

Highly Efficient Syntheses of β -Cyanoketones via Conjugate Addition of Me_3SiCN to Aromatic Enones

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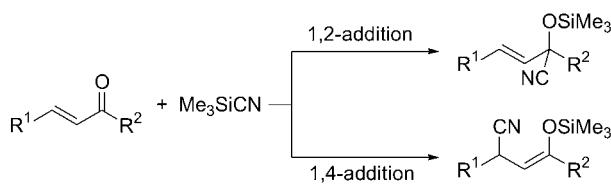
An efficient 1,4-addition of Me_3SiCN to aromatic enones has been achieved with excellent yields (91%—99%) using CsF (1 mol%) as the catalyst and H_2O (4 equiv.) as the additive in refluxing dioxane within 7 h. The perfect regioselectivity is proposed accounting from H_2O -facilitated reversion of the 1,2-adduct in the presence of CsF and subsequent irreversible 1,4-addition reaction.

Keywords 1,4-addition, regioselectivity, enones, cyanides, CsF

Introduction

Among the most widely used methods for the construction of carbon-carbon bonds are conjugate addition reactions of carbon nucleophiles to α,β -unsaturated carbonyl compounds.¹ While transition metal-catalyzed 1,4-addition of aryl² and alkyl reagents is well documented,³ the regioselective 1,4-addition rather than 1,2-addition of weak nucleophiles such as cyanide to α,β -unsaturated carbonyl compounds remains challenging (Scheme 1).

Scheme 1



In the literature, 1,4-addition of cyanide to enones has been widely employed in syntheses of biologically active molecules⁴ and complex natural products.⁵ In this framework, mild cyanide source such as Me_3SiCN ⁶ and Et_2AlCN ⁷ are frequently involved with catalysts such as Et_3Al ,^{6,9a} $\text{Pd}(\text{OAc})_2$,⁸ and Lewis acids.⁹ Ionic liquid and microwave have also been applied to this reaction in line of the concept of green chemistry.^{10,11} Recently, Shibasaki and co-workers developed an entirely distinct $\text{Ni}(0)$ -cyclooctadiene (COD) complex in the elegant synthesis of Tamiflu,¹² an anti-influenza drug, and subsequent $\text{Ni}(0)$ and $\text{Gd}(\text{OTf})_3$ as the cooperative catalyst in the 1,4-addition of Me_3SiCN to aliphatic enones with good substrate generality.¹³ The first catalytic enanti-

oselective version of conjugate addition of cyanide to enones is also described by Shibasaki.¹⁴ Despite these convincing achievements, practical regioselective 1,4-addition of Me_3SiCN to enones is still demanding.¹⁵

Due to special property and low nucleophilicity of fluoride ion, cesium fluoride is extensively used in organic synthesis.^{16–18} Though CsF -catalyzed silylcyanation of ketones¹⁷ and Michael reaction¹⁸ have been presented, to the best our knowledge, CsF is scarcely applied to the 1,4-addition of cyanide to α,β -unsaturated carbonyl compounds. Herein, we report in full length an efficient CsF -catalyzed 1,4-addition of Me_3SiCN to aromatic enones in the presence of water as well as the insight of the role of water.¹⁹

Results and discussion

Model reaction is conducted with chalcone (**1a**) and Me_3SiCN under argon. Initially, various catalysts are screened in dioxane at reflux temperature (Table 1). Without any catalyst added, just trace of product **2a** can be detected by TLC (thin layer chromatography) (Entry 1). Considering high affinity of silicon for fluoride anion,²⁰ we presume that fluorides could be used to activate Me_3SiCN in this transformation.¹⁶ Then, various fluorides are examined (Entries 2–4). Thus, 41% yield is obtained with hydrated KF (20 mol%, Entry 2) while Bu_4NF gives moderate 75% yield (Entry 3). Exhilaratingly, the reaction proceeds smoothly in the presence of CsF to afford the product **2a** in 92% yield (Entry 4). Comparing the results of KF and CsF , a possible ‘cesium effect’ cannot be ruled out.²¹ Nevertheless, a control experiment using CsCl yields the product in only 16% yield (Entry 5). More basic monohydrated CsOH

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gives an inferior result (Entry 6).

Table 1 Screening in the model reaction

 1a	$\xrightarrow[\text{(2) } 1 \text{ mol}\cdot\text{L}^{-1} \text{ HCl, r.t.}]{\text{(1) cat. (20 mol\%)} \text{ Me}_3\text{SiCN (2.2 equiv.) dioxane, reflux, 5.5 h}}$	 2a
Entry ^a	Catalyst	Yield ^b /%
1	none	trace
2	KF·2H ₂ O	41
3	Bu ₄ NF	75
4	CsF	92
5	CsCl	16
6	CsOH·H ₂ O	86

^a Reaction conditions: chalcone **1a** (0.15 mmol), Me₃SiCN (0.33 mmol, 2.2 equiv.), CsF (20 mol%), dioxane (1.5 mL), reflux, 5.5 h. ^b Isolated yield.

With CsF as the catalyst, the effects of solvent and reaction temperature on the model reaction are investigated (Table 2). First, various solvents are evaluated at reflux temperature (Entries 1–4). When CH₂Cl₂ is used as the solvent, no reaction happens (Entry 1). 30% yield is obtained in THF (Entry 3) while trace product in toluene (Entry 2). Although having similar boiling point to toluene, dioxane gives the excellent yield of 92% (Entry 4). Second, the effect of reaction temperature is examined in dioxane. Decrease of reaction temperature from 102 to 0 °C leads to sharp drop in yield (Entries 4–6). High temperature is required for high yield in dioxane.

Table 2 Effects of solvent and reaction temperature on the CsF-catalyzed 1,4-addition of Me₃SiCN to chalcone (**1a**)

 1a	$\xrightarrow[\text{(2) } 1 \text{ mol}\cdot\text{L}^{-1} \text{ HCl, r.t.}]{\text{(1) CsF (20 mol\%)} \text{ Me}_3\text{SiCN (2.2 equiv.) solvent, 5.5 h}}$	 2a	
Entry ^a	Solvent	Temp./°C	Yield ^b /%
1	CH ₂ Cl ₂	40	0
2	toluene	110	trace
3	THF	66	30
4	dioxane	102	92
5	dioxane	40	7
6	dioxane	0	0

^a Reaction conditions: chalcone **1a** (0.15 mmol), Me₃SiCN (0.33 mmol, 2.2 equiv.), catalyst (20 mol%), solvent (1.5 mL), 5.5 h.

^b Isolated yield.

To obtain the optimum reaction conditions further optimization focusing on catalyst loading and concentration of chalcone is performed (Table 3). Reasonably, as reducing catalyst loading from 20 mol% to 5 mol% without any additive at 0.1 mol·L⁻¹ concentration of chalcone, the yield of product **2a** decreases gradually from 92% to 84% with a longer reaction time (Entries

2–3 vs. Entry 1). Subsequent increasing the concentration of chalcone to 0.15 and 0.3 mol·L⁻¹, the model reaction produces lower yield even with a longer reaction time (Entries 4–6 vs. Entries 1–3). Considering proton might be needed to complete the reaction sequence, water as protonic additive is added (Entries 7–9). Dramatically, the reaction proceeds much fast and cleanly affording almost quantitative yields with 4 equiv. of water within 4 h even catalyst loading down to 1 mol% at concentrated conditions (Entries 7–9). Additionally, comparable result is obtained when the reaction is conducted under open-to-air conditions (Entry 9).

Table 3 Effects of catalyst loading and concentration of chalcone on the CsF-catalyzed 1,4-addition of Me₃SiCN to chalcone (**1a**)

 1a	$\xrightarrow[\text{(2) } 1 \text{ mol}\cdot\text{L}^{-1} \text{ HCl, r.t.}]{\text{(1) CsF (x mol\%)} \text{ Me}_3\text{SiCN (2.2 equiv.) dioxane, reflux}}$	 2a		
Entry ^a	CsF ^b /mol%	Concn. ^c / (mol·L ⁻¹)	Additive ^d / equiv.	Time/h
1	20	0.1		5.5
2	10	0.1		7
3	5	0.1		7
4	20	0.15		9.5
5	10	0.15		9.5
6	5	0.3		9.5
7	20	0.1	H ₂ O (4)	4
8	5	0.3	H ₂ O (4)	4
9 ^e	1	0.3	H ₂ O (4)	4

^a Unless otherwise noted, all reactions are conducted with chalcone (**1a**) and Me₃SiCN (2.2 equiv.) in refluxing dioxane under argon.

^b Relative to **1a**. ^c Concentration of chalcone. ^d Isolated yield. ^e Performed open to air.

To insight the role of additive, other proton resources are introduced into the reaction mixture with results listed in Table 4. Without any proton additive, the yield is 52% (Entry 1). Increasing the amount of H₂O from 0.3 to 1 equiv., the yield of **2a** increases gradually from 59% to 70% (Entries 2 and 3). Other proton sources such as alcohol and phenol (2,6-dimethylphenol) give inferior yields (Entries 4 and 5). It implies that H₂O is not only used to provide proton.²² The optimum yield is obtained with 4 equiv. of water (Entry 6). However, using excessive amount of H₂O reduces the yield (Entry 7).

With optimal reaction conditions in hands: enone (0.3 mmol), Me₃SiCN (2.2 equiv.), CsF (1 mol%), H₂O (4 equiv.), dioxane (1 mL), substrate concentration (0.3 mol·L⁻¹), at reflux reaction temperature, the substrate generality is evaluated (Table 5). In general, chalcone derivatives give excellent yields (91%–99%) at varying reaction rate (Entries 1–9). With electron-donating substituent, the reactions proceed slowly than chalcone

Table 4 Effect of protonic additive on the CsF-catalyzed 1,4-addition of Me_3SiCN to chalcone (**1a**)

Entry ^a	Additive ^b	Yield ^c /%	<chem>CC(=O)c1ccccc1C=Cc2ccccc2</chem>	<chem>CC(CN)C(=O)c1ccccc1C=Cc2ccccc2</chem>
			1a	2a
1 ^d	None	52		
2 ^d	H_2O (0.3 equiv.)	59		
3	H_2O (1 equiv.)	70		
4 ^d	<i>i</i> -PrOH (1 equiv.)	55		
5 ^d	DMP (1 equiv.)	64		
6	H_2O (4 equiv.)	99		
7	H_2O (0.2 mL)	77		

^a Conditions: **1a** (62.5 mg, 0.3 mmol), CsF (0.5 mg, 0.003 mmol, 1 mol%), Me_3SiCN (84 μL , 0.66 mmol, 2.2 equiv.), dioxane (1.0 mL), under argon, 4 h. ^b Relative to **1a**. ^c Isolated yield. ^d Quenched with 1 mol•L⁻¹ HCl. DMP=2,6-dimethylphenol.

(Entries 2—5 vs. Entry 1). On the other hand, electron-deficient α,β -unsaturated enones are converted into β -cyanoketones much faster (Entries 6—9). β -Alkyl substituted enone **1j** also gives excellent yield under the optimal reaction conditions (Entry 10). However, aliphatic enones can not be converted to the product under these conditions.

Table 5 Scope of substrate

Entry ^a	Product	Time/h	Yield ^b /%	<chem>CC(=O)c1ccccc1C=Cc2ccccc2</chem>	<chem>CC(CN)C(=O)c1ccccc1C=Cc2ccccc2</chem>
				1a — 1j	2a — 2j
1 ^{c,d}	2a R ¹ =Ph, R ² =H	4	99		
2	2b R ¹ = <i>o</i> -MeOC ₆ H ₄ , R ² =H	7	99		
3	2c R ¹ = <i>m</i> -MeOC ₆ H ₄ , R ² =H	5	99		
4	2d R ¹ = <i>p</i> -MeOC ₆ H ₄ , R ² =H	7	99		
5	2e R ¹ = <i>p</i> -MeC ₆ H ₄ , R ² =H	6	99		
6	2f R ¹ = <i>o</i> -ClC ₆ H ₄ , R ² =H	1.5	99		
7	2g R ¹ = <i>o,p</i> -Cl ₂ C ₆ H ₃ , R ² =H	1.5	99		
8	2h R ¹ = <i>m</i> -O ₂ NC ₆ H ₄ , R ² =H	1.5	91		
9	2i R ¹ = <i>o</i> -ClC ₆ H ₄ , R ² =NO ₂	1	93		
10	2j R ¹ =Me, R ² =H	1.5	97		

^a Conditions: enone (0.3 mmol), CsF (0.5 mg, 0.003 mmol, 1 mol%), Me_3SiCN (84 μL , 0.66 mmol, 2.2 equiv.), H_2O (22 μL , 1.2 mmol, 4 equiv.), dioxane (1.0 mL), under argon. ^b Isolated yield. ^c Comparable results are obtained under open-to-air condition. ^d Comparable results are obtained with 1.5 equiv. of Me_3SiCN .

In the literature, 1,4-regioselectivity of this reaction

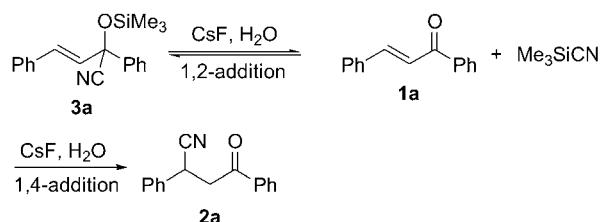
is based on the thermodynamic stability,⁷ cyanide rearrangement¹⁴ and kinetic control.¹³ Although CsF has been used to catalyze the 1,2-addition of Me_3SiCN to α,β -unsaturated ketones,^{17b} no 1,2-adduct is produced by TLC analysis during the course of the reaction under the present reaction conditions. It is supposed that 1,2-adducts should be rapidly converted into 1,4-adducts via certain way¹⁴ if they are formed in this protocol.

To the mechanistic insight, *O*-trimethylsilyl cyanohydrin **3a**, the 1,2-addition product,²³ is prepared and tested under the reaction conditions (Table 6). Those results indicate that H_2O presumably partly facilitates reversion of *in situ* formed 1,2-adduct (**3a**) back to **1a** in the presence of CsF, which is followed by the subsequent irreversible formation of 1,4-addition product **2a** in 65% yield (Entry 1 vs. Entry 2). Side evidence comes from that the reversion is restrained by additional 2.2 equiv. of Me_3SiCN which would drive the equilibrium to left side (Entry 3). However, no reaction occurs in the absence of CsF (Entries 4 and 5). Referring to Entry 1 in Table 4, it is concluded that water assists the catalyst CsF to convert enone into 1,4-adduct completely (Scheme 2). So, the key factors to the perfect 1,4-selectivity are: (1) CsF rapidly catalyzing irreversible 1,4-addition at high temperature, and (2) H_2O facilitating reversion of the possible 1,2-addition in the presence of CsF.

Table 6 Control experiments

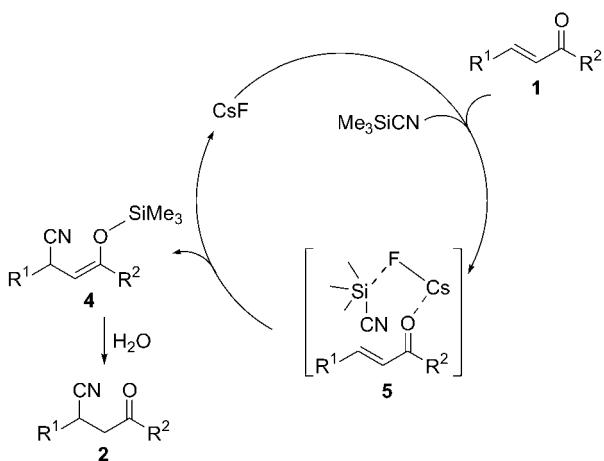
Entry ^a	H_2O (x equiv.) ^b	Me_3SiCN (y equiv.) ^b	<chem>CC(=O)c1ccccc1C=Cc2ccccc2</chem>	<chem>CC(CN)C(=O)c1ccccc1C=Cc2ccccc2</chem>	<chem>CC(=O)c1ccccc1C=Cc2ccccc2</chem>	<chem>CC(CN)C(=O)c1ccccc1C=Cc2ccccc2</chem>	<chem>CC(=O)c1ccccc1C=Cc2ccccc2</chem>
			1a ^c /%	2a ^c /%	4a ^d /%		
1	0	0	trace	0	0		
2	4	0	trace	65	0		
3	4	2.2	trace	10	0		
4 ^e	4	2.2	0	0	0		
5 ^e	4	0	0	0	0		

^a Reaction conditions: **3a** (30.7 mg, 0.1 mmol), dioxane (1 mL), under argon, 4 h. ^b Relative to **3a**. ^c Isolated yield. ^d Monitored by TLC. ^e Without CsF.

Scheme 2 Role of water

On the basis of experimental results, CsF is proposed to act as a bifunctional catalyst,²⁴ in which Me₃SiCN is activated by fluoride ion in a manner of hypervalent silicon intermediate and enone by cesium ion.²⁵ A plausible catalytic cycle is shown in Scheme 3. By taking advantage of the intensive studies on hypervalent silicon intermediates,²⁵ transition state **5** is formed. In this manner, the fluoride ion as a Lewis base might favor the formation of a pentacoordinate silicon intermediate with Me₃SiCN, meanwhile, the cesium ion as a Lewis acid might serve to activate the carbonyl substrate in the manner of dual activation.²⁴ The activated nucleophile and electrophile make the 1,4-addition easily to give the silyl enol ether **4** with high regioselectivity, which is also promoted by the subsequent protonation of **4** furnishing the corresponding product **2** and regenerating catalyst CsF.

Scheme 3 Proposed catalytic cycle



Experimental

¹H NMR spectra are recorded on a Bruker AVIII 400 spectrometer, operating at 400 MHz for ¹H NMR, and 100 MHz for ¹³C NMR. Chemical shifts for ¹H NMR and ¹³C NMR spectra are reported as δ downfield from Me₄Si and relative to the signal of CDCl₃. The IR spectra are recorded on a PerkinElmer Spectrum One with KBr pellets. The elemental analyses are performed on an Elementar Vario MICRO CUBE instrument. All melting points are determined on a XT4A melting point apparatus without correction. Analytical thin layer chromatography (TLC) is performed using F254 pre-coated silica gel plate. Column chromatography is performed with silica gel (200–300 mesh). Petroleum ether (PE) used has a boiling point range of 60–90 °C.

All reactions are carried out under argon atmosphere using typical vacuum-line techniques unless otherwise noted. Me₃SiCN and CsF are purchased from Alfa Aesar and used directly. All dry solvents are distilled under argon prior to use. Enones **1a**–**1j** are synthesized according to reported procedure.²⁶

General procedure for the 1,4-addition of Me₃SiCN to enones **1a**–**1j**

After CsF (0.5 mg, 0.003 mmol, 1 mol%), enone (**1**, 0.3 mmol), and 1 mL dioxane were placed in a dry Schlenk tube equipped with cold finger under argon, Me₃SiCN (84 μ L, 0.66 mmol, 2.2 equiv.) and H₂O (22 μ L, 1.2 mmol, 4 equiv.) were added. The reaction mixture was stirred at reflux until the reaction was completed (monitored by TLC). 2 mL H₂O was added, and the resulting mixture was extracted with EtOAc (5 mL) (Caution! HCN generated in the reaction mixture is highly toxic. Those operations should be conducted in a well-ventilated hood). The extract was washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated. The crude products were purified by flash chromatography on silica gel (PE-EtOAc, 20 : 1, V : V, unless otherwise noted) to afford pure products **2**.

4-Oxo-2,4-diphenylbutanenitrile (2a)¹¹ White solid, yield 99%, m.p. 120–122 °C (Lit.¹¹ 122–125 °C); ¹H NMR (CDCl₃, 400 MHz) δ : 3.52 (dd, J =6.0, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.74 (dd, J =8.0, 18.0 Hz, 1H, NCCHCH_AH_BCO), 4.57 (dd, J =6.0, 8.0 Hz, 1H, NCCHCH_AH_BCO), 7.34–7.49 (m, 7H, ArH), 7.58–7.62 (m, 1H, ArH), 7.92–7.94 (m, 2H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ : 31.9, 44.5, 120.6, 127.5, 128.1, 128.4, 128.8, 129.3, 133.9, 135.3, 135.8, 194.6; IR (KBr) v: 1681, 2236 cm⁻¹.

2-(2-Methoxyphenyl)-4-oxo-4-phenylbutanenitrile (2b)⁷ White solid, yield 99%, m.p. 84–86 °C; ¹H NMR (CDCl₃, 400 MHz) δ : 3.50 (dd, J =4.8, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.65 (dd, J =8.8, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.87 (s, 3H, OCH₃), 4.78 (dd, J =4.8, 8.8 Hz, 1H, NCCHCH_AH_BCO), 6.91–7.02 (m, 2H, ArH), 7.31–7.35 (m, 1H, ArH), 7.45–7.51 (m, 3H, ArH), 7.56–7.61 (m, 1H, ArH), 7.93–7.95 (m, 2H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ : 27.5, 42.2, 55.6, 111.0, 120.5, 121.1, 123.2, 128.1, 128.7, 129.0, 129.8, 133.6, 136.0, 156.3, 195.3; IR (KBr) v: 1685, 2245 cm⁻¹.

2-(3-Methoxyphenyl)-4-oxo-4-phenylbutanenitrile (2c)⁷ White solid, yield 99%, m.p. 106–108 °C; ¹H NMR (CDCl₃, 400 MHz) δ : 3.50 (dd, J =6.0, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.72 (dd, J =8.0, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.82 (s, 3H, OCH₃), 4.55 (dd, J =6.0, 8.0 Hz, 1H, NCCHCH_AH_BCO), 6.86–6.88 (m, 1H, ArH), 6.96–7.02 (m, 2H, ArH), 7.28–7.32 (m, 1H, ArH), 7.45–7.49 (m, 2H, ArH), 7.58–7.62 (m, 1H, ArH), 7.92–7.94 (m, 2H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ : 31.9, 44.5, 55.4, 113.3, 113.8, 119.6, 120.5, 128.1, 128.8, 130.4, 133.9, 135.8, 136.7, 160.2, 194.6; IR (KBr) v: 1678, 2236 cm⁻¹.

2-(4-Methoxyphenyl)-4-oxo-4-phenylbutanenitrile (2d)⁷ White solid, yield 99%, m.p. 111–113 °C (Lit.¹¹ 113–114 °C); ¹H NMR (CDCl₃, 400 MHz) δ : 3.49 (dd, J =6.4, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.73 (dd, J =7.6, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.80 (s, 3H, OCH₃), 4.53 (dd, J =6.4, 7.6 Hz, 1H, NCCHCH_AH_BCO), 6.89–6.92 (m, 2H, ArH), 7.33–7.36 (m, 2H, ArH), 7.45–7.49 (m, 2H, ArH), 7.57–7.61 (m, 1H, ArH), 7.91–

7.93 (m, 2H, ArH); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 31.2, 44.6, 55.4, 114.6, 120.9, 127.2, 128.1, 128.7, 128.8, 133.8, 135.8, 159.6, 194.7; IR (KBr) ν : 1677, 2234 cm^{-1} .

4-Oxo-4-phenyl-2-p-tolylbutanenitrile (2e)^{11,27}

White solid, yield 99%, 129—131 °C (Lit.¹¹ 135—137 °C); ^1H NMR (CDCl_3 , 400 MHz) δ : 2.35 (s, 3H, CH_3), 3.49 (dd, $J=6.4$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.70 (dd, $J=8.0$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 4.53 (dd, $J=6.4$, 8.0 Hz, 1H, NCCHCH_AH_BCO), 7.19 (d, $J=8.0$ Hz, 2H, ArH), 7.31 (d, $J=8.0$ Hz, 2H, ArH), 7.45—7.48 (m, 2H, ArH), 7.57—7.61 (m, 1H, ArH), 7.91—7.93 (m, 2H, ArH); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 21.0, 31.5, 44.6, 120.8, 127.4, 128.1, 128.8, 129.9, 132.3, 133.8, 135.8, 138.3, 194.7; IR (KBr) ν : 1674, 2239 cm^{-1} .

2-(2-Chlorophenyl)-4-oxo-4-phenylbutanenitrile (2f)^{7,28} White solid, yield 99%, m.p. 100—102 °C (Lit.²⁸ 106—108 °C); ^1H NMR (CDCl_3 , 400 MHz) δ : 3.53 (dd, $J=4.8$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.68 (dd, $J=9.2$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 4.93 (dd, $J=4.8$, 9.2 Hz, 1H, NCCHCH_AH_BCO), 7.29—7.38 (m, 2H, ArH), 7.42—7.50 (m, 3H, ArH), 7.58—7.62 (m, 1H, ArH), 7.67—7.69 (m, 1H, ArH), 7.94—7.96 (m, 2H, ArH); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 30.1, 42.4, 119.7, 127.8, 128.1, 128.8, 129.5, 129.9, 130.3, 132.7, 133.9, 135.6, 194.4; IR (KBr) ν : 1686, 2247 cm^{-1} .

2-(2,4-Dichlorophenyl)-4-oxo-4-phenylbutanenitrile (2g) White solid, yield 99%, m.p. 90—91 °C; ^1H NMR (CDCl_3 , 400 MHz) δ : 3.52 (dd, $J=4.8$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.67 (dd, $J=9.2$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 4.88 (dd, $J=4.8$, 9.2 Hz, 1H, NCCHCH_AH_BCO), 7.33—7.36 (m, 1H, ArH), 7.45—7.50 (m, 3H, ArH), 7.59—7.63 (m, 2H, ArH), 7.93—7.95 (m, 2H, ArH); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 29.7, 42.2, 119.3, 128.08, 128.11, 128.9, 130.1, 130.5, 131.3, 133.5, 134.0, 135.3, 135.5, 194.1; IR (KBr) ν : 1682, 2247 cm^{-1} . Anal. calcd for $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{NO}$: C 63.18, H 3.65, N 4.60; found C 63.06, H 3.73, N 4.65.

2-(3-Nitrophenyl)-4-oxo-4-phenylbutanenitrile (2h)

The purification of **2h** was performed by column chromatography with PE-EtOAc ($V:V$, 10 : 1) as the eluent. Yellowish solid, yield 91%, m.p. 132—133 °C; ^1H NMR (CDCl_3 , 400 MHz) δ : 3.61 (dd, $J=6.8$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.80 (dd, $J=6.8$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 4.72 (t, $J=6.8$ Hz, 1H, NCCHCH_AH_BCO), 7.47—7.51 (m, 2H, ArH), 7.59—7.64 (m, 2H, ArH), 7.83—7.85 (m, 1H, ArH), 7.92—7.94 (m, 2H, ArH), 8.20—8.23 (m, 1H, ArH), 8.33—8.34 (m, 1H, ArH); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 31.6, 43.9, 119.5, 122.8, 123.6, 128.1, 129.0, 130.4, 133.9, 134.2, 135.3, 137.4, 148.7, 193.8; IR (KBr) ν : 1680, 2245 cm^{-1} . Anal. calcd for $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$: C 68.56, H 4.32, N 9.99; found C 68.41, H 4.45, N 10.09.

2-(2-Chlorophenyl)-4-(4-nitrophenyl)-4-oxobutanenitrile (2i) The purification of **2i** was performed by column chromatography with PE-EtOAc ($V:V$, 10 : 1) as the eluent. White solid, yield 93%, m.p. 126—127

°C; ^1H NMR (CDCl_3 , 400 MHz) δ : 3.57 (dd, $J=4.4$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 3.71 (dd, $J=9.6$, 18.0 Hz, 1H, NCCHCH_AH_BCO), 4.93 (dd, $J=4.4$, 9.6 Hz, 1H, NCCHCH_AH_BCO), 7.33—7.40 (m, 2H, ArH), 7.44—7.46 (m, 1H, ArH), 7.69—7.71 (m, 1H, ArH), 8.10—8.13 (m, 2H, ArH), 8.32—8.35 (m, 2H, ArH); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 30.0, 42.9, 119.2, 124.1, 127.9, 129.2, 129.5, 130.2, 130.4, 132.1, 132.6, 139.9, 150.8, 193.1; IR (KBr) ν : 1691, 2252 cm^{-1} . Anal. calcd for $\text{C}_{16}\text{H}_{11}\text{ClN}_2\text{O}_3$: C 61.06, H 3.52, N 8.90; found C 61.88, H 3.84, N 8.87.

2-Methyl-4-oxo-4-phenylbutanenitrile (2j)¹⁴

Colorless oil, yield 97%; ^1H NMR (CDCl_3 , 400 MHz) δ : 1.35 (d, $J=6.8$ Hz, 3H, CH_3), 3.14 (dd, $J=6.4$, 17.2 Hz, 1H, NCCHCH_AH_BCO), 3.27 (dd, $J=6.4$, 13.2 Hz, 1H, NCCHCH_AH_BCO), 3.34 (m, 1H, NCCHCH_AH_BCO), 7.40—7.44 (m, 2H, ArH), 7.52—7.55 (m, 1H, ArH), 7.87—7.89 (m, 2H, ArH); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 17.9, 20.5, 42.2, 122.6, 128.0, 128.8, 133.8, 135.9, 195.1; IR (film) ν : 1686, 2236 cm^{-1} .

Conclusion

In conclusion, the highly regioselective 1,4-addition of Me_3SiCN to aromatic enones has been achieved with good substrate generality. The 1,4-adducts are obtained in excellent yields with 1 mol% of CsF as the catalyst and 4 equiv. of H_2O as the additive. Further mechanism elucidation and extension to asymmetric version of this protocol are under way in our group.

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