and electron-transport materials, etc.[5] Among them, electron-withdrawing 2,1,3-benzothiadiazole (BTD) has been widely incorporated into polymers[6] and small molecules[7] used as DSC sensitizers,[8] 2PA chromophores,[9] or emitters in organic light-emitting diodes (Figure 1).[10] For example, polyfluorene (PF)

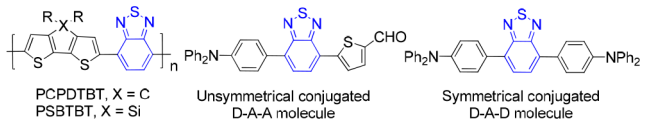
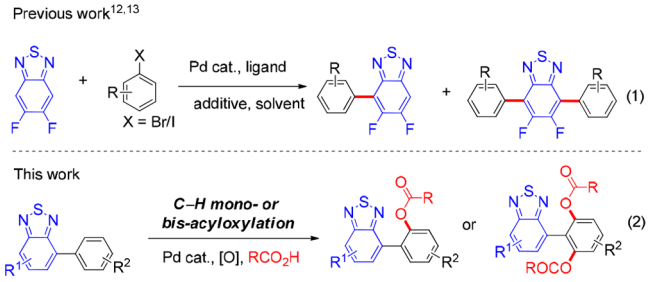


Figure 1. Representative BTD-containing molecules used in optoelectronic materials.

based materials have been explored as blue light emitting materials in polymer light emitting diodes (PLEDs) due to their superior properties, and BTD, which is a narrow bandgap moiety, has often been incorporated into the PF backbone or side chain to tune the emission colors.[11]

Although BTD moieties are among the most important cores in organic materials for optoelectronics, studies concerning their efficient synthesis or structure modification are relatively limited. Because of the synthetic challenges, most of these studies have been only focused on the preparation and investigation of the photophysical properties of 4,7-diaylated BTD derivatives. Moreover, to our knowledge, there are only two similar examples that employ BTD as a modifiable directing group for the direct C−H functionalization of the BTD ring, which were reported by Marder[12] and Zhang,[13] respectively, for the direct *ortho*-arylation of difluoro-BTD under palladium catalysis (Scheme 1, eq 1). In these examples, although the

Scheme 1. Double Functions of BTD Derivatives as Both a Modifiable Directing Group and an Important Fragment of Functional Materials



monofluoro-BTD and nonfluorinated BTD substrates are much less effective probably due to the unfavorable cyclopalladation, we are still inspired to develop a more general and efficient arene C−H functionalization strategy for the diversified modification of the valuable functionalized BTD molecules, which would offer a rational tailoring of their electronic properties by combining the double functions of BTD as both a modifiable directing group for C−H activation[14] and one of the most important cores for functional materials (Scheme 1, eq 2).

Transition-metal-catalyzed, ligand-directed C−H acyloxylation has emerged as a powerful tool for the direct conversion of arenes into various valuable oxygenated aromatic derivatives.[15] Recently, the Mei group reported the oxime-directed sp^3 C−H acyloxylation under electrochemical paladium catalysis.[16]

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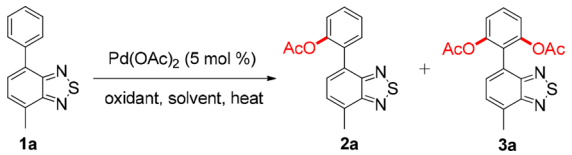
Although a variety of other directing groups such as pyridine,[17] pyrimidine,[18] pyrazole,[19] oxazoline,[20] amide,[21] diphenylphosphine oxide,[22] and pyridyldiisopropylsilyl (PyDipSi)[23] have been shown to be efficient in these reactions, there are still some challenges that need to be addressed. First, the acyloxylation of strong electron-withdrawing substrates is much less effective. Second, the control of reaction selectivity between mono- and bis-acyloxylation is still problematic. Third, the examples about iterative double C−H acyloxylation of arenes are very rare. Finally, the removal or conversion of most directing groups into other desired functionalities is not trivial. Due to the important applications of functionalized BTD derivatives in material chemistry, we are interested in addressing these problems by employing the BTD moiety as a modifiable directing group for the direct arene C−H acyloxylation.

We initiated the investigation by reacting the readily available 4-methyl-7-phenyl-BTD **1a** with $PhI(OAc)_2$ (PIDA) under palladium catalysis at 120 °C (Table 1).

Table 1. Reaction Optimization[a]



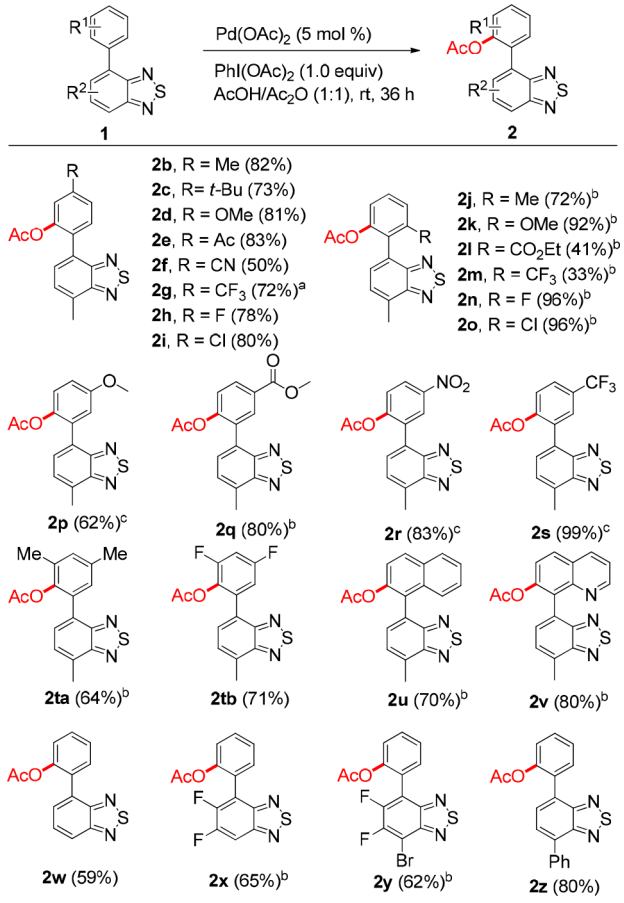
entry	PIDA (equiv)	solvent	yield[b] (%)	2a/3a[c]
1	3.0	MeCN	42	
2	3.0	DCE	62	
3	3.0	Ac_2O	70	1:1
4	3.0	AcOH	72	1:35
5	**3.0**	**AcOH/Ac_2O (1:1)**	**91**	**1:45**
6[d]	3.0	AcOH/Ac_2O (1:1)	99	1:10
7	2.0	AcOH/Ac_2O (1:1)	98	1:3
8	1.0	AcOH/Ac_2O (1:1)	88	6:1
9[e]	**1.0**	**AcOH/Ac_2O (1:1)**	**91**	**20:1**
10[f]	1.0	AcOH/Ac_2O (1:1)		
11		AcOH/Ac_2O (1:1)		
12[g]	1.0	AcOH/Ac_2O (1:1)	82	40:1

[a]Reaction conditions: 0.2 mmol of **1a**, $Pd(OAc)_2$ (5 mol %), PIDA (*x* equiv), solvent (2.0 mL), 120 °C, 16 h. [b]Isolated overall yield. [c]The ratio of **2a** to **3a** was determined by the isolated yields of the products. [d]150 °C. [e]The reaction was conducted at rt for 36 h. [f]In the absence of Pd cat. [g]5 mmol gram scale.

With MeCN as the solvent, the acetate was obtained in 42% yield (Table 1, entry 1). The yield could be improved to 62% with DCE as the solvent (Table 1, entry 2). With Ac_2O as the solvent, it was found that a 1:1 mixture of mono- and bis-acetates was isolated in 70% yield (Table 1, entry 3). By switching the solvent from Ac_2O to AcOH, the selectivity was improved to 1:35 with the bis-acetate **3a** as the major product (Table 1, entry 4). Pleasingly, the selectivity could be further improved to 1:45 with a 91% overall yield with a mixture of AcOH/Ac_2O (1:1) as the solvent (Table 1, entry 5). It was found that both the yield and selectivity were decreased by further changing the ratio of solvents (not shown). By raising the reaction temperature to 150 °C, the selectivity was decreased significantly, although the overall yield was improved to 99% (Table 1, entry 6). By reducing the amounts of PIDA (1.0 equiv), the amount of isolated bis-acetate **3a** decreased, and the major compound isolated was the monoacetoxylated **2a** (Table 1, entries 7 and 8). The selectivity can be improved to 20:1 in 91% overall yield when the reaction was conducted at rt (Table 1, entry 9). No reaction occurred in the absence of either the palladium catalyst or oxidant (Table 1, entries 10 and 11). Finally, to demonstrate the scalability of this reaction, a 5 mmol gram scale reaction was conducted, and the monoacetate **2a** was isolated almost exclusively in very good yield (Table 1, entry 12).

With the optimum conditions in hand, we first examined the scope of this novel monoacyloxylation reaction (Scheme 2).

Scheme 2. Mono-acetoxylation of BTD-arene Derivatives



[a]60 °C. [b]$PhI(OAc)_2$ (1.2 equiv), 120 °C, 16 h. [c]$PhI(OAc)_2$ (3.0 equiv), 120 °C, 16 h.

First, the substrates with a substituent on the *para*-position of the phenyl ring were tested. Simple alkyl (**2b**,**c**), strong electron-donating (**2d**), strong electron-withdrawing (**2e**−**g**), and halogen substituents (**2h**,**i**) were all tolerated under the reaction conditions, affording the corresponding products in good yields. For the substrates with a substituent on the *ortho*-position of the phenyl ring, all gave the corresponding products in good to excellent yields (**2j**−**k** and **2n**−**o**) except the substrates with strong electron-withdrawing substituents (**2l**−**m**) by conducting the reactions at an elevated temperature (120 °C). For the substrates with a substituent on the *meta*-position of the phenyl ring, surprisingly, the substrates with electron-withdrawing substituents (**2q**−**s** and **2tb**) gave the corresponding products in much higher yields than those with electron-donating substituents (**2p** and **2ta**), whereas in the literature the acyloxylation of strong electron-withdrawing substrates was normally much less extensively reported.[15−22] The BTD-naphthalene **2u** and quinolone **2v** substrates were effective as

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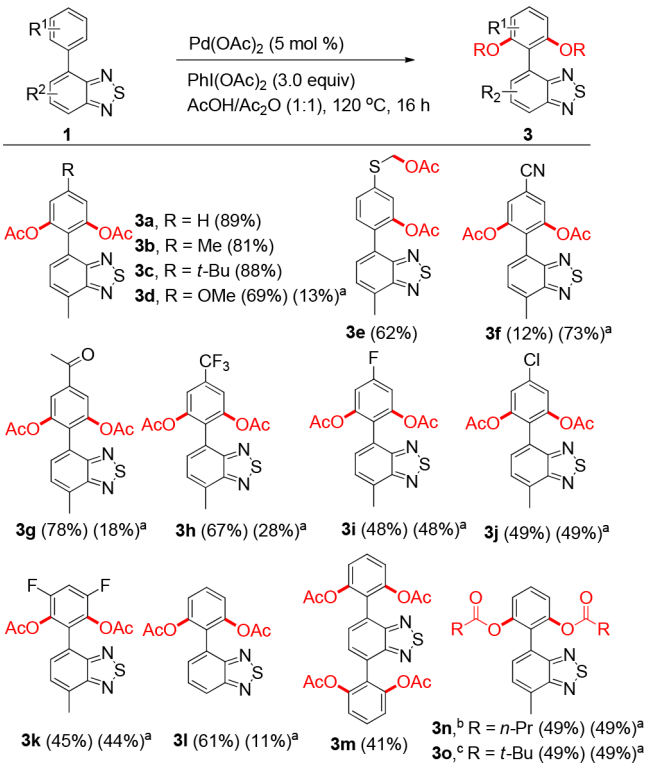
well. If there is no substituent on the 4-position of BTD, the acetoxylation still took place regioselectively on the 7-phenyl ring (**2w**–**x**) other than the BTD ring itself. Both fluoro- and bromo- functional groups were tolerated on the BTD ring under the reaction conditions, which could work as functional handles for further transformations (**2y**). For the symmetrical BTD-arene substrate, the monoacetoxylation still can be achieved very well under the optimized conditions (**2z**).

The substrate scopes for the bis-acyloxylation were then examined under the optimized reaction conditions (Scheme 3).

Scheme 3. Bis-acyloxylation of BTD-arene Derivative

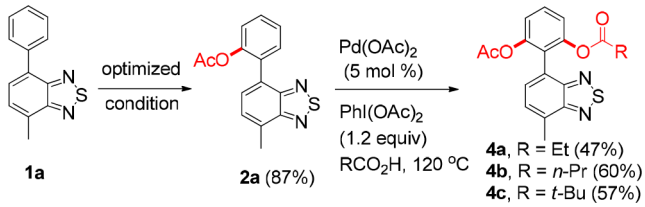


[a]Yield of monoacyloxylated product. [b]*n*-$PrCO_2H$ was used as the solvent. [c]*t*-$BuCO_2H$ was used as the solvent.

The substrates with simple alkyl substituents gave the bis-acetates almost exclusively in very good yields by using 3.0 equiv of PIDA (**3a**–**c**). For the substrate with a strong electron-donating methoxy group, a separable mixture of bis- and monoacetylated products (5.3:1) was obtained in 82% overall yield (**3d**). Interestingly, both sp^3 and sp^2 C–H acetoxylation occurred for the substrate with a methylthio group (**3e**). Surprisingly, the monoacetate was obtained as the major product for the substrate with a cyano group (**3f**). For the substrates with other strong electron-withdrawing groups, a separable mixture of products was obtained in excellent overall yields with the bis-acetate as the major one (**3g**,**h**). The reactions gave an almost 1:1 separable mixture of bis- and monoacetates in excellent yields for the substrates with halogen substituents (**3i**–**k**). The bis-acetoxylation still can be achieved if there is no substituent on the 4-position of BTD (**3l**). For the symmetrical BTD-arene substrate, tetra-acetate was obtained in an unoptimized 41% yield (**3m**). Finally, we showed that the other acyloxylated products can be obtained as well in almost quantitative yield by changing the solvent to the other acids, respectively (**3n**,**o**), which demonstrated in this study that the acyloxy group could come from the solvent directly other than the oxidant.

We already demonstrated that the BTD moiety, as both an important fragment in material chemistry and C–H activation directing group, is effective for selective mono- and bis-acyloxylation. We next want to further demonstrate that the iterative double C–H acyloxylation can be achieved as well (Scheme 4). First, with a mixture of AcOH and Ac_2O as the

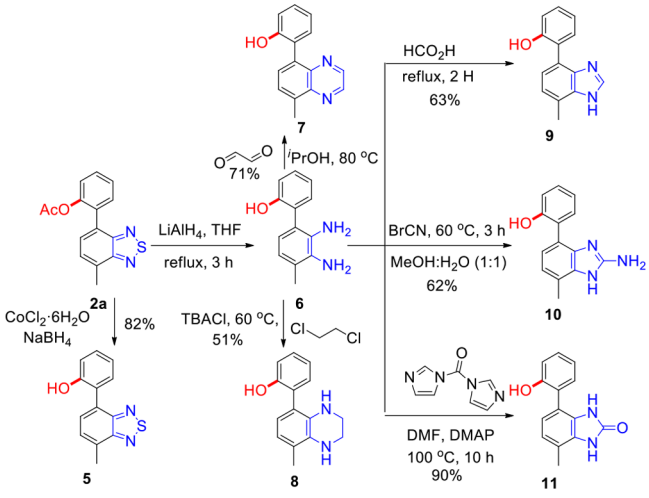
Scheme 4. Iterative Double Acyloxylation of BTD-arene Derivatives



solvent the monoacetate **2a** was obtained under the optimized conditions at rt. Then the compound **2a** was treated with the palladium-catalyzed acyloxylation conditions again in the presence of different solvent at 120 °C, and various asymmetric bis-acyloxylated BTD-arene products **4a**–**c** were obtained successfully.

Finally, we demonstrate that the BTD directing group can be easily modified and the acyloxylated product **2a** could be transformed into various valuable functionalized (hetero)biaryls (Scheme 5).[24] It was found that the acetoxyl group of **2a** can be

Scheme 5. Further Diversity-Oriented Transformations into Various Valuable (Hetero) Biaryls



selectively reduced to give the hydroxylated BTD product **5** in the presence of $CoCl_2{\cdot}6H_2O$ and $NaBH_4$. With LAH as the reducing reagent, both the acetoxyl group and BTD moiety were reduced in one pot to give the diaminobiphenyl **6**. Starting with compound **6**, a diversity-oriented synthesis of various valuable functionalized heterobiaryls **7**–**11** can be achieved readily. For example, by reacting **6** with glyoxal the quinoxaline derivative **7** was prepared in good yield, which could be employed as a PFKFB3 inhibitor. The azabicyclic compounds **9**–**11** were also obtained successfully under different reaction conditions, which could be used as BET inhibitors.[25]

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In summary, we have developed an efficient protocol for the highly selective arene C−H mono- and bis-acyloxylation of BTD derivatives by combining the double functions of BTD moiety as both an important fragment of material chemistry and a modifiable directing group, which would allow the rational tailoring of their electronic properties. Different acyloxy groups can be introduced by simply changing the corresponding solvents. We also demonstrated that an iterative double acyloxylation can be achieved. Finally, by diversity-oriented modification of the benzothiadiazole directing group the acyloxylated products can be readily converted into various valuable functionalized (hetero)biaryls. The asymmetric version of this protocol for the synthesis of functionalized chiral (hetero)biaryls and screening of these diversified compounds for potential applications in optoelectronics are ongoing, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02414.

Experimental procedures and spectroscopic characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail:zhangfengzhi@zjut.edu.cn.

ORCID

Fengzhi Zhang: 0000-0001-9542-6634

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Henson, Z. B.; Müllen, K.; Bazan, G. C. *Nat. Chem.* **2012**, *4*, 699. (b) Li, G.; Zhu, R.; Yang, Y. *Nat. Photonics* **2012**, *6*, 153.

(2) Hagfeldt, A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. *Chem. Rev.* **2010**, *110*, 6595.

(3) Dalton, L. R.; Sullivan, P. A.; Bale, D. *Chem. Rev.* **2010**, *110*, 25.

(4) Pawlicki, M.; Collins, H. A.; Denning, R. G.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3244.

(5) Anthony, J. E.; Facchetti, A.; Heeney, M.; Marder, S. R.; Zhan, X. *Adv. Mater.* **2010**, *22*, 3876.

(6) (a) Zhou, H.; Yang, L.; Stuart, A. C.; Price, S. C.; Liu, S.; You, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 2995. (b) You, J.; Dou, L.; Yoshimura, K.; Kato, T.; Ohya, K.; Moriarty, T.; Emery, K.; Chen, C.-C.; Gao, J.; Li, G.; Yang, Y. *Nat. Commun.* **2013**, *4*, 1446.

(7) (a) Lin, L.-Y.; Chen, Y.-H.; Huang, Z.-Y.; Lin, H. W.; Chou, S.-H.; Lin, F.; Chen, C.-W.; Liu, Y.-H.; Wong, K.-T. *J. Am. Chem. Soc.* **2011**, *133*, 15822. (b) van der Poll, T. S.; Love, J. A.; Nguyen, T.-Q.; Bazan, G. C. *Adv. Mater.* **2012**, *24*, 3646.

(8) (a) Velusamy, M.; Thomas, K. R. J.; Lin, J. T.; Hsu, Y.-C.; Ho, K.-C. *Org. Lett.* **2005**, *7*, 1899. (b) Zhu, W.; Wu, Y.; Wang, S.; Li, W.; Li, X.; Chen, J.; Wang, Z.-S.; Tian, H. *Adv. Funct. Mater.* **2011**, *21*, 756.

(9) Kato, S.-I.; Matsumoto, T.; Shigeiwa, M.; Gorohmaru, H.; Maeda, S.; Ishi-i, T.; Mataka, S. *Chem. - Eur. J.* **2006**, *12*, 2303.

(10) Chen, L.; Zhang, B.; Cheng, Y.; Xie, Z.; Wang, L.; Jing, X.; Wang, F. *Adv. Funct. Mater.* **2010**, *20*, 3143.

(11) Kim, K.; Inagaki, Y.; Kanehashi, S.; Ogino, K. J. *J. Appl. Polym. Sci.* **2017**, *134*, 45393 and references cited therein.

(12) Zhang, J.; Chen, W.; Rojas, A. J.; Jucov, E. V.; Timofeeva, T. V.; Parker, T. C.; Barlow, S.; Marder, S. R. *J. Am. Chem. Soc.* **2013**, *135*, 16376.

(13) He, C.-Y.; Wu, C.-Z.; Qing, F.-L.; Zhang, X. *J. Org. Chem.* **2014**, *79*, 1712.

(14) For reviews, see: (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Zhang, F.; Spring, D. R. *Chem. Soc. Rev.* **2014**, *43*, 6906. (f) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107 and references cited therein.

(15) (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Wu, Y.; Wan, Y.; Zhang, F. *Curr. Org. Synth.* **2018**, *15*, 781 and references cited therein.

(16) (a) Yang, Q.-L.; Li, Y.-Q.; Ma, C.; Fang, P.; Zhang, X.-J.; Mei, T.-S. *J. Am. Chem. Soc.* **2017**, *139*, 3293. (b) Sauermann, N.; Meyer, T. H.; Tian, C.; Ackermann, L. *J. Am. Chem. Soc.* **2017**, *139*, 18452.

(17) (a) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (b) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. (c) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (d) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136. (e) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466.

(18) (a) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (b) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (c) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966.

(19) (a) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (b) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (c) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726. (d) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066.

(20) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem.* **2010**, *122*, 1297.

(21) (a) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (b) Sun, C.-L.; Liu, N.; Yu, D.-G.; Wang, Y.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 184.

(22) (a) Wang, H.-L.; Hu, R.-B.; Zhang, H.; Zhou, A.-X.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 5302. (b) Zhang, H.-Y.; Yi, H.-M.; Wang, G.-W.; Yang, B.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 6186. (c) Zhang, H.; Hu, R.-B.; Zhang, X.-Y.; Li, S.-X.; Yang, S.-D. *Chem. Commun.* **2014**, *50*, 4686. (d) Li, S.-X.; Ma, Y.-N.; Yang, S.-D. *Org. Lett.* **2017**, *19*, 1842.

(23) (a) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270. (b) Dudnik, A. S.; Chernyak, N.; Huang, C.; Gevorgyan, V. *Angew. Chem.* **2010**, *122*, 8911. (c) Gulevich, A. V.; Melkonyan, F. S.; Sarkar, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2012**, *134*, 5528. (d) Sarkar, D.; Melkonyan, F. S.; Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 10800. (e) Sarkar, D.; Gulevich, A. V.; Melkonyan, F. S.; Gevorgyan, V. *ACS Catal.* **2015**, *5*, 6792. (f) Wang, Y.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2017**, *56*, 3191.

(24) (a) Zhang, F.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768. (b) Zhang, F.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 4745. (c) Xie, H.; Ding, M.; Liu, M.; Hu, T.; Zhang, F. *Org. Lett.* **2017**, *19*, 2600. (d) Xie, H.; Yang, S.; Zhang, C.; Ding, M.; Liu, M.; Guo, J.; Zhang, F. *J. Org. Chem.* **2017**, *82*, 5250.

(25) Liu, S.; Quinn, J. F.; Bryan, C.; Wang, R.; May, X.; Martin, G. S.; Zhao, H.; Ellis, M.; Wagner, G. S.; Gregory, S.; Young, P. R. Zenith Epigenetics Corp. PCT Int. Appl. 2015004533, 2015.

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