Chapter-III

Scandium(III) triflate catalyzed 1,4-addition of cyano group to enones using tetraethylammonium cyanide as the cyanide source

3.1 Lewis acid Sc(OTf)₃

The quest for better and efficient catalysts for various organic reactions, both new and old is never ending. In particular, Lewis acid catalysis has been extensively explored and continues to be, as evident by the plethora of books and publications in this area.¹ Among the requirements of a good Lewis acid catalyst, their ability to be used in catalytic amounts, stability, reusability as well as specificity in promoting just the desired reaction and none other are most important. Sc(OTf)₃ is a new type of Lewis acid that is different from other typical Lewis acids such as AlCl₃, BF₃, SnCl₄, etc. While most Lewis acids are decomposed or deactivated in the presence of water, Sc(OTf)₃ is more stable and works as a Lewis acid in water solutions. While the element scandium (Sc) is in group 3 and lies above La and Y, its radius is appreciably smaller than those of any other rare earth elements. The chemical behavior of scandium is known to be intermediate between that of aluminium and lanthanides.² Scandium has been uncommon probably due to the lack of rich sources and the difficulties in separation, and its use in organic synthesis is rather limited although unique characteristics might be expected. In 1993, Kobayashi was the first to introduce scandium trifloromethanesulfonate [Sc(OTf)₃] as a promising Lewis acid in organic synthesis.³,⁴

Most of the studies have shown that Scandium(III) triflate is an effective catalyst that is mild as well as nonhydrolysable in aqueous medium. It has been shown that Scandium(III) triflate can be used as a catalyst for a variety of organic
transformations.\textsuperscript{5} Scandium(III) triflate can be used in catalytic amounts, is stable up to 280 °C and can be easily recovered thus rendering itself as a reusable, safe and environmentally benign catalyst.\textsuperscript{6} It is also easily accessible by reacting either metallic scandium or its chloride with trifluoromethane sulfonic acid. Scandium(III) triflate has been extensively used for various condensation-cyclization reactions to afford the corresponding heterocycles, alkylation, Friedel-Crafts acylation, Fries rearrangement, Diels-Alder reaction, etc. It has also proved to be a superior catalyst for the Strecker reaction.\textsuperscript{7}

Many nitrogen-containing compounds such as imines and hydrazones are also successfully activated by using a small amount of Sc(OTf)\textsubscript{3} in both organic and aqueous solvents. In addition, Sc(OTf)\textsubscript{3} can be recovered after reactions and can be reused. While lanthanum triflate [Ln(OTf)\textsubscript{3}] has similar properties, the catalytic efficiency of Sc(OTf)\textsubscript{3} is higher than that of Ln(OTf)\textsubscript{3} in several cases. In this chapter, we have described a convenient method of cyanation of chalcones with TEACN using Sc(OTf)\textsubscript{3} as an efficient catalyst, where the 1,4- adducts were formed selectively.

3.2 Review of a few reported methods for the applications of Sc(OTf)\textsubscript{3} as catalyst

Aldol reactions in organic solvents

Sc(OTf)\textsubscript{3} was found to be an effective catalyst in aldol reactions of silyl enol ethers with aldehydes.\textsuperscript{8} The activities of typical rare earth triflates [Sc, Y and Yb(OTf)\textsubscript{3}] were evaluated with the reaction of 1-trimethylsiloxy cyclohexane and benzaldehyde in dichloromethane. While the reaction scarcely proceeded at -78 °C in the presence of Y(OTf)\textsubscript{3} and Yb(OTf)\textsubscript{3},\textsuperscript{9} the aldol adduct was obtained in 81% yield in the presence of Sc(OTf)\textsubscript{3}. 

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Aldol reactions in aqueous medium

The importance of aqueous reactions is now generally recognized, and development of carbon-carbon bond forming reactions that can be carried out in aqueous media emerges as one of the most challenging topics in organic synthesis.\textsuperscript{10,11} It was found that Sc(OTf)\textsubscript{3} was effective in the aldol reactions of silyl enolates with aldehydes in aqueous media (water/THF).\textsuperscript{8} The reactions of aromatic and aliphatic aldehydes such as benzaldehyde and 3-phenylpropanaldehyde with silyl enolates were successfully carried out in aqueous solvents.

The Michael addition reactions of silyl enol ethers or ketene silyl acetals with $\alpha$, $\beta$-unsaturated carbonyl compounds are among the most common carbon-carbon bond forming processes in organic synthesis. Sc(OTf)\textsubscript{3} was found to be an effective and reusable catalyst in these reactions.\textsuperscript{12} The reactions proceed smoothly in the presence of catalytic amount of Sc(OTf)\textsubscript{3} under extremely mild conditions to give the corresponding 1,5-dicarbonyl compounds in high yields after acid work-up.
Scheme 3.3. Sc(OTf)₃ catalyzed Michael reactions of silyl enol ethers with α, β-unsaturated carbonyl compounds

Allylation reactions

Synthesis of homoallylic alcohols by the reaction of organometallic allyl compounds is one of the most important processes in organic synthesis.¹² The allylation reactions of carbonyl compounds with tetrallyltin proceeded smoothly under the influence of a catalytic amount of Sc(OTf)₃¹³ to afford the homoallylic alcohols, in high yields under extremely mild conditions.¹⁴

Scheme 3.4. Sc(OTf)₃ catalyzed allylation reactions of carbonyl compounds

Friedel-Crafts acylation and Fries rearrangement

While Friedel-Crafts acylation reactions are fundamental and important processes in organic synthesis as well as in industrial chemistry,¹⁵ more than a stoichiometric amount of a Lewis acids such as AlCl₃ or BF₃ is needed due to the consumption of the Lewis acid by the coordination with the aromatic ketones produced. But a small amount of Sc(OTf)₃ was enough to catalyze the Friedel-Crafts acylation reactions.¹⁶,¹⁷ The catalytic activity of Sc(OTf)₃ was found to be much higher than that of Ln(OTf)₃ in this case too.
Diels-Alder reaction

The Diels-Alder reaction is one of the most useful synthetic conversions used to form cyclic structures. Diels- Alder reaction is reversible, and the lowest quantity of catalysts allow the reaction to proceed at room temperature or below with satisfactory yields.\textsuperscript{18}

Asymmetric Sc(OTf)\textsubscript{3} catalysts

Recently, some efficient asymmetric Diels-Alder reactions catalyzed by chiral Lewis acids have been reported.\textsuperscript{19} Although rare-earth compounds were expected to be promising Lewis acid reagents, only a few asymmetric Diels-Alder reactions were catalyzed by chiral rare-earth Lewis acid triflates especially, Yb(OTf)\textsubscript{3} and Sc(OTf)\textsubscript{3}. The chiral Scandium catalyst could be prepared from Sc(OTf)\textsubscript{3}, (R)-BINOL, and a tertiary amine in dichloro methane.\textsuperscript{20} The catalyst was also found to be effective for the Diels-Alder reactions of an acrylic acid derivative with dienes.
Kobayashi et al. have reported a chiral scandium catalyst for enantioselective Diels-Alder reactions. This catalyst prepared from scandium triflate \((\text{Sc(OTf)}_3)\), (R)-(+)-1,1-bi-2-naphthol, and a tertiary amine in dichloromethane, was quite effective in the enantioselective Diels-Alder reaction of acyl-1,3-oxazolidin-2-ones with dienes, and the corresponding Diels-Alder adducts were obtained in high yields with high diastereo- and enantioselectivities.\(^{20,21}\)

![Fig. 3.1. Chiral scandium catalyst](image)

Scheme 3.7. Chiral scandium catalyst in Diels-Alder reaction

3.3 Chalcones

Chalcones are the main precursors for the biosynthesis of flavonoids and isoflavonoids.\(^{22}\) Chalcones comprise of a three carbon \(\alpha\), \(\beta\)-unsaturated carbonyl system. These are the condensation products of aromatic aldehydes with acetophenones in the presence of a catalyst.\(^{23}\) They undergo a variety of chemical reactions and are found beneficial in the synthesis of pyrazoline, isoxazole and pyrimidine, an assortment of heterocyclic compounds. Chalcones play pivotal role in synthesizing a range of remedial compounds. Chalcones act as mediators in the synthesis of beneficial therapeutic compounds. Special attention has been given to
chalcones due to their simple structures and diverse pharmacological activities. Worth mentioning activities of chalcones are in antiinflammatory, antifungal, antibacterial, antimalarial, antitumor, antimicrobial, antiviral, antitubercular, antioxidant, antimitotic, antileishmanial, antiplatelet, anticancer and antihypertensive activities.

Owing to the above stated reasons, the synthesis of chalcones and chalcone based functionalized derivatives had remained primary objective for a long time. They have exhibited impressive curative efficacy for the treatment of numerous diseases. Chalcone based derivatives have gained focus since they possess simple structures and sundry pharmacological actions. A number of techniques and schemes have been reported for the synthesis of these compounds. Chalcones and their derivatives find application as

< Artificial sweeteners, scintillator
< Polymerization catalyst, fluorescent whitening agent, organic brightening agent, stabilizer against heat, visible light, ultraviolet light and aging.
< 3,2’,4’,6’-tetrahydroxy-4-propoxy-dihydrochalcone-4-β-neohesperidoside has been used as a synthetic sweetener and is 2200 times sweeter than glucose.
< Chalcones are reactive towards several reagents e.g. (a) phenyl hydrazine, (b) 2-amino thiophenol, etc.
< The chalcones have been found useful in elucidating structure of natural products like hemlock tannin, cyanomaclurin, ploretin, eriodictyol, homo eriodictyol, naringenin, etc.
3.3.1 Chemistry of chalcones

The name “Chalcones” was given by Kostanecki and Tambor.\(^{48}\) The chemistry of Chalcones has generated intensive scientific studies throughout the world, especially, interest has been focused on the synthesis and biodynamic activities of chalcones. These compounds are also known as benzalacetophenone or benzyldene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcone bears a very good synthon so that a variety of novel heterocycles with good pharmaceutical profile can be designed. Chalcones are unsaturated ketones containing the reactive ketoethylenic group –CO-CH=CH-. These are coloured compounds because of the presence of the chromophore -CO-CH=CH-, and the colour depends on the presence of other auxochromes. Different methods are available for the preparation of chalcones.\(^ {49}\) Chalcones are used to synthesize several derivatives like cyanopyridines, pyrazolines isoxazoles and pyrimidines having different heterocyclic ring systems.\(^ {50}\)

![Fig. 3.2. Chemical structure of chalcone](image)

3.3.2 Nomenclature of Chalcone

Different methods of nomenclatures for chalcone were suggested at different times. The following pattern has been adopted by “Chemical Abstracts” published by American chemical society.

![Fig. 3.3. Nomenclature of chalcone](image)
3.3.3 General synthetic methods of chalcones

Claisen-Schmidt reaction

A variety of methods are available for the synthesis of chalcones and the most convenient method is the one that involves the Claisen-Schmidt condensation of equimolar quantities of a substituted acetophenone with substituted aldehydes in the presence of aqueous alcoholic alkali. Amongst all the stated methods, Aldol condensation and Claisen-Schmidt condensation still hold high position. Other renowned techniques include Suzuki reaction, Wittig reaction, Friedel-Crafts acylation with cinnamoyl chloride, Photo-Fries rearrangement of phenyl cinnamates, etc.

In the Claisen-Schmidt reaction, the concentration of alkali used usually ranges between 10 and 60 %. The reaction is carried out at about 50 °C for 12-15h or at room temperature for one week. Under these conditions, the Cannizaro Reaction also takes place and thereby decreases the yield of the desired product. To avoid the disproportionation of aldehyde in the above reaction, the use of benzylidene-diacetate in the place of aldehyde has been recommended.
3.4 1,4-Addition on α, β-unsaturated compounds

1,4-Conjugate addition of nucleophiles to the β-position of α, β-unsaturated carbonyl compounds is one of the most frequently used reactions for bond formation. Originally⁵⁷ the Michael reaction was restricted to the conjugate addition of an enolate to an α, β-unsaturated carbonyl group. Michael donors that contain active methylene centers can be directly applied, whereas simple carbonyl compounds had generally to be activated into more reactive species such as enolates or enamines. Now “Michael reaction” is often referred to the 1,4-addition of every nucleophile and a prefix indicating the nucleophilic species is generally added (e.g., oxo-, thia- or aza- for oxygen, sulfur and nitrogen nucleophiles, respectively). However 1,4-conjugate addition reaction is the most correct name. Among the most powerful methods in asymmetric synthesis is the enantioselective 1,4-addition of carbon nucleophiles to α, β-unsaturated compounds in which a C-C bond and a new stereogenic centre are formed.⁵⁸ Conjugate addition has developed into one of the most widely used methods for asymmetric carbon-carbon bond formation in organic chemistry. This transformation involves the reaction of a nucleophile and α, β-unsaturated system activated by an electron-withdrawing group (EWG). The addition takes place at the β-carbon of the unsaturated system, resulting in the formation of a stabilized carbanion. After protonation of the carbanion, the β-adduct is formed with a single stereogenic centre, whereas quenching with an electrophile (E⁺) results in the α, β-di-substituted product with two newly created stereocentres.

A typical problem associated with conjugate addition to α, β-unsaturated carbonyl compounds is the regioselectivity of the nucleophilic addition. Addition of a soft nucleophile occurs preferably at the β- or 4-position of the unsaturated system,
resulting in the 1,4-adduct, while 1,2-addition is favoured if hard nucleophiles are used (Scheme 3.10).

![Scheme 3.10. Addition of hard or soft nucleophiles to α, β-unsaturated carbonyl compounds](image)

The first example of an un-catalyzed conjugate addition reaction was reported in 1883 by Kommenos where he described the addition of diethyl sodiomalonate to diethyl ethyldienemalonate. The tremendous versatility and scope of the Michael addition using a variety of (soft) nucleophiles and the copper-mediated conjugate addition of a range of (hard) organometallic reagents, as well as various related methods, are testimony to the importance of these C-C bond formations.

![Scheme 3.11. 1,4-Conjugate addition of α, β-unsaturated carbonyl compounds](image)

3.5 Importance of nitriles in organic chemistry

The cyano group serves as a stable and useful key functional group for the synthesis of biologically important compounds. The reduction of the nitrile group (RCN), depending on the nature of the reducing agent and experimental conditions, can produce amines, aldehydes, primary alcohol, imines or alkanes (RCH₃ or RH).
Hydrogen cyanide (HCN) was the most commonly used industrial reagent for the introduction of cyano group.\textsuperscript{61} However, due to toxicity and to follow abundant precautions in handling HCN, newer methods have been developed to substitute it with other potentially less harmful and easily manageable reagents. Cyanide sources like, trimethylsilyl cyanide (TMSCN), tetrethyl ammonium cyanide (TEACN), tetrabutyl ammonium cyanide, etc., along with or without catalysts have been reported for the introduction of cyano group.\textsuperscript{62} Depending on the reaction conditions, the hydrocyanation of unsaturated carbonyl compounds lead to \(\beta\)-cyanoketones, \(\beta\)-cyano-cyanohydrins, or vinyl cyanohydrins as a result of 1,2- or 1,4-additions.\textsuperscript{63} The conjugate addition of cyano to \(\alpha\), \(\beta\)-unsaturated carbonyl compounds is one of the most important carbon-carbon bond formation reactions because, the resulting \(\beta\)-cyano adducts can be converted into biologically important \(\gamma\)-amino butyric acids under reducing conditions (GABA analogues).\textsuperscript{64} The conjugate hydrocyanation reaction of enones is recently employed for the total synthesis of natural products like terpenes, alkaloids, steroids etc.\textsuperscript{65}

The reactions of enones with TMSCN in the presence of base catalysts provided selectively the 1,2-adducts which also serve as a method of protection of the carbonyl groups.\textsuperscript{66} In contrast, employing Lewis acid catalysts such as \(\text{Et}_2\text{AlCN},\textsuperscript{67} \text{Et}_3\text{Al},\textsuperscript{68} \text{AlCl}_3,\) \(\text{SnCl}_2,\textsuperscript{69} \text{Pd(OAc})_2,\textsuperscript{70}\) ionic liquids\textsuperscript{71} and microwave irradiation,\textsuperscript{72} resulted in the selective 1,4-additions. Recently, Shibasaki and co-workers employed \(\text{Ni(0)}\) and \(\text{Gd(OTf})_3\) as the co-catalysts in the 1,4-addition of cyanide using TMSCN, and the catalytic enantioselective conjugate addition of cyanide to enones was also disclosed.\textsuperscript{73} Asymmetric catalytic hydrocyanation of \(\alpha,\beta\)-unsaturated ketones by using \(\text{Me}_3\text{SiCN}\) and \([\text{Ru(phgly})_2(\text{binap})]/\text{Li salt}\) has been
very recently reported.\textsuperscript{74} Yanagisawa and co-workers described that, un-activated arylalkenes could be effectively converted to benzylic nitriles in the presence of triflic acid and TMSCN.\textsuperscript{75} Very recently, Fu-Xue Chen and co-workers reported the 1,4-addition of TMSCN to enones in presence of Cs\textsubscript{2}CO\textsubscript{3} and CsF catalysts.\textsuperscript{76} Despite these achievements, practical regioselective 1,4-hydrocyanation of enones using newer cyanide sources is still demanding. Scandium(III) triflate has been extensively used as an efficient Lewis acid catalyst for various organic reactions.\textsuperscript{77}

3.5.1 Review of literature for the 1,4-conjugative addition of cyano group to \( \alpha, \beta \)-unsaturated carbonyl compounds

Yasutaka Ishii et al., reported a new method using acetone cyanohydrin and isopropenyl acetate for the hydrocyanation of carbonyl compounds catalyzed by Cp\textsuperscript{+}Sm(thf)\textsubscript{2} under ambient conditions.\textsuperscript{78}

![Scheme 3.12. Hydrocyanation of carbonyl compounds with acetone cyanohydrins](image)

The Michael addition of hydrogen cyanide to \( \alpha, \beta \)-unsaturated carbonyl compounds was promoted by Cp\textsuperscript{+}Sm(thf)\textsubscript{2}. Several \( \alpha, \beta \)-unsaturated carbonyl compounds were reacted with acetone cyanohydrin in the presence of Cp\textsuperscript{+}Sm(thf)\textsubscript{2} at room temperature for 15h.\textsuperscript{78}

![Scheme 3.13. Hydrocyanation of enones with acetone cyanohydrin](image)
Fu-Xue Chen et al., have described the facile enantioselective 1,4-addition of TMSCN to aromatic enones using chiral sodium phosphate. Thus, in presence of 20mol% of sodium salt generated in-situ from (R)-3,3’-di(1-diadamandyl)-1,1’-binapthyl-2-2’-diylphosphoric acid and NaOH, β-cyano ketones were obtained at 80 °C in toluene.79

![Scheme 3.14. Asymmetric 1,4-addition of cyanide to chalcones](image)

Cyanotrimethylsilane added to α, β-unsaturated ketones in conjugative manner under the catalytic action of Lewis acid as triethylaluminium, aluminium chloride and SnCl₂. Hydrolysis of the products yielded β-cyano ketones which were identical to the hydrocyanated products of the starting enones.80

![Scheme 3.15. Lewis acid catalyzed synthesis of β-cyano ketones](image)

Eric Jacobsen et al., have reported highly enantioselective conjugative cyanation of unsaturated imides using co-operative dual catalysis. Reactions were carried out for 24h at room temperature in presence of dual catalyst and trimethylsilylcyanide as cyanide source.81

![Scheme 3.16. Asymmetric hydrocyanation of unsaturated imides using co-operative dual catalyst](image)
3.6 Results and Discussion

Earlier methods for 1,4-addition of cyano group to α, β-unsaturated compounds used cyanide sources like trimethylsilylcyanide, KCN, NaCN, with various metal and Lewis acid catalysts. Further, most of these methods will liberate free HCN making them not environmentally friendly and require more safety protocols. Herein, we report a simple, convenient and milder method for the 1,4-addition of cyanide to α, β-unsaturated enones using tetraethylammonium cyanide as the cyanide source using Sc(OTf)₃ as the Lewis acid catalyst without the liberation of any HCN. This method selectively leads to 1,4-addition of cyanide to enones resulting in moderate to high yield of the products. The reaction procedures were easy and in most of the cases the products were obtained in high purity that needed no further purification processes.

![Scheme 3.17. Sc(OTf)₃-catalyzed 1,4-addition of TEACN with chalcones](image)

In order to determine the most appropriate reaction conditions and to evaluate the efficiency of scandium(III) triflate as catalyst for the hydrocyanation, synthesis of 4-oxo-2,4-diphenylbutanenitrile was taken as a model reaction (Entry 8, Table 3.3). Among the tested solvents, DMF (Table 3.1, Entry 5) gave the best results for the hydrocyanation of (E)-chalcone (1.0 equiv) using TEACN (1.0 equiv) and Sc(III) triflate (30% weight of chalcone taken).
The use of chlorinated solvents like DCM, EDC, CHCl₃, etc., or hydrocarbons as solvent did not provide good yields of the expected product.

Table 3.1. Effect of solvent in the 1,4-addition of cyano group to enones with TEACN/Sc(III) triflate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>Sc(III)OTf</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>Sc(III)OTf</td>
<td>12</td>
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</tr>
<tr>
<td>3</td>
<td>EDC</td>
<td>Sc(III)OTf</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>Sc(III)OTf</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>Sc(III)OTf</td>
<td>2-3</td>
<td>72-92</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>Sc(III)OTf</td>
<td>3-6</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
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</tr>
<tr>
<td>8</td>
<td>DCM</td>
<td>Sc(III)OTf</td>
<td>8</td>
<td>27</td>
</tr>
</tbody>
</table>

*All reactions were conducted with 30% of catalyst, 1 mmol of chalcone (benzylidene acetophenone) and 1 mmol of TEACN in 30 vol. of solvent.

This may be attributed to the poor solubility of TEACN in these solvents which has resulted in a heterogeneous reaction mixture (TEACN is not freely soluble in non-polar solvents) leading to the reduction in its reactivity. It is noteworthy that the order of addition of reagents was also very important for the success of the reaction. Initially, a mixture of TEACN and chalcones should be prepared in DMF at -5 °C to 0 °C by stirring for 10min followed by the addition of scandium(III) triflate. If scandium(III) triflate has been added at the beginning, no reaction was observed. The catalytic activities of various triflates and other catalysts were also investigated using a loading of 30% of the respective catalyst (Table 3.2) wherein, almost all of the catalysts (except Scandium(III) triflate) studied were found to be ineffective for the cyano addition to chalcones with TEACN as cyanide source. Though the TMS(OTf) gave modest yield of the desired product (Entry 3), it is having difficulty in
handling due to its ready hydrolysis. Zn(OTf)₂ afforded only a trace of the product whereas, the other lanthanide triflate, namely, the ytterbium triflate also resulted in moderate yields leading to the conclusion that Sc(III) triflate is the promising catalyst for this reaction.

Table 3.2. Effect of different catalysts on 1,4-addition of cyano group to enones with TEACN/ Sc(III) triflate

<table>
<thead>
<tr>
<th>Entryᵃ</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(III) OTf</td>
<td>2-3</td>
<td>72-92</td>
</tr>
<tr>
<td>2</td>
<td>Yb(III) OTf</td>
<td>2-3</td>
<td>30-40</td>
</tr>
<tr>
<td>3</td>
<td>TMS (OTf)</td>
<td>3-6</td>
<td>56-70</td>
</tr>
<tr>
<td>4</td>
<td>Zn(OTf)₂</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>Iodine</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
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<td>TFA</td>
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<tr>
<td>8</td>
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<td>--</td>
</tr>
<tr>
<td>9</td>
<td>TBAF</td>
<td>12</td>
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</tbody>
</table>

ᵃAll reactions were conducted with 30% of catalyst, 1 mmol of chalcone (benzylideneacetophenone) and 1 mmol of TEACN in 30 vol. of solvent.

In order to extend the scope of the scandium(III) triflate catalyzed hydrocyanation reaction, various chalcones were subjected to the reaction (Table 3.3). Interestingly, no substituent effects on the yields were noted. Thus, the chalcones with either electron withdrawing or electron donating groups at any positions, gave the 1,4-adducts in good to moderate yields (Table 3.3, Entries 1-14). It was observed that no 1,2-adduct was obtained in any of the reactions. In order to clarify the scope and limitation of the present method, some reactions of the enones other than chalcones were performed under same reaction conditions. Unfortunately, cyclohexenone and α, β-unsaturated esters such as methyl cinnamate did not undergo 1,4-addition at all, and the starting materials were recovered.
The mechanism of the reaction is not completely understood at this stage. However, since the order of the addition of reagents is crucial for the success of the reaction, we can give a reasonable explanation as shown in the Scheme 3.18. It has been observed that if scandium(III) triflate is added at the beginning no reaction takes place. Besides, there should be an induction period of 10min after addition of TEACN to chalcones and before addition of the triflate salt. These two facts indicate that a weak interaction is needed between chalcone and TEACN at the beginning of the reaction to initiate the transfer of cyano group. Once scandium(III) triflate is added it coordinates with the carbonyl oxygen and helps the delocalization of electron through a six member cyclic transition state (Scheme 3.18) and in this course the cyanide is added in 1,4-fashion rather than the 1,2-fashion. Finally, during quenching the neutral product is generated. This model thus takes into account the importance of the order of addition of reagents and selectivity of the reaction. If scandium(III) triflate is added at the beginning it gives rise to a strong interaction with the carbonyl oxygen and does not allow the TEACN salt to interact with the chalcone. Hence no reaction takes place.
Table 3.3. Synthesis of 4-oxo-2,4-diphenylbutanenitrile derivatives

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Chalcones</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield&lt;sup&gt;c&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
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<td><img src="image" alt="Chalcone 1a" /></td>
<td>3</td>
<td><img src="image" alt="Product 2a" /></td>
<td>74&lt;sup&gt;y&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Chalcone 1b" /></td>
<td>3</td>
<td><img src="image" alt="Product 2b" /></td>
<td>72&lt;sup&gt;y&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Chalcone 1c" /></td>
<td>3</td>
<td><img src="image" alt="Product 2c" /></td>
<td>75&lt;sup&gt;y&lt;/sup&gt;</td>
</tr>
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\*All reactions were conducted with 30% of catalyst, 1 mmol of chalcone and 1 mmol of TEACN in 30 volume of dry DMF. \*New compounds, \*Isolated yield.

3.7 Conclusion

The present investigation has demonstrated that the use of TEACN/scandium(III) triflate offers a novel, simple, and convenient method for the conversion of wide varieties of chalcones to their corresponding β-cyanoketones, without the liberation of HCN gas. This method shows excellent selectivity giving the 1,4-adduct in good yields. The ready availability of the reagents, easy handling of them, the absence of generation of HCN during the reaction, mild reaction conditions and high yield of the product make this method attractive for direct synthesis of cyano substituted 1,4-adducts from enones.
3.8 Experimental Section

All the melting points of the products were measured on an Buchi melting point (B-545) apparatus. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Bruker 400MHz instrument using CDCl\(_3\) as the solvent with tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on an Agilent 6330 ion trap instrument. Elemental analysis for C, H and N were obtained using a Vario-microcube CHN-O-Rapid analyzer. TEACN from Alfa Aesar (purity > 97%), and Scandium(III) triflate from Aldrich (purity>98%) were used as procured.

3.8.1 General synthetic procedure

The chalcones used in the present study have been prepared as per literature procedures. TEACN (0.075gm, 0.48 mmol) was dissolved in DMF (3 mL, 30 vol) at room temperature, then cooled to -5 °C to 0 °C. To that, chalcone (0.1gm, 0.48 mmol) was added and stirred maintaining the temperature between -5 °C to 0 °C for 10min and then, Sc(III) triflate (0.03gm, 30% weight of chalcones taken) was added at 0 °C, and the reaction mixture was slowly warmed to 25 °C. It was stirred for appropriate time at 25 °C under N\(_2\) atmosphere. The reaction was monitored by thin layer chromatography. After completion (about 3h), the reaction mixture was quenched with 5 mL water and extracted with diethyl ether (3×5 mL). The combined organic layer was dried (over anhydrous MgSO\(_4\)), filtered, concentrated and purified by column chromatography with silica gel 230-400 mesh (hexane/ethyl acetate 8:2) to give the desired product.

3.8.2 Spectral data

4-Oxo-4-phenyl-2-(2-(trifluoromethyl)phenyl)butanenitrile (Entry 1, Table 3.3):

Yellow Colour Oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 3.42\) (dd, J = 3.6, 18.0 Hz,1H),
3.72 (dd, J = 10.4, 18.0 Hz, 1H), 4.89 (dd, J = 3.6, 10.4 Hz, 1H), 7.48–7.54 (m, 3H, ArH), 7.62–7.65 (t, 1H, ArH), 7.67–7.71 (t, 1H, ArH), 7.74–7.76 (d, 1H, ArH), 7.84–7.86 (d, 1H, ArH), 7.95–7.97 (d, 1H, ArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 28.81, 44.70, 120.01, 123.79 (q, J = 273.82 Hz, CF$_3$), 126.84 (q, J = 6.03 Hz, ortho carbon to CF$_3$), 127.61, 127.92, 128.12, 128.75, 129.88, 132.95, 133.96, 135.43, 193.91 ppm. $^{19}$F NMR (376 MHz, CDCl$_3$) δ = −59.22 ppm. MS: m/z = 303.29 (M)$^+$. Anal. Calcd. for C$_{17}$H$_{12}$F$_3$NO: C: 67.33; H: 3.99; N: 4.62%; Found: C: 67.30; H: 3.93; N: 4.64%.

2-(5-Chloro-2-(trifluoromethyl)phenyl)-4-oxo-4-phenylbutanenitrile (Entry 2, Table 3.3): Yellow pasty mass. $^1$H NMR (400 MHz, CDCl$_3$): δ = 3.43 (dd, J = 4, 18 Hz, 1H), 3.77 (dd, J = 10.4, 18 Hz, 1H), 4.89 (dd, J = 3.6, 10.4 Hz, 1H), 7.46–7.49 (t, 3H, ArH), 7.61–7.64 (m, 1H, ArH) 7.68–7.73 (d, 1H, ArH), 7.83 (s, 1H, ArH), 7.95–7.99 (d, 2H, ArH) ppm. $^{13}$C NMR (100.66 MHz, CDCl$_3$) δ = 28.74, 44.41, 119.46, 123.51 (q, J = 273.79 Hz, CF$_3$), 126.24 (q, J = 31.2 Hz, C-CF$_3$), 128.28 (q, J = 5Hz, Ortho carbon to CF$_3$) 128.62, 128.91, 129.07, 130.18, 134.15, 135.25, 135.90, 136.53, 139.40, 193.50 ppm. MS: m/z = 337.04 (M)$^+$. Anal. Calcd. for C$_{17}$H$_{13}$ClF$_3$NO: C: 60.46; H: 3.28; N: 4.15%; Found: C: 60.43; H: 3.26; N: 4.18%.

2-(4-Bromo-2-fluorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 3, Table 3.3): White solid; mp = 118.2–119.7 ºC, $^1$H NMR (300 MHz, CDCl$_3$): δ = 3.56 (dd, J = 5.73, 18 Hz, 1H), 3.72 (dd, J = 8, 18 Hz, 1H), 4.70 (dd, J = 5.7, 7.8 Hz, 1H), 7.26–7.34 (m, 2H, ArH ), 7.43–7.51 (m, 3H, ArH), 7.59–7.64 (m, 1H, ArH), 7.91–7.94 (d, 2H, ArH) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ = 26.35, 42.05, 118.92, 119.59, 119.91, 121.32, 123.04, 128.02, 128.82, 130.73, 134.00, 135.32, 159.64
(broad d, J = 251.25Hz, F attached Carbon), 194.07 ppm. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -114.04$ppm. MS: m/z = 332.17 (M)$^+$. Anal Calcd. for C$_{16}$H$_{11}$BrFNO: C: 57.85; H: 3.34; N: 4.22%. Found: C: 57.82; H: 3.31, N: 4.25%.

2-(4-Fluorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 4, Table 3.3): White Solid; mp = 100.7–101.6 °C (lit. $^{82,83}$ mp 101.9-102.5 °C); $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 3.51$ (dd, J = 6.3, 18 Hz,1H), 3.71 (dd, J = 7.5, 18 Hz, 1H), 4.55–4.59 (t, 1H), 7.05–7.10 (m, 2H, ArH), 7.38–7.58 (m, 5H, ArH), 7.60–7.61 (dd, 2H, ArH), ppm.$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta = 31.19, 44.44, 116.26, 120.46, 128.08, 128.87, 129.28, 131.05, 133.99, 135.62, 162.53$ (broad d, J = 246.75Hz, F attached Carbon), 194.41 ppm.$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -112.04$ppm. MS:m/z = 253.27 (M)$^+$. Anal. Calcd. for C$_{16}$H$_{12}$F NO: C: 75.88; H: 4.78; N: 5.53%; Found: C: 75.86; H: 4.76, N: 5.51%.

2-(3-Chlorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 5, Table 3.3): Yellow Solid; mp = 101–102.8 °C, $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 3.50$ (dd, J = 6.4, 18 Hz,1H), 3.71 (dd, J = 7.2, 18 Hz, 1H), 4.58 (dd, J= 7.2, 14 Hz, 1H), 7.35–7.44 (m, 3H, ArH), 7.45–7.49 (m, 1H, ArH), 7.56–7.67 (m, 2H, ArH), 7.90–7.92 (m, 1H, ArH ), 7.99–8.04 (m, 1H, ArH), 8.01–8.10 (m, 1H, ArH) ppm.$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 31.32, 44.31, 119.7, 127.75, 128.23, 128.84, 129.43, 129.90, 130.04, 132.41, 133.8, 135.61, 194.42 ppm. MS: m/z = 269.32 (M)$^+$. Anal. Calcd. for C$_{16}$H$_{12}$ClNO: C: 71.25; H: 4.48; N: 5.19%; Found: C: 71.28; H: 4.45, N: 5.16%.

2-(4-Chlorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 6, Table 3.3): White Solid; mp = 111.2–111.9 °C, (lit. $^{82,84}$ mp 112-113 °C);$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 3.50$ (dd, J = 6.4 19.6 Hz,1H), 3.71 (dd, J = 7.2, 14.4 Hz, 1H), 4.57 (dd, J = 6.58, 13.6 Hz,1H), 7.35–7.44 (m, 3H, ArH), 7.59–7.62 (m, 1H, ArH), 7.90–7.93 (m, 2H,
ArH), 7.99–8.01 (m, 2H, ArH), 8.01–8.10 (dd, 1H, ArH) ppm. $^{13}$C NMR (100MHz, CDCl$_3$) δ = 31.32, 44.33, 120.96, 126.82, 128.50, 128.56, 128.61, 128.67, 128.97, 133.77, 134.06, 134.48, 135.55, 194.43 ppm. MS: m/z = 269.32 (M$^+$). Anal. Calcd. for C$_{16}$H$_{12}$Cl NO: C: 71.25; H: 4.48; N: 5.19%; Found: C: 71.28; H: 4.45, N: 5.16%.

4-Oxo-4-phenyl-2-p-tolylbutanenitrile (Entry 7, Table 3.3): White Solid; mp = 129.3–131.7 °C, (lit.$^{82,83,80b}$ mp 129-131 °C); $^1$H NMR (400 MHz, CDCl$_3$): δ = 2.42 (s, 3H), 3.41 (dd, J = 5.2, 17.2 Hz, 1H), 3.74 (dd, J = 9.2 18 Hz, 1H), 4.71 (dd, J = 5, 8.8 Hz,1H), 7.20–7.27 (m, 2H, ArH),7.28–7.29(m, 1H, ArH), 7.46–7.51(m, 3H, ArH),7.61–7.93 (m, 1H, ArH),7.94–7.96 (m, 2H, ArH) ppm.$^{13}$C NMR (100 MHz, CDCl$_3$) δ = 19.27, 28.75, 43.10, 120.72, 127.04, 127.50, 128.13, 128.48, 128.87, 131.27, 133.40, 133.94, 135.68, 194.77 ppm. MS: m/z = 249.32 (M$^+$). Anal Calcd. for C$_{17}$H$_{15}$NO: C: 81.90; H: 6.06; N: 5.62%; Found: C: 81.87; H: 6.00, N: 5.59%.

4-Oxo-2,4-diphenylbutanenitrile (Entry 8, Table 3.3): White Solid; mp = 121–123.4 °C, (lit.$^{82,83}$ mp 122-125 °C);$^1$H NMR (400 MHz, CDCl$_3$): δ = 3.49 (dd, J = 6, 18.0 Hz,1H), 3.70 (dd, J = 8, 18.0 Hz,1H), 4.56 (dd, J = 6.0, 8.0 Hz,1H), 7.34–7.49 (m, 7H, ArH), 7.57–7.60 (m, 1H, ArH), 7.89–7.92 (m, 2H, ArH)ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 31.38, 44.31,120.9, 127.5, 128.09, 128.88, 128.95, 129.45, 134.03, 135.3, 135.8, 194.6 ppm. MS: m/z = 235.29 (M$^+$). Anal. Calcd. for C$_{16}$H$_{13}$NO: C: 81.68; H: 5.57; N: 5.95%; Found: C: 81.64; H: 5.53, N: 5.98%.

4-(1-Cyano-3-oxo-3-phenylpropyl)benzonitrile (Entry 9, Table 3.3): Yellow Solid; mp = 134.7–135.2 °C, (lit.$^{83}$ mp 136.8-137.3 °C); $^1$H NMR(400 MHz, CDCl$_3$): δ = 3.55 (dd, J = 6.8, 18 Hz ,1H), 3.75 (dd, J = 6.8, 18 Hz, 1H) , 4.67 (dd, J = 6.8, 13.8 Hz, 1H), 7.46–7.50 (m, 2H, ArH), 7.58–7.61 (m, 3H, ArH), 7.69–7.71 (m, 2H, ArH), 7.90–7.92 (m, 2H, ArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) δ =
28.97, 43.82, 113. 34, 128.11, 128.44, 129.61, 129.85, 129.50, 131.27, 133.03, 133.96, 194.96ppm. MS: m/z = 260.30(M)⁺. Anal. Calcd. for C₁₇H₁₂N₂O: C: 78.44; H: 4.65; N: 10.76 %; Found: C: 78.40; H: 4.63, N: 10.64%.

2-(2,4-Dichlorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 10, Table 3.3):
White Solid; mp = 89.2–90.1 °C, (lit.⁸⁸ mp 90-91 °C); ¹H NMR (400 MHz, CDCl₃): δ = 3.53 (dd, J = 4.6, 18 Hz, 1H), 3.69 (dd, J = 9.2, 18.0 Hz, 1H), 4.88 (dd, J = 5.2, 12.0 Hz, 1H), 7.34–7.37 (m, 1H, ArH), 7.40–7.48 (m, 3H, ArH), 7.65–7.69 (m, 2H, ArH), 7.72–7.74 (m, 1H, ArH), 7.93–7.95 (m, 1H, ArH) ppm.¹³C NMR (100 MHz, CDCl₃) δ = 28.91, 44.68, 118.9, 126.86, 128.10, 128.72, 128.85, 129.87, 131.30, 132.92, 133.96, 135.2, 135.5, 193.86, ppm. MS: m/z = 303.39 (M)⁺. Anal. Calcd. for C₁₆H₁₁Cl₂ NO: C: 63.18; H: 3.65; N: 4.60 %. Found: C: 63.12; H: 3.71, N: 4.64%.

2-(2-Chlorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 11, Table 3.3): White Solid; mp = 107.1–108.4 °C, (lit.⁸⁶ mp 106-108 °C); ¹H NMR (400 MHz, CDCl₃): δ = 3.50 (dd, J = 6.4, 18 Hz, 1H), 3.71 (dd, J = 7.2, 18 Hz, 1H), 4.57 (dd, J = 8, 12 Hz, 1H), 7.35–7.39 (m, 4H, ArH), 7.40–7.49 (m, 2H, ArH), 7.59–7.62 (m, 1H, ArH), 7.91 (dd, J = 1, 8.4 Hz, 2H, ArH) ppm.¹³C NMR (100 MHz, CDCl₃) δ = 31.38, 44.31, 119.7, 127.4, 128.09, 128.88, 128.95, 129.45, 130.7, 132.6, 134.0, 135.9, 194.3 ppm. MS: m/z = 269.014(M)⁺. Anal. Calcd. for C₁₆H₁₂ClNO: C: 71.25; H: 4.48; N: 5.19 %; Found: C: 71.21; H: 4.43, N: 5.16%.

2-(4-Methylnaphthalen-1-yl)-4-oxo-4-phenylbutanenitrile (Entry 12, Table 3.3):
Yellow Solid Mp = 132.4–134.7 °C, ¹H NMR (400 MHz, CDCl₃): δ = 2.71 (s, 3H), 3.56 (dd, J = 4, 18 Hz, 1H), 3.86 (dd, J = 9.6, 18 Hz, 1H), 5.31 (dd, J = 3.8, 10 Hz, 1H), 7.35–7.37 (m, 1H, ArH), 7.44–7.46 (m, 2H, ArH), 7.48–7.61 (m, 3H, ArH), 104
7.67–7.69 (m, 1H, ArH), 7.93–7.96 (m, 3H, ArH), 7.97–8.07 (m, 1H, ArH) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$) δ = 19.517, 28.971, 43.836, 12.79, 122.51, 125.54, 125.61, 126.13, 126.86, 128.15, 128.83, 129.73, 133.29, 133.90, 135.70, 194.98 ppm; MS: m/z = 299.38 (M$^+$). Anal. Calcd. for C$_{21}$H$_{17}$NO: C: 84.25; H: 5.72; N: 4.68; O: 5.34%; Found: C: 84.28; H: 5.69, N: 4.68%.

4-(4-Bromophenyl)-4-oxo-2-phenylbutanenitrile (Entry 13, Table 3.3): Yellow Solid; mp = 119.4–121.5 °C, (lit.$^{82}$ mp 122-124 °C); $^1$H NMR (400 MHz, CDCl$_3$): δ = 3.45 (dd, J = 6, 18 Hz, 1H), 3.68 (dd, J = 8, 19.6 Hz, 1H), 4.54 (dd, J = 7.2, 8 Hz, 1H), 7.34–7.43 (m, 5H, ArH), 7.60–7.62 (m, 2H, ArH), 7.77–7.79 (m, 2H, ArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 31.28, 44.50, 120.30, 127.48, 128.0, 128.49, 129.04, 129.35, 129.56, 132.22, 134.20, 135.05, 194.28 ppm. MS: m/z = 314.18 (M$^+$). Anal Calcd. for C$_{18}$H$_{12}$BrNO: C: 61.17; H: 3.85; N: 4.46%; Found: C: 61.15; H: 3.88, N: 4.49%.

4-(3-Bromophenyl)-4-oxo-2-phenylbutanenitrile (Entry 14, Table 3.3): Yellow Solid; mp = 85.7–86.4 °C (lit.$^{82}$ mp 86–87 °C); $^1$H NMR (400 MHz, CDCl$_3$): δ = 3.45 (dd, J = 6, 18 Hz, 1H), 3.69 (dd, J = 8, 19.6 Hz, 1H), 4.52 (dd, J = 5.97, 18 Hz, 1H), 7.36–7.45 (m, 5H, ArH), 7.70–7.72 (m, 2H, ArH), 7.80–7.84 (m, 2H, ArH) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) δ = 31.28, 44.50, 120.30, 127.45, 128.0, 128.46, 129.01, 129.35, 129.56, 132.22, 134.23, 135.05, 194.28 ppm. MS: m/z = 314.18 (M$^+$).
3.8.3 Spectra for novel compounds

Fig. 3.4. $^1$H and $^{13}$C-NMR spectra of 2-(4-fluorophenyl)-4-oxo-4-phenyl butanenitrile
(Entry 4, Table 3.3)
Fig. 3.5. $^{19}$F-NMR spectrum of 2-(4-fluorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 4, Table 3.3)
Fig. 3.6. $^1$H and $^{13}$C-NMR spectra of 4-oxo-4-phenyl-2-(2 ( trifluoromethyl)phenyl)butanenitrile.  
(Entry 1, Table 3.3)
Fig. 3.7. $^{13}$C-NMR spectrum (expansion) of 4-oxo-4-phenyl-2-(2-(trifluoromethyl)phenyl)butanenitrile (Entry 1, Table 3.3)
Fig. 3.8. $^1$H and $^{13}$C NMR spectra of 2-(5-chloro-2-(trifluoromethyl)phenyl)-4-oxo-4-phenylbutanenitrile (Entry 2, Table 3.3)
Fig. 3.9. $^{13}$C-NMR spectrum (expansion) of 2-(5-chloro-2-(trifluoromethyl) phenyl)-4-oxo-4-phenylbutanenitrile (Entry 2, Table 3.3)
Fig. 3.10. $^1$H and $^{13}$C-NMR spectra of 2-(4-bromo-2-fluorophenyl)-4-oxo-4-phenylbutanenitrite
(Entry 3, Table 3.3)
Fig. 3.11. $^{13}$C-NMR spectrum (expansion) of 2-(4-bromo-2-fluorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 3, Table 3.3)
Fig. 3.12. $^{19}\text{F}-\text{NMR}$ spectrum (expansion) of 2-(4-bromo-2-fluorophenyl)-4-oxo-4-phenylbutanenitrile (Entry 3, Table 3.3)
3.9 References


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