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Letter

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A Catalytic Peterson-like Synthesis of Alkenyl Nitriles

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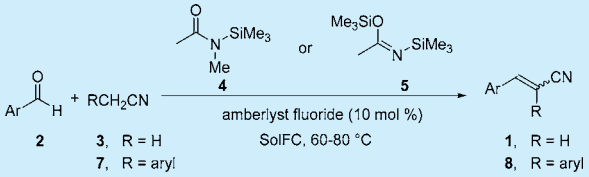
Supporting Information

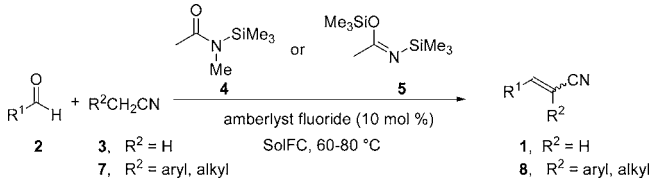
ABSTRACT: A heterogeneous fluoride catalyst was found to enable the straightforward formation of alkenyl nitriles from the reaction of aldehydes and simple or substituted acetonitriles, in the presence of commercially available silazanes and in solvent-free conditions. The protocol afforded the products in good to excellent yields with selectivity values dependent on the nature of the substrates. It represents an alternative to classic approaches using stoichiometric strong bases, and the catalyst can be easily recovered and reused for consecutive cycles.



Alkenyl nitriles represent important building blocks in synthetic organic chemistry, particularly as electrophilic partners in nucleophilic conjugate addition reactions.[1] Moreover, alkenyl nitriles are found in a number of natural products,[2] especially nitrilosides, and pharmaceutically important compounds,[3] such as the anti-HIV non-nucleoside reverse transcriptase inhibitor rilpivirine[4] and the antiparkinson agent entacapone.[5] The standard procedure for the preparation of alkenyl nitriles employs sodium or potassium hydroxide to promote the condensation between acetonitrile and carbonyl compounds.[6] However, side reactions are common under these conditions. These include the aldol reaction (for enolizable carbonyl compounds), the self-condensation of nitriles, and the Cannizzaro reaction. It is not surprising then that considerable research efforts have been devoted to the definition of more efficient methodologies for the preparation of alkenyl nitriles.[7] Among these, particularly interesting procedures are those based on the Wittig–Horner[7c,o] and the Peterson reactions,[7m] the carbocyanation of alkynes,[7l] and the iron-catalyzed oxidative functionalization of alkenes.[7j] However, most of these procedures suffer from serious drawbacks, such as the use of toxic reagents, the need for stoichiometric organometallic reagents, and the frequently observed unsatisfactory yields.

In this letter, we present a novel, simple, and mild protocol for the olefination reaction toward the synthesis of alkenyl nitriles **1** or **8**, starting from aldehydes **2** and acetonitrile **3** or substituted acetonitriles **7** (Scheme 1). This novel approach is based on the ability of a fluoride ion to activate a Si–N bond.[8] The reaction works efficiently in the absence of an additional reaction medium (solvent-free conditions, SolFC) and involves the use of silazanes **4**–**5** as trimethylsilyl sources and the use of a polystyrene supported tetraalkylammonium fluoride (amberlyst fluoride, Amb-F, **6**) as the catalyst. This protocol offers the great advantages of using simple nitriles as a reactant without any time-consuming and costly functionalization and avoiding the use of highly reactive organometallic reagents or superbases. Moreover, the use of a solid catalyst simplifies the purification and allows the recovery and recycle of the fluoride ion source.

Scheme 1. Amb-F Catalyzed Synthesis of Alkenyl Nitriles Using Aldehydes and Nitriles



We first focused on the scope of the reaction between unsubstituted acetonitrile and a wide range of aromatic and heteroaromatic aldehydes (Table 1). Either *N*-methyl-*N*-trimethylsilylacetamide (MTSA, **4**) or *N*,*O*-bis-trimethylsilylacetamide (BSA, **5**) were used as silazane bases, with **4** generally giving better results, especially in terms of a clean reaction profile and ease of purification of the reaction mixture. The reaction affords the products in good to excellent yields (up to 93%), and both electron-rich (Table 1, entries 1–5 and 10–12) and electron-poor aldehydes (Table 1, entries 6–8 and 13) could be used as substrates. The reaction with 4-bromobenzaldehyde (**2f**) (Table 1, entry 6) required an increased amount of acetonitrile, because of the competing nucleophilic addition of the silazane on the carbonyl. Anyway, it should be noted that highly concentrated conditions are crucial for the efficiency of the process, and a larger excess of **3** is detrimental to the reactivity.

Cinnamaldehyde (**2i**) was also employed, showing a complete preference for carbonyl olefination over conjugate addition (Table 1, entry 9). Olefination of aromatic heterocyclic aldehydes **2k**–**m** proved to be very satisfying (Table 1, entries 11–13), especially with 2-pyridinecarboxaldehyde (**2m**) (Table 1, entry 13). The reaction with indole-3-carboxaldehyde (**2n**) (Table 1,

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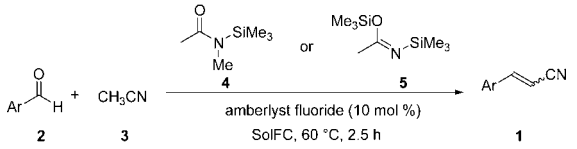
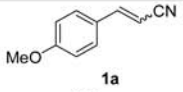
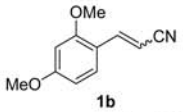
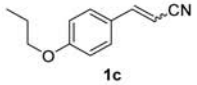
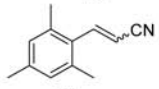
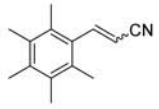
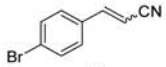
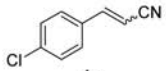
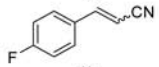
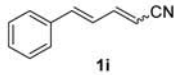
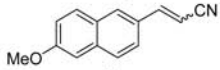
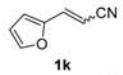
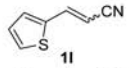
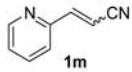
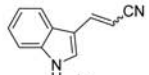
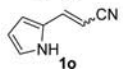
Table 1. Amb-F-Catalyzed Preparation of Alkenylnitriles 1 from Aromatic Aldehydes 2 Using Silazanes 4 or 5 under SolFC[a]



entry	reagent	product	silazane	*E*/*Z*	yield (%)
1	**2a**	 **1a**	**4**	70:30	87
2	**2b**	 **1b**	**5**	73:27	92
3	**2c**	 **1c**	**4**	72:28	77
4	**2d**	 **1d**	**5**	80:20	72
5	**2e**	 **1e**	**5**	84:16	72
6[b]	**2f**	 **1f**	**4**	68:32	83
7	**2g**	 **1g**	**5**	71:29	83
8	**2h**	 **1h**	**5**	74:26	70
9	**2i**	 **1i**	**5**	50:50	70
10	**2j**	 **1j**	**4**	74:26	88
11	**2k**	 **1k**	**4**	70:30	81
12	**2l**	 **1l**	**4**	71:29	75
13	**2m**	 **1m**	**4**	84:16	93
14[c]	**2n**	 **1n**	**4**	-	-
15[c]	**2o**	 **1o**	**4**	-	-

[a]Reaction conditions: **2** (0.5 mmol), **3** (5 mmol, 10 equiv), **4** or **5** (1 mmol, 2 equiv). [b]20 equiv of **3**. [c]Deprotonation/silylation of **2** (no formation of product **1**).

entry 14) and pyrrole-2-carboxaldehyde (**2o**) (Table 1, entry 15) led to the immediate and irreversible deprotonation/silylation of the relatively acidic nitrogen, as revealed by GC-MS analysis. Use of an excess of 4 equiv of **4** led to complex reaction mixtures. These results indicate the involvement of a strong base in the reaction.

A slight preference for the formation of the *E* isomer was generally observed, with the selectivity depending on the substrate. The highest levels of selectivity were found for the reactions of pentamethylbenzaldehyde (**2e**) (Table 1, entry 5) and pyridine-2-carboxaldehyde (**2m**) (Table 1, entry 13). The generally moderate selectivity might be ascribed to the limited steric hindrance exerted by acetonitrile. Indeed, performing the reaction with bulkier nitriles gives much higher levels of selectivity (*vide infra*).

Having established the scope of the reaction with acetonitrile (**3**) we decided to investigate whether the protocol could be extended to substituted acetonitriles **7** to afford trisubstituted alkenylnitriles (Table 2).

The reaction promoted by silazane **4** works efficiently on benzyl nitriles, with yields ranging from good to excellent (68%−99%). Electron-rich and -poor aromatic aldehydes, as well as heteroaromatic aldehydes, could be used in combination with substituted or unsubstituted benzyl nitriles. The use of an excess of nitrile was not necessary in this case, as all the reactions could be carried out with equimolar amounts of the two coupling partners. As expected, the higher steric demands of benzyl nitriles lead to much higher selectivity compared to the reactions with acetonitrile. Indeed, in most of the cases only one of the two possible geometrical isomers was detected.[9] The methodology could be extended also to alkyl-substituted acetonitriles (Table 2, entries 12−13) and alkyl aldehydes (Table 2, entries 14−15).

We also tested whether this protocol could be applied to ketones, subjecting acetophenone (**9**) to normal reaction conditions using silazane **4** and acetonitrile (**3**) as coupling partners (Scheme 2). Gratifyingly, the product was obtained in 90% yield after 2.5 h with an *E*/*Z* ratio of 7.2:1. In line with the hypothesis that the selectivity depends on the steric hindrance of the reactants, the isomer ratio observed for this reaction lies in between the average ratio of the reactions between aldehydes and acetonitrile and that obtained for reactions between aldehydes and benzyl nitriles.

A tentative mechanism for the reaction is reported in Scheme 3. The process is initiated by the fluoride anion mediated activation of the silazane,[10] to generate a basic amide (**11**). Here we should mention that no reaction occurred without catalyst **6**. Additional proof of the activation of the silazane, with the likely formation of intermediate **11**, is the formation of the side product deriving from the addition of the silazane on the carbonyl moiety when the reaction is performed on highly electrophilic aldehydes such as 4-bromobenzaldehyde (**2f**).

Amide **11** is in turn responsible for deprotonating acetonitrile **3** (or nitriles **7**), with the assistance of the cationic resin which stabilizes the generated carbanion **12**. At this stage, the reaction is likely to proceed through two possible pathways: namely, direct attack of the carbanion on the carbonyl substrate, with the assistance of a trimethylsilyl group in stabilizing the negative charge on the oxygen (from **12** to **15** in Scheme 3), or through the formation of trimethylsilylacetonitrile intermediate **16**. The latter is known to react with aldehydes to give the corresponding *β*-trimethylsilyloxynitriles **15**, in different reaction conditions.[11] Accordingly, we believe that also this process may proceed through a fluoride ion activated silicon pentavalent species derived from the attack of the fluoride ion on **16**.

In several cases, we observed the formation of intermediate **15** in the reaction mixtures, especially in the early stages of the

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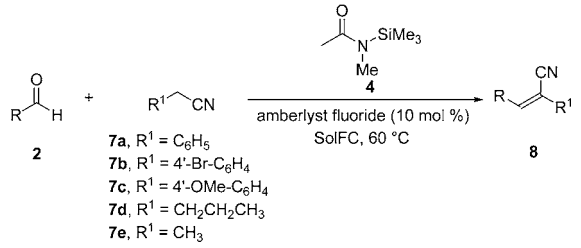
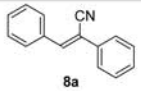
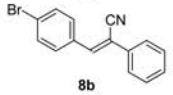
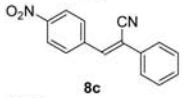
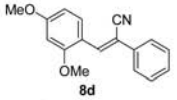
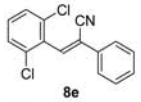
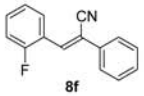
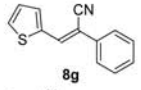
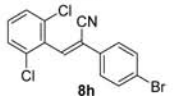
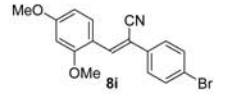
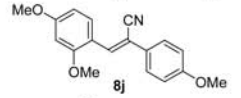
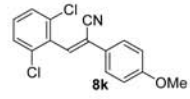
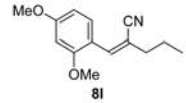
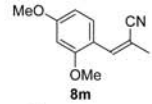
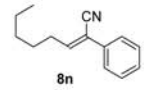
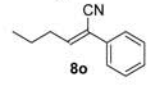
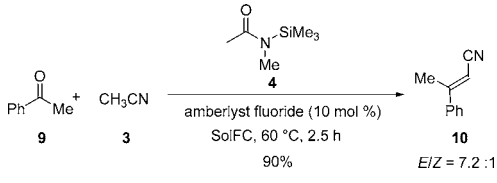
Table 2. Amb-F-Catalyzed Preparation of Alkenylnitriles 8 from Aldehydes 2 and Substituted Acetonitriles 7, Using Silazane 4 under SolFC[a]



entry	product	time (h)	Z/E[b]	yield (%)
1	 8a	24	98:2	80
2	 8b	1	98:2	76
3	 8c	1	-[c]	68
4	 8d	24	-[c]	88[d]
5	 8e	4	-[c]	94
6	 8f	20	-[c]	85
7	 8g	24	97:3	97
8	 8h	2	-[c]	98
9	 8i	1	-[c]	99
10	 8j	48	-[c]	89[d]
11	 8k	6	-[c]	96
12[e]	 8l	24	88:12	70
13[e]	 8m	24	79:21	71
14	 8n	24	96:4	62
15	 8o	24	94:6	64

[a]Reaction conditions: **2** (0.5 mmol), **7** (0.5 mmol), **4** (1 mmol, 2 equiv). [b]Determined by gas chromatography. [c]The minor isomer was not detected. [d]Reaction conducted at 80 °C. [e]10 equiv of nitrile were used.

Scheme 2. Amb-F-Catalyzed Olefination of Acetophenone (9) with Acetonitrile (3) under SolFC



reaction, confirming its involvement in the reaction mechanism. Finally, activation of the second equivalent of the silazane should provide both the base and an electrophilic silyl group to readily provide the β-elimination product **1**. It is important to note that 2 equiv of silazane are necessary for the reaction to go to completion. To further prove the role of **15** as an intermediate, we first synthesized **15a** (R = *p*-MeO-C_6H_4-) (Scheme 3) by reaction of *p*-anisaldehyde **2a** with trimethylsilylacetonitrile **16**, in SolFC and with 10 mol % of Amb-F **6** as the catalyst. The reaction went to completion in 5 min. Then, intermediate **15a** was treated with 1 equiv of silazane **4** and a catalytic amount of Amb-F **6**. The reaction

Scheme 3. Proposed Mechanism for the Reported Peterson-like Olefination

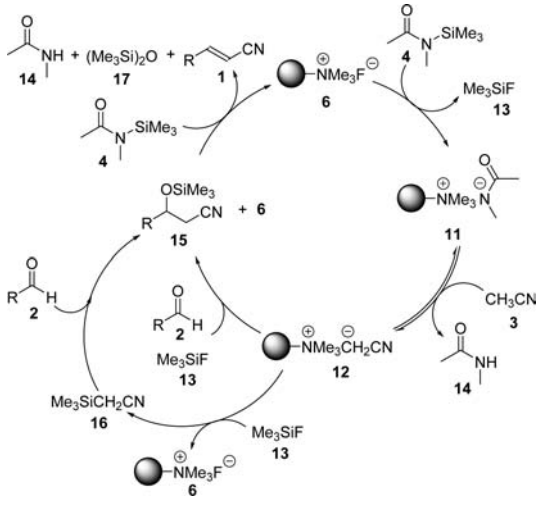


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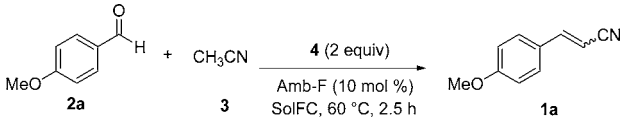
Table 3. Catalyst Recycling in the Olefination Reaction of *p*-Anisaldehyde (2a)[a]



run	conversion (%)[b]	isolated yield (%)	*Z*/*E*
1	89	87	2.3
2	90	85	2.3
3	90	87	2.3

[a]Reaction conditions: **2a** (1 mmol), **3** (10 mmol, 10 equiv), **4** (2 mmol, 2 equiv); between each run the catalyst was washed 3 times with dichloromethane, dried with a nitrogen flow, and directly reused. [b]Determined by gas chromatography.

quickly afforded product **1a** in good yield (83%), also confirming the role of the second equivalent of silazane.[12]

To establish that the fluoride ion is restored to the catalyst, we tested the possibility of using catalyst **6** for three consecutive reaction runs (Table 3). Complete retention of the activity was observed. Moreover, the composition of the catalyst did not show any appreciable modification, as revealed by elemental analysis.

The search for simple, effective, and inexpensive methodologies for the synthesis of valuable products or intermediates is a topic of great importance;[13] herein, we reported a mild, simple, and efficient protocol for the synthesis of alkenyl nitriles starting from aldehydes and simple or substituted acetonitriles. The reaction requires solvent-free conditions and makes use of a commercially available and bench stable catalyst (Amberlyst Fluoride) and silazanes. Preliminary results show that the protocol also works on ketones, but further investigations are necessary to explore the scope of the reaction. Finally, the reaction mechanism has been discussed with support from experiments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01121.

Characterization data and copies of the ^{1}H and ^{13}C NMR spectra for all compounds **1a**−**m**, **8a**−**o**, and **10** (PDF)

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Notes

The authors declare no competing financial interest.

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