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Three-component carbon–carbon bond-forming reactions catalyzed by a Brønsted acid–surfactant-combined catalyst in water

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This paper is dedicated to Professor Henri B. Kagan on the occasion of the recognition of his work by the prestigious Tetrahedron Prize, 1999

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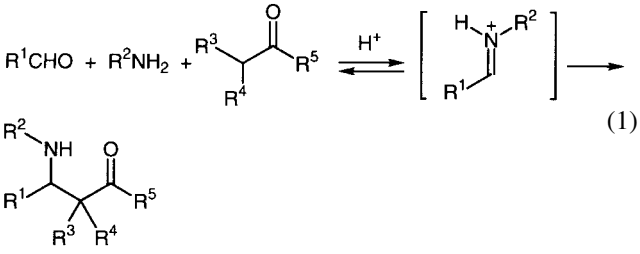
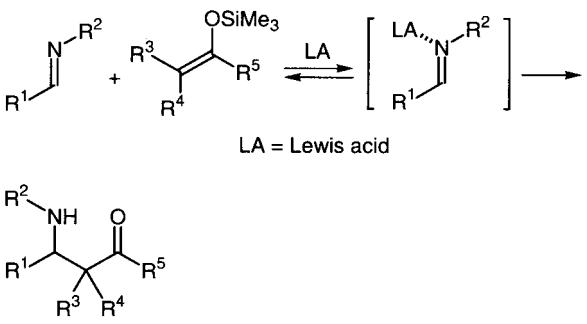
Abstract—Reactions of aldehydes, amines, and various nucleophiles such as silyl enolates, ketones, Danishefsky's diene, and allyltribuyltin in water were successfully carried out in the presence of *p*-dodecylbenzenesulfonic acid (DBSA) as a Brønsted acid–surfactant-combined catalyst.

1. Introduction

Mannich and related reactions provide basic and useful methods for the synthesis of β-amino carbonyl compounds, which constitute various pharmaceuticals, natural products, and versatile synthetic intermediates.[1] Conventional protocols for proton-catalyzed three-component Mannich-type reactions of aldehydes, amines, and ketones in organic solvents (Eq. (1)) include some severe side reactions and have some substrate limitations, especially for enolizable aliphatic aldehydes. Therefore, some modern variants of Mannich reactions have been developed so far.[2] Among them, Lewis acid-mediated reactions of pre-formed imines and silyl enolates (Eq. (2)) as substrates provide one of the most efficient methods.[3] Furthermore, three-component Mannich-type reactions of aldehydes, amines, and silyl enolates have also been reported and greatly extended their synthetic utility.[4]



(1)



(2)

Recently, organic reactions in water without use of harmful organic solvents have attracted much attention, because water is a cheap, safe, and environmentally benign solvent.[5] In the course of our investigations to develop new synthetic methods in water, we have recently found that a combination of a water-stable Lewis acid (e.g. scandium triflate) and an anionic surfactant (e.g. sodium dodecyl sulfate (SDS)) provides an efficient system for some Lewis acid-catalyzed reactions in water.[6] Moreover, we have also synthesized more simplified catalysts, 'Lewis acid–surfactant-combined catalysts (LASCs)', such as scandium tris(dodecyl sulfate) ($Sc(DS)_3$).[7] These LASCs form stable colloidal dispersion systems with organic substrates and function as effective Lewis acids in water. These catalytic systems have been successfully applied to three-component Mannich-type reactions of aldehydes, amines, and silyl enolates in water.[6c,7f]

As an extension of these studies, we planned to develop a 'Brønsted acid–surfactant-combined catalyst (BASC)', composed of a Brønsted acidic group and a hydrophobic moiety. Although conventional procedures of Mannich-type

Keywords: surfactant; Brønsted acid; Mannich reaction; silyl enolate; colloidal dispersion.

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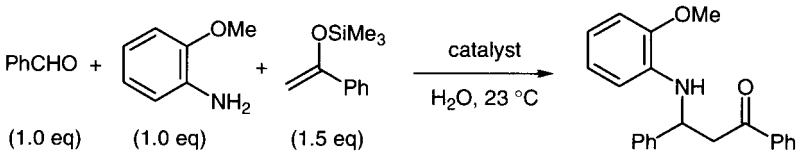
Table 1. Mannich-type reactions in the presence of various catalysts in water



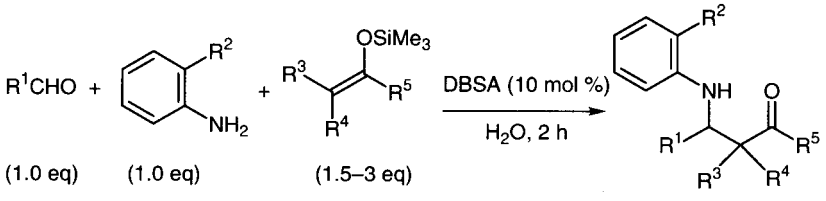
Entry	Catalyst (mol%)	Time (min)	Yield (%)
1	SDS (30)	20	8
2	SDS (30)+HCl (10)	20	29
3	$Sc(DS)_3$ (10)	20	38
4	DBSA (10)	20	69
5	DBSA (10)	120	83
6	TsOH (10)	120	Trace
7	$C_{11}H_{23}COOH$ (10)	120	6

reactions use a Brønsted acid catalyst, they need organic solvents for water-insoluble substrates. We expected that a BASC would efficiently catalyze Mannich-type reactions in water by activating the intermediate imines and by creating effective colloidal dispersions.[8] Here we report BASC-catalyzed reactions of aldehydes, amines, and silyl enolates, parent ketones, Danishefsky's diene, or allyltributyltin in water.[9] In addition, microscopic observation of colloidal particles created by the BASC and organic substrates is presented.

2. Results and discussion

First, we searched an efficient catalyst for Mannich-type reactions of silyl enolates with imines generated in situ from aldehydes and amines in water. Various catalysts were tested for the reaction of benzaldehyde, *o*-anisidine, and 1-phenyl-1-(trimethylsiloxy)ethene in water, and selected examples are summarized in Table 1. Although the reaction in the presence of SDS alone afforded the desired β-amino ketone in a very low yield (entry 1), addition of a catalytic amount of HCl slightly improved the yield (entry 2). This result suggests that a combination of a Brønsted acid and an anionic surfactant leads to an effective catalyst for this Mannich-type reaction. We then tested *p*-dodecylbenzenesulfonic acid (DBSA),[10] which was expected to behave both as a Brønsted acid and as a surfactant. Indeed, DBSA (10 mol%) was found to be a good catalyst for the reaction (entry 4), and even better than a surfactant-type Lewis acid, $Sc(DS)_3$ (entry 3). It is noteworthy that hydrolysis of the silyl enolate was not a severe problem even in the presence of the Brønsted acid. Elongation of the reaction time led to an improved yield (entry 5). Interestingly, *p*-toluenesulfonic acid (TsOH), which has a shorter alkyl chain than DBSA does, gave only a trace amount of the product (entry 6). This result indicates that the long alkyl chain of DBSA is indispensable for efficient catalysis probably due to the formation of hydrophobic colloidal particles in water. A carboxylic acid having a long alkyl chain, lauric acid, was much less effective (entry 7) than DBSA, suggesting that the strong acidity of DBSA is essential for the catalysis. The reaction proceeds through the imine formation of the aldehyde and

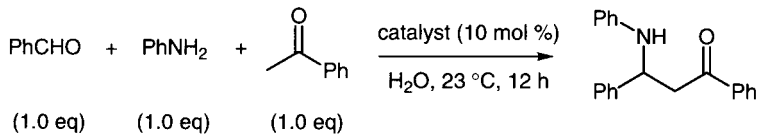
Table 2. Mannich-type reactions catalyzed by DBSA in water using silyl enolates as nucleophilic substrates



Entry	R^1	R^2	R^3	R^4	R^5	Temp. (°C)	Yield (%)
1[a]	Ph	OMe	H	H	Ph	23	83
2[b,c]	Ph	OMe	Me	H	Ph	23	81
3[c]	Ph	OMe	Me	Me	OMe	23	68
4[c]	Ph	OMe	Me	Me	OMe	0	90
5[c]	2-Furyl	OMe	Me	Me	OMe	0	84
6[c]	PhCH=CH	OMe	Me	Me	OMe	0	63
7[c]	$(CH_3)_2CHCH_2$	OMe	Me	Me	OMe	0	88
8[c]	*c*-Hex	OMe	Me	Me	OMe	0	0
9[a,c]	Ph	OMe	H	H	SEt	23	78
10[a,c]	Ph	H	Me	Me	OMe	0	91

[a] Silyl enolate (1.5 equiv.).
[b] 18 h.
[c] Silyl enoalte (3.0 equiv.).

Table 3. Mannich-type reactions in the presence of various catalysts in water



Entry	Catalyst	Yield (%)
1	DBSA	69
2	$Sc(DS)_3$	54
3	$Cu(DS)_2$	40
4	TsOH	0
5	SDS	5
6	TsOH+SDS	56
7[a]	DBSA	9
8[b]	DBSA	4

[a] In MeOH.
[b] In CH_2Cl_2.

the amine, protonation of the imine, and the attack of the silyl enolate to the protonated imine. This dehydrative imine formation in water is a characteristic feature of our colloidal dispersion system for reactions of imines.[6c,d,7f]

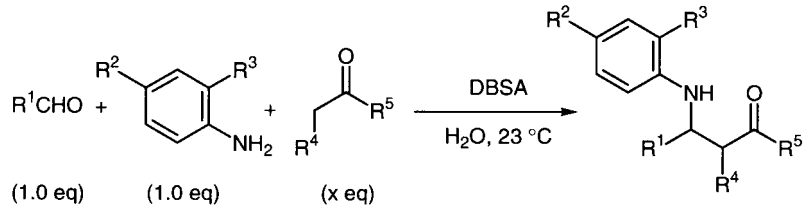
DBSA was found to be applicable to the reactions of various substrates in water, and the results are shown in Table 2. Not only benzaldehyde (entries 1–4, 9, and 10) but also heteroaromatic (entry 5), α,β-unsaturated (entry 6), and aliphatic aldehydes (entry 7) afforded the desired products in good yields, although cyclohexanecarbaldehyde did not react under these conditions (entry 8) presumably because of its steric hindrance. As for silyl enolates, those derived from ketones (entries 1 and 2), an ester (entries 3–7, and 10), and a thioester (entry 9) could be used successfully. Note that such water-sensitive substrates reacted smoothly, and that neither aldol products nor deamination products were obtained under these conditions. As for amines, aniline (entry 10) as well as *o*-anisidine worked well. It should be mentioned that *o*-methoxyphenyl groups of the products in entry 1–9 can be easily removed to give the corresponding primary amines.[11c] Unfortunately, aliphatic amines did not afford the desired Mannich adducts under the conditions in Table 2 probably due to electronic property of the substituents on the nitrogen atoms. For some cases, the reaction temperature affected the yields of the Mannich adducts. For example, in the case of entries 3 and 4, lower temperature resulted in a better yield. This improvement of the yield is attributed to slow hydrolysis of the silyl enolate at lower temperature.

Although the reaction system stated above has extended the substrate applicability in Mannich reactions in water, there is still a drawback that the silyl enolates, which are prepared from the corresponding carbonyl compounds usually under anhydrous conditions,[12] have to be used. From atom-economical and practical points of view, it is desirable to develop an efficient system for Mannich-type reactions in which the parent carbonyl compounds are directly used. Therefore, we next investigated three-component Mannich-type reactions in water using ketones, instead of silyl enolates, as nucleophilic components.

The reaction of benzaldehyde, aniline, and acetophenone in the presence of an acid catalyst in water was selected as a model reaction. Among the Brønsted and Lewis acid catalysts tested, DBSA was found to be, again, the most efficient catalyst (Table 3, entry 1). LASCs such as $Sc(DS)_3$ and copper bis(dodecyl sulfate) ($Cu(DS)_2$)[7g,13] were less effective (entries 2 and 3) than DBSA. It should be noted that TsOH did not afford the desired product (entry 4) as in the reaction in Table 1. DBSA formed a white turbid reaction mixture, while TsOH formed two immiscible layers. This result indicates that the long alkyl chain of DBSA is necessary for the formation of the colloidal dispersion that is assumed to lead to the efficient catalysis. A combination of TsOH and SDS, which formed colloidal dispersion in the presence of the substrates, afforded the adduct in a modest yield (entry 6), confirming the importance of both a Brønsted acidic group and an anionic surfactant. Interestingly, the efficient catalysis by DBSA was not observed in the reactions carried out in organic solvents such as MeOH (entry 7) and dichloromethane (entry 8). This solvent effect shows the unique property of water to induce hydrophobic interactions between the substrates and the catalyst. We assume that the nucleophilic species in this reaction is the enol that is in equilibrium with the ketone, although it cannot be ruled out that the enamine derived from the ketone and the amine is involved as the nucleophile.

The reactions of various aldehydes, amines, and ketones were found to be efficiently catalyzed by DBSA at ambient temperature in water (Table 4). The following features are noteworthy in these reactions: (1) A 1:1:1 mixture of benzaldehyde, *p*-anisidine, and acetophenone with 10 mol% of DBSA gave the Mannich adduct in 63% yield (entry 5), in contrast to 30% yield by a conventional HCl-catalyzed reaction in EtOH (18 h).[1] (2) In the case of the substrates shown in entries 6, 8, and 9, only 1 mol% of DBSA was sufficient to catalyze the reactions. (3) The reactivity order of the amines is *p*-chloroaniline>aniline>*p*-anisidine>*o*-anisidine, indicating the importance of the electronic and steric nature of the amines. (4) In the reaction of 2-butanone (entries 11 and 12), the adduct aminoalkylated at the less substituted α-carbon was formed preferentially. (5) Not only benzaldehyde but also heteroaromatic aldehydes such as 2-furfural and 2-pyridinecarbaldehyde worked well (entries 13 and 14). (6) For enolizable aliphatic aldehydes

Table 4. Mannich-type reactions catalyzed by DBSA in water using ketones as nucleophilic substrates



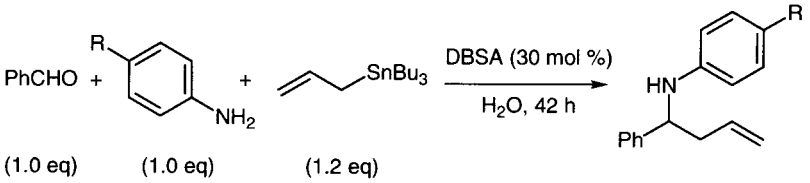
Entry	R^1	R^2	R^3	R^4	R^5	Ketone (equiv.)	DBSA (mol%)	Time (h)	Yield (%)
1	Ph	H	H	H	Ph	1	10	12	69
2	Ph	H	H	H	Ph	1	10	24	81
3	Ph	H	OMe	H	Ph	1	10	12	35
4	Ph	OMe	H	H	Ph	1	10	12	45
5	Ph	OMe	H	H	Ph	1	10	24	63
6	Ph	H	H	$-(CH_2)_4-$		5	1	1	97[a]
7	Ph	OMe	H	$-(CH_2)_4-$		5	10	12	81[b]
8	Ph	Cl	H	$-(CH_2)_4-$		5	1	1	>99[c]
9	Ph	OMe	H	$-(CH_2)_5-$		5	1	12	89[d]
10	Ph	Cl	H	Me	Ph	1	10	47	73[e]
11	Ph	H	H	H	Et	5	10	24	84[f]
12	Ph	H	H	H	Et	10	10	24	92[g]
13	2-furyl	H	H	$-(CH_2)_4-$		5	10	24	87[h]
14	2-pyridyl	H	H	$-(CH_2)_4-$		5	10	12	78[i]
15	Me_2CH	H	H	$-(CH_2)_4-$		5	10	12	trace
16[j]	Me_2CH	H	H	$-(CH_2)_4-$		5	10	12	71[k]
17[j]	Me_2CH	Cl	H	$-(CH_2)_4-$		5	10	12	66[l]
18	*c*-Hex	H	H	$-(CH_2)_4-$		5	10	12	0

[a] Diastereomer ratio (dr)=74:26.
[b] dr=68:32.
[c] dr=70:30.
[d] dr=81:19.
[e] dr=58:42.
[f] Regioisomer ratio=87:13.
[g] Regioisomer ratio=89:11.
[h] dr=67:33.
[i] dr=69:31.
[j] The aldehyde was slowly added to the reaction mixture during 9 h, and then the whole was stirred for 3 h.
[k] dr=65:35.
[l] dr=62:38.

such as isovaleraldehyde, the reaction procedure mentioned above afforded a complicated mixture of several compounds, and only a trace amount of the desired adduct was obtained probably due to self-condenzation of the aldehyde (entry 15). Therefore, we tried slow addition of the aldehyde to a mixture of the amine, the ketone, and DBSA in water. Indeed, this procedure greatly improved the yields up to 71% (entries 16 and 17). (7) For the reactions of cyclohexanone, cycloheptanone, and 2-butanone, 5 equiv. of the ketones were needed to avoid polyaminoalkylation. (8) Cyclohexanecarbaldehyde did not react under these conditions as in the case of Table 2, entry 8. (9) Reactions with esters or thioesters, instead of ketones, did not proceed under these conditions. (10) Ten-mmol-scale reactions were also carried out without any difficulties. For example, the reaction of benzaldehyde (10 mmol), aniline (10 mmol), and acetophenone (10 mmol) in the presence of 10 mol% of DBSA afforded the desired product in 82% yield (24 h).

The aza Diels–Alder reactions of imines with Danishefsky's

Table 5. Allylation reactions catalyzed by DBSA in water



Entry	R	Temp. (°C)	Yield (%)
1	H	30	67
2	Cl	30	68
3	OMe	40	57

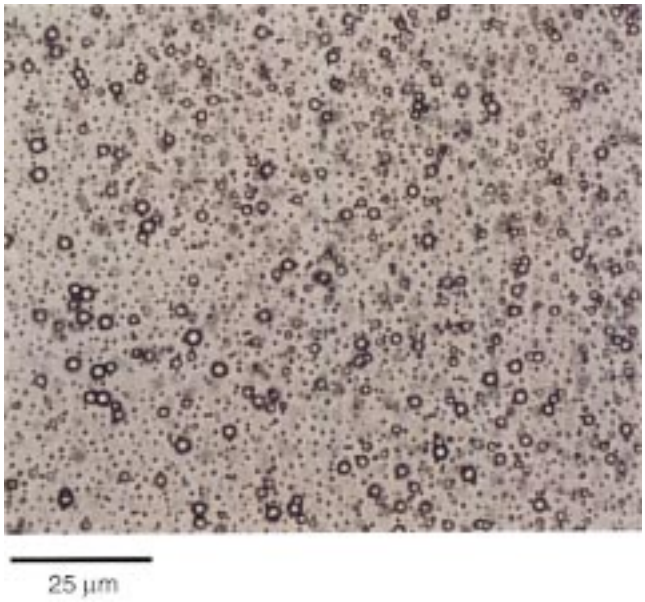
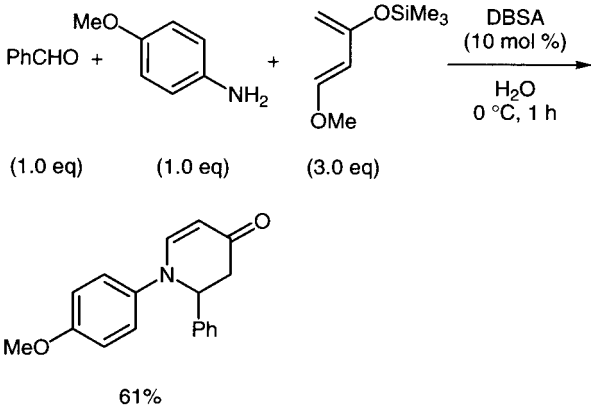


Figure 1. Mixture of DBSA (16.7 mM), benzaldehyde (167 mM), and aniline (167 mM) as detected by light microscopy.

diene are useful for the synthesis of pyridone derivatives.[14] DBSA could be also applied to the reaction in water.[8b] Although 3 equiv. of the water-sensitive diene was needed, the desired dihydro-4-pyridone was obtained in good yield as shown in Eq. (3).



(3)

The reactions of imines with allylmetals provide important routes for the synthesis of homoallylic amines.[15] Recently, we have reported that three-component reactions of aldehydes, amines, and allyltributyltin proceed smoothly in water in the presence of $Sc(OTf)_3$ and SDS to give the corresponding homoallylic amines.[6d] The reactions were also catalyzed by DBSA in water (Table 5). Although the desired products were obtained in modest to good yields, the reactions were slow compared with the $Sc(OTf)_3$/SDS system. As the DBSA-catalyzed allylation reactions proceeded, turbid reaction mixtures became two phase-systems in which the organic substances were separated from the aqueous phase. We have not yet understood the reason for this phase separation, which may be related to the lower reaction rates.

In the DBSA-catalyzed reactions stated in this article, most of the reaction mixtures became turbid, and formation of these colloidal dispersions is a characteristic feature for the present reaction system. Quite recently, we undertook microscopic observation of the colloidal dispersion formed from a LASC and an organic substrate in water and confirmed the formation of spherical colloidal particles.[7f] Thus, we then tried to observe the DBSA-induced colloidal particles. Indeed, light microscopic observation of the colloidal dispersion formed from DBSA (10 mol%), benzaldehyde (1 equiv.), and aniline (1 equiv.) in water revealed that spherical particles were formed (Fig. 1) as in the case of LASCs. It is suggested that most of the substrates and catalyst molecules are concentrated in the spherical particles, which act as a hydrophobic reaction site and enable the rapid reactions in water.

3. Conclusions

Three-component reactions of aldehydes, amines, and various nucleophiles are efficiently catalyzed by DBSA, a BASC, in water. Aromatic, heteroaromatic, and aliphatic aldehydes can be successfully used as the aldehyde component. Moreover, these reactions, which proceed sluggishly in organic solvents, attest to the unique property of water as a reaction medium. DBSA forms stable colloidal particles in the presence of the substrates in water, and this colloid formation plays an important role in acceleration of the reactions. In contrast to Lewis acid-catalyzed reactions of imines, DBSA-catalyzed reactions need no metal catalysts, some of which are expensive or toxic.

Whereas, the advantages of organic reactions in water are now well recognized, most organic substrates are insoluble in water and, as a result, water cannot be used as a reaction medium in many cases. The use of surfactant-type catalysts is a solution for this problem.[8,16] We hope that, in the light of the increased demand for reduction of organic solvents in industry, the surfactant-aided Brønsted acid catalysis described here will lead to a green technique for practical organic synthesis.

4. Experimental

4.1. General procedure for Mannich-type reactions of aldehydes, amines, and silyl enolates

An amine (0.25 mmol), a silyl enolate (0.38–0.75 mmol), and an aldehyde (0.25 mmol) were successively added to a solution of DBSA (0.025 mmol) in water (1.5 mL). The resulting mixture was stirred at 23°C for 2 h, and then quenched with saturated aq. $NaHCO_3$ (5 mL) and brine (5 mL). The mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, concentrated, and purified by silica gel chromatography to give the desired product.

4.2. General procedure for Mannich-type reactions of aldehydes, amines, and ketones

To a solution of DBSA (0.0025–0.075 mmol, 1–30 mol%) in H_2O (1.5 mL) were added an amine (0.25 mmol), an

aldehyde (0.25 mmol), and a ketone (0.25–2.50 mmol) successively at 23°C. After stirring at the same temperature for the period of time listed in Table 4, a saturated aq. $NaHCO_3$ solution (5 mL) and brine (5 mL) were added, and the mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography gave the desired product.

4.3. Procedure for aza Diels–Alder reaction of benzaldehyde, *p*-anisidine, and Danishefsky's diene

To a solution of DBSA (0.050 mmol, 20 mol%) in H_2O (1.5 mL) were added the amine (0.25 mmol), the aldehyde (0.25 mmol), and the diene (0.75 mmol) successively at 0°C. After stirring at the same temperature for 1 h, a saturated aq. $NaHCO_3$ solution (5 mL) and brine (5 mL) were added, and the mixture was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography gave the desired product.

4.4. General procedure for allylation reactions of benzaldehyde, amines, and allyltributyltin

To a solution of DBSA (0.075 mmol, 30 mol%) in H_2O (1.5 mL) were added an amine (0.25 mmol), benzaldehyde (0.25 mmol), and allyltributyltin (0.30 mmol) successively at 30 or 40°C. After stirring at the same temperature for the period of time listed in Table 5, a saturated aq. $NaHCO_3$ solution (5 mL) and brine (5 mL) were added, and the mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography gave the desired product.

4.4.1. 3-(2′-Methoxyphenyl)amino-2-methyl-1,3-diphenyl-1-propanone. ^{1}H NMR ($CDCl_3$, 400 MHz) one diastereomer: δ 1.22 (3H, d, J=7.1 Hz), 3.75 (3H, s), 3.95–3.99 (1H, m), 4.71 (1H, d, J=6.8 Hz), 5.4 (1H, br), 6.40 (1H, dd, J= 7.8, 1.2 Hz), 6.54–6.76 (3H, m), 7.13–7.51 (8H, m), 7.81 (2H, d, J=8.6 Hz); the other diastereomer: δ 1.29 (3H, d, J=6.8 Hz), 3.86 (3H, s), 3.95–3.99 (1H, m), 4.78 (1H, d, J=5.9 Hz), 5.0 (1H, br), 6.24 (1H, dd, J=7.6, 1.7 Hz), 6.54–6.76 (3H, m), 7.13–7.51 (8H, m), 7.87 (2H, d, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) a mixture of two diastereomers: δ 12.40, 16.29, 46.65, 47.44, 55.53, 55.60, 59.19, 60.94, 109.37, 109.46, 110.90, 111.14, 114.97, 116.33, 116.55, 118.41, 120.94, 121.06, 126.88, 126.90, 127.12, 127.20, 128.18, 128.20, 128.44, 128.48, 128.51, 128.62, 133.01, 136.46, 137.01, 137.06, 137.28, 141.79, 141.81, 146.85, 146.95, 202.37, 203.48; HRMS calcd for $C_{23}H_{23}NO_2(M^+)$: 345.1729. Found: 345.1690.

4.4.2. Ethyl [3-(2′-methoxyphenyl)amino-3-phenyl]thiopropanoate. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (3H, t, J=7.5 Hz), 2.83 (2H, q, J=7.5 Hz), 2.99 (1H, dd, J=5.7, 14.6 Hz), 3.04 (1H, dd, J=7.9, 14.6 Hz), 3.84 (3H, s), 4.86 (1H, dd, J=5.7, 7.9 Hz), 5.02 (1H, brs), 6.39 (1H, dd, J=7.7, 1.7 Hz), 6.61 (1H, dt, J=1.7, 7.5 Hz), 6.69 (1H, dt, J=1.7, 7.5 Hz), 6.74 (1H, dd, J=1.7, 7.5 Hz), 7.19–7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.51, 23.46, 51.74, 55.26, 55.43, 109.37, 111.10, 116.81, 121.01, 126.21, 127.32, 128.64, 136.52, 142.03, 146.81, 196.89; HRMS calcd for $C_{18}H_{21}NO_2S(M^+)$: 315.1293. Found: 315.1276.

4.4.3. 2-[1′-(*N*-*p*-Methoxyphenylamino)-1′-phenyl]methylcyclohexanone. ^{1}H NMR ($CDCl_3$, 300 MHz, major/minor=68:32) δ 1.61–1.88 (6H, m), 2.31–2.43 (2H, m), 2.71–2.72 (1H, m), 3.65 (major, 2.04H, s), 3.66 (minor, 0.96H, s), 4.5 (1H, br), 4.54 (major, 0.68H, d, J=7.3 Hz), 4.73 (minor, 0.32H, d, J=4.2 Hz), 6.47–6.52 (2H, m), 6.62–6.67 (2H, m), 7.19–7.36 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz, major/minor=68:32) δ 23.65, 24.86, 27.05, 27.89, 28.45, 31.19, 41.73, 42.40, 55.63, 55.65, 56.73, 57.52, 58.16, 58.96, 114.61, 114.66, 114.80, 115.17, 115.57, 116.38, 126.91, 127.12, 127.36, 127.51, 128.32, 128.42, 141.43, 141.69, 141.76, 141.87, 152.14, 152.25, 211.46, 212.87; IR (neat) 3364, 2935, 1706, 1604, 1512 cm^{-1}; MS (EI) m/z 309 (M^+).

4.4.4. 2-[1′-(*N*-*p*-Methoxyphenylamino)-1′-phenyl]methylcycloheptanone. ^{1}H NMR ($CDCl_3$, 300 MHz, major/minor=81:19) δ 1.20–2.48 (10H, m), 2.82–2.88 (1H, m), 3.65 (3H, s), 4.43 (major, 0.81H, d, J=7.9 Hz), 4.57 (minor, 0.19H, d, J=4.6 Hz), 4.6 (1H, br), 6.46–6.49 (2H, m), 6.62–6.67 (2H, m), 7.17–7.32 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz, major/minor=81:19) δ 24.95, 25.05, 27.31, 27.82, 28.54, 28.86, 29.27, 29.77, 42.57, 44.14, 55.67, 58.41, 58.71, 61.04, 61.15, 114.68, 114.87, 114.93, 127.23, 128.37, 128.48, 140.75, 141.05, 141.20, 141.58, 152.01, 215.64, 216.21; IR (neat) 3387, 2929, 1696, 1512 cm^{-1}; MS (EI) m/z 323 (M^+).

4.4.5. 3-(*N*-*p*-Chlorophenylamino)-2-methyl-1,3-diphenyl-1-propanone. ^{1}H NMR ($CDCl_3$, 300 MHz, major/minor=58:42) δ 1.20 (1.26H, d, J=6.8 Hz), 1.29 (1.74H, d, J=7.0 Hz), 3.94–3.98 (1H, m), 4.5 (0.42H, br), 4.65 (0.58H, d, J=5.9 Hz), 4.69 (0.42H, d, J=4.9 Hz), 5.3 (0.58H, br), 6.37 (1.16H, d, J=8.8 Hz), 6.44 (0.84H, d, J=8.8 Hz), 6.94–7.56 (10H, m), 7.72 (1.16H, d, J=7.5 Hz), 7.92 (0.84H, d, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, major/minor=58:42) δ 11.39, 16.75, 46.32, 46.74, 59.29, 61.26, 114.48, 114.88, 116.16, 120.18, 121.74, 122.27, 126.65, 126.74, 127.38, 127.39, 128.10, 128.20, 128.54, 128.60, 128.69, 128.73, 128.78, 128.83, 129.05, 133.22, 133.35, 136.10, 137.00, 140.97, 141.37, 145.74, 145.77, 202.59, 204.05; IR (film) 3401, 1675, 1597, 1499 cm^{-1}; MS (EI) m/z 349 (M^+).

4.4.6. 2-[1′-(2-Furyl)-1′-*N*-phenylamino]methylcyclohexanone. ^{1}H NMR ($CDCl_3$, 300 MHz, major/minor=67:33) δ 1.60–2.40 (8H, m), 2.89–2.99 (1H, m), 4.5 (1H, br), 4.81 (0.67H, d, J=5.3 Hz), 4.87 (0.33H, d, J=4.7 Hz), 6.17–6.26 (2H, m), 6.61–6.71 (3H, m), 7.10–7.29 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz, major/minor=67:33) δ 24.23, 24.65, 26.82, 27.56, 29.63, 30.76, 42.04, 42.18, 51.88, 52.14, 54.02, 54.41, 106.83, 107.11, 110.28, 113.65, 113.96, 117.95, 118.11, 129.11, 129.13, 141.11, 141.24, 147.12, 147.16, 154.60, 154.83, 210.93, 211.76; IR (neat) 3362, 2938, 1673, 1597, 1500 cm^{-1}; MS (EI) m/z 269 (M^+).

4.4.7. 2-[1′-*N*-phenylamino-1′-(2-pyridyl)]methylcyclohexanone. The major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66–1.72 (3H, m), 1.90–2.10 (3H, m), 2.28–2.37 (2H, m), 3.30–3.34 (1H, m), 4.79 (1H, d, J=3.9 Hz), 5.18 (1H, br), 6.60 (2H, d, J=8.3 Hz), 6.65 (1H, t, J=8.3 Hz), 7.08–7.13 (3H, m), 7.47 (1H, d, J=7.8 Hz), 7.57 (1H, t, J=7.8 Hz), 8.51 (1H, d, J=4.6 Hz); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 24.68, 27.74, 31.64, 42.51, 55.42, 58.71, 113.12, 117.35, 121.81, 121.90, 129.31, 136.46, 147.38, 148.75, 161.28, 213.07; IR (film) 3396, 2936, 1703, 1603, 1501 cm^{-1}; MS (EI) *m/z* 280 (M^+). The minor isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.61–1.69 (3H, m), 1.89–1.91 (1H, m), 2.04–2.07 (1H, m), 2.25–2.42 (3H, m), 3.08 (1H, dt, *J*=11.7, 6.3 Hz), 4.54 (1H, br), 4.96 (1H, d, *J*=6.3 Hz), 6.63–6.68 (3H, m), 7.08–7.12 (3H, m), 7.41 (1H, d, *J*=7.8 Hz), 7.56 (1H, t, *J*=7.8 Hz), 8.51 (1H, d, *J*=4.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.02, 27.68, 29.82, 42.49, 56.05, 57.87, 113.99, 117.77, 122.00, 123.09, 129.14, 136.32, 147.62, 149.02, 161.51, 211.67; IR (film) 3391, 2934, 1706, 1599, 1502 cm^{-1}; MS (EI) *m/z* 280 (M^+).

4.4.8. 2-(3′-Methyl-1′-*N*-phenylamino)butylcyclohexanone. ^1H NMR ($CDCl_3$, 300 MHz, major/minor=65:35) δ 0.86–0.93 (6H, m), 1.23–2.61 (12H, m), 3.58–3.64 (0.35H, m), 3.77–3.82 (0.65H, m), 3.90 (1H, br), 6.54 (2H, d, *J*=8.6 Hz), 6.61 (1H, t, *J*=8.6 Hz), 7.12 (2H, t, *J*=8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, major/minor=65:35) δ 21.75, 22.19, 23.38, 23.73, 24.96, 25.04, 25.21, 25.30, 27.11, 27.36, 29.82, 30.56, 42.01, 42.59, 42.65, 42.80, 51.03, 51.80, 53.38, 54.00, 112.53, 112.81, 116.48, 116.70, 129.34, 148.09, 148.20, 212.58, 213.01; IR (neat) 3386, 2939, 1689, 1600, 1500 cm^{-1}; MS (EI) *m/z* 259 (M^+).

4.4.9. 2-[1′-(*N*-*p*-Chlorophenylamino)-3′-methyl]butylcyclohexanone. ^1H NMR ($CDCl_3$, 400 MHz, major/minor=62:38) δ 0.86–0.91 (6H, m), 1.23–2.57 (12H, m), 3.55–3.58 (0.38H, m), 3.67–3.69 (0.62H, m), 4.0 (1H, br), 6.46 (1.24H, d, *J*=8.8 Hz), 6.51 (0.76H, d, *J*=8.8 Hz), 7.05 (1.24H, d, *J*=8.8 Hz), 7.06 (0.76H, d, *J*=8.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz, major/minor=62:38) δ 21.70, 22.17, 22.52, 23.23, 23.59, 24.94, 25.04, 25.15, 25.24, 26.99, 27.40, 30.32, 41.83, 42.52, 42.69, 42.85, 51.76, 52.14, 53.49, 53.81, 113.58, 114.04, 129.11, 146.58, 146.67, 212.40, 212.99; IR (neat) 3387, 2951, 2865, 1703, 1597, 1500 cm^{-1}; MS (EI) *m/z* 293 (M^+).

For the other Mannich adducts in Table 2, entries 1,[7f] 3–7,[7f] and 10[17] and Table 4, entries 1,[1e] 4,[1e] 6, [1e,f] 8,[1f] 10,[18] and 11,[1e] their spectral data have been reported.

4.4.10. 2,3-Dihydro-*N*-(4-methoxyphenyl)-2-phenyl-4-pyridone. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.77 (1H, dd, *J*=16.4, 3.9 Hz), 3.26 (1H, dd, *J*=16.3, 7.1 Hz), 3.76 (3H, s), 5.18 (1H, dd, *J*=7.1, 3.8 Hz), 5.23 (1H, d, *J*=7.7 Hz), 6.77–6.87 (2H, m), 6.93–7.03 (2H, m), 7.22–7.40 (5H, m), 7.54 (1H, d, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.5, 55.5, 62.4, 101.7, 114.6, 121.1, 126.3, 127.9, 128.9, 138.2, 138.3, 149.6, 156.9, 190.1; IR (neat) 2926, 2935, 1641, 1573, 1510, 1248 cm^{-1}; HRMS calcd for $C_{18}H_{17}NO_2$ (M^+): 279.1259. Found: 279.1263.

4.4.11. 1-Phenyl-1-phenylamino-3-butene. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.47–2.69 (2H, m), 4.20 (1H, br), 4.41 (1H, dd, *J*=5.1, 7.9 Hz), 5.17 (1H, d, *J*=9.2 Hz), 5.21 (1H, d, *J*=15.2 Hz), 5.75–5.86 (1H, m), 6.52 (2H, d, *J*=7.1 Hz), 6.69 (1H, t, *J*=7.1 Hz), 7.10 (2H, t, *J*=7.1 Hz), 7.25 (1H, t, *J*=7.1 Hz), 7.27–7.41 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.27, 57.13, 113.47, 117.37, 118.28, 126.28, 126.96, 128.55, 129.03, 134.62, 143.49, 147.27; IR (neat) 3410, 3224, 1601 cm^{-1}; HRMS calcd for $C_{16}H_{17}N$ (M^+): 223.1361. Found: 223.1395.

4.4.12. 1-(*p*-Chlorophenyl)amino-1-phenyl-3-butene. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.36–2.43 (1H, m), 2.49–2.56 (1H, m), 4.10 (1H, br), 4.26 (1H, dd, *J*=5.1, 8.1 Hz), 5.07 (1H, d, *J*=8.8 Hz), 5.10 (1H, d, *J*=15.6 Hz), 6.32 (2H, d, *J*=8.8 Hz), 6.92 (2H, d, *J*=8.8 Hz), 7.13–7.28 (5H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.18, 57.13, 114.53, 118.49, 121.94, 126.19, 127.12, 128.63, 128.85, 134.36, 142.94, 145.78; IR (neat) 3416, 3027, 1600, 1506 cm^{-1}; HRMS calcd for $C_{16}H_{16}ClN$ (M^+): 257.0971. Found: 257.0931.

4.4.13. 1-(*p*-Methoxyphenyl)amino-1-phenyl-3-butene. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42–2.52 (1H, m), 2.55–2.63 (1H, m), 3.67 (3H, s), 3.9 (1H, br), 4.30 (1H, dd, *J*=7.7, 5.3 Hz), 5.13 (1H, dd, *J*=9.3, 0.6 Hz), 5.17 (1H, dd, *J*=16.7, 1.5 Hz), 5.69–5.83 (1H, m), 6.45 (2H, d, *J*=9.0 Hz), 6.67 (2H, d, *J*=9.0 Hz), 7.19–7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.33, 55.68, 57.98, 114.67, 114.70, 118.22, 126.33, 126.91, 128.52, 134.74, 141.48, 143.70, 151.98; IR (neat) 3401, 2929, 2831, 1510, 1237 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO$ (M^+): 253.1467. Found: 253.1448.

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