

PAPER

View Article Online
View Journal | View IssueCite this: *RSC Adv.*, 2018, 8, 16019

Received 17th March 2018

Accepted 13th April 2018

DOI: 10.1039/c8ra02353k

rsc.li/rsc-advances

Cs₂CO₃-promoted defluorination and functionalization of α -CF₃ carbonyl compounds in the presence of *N*-, *O*-, and/or *S*-nucleophiles†

Yue Wu, Bingbing Zhang, Yinying Zheng, Yuheng Wang and Xinsheng Lei *

A simple, efficient, and mild method for defluorination and functionalization of 3,3,3-trifluoro carbonyl compounds has been developed. In the present method, Cs₂CO₃ can easily convert α -trifluoromethyl esters, amides, and ketones into β,β -*S*-, *O*- and/or *N*-substituted α,β -unsaturated carbonyl compounds in the presence of *N*-, *O*-, and *S*-nucleophiles with moderate to excellent yields, and furthermore, this transformation with α -trifluoromethyl ester and a series of 2-aminophenols can result in benzooxazoles in good yields.

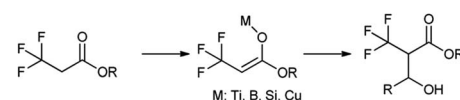
Introduction

In the past six decades, hydrofluorocarbons have been widely used in pharmaceuticals, agrochemicals, materials, refrigeration, and air conditioning. Introduction of C–F bonds into pharmaceuticals or materials can modify the acidity, lipophilicity, conformation and metabolism of pharmaceuticals,^{1–3} improve the hydrophobic properties, chemical inertness, and elasticity of materials,^{4,5} and sometimes enhance their special water-/stain-resistant and non-sticky characteristics.^{6,7} This “fluorine effect” or “fluorine magic” stems from a very short bond length, low polarizability, being fairly inert and the strong inductive effects of the C–F bond.^{8,9}

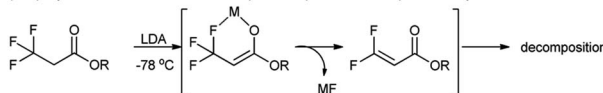
Logically, chemical inertness of C–F bond will make hydrofluorocarbons resistant to biotransformation or biodegradation.^{10,11} Thus, continual and increasing use of hydrofluorocarbons in modern life has implications for the environment and human health that urgently require attention.^{12,13} In light of the environmental concerns associated with organofluorine compounds,^{14,15} the development of novel synthetic methods for the C–F cleavage and subsequent functionalization is highly required.¹⁶

3,3,3-Trifluoropropanoic acid derivatives are one of the very important building blocks to incorporate one CF₃ group into organic molecules. The exploitation of their α -CF₃ enolates as active nucleophiles for the introduction of a CF₃ group have been achieved (Fig. 1, path a),^{17–21} but their defluorination and functionalization are only scarcely explored,²² because their direct

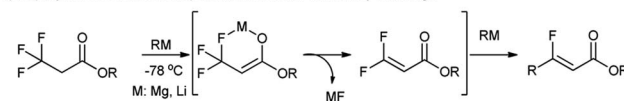
defluorinations usually require strong basic conditions²³ and the resultant β,β -difluoro- α,β -unsaturated carbonyl compounds are prone to subsequent decomposition even at a low temperature (path b).²⁴ Recently, defluorination and functionalization of 3,3,3-trifluoropropanoic acid derivatives have been reported at –78 °C to prepare monofluoroalkenes *via* elimination and addition with organolithium or Grignard reagents as *C*-nucleophiles (path c).²⁵ These results prompted us to examine defluorination and functionalization of α -CF₃ carbonyl compounds with other nucleophiles such as *S*-, *O*-, and *N*-nucleophiles. Herein, we described an efficient and mild defluorinated and functionalized method of α -CF₃ carbonyl compounds *via* a Cs₂CO₃-promoted elimination/addition in the presence of a series of *N*-, *O*-, *S*-nucleophiles.

a) Introduction of a CF₃ group upon enolization by TCl₄ or TMSOTf/Et₃N

b) Rapidly fluoride elimination and decomposition upon enolization promoted by LDA



c) Rapidly-fluoride elimination upon enolization and addition by RLi/RMgX



d) Current work: defluorination and functionalization promoted by a mild base

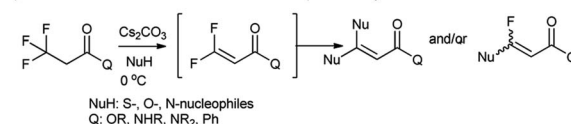


Fig. 1 The enolization and defluorination of 3,3,3-trifluoropropanoic acid derivatives.

School of Pharmacy, Fudan University, 826 Zhangheng Road, Pudong Zone, Shanghai 201203, China. E-mail: leixs@fudan.edu.cn; Fax: +86 21 5198 0128; Tel: +86 21 5198 0128

† Electronic supplementary information (ESI) available. CCDC 1815972. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ra02353k

Results and discussion

We initiated our work by studying the reaction of ethyl 3,3,3-trifluoropropanoate (**1a**) and 4-mercaptotoluene (**2a**) under the basic conditions. As shown in Table 1, in the presence of NaHMDS, the reaction was run at rt for 2 h, and expectedly, **2a** was not consumed because of the almost quantitative recovery of **2a**. When the reaction was run at 0 °C, only a small amount of defluorinated product could be isolated (entry 1, 37%), and its structure was subsequently determined as **3aa**. Decreasing reaction temperature to −78 °C, only **3aa** could be isolated in a higher yield (entry 2, 46%), but the partial-defluorinated product, such as **4aa**, was still not isolated. Increasing the amount of **2a** did not improve the reaction (entry 3, 47%), instead, increasing the amount of NaHMDS could increase the yield of **3aa** up to 88%, albeit without **4aa**. LDA had a similar performance to NaHMDS (entry 5, 64%). The above results implied that those bases might rapidly transform the ester into active β,β -difluoro- α,β -unsaturated carbonyl compounds, and then this unstable intermediate could be trapped by **2a** to some extent while it was prone to decompose.

Based on the facts that only the trace partial-defluorinated product was observed and the major full-defluorinated product, as one kind of α -oxoketene-*S,S*-acetals, might be one potentially versatile three-carbon building blocks for the construction of various heterocyclic systems,²⁶ we turned to

optimize the full-defluorinated reaction by screening a variety of other bases for the reaction.

As shown in Table 1, *t*-BuOK gave a moderate yield (entry 6, 54%) at 0 °C, but a higher or lower temperature led to a poorer yield (at rt or −78 °C). Similarly, MeONa could give the almost same result (entry 7, 56%). The weaker bases, such as Na₂CO₃, AcONa and Et₃N, could not initiate the reaction (entry 8, 10, 11) while K₂CO₃ just resulted in a very low yield (entry 9, 15%). To our delight, Cs₂CO₃ gave the almost quantitative yield and its amount could be reduced from 3.0 to 2.0 equivalents (entry 12, 98% vs. 96%). Subsequently, the solvent screening demonstrated that neither DMF nor EtOH was good to the reaction (entry 13, 15), and DMSO just gave a slightly decreased yield (entry 14, 74%). As a result, THF was chosen as the optimized solvent for the reaction, but therein, elevating the temperature seemed to have an adverse effect on the reaction (entry 16).

With the optimized condition in hand, we subsequently examined the nucleophile scope with a variety of mono-dentate *S*-, *O*-, and *N*-nucleophiles, and the results were depicted in Table 2. For the *S*-containing nucleophiles, aryl thiols generally gave their defluorinated products in good to excellent yields (**3aa**–**3af**, 46–96%), and the substituent electronic effect in the

Table 1 The optimization on the reaction condition for the defluorination and functionization of 3,3,3-trifluoropropanoic acid derivatives

Entry	1a/2a/base (eq.)	Base	Temp.	Solvent	Yield (3aa) ^{a,b}
1	1.0/1.0/2.0	NaHMDS	0 °C	THF	37%
2	1.0/1.0/2.0	NaHMDS	−78 °C	THF	46%
3	1.0/2.0/2.0	NaHMDS	−78 °C	THF	47%
4	1.0/2.0/3.0	NaHMDS	−78 °C	THF	88%
5	1.0/1.0/3.0	LDA	−78 °C	THF	64%
6	1.0/2.0/3.0	<i>t</i> -BuOK	0 °C	THF	54%
7	1.0/2.0/3.0	MeONa	0 °C	THF	56%
8	1.0/2.0/3.0	Na ₂ CO ₃	0 °C	THF	ND ^c
9	1.0/2.0/3.0	K ₂ CO ₃	0 °C	THF	15%
10	1.0/2.0/3.0	AcONa	0 °C	THF	ND ^c
11	1.0/2.0/3.0	NEt ₃	0 °C	THF	ND ^c
12	1.0/2.0/2.0	Cs ₂ CO ₃	0 °C	THF	96%
13	1.0/2.0/2.0	Cs ₂ CO ₃	0 °C	DMF	30%
14	1.0/2.0/2.0	Cs ₂ CO ₃	0 °C	DMSO	74%
15	1.0/2.0/2.0	Cs ₂ CO ₃	0 °C	EtOH	ND ^c
16	1.0/2.0/2.0	Cs ₂ CO ₃	25 °C	THF	43%

^a Reaction conditions: to a solution of **1a** (1.0 mmol), **2a** in anhydrous THF (10 mL) was added one kind of base in one portion at the suitable temperature under Ar, and the reaction mixture was stirred for the indicated time. ^b The isolated yield based on **1a**. ^c Not detected.

Table 2 The substrate scope of defluorination and functionization of 3,3,3-trifluoropropanoic acid derivatives with mono-dentate nucleophiles

Reaction scheme	
$\text{F}_3\text{C}-\text{CH}_2-\text{C}(=\text{O})-\text{OR}_1 + \text{R}_2-\text{AH} \xrightarrow[\text{THF, 0 } ^\circ\text{C, 2 h}]{\text{Cs}_2\text{CO}_3 (3.0 \text{ eq.})} \text{R}_2-\text{CH}=\text{C}(\text{OR}_1)-\text{C}(=\text{O})-\text{OR}_1 + \text{F}_2\text{C}-\text{CH}=\text{C}(\text{OR}_1)-\text{C}(=\text{O})-\text{OR}_1$	
1	2
3	4

^a Reaction conditions: a solution of **1** (1.0 mmol), **2** (2.0 mmol) and Cs₂CO₃ (2.0 mmol) in anhydrous THF (10 mL) was stirred at 0 °C for 2 h at under Ar. ^b The isolated yield based on **1**. ^c The reaction was run at 45 °C. ^d The reaction was run at 45 °C in anhydrous DMSO.



aryl ring may have little influence on the reaction, instead, the bulkier nucleophile seems to have a slight effect on the reaction (**3ac**, 46%). This reaction could successfully be expanded to the aliphatic thiol (**3ag**, 89%).

On the other hand, for the different 3,3,3-trifluoropropanoyl esters, the reaction also gave the similar results in the case of benzyl ester and β -naphthalenyl ester (**3ba**, 43%; **3ca**, 71%). *N,N*-substituted 3,3,3-trifluoropropanamide was able to carry out this transformation with a lower yield (**3da**, 34%). In contrast, the *N*-monosubstituted amide only produced a trace amount of the desired product at 0 °C, but could afford the product at 45 °C in DMSO (**3fa**, 79%).

Furthermore, the *O*- and *N*-containing nucleophiles were tested in the reaction, for example, *p*-cresol successfully afforded the defluorinated product at a higher temperature (**3ai**, 90% at 45 °C). However, in terms of the *N*-containing nucleophile, *p*-toluidine did not afford the desired compound (**3aj**, trace) under Cs_2CO_3 -, NaHMDS -, or *t*-BuOK-promoted conditions, possibly due to poor nucleophilicity of the amine or instability of **3aj**. In contrast, the amide was able to produce the partial-defluorinated product (**4ak**, 61%) with *Z*-configuration. To our surprise, α - CF_3 ketone was also proved flexible in the reaction, for example, 3,3,3-trifluoro-1-phenylpropan-1-one could react with **2a** under the standard condition, and then gave **3ga** in 53% yield.

Next, this defluorinative functionalization was switched from those mono-dentate nucleophiles to the bidentate nucleophiles, the results were depicted in Table 3. When one equivalent of catechol was used as one *O,O*-bidentate nucleophile, the reaction did not occur at 0 °C, but at a higher temperature (45 °C) the cyclized compound was smoothly produced (**5am**, 83%). Similarly, 2-mercaptophenol, one *O,S*-bidentate nucleophile, could smoothly afford the corresponding product (**5an**, 66%), and interestingly, the single crystal X-ray diffraction experiment demonstrated that the stereo configuration between H atom at the olefin and O atom at the heterocycle was *syn*-configuration,²⁷ indicating there evidently existed bulkier repulse between H atom and S atom.

Unexpectedly, 2-aminothiophenol, as one *N,S*-bidentate nucleophile, did not give the desired product, instead, it resulted in the undesired product (**3ao**, 71%), possibly due to the weaker nucleophilicity of amine than that of thiol. Furthermore, the reaction using benzene-1,2-diamine as one *N,N*-bidentate nucleophile led to complicated products (**5ap**, trace).

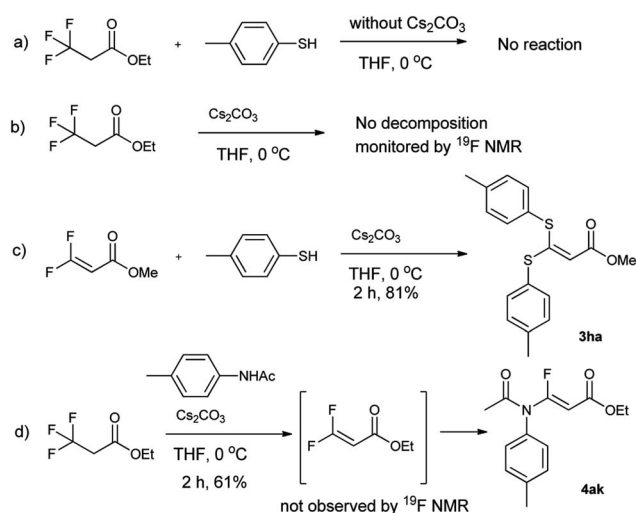
Interestingly, 2-aminophenol, as one *N,O*-bidentate nucleophile, produced the benzoxazole derivative at 45 °C in a good yield (**5aq**, 81%) *via* defluorinative substitution, intramolecularly defluorinative substitution and aromatization. To our delight, a set of 2-aminophenols substituted at the aromatic ring could easily produce the corresponding ethyl 2-(benzo[*d*]oxazol-2-yl)acetates in moderate to good yields (**5aq–5ay**, 44–81%). However, when one *C,O*-bidentate nucleophile, such as methyl 2-(2-hydroxyphenyl)acetate, was used in the reaction, only O atom instead of C atom acted as the nucleophile (**3az**, 70%).

Table 3 Defluorination and functionization of ethyl 3,3,3-trifluoropropanoate with some bidentate nucleophiles^a

	<p>5am: 83% 5an: 66% 5ao: 71% 5ap: trace 5aq: 81% 5as: 80% 5at: 75% 5au: 76% 5av: 44% 5aw: 55% 5ax: 51% 5ay: 47% 3az: 70% 3ga: 53%</p>

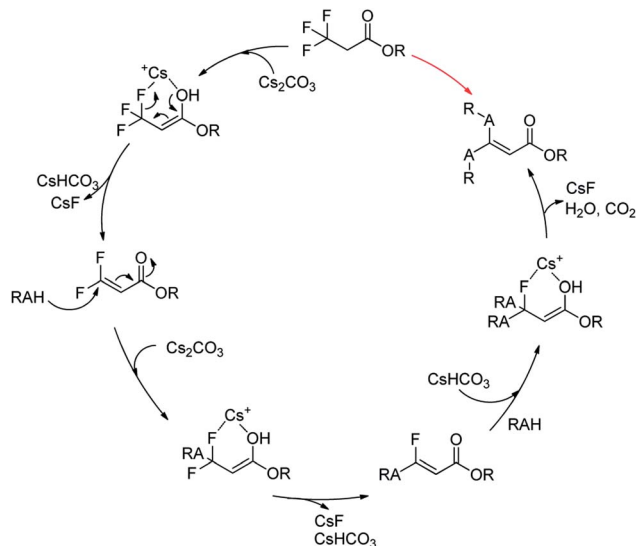
^a Reaction conditions: a solution of **1a** (1.0 mmol), **2** (1.0 mmol) and Cs_2CO_3 (2.0 mmol) in anhydrous THF (10 mL) was stirred at 45 °C for 2 h under Ar. The isolated yield based on **1a**.

To understand the reaction mechanism, the control experiments were performed, as shown in Scheme 1. If the reaction was run in absence of Cs_2CO_3 , the reaction did not occur (Scheme 1a). Meanwhile the trifluoropropanoate ester was not decomposed by Cs_2CO_3 in the absence of nucleophile (Scheme 1b), although decomposition occurred with a strong base (such as NaHMDS). On the other hand, if methyl 3,3-difluoroacrylate was subjected to the same basic condition, the desired compound (**3ha**) could be produced (Scheme 1c), strongly



Scheme 1 The control experiments.





Scheme 2 A plausible mechanism of the defluorination and functionalization of ethyl 3,3,3-trifluoropropanoylete.

indicating the 3,3-difluoroacrylate was the intermediate. Although we attempted to isolate the corresponding 3,3-difluoroacrylamide or monitor other fluoro organic compounds by ^{19}F NMR in the case of **4ka**, unfortunately we did not succeed (Scheme 1d).

Together with the above results, we proposed a plausible mechanism (Scheme 2).²²⁻²⁴ At first, Cs_2CO_3 promoted the dehydrofluorinative elimination of trifluoropropanoylate ester in the presence of one suitable nucleophile, and the resultant 3,3-difluoroacrylate ester was rapidly added by the nucleophile, then the adduct continued to rapidly undergo elimination to afford α,β -unsaturated monofluorinated carbonyl compound, and in general, the further addition and dehydrofluorinative elimination continued to occur and finally resulted in the full-defluorinated product.

Conclusions

In conclusion, we have developed an efficient defluorinated and functionized method of 3,3,3-trifluoropropanoic acid derivatives, and in this method, a mild base (Cs_2CO_3) enables to promote defluorination and functionalization of the β,β,β -trifluoro carbonyl compounds in the presence of a series of *N*-, *O*-, *S*-nucleophiles. By the current method, the α -trifluoromethyl carbonyl compounds easily afford β,β -*N*-, *O*-, and/or *S*-substituted α,β -unsaturated products in moderate to excellent yields, and α -trifluoromethyl ester can also be transformed into the corresponding benzooxazoles in good yields when 2-aminophenols were used as nucleophiles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank National Natural Foundation of China (No. 21472024 and No. 21242008) for the financial support.

Notes and references

- 1 Y. Zhou, J. Wang, Z. N. Gu, S. N. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422.
- 2 D. E. Yerien, S. Bonesi and A. Postigo, *Org. Biomol. Chem.*, 2016, **14**, 8398.
- 3 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
- 4 Z. L. Chu and S. Seeger, *Chem. Soc. Rev.*, 2014, **43**, 2784.
- 5 M. Pagliaro and R. Ciriminna, *J. Mater. Chem.*, 2005, **15**, 4981.
- 6 I. T. Horváth, *Acc. Chem. Res.*, 1998, **31**, 641.
- 7 W. Zhang, *Chem. Rev.*, 2009, **109**, 749.
- 8 C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2015, **115**, 765, and references therein.
- 9 C. F. Ni and J. B. Hu, *Chem. Soc. Rev.*, 2016, **45**, 5441.
- 10 D. O'Hagan and H. Deng, *Chem. Rev.*, 2014, **115**, 634.
- 11 C. D. Murphy, *Appl. Microbiol. Biotechnol.*, 2016, **100**, 2617.
- 12 N. Khalil, A. Chen, M. Lee, S. A. Czerwinski, J. R. Ebert, J. C. DeWitt and K. Kannan, *Environ. Health Perspect.*, 2016, **124**, 81.
- 13 H. Fromme, S. A. Tittlemier, W. Voelkel, M. Wilhelm and D. Twardella, *Int. J. Hyg. Environ. Health*, 2009, **212**, 239.
- 14 K. Kato, L. Y. Wong, L. T. Jia, Z. Kuklenyik and A. M. Calafat, *Environ. Sci. Technol.*, 2011, **45**, 8037.
- 15 A. Rotander, A. Kärman, B. van Bavel, A. Polder, F. Rigét, A. Auðunsson, G. Vikingsson, G. W. Gabrielsen, D. Bloch and M. Damh, *Chemosphere*, 2012, **86**, 278.
- 16 O. Eisenstein, J. Milani, N. Robin and R. N. Perutz, *Chem. Rev.*, 2017, **117**, 8710, and references therein.
- 17 (a) A. Matsuzawa, H. Noda, N. Kumagai and M. Shibasaki, *J. Org. Chem.*, 2017, **82**, 8304; (b) L. Brewitz, F. A. Arteaga, L. Yin, K. Alagiri, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2015, **137**, 15929; (c) P. V. Ramachandran, B. Otoo and P. B. Chanda, *Tetrahedron Lett.*, 2015, **56**, 3019; (d) L. Yin, L. Brewitz, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2014, **136**, 17958; (e) J.-L. Chen, Z.-W. You and F.-L. Qing, *J. Fluorine Chem.*, 2013, **155**, 143; (f) P. V. Ramachandran, G. Parthasarathy and P. D. Gagare, *Tetrahedron Lett.*, 2011, **52**, 6055; (g) P. V. Ramachandran, G. Parthasarathy and P. D. Gagare, *Tetrahedron Lett.*, 2011, **52**, 5359; (h) P. V. Ramachandran, G. Parthasarathy and P. D. Gagare, *Org. Lett.*, 2010, **12**, 4474.
- 18 K. Uneyama, T. Katagiri and H. Amii, *Acc. Chem. Res.*, 2008, **41**, 817, and references therein.
- 19 (a) A.-L. Dreier, B. Beutel, C. Mück-Lichtenfeld, A. V. Matsnev, J. S. Thrasher and G. Haufe, *J. Org. Chem.*, 2017, **82**, 1638; (b) A. Saito, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2017, **56**, 5551; (c) F. Grellepois, V. Kikelj, N. Coia and C. Portella, *Eur. J. Org. Chem.*, 2012, 509.

- 20 (a) H.-W. Liang, W. Ding, K. Jiang, L. Shuai, Y. Yuan, Y. Wei and Y.-C. Chen, *Org. Lett.*, 2015, **17**, 2764; (b) J. Xie, P. Xu, H. Li, Q. Xue, H. Jin, Y. Cheng and C. Zhu, *Chem. Commun.*, 2013, **49**, 5672; (c) Y. Guo, X. Zhao, D. Zhang and S.-I. Murahashi, *Angew. Chem., Int. Ed.*, 2009, **48**, 2047.
- 21 (a) A. Gómez-Palomino, M. Pellicena, J. M. Romo, R. Solà, P. Romea, F. Urpí and M. Font-Bardía, *Chem. – Eur. J.*, 2014, **20**, 10153; (b) J. K. Augustine, A. Bombrun, B. Ramappa and C. Boodappa, *Tetrahedron Lett.*, 2012, **53**, 4422; (c) E. Yoshioka, S. Kohtani and H. Miyabe, *Angew. Chem., Int. Ed.*, 2011, **50**, 6038; (d) Y. Liu, H. Lai, B. Rong, T. Zhou, J. Hong, C. Yuan, S. Zhao, X. Zhao, B. Jiang and Q. Fang, *Adv. Synth. Catal.*, 2011, **353**, 3161.
- 22 (a) H. Liu, S. Song, C.-Q. Wang, C. Feng and T.-P. Loh, *ChemSusChem*, 2017, **10**, 58; (b) K. N. Nandeesh, H. A. Swarup, N. C. Sandhya, C. D. Mohan, C. S. P. Kumar, M. N. Kumara, K. Mantelingu, S. Ananda and K. S. Rangappa, *New J. Chem.*, 2016, **40**, 2823.
- 23 Y. Itoh, M. Yamanaka and K. Mikami, *J. Am. Chem. Soc.*, 2004, **126**, 13174.
- 24 (a) K. K. Nanda and B. W. Trotter, *Tetrahedron Lett.*, 2008, **48**, 5332; (b) T. Yokozawa, T. Nakai and N. Ishikawa, *Tetrahedron Lett.*, 1984, **25**, 3987; (c) T. Yokozawa, T. Nakai and N. Ishikawa, *Tetrahedron Lett.*, 1984, **25**, 3991.
- 25 M. Lecea, A. Grassin, L. Ferreiro-Mederos, S. Choppin, A. Urbano, M. C. Carreno and F. Colobert, *Eur. J. Org. Chem.*, 2013, 4486.
- 26 (a) D. Cheng, L. Wu, Z. Deng, X. Xu and J. Yan, *Adv. Synth. Catal.*, 2017, **359**, 4317; (b) L. Zhu, H. Yu, Q. Guo, Q. Chen, Z. Xu and R. Wang, *Org. Lett.*, 2015, **17**, 1978; (c) B. Liu, G. Zheng, X. Liu, C. Xu, J. Liu and M. Wang, *Chem. Commun.*, 2013, **49**, 2201; (d) G. K. Verma, R. K. Verma and M. S. Singh, *RSC Adv.*, 2013, **3**, 245, and references therein; (e) G. K. Verma, R. K. Verma, G. Shukla, N. Anugula, A. Srivastava and M. S. Singh, *Tetrahedron*, 2013, **69**, 6612; (f) D. Liang, M. Wang, B. Bekturhun, B. Xiong and Q. Liu, *Adv. Synth. Catal.*, 2010, **352**, 1593.
- 27 Crystallographic data for compound **5an**: CCDC 1815972.

