Highly Efficient and Environmentally Benign Catalytic Enamine Reaction of Unmodified Aldehydes and its Application to Terpenoid Syntheses

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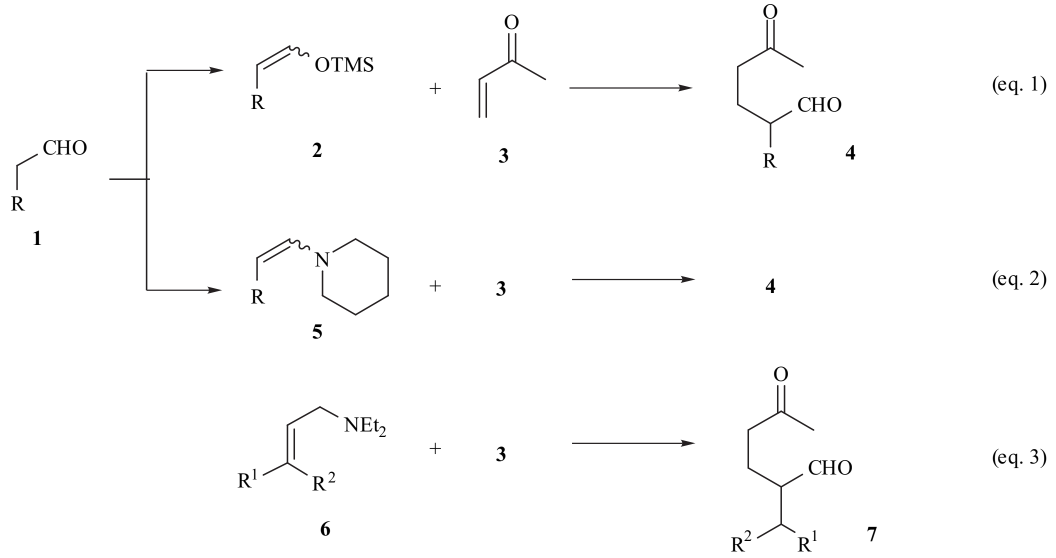
Abstract: Unmodified aldehydes add in 1,4-manner to electron deficient olefins in the presence of a catalytic amount of diethylaminotrimethylsilane. Reaction with methyl α-haloacrylates provided formylcyclopropanecarboxylates by domino conjugate addition–alkylation. Aldol condensation afforded unsaturated aldehydes. The reaction was revealed to proceed *via* catalytic enamine pathway. Total syntheses of several bisabolane type sesquiterpenoids have been accomplished according to this protocol.

Keywords: Diethylaminotrimethylsilane, 1,4-conjugate addition, cyclopropanation, aldol condensation, enamine reaction, bisabolane sesquiterpenoid.

INTRODUCTION

Aldehyde is a very versatile substrate as an electrophile and thus has been mainly used as an acceptor of nucleophile. On the other hand, there have been not enough examples to employ aldehyde as a nucleophile, which is due to the difficulty to generate enolate or enol of aldehyde directly and quantitatively in addition to the difficulty to control the reactivity of these species due to the competitive side reactions [1]. In order to use aldehyde as a nucleophile, aldehyde has been transformed once into its synthone such as a silylenol ether or enamine. However, there are several disadvantages in employing such aldehyde equivalents. Silylenol ether of aldehyde is not easily obtained in satisfactory yield. In addition, strong Lewis acid such as $BF_3 \cdot OEt_2$ is required for nucleophilic reaction [2], which limits application of the reaction to multifunctional compounds having acid sensitive substituents (Scheme **1**, eq. **1**). Similarly, synthesis of aldehyde enamine is not usually efficient because of the instability of aldehyde itself and the very sensitive nature of the enamine toward moisture. As a result, the examples of nucleophilic reaction of aldehyde enamine are not well precedented (Scheme **1, eq. 2**) [3]. Then, an alternative method was devised by the Ru catalyzed isomerization of allylamine leading to aldehyde enamine, though the process is not generally applicable to various substrates. The enamine thus formed was utilized *in situ* for 1,4-conjugate addition to vinylketone (Scheme. **1**, eq. **3**) [4].



Scheme 1.

These issues prompted us to investigate more efficient nucleophilic reaction of aldehyde and we have corroborated several novel nucleophilic reactions of unmodified aldehyde

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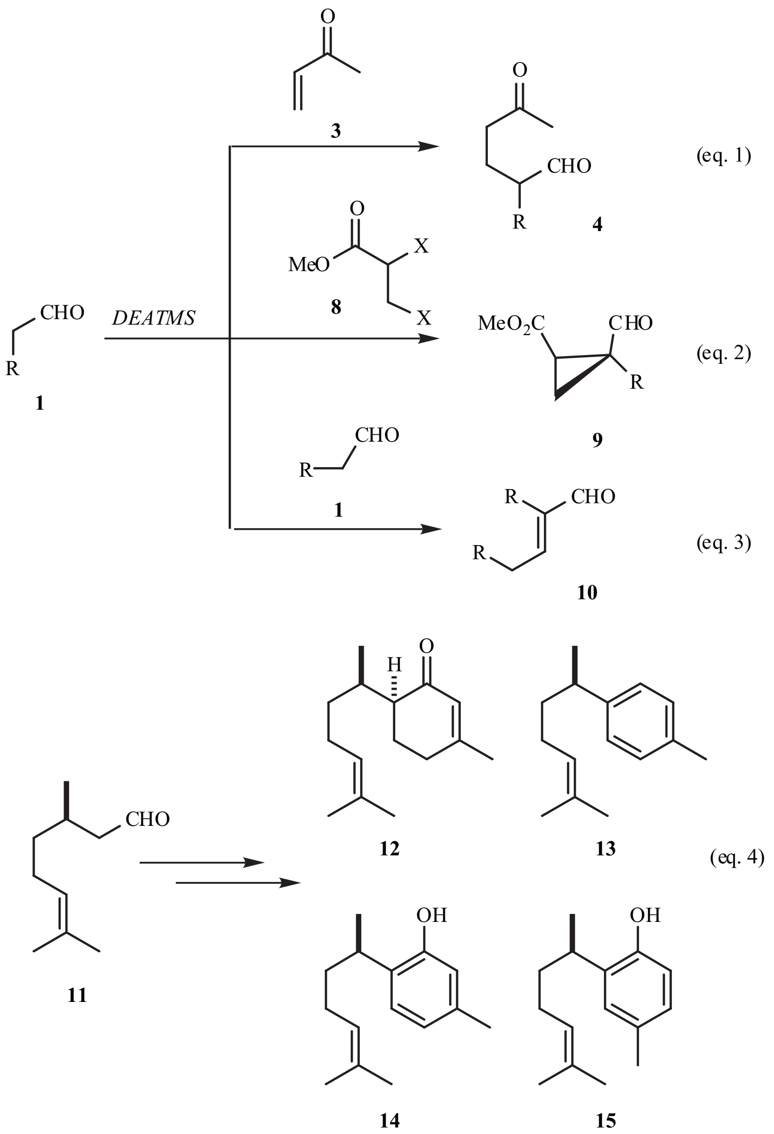


Scheme 2.

employing diethylaminotrimethylsilane (DEATMS). In this article, our results on 1,4-conjugate addition (Scheme **2,** eq. **1**), domino 1,4-addition–substitution (Scheme. **2,** eq. **2**) and aldol condensation (Scheme **2,** eq. **3**) of unmodified aldehyde are reviewed as well as development of the environmentally benign procedures and application of 1,4-conjugate addition product to several bisabolane sesquiterpenoids (Scheme **2,** eq. **4**).

1. DIRECT 1,4-CONJUGATE ADDITION OF UNMODIFIED ALDEHYDE [5]

The reaction of decanal **1** and 3-buten-2-one **3** (MVK) was employed as a probe to investigate optimized reaction condition for 1,4-conjugate addition of unmodified aldehydes **1** (Scheme **1**, eq. **1**). After testing various reagents, DEATMS was found to give the 1,4-conjugate addition product **4** in satisfactory yield (Table **1.**, entry 8). The reaction proceeded well with 0.5 equiv of DEATMS without solvent at room temperature. The product was isolated by medium pressure liquid chromatography (LC) without aqueous work-up. The reaction as well as the isolation procedure were very simple. Several results with other aldehydes are listed in Table **2**.

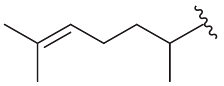
Table 1. Investigation of Reagents for 1,4-Addition[a]

Entry	Reagent	Yield (%)[b]
1	None	0[c]
2	TMSCl	0[c]
3	NEt_3	0[c]
4	$N(TMS)_3$	0[c]
5	C_4H_8NTMS	29
6	Et_2NH	35
7	$Me_2Si(NMe_2)_2$	46 (80)[d]
8	DEATMS	67

[a] Reaction was carried out without solvent. [b] Yield is based on aldehyde **1**. [c] Decylaldehyde was recovered completely. [d] Yield in parentheses based on the aldehyde consumed.

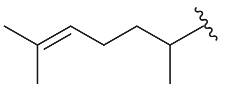
Aminosilane reagents can be easily obtained by the silylation of the corresponding amines. These compounds have been previously employed for the functional group transformations such as silylation of alcohol or amine [6], hydrolysis of ester [7], or ring opening of epoxide [8]. On the other hand, examples as the reagents for carbon-carbon bond forming reactions were rare except the reaction *via* iminium cation formation [9]. DEATMS is commercially available or prepared according to the procedure in *Organic Syntheses* [10].

Table 2. 1,4-Addition of Aldehydes 1 to Vinylketones 3^a

Entry	Aldehyde **1** R =	Ketoaldehyde **4** Yield (%)^b
1	C_8H_{17}	**a** 67
2	C_8H_{17}	**a** 22^c
3	C_8H_{17}	**b** 15^d
4	C_6H_{13}	**c** 49
5	C_8H_{17}	**d** 35^e
6	*i*-Pr	**e** 22
7	$PhCH_2$	**f** 58
8		**g** 13

^{a}All reactions were carried out at room temp. overnight with 3-buten-2-one **3** (MVK) and 0.5 mol equiv. of DEATMS without solvent. All reagents were used directly from bottles. ^{b}Yield is based on aldehyde **1**. ^{c}DEATMS (0.2 mol equiv.) was used. ^{d}3-Penten-2-one was used. ^{e}3-Methyl-3-buten-2-one was used.

Table 3. 1,4-Addition of Aldehydes 1 to Electron Deficient Olefins in CH_3CN at Reflux^a

Entry	**Aldehyde 1** **R =**	**Olefin**	**Product** **Yield (%)^b**
1	C_8H_{17}	MVK **3**	**4a**
2	C_8H_{17}	**3**	54^c
3	C_8H_{17}	**3**	**a** 66^d
4	*i*-Pr	**3**	**a** 78
5	$PhCH_2$	**3**	**e** 64
6	$THPOC_3H_6$	**3**	**f** 59
7		**3**	**g** 96^d
8	$AcOC_8H_{16}$	**3**	**h** 89
9	C_8H_{17}	4-Penten-3-one **16**	**i** 76
10	$PhCH_2$	**16**	**j** 76
11	C_8H_{17}	Phenylvinylsulfone **17**	**k** 68
12	$PhCH_2$	**17**	**l** 32
13	C_8H_{17}	Methyl acrylate	**m** 34
14	C_8H_{17}	**3**	**n** 55 **d** 20

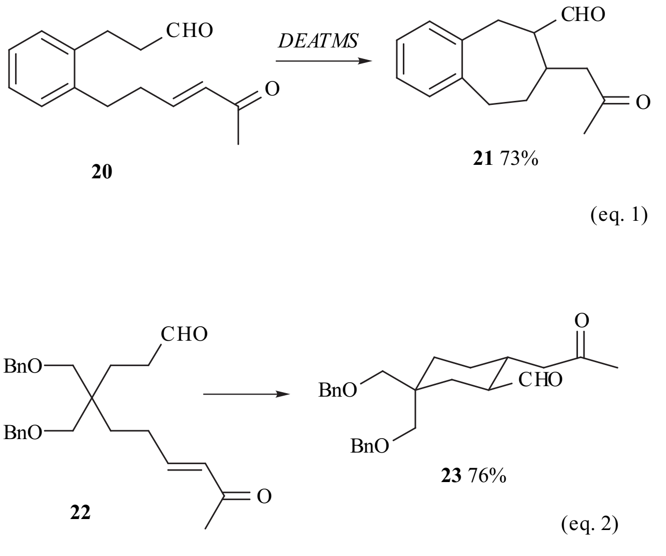
^{a}A mol equiv. of DEATMS was used. ^{b}Yield is based on aldehyde **1**. $^c CH_2Cl_2$ was employed as solvent. ^{d}10 mol. % of DEATMS was used.

However, under these reaction conditions, the reaction of the aldehydes having the substituents at β position of the formyl group resulted in low yields (Table **2.**, entries 6 and 8). This drawback was solved heating the reaction mixture in acetonitrile. Representative results are shown in Table **3**. This reaction condition was easily applicable to a larger scale reaction. In the case of the reaction of 0.5 mol of citronellal **11** with MVK **3**, the amount of DEATMS was enough to be 0.1 eq and 1,4-conjugate addition product **4** was obtained in 96% yield after distillation (Table **3.**, entry 7) [11]. The reaction condition was so mild that the aldehydes having OTHP or OAc substituent provided the products **4** without decomposition (Table **3**, entries 6 and 8). In all cases, aqueous work-up was not required. After evacuation, medium pressure LC or distillation of the residue was sufficient to obtain pure products.

Among various 1,4-acceptors investigated, MVK **3** was the most suitable along with other electron deficient olefins such as 4-penten-3-one (EVK) **16**, phenylvinylsulfone **17** or methyl acrylate (Table **3.**, entries 9 ~ 14).

α-Methylencycloalkanones were prepared *in situ* from the mesylates **18** [12] by DEATMS. These enones having the *s-cis* configuration were all reactive 1,4-acceptors (Table **4**). All products **19** were mixtures of diastereomers. These compounds **19** were precursors of bicyclo[n.3.1] derivatives, which are expected to be good starting materials for the syntheses of bridged molecules by intramolecular aldol reaction.

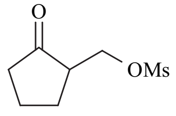
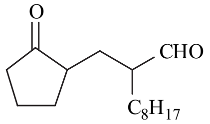
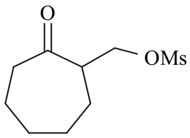
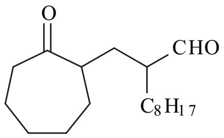
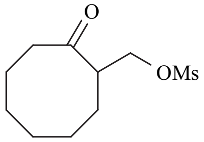
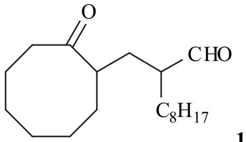
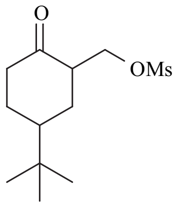
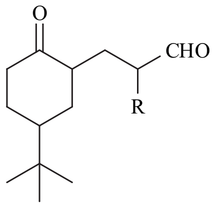
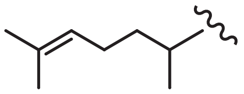
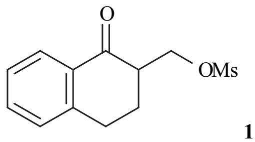
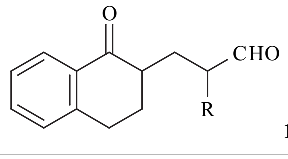
Intramolecular 1,4-conjugate addition was also possible, which enabled synthesis of 6 or 7 membered ring compound (Scheme **3**). In the reaction in eq. **2**, a single diastereomer **23** was obtained.



Scheme 3.

There have been a few precedents of 1,4-conjugate addition of unmodified aldehydes [13]. In most cases, subsequent reaction such as intramolecular aldol condensation has proceeded in one-pot operation. The examples of clean isolation of 1,4-adduct **4** are rare. Thus, present protocol is relevant in preparation of 5-ketoaldehydes **4**, which are very versatile starting materials for various synthetic transformations.

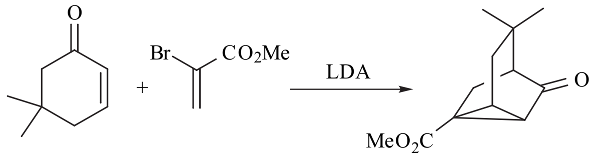
Table 4. 1,4-Addition of Aldehydes 1 to α-Methylenecycloalkanones[a]

Entry	Mesylate **18**	Product **19**[b,c]
1	 **18a**	 **19a** 67% (46%)[d]
2	 **18b**	 **19b** 47%
3	 **18c**	 **19c** 69%
4	 **18d**	 **19d** R = C_6H_{17}, 77% (52%)[e]
5	**18d**	**e** R = $AcOC_8H_{16}$, 67%
6	**18d**	**f** R = $THPOC_3H_6$, 65%
7	**18d**	**g** R = $PhCH_2$, 56%
8	**18d**	**h** R =  , 45%
9	 **18e**	 **19i** R = C_6H_{17}, 83%
10	**18e**	**19j** R = $PhCH_2$, 76%

[a] DEATMS (2.4 equiv.) was used in CH_2Cl_2. [b] Yield is based on mesylate **18**. [c] A mixture of diastereomers was obtained. [d] Reaction was carried out in CH_3CN. [e] An equivalent amount of DBU and DEATMS were used in CH_2Cl_2.

2. DOMINO 1,4-ADDITION—SUBSTITUTION OF UNMODIFIED ALDEHYDE [14]

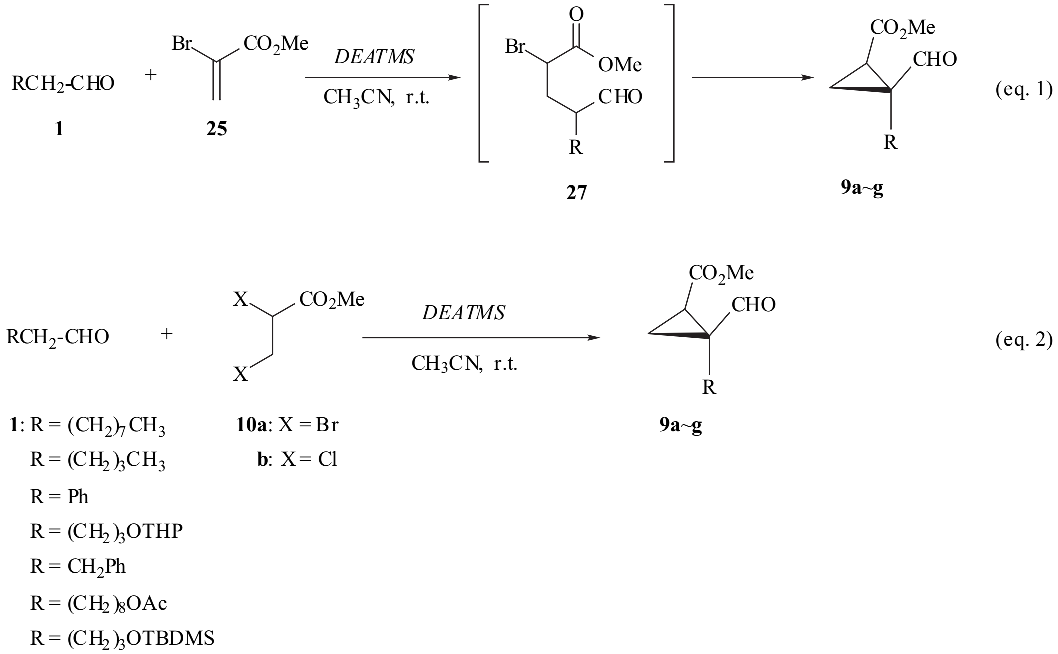
The domino reaction, a consecutive multi bond forming reaction in one-pot operation as a result of previous reaction, has attracted much attention specially in view of efficiency as well as sustainable aspect of organic reactions. Among them, the nucleophilic domino reaction has been developed for its efficiency in construction of the polycyclic carbon frameworks. Still much effort has been devoted for new methodologies and their application to natural product syntheses [15]. For example, the kinetic enolate of cyclohexenone **24** reacted with α-halo-α,β-unsaturated esters **25** to give tricyclo[3.2.1.0^{2,7}]octane derivatives **26** as a result of domino double 1,4-conjugate addition followed by intramolecular substitution (Scheme **4**) [16].



24 **25** **26** (62%)

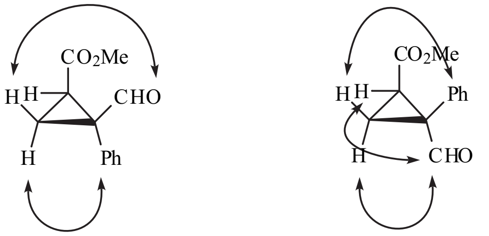
Scheme 4.

Reaction of unmodified aldehyde **1** with the α-halo-α,β-unsaturated esters **25** in the presence of DEATMS in acetonitrile furnished formylcyclopropanecarboxylate **9** by



Scheme 5.

the domino 1,4-addition—substitution reaction (Scheme **5, eq. 1**). The product was a mixture of diastereomers in which major isomer had *syn* stereochemistry between the formyl and ester groups according to nOe measurements (Fig. **1**).



9c (a major diastereomer) **9c** (a minor diastereomer)

Fig. (1). Selected nOe Correlations.

After several experiments, it was found that the α-haloacrylate **25** generated *in situ* from 2,3-dihalopropanoate **10** by DEATMS provided better yields rather than the unsaturated ester **25** (Scheme **5,** eq. **2**, Table **5**) probably due to instability of the ester **25**. 2,3-Dichloropropanoate **10b** gave better yields than 2,3-dibromopropanoate **10a** (Table **5**., entries 8 ~ 13) owing to the better stability of the resulting α-chloroacrylate **25**.

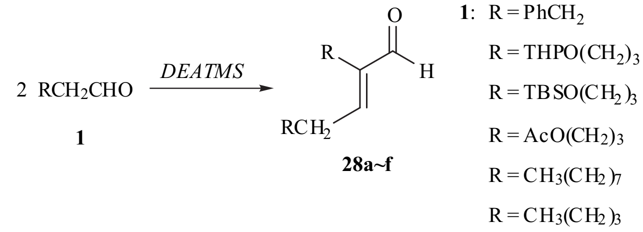
3. ALDOL CONDENSATION OF UNMODIFIED ALDEHYDE [17]

The reaction condition for the aldol condensation of unmodified aldehyde so far has lacked generality and mildness since inorganic bases were usually used [18]. Recently Mahrwald [19] and Tanabe [20] reported milder reaction conditions employing titanium tetrachloride/amine and subsequently by Okano [21] using La(OiPr)3. At the same time, Saito [22] reported the synthesis of α,β-unsaturated aldehyde (enals) employing pyrrolidine/benzoic acid.

Table 5. Synthesis of Methyl Formylcyclopropanecarboxylate 9^a

Entry	Aldehyde 1 R =	Dihaloester 10	Times (h)	Yield (%)^{b,c}
1	C_8H_{17}	**10a**	1.5	64 (1.4 : 1)
2	C_8H_{17}	**10a**	2.5	42 (1.4 : 1)^{d,e}
3	C_8H_{17}	**10a**	15.5	41 (0.74 : 1)^f
4	C_8H_{17}	**10a**	1	62 (2.1 : 1)
5	Ph	**10a**	2	30 (0.6 : 1)^d
6	$THPOC_3H_6$	**10a**	5	30 (1.8 : 1)
7	$PhCH_2$	**10a**	20.5	25 (1 : 1)
8	C_8H_{17}	**10b**	4	65 (1.6 : 1)
9	C_4H_9	**10b**	4	57 (2 : 1)
10	$THPOC_3H_6$	**10b**	2	61 (3.6 : 1 : 1)
11	$PhCH_2$	**10b**	3	58 (1.3 : 1)
12	$AcOC_8H_{16}$	**10b**	4	64 (1.7 : 1)
13	$TBDMSOC_3H_6$	**10b**	11	69 (1.2 : 1)

^{a}Reaction was carried out in the presence of 2.4 equiv. of DEATMS in CH_3CN. ^{b}Yield is based on aldehyde **1**. ^{c}A mixture of diastereomers was isolated. Ratio was determined by NMR. ^{d}Reaction was carried out in CH_2Cl_2. ^{e}Diastereomers were separated by MPLC. ^{f}Reaction was carried out without solvent.



Scheme 6.

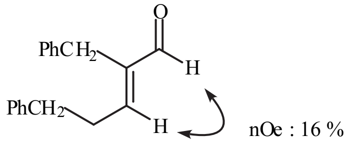
DEATMS is also effective for the self-aldol condensation of unmodified aldehyde leading to enal **28**. Heating with 0.5 mol equiv of DEATMS, the self-aldol condensation of aldehyde **1** followed by dehydration proceeded to give the enal **28** in acceptable yield (Scheme **6**, Table **6**).

Table 6. Intermolecular Self-Aldol Condensation of Various Aldehydes[a,b]

Entry	Aldehyde **1** R =	Enal **28**	Yield (%)
1	$PhCH_2$	**28a**	51
2	$THPOC_3H_6$	**28b**	49[c]
3	$TBDMSOC_3H_6$	**28c**	47
4	$AcOC_3H_6$	**28d**	44
5	C_8H_{17}	**28e**	54[d]
6	C_4H_9	**28f**	27

[a]Half equiv. of DEATMS was used unless otherwise specified. [b]Reaction was carried out at 50 °C for 16 h. [c]CH_3CN was employed as solvent. [d]An equiv. amount of DEATMS was used.

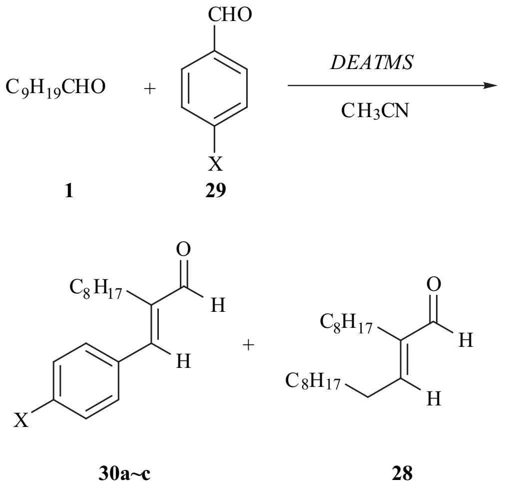
NOe experiment revealed that the geometry of the enal **28** was *E* (Fig. **2**). The reaction condition was so mild that the aldehydes having OTHP, OTBDMS or OAc substituent gave the enals **28** (Table **6.**, entries 2 ~ 4).



28a

Fig. (2).

Intermolecular cross aldol condensation was also possible (Scheme **7**, Table **7**). In this case also, *E*-isomer was obtained as a major isomer.



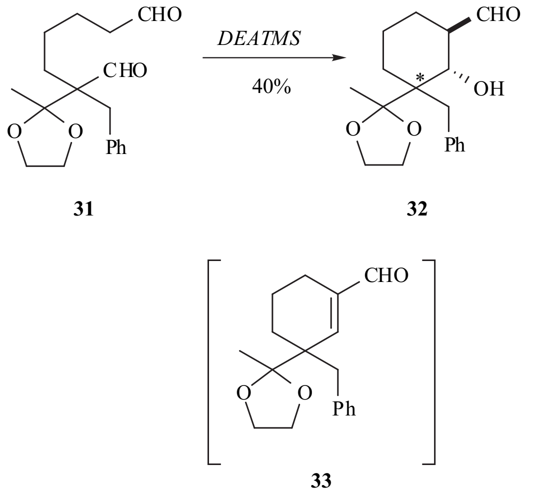
Scheme 7.

Next scheme is the example of intramolecular aldol condensation to afford the aldol product **32** as a single stereoisomer (Scheme **8**). Dehydration product **33** was not obtained.

Table 7. Intermolecular Cross-Aldol Condensation[a,b,c]

Entry	Arylaldehyde **29** X =	Yield (%) *E*-**30**	 *Z*-**30**	 **28**
1	**a** NO_2	81	10	–
2	**b** Cl	60	–	–
3	**b** Cl	25[d]	–	–
4	**c** MeO	20	2[e]	41

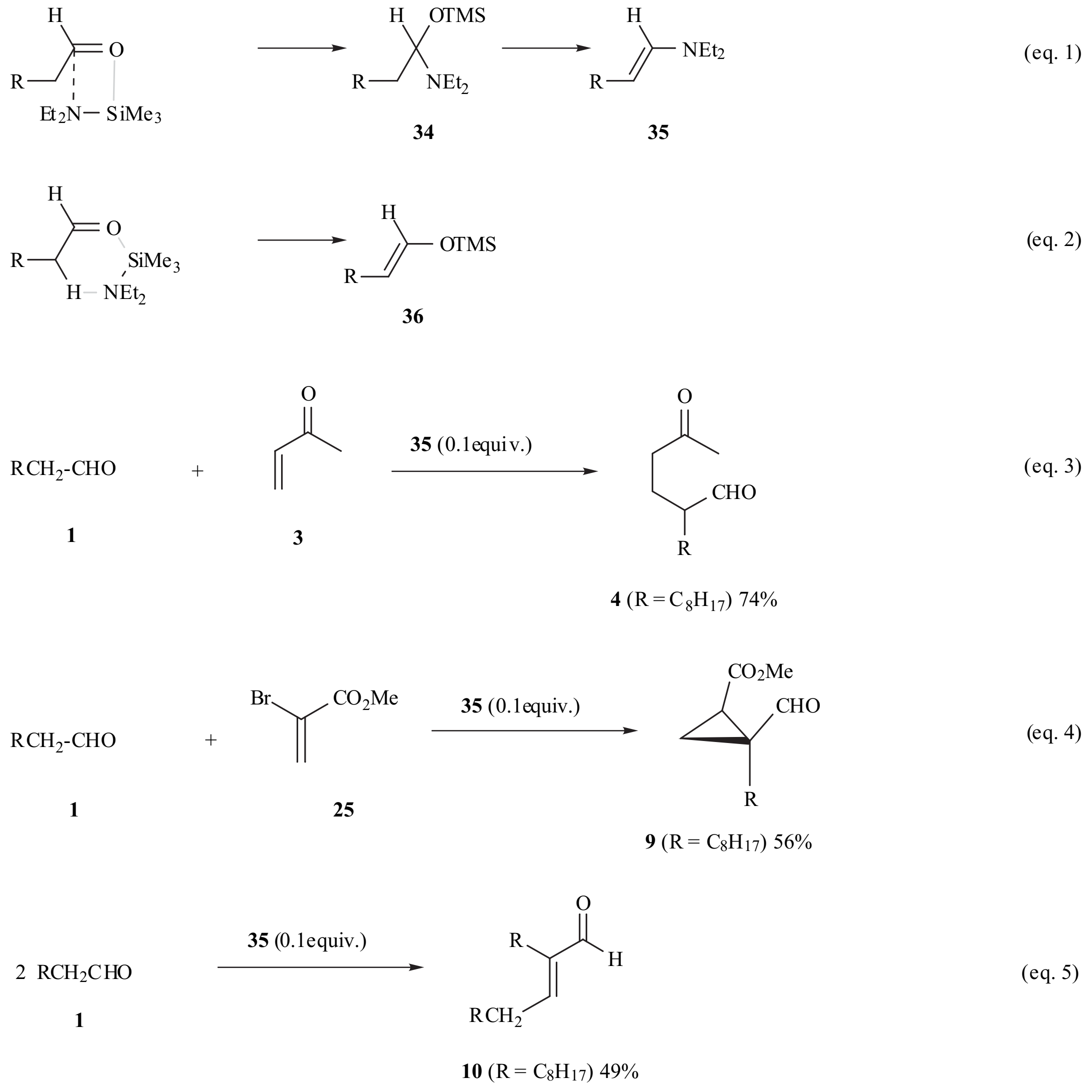
[a]Molecular sieves powder 4A (50 mg/mmol of aldehyde) was added. [b]Two equiv. of DEATMS was used. [c]Resulting slurry was heated at reflux for 20~24 h. [d]Reaction was carried out without solvent and MS 4A. [e]Anisaldehyde **29c** was recovered in 78% yield.



Scheme 8.

4. REACTION PATHWAY [5]

One obvious question is the role of DEATMS for the 1,4-conjugate addition reaction. On the reaction of aminosilane derivative and ketone, there have been two inconsistent reports at the same time. Hellberg and Juarez [23] reported the formation of silylenol ether in the presence of *p*-toluenesulfonic acid, while Weinreb *et al.* [24] reported formation of enamine. To this end, the reaction of decanal **1** and DEATMS was monitored in NMR tube in deuteriochloroform at room temperature in 22 hr and the formation of enamine **35** ($R = C_8H_{17}$) was observed judging from the chemical shift values of the olefinic protons [4.18 (dt, *J* = 13.8 and 7 Hz) and 5.86 (d, *J* = 13.8 Hz)] [8, 25]. The ratio of enamine **35** ($R = C_8H_{17}$) and starting decanal **1** was 1.3 : 1. Silylenol ether **36** of decanal **1** was not formed at all. While, deuterium exchange of α-protons of decanal **1** was not observed in the presence of D_2O and DEATMS in deuteriochloroform. According to *ab initio* calculations [MP2/6-31G(d) level], electron densities (Mulliken population) of nitrogen atom of dimethylaminotrimethylsilane and dimethylamine were the same (–0.59). Comparison of charge separation between nitrogen and hetero atoms revealed that the separation was larger in dimethylaminotrimethylsilane than fluorotrimethylsilane, which is a stronger Lewis acid than the former. These outcomes support the preferential formation of enamine **35** (Scheme **9.**, eqs. **1** and **2**).



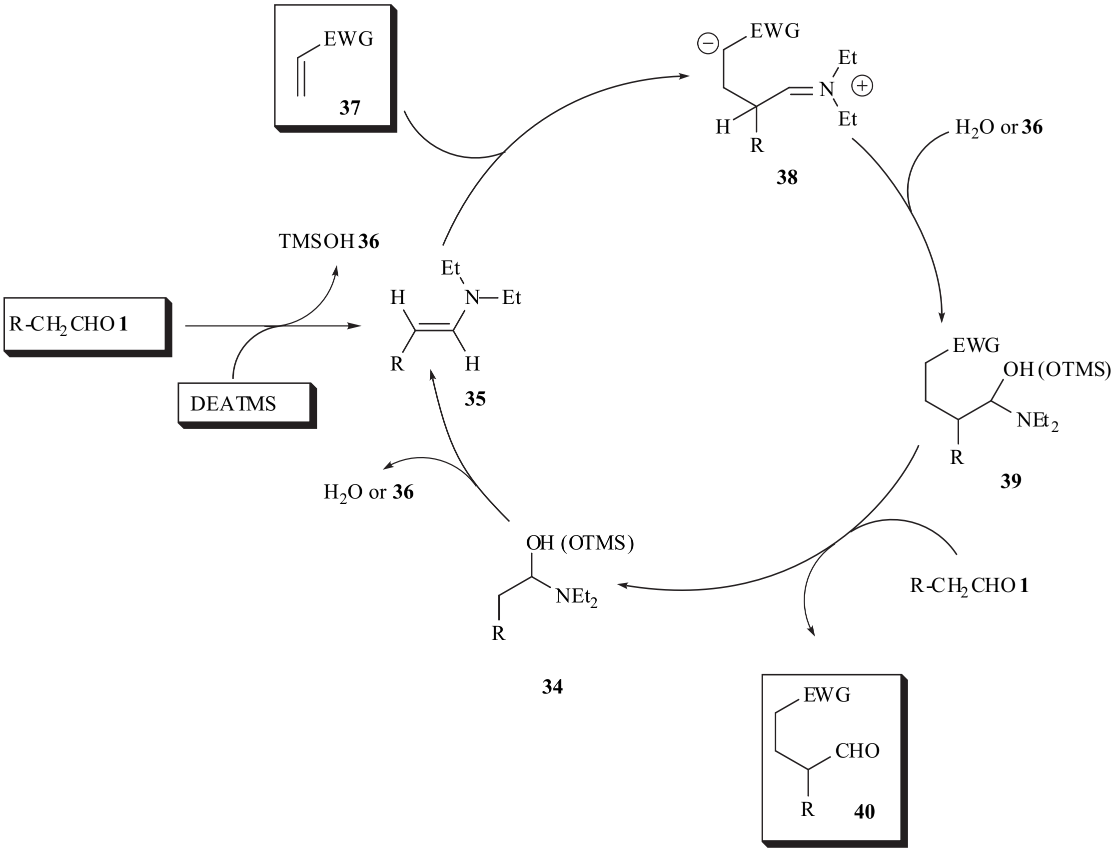
Scheme 9.

In the reaction of citronellal **11** and MVK **3**, the 5-ketoaldehyde **4** was obtained in 96% yield even using 0.1 equiv of DEATMS (Table **3.**, entry 7). This result suggests that DEATMS or other related intermediate works as a catalyst. Based on these findings, the diethylaminoenamine **35a** of decanal **1** was prepared according to the procedure of Stork [3]. NMR measurement soon after bulb to bulb distillation indicated that the product was a mixture of the enamine **35**, decanal **1** and diethylamine (DEA) (ratio: **35**: **1**: DEA = 1: 0.85: 0.7). Deducing from extremely volatile nature of DEA, hydrolysis of the enamine **35** occurred during sampling into NMR tube, though all glass apparatus were rinsed with aq. ammonium hydroxide and dried under reduced pressure. Then, in the presence of 0.1 equiv of decanal enamine **35**, the reaction of decanal **1** and MVK **3** in acetonitrile at reflux temperature provided the 1,4-conjugate addition product **4a** (R = C_8H_{17}) in 74% yield (Scheme **9, eq. 3**). Thus, the reaction pathway of the present reaction is proposed to proceed *via* enamine **35** as a catalyst, which was generated by DEATMS. **36** generated after enamine formation is easily dehydrated into trimethylsiloxane either under an acidic or a basic reaction condition [26] to generate water, which was supposed to play an important role to complete catalytic cycle, since molecular sieves powder decreased the yield of 1,4-conjugate addition product to 47% in the reaction of citronellal **11** and MVK **3** in toluene. Later on, it was found that 1,4-conjugate addition proceeded similarly by a catalytic amount of DEA (*vide infra*).

Based on the results cited above, the reaction pathway of the present 1.4-conjugate addition is drawn in Scheme **10**. In this reaction, the diethylaminoenamine **35** is regenerated and works as a reactive intermediate to initiate the next catalytic cycle. Fair instability of the diethylaminoenamine **35** might play an important role to drive the catalytic cycle.

Similarly, 0.1 equiv of decanal diethylaminoenamine **35a** promoted the domino 1,4-conjugate addition–substitution reaction of decanal **1** with α-bromoacrylate **25** to afford the formylcyclopropanoate **9a** in 56% yield (Scheme **9**, eq. 4).

Self-aldol condensation of decanal **1** was also catalyzed by pyrrolidino- or diethylaminoenamine **35** of decanal **1** to give the enal **28e** in 99 and 49% yields, respectively (Scheme **9**, eq. **5**). This aldol condensation was suppressed by molecular sieves powder, indicating importance of the presence of a small amount of water.

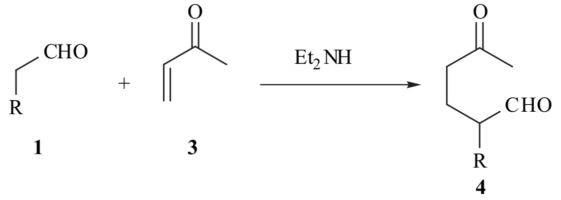


Scheme 10. Plausible reaction pathway.

These results suggest that both domino 1,4-conjugate addition–substitution reaction and aldol condensation proceeds *via* catalytic enamine pathway.

5. 1,4-CONJUGATE ADDITION REACTION CATALYZED BY DIETHYLAMINE [27]

Since DEATMS mediated nucleophilic reactions of unmodified aldehydes were exemplified to proceed *via* catalytic enamine pathway, it was anticipated that DEA also acts as a catalyst though DEA was not a good mediator in the absence of solvent (Table **1.**, entry 6). In using a catalytic amount of volatile DEA, the reaction condition was investigated in a sealed tube employing citronellal **11** as a model substrate (Scheme **11**). Among solvents investigated, THF, toluene or acetonitrile gave in satisfactory yields 1,4-conjugate addition product **4** heating with 0.2 equiv of DEA (Table **8**).



Scheme 11.

Present reaction conditions were applicable to other aldehydes **1** especially to the aldehydes having acid or base sensitive substituents (Scheme **11**, Table **9.**, entries 4 ~ 6), which showed similar mild reactivity in the reactions with DEATMS.

Table 8. Optimization of Reaction Condition in 1,4-Addition of Citronellal 11 to MVK 3

Entry[a]	Solvent	Amount of amine (equiv.)	Product 4	
			Time (h)	Yield (%)
1	CH_3CN	0.1	50	66
2[b]	–	1.0	23	28 (37)[c]
3	CH_3CN	0.2[d]	5	7[e]
4	*n*-hexane	0.1	16	10[f]
5	THF	0.1	19	43 (66)[c]
6	CH_2Cl_2	0.1	15.5	45 (65)[c]
7	CH_3CN	0.1	16.5	50 (55)[c]
8	CH_3CN	0.2	41	73
9[g]	Toluene	0.2	16	29 (59)[c]
10	Toluene	0.2	24	87
11[h]	Toluene	0.2	25	45 (80)[c]

[a]Reaction was carried out with DEA and 1.6 equiv. of MVK **3** at 80 °C in a sealed tube. [b]Reaction was carried out in an open vessel. [c]Yield in parentheses was based on starting material consumed. [d]Pyrrolidine was used. [e]Citronellal **11** decomposed. [f]Citronellal **11** could not be separable from by-product. [g]Reaction was carried out at 130 °C. [h]Reaction was carried out in the presence of 4A sieves.

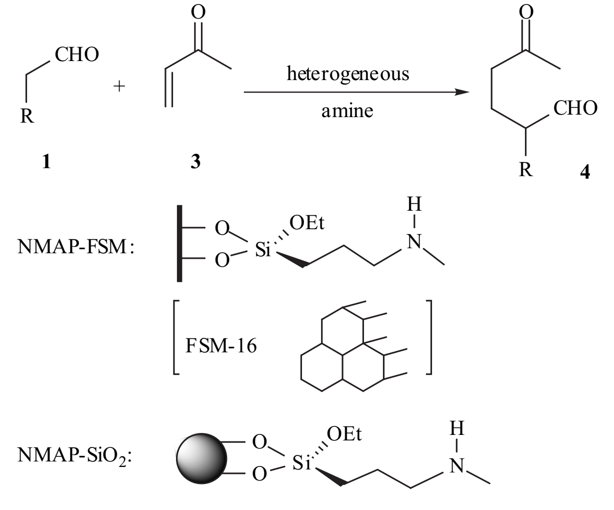
Table 9. 1,4-Addition of Various Aldehydes 1 to MVK 3

Entry[a]	Aldehyde **1** R =	Product **4** THF	Yield (%)[b] Toluene
1	C_8H_{17}	73	47
2	*i*-Pr	28	30
3	$PhCH_2$	62	60
4	$AcOC_8H_{16}$	61 (63)[b]	80 (83)[b]
5	$THPOC_3H_6$	55 (73)[b]	76
6	$TBDMSOC_8H_{16}$	–	75

[a] Reaction was carried out with 1.5 equiv. of MVK **3** in the presence of 0.2 equiv. of Et_2NH at 80 °C for 16 h in a sealed tube. [b] Yield in parentheses based on starting material consumed.

6. 1,4-CONJUGATE ADDITION [28] AND ALDOL CONDENSATION [29] CATALYZED BY AMINE IMMOBILIZED ON SILICA

From environmental and economical point of view, the use of heterogeneous catalyst offers several advantages, e.g., simple reaction procedure with easy work-up or repeated use of the catalyst. Contrary to the satisfactory results on Knoevenagel or aldol condensation, traditional inorganic solid bases have not been suitable for 1,4-conjugate addition reactions. Actually, MgO or hydrotalcite did not give any desired 1,4-addition product as shown in entries 1 and 2 in Table **10**.



Scheme 12.

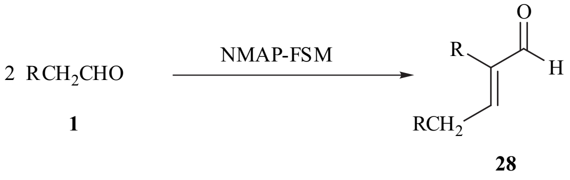
Based on the results of the catalytic enamine reactions cited above, *N*-methylamino residue was grafted on amorphous silica (NMAP-SiO_2) or FSM-16 (NMAP-FSM) which is a synthetic mesoporous silica and currently attracts much attention as a nano-order reaction vessel due to high surface area, large pore sizes and ordered structure. In refluxing toluene solution, the 1,4-addition of *n*-decanal **1** to MVK **3** proceeded in the presence of 10 mol% of NMAP-FSM in 57% yield (Scheme **12.**, entry 4, Table **10**). Re-use of the catalyst was possible up to 4 re-uses without appreciable decrease of catalytic activity after washing with dilute aq. K_2CO_3 in each cycle. In Table **10**, entry 10, a turnover number (TON) of 400 was obtained, which is unusually higher compared to other basic catalysts.

Table 10. 1,4-Addition of Aldehydes 1 to Vinylketones 3 Catalyzed by Immobilized Amine on Silica

Entry[a]	**Catalyst**	**Aldehyde 1 R =**	**Vinylketone 3**	**Yield (%)[b]**
1	MgO	C_8H_{17}	MVK	0
2	Hydrotalcite			0
3	NMAP-SiO_2			44
4	NMAP-FSM			57
5[b]	1st re-use			72
6[b]	2nd re-use			64
7[b]	3rd re-use			63
8[c]	NMAP-FSM	C_4H_9		87
9[c]	NMAP-FSM		EVK	93
10[d]	NMAP-FSM			40

[a] Reaction was carried out with 1.5 equiv. of MVK **3** in toluene at reflux. Amount of the catalyst was 10 mol%. [b] The catalyst was washed with dilute aq. K_2CO_3 prior to re-use. [c] Amount of the catalyst was 1 mol%. [d] Amount of the catalyst was 0.1 mol%.TON value was 400.

Employing the same catalyst, self-aldol condensation of unmodified aldehydes **1** are examined (Scheme **13**). Re-use of the catalyst was also realized as shown in Table **11.**, entries 4-7. Efficiency as well as higher reactivity of the NMAP-FSM than inorganic bases was thus demonstrated.



Scheme 13.

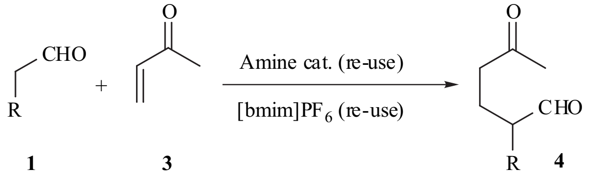
Table 11. Self-Aldol Condensation of Aldehydes 1 Catalyzed by Immobilized Amine on Silica

Entry[a]	Catalyst	Aldehyde **1** R =	Yield (%)
1	MgO	C_4H_9	26
2	Hydrotalcite		11
3	NMAP-SiO_2		69
4	NMAP-FSM		85
5[b]	1st re-use		81
6[b]	2nd re-use		83
7[b]	3rd re-use		77
8[c]	NMAP-FSM	C_2H_5	84
9[c]	NMAP-FSM	C_6H_{13}	93
10	NMAP-FSM	C_8H_{17}	56

[a] Reaction was carried out in toluene at reflux temp. Amount of the catalyst was 5 mol%. [b] The catalyst was washed with dilute aq. K_2CO_3 prior to re-use. [c] Amount of the catalyst was 10 mol%.

7. 1,4-CONJUGATE ADDITION [30] AND ALDOL CONDENSATION IN IONIC LIQUID CATALYZED BY AMINE ON IMMOBILIZED SILICA [31]

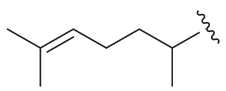
Room temperature organic ionic liquid (molten salt) has been highlighted from various scientific field and has attracted much attention especially as environmentally benign organic media because of non-volatility, low lipophilicity and low hydrophobicity. Such characteristics prompted utilization as a new media in synthetic organic chemistry [32]. Since the 1,4-conjugate addition reaction of unmodified aldehyde **1** proceeds efficiently in acetonitrile, highly polar ionic liquid must be an alternative candidate (Scheme **14**). Among ionic liquid, [bmim]PF$_6$ was employed because of very low lipophilicity and hydrophobicity, which makes extraction easier with organic solvent as well as water.



1 **3** **4**

Scheme 14.

Table 12. 1,4-Addition of Aldehydes 1 in [bmim]PF$_6$^{a}

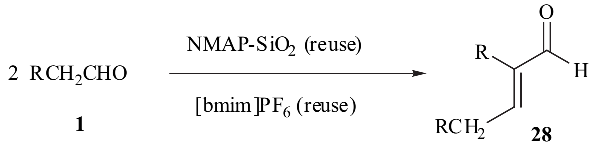
Entry	Amine (0.2 equiv.)	Aldehyde 1 R =	Yield (%)^b
1	–		0
2	NMAP-FSM^b		20
3	NMAP-SiO$_2$^{c}		62
4	DEATMS		85
5	DEA		71
6		*i*-Pr	50^d
7		C$_8$H$_{17}$	61(58)^d
8		PhCH$_2$	60
9		AcOC$_8$H$_{16}$	56
10		THPOC$_8$H$_{16}$	68
11		TBDMSOC$_8$H$_{16}$	75

[a]Reaction was carried out at 80 °C under nitrogen. [b]Nitrogen contents of per gram of the support was 0.5 mmol/g. [c]Nitrogen contents of per gram of the support was 0.8 mmol/g. [d]Product was distilled from [bmim]PF$_6$ *in vacuo*.

Reactivity of various secondary amine bases in [bmim]PF$_6$ was examined at first (Table **12**, entries 1 ~ 5). Optimized reaction condition was investigated by the reaction of citronellal **11** and MVK **3**. The reaction was carried out in the presence of 0.2 equiv of amine catalyst at 80 °C (Table **12**). The product was partitioned into diethyl ether several times. After evaporation of ether, pure 5-ketoaldehyde **4** was obtained by medium pressure LC purification. At room temperature or without amine, citronellal **11** was completely recovered. Consequently, DEA was employed for further reaction because of better yields in the reaction with other aldehydes **1** (Table **12.**, entries 6 ~ 12). In entries 6 and 7, the 1,4-conjugate addition product **4** was directly isolated from [bmim]PF$_6$ by bulb to bulb distillation. The reaction condition is mild enough to give products **4** starting from the aldehydes **1** with acid or base sensitive protecting groups (Table **12**., entries 9 ~ 11). The reaction was carried out simply in a test tube covered with septum in spite of highly volatile nature of DEA. Sealed tube was not required, which is another advantage in the reaction in ionic liquid.

[Bmim]PF$_6$ was re-used five times in DEA catalyzed reactions of citronellal **11** and MVK **3** in 62 ~ 71% yield, adding DEA freshly in each cycle. Employing NMAP-SiO$_2$, not only ionic liquid but also the catalyst was recycled intact four times in moderate yields (46 ~ 59% yield) without any further treatment to re-activate the catalyst after the reaction.

Such recycle of the catalyst as well as ionic liquid were further elaborated in self-aldol condensation (Scheme **15**), in which representative results are compiled in Table **13**. The reaction system continuously worked well until 8 recycles after heating the system *in vacuo* in order to remove H$_2$O generated in the previous reaction. In cycle 7, inherent low reactivity of cross aldol reaction resulted in low yield. Actually, re-use of the same catalyst in cycle 8 for self-aldol condensation recorded higher yield back. In order to make decantation of ether layer easier from lower ionic liquid layer, powdery NMAP-SiO$_2$ was pressed as cylindrical pellets, since powdery NMAP-SiO$_2$ has been floating between ether and ionic liquid layers during product partition. Mechanical stability of NMAP-SiO$_2$ increased by plasticizing into pellets.



1 **28**

Scheme 15.

Table 13. NMAP-SiO$_2$ Catalyzed Self-Aldol Condensation of Aldehyde 1 in [bmim]PF$_6$

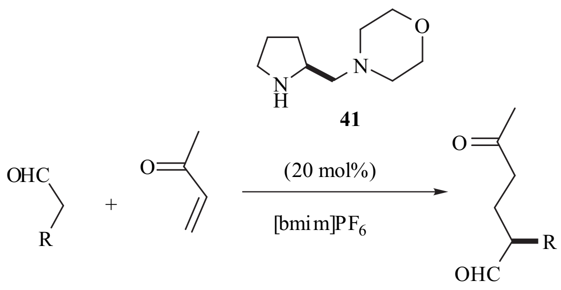
Cycle^a	Aldehyde **1** R =	Time (h)	Yield (%)^c
1^b	C$_8$H$_{17}$	5	83
2		5	70
3		5	82
4		5	81
5		5	70
6	PhCH$_2$	21	81
7	Cross aldol^d	19	22
8	TBDMSOC$_3$H$_6$	7	82
9	THPOC$_8$H$_{16}$	20(5)^e	58(78)^e
10	AcOC$_3$H$_6$	24	44
11		48	51

[a]Reaction was carried with 0.2 equiv. of the catalyst at 80 °C in [bmim]PF$_6$ under nitrogen atmosphere. [b]After cycle 1, the same reaction system was evacuated at 1.5 mmHg at 70 °C and re-used for subsequent reaction. [c]Yields were for isolated pure products by decantation with ether followed by medium pressure LC. [d]Reaction of *p*-nitrobenzaldehyde and acetone (10 equiv.) gave *p*-nitrtobenzalacetone. [e]New catalyst was used.

The reaction system made up heterogeneous catalyst and ionic liquid might be developed into an efficient continuous reactor combining direct distillation of the products from ionic liquid.

8. CATALYTIC ASYMMETRIC 1,4-CONJUGATE ADDITION IN IONIC LIQUID [33]

The asymmetric conjugate addition of unmodified aldehyde **1** to MVK **3** in [bmim]PF_6 was effected to afford optically active-5-keto-aldehyde **4** in up to 51% ee in the presence of 20 mol% of optically active pyrrolidine derivative **41** [34] derived from L-proline (Scheme **16**, Table **14**). The enantiomeric excess of the products were obtained by HPLC analysis of the corresponding benzoate **42**. The absolute stereostructure of **4a** was determined to be *S* by Kusumi's PGME method [35] after transformation of **4a** into PGME-ester **43** (Fig. **3**). Formation of the keto-aldehyde **4a** is explained by initial approach of MVK **3** to less hindered *Si*-face of *E*-enamine **44** to avoid bulkiness of the morpholine residue on pyrrolidine ring (Fig. **3**). Use of ionic liquid and cyclic amine was important to promote the reaction at room temperature or below thereby avoiding racemization of the resulting chiral keto-aldehyde **4**. .



1a: R = C_8H_{17} **3** **4a**
b: R = $PhCH_2$ **b**
c: R = $AcOC_3H_6$ **c**
d: R = C_4H_9 **d**
e: R = $TBSOC_3H_6$ **e**

Scheme 16.

Table 14. Catalytic Enantioselective1,4-Addition of Various Aldehydes 1

Entry[a]	Aldehyde 1 R =	Product 4	Yield (%)	ee(%)
1	C_8H_{17}	a	29	42
2[b]	$PhCH_2$	f	29	59
3	$PhCH_2$	f	72	24
4	$AcOC_3H_6$	i	22	44
5	C_4H_9	o	46	42
6	$TBDMSOC_3H_6$	p	17	51

[a] All reactions were carried out at room temp. for 48 h in the presence of 20 mol% of the diamine catalyst. [b] Reaction was carried out at 2 °C without solvent.

Meanwhile, higher enantiomeric induction of 79% was reported recently by Melchiorre and Jorgensen in THF and hexafluoro-2-propanol employing (2*S*,5*S*)-2,5-diphenylpyrrolidine as a catalyst [36].

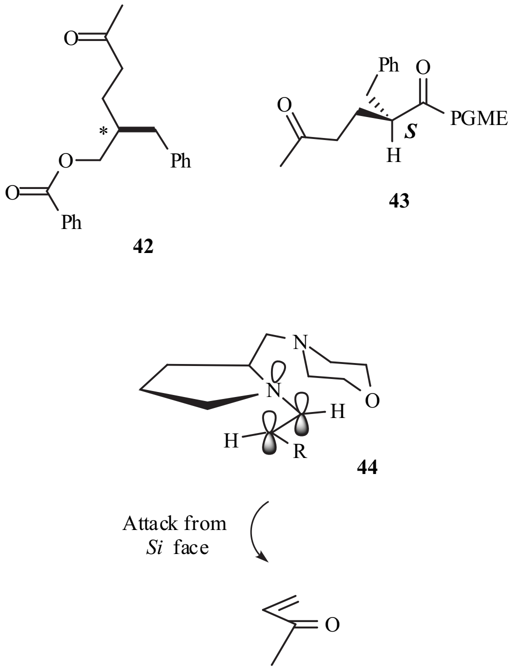


Fig. (3).

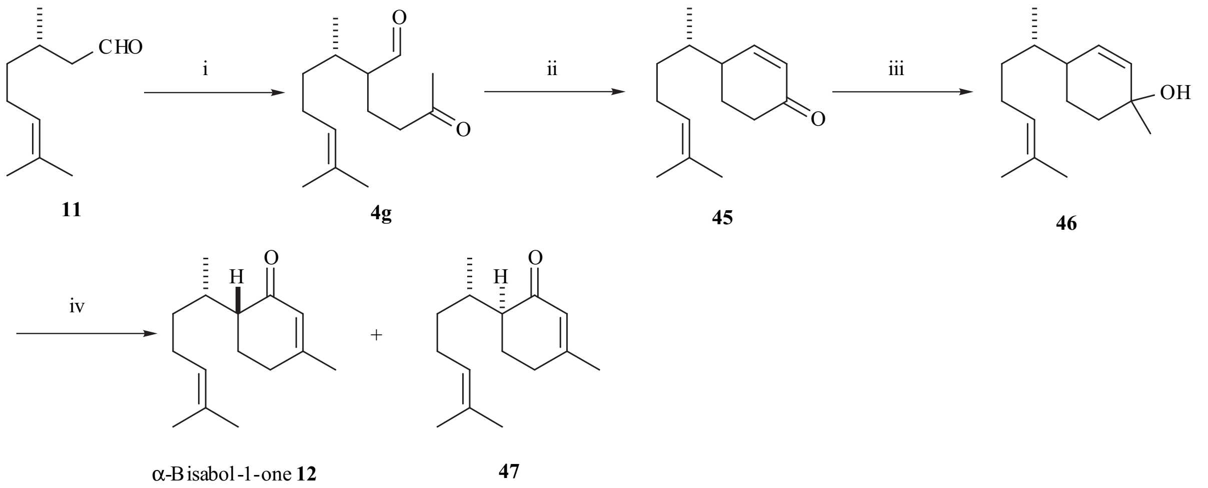
9. APPLICATION TO THE TOTAL SYNTHESES OF BISABOLANE TYPE SESQUITERPENOIDS [37]

The 5-ketoaldehydes **4** thus prepared can be easily transformed into 4-substituted cyclohexenone by intramolecular aldol condensation. Starting from (*R*)/(*S*)-citronellal **11** as a chiral source, total syntheses of several bisabolane sesquiterpenoids have been achieved. Bisabolane sesquiterpenoids have been found in terrestrial as well as marine organisms and some of them show intriguing bioactivities in spite of simple structure. Though there have been several synthetic precedents on the present target molecules, present synthetic sequences became shorter improving overall yields much better. Other notable feature is that these total syntheses have been accomplished without any protecting groups.

9.1 Total synthesis of (+)/(–)-α-bisabol-1-one 12

α-Bisabol-1-one **12** was at first isolated from *Stevia purpurea* [38] and later on both diastereomer **12** and **47** were isolated from Brazilian Lantana oil [39]. There is one report on total synthesis of optically active compound [40].

To begin with, intramolecular aldol condensation of the 5-ketoaldehyde **4g** prepared by the reaction of (*S*)-citronellal **11** and MVK **3** was investigated and satisfactory result was obtained, using basic phase transfer catalyst to give cyclohexenone **45**. Methylation and subsequent allylic oxidation by PCC provided a diastereomeric mixture of the desired compound **12** and **47,** which were separable by medium pressure LC. The overall yield from citronellal **11** was 78%. Starting from (*R*)-citronellal **11**, *ent*-**12** and *ent*-**47** were also synthesized (Scheme **17**).

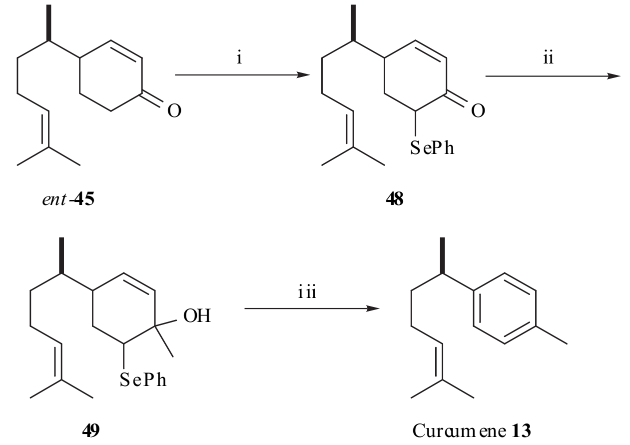


Scheme 17. Reagents and conditions; i, MVK, DEATMS (0.2 equiv.), MeCN, reflux, 20 h, >99%; ii, KOH, *n*-Bu_4NOH, THF, Et_2O, reflux, 4 h, 89%; iii, MeLi, Et_2O, >99%; iv, PCC, CH_2Cl_2, 89%.

9.2 Total Synthesis of (–)-Curcumene 13

Curcumene **13** isolated from *Curcuma aromatica* [41] have already been synthesized in either racemic as well as natural enantiomeric form [42].

Kinetic enolate of cyclohexenone *ent*-**45**, a synthetic intermediate for bisabol-1-one **12**, was treated with benzeneselelenyl chloride to give phenylselenide **48,** which was reacted with methyllithium. Treatment of the resulting alcohol **49** with PCC resulted in three contiguous reactions in one-pot operation, *i.e.* oxidation of selenide followed by elimination of selenoxide and subsequent dehydration to furnish curcumene **13**. The overall yield from citronellal **11** was 43% (Scheme **18**). Attempts to shorten synthetic sequence, namely dehydration of alcohol *ent*-**46** and subsequent DDQ oxidation, resulted in formation of complex mixture.

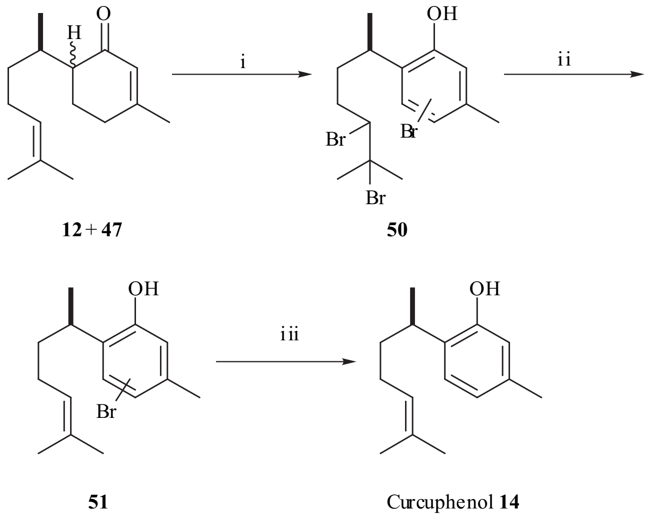


Scheme 18. Reagents and conditions; LDA, THF then PhSeCl, 84%; ii, MeLi, Et_2O, 86%; iii, PCC, CH_2Cl_2, 75%.

9.3 Total Synthesis of (–)-Curcuphenol 14

Curcuphenol **14** was isolated from marine sponge *Didiscus flavus* and also plant *Lasianthaea podocephala* [43]. It is interesting to note that (*S*)-enantiomer has antitumor activity while (*R*)-enantiomer exhibits antiviral activity. There have been four total syntheses so far [44].

It was anticipated that aromatization of a mixture of *ent*-**12** and its diastereomer *ent*-**47** could lead to curcuphenol **14**. However, attempted oxidation by DDQ, chemical manganese dioxide [45], or sulfur resulted in complete recovery. Attempted generations of kinetic enolate of *ent*-**47** were unsuccessful probably due to steric reason. Fortunately aromatization using copper bromide [46] provided phenol **50**, though aromatic nucleus and double bond in the side chain were brominated. Regeneration of the double bond by zinc/acetic acid and subsequent removal of the bromine atoms from aromatic nucleus by lithiation completed the total synthesis of (–)-curcuphenol **14** in 44% overall yield in 3 steps (Scheme **19**).

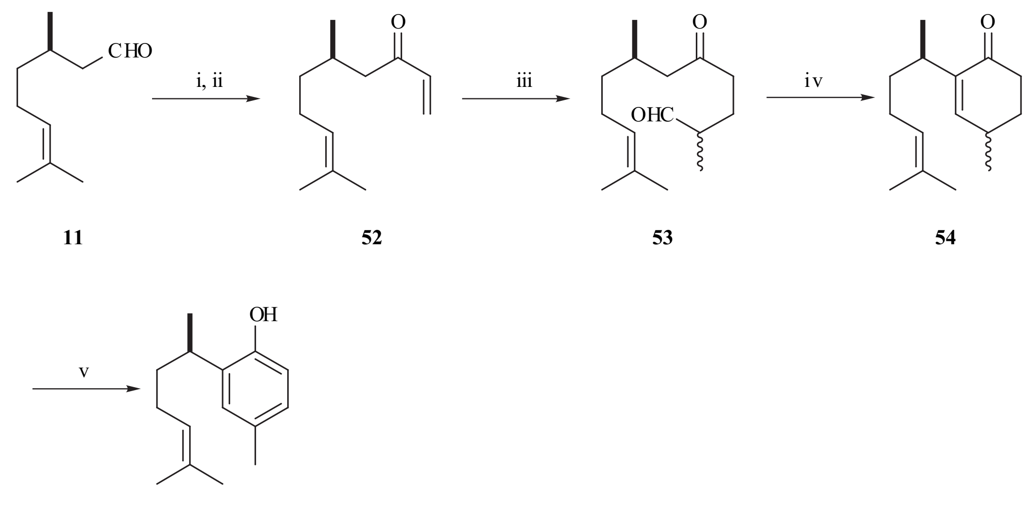


Scheme 19. Reagents and conditions; i, $CuBr_2$, MeCN; ii, Zn, AcOH, Et_2O; iii, *t*-BuLi, THF, 44% in three steps.

9.4 Total Synthesis of (+)/(–)-Elvirol 15

Elvirol **15** was isolated from *Elvira biflora* [47] and total synthesis of racemic **15** has already been reported [48]. Syntheses of both enantiomers were reported at the same time with present synthesis [49].

Vinylketone **52** requisite for 1,4-conjugate addition was prepared by vinylation of (*R*)-citronellal **11** followed by



Elvirol **15**

Scheme 20. Reagents and conditions; i, vinylmagnesium bromide, THF, 0 °C, >99%; ii, TPAP, NMO, CH_2Cl_2, 0 °C; iii, DEA, propionaldehyde, MeCN, sealed tube, 80 °C, 24 h, 48% in two steps; iv, 5% KOH, n-Bu_4NOH, THF, Et_2O, reflux, 93%; v, LDA, HMPA, THF, PhSeCl, 94%; vi, 30% H_2O_2, pyridine, CH_2Cl_2, 0 °C, 58%.

TPAP oxidation. Without purification due to volatility of **52**, 1,4-conjugate addition of propionaldehyde in the presence of DEA in a sealed tube provided 5-ketoaldehyde **53**. Intramolecular aldol condensation by phase transfer catalyst lead to enone **54**. Phenylselenylation and subsequent oxidation furnished (+)-elvirol **15** in 5 steps in 24% overall yield from (*R*)-citronellal **11**. Starting from (*S*)-citronellal **11**, *ent*-**15** was also synthesized (Scheme **20**).

10. CONCLUSION

A series of the present methodologies offers new protocol for nucleophilic reactions of unmodified aldehydes whose reactivities so far have been difficult to control. The reaction condition is mild enough to afford the desired products in excellent to acceptable yields, keeping acid sensitive OTHP, OTBDMS or base sensitive OAc group intact without substantial deprotection. Products thus obtained are very versatile synthetic intermediates for various synthetic transformations, which were exemplified by the total syntheses of some bisabolane type sesquiterpenoids. The reaction can be carried out without solvent if desired. Synthetic operation is very simple. After mixing reagents directly from bottles, bulb to bulb distillation or medium pressure LC is sufficient for product isolation. No aqueous work-up is required. When ionic liquid is used as a reaction media, direct distillation from reaction vessel is possible. In addition, waste disposals are less toxic amine and siloxane which can be trapped easily. Moreover, combining heterogeneous catalyst and ionic liquid, the whole system is recyclable and thus economical and environmentally benign. The system is expected to exploit a potentially sustainable reactor.

Contribution of DEATMS, DEA and heterogeneous amine as organocatalysts is elucidated by this project. New reactivity, milder reaction condition, simple synthetic operation and green sustainable character, all these features would rank present protocol in highly practical level.

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REFERENCES

[1] Brettle, R. in *Comprehensive Organic Chemistry*, Stoddart, J.F., Ed.; Pergamon Press: Oxford, **1979**; Vol. 1, p. 943.
[2] Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron*, **1986**, *42*, 4777.
[3] (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc*., **1963**, 85, 207. (b) Brown, M. *J. Org. Chem*., **1968**, *33*, 162.
[4] Nakajima, T.; Maruyama, Y.; Shimizu, I. *Abstracts of Papers of 65th Annual Meeting of Chemical Society of Japan*; Tokyo, **1993**; Vol. II, pp. 335.
[5] Hagiwara, H.; Komatsubara, N.; Ono, H.; Okabe, T.; Hoshi, T.; Suzuki, T.; Ando, M.; Kato, M. *J. Chem. Soc., Perkin Trans.1*, **2001**, 316.
[6] (a) Evans, D. A.; Bartoli, J.; *Tetrahedron Lett*., **1982**, *23*, 807. (b) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc*., **1987**, *109*, 1564. (c) Hamada, Y.; Yamamoto, Y.; Shimizu, H. *J. Organomet. Chem*., **1996**, *510*, 1. (d) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc.: New York, **1991**.
[7] Yamamoto, Y.; Shimizu, H.; Hamada, Y. *J. Organomet. Chem*., **1996**, *509*, 119.
[8] (a) Yamamoto, Y.; Shimizu, H.; Matui, C.; Chinda, M. *Main Group Chem*., **1996**, *1*, 409. (b) Ipaktschi, J.; Heydari, A. *Chem. Ber*., **1993**, *120*, 1905. (c) Papini, A.; Ricci, A.; Taddei, M.; Seconi, G.; Dembech, P. *J. Chem. Soc., Perkin Trans 1*, **1984**, 2261.
[9] Saidi, M. R.; Mojtahedi, M. M.; Bolourtchian, M. *Tetrahedron Lett.*, **1997**, *38*, 8071.
[10] Middleton, W. J.; Bingham, E. M. In *Org. Synth.*; Ed.; Noland, W. E., John Wiley & Sons: New York, **1988**; Collective volume 6, p. 440.
[11] Hagiwara, H.; Ono, H.; Hoshi, T. *Org. Synth*., **2003**, *80*, 195.
[12] Master's thesis of Komatsubara, N., Niigata University, **1999**.
[13] Franke, W.; Bueren, J. *Chem. Abst*., **1953**, *37*, 2205a. ; Eliel, E.; Lukach, C.A. *J. Am. Chem. Soc*., **1957**, *79*, 5986. ; Cook, K. L.;

Waring, A.J. *J. Chem. Soc., Perkin Trans 1*, **1973**, 529. ; Pesaro, M.; Bachman, J. –P. *J. Chem. Soc., Chem. Commun.*, **1978**, 203.

[14] Hagiwara, H.; Komatsubara, N.; Hoshi, T.; Suzuki, T.; Ando, M. *Tetrahedron Lett*., **1999**, *40*, 1523.

[15] Tietze, L.; Beifuss, U. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 131.

[16] Hagiwara, H. *J. Synth. Org. Chem., Japan*, **1992**, *50*, 713.

[17] Hagiwara, H.; Ono, H.; Komatsubara, N.; Hoshi, T.; Suzuki, T.; Ando, M. *Tetrahedron Lett*., **1999**, *40*, 6627.

[18] Heathcock, C. H. In *Comprehensive Organic Synthesis*, Ed.; Trost, B. M.; Fleming, I.: Pergamon Press, Oxford, **1991**, vol 2, p.133.

[19] Mahrwald, R.; Costisella, B.; Gündogan, B. *Synthesis*, **1998**, 262.

[20] Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett*., **1997**, *38*, 8727.

[21] Okano, T.; Satou, Y.; Tamura, M.; Kiji, J. *Bull. Chem. Soc., Jpn.*, **1997**, *70*, 1879.

[22] Ishikawa, T.; Uedo, E.; Okada, S.; Saito, S. *Synthesis*, **1999**, 450.

[23] (a) Hellberg, L. H.; Juarez, A. *Tetrahedron Lett*., **1974**, *40*, 3553. ; (b) Fiorenza, M.; Ricci, A.; Romanelli, M. N.; Taddei, M.; Dembech, P.; Seconi, G. *Heterocycles*, **1982**, *19*, 2327. ; (c) Yamamoto, Y.; Matui, C. *Organometallics*, **1997**, *16*, 2204.

[24] Comi, R.; Franck, R. W.; Reitano, M.; Weinreb, S. M. *Tetrahedron Lett.*, **1973**, *33*, 3107.

[25] Tani, K.; Yamagata, T.; Otshuka, S.; Kumobayashi, H.; Akutagawa, S. In *Org. Synth.*, Ed.; Freeman, J. P.; John Wiley & Sons: New York, Collective volume 8, **1993**, p. 183.

[26] Birkofer, L.; Stuhl, O. In *The Chemistry of Organosilicon Compounds Part 1*, Ed.; Patai, S.; Rappoport, Z.; John Wiley & Sons Ltd, **1989**, p. 655.

[27] Hagiwara, H.; Okabe, T.; Hakoda, K.; Hoshi, T.; Ono, H.; Kamat, V. P.; Suzuki, T.; Ando, M. *Tetrahedron Lett*., **2001**, *42*, 2705.

[28] Shimizu, K.; Suzuki, H.; Hayashi, E.; Kodama, T.; Hagiwara, H.; Kitayama, Y. *J. Chem. Soc., Chem., Commun.*, **2002**, 1068.

[29] Shimizu, K.; Hayashi, E.; Inokuchi, T.; Kodama, T.; Hagiwara, H.; Kitayama, Y. *Tetrahedron Lett*., **2002**, *43*, 9073.

[30] Hagiwara, H.; Tsuji, S.; Okabe, T.; Hoshi, T.; Suzuki, T.; Suzuki, H.; Shimizu, K.; Kitayama, Y. *Green Chemistry,* **2002**, *4*, pp. 461-463.

[31] Hamaya, J.; Hoshi, T.; Suzuki, T.; Shimizu, K.; Kitayama, Y.; Hagiwara, H. *Synlett*, **2003**, 873.

[32] Welton, T. *Chem. Rev.,* **1999**, *99*, 2071. ; Wasserscheid, P.; Keim,, W. *Angew. Chem., Int. Ed. Engl*., **2000**, *39*, 3773. ; Sheldon, R. *Chem. Commun*., **2001**, 2399; Gordon, C. M. *Appl. Catal. A, General*, **2001**, *222*, 101.

[33] Hagiwara, H.; Okabe, T.; Hoshi, T.; Suzuki, T. *Journal of Molecular Catalysis A, Chemical,* **2004**, *in press.*

[34] Asami, M. *Bull. Chem. Soc., Jpn*., **1990**, *63*, 721; Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron*, **2002**, *58*, 8167.

[35] Nagai, Y.; Kusumi, T. *Tetrahedron Lett*., **1995**, *36*, 1853. ; Yabuuchi, T.; Kusumi, T. *J. Org. Chem.,* **2000**, *65*, 397.

[36] Melchiorre, P.; Jorgensen, K. A. *J. Org. Chem*., **2003**, *68*, 4151.

[37] Hagiwara, H.; Okabe, T.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1,* **2002**, 895.

[38] Bohlmann, F.; Zdero, C.; Schoneweiss, S. *Chem. Ber*., **1976**, *109*, 3366.

[39] Weyerstahl, P.; Marschall, H.; Eckhard, A.; Christiansen, C. *Flavour Fragr. J.,* **1999**, *14*, 15.

[40] Ghisalberti, E. L.; Jefferies, P. R.; Stuart, A. D. *Aust. J. Chem*., **1979**, *32*, 1627.

[41] (a) Damodaran, N. P.; Dev, S. *Tetrahedron*, **1968**, *24*, 4113. (b) Honwad, V. K.; Rao, A. S.; *ibid*., **1964**, *20*, 2921.

[42] (a) Fuganti, C.; Serra, S.; Dulio, A. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 279. (b) Fuganti, C.; Serra, S. *Synlett*., **1998**, 1252. (c) Chavan, S. P.; Dhondge, V. J.; Patil, S. S.; Rao, Y. T. S. *Tetrahedron: Asymm*., **1997**, *8*, 2517. (d) Takano, S.; Yanase, M.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem., Commun*., **1998**, 1538. (e) Honda, Y.; Sasaki, M.; Tsuchihashi, G. *Chem. Lett*., **1985**, 1153. (f) Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett*., **1982**, *23*, 5567. (g) Tamao, K.; Hayashi, T.; Matsumoto, H.; Yamamoto, H.; Kumada, M. *Tetrahedron Lett*., **1979**, *20*, 2155. (h) Joshi, G. D.; Kulkarni, S. N. *Indian J. Chem*., **1968**, *6*, 127.

[43] Weight, A. E.; Pomponi, S. A.; McConnell, O. L.; Kohmoto, S.; McCarthy, P. J. *J. Nat. Prod*., **1987**, 50, 976 and references cited therein.

[44] (a) Kimachi, T.; Takemoto, Y. *J. Org. Chem*., **2001**, *66*, 2700. (b) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin 1,* **2000**, 3758. (c) Sugahara, T.; Ogasawara, K. *Tetrahedron: Asymm*., **1998**, *9*, 2215.

[45] (a) Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shioiri, T. *Synlett*, **1998**, 35. (b) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc*., **1998**, *120*, 12777.

[46] Rao, P. N.; Cessac, J. W.; Kim, H. K. *Steroids*, **1994**, *59*, 621.

[47] Bohlmann. F.; Grenz, M. *Tetrahedron Lett*., **1969**, *10*, 1005.

[46] (a) Dennison, N. R.; Mirrington, R. N.; Stuart, A. D. *Aust. J. Chem*., **1975**, 28, 1339. (b) Pednekar, P. R.; Chakravarti, K. K. *Indian J. Chem*., **1980**, 19B, 1076. (c) Bohlmann, F.; Kornig, D. *Chem. Ber*., **1974**, *107*, 1777.

[47] Ono, M.; Suzuki, K.; Tanaka, S.; Akita, H. *Tetrahedron:Asymm*., **2001**, *12*, 2597.

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