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L-Proline-Catalyzed Activation of Methyl Ketones or Active Methylene Compounds and DMF-DMA for Syntheses of (2*E*)-3-Dimethylamino-2-propen-1-ones

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A cascade organocatalysis is reported for the nucleophilic and electrophilic dual activation taking place in the reaction of methyl ketones or active methylene compounds with DMF-DMA (*N*,*N*-dimethylformamide dimethyl acetal). L-Proline serves as an efficient organocatalyst in the covalent and noncovalent synchronous mode for the ambiphilic activation of various aryl, heteroaryl, and styryl methyl ketones, cyclic ketones, and 1,3-diketones with DMF-DMA to achieve the convenient syntheses of the versatile synthons (2*E*)-1-aryl/heteroaryl/styryl-3-(dimethylamino)-2-propen-1-ones, (*E*)-α-[(dimethylamino)formylidene]cycloalkanones, and (*E*)-2-(dimethylamino)formylidene-1,3-diketones in high yields under solvent-free conditions.

Introduction

Noncovalent synthesis is nature's strategy to construct complex molecular architectures for various biological functions and is the central theme of drug–receptor interactions.[1] The hydrogen bond (HB) is the backbone of noncovalent synthesis,[2] and the emerging area of organocatalysis[3] relies on hydrogen-bonded assemblies of small molecules. Herein, we describe the cooperative formation of the HB-assisted cascade organocatalyzed reaction for ambiphilic dual activation during the L-proline-mediated condensation of active methylene compounds with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) to give (2*E*)-3-(dimethylamino)-2-propen-1-ones. These compounds are useful starting materials for preparing various heterocyclic scaffolds,[4] new chemical entities for new therapeutic indications,[5] and the antileukemic drug imatanib[6] (see Scheme 1).

The (2*E*)-3-(dimethylamino)-2-propen-1-ones, represented by the general structural formula **A**, are obtained by the condensation of active methylene compounds with DMF-DMA, DMF-DEA (*N*,*N*-dimethylformamide diethyl acetal), *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent), or tris(dimethylamino)methane (TRIS-DMAM, see Scheme 2).[7]

The various drawbacks associated with reported synthetic protocols, such as the use of an excess amount of DMF-DMA (1.5–4 equiv.)[7c,7i,7j,7l–7n] and high boiling solvents such as DMF or xylene[6,7i–7k] that are difficult to recover as well as the requirement of a long reaction time (7–20 h),[7a–7e,7i,7j] high temperature (110–180 °C),[7f,7i,7j] and special apparatus such as a microwave oven or reactor,[7g,7h] press the need for convenient and better methodology to prepare these versatile synthons. We realized that there are a limited number of reports on the use of a catalyst that would facilitate the condensation of the carbonyl substrate with DMF-DMA under milder conditions, for example, at lower temperatures and shorter time periods, to give improved product yields.[8] The recent report[9] on the use of stoichiometric amounts of the room-temperature ionic liquid (IL) [bmim][BF_4] (bmim = 1-butyl-3-methylimidazolium) at 100 °C for 6 h highlights the possibility of the general effect of an IL as a medium for the desired transformation rather than a true representation of the nonsolvent (catalytic) use of ILs.[10] It was anticipated that the presence of a suitable catalyst would generate the enolate of the active methylene compound, facilitate the subsequent nucleophilic displacement of the methoxy group in DMF-DMA, and accelerate the condensation reaction. In this context, we recently found that *N*-methylimidazole (MeIm) is an effective promoter for the desired transformation.[11] However, the requirement of a stoichiometric amount of MeIm underlines the scope of the use of a substoichiometric amount of a catalytic agent.

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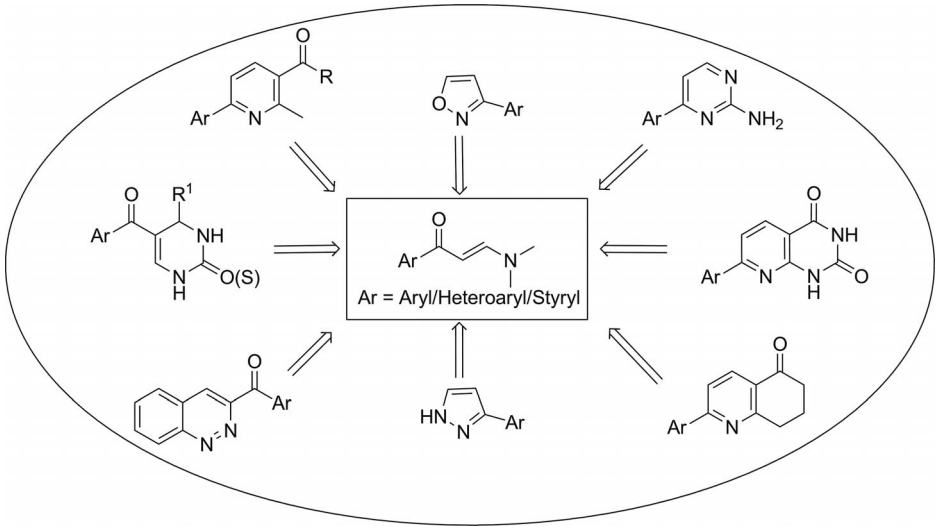
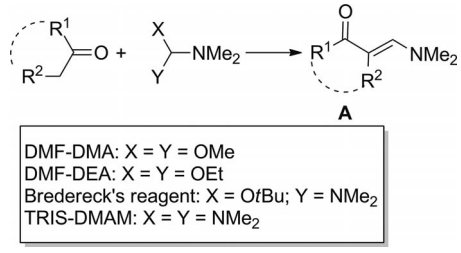


Scheme 1. (2*E*)-3-(Dimethylamino)-2-propen-1-ones as a versatile synthon for heterocyclic scaffolds.

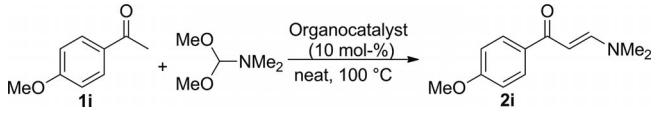


Scheme 2. Synthesis of (2*E*)-3-(dimethylamino)-2-propen-1-ones.

Results and Discussion

We reasoned that using an organocatalyst that does not involve a proton exchange with the active methylene compound, but instead forms a covalent bond to generate the enolate equivalent, might feasibly be regenerated after the enolate equivalent undergoes a reaction with the electrophile (DMF-DMA). Such a strategy is observed during enamine-mediated reactions where the secondary amine pyrrolidine is used as the enamine-forming agent.[12] The presence of an additional structural feature in the enamine-forming agent that could simultaneously activate the acetal moiety of DMF-DMA would offer the dual benefit of nucleophilic and electrophilic activation. The proline moiety offers this framework of dual activation, and it has been demonstrated that proline-catalyzed aldol reactions proceed through an enamine intermediate.[13] To implement a dual activation strategy,[14] we chose 4-methoxyacetophenone (**1i**) as the model substrate and treated it with DMF-DMA under various conditions in the presence of various organocatalysts bearing the pyrrolidine moiety. The results are summarized in Table 1.

Table 1. Reaction of 4-methoxyacetophenone (**1i**) with DMF-DMA in the presence of various organocatalysts to form **2i**.[a]



Entry	Catalyst	% Yield[b]
1	no catalyst	20
2	L-proline	82
3	L-prolinamide	52 (77)[c]
4	L-proline methyl ester	32
5	*N*-methyl-L-proline	25
6	L-pyroglutamic acid	32
7	pyrrolidine	25
8	glycine	32
9	phenylalanine	31
10	acetic acid	28
11	pyrrolidine + acetic acid	45

[a] 4-Methoxyacetophenone (**1i**, 0.375 g, 2.5 mmol) was treated with DMF-DMA (0.35 g, 3.0 mmol, 1.2 equiv.) in the presence of different organocatalysts (10 mol-%) at 100 °C for 3 h. [b] Yield of **2i** after chromatographic purification. [c] Yield of **2i** after 5 h.

The desired product (2*E*)-3-(dimethylamino)-1-(4-methoxyphenyl)-2-propen-1-one (**2i**) was obtained in 82% yield, upon performing the reaction in the presence of L-proline (10 mol-%) at 100 °C for 3 h (complete consumption of **1i**, TLC; see Table 1, Entry 2). The poor yield (20%) obtained in the absence of any catalyst (see Table 1, Entry 1) demonstrated the catalytic assistance provided by L-proline. Other organocatalysts having the pyrrolidine framework but devoid of the carboxylic acid moiety or the NH hydrogen atom either afforded inferior yields or did not exhibit any significant catalytic activity (see Table 1, Entries 3–7).

To determine the best operative conditions for the catalysis by L-proline, the reactions of **1i** with DMF-DMA were

performed under different conditions such as varying the amounts of organocatalyst, the reaction temperature, and the reaction time (see Table 2). The optimal amount of the organocatalyst L-proline was 10 mol-%, as no significant increase in the product yield was observed by using larger quantities (15–20 mol-%). However, the yield decreased when L-proline was used in smaller amounts (1–5 mol-%). The optimal reaction temperature was 80 °C, with no further increase in product yield by increasing the reaction temperature to 120 °C. However, the reaction did not proceed upon reducing the reaction temperature to room temp. or 50 °C.

Table 2. L-Proline-catalyzed reaction of **1i** with DMF-DMA to form **2i** under different conditions.[a]

Entry	L-Proline [mol-%][b]	Temp [°C]	Time [h]	% Yield[c]
1	1.0	100	3	25
2	2.5	100	3	30
3	5	100	3	50
4	10	100	3	82
5	15	100	3	82
6	20	100	3	82
7	10	room temp.	3	trace
8	10	50	3	12
9	10	80	3	82
10	10	100	3	82
11	10	120	3	82
12	10	80	0.5	trace
13	10	80	1	25
14	10	80	2	55
15	10	80	3	82
16	10	80	4	82
17	10	80	5	82
18	0	80	3	20

[a] **1i** (0.375 g, 2.5 mmol) was treated with DMF-DMA (0.35 g, 3.0 mmol, 1.2 equiv.) in the presence of L-proline under various conditions. [b] Amount of catalyst used with respect to **1i**. [c] Yield of **2i** after chromatographic purification.

Next, the condensation of **1i** with DMF-DMA was carried out in various solvents (nonpolar, weakly polar, polar aprotic, and polar protic) to determine its effect on the reaction. In general, using a solvent was detrimental to the reaction, as no significant catalytic activity was exhibited by L-proline or prolinamide (see Table 3).

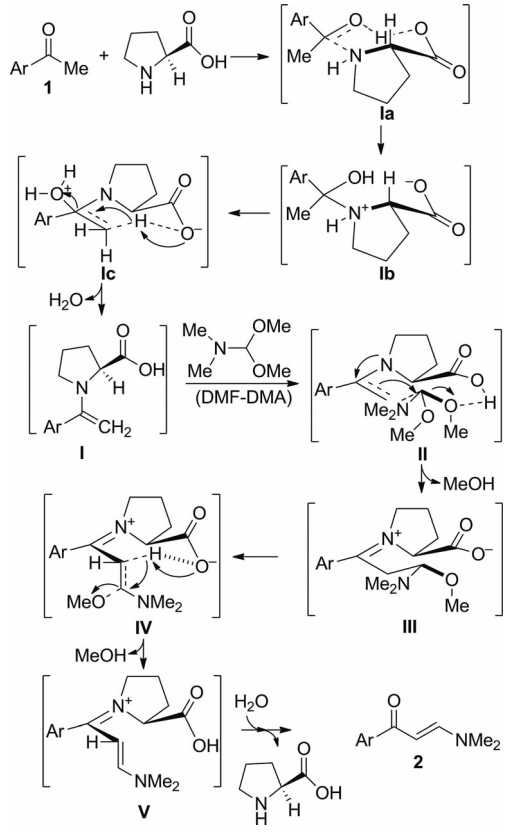
The catalytic role of L-proline is depicted in Scheme 3. Nucleophilic activation of the carbonyl group of ketone **1** takes place by a condensation with the pyrrolidine moiety of L-proline through the cooperatively formed hydrogen-bonded intermediates **Ia** and **Ic** to give enamine **I** (nucleophilic activation).[15] The carboxylic acid hydrogen atom of **I**, in turn, forms a hydrogen bond with one of the methoxy groups of DMF-DMA, which increases the potential (electrophilic activation) for its removal through a nucleophilic attack by the α-carbon atom in the enamine **I** moiety of intermediate **II** to generate imminium intermediate **III**. The carboxylate anion in **III** then abstracts one of the α-hydrogen atoms of the imminium moiety through hydrogen-bonded intermediate **IV**. This is followed by the nucleophilic removal of the OMe group to generate imminium species **V**, which upon subsequent hydrolytic cleavage by the water

Table 3. L-Proline-catalyzed reaction in various solvents of **1i** with DMF-DMA to form **2i**.[a]

Entry	Solvent	Temp [°C]	% Yield[b]
1	neat	80	82
2	toluene	80	20
3	1,4-dioxane	80	0
4	THF	reflux[c]	30
5	DCE	reflux[c]	0
6	$CHCl_3$	reflux[c]	0
7	MeCN	80	30
8	DMF	80	35
9	EtOH	80	10
10	H_2O	80	0
11	H_2O	80	0[d]

[a] **1i** (0.375 g, 2.5 mmol) was treated with DMF-DMA (0.35 g, 3.0 mmol, 1.2 equiv.) in the presence of L-proline (10 mol-%) in different solvents at 80 °C for 3 h. [b] Yield of **2i** after chromatographic purification. [c] The bath temperature was 80 °C. [d] The reaction was performed in using L-prolinamide as the organocatalyst.

molecule, initially generated during the enamine formation, leads to enaminone **2**. This sequence of events demonstrates the role of proline in the ambiphilic dual (i.e., nucleophilic and electrophilic) activation through a cooperatively formed hydrogen-bond-assisted cascade catalysis.



Scheme 3. The catalytic role of L-proline during the reaction of aryl methyl ketones with DMF-DMA to form an enaminone.

The importance and necessity of this nucleophilic activation through the intermediacy of the enamine and imminium ions is demonstrated by observing that other amino acids unable to generate intermediates **I**–**V** were ineffective

in the reaction (see Table 1, Entries 8 and 9). The insignificant catalytic potential of HOAc (see Table 1, Entry 10) indicated that a general Brønsted acid catalyzed mechanism is not operative. The lack of an appreciable catalytic effect

Table 4. L-Proline-catalyzed synthesis of 3-(dimethylamino)propenones from different methyl ketones and active methylene compounds.[a]

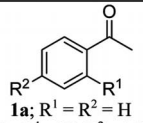
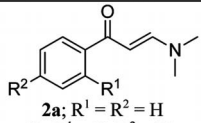
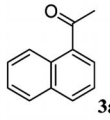
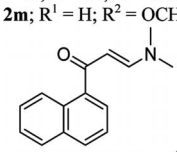
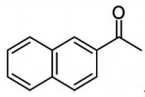
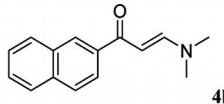
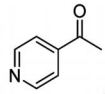
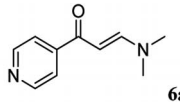
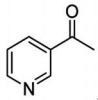
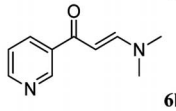
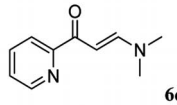
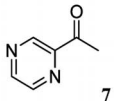
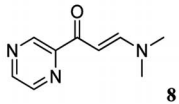
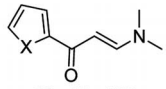
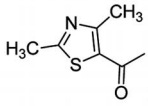
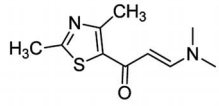
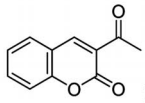
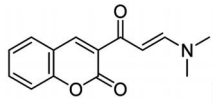
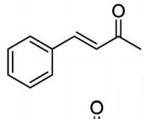
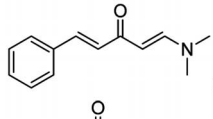
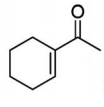
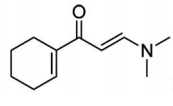
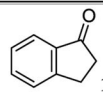
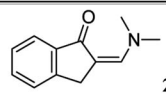
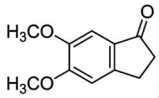
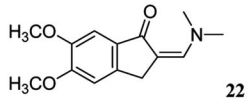
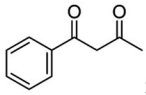
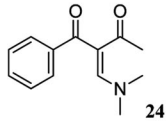
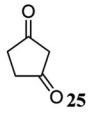
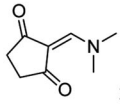
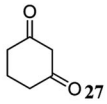
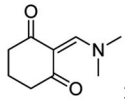
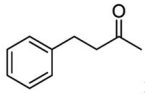
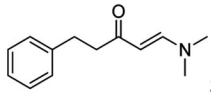
Entry	Substrate	Product	Time (h)	Yield (%)[b,c]
				
1	**1a**; $R^1 = R^2 = H$	**2a**; $R^1 = R^2 = H$	1	90
2	**1b**; $R^1 = H$; $R^2 = Me$	**2b**; $R^1 = H$; $R^2 = Me$	1	88
3	**1c**; $R^1 = H$; $R^2 = F$	**2c**; $R^1 = H$; $R^2 = F$	1	93
4	**1d**; $R^1 = H$; $R^2 = Cl$	**2d**; $R^1 = H$; $R^2 = Cl$	1	92
5	**1e**; $R^1 = H$; $R^2 = Br$	**2e**; $R^1 = H$; $R^2 = Br$	2	90
6	**1f**; $R^1 = H$; $R^2 = I$	**2f**; $R^1 = H$; $R^2 = I$	1.5	91
7	**1g**; $R^1 = H$; $R^2 = NO_2$	**2g**; $R^1 = H$; $R^2 = NO_2$	1	95
8	**1h**; $R^1 = H$; $R^2 = CF_3$	**2h**; $R^1 = H$; $R^2 = CF_3$	1	92
9	**1i**; $R^1 = H$; $R^2 = OCH_3$	**2i**; $R^1 = H$; $R^2 = OCH_3$	3	80
10	**1j**; $R^1 = R^2 = OCH_3$	**2j**; $R^1 = R^2 = OCH_3$	3	78
11	**1k**; $R^1 = H$; $R^2 = OH$	**2k**; $R^1 = H$; $R^2 = OH$	3	0
12	**1l**; $R^1 = H$; $R^2 = NH_2$	**2l**; $R^1 = H$; $R^2 = NH_2$	3	0
13	**1m**; $R^1 = H$; $R^2 = OCH_2Ph$	**2m**; $R^1 = H$; $R^2 = OCH_2Ph$	2	76
14	 **3a**	 **4a**	2	88
15	 **3b**	 **4b**	2.5	91
16	 **5a**	 **6a**	1	88
17	 **5b**	 **6b**	1	85
18	 **5c**	 **6c**	1	89
19	 **7**	 **8**	1.5	90
				
20	**9a**; X = NH	**10a**; X = NH	1.5	90
21	**9b**; X = O	**10b**; X = O	1.5	85
22	**9c**; X = S	**10c**; X = S	1.5	90
23	 **11**	 **12**	1	82
24	 **13**	 **14**	1.5	92
25	 **15**	 **16**	2	82
26	 **17**	 **18**	2	82

Table 4. *(continued)*

Entry	Substrate	Product	Time (h)	Yield (%)[b,c]
27	 **19**	 **20**	2	80
28	 **21**	 **22**	2.5	88
29	 **23**	 **24**	2	85[d] (32)[e]
30	 **25**	 **26**	2	82[d] (38)[e]
31	 **27**	 **28**	2	80[d] (35)[e]
32	 **29**	 **30**	5	62[f]

[a] The methyl ketone/active methylene compound (2.5 mmol) was treated with DMF-DMA (3.0 mmol, 1.2 equiv.) in the presence of L-proline (10 mol-%) at 80 °C (oil bath) under neat conditions. [b] Yield of the corresponding enaminone obtained after purification. [c] The products were characterized by IR, NMR, and MS. [d] The enaminone formation occurred selectively at the methylene group flanked by the two carbonyl groups. [e] Yield of the corresponding product upon performing the reaction in the absence of L-proline. [f] The product was identified as 1-(dimethylamino)-5-phenylpent-1-en-3-one.

by pyrrolidine (see Table 1, Entry 7) justifies the critical role of the HB-assisted activation of DMF-DMA. On the other hand, when a combination of pyrrolidine and acetic acid was used (see Table 1, Entry 11), the increase in the product yield (although moderately because of intermolecular participation) justifies the combined and synergistic effects of the pyrrolidine and carboxylic acid moieties of L-proline.

The implication of the nucleophilic and electrophilic dual activation during the progress of the reaction is further demonstrated by the insignificant catalytic effects from L-proline methyl ester (see Table 1, Entry 4), *N*-methyl-L-proline (see Table 1, Entry 5), and L-pyroglutamic acid (see Table 1, Entry 6). In case of L-proline methyl ester, the electrophilic activation of DMF-DMA is not feasible because of the lack of HB formation through the carboxylic acid hydrogen atom, whereas for *N*-methyl-L-proline and L-pyroglutamic, the formation of the enamine and imminium ion is not possible. The appreciable catalytic potential of L-prolinamide (see Table 1, Entry 3) is justified by the fact that the amide hydrogen atoms are capable of forming a hydrogen bond with DMF-DMA. However, because of the poor HB donor ability of the amide hydrogen atom in comparison to the carboxylic acid hydrogen atom, the L-prolinamide-catalyzed reaction takes a longer time and affords a lower yield. The lack of formation of the desired product in solvents such as toluene, MeCN, 1,4-dioxane, THF (tetrahydrofuran), DMF, DCE (dichloroethylene), and $CHCl_3$ could be a result of the insolubility of L-proline. However, the lack of appreciable product formation in various solvents may not be because of the solubility or the effective reaction temperature (that depends on the b.p. of the solvent). It is possible that the polar character (and competitive HB formation ability) of such solvents may not provide the conducive environment for formation of the hydrogen-bonded assemblies (i.e., the effective catalytic species), leading to the lack of formation of the desired product. Hence, no appreciable catalytic influence in water and EtOH (in which it is soluble) is observed because of the interference in the formation of hydrogen-bonded adducts **Ia**, **Ic**, **II**, and **IV** in protic polar solvents (see Scheme 3).

The generality of this organocatalytic protocol was tested in the reaction of versatile active methylene compounds with DMF-DMA (see Table 4), affording the desired enaminones in 76–80% yields. The reaction worked well with active methylene compounds containing other functional groups such as those with a halogen, nitro, alkoxy, methyl, or trifluoromethyl group, and so forth. However, no product formation took place in case of 4-hydroxyacetophenone or 4-aminoacetophenone (see Table 4, Entries 11 and 12). Carbonyl substrates bearing an alkoxy group took longer reaction times (see Table 4, compare Entries 1, 9, and 10). For 1,3-dicarbonyl compounds (see Table 4, Entries 29–31), the regioselective enaminone formation took place with the active methylene group flanked by the two carbonyl groups. No aqueous workup was necessary to isolate the product. The crude reaction mixture was passed through a flash chromatography column, and the desired product was eluted with EtOAc/hexane.

The lack of product formation in case of 4-hydroxyacetophenone and 4-aminoacetophenone (see Table 4, Entries 11 and 12) could be, because the competitive HB formation of the hydroxy and amino group, respectively, with the carboxylic hydrogen atom of L-proline interferes with the HB-assisted activation of DMF-DMA. The retarding effect exhibited by aryl methyl ketones with an alkoxy substituent on the aryl moiety (see Table 4, compare Entry 1 with 9 and 10, and Entry 27 with 28) may also be, because of the competitive HB formation with the carboxylic acid hydrogen atom in L-proline.

Conclusions

We have described the use of L-proline as an efficient organocatalyst for the convenient syntheses of (2*E*)-3-(dimethylamino)-2-propen-1-ones. The condensation of aryl, heteroaryl, and styryl methyl ketones, cyclic ketones, and 1,3-diketones under solvent-free conditions afforded products in high yields and short reaction times. The organocatalytic role of L-proline has been envisaged in the synchronous mode of covalent and noncovalent dual activation of the methyl ketones or active methylene compounds with DMF-DMA. The reaction represents an organocatalytic cascade sequence through a cooperatively formed HB-assisted ambiphilic (nucleophilic and electrophilic) activation of methyl ketones or active methylene compounds with DMF-DMA.

Experimental Section

General Methods: The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectroscopic data were recorded with a Bruker Avance DPX 300 NMR spectrometer, using $CDCl_3$ as the solvent and TMS as an internal standard. *J* values are given in Hz. The IR spectra were recorded with a Nicolet Impact 410 FTIR spectrometer, and the samples were either KBr pellets (for solids) or neat (for liquids). Mass spectra were recorded with a GC–MS QP 5000 (Shimadzu, for EI) and Finnigan MAT-LCQ [for APCI (atmospheric pressure chemical ionization)] mass spectrometers. The reactions were monitored by using TLC (Merck®, Silica gel 60 F_{254}). Evaporation of solvents was performed at reduced pressure, using a rotary evaporator.

Typical Experimental Procedure for the Synthesis of 3-(Dimethylamino)-1-(4-methoxyphenyl)prop-2-en-1-one: Table 4, Entry 9. To a magnetically stirred mixture of 4-methoxyacetophenone (**1i**, 0.37 g, 2.5 mmol) and DMF-DMA (0.39 mL, 357 mg, 3 mmol, 1.2 equiv.) at 80 °C (oil bath) was added L-proline (29 mg, 0.25 mmol, 10 mol-%), and the mixture was stirred for 2 h. The mixture was concentrated in vacuo to remove the volatile components (excess amount of DMF-DMA and the liberated methanol), and the crude product was purified by flash chromatography (EtOAc/hexane) to afford 3-(dimethylamino)-1-(4-methoxyphenyl)-prop-2-en-1-one (**2i**) as reddish brown viscous solid[8] (0.41 g, 80%). IR (KBr): $\tilde{\nu}_{max}$ = 2930, 1635, 1605, 1432, 1350, 1252, 1210, 1105, 1032, 892, 835 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.91 (m, 2 H), 7.79 (d, *J* = 12.3 Hz, 1 H), 6.89–6.92 (m, 2 H), 5.71 (d, *J* = 12.3 Hz, 1 H), 3.84 (s, 3 H), 3.10 (s, 3 H), 2.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.5, 161.9, 153.8, 133.1, 129.5, 113.3, 91.7, 55.3, 44.9, 37.1 ppm. MS (APCI): *m/z* = 206.25 [M + H]$^+$. HRMS (ESI): calcd. for $C_{12}H_{15}NO_2Na$ [M + Na]$^+$ 228.0995; found 228.0998.

Supporting Information (see footnote on the first page of this article): Spectral data for all compounds and scanned spectra.

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