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PAPER

An environmentally friendly Mukaiyama aldol reaction catalyzed by a strong Brønsted acid in solvent-free conditions†

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o-Benzenedisulfonimide, a new strong bench-stable Brønsted acid, has been shown to efficiently catalyze the Mukaiyama aldol reaction of aldehydes or dimethyl acetals with silyl enol ethers under mild solvent-free reaction conditions.

Introduction

The Mukaiyama aldol reaction[1] is one of the most powerful carbon-carbon bond-forming reactions. The interest in the synthetic developments of this reaction is high, because of the widespread presence of the aldol motif in natural products. The reaction occurs between silyl enol ethers or ketene silyl acetals and carbonyl compounds to afford β-hydroxy ketones or β-trimethylsilyloxy esters, respectively. The advantages of the Mukaiyama reaction over the direct cross-aldol reaction are its milder reaction conditions, nonreversibility, high product yields and lower amounts of dehydration side-products. The aforementioned enol equivalents are stable enough to be easily prepared and stored, but a catalyst is needed to obtain the aldol reaction. Normally Lewis acid or Lewis base catalysts are used in catalytic loadings to activate the electrophilic carbonyl substrate or the nucleophilic silyl enol equivalent, respectively, so a huge number of examples has been reported in the literature.[2] By contrast, in the last decade very few Brønsted acids have been used as catalysts in this reaction.

N,*N*-Bis(trifluoromethanesulfonyl) squaramide has recently been reported as a strong bench-stable Brønsted acid and applied in catalytic amounts (1 mol %) to Mukaiyama aldol and Mukaiyama-Michael reactions between trimethylsilyl enol ethers and aromatic aldehydes (or electron-deficient ketones) and α,β-unsaturated ketones, respectively.[3a] The reaction mechanism was investigated, since it is known that the Mukaiyama aldol reaction may be promoted by either a true Brønsted acid catalyst or a Lewis acid catalyst which corresponds to the *in situ* silylated Brønsted acid.[3b] On the basis of the observed results, a real Brønsted acid catalysis is however preferred by the authors. The same authors have also developed the synthesis of *N*,*N*-bis(perfluoroalkanesulfonyl) squaric acid diamides and applied them as catalysts in two Mukaiyama reactions and in a carbonyl-ene reaction.[3c,d]

Extraordinarily bulky tris(trimethylsilyl)silyl (TTMSS) enol ethers of acetaldehyde and propanal have been successfully reacted with a variety of aliphatic aldehydes in the presence of bis(trifluoromethanesulfonyl)imide (triflimide, $HNTf_2$)[3b] as the catalyst (0.05 mol %). Identical results were obtained by using $TTMSSNTf_2$. This finding was explained with the silyl triflimide as the likely true self-repairing catalyst.

A chiral 3,3′-disubstituted 1,1′-binaphthyl-2,2′-disulfonimide has been reported as the catalyst (2–5 mol %) in an asymmetric application of the Mukaiyama reaction.[4] Ketene silyl acetals were used as enol equivalents in the reaction with aromatic, α,β-unsaturated and aliphatic aldehydes with high enantioselectivity. A Lewis acid mechanism, supported by NMR studies, was proposed. This involved an intermediate *N*-silyl disulfonimide as the actual catalyst.

Rawal and coworkers have reported the catalytic use of α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) family diols (20 mol %) in both diastereoselective and enantioselective Mukaiyama aldol reactions[5a,b] and in vinylogous Mukaiyama aldol reactions.[5c] The hydrogen bond between the chiral diols and the carbonyl substrates (aromatic aldehydes or β-ketoesters) generates highly ordered transition states. These are responsible for the high enantioselectivity observed in the reaction products when using hetero-atom substituted ketene acetals. Several bis-sulfonamides have also been reported to activate, through hydrogen bonding, the carbonyl group of aromatic aldehydes in the Mukaiyama reaction with silyl ketene acetals.[6] Brønsted acid assisted chiral Lewis acid catalysts, namely chiral acyloxyboranes derived from tartaric acid, have also been reported to efficiently catalyze the Mukaiyama aldol reaction of aldehydes with trimethylsilyl enol ethers[7a–b] or ketene silyl acetals.[7c] The high and enantioselective reactivity of these catalysts was attributed to the intramolecular hydrogen bonding of a terminal carboxylic group.

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Finally, catalytic amounts of benzoic acid improved a boron enolate-mediated diastereoselective Mukaiyama aldol reaction between silyl enol ethers and aromatic aldehydes, in the presence of aryl borinic acids as boron source and a surfactant in water. The role of the weak Brønsted acid was presumed to be the acceleration of the Si–B exchange step through the protonation of the hydroxyl group of the borinic acid.[8]

We have recently described the usefulness of a new strong Brønsted acid, namely *o*-benzenedisulfonimide (**1**) (Fig. 1), in organic synthesis.[9] Compared to Lewis acid metal catalyzed reactions, this compound has proved to be a more efficient and recyclable organocatalyst in many acid-catalyzed organic reactions in environmentally friendly conditions.[9d,f–h,j]

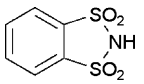


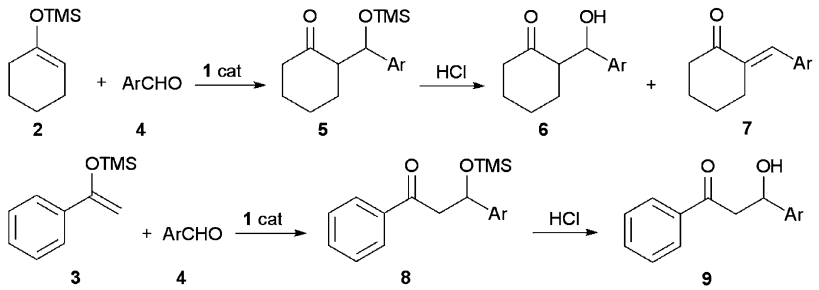
Fig. 1 *o*-Benzenedisulfonimide (**1**).

Herein we wish to report that **1** can catalyze the Mukaiyama aldol reaction between silyl enol ethers **2** (or **3**) and carbonyl compounds **4** in mild and solvent-free reaction conditions in very low amounts. Reaction conditions were also extended to acetals **13**. In an interesting variation of the Mukaiyama aldol reaction, dimethyl acetals were used as highly electrophilic aldehyde surrogates.[10a] Enol silanes were formed *in situ*[10b] and one-pot reacted with the dimethyl acetals of aromatic or aliphatic aldehydes. These, activated by a Lewis acid catalyst, gave oxocarbenium ions which are a class of electrophiles that is known to undergo Mukaiyama-type addition.

Results and discussion

Initially, in order to optimize the reaction conditions, the model reaction of 1-trimethylsilyloxycyclohex-1-ene (**2**) or 1-trimethylsilyloxystyrene (**3**) and 4-chlorobenzaldehyde (**4a**; Ar = 4-ClC_6H_4) catalyzed by **1** was studied under different reactant ratios and conditions (Scheme 1). The intermediate trimethylsilyl derivatives **5a** and **8a** were not isolated and so were immediately hydrolyzed to the aldol products **6a** and **9a**.

The most representative results, obtained from trimethylsilyl enol ethers **2** (entries 1–5) and **3** (entries 6–9), are reported in Table 1 and can be summarized as follows. The optimal reactant ratios between the enol equivalents and aldehyde **4a** were 2 : 1 and 1.3 : 1, respectively. Polar or slightly polar solvents were tested, but the best results were obtained in solvent-free reaction conditions. The effect of the catalytic amount of **1** was also studied. In the presence of solvents, larger quantities of catalyst were used, without producing significant product yields. In the optimized reaction conditions, *i.e.* without any solvent, **1** was used in 1 mol % starting from **2** and 2 mol % from **3**. All the reactions were carried out at rt and reached completion in short times. When **2**



4a: Ar = 4-ClC_6H_4; **4b**: Ar = 4-$MeOC_6H_4$; **4c**: Ar = C_6H_5; **4d**: Ar = 4-$NO_2C_6H_4$; **4e**: Ar = 4-NCC_6H_4; **4f**: Ar = 2-MeC_6H_4; **4g**: Ar = 2-$CF_3C_6H_4$; **4h**: Ar = 2-thienyl; **4i**: Ar = cinnamyl

Scheme 1 Mukaiyama aldol reaction between enol equivalents **2** or **3** and aldehydes **4**.

Table 1 Mukaiyama aldol trial reactions of **2** (or **3**) with **4a**

Entry	Reactant ratio[a]	**1** (mol %)	Solvent/t (h)	Products, Yields (%)[b]	*dr*[c]
1	**2**:**4a** = 1.1 : 1	1	Neat/4	**6a**, 49 **7a**, 11	57 : 43
2	**2**:**4a** = 1.5 : 1	1	Neat/4	**6a**, 56 **7a** (n.d.)	55 : 53
3	**2**:**4a** = 2 : 1	1	Neat/4	**6a**, 68 **7a**, 5	50 : 50
4	**2**:**4a** = 2 : 1	1–10	CH_2Cl_2/48	[d]	
5	**2**:**4a** = 2 : 1	1–5	Tol/5	[d]	
6	**3**:**4a** = 1.1 : 1	1–10	MeCN/5	[e]	
7	**3**:**4a** = 1.1 : 1	1–10	CH_2Cl_2/48	[e]	
8	**3**:**4a** = 1.1 : 1	1–5	Neat/2	**9a**, 60	
9	**3**:**4a** = 1.3 : 1	2	Neat/2	**9a**, 87	
10	**2**:**4a** = 2 : 1	2[f]	Neat/2	**6a**, 38 **7a**, 5	50 : 50
11	**3**:**4a** = 1.3 : 1	4[f]	Neat/4	**9a**, 63	

[a] Unless otherwise stated, the reactions were carried out on 2 mmol of **4a**, at rt (20–25 °C). After completion of the reaction, the reaction mixture was treated with 2 N HCl (2 mL) to hydrolyze **5a** to **6a** or **8a** to **9a**. [b] Products identified by ^1H and ^{13}C NMR spectra; yields % of isolated products (flash chromatography; PE/AcOEt = 7 : 3). [c] dr (*syn*/*anti*) determined by ^1H NMR spectroscopy. [d] Expected products were identified, but in low amounts. [e] In MeCN **3** decomposes completely to acetophenone, whilst in CH_2Cl_2 the acid hydrolysis of **8a** does not proceed to completion. [f] 2,4-Dinitrobenzenesulfonic acid was used as the catalyst.

Table 2 Mukaiyama aldol reaction of enol ethers **2** or **3** with aldehydes **4**

Entry	Reactants[a]		**1** (mol %)	t (h)	Products, Yields (%);[b] overall yield	*dr*[c]	Lit. [%][d]
1	**2**	**4a**	1	4	**6a**, 68; **7a**, 5; overall 73	50 : 50	
2	**2**	**4b**	2	4	**6b**, 68; **7b**, 16; overall 84	59 : 41	
3	**2**	**4c**	2	6	**6c**, 51; **7c**, 19; overall 70	57 : 43	58(56 : 44),[8] 87 (80 : 20)[3a]
4	**2**	**4d**	3	3[e]	**6d**, 48; **7d**, 15; overall 63	50 : 50	
5	**2**	**4e**	5	6	**6e**, 48; **7e**, 14; overall 62	46 : 54	
6	**3**	**4a**	2	2	**9a**, 87		97[3d]
7	**3**	**4b**	2	1	**9b**, 88		93[3a,d]
8	**3**	**4c**	3	2	**9c**, 80		96[3a,d]
9	**3**	**4d**	4	2	**9d**, 91		98[3a,d]
10	**3**	**4e**	4	2	**9e**, 96		
11	**3**	**4f**	2	3	**9f**, 98		95[3a,d]
12	**3**	**4g**	4	6	**9g**, 80		
13	**3**	**4h**	4	1	**9h**, 89		91[3d]
14	**3**	**4i**	1	1.5	**9i**, 80; **10**, 16		92[3d]
15	**3**	**11**[g]	2	24	**12**,[f] 32		

[a] Unless otherwise stated, the reactions were carried out on 2 mmol of **4**, at rt (20–25 °C). The reactant ratio was **2**: **4** = 2 : 1 and **3**: **4** = 1.3 : 1. After completion of the reaction, the reaction mixture was treated with 2 N HCl (2 mL) to hydrolyze **5** to **6** or **8** to **9**. [b] Yields % refer to isolated products (flash chromatography; eluent: PE:AcOEt = 7 : 3 in entries 1–5, 7, 9–10, 14 and PE:AcOEt = 8 : 2 in entries 6, 8, 11–13). [c] dr (*syn*/*anti*) determined by ^{1}H NMR spectroscopy. [d] Yields obtained in Brønsted acid-catalyzed Mukaiyama aldol reactions; dr in parentheses. [e] Reaction temperature was 50 °C. [f] Hexanal (**11**) was the starting aldehyde.

was the starting enol equivalent, *syn* and *anti* diastereomers **6a** were obtained, but no significant stereocontrol of the Mukaiyama aldol reaction was observed in the presence of **1** as the catalyst. All these reactions gave the by-product **7a**, as an acid-catalyzed dehydration product of the aldol **6a**.

In order to evaluate the role of the acidity of **1** on the catalytic activation of the Mukaiyama reaction, the optimized conditions of entries 3 and 9 were tested in the presence of 2,4-dinitrobenzenesulfonic acid, a Brønsted acid commonly used as an organocatalyst.[11] As reported in entries 10 and 11 respectively, greater amounts of catalyst were used, longer reaction times and lower product yields were observed.

The optimized reaction conditions were then applied to the Mukaiyama aldol reaction of a number of representative aromatic aldehydes. Aldehydes **4b–g**, bearing both electron-donating or electron-withdrawing substituents (Scheme 1), were reacted with the enol equivalents **2** (Table 2, entries 1–5) and **3** (Table 2, entries 6–12).

In general, larger amounts of catalyst (entries 4–5 and 9–10) and heating (entry 4) were required in the presence of electron-withdrawing groups. Lower yields and lower overall conversions were also observed. Dehydration products **7** were always isolated along with the predominant aldol products when **2** was reacted (entries 1–5), whereas, higher selectivity and better aldol product yields were obtained from **3**. *o*-Substituted aldehydes were also reacted with **3** (**4f** and **4g**; entries 11–12). Longer reaction times were required and, due to the electron-withdrawing effect of the substituent group on **4g**, a larger amount of catalyst was needed.

In the light of these results, the applicability of the acid catalyzed Mukaiyama reaction of **3** with a heteroaromatic and an α,β-unsaturated aldehyde was studied (2-thiophenecarboxaldehyde, **4h** and cinnamaldehyde, **4i**). Good results were also obtained in these cases. Interestingly, in the reaction with **4i**, 5-oxo-3,5-diphenylpentanal (**10**) (Fig. 2) was isolated as the Mukaiyama-Michael addition product in 16% yield (entry 14). In order to favor the 1,2-addition over to the 1,4-, the reaction temperature was

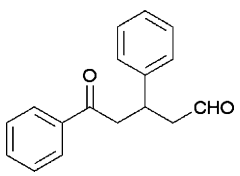


Fig. 2 5-Oxo-3,5-diphenylpentanal (**10**).

lowered to 0 °C and then to −30 °C, but no appreciable variation in the ratio of **9i** to **10** was observed.

The literature yields of the aldol products **6** and **9**, obtained in Brønsted acid catalyzed Mukaiyama reactions, are also reported in Table 2 for ease of comparison. Only few examples have been recovered and the yields are comparable.

Owing to these encouraging results, some aliphatic aldehydes were then tested, although only the bulky tris(trimethylsilyl)silyl enol ethers of acetaldehyde and propanal have so far been reported to react in a Mukaiyama reaction with aliphatic aldehydes under similar reaction conditions ($HNTf_2$ or $TTMSSNTf_2$ as the catalysts).[3b]

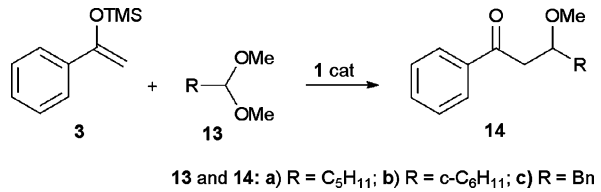
Unfortunately, phenylacetaldehyde, cyclohexanecarbaldehyde, and pivalaldehyde never reacted, even under various reaction conditions (neat or in MeCN, in the presence of 2–5 mol % of **1** at rt or by heating to 50 °C, prolonged times). Only hexanal (**11**) gave the expected aldol product **12** in reaction with **3** in 32% yield (Table 2, entry 15). Keeping in mind that dimethyl acetals have been used as aldehyde surrogates,[10a] the dimethyl acetals of some aliphatic aldehydes were then reacted with **3** in neat conditions and in the presence of **1** as the catalyst (Scheme 2). The reaction was achieved, although modest to good results were obtained, as reported in Table 3.

Furthermore, although (*R*)-2,2′-binaphthyldisulfonimide **15**[12] (Fig. 3) does not show any evidence of an enantiomeric induction, the model Mukaiyama reaction between **2** and **4a** was carried out in its presence in the same optimized catalytic amounts of **1**. Binaphthyl-derived chiral disulfonimides have recently received

Table 3 Mukaiyama aldol-type reaction of **3** with dimethyl acetals **13**

Entry	Reactants[a]		**1** (mol %)	t (h)	Yields[b] of **14** (%)
1	**3**	**13a**	2	30	**14a**, 81
2	**3**	**13b**	2	4	**14b**, 61
3	**3**	**13c**	3	24	**14c**, 33

[a] The reactions were carried out on 2 mmol of **13**, at rt (20–25 °C). The reactant ratio was **3**: **13** = 1.3 : 1. [b] Yields % refer to isolated products (flash chromatography; eluent: PE:AcOEt = 9 : 1).



Scheme 2 Mukaiyama-aldol type reaction catalyzed by **1**.

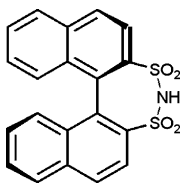
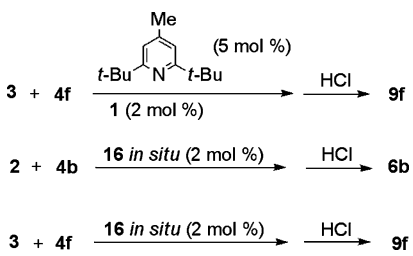


Fig. 3 (*R*)-2,2′-Binaphthyldisulfonimide (**15**).

growing interest as Brønsted acid organocatalysts.[4,13] In general, the presence of bulky aryl substituents at the 3,3′-positions is needed for effective enantioselective catalysis. So it was not a surprise to isolate, from the reaction mixture, a diastereomeric mixture of *syn* and *anti* **6a** in a ratio which was unaltered with respect to entry 1 in Table 2.

Finally, some mechanistic studies have been undertaken in order to clarify the real nature of the catalyst involved. The results are reported in Table 4 and illustrated in Scheme 3.



Scheme 3 Mechanistic studies between **2** or **3** and **4b** or **4f**.

In order to differentiate between Lewis and Brønsted acid catalysis, the reaction between 1-trimethylsilyloxystyrene (**3**) and 2-methylbenzaldehyde (**4f**) was first performed in the presence of 2,6-di-*t*-butyl-4-methylpyridine (DBMP) (Table 4, entry 1). This hindered base is known to act as a proton scavenger that inhibits any protic acid catalysis.[3a–b,4] Under reaction conditions of entry 11, Table 2, and in the presence of 5 mol % of DBMP, the reaction did not proceed to completion within the same time (1 h). Moreover, when it was quenched after 24 h, traces of **3** and low amounts of **4f** were still recovered. Acid hydrolysis gave the aldol product **9f** in a 83% yield.

Then, in order to assess the transfer of the trimethylsilyl group from **2** or **3** to **1** and therefore the *in situ* formation of the Lewis acid catalyst **16**, **1** (1.0 equiv) was added to the enol ether **2** (or **3**). ^{1}H NMR spectra (anhydrous $CDCl_3$) showed the immediate hydrolysis of the silyl enol ethers **2** or **3** (with the respective disappearance of singlets at 0.12 ppm and 0.23 ppm) and the appearance of a new singlet centered at 0.59 ppm, which has been attributed to the Me_3Si group of *N*-trimethylsilyl-1,2-benzenedisulfonimide (**16**) (Fig. 4).[14] Afterwards, a 1 : 1 mixture of **1** and **2** (or **3**) (2 mol % with respect to remaining reagents) was prepared and then **2** and **4b** (or **3** and **4f**) were added. ^{1}H NMR spectra of both reaction mixtures showed the immediate formation of **16** and both reactions proceeded in a similar fashion. In both cases, the reagent **2** (or **3**) was consumed more quickly, but with lower product yields with respect to results obtained previously (see entries 2 and 3 of Table 4 and entries 2 and 11 of Table 2).

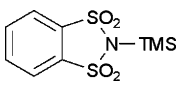


Fig. 4 *N*-Trimethylsilyl-1,2-benzenedisulfonimide (**16**).

Finally, several attempts were made to prepare and isolate derivative **16** by treating **1** with allyltrimethylsilane in MeCN at rt, but unsuccessfully.[15] Although ^{1}H NMR spectra showed a singlet

Table 4 Mechanistic studies

Entry	Reactants[a]		**1** (mol %)	t (h)	Products; Yields (%)[b]
1	**3**	**4f**	2[c]	24	**9f**; 83
2	**2**	**4b**	2[d]	2	**6b**, 60 (54 : 46);[e] **7b**, 23
3	**3**	**4f**	2[d]	0.3	**9f**; 83

[a] The reactions were carried out on 2 mmol of **4**, at rt (20–25 °C), following reaction conditions as in Table 2. [b] Yields % refer to isolated products (flash chromatography; eluent: PE:AcOEt = 8 : 2 in entries 1–3 and PE:AcOEt = 7 : 3 in entry 2). [c] The reaction was run in the presence of 4-methyl-2,6-di(t-butyl)pyridine 5 mol %. [d] Reactions performed by previously preparing *in situ* Lewis acid **16** as the catalyst. [e] In parentheses dr (*syn*/*anti*) determined by ^{1}H NMR spectroscopy.

at 0.59 ppm, other signals, probably due to the decomposition of **16**, were always predominant.

Compared to literature reports, our results are in better agreement with those of Yamamoto and coworkers[3a,3d] (which obtained them by using the same silyl enol ether as the enol equivalent) than with those of List and coworkers.[4] In our conditions, the *in situ* formed Lewis acid catalyst appears to be less efficient than the parent imide. This behaviour could be interpreted as a result of many possible reasons. The low nucleophilicity of its conjugate base could prevent the inter and intramolecular transfer of the silyl group. This topic has been previously discussed in Mukaiyama reactions induced by silyl Lewis acid catalysts with conjugate bases of various nucleophile strengths.[16] In neat conditions, acid **1** could activate electrophilic aldehydes through hydrogen bonding. Nevertheless, experimental findings suggest that the Brønsted acid itself is a more efficient catalyst than the silylated one.

Conclusions

In summary, a new application of the organocatalyst *o*-benzenedisulfonimide (**1**) has been reported. This strong bench-stable Brønsted acid has been shown to efficiently catalyze the Mukaiyama aldol reaction between various aromatic aldehydes and silyl enol ethers as enol equivalents, in solvent-free conditions. In the case of less reactive aliphatic aldehydes, the corresponding dimethyl acetals have been used as source of highly electrophilic oxocarbenium ions, in the presence of catalytic amounts of **1**. Mechanistic studies are in better agreement with the involvement of a Brønsted acid than a Lewis acid catalysis.

Experimental

General experimental

All the reactions were conducted in vials using analytical grade reagents, and were monitored by GC and GC-MS spectrometry. GC-MS spectra were recorded with an AT5973N mass selective detector connected to an AT6890N GC cross-linked methyl silicone capillary column. IR spectra were recorded using a Perkin Elmer Spectrum BX FT-IR spectrometer in neat conditions or as solutions in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Bruker Avance 200 spectrometer at 200 MHz and 50 MHz, respectively; chemical shifts are given in ppm relative to $CDCl_3$. TLC were performed on Fluka silica gel TLCPET foils GF 254, 2–25 μm, layer thickness 0.2 mm, medium pore diameter 60 A°. Plates were visualized using UV light (254 nm) or treatment with an appropriate revelatory agent (*p*-anisaldehyde), followed by heating. Column flash chromatography was carried out on SiO_2 (particle size 0.032–0.063 mm/230–400 mesh). Petroleum ether refers to the fraction boiling in the range 40–60 °C and is abbreviated as PE. Commercially available reagents and solvents were purchased from Aldrich and were used without purification or distillation prior to use; Dowex 50 × 8 ion-exchange resin was purchased from Fluka. *o*-Benzenedisulfonimide (**1**) was prepared as described in literature.[17] Moisture-sensitive **3** was prepared following literature;[18] flasks and all equipment used for its generation were dried by electric heat gun under Ar; THF was distilled from Na/benzophenone ketyl. Acetal **13a** was prepared following a previously optimized procedure.[9b] Structure and purity of all isolated products were confirmed by comparison of their physical and spectral data (IR, MS and ^1H NMR) with those reported in literature. See ESI for details.†

General procedure for Mukaiyama aldol reaction

A mixture of aldehyde **4** (2.0 mmol), trimethylsilyl enol ether **2** (0.68 g, 4.0 mmol) or **3** (0.50 g, 2.6 mmol), and *o*-benzenedisulfonimide (**1**, mol % as in Table 2) was stirred at r.t. in a vial until TLC and GC analyses showed almost complete conversion of **4**. The reaction mixture was then treated with 2 N HCl (2 mL) and stirred at rt for 5–20 min. After TLC analyses showed complete hydrolysis of **5** to **6** (or **8** to **9**), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with aqueous $NaHCO_3$ (20 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography on a short column of silica gel (eluent reported in footnote of Table 2).

Representative experimental data: 2-[(4-chlorophenyl)-(hydroxy)methyl]cyclohexan-1-one (6a). White solid, 68% yield; dr (*syn*/*anti*) = 50 : 50, determined by ^1H NMR analysis of title compound isolated partially as pure *syn* and *anti* diastereomers, and partially as a mixture.

syn-**6a**:[19] ^1H NMR (200 MHz, $CDCl_3$): δ = 1.13–1.25 (m, 1H), 1.40–1.88 (m, 5H), 1.98–2.10 (m, 1H), 2.30–2.50 (m, 3H), 5.29 (d, *J* = 2.4 Hz, 1H), 7.12–7.28 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.7, 25.8, 27.7, 42.5, 56.8, 69.9, 127.0 (2C), 128.1 (2C), 132.1, 139.8, 214.4. FT-IR ($CHCl_3$, cm^{-1}): 3584, 3539, 3016, 2946, 2870, 1698, 1494, 1208, 1091, 702.

anti-**6a**:[19] ^1H NMR (200 MHz, $CDCl_3$): δ = 1.11–1.40 (m, 1H), 1.42–1.80 (m, 5H), 1.98–2.10 (m, 1H), 2.15–2.55 (m, 3H), 4.70 (d, *J* = 8.8 Hz, 1H), 7.14–7.29 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.5, 27.5, 30.5, 42.4, 57.1, 73.8, 128.2 (2C), 128.3 (2C), 133.3, 139.4, 215.1. FT-IR ($CHCl_3$, cm^{-1}): 3584, 3539, 3025, 2946, 2869, 1697, 1491, 1211, 1089, 781.

2-(4-Chlorobenzylidene)cyclohexan-1-one (7a)[20]. Yield 5%. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.64–1.74 (m, 2H), 1.78–1.90 (m, 2H), 2.45 (t, *J* = 6.8 Hz, 2H), 2.71 (td, *J* = 6.4 and 2.2 Hz, 2H), 7.20–7.30 (m, 4H), 7.34 (t, *J* = 2.2 Hz, 1H). MS *m*/*z* (%): 220 [M+](88), 129 (100).

3-(4-Chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (9a)[3d,21]. White needles, mp 99.4–100.4 °C (CH_2Cl_2–PE) [lit.[22] 96–96.5 °C]. Yield 87%.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.20 (br s, 1H), 3.28 (d, *J* = 6.0 Hz, 2H), 5.20–5.31 (m, 1H), 7.26–7.32 (m, 4H), 7.35–7.45 (m, 2H), 7.48–7.55 (m, 1H), 7.80–7.93 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 47.1, 69.2, 127.0 (2C), 128.0 (2C), 128.5 (2C), 128.6 (2C), 133.1, 133.6, 136.2, 141.3, 199.8. FT-IR ($CHCl_3$, cm^{-1}): 3584, 3550, 3010, 2905, 1677, 1598, 1582, 1494, 1450, 1093, 1014, 800, 668.

General procedure for Mukaiyama aldol-type reaction

A mixture of aldehyde dimethyl acetal **13** (2.0 mmol), trimethylsilyl enol ether **3** (0.50 g, 2.6 mmol), and *o*-benzenedisulfonimide (**1**, mol % as in Table 3) was stirred at rt in a vial until TLC and GC analyses showed almost complete conversion of **13**. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic

extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography on a short column of silica gel (eluent reported in footnote of Table 3).

Representative experimental data: 3-cyclohexyl-3-methoxy-1-phenylpropan-1-one (14b)[10b]. Colorless oil, 61% yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90–1.18 (m, 5H), 1.45–1.72 (m, 6H), 2.84 (dd, *J* = 16.2 and 4.0 Hz, 1H), 3.13 (overlapped dd, *J* = 16.2 and 7.8 Hz, 1H), 3.23 (s, 3H), 3.59–3.68 (m, 1H), 7.32–7.46 (m, 3H), 7.85–7.92 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.1 (2C), 26.4, 28.3, 28.42, 40.6, 41.7, 58.1, 81.6, 128.0 (2C), 128.3 (2C), 132.7, 137.3, 199.2. MS *m/z* (%): 246 [M^+] (2), 231 [M^+−15] (10), 105 (100). FT-IR ($CHCl_3$, cm^{-1}): 3013, 2905, 2856, 1684, 1598, 1582, 1450, 1232, 1095.

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