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# A novel and green protocol for two-carbon homologation: a direct amino acid/$K_2CO_3$-catalyzed four-component reaction of aldehydes, active methylenes, Hantzsch esters and alkyl halides

Dhevalapally B. Ramachary,* M. Kishor and K. Ramakumar

*School of Chemistry, University of Hyderabad, Central University (P.O.), Hyderabad 500 046, India*

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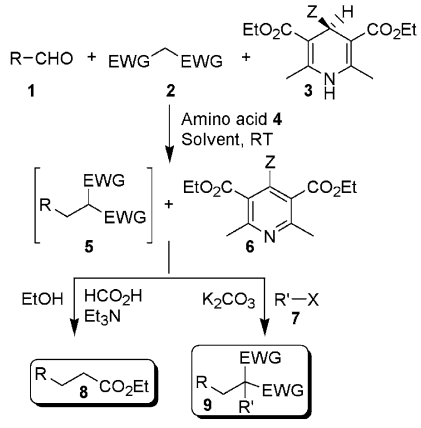
**Abstract**—A novel and green approach for the two-carbon homologation of aldehydes using amino acid catalysis has been developed and further extended to the generation of pharmaceutically active cyano-esters via four-component reactions in one-pot.


Two-carbon homologation is a very important transformation in synthetic organic chemistry and numerous methods[1] are available although most involve redox functional group transformations rather than carbon–carbon bond formation. In this regard, the development of two-carbon homologation through carbon–carbon bond formation using organocatalytic tandem methodology[2] can provide an expedient access to homologated products from simple starting materials.

As part of our program to engineer direct organocatalytic tandem or multi-component reactions,[2a–e] we report the first organocatalytic, regioselective, tandem Knoevenagel and hydrogenation (K/H), Knoevenagel/hydrogenation/hydrolysis (K/H/H) and Knoevenagel/hydrogenation/alkylation (K/H/A) reactions that produce highly substituted two-carbon homologated esters **5**, **8** and **9**, respectively, from commercially available aldehydes **1a**–**t**, active methylenes **2a**–**h**, Hantzsch 1,4-dihydropyridine esters **3a**–**b**, alkyl halides **7a**–**d** and amino acids **4a**–**b** as shown in Scheme 1. Homologated esters **5** and **9** are attractive intermediates in medicinal chemistry, and analogues thereof have broad utility in pharmaceutical chemistry[3] (herbicidal, anti-diabetic, analgesic, anti-inflammatory and anti-thrombotics) and in organic synthesis. Hence, new methods for their syntheses have continued to attract considerable interest.




***Substrates and Catalysts Screened:***

| | |
|---|---|
| **1a** R = $C_6H_5$ | **1s** R = $(CH_3)_2CH$ |
| **1b** R = 2-$ClC_6H_4$ | **1t** R = $(CH_3)_2CHCH_2$ |
| **1c** R = 4-$ClC_6H_4$ | **2a** *N,N*-Dimethylbarbituric acid |
| **1d** R = 4-$FC_6H_4$ | **2b** Meldrum's acid |
| **1e** R = 2-$NO_2C_6H_4$ | **2c** Indandione |
| **1f** R = 3-$NO_2C_6H_4$ | **2d** Diethyl malonate |
| **1g** R = 4-$NO_2C_6H_4$ | **2e** Ethyl cyanoacetate |
| **1h** R = 4-$MeC_6H_4$ | **2f** Malononitrile |
| **1i** R = 4-$BrC_6H_4$ | **2g** Ethyl nitroacetate |
| **1j** R = 2,4,6-$(CH_3)_3C_6H_2$ | **2h** Barbituric acid |
| **1k** R = 1-Naphthalenyl | **3a** Z = H |
| **1l** R = 9-Anthracenyl | **3b** Z = Ph |
| **1m** R = *trans*-$C_6H_5CH$=CH | **4a** L-Proline |
| **1n** R = $C_6H_5CH_2CH_2$ | **4b** Glycine |
| **1o** R = 2-Furanyl | **7a** MeI |
| **1p** R = 2-Thiophenyl | **7b** EtBr |
| **1q** R = 4-$MeOC_6H_4$ | **7c** $H_2C$=$CHCH_2Br$ |
| **1r** R = 4-$NCC_6H_4$ | **7d** HCCCH$_2$Br |

**Scheme 1.** Direct organocatalytic K/H, K/H/H and K/H/A reactions in one-pot.

*Keywords*: Amino acids; Hantzsch ester; Multi-component reactions; Organocatalysis; Two-carbon homologation.

* Corresponding author. Tel.: +91 40 23134816; fax: +91 40 23012460; e-mail: ramsc@uohyd.ernet.in

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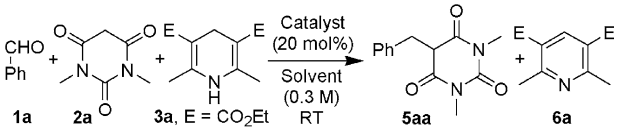
This letter outlines that amino acid **4** or Hantzsch ester **3** catalyzes the tandem Knoevenagel condensation[2c] of aldehydes **1** with the active methylenes **2** to form Knoevenagel products **10**,[4] which then undergo regioselective hydrogenation with the NADH mimic[5] organic hydride Hantzsch esters **3** to produce homologated esters **5** in good to excellent yields. Esters **5** could be converted into compounds **8** and **9** via hydrolysis and alkylation reactions catalyzed by acid and base, respectively, in good to excellent yields over the three-step sequence (Scheme 1).

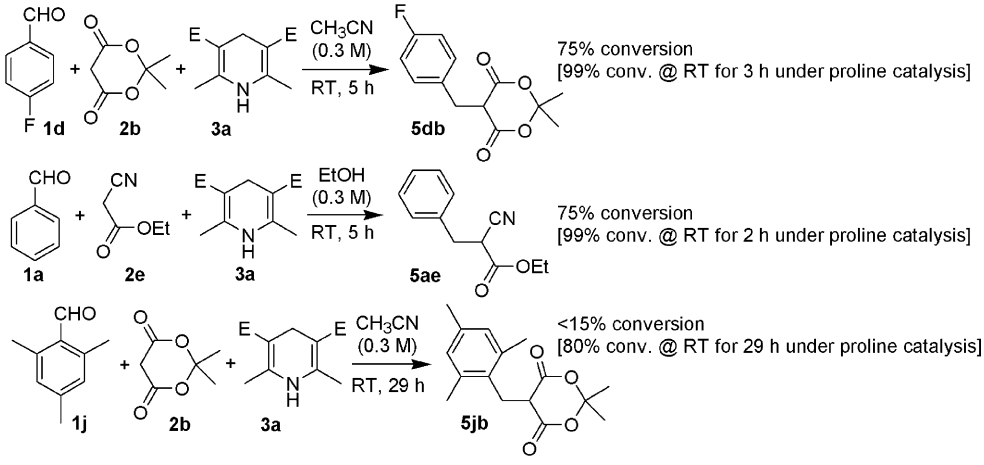
We were pleased to find that the one-pot reaction of benzaldehyde **1a**, *N*,*N*-dimethylbarbituric acid **2a** and Hantzsch ester **3a** with a catalytic amount of L-proline **4a** in EtOH at 25 °C for 2–14 h furnished the homologated product 5-benzyl-1,3-dimethyl-pyrimidine-2,4,6-trione **5aa** as a single isomer, with 99% conversion (Table 1, entry 1). The same reaction, catalyzed by L-proline **4a** in EtOH at 25 °C under tandem conditions, furnished the product **5aa** with 98% conversion in less time (Table 1, entry 7), perhaps due to the catalytic nature of the Hantzsch ester **3a** in the tandem K/H reaction. Interestingly, the tandem K/H reaction of **1a**, **2a** and **3a** without catalyst at 25 °C for 5 h furnished the expected product **5aa** with 99% conversion (Table 1, entry 10) and this is the best demonstration of the catalytic nature of reagent **3a** in tandem reactions. Interestingly, there is a little solvent effect on the proline catalyzed tandem K/H reaction of **1a**, **2a** and **3a** as shown in Table 1. The one-pot K/H reaction of **1a**, **2a** and **3a** in $H_2O$ without catalyst furnished the expected

**Table 1.** Optimization of the direct organocatalytic tandem Knoevenagel and hydrogenation reactions of **1a**, **2a** and **3a**[a]




| Entry | Catalyst | Solvent | Ester **3a** (equiv) | Time (h) | Conversion (%)[b] |
|---|---|---|---|---|---|
| 1 | **4a** | EtOH | 1.06 | 2–14 | 99 |
| 2 | **4a** | MeOH | 1.06 | 4–6 | 82 |
| 3 | **4a** | DMF | 1.06 | 3–6 | 99 |
| 4 | **4a** | DMSO | 1.06 | 4–6 | 90 |
| 5 | **4a** | $CHCl_3$ | 1.06 | 3–6 | 98 |
| 6 | **4a** | $CH_3CN$ | 1.06 | 2–14 | 99 |
| 7 | **4a** | EtOH | 1.00 | 2 | 98 |
| 8 | **4a** | $CH_3CN$ | 1.00 | 2 | 97 |
| 9[c] | **4b** | EtOH | 1.00 | 3 | 99 |
| 10 | — | $CH_3CN$ | 1.00 | 5 | 99 |
| 11[d] | — | $CH_3CN$ | — | 48 | — |
| 12 | — | $H_2O$ | 1.00 | 0.25–2 | 99 |

[a] Experimental conditions: Method **A**: A mixture of **1a** (0.3 mmol), **2a** (0.3 mmol) and catalyst **4** (20 mol %) was stirred at room temperature for 2–4 h then **3a** was added and stirring continued at the same temperature: Method **B**: All reactants **1a**, **2a**, **3a** and catalyst **4** were mixed at the same time and stirred at room temperature.
[b] Determined by $^1$H NMR spectroscopy.
[c] Product **5aa** was isolated as a 1:1 mixture of keto and enol forms.
[d] Knoevenagel product did not form.

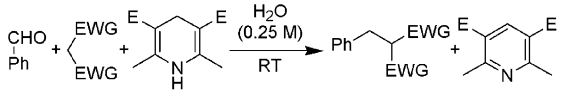



**Scheme 2.** Dual role of Hantzsch ester **3a** as a catalyst and reagent in the tandem Knoevenagel/hydrogenation reactions.

homologated product **5aa** with very good conversion and these are the optimal reaction conditions for the construction of C–C and C–H bonds under green reaction conditions (Table 1, entry 12). The simple amino acid, glycine also catalyzed the tandem K/H reaction to furnish homologated product **5aa** with 99% conversion as a 1:1 ratio of keto/enol forms (Table 1, entry 9). The best conditions for the tandem K/H reaction of **1a**, **2a** and **3a** in $CH_3CN$, EtOH or $H_2O$ at 25 °C to furnish **5aa** with excellent conversions required the presence of the amino acid (entries 7 and 8), but not in the cases of entries 10 and 12.

Following these promising results, we proceeded to investigate the scope and limitations of the tandem K/H reaction with a range of aldehydes **1a**–**t**, active methylenes **2a**–**h** and Hantzsch esters **3a**–**b** with and without catalyst (Scheme 2, Tables 2 and 3). Unfortunately, tandem K/H reaction of **1a**, **2a** and 4-phenyl Hantzsch ester **3b** with and without proline catalysis did not furnish the expected tandem product **5aa** and furnished only the Knoevenagel product, 5-benzylidene-1,3-dimethylpyrimidine-2,4,6-trione (results not shown). Tandem K/H reactions of 4-fluorobenzaldehyde **1d**, Meldrum's acid **2b** and Hantzsch ester **3a** in $CH_3CN$ at 25 °C for 5 h and benzaldehyde **1a**, ethyl cyanoacetate **2e** and Hantzsch ester **3a** in EtOH at 25 °C for 5 h furnished the tandem products 5-(4-fluoro-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **5db** and ethyl benzyl-cyano-acetate **5ae** with 75% conversions, respectively. However, the same reactions under proline catalysis furnished the expected products **5db** and **5ae** with 99% conversion and in shorter times (Scheme 2). The regioselective one-pot K/H reaction of benzaldehyde **1a** and Hantzsch ester **3a** with a variety of active methylene compounds **2a**–**h** was screened in $H_2O$ at 25 °C without catalysis, which furnished the expected homologated products **5aa**–**ah** in very good to poor yields as shown in Table 2. After testing the autocatalytic nature of the Hantzsch ester **3a** and $H_2O$ promoted reactions in one-pot K/H reactions with different aldehydes **1** and active methylenes **2** as shown in Scheme 2 and Table 2, we generated a library of homologated esters **5** under proline catalysis.

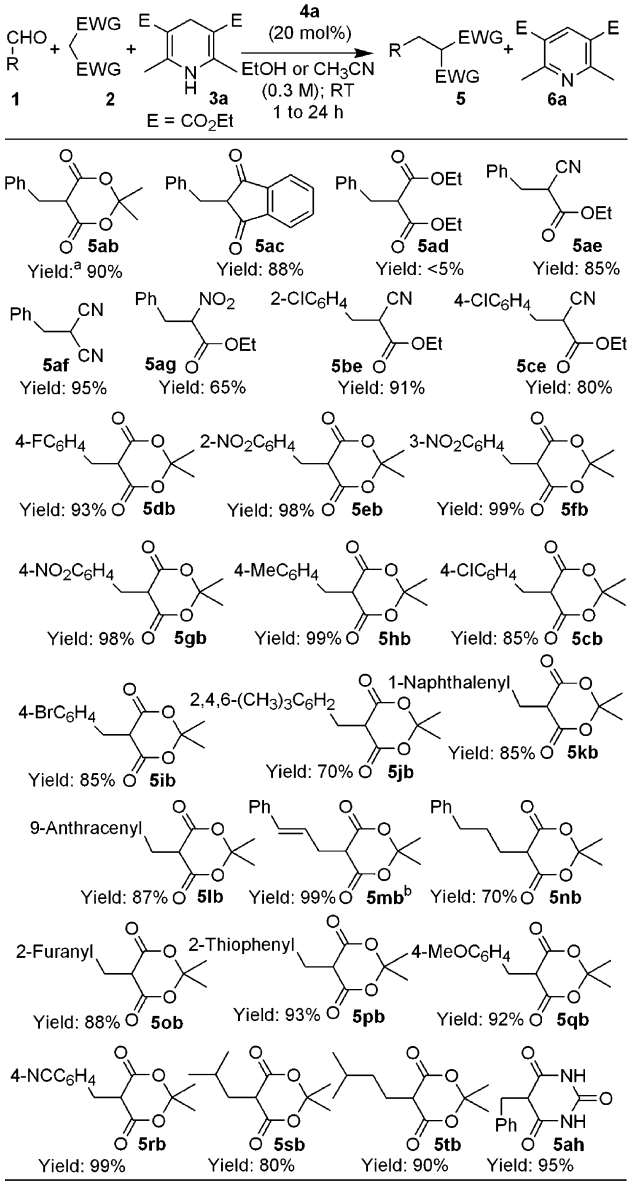
**Table 2.** Tandem Knoevenagel/hydrogenation reactions of **1a**, **2** and **3a** in $H_2O$[a]




| Entry | Active methylene **2** | Time (h) | Conversion (%)[b] |
|---|---|---|---|
| 1 | **2a** | 0.25–2 | 99 |
| 2 | **2b** | 1–16 | 85 |
| 3 | **2c** | 3–25 | 40 |
| 4[c] | **2d** | 5–40 | — |
| 5[c] | **2e** | 3–54 | 40 |
| 6 | **2f** | 2–25 | 60 |
| 7[c] | **2g** | 48 | <25 |
| 8 | **2h** | 0.5–4 | 99 |

[a] A mixture of **1a** (0.5 mmol) and **2** (0.5 mmol) was stirred at room temperature for 0.25–5 h then **3a** was added and stirring continued at the same temperature.
[b] Determined by $^1H$ NMR spectroscopy.
[c] Knoevenagel product formation was very poor.

**Table 3.** Chemically diverse libraries of two-carbon homologated esters **5**




[a] Yield refers to the column purified product.
[b] A 1:2.5 ratio of completely reduced **5nb** and 1,2-reduction **5mb** products were formed (see Supplementary data).

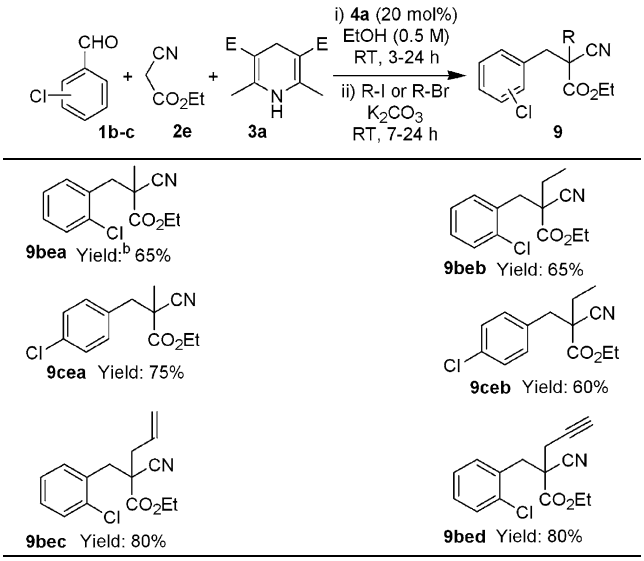
The results in Table 3[6,7] demonstrate the broad scope of this reductive methodology covering a structurally diverse group of activated aldehydes **1a**–**t** and methylenes **2a**–**h** with many of the yields obtained being very good, or indeed better, than previously published homologation reactions starting from the corresponding aldehydes. Although diethyl malonate **2d** did not react efficiently using this methodology, we have found that **2d** did not undergo Knoevenagel condensation either.

Tandem K/H reaction of *E*-cinnamaldehyde **1m**, Meldrum's acid **2b** and Hantzsch ester **3a** furnished the regioselectively hydrogenated ester **5mb** and completely hydrogenated ester **5nb** in a 2.5:1 ratio in 99% yield (Table 3; Scheme 3). Homologated esters 2-benzyl-indan-1,3-dione **5ac** and 5-(4-cyano-benzyl)-2,2-dimethyl-[1,3]dioxane-4,6-dione **5rb** are important intermediates for herbicidal[3a] and anti-thrombotic[3c] chemicals; tandem ester 5-anthracen-9-ylmethyl-2,2-dimethyl-[1,3]dioxane-4,6-dione **5lb** is a very useful intermediate to prepare dienophile scavengers,[3d] emphasizing the value of this approach. Tandem K/H ester 5-benzyl-2,2-dimethyl-[1,3]dioxane-4,6-dione **5ab** was converted into the two-carbon homologated ester ethyl 3-phenyl-propionate **8a** via a tandem K/H/H sequence in good yield with $HCO_2H/Et_3N$ in one-pot as shown in Scheme 4.

Based on the results of the proline-catalyzed three-and four-component K/H and K/H/H reactions with various aldehydes **1a–t** and active methylenes **2a–h**, we also engineered a novel proline/$K_2CO_3$-catalyzed four-component K/H/A reaction of aldehydes **1**, ethyl cyanoacetate **2e**, Hantzsch ester **3a** and alkyl halides **7a–d** in one-pot (Table 4).[6,7] Highly substituted cyano-esters **9** containing a quaternary carbon were constructed in good yields with various substituents as shown in Table 4 and this process is the first example of the utility of the proline/$K_2CO_3$ combination in catalysis. One-pot cyano-esters **9** have direct applications in pharmaceutical chemistry.[3b]

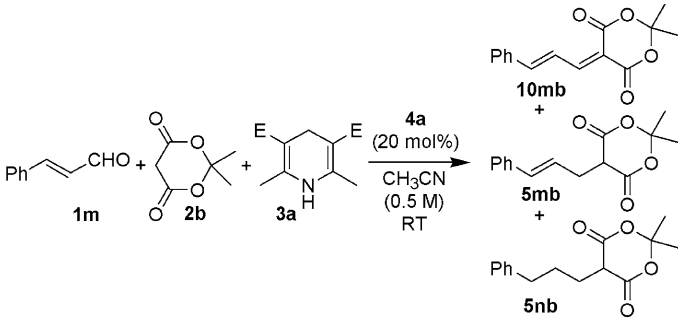
In summary, we have developed the first examples of amino acid-catalyzed direct tandem K/H, K/H/H and K/H/A reactions. This experimentally simple and environmentally friendly approach can be used to construct highly substituted homologated esters in a regioselective fashion, which are useful in pharmaceutical chemistry. For the first time in organocatalysis, the reagent has acted as a catalyst in tandem reactions and this is a very good example of autocatalysis. Further work is in progress to utilize an asymmetric version of this tandem process.

**Table 4.** Generation of chemically diverse libraries of analgesic and anti-inflammatory cyano-esters **9** via proline/$K_2CO_3$-catalyzed tandem Knoevenagel/hydrogenation/alkylation reactions[a]



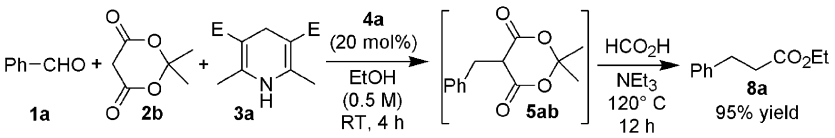

[a] A mixture of **1b–c** (0.5 mmol), **2e** (0.5 mmol), **3a** (0.5 mmol) and catalyst **4a** (20 mol %) was stirred at room temperature for 3–24 h then R-I or R-Br **7a–d** (2.5 mmol) and $K_2CO_3$ (0.4 g) were added and stirring continued at the same temperature.

[b] Yield refers to the column purfied product.




| Entry | 1m | 2b | 3a | Time/h | Yield (%) | | |
|---|---|---|---|---|---|---|---|
| | | | | | 10mb | 5mb | 5nb |
| 1 | 0.5 | 0.5 | 0.5 | 0.75 | 27 | 53 | 20 |
| 2 | 0.5 | 0.5 | 1.0 | 2.0 | 0 | 71 | 28 |

**Scheme 3.** Direct organocatalytic tandem Knoevenagel/hydrogenation of **1m**, **2b** and **3a**.




**Scheme 4.** Direct organocatalytic two-carbon homologation reaction in one-pot.

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## Supplementary data

Experimental procedures and analytical data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.tetlet.2005.11.128.

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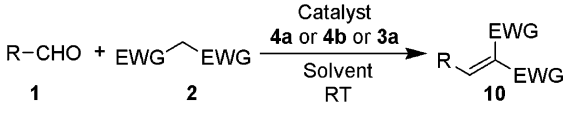
4. The amino acids proline **4a** and glycine **4b** and Hantzsch ester **3a** catalyzed the Knoevenagel condensation of aldehydes **1a**–**t** with active methylenes **2a**–**h** to furnish in situ Knoevenagel products **10** in very good yields (see Eq. 1).




(1)

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6. General experimental procedures for the two-carbon homologation reactions: Amino acid-catalyzed Knoevenagel/hydrogenation reactions in one-pot: To 0.3 mmol of aldehyde **1** and 0.3 mmol of active methylene compound **2** was added 1.0 mL of solvent, and then the amino acid catalyst **4** (0.06 mmol) was added and the reaction mixture was stirred at 25 °C for 0.25–5 h. Hantzsch ester **3a** (0.3 mmol) was added and stirring continued for the time indicated in Tables 1, 2 or 3. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up and pure one-pot products **5** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate). Amino acid-catalyzed tandem Knoevenagel/hydrogenation reactions: To 0.3 mmol of aldehyde **1**, 0.3 mmol of active methylene compound **2** and 0.3 mmol of Hantzsch ester **3a** was added 1.0 mL of solvent, and then the amino acid catalyst **4** (0.06 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1, 2 or 3. The crude reaction mixture was purified as before. Amino acid-catalyzed Knoevenagel/hydrogenation/hydrolysis reactions in one-pot: To 0.5 mmol of aldehyde **1**, 0.5 mmol of active methylene compound **2** and 0.5 mmol of Hantzsch ester **3a** was added 1.0 mL of EtOH followed by the amino acid catalyst **4** (0.1 mmol) and the reaction mixture was stirred at 25 °C for the time indicated in Table 3. To the crude reaction mixture was added 0.5 mL of $HCO_2H$, 1.8 mL of $Et_3N$ and stirring continued at 120 °C for 12 h. The crude reaction mixture was worked up with aqueous $NaHCO_3$ and $NH_4Cl$ solutions and the aqueous layer was extracted with dichloromethane ($2 \times 20$ mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure products **8** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate). Amino acid/$K_2CO_3$-catalyzed Knoevenagel/hydrogenation/alkylation reactions in one-pot: To 0.5 mmol of aldehyde **1**, 0.5 mmol of active methylene compound **2** and 0.5 mmol of Hantzsch ester **3a** was added 1.0 mL of solvent followed by the proline catalyst **4a** (0.1 mmol) and the reaction mixture was stirred at 25 °C for 3–24 h. Then R-I or R-Br **7** (2.5 mmol) and $K_2CO_3$ (0.4 g) were added and stirring continued at the same temperature for 7–24 h. The crude reaction mixture was worked up with aqueous $NH_4Cl$ solution and the aqueous layer was extracted with dichloromethane ($2 \times 20$ mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Pure products **9** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).
7. All new compounds were characterized on the basis of IR, $^1H$ and $^{13}C$ NMR and LRMS data. Spectral data for selected compounds: **5db:** IR (neat): 1786, 1739 (O—C=O), 1602 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.29 (2H, m, Ar-*H*), 6.96 (2H, t, $J = 8.8$ Hz, Ar-*H*); 3.75 (1H, t, $J = 4.8$ Hz, C*H*), 3.45 (2H, d, $J = 4.8$ Hz, $CH_2$), 1.73 (3H, s, $CH_3$), 1.53 (3H, s, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$, DEPT-135) $\delta$ 165.1 (C, 2×O—C=O), 161.9 (C, d, $J = 244.3$ Hz, *C*-F), 132.7 (C, d, $J = 3.4$ Hz), 131.5 (2×CH, d, $J = 7.9$ Hz), 115.3 (2×CH, $J = 21.1$ Hz), 105.2 (C, O–*C*–O), 48.1 (CH), 31.2 ($CH_2$), 28.3 ($CH_3$), 27.2 ($CH_3$); HRMS: *m/z* calcd for $C_{13}H_{13}FO_4$ ($M^+$): 252.0798; found: 252.0790. **9bec**: IR (neat): 2229 (C≡N), 1734 (O—C=O), 1608 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.40 (2H, m, Ar-*H*), 7.25 (2H, m, Ar-*H*); 5.85 (1H, m, olefinic-*H*), 5.26 (2H, m, olefinic-*H*), 4.21 (2H, q, $J = 7.2$ Hz, $OCH_2CH_3$), 3.37 (2H, AB q, $J = 14.0$ Hz, Ph-$CH_2$), 2.82 (1H, dd, $J = 14.0$, 7.6 Hz), 2.56 (1H, dd, $J = 14.0$, 7.6 Hz), 1.22 (3H, t,

$J = 7.2$ Hz, $OCH_2CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$, DEPT-135) $\delta$ 167.8 (C, O—C═O), 134.9 (C), 132.2 (C), 131.4 (CH), 130.5 (CH), 129.8 (CH), 129.1 (CH), 126.9 (CH), 121.1 ($CH_2$), 118.1 (C, $C{\equiv}N$), 62.9 ($CH_2$, $OCH_2CH_3$), 50.2 (C), 41.0 ($CH_2$), 38.4 ($CH_2$), 13.9 ($CH_3$, $OCH_2CH_3$); HRMS: $m/z$ calcd for $C_{15}H_{16}NO_2ClNa$ (M+Na): 300.0700; found: 300.0757. **9bed**: IR (neat): 2251 (C≡N), 1745 (O—C═O) $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (2H, m, Ar-*H*), 7.27 (2H, m, Ar-*H*); 4.27 (2H, q, $J = 7.2$ Hz, $OCH_2CH_3$), 3.52 (1H, d, $J = 14.4$ Hz, Ph-$CH_2$), 3.40 (1H, d, $J = 14.4$ Hz, Ph-$CH_2$), 2.95 (1H, dd, $J = 14.8$, 2.0 Hz), 2.76 (1H, dd,$J = 14.8$, 2.0 Hz), 2.25 (1H, t, $J = 2.8$ Hz, $CH_2C{\equiv}C{-}H$), 1.22 (3H, t, $J = 7.2$ Hz, $OCH_2CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$, DEPT-135) $\delta$ 166.9 (C, O—C═O), 134.9 (C), 131.8 (CH), 131.6 (C), 129.8 (CH), 129.4 (CH), 127.0 (CH), 117.5 (C, $C{\equiv}N$), 76.9 (C, $CH_2C{\equiv}C$-H), 73.3 (CH, $CH_2C{\equiv}C{-}H$), 63.4 ($CH_2$, $OCH_2CH_3$), 49.4 (C), 37.7 ($CH_2$), 26.6 ($CH_2$), 13.8 ($CH_3$, $OCH_2CH_3$); HRMS: $m/z$ calcd for $C_{15}H_{14}NO_2ClNa$ (M+Na): 298.0600; found: 298.0603.