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Stereoselective formation of *Z*-monofluoroalkenes by nickel-catalyzed defluorinative coupling of *gem*–difluoroalkenes with lithium organoborates

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ABSTRACT

A method for stereoselective construction of *Z*-monofluoroalkenes by nickel-catalyzed defluorinative coupling of *gem*–difluoroalkenes in mild conditions was described. The combination of lithium organoborate and $ZnBr_2$ generated *in situ* lithium aryl zincates, which facilitates the transmetalation step of the nickel-catalyzed cross coupling reaction.

Due to similarity in spatial configuration and electrical distribution, monofluoroakene is often considered by medicinal chemists as a more lipophilic and metabolically more stable bioisostere of an amide in peptides [1–4], which was recently demonstrated to be a new type of powerful therapeutic agents for the treatment of human diseases [5–12]. Nevertheless, stereoselective preparation of (*Z*)- or (*E*)-monofluoroalkenes by classic Wittig reaction or Julia-Kocienski olefination was rather difficult, as reported previously [13–15]. Instead, an approach that utilized easily available *gem*–difluoroalkene as a proper precursor and an appropriate coupling partner under transition metal catalysis have emerged recently as an efficient method for the preparation of (*Z*)- or (*E*)-monofluoroalkenes in high stereoselectivity [4]. In this respect, several different types of commonly used coupling partners including Grignard reagents [16,17], organozinc reagents [18], alkyl halide [19], silicon reagents [20], organoboron reagents [21,22] have been successfully identified to be suitable for such a transformation to give defluorinative alkylation, silylation or boronization in high yields and excellent stereoselectivity. For instance, in 2015, Cao and coworkers reported a nickel-catalyzed highly *Z*-selective defluoroarylation of *gem*–difluoroalkenes with arylboronic acids [21]. Meanwhile, Toste and coworkers reported a palladium-catalyzed defluorinative coupling of *gem*–difluoroalkenes with aryl boronic acids, which was proposed to proceed through a β-fluoride elimination of a Pd(II) intermediate [22].

Very recently, during the development of nickel-catalyzed asymmetric cross-coupling reaction for the construction of fluoroalkyl-substituted stereogenic centers, we discovered that the combination of lithium organoborate with zinc bromide generated a zincate species which was more reactive toward transmetalating the aryl group from boron to nickel [23–26]. Inspired by such a phenomenon, we questioned ourselves whether such an *in situ* generated zincate species could be used in the coupling with *gem*–difluoroalkenes to stereoselectively generate monofluoroalkenes. Herein, we reported that in the presence of a nickel catalyst, coupling of *gem*–difluoroalkenes with a combination of various readily available "ate-type" aryl pinacol boronates and $ZnBr_2$ occurred smoothly under mild conditions to give *Z*-monofluoroalkenes in good yields and excellent stereoselectivity (Scheme 1).

We chose the reaction of 2-(2,2-difluorovinyl)naphthalene **1a** with lithium organoborate, which was easily formed *in situ* by mixing phenylboronic acid pinacol ester with *n*-BuLi under −20 °C [27,28], as the model reaction to optimize the reaction conditions. We initially discovered that in the presence of 5.0 mol% $NiBr_2$•DME and 2.5 mol% of 4,4′-dimethyl-2,2′-bipyridine ligand **L1**, reaction of 2-(2,2-difluorovinyl)naphthalene **1a** with lithium phenylorganoborate **2a** and 50 mol% of $ZnBr_2$ in a number of common organic solvents, such as Et_2O, THF, DME, DMF or toluene did not pro-

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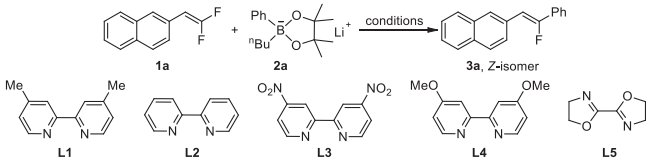
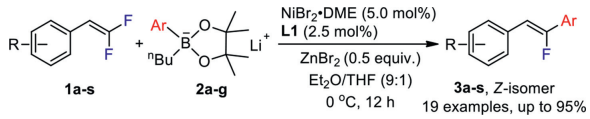
Table 1
Optimization of the reaction conditions for nickel-catalyzed defluorinative coupling of *gem*–difluoroalkenes.



Entry	Catalyst (5.0 mol%)	Ligand (2.5 mol%)	Solvent	Addictive (50 mol%)[a]	Temp (°C)	Yield (%) (*Z*/*E*)[b]
1	$NiBr_2$•DME	**L1**	Et_2O	$ZnBr_2$	0	22 (> 20:1)
2	$NiBr_2$•DME	**L1**	THF	$ZnBr_2$	0	16 (> 20:1)
3	$NiBr_2$•DME	**L1**	DME	$ZnBr_2$	0	45 (> 20:1)
4	$NiBr_2$•DME	**L1**	DMF	$ZnBr_2$	0	0 (> 20:1)
5	$NiBr_2$•DME	**L1**	Toluene	$ZnBr_2$	0	8 (> 20:1)
6	$NiBr_2$•DME	**L1**	Et_2O/THF (9:1)	$ZnBr_2$	0	94 (> 20:1)
7	$NiBr_2$•DME	**L1**	Et_2O/THF (4:1)	$ZnBr_2$	0	90 (> 20:1)
8	$NiBr_2$•DME	**L1**	Et_2O/THF (1:1)	$ZnBr_2$	0	80 (> 20:1)
9	NiI_2	**L1**	Et_2O/THF (9:1)	$ZnBr_2$	0	15 (> 20:1)
10	$NiCl_2$•DME	**L1**	Et_2O/THF (9:1)	$ZnBr_2$	0	88 (> 20:1)
11	$Ni(OAc)_2$	**L1**	Et_2O/THF (9:1)	$ZnBr_2$	0	85 (> 20:1)
12	$Ni(cod)_2$	**L1**	Et_2O/THF (9:1)	$ZnBr_2$	0	48 (> 20:1)
13	$NiBr_2$•DME	**L2**	Et_2O/THF (9:1)	$ZnBr_2$	0	82 (> 20:1)
14	$NiBr_2$•DME	**L3**	Et_2O/THF (9:1)	$ZnBr_2$	0	10 (> 20:1)
15	$NiBr_2$•DME	**L4**	Et_2O/THF (9:1)	$ZnBr_2$	0	41 (> 20:1)
16	$NiBr_2$•DME	**L5**	Et_2O/THF (9:1)	$ZnBr_2$	0	29 (> 20:1)
17	$NiBr_2$•DME	**L1**	Et_2O/THF (9:1)	$ZnBr_2$	r.t.	60 (> 20:1)
18	$NiBr_2$•DME	**L1**	Et_2O/THF (9:1)	ZnI_2	0	69 (> 20:1)
19	$NiBr_2$•DME	**L1**	Et_2O/THF (9:1)	$Zn(OTf)_2$	0	
20	$NiBr_2$•DME	**L1**	Et_2O/THF (9:1)	$MgBr_2$	0	
21			Et_2O/THF (9:1)	$ZnBr_2$	0	
22		**L1**	Et_2O/THF (9:1)	$ZnBr_2$	0	
23	$NiBr_2$•DME		Et_2O/THF (9:1)	$ZnBr_2$	0	10 (>20:1)
24	$NiBr_2$•DME	**L1**	Et_2O/THF (9:1)		0	

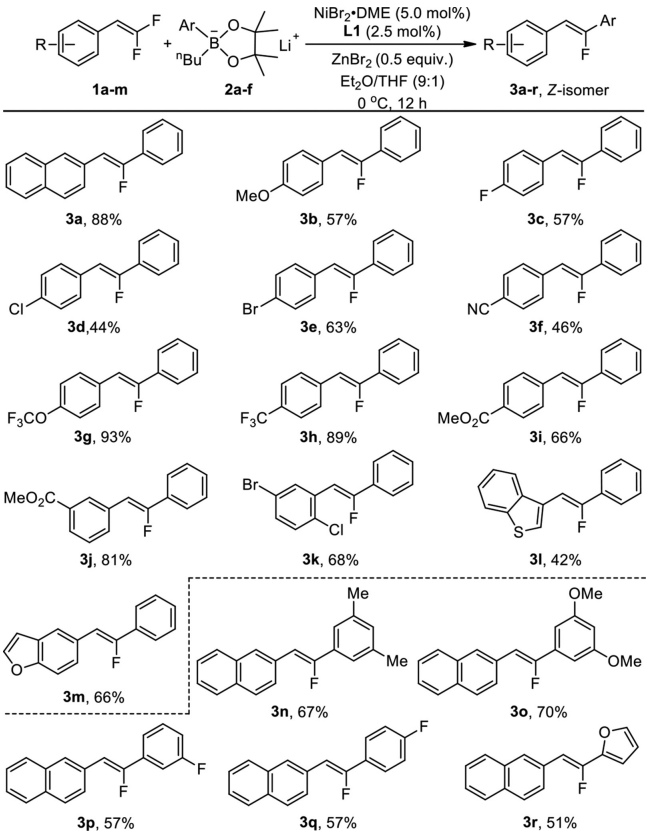
[a] Reaction conditions: 2-(2,2-difluorovinyl)naphthalene (0.2 mmol, 1.0 equiv.), boron compound (0.6 mmol, 3.0 equiv.), [Ni] (5.0 mol%), ligand (2.5 mol%), $ZnBr_2$ (0.5 equiv.), solvent (2.0 mL) at temperature indicated for 12 h
[b] Yields of **3a** and the ratio of *Z*/*E* were determined by ^{19}F NMR spectroscopy in the presence of fluorobenzene as an internal standard.



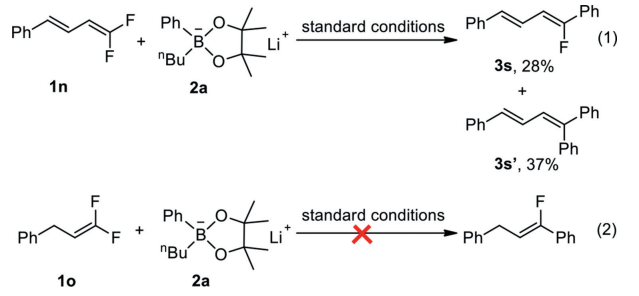
Scheme 1. Nickel-catalyzed defluorinative coupling of *gem*–difluoroalkenes with lithium organoborate.

ceed into full conversion after 12 h at 0 °C and the yields for the desired to monofluoroalkene **3a** were low (Table 1, entries 1–5). However, stereoselectivity of the reaction was excellent since only *Z*-monofluoroalkene **3a** was observed in ^{19}F NMR spectroscopies. To our delight, when a mixed solvent of Et_2O/THF (9:1) was employed, the yield of compound **3a** was significantly improved to 94% along the formation of single *Z*-isomer (Table 1, entry 6). Decreasing the ratio of Et_2O in the mixed solvents from 9:1 to 4:1 has little effect on the yield and selectivity of the reaction. Yet, further decrease the ratio of Et_2O in the mixed solvents to 1:1 led to significantly decrease the yield of the reaction to 80% (Table 1, entries 7 and 8). The choice of different nickel catalyst precursors and ligands played an essential role for the high yielding formation of compound **3a**. When NiI_2 was used as the catalyst precursor, the yield decreased dramatically (Table 1, entry 9). On the other hand, reactions using $NiCl_2$•DME or $Ni(OAc)_2$ as the catalyst gave the coupled products in slightly lower yields (Table 1, entries 10 and 11). In contrast, when a Ni(0) complex $Ni(cod)_2$ was used as the precursor, the yield of the reaction deceased significantly to 48% (Table 1, entry 12). Likewise, the electronic properties of the ligand were also equally important for the high yields of the reaction. Using either more electron-donating or electron-poor bipyridine derivatives resulted in lower yields (Table 1, entries 13–16). Further optimization disclosed that the reaction conducted at room temperature gave lower yield (Table 1, entry 17). In addition, it was found that reaction using ZnI_2 as an additive gave the defluoroarylation product **3a** in slightly low yields, while reactions using other additives such as $Zn(OTf)_2$ or $MgBr_2$ were not effective at all (Table 1, entries 18–20). Our initially studies showed that the amount of $ZnBr_2$ was important for the conversion of the reaction. Nevertheless, it was found that the yields decreased with the increase of the amount of $ZnBr_2$ to 0.8 or 1.5 equiv. The effect of the addition of $ZnBr_2$ to a solution of lithium aryl borate has been reported to generate lithium aryl zincates $[Ph_xZnBr_y]^{n-}$ ($n = x + y - 2$) [29], which facilitates the transmetalation step of the nickel-catalyzed cross coupling reaction [24]. Alternatively, $ZnBr_2$ might act as a Lewis acid to abstract the bromide on the nickel metal center to facilitate the transmetalation step. Finally, control experiments showed that reactions in the absence of either nickel precursor, the ligand or additive $ZnBr_2$ occurred in less than 10% yield (Table 1, entries 21–24).

Having identified the suitable conditions for highly stereoselective formation of *Z*-monofluoroalkene **3a**, we next examined the generality of the nickel-catalyzed defluorinative coupling of diverse *gem*–difluoroalkenes with a variety of aryl lithium organoborates under the optimized reaction conditions as shown in entry 6 in Table 1. As summarized in Scheme 1, in general, *gem*–difluoroalkenes with electron-donating or electron-withdrawing substituents at *ortho*-, *meta*- or *para*-position of the aryl moiety reacted smoothly to give the corresponding *Z*-monofluoroalkenes **3a-k** in medium to good yields. For instance, reactions of lithium phenyl *n*–butyl borate **2a** with *gem*–difluoroalkenes bearing an electron-donating *para*-methoxyl group occurred to give compound **3b** in 57% yield, while reaction with *gem*–difluoroalkenes bear-



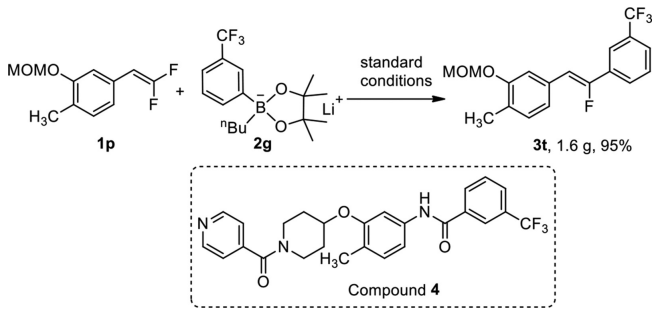
Scheme 2. Nickel-catalyzed defluorinative coupling of *gem*–difluoroalkenes with lithium organoborates. Reaction conditions: *gem*–difluoroalkenes (0.3 mmol), boron compound (0.9 mmol), $NiBr_2$•DME (5.0 mol%), **L1** (2.5 mol%), $ZnBr_2$ (0.5 equiv.) in Et_2O/THF (9:1) at 0 °C for 12 h. Isolated yields.



Scheme 3. Reactions with other *gem*–difluoroalkenes.

ing an electron-withdrawing *para*-cyanophenyl group occurred to give compound **3f** in 46% yield (Scheme 2, **3b** and **3f**). *gem*–Difluoroalkenes with a heteroaryl substituent such as benzothiophene or benzofuran also reacted smoothly to afford the corresponding *Z*-monofluoroalkenes **3l** and **3m** in 42% and 66% yields, respectively (Scheme 2, **3l** and **3m**). On the other hand, aryl boronic acid pinacol esters bearing methyl, methoxyl, fluoro and furan also reacted with *gem*–difluoroalkenes **1a** to afford the defluorinative coupling products **3n**-**3r** in 51%–70% yields (Scheme 2, **3n**-**3r**). Because of the benign nature of the combination of lithium aryl borates and $ZnBr_2$, a variety of common functional groups such as fluoride (**3c**, **3p**, **3q**), chloride (**3d**, **3k**), bromide (**3e**, **3k**), cyano (**3f**) and ester (**3i**, **3j**) were compatible, which would allow for further functional group transformation.

To further expand the scope of the reaction, we also explored other *gem*–difluoroalkenes including conjugated *gem*–difluoroalkene **1n** and alkyl *gem*–difluoroalkene **1o** (Scheme 3). We



Scheme 4. Application of nickel-catalyzed defluorinative coupling of *gem*–difluoroalkenes.

found that conjugated *gem*–difluoroalkene **1n** reacted under the optimized conditions to give compound **3s** in 28% yield, along with a secondary defluoroarylative product **3s'** in 37% yield, while *gem*–difluoroalkene **1o** with an alkyl group did not react under the optimal conditions at all.

As we mentioned in the introduction, monofluoroalkene is considered to be bioisostere of amide bond that is widespread presence in a number of bioactive compounds with diverse pharmacological activities, such as anti-cancer [30,31], anti-diabetic [32,33]. In 2016, Liu and coworkers reported that compound **4** was a more selective c-KIT inhibitor than Imatinib and Sunitinib for gastrointestinal stromal tumors (GISTs), which completely abolished ABL and FLT3 kinase [34]. To demonstrate the applicability of the current protocol, we synthesized a *Z*-monofluoroalkene mimic of the core structure of compound **4**, as shown in Scheme 4. Treatment of 4-(2,2-difluorovinyl)-2-(methoxymethoxy)-1-methylbenzene **1o** with lithium *m*-trifluoromethylphenyl borate under standard conditions occurred smoothly to give corresponding product **3t** in 95% yield (Scheme 4). Notably, this gram-scale reaction afforded the desired defluoroarylated product in pure *Z*-isomer.

In summary, a highly *Z*-selective construction of monofluoroalkenes *via* a nickel-catalyzed coupling of lithium organoborate with *gem*–difluoroalkenes was reported. In this reaction, the presence of $ZnBr_2$ as an additive was crucial to achieve high reactivity and selectivity. The absence of base to activate organoboron and mild conditions allow the tolerance among a variety of useful functional groups in this coupling reaction. The applicability of the current method was demonstrated in the gram-scale synthesis of the monofluoroalkene mimic of the core structure of drug molecule compound **4**. Expanding the scope of the reaction with fluorinated arenes and heteroarenes are currently undergoing in our laboratory.

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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.01.020.

References

[1] K. Zhao, D. Lim, T. Funaki, J.T. Welch, Bioorg. Med. Chem. Lett. 11 (2003) 207–215.
[2] P. Van der Veken, K. Senten, I. Kertesz, et al., J. Med. Chem. 48 (2005) 1768–1780.
[3] N. Asakura, Y. Usuki, H. Iio, T. Tanaka, J. Fluorine Chem. 127 (2006) 800–808.
[4] J.J. Urban, B.G. Tillman, W.A. Cronin, J. Phys. Chem. A 110 (2006) 11120–11129.
[5] S. Couve-Bonnaire, D. Cahard, X. Pannecoucke, Org. Biomol. Chem. 5 (2007) 1151–1157.
[6] B. Zajc, R. Kumar, Synthesis 2010 (2010) 1822-1836.
[7] H.J. Tsai, Tetrahedron Lett. 37 (1996) 629–632.
[8] H. Yanai, T. Taguchi, Eur. J. Org. Chem. (2011) 5939–5954 2011.
[9] G. Landelle, M. Bergeron, M.O. Turcotte-Savard, J.F. Paquin, Chem. Soc. Rev. 40 (2011) 2867–2908.
[10] A.K. Ghosh, B. Zajc, Org. Lett. 8 (2006) 1553–1556.
[11] B. Zajc, S. Kake, Org. Lett. 8 (2006) 4457–4460.
[12] Y.C. Zhao, F.Z. Jiang, J.B. Hu, J. Am. Chem. Soc. 137 (2015) 5199–5203.
[13] F. Liao, J. Yu, J. Zhou, Chin. J. Org. Chem. 37 (2017) 2175–2186.
[14] X. Zhang, S. Cao, Tetrahedron Lett. 58 (2017) 375–392.
[15] J. Paquin, M. Drouin, J. Hamel, Synthesis (Mass) 50 (2018) 881–955.
[16] W. Dai, J. Xiao, G. Jin, et al., J. Org. Chem. 79 (2014) 10537–10546.
[17] W. Dai, H. Shi, X. Zhao, S. Cao, Org. Lett. 18 (2016) 4284–4287.
[18] J. Zhang, B. Wang, Y. Liu, S. Cao, Chin, J. Org. Chem. 39 (2019) 249–256.
[19] X. Lu, Y. Wang, B. Zhang, et al., J. Am. Chem. Soc. 139 (2017) 12632–12637.
[20] D. Tan, E. Lin, W.W. Ji, et al., Adv. Synth. Catal. 360 (2018) 1032–1037.
[21] Y. Xiong, T. Huang, X. Ji, J. Wu, S. Cao, Org. Biomol. Chem. 13 (2015) 7389–7392.
[22] R.T. Thornbury, F.D. Toste, Angew. Chem. Int. Ed. 55 (2016) 11629–11632.
[23] W.C. Huang, X. Wan, Q. Shen, Angew. Chem. Int. Ed. 56 (2017) 11986–11989.
[24] W.C. Huang, M. Hu, X.B. Leng, Q. Shen, Nat. Commun. 10 (2019) 2963.
[25] S.S. Liu, W.C. Huang, D.C. Wang, et al., Org. Chem. Front. 10 (2019) 2630–2634.
[26] W.C. Huang, X.L. Wan, Q. Shen, Org. Lett. 22 (2020) 4327–4332.
[27] Y. Kobayashi, R. Mizojiri, Tetrahedron Lett. 37 (1996) 8531–8534.
[28] Y. Kobayashi, Y. Nakayama, R. Mizojiri, Tetrahedron 54 (1998) 1053–1062.
[29] R.J. Procter, J.J. Dunsford, P.J. Rushworth, et al., Chem. Eur. J. 23 (2017) 15889–15893.
[30] S. Osada, S. Sano, M. Ueyama, et al., Bioorg. Med. Chem. 18 (2010) 605–611.
[31] J. Kanazawa, T. Takehashi, S. Akinaga, et al., Anticancer Drugs 9 (1998) 653–657.
[32] T. Deng, S. Shan, Z. Li, et al., Biol. Pharm. Bull. 28 (2005) 1192–1196.
[33] S.D. Edmondson, L. Wei, J. Xu, et al., Bioorg. Med. Chem. Lett. 18 (2008) 2409–2413.
[34] Q. Wang, F. Liu, B. Wang, et al., J. Med. Chem. 59 (2016) 3964–3979.