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Coupling of Trifluoroacetaldehyde *N*-Triftosylhydrazone with Organoboronic Acids for the Synthesis of *gem*-Difluoroalkenes

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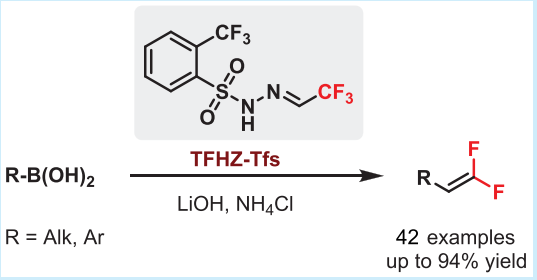
Supporting Information

ABSTRACT: The synthesis of alkyl *gem*-difluoroalkenes remains a difficult task in organic synthesis. Here, we report a general and efficient approach for tackling this problem by *gem*-difluoroolefination of trifluoroacetaldehyde *N*-triftosylhydrazone with organoboronic acids. This protocol is operationally simple, free of transition metals, and suitable for a broad range of organoboronic acids. Moreover, the utility of the products was demonstrated by further conversion of the *gem*-difluorovinyl group.



gem-Difluoroalkenes are ubiquitous structural units in biologically active molecules, pharmaceuticals, agrochemicals, and organic materials (Figure 1).[1] They are also important motifs

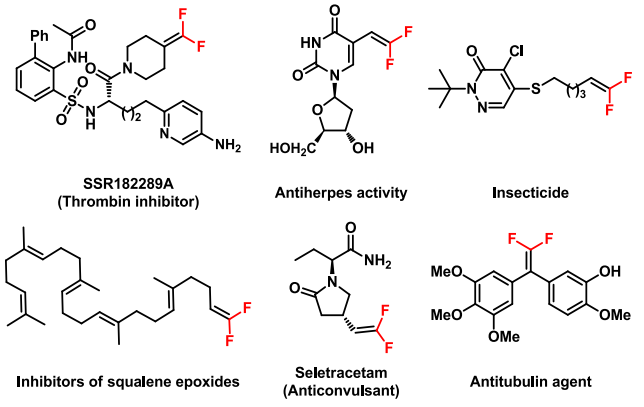


Figure 1. Biologically active molecules containing a *gem*-difluorovinyl moiety.

in the design of mechanism-based enzyme inhibitors[1c,2] and are known to act as bioisosteres of carbonyl groups.[3] Moreover, *gem*-difluoroalkenes are versatile building blocks in organic synthesis.[4] Consequently, a number of elegant methods for their synthesis have been developed. Among these, the construction of *gem*-difluoroalkenes from diazo compounds has attracted considerable attention in recent years.[5] For instance, Wang, Hu, and others demonstrated a cross-carbene type coupling of diazo compounds with difluorocarbene precursors to access *gem*-difluoroalkenes (Figure 2a).[5a−f] Despite their versatility, these methodologies are viable for only diazo compounds bearing at least one EWG

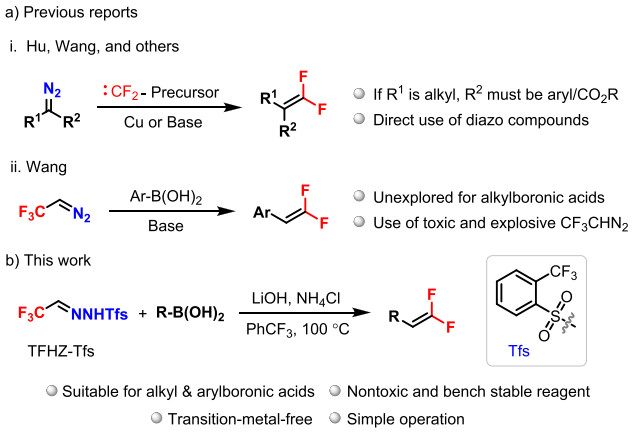


Figure 2. Coupling strategies for the synthesis of *gem*-difluoroalkenes using diazo compounds.

or an aryl ring. In addition, homodimerization and cyclopropanation yield the side products. Recently, Wang and coworkers reported a seminal coupling reaction of trifluorodiazoethane (CF_3CHN_2) and arylboronic acids leading to *gem*-difluoroalkenes (Figure 2a).[5g] However, this method required the direct use of toxic and explosive CF_3CHN_2. A survey of the chemistry of *gem*-difluoroalkenes revealed that alkyl *gem*-difluoroalkenes were more abundant in biologically active compounds than aryl *gem*-difluoroalkanes (Figure 1).[1] Nevertheless, the synthesis of alkyl *gem*-difluoroalkenes remains a difficult task in organofluorine chemistry. As part of our continued interest in the room-temperature decomposition of

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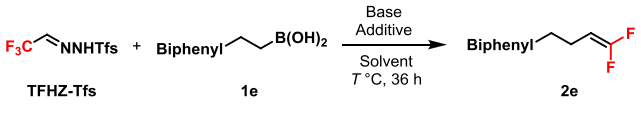
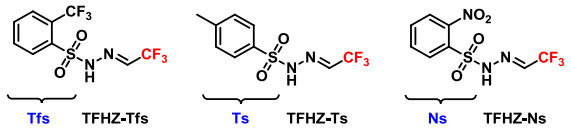
N-sulfonylhydrazones, we recently disclosed a nontoxic and bench-stable trifluoroacetaldehyde *N*-triftosylhydrazone (TFHZ-Tfs) as a CF_3CHN_2 surrogate, which afforded CF_3CHN_2 in situ under basic conditions. In addition, TFHZ-Tfs was successfully employed in the *gem*-difluoroolefination of X−H bonds (X = N, O, S, or Se).[6] Encouraged by these results, we envision that *gem*-difluoroolefination of trifluoroacetaldehyde *N*-sulfonylhydrazones with organoboronic acids might be possible. An investigation of this hypothesis led to the development of a highly efficient transition metal free *gem*-difluoroolefination of TFHZ-Tfs with organoboronic acids, which represents a novel method for accessing alkyl and aryl *gem*-difluoroalkenes (Figure 2b).

We started our study using TFHZ-Tfs and biphenyl ethyl boronic acid (**1e**) as standard substrates. As shown in Table 1,

Table 1. Optimization of the Reaction Conditions[a]



entry	base	additive	solvent	T (°C)	yield of **2e** (%)[b]
1	K_2CO_3	–	$PhCF_3$	100	trace
2	*t*-BuOLi	–	$PhCF_3$	100	30
3	*t*-BuOK	–	$PhCF_3$	100	trace
4	*t*-BuONa	–	$PhCF_3$	100	25
5	LiOH	–	$PhCF_3$	100	36
6	LiOH	–	1,4-dioxane	100	0
7	LiOH	–	DMSO	100	0
8	LiOH	–	toluene	100	trace
9	LiOH	NH_4OAc	$PhCF_3$	100	80
10	LiOH	NH_4I	$PhCF_3$	100	88
11	LiOH	NH_4Cl	$PhCF_3$	100	95 (90)[c]
12	LiOH	NH_4Cl	$PhCF_3$	80	trace
13	LiOH	NH_4Cl	$PhCF_3$	120	82
14	LiOH	LiCl	$PhCF_3$	100	0
15[d]	LiOH	NH_4Cl	$PhCF_3$	100	38
16[e]	LiOH	NH_4Cl	$PhCF_3$	100	54
17[f]	LiOH	NH_4Cl	$PhCF_3$	100	37

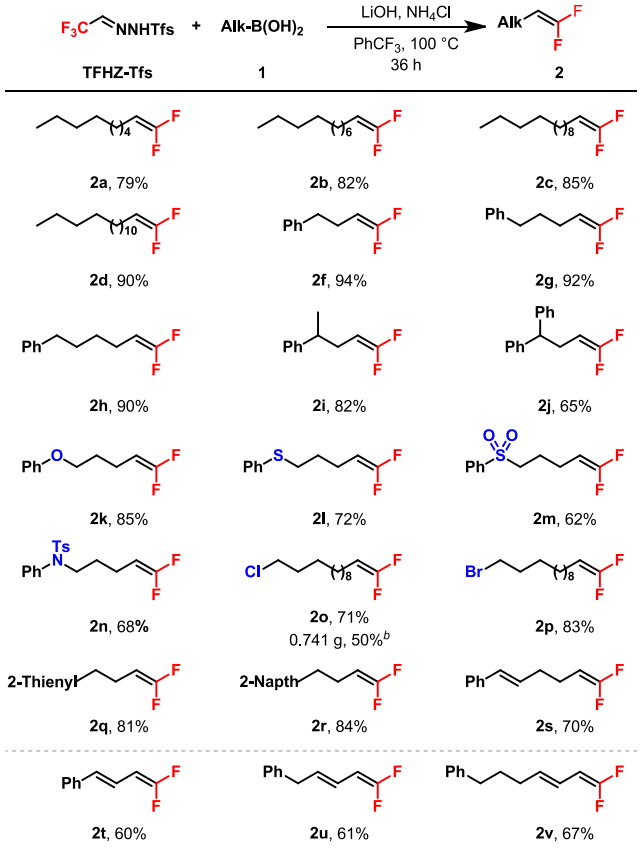


[a]Reaction conditions: **1e** (0.25 mmol), TFHZ-Tfs (0.625 mmol, 2.5 equiv), base (2.0 mmol, 8.0 equiv), and additive (1.0 mmol, 4.0 equiv) in 5 mL of solvent for 36 h under Ar. [b]Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield in parentheses. [d]Reaction conducted with TFHZ-Ts. [e]Reaction conducted with TFHZ-Ns. [f]Reaction conducted directly with CF_3CHN_2 using Wang's method.[5g]

the reaction gave desired product **2e** in very low yields when carbonate and various *tert*-butoxides were used as the base (entries 1−4). With LiOH in place of carbonate and *tert*-butoxides, a slight increase in the yield was observed (entry 5). The use of nonfluorinated solvents had a detrimental effect on the reaction outcome (entries 6−8). Notably, the addition of NH_4OAc or NH_4I as an additive significantly improved the yield (entries 9 and 10). The best yield (95%) was achieved by employing NH_4Cl as an additive (entry 11). The judicious optimization of the temperature showed that 100 °C is crucial for obtaining *gem*-difluoroalkenes in high yield (entries 11−13). When the ammonium salts were replaced with LiCl, the reaction failed to provide the desired product (entry 14). The use of TFHZ-Ts or TFHZ-Ns as a substitute for TFHZ-Tfs resulted in lower yields (entry 15 or 16, respectively). When **1e** was subjected to the method reported by Wang et al.,[5g] the product was delivered in a lower yield (entry 17). Presumably, the slow release of CF_3CHN_2 from TFHZ-Tfs may favor the *gem*-difluoroolefination in the case of alkylboronic acids. We thus selected the reaction conditions listed in entry 11 of Table 1 as the optimum conditions for the subsequent assessment of the substrate scope.

Adopting the optimized conditions obtained above (Table 1, entry 11), we next investigated the substrate scope of the *gem*-difluoroolefination of TFHZ-Tfs with alkylboronic acids (Scheme 1). Straight-chain alkylboronic acids with various

Scheme 1. *gem*-Difluoroolefination of TFHZ-Tfs with Alkylboronic Acids[a]



[a]Reaction conditions: **1** (0.25 mmol), TFHZ-Tfs (0.625 mmol, 2.5 equiv), LiOH (2.0 mmol, 8.0 equiv), and NH_4Cl (1.0 mmol, 4.0 equiv) in 5 mL of trifluorotoluene at 100 °C for 36 h under Ar. Yields are of isolated products. [b]Reaction conditions: **1o** (6.0 mmol), TFHZ-Tfs (15.0 mmol, 2.5 equiv), LiOH (48.0 mmol, 8.0 equiv), and NH_4Cl (24.0 mmol, 4.0 equiv) in 100 mL of trifluorotoluene at 100 °C for 48 h under Ar.

chain lengths were quite compatible with this method and were converted to **2a−2d** in 79−90% yields. It is worth mentioning that long-chain aliphatic *gem*-difluoroalkene frameworks are found in notable bioactive compounds (Figure 1).[1a−d] Alkylboronic acids featuring a phenyl group at the terminal carbon of their alkyl chain were successfully converted

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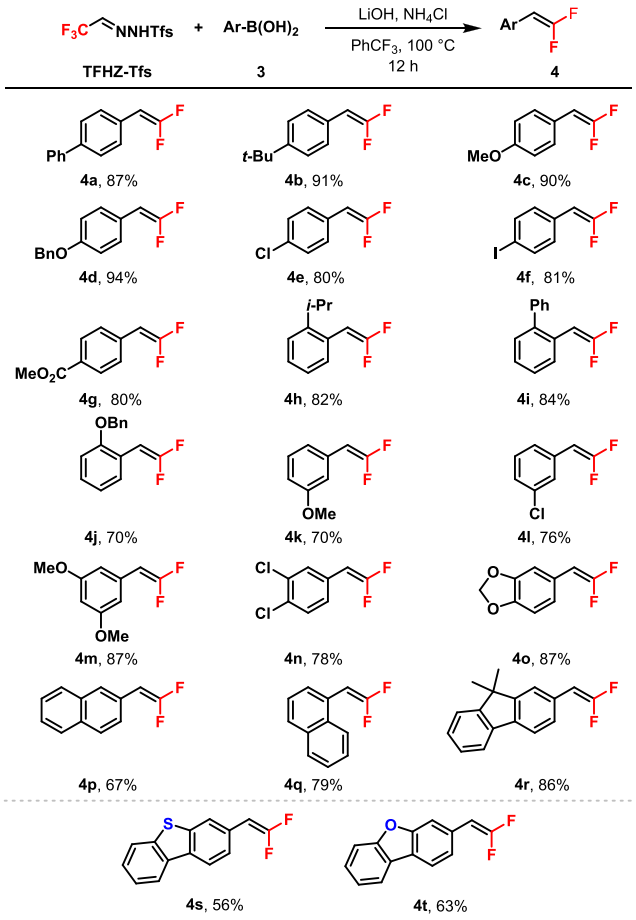
to the desired products with high yields (**2f**–**2j**). Alkylboronic acids containing a variety of functional groups at the terminal carbon, such as ether, sulfide, sulfone, sulfonamide, and halogens, also proved to be suitable reaction partners, leading to the desired products **2k**–**2p** in 62–85% yields. Moreover, alkylboronic acids holding 2-thienyl, 2-naphthyl, and styrene moieties at the terminal carbon reacted smoothly to form the desired products in good yields (**2q**–**2s**). In addition to alkylboronic acids, alkenylboronic acids were also competent substrates, furnishing products **2t**–**2v** in moderate yields under identical reaction conditions.

The results presented above prompted us to investigate the scope of arylboronic acids (Scheme 2). Delightfully, in this case the base and additive loading could be reduced to 6.0 and 3.0 equiv, respectively, and the reaction was complete within 12 h. Initially, we studied the effect of the substituents on the benzene ring of arylboronic acids. The electronic properties, position, and number of substituents on the benzene ring have very little influence on the *gem*-difluoroalkene formation, and the corresponding products were furnished in good to high yields (**4a**–**4n**, 70–94% yields). Similarly, 1,3-benzodioxole-5-boronic acid was used in the reaction to provide product **4o** in 87% yield. Naphthyl boronic acids smoothly participated in the reaction and delivered the corresponding products in good yields (**4p** and **4q**). Furthermore, we tested a boronic acid containing a fluorene ring, and it gave **4r** in 86% yield. Interestingly, boronic acids bearing dibenzo-fused heterocycles could also be employed to construct *gem*-difluoroalkenes without any difficulties (**4s** and **4t**).

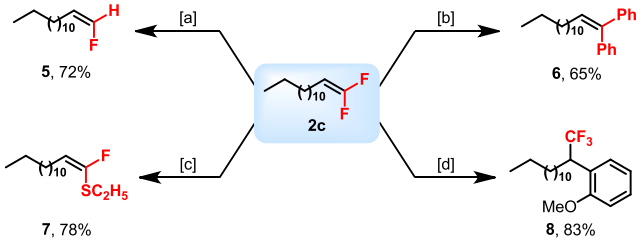
To further assess the utility of the described *gem*-difluoroolefination, we performed a series of synthetic manipulations of the *gem*-difluorovinyl group (Scheme 3).

Scheme 2. *gem*-Difluoroolefination of TFHZ-Tfs with Arylboronic Acids[a]



[a]Reaction conditions: **3** (0.3 mmol), TFHZ-Tfs (0.75 mmol, 2.5 equiv), LiOH (1.8 mmol, 6.0 equiv), and NH_4Cl (0.9 mmol, 3.0 equiv) in 4.5 mL of trifluorotoluene at 100 °C for 12 h under Ar. Yields are of isolated products.

Scheme 3. Synthetic Applications of 2c[a]

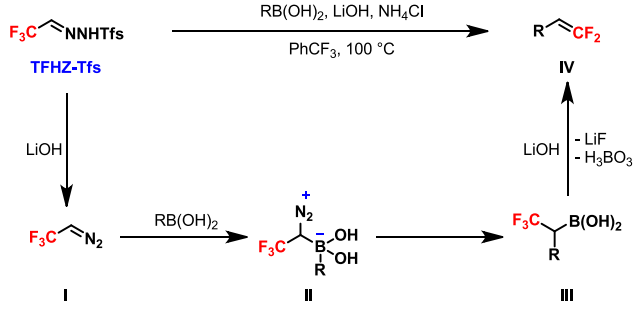


[a]Reaction conditions: (a) **2c** (0.2 mmol), CuTc (10 mol %), Xantphos (10 mol %), *t*-BuOLi (0.6 mmol, 3.0 equiv), and B_2nep_2 (0.6 mmol, 3.0 equiv) in DMA (1.0 mL) at 40 °C for 16 h under Ar; (b) **2c** (0.5 mmol), PhMgBr (3.0 equiv), and $NiCl_2$(dppp) (4 mol %) in THF (2.5 mL) at rt for 1 h under Ar; (c) **2c** (0.2 mmol), EtSH (0.4 mmol, 2.0 equiv), and Cs_2CO_3 (0.6 mmol, 3.0 equiv) in DMF (2.0 mL) at rt for 15 h; (d) **2c** (0.3 mmol, 2.0 equiv), 2-iodoanisole (0.15 mmol), $[allylPdCl]_2$ (2.5 mol %), XPhos (10 mol %), and AgF (0.18 mmol, 1.2 equiv) in cyclohexane (1.0 mL) at 80 °C for 12 h under N_2.

For example, *gem*-difluoroalkene **2c** readily underwent Cu-catalyzed hydrodefluorination to produce *Z*-fluoroalkene **5** in 72% yield (Scheme 3a).[4f] Also, **2c** smoothly underwent a double cross-coupling with Grignard reagents in the presence of a Ni catalyst (Scheme 3b).[7] Upon treatment with thiols, the compound underwent direct nucleophilic substitution to produce *α*-fluorovinyl thioether **7** in 78% yield with excellent *Z* selectivity (Scheme 3c).[8] Moreover, we were pleased to find that **2c** could readily undergo a Pd-catalyzed fluoroarylation to deliver **8** in 83% yield (Scheme 3d).[4i]

On the basis of the aforementioned results and previous reports,[5g,6,9] we proposed a possible reaction mechanism (Scheme 4). Initially, CF_3CHN_2 (**I**) is generated from TFHZ-Tfs under basic conditions. Thereafter, nucleophilic addition of CF_3CHN_2 (**I**) to the electron-deficient boron atom of the boronic acid afforded a tetracoordinate boronate intermediate (**II**). The subsequent 1,2-shift of the carbon ligand from boron to carbon followed by elimination of N_2 afforded intermediate

Scheme 4. Proposed Reaction Mechanism



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III. Finally, intermediate **III** underwent β-fluoride elimination in the presence of a base to deliver the *gem*-difluoroalkene (**IV**).

A novel transition metal free *gem*-difluoroolefination of TFHZ-Tfs with organoboronic acids was successfully developed. The protocol notably provides an efficient approach to access alkyl *gem*-difluoroalkenes, which were previously challenging to prepare. Moreover, the reaction is suitable for a wide range of organoboronic acids, and the utility of the products was established by further transformations of the *gem*-difluorovinyl group. In view of the bench-stable and nontoxic TFHZ-Tfs reagent, ready availability of boronic acids, and biological significance and versatile transformations of *gem*-difluoroalkenes, this method would find wide applications in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03740.

Experimental procedures and copies of spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Bobek, M.; Kavai, I.; De Clercq, E. *J. Med. Chem.* **1987**, *30*, 1494. (b) Pan, Y.; Qiu, J.; Silverman, R. B. *J. Med. Chem.* **2003**, *46*, 5292. (c) Altenburger, J.-M.; Lassalle, G. Y.; Matrougui, M.; Galtier, D.; Jetha, J.-C.; Bocskei, Z.; Berry, C. N.; Lunven, C.; Lorrain, J.; Herault, J.-P.; Schaeffer, P.; O'Connor, S. E.; Herbert, J.-M. *Bioorg. Med. Chem.* **2004**, *12*, 1713. (d) Moore, W. R.; Schatzman, G. L.; Jarvi, E. T.; Gross, R. S.; McCarthy, J. R. *J. Am. Chem. Soc.* **1992**, *114*, 360. (e) Messaoudi, S.; Treguier, B.; Hamze, A.; Provot, O.; Peyrat, J.-F.; De Losada, J. R.; Liu, J.-M.; Bignon, J.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *J. Med. Chem.* **2009**, *52*, 4538. (f) Fujii, K.; Nakamoto, Y.; Hatano, K.; Kanetsuki, Y. JP2006036706A.

(2) (a) McDonald, I. A.; Lacoste, J. M.; Bey, P.; Palfreyman, M. G.; Zreika, M. *J. Med. Chem.* **1985**, *28*, 186. (b) Weintraub, P. M.; Holland, A. K.; Gates, C. A.; Moore, W. R.; Resvick, R. J.; Bey, P.; Peet, N. P. *Bioorg. Med. Chem.* **2003**, *11*, 427.

(3) (a) Motherwell, W. B.; Tozer, M. J.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1437. (b) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (c) Magueur, G.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Fluorine Chem.* **2006**, *127*, 637. (d) Leriche, C.; He, X.; Chang, C.-W.; Liu, H.-W. *J. Am. Chem. Soc.* **2003**, *125*, 6348.

(4) For selected reviews, see: (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. *Chem. Soc. Rev.* **2011**, *40*, 2867. (c) Zhang, X.; Cao, S. *Tetrahedron Lett.* **2017**, *58*, 375. For selected papers, see: (d) Ichikawa, J. *J. Fluorine Chem.* **2000**, *105*, 257. (e) Unzner, T. A.; Magauer, T. *Tetrahedron Lett.* **2015**, *56*, 877. (f) Hu, J.; Han, X.; Yuan, Y.; Shi, Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 13342. (g) Sakaguchi, H.; Uetake, Y.; Ohashi, M.; Niwa, T.; Ogoshi, S.; Hosoya, T. *J. Am. Chem. Soc.* **2017**, *139*, 12855. (h) Zhu, C.; Song, S.; Zhou, L.; Wang, D.-X.; Feng, C.; Loh, T.-P. *Chem. Commun.* **2017**, *53*, 9482. (i) Tang, H.-J.; Lin, L.-Z.; Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2017**, *56*, 9872. (j) Lu, X.; Wang, Y.; Zhang, B.; Pi, J.-J.; Wang, X.-X.; Gong, T.-J.; Xiao, B.; Fu, Y. *J. Am. Chem. Soc.* **2017**, *139*, 12632.

(5) (a) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 17302. (b) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J. *J. Am. Chem. Soc.* **2015**, *137*, 14496. (c) Zhang, Z.; Yu, W.; Wu, C.; Wang, C.; Zhang, Y.; Wang, C. *Angew. Chem., Int. Ed.* **2016**, *55*, 273. (d) Nenajdenko, V. G.; Varseev, G. N.; Korotchenko, V. N.; Shastin, A. V.; Balenkova, E. S. *J. Fluorine Chem.* **2003**, *124*, 115. (e) Zheng, J.; Lin, J.-H.; Yu, L. Y.; Wei, Y.; Zheng, X.; Xiao, J.-C. *Org. Lett.* **2015**, *17*, 6150. (f) Zhang, Z.; Zhou, q.; Yu, W.; Li, T.; Wu, G.; Zhang, Y.; Wang, J. *Org. Lett.* **2015**, *17*, 2474. (g) Wu, G.; Deng, Y.; Wu, C.; Wang, X.; Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2014**, *2014*, 4477. (h) Lan, Y.; Yang, F.; Wang, C. *ACS Catal.* **2018**, *8*, 9245. (i) Lin, Z.; Lan, Y.; Wang, C. *ACS Catal.* **2019**, *9*, 775. (j) Ichitsuka, T.; Fujita, T.; Ichikawa, J. *ACS Catal.* **2015**, *5*, 5947. (k) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641. (l) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. *Org. Lett.* **2010**, *12*, 1444. (m) Gao, B.; Zhao, Y.; Hu, M.; Ni, C.; Hu, J. *Chem. - Eur. J.* **2014**, *20*, 7803. (n) Gao, B.; Zhao, Y.; Hu, J.; Hu, J. *Org. Chem. Front.* **2015**, *2*, 163. (o) Lang, S. B.; Wiles, R. J.; Kelly, C. B.; Molander, G. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 15073. (p) Chen, H.; Anand, D.; Zhou, L. *Asian J. Org. Chem.* **2019**, *8*, 661. (q) Xiao, T.; Li, L.; Zhou, L. *J. Org. Chem.* **2016**, *81*, 7908. (r) Fuchibe, K.; Takahashi, M.; Ichikawa, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 12059. (s) Fuchibe, K.; Hatta, H.; Oh, K.; Oki, R.; Ichikawa. *Angew. Chem., Int. Ed.* **2017**, *56*, 5890. (t) Fujita, T.; Ichitsuka, T.; Fuchibe, K.; Ichikawa, J. *Chem. Lett.* **2011**, *40*, 986. (u) Han, S. Y.; Jeong, I. H. *Org. Lett.* **2010**, *12*, 5518. (v) Han, S. Y.; Lee, H. Y.; Jeon, J. H.; Jeong, I. H. *Tetrahedron Lett.* **2012**, *53*, 1833.

(6) Zhang, X.; Liu, Z.; Yang, X.; Dong, Y.; Virelli, M.; Zanoni, G.; Anderson, E. A.; Bi, X. *Nat. Commun.* **2019**, *10*, 284.

(7) Dai, W.; Zhang, X.; Zhang, J.; Lin, Y.; Cao, S. *Adv. Synth. Catal.* **2016**, *358*, 183.

(8) Cong, Z.-S.; Li, Y.-G.; Chen, L.; Xing, F.; Du, G.-F.; Gu, C.-Z.; He, L. *Org. Biomol. Chem.* **2017**, *15*, 3863.

(9) (a) Peng, C.; Zhang, W.; Yan, G.; Wang, J. *Org. Lett.* **2009**, *11*, 1667. (b) Li, H.; Zhang, Y.; Wang, J. *Synthesis* **2013**, *45*, 3090. (c) Barluenga, J.; Tomas-Gamasa, M.; Aznar, F.; Valdes, C. *Nat. Chem.* **2009**, *1*, 494. (d) Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 5953. (e) Li, H.; Wang, L.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2943. (f) Argintaru, O. A.; Ryu, D.; Aron, I.; Molander, G. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 13656.

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