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Temperature-controlled Mukaiyama aldol reaction of cyclododecanone (CDD) with aromatic aldehydes promoted by TMSCI via $(TMS)_3\text{Si-intermediate generated in situ}$

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An alternative path with temperature dependency for obtaining direct chemo, regio and diastereoselective monobenzylidene and $\beta$-hydroxy carbonyl derivatives, has been developed. In the present work, an attempt has been made to synthesize a precursor containing organometallic compound trimethylsilyl chloride (TMSCI) and cyclododecanone (CDD). Unexpectedly, this precursor exhibited temperature dependent chemoselective structures. At 35-40°C, in situ formation of super silyl groups (TTMSS) from trimethylsilyl chloride stabilized the positive charge on the $\alpha$-corner (C) side (sterically hindered side) of CH$_2$ group (1b) in zwitterionic CDD, leading to monobenzylidene derivatives (enones). At -20°C, interestingly, TMSCI stabilized silyl enol ether, which in turn produced $\beta$-hydroxy carbonyl derivatives (Mukaiyama aldol product) in $\alpha$-less hindered (S) side (sterically less hindered side) of the CH$_2$ group. When we tried the reaction with TTMSSH instead of TMSCI, we failed to get either enones or aldol addition products. Tris(trimethylsilyl)silyl (TTMSSH) stabilized the positive charge on the $\alpha$-less hindered (S) side of the CH$_2$ group. In the present protocol, the formation of monobenzylidene derivatives occurred in one step, whereas the methods available so far have involved more than three steps. From this, it is clear that temperature is the only factor that changes the course of the reaction. In order to get diastereoselectivity in Mukaiyama aldol reaction, sodium iodide was added. In monobenzylidene derivatives, the E-isomer is predominant (97-99 %) while in the case of Mukaiyama aldol product, the anti-isomer is predominant (85-99 %).

Introduction

Although aldol reaction is one of the most versatile tools for creating new carbon-carbon bonds $^1$, its utility has several limitations because it is very difficult to control the course of the reaction $^2$. It has been known for a long time that silyl enol ethers are useful intermediates in organic synthesis as well as in the synthesis of natural products $^3$. In many aldol reactions, even though the equilibrium is centered on the aldol anion, the reaction could not be controlled, and many times undesirable products were formed by self or poly condensation $^{1b-d}$. Different methodologies have been devised to get chemo, regio and diastereoselective aldol products in cyclic (5-8) and acyclic ketones $^{4a-d}$. Wittig developed direct aldol reaction procedure using enolate intermediate in the place of lithio derivatives and some interesting applications were also developed by other chemists $^{4e}$. For example, enol ether derivatives $^5$, enol ether/acetalts $^5$, enol silyl ethers/TiCl$_4$ $^{4c}$, Li-Me enol ether $^{6a}$, TiCl$_4$-n-Bu$_3$NI $^{6b}$ or with various catalysts $^{6c}$, trimethylsilyl triflates $^7$ have proven the usefulness of regio, and sometimes diastereoselective synthesis of aldol-type compounds. Unless some deliberate measures are taken for stereoselectivity, the enolate anions with different metal cations do not undergo controlled aldol reactions. Finally, preformed lithium $^8$, aluminum $^9$, boron $^{10}$, tin $^{11}$, zirconium enolates $^{12a}$, MeLi/TMS-enol ethers $^{12b}$ and TiCl$_4$ – Bu3N-mediated aldol reactions $^{12}$ were also received much attention in relation to the stereochemical problems. Consequently, the preparation of the enones usually requires more than two steps $^{13}$, i.e. aldol addition followed by dehydration $^{14}$.

The aldol addition is readily reversible $^{15}$ and hence, to avoid this, the Mukaiyama approach starting from the –OTMS of the ketone $^{16}$ has gained prominence $^{17}$. Silylation of the ketone introduced another step and lowered the atom economy $^{18}$. Many new methodologies have been developed to get enones selectively by using preformed alkenyl trichloroacetates in the presence of dibutyltin dimethoxide in THF/CH$_2$OH $^{19}$. The recent success of tris(trimethylsilyl)silyl-governed aldehyde cross-aldol cascade reaction $^{19d}$ and syn 1,3-diol $^{19e}$ has led to high diastereoselectivity. The “super silyl group” is superior to the organotin and tributyltin groups for tuning the aldol reactions $^{19c,d}$. The treatment of commercially available vsiodomeric ketone $^{20}$ with carbonyl compounds in the presence of enol silyl ether/Ni (CO)$_3$ at 80°C produced the corresponding enones in less yield $^{20}$. A freshly prepared N-(1-cyclohexen-1-yl)morpholine reacted with benzaldehyde in the presence of toluene at reflux condition yielding enone $^{21}$. Kreher and coworkers reported the monoarylidene derivatives using 12 mol equiv of N,N-
dimethylammonium N',N'' dimethylcarbamate (DIMCARB) as a catalyst to stabilize the aminal followed by the addition of aldehyde to get high selectivity of E and Z isomers 22. All the reaction procedures attracted only the small ring cyclic (5-8) and acyclic ketones.

In large ring ketones, certain catalysts do not work much efficiently 23. This prompted us to select CDD 23,24. We recently reported a new series of unique aldol reactions in CDD, and we have tried to extend that method for the preparation of monobenzylidene derivative. We have been struggling to get acyclic ketones.

Unsymmetrical and sterically hindered ketones such as (TBS) enol ethers were found to give predominantly fluoro-mediated generation of nucleophiles has been reported five decades back, when Zakharkin et al., 25 reported that cyclododecanone is known for W shaped zwitter ion in solution

Therefore, an alternative synthetic approach for the preparation of the monobenzylidene derivative. We have been struggling to get acyclic ketones. Efficiently dimethylammonium N',N'' dimethylcarbamate (DIMCARB) as a catalyst to the tune of 5 mol% was required for the completion of the reaction even after 3 days.

We found that Mukaiyama aldol reaction using organosilane reagent was the most suitable one for the current study. Therefore, an alternative synthetic approach for the preparation of aldol condensation and addition products was separately developed with temperature dependency in one-pot manner. This aldol reaction showed a number of fascinating properties, the full details of which are illustrated in scheme 1.

Scheme 1 Protocols for formation of chemo, regio and diastereoselectivity of C＝C & C＝C bond formation.

**Results and discussion**

Cyclododecanone is known for W shaped zwitter ion in solution phase 26, and the organometallic reagent TTMSS (from in situ generation of TMSCl) forms a bond with keto group of CDD, since TMSCl is known for homobond cleavage of Si-CI linkage. The exploitation of this property for protonolysis of Si-O 27 has been known for a long time, and the potential of the fluoro-mediated generation of nucleophiles has been demonstrated in regio-specific enolate formation. 28 This work involved chloro-mediated enolate formation. The N-heterocyclic carbenes were also demonstrated as catalysts for the formation of corresponding silyl enol ether at 23°C in THF regio-specifically.

In symmetrical ketones TMSCl and tert-butyldimethylsilyl (TBS) enol ethers were found to give predominantly E isomer. 29 Unsymmetrical and sterically hindered ketones such as propiophene, 2-methylcyclohexanone and cyclobutanone 30 afforded the mixture E/Z-silyl enol ether mainly consisting of Z-isomer, and this selectivity also held true for the reaction with 3-pentanone. 31 In the case of 3-pentanone, a catalyst to the tune of 5 mol% was required for the completion of reaction even after 3 days.

<table>
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<th>Entry</th>
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<th>Yield %</th>
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<td>-</td>
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<td>4</td>
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<td>EtOH</td>
<td>70</td>
<td>48</td>
<td>18</td>
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*Unless otherwise noticed, the reaction was carried out using various catalysts, CDD (5 mmol), and parent benzaldehyde 2d (5 mmol) in different solvents at different temperature for 24-48 h. 10 mol% piperidine was used. N-methylimidazole 10 mol% was used. The reaction was carried out at -20°C. Immediate addition (i.e. without preformed enolate) of 2d mixture of product (anti/syn: 50/50) 1 equiv. of Na was added. 1 isolated yield.

The reaction between cyclododecanone and parent benzaldehyde (2d) was examined with respect to a variety of acids, bases, metal salts and metal oxides as catalysts, and with various solvents. In all the cases, product was not formed (Table 1, entries 1-11). However, NH2OAc initiated the reaction but the consumption of the starting materials at 70°C in EtOH was sluggish. It led to the mixture of products mainly consisting of macro acyclic Mannich product 32 and very less amount of enones, as shown in Table 1, entries 12-14 (10-18 %), and in scheme 2. In some instances, HCl gas gave chemo selective product 33 of enones. But this method too did not work in our experiment even after passing HCl gas for a long time (Table 1, entry 15). In our earlier work, the aldol addition reaction in cyclododecanone 23 proceeded with strong bases such as NaOH, LiOH & KOH at ambient temperature Table 1, entries 16 & 17.

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But the enones were not formed.

Scheme 2 Synthesis of enone from cyclododecanone and aldehydes catalyzed by NH$_2$OAc

Hence, two extreme reaction conditions using temperature as a key factor for getting enone and aldol product (Mukaiyama aldol product) are illustrated in Table 2 & 3. Chlorotrimethylsilane was used to get the chemo, regio and stereo controlled products in case of both enone and aldol product. Enone was formed on treatment of CDD with chlorotrimethylsilane in CH$_2$CN at 35-40°C with stirring for 18 hours and on adding benzaldehyde 2d to the reaction mixture (yield 83% with high diastereoselectivity (E/Z >99/1)) for 26 hours as shown in Table 1, entry 24. Aldol reaction in cyclic or acyclic ketones with carbonyl compounds in the presence of TMSCl/acid, ketone could give the silylating as well as aldol addition products but not enone. But in the case of CDD, catalyst (in situ generation of TTMSS from TMSCl) played a major role, both in selectivity and yield, under the given reaction condition (35-40°C).

Hence, using the optimum reaction condition (Table 1, entry 24) we employed the Mukaiyama aldol reaction in the presence of sodium iodide 38a at low temperature. NaI was added to get the diastereoselectivity. We tried the same reaction with tris(trimethylsilyl) silane (TTMSSH) instead of TMSCl (Table 1, entry 25) but the reaction did not proceed, and we failed to get either enone or aldol addition product due to steric hindrance of cyclododecanone and bulkiness of the super silyl groups (TTMSSH). This is in line with the report by Ramachandran et al., that enolization of tert-butyl 2-phenylacetate with bulky group TTMSSH. This is in line with the report by Ramachandran et al., that enolization of tert-butyl 2-phenylacetate with bulky group

The Mukaiyama aldol reaction was preformed with (cyclododecyl)trimethylsilane 1c (Table 3) (CDD/NaI equiv. molar ratio) and benzaldehyde 2d as a model reaction, where the TMSCl was employed as the one of the reactants. This synthetic protocol gave satisfactory results (5) when the reaction was carried out with 2 equivalents of TMSCl/NaI under stirring condition for 8 hours at -20°C. In some instances, immediate addition (i.e. without preformed enolate) of 2d to CDD/TMSCl/NaI led to the mixture of product (1:1 anti/syn product). This problem was specific when the amount of TMSCl was small (1 equiv) as shown in Table 1, entry 18. Another point of interest demonstrated by the present reaction condition to controlling the stereoechemical course of the reaction by adding NaI was due to the formation of stable 1c $^{34}$. From these points, it is very clear that TMSCl/NaI/CH$_2$CN (2 equiv.) played a crucial role in Mukaiyama aldol addition reaction and that the reactions (Table 1, entry 24) were quite clean under the optimum condition described above.

We carried out the Mukaiyama aldol reaction under conventional condition, i.e. after the isolation of (cyclododecyl)trimethylsilane 1c or (cyclohex-1-en-1-yloxy)trimethylsilane and reacted with benzaldehyde 2d in the presence of 2 equivalent of TMSCl and 1 equivalent of NaI or 2 equivant of TMSCl in CH$_2$CN stirring at room temperature or -20°C yielded Mukaiyama aldol product in both the cases as shown in Scheme 3. We try to prepare tris(methylsilylenol ether of cyclododecanone under the similar condition but we couldn’t get the expected intermediate.

Scheme 3 Synthesis of Mukaiyama aldol or enone from isolated silyl enol ether of CDD and benzaldehyde.

Table 2. shows the Chemo selective synthesis of monobenzylidenecyclododecanones (enones) derivatives at room temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>R = alkyl or aryl</th>
<th>3</th>
<th>T/h</th>
<th>Yield (%)</th>
<th>E/Z (%)</th>
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<tbody>
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<td>n-C$_3$H$_7$</td>
<td>3a</td>
<td>22</td>
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<td>1/99</td>
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<tr>
<td>2</td>
<td>n-C$_3$H$_7$</td>
<td>3b</td>
<td>20</td>
<td>87</td>
<td>1/99</td>
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<tr>
<td>3</td>
<td>Iso-C$_3$H$_7$</td>
<td>3c</td>
<td>21</td>
<td>70</td>
<td>1/99</td>
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<td>C$_6$H$_5$</td>
<td>3d</td>
<td>26</td>
<td>83</td>
<td>99/1</td>
</tr>
<tr>
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<td>2-CH$_2$-C$_6$H$_5$</td>
<td>3e</td>
<td>24</td>
<td>87</td>
<td>99/1</td>
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<tr>
<td>6</td>
<td>2-OCH$_3$-C$_6$H$_5$</td>
<td>3f</td>
<td>28</td>
<td>65</td>
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ARTICLE TYPE

Monobenzylidene product formation

The versatility of the protocol was fully established by evaluating a variety of aldehydes as shown Table 2&3 respectively. By employing cyclododecanone as the nucleophile, a wide range of the substituent patterns with electron-donating and withdrawing substituents on aromatic ring were well tolerated. It afforded the desired enone product 3 with moderate to good yield and high selectivity (Table 2, 3a-3r, 53% to 87% yield, E/Z = 97/3 to >99). The selectivity was reverse in the case of aliphatic aldehydes such as propionaldehyde, isopropylaldehyde and n-butylaldehyde (Z/E = 99%). In general, aromatic substituted aldehydes gave higher yields than the aliphatic one. The formation enones was practically not possible in other ketones (5-8 homologues and acyclic ketones) due to the non-formation of Mukaiyama aldol products.

Mukaiyama aldol products

As evident from Table 3, the product yield and the selectivity depended on the benzaldehyde ring substituent and its bulkiness. Unsubstituted benzaldehyde and 1-naphthaldehyde yielded only anti isomer predominantly (>99 %) but the yield was decreased in 2u (1-naphthaldehyde) when compared to 2d (benzaldehyde). All the electron withdrawing and donating substituents on para position gave relatively higher yield (>80 %) and good selectivity (>99 anti isomer) compounds 5l, 5m, 5o, 5r, 5t.

Table 3. Anti&regio-selective Mukaiyama aldol reactions of cyclododecanone with aldehyde using TMSCl as catalyst at -20°C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R = aryl</th>
<th>5</th>
<th>T/h</th>
<th>Yield (%)</th>
<th>anti/syn (%)</th>
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<td>1</td>
<td>C₆H₅</td>
<td>2d</td>
<td>24</td>
<td>81</td>
<td>99/1</td>
</tr>
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</table>

*a Unless otherwise noted, all the reaction were carried out with CDD 1 (5 mmol), benzaldehydes 2 (5 mmol) and TMSCl (10 mmol) in 2 mL of dry CH₂CN at 35-40°C; given all the compounds are isolated yield; chemo and E/Z isomer ratio were determined by ¹H NMR. The compounds 3a-c having Musk odor.
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caused a mixture of anti and syn Mukaiyama aldol product (50%) only.

Plausible mechanism

Formation of enone: The enones were formed through preformed 1-(trimethylsiloxy)-1-cyclododecene at the α-corner (C) side of CDD ring. Hence, we decided to isolate the 1-(trimethylsiloxy)-1-cyclododecene, and for this, we carried out reaction in CDCl₃ with CDD (5 mmol) and TMSCl (10 mmol) at 35-40°C for 18 hours with stirring. After 18 hours, the crude mixture (CDCl₃ portion) was analyzed by NMR spectroscopy. The NMR result revealed that 1-(trimethylsiloxy)-1-cyclododecene had not been formed. It showed that α-corner side CH₃ group of carbon atom containing hydrogen atoms were strongly affected, and also that variation in the splitting pattern occurred due to the coordination of electrophilic silicon to the C side of CH₃ group and also the TMSCl was completely converted into intermediate of Tris(trimethylsilyl)siloxy-CDD 1b (TTMSS-CDD). This discussion has been held to be true since in ¹³C spectra also the C side of CH₃ was shifted to about 2 ppm in shielding region and C=O groups were shifted to about 2 ppm in shielding region from the original one (CDD) as shown in the supporting information. The above results supported that the formation of CDD-super silyl groups intermediate 1b without any doubts as shown in figure 1.

TTMSS stabilized the mobile equilibrium of CDD, and this might be due to one electron-transfer mechanism ¹⁹. One electron transfer took place from Si-metal ¹⁹ to the C side of the CH₃ group and the oxonium ion (C=O) coordinated with an electrophilic silicon atom of TTMSS where excess of chloride atom acted as a counter anion (1b) as shown in figure 2. However, it was confirmed that the CDD existed as zwitter ion.

The literature reports confirm that in the solution phase, the cyclododecanone was in W-shape zwitter ion state ²⁰, which was in mobile equilibrium with shifting of positive charge between C side CH₃, carbon atom of CDD and α-less hindered (S) side CH₂. TTMSS stabilized the positive charge on the C side of the CH₃ group. The first, mechanistic detail of the 1b induced reactions was investigated to clarify the transformation of electrons from silicon atom to the C side of CH₂ group in CDD.

Hence, removal of the TTMSS was done by a simple workup. The reaction mixture was diluted with hexane and the solvent was removed, and the obtained white solid was analyzed by NMR. The results were compared with original one (pure CDD). The ¹H NMR spectrum of CDD showed different splitting patterns for C side CH₃ and α-less hindered (S) side CH₂. Two specific pentets were given for these two CH₃ groups as shown in figure S1A ²⁵. Whereas in the case of CDD, it reacted with TMSCl (in situ generation of TTMSS). The ¹H NMR spectrum showed one triplet (A) and one sextet (B), clearly indicating that the shifting of positive charge was stabilized by TTMSS, and therefore we got a triplet in C side of CH₃ group (figure S1B).

Next, we carried out the reaction between preformed 1b and activated TTMSS-benzaldehyde 3d generating a siloxocarbenium ion intermediate 1d. The carbonyl group of benzaldehyde (2) approached the CDD from C side of the CH₂ group. TTMSS was released from 1d to the reaction medium to give Tris(trimethylsilyl)silyl aldolate 1e (confirmed by ¹H & ¹³C NMR shown in SI) by the intramolecular transfer of chloride.
anion (-Cl) to the silicon atom. Hence, the intermolecular hydrogen bond formation between C=O and OH of aldol adduct was negligible due to backward pointing of OH to the C=O group and bulkiness of the super silyl groups (TTMSS), thereby preventing the aldol adduct formation in sterically congested CDD ring. Hence, we obtained a dehydrated product which was formed by overcoming the H-bond formation. Therefore, we infer that the in situ formation of TTMSS from TMSCl plays a major role in the formation of enones.

Figure 1: The reaction was carried out in CDCl$_3$ and the NMR recorded in CDCl$_3$. (a) Spectrum of commercially available TTMSSH (b) Spectrum indicating cyclododecanone (c) Spectrum indicating the stabilization of positive charge on the α-corner side of the CH$_2$ group after the removal of silyl groups. (d) Spectrum of in situ formation of TTMSS-CDD intermediate 1b (e) Spectrum indicating the formation of TTMSS-CDD (1bb) from TTMSSH and this has stabilized the positive charge on the α-less hindered side of the CH$_2$ group. (f) Spectrum indicating the in situ formation of TTMSS-CDD from TMSCl after the addition of benzaldehyde and it can generate a siloxocarbenium ion intermediate 1e (g) Formation of TTMSS-CDD from TTMSSH and after the addition of benzaldehyde it has not generated the siloxocarbenium ion aldol adducts (The full spectrum has been given in supporting information).

In situ formation of tris(trimethylsilyl)siloxy-cyclododecanone 1b (TTMSS-CDD) was confirmed by formation of tris(trimethylsilyl)siloxy-cyclododecanone 1bb (TTMSS-CDD) from commercial sources of tris(trimethylsilyl)isilane (TTMSSH). The reaction was simultaneously carried out using commercially available Tris(trimethylsilyl)isilane (TTMSSH) and cyclododecanone at same reaction conditions to confirm the formation of TTMSS-CDD (1b) intermediate. It clearly indicated that TTMSS-CDD was formed, but the stabilization of positive charge occurred in α-less hindered side (1bb) instead of α-corner side (1b), and this has been identified from $^1$H & $^{13}$C NMR spectrum. It showed that the marginal peak shifted from 1b and the original one (CDD). After the addition of benzaldehyde 2, the expected product was not formed (either enone or aldol addition) and this could be due to the bulkiness of the super silyl group (TTMSSH) and ring strain in the CDD ring. The resulting attachment of TTMSSH to CDD in α-less hindered side prevented the attack of carbonyl carbon of benzaldehyde toward the nucleophilic carbon as shown in figure 2. Even though we tried to generate an in situ formation of TTMSS-cyclohexanone from TMSCl in cyclohexane at same reaction condition, we failed to get the expected product. Herein, CDD might act as a radical initiator.

Formation of Mukaiyama aldol product: Enol silyl ether (E) was formed from α-less hindered (S) side when the reaction was carried out with CDD 1 (5 mmol), NaI (5 mmol) and TMSCl (10 mmol) in dry acetonitrile with stirring for 8 hours in -20°C to give a corresponding 1-(trimethylsiloxy)-1-cyclododecene and this was well documented 34. The addition of benzaldehyde produced an anti-aldol product with a diastereoselectivity up to 99% via the Mukaiyama aldol reaction. These are illustrated in figure 1. This mechanism is similar to the one that we had previously reported.
**Conclusion**

In summary, this is the first report of Mukaiyama aldol reaction and aldol condensation involving CDD on a substantial scale, employing ordinary laboratory equipment and readily available starting materials. Various β-hydroxy carbonyl compounds and α,β-unsaturated ketones with high chemo, regio and diastereoselective products were obtained with fair to good yield. Temperature was the only deciding factor which played a curial role. The nucleophile attack from α-corner (C) side led to enones, while from the α-less hindered (S) side it led to Mukaiyama aldol product. The formation of dehydrated product was due to the absence of hydrogen bonding between –C=O and –OH groups of aldol adduct. This was because of the *in situ* formation of "super silyl group" (TTMSS) from O-SiMe₃ linkage on C side of CH₂ group in sterically congested CDD 1. Even intermediate 1b was confirmed by reaction with TTMSH and CDD but this stabilized the positive charge on α-less hindered side of the CH₂ group.

The present synthetic protocol is superior to other methodologies already reported for CDD because of the one-pot manner, mildness of the TMSCl and high product selectivity. We believe that this will lead to an increase in the scope and synthetic utility of silyl enol ethers of CDD for creating new protocols.

**General Information**

All Chemicals were purchased from commercial sources and they were used without further purification unless otherwise specified. TLC - Thin layer chromatography was performed on pre-coated silica gel on alumina plates using UV light to visualize the course of reaction. Purification of reaction mixture was carried out by chromatography on silica gel and isolated yields after column chromatography are reported. Melting points were determined using microprocessor digital melting point apparatus, and they are uncorrected. IR spectra were recorded in the range 4000-400 cm⁻¹ using KBr pellet technique. ¹H NMR and ¹³C NMR spectra were recorded at room temperature on a 400 MHz using CDCl₃ as the solvent with TMS as an internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, multiplet, br = broad. HRMS analysis was obtained from double focusing electron impact method. Reactions involving air- or moisture-sensitive compounds were conducted in appropriate shielded two neck round-bottomed flasks with magnetic stirring bars and placed in 4 A molecular sieves. CH₂CN and DCM were distilled successively from P₂O₅ and k₂CO₃.

**Experimental Section**

Illustrative procedure for the preparation of the enone (3a–q): 4Å molecular sieves, 2 mL of CH₂CN, 10 mmol of trimethylsilyl chloride and 5 mmol of cyclododecanone were placed in a dry, two-necked RB flask with stopcock, equipped with mechanical stirrer. The mixture was stirred at room temperature for 18 hours. Aldehyde (5 mmol) was added to the preformed intermediate over a period of 1 minute and the stirring was continued at 35–40°C, until the aldehyde was consumed. This process was monitored by TLC. The 4Å molecular sieves were removed through filtration. HCl solution (1N, 4mL) was added to the reaction mixture and stirred at 35–40°C for 1-2 min. Saturated NaHCO₃ aq solution (4 mL) and water (4 mL) were added. DCM (10 mL X 2) was added, and the aqueous layer was extracted with DCM. Organic layer was dried over anhydrous Na₂SO₄ and the solvent was removed under vacuum to give the crude residue, which was then subjected to column chromatography (hexane/ethylacetate) to give expected product in moderate to good yield as indicated in Table 2.

**Synthesis of (E)-1-(2-bromobenzyldiene)cyclododecanone (3h)**

The crude product was subjected to column chromatography on silica gel (n-hexane/EtOAc, 8/2) to afford the enone product 3h (1.29 g, 74% E/Z = 98/2), Rr 0.6 (n-hexane/EtOAc, 4/1); mp: 111–113°C. ¹H NMR (400 MHz, CDCl₃): δ = 7.56-7.54 (d, J = 8Hz, 1H, CH₂); 6.95 (bs, 2H, CH₂); 6.89-6.87 (d, J = 8.8Hz, 1H, CH₂); 6.73-6.75 (t, J = 13.6Hz, 2H, CH₂); 4.73-4.75 (t, J = 11.2Hz, 2H, CH₂); 1.81 (bs, 2H, CH₂); 1.24-1.16 (m, 13H, CH₃); 1.04 (bs, 2H, CH₂). ¹³C NMR (100 MHz, CDCl₃): δ = 205.6 (C=O), 142.8 (C=C al-ri), 138.1, 136.6 (C=CH₂), 132.6, 130.5, 129.4, 127.1, 124.0, 38.8 (α-CH₂), 26.6, 26.5, 25.4, 24.4, 24.2, 24.1, 24.0, 23.1, 22.6. HRMS (EI) m/z: Calc. for C₂₉H₂₇BrO 434.1089 [M] +; Found 434.1086.

Illustrative procedure for the Mukaiyama aldol reaction (5): In a dry two-necked RB flask with stopcock placed in a ice/NaCl, equipped with mechanical stirrer, 4Å molecular sieves, 2 mL of CH₂CN, 10 mmol of trimethylsilyl chloride and 5 mmol of Na₂CO₃ were added. This mixture was stirred at 20°C for 8 hours. Aldehyde (5 mmol) was added to the preformed enol silyl ether over the period of 1 minute and the stirring was continued at -20°C, until the aldehydes were consumed. This process was monitored by TLC. The 4Å molecular sieves were removed through filtration. HCl solution (1N, 4mL) was added to the reaction mixture and was stirred at -20°C for 1-2 min. Saturated NaHCO₃ aq solution (4 mL) and water (4 mL) were added. Next, DCM (10 mL X 2) was added and the aqueous layer was extracted with DCM. The organic layer was dried over anhydrous Na₂SO₄ and the solvent was distilled successively from P₂O₅ and k₂CO₃.

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The crude product was subjected to column chromatography on silica gel (4:1 n-hexane/ethylacetate) to afford Mukaiyama-aldol product Sh (132g, 72%, dr= 99/2); Rr 0.7 (4:1 hexane:EtOAc); Mp. 136-138°C; FT-IR (KBr) ν = 3402.0 (OHi), 3052.7, 2920.7, 2852.7, 1681.5 (C=O), 1589.9, 821.0, 730.4, 599.6. 1H NMR (400 MHz, CDCl3); J = 5.7-5.55 (d, J = 8Hz, 1H, CH3); 7.45-7.43 (t, J = 4Hz, 1H, CH3); 5.24 (s, 2H, β-CH2α). 13C NMR (100 MHz, CDCl3); δ = 215.6 (C-O), 141.4, 132.9, 129.2, 128.0, 127.9, 122.6, 74.1 (β-CH3α), 56.7 (α-CH3α), 40.6 (α-CH3), 28.0, 26.3, 25.6, 24.5, 24.4, 24.2, 23.8, 22.6, 21.7. HRMS (EI) m/z: Calc. for C12H10BrO2: 266.0229; Found: 266.0271.

Notes and references

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4. Electronic Supplementary Information (ESI) available: [1H NMR, and 13C NMR of the newly synthesized compounds and mechanistic proofs].

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Graphical Abstract

Temperature-controlled Mukaiyama aldol reaction of cyclododecanone (CDD) with aromatic aldehydes promoted by TMSCl via (TMS)_3Si- intermediate generated in situ†

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A temperature controlled chemo, regio and diastereoselective synthesis of enones and Mukaiyama aldol reaction have been developed in sterically hindered CDD using organosilane as a catalyst. At 38°C in situ formation of super silyl groups (TTMSS) from TMSCl stabilized the positive charge on the α-corner (C) side of CH₂ group in zwitterionic CDD, leading to enones. At -20°C, interestingly, TMSCl stabilized silyl enol ether, which produced Mukaiyama aldol product in α-less hindered (S) side of the CH₂ group.