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# Dual Role of Ethyl Bromodifluoroacetate in the Formation of Fluorine-containing Heteroaromatic Compounds

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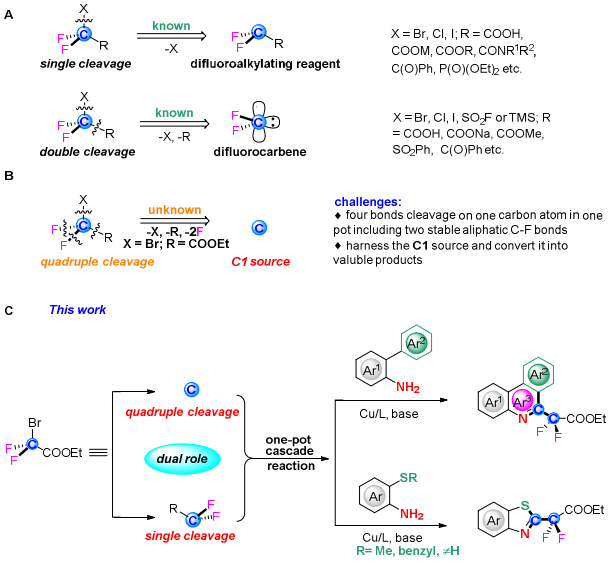
**An efficient one-pot cascade process via unprecedented quadruple cleavage of $BrCF_2COOEt$ with primary amines to afford valuable fluorine-containing heterocycles is described, in which $BrCF_2COOEt$ plays dual role as C1 synthons and difluoroalkylating reagent for the first time. Mechanistic studies supported by DFT calculations suggest that base plays an active role to form the key intermediate isocyanides, generated *in-situ* from primary amines and difluorocarbene.**

C-F bonds are one of the strongest bonds that are ever formed in substances,[1] which make them inert and chemically stable. Therefore, activation of C-F bonds[2] has gained significant attentions. The activation of C-F bonds on arylfluorides has long been studies[2a,2b,2d], but research on $C(sp^3)$-F bonds scission[2c,3] is relatively rare, strong nucleophiles, air- and moisture sensitive organometallic reagents (organolithium or Grignard reagents) or high temperature, have been employed.[2h,4] Thus cleavage of C-F bonds under mild and operational simple conditions still remains a fundamental and ongoing issue.

Halodifluoromethyl compounds (halo = Br, I or Cl) have been widely employed as difluoroalkylating reagents[5] as well as difluorocarbene synthons,[6] and many difluoroalkylation or difluoromethylation reactions have been developed with them via either single C-X bond cleavage or double C-X and C-R bonds cleavage (Scheme 1A).[5,6] However, despite the great advances on difluoroalkylation/difluorometylation with halodifluoromethyl compounds, quadruple cleavage on the same carbon atom leading to a novel C1 source, to our knowledge, has not yet been reported (Scheme 1B). Recently, our research group has developed several difluoroalkylation




**Scheme 1**. **A**) Single and double cleavage in halodifluoromethyl compounds; **B**) Quadruple cleavage in halodifluoromethyl compound **C**) Cascade approaches to access valuable products from arylamines with ethyl bromodifluoroacetate.

reactions with $BrCF_2COOEt$ via radical process with $Cu/B_2pin_2$ catalytic system.[5k-5n,7] Herein, we report two unusual cascade reactions via unprecedented quadruple cleavage of $BrCF_2COOEt$ with primary amines to access various phenanthridines and benzothiazoles (Scheme 1C). These novel transformations have several significant merits: (1) these reactions proceed via an isocyanide intermediate which are widely used in organic synthesis.[8] Notably, these are the first examples in which isocyanides were formed in situ, and subsequently fully converted into valuable products.; (2) two molecules of $BrCF_2COOEt$ were involved in the synthesis of 6-difluoroacetate phenanthridines and 2-difluoroacetate benzothiazoles: one serves as C1 source by the cleavage of two C-F bonds, one C-Br bond and one C-COOEt bond, another one acts as a normal difluoroalkylation reagent. To our knowledge, the current protocol represents the first example for using

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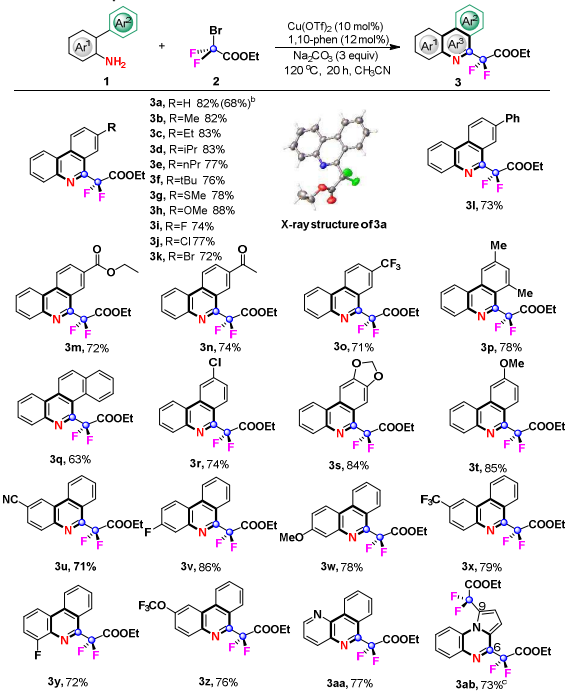
$BrCF_2COOEt$ as a dual role in one reaction. (3) a novel mechanism is proposed via DFT calculations, which represents a highly attractive and efficient strategy for both isocyanide chemistry and fluorine chemistry, thus might promote the discovery of new methodologies with this unusual C-F bond cleavage strategy.

We commenced our study by utilizing 2-phenylaniline (**1a**) and $BrCF_2COOEt$ as model substrates for optimization of the reaction (see SI for details). After many attempts, to our delight, the use of $Cu(OTf)_2$/1,10-phen catalytic system, the tandem transformation could afford the desired product **3a** in 82% yield by using $Na_2CO_3$ as base in $CH_3CN$ at 120 °C. Under the optimal reaction conditions, the substrate scope of amines in this novel cascade process was subsequently investigated (Scheme 2). Firstly, various amines with different substituents on the $Ar^2$ ring were investigated, where C-H bond activation occurred. Various groups of $Ar^2$ ring were well compatible, rendering the target molecules in good to excellent yields (**3a**-**3q**). The structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis.[9] Of note, it is possible to provide two isomers when the substrates bearing substituent on the *meta*-position of the $Ar^2$ ring are used. However, gratifyingly, excellent regioselectivity was observed with these substrates in our transformation, and the products with C-H cyclization occurring *para*- to the substitute group was predominant (**3r**-**3t**), which suggested that the C-H activation was sensitive to the steric environment. Subsequently, the substituent effect on the $Ar^1$ ring

**Scheme 2.** The substrate scope of amines for the synthesis of 6-difluoroacetate phenanthridines[a]

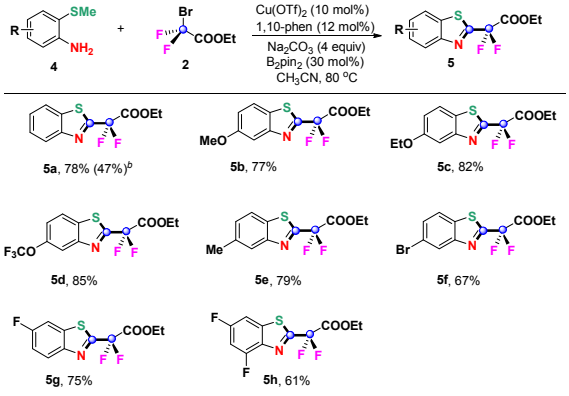



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $Cu(OTf)_2$ (10 mol%), 1,10-phen (12 mol%), $Na_2CO_3$ (3 equiv), $CH_3CN$ (2 mL) under $N_2$ atmosphere 120 °C for 20 h, isolated yield. [b] **1a** (2 mmol). [c] **2** (4 equiv).

was explored. Not surprisingly, the cascade transformations proceeded smoothly as well and delivered the corresponding products (**3u**-**3z**) in 71-86% yields. To our delight, the heterocyclic amines such as 2-phenylpyridin-3-amine and 2-(1*H*-pyrrol-1-yl)aniline were also amenable to this reaction, giving the products **3aa** and **3ab** in decent yields. Most remarkably, for 2-(1*H*-pyrrol-1-yl)aniline, the cascade process didn't stay at mono-substitution, instead, further difluoroalkylation occurred on another C-H bond which adjacent to N-atom of pyrrole ring, leading to 6,9-difluoroalkylative product **3ab** when 4 equivalents of $BrCF_2COOEt$ was used.

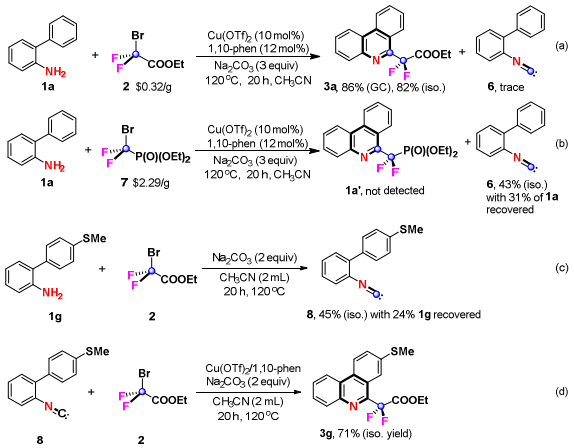
The successful examples encouraged us to further apply our dual-role strategy of $BrCF_2COOEt$ for the construction of 2-difluoroacetate benzothiazoles or benzoxazoles from 2-thiol aniline or 2-hydroxy aniline, since these types of compounds are prevalent scaffolds in many bioactive molecules,[10] the incorporation of fluorine atom in the above two types of heterocyclic compounds might significantly alter the property of these compounds. With these in mind, initial attempts with above two types of anilines as starting materials under our standard conditions were conducted. Unfortunately, no desired 2-difluoroacetate benzazoles and benzothiazoles were obtained, and only trace amount of corresponding 2-difluoroacetate target molecules were detected. Inspired by our recent progress on the radical cyclization of 2-alkynyl thioanisoles,[11] we changed 2-thiol aniline into 2-amino thioanisole. To our delight, 2-amino thioanisole **4a** could smoothly convert into target 2-difluoroacetate benzothiazole **5a** under the standard conditions. A brief survey on the parameters of the reaction indicated that 30 mol% of $B_2pin_2$[5k-5n] could significantly promote the transformation (see SI), rendering 2-difluoroacetate benzothiazoles (**5**) in decent yields with good functional group tolerance (Scheme 3).

**Scheme 3.** 2-Difluoroacetate benzothiazoles formation from 2-aminothioanisoles and ethyl bromodifluoroacetate with the latter one serving as dual roles[a]



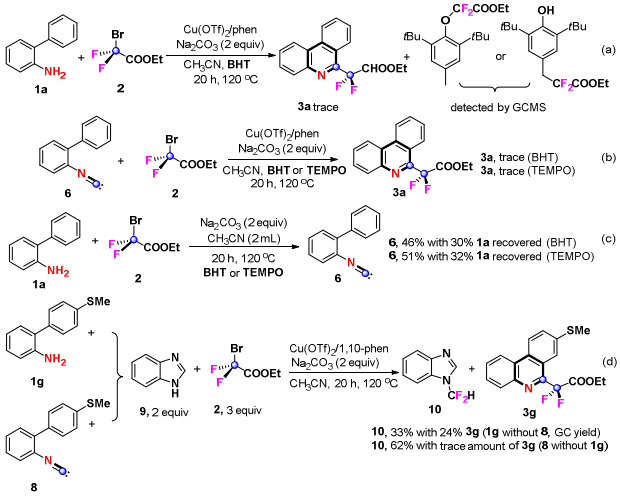

[a] Reaction conditions: **4** (0.2 mmol), ethyl bromodifluoroacetate (**2**) (3 equiv), $Cu(OTf)_2$ (10 mol%), 1,10-phen (12 mol%), $B_2pin_2$ (30 mol%), $Na_2CO_3$ (4 equiv), $CH_3CN$ (2 mL) under $N_2$ atmosphere at 80 °C for 24 h. Isolated yields. [b] 2-(benzylthio)aniline as a substrate.

In order to understand the source of the extra carbon, different difluoromethyl compounds and solvent were further screened (SI). The formation of 6-substituted phenanthridine **3a** and the trace amount of **6** were observed under the optimized conditions. When (bromodifluoromethyl)phosphonate **7** was subjected to the above reaction, isocyanide **6** was obtained in 43% isolated yield with 31% of amine **1a** recovered (Scheme 4b). In addition, corresponding isocyanides **8** was obtained in 45% isolated yield, with 24% of starting material amines **1g** recovered in the absence of Cu catalyst




**Scheme 4.** Control experiments to figure out the key intermediate for this transformation.

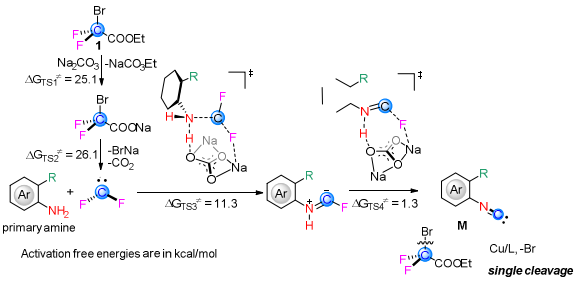
and ligand (Scheme 4c). These results implied the extra carbon in both **3a** and **6** should come from the carbon which is bound to two fluorine atoms in $BrCF_2COOEt$ and base itself could promote the formation of isocyanide slowly, yet Cu salt and ligand will lead to the sequential cyclization and difluoroacetylation of isocyanide. Not surprisingly, the formation of phenanthridine actually could accelerate the speed for the generation of isocyanide. Based on the above experiments, isocyanide might be the key intermediate for this cascade transformation. To verify our hypothesis, the isocyanides **8** was subjected to the optimized conditions with $BrCF_2COOEt$ (SI). Gratifyingly, the corresponding desired product **3g** was obtained in good yield (Scheme 4d). These results clearly demonstrated that isocyanides are the key intermediates for this tandem transformation.




**Scheme 5.** Control experiments and radical trapping experiments.

Radical trapping experiments were then carried out under various conditions in order to thoroughly understand the mechanism of this transformation (Scheme 5a-c). For phenanthridine synthesis, when aryl amine **1a** or the corresponding isocyanide **6** was exposed to the standard conditions in the presence of radical scavenger (BHT or TEMPO), no desired product was obtained (Scheme 5a-5b). Next, when reaction was performed with aryl amine **1a** and $BrCF_2COOEt$ in the absence of Cu salt and ligand, satisfactory yields of isocyanide **6** was obtained with both BHT and TEMPO cases (Scheme 5c). Above results suggested the formation of isocyanide is a radical free process, while the subsequent cyclization and difluoroalkylation step should be a SET pathway. In order to trap the possible intermediate (SI), carbene scavenger benzimidazole (**9**) was added to the reaction for the synthesis of 6-difluoroacetate phenanthridine with **1g** as the substrate, notably, **3g** was obtained in 24% yield along with the formation of 1-(difluoromethyl)-1*H*-benzo[*d*]imidazole **10**. Interestingly, the yield of **10** was increased to 62% and trace amount of the desired product **3g** was detected when the reactant was corresponding isocyanide **8** (Scheme 5d). All the three control experiments clearly indicated that difluorocarbene ($:CF_2$) was generated in situ during this transformation.

On the basis of the above results and literature, the reaction is proposed to occur by an isocyanide intermediate which was generated from a difluorocarbene and primary amine with the help of base (Scheme 6). To investigate the formation of difluorocarbene and isocyanide intermediate, DFT calculations were performed[12] (SI). Computational results suggest that the $BrCF_2COOEt$ reacts with $Na_2CO_3$ to generate $BrCF_2COONa$ which undergoes further decarboxylation and debromination processes to afford difluorocarbene. The activation free energy of the generation of difluorocarbene is 26.1 kcal/mol which can be overcome under the reaction condition. Subsequently, difluorocarbene reacts with amine substrate in the presence of $Na_2CO_3$. Computations reveal that the formation of C-N bond, the N-H and C-F bonds activation by $Na_2CO_3$ occur in a concerted way (**TS3**), leading to N-(fluoromethylene)arylaminium (**P**), $NaHCO_3$ and NaF. Then **P** easily decomposes to isocyanide **M** via N-H and C-F bonds cleavage by $Na_2CO_3$. Calculation results indicate the formation of isocyanide intermediate from difluorocarbene and amine with the assistance



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eventually delivering valuable products.

We have developed a novel and unusual C-F bond activation from $BrCF_2COOEt$ and primary amines, rendering straightforward synthetic methods toward two types of valuable heteroaromatic rings. These protocols proceed via an isocyanide intermediate which is generated in situ between $BrCF_2COOEt$ and primary amines in basic conditions. This is the first example that $BrCF_2COOEt$ performs two role as a C1 source and difluoroalkylating reagent in synthetic chemistry. A novel mechanism based on experimental observations and DFT calculations is proposed which might nourish both isocyanide chemistry and fluorine chemistry to discover more new methodologies through C-F bond cleavage under operational simple and relative mild conditions from simple starting materials. Further studies towards the detailed mechanism and transformation as well as exploration on new methodologies on this unusual quadruple cleavage on one carbon in difluoromethane compounds are under way in our laboratory.

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## Conflicts of interest

The authors declare no competing financial interest.

## Notes and references

1 (a) R. T. Blickenstaff and B. Orwig, *J. Org. Chem*. 1967, **32**, 815-816. (b) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*. 2011, **473**, 470. (c) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.* 2011, **111**, 4475-4521. (d) Q. Liu, Y. Wu, P. Chen and G. Liu, *Org. Lett.* 2013, **15**, 6210-6213.

2 a) M. Aizenberg and D. Milstein, *Science*. 1994, **265**, 359-361. (b) M. Aizenberg and D. Milstein, *J. Am. Chem. Soc.* 1995, **117**, 8674-8675. (c) J. Burdeniuc and R. H. Crabtree, *J. Am. Chem. Soc.* 1996, **118**, 2525-2526. (d) B. L. Edelbach, B. M. Kraft and W. D. Jones, *J. Am. Chem. Soc.* 1999, **121**, 10327-10331. (e) V. P. W. Böhm, C. W. K. Gstöttmayr, T. Weskamp and W. A. Herrmann, *Angew. Chem. Int. Ed.* 2001, **40**, 3387-3389. (f) T. Iida, R. Hashimoto, K. Aikawa, S. Ito and K. Mikami, *Angew. Chem. Int. Ed*. 2012, **51**, 9535-9538. (g) J. Terao, A. Ikumi, H. Kuniyasu and N. Kambe, *J. Am. Chem. Soc.* 2003, **125**, 5646-5647.

3 (a) J. Ichikawa, R. Nadano, and N. Ito, *Chem. Commun.* 2006, 4425-4427. (b) T. Narumi, K. Tomita and E. Inokuchi, K. Kobayashi, S. Oishi, H. Ohno, and N. Fujii, *Org. Lett.* 2007, **9**, 3465-3468.

4 (a) J. L.Kiplinger, T. G. Richmond and C. E. Osterberg, *Chem. Rev.* 1994, **94**, 373-431. (b) M. Ohashi, T. Kambara, T. Hatanaka, H. Saijo, R. Doi and S. Ogoshi, *J. Am. Chem. Soc.* 2011, **133**, 3256-3259. (c) T. Ichitsuka, T. Fujita, T. Arita and J. Ichikawa, *Angew. Chem. Int. Ed.* 2014, **53**, 7564-7568.

5 (a) Q. Zhou, A. Ruffoni, R. Gianatassio, Y. Fujiwara, E. Sella, D. Shabat and P. S. Baran, *Angew. Chem. Int. Ed.* 2013, **52**, 3949-3952. (b) V. D. Romanenko and V. P. Kukhar, *Chem. Rev.* 2006, **106**, 3868-3935. (c) Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang and X. Zhang, *Angew. Chem. Int. Ed.* 2014, **53**, 1669-1673. (d) Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan and X. Zhang, *Angew. Chem. Int. Ed*. 2014, **53**, 9909-9913. (e) Z. Feng, Q.-Q. Min, H.-Y. Zhao, J.-W. Gu and X. Zhang, *Angew. Chem. Int. Ed.* 2015, **54**, 1270-1274. *(*f) J.-W. Gu, Q.-Q. Min, L.-C. Yu and X. Zhang, *Angew. Chem. Int. Ed.* 2016, **55**, 12270-12274. (g) G. Li, T. Wang, F. Fei, Y.-M. Su, Y. Li, Q. Lan and X.-S. Wang, *Angew. Chem. Int. Ed.* 2016, **55**, 3491-3495. (h) P. Xu, G. Wang, Y. Zhu, W. Li, Y. Cheng, S. Li and C. Zhu, *Angew. Chem. Int. Ed.* 2016, **55**, 2939-2943. (i) J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph and A. S. K. Hashmi, *Angew. Chem. Int. Ed.* 2016, **55**, 2934-2938. (j) J. Liu, W. Ding, Q.-Q. Zhou, D. Liu, L.-Q. Lu and W.-J. Xiao, *Org. Lett.* 2018, **20**, 461-464. (k) M. Ke, Q. Feng, K. Yang and Q. Song, *Org. Chem. Front.* 2016, **3**, 150-155. (l) M. Ke and Q. Song, *J. Org. Chem.* 2016, **81**, 3654-3664. (m) M. Ke and Q. Song, *Chem. Commun.* 2017, **53**, 2222-2225. (n) M. Ke and Q. Song, *Adv. Synth. Catal.* 2017, **359**, 384-389.

6 (a) H. Amii, T. Kobayashi, Y. Hatamoto and K. Uneyama, *Chem. Commun.* 1999, 1323-1324. (b) V. D. Romanenko and V. P. Kukhar, *Chem. Rev.* 2006, **106**, 3868-3935. (c) R. Doi, K. Kikushima, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.* 2015, **137**, 3276-3282. (d) M. Zhou, C. Ni, Z. He and J. Hu, *Org. Lett.* 2016, **18**, 3754-3757. (e) Q. Xie, C. Ni, R. Zhang, L. Li, J. Rong and J. Hu, *Angew. Chem. Int. Ed.* 2017, **56**, 3206-3210. (f) W. Miao, Y. Zhao, C. Ni, B. Gao, W. Zhang and J. Hu, *J. Am. Chem. Soc.* 2018, **140**, 880-883. (g) D. O'Hagan, *Chem. Soc. Rev.* 2008, **37**, 308-319. (g) N. A. Meanwell, *J. Med. Chem.* 2011, **54**, 2529-2591.

7 W. Fu, Q. Song, *Org. Lett.* 2018, **20**, 393-396.

8 (a) M. Tobisu, K. Koh, T. Furukawa and N. Chatani, *Angew. Chem. Int. Ed.* 2012, **51**, 11363-11366. (b) H. Jiang, Y. Cheng, R. Wang, M. Zheng, Y. Zhang and S. Yu, *Angew. Chem. Int. Ed.* 2013, **52**, 13289-13292. (c) D. Leifert, C. G. Daniliuc and A. Studer, *Org. Lett.* 2013, **15**, 6286-6289. (d) J. Liu, Z. Fang, Q. Zhang, Q. Liu and X. Bi, *Angew. Chem. Int. Ed.* 2013, **52**, 6953-6957. (e) H. Jiang, Y. Cheng, R. Wang, Y. Zhang and S. Yu, *Chem. Commun.* 2014, **50**, 6164-6167. (f) X. Sun and S. Yu, *Org. Lett.* 2014, **16**, 2938-2941.

9 (a) CCDC 1820711 (**B1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. (b) W. Wan, X. Xu, Y. Chen, H. Jiang, H. Deng and J. Hao, *Eur. J. Org. Chem.* 2017, **2017**, 3145-3151. (c) J.-W. Gu, X. Zhang, *Org. Lett.* 2015, **17**, 5384-5387.

10 (a) T. Nakanishi and M. Suzuki, *Org. Lett.* 1999, **1**, 985-988. (b) H. Fuchino, M. Kawano, K. M. Yasumoto and S. Sekita, *Chem. Pharm. Bull.* 2010, **58**, 1047-1050. (c) K. Li, K. J. Frankowski and D. N. Frick, *J. Med. Chem*. 2012, **55**, 3319-3330. (d) T. Nakanishi and M. Suzuki, *J. Nat. Prod.* 1998, **61**, 1263-1267. (e) T. Nakanishi, A. Masuda, M. Suwa, Y. Akiyama, N. Hoshino-Abe and M. Bioorg. Suzuki, *Med. Chem. Lett.* 2000, **10**, 2321-2323. (f) E. Feng, H. Huang, Y. Zhou, D. Ye, H. Jiang and H. Liu, *J. Comb. Chem.* 2010, **12**, 422-429.

11 (a) J. Xu, X. Yu, J. Yan and Q. Song, *Org. Lett*. 2017, **19**, 6292-6295. (b) J. Yan, J. Xu, Y. Zhou, J. Chen, and Q. Song, *Org. Chem. Front.*, 2018, DOI:10.1039/C8QO00147B.

12 All DFT calculations were performed at the SMD-M06-2X/6-311G++(d,p)//B3LYP/6-31G+LAN2DZ level of theory using Gaussian 09, M. J. Frisch, et al. Gaussian, Inc., Wallingford CT, 2009. Computational details, numerical results and complete citation of Gaussian 09 are provided in the Supporting Information.