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View Article Online
DOI: 10.1039/C9NJ02370D

ARTICLE

Stereoselective synthesis of α-fluoroacrylonitriles through organocatalytic cyanation of *gem*-difluoroalkenes and TMSCN

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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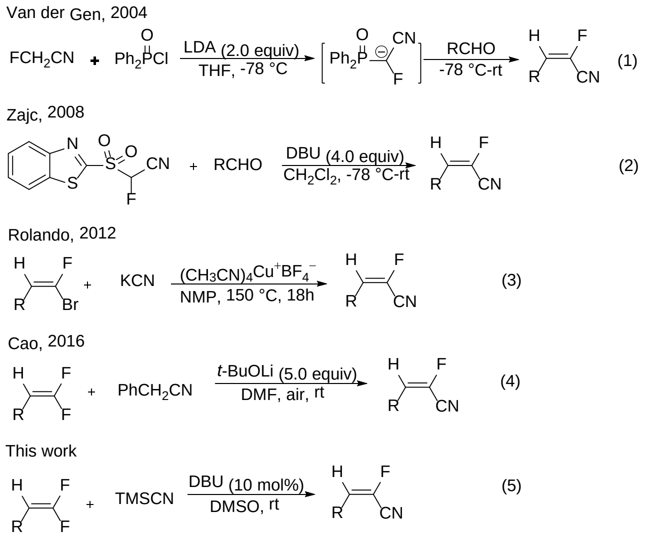
An organocatalytic cyanation reaction of gem-difluoroalkenes was developed. Under the catalysis of 10 mol% DBU, *gem*-difluoroalkenes undergo nucleophilic addition-β-elimination reaction with trimethylsilyl cyanide to provide α-fluoroacrylonitriles in 50%-98% yields with excellent *Z/E* selectivity.

Introduction

The monofluoroalkene is an important structural motif found in many agrochemicals, pharmaceuticals and functional materials.[1] Owing to its unique physical and chemical properties, this fluorinated unit has been used widely in the synthesis of peptide mimics[2] and served as the amide bioisosteres[3] in medicinal chemistry. Moreover, they can also serve as fluorinated building blocks in organic synthesis.[4] Therefore, considerable efforts have been exerted to develop new methods for the synthesis of these important frameworks.[5] Among them, transition-metal and organocatalysts catalyzed C-F bond functionalization of gem-difluoroalkenes with different nucleophiles provides a powerful and effective strategy for the synthesis of functionalized monofluoroalkenes.[6] On the other hand, the acrylonitrile is another common structural subunit existing in different biologically active compounds and pharmaceuticals.[7] The cyano group can feasibly transfer to other useful functional moieties, such as amine, amidine and carboxylic acid.[8] The significance of this motif has attracted considerable attention from organic chemists. In the past decade, transition-metal catalyzed cyanation of alkenes and alkenyl halides have been extensively developed, which provides facile access to different acrylonitrile derivatives.[9] Despite numerous achievements accomplished in this research field, the synthesis of fluorinated acrylonitriles remains far less examined. In 2004, Van der Gen and co-workers[10] reported a Horner-wittig reaction of (diphenylphosphinoyl)fluoroacetonitrile and aldehydes, which produced α-fluoroacrylonitriles in moderate yield and low *Z/E* selectivity (Scheme 1, eq 1). In 2008, Zajc and co-workers[11] prepared a stable reagent (1,3-benzothiazol-2-ylsulfonyl)fluoroacetonitrile via multistep reactions. In the presence of 4.0 equivalents of DBU, this reagent can undergo fluoro-Julia olefination with aldehydes to provide α-fluoroacrylonitriles in high yields with good *Z*-selectivity (Scheme 1, eq 2). Recently, Rolando and co-workers[12] developed the copper-catalyzed coupling reaction of alkenyl halide and potassium cyanide, which gave α-fluoroacrylonitriles in high yield (Scheme 1, eq 3). Interestingly, using benzyl nitrile as a cyanating reagent, Cao and co-workers[13] developed a highly stereoselective cyanation of *gem*-difluoroalkenes (Scheme 1, eq 4).



Scheme 1 Different synthesis methods of α-fluoroacrylonitriles

However, these methods often suffer from some drawbacks, such as harsh reaction conditions, the use of highly toxic cyanating reagent and the addition of excess of additives. Therefore, the development of more convenient and mild method for the synthesis of α-fluoroacrylonitriles is still highly significnce. In line with our continue interest of the functionalization of C-F bonds of gem-difluoroalkenes[14] and N-heterocyclic carbene-catalyzed activation of silylated

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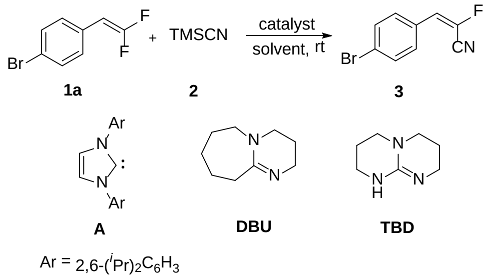
DOI: 10.1039/C9NJ02070D

reagents,[15] we envisioned that NHCs or other strong Brønsted bases could catalyze the cyanation reaction of gem-difluoroalkenes and TMSCN to produce fluorinated acrylonitriles (Scheme 1, eq 5). And herein, we wish to report this result.

Experimental

Our initial studies were carried out with the readily available *gem*-difluoroalkene **1a** and TMSCN as the model substrates. In the presence of 10 mol% NHC **A**,[16] the reaction hardly proceeded in THF and only trace amount of fluorinated acrylonitrile **3a** was observed by GC-MS (Table 1, entry 1). The following studies indicated that the reaction media has obvious influence on the reaction yield and the polar aprotic solvents, DMF and DMSO are suitable for the transformation (Table 1, entries 2-5). Basesd on these results, a series of organic bases and inorganic bases were then screened for the reaction. Both triethylamine and Hunig's base showed low efficiency (Table 1, entries 6 and 7. Strong Brønsted bases, such as *t*-BuOK, DBU and TBD, catalyzed the reaction efficiently and DBU gave the highest yield (Table 1, entries 8-10). Carbonates and fluorides can also catalyze the reaction in good efficiency (Table 1, entries 11-13). Reducing the DBU loading to 5 mol% or lowering the amount of TMSCN to 1.5 equivalents led to prolonged reaction time and decreased reaction yield (Table 1, entries 14 and 15). Finally, the control experiment showed that in the absence of a Brønsted base, the reaction was unsuccessful (Table 1, entry 16). The configurations of *Z*- and *E*-isomers were determined by the comparison of their ^{1}H NMR data with literature reports.[12] The $^{3}J_{H\text{-}F}$ coupling constant of the *Z*-isomer are generally more than 30 Hz, while the $^{3}J_{H\text{-}F}$ coupling constant of the *E*-isomer are less than 20 Hz.[11]

Table 1. Optimization of the reaction conditions[a]

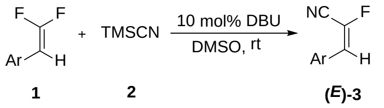


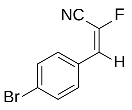
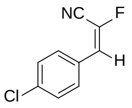
Entry	Conditions	Time/h	**2** (equiv)	Yield(%)[b]	*E/Z*[c]
1	**A** (10 mol%), THF	24	2	< 10	/
2	**A** (10 mol%), DCM	24	2	18	>20:1
3	**A** (10 mol%), CH_3CN	24	2	27	>20:1
4	**A** (10 mol%), DMF	12	2	53	>20:1
5	**A** (10 mol%), DMSO	12	2	66	>20:1
6	Et_3N (10 mol%), DMSO	12	2	34	>20:1
7	DIPEA (10 mol%), DMSO	12	2	34	>20:1
8	*t*-BuOK (10 mol%), DMSO	12	2	70	>20:1
9	DBU (10 mol%), DMSO	12	2	84	>20:1
10	TBD (10 mol%), DMSO	12	2	67	>20:1
11	Cs_2CO_3 (10 mol%), DMSO	12	2	64	>20:1
12	K_2CO_3 (10 mol%), DMSO	12	2	59	>20:1
13	KF(10 mol%), DMSO	12	2	64	>20:1
14	DBU (5 mol%), DMSO	24	2	70	>20:1
15	DBU (10 mol%), DMSO	24	1.5	72	>20:1
16	No base, DMSO	24	2	0	/

[a] **1a** (0.2 mmol), base (10 mol%), solvent (2.0 mL). [b] Isolated total yield of two diastereomers. [c] Determined by ^{19}F NMR analysis of the crude product.

With the optimized reaction conditions in hand, we then evaluated the substrate scope of the cyanation reaction and the results are summarized in Table 2. gem-Difluoroalkenes with electron-withdrawing substituents on the aryl rings gave the corresponding products in higher yields than those bearing electron-donating substituents (Table 2, entries 1-4). In addition, different positions of the substituents can be well tolerated for the reaction (Table 2, entries 5-9). Interestingly, when the strong electron-withdrawing nitro group substituted gem-difluoroalkene **1j** was used for the reaction, the desired product was obtained in high yield but with opposite *Z/E* selectivity (Table 2, entry 10). We reasoned that the nitro group can stablize the benzyl anion intermediate and facilate the β-elimination of fluoride, and as a result, giving the thermodynamically favorable *Z*-isomer as the major product. Both α-naphthyl and β-naphthyl substituted gem-difluoroalkenes performed very well to produce the corresponding products **3l** and **3m** in 70% and 77% yields (Table 2, entries 11 and 12). Biphenyl substituted substrate was proven to be a good candidate for the reaction, affording **3p** in 85% yield (Table 2, entry 13). Heteroaryl substituted gem-difluoroalkene underwent the reaction to provide **3q** in 83% yield (Table 2, entry 14). Electron-donating,-neutral and -withdrawing groups substituted symmetrical gem-difluoroalkenes were all suitable for the reaction, giving the corresponding products in excellent yields (Table 2, entries 15-18).

Table 2. Evaluation of the substrate scope [a]



Entry	Product	Yield of 3(%)[b]	*E/Z* [c]
1		**3a**, 84	>20:1
2		**3b**, 75	>20:1

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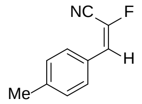
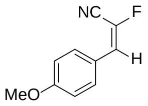
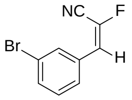
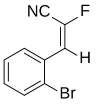
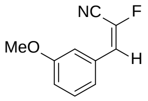
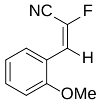
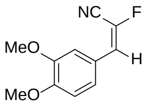
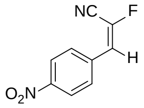
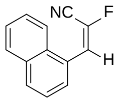
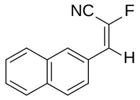
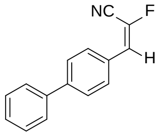
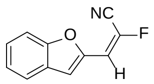
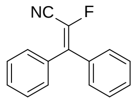
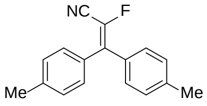
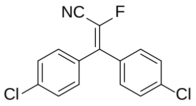
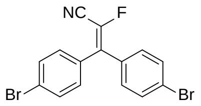
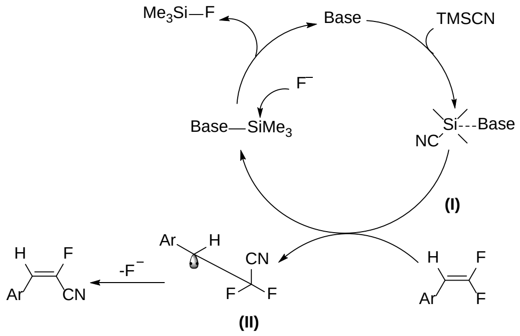
3		**3c**, 59	>20:1
4		**3d**, 52	>20:1
5		**3e**, 77	>20:1
6		**3f**, 65	>20:1
7		**3g**, 87	>20:1
8		**3h**, 81	>20:1
9		**3i**, 50	13:1
10		**3j**, 84	1:5
11		**3k**, 70	>20:1
12		**3l**, 77	>20:1
13		**3m**, 85	>20:1
14		**3n**, 83	>20:1
15		**3o**, 96	/
16		**3p**, 93	/
17		**3q**, 98	/
18		**3r**, 95	/

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.4 mmol), DBU (10 mol%), DMSO (2.0 mL), 12 h, room temperature. [b] Isolated total yield of two diastereomers. [c] *E/Z* was determined by ^{19}F NMR analysis of the crude reaction mixture.

Based on previous literature report,[17] a plausible reaction mechanism was proposed as depicted in Scheme 2. The Brønsted base attacks the silicon atom of TMSCN to generate the reactive hypervalent silicon species **I**, which might trigger the following nucleophilic addition with *gem*-difluoroalkene to form carbanion intermediate **II**, and after the β-elimination of the fluoride anion, to produce the final product.



Scheme 2 Proposed mechanism.

The rotation of intermediate **II** would form two possible conformational intermediates **III** and **IV** (Figure 1). In order to minimize the electronic repulsion[13] between the fluoride atom and the aryl group, the elimination process of intermediate **II** preferentially proceeds via model **III** and as a result, to produce the *E*-isomer as the major product.

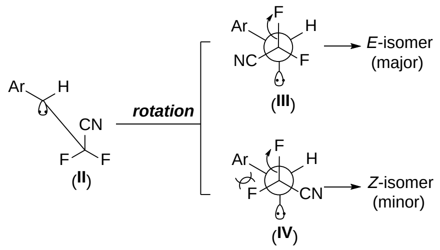


Figure 1 Two possible conformational models

Conclusions

In conclusion, an organocatalytic functionalization of *gem*-difluoroalkenes has been described. The mild and transition-metal free conditions, simple procedure and generally high yield and excellent *Z/E* selectivity provide a new protocol for the synthesis of fluorinated acrylonitriles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No.21662029), the Young Scientists Foundation of Shihezi University (Nos. RCZX201546, 2015ZRKXJQ05), the Excellent Young Teachers Plan of Bingtuan (2017CB001, CZ027203) and the International Cooperation Project of Shihezi University (No.GJHZ201801)

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DOI: 10.1039/C9NJ02370D

DBU-catalyzed cyanation of *gem*-difluoroalkenes with TMSCN highly stereoselective synthesis of α-fluoroacrylonitriles