Michael Additions of Aldehydes and Ketones to β-Nitrostyrenes in an Ionic Liquid

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Michael additions of different aldehydes and ketones to β-nitrostyrene and 2-(β-nitrovinyl)thiophene in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) were studied. β-Nitrostyrene was a better acceptor than 2-(β-nitrovinyl)thiophene, in terms of both reactivity and selectivity. Aldehydes proved to be better donors than ketones, which were themselves better than β-diketones. L-proline proved to be the best catalyst among seven organocatalysts tested.

Introduction

The Michael addition is one of the most frequently used C−C bond-forming reactions in organic synthesis.[1−5] Great progress has been achieved in the asymmetric version of this reaction[6−8] and the asymmetric Michael addition to nitroalkenes has also been described.[9] Among the most frequently used catalysts in asymmetric Michael additions are Cinchona alkaloids and their derivatives[10,11] as well as BINOL-based heterobimetallic catalysts.[12] Asymmetric reactions catalysed by small organocatalysts have become very attractive in recent years,[13−17] and this type of catalysis has also been used for Michael additions of aldehydes and ketones to nitrostyrenes.[18−21] DMSO and chloroform are the most frequently employed solvents in proline-catalysed reactions, although methanol is also a suitable solvent. This was recently shown by Enders in a thorough study of the solvent effect on the course of L-proline-catalysed reactions.[22] Barbas III[18] has also used THF as the solvent, but the yield with L-proline was just 5% and (*S*)-2-(morpholinomethyl)pyrrolidine had to be used as the catalyst to achieve high yields. Reaction times of such reactions are generally long (2−4 days) and the yields can reach up to 85%. The best selectivities for such reactions were described by Enders[21] who reached a diastereomeric ratio (*dr*) of approx. 80:20 and *ee* values varying from 25 to 78%.

In recent years, ionic liquids have emerged as frequently used "green" solvents for many organic reactions including transition metal-catalysed reactions.[22−26] Ionic liquids have also been used for quinidinium bromide-catalysed Michael addition of dimethyl malonate to chalcone[27] and addition of thiols to α,β-unsaturated ketones.[28] We[29] and, simultaneously, Loh et al.[30] have found that ionic liquids are also excellent solvents for proline-catalysed aldol reactions. Following this line, the aim of the work described here was to explore whether ionic liquids can also be used as solvents for L-proline-catalysed Michael additions to β-nitrostyrenes.

Results and Discussion

We started our investigation with an examination of the catalytic efficacy of several chiral amino acids or compounds derived from them. The reaction of β-nitrostyrene (**1a**) with isobutyraldehyde (**2b**) (Scheme 1) was used to test the catalytic activity of seven different small organic molecules (**CAT1** − **CAT7**) (Figure 1). All reactions were performed in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) as the solvent in the presence of 5 mol % of a catalyst.

The results given in Table 1 show that the best catalyst proved to be simple L-proline (**CAT1**). The second best was 2-(*N*-morpholinomethyl)pyrrolidine (**CAT4**). While most of the other catalysts were more or less inactive, *trans*-4-hydroxy-L-proline (**CAT3**) exhibited significant activity at elevated temperatures (80 °C). The attempt to use free **CAT4** (without TfOH) was also promising, because 45% yield of the product was isolated after 22 h at room temperature, but all of the catalyst together with the product was extracted into diethyl ether and no re-use of the catalytic system was possible.

As mentioned above, there are several papers[18−21] describing L-proline-catalysed additions of aldehydes or ke-

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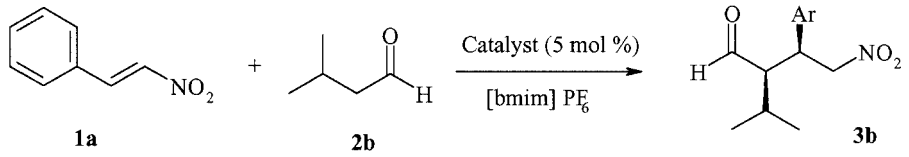


1a 2b 3b

Scheme 1

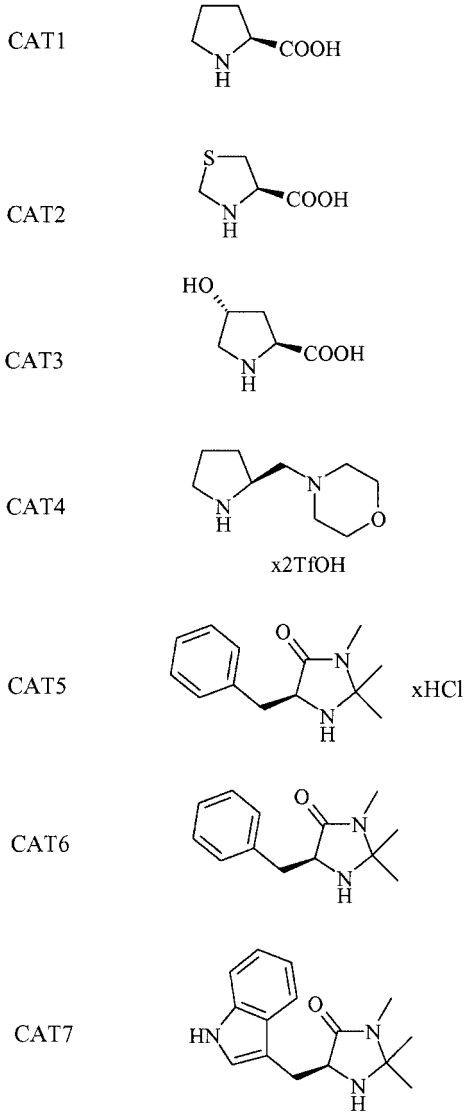


Figure 1. Structure of the catalysts

tones to β-nitrostyrenes, but usually either aldehydes[18] or ketones[19,21] were studied, and therefore no direct comparison of their reactivity could be made. Moreover, other Michael donors such as β-diketones have never been tested. For this reason, we decided to examine the reactivity of a broad range of Michael donors (Figure 2, **2a**−**2v**) in the addition to β-nitrostyrene (**1a**) according to Scheme 2. Again, [bmim]PF_6 was used as the solvent in the presence of 5 mol % of L-proline as a catalyst.

Table 1. Results of the catalysts screening

Entry	Catalyst	*t* (°C)/Time (h)	Yield (%)	*dr* (*syn*/*anti*) (NMR)
1	CAT1	room temp./22	83	9:1
2	CAT2	room temp./22	0	–
3	CAT2	80/12	16	10:1
4	CAT3	room temp./22	0	–
5	CAT3	80/12	51	4:3
6	CAT4	room temp./100	34	3:1
7	CAT4[a]	room temp./22	45	3:1
8	CAT4[a]	room temp./48	45	3:1
9	CAT5	room temp./22	0	–
10	CAT6	room temp. /22	0	–
11	CAT7	room temp. /22	0	–

[a] A naked CAT4 (not containing TfOH) was used in this experiment. This catalyst is very soluble in diethyl ether so the IL/catalyst system cannot be re-used.

The results given in Table 2 show that the reactions proceeded well using just 5 mol % of L-proline as the catalyst, and reasonable yields of the products were isolated after 24 h at room temperature. Obviously, there is a big difference from the published systems, where 15−20 mol % of catalyst were necessary to obtain reasonable conversions within 2−3 days. In comparison to simple propionic aldehyde (**2a**), aldehydes **2b**−**2e** give high yields, an exception being 3,3-dimethylbutanal (**2f**) in which case no reaction was observed even at higher temperature. This can be rationalised by assuming that a bulky *tert*-butyl group precluded the formation or conversion of the suggested enamine intermediate.[21] Two further experiments were performed. In an ionic liquid−chloroform system (Table 2, Entry 7) the same results were achieved as in the pure ionic liquid. The two phase ionic liquid/water system was less effective (Table 2, Entry 8).2

Interesting results were also observed for Michael additions of cyclic ketones **2g**−**2j**. While the reaction of cyclopentanone (**2h**) proceeded smoothly at room temperature, which is in agreement with refs.[20,21], elevated temperatures were necessary to obtain good results with cyclobutanone (**2g**), cyclohexanone (**2i**) and cycloheptanone (**2j**). We cannot explain this observation. One could only speculate about subtle differences in the rate of formation and conversion of the cyclic enamine intermediates.

Acyclic ketones **2k**−**2n**, especially those with bulky substituents, proved to be less reactive than aldehydes and also less reactive than cyclic ketones, which is reflected by lower product yields even at elevated temperatures. It is worth

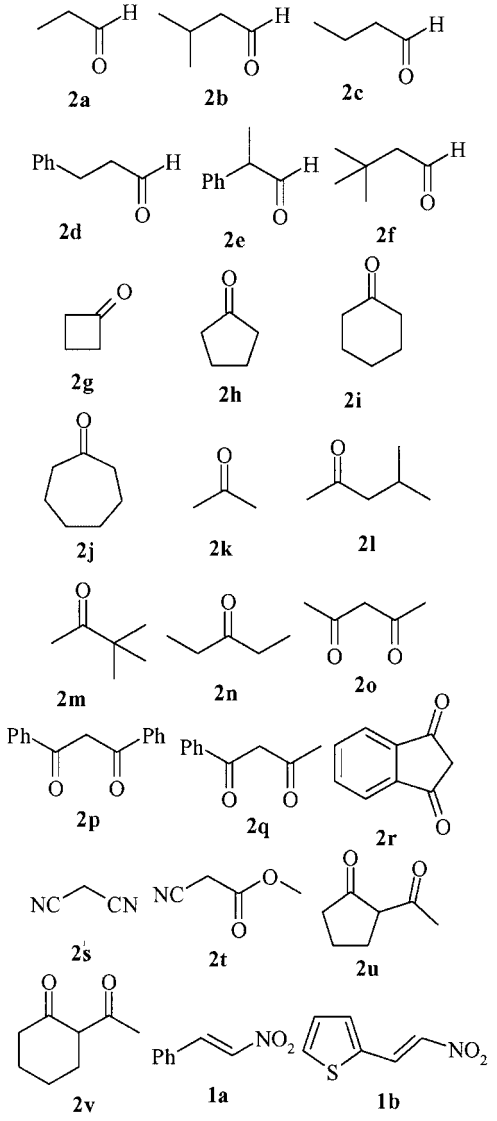
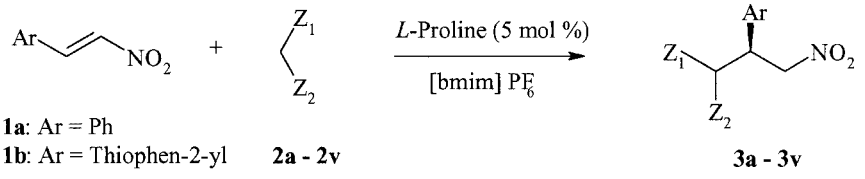


Figure 2. Structure of the reagents

Table 2. Results of Michael additions to β-nitrostyrene **1a**

Entry	Reagent	*t* (°C)/Time (h)	Yield (%)	*dr* (*syn*/*anti*) (NMR)
1	**2a**	room temp./22	58	3:1
2	**2b**	room temp./22	83	9:1
3	**2b**	room temp./22	70[a]	6:1
4	**2b**	room temp./22	61[b]	5:1
5	**2c**	room temp./22	89	6:1
6	**2d**	room temp./22	93	5:1
7	**2d**	room temp./12	90[c]	5:1
8	**2d**	room temp./12	79[d]	5:1
9	**2e**	room temp./22	64	8:1
10	**2f**	room temp./24	0	–
11	**2f**	80/24	0	–
12	**2g**	room temp./36	0	–
13	**2g**	70/12	53	4:3
14	**2h**	room temp./14	69	3:2
15	**2i**	room temp./36	4	n.d.
16	**2i**	80/14	87	5:1
17	**2j**	room temp./36	0	–
18	**2j**	70/14	67	6:1
19	**2k**	room temp./22	35	n.d.
20	**2k**	80 /22	77	n.d.
21	**2l**	room temp./22	0	–
22	**2l**	80/22	23	n.d.
23	**2m**	room temp./22	0	–
24	**2m**	80/22	5	n.d.
25	**2n**	room temp./22	0	–
26	**2n**	80/22	25	1:1
27	**2o**	room temp./14	45	–
28	**2p**	room temp./14	9	–
29	**2p**	80/22	38	–
30	**2q**	room temp./12	17	3:2
31	**2q**	80/22	51	3:2
32	**2r**	room temp./14	55	–
33	**2s**	room temp./14	80	–
34	**2t**	room temp./14	81	3:2
35	**2u**	room temp./14	41	12:1
36	**2v**	room temp./36	0	–
37	**2v**	80/48	0	–

[a] 1st re-use of the IL – L-proline system. [b] 2nd re-use of the IL – L-proline system. [c] Reaction was performed in [bmim]PF_6: $CHCl_3$ (1:1). [d] Reaction was performed in [bmim]PF_6: H_2O (1:1) two phase system.



Scheme 2

noting that the reactions are clean and no side-products were detected. The low yields of the product can be raised either by prolonging the reaction time or by performing the reaction at higher temperature (see below).

It is interesting to compare the results achieved with different β-diketones (**2o**–**2r**, **2u**, **2v**). Among the acyclic β-diketones, acetylacetone (**2o**) gave rise to the highest yield. The lower reactivity of β-diketones may be rationalised by the assumption that they are enolised and their enols are stabilised by strong intramolecular hydrogen bonding. This precludes the formation of the enamine which was suggested as an intermediate[21] in L-proline-catalysed reactions. This could explain the observed reactivity order **2o** > **2q** > **2p**. In the case of the cyclic β-diketones **2r**, **2u**, **2v**, accordingly, a very good yield was achieved with indane-1,3-dione (**2r**) which is "unhindered" because its enol form

cannot be stabilised by intramolecular hydrogen bonding. In contrast, 2-acetylcyclohexan-1-one (**2v**) did not react even at elevated temperatures, possibly because its geometry allows the formation of a hydrogen bond-stabilised enol. This assumption is also supported by the fact that high yields of the products resulted from the reactions of malonodinitrile (**2s**) and methyl cyanoacetate (**2t**), neither of which can form hydrogen bond-stabilised enolates. The structures of the reaction products formed by addition to **1a** and **1b** are given in Figure 3.

In order to probe the generality of the reactivity pattern observed so far for reagents **2a**−**2v**, we also performed several reactions using 2-(2-nitrovinyl)thiophene (**1b**) as a Michael acceptor. Indeed, as the results given in Table 3 demonstrate, the same reactivity pattern was observed, 2-(2-nitrovinyl)thiophene (**1b**) just being a little less reactive than β-nitrostyrene (**1a**). The ratio of *syn*/*anti* diastereomers was determined by NMR and in some cases also by HPLC measurements, which resulted in some different *dr* values in Table 2 and Table 4. From the results given in Tables 2 and 3 it follows that formation of the *syn* diastereomer is strongly favored, which is consistent with refs.[18−21] The absolute configuration of the main products was suggested in analogy with refs.[18−21]

We next examined the stereoselectivity of L-proline-catalysed Michael additions, and therefore determined the *ee* of selected samples by HPLC measurements (Table 4). While all samples were pure according to TLC and NMR, the HPLC measurements were complicated by UV-active trace impurities and the tendency of some samples to slowly decompose. Nevertheless, the results given in Table 4 are significant and clearly show that only low or medium stereoselectivities were obtained, even when 20 mol % of L-proline or a great excess of aldehyde was used (entries 3 and 4). Thanks to a referee comment we also performed reactions in four other ionic liquids, namely: 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4), 1,3-dibutylimidazolium bromide ([dbim]Br), 1,3-dibutylimidazolium hexafluorophosphate ([dbim]PF_6) and 1-butyl-3-methylimidazolium laurate ([bmim] laurate). Chemical yields were in most cases very high (95%) although with [bmim] laurate the yield was 82%. Table 4, entries 20−23, show that *ee* values are similar to those achieved in experiments using [bmim]PF_6 as the solvent, the exception being [bmim] laurate in which 58% *ee* was achieved. We have to add that this ionic liquid is very miscible with organic solvents and the product had to be isolated by flash chromatography on silica gel.

Comparing our results with those published we can state that by using an ionic liquid as a solvent we have reached similar results (*dr*, *ee*) to those described by Alexakis,[20] who used 15 mol % of L-proline in DMSO, and by Enders,[21] who used 20−15 mol % of L-proline in methanol. On the other hand our yields are lower that those reported by Enders.[21] Better results with respect to both yields and selectivities were only described by Barbas,[18] who used 20 mol % of (*S*)-2-(morpholinomethyl)pyrrolidine as catalyst and THF as solvent.

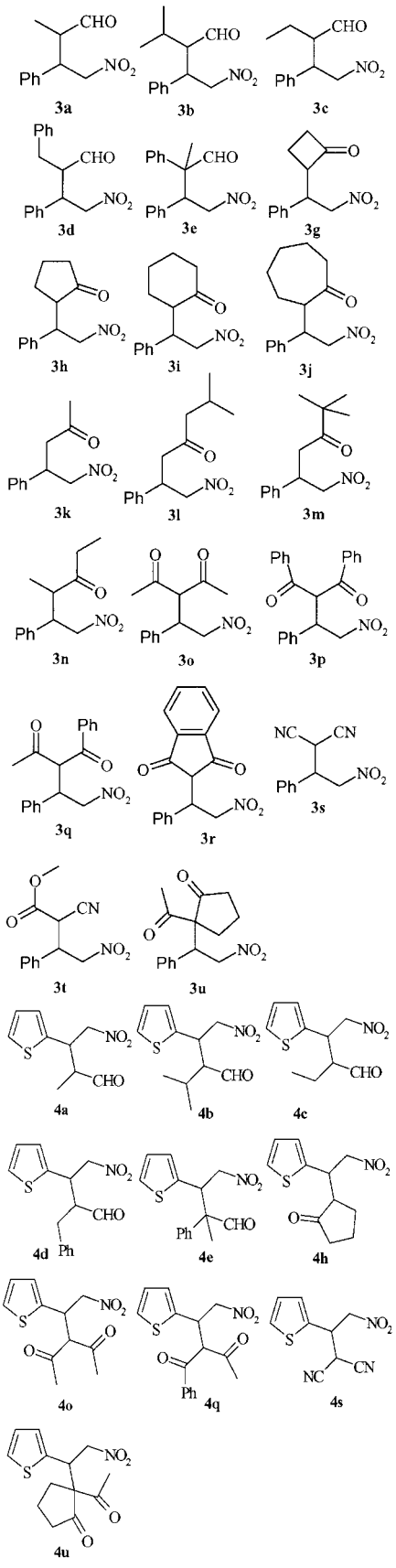


Figure 3. Structure of products

Table 3. Results of Michael addition to 2-(2-nitrovinyl)thiophene **1b**

Entry	Reagent	*t* (°C)/Time (h)	Yield (%)	*dr* (*syn*/*anti*) (NMR)
1	**2a**	room temp./22	73	5:4
2	**2b**	room temp./22	91	10:1
3	**2c**	room temp./22	81	5:1
4	**2d**	room temp./22	85	5:1
5	**2e**	room temp./22	29	20:1
6	**2f**	room temp./24	0	–
7	**2f**	80/24	0	–
8	**2h**	room temp./12	42	4:1
9	**2o**	room temp./12	14	10:1
10	**2q**	room temp./12	11	3:2
11	**2s**	room temp./12	70	20:1
12	**2u**	room temp./12	40	8:1

Table 4. Determination of *ee* of the chosen samples by HPLC

Entry	Reagents	*t* (°C) /Time (h)	*dr* (*syn*/*anti*)	*ee* (*syn*) (%)
1	**1a**+**2a**	room temp./22	n.d.	12
2	**1a**+**2b**	room temp./22	≥25:1	43
3	**1a**+**2b**	room temp./22	25:1	39[a]
4	**1a**+**2b**	room temp./22	25:1	42[b]
5	**1a**+**2c**	room temp./22	"signif."	38
6	**1a**+**2d**	room temp./22	"high"	31
7	**1a**+**2e**	room temp./22	n.d.	3
8	**1a**+**2h**	room temp./14	2:1	32[c]
9	**1a**+**2i**	70/14	4:1	very low[c]
10	**1a**+**2k**	80/22	n.d.	3[d]
11	**1a**+**2n**	80/22	n.d.	60
12	**1a**+**2o**	room temp./14	n.d.	10[d]
13	**1a**+**2q**	room temp./14	n.d.	8[d]
14	**1a**+**2r**	room temp./14	n.d.	17[d]
15	**1b**+**2a**	room temp./22	2.5:1	28
16	**1b**+**2b**	room temp./22	3:1	25
17	**1b**+**2c**	room temp./22	3:1	25
18	**1b**+**2d**	room temp./22	1.5:1	36[c]
19	**1b**+**2e**	room temp./22	n.d.	5
20	**1a**+**2b**	room temp./12	25:1	43[e]
21	**1a**+**2b**	room temp./12	25:1	41[f]
22	**1a**+**2b**	room temp./12	25:1	35[g]
23	**1a**+**2b**	35/12	25:1	58[h]

[a] Reaction was performed with 20 mol % of L-proline and 1.5 equiv. of aldehyde. [b] Reaction was performed with 5 mol % of L-proline and 10 equiv. of aldehyde. [c] *ee* was determined by HPLC using a refractometer as detector. [d] *ee* was determined by NMR (chiral NMR shift reagent). [e] [bmim]BF_4 was used as the solvent. [f] [dbim]Br was used as the solvent. [g] [dbim]PF_6 was used as the solvent. [h] [bmim] laurate was used as the solvent.

Conclusions

The ionic liquid [bmim]PF_6 was shown to be a good solvent for L-proline-catalysed Michael additions of different donors (carbonyl compounds) to β-(nitrovinyl)arenes. Just 5 mol % of L-proline are necessary to reach reasonable to high yields in a short reaction time (1 day instead of 2–3 days in other solvents). L-Proline was found to be the best among seven catalysts tested.

β-Nitrostyrene (**1a**) proved to be a better acceptor than 2-(2-nitrovinyl)thiophene (**1b**), in terms of both reactivity and selectivity. Aldehydes proved to be much better donors than ketones, which were themselves better than β-diketones, indane-1,3-dione being the exception. Reactions with ketones require elevated temperatures to achieve good yields of products.

Experimental Section

Starting materials, that is nitrostyrene, 2-(2-nitrovinyl)thiophene, aldehydes and ketones together with L-proline and *trans*-4-hydroxy-L-proline and (*R*)-(−)thiazolidine-4-carboxylic acid, were commercial products (Aldrich) and used as received.

NMR spectra were measured on a Varian Gemini 2000 spectrometer operating at 300 MHz; tetramethylsilane was used as an internal standard. The NMR spectra of the main (syn) isomer are always given. MS spectra were measured on a Micromass ZMD ESI (80 eV) system; substances were dissolved in an acetonitrile/water (80:20) mixture, with the exception of compounds **3d**, **4d** and **4e**, which were dissolved in chloroform, and 100% methanol was used as the mobile phase. HPLC was performed on a Merck–Hitachi. HPLC-system with Pump L-6200A, UV-Detector L-4000A, RF-Detector RI-71 and software HPLC-Manager D-6000 using Diacel Chiralpak AD-H 250×4 mm column equipped with Macherey–Nagel Nucleosil 100–5 11×3 mm precolumn. Hexane/2-propanol 90:10 was used as the eluent. A UV detector was used in most cases, but in the case of cyclic ketones a refractory detector has to be used. (*S*)-2-(morpholinomethyl)pyrrolidine was prepared according to ref.[31], 1-methyl-2,2-dimethyl-4-[(*S*)-benzyl]-pyrimidine-5-one (CAT6) was prepared according to ref.[32] and CAT7 was prepared analogously to CAT6.

General Experimental Procedure: L-Proline (5.75 mg, 5 mol %) and the chosen donor (**2**) (1.5 equiv.) were added to the degassed ionic liquid [bmim]PF_6 (1 mL) and the mixture was stirred for 15 min at room temp. Acceptor (**1**) (1 mmol) was then added and the reaction mixture was stirred intensively for the chosen time at the chosen temperature (see Tables). The product was extracted in several portions of diethyl ether and the extract was chromatographed on SiO_2 column using hexane/dichloromethane, 2:1 as the eluent when aldehydes were used as donors and hexane/ethyl acetate, 4:1 in all other cases. Products were isolated as pure materials and their structure was proved by ^{1}H NMR spectra and, in the case of new compounds, also by mass spectrometry.

2-Methyl-4-nitro-3-phenylbutyraldehyde (3a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 1.5 Hz, 1 H), 7.36–7.29 (m, 3 H), 7.17–7.16 (m, 2 H), 4.80 (dd, *J* = 12.9, 5.5 Hz, 1 H), 4.69 (dd, *J* = 12.9, 9.2 Hz, 1 H), 3.81 (ddd, *J* = 9.2, 9.2, 5.5 Hz, 1 H), 2.80–2.75 (m, 1 H), 1.01 (d, *J* = 7.4 Hz, 3 H), in agreement with ref.[18]

2-Isopropyl-4-nitro-3-phenylbutyraldehyde (3b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.93 (d, *J* = 2.6 Hz, 1 H), 7.36–7.29 (m, 3 H), 7.20–7.18 (m, 2 H), 4.67 (dd, *J* = 12.5, 4.4 Hz, 1 H), 4.58 (dd, *J* = 12.5, 10.2 Hz, 1 H), 3.90 (ddd, *J* = 10.2, 10.2, 4.4 Hz, 1 H), 2.79–2.75 (m, 1 H), 1.76–1.69 (m, 1 H), 1.10 (d, *J* = 7.2 Hz, 3 H), 0.89 (d, *J* = 7.2 Hz, 3 H), in agreement with ref.[18]

2-Ethyl-4-nitro-3-phenylbutyraldehyde (3c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.72 (d, *J* = 2.6 Hz, 1 H), 7.36–7.28 (m, 3 H), 7.19–7.17 (m, 2 H), 4.72 (dd, *J* = 12.8, 4.9 Hz, 1 H), 4.63 (dd, *J* = 12.8, 9.7 Hz, 1 H), 3.79 (ddd, *J* = 9.7, 9.7, 4.9 Hz, 1 H), 2.71–2.66

(m, 1 H), 1.53−1.49 (m, 2 H), 0.83 (dd, 3 H, J = 7.5, 7.5 Hz), in agreement with ref.[18]

2-Benzyl-4-nitro-3-phenylbutyraldehyde (3d): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.717 (d, J = 2.1 Hz, 1 H), 7.382−7.226 (m, 10 H), 4.73 (dd, J = 6, 2.4 Hz, 2 H), 3.836 (m, 1 H), 3.13 (m, 1 H), 2.77 (t, 2 H). MS (neg. mode): m/z = 318 [M + Cl^-]. $C_{17}H_{17}NO_3$ (283.33): calcd. C 72.07, H 6.05, N 4.94; found C 72.37, H 6.09, N 4.98.

2-Methyl-4-nitro-2,3-diphenylbutyraldehyde (3e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.558 (d, J = 2.0 Hz, 1 H), 7.945−7.280 (m, 10 H), 5.065 (dd, J = 11.7, 1.2 Hz, 1 H), 4.822 (dd, J = 9.6, 3.6 Hz, 1 H), 4.222 (dd, J = 11.4, 3.6 Hz, 1 H), 9.717 (s, 3 H), in agreement with ref.[33]

2-(2-Nitro-1-phenylethyl)cyclobutanone (3g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.348−7.202 (m, 5 H), 5.101−5.044 (dd, J = 12.6, 4.2 Hz, 1 H), 4.678−4.603 (dd, J = 9.9, 2.7 Hz, 1 H), 3.725−3.620 (m, 2 H), 3.119−2.982 (m, 2 H), 2.082−2.067 (m, 1 H), 1.731−1.67 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): 137.166, 129.317, 129.302, 128.377, 127.766, 127.750, 77.710, 60.100, 44.685, 44.483, 16.043 ppm. MS (neg. mode): m/z = 220 [M − H^+]. $C_{12}H_{13}NO_3$ (219.24): calcd. C 65.74, H 5.98, N 6.39; found C 65.79, H 6.02, N 6.31.

2-(2-Nitro-1-phenylethyl)cyclopentanone (3h): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.320−7.149 (m, 5 H), 5.328 (dd, J = 12.9, 7.5 Hz, 1 H), 5.032 (d, J = 7.5 Hz, 1 H), 4.718 (dd, J = 12.9, 9.9 Hz, 1 H), 3.833 (m, 1 H, minor), 3.686 (m, 1 H, major), 2.411−0.902 (m, 6 H, cycl), in agreement with ref.[34]

2-(2-Nitro-1-phenylethyl)cyclohexanone (3i): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.325−7.155 (m, 5 H), 4.673 (dd, J = 9.9, 2.4 Hz, 1 H), 4.096 (m, 1 H, minor), 3.770 (m, 1 H, major), 2.735−1.264 (m, 9H cycl), in agreement with ref.[20]

2-(2-Nitro-1-phenylethyl)cycloheptanone (3j): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.336−7.160 (m, 5 H), 4.658 (dd, J = 8.1, 4.8 Hz, 2 H), 3.691 (m, 1 H), 3.036 (m, 1 H), 2.548 (m, 3 H), 1.904−1.509 (m, 5 H), 1.246 (m, 2 H), in agreement with ref.[34]

5-Nitro-4-phenylpentane-2-one (3k): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.334−7.200 (m, 5 H), 4.688 (dd, J = 6.9, 3.5 Hz, 1 H), 4.608 (dd, J = 7.5, 3.5 Hz, 1 H), 4.008 (m, 1 H), 2.931 (d, J = 6.9 Hz, 2 H), 2.120 (s, 3 H), in agreement with ref.[20]

2-Methyl-7-nitro-6-phenylheptane-4-one (3l): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.322−7.221 (m, 5 H), 4.663 (dd, J = 16.8, 6.9 Hz, 1 H), 4.604 (dd, J = 16.8, 6.9 Hz, 1 H), 4.018 (m, 1 H), 2.864 (dd, J = 2.1, 1.8 Hz, 2 H), 2.216 (dd, J = 7.5, 2.7 Hz, 2 H), 2.070 (m, 1 H), 0.848 (d, J = 6.6 Hz, 6 H). MS (neg. mode): m/z = 248 [M − H^+]. $C_{14}H_{19}NO_3$ (249.31): calcd. C 67.45, H 7.68, N 5.62; found C 67.51, H 7.62, N 5.59.

2,2-Dimethyl-6-nitro-5-phenylhexane-3-one (3m): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.631 (m, 5 H), 4.120 (m, 2 H), 3.665 (t, 2 H), 3.065 (m, 1 H), 0.905 (s, 9 H), in agreement with ref.[35]

4-Methyl-6-nitro-5-phenylhexane-3-one (3n): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.333−7.239 (m, 3 H), 7.174−7.148 (m, 2 H), 4.629 (dd, J = 12.9, 5.1 Hz, 2 H), 3.704 (m, 1 H), 3.001 (m, 1 H), 2.575 (m, 1 H), 2.430 (m, 1 H), 1.075 (t, 3 H), 0.970 (d, J = 7.2 Hz, 3 H), in agreement with ref.[20]

3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (3o): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.367−7.169 (m, 5 H), 4.620 (m, 2 H), 4.395 (d, J = 10.8 Hz, 1 H), 4.282−4.204 (m, 1 H), 2.298 (s, 3 H), 1.944 (s, 3 H), in agreement with ref.[21]

2-(2-Nitro-1-phenylethyl)-1,3-diphenylpropane-1,3-dione (3p): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.876 (dd, J = 7.2, 1.2 Hz, 2 H), 7.847 (dd, J = 7.2, 1.2 Hz, 2 H), 7.58 (m, 2 H), 7.419 (m, 4 H), 7.225 (m, 5 H), 5.849 (d, J = 7.8 Hz, 1 H), 5.008 (d, J = 6.6 Hz, 2 H), 4.658 (m, 1 H). MS (neg. mode): m/z = 372 [M − H^+]. $C_{23}H_{19}NO_4$ (373.41): calcd. C 73.98, H 5.13, N 3.75; found C 74.05, H 5.17, N 3.81.

2-(2-Nitro-1-phenylethyl)-1-phenylbutane-1,3-dione (3q): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.031−7.27 (m, 10 H), 5.203 (m, 1 H), 4.781 (m, 2 H), 4.540 (m, 1 H, major), 4.416 (m, 1 H, minor), 2.231 (s, 1 H, minor), 1.940 (s, 1 H, major), in agreement with ref.[36]

2-(2-Nitro-1-phenylethyl)indan-1,3-dione (3r): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.876−7.739 (m, 5 H), 7.259−7.153 (m, 5 H), 5.335 (dd, J = 13.5, 5.1 Hz, 1 H), 5.085 (dd, J = 13.5, 7.5 Hz, 1 H), 4.438 (m, 1 H), 3.450 (d, J = 3.6 Hz, 1 H), in agreement with ref.[37]

2-(2-Nitro-1-phenylethyl)malononitrile (3s): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.489−7.340 (m, 5 H), 4.955 (dd, J = 11.4, 8.1 Hz, 2 H), 4.435 (d, J = 5.7 Hz, 1 H), 7.876 (m, 1 H), in agreement with ref.[38]

Methyl 2-Cyano-4-nitro-3-phenylbutyrate (3t): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.403−7.304 (m, 5 H), 5.000−4.844 (m, 2 H), 4.228−4.159 (m, 1 H), 4.150 (d, J = 12 Hz, 1 H major), 3.950 (d, J = 12 Hz, 1 H, minor), 3.785 (s, 3 H, minor), 3.697 (s, 3 H, major), in agreement with ref.[39]

2-Acetyl-2-(2-nitro-1-phenylethyl)cyclopentanone (3u): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.300−7.28 (m, 5 H), 4.868 (dd, J = 11.4, 2.1 Hz, 1 H), 4.521 (dd, J = 13.5, 3.9 Hz, 1 H), 4.419 (dd, J = 13.5, 3.9 Hz, 1 H), 2.613 (m, 1 H), 2.337 (s, 3 H), 2.241 (m, 1 H), 2.037 (m, 1 H), 1.719 (m, 3 H), in agreement with ref.[40]

2-Methyl-4-nitro-3-(thiophen-2-yl)butyraldehyde (4a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.703 (d, J = 1.2 Hz, 1 H, major), 9.630 (d, J = 1.2 Hz, 1 H, minor), 7.255 (d, J = 2.4 Hz, 1 H), 6.946 (m, 2 H), 4.795 (m, 2 H), 4.234 (m, 1 H), 2.815 (m, 1 H), 1.128 (d, J = 7.2 Hz, 3 H, minor), 1.148 (d, J = 7.2 Hz, 3 H, major). MS (neg. mode): m/z = 212 [M − H^+]. $C_9H_{11}NO_3S$ (213.26): calcd. C 50.69, H 5.20, N 6.57, S 15.04; found C 50.75, H 5.28, N 6.62, S 15.24.

2-Isopropyl-4-nitro-3-(thiophen-2-yl)butyraldehyde (4b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.913 (d, J = 2.4 Hz, 1 H, major), 9.630 (d, J = 2.4 Hz, 1 H, minor), 7.263 (d, J = 5.7 Hz, 1 H), 6.937 (m, 2 H), 4.236 (m, 1 H), 2.822 (dd, J = 4.5, 1.8 Hz, 1 H), 1.919 (m, 1 H), 1.169 (d, J = 6.9 Hz, 3 H), 0.936 (d, J = 6.9 Hz, 3 H), in agreement with ref.[18]

2-Ethyl-4-nitro-3-(thiophen-2-yl)butyraldehyde (4c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.722 (d, J = 1.8 Hz, 1 H, major), 9.616 (d, J = 1.8 Hz, 1 H, minor), 7.244 (d, J = 5.7 Hz, 1 H), 6.953 (m, 2 H), 4.725 (m, 2 H), 4.190 (m, 1 H), 2.707 (m, 1 H), 1.663 (q, 2 H), 1.039 (t, 3 H, minor), 0.944 (t, 3 H, major). MS (neg. mode): m/z = 226 [M − H^+]. $C_{10}H_{13}NO_3S$ (227.28): calcd. C 52.85, H 5.77, N 6.16, S 14.11; found C 52.90, H 5.74, N 6.10, S 14.17.

2-Benzyl-4-nitro-3-(thiophene-2-yl)butyraldehyde (4d): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.707 (d, J = 1.8 Hz, 1 H), 7.296−7.229 (m, 5 H), 7.126 (d, 1 H), 6.984 (m, 2 H), 4.713 (m, 2 H), 4.236 (m, 1 H), 3.137 (m, 1 H), 2.869 (d, J = 7.5 Hz, 2 H). MS (neg. mode): m/z = 324 [M + Cl^-]. $C_{15}H_{15}NO_3S$ (289.36): calcd. C 62.26, H 5.23, N 4.84, S 11.08; found C 62.22, H 5.29, N 4.89, S 11.14.

2-Methyl-4-nitro-2-phenyl-3-(thiophen-2-yl)butyraldehyde (4e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.562 (d, *J* = 1.2 Hz, 1 H), 7.388−7.128 (m, 6 H), 6.808 (dd, *J* = 5.1, 3.6 Hz, 1 H), 6.684 (d, *J* = 2.7 Hz, 1 H), 4.923 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.707 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.532 (2d, 1 H, *J* = 3.6 Hz), 1.603 (s, 3 H). MS (neg. mode): *m*/*z* = 324 [M + Cl^-]. $C_{15}H_{15}NO_3S$ (289.36): calcd. C 62.26, H 5.23, N 4.84, S 11.08; found C 62.31, H 5.27, N 4.90, S 11.14.

2-[2-Nitro-1-(thiophen-2-yl)ethyl]cyclopentanone (4h): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 1 Hz, 1 H), 6.946 (d, *J* = 3.3 Hz, 1 H), 6.874 (d, *J* = 6 Hz, 1 H), 4.969 (dd, *J* = 12.9, 6.3 Hz, 1 H), 5.018 (m, 1 H), 4.702 (dd, *J* = 12.9, 9.3 Hz, 1 H), 4.155 (m, 1 H), 2.405−2.208 (m, 2 H), 2.122−2.088 (m, 2 H), 1.772−1.753 (m, 2 H). MS (neg. mode): *m*/*z* = 238 [M − H^+]. $C_{11}H_{13}NO_3S$ (239.30): calcd. C 55.21, H 5.48, N 5.85, S 13.40; found C 55.33, H 5.42, N 5.72, S 13.36.

3-(2-Nitro-1-thiophen-2-ylethyl)pentane-2,4-dione (4o): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.240 (d, *J* = 0.9 Hz, 1 H), 6.937−6.696 (m, 2 H), 4.673−4.651(dd, *J* = 6.6, 1.5 Hz, 2 H), 4.580−4.529 (m, 1 H), 4.420−4.386 (d, *J* = 10.2 Hz, 1 H), 2.305 (s, 3 H), 7.240 (s, 3 H), in agreement with ref.[41]

2-[2-Nitro-1-(thiophen-2-yl)ethyl]-1-phenylbutane-1,3-dione (4q): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.039 (d, *J* = 7.2 Hz, 1 H), 8.015 (d, *J* = 7.5 Hz, 1 H), 7.926−6.180 (m, 6 H), 5.307 (2d, 1 H, *J* = 9.3 Hz), 4.780 (m, 3 H), 2.480 (s, 3 H,minor), 2.046 (s, 3 H, major). MS (neg. mode): *m*/*z* = 316 [M − H^+]. $C_{16}H_{15}NO_4S$ (317.37): calcd. C 60.55, H 4.76, N 4.41, S 10.10; found C 60.49, H 4.62, N 4.82, S 10.28.

2-[2-Nitro-1-(thiophen-2-yl)ethyl]malononitrile (4s): ^{1}H NMR (300 MHz, DMSO): δ = 7.625 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.280 (d, *J* = 3 Hz, 1 H), 7.112 (dt, 1 H, *J* = 3.6 Hz), 5.411 (d, *J* = 6.6 Hz, 1 H), 5.188 (dd, *J* = 8.7, 5.7 Hz, 1 H), 5.389 (dd, *J* = 8.7, 5.7 Hz, 1 H). MS (neg. mode): *m*/*z* = 220 [M − H^+]. $C_9H_7N_3O_2S$ (221.24): calcd. C 48.86, H 3.19, N 18.99, S 14.49; found C 48.73, H 3.29, N 19.01, S 14.78.

2-Acetyl-2-[2-nitro-1-(thiophen-2-yl)ethyl]cyclopentanone (4u): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.250 (d, *J* = 0.9 Hz, 1 H), 6.959−6.941 (2d, 2 H, *J* = 5.4 Hz), 4.786−4.742 (dt, *J* = 11.1, 2.1 Hz, 1 H), 4.655−4.491 (dd, 2 H, *J* = 13.8, 3 Hz), 2.600 (m, 1 H), 2.294 (s, 3 H), 2.210 (m, 1 H), 1.874 (m, 2 H), 1.855 (m, 2 H). MS (neg. mode): *m*/*z* = 280 [M − H^+]. $C_{13}H_{13}NO_4S$ (281.33): calcd. C 55.50, H 5.37, N 4.98, S 11.40; found C 55.53, H 5.35, N 4.94, S 11.43.

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