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

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An alternative method with temperature dependency for obtaining direct chemo-, regio- and diastereoselective monobenzylidene and β-hydroxy carbonyl derivatives has been developed. In the present work, an attempt has been made to synthesize a precursor containing an organometallic compound, trimethylsilyl chloride (TMSCl), 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 α-corner (C) side (sterically hindered side) of the CH_2 group (**1b**) in zwitterionic CDD, leading to monobenzylidene derivatives (enones). At −20 °C, interestingly, TMSCl stabilized silyl enol ethers, which in turn produced β-hydroxy carbonyl derivatives (Mukaiyama aldol products) in the α-less hindered (S) side (sterically less hindered side) of the CH_2 group. When we tried the reaction with TTMSSH instead of TMSCl, we failed to get either enones or aldol addition products. Tris(trimethylsilyl)silane (TTMSSH) stabilized the positive charge on the α-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 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 achieve diastereoselectivity in the Mukaiyama aldol reaction, sodium iodide was added. In monobenzylidene derivatives, the *E*-isomer is predominant (97–99%), while in the case of Mukaiyama aldol products, the *anti*-isomer is predominant (85–99%).

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Introduction

Although aldol reactions are one of the most versatile tools for creating new carbon–carbon bonds,[1] their 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 polycondensation.[1b–d] Different methodologies have been devised to get chemo-, regio- and diastereoselective aldol products using cyclic (5–8) and acyclic ketones.[4a–d] Wittig developed a direct aldol reaction procedure using enolate intermediates in place of lithio derivatives and some interesting applications were also developed by other chemists.[4e] For example, enol ether derivatives,[5] enol ether/acetals,[5] enol silyl ethers/$TiCl_4$,[4c] Li–Me enol ethers,[6a] $TiCl_4$-*n*-Bu_4NI[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] and zirconium enolates,[12a] MeLi/TMS-enol ethers[12b] and $TiCl_4$–Bu_3N-mediated aldol reactions[12c] have also received much attention in relation to the stereochemical problems. Consequently, the preparation of 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

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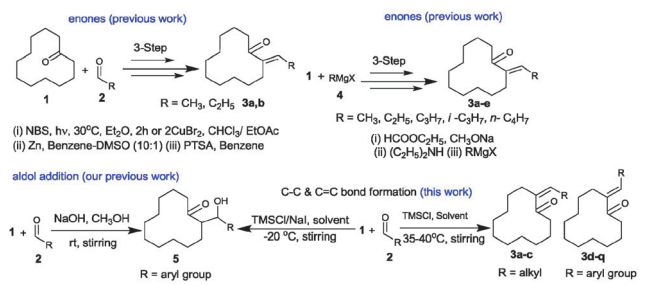
selectively by using preformed alkenyl trichloroacetates in the presence of dibutyltin dimethoxide in THF/CH_3OH.[19] The recent success of tris(trimethylsilyl)silyl-governed aldehyde cross-aldol cascade reaction[19d] and *syn* 1,3-diol[19e] has led to high diastereoselectivity. The ''super silyl group'' is superior to the organotin and tributyltin groups in tuning the aldol reactions.[19f,g] The treatment of commercially available α-iodomercuric ketone with carbonyl compounds in the presence of enol silyl ether/$Ni(CO)_4$ at 80 °C produced the corresponding enones in lower yield.[20] A freshly prepared *N*-(1-cyclohexen-1-yl)morpholine reacted with benzaldehyde in the presence of toluene under reflux conditions yielding enones.[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 used 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[25] a new series of unique aldol reactions of CDD, and we have tried to extend that method for the preparation of monobenzylidene derivatives. We have been struggling to get an enone product using the one-pot strategy for the past 3 years with various substituents on the benzaldehyde ring. There are a few types of synthetic approaches to get aldol condensation and addition reaction products using the reaction of cyclododecanone with aliphatic aldehydes. This was reported five decades back, when Zakharkin *et al.*[26a] synthesized musk odored compounds involving more than three steps. Paul *et al.*[26b] reacted **1** with ethylformate in the presence of CH_3ONa, which gave 2-hydroxymethylene cyclododecanone in the first step. Then, this was treated with diethylamine to yield 2-*N*-dimethylaminomethylenecyclododecanone followed by treatment with alkyl magnesium halides **4** yielding 2-alkylidenocyclododecanone (**3a–e**) (Scheme 1) with pleasant musk odor.[26b]

We found that Mukaiyama aldol reaction using an organosilane reagent as a catalyst 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 a one-pot manner. This aldol reaction showed a number of fascinating properties, full details of which are illustrated in Scheme 1.



Scheme 1 Protocols for the chemo-, regio- and diastereoselective formation of C=C and C–C bonds.

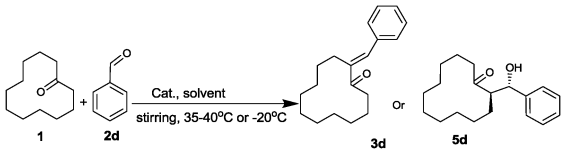
Results and discussion

Cyclododecanone is known for its W shaped zwitterions in the solution phase,[24b] and the organometallic reagent TTMSS (*in situ* generated from TMSCl) forms a bond with the keto group of CDD, since TMSCl is known for the homolytic bond cleavage of Si–Cl linkage.[27] The exploitation of this property for the protonolysis of Si–O[28] 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.[29] This work involved chloro-mediated enolate formation. N-heterocyclic carbenes were also demonstrated as catalysts for the formation of corresponding silyl enol ethers at 23 °C in THF *regio*-specifically.[30] In symmetrical ketones TMSCl and *tert*-butyldimethylsilyl (TBS) enol ethers were found to give predominantly *E* isomers.[31] Unsymmetrical and sterically hindered ketones such as propiophenone,[32] 2-methylcyclohexanone[33] and cyclododecanone[34] afforded a mixture of *E*/*Z*-silyl enol ethers mainly consisting of *Z*-isomers, and this selectivity also held true for the reaction with 3-pentanone.[35] In the case of 3-pentanone, a 5 mol% catalyst was required for the completion of the reaction even after 3 days.

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, products were not formed (Table 1, entries 1–11). However, NH_4OAc initiated the reaction but the consumption of the starting materials at 70 °C in EtOH was sluggish. It led to a mixture of products mainly consisting of a macro acyclic Mannich product[36] and a very small amount of enones, as shown in Table 1, entries 12–14 (10–18%), and in Scheme 2. In some instances, HCl gas gave chemoselective products[37] of enones. But this method also 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 of cyclododecanone[25] proceeded with strong bases such as NaOH, LiOH and KOH at ambient temperature (Table 1, entries 16 and 17). But the enones were not formed.

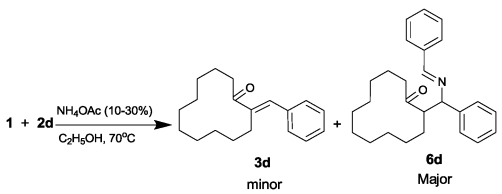
Hence, two extreme reaction conditions using temperature as a key factor for getting enones and aldol products (Mukaiyama aldol products) are illustrated in Tables 2 and 3. Chlorotrimethylsilane was used to get the chemo-, regio- and stereocontrolled products in the case of both enone and aldol products. Enone was formed upon treatment of CDD with chlorotrimethylsilane in CH_3CN at 35–40 °C with stirring for 18 hours and upon 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 reactions of cyclic or acyclic ketones with carbonyl compounds in the presence of TMSCl/acid, ketone could give the silylation as well as aldol addition products but not enones. But in the case of CDD, the catalyst (*in situ* generation of TTMSS from TMSCl)

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Cat. load. mol%	Solvents	Temp. (°C)	*T*/h	Yield%[g] 3d	5d
1	$ZnCl_2$	10[b]	EtOH	r.t.	24	—	—
2	AcOH	10	EtOH	r.t.	24	—	—
3	$FeCl_3{\cdot}6H_2O$	10[c]	DCM	r.t.	24	—	—
4	CuI	10[c]	DCM	r.t.	24	—	—
5	$AlCl_3$	10	EtOH	r.t.	24	—	—
6	Al_2O_3	10	EtOH	r.t.	24	—	—
7	$CoAlO_4$	10	EtOH	r.t.	24	—	—
8	$NiAlO_4$	10	EtOH	r.t.	24	—	—
9	MgO	10	EtOH	r.t.	24	—	—
10	Zeolite-Y	10	EtOH	r.t.	24	—	—
11	$FeCl_3$–SiO_2	10	DCM	r.t.	24	—	—
12	NH_4OAc	10	EtOH	70	48	10	—
13	NH_4OAc	20	EtOH	70	48	15	—
14	NH_4OAc	30	EtOH	70	48	18	—
15	HCl (gas)	Over 45 min gas has been passed	MeOH	r.t.	24	—	—
16	KOH	1	MeOH	r.t.	24	—	78
17	NaOH	1	MeOH	r.t.	24	—	86
18	TMSCl	1 (eq.)	DCM	r.t.	26	55	63[d,e,f]
19	TMSCl	10	DCM	r.t.	24	20	—
20	TMSCl	20	DCM	r.t.	26	28	—
21	TMSCl	40	DCM	r.t.	26	40	—
22	TMSCl	60	DCM	r.t.	26	49	—
23	TMSCl	2 (eq.)	DCM	r.t.	26	78	—
24	TMSCl	2 (eq.)	CH_3CN	r.t.	26	83	81[d,e]
25	TTMSSH	2 (eq.)	DCM	r.t.	30	—	—

[a] Unless otherwise noted, the reaction was carried out using various catalysts, CCD **1** (5 mmol) and parent benzaldehyde **2d** (5 mmol), in different solvents at different temperatures for 24–48 h. [b] 10 mol% piperidine was used. [c] *N*-Methylimidazole 10 mol% was used. [d] The reaction was carried out at −20 °C. [e] Immediate addition (*i.e.* without preformed enolate) of the **2d** mixture of the product (*anti*/*syn*: 50/50). [f] 1 equivalent of NaI was added. [g] Isolated yield.



Scheme 2 Synthesis of enones from cyclododecanone and aldehydes catalyzed by NH_4OAc.

played a major role, both in selectivity and yield, under the given reaction conditions (35–40 °C).

Hence, using the optimum reaction conditions (Table 1, entry 24) we employed the Mukaiyama aldol reaction in the presence of sodium iodide[38a] at low temperature. NaI was added to achieve 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 enones or aldol addition products due to the steric hindrance of cyclododecanone and bulkiness of the super silyl groups (TTMSSH). This is in line with the report by Ramachandran *et al.*, where enolization of *tert*-butyl 2-phenylacetate with the bulky group of CHX_2BOTf in CH_2Cl_2 and aldolization with benzaldehyde with stirring at 0 °C did not yield the desired aldol product.[38b]

The Mukaiyama aldol reaction was preformed with (cyclododecyloxy)trimethylsilane **1c** (Table 3) (CDD/NaI equiv. molar ratio) and benzaldehyde **2d** as a model reaction, where 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 conditions 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 products (1 : 1 *anti*/*syn* product). This problem was specific when the amount of TMSCl was low (1 equiv.) as shown in Table 1, entry 18. The present reaction conditions demonstrated that the control of the stereochemical course of the reaction by adding NaI was due to the formation of stable **1c**.[34] From these results, it is very clear that TMSCl/NaI/CH_3CN (2 equiv.) played a crucial role in the Mukaiyama aldol addition reaction and that the reaction (Table 1, entry 24) was quite clean under the optimum conditions described above.

We carried out the Mukaiyama aldol reaction under conventional conditions, *i.e.* after the isolation of (cyclododecyloxy)-trimethylsilane **1c** or (cyclohex-1-*en*-1-yloxy)trimethylsilane which reacted with benzaldehyde **2d** in the presence of 2 equivalents of

Table 2 Chemoselective synthesis of monobenzylidenecyclododecanone (enones) derivatives at room temperature[a]

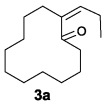
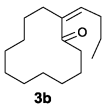
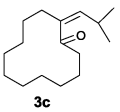
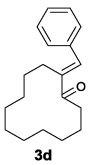
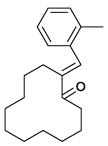
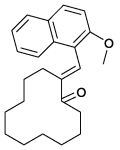
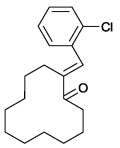
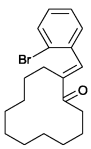
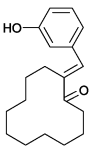
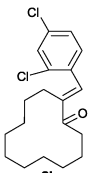
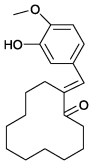
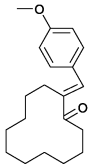
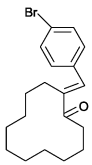
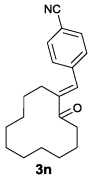
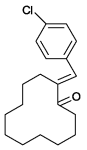
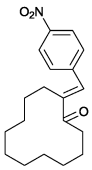
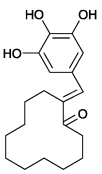
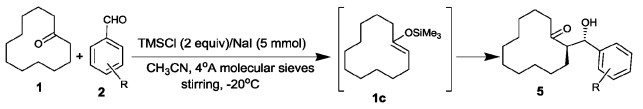
Entry	R = alkyl or aryl	3	*T*/h	Yield (%)	*E*/*Z* (%)
1	*n*-C_2H_5	 3a	22	82	1/99
2	*n*-C_3H_7	 3b	20	87	1/99
3	iso-C_3H_7	 3c	21	70	1/99
4	C_6H_5	 3d	26	83	99/1
5	2-CH_3-C_6H_5	 3e	24	87	99/1
6	2-OCH_3-$C_{10}H_6$	 3f	28	65	99/1
7	2-Cl-C_6H_5	 3g	35	77	99/1
8	2-Br-C_6H_5	 3h	33	74	98/2
9	3-OH-C_6H_5	 3i	29	67	99/1
10	2,4-Cl-C_6H_4	 3j	31	70	99/1

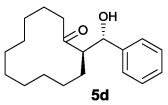
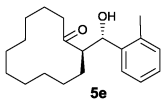
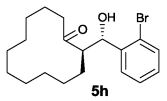
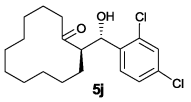
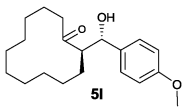
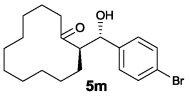
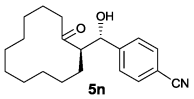
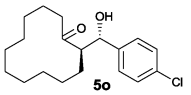
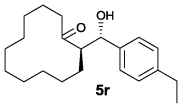
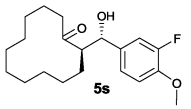
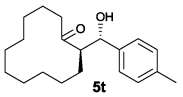
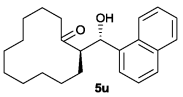
Table 2 (*continued*)

Entry	R = alkyl or aryl	3	*T*/h	Yield (%)	*E*/*Z* (%)
11	3-OH, 4-OCH_3-C_6H_4	 3k	32	58	97/3
12	4-OCH_3-C_6H_5	 3l	23	69	97/3
13	4-Br-C_6H_5	 3m	25	78	99/1
14	4-CN-C_6H_5	 3n	28	59	99/1
15	4-Cl-C_6H_5	 3o	26	81	99/1
16	4-NO_2-C_6H_5	 3p	32	73	99/1
17	3,4,5-Tri-OH-C_6H_2	 3q	30	53	99/1

[a] Unless otherwise noted, all the reactions were carried out with CDD **1** (5 mmol), benzaldehydes **2** (5 mmol) and TMSCl (10 mmol) in 2 mL of dry CH_3CN at 35–40 °C; the isolated yields of all the compounds are given; chemoselectivity and the *E*/*Z* isomer ratio were determined by ^1H NMR. Compounds **3a–c** have musk odor.

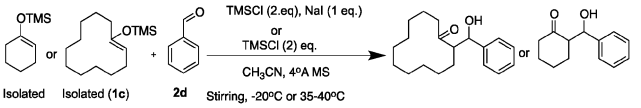
Table 3 *Anti* and *regio*-selective Mukaiyama aldol reactions of cyclododecanone with aldehydes using TMSCl as a catalyst at −20 °C[a]



Entry	R = aryl	5	*T*/h	Yield (%)	*Anti*/*syn* (%)
1	C_6H_5	 **5d**	24	81	99/1
2	2-CH_3-C_6H_5	 **5e**	23	83	99/1
3	2-Br-C_6H_5	 **5h**	21	72	98/2
4	2,4-Cl-C_6H_4	 **5j**	28	56	98/2
5	4-OCH_3-C_6H_5	 **5l**	27	86	99/1
6	4-Br-C_6H_5	 **5m**	22	82	99/1
7	4-CN-C_6H_5	 **5n**	34	63	85/15
8	4-Cl-C_6H_5	 **5o**	22	80	98/2
9	4-C_2H_5-C_6H_5	 **5r**	29	79	99/1
10	2,4-Cl-C_6H_4	 **5s**	38	59	89/11
11	4-CH_3-C_6H_5	 **5t**	23	87	99/1
12	$C_{10}H_7$	 **5u**	26	66	99/1

[a] Unless otherwise noted, all the reactions were carried out with CDD 1 (5 mmol), aromatic benzaldehydes (5 mmol), NaI (5 mmol) and TMCl (10 mmol) in 2 mL of dry CH_3CN at −20 °C. Isolated yields of all the derivatives are given. The *anti*/*syn* ratios were determined by the NMR spectroscopic technique.

TMSCl and 1 equivalent of NaI or 2 equivalents of TMSCl in CH_3CN stirring at room temperature or −20 °C yielding the Mukaiyama aldol product in both the cases as shown in Scheme 3.



Scheme 3 Synthesis of Mukaiyama aldols or enones from isolated silyl enol ethers of CDD and benzaldehyde.

We tried to prepare the tristrimethylsilylenol ether of cyclododecanone under similar conditions but we could not get the expected intermediate.

Monobenzylidene product formation

The versatility of the protocol was fully established by evaluating a variety of aldehydes as shown in Tables 2 and 3 respectively. By employing cyclododecanone as the nucleophile, a wide range of electron-donating and withdrawing substituents on the 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 aldehydes. The formation of enones was practically not possible using other ketones (5–8 homologues and acyclic ketones), as **1b** was not formed (Fig. 2), which was formed under the present reaction conditions. Using CDD, due to its dissimilar α and α′-CH_2 groups, the product formation was possible.

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*-isomers predominately (>99%) but the yield was decreased for **2u** (1-naphthaldehyde) when compared to **2d** (benzaldehyde). All the electron withdrawing and donating substituents at the *para* position gave a relatively high yield (>80%) and good selectivity (>99 *anti*-isomer) for compounds **5l**, **5m**, **5o**, **5r**, and **5t**.

The yield and *anti*/*syn* ratio were decreased (63% and 85/15%) in the case of 4-cyanobenzaldehyde **2n**. On the other hand, *ortho* substituted aldehydes gave moderate to good yield, and the *anti*-product was obtained predominantly (Table 3, entries 2 and 3). In contrast, di-substituted benzaldehydes gave low yield and less selectivity (compounds **5j** and **5s**). We examined the reaction using an excess of **2j** (2,4-dichlorobenzaldehyde). In fact, 1.4 equiv. of **2j** gave a mixture of products mainly consisting of ∼81% aldol products and ∼19% enones. On the other hand, excess of TMSCl resulted in a mixture of *anti* and *syn* Mukaiyama aldol products (50%) only.

Plausible mechanism

Formation of enones. The enones were formed through preformed 1-(trimethylsi1oxy)-1-cyclododecene at the α-corner (C) side of the CDD ring. Hence, we decided to isolate the 1-(trimethylsi1oxy)-1-cyclododecene, and for this, we carried

out reaction in $CDCl_3$ with CDD (5 mmol) and TMSCl (10 mmol) at 35–40 °C for 18 hours with stirring. After 18 hours, the crude mixture ($CDCl_3$ portion) was analyzed by NMR spectroscopy. The NMR results revealed that 1-(trimethylsi1oxy)-1-cyclododecene had not been formed. It showed that the α-corner side of the CH_2 group of the carbon atom containing hydrogen atoms was strongly affected, and also that variation in the splitting pattern occurred due to the coordination of electrophilic silicon to the C side of the CH_2 group and also the TMSCl was completely converted into an intermediate of tris(trimethylsilyl)-siloxy-CDD **1b** (TTMSS-CDD). This discussion has been held to be true since in ^{13}C spectra also the C side of CH_2 was shifted to about 2 ppm in the shielding region and C═O groups were shifted to about 2 ppm in the shielding region from the original one (CDD) as shown in the ESI.† The above results supported the formation of CDD-super silyl group intermediate **1b** without any doubt as shown in Fig. 1.

TTMSS stabilized the mobile equilibrium of CDD, and this might be due to the one electron-transfer mechanism.[39] One electron transfer took place from Si-metal[39b] to the C side of the CH_2 group and the oxonium ion (C···O) coordinated with an electrophilic silicon atom of TTMSS where an excess of chlorine atom acted as a counter anion (**1b**) as shown in Fig. 2. However, it was confirmed that the CDD existed as zwitterions. The literature reports confirm that in the solution phase, cyclododecanone was in the W-shape zwitterion state,[24a,b] which was in mobile equilibrium with shifting of the positive charge between the C side of CH_2, the carbon atom of CDD and the α-less hindered (S) side of CH_2. TTMSS stabilized the positive charge on the C side of the CH_2 group. At first, mechanistic details of the **1b** induced reactions were investigated to clarify the transfer of electrons from the silicon atom to the C side of the CH_2 group in CDD.

Hence, the removal of 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 the original one (pure CDD). The ^1H NMR spectrum of CDD showed different splitting patterns for the C side of CH_2 and the α-less hindered (S) side of CH_2. Two specific pentets were obtained for these two CH_2 groups as shown in Fig. S1A (ESI†).[25] Whereas in the case of CDD, it reacted with TMSCl (*in situ* generation of TTMSS).

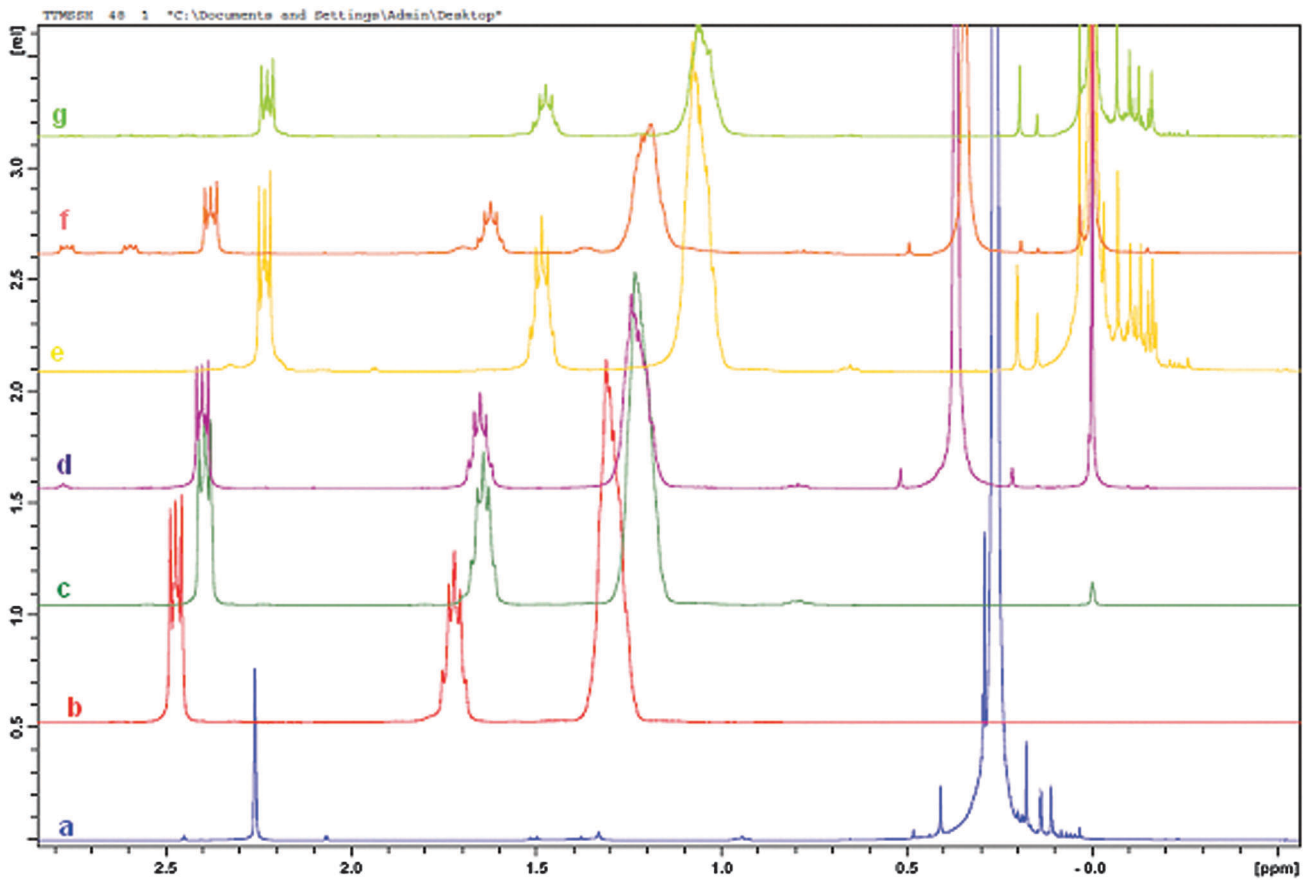


Fig. 1 The reaction was carried out in $CDCl_3$ and the NMR recorded in $CDCl_3$. (a) Spectrum of commercially available TTMSSH. (b) Spectrum indicating cyclododecanone. (c) Spectrum indicating the stabilization of the positive charge on the α-corner side of the CH_2 group after the removal of silyl 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 is given in the ESI†).

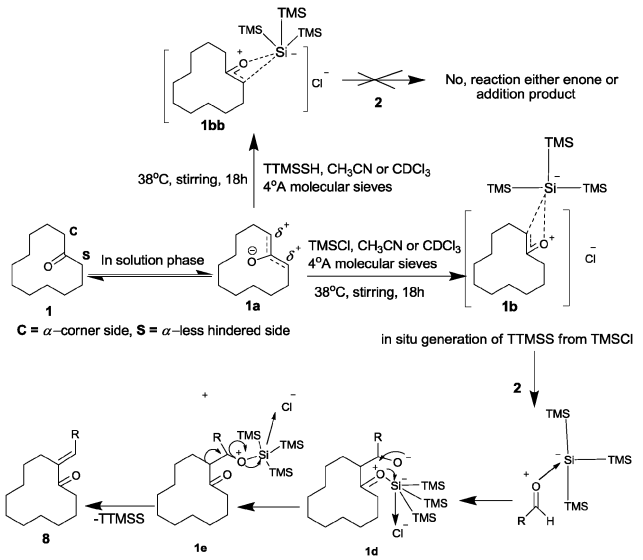


Fig. 2 Plausible mechanistic pathway for the formation of enones and Mukaiyama aldol reaction.

The ^{1}H NMR spectrum showed one triplet (A) and one sextet (B), clearly indicating that the shifting of the positive charge was stabilized by TTMSS, and therefore we got a triplet in the C side of the CH_2 group (Fig. S1B, ESI†).

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 the C side of the CH_2 group. TTMSS was released from **1d** to the reaction medium to give Tris(trimethylsilyl)silyl aldolate **1e** (confirmed by ^{1}H and ^{13}C NMR shown in the ESI†) by the intramolecular transfer of chloride anions ($-Cl^{-}$) to the silicon atom. Hence, the intermolecular hydrogen bond formation between C═O and OH of the 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 the 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.

In situ formation of tris(trimethylsilyl)siloxy-cyclododecanone **1b** (TTMSS-CDD) was confirmed by the formation of tris(trimethylsilyl)siloxy-cyclododecanone **1bb** (TTMSS-CDD) from commercial sources of tris(trimethylsilyl)silane (TTMSSH). The reaction was simultaneously carried out using commercially available Tris(trimethylsilyl)silane (TTMSSH) and cyclododecanone under the same reaction conditions to confirm the formation of the TTMSS-CDD (**1b**) intermediate. It clearly indicated that TTMSS-CDD was formed, but the stabilization of the positive charge occurred in the α-less hindered side (**1bb**) instead of the α-corner side (**1b**), and this has been identified from ^{1}H and ^{13}C NMR spectra. 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 the α-less hindered side prevented the attack of the carbonyl carbon of benzaldehyde toward the nucleophilic carbon as shown in Fig. 2. Even though we tried to generate an *in situ* formation of TTMSS-cyclohexanone from TMSCl in cyclohexanone under the same reaction conditions, we failed to get the expected product. Herein, CDD might act as a radical initiator.

Formation of Mukaiyama aldol products. Enol silyl ether (*E*) was formed from the 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 at −20 °C to give a corresponding 1-(trimethylsi1oxy)-1-cyclododecene and this was well documented.[34] The addition of benzaldehyde produced an *anti*-aldol product with a diastereoselectivity of up to 99% *via* the Mukaiyama aldol reaction. These are illustrated in Fig. 1. This mechanism is similar to the one that we had previously reported.[25]

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 diastereoselectivity were obtained with fair to good yield. Temperature was the only deciding factor, which played a crucial role. The nucleophile attack from the α-corner (C) side led to enones, while from the α-less hindered (S) side led to Mukaiyama aldol products. The formation of a dehydrated product was due to the absence of hydrogen bonding between –C═O and –OH groups of the aldol adduct. This was because of the *in situ* formation of a ''super silyl group'' (TTMSS) from O–SiMe_3 linkage in **1b** on the C side of the CH2 group in sterically congested CDD **1**. Even intermediate **1b** was confirmed by reaction with TTMSSH and CDD but this stabilized the positive charge on the α-less hindered side of the CH_2 group.

The present synthetic protocol is superior to other methodologies already reported for CDD, because it proceeded in a one-pot manner, and also because of the mildness of 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 a pre-coated silica gel on alumina plates using UV light to visualize the course of reaction. Purification of the reaction mixture was carried out by chromatography on silica gel and isolated yields after column chromatography are reported. Melting points were determined using a microprocessor digital

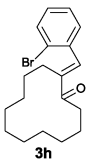
melting point apparatus, and they are uncorrected. IR spectra were recorded in the range 4000–400 cm^{-1} using a KBr pellet technique. ^1H NMR and ^{13}C NMR spectra were recorded at room temperature on a 400 MHz instrument using $CDCl_3$ as the solvent with TMS as an internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, multiplet, br = broad. HRMS analysis was performed using a double focusing electron impact method. Reactions involving air- or moisture-sensitive compounds were conducted in appropriate shielded two neck round-bottomed flasks equipped with magnetic stirring bars and placed in 4 Å molecular sieves. CH_3CN and DCM were distilled successively from P_2O_5 and K_2CO_3.

Experimental section

Illustrative procedure for the preparation of the enone (3a–q)

4 Å molecular sieves, 2 mL of CH_3CN, 10 mmol of trimethylsilyl chloride and 5 mmol of cyclododecanone were placed in a dry, two-necked RB flask with stopcock, equipped with a 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 stirring was continued at 35–40 °C, until the aldehyde was consumed. This process was monitored by TLC. Then 4 Å molecular sieves were removed through filtration. HCl solution (1 N, 4 mL) was added to the reaction mixture and stirred at 35–40 °C for 1–2 min. Saturated $NaHCO_3$ aq solution (4 mL) and water (4 mL) were added. DCM (10 mL × 2) was added, and the aqueous layer was extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to give the crude residue, which was then subjected to column chromatography (hexane/ethylacetate) to give the expected product in moderate to good yield as indicated in Table 2.

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



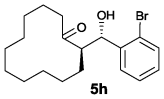
3h

The crude product was subjected to column chromatography on a silica gel (*n*-hexane/EtOAc, 8/2) to afford the enone product 3 h (1.29 g, 74% *E*/*Z* = 98/2), R_f 0.6 (*n*-hexane/EtOAc, 4/1); mp: 111–113 °C; ref. 25 FT-IR (KBr) ν = 3064.8, 2938.1, 2860.8, 1661.5 (C═O), 1464.8, 765.7, 742.3. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.54 (d, J = 8 Hz, 1H, CH_{Ar}); 7.33 (bs, 1H, $CH_{vinylic}$); 7.27–7.23 (t, J = 16 Hz, 1H, CH_{Ar}); 7.19–7.17 (d, J = 8 Hz, 1H, CH_{Ar}), 7.13–7.09 (t, J = 17.6 Hz, 1H, CH_{Ar}), 2.80–2.77 (t, J = 13.6 Hz, 2H, CH_{2ali}); 2.46–2.43 (t, J = 11.2 Hz, 2H, CH_{2ali}); 1.81 (bs, 2H, CH_{2ali}); 1.24–1.16 (m, 13H, CH_{2ali}); 1.04 (bs, 2H, CH_{2ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.6 (C═O), 142.8 (C═C ali-ring), 138.1, 136.6 (C═$C_{vinylic}$), 132.6, 130.5, 129.4, 127.1, 124.0, 38.8 (α'-CH_2), 26.6, 26.5, 25.4, 24.4, 24.2, 24.1, 24.0, 23.1, 22.6. HRMS (EI) *m*/*z*: calc. for $C_{19}H_{25}BrO$ 348.1089 $[M]^+$; found 348.1086.

Illustrative procedure for the Mukaiyama aldol reaction (5)

In a dry two-necked RB flask with stopcock placed in an ice/NaCl mixture, equipped with a mechanical stirrer, 4 Å molecular sieves, 2 mL of CH_3CN, 10 mmol of trimethylsilyl chloride, 5 mmol of NaI and 5 mmol of cyclododecanone were added. This mixture was stirred at −20 °C for 8 hours. Aldehyde **2** (5 mmol) was added to the preformed enol silyl ether over the period of 1 minute and stirring was continued at −20 °C until the aldehydes were consumed. This process was monitored by TLC. Then 4 Å molecular sieves were removed through filtration. HCl solution (1 N, 4 mL) was added to the reaction mixture and was stirred at −20 °C for 1–2 min. Saturated $NaHCO_3$ aq solution (4 mL) and water (4 mL) were added. Next, DCM (10 mL × 2) was added and the aqueous layer was extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to give the crude residue, which was finally subjected to column chromatography (hexane/ethylacetate). This produced the expected product in moderate to good yield as indicated in Table 3.

Synthesis of 2-((2-bromophenyl)(hydroxy)methyl)cyclododecanone (5h).



5h

The crude product was subjected to column chromatography on a silica gel (4 : 1 *n*-hexane/ethylacetate) to afford the Mukaiyama aldol product 5 h (1.32 g, 72%, dr = 98/2); R_f 0.7 (4 : 1 hexane : EtOAc); Mp: 136–138 °C; FT-IR (KBr) ν = 3402.0 (OH), 3052.7, 2929.7, 2852.7, 1685.1 (C═O), 1589.9, 821.0, 730.4, 599.6. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.55 (d, J = 8 Hz, 1H, CH_{Ar}); 7.45–7.43 (d, J = 8 Hz, 1H, CH_{Ar}); 7.36–7.33 (m, 1H, CH_{Ar}); 7.18–7.15 (t, 14 Hz, 1H, CH_{Ar}); 5.24 (s, 1H, β-CH_{chiral}), 3.22 (s, 2H, CH_{2ali}), 2.56–2.50 (dd, J = 15.2, 8.8 Hz, 1H, CH_{2ali}); 2.33–2.27 (dd, J = 14, 4 Hz, 1H, CH_{2ali}), 1.87–1.86 (d, J = 4 Hz, 1H, CH_{2ali}) 1.72 (bs, 1H, β-OH); 1.64 (bs, 1H CH_{2ali}); 1.64–1.48 (bs, 1H, CH_{2ali}); 1.32 (bs, 14H, CH_{2ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.6 (C═O), 141.4, 132.9, 129.2, 128.0, 127.9, 122.6, 74.1 (β-CH_{chiral}), 56.7 (α-CH_{chiral}), 40.6 (α'-CH_2), 28.0, 26.3, 25.6, 24.5, 24.4, 24.2, 23.8, 22.6, 21.7. HRMS (EI) *m*/*z*: calc. for $C_{19}H_{27}BrO_2$ 366.1194 $[M]^+$; found 366.1189.

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