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Lewis Base Catalyzed Mannich-Type Reactions between Trimethylsilyl Enol Ethers and Aldimines

Hidehiko Fujisawa, Eiki Takahashi, and Teruaki Mukaiyama*[a]

Abstract: Lewis base catalyzed Mannich-type reaction between trimethylsilyl enol ethers and *N*-tosylaldimines is described. Nitrogen anions generated from amides or imides such as lithium benzamide or potassium phthalimide are found to be effective Lewis base catalysts in DMF at room temperature to afford the corresponding β-amino carbonyl compounds in good to high yields; the oxygen anion generated from carboxylic acids such as lithium acetate was also found to be effective in dry DMF. The above-mentioned lithium acetate-catalyzed Mannich-type reaction between aldimines and various trimethylsilyl (TMS) enol ethers such as silyl ketene acetal proceeded smoothly even in water-containing DMF. Then, Lewis base catalyzed three-component Mannich-type reactions of TMS enol ether, tosylamide, and aromatic aldehyde having electron-withdrawing group such as *p*-nitrobenzaldehyde were investigated. The reaction proceeded smoothly to afford the corresponding β-amino ester in good yield. Further, ammonium carboxylates such as tetrabutyl ammonium acetate or tetrabutyl ammonium benzoate were found to be more effective Lewis base catalysts in the above-mentioned Mannich-type reaction. The synthesis proceeded in various solvents at lower temperatures. The reaction between aldimines and TMS enol ethers generated from thioester and various ketones such as propiophenone or cyclohexanone also proceeded smoothly to afford the corresponding β-amino carbonyl compounds in high yields with good to high *anti*-selectivities.

Keywords: enols · Lewis bases · Mannich bases

Introduction

Mannich-type reaction of aldimine with silyl enol ether is one of the most important tools for the construction of β-amino carbonyl compounds to provide useful routes for the synthesis of β-amino esters that are important precursors of various β-lactams and β-amino acids. In general, Mannich-type reactions proceed via the electrophilic activation step of Mannich acceptor with Lewis acids. Ojima et al. first reported in 1977 that the Mannich-type reaction between benzylideneaniline and silyl ketene acetal was accelerated by using stoichiometric amounts of $TiCl_4$.[1] After this report, various Lewis acid-mediated Mannich-type reactions have been developed.[2] In 1994, Yamamoto and co-workers reported that the enantioselective reactions of imines with a silyl ketene acetal using a stoichiometric amount of a Brønsted acid-assisted chiral Lewis acid generated from a BINOL.[3] In most cases, a Lewis acid was often trapped by the nitrogen atom of starting aldimines or produced amines, which therefore, made it difficult to perform Mannich-type reaction by using catalytic amounts of Lewis acid. However, there is a successful Mannich-type reaction reported by Kobayashi et al. using a catalytic amount of Lewis acid such as scandium trifluoromethanesulfonate or lanthanoid trifluoromethanesulfonate in 1995.[4] Recently, enantioselective Mannich-type reaction using chiral Lewis acid has been studied intensively.[5] For example, Kobayashi et al. succeeded in the first catalytic enantioselective Mannich-type reactions of imines with silyl enol ethers using chiral zirconium catalyst in 1997. Further, Akiyama et al. reported enantioselective Mannich-type reaction by using the chiral Brønsted acid generated from BINOL.[6]

For Mannich-type reaction via the nucleophilic activation of silyl enol ether, on the other hand, there is only a few examples. Exceptions include results by Sodeoka and co-workers who reported on reactions of imines using nucleophilic Pd enolate formed by the transmetalation of silyl enol ethers with a Pd complex[7] and Hosomi and co-workers who reported that Lewis base catalyzed Mannich-type reactions carried out by using dimethyl silyl enol ether which

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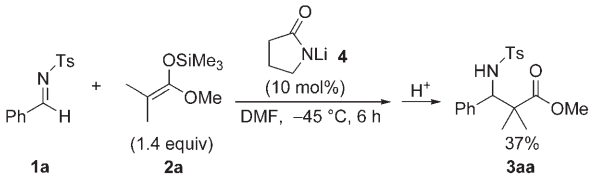
readily formed hypervalent silicon intermediate with Lewis base such as diisopropylethylamine or calcium chloride.[8]

In the course of our investigation for the activation of trimethylsilyl (TMS) enol ether with Lewis base catalysts, nitrogen anions generated from amines, amides, and imides or oxygen anions generated from carboxylic acids are found to be effective and thus worked rather well as strong activators in aldol[9] and Michael reactions[10] as Lewis base catalysts. Then, in order to show the extended usefulness of organic anions as Lewis base catalysts in organic reactions, Mannich-type reaction catalyzed by these Lewis bases was planned. Since the above-mentioned undesirable interactions of a catalyst with starting aldimines or produced amines are not considered when a Lewis base was used as a promoter of the reaction, the reaction was expected to proceed in the presence of a catalytic amount of Lewis base, which would promote the reaction by activating the silyl enol ethers.

In this paper, we would like to describe a new catalytic Mannich-type reaction of TMS enol ethers with *N*-tosylaldimine by using Lewis base catalysts such as lithium benzamide (PhCONHLi), lithium acetate (AcOLi), tetramethylammonium acetate ($AcONBu_4$), or tetrabutylammonium benzoate ($PhCOONBu_4$).[11]

Results and Discussion

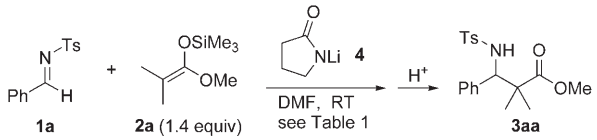
Nitrogen anions generated from amides or imides-catalyzed Mannich-type reaction between *N*-tosylaldimine and trimethylsilyl enol ethers in DMF: In the first place, a reaction between *N*-tosylaldimine **1a** and TMS enol ether **2a** by using 10 mol% lithium pyrrolidone (**4**) at −45 °C in DMF was investigated as a model, and the corresponding β-amino ester **3aa**[12] was obtained in 37% yield (Scheme 1).



Scheme 1. Mannich-type reaction of **1a** with **2a** catalyzed by lithium 2-pyrrolidone.

This indicated that the Lewis base could catalyze this reaction. Then, reaction conditions of the above reaction were screened (Table 1). At first, reaction temperature was examined by using 10 mol% **4**. It was found that the reaction was accelerated by temperatures above 0 °C and that the best results were obtained when the reaction was carried out at room temperature. Similarly, a good result was obtained even when 5 mol% **4** were used (entry 5). In the absence of the catalyst, the reaction proceeded slowly to afford **3aa** only in 24% yield after 6 h at room temperature (entry 6).

Table 1. Screening of reaction conditions of Mannich-type reaction of **1a** with **2a** catalyzed by **4**.



Entry	**4** [mol%]	*T* [°C]	*t* [h]	Yield [%][a]
1	10	0	6	83
2	10	RT	3	55
3	10	RT	6	89
4	10	50	2	82
5	5	RT	6	88
6	–	RT	6	24

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

Next, various catalysts were screened in the reaction of aldimine **1a** with TMS enol ether **2a** (Table 2). It was suggested that this reaction is influenced by the nature of the catalyst. Lithium diphenylamide, effective Lewis base catalyst in aldol reaction, turned out to be inefficient in this reaction. Both lithium 2-oxazolidone and $CF_3CONHLi$ showed lower reactivities than lithium 2-pyrrolidone (**4**). PhCONHLi (**5**) was found to be the most effective catalyst to promote the reaction smoothly and afforded **3aa** in a quantitative yield. Lithium amide **5** showed a higher reactivity compared with the corresponding thioamide of PhCSNHLi. This indicated that the lithium salt of amide is more reactive in Mannich-type reaction than that of thioamide. Electronic effect of aromatic ring of **5** was investigated and the better results were obtained when aromatic ring with electron-withdrawing group was employed (entries 7–10). That is, the low nucleophilic nitrogen anion of aromatic amides has better reactivity than the highly nucleophilic ones. Subsequently, the nitrogen anion of imides was considered as they have a lower nucleophilicity than that of amides. Actually, lithium salts of various imides worked as effective Lewis base catalysts for the above reaction (entries 11, 13, and 14); commercially available potassium salt of phthalimide was also found useful (entry 12).

When the reaction of TMS enol ether **2a** with *N*-alkylaldimines such as *N*-methyl, *N*-allyl, *N*-*tert*-butyl, or *N*-benzylaldimines, was carried out in the presence of 10 mol% **5** at room temperature, the corresponding Mannich adduct was not detected. In order to increase the electrophilicity of the imine, *N*-tosylaldimines was employed next. The reactions of various *N*-tosylaldimines with TMS enol ether **2a** were examined by using 10 mol% **5** or **6** at room temperature in DMF (Table 3). Various aromatic *N*-tosylaldimines smoothly reacted with **2a** to afford the corresponding β-amino esters in high yields. When the aromatic aldimines having electron-donating group were used as Mannich acceptors, the reactions proceeded slower compared with those using the aldimines having electron-withdrawing group. These results indicated that the reaction rates were influenced by the electrophilicities of aldimines. The present Lewis base catalyzed reaction is considered to have a remarkable advantage in

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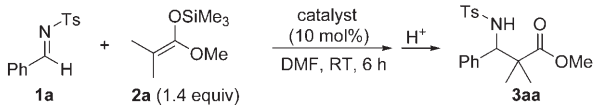
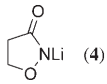
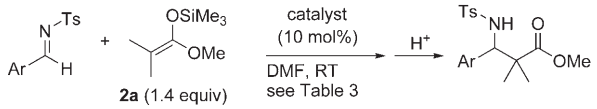
Table 2. Screening of the catalyst.



Entry	Catalyst	Yield [%][a]
1	Ph_2NLi	20
2		89
3	NLi (**4**)	57
4	$CF_3CONHLi$	79
5	PhCONHLi (**5**)	quant.
6	PhCSNHLi	80
7	4-$MeOC_6H_4CONHLi$	87
8	3,4,5-$(MeO)_3C_6H_2CONHLi$	75
9	4-$ClC_6H_4CONHLi$	quant.
10	4-$O_2NC_6H_4CONHLi$	93
11	phthalimide Li[b]	96
12	phthalimide K[c] (**6**)	96
13	maleimide Li[d]	quant.
14	succinimide Li[e]	quant.

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b] Lithium salt of phthalimide. [c] Potassium salt of phthalimide. [d] Lithium salt of maleimide. [e] Lithium salt of succinimide.

Table 3. Mannich-type reaction using various aldimines.



Entry	Ar	Catalyst	t [h]	Product	Yield [%][a]
1	4-ClC_6H_4 (**1b**)	**5**	6	**3ba**	95
2	4-ClC_6H_4 (**1b**)	**6**	3	**3ba**	quant.
3	4-$O_2NC_6H_4$ (**1c**)	**5**	6	**3ca**	89
4	4-$O_2NC_6H_4$ (**1c**)	**6**	3	**3ca**	80
5	4-$MeOC_6H_4$ (**1d**)	**5**	6	**3da**	87
6	4-$MeOC_6H_4$ (**1d**)	**6**	9	**3da**	92
7	4-$Me_2NC_6H_4$ (**1e**)	**5**	6	**3ea**	68
8	4-$Me_2NC_6H_4$ (**1e**)	**6**	16	**3ea**	84
9	4-pyridyl (**1f**)	**5**	6	**3fa**	70
10	4-pyridyl (**1f**)	**6**	3	**3fa**	81

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

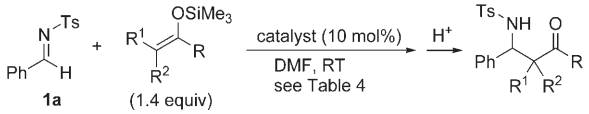
forming β-amino esters especially when the aldimines have basic function in the same molecule. The reactions in the presence of **5** or **6** as a Lewis base proceeded smoothly to afford the Mannich adducts in high yields as expected (entries 7–10).

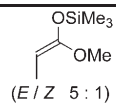
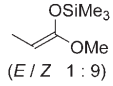
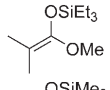
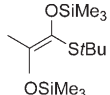
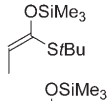
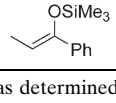
Lewis base catalyzed Mannich-type reaction was further examined by using several silyl enol ethers (Table 4) such as TMS enol ethers generated from methyl propionate. Although the reaction rate of enol ether (*E*)-**2b** was faster than that of *Z*-type (*Z*)-**2b**, the Mannich adducts **3ab**[13] were obtained in good yields with moderate *anti*-selectivity irrespective of the geometries of the above two silyl enol ethers (entries 1–4). In addition, the above reaction proceeded smoothly to afford **3aa** in good yield even when triethylsilyl (TES) enol ether **2a**-TES was used instead of TMS enol ether **2a** (entry 5). Trimethylsilyl enol ethers generated from thioesters or ketones are also applied to the present Mannich-type reaction. When TMS enol ethers generated from *S*-*tert*-butyl thiopropionate or propiophenone were employed, the corresponding Mannich adducts were obtained in good yields with moderate *anti*-selectivities (entries 8 and 9).[8]

Thus, nitrogen anions generated from amides or imides such as PhCONHLi or potassium salt of phthalimide were the effective Lewis base catalysts, which promoted the Mannich-type reaction of *N*-tosyl aldimines with TMS enol ethers.

Lithium acetate-catalyzed Mannich-type reaction between *N*-tosylaldimine and trimethylsilyl enol ethers in DMF: In the course of our investigation for the activation of TMS enol ether with a Lewis base catalyst, the carboxylate anions were found to work effectively as Lewis base catalysts to promote the aldol (Scheme 2) and Michael reactions

Table 4. Lewis base catalyzed Mannich-type reaction of **1a** with various silyl enolates.



Entry	Silyl enolate		Cat.	t [h]	Product	Yield [%][a]	*anti*/*syn*
1	 (E / Z 5 : 1)	(*E*)-**2b**	**5**	6	**3ab**	70	1.8:1
2			**6**	6	**3ab**	52	1.6:1
3	 (E / Z 1 : 9)	(*Z*)-**2b**	**5**	24	**3ab**	59	1.8:1
4			**6**	24	**3ab**	67	1.6:1
5		**2a**-TES	**6**	12	**3aa**	87	–
6		**2c**	**5**	6	**3ac**	quant.	–
7			**6**	4	**3ac**	83	–
8		**2d**	**5**	3	**3ad**	80	1.6:1
9		**2e**	**6**	3	**3ae**	72	2.1:1

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

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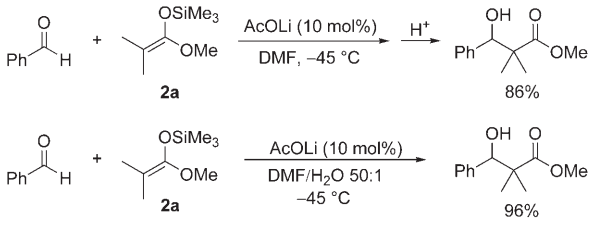
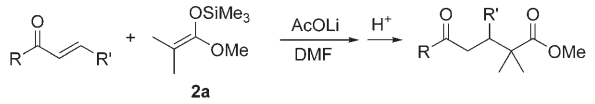


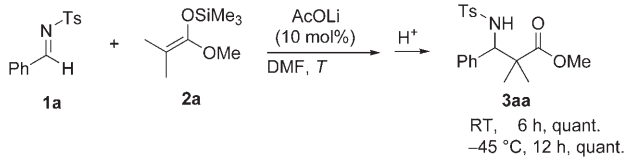
Scheme 2. Aldol reaction catalyzed by AcOLi in dry DMF and DMF/H_2O.

(Scheme 3). Subsequently, the carboxylate anions were expected to work as effective Lewis base catalysts for the Mannich-type reaction. In addition, the above catalysts are readily available, inexpensive and are used under mild conditions because of their weak basicity. They are very useful from an environmental point of view for their low toxicity and are disposable without any special precautions. Then, Mannich-type reaction of aldimines with TMS enol ethers catalyzed by metal carboxylates such as AcOLi was considered.



Scheme 3. Michael reaction catalyzed by AcOLi.

In the first case, reactions between *N*-tosylaldimine **1a** and TMS enol ether **2a** were investigated in the presence of 10 mol% of AcOLi at room temperature and the corresponding Mannich adducts were obtained in quantitative yields (Scheme 4). Interestingly the above reaction, when

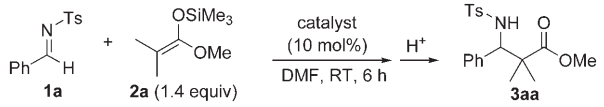


Scheme 4. Mannich-type reaction of **1a** with **2a** catalyzed by AcOLi.

using AcOLi, proceeded smoothly even at −45 °C and lithium 2-pyrrolidone was less effective at the temperature in spite of the weaker nucleophilicity of the lithium carboxylate than of lithium 2-pyrrolidone. These results indicate that lithium carboxylates could be used as favorable catalysts of this reaction.

Next, Mannich-type reaction using lithium carboxylates was investigated and various lithium carboxylates were found to be effective Lewis base catalysts to promote the above reaction (Table 5). When lithium carboxylates generated from aliphatic carboxylic acid such as hexanoic acid or isobutylic acid were employed, the Mannich adduct was afforded in high yields. On the other hand, the yield was moderate when a hindered lithium pivalate (*t*BuCOOLi) was used. Various lithium carboxylates generated from aromatic carboxylic acids were also effective as Lewis base catalysts and accelerated the present Mannich-type reactions. However, the yield remained moderate when the reaction was carried out with the low-nucleophilic lithium carboxylates such as lithium 4-nitrobenzoate.

Table 5. Screening of various lithium carboxylates.

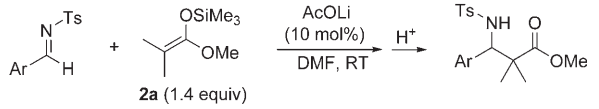


Entry	Catalyst	Yield [%][a]
1	AcOLi	quant.
2	$CH_3(CH_2)_4COOLi$	quant.
3	*i*PrCOOLi	quant.
4	*t*BuCOOLi	63
5	PhCOOLi	quant.
6	4-MeC_6H_4COOLi	quant.
7	4-$MeOC_6H_4COOLi$	quant.
8	4-$Me_2NC_6H_4COOLi$	quant.
9	4-FC_6H_4COOLi	quant.
10	4-ClC_6H_4COOLi	quant.
11	2,6-$Cl_2C_6H_3COOLi$	96
12	4-$O_2NC_6H_4COOLi$	79

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

Next, the reactions of *N*-tosylaldimines were investigated with TMS enol ether **2a** in the presence of 10 mol% AcOLi in DMF (Table 6). Most aromatic *N*-tosylaldimines reacted

Table 6. AcOLi-catalyzed Mannich-type reaction.



Entry	Ar	*t* [h]	Product	Yield [%][a]
1	4-ClC_6H_4 (**1b**)	3	**3ba**	97
2	4-$O_2NC_6H_4$ (**1c**)	3	**3ca**	96
3	4-$MeOC_6H_4$ (**1d**)	6	**3da**	quant.
4	4-$Me_2NC_6H_4$ (**1e**)	6	**3ea**	78
5	4-pyridyl (**1f**)	3	**3fa**	77

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

smoothly with **2a** to afford the corresponding β-amino esters in high yields. The corresponding Mannich adducts were also obtained in high yields even when aromatic aldimines with electron-donating or -withdrawing groups were used for the acceptors. It is noteworthy to point out that the corresponding β-amino esters were also obtained in good yields when aldimines having a basic part such as dimethylamino or pyridyl function within the same molecule were used (entries 4 and 5).

Lithium acetate-catalyzed Mannich-type reaction was further examined by using various silyl enol ethers (Table 7) and they all reacted smoothly with **1a** to afford the corre-

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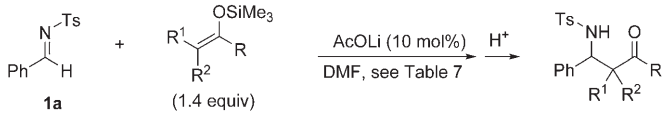
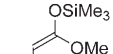
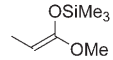
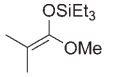
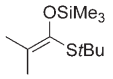
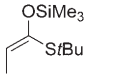
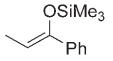
Table 7. AcOLi-catalyzed Mannich-type reaction of **1a** with various silyl enolates.



Entry	Silyl enolate		T [°C]	t [h]	Product	Yield [%][a]	*anti*/*syn*
1			RT	6	**3ab**	84	1.6:1
2	(E / Z 5 : 1)		−20	24	**3ab**	quant.	4.2:1
3	 (E / Z 1 : 9)	(*Z*)-**2b**	−20	24	**3ab**	quant.	1.6:1
4		**2a**-TES	RT	12	**3aa**	quant.	–
5		**2c**	RT	6	**3ac**	quant.	–
6		**2d**	RT	3	**3ad**	quant.	3.0:1
7			−45	6	**3ad**	85	3.1:1
8		**2e**	RT	3	**3ae**	quant.	3.0:1
9			−20	24	**3ae**	quant.	5.4:1

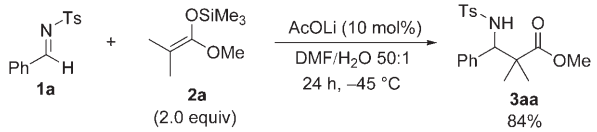
[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

sponding β-amino esters in excellent yields. When TMS enol ethers derived from methyl propionate (*E*)-**2b** or (*Z*)-**2b** were used, the reaction proceeded smoothly at −20 °C to afford **3ab** in quantitative yields with moderate *anti*-selectivity irrespective of the geometry of the enol ethers (entries 1 and 2). The reactions also proceeded smoothly to afford the corresponding adducts in high yields with moderate *anti*-selectivities in the cases when TMS enol ethers generated from thioesters or ketones were used.

Lithium acetate-catalyzed Mannich-type reaction between *N*-tosylaldimine and TMS enol ethers in water-containing DMF: Recently, a reaction in water or water-containing solvent has attracted much attention in connection with economical and environmentally-benign synthetic methods. The Mannich-type reactions between aldimines and silyl enol ethers are difficult to perform in water and water-containing solvent because silyl enol ethers and aldimines are both extremely sensitive to water. Therefore, methods for Mannich-type reactions in water and water-containing solvents are rare, except those reported by Kobayashi et al. in which Lewis acid-catalyzed Mannich-type reactions were carried out in emulsified spheres using surfactants[14] or Akiyama et al. in which Brønsted acid-catalyzed Mannich-type reactions were carried out between aldimines and silyl enol ethers such as silyl ketene acetal in water or water-containing solvent.[6]

It was shown in the previous reports that AcOLi was an effective Lewis base catalyst to promote the aldol reactions between aldehydes and silyl enol ethers even in water-containing DMF because the catalyst is weakly-basic and is stable towards water. Therefore, AcOLi was expected to work as an effective Lewis base catalyst for Mannich-type reaction between aldimines and silyl enol ethers similar to the aldol reactions. The above anions are readily available, inexpensive and are used under mild conditions in water-containing solvent because they are weakly basic and are stable in water. Subsequently, Mannich-type reactions between TMS enol ethers and aldimines by using a catalytic amount of LiOAc in water-containing DMF were examined.

First, the Mannich-type reaction of *N*-tosylaldimine **1a** with two equivalents of TMS enol ether **2a** was investigated in the presence of 10 mol% AcOLi at −45 °C for 24 h in DMF/H_2O (50:1); the corresponding β-amino ester **3aa** was afforded in 84% yield (Scheme 5).



Scheme 5. Mannich-type reaction catalyzed by AcOLi in DMF/H_2O.

Next, optimization of the reaction conditions of LiOAc-catalyzed Mannich-type reaction in water-containing DMF was investigated in order to improve the yield (Table 8). When the reaction of *N*-tosylaldimine **1a** with two equivalents of TMS enol ether **2a** in the presence of 10 mol% of AcOLi was investigated in DMF/H_2O (50:1) for 6 h at room temperature, the reaction proceeded even at that temperature and afforded Mannich adduct **3aa** in 65% yield. The yield of **3aa** increased up to 76% when 30 mol% of AcOLi was used whereas the use of 100 mol% AcOLi under the same reaction conditions did not improve the yield. Mannich adduct **3aa** was obtained in the same yields as shown in Scheme 5 when the reaction was carried out under similar conditions for 12 h. The adduct **3aa** was afforded in high yields even when the volume ratio of DMF and H_2O was changed from 50:1 to 20:1 at −45 °C. These results indicate that the AcOLi-catalyzed Mannich-type reaction in water-containing DMF carried out at −45 °C was more effectively catalyzed compared with that carried out in water-containing DMF at room temperature. This is the first example of the Lewis base catalyzed Mannich-type reaction using silyl enol ethers derived from carboxylic esters in a homogeneous water-containing solvent.

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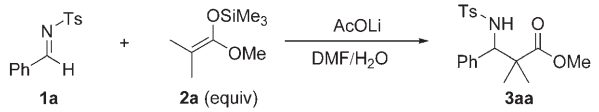
Table 8. AcOLi-catalyzed Mannich-type reaction in DMF/H_2O.



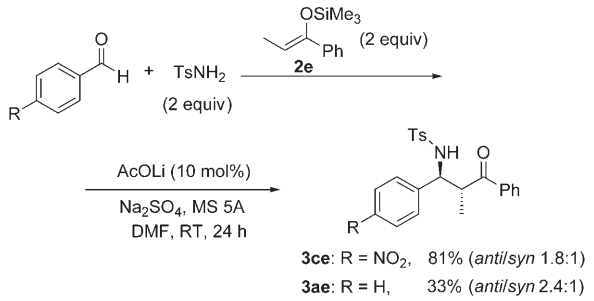
Entry	**2a** [equiv]	AcOLi [mol%]	DMF/H_2O (volume ratio)	T [°C]	t [h]	Yield [%][a]
1	1.4	10	50:1	RT	6	65
2	2.0	10	50:1	RT	6	65
3	2.0	30	50:1	RT	6	76
4	2.0	100	50:1	RT	6	77
6	2.0	10	20:1	RT	6	62
5	2.0	10	100:1	RT	6	79
7	1.4	10	50:1	−45	12	76
8	2.0	10	50:1	−45	12	84
9	2.0	10	50:1	−45	24	84
10	2.0	10	100:1	−45	12	88
11	2.0	10	20:1	−45	12	79

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

Reactions in water-containing DMF by using several TMS enol ethers were studied next (Table 9). Various TMS enol ethers reacted smoothly to afford the corresponding Mannich adducts in good to high yields. When TMS enol ether generated from *S-tert*-butyl thioisobutyrate (**2c**) was employed, the corresponding adduct **3ac** was afforded in moderate yields (entry 1). Trimethylsilyl enol ether generated from methyl propionate [(*E*)-**2b**], *S-tert*-butyl propanethionate (**2d**) or propiophenone (**2e**) was used, the reactions proceeded smoothly to afford the corresponding adducts in good yields with moderate *anti*-selectivities. It was also found that the selectivity was influenced both by water contained in the solvent and also by the silyl enol ethers employed. That is, when silyl enol ether (*E*)-**2b** was employed in water-containing DMF, the yield and ratio of *anti*-isomer decreased compared with the case in dry DMF whereas the ratio increased with the use of silyl enol ether **2d**.

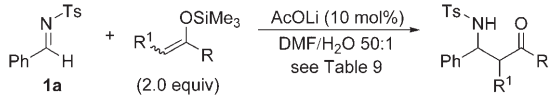
Lewis base catalyzed three-component Mannich-type reaction of aldehyde, *p*-toluenesulfonamide, and TMS enol ethers: Next, Lewis base catalyzed three-component Mannich-type reaction of TMS enol ether with imine generated in situ from aldehyde and amine was considered.

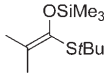
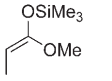
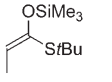
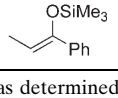
First, a three-component reaction of 4-nitrobenzaldehyde, *p*-toluenesulfonamide and TMS enol ethers was investigated in the presence of 10 mol% AcOLi at room temperature. Mannich adduct **3ce** was afforded in 64% yield with moderate *anti*-selectivity. Further, in order to accelerate the formation of the corresponding imine, anhydrous sodium sulfate and 5 Å molecular sieves were added and the yield was thus improved, that is, the reaction proceeded smoothly at room temperature in 24 h to afford the adduct **3ce** in 81% yield (Scheme 6). However, when the above reaction was investigated at



Scheme 6. Three-component Mannich-type reaction catalyzed by AcOLi.

Table 9. AcOLi-catalyzed Mannich-type reaction using various silyl enolates in DMF/H_2O.



Entry	Silyl enolate		T [°C]	t [h]	Product	Yield [%][a]	*anti*/*syn*
1		(**2c**)	−20	12	**3ac**	66	–
2		[(*E*)-**2b**]	−20	24	**3ab**	74	1.6:1
3		(**2d**)	−45	6	**3ad**	quant.	5.5:1
4		(**2e**)	−20	12	**3ae**	quant.	5.8:1

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

lower temperatures the corresponding adduct **3ce** was not detected. The reaction which used benzaldehyde under the same conditions gave the adduct in a lower yield.

Therefore it appeared that the higher reaction temperature and use of an aldehyde with high electrophilicity were necessary to accomplish the above three-component Mannich-type reaction since the formation of *N*-tosylimine was difficult because of low nucleophilicity of *p*-toluenesulfonamide.

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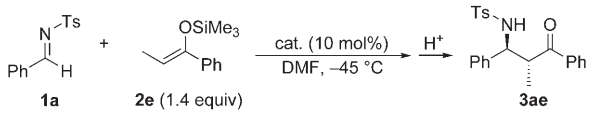
Carboxylate anion-catalyzed *anti*-selective Mannich-type reaction between TMS enol ethers and *N*-tosylaldimines: Diastereoselective Mannich-type reactions using several carboxylate anions were planned in order to further extend the synthetic utility of Lewis base catalyzed Mannich-type reaction. When the reaction of *N*-tosylaldimine **1a** with TMS enol ether **2e** was carried out in the presence of 10 mol% AcOLi at room temperature, the corresponding adduct **3ae** was afforded in high yield with moderate *anti*-selectivity (*anti*/*syn* 75:25) as shown in Table 7. Further, the selectivity increased up to 84:16 when the above reaction was performed at −20°C. This indicates that the selectivity can be controlled when the reaction was carried out at lower reaction temperatures.

Then, the reaction of *N*-tosylaldimine **1a** with TMS enol ether **2e** was investigated at −45°C in the presence of 10 mol% AcOLi and the corresponding Mannich adduct was obtained with high *anti*-selectivity (*anti*/*syn* 94:6) although the yields remained low (20%; see Table 10, entry 1). It was therefore concluded that high yields and high selectivities could be achieved if the reaction was investigated in the presence of a catalyst of higher nucleophilicity at low temperatures. Subsequently the effect of countercations of the catalyst was examined (Table 10). It was revealed that the potassium or ammonium ion worked as a useful countercation of the catalysts as the reaction proceeded smoothly at lower temperature to afford the corresponding Mannich adduct in good yields with excellent *anti*-selectivity. The isomerization of **3ae**[8] formed did not take place during the reaction because the ratio was maintained even when reaction time was changed (entries 7–10). This reaction was also accelerated even in THF when $PhCOONBu_4$ was used. When a Lewis base having metal countercation such as potassium cation was used (entries 4 and 11), on the other hand, a highly Lewis basic solvent such as DMF was essential for the catalytic reaction.

Table 10. Screening of Lewis base catalyst for *anti*-selective Mannich-type reaction of **1a** with **2e**.

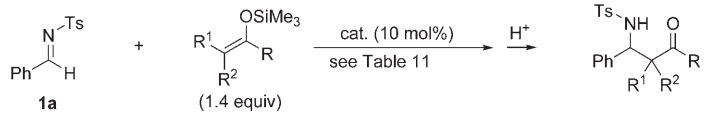


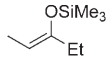
Entry	Catalyst	t [h]	Yield [%][a]	*anti*/*syn*
1	AcOLi	12	20	94:6
2	AcONa	24	11	96:4
3	AcOK	24	quant.	94:6
4	AcOK	12	n.d.[b,c]	–
5	$AcONMe_4$	12	93	92:8
6	$PhCOONBu_4$	2	17	95:5
7	$PhCOONBu_4$	6	38	96:4
8	$PhCOONBu_4$	24	quant.	96:4
9	$PhCOONBu_4$	48	quant.	96:4
10	$PhCOONBu_4$	24	34[b]	93:7

[a] Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b] THF was used instead of DMF. [c] n.d.: not detected.

Next, Lewis base catalyzed *anti*-selective Mannich-type reaction was examined by using several silyl enol ethers (Table 11). It was found that the ratio of *anti*-selectivity was influenced by the nature of silyl enol ethers as well as the reaction conditions. When the reactions of TMS enol ether **2d** with aldimine **1a** were carried out by using 10 mol% AcOLi, AcOK, or $PhCOONBu_4$ in DMF, the Mannich adducts were afforded in high yields with moderate *anti*-selectivity (entries 1–3). The solvent effect was examined by using $PhCOONBu_4$. The reaction proceeded in various solvents; THF, MeCN, and 1,4-dioxane were also suitable for this reaction. On the other hand, the reaction in Et_2O, toluene, or CH_2Cl_2 afforded the desired adduct **3ad**[8] in lower yields; no adduct was detected when EtOH was used.

Table 11. Lewis base catalyzed *anti*-selective Mannich-type reaction of **1a** with various silyl enolates.



Entry	Silyl enolate		Catalyst	Solvent	T [°C]	t [h]	Product	Yield [%][a]	*anti*/*syn*
1			AcOLi	DMF	−45	6	**3ad**	85	76:24
2			AcOK	DMF	−45	12	**3ad**	quant.	75:25
3			$PhCOONBu_4$	DMF	−45	24	**3ad**	92	76:24
4		(**2d**)	$PhCOONBu_4$	THF	−45	24	**3ad**	98	90:10
5			$PhCOONBu_4$	MeCN	−45	24	**3ad**	92	81:19
6			$PhCOONBu_4$	Et_2O	−45	24	**3ad**	44	86:14
7			$PhCOONBu_4$	toluene	−45	24	**3ad**	6	76:24
8			$PhCOONBu_4$	CH_2Cl_2	−45	24	**3ad**	6	86:14
9			$PhCOONBu_4$	1,4-dioxane	RT	6	**3ad**	91	88:12
10			$PhCOONBu_4$	EtOH	−45	12	**3ad**	n.d.[b]	–
11		(**2f**)	$PhCOONBu_4$	DMF	−20	24	**3af**	quant.	89:11
12			$PhCOONBu_4$	THF	−20	24	**3af**	60	93:7
13		(**2g**)	$PhCOONBu_4$	DMF	−20	24	**3ag**	98	>99:1
14			$PhCOONBu_4$	THF	−20	24	**3ag**	93	>99:1

[a] Yield determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b] n.d. = not detected.

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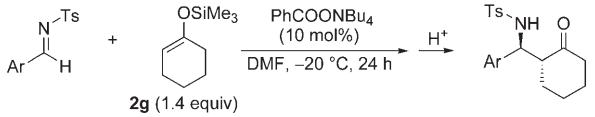
Reactions of aldimine **1a** with TMS enol ether **2f** in DMF proceeded smoothly to afford the corresponding adduct **3af** in good yield with moderate *anti*-selectivity. The selectivity was improved when the above reactions were carried out in THF, but the yields were lower. Thus, it was noted that high yields and excellent selectivity were attained in the case when TMS enol ether derived from cyclohexanone **2g** was used.[8]

Further, the reactions of TMS enol ether **2g** with various aldimines were further investigated by using 10 mol% $PhCOONBu_4$ in DMF at −20 °C (Table 12).[8] Aromatic aldimines having an electron-withdrawing or -donating group proceeded smoothly to afford the desired adducts in good to high yields with excellent *anti*-selectivities (entries 1–5). When conjugated aldimine **1i** was used, only 1,2-addition took place to afford adduct **3ig** in good yields with excellent *anti*-selectivity (entry 6). When aldimines having a basic part such as pyridyl function within the same molecule was used, the corresponding adduct **3fg** were obtained in good to high yields with excellent *anti*-selectivity, respectively (entries 7 and 8).

Table 12. *anti*-Selective Mannich-type reaction of various aldimines with **2g** catalyzed by $PhCOONBu_4$.



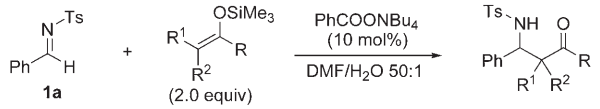
2g (1.4 equiv)

Entry	Ar	Product	Yield [%][a]	*anti*/*syn*
1	4-$ClOC_6H_4$ (**1b**)	**3bg**	quant.	>99:1
2	4-NCC_6H_4 (**1g**)	**3gg**	quant.[b]	>99:1
3	4-$NO_2C_6H_4$ (**1c**)	**3cg**	92	>99:1
4	4-MeC_6H_4 (**1h**)	**3hg**	98	>99:1
5	4-$MeOC_6H_4$ (**1d**)	**3dg**	quant.	>99:1
6	(*E*)-PhCH=CH (**1i**)	**3ig**	quant.[b]	>99:1
7	4-pyridyl (**1f**)	**3fg**	90	>99:1

[a] Yield determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b] 5 mol% catalyst was used.

Next, Lewis base catalyzed Mannich-type reaction was investigated by using $PhCOONBu_4$ in water-containing solvent (Table 13). The reactions of TMS enol ether **2a** or **2c** with aldimine **1a** were carried out by using 10 mol% $PhCOONBu_4$ in water-containing DMF, and the Mannich adducts were afforded in high yields (entries 1 and 2). Reaction of aldimine **1a** with TMS enol ether **2d** in water-containing DMF proceeded smoothly to afford **3ad** in good yield with moderate *anti*-selectivity while the yield lowered in the case when the reaction was carried out in water-containing THF (entries 3 and 4). The reaction of **1a** with TMS enol ether **2e** or **2g** in water-containing DMF afforded the corresponding adducts in moderate yields with high *anti*-selectivities.

Table 13. Mannich-type reaction of **1a** with various TMS enolates in DMF/H_2O catalyzed by $PhCOONBu_4$.



Entry	Silyl enolate		*T* [°C]	*t* [h]	Product	Yield [%][a]	*anti*/*syn*
1		(**2a**)	−45	12	**3aa**	77	–
2		(**2c**)	−20	12	**3ac**	89	–
3		(**2d**)	−45	6	**3ad**	92	84:16
4			−45	6	**3ad**	29[b]	92:8
5		(**2e**)	−45	12	**3ae**	54[c]	94:6
6		(**2g**)	−20	12	**3ag**	65	>99:1
7			−20	12	**3ag**	28[b]	>99:1

[a] Yield determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b] In THF. [c] $AcONMe_4$ was used.

Thus, it was shown that a ammonium carboxylate such as $PhCOONBu_4$ or $AcONMe_4$ also worked as efficient catalysts for the Mannich-type reaction even in water-containing DMF and that their selectivities could be influenced by the nature of silyl enol ether employed similar to the results obtained in dry DMF.

Assumed mechanism of Lewis base catalyzed Mannich-type reaction: The present Lewis base catalyzed Mannich-type reaction in DMF is assumed to proceed in a pathway similar to that of previously reported Lewis base catalyzed aldol reactions (Scheme 7): that is, a nitrogen or oxygen anion of the catalysts such as lithium benzamide, potassium phthalimide, AcOLi, or $PhCOONBu_4$ coordinated to the silicon atom of the TMS enol ether to form pentacoordinated hypervalent silicon intermediate **A** and further coordination of the Lewis basic solvent such as DMF to **A** and formed a hexacoodinated hypervalent silicon intermediate **B**. Nucleophilicity of the enol ether then increased enough to attach the *N*-tosylimine to afford **C** and silylated Lewis base (Me_3Si-LB). Subsequent silylation of **C** by Me_3Si-LB thus-formed afforded **D** along with regeneration of Lewis base (X-LB).

Alternative mechanism for regeneration of the catalyst in water containing DMF was shown in the Scheme 8. By the time that **C** and $AcOSiMe_3$ are formed, the same reaction pattern is considered similar to the one under non-aqueous conditions. In the presence of H_2O, **C** is rapidly hydrolyzed to produce Mannich adduct **E** and LiOH, and $AcOSiMe_3$ is

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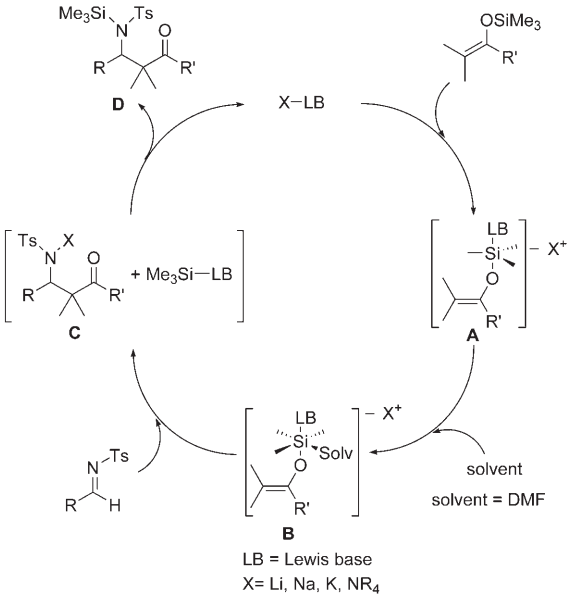
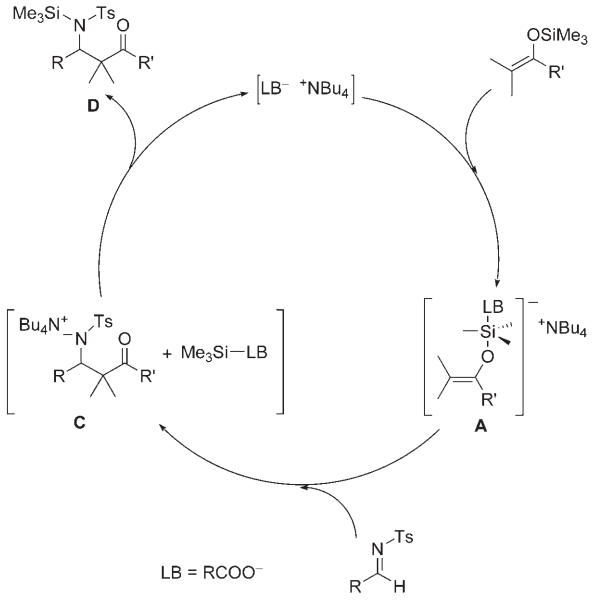
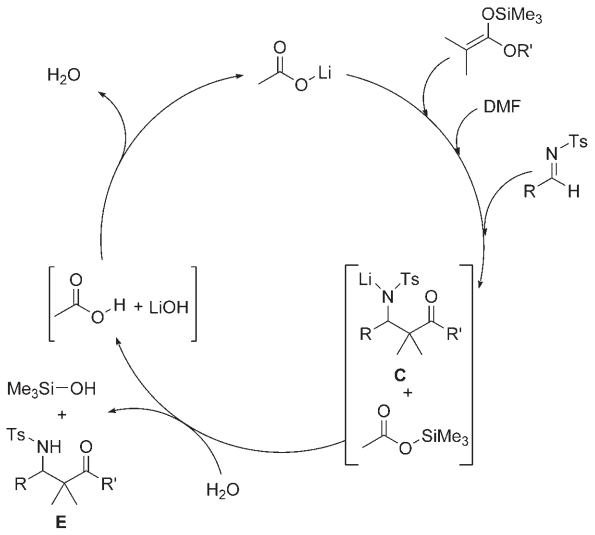


Scheme 7. Assumed catalytic cycle of Lewis base catalyzed Mannich-type reaction in DMF.



Scheme 9. Assumed catalytic cycle of ammonium carboxylate-catalyzed Mannich-type reaction in THF.



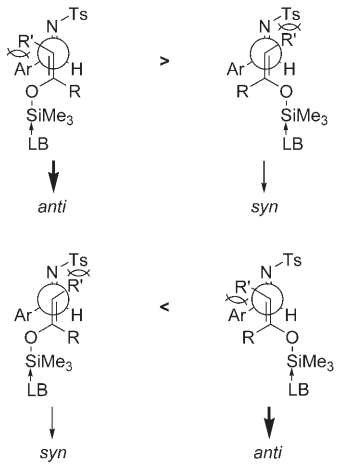
Scheme 8. Assumed catalytic cycle of AcOLi-catalyzed Mannich-type reaction in water-containing DMF.

simultaneously hydrolyzed to AcOH and $HOSiMe_3$. Subsequent neutralization of LiOH with AcOH regenerates the Lewis base catalyst of AcOLi to establish a catalytic cycle.

When a metal cation was used as a counterpart of the catalyst, a highly Lewis basic solvent such as DMF was necessary for the promotion of the reaction. On the other hand, the reaction proceeded in various solvents when an ammonium cation was used as a counterpart of the carboxylate catalyst. The results indicated that the reaction using ammonium carboxylate is assumed to proceed directly via pentacoordinated hypervalent silicon intermediate **A** without further coordination of a Lewis acid solvent because the silicate is fully nucleophilic to react with *N*-tosylimines (Scheme 9).

The reaction using ammonium carboxylate in DMF showed higher reactivity than in THF. In this case, the formation of highly nucleophilic hexacoordinated hypervalent silicon intermediate **B** by further coordination of DMF to the pentacoordinated silicon intermediate **A** is considered and it successively follows the same mechanism similar to that shown in Scheme 7.

The reaction was assumed to proceed via acyclic transition states (Scheme 10) since the silyl enol ether derived from methyl propionate gave the corresponding Mannich adducts with moderate *anti*-selectivities irrespective of geometries of the silyl enol ethers (Table 4, entries 1–4, Table 7, entries 1–3). It was then considered that the selectivities were achieved by the steric effect caused by the repulsion of a Ts group of imine and a substituent R′ of the enol ether which was stronger than the steric hindrance between an Ar of imine and R of silyl enolate.



Scheme 10. *anti*-Selectivity from *E*- and *Z*-enol ether.

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Conclusion

Lewis base catalyzed Mannich-type reaction between TMS enol ethers and aldimines was established. Nitrogen anions generated from amides or imides and oxygen anions generated from carboxylic acids are found to be effective as Lewis base catalysts to promote the reaction. This method is quite practical and is applicable to the synthesis of various β-amino esters since its reaction conditions are not strictly anhydrous and the reaction proceeded smoothly by using a mild and readily available Lewis base catalyst.

Experimental Section

General methods: All melting points were determined on a Yanagimoto micromelting point apparatus (Yanaco MP-S3) and are not corrected. IR spectra were recorded on a Horiba FT300 FT-IR spectrometer or JASCO FT/IR-410. ^{1}H NMR spectra were recorded on a JEOL JNM EX270 L (270 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on EX270 L (68 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; $\delta = 77.0$ ppm). High resolution mass spectra (HRMS) were recorded on a Jeol JMS-DX303 or LCT (micromass) and were performed by Toray Research Center, Inc. Analytical TLC was performed on Merck preparative TLC plates (silica gel 60 GF254, 0.25 mm). Column chromatography was carried out on Merck silica gel 60 (0.063–0.200 mm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. Anhydrous solvents such as DMF or THF were purchased from Kanto Chemical. Potassium salt of phthalimide, AcOLi, AcONa, AcOK, PhCOOLi, $AcONMe_4$, and $PhCOONBu_4$ were purchased from Tokyo Kasei Kogyo, Wako Pure Chemical Industries, or Aldrich Chemical. All reagents were purchased from Tokyo Kasei Kogyo, Kanto Chemical, Kokusan Chemical, Wako Pure Chemical Industries or Aldrich Chemical. Aldimines were made by known methods and they were used after purification by recrystallization. Silyl enol ethers were prepared by usual methods.

General procedure for commercially available solid Lewis base catalysts: A solution of silyl enol ether (0.28 mmol) in DMF (0.6 mL) and a solution of *N*-tosylaldimine (0.2 mmol) in DMF (0.6 mL) at an appropriate temperature were added successively to a stirred solution (or suspension) of Lewis base (0.02 mmol) in DMF (0.3 mL). The mixture was stirred for an appropriate time at the same temperature, and quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt and organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding Mannich adduct.

General procedure for other Lewis base catalysts

Catalyst preparation: MeLi in Et_2O (1.20 M, 0.5 mL, 0.6 mmol) was added at 0 °C to a solution of amides, imides, or carboxylic acids (0.63 mmol) in Et_2O (5.5 mL) and the mixture was stirred for 30 min to prepare a 0.1 M solution (or fine suspension) of Lewis base catalyst.

General procedure of lithium salt-catalyzed Mannich-type reaction: An solution (or fine suspension) of Lewis base catalyst (0.1 M, 0.2 mL, 0.02 mmol) in Et_2O was evaporated under reduced pressure and the residue was dissolved in DMF (0.2 mL). The solution of a silyl enol ether (0.28 mmol) in DMF (0.6 mL) was added at an appropriate temperature. After the mixture was stirred for 5 min, a solution of *N*-tosylaldimine (0.2 mmol) in DMF (1.4 mL) was added slowly over 5 min at the temperature. The mixture was stirred for an appropriate time at the same temperature, and quenched with saturated aqueous NH_4Cl. The mixture was extracted with AcOEt and organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding Mannich adduct.

Methyl 2,2-dimethyl-3-phenyl-3-(tosylamino)propanoate (3aa): White powder; m.p. 133.0 °C; ^{1}H NMR: $\delta = 1.01$ (s, 3H), 1.28 (s, 3H), 2.26 (s, 3H), 3.61 (s, 3H), 4.39 (d, $J = 10.0$ Hz, 1H), 6.33 (d, $J = 10.0$ Hz, 1H), 6.89–7.07 (m, 7H), 7.41 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR: $\delta = 21.3$, 22.2, 24.2, 47.1, 52.0, 64.5, 126.6, 127.1, 127.6, 127.7, 128.7, 136.8, 137.2, 142.3, 176.1; IR (neat): $\tilde{\nu} = 3261$, 2956, 1726, 1472, 1456, 1325, 1159 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{19}H_{23}NO_4SNa$: 384.1245; found: 384.1261 $[M+Na]^+$.

Methyl 3-(4-chlorophenyl)-2,2-dimethyl-3-(tosylamino)propanoate (3ba): White powder; m.p. 160.0 °C; ^{1}H NMR: $\delta = 1.05$ (s, 3H), 1.33 (s, 3H), 2.32 (s, 3H), 3.61 (s, 3H), 4.28 (d, $J = 9.5$ Hz, 1H), 6.12 (d, $J = 9.5$ Hz, 1H), 6.82–6.85 (m, 2H), 6.98–7.02 (m, 4H), 7.35–7.38 (m, 2H); ^{13}C NMR: $\delta = 21.4$, 22.3, 24.6, 46.8, 52.1, 64.2, 121.3, 126.6, 128.9, 129.5, 130.7, 135.9, 137.1, 142.8, 176.0; IR (neat): $\tilde{\nu} = 3346$, 2992, 2973, 1714, 1336, 1158, 1144 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{19}H_{21}ClNO_4S$: 394.0880; found: 394.0911 $[M-H]^-$.

Methyl 2,2-dimethyl-3-(4-nitrophenyl)-3-(tosylamino)propanoate (3ca): White powder; m.p. 193.0 °C; ^{1}H NMR: $\delta = 1.07$ (s, 3H), 1.36 (s, 3H), 2.28 (s, 3H), 3.62 (s, 3H), 4.41 (d, $J = 9.2$ Hz, 1H), 6.32 (d, $J = 9.2$ Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 7.14 (d, $J = 8.6$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.92 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR: $\delta = 21.4$, 22.5, 24.8, 46.9, 52.4, 64.2, 122.9, 126.7, 129.0, 129.1, 137.1, 143.3, 144.6, 146.9, 175.8; IR (neat): $\tilde{\nu} = 3258$, 3074, 2953, 1739, 1522, 1350, 1160 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{19}H_{21}N_2O_6S$: 405.1120; found: 405.1137 $[M-H]^-$.

Methyl 3-(4-methoxyphenyl)-2,2-dimethyl-3-(tosylamino)propanoate (3da): White powder; m.p. 116.0 °C; ^{1}H NMR: $\delta = 1.08$ (s, 3H), 1.27 (s, 3H), 2.28 (s, 3H), 3.61 (s, 3H), 3.71 (s, 3H), 4.32 (d, $J = 9.7$ Hz, 1H), 6.22 (d, $J = 9.7$ Hz, 1H), 6.56 (d, $J = 8.6$ Hz, 2H), 6.81 (d, $J = 8.6$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR: $\delta = 21.4$, 22.4, 24.5, 47.3, 52.1, 55.2, 64.2, 113.1, 126.8, 128.8, 128.9, 129.2, 137.6, 142.3, 158.7, 176.3; IR (neat): $\tilde{\nu} = 3258$, 2953, 1739, 1615, 1522, 1350, 11591 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{20}H_{24}NO_5S$: 390.1375; found: 390.1366 $[M-H]^-$.

Methyl 3-[4-(dimethylamino)phenyl]-2,2-dimethyl-3-(tosylamino)propanoate (3ea): White powder; m.p. 158.0 °C; ^{1}H NMR: $\delta = 1.07$ (s, 3H), 1.30 (s, 3H), 2.27 (s, 3H), 2.86 (s, 6H), 3.60 (s, 3H), 4.23 (d, $J = 9.6$ Hz, 1H), 5.90 (d, $J = 9.6$ Hz, 1H), 6.37 (d, $J = 8.7$ Hz, 2H), 6.71 (d, $J = 8.7$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR: $\delta = 21.4$, 22.4, 24.7, 40.5, 47.4, 52.0, 55.2, 64.5, 111.7, 124.8, 126.8, 128.5, 128.8, 137.8, 141.9, 149.6, 176.6; IR (neat): $\tilde{\nu} = 3293$, 2941, 1739, 1617, 1529, 1460, 1321, 1157 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{21}H_{29}N_2O_4S$: 405.1848; found: 405.1837 $[M+H]^+$.

Methyl 2,2-dimethyl-3-(pyridin-4-yl)-3-(tosylamino)propanoate (3fa): White powder; m.p. 169.0 °C; ^{1}H NMR: $\delta = 1.10$ (s, 3H), 1.31 (s, 3H), 2.30 (s, 3H), 3.62 (s, 3H), 4.36 (d, $J = 9.5$ Hz, 1H), 6.54 (d, $J = 9.5$ Hz, 1H), 6.89 (d, $J = 5.7$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 7.45 (d, $J = 8.4$ Hz, 2H), 8.30 (d, $J = 5.7$ Hz, 2H); ^{13}C NMR: $\delta = 21.4$, 22.4, 24.4, 46.8, 52.3, 63.7, 123.0, 126.7, 129.1, 137.0, 143.2, 146.0, 149.2, 175.7; IR (KBr): $\tilde{\nu} = 3443$, 3044, 2869, 1733, 1600, 1455, 1327, 1258, 1157 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{18}H_{21}N_2O_4S$: 361.1222; found: 361.1262 $[M-H]^-$.

S-*tert*-butyl 2,2-dimethyl-3-phenyl-3-(tosylamino)propanethioate (3ac): White powder; m.p. 129.0 °C; ^{1}H NMR: $\delta = 1.13$ (s, 3H), 1.31 (s, 3H), 1.39 (s, 9H), 2.26 (s, 3H), 4.30 (d, $J = 9.2$ Hz, 1H), 6.30 (d, $J = 9.2$ Hz, 1H), 6.88–7.26 (m, 7H), 7.37 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR: $\delta = 21.4$, 22.6, 25.4, 29.5, 48.1, 53.3, 65.6, 126.7, 127.1, 127.5, 128.2, 128.8, 136.9, 137.6, 142.3, 207.4; IR (neat): $\tilde{\nu} = 3257$, 2960, 1675, 1159 cm^{-1}; HRMS: *m*/*z*: calcd for $C_{22}H_{28}NO_3S_2^-$: 418.1511; found: 418.1530 $[M-H]^-$.

Methyl 2-methyl-3-phenyl-3-(tosylamino)propanoate (3ab): Obtained as mixture of diastereomers (major/minor 64:36); colorless oil; ^{1}H NMR (diastereomers): $\delta = 1.11$–1.15 (m, 3H), 2.31 (s, 2H), 2.33 (s, 1H), 2.80–2.97 (m, 1H), 3.48 (s, 1H), 3.55 (s, 2H), 4.45–4.56 (m, 1H), 5.60 (d, $J = 8.8$ Hz, 0.3H), 5.72 (d, $J = 8.8$ Hz, 0.7H), 6.96–7.14 (m, 7H), 7.48–7.52 (m, 2H); ^{13}C NMR (diastereomers): $\delta = 13.7$, 15.4, 21.4, 21.6, 46.0, 46.1, 51.8, 51.9, 59.7, 60.0, 126.2, 126.4, 126.8, 126.9, 127.2, 127.3, 128.1, 128.3, 129.0,

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129.1, 137.0, 137.5, 137.8, 138.5, 142.5, 142.8, 173.6, 174.8; IR (neat): $\tilde{\nu}$ = 3241, 2981, 2953, 1739, 1452 cm^{-1}.

***S-tert*-butyl 2-methyl-3-phenyl-3-(tosylamino)propanethioate (*anti*-3ad)**: White powder; m.p. 185.0 °C; ^{1}H NMR: δ = 1.14 (d, J = 6.9 Hz, 3H), 1.33 (s, 9H), 2.31 (s, 3H), 2.26 (s, 3H), 2.82 (dq, J = 5.9, 6.9 Hz, 1H), 4.48 (dd, J = 5.9, 8.6 Hz, 1H), 5.97 (d, J = 8.6 Hz, 1H), 6.98–7.14 (m, 7H), 7.49 (d, J = 8.1 Hz, 2H); ^{13}C NMR: δ = 16.4, 21.5, 29.5, 48.7, 53.5, 60.7, 126.5, 126.8, 127.2, 128.1, 129.0, 137.8, 138.8, 142.6, 203.4; IR (neat): $\tilde{\nu}$ = 3280, 2963, 1714, 1666, 1449, 1362, 1319, 1160 cm^{-1}.

***S-tert*-butyl 2-methyl-3-phenyl-3-(tosylamino)propanethioate (*syn*-3ad)**: White powder; m.p. 145.0 °C; ^{1}H NMR: δ = 1.20 (d, J = 7.0 Hz, 3H), 1.23 (s, 9H), 2.33 (s, 3H), 2.81 (dq, J = 7.0, 7.8 Hz, 1H), 4.41 (t, J = 7.8 Hz, 1H), 5.59 (bs, 1H), 6.97–6.98 (m, 2H), 7.06–7.11 (m, 5H), 7.51 (d, J = 8.1 Hz, 2H); ^{13}C NMR: δ = 14.3, 21.5, 29.4, 48.2, 54.2, 60.3, 127.1, 127.2, 127.3, 127.9, 129.1, 137.0, 138.2, 142.9, 201.7; IR (neat): $\tilde{\nu}$ = 3249, 2970, 1734, 1676, 1559, 1507, 1456, 1161 cm^{-1}; HRMS: m/z: calcd for $C_{21}H_{26}NO_3S_2$: 404.1354; found: 404.1398 [M−H]$^-$.

2-Methyl-1,3-diphenyl-3-(tosylamino)propan-1-one (*anti*-3ae): White powder; m.p. 158.0 °C; ^{1}H NMR: δ = 1.29 (d, J = 7.0 Hz, 3H), 1.57 (s, 3H), 2.31 (s, 3H), 3.89 (dq, J = 4.6, 7.0 Hz, 1H), 4.71 (dd, J = 4.6, 8.8 Hz, 1H), 6.42 (d, J = 8.8 Hz, 1H), 7.02–7.08 (m, 7H), 7.32–7.38 (m, 2H), 7.45–7.53 (m, 3H), 7.65–7.69 (m, 2H); ^{13}C NMR: δ = 16.8, 21.5, 46.0, 60.7, 126.5, 126.8, 127.0, 128.1, 128.1, 128.5, 129.0, 133.3, 136.1, 137.8, 139.3, 142.5, 203.6; IR (neat): $\tilde{\nu}$ = 3254, 3061, 2967, 1683, 1446, 1324, 1153 cm^{-1}.

Methyl-1,3-diphenyl-3-(tosylamino)propan-1-one (*syn*-3ae): White powder; m.p. 136.0 °C; ^{1}H NMR: δ = 1.29 (d, J = 7.0 Hz, 3H), 1.57 (s, 3H), 2.31 (s, 3H), 3.89 (dq, J = 4.6, 7.0 Hz, 1H), 4.71 (dd, J = 4.6, 8.8 Hz, 1H), 6.42 (d, J = 8.8 Hz, 1H), 7.02–7.08(m, 7H), 7.32–7.38 (m, 2H), 7.45–7.53 (m, 3H), 7.65–7.69 (m, 2H); ^{13}C NMR: δ = 14.7, 21.5, 46.7, 59.7, 126.9, 127.0, 127.1, 127.9, 128.0, 128.4, 129.1, 133.0, 135.7, 136.8, 139.4, 142.8, 201.4; IR (neat): $\tilde{\nu}$ = 3335, 2969, 1674, 1326, 1157 cm^{-1}; HRMS: m/z: calcd for $C_{23}H_{22}NO_3S$: 392.1320; found: 392.1357 [M−H]$^-$.

2-Methyl-3-(4-nitrophenyl)-1-phenyl-3-tosylaminopropan-1-one (*anti*-3ce): White powder; m.p. 133.0 °C; ^{1}H NMR: δ = 1.35 (d, J = 7.0 Hz, 3H), 1.57 (s, 3H), 3.91 (m, 1H), 4.80 (dd, J = 4.1, 8.6 Hz, 1H), 6.68 (d, J = 8.6 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 7.25–7.28 (m, 2H), 7.34–7.40 (m, 2H), 7.50–7.57 (m, 3H), 7.68 (d, J = 7.3 Hz, 2H), 7.93 (d, J = 8.6 Hz, 2H); ^{13}C NMR: δ = 17.0, 21.5, 45.6, 60.1, 123.3, 126.7, 127.5, 128.1, 128.7, 129.3, 134.0, 135.3, 137.6, 143.3, 146.7, 147.0, 202.9; IR (KBr): $\tilde{\nu}$ = 3421, 3004, 2361, 1714, 1360, 1223 cm^{-1}; HRMS: m/z: calcd for $C_{23}H_{21}N_2O_5S$: 437.1171; found: 437.1187 [M]$^+$.

2-Methyl-1-phenyl-1-(tosylamino)pentan-3-one (*anti*-3af): White powder; m.p. 125.0 °C; ^{1}H NMR: δ = 0.85 (t, J = 7.3 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 2.02 (dq, J = 7.3, 18.9 Hz, 1H), 2.30 (s, 3H), 2.39 (dq, J = 7.3, 18.9 Hz, 1H), 2.96 (dq, J = 5.9, 7.0 Hz, 1H), 4.50 (dd, J = 5.9, 8.9 Hz, 1H), 6.32 (d, J = 8.9 Hz, 1H), 6.96–7.11(m, 7H), 7.46 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 7.19, 15.5, 21.4, 36.1, 51.1, 60.4, 126.3, 126.7, 127.1, 128.1, 128.9, 137.6, 139. 1, 142.5, 214.9; IR (neat): $\tilde{\nu}$ = 3276, 3059, 2976, 2935, 1699, 1451,1326, 1160 cm^{-1}.

2-Methyl-1-phenyl-1-(tosylamino)pentan-3-one (*syn*-3af): White powder; m.p. 135.0 °C; ^{1}H NMR: δ = 0.78 (t, J = 7.3 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 2.00 (dq, J = 7.3, 18.9 Hz, 1H), 2.23 (dq, J = 7.3, 18.9 Hz, 1H), 2.33 (s, 3H), 2.91 (dq, J = 7.0, 7.6 Hz, 1H), 4.43 (dd, J = 7.6, 8.0 Hz, 1H), 5.31 (d, J = 8.0 Hz, 1H), 6.91–7.12 (m, 7H), 7.48 (d, J = 8.1 Hz, 2H); ^{13}C NMR: δ = 7.16, 13.6, 21.4, 35.7, 51.5, 59.6, 126.8, 126.9, 127.3, 128.1, 129.0, 136.8, 138.5, 142.8, 212.5; IR (KBr): $\tilde{\nu}$ = 3275, 2982, 1707, 1449, 1332, 1159 cm^{-1}; HRMS: m/z: calcd for $C_{19}H_{22}NO_3S$: 344.1320; found: 344.1355 [M−H]$^-$.

2-(1-Phenyl-1-tosylaminomethyl)cyclohexanone (*anti*-3ag): White powder; m.p. 146.0 °C; ^{1}H NMR: δ = 1.55–2.01 (m, 6H), 2.22–2.30 (m, 5H), 2.74 (dt, J = 5.1, 10.5 Hz, 1H), 4.43 (dd, J = 5.1, 8.4 Hz, 1H), 6.15 (d, J = 8.4 Hz, 1H), 7.00–7.08 (m, 7H), 7.44 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.4, 24.4, 28.0, 32.2, 42.5, 56.7, 59.1, 126.8, 126.9, 127.0, 127.9, 128.9, 137.4, 138.8, 142.6, 212.4; IR (neat): $\tilde{\nu}$ = 3282, 2940, 1710, 1446, 1157 cm^{-1}.

2-[1-(4-Chlorophenyl)-1-tosylaminomethyl]cyclohexanone (*anti*-3bg): White powder; m.p. 148.0 °C; ^{1}H NMR: δ = 1.57–2.08 (m, 6H), 2.22–2.37 (m, 5H), 2.72 (dt, J = 5.3, 10.5 Hz, 1H), 4.43 (dd, J = 5.1, 8.0 Hz, 1H), 6.20 (d, J = 8.0 Hz, 1H), 6.98–7.10 (m, 6H), 7.45 (d, J = 8.2 Hz, 2H); ^{13}C NMR: δ = 21.4, 24.4, 27.9, 32.1, 42.4, 56.4, 58.5, 126.8, 127.9, 128.5, 129.0, 132.7, 137.2, 137.3, 142.9, 212.2; IR (neat): $\tilde{\nu}$ = 3243, 2942, 2863, 1704, 1600, 1490, 1153 cm^{-1}; HRMS: m/z: calcd for $C_{20}H_{21}ClNO_3S$: 390.0931; found: 390.0951 [M−H]$^-$.

2-[1-(4-Cyanophenyl)-1-tosylaminomethyl]cyclohexanone (*anti*-3gg): White powder; m.p. 141.0 °C; ^{1}H NMR: δ = 1.54–2.38 (m, 10H), 2.72–2.82 (m, 1H), 4.42–4.52 (m, 1H), 6.16–6.28 (m, 1H), 7.10 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H); ^{13}C NMR: δ = 21.5, 24.7, 27.9, 32.5, 42.7, 56.4, 58.8, 110.7, 118.4, 126.8, 127.9, 128.0, 129.2, 131.7, 143.3, 144.6, 211.9; IR (KBr): $\tilde{\nu}$ = 3278, 2943, 2866, 2227, 1699, 1434, 1337, 1160 cm^{-1}.

2-[1-(4-Nitrophenyl)-1-tosylaminomethyl]cyclohexanone (*anti*-3cg): White powder; m.p. 175.0 °C; ^{1}H NMR: δ = 1.58–2.34 (m, 11H), 2.74–2.84 (m, 1H), 4.48 (dd, J = 4.1, 8.4 Hz, 1H), 6.13 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 8.6 Hz, 2H); ^{13}C NMR: δ = 21.4, 24.8, 27.9, 32.5, 42.7, 56.4, 58.8, 123.0, 123.1, 126.8, 126.9, 128.0, 128.1, 129.2, 129.3, 137.4, 143.9, 147.1, 147.2, 212.2; IR (KBr): $\tilde{\nu}$ = 3286, 2932, 2863, 1708, 1601, 1522, 1347, 1317, 1152 cm^{-1}.

2-[1-(4-Methylphenyl)-1-tosylaminomethyl]cyclohexanone (*anti*-3hg): White powder; m.p. 128.0 °C; ^{1}H NMR: δ = 1.59–2.34 (m, 14H), 2.72 (dt, J = 5.4, 10.8 Hz, 1H), 4.38 (dd, J = 5.4, 7.8 Hz, 1H), 6.03 (d, J = 7.8 Hz, 1H), 6.88–6.96 (m, 4H), 7.05 (d, J = 7.8 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.1, 21.4, 24.5, 28.0, 32.3, 42.6, 55.7, 58.9, 126.9, 127.1, 128.5, 128.7, 128.8, 129.0, 135.9, 136.7, 137.4, 142.6, 212.5; IR (KBr): $\tilde{\nu}$ = 3358, 3201, 2942, 2864, 1707, 1338, 1156 cm^{-1}.

2-[1-(4-Methoxyphenyl)-1-tosylaminomethyl]cyclohexanone (*anti*-3dg): White powder; m.p. 129.0 °C; ^{1}H NMR: δ = 1.59–2.42 (m, 11H), 2.72 (dt, J = 5.4, 10.8 Hz, 1H), 3.72 (s, 3H), 4.41 (dd, J = 5.2, 7.6 Hz, 1H), 6.20 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.4, 24.1, 27.9, 31.4, 42.2, 55.1, 56.7, 58.4, 113.2, 126.2, 126.8, 128.2, 128.9, 129.4, 130.7, 137.3, 142.4, 158.3, 212.6; IR (KBr): $\tilde{\nu}$ = 3300, 1710, 1605, 1149 cm^{-1}.

2-(*trans*-3-Phenyl-1-tosylaminopropan-2-en)cyclohexanone (*anti*-3ig): White powder; m.p. 170.0 °C; ^{1}H NMR: δ = 1.62–2.40 (m, 12H), 2.56–2.62 (m, 1H), 3.89 (ddd, J = 3.3, 7.6, 9.4 Hz, 1H), 5.54 (d, J = 9.4 Hz, 1H), 5.87–6.03 (m, 2H), 6.98–7.01 (m, 2H), 7.10–7.26 (m, 5H), 7.47 (d, J = 8.4 Hz, 2H); ^{13}C NMR: δ = 21.4, 25.0, 27.8, 31.8, 42.9, 56.0, 58.2, 126.2, 127.2, 127.3, 127.6, 128.2, 129.3, 131.8, 135.9, 137.8, 143.1, 212.4; IR (KBr): $\tilde{\nu}$ = 3298, 2936, 1694, 1596, 1494, 1449, 1160 cm^{-1}.

2-[1-(Pyridin-4-yl)-1-tosylaminomethyl]cyclohexanone (*anti*-3fg): White powder; m.p. 195.0 °C; ^{1}H NMR: δ = 1.60–2.41 (m, 11H), 2.76–2.84 (m, 1H), 4.43 (dd, J = 3.8, 9.2 Hz, 1H), 6.27 (d, J = 9.2 Hz, 1H), 7.01 (d, J = 5.7 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 8.33 (d, J = 5.7 Hz, 2H); ^{13}C NMR: δ = 21.5, 24.8, 27.9, 32.7, 42.7, 56.3, 58.2, 122.0, 126.7, 129.2, 137.4, 143.3, 148.4, 149.2, 211.6; IR (KBr): $\tilde{\nu}$ = 3037, 2947, 2854, 1713, 1601, 1420, 1326, 1152 cm^{-1}; HRMS: m/z: calcd for $C_{19}H_{23}O_3N_2S$: 359.1429; found: 359.1437 [M+H]$^+$.

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