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ORIGINAL PAPER

Synthesis of β-hydroxy-α,β-unsaturated carbonyl compounds via the Morita–Baylis–Hillman reaction of paramagnetic aldehydes

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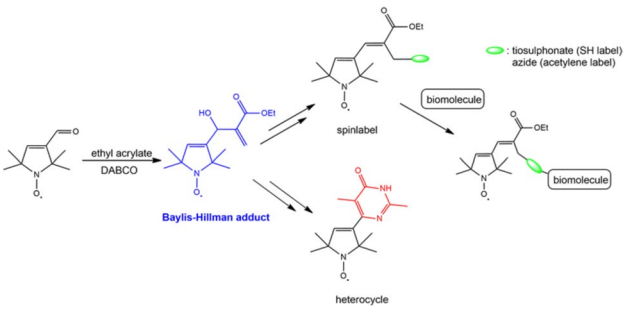
Abstract

To investigate the possibilities of carbon–carbon bond formation in the presence of nitroxides, a novel group of paramagnetic Morita–Baylis–Hillman adducts were synthesized from the reaction starting with five- and six-membered cyclic nitroxide aldehydes and various activated alkenes in the presence of a base, affording β-hydroxy-α,β-unsaturated carbonyls. These adducts could serve as valuable building blocks in nitroxide chemistry. To extend our study, a Morita–Baylis–Hillman alcohol was converted into an iodine derivative, a key intermediate for nucleophilic substitution, forming new cysteine and alkyne spin labels. Additionally, the paramagnetic acrylate adduct was transformed into a β-ketoester, which could be a starting material for synthesizing new heterocyclic compounds bearing a nitroxide moiety.

Graphical abstract



Keywords Alkenes · Carbonyl compounds · Radicals · Morita–Baylis–Hillman reaction · Carbon–carbon bond formation · Spin label

Introduction

One of the most important and practical methods in organic synthesis is carbon–carbon bond formation due to its chemical stability. The Morita–Baylis–Hillman (MBH) coupling reaction is one such method [1, 2], which has increased importance and utilization over the past four decades. The reaction takes place between aldehydes and activated olefins containing an electron-withdrawing group in the presence of a Lewis base catalyst. Among several advantages of the MBH reaction (such as atom economy and organocatalysis), the highly functionalized adducts with β-hydroxy-α-methylene (or β-amino-α-methylene) and electron-withdrawing moiety make the reaction a valuable carbon–carbon bond-forming technique. Thus, MBH adducts are useful substrates to various reactions and have been extensively reviewed in the literature [3–5] as the application and scope of the reaction itself [6–8].

Nitroxide free radicals are one of the most widely studied stable radicals; however, achieving carbon–carbon bond formation in the presence of amphiphilic nitroxide free radicals remains challenging. In our laboratory, several

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publications have been reported over the last three decades on carbon–carbon bond-forming reactions in the presence of nitroxide moieties. These include classic organometallic reactions such as Grignard and lithium organic reactions [9, 10], condensation reactions [9], Cu– and Pd–catalyzed cross-coupling reactions [11–13], and reactions of paramagnetic α,β-ketophosphonates with carbonyl compounds [14]. These reactions have enabled us to access various new paramagnetic building blocks for synthesizing biomolecules and spin labels. Our objective was to develop a new methodology for forming carbon–carbon bonds in the presence of pyrroline- and tetrahydropyridine-nitroxide aldehydes, aiming to access new paramagnetic building blocks. We aimed to functionalize these new compounds further.

The MBH reaction of (4-acryloxy-2,2,6,6-tetramethylpiperidine-1-yl)oxydanyl has been reported with various aldehydes, resulting in new paramagnetic aliphatic, aryl, and heterocyclic MBH adducts [15]. However, to our knowledge, this reaction has not been extended to applying paramagnetic aldehydes. This paper reports the synthesis of new β-hydroxy-α,β-unsaturated carbonyl, and nitrile compounds via MBH reaction from nitroxide aldehydes as starting substances.

Results and discussion

To perform a Morita–Baylis–Hillman reaction, we synthesized the paramagnetic acrylic ester **2** via an esterification of [3-(hydroxymethyl)−2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yl]oxydanyl (**1**) [16] with acryloyl chloride. Compound **2** was reacted with an excess of benzaldehyde without any auxiliary solvent in the presence of 0.2 equiv. 1,4-diazabicyclo[2.2.2]octane (DABCO) to access the paramagnetic MBH adduct **3**, in 72% yield, similar to Zakrzewski's work (Scheme 1) [15].

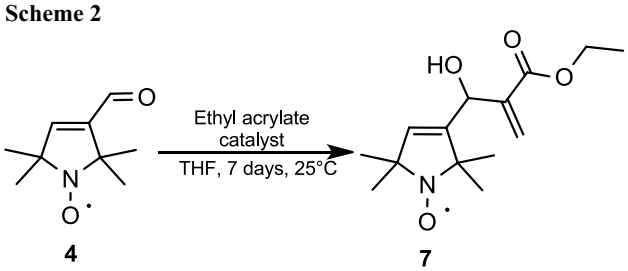
Nevertheless, these types of MBH adducts are limited as building blocks because the nitroxide moiety is connected to the active center of the adduct via an ester function, making them less stable and consumable. We wished to synthesize new paramagnetic Morita–Baylis–Hillman adducts where the C–C bond is formed directly between the nitroxide and the alkene. To produce such MBH adducts, we chose five- and six-membered aldehydes containing nitroxide free radical scaffolds **4**–**6** [16–18] as starting substrates. We applied but-3-ene-2-one (methyl vinyl ketone, MVK), acrylonitrile, methyl and ethyl acrylate as olefins in the presence of DABCO catalyst.

The amount of catalyst was optimized in the reaction of aldehyde **4** and three equiv. of ethyl acrylate (Scheme 2), increasing from 0.01 equiv. to 1.00 equiv. in three steps, with the best yield achieved using 0.5 equiv. of catalyst. Although DABCO is the most commonly used catalyst for this reaction, several Lewis bases have been published previously. To improve yields, we tested the effect of seven different catalysts. Our results demonstrated that DABCO was the most effective catalyst, yielding 42%. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) [19] provided a yield of 21%, while 4-dimethylaminopyridine (DMAP) [20] yielded only 18%. Reactions catalyzed by triazabicyclodecene (TBD) [21], *N*,*N*′-diisopropylethylamine (DIPEA), quinoline, and PCy_3 [1], did not yield the desired product under these conditions (Table 1).

To extend this procedure for novel paramagnetic MBH adducts starting from nitroxide aldehyde electrophiles (Scheme 3), compounds **4**–**6** were reacted with 3 equiv. of electrophiles (MVK, acrylonitrile, and acrylate esters) in the presence of 0.5 equiv. of DABCO at room temperature for seven days.

The MBH adducts **7**–**14** were obtained with low to acceptable yield. The reactions of tetrahydropyridinyl nitroxide **5** yielded lower (8–15%) than the pyrroline derivatives

Scheme 2



Scheme 1

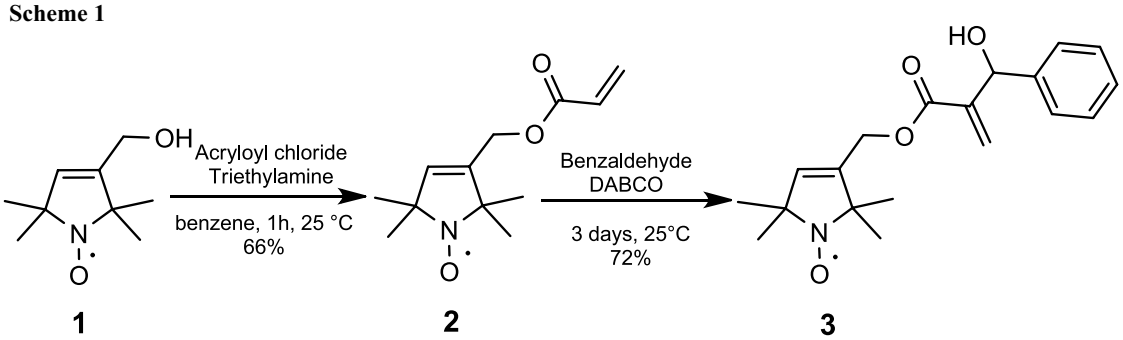


Table 1 Optimization of the reaction conditions

Product	DABCO/equiv	Yield/%	Catalyst	Yield/%
7	0.05	18	DABCO	42
7	0.1	17	DMAP	18
7	0.5	42	DBU	21
7	1	28	TBD	0
			DIPEA	0
			Quinoline	0
			Tricyclohex-ylphosphine	0

The bold values indicate the number of new compounds

Scheme 3

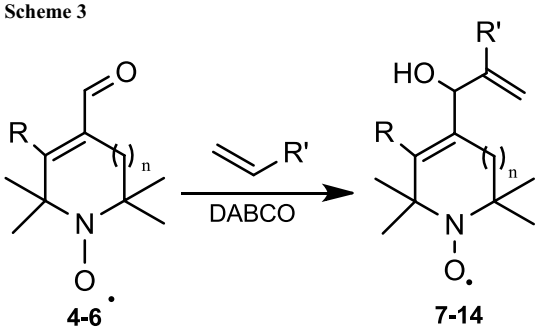


Table 2 Yields of MBH adducts **7**–**14**, the reaction was performed (a) in the presence of 3 equiv. of alkene and 0.5 equiv. of DABCO; (b) in the presence of 1.5 equiv. of alkene and 0.25 equiv. of DABCO; (c) in the presence of 1.5 equiv. of alkene, 0.5 equiv. of DABCO; (d) in the presence of 1.5 equiv. of alkene, 1 equiv. of DABCO and 2 cm^3 of triethanolamine

	R	R′	n	%
4	H	–	0	–
5	H	–	1	–
6	Br	–	0	–
7[a]	H	COOEt	0	42
8[b]	H	COOEt	1	15
9[d]	Br	COOMe	0	23
10[c]	H	$COCH_3$	0	15
11[c]	H	$COCH_3$	1	9
12[a]	H	CN	0	20
13[b]	H	CN	1	8
14[d]	Br	CN	0	17

The bold values indicate the number of new compounds

8, **11**, **13** (15, 9, 42%). Regarding the electrophiles, reactions with acrylate esters achieved higher yields than those with MVK or acrylonitrile. In cases where the yields were lower, signs of the aldehyde or nucleophile decomposition were observed, and minor reaction modifications were needed (a–d) (Table 2). The amount of the catalyst and nucleophile had to be decreased in the case of the tetrahydropyridine nitroxide aldehydes because of the instability and increased reactivity of the more flexible six-membered rings. Thus, side products were formed. In the reactions with but-3-ene-2-one and acrylonitrile, the amount of alkene also had to be decreased. The more reactive alkene can cause the formation of unwanted double-MBH adducts [22], and alkene polymerization can also occur. The reactions of bromo-aldehyde **6** did not yield the corresponding MBH adducts in THF. Therefore, triethanolamine was added as an auxiliary base, and the reactions were performed under an argon atmosphere. Using this method, we obtained the bromo-containing adducts **9** and **14** in low yields. The reaction of aldehyde **4** and ethyl acrylate showed the most stable condition without forming any side products. Therefore, we increased the reaction time; in this way, we obtained the adduct **7** with 82% yield and an almost complete conversion after 60 days. The yields show the amount of isolated racemic mixture. From our view, enantioselective synthesis was not crucial.

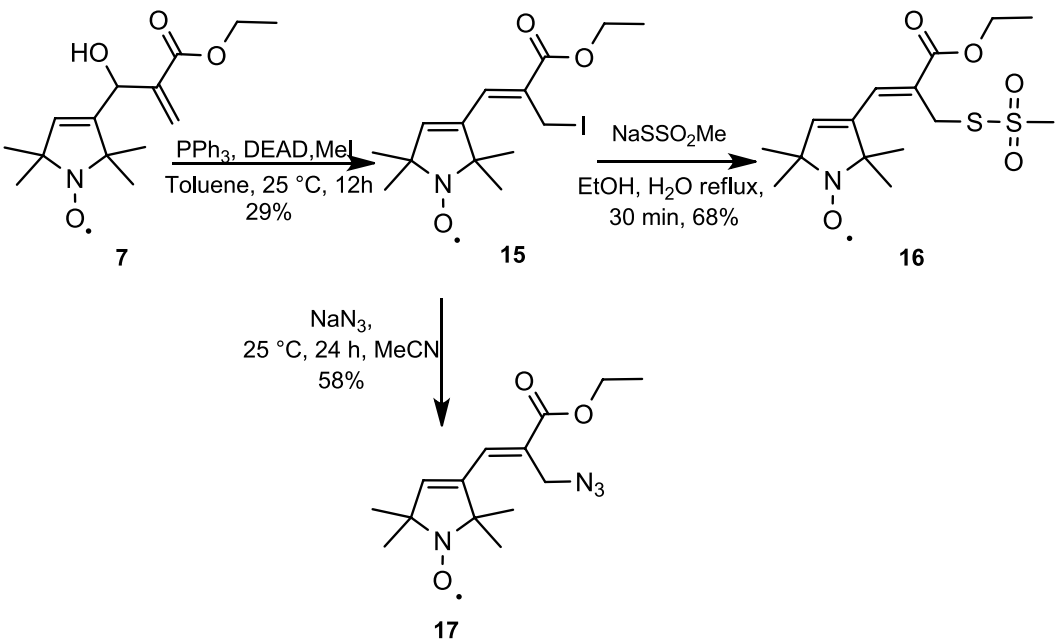
Since the MBH adducts are highly functionalized compounds, we also aimed to convert them into different spin labels. To achieve this, the first step was to convert adduct **7** into a compound prone to nucleophilic substitution.

The conversion of the hydroxyl group into an acetate leaving group is a standard procedure in the nucleophilic substitution of MBH adducts [23, 24]. However, our adducts either did not react with acetic anhydride, or the forming acetate was not reactive in further transformation, so we decided to use the Mitsunobu reaction. Compound **7** was treated with diethyl azodicarboxylate (DEAD), and iodomethane yielding the corresponding iodine compound **15**, which underwent an allylic rearrangement proved by the NMR shifts. The nucleophilic substitution of compound **15** with sodium methanethiosulfonate and sodium azide produced the paramagnetic thiosulfonate **16** and azide **17**, respectively, affording cysteine and alkyne labels with an ethyl ester group in β-position (Scheme 4).

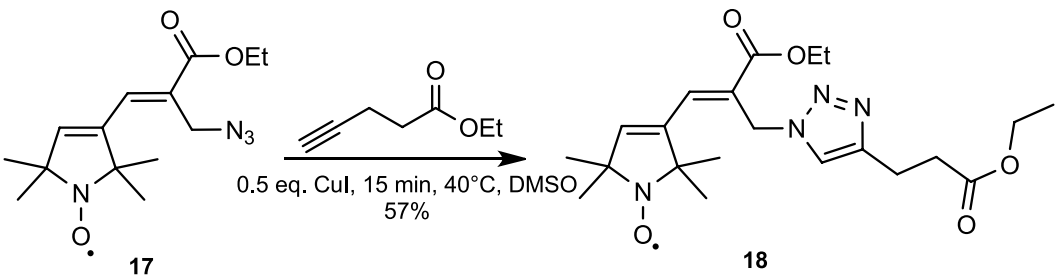
Ethyl pent-4-ynoate was used to test the reactivity of azide **17** in a CuI-catalyzed azide-alkyne cycloaddition reaction. After 15 min at 40 °C, the reaction was complete, and the corresponding paramagnetic 1,2,3-triazole **18** was obtained with 57% yield (Scheme 5).

The 1,3-dicarbonyl compounds are essential building blocks in heterocyclic chemistry. Therefore, several conditions have been tested to access a *β*-ketoester by oxidizing the secondary alcohol of the MBH adduct. Treatment with activated MnO_2 or Dess-Martin periodinane resulted in a mixture of inseparable products. To avoid the more reactive conjugated system, we first reduced the double bond between the alcohol and ester functions using an H-Cube mini flow reactor with a 10% Pd/C catalyst under mild conditions (**19**). The reduction afforded diastereomers in a 1:0.4 ratio in excess with the less polar diastereomer, shown by the quintet of the proton of the methyl propanoate on the ^{1}H NMR spectrum (Fig. 1). To record a clear ^{1}H NMR and ^{13}C NMR spectrum, a small amount of the major diastereomer

Scheme 4



Scheme 5



was isolated by flash column chromatography. For further synthesis, we used the diastereomeric mixture because, in the following oxidation, the compounds lose the stereogenic center on the β-carbon of the ester.

Additionally, we sought a more selective oxidative transformation. In the past decade, 2-iodoxybenzoic acid (IBX) has been used to oxidize MBH adducts [25, 26]. Due to its potentially explosive nature, IBX was prepared 'in situ' to oxidize the selectively reduced paramagnetic MBH alcohol **19** under mild conditions [27]. To prepare IBX, we used 2.0 equiv. of 2-iodosobenzoic acid (IBA) and 1.1 equiv. of oxone in acetonitrile, in the presence of compound **19** under reflux condition for 2 h. After completion of the reaction, we isolated the *β*-ketoester **20** with good yield (87%). Since the presence of the unpaired electron makes it impossible to characterize the stable free radicals with NMR spectroscopy directly, the compounds were recorded in the presence of 1,2-diphenylhydrazine, a method developed for nitroxides by Keana et al. [28]. The *β*-ketoester **20** showed high reactivity with the binucleophile, resulting in byproducts during the 'in situ' reduction with hydrazobenzene. To obtain a clear NMR recording of the ketoester, we synthesized the *O*-acetyl derivative of compound **20** via the reduction with ascorbic acid followed by the acylation with acetyl chloride [29]. Using this method, compound **21** was collected with a 62% yield. Treatment of compound **20** with acetamidine hydrochloride in the presence of DBU yielded the paramagnetic pyrimidine derivative **22** (Scheme 6) [30].

Conclusion

In summary, we presented a novel group of paramagnetic Morita–Baylis–Hillman adducts synthesized from tetrahydropyridine and pyrroline nitroxide aldehydes (**4**–**6**) and various activated alkenes in the presence of DABCO. Yields ranged from low to moderate across the reactions. The most stable reaction condition was observed in the reaction of

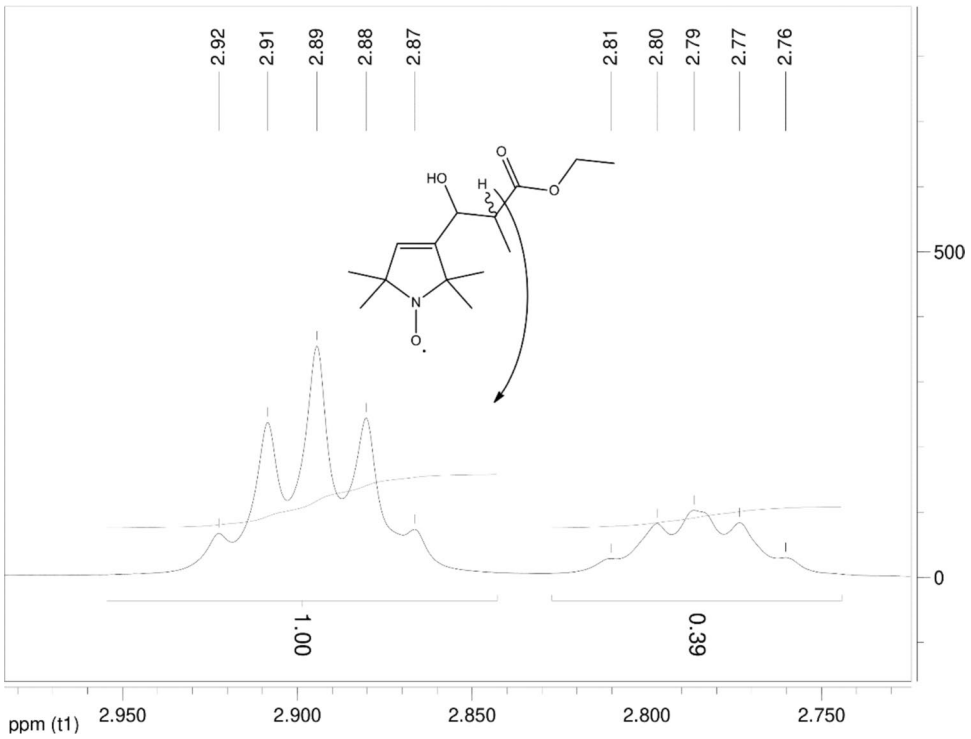
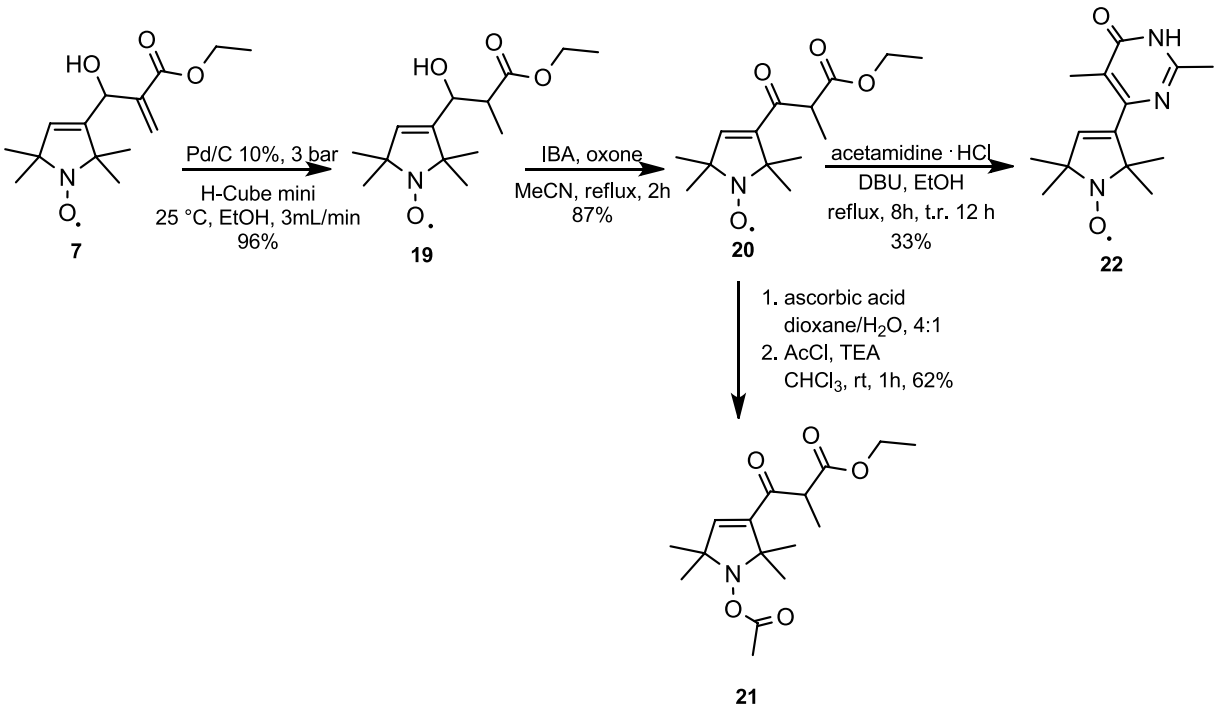


Fig. 1 Diastereomer ratio after the reduction of compound **7** presented by the integral of the quintet peak on ^{1}H NMR spectrum

Scheme 6



aldehyde **7** and ethyl acrylate, yielding high yield and nearly complete conversion over two months. Functionalization of MBH adduct **7** resulted in the cysteine label thiosulfonate **16** and the azide **17**, which can serve as a spin label for biomolecules tagged with an acetylene function. Compound **7** was also converted to the β-ketoester **20**, a potential building block for synthesizing heterocyclic compounds bearing a nitroxide moiety. To demonstrate this, we converted this compound to the pyrimidone derivative **22** in the presence of DBU and acetamidine hydrochloride.

Experimental

The mass spectra were recorded on a Shimadzu GCMS-2020 spectrometer in electron ionization (EI) mode (70 eV). Elemental analyses were carried out with a Fisons EA 1110 CHNS elemental analyzer. The melting points were determined using a Boetius micro-melting point apparatus. The NMR spectra were recorded on a Bruker Avance III Ascend 500 system operated at 500 MHz for ^{1}H and 125 MHz for ^{13}C at 298 K. The in-situ reduction of the nitroxides was achieved by adding five equivalents of hydrazobenzene (DPPH/radical). The infrared (IR) spectra were obtained using a Bruker Alpha FT-IR instrument with an attenuated total reflectance support on a diamond plate. Flash column chromatography was performed on the Merck Kieselgel 60 (0.040–0.063 mm) column. Qualitative thin layer chromatography (TLC) was carried out on commercially available plates (20.0 cm × 20.0 cm × 0.02 cm) coated with Merck Kieselgel. Compounds **1** [26], **4** [26], **5** [27], and **6** [28] were synthesized as described previously. All the other reagents were purchased from Sigma Aldrich, Molar Chemicals, or TCI.

(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-methyl acrylate (2, $C_{12}H_{18}NO_3$) A solution of alcohol **1** (1.7 g, 10.0 mmol), acryloyl chloride (996 mg, 10.8 mmol), triethylamine (3.0 g, 30.0 mmol) in benzene (30 cm^3) was stirred at room temperature for 1 h. The precipitated salts were filtered off. The solvent was evaporated. 5% aq. H_2SO_4 (15 cm^3) was added and extracted with EtOAc (3 × 20 cm^3). The organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography on silica (hexane/Et_2O, 2:1). Yellow oil; yield 1.47 g (66%); TLC: R_f = 0.37 (hexane/EtOAc, 2:1); IR: $\overline{\nu}$ = 2976, 1726, 1635, 1620 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 6.53 (d, 1H, J = 17 Hz), 6.25 (dd, 1H, J_1 = 10 Hz, J_2 = 7 Hz), 5.92 (d, 1H, J = 11 Hz), 5.67 (s, 1H), 4.78 (s, 2H), 1.37 (s, 6H), 1.34 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 165.9, 139.2, 132.5, 131.2, 128.4, 70.0, 67.9, 60.8, 25.8 (2C), 24.8 (2C) ppm; MS (EI): *m/z* (%) = 224 (M^+, 7), 209 (3), 138 (5), 122 (29), 107 (100), 55 (29), 44 (11).

(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)-methyl 2-[hydroxy(phenyl)methyl]acrylate (3, $C_{19}H_{24}NO_4$) A mixture of benzaldehyde (3.120 g, 29.4 mmol), compound **2** (1.12 g, 5.0 mmol), and DABCO (280 mg, 2.5 mmol) was stirred at room temperature for 3 days. The crude product was purified by flash chromatography on silica (hexane/Et_2O, 2:1 and hexane/EtOAc, 2:1). Yellow crystals; yield 1.18 g (72%); m.p.: 78–81 °C; TLC: R_f = 0.24 (hexane/EtOAc, 2:1); IR: $\overline{\nu}$ = 3361, 2984, 1721, 1636, 1626, 1436 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.47 (d, 2H, J = 6.9 Hz); 7.43 (t, 1H, J = 7), 7.37 (d, 2H, J = 7 Hz), 6.47 (s, 1H), 5.99 (s, 1H), 5.69 (s, 1H), 5.45 (s, 1H), 4.71 (dd, 2H, J_1 = 14 Hz, J_2 = 7 Hz), 1.30 (s, 6H), 1.29 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 165.9, 142.1, 141.4, 138.9, 132.5, 128.6 (2C), 128.0, 126.8 (2C), 126.3, 73.2, 69.9, 67.9, 61.0, 25.7, 25.6, 24.7, 24.7 ppm; MS (EI): *m/z* (%) = 330 (M^+, 8), 316 (9), 281 (17), 253 (10), 207 (44), 138 (24), 107 (100), 44 (95).

Ethyl 2-[hydroxy(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl]acrylate (7, $C_{14}H_{22}NO_4$) A solution of aldehyde **4** (840 mg, 5.0 mmol), ethyl acrylate (1.50 g, 15.0 mmol), and DABCO (280 mg, 2.5 mmol) in THF (2 cm^3) was stirred at room temperature for 7 days. The solvent was evaporated from the resulting mixture, and the crude product was purified by flash chromatography on silica (hexane/Et_2O, 4:1 and hexane/EtOAc, 4:1). Yellow crystals; yield 568 mg (42%) [under the same reaction conditions, with an extended reaction time of 2 months, the isolated yield is 1.1 g (82%)]; TLC: R_f = 0.35 (hexane/EtOAc, 2:1); IR: $\overline{\nu}$ = 3401, 2977, 1715, 1632 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 6.42 (s, 1H), 5.99 (s, 1H), 5.58 (s, 1H), 5.08 (s, 1H), 4.31 (q, 2H, J = 7 Hz), 1.46 (s, 3H), 1.37 (t, 3H, J = 7 Hz), 1.36 (s, 3H), 1.32 (s, 3H), 1.3 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 166.4, 145.0, 141.4, 131.8, 125.8, 70.6, 68.0, 67.4, 61.0, 25.8, 25.6, 25.4, 24.9, 14.3 ppm; MS (EI): *m/z* (%) = 268 (M^+, 38), 238 (8), 223 (42), 205 (22), 192 (38), 177 (34), 149 (41), 126 (58), 109 (81), 83 (53), 67 (100), 55 (68), 43 (48), 41 (50).

Ethyl 2-[hydroxy(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]acrylate (8, $C_{15}H_{24}NO_4$) A solution of aldehyde **5** (910 mg, 5.0 mmol), ethyl acrylate (750 mg, 7.5 mmol), and DABCO (140 mg, 1.25 mmol) in THF (2 cm^3) was stirred at room temperature for 7 days. The solvent was evaporated from the resulting mixture, and the crude product was purified by flash chromatography on silica (hexane/Et_2O, 4:1 and hexane/EtOAc, 4:1). Orange oil; yield 37 mg (15%); TLC: R_f = 0.30 (hexane/EtOAc, 2:1); IR: $\overline{\nu}$ = 3415, 2977, 1716, 1629 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 6.38 (s, 1H), 5.93 (s, 1H), 5.64 (s, 1H), 4.97 (s, 1H), 4.28 (q, 2H, J = 7 Hz), 2.10 (dd, 2H, J_1 = 18 Hz, J_2 = 21 Hz), 1.36 (t, 3H, J = 7 Hz), 1.34 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 166.5, 140.8, 131.9, 130.9, 125.6, 73.7, 61.0, 59.6, 57.5, 39.2, 26.0 (2C), 24.8 (2C), 14.3 ppm; MS (EI): *m/z* (%) = 282 (M^+, 20), 268 (14), 252 (11), 219 (16), 179 (21), 154 (100), 107 (78), 81 (77), 55 (64), 41 (70).

Methyl 2-[(4-bromo-1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)(hydroxy)methyl]acrylate (9,

$C_{13}H_{19}BrNO_4$) A solution of bromo aldehyde **6** (1.000 g 4.0 mmol), methyl acrylate (517 mg, 6.0 mmol), DABCO (448 mg, 4.0 mmol) in triethanolamine (2 cm^3) was stirred under Ar atmosphere for 7 days. 2% aq. HCl solution (10 cm^3) was added to the mixture and extracted with Et_2O (3×20 cm^3). The Et_2O was evaporated, and the crude product was purified by flash chromatography on silica (hexane/Et_2O, 4:1 and hexane/EtOAc, 4:1). Yellow crystals; yield 305 mg (23%); m.p.: 87–89 °C; TLC: $R_f = 0.47$ (hexane/EtOAc, 2:1); IR: $\overline{\nu}$ = 3359, 2975, 1731, 1636 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 6.42$ (s, 1H), 5.96 (s, 1H), 5.48 (s, 1H), 3.84 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 167.0$, 139.8, 139.0, 127.0, 126.5, 71.3, 70.7, 68.5, 52.2, 25.1, 25.0, 24.7, 24.4 ppm; MS (EI): *m/z* (%) = 332 (M^+, 75), 334 (73), 319 (20), 317 (20), 286 (15), 284 (15), 286 (15), 284 (15), 238 (18), 220 (53), 205 (69), 191 (27), 145 (74), 108 (100), 55 (37), 43 (47), 41 (48).

General procedure for Baylis–Hillman reaction of aldehydes 4 and 5 with methyl vinyl ketone

A solution of aldehyde **4** or **5** (5.0 mmol), methyl vinyl ketone (525 mg, 7.5 mmol), DABCO (280 mg, 2.5 mmol) in THF (2 cm^3) was stirred at room temperature for 7 days. The solvent was evaporated from the resulting mixture, and the crude product was purified by flash chromatography on silica (hexane/Et_2O, 4:1 and hexane/EtOAc, 4:1).

3-[Hydroxy(1-oxyl-2,2,5,5,-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl]but-3-ene-2-one (10, $C_{13}H_{20}NO_3$) Yellow crystals; yield 176 mg (15%); m.p.: 112–115 °C; TLC: $R_f = 0.24$ (chloroform/Et_2O, 2:1); IR: $\overline{\nu}$ = 3319, 2978, 1711, 1671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 6.23$ (s, 1H), 6.14 (s, 1H), 5.54 (s, 1H), 5.12 (s, 1H), 2.42 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 200.0$, 145.2, 131.5, 126.8, 126.7, 70.7, 67.6, 67.5, 26.6, 26.0, 25.5, 25.2, 25.0 ppm; MS (EI): *m/z* (%) = 238 (M^+, 18), 224 (7), 193 (35), 165 (42), 67 (48), 43 (100).

3-[Hydroxy(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)methyl]but-3-ene-2-one (11, $C_{14}H_{22}NO_3$) Brown oil; yield 278 mg (21%); TLC: $R_f = 0.18$ (hexane/EtOAc, 2:1); IR: $\overline{\nu}$ = 3423, 2975, 1711, 1676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 6.41$ (s, 1H), 5.97 (s, 1H), 5.56 (s, 1H), 5.05 (s, 1H), 4.28 (q, 2H, $J = 7$ Hz), 1.44 (s, 3H), 1.34–1.37 (m, 6H), 1.31 (s, 3H), 1.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 166.4$, 145.0, 141.4, 131.8, 125.8, 70.6, 68.0, 67.4, 61.0, 25.8, 25.5, 25.4, 24.8, 14.3 ppm; MS (EI): *m/z* (%) = 252 (M^+, 11), 238 (4), 222 (11), 154 (52), 123 (21), 81 (39), 55 (25), 43 (100).

2-[Hydroxy(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)methyl]acrylonitrile (12, $C_{12}H_{17}N_2O_2$) A solution of aldehyde **4** (840 mg, 5.0 mmol), acrylonitrile (795 mg, 15.0 mmol), and DABCO (280 mg, 2.5 mmol) in THF (2 cm^3) was stirred at room temperature for 7 days. The solvent was evaporated from the resulting mixture, and the crude product was purified by flash chromatography on silica (hexane/Et_2O, 4:1 and hexane/EtOAc, 4:1). Yellow crystals; yield 215 mg (20%); m.p.: 80–82 °C; TLC: $R_f = 0.21$ (hexane/EtOAc, 2:1); IR: $\overline{\nu}$ = 3370, 2977, 2227, 1734, 1648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 6.09$ (s, 1H), 6.07 (s, 1H), 5.80 (s, 1H), 4.74 (s, 1H), 1.40–1.34 (m, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 142.9$, 133.9, 130.4, 125.8, 116.8, 70.2, 68.9, 67.7, 25.7, 25.4, 25.4, 24.7 ppm; MS (EI): *m/z* (%) = 221 (M^+, 23), 206 (7), 191 (10), 176 (21), 148 (27), 109 (61), 91 (25), 81 (29), 67 (100), 55 (34), 43 (50), 41 (47).

2-[Hydroxy(1-oxyl-2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridine-4-yl)methyl]acrylonitrile (13, $C_{13}H_{19}N_2O_2$) A solution of aldehyde **5** (910 mg, 5.0 mmol), acrylonitrile (398 mg, 7.5 mmol), and DABCO (140 mg, 1.25 mmol) in THF (2 cm^3) was stirred at room temperature for 7 days. The solvent was evaporated from the resulting mixture, and the crude product was purified by flash chromatography on silica (hexane/Et_2O, 4:1 and hexane/EtOAc, 4:1). Yellow crystals; yield 90 mg (8%); m.p.: 123–125 °C; TLC: $R_f = 0.32$ ($CHCl_3$/Et_2O, 2:1); IR: $\overline{\nu}$ = 3352, 2991, 2227, 1684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 6.11$ (s, 1H), 6.07 (s, 1H), 5.70 (s, 1H), 4.64 (s, 1H), 2.04 (dd, 2H, $J_1 = 17$ Hz, $J_2 = 47$ Hz), 1.35 (s, 6H, CH_3), 1.25 (s, 3H), 1.24 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 134.2$, 130.1, 129.4, 124,8, 116.9, 74.8, 59.8, 57.5, 37.9, 26.4 (2C), 25.5 (2C) ppm; MS (EI): *m/z* (%) = 235 (M^+, 5), 221 (100), 189 (39), 154 (8), 107 (24), 81 (50), 59 (42).

2-[(4-Bromo-1-hydroxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)(hydroxy)methyl]acrylonitrile (14, $C_{12}H_{16}BrN_2O_2$) A mixture of bromo aldehyde **6** (1.000 g, 4.0 mmol), acrylonitrile (318 mg, 6.0 mmol), DABCO (448 mg, 4.0 mmol), and triethanolamine (2 cm^3) was stirred at room temperature under Ar atm. for 7 days. 2%, aq. HCl solution (10 cm^3) was added to the mixture and extracted with Et_2O (3×20 cm^3). The Et_2O was evaporated, and the crude product was purified by flash chromatography on silica (hexane/Et_2O, 4:1, and hexane/EtOAc, 4:1). Yellow crystals; yield 205 mg (17%); m.p.: 94–96 °C; TLC: $R_f = 0.44$ (hexane/EtOAc, 2:1); IR: $\overline{\nu}$ = 3303, 2981, 2231, 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 6.21$ (s, 1H), 6.13 (s, 1H), 5.17 (s, 1H) 1.40 (s, 6H), 1.35 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 138.7$, 130.7, 128.5, 123.9, 116.9, 71.0, 70.8, 68.8, 25.2, 25.1, 24.9, 23.7 ppm; MS (EI): *m/z* (%) = 299 (M^+, 63), 301 (64), 286

(54), 284 (51), 271 (13), 220 (2), 205 (54), 203 (54), 190 (53), 148 (54), 108 (100), 93 (90), 65 (55), 41 (88).

Ethyl 3-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)−2-(iodomethyl)acrylate (15, $C_{14}H_{21}INO_3$) To a stirred solution of compound **4** (300 mg, 1.1 mmol) and PPh_3 (314 mg, 1.2 mmol) in benzene (10 cm^3), a solution of DEAD (620 mg, 1.4 mmol, in 40% toluene) in benzene (5 cm^3) was added dropwise at 0 °C under N_2. After 10 min of the complete addition, a solution of CH_3I (170 mg, 1.2 mmol) in benzene (5 cm^3) was added dropwise. After the addition was completed, the mixture was held for 30 min at 0 °C, and stirring was continued for 24 h at r.t.. The solvent was evaporated, and the residue was partitioned between H_2O (20 cm^3) and EtOAc (3 × 20 cm^3). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated, and the crude was purified by flash column chromatography (hexane/Et_2O, 4:1). Yellow crystals; yield 108 mg (29%); m.p.: 53–55 °C; TLC: R_f = 0.33 (hexane/Et_2O, 2:1); IR: $\overline{\nu}$ = 2976, 1708, 1632 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.09 (s, 1H), 6.23 (s, 1H), 4.37 (q, 2H, J = 6.8 Hz), 4.36 (s, 2H), 1.41 (t, 3H, J = 7 Hz), 1,40 (s, 6H), 1,33 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 165.6, 140.0, 137.6, 133.0, 132.8, 71.5, 68.9, 61.5, 25.7 (2C), 25.2 (2C), 14.3, −0.9 ppm; MS (EI): *m/z* (%) = 378 (M^+, 10.8), 364 (3.6), 251 (6.3), 237 (6.6), 221 (47.7), 138 (43.8), 105 (40.7), 57 (100).

Ethyl 3-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)−2-[[(methylsulfonyl)thio]methyl]acrylate (16, $C_{15}H_{24}NO_5S_2$) A solution of compound **15** (378 mg, 1.0 mmol), sodium methanethiosulfonate (150 mg, 1.2 mmol), and water (2 cm^3) in ethanol (20 cm^3) was refluxed for 30 min, then diluted with brine (10 cm^3) and extracted with ether (3 × 10 cm^3). The organic phase was dried and evaporated and the crude product was purified by flash column chromatography (hexane/EtOAc, 2:1). Yellow crystals; yield 245 mg (68%); m.p.: 58–60 °C; TLC: R_f = 0.67 ($CHCl_3$/Et_2O, 4:1); IR: $\overline{\nu}$ = 2976, 1707, 1625 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.29 (s, 1H), 6.06 (s, 1H), 4.37 (s, 4H), 3.46 (s, 3H), 1.41 (s, 9H), 1.35 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 165.9, 139.2, 138.1, 136.2, 128.0, 71.2, 68.9, 61.8, 50.5, 33.8, 25.7 (2C), 25.2 (2C), 14.3 ppm; MS (EI): *m/z* (%) = 362 (M^+, 12.6), 348 (10.3), 316 (11.5), 253 (33.6), 97 (52.4), 57 (100).

Ethyl (*E*)−2-(azidomethyl)−3-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)acrylate (17, $C_{14}H_{21}N_4O_3$) A mixture of compound **15** (150 mg, 0.4 mmol) and NaN_3 (40 mg, 0.6 mmol) in acetonitrile (10 cm^3) was stirred at r.t. for 24 h. The solvent was evaporated, water was added (15 cm^3) and extracted with Et_2O (3 × 10 cm^3). The organic phase was dried ($MgSO_4$) and the solvent was evaporated; the crude product was purified by flash chromatography (hexane/Et_2O, 4:1). Yellow oil; yield 68 mg (58%); TLC: R_f = 0.38 (hexane/Et_2O, 1:1); IR: $\overline{\nu}$ = 2975, 2094, 1709, 1630 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.33 (s, 1H), 5.97 (s, 1H), 4.38 (q, 2H, J = 7 Hz), 4.18 (s, 2H), 1.42 (t, 3H, J = 7 Hz), 1.37 (s, 6H), 1.33 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 166.5, 139.4, 137.9, 137.0, 129.6, 71.1, 68.8, 61.6, 47.1, 25.7 (2C), 25.0 (2C), 14.3 ppm; MS (EI): *m/z* (%) = 293 (M^+, 26.6), 279 (2.8), 235 (18.3), 220 (27.4), 162 (66.0), 120 (80.2), 57 (100).

Ethyl (*E*)−2-[(4-(3-ethoxy-3-oxopropyl)−1*H*−1,2,3-triazol-1-yl)methyl]−3-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)acrylate (18, $C_{21}H_{31}N_4O_5$) A solution of azide **16** (150 mg, 0.5 mmol), ethyl 4-pentynoate (126 mg, 1.0 mmol), and CuI (48 mg, 0.25 mmol) were stirred in DMSO (15 cm^3) at 40 °C for 15 min. The solution was diluted with water (15 cm^3) and extracted with EtOAc (3 × 15 cm^3). The organic phase was dried ($MgSO_4$), evaporated and the crude product was purified by flash chromatography (hexane/EtOAc, 2:1). Yellow crystals; yield 120 mg (57%); m.p.: 48–50 °C; TLC: R_f = 0.52 ($CHCl_3$:Et_2O, 2:1); IR: $\overline{\nu}$ = 2922, 1710, 1638, 1553 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 7.43 (s, 1H), 7.12 (t, 1H, J = 7 Hz), 6.15 (s, 1H), 5.25 (s, 2H), 4.16 (q, 2H, J = 6 Hz), 4.05 (q, 2H, J = 7 Hz), 2.89 (t, 2H, J = 6 Hz), 2.65 (t, 2H, J = 6 Hz), 1.20–1.15 (m, 18H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 172.5, 165.9, 148.0, 145.7, 139.4, 138.5, 137.4, 128.6, 70.3, 67.9, 61.5, 60.4, 46.8, 33.6, 26.0 (2C), 25.3 (2C), 21.1, 14.6, 14.4 ppm; MS (EI): *m/z* (%) = 419 (M^+, 16.5), 389 (20.0), 374 (17.2), 318 (1.6), 220 (96.6), 205 (90.6), 174 (44.6), 147 (100), 107 (76.1).

Ethyl 3-hydroxy-3-(1-oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)−2-methylpropanoate (19, $C_{14}H_{24}NO_4$) Compound **4** (450 mg, 1.7 mmol) was dissolved in dry ethanol (30 cm^3) and reduced in catalytic flow reaction (H-Cube Mini, Pd/C 10%, 3 bar, 3 cm^3/min, 25 °C). The solvent was evaporated, the residual material was dissolved in $CHCl_3$ (15 cm^3), PbO_2 (813 mg, 3.4 mmol) was added, and stirred on r.t. for 1 h. The mixture was filtered on celite and evaporated. The reaction formed diastereomers, which were not separated; the racemic mixture was used for further synthesis. To give a clear NMR spectrum, a small amount of the less polar diastereomer was isolated by flash chromatography. Yellow oil; yield 400 mg (88%); TLC: R_f = 0.46 ($CHCl_3$/Et_2O, 2:1); IR: $\overline{\nu}$ = 3415, 2976, 1728, 1639 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 5.67 (s, 1H), 4.33 (m, 3H), 2.97 (quin, 1H, J = 7 Hz), 1.56–1.39 (m, 18H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + $(PhNH)_2$): δ = 176.2, 145.0, 130.9, 71.8, 70.3, 68.5, 60.9, 44.2, 25.8, 25.4, 25.0, 24.9,

15.4, 14.4 ppm; MS (EI): *m/z* (%) = 270 (M^+, 17.7), 256 (15.2), 240 (8.4), 225 (7.0), 139 (100), 126 (65.2).

Ethyl 3-(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)−2-methyl-3-oxopropanoate (20, $C_{14}H_{22}NO_4$) A solution of diastereomeric mixture **19** (150 mg, 0.6 mmol), 2-iodosylbenzoic acid (IBA, 290 mg, 1.1 mmol), and oxone (405 mg, 0.7 mmol) in acetonitrile (10 cm^3) was stirred under reflux conditions for 2 h. After the reaction completion, the mixture was allowed to cool down to room temperature, the IBA was filtered off, washed with acetonitrile, and the solvent was evaporated. The residual material was solved in EtOAc (15cm^3) and washed with 10% aq. Na_2CO_3 solution (20 cm^3). The organic phase was dried ($MgSO_4$), filtered, and evaporated, the crude product was purified by flash chromatography (hexane/EtOAc, 2:1). Yellow crystals; yield 130 mg (87%); m.p.: 39–41 °C; TLC: $R_f = 0.44$ (hexane/EtOAc, 2:1); IR: $\overline{\nu}$ = 2922, 1734, 1677, 1618, 1458 cm^{-1}; MS (EI): *m/z* (%) = 268 (M^+, 8.5), 238 (2.1), 220 (22.0), 137 (54.4), 109 (100), 67 (54.6). NMR spectra were not recorded because compound **20** gave in situ byproduct with hydrazobenzene.

Ethyl 3-(1-acetoxy-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)−2-methyl-3-oxopropanoate (21, $C_{16}H_{25}NO_5$) To a solution of compound **20** (161 mg, 0.6 mmol) in 1,4-dioxane (20 cm^3), water (5 cm^3) and ascorbic acid (528 mg, 3.0 mmol) was added and stirred for five min at 40 °C. The solution was extracted with $CHCl_3$, and the organic phase was directly added to the mixture of $MgSO_4$ (1.000 g, 8.3 mmol) and triethylamine (121 mg, 1.2 mmol) under N_2 atmosphere. Acetyl chloride (94 mg, 1.2 mmol) was added to the solution at 0 °C and continuously stirred on r.t. under N_2 atmosphere for 1 h. The $MgSO_4$ was filtered off, the solvent was evaporated, and the residue material was washed with brine and extracted with EtOAc (3 × 20 cm^3). The organic phase was dried on $MgSO_4$, filtered, and the crude product was purified by flash column chromatography (hexane/Et_2O, 2:1). Colorless oil; yield 116 mg (62%); TLC: $R_f = 0.37$ (hexane/Et_2O, 1:1); IR: $\overline{\nu}$ = 3458, 2977, 1773, 1753, 1717, 1632 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 6.56$ (s, 1H), 4.19–4.14 (m, 2H), 3.98–3.95 (m, 1H), 2.15 (s, 3H), 1.41–1.36 (m, 12H), 1.30 (s, 3H), 1.24 (t, 3H, $J = 8$ Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 192.7$, 171.0, 170.6, 145.5, 142.6, 71.5, 68.8, 61.4, 49.3, 28.2, 22.5, 19.1 (2C), 14.1 (2C), 13.1 ppm; MS (EI): *m/z* (%) = 296 (M^+−15, 10.8), 269 (19.9), 254 (100), 168 (12.2), 152 (65.3), 126 (58.6).

6-(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-3-yl)−2,5-dimethylpyrimidin-4(3*H*)-one (22, $C_{14}H20N3O2$) A solution of β-ketoester **20** (213 mg, 0.8 mmol), acetamidine hydrochloride (85 mg, 0.9 mmol), and DBU (228 mg, 1.5 mmol) in EtOH (10 cm^3) was refluxed for 8 h and continuously stirred on room temperature overnight under N_2 atmosphere. The solvent was evaporated, and the crude material was purified by flash column chromatography (hexane:EtOAc, 2:1 and $CHCl_3$:Et_2O, 10:1). Pale yellow crystals; yield 65 mg (31%); m.p.: 187–189 °C; TLC: $R_f = 0.55$ ($CHCl_3$:Et_2O:MeOH, 4:1.5:0.5); IR: $\overline{\nu}$ = 2922, 1734, 1677, 1618, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3 + (PhNH)_2$): $\delta = 5.67$ (s, 1H), 2.24 (s, 3H), 1.96 (s, 3H), 1.26 (s, 6H), 1.21 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3 + (PhNH)_2$): 163.6, 156.7, 154.7, 141.8, 136.4, 119.4, 71.4, 67.4, 26.1 (2C), 25.6 (2C), 21.5, 12.9 ppm; MS (EI): *m/z* (%) = 262 (M^+, 13.0), 232 (67.9), 217 (100), 189 (37.8), 149 (49.2), 57 (81.8).

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