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Full ARTICLE

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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An alternative path 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 organometallic compound trimethylsilyl chloride (TMSCl) and cyclododecanone (CDD). Unexpectedly, this precursor exhibited temperature dependent chemoselective structures. At 35-40ºC, 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 CH_2 group (**1b**) in zwitterionic CDD, leading to monobenzylidene derivatives (enones). At -20ºC, interestingly, TMSCl stabilized silyl enol ether, which in turn produced *β*-hydroxy carbonyl derivatives (Mukaiyama aldol product) in *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 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

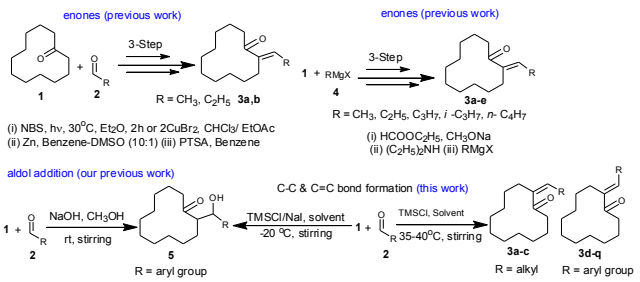
Although aldol reaction is one of the most versatile tools for creating new carbon-carbon bonds [1], its utility has several limitations because it is very difficult to control the course of the reaction [2]. It has been known for a long time that silyl enol ethers are useful intermediates in organic 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/acetals [5], enol silyl ethers/$TiCl_4$ [4c], Li-Me enol ether [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], zirconium enolates [12a], MeLi/TMS-enol ethers [12b] and TiCl4 – Bu3N-mediated aldol reactions [12c] 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_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 for 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 80ºC 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 [25] 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 enone product in one-pot strategy for the past 3 years with various substituents on benzaldehyde ring. There are a few types of synthetic approaches to get aldol condensation and addition reaction in 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 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**.

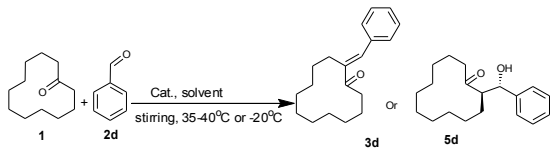


Scheme 1 Protocols for formation of chemo, regio and diastereoselectivity of C=C & C-C bond formation.

Results and discussion

Cyclododecanone is known for W shaped zwitter ion in solution phase [24b], and the organometallic reagent TTMSS (from in situ generation of TMSCl) forms a bond with keto group of CDD, since TMSCl is known for homolytic bond cleavage of Si-Cl linkage [27]. The exploitation of this property for 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. The N-heterocyclic carbenes were also demonstrated as catalysts for the formation of corresponding silyl enol ether at 23°C in THF *regio*-specifically [30]. In symmetrical ketones TMSCl and tert-butyldimethylsilyl (TBS) enol ethers were found to give predominantly *E* isomer [31]. Unsymmetrical and sterically hindered ketones such as propiophenone [32], 2-methylcyclohexanone [33] and cyclododecanone [34] 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 [35]. 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 1 Optimization of reaction conditions [a]



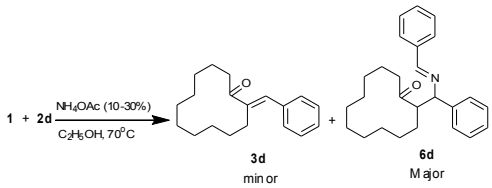
Entry	Catalyst	Cat.load. mol %	Solvents	Temp. (°C)	T/h	Yield % [g]	
						3d	5d
1	$ZnCl_2$	10 [b]	EtOH	r.t	24	-	-
2	AcOH	10	EtOH	r.t.	24	-	-
3	$FeCl_3.6H_2O$	10 [c]	DCM	r.t	24	-	-
4	CuI	10 [c]	DCM	r.t.	24	-	-
5	$AlCl_3$	10	EtOH	r.t	24	-	-
6	Al_2O_3	10	EtOH	r.t.	24	-	-
7	$CoAlO_4$	10	EtOH	r.t	24	-	-
8	$NiAlO_4$	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 noticed, the reaction was carried out using various catalysts, CCD **1** (5 mmol), and parent benzaldehyde **2d** (5 mmol) in different solvents at different temperature 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 **2d** mixture of product (anti/syn: 50/50) [f] 1 equivalence of NaI was added. [g] isolated yield.

The reaction between cyclododecanonene 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, NH_4OAc 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 [36] 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 [37] 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 [25] proceeded with strong bases such as NaOH, LiOH & KOH at ambient temperature Table **1**, entries **16**&**17**.

But the enones were not formed.

Scheme 2 Synthesis of enone from cyclododecanone and aldehydes catalyzed by NH_4OAc



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_3CN 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 hinderance 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 of CHX_2BOTf in CH_2Cl_2 and aldolization with benzaldehyde stirring at 0°C the reaction 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 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 stereochemical 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_3CN (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 (cyclododecyloxy)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 equivaent of TMSCl in CH_3CN stirring at room temperature or -20°C yielded Mukaiyama aldol product in both the cases as shown in Scheme **3**. We try to prepare tristrimethylsilylenol ether of cyclododecanone under the similar condition but we couldn't get the expected intermidate.

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

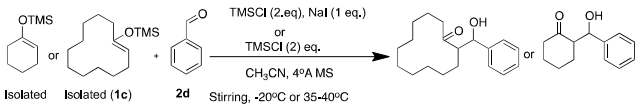
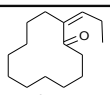
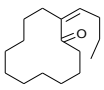
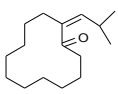
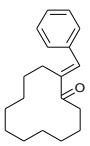
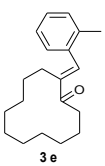
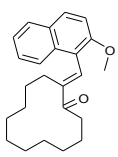
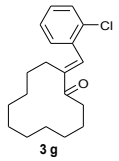
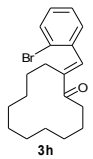
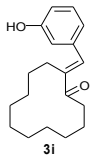
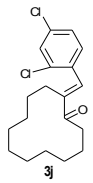
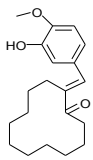
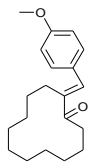
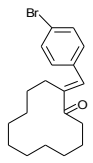
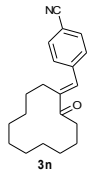
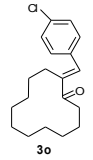
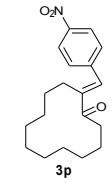
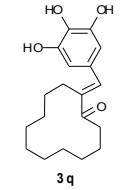


Table 2. shows the Chemo selective synthesis of monobenzylidenecyclododecanones (enones) derivatives at room temperature [a]

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	 3 e	24	87	99/1
6	2-OCH_3-$C_{10}H_6$	 3f	28	65	99/1

7	2-Cl-C_6H_5	 3 g	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
11	3-OH, 4-OCH_3-C_6H_4	 3 k	32	58	97/3
12	4-OCH_3-C_6H_5	 3l	23	69	97/3
13	4-Br-C_6H_5	 3 m	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	 3 q	30	53	99/1

[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 CH_3CN at 35-40°C; given all the compounds are isolated yield; chemo and E/Z isomer ratio were determined by ^{1}H NMR. The compounds **3a-c** having Musk odor.

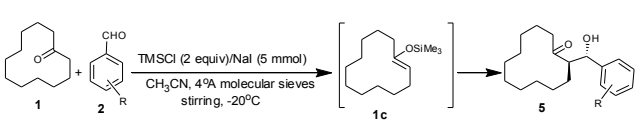
Monobenzylidene product formation

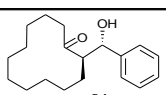
The versatility of the protocol was fully established by evaluating a variety of aldehydes as shown Table **2**&**3** respectively. By employing cyclododecanone as the nuclophile, a wide range of the substituent patterns with electron-donating and withdrawing substituents on aromatic ring were well tolerated. 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 **1b** (Fig.2), which was formed in the present reaction condition. In CDD, due to dissimilar α, α'-CH_2 groups, the product formation was possible.

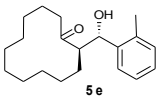
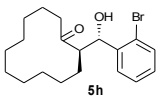
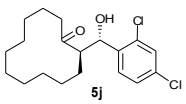
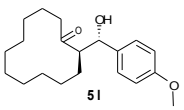
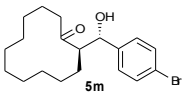
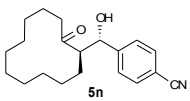
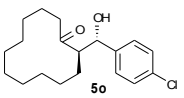
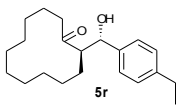
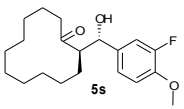
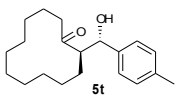
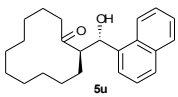
Mukaiyama aldol products

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 isomer predominately (>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 Mukaiyamaaldol reactions of cyclododecanone with aldehyde using TMSCl as 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-CH3-C_6H_5	 **5t**	23	87	99/1
12	$C_{10}H_7$	 **5u**	26	66	99/1

[a] Unless otherwise noted, all the reaction were carried with CDD 1 (5mmol), aromatic benzaldehydes (5 mmol), NaI (5 mmol) and TMCl (10 mmol) in 2 mL of dry CH_3CN at -20°C. All derivatives are isolated yield. The anti/syn ratios were determined by NMR spectroscopic technique.

The yield and anti/syn ratio was decreased (63 % & 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 & 3). In contrast, di-substituted benzaldehydes gave low yield and less selectivity (compounds **5j**&**5s**). We examined the reaction using excess of **2j** (2,4-dichlorobenzaldehyde). In fact, 1.4 equiv of **2j** gave a mixture of product mainly consisting of aldol product ~81% and ~19% of enone. On the other hand, excess of TMSCl caused a mixture of anti and syn Mukaiyama aldol product (50%) only.

Plausible mechanism

Formation of enone: The enones were formed through preformed 1-(trimethylsi1oxy)-1-cyclododecene at the α-corner (C) side of 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 for18 hours with stirring. After 18 hours, the crude mixture ($CDCl_3$ portion) was analyzed by NMR spectroscopy. The NMR result revealed that 1-(trimethylsi1oxy)-1-cyclododecene had not been formed. It showed that α-corner side CH_2 group of carbon atom containing hydrogen atoms were strongly affected, and also that variation in the splitting pattern occured due to the coordination of electrophilic silicon to the C side of CH_2 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 ^{13}C spectra also the C side of CH_2 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 [39]. One electron transfer took place from Si-metal [39b] to the C side of the CH_2 group and the oxonium ion (C$\dashv\!\!-$O) coordinated with an electrophilic silicon atom of TTMSS where excess of chlorine 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 [24a,b], which was in mobile equilibrium with shifting of positive charge between C side CH_2, carbon atom of CDD and α-less hindered (S) side CH_2. TTMSS stabilized the positive charge on the C side of the CH_2 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 CH_2 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 CH_2 and α-less hindered (S) side CH_2. Two specific pentets were given for these two CH_2 groups as shown in figure S**1A** [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 CH_2 group (figure S**1B**).

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**) approachedthe CDD from 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 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 CH2 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)silane (TTMSSH)

The reaction was simultaneously carried out using commercially available Tris(trimethylsilyl)silane (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 ^1H &^{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 cyclohexanone at same reaction condition, we failed to get the expected product. Herein, CDD might act has 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-(trimethylsi1oxy)-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 [25].

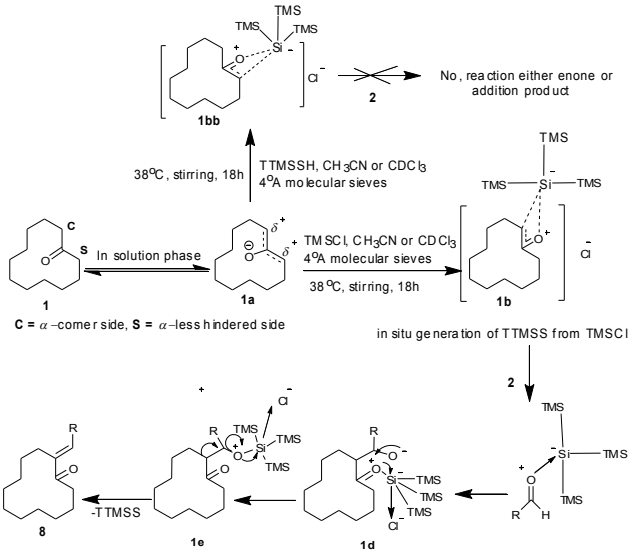


Figure 2. Plausible mechanistic path way for the formation of enone and Mukaiyamaaldol reaction

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-SiMe_3 linkage in the **1b** on C side of 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 α-less hindered side of the CH_2 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.

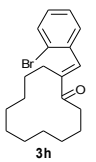
General Information

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 4000-400cm^{-1} using KBr pellet technique. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on a 400 MHz 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 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. 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): 4Å 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 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 $NaHCO_3$ 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 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 expected product in moderate to good yield as indicated in Table **2**.

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



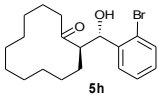
3h

The crude product was subjected to column chromatography on silica gel (n-hexane/EtOAc, 8/2) to afford the enone product 3h (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) υ = 3064.8, 2938.1, 2860.8, 1661.5 (C=O), 1464.8, 765.7, 742.3. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.56-7.54 (d, J = 8Hz, 1H, CH_{Ar}); 7.33 (bs, 1H, $CH_{vinylic}$); 7.27-7.23 (t, J = 16Hz, 1H, CH_{Ar}); 7.19-7.17 (d, J = 8Hz, 1H, CH_{Ar}), 7.13-7.09 (t, J = 17.6Hz, 1H, CH_{Ar}), 2.80-2.77 (t, J = 13.6Hz, 2H, CH_{2ali}); 2.46-2.43 (t, J = 11.2Hz, 2H, $CH2_{ali}$); 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 a ice/NaCl, equipped with mechanical stirrer, 4Å 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 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 $NaHCO_3$ 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 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 silica gel (4:1 n-hexane/ethylacetate) to afford Mukaiyamaaldol product 5h (1.32g, 72%, *dr*= 98/2); R_f 0.7 (4:1 hexane:EtOAc); Mp: 136-138°C; FT-IR (KBr) υ = 3402.0 (OH), 3052.7, 2929.7, 2852.7, 1685.1 (C=O), 1589.9, 821.0, 730.4, 599.6. ^{1}H NMR (400 MHz, CDCl3): δ = 7.57-7.55 (d, J = 8Hz, 1H, CH_{Ar}); 7.45-7.43 (d, J = 8Hz, 1H, CH_{Ar}); 7.36-7.33 (m, 1H, CH_{Ar}); 7.18-7.15 (t, 14Hz, 1H, CH_{Ar}); 5.24 (s, 1H, β-CH_{chiral}), 3.22 (s, 2H, CH_{2ali}), 2.56-2.50 (dd, J = 15.2, 8.8Hz, 1H, CH_{2ali}); 2.33-2.27 (dd, J = 14, 4Hz, 1H, CH_{2ali}), 1.87-1.86 (d, J = 4Hz, 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.

Notes and references

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† Electronic Supplementary Information (ESI) available: [^{1}H NMR,and ^{13}C NMR of the newly synthesized compounds and mechanistic proofs]. See DOI: 10.1039/b000000x/

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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 CH_2 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 CH_2 group.