Published in final edited form as:

Chem Commun (Camb). 2015 January 25; 51(7): 1267–1270. doi:10.1039/c4cc08257e.

Synthesis of enaminones and their difluoroboron complexes through domino aryl migration†

Zheng Yang^a, Bo Jiang^{a,*}, Wen-Juan Hao^a, Peng Zhou^a, Shu-Jiang Tu^{a,*}, and Guigen Li^{b,c,*}

^aJiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou, 211116, P. R. China

^bInstitute of Chemistry & BioMedical Sciences, Nanjing University, Nanjing 210093, P. R. China

^cDepartment of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

Abstract

A new domino strategy for selective synthesis of enaminones and their difluoroboron complexes through aryl migration has been developed. The reaction features low-cost and readily accessible starting materials, reliable scalability, and bond-forming efficiency as well as simple one-pot operation, which makes this strategy highly viable for future applications.

The difluoroboron complexes have gained considerable attention in organic, biomedical and material sciences due to their high thermal stability and excellent photophysical properties.¹ They can serve as biochemical labeling markers,² bioimaging probes and³ photodynamic therapy agents.⁴ In fact, they have been widely utilized in research on light emitting devices,⁵ solar cells⁶ and energy transfer casettes.⁷ Enaminones are also important building blocks in organic and pharmaceutical chemistry.¹⁰ Recent studies show that enaminones can exhibit excellent anticonvulsant activity¹¹ and modulate $\alpha 7$ nicotinic acetylcholine receptors (nAChRs).¹² Obviously, β -ketoiminate complexes anchored with difluoroboron represents a family of important structural motifs that show air-stable and electrochemical properties.⁸ Many efforts have been devoted to the synthesis and applications of difluoroboron complexes in the past decade.⁹ A literature survey on this topic shows that the synthesis of difluoroboron β -ketoiminates involves the preparation of enaminones followed by the treatment with BF_3 .⁹ There has not been a report on domino reaction approaches to enaminone-difluoroboron complexes in a simple one-pot operation. During our ongoing domino projects, we found a new methodology for the synthesis of these stable complexes as shown in Scheme 1.

Initially, we designed our strategy by reacting phenyl(3-phenyloxiran-2-yl)methanone **1a** with 4-chloroaniline **2a** as model substrates in 1,4-dioxane at 80 °C in the presence of 1.2 equiv of BF_3 (THF as both B/F source and Lewis acid promoter (Table 1, entry 1). To our

jiangchem@jsnu.edu.cn (B. Jiang); laotu@jsnu.edu.cn (S.-J. Tu); Tel./fax: +8651683500065. guigen.li@ttu.edu.

†We would like to dedicate this work to Professor Iwao Ojima for celebrating his 70th Birthday.

Electronic supplementary information (ESI) available. CCDC 1007344 (**3d**) and 1007345 (**4a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/

delight, the desired difluoroboron product **3a** was obtained in 64% yield under above conditions for the first trial. The use of BF₃(AcOH (1.2 equiv.) to replace BF₃(THF resulted in a slightly higher yield of **3a** (70%) (Table 1, entry 2). In another case, the reaction worked more efficiently, providing a 78% chemical yield of product **3a** in 1,4-dioxane at 80 °C when BF₃(Et₂O (1.2 equiv.) was employed (Table 1, entry 3). Then we examined the effect of different amounts of BF₃(Et₂O. It was found that more or less 1.2 equiv of BF₃(Et₂O both give slightly lower yields (Table 1, entries 4 and 5). Next, different solvents, such as CH₃CN, 1,2-dichloroethane (DCE), and EtOH, were investigated under the above condition. All of these solvents led to much lower yields of the desired product **3a**. With substrates **1a** and **2a**, a lower yield of **3a** was isolated while the reaction was performed at higher (100 °C) or lower (60 °C) temperatures (Table 1, entries 9–10).

With these optimal conditions in hands, the generality and scope of this domino reaction were explored by using different oxirane derivatives **1** and substituted arylamines **2** in the presence of BF₃·Et₂O. As revealed in Table 2, various arylamines **2** bearing chloro, bromo, methyl, or methoxyl group can be transformed into highly functionalized difluoroboron complexes **3** that offer further flexibility for structural modifications. In the meanwhile, a variety of substituted oxirane derivatives bearing electron-withdrawing or electron-donating groups can all tolerate the reaction conditions. Notably, the bulky 2,3- and 2,4-dichlorophenyl substituted oxirane derivatives **2b** and **2c** were all proven to be successful in the reaction and can be readily converted into the corresponding difluoroboron complexes **3h–3j** in 64–74% yields. Obviously, the present protocol provides a new and straightforward pathway for constructing polyfunctionalized difluoroboron complexes, although aliphatic amines such as benzylamine, ethylamine and cyclopropanamine have not been proven to work for this reaction.

Interestingly, we found when 0.2 equiv of BF₃(Et₂O were used for the reaction of **1a** with **2a**, *N*-aryl enaminones **4a** with a *Z/E* ratio of 6/1 can be isolated in 28% chemical yield. The attribution of stereoselectivity of *N*-aryl enaminones **4a** was characterized by its spectroscopic analysis and was further confirmed by single crystal X-ray diffraction (Figure 2). Encouraged by these useful results, we further turned our attention on the optimization of reaction conditions for the synthesis of **4a**. We found when the amount of BF₃(Et₂O was increased to 0.5 equiv., no increase in chemical yield was observed. The loading of BF₃(Et₂O was continuously increased to 0.8 equiv., the yield of **4a** was still remained similar, but it led to an increasing yield of product **3a**. However, when acetylacetone (Hacac) was added into the above system, the yield of **4a** was dramatically improved. We found that the combination with 1.2 equivalents of acetylacetone and BF₃(Et₂O in this reaction gave the highest yield of **4a** (70%). Under these optimized conditions, a set of new *N*-aryl enaminones **4** were provided with 52–76% yields and *Z/E* between 67/1 and 5/1. We believe this high stereoselectivity was attributed to the further formation of intramolecular hydrogen bonds. The influence of substituted aromatic amines was explored, employing **1a** with different functionalities on the aromatic ring including methoxy, chloro, bromo and iodo groups. The results indicated that both electron-withdrawing and electron-donating groups are suitable substrates, affording the corresponding *N*-aryl enaminones **4a–4i** with high stereoselectivity through a BF₃·Et₂O-promoted aryl migration. Notably, sterically

bulky 2-iodoaniline **2h**, 2-(phenylethynyl)aniline **2i**, and naphthalen-1-amine **2j** were found to only convert into the corresponding *N*-aryl enaminones **4g–4i** and provided higher *Z/E* selectivity than that of *para*-substituted arylamines. Furthermore, the substituents on the phenyl ring of oxirane derivatives **1** did not hamper the reaction process.

To further study this reaction, the treatment of *N*-4-chlorophenyl enaminone **4a** with BF₃(Et₂O) was performed in 1,4-dioxane at 80 °C for 6 hours. It was found that functionalized difluoroboron ketoiminates **3a** was obtained in 85% yield (Scheme 3, eq 1). In order to better understand the role of acetylacetone, the treatment of **1a** with **2a** in the presence of 1.2 equiv of difluoroboron diketonates **5** did not afford the corresponding *N*-4-chlorophenyl enaminone **4a** (eq 2), which indicates that difluoroboron diketonates **5** did not promote aryl migration process. The reaction of **1a** in the presence of 1.2 equivalents of acetylacetone and BF₃(Et₂O) generated migration product **6a** in 88% yield (eq 3), which was trapped by arylamine **2a**, affording product **4a** in 86% yield (eq 4).¹⁴ These experiments suggested that aryl migration occurred prior to amination step.

On the basis of the above observations, we proposed mechanistic processes as shown in Scheme 4. Ring-opening of oxirane derivatives **1** and aryl migration promoted by BF₃·Et₂O resulted in 3-oxopropanals **A**,¹³ which is followed tautomerization to 3-hydroxyprop-2-en-1-one intermediate **B**. The enaminones **4** were formed by the reaction between intermediate **B** and arylamines **2**, which were converted into the final difluoroboron ketoiminates **3** by the treatment with BF₃·Et₂O.

Conclusions

In conclusion, we have established a new and chemoselective domino strategy for an efficient accesses to enaminones and their difluoroboron complexes through aryl migration process. The former process simultaneously installs C–N and O–B bonds through aryl migration, allowing us to build blocks of difluoroboron ketoiminates with a wide diversity in substituents. The mild reaction conditions, reliable scalability, and good selectivity as well as simple one-pot operation make this strategy highly viable for future applications. A detailed application of difluoroboron ketoiminates is currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We are grateful for financial support from the NSFC (No. 21232004, 21272095, 21102124 and 21332005), PAPD of Jiangsu Higher Education Institutions., the Qing Lan Project (12QLG006), Robert A. Welch Foundation (D-1361, USA) and NIH (R33DA031860, USA), Graduate Education Innovation Project of Jiangsu Province (No. CXZZ14_0985).

Notes and references

- (a) Ni Y, Wu J. *Org. Biomol. Chem.* 2014; 12:3774. [PubMed: 24781214] (b) Lu H, Mack J, Yang Y, Shen Z. *Chem. Soc. Rev.* 2014 ASAP. (c) Ulrich G, Ziesel R, Harriman A. *Angew. Chem., Int. Ed.* 2008; 47:1184. (d) Loudet A, Burgess K. *Chem. Rev.* 2007; 107:4891. [PubMed: 17924696]

2. (a) Loudet A, Burgess K. *Chem. Rev.* 2007; 107:4891. [PubMed: 17924696] (b) Wu L, Loudet A, Barhoumi R, Burghardt R, Burgess K. *J. Am. Chem. Soc.* 2009; 131:9156. [PubMed: 19566090]
3. (a) Urano Y, Asanuma D, Hama Y, Koyama Y, Barrett T, Kamiya M, Nagano T, Watanabe T, Hasegawa A, Choyke PL, Kobayashi H. *Nat. Med.* 2009; 15:104. [PubMed: 19029979] (b) Han J, Loudet A, Barhoumi R, Burghardt RC, Burgess K. *J. Am. Chem. Soc.* 2009; 131:1642. [PubMed: 19146412]
4. (a) Myochin T, Hanaoka K, Komatsu T, Terai T, Nagano T. *J. Am. Chem. Soc.* 2012; 134:13730. [PubMed: 22830429] (b) Yogo T, Urano Y, Ishitsuka Y, Maniwa F, Nagano T. *J. Am. Chem. Soc.* 2005; 127:12162. [PubMed: 16131160] (c) Atilgan S, Ekmekci Z, Dogan AL, Guc D, Akkaya EU. *Chem. Commun.* 2006:4398.
5. Bonardi L, Kanaan H, Camerel F, Jolinat P, Retailleau P, Ziessel R. *Adv. Funct. Mater.* 2008; 18:401.
6. Erten-Ela S, Yilmaz D, Icli B, Dede Y, Icli S, Akkaya UE. *Org. Lett.* 2008; 10:3299. [PubMed: 18588306]
7. (a) Ulrich G, Goze C, Guardigli M, Roda A, Ziessel R. *Angew. Chem., Int. Ed.* 2005; 44:3694.(b) Loudet A, Bandichhor R, Wu L, Burgess K. *Tetrahedron.* 2008; 64:3642. [PubMed: 19458781]
8. (a) Kuhn N, Kuhn A, Boese R, Augart N. *J. Chem. Soc., Chem. Commun.* 1989:975.(b) Chow YL, Johansson CI, Zhang Y-H, Gautron R, Yang L, Rassat A, Yang S-Z. *J. Phys. Org. Chem.* 1996; 9:7. (c) Belford RL, Martell AE, Calvin M. *J. Inorg. Nucl. Chem.* 1956; 2:11.
9. (a) Zhou Y, Xiao Y, Chi S, Qian X. *Org. Lett.* 2008; 10:633. [PubMed: 18201096] (b) Macedo FP, Gwengo C, Lindeman SV, Smith MD, Gardinier JR. *Eur. J. Inorg. Chem.* 2008:3200.(c) Chen J, Burghart A, Wan C, Thai L, Ortiz C, Reibenspies J, Burgess K. *Tetrahedron Lett.* 2000; 41:2303.(d) Feng J, Liang B, Wang D, Xue L, Li X. *Org. Lett.* 2008; 10:4437. [PubMed: 18798646] (e) Xia M, Wu B, Xiang G. *J. Fluorine Chem.* 2008; 129:402.
10. (a) Jiang B, Wang X, Xu H-W, Tu M-S, Tu S-J, Li G. *Org. Lett.* 2013; 15:1540. [PubMed: 23506186] (b) Fu L-P, Shi Q-Q, Shi Y, Jiang B, Tu S-J. *ACS Comb. Sci.* 2013; 15:135. [PubMed: 23339825] (c) Jiang B, Li Q-Y, Tu S-J, Li G. *Org. Lett.* 2012; 14:5210. [PubMed: 23025431] (d) Jiang B, Li Y, Tu M-S, Wang S-L, Tu S-J, Li G. *J. Org. Chem.* 2012; 77:7497. [PubMed: 22852549]
11. (a) Edafiogho IO, Qaddoumi MG, Ananthalakshmi KVV, Phillips OA, Kombian SB. *Eur. J. Med. Chem.* 2014; 76:20. [PubMed: 24565570] (b) Okoro CO, Apraku J, Okoromoba EO, Fadeyi OO. *Lett. Drug Des. Discov.* 2013; 10:1024.(c) Garro Martinez JC, Vega-Hissi EG, Andrada MF, Spedaletti C, Estrada MR. *Med. Chem. Res.* 2014; 23:2528.
12. Hogenkamp DJ, Ford-Hutchinson TA, Li W-Y, Whittemore ER, Yoshimura RF, Tran MB, Johnstone TBC, Bascom GD, Rollins H, Lu L, Gee KW. *J. Med. Chem.* 2013; 56:8352. [PubMed: 24098954]
13. For the selected examples, see: House HO. *J. Am. Chem. Soc.* 1954; 76:1235. Mathew P, Mathew D, Asokan CV. *Synth. Commun.* 2007; 37:661. Ruan L, Shi M, Li N, Ding X, Yang F, Tang J. *Org. Lett.* 2014; 16:733. [PubMed: 24476013]
14. (a) Gudla V, Balamurugan R. *Tetrahedron Lett.* 2012; 53:5243.(b) Procopio A, Dalpozzo R, De Nino A, Nardi M, Sindona G, Tagarelli A. *Synlett.* 2004:2633.(c) Bargagna A, Schenone P, Bondavalli F, Longobardi M. *J. Heterocyclic Chem.* 1980; 17:1201.(d) Bhatia KA, Eash KJ, Leonard NM, Oswald MC, Mohan RS. *Tetrahedron Lett.* 2001; 42:8129.

Figure 1.
The ORTEP Drawing of **3d**

Figure 2.
The ORTEP Drawing of **4a**

Scheme 1.
Selective synthesis of compounds **3** and **4**.

4a, 4-Cl, 70%^a, *Z/E* = 6:1^b

4b, 3,4-Cl₂, 73%, *Z/E* = 7:1

4c, 4-Br, 68%, *Z/E* = 6:1

4d, 3-Br, 64%, *Z/E* = 32:1

4e, H, 52%, *Z/E* = 5:1

4f, 4-MeO, 62%, *Z/E* = 18:1

4g 2-I, 63%, *Z/E* = 55:1

4j, 4-Cl, 76%, *Z/E* = 10:1

4k, 4-Br, 72%, *Z/E* = 11:1

^aTotal yield of two isomers; ^bBased on ¹H NMR analysis

Scheme 2.

Domino synthesis of *N*-aryl enaminones **4**

Scheme 3.
Controlling reactions for the formation of **3a** and **4a**

Scheme 4.
Proposed mechanism for forming products **3** and **4**

Table 1

Optimization of reaction conditions

Entry	Promoter (equiv.)	Solvent	T/ °C	Yield ^a /%
1	$\text{BF}_3 \cdot \text{THF}$ (1.2)	1,4-Dioxane	80	64
2	$\text{BF}_3 \cdot \text{AcOH}$ (1.2)	1,4-Dioxane	80	70
3	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2)	1,4-Dioxane	80	78
4	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.5)	1,4-Dioxane	80	75
5	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.0)	1,4-Dioxane	80	71
6	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2)	CH_3CN	80	29
7	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2)	DCE	80	36
8	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2)	EtOH	80	42
9	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2)	1,4-Dioxane	100	20
10	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2)	1,4-Dioxane	60	26

^a Isolated yield

Table 2

One-pot synthesis of difluoroboron ketoiminates