Multi-catalysis cascade reactions based on the methoxycarbonylketene platform: diversity-oriented synthesis of functionalized non-symmetrical malonates for agrochemicals and pharmaceuticals†

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In this paper we describe new multi-catalysis cascade (MCC) reactions for the one-pot synthesis of highly functionalized non-symmetrical malonates. These metal-free reactions are either five-step (olefination/hydrogenation/alkylation/ketenization/esterification) or six-step (olefination/hydrogenation/alkylation/ketenization/esterification/alkylation), and employ aldehydes/ketones, Meldrum's acid, 1,4-dihydropyridine/*o*-phenylenediamine, diazomethane, alcohols and active ethylene/acetylenes, and involve iminium-, self-, self-, self- and base-catalysis, respectively. Many of the products have direct application in agricultural and pharmaceutical chemistry.

Introduction

2-Alkylmalonates are an important class of compounds that display a large spectrum of biological applications, and are widely used as intermediates for pharmaceuticals and agrochemicals.[1] Compounds containing 2-alkyl- and 2-arylmalonates have also found pharmaceutical applications as glucocorticoid receptor modulators, peptide deformylase inhibitors, HIV-1 and HIV-2 protease inhibitors, potent dual ACE/NEP inhibitors, anti-diabetic agents, ligands for the neuromodulatory receptor and in organic synthesis (see Fig. 1).[1] As such, the development of new and more general methods for their diversity-oriented preparation is of significant interest.[2] The conventional route to 2-alkylmalonates is the alkylation of symmetrical malonates with alkyl halides under dry conditions, but this has limited scope with respect to yield, generality, and experimental simplicity.

Recently, acylketenes (**B**) have often been employed as reactive electrophiles to trap alcohols to construct β-ketoesters (**C**) by concerted addition of an oxygen nucleophile (Scheme 1).[3] Thermolysis of 6-alkyl-1,3-dioxin-4-one derivatives (**A**) is the most common method used for the generation of **B**, and Boeckman and co-workers pioneered the application of reactive acylketene species in the synthesis of complex molecules such as macrocyclic lactones and lactams.[3] *In situ* generation of alkyloxycarbonylketenes (**B′**) from 6-alkyloxy-1,3-dioxin-4-one (**A′**) is hardly known, but the rate of the cycloreversion reaction of **A′** → **B′** is rapid below 25 °C relative to **A** → **B**, because of electronic factors (Scheme 1).[4] In this paper, we have used a new reactive species – alkyloxycarbonylketenes (**B′**) – to generate a library of non-symmetrical 2-alkylmalonates (**C′**) by *in situ* generation, cycloreversion and alcohol addition (**A′** → **C′**) in one pot under ambient conditions.

As part of our program to engineer direct multi-catalysis cascade (MCC) reactions,[5] we were exploring the *in situ* generation and application of the methoxycarbonylketenes (**12**), as shown in Scheme 2. We expected that the reaction of **1** with **2**/**6**, **3**, **4**,

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† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds; NMR spectra. CCDC reference number 713797 (**18ea**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b901652j

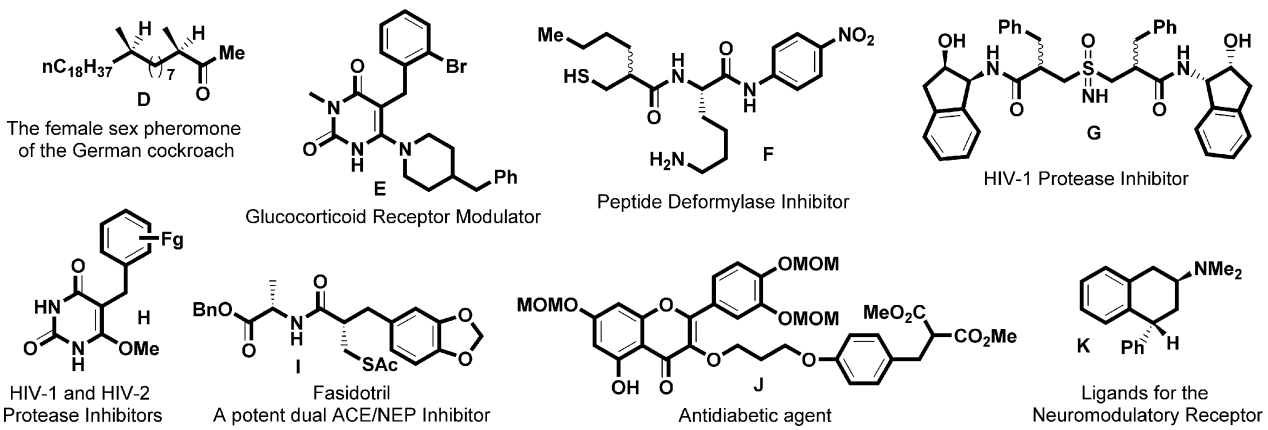
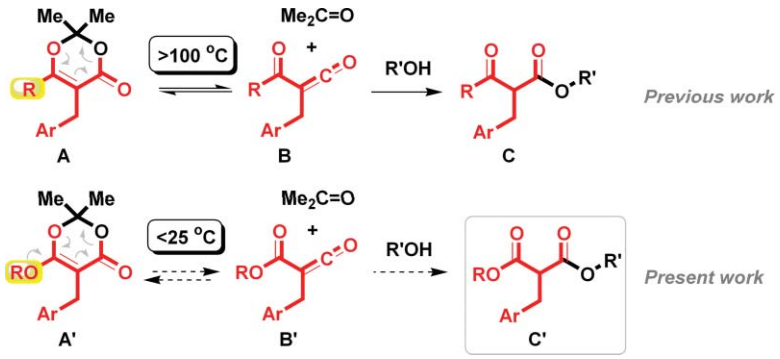
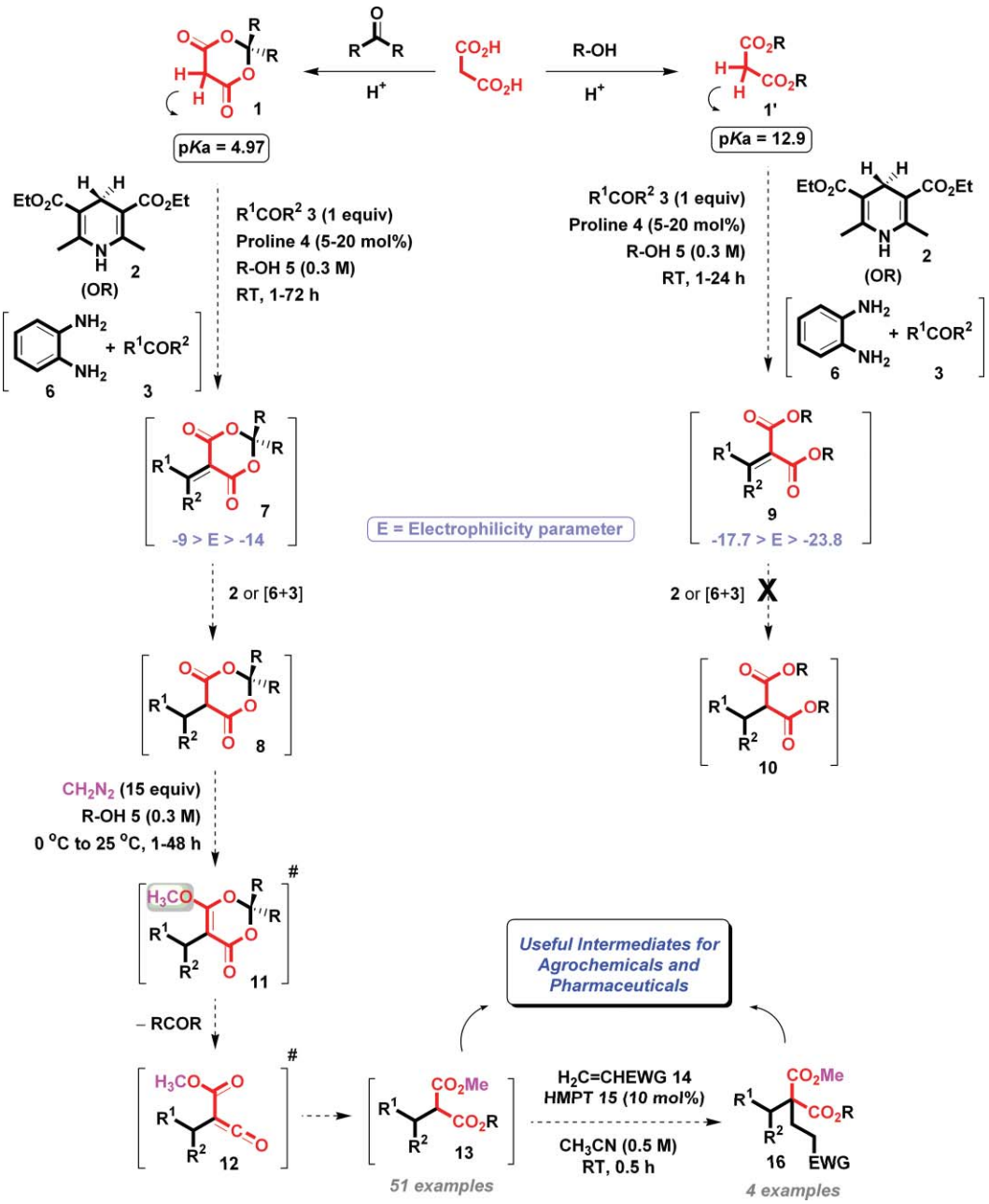


Fig. 1 Generation of a library of pharmaceutically attractive molecules from 2-alkylmalonates.

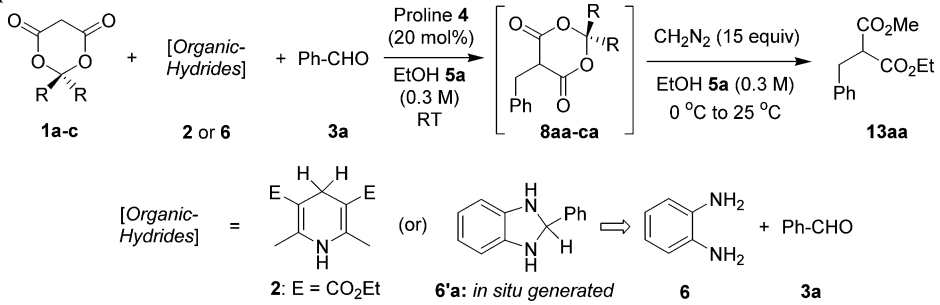


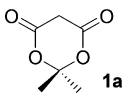
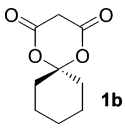
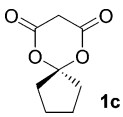
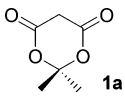
Scheme 1 Synthesis of non-symmetrical malonates *via* alkyloxycarbonylketenes generated from 6-alkyloxy-[1,3]dioxin-4-one.



Scheme 2 One-pot multi-catalysis cascade (MCC) reactions.

Table 1 Preliminary optimization of MCC reactions



Entry	Cyclic malonate	Organic hydride	Time (h) O/H step	Time (h) A/K/E step	Product	Yield (%)[a]
1[b]	 **1a**	**2**	2	2	**13aa**	90
2[b]	 **1b**	**2**	0.5	1	**13aa**	89
3[b]	 **1c**	**2**	0.5	1	**13aa**	65
4[c]	 **1a**	**6′a**	1.5	1	**13aa**	65

[a] Yield refers to the column-purified product. [b] All reactants **1a–c**, **2**, **3a** and catalyst **4** were mixed at the same time in the solvent and stirred at 25 °C; 15 equiv of ethereal diazomethane was then added and the mixture stirred at 25 °C. [c] All reactants **1a**, **6**, **3a** (2 equiv) and catalyst **4** were mixed at the same time in the solvent and stirred at 25 °C; 15 equiv of ethereal diazomethane was then added and the mixture stirred at 25 °C.

and **5** would lead to 5-alkyl-2,2-dialkyl-[1,3]dioxane-4,6-diones **8** *via* olefin intermediate **7**. Further *in situ* treatment of **8** with CH_2N_2 and **5** ought to lead to non-symmetrical malonates **13** *via* chemoselective generation of key intermediates **12** from **11**. Final HMPT-mediated alkylation of **13** with active ethylene/acetylenes **14** should give non-symmetrical 2,2-dialkylated malonates **16**.

Incidentally, the amino acid-/self-catalyzed olefination/hydrogenation reaction sequence did not work with dialkylmalonates **1′**, instead furnishing only the olefin product **9** in good yield. This may be because the dialkyl benzylidenemalonates **9** are more than 10^{10} times less reactive than benzylidene Meldrum's acids **7** and their cyclic counterparts **7** with organic hydrides **2** (Scheme 2).[6]

Considering the main reaction sequence, the *in situ* generation of methoxycarbonylketenes **12** – and reaction with various alcohols **5** – was very fast at ≤25 °C compared to acylketenes **B**. This unexpectedly high reactivity makes this route a useful way of preparing **12**, and further reaction to give either (a) 2-alkylmalonates **13** (by olefination/hydrogenation/alkylation/ketenization/esterification (O/H/A/K/E)) or (b) 2,2-dialkylmalonates **16** (with a final alkylation step (A)). Overall, the route employs aldehydes/ketones **3**, Meldrum's acid **1**, 1,4-dihydropyridine **2**/*o*-phenylenediamine **6**, diazomethane, alcohols **5** and active ethylene/acetylenes **14**, and does not involve any metal catalysts. It also generates a quaternary center, two carbon–carbon σ-bonds and two carbon–oxygen σ bonds. We report herein our findings regarding this new organocatalytic one-pot cascade sequence.

Results and discussion

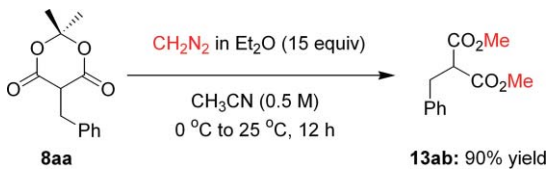
Reaction optimization for the one-pot MCC reactions

First we focused on the optimization of the synthesis of ethyl methyl 2-benzylmalonate **13aa** from **1**, **2**/**6** and **3a** by amino acid-catalysis in ethanol **5a**, by looking at the effect of the cyclic nature of **1** and the hydrogen donor ability of **2**/**6**. We therefore tested three known and novel cyclic Meldrum's acids **1a–c** and organic hydrides **2** (or *in situ*-generated **6′a**) for the O/H cascade followed by the A/K/E cascade with benzaldehyde **3a** and ethereal diazomethane in ethanol **5a**, as shown in Table 1. Interestingly, the proline-catalyzed O/H cascade of Meldrum's acid **1a** and benzaldehyde **3a** with Hantzsch ester **2** in ethanol at 25 °C for 2 h furnished the expected reductive alkylation product **8aa** in >99%

conversion, which on *in situ* treatment with ethereal diazomethane at 0 → 25 °C for 2 h furnished the expected product **13aa** in 90% yield (entry 1). The O/H/A/K/E reaction of Meldrum's acid analogues **1b,c** with **2**, **3a**, **5a** and diazomethane catalyzed by **4** in ethanol at 0 → 25 °C for 1 h furnished **13aa** in lower yield – 89% and 65% respectively (entries 2 and 3). However, the reaction rate with **1b,c** was 4-fold higher than for **1a**.

Interestingly, proline-catalyzed cascade O/H reaction of Meldrum's acid **1a** and two equivalents of benzaldehyde **3a** with *o*-phenylenediamine **6** in ethanol at 25 °C for 1.5 h furnished the expected reductive alkylation product **8aa** in >99% conversion, which on *in situ* treatment with ethereal diazomethane at 0 → 25 °C for 1 h furnished the expected product **13aa**, but in only 65% yield (entry 4). From these preliminary results, it was clear that **1a** or **1b** and **2** are suitable for the MCC reactions.

After this preliminary investigation, we proceeded to investigate the scope and limitations of the O/H/A/K/E cascade reaction of **1a**, **2**, **3a** and diazomethane with a range of alcoholic solvents **5a–j** under catalysis by proline at 25 °C (Table 2). Larger alkyl alcohols **5c–h** furnished MCC products **13ac–ah** in lower yield than smaller alkyl alcohols **5a,b** in the cascade O/H/A/K/E reactions. The reason may be due to moderate steric hindrance with larger alkyl groups. Also we observed that the rate of the cascade *O*-methylation reaction of **8aa** with CH_2N_2 in MeOH appeared to be slow compared to other alcoholic solvents – unreacted cascade product **8aa** was isolated in 15% yield after 6 h (entry 2). However, extension of the reaction time up to 26 h in MeOH furnished the expected product **13ab** in 85% yield (result not shown in Table 2). This may be due to the existence of more interactions between the intermediates and methanol compared to other solvents. Interestingly, the MCC reaction of **1a**, **2**, **3a**, **4** and diazomethane in benzyl alcohol **5i** furnished the expected product **13ai** along with the unexpected product dimethyl 2-benzylmalonate **13ab** in good yield with a 6:1 ratio (entry 9). Generation of **13ab** was also observed in other solvents, such as (*S*)-ethyl lactate **5j** and CH_3CN (entries 10–12). Formation of **13ab** in solvents like **5i**, **5j** and CH_3CN can be explained by the lower nucleophilicity of **5i** and **5j** compared to methanol **5b**, and a small amount of methanol being present in the ethereal diazomethane solution (generated *in situ* from the reaction of NMU with aqueous KOH in ether at low temperature[7]). Unexpected formation of **13ab** from above reactions was confirmed by controlled experiment as shown in Scheme 3, which proved that significant amount of methanol **5b** is present in the ethereal diazomethane solution.[7] The mixture of compounds **13ai**/**13ab** obtained from benzyl alcohol could be transformed into the useful diols **17a** with good yield, as shown in Scheme 4.

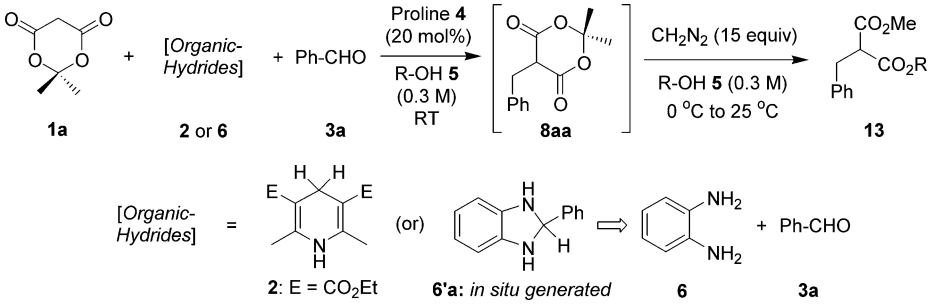


Scheme 3

Development of product-specific MCC reactions

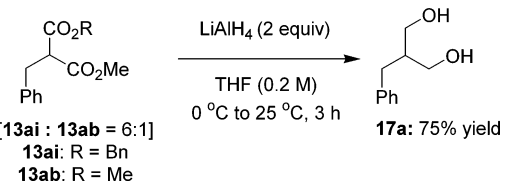
We then decided to investigate the scope and limitations of the MCC reaction with a range of aldehydes/ketones **3a–k′**,

Table 2 Optimization of MCC reactions



Entry	Organic hydride	R–OH	Time (h) O/H step	Time (h) A/K/E step	Product	Yield (%)[a]
1	**2**	EtOH **5a**	2	2	**13aa**	90
2[b]	**2**	MeOH **5b**	2	6	**13ab**	75
3	**2**	*n*-PrOH **5c**	2	2	**13ac**	70
4	**2**	*i*-PrOH **5d**	2	2	**13ad**	65
5	**2**	*n*-BuOH **5e**	2	2	**13ae**	65
6	**2**	*t*-BuOH **5f**	2	2	**13af**	65
7	**2**	$H_2C{=}CHCH_2OH$ **5g**	1.5	1	**13ag**	70
8	**2**	$HC{\equiv}C{-}CH_2OH$ **5h**	1.5	1	**13ah**	70
9[c]	**2**	BnOH **5i**	1.5	1	**13ai** + **13ab**	80
10[d]	**6′a**	(*S*)-$CH_3CH(OH)CO_2Et$ **5j**	15	6	**13ab**	89
11	**6′a**	CH_3CN	15	12	**13ab**	90
12	**2**	CH_3CN	3	6	**13ab**	75

[a] Yield refers to the column-purified product. [b] Un-reacted cascade O/H product **8aa** were isolated in 15% yield. [c] Compounds **13ai** and **13ab** were furnished in 6:1 ratio. [d] (*S*)-Ethyl lactate **5j** was taken as 5 equiv in CH_3CN (0.5 M).



Scheme 4

Meldrum's acid analogues **1a–e** and alcohols **5** under catalysis by proline and ambient conditions (Scheme 5 and Table 3). As shown in Scheme 5, MCC reaction of *N*,*N*-dimethylbarbituric acid **1d**, **2**, **3a**, **4**, **5a** and diazomethane furnished the single uracil derivative **18da** with 98% yield. Same MCC reaction with barbituric acid **1e** furnished the 2(1*H*)-pyrimidinone derivative **18ea** as major single product with 70% yield and 5-benzyl-2,6-dimethoxy-3-methyl-3*H*-pyrimidin-4-one **19ea** with ≤5% yield out of 24 expected products from the designed reaction as shown in Scheme 5. 5-Benzylpyrimidine-2,4,6-trione **8ea**, which is generated *in situ* from the O/H cascade reaction, has many active sites toward methylation with diazomethane, but the only major product was 5-benzyl-2,6-dimethoxy-3*H*-pyrimidin-4-one **18ea**, which was confirmed by X-ray structural analysis (see Fig. 2).† Interestingly, we did not observe the formation of ketenes from **18**. Uracil and 2(1*H*)-pyrimidinone derivatives **18** are useful compounds as agrochemical fungicides and potent HIV-1 and HIV-2 inhibitors, and they also have good anti-viral and anti-bacterial activity.[1] Our product-specific MCC technology may be suitable to develop a large number of diverse-compounds of **18** to screen and identify suitable bioactive products.

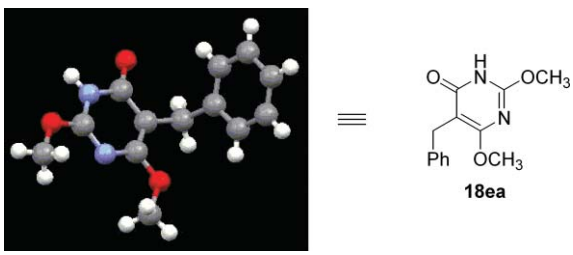


Fig. 2 Crystal structure of 5-benzyl-2,6-dimethoxy-3*H*-pyrimidin-4-one (**18ea**).

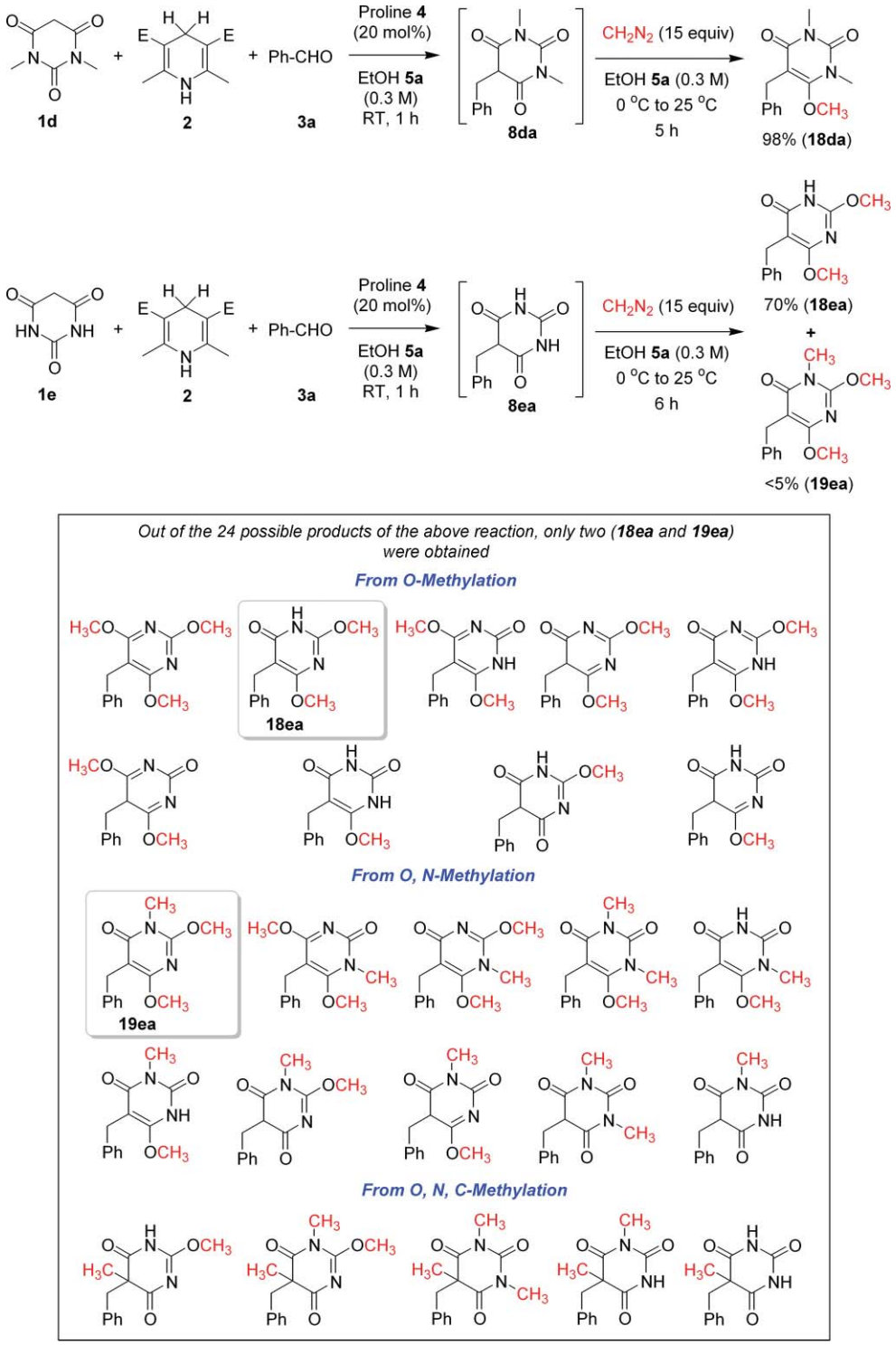
Diversity-oriented synthesis of MCC products 13aa–13k′a

We then generated a useful library of MCC products **13** under proline-/self-/self-/self-/self-catalysis. The results in Table 3 demonstrate the broad scope of this reductive MCC methodology covering a structurally diverse group of aldehydes **3a–f′**, less reactive ketones **3g′–k′** and alcohols **5a–i**, with many of the yields obtained being better than previously published reactions starting from the corresponding symmetric malonates **1′**. A large number of non-symmetrical 2-alkylmalonates **13** are not known, and our MCC methodology is first to prepare them with good yields. A series of substituted aromatic aldehydes **3a–v**, hetero-aromatic aldehydes **3w–x**, aliphatic aldehydes **3y–f′** and ketones **3g′–k′** were treated with Meldrum's acid **1a** (1.0 equiv), Hantzsch ester **2** (1.0 equiv) and diazomethane (15 equiv) catalyzed by 5–20 mol% of proline **4** at 25 °C in EtOH **5a**, MeOH **5b** or BnOH **5i** (Table 3). Ethyl methyl 2-arylmalonates **13aa–xa** and ethyl methyl 2-alkylmalonates **13ya–k′a** were obtained as single products with excellent yields. To show the applicability of this method, we carried out the large-scale (10 mmol) synthesis of MCC product **13aa** with very good yield. The fact that the MCC reaction of substrates such as **3g**, **3n**, **3g′**, **3h′** and **3j′** in BnOH furnished only the desired products **13gi–13j′i** without side products may be due to the substrate electronic factors and also the amount of methanol available in the ethereal diazomethane solution, which is proved by the reaction shown in Scheme 6. Reaction of **1a**, **3g** (2 equiv), **6**, **4** and CH_2N_2 in CH_3CN furnished the expected product **13gb** in lower yield (30%) compared to simple benzaldehyde **3a** (see Scheme 6 and Table 2, entries 11–12).

MCC reactions with active functional groups

Interestingly, proline-catalyzed MCC reaction of Meldrum's acid **1a**, Hantzsch ester **2**, 2-hydroxybenzaldehyde **3h** and diazomethane at 25 °C in EtOH **5a** furnished the MCC product **13ha** in 80% yield *via* an unexpected intermediate of the O/H/H cascade, 2-(2-hydroxybenzyl)malonic acid mono-ethyl ester **20ha**, instead of the expected ketene intermediate **12ha** (Table 3 and Scheme 7). But the same reaction with 3-hydroxybenzaldehyde **3i** or 4-hydroxybenzaldehyde **3j** proceeded *via* ketene intermediates **12ia** and **12ja** respectively, furnishing the expected MCC products **13ia** and **13ja** with good yields, as shown in Table 3. Also, MCC reaction of Meldrum's acid **1a** with 2-hydroxy-benzaldehyde **3h** and Hantzsch ester **2** at 25 °C in water furnished the unexpected intermediate 2-oxochroman-3-carboxylic acid **21ha**, which on *in situ* treatment with sodium hydroxide furnished the 2-(2-hydroxy-benzyl)-malonic acid **22ha** with very good yield (Scheme 7). Reaction of **22ha** with diazomethane furnished the unexpected methylated product **13l′b** along with expected product **13hb** in good yield, may be due to the co-operative catalysis from hydrogen bonding. Unexpected intermediates **20ha** and **21ha** were isolated and characterized by NMR analysis.[5f] Formation of unexpected cascade O/H/H intermediates from **1a**, **2** and **3h** under proline- and self-catalysis in EtOH and H_2O can be explained as shown in **TS-1** and **TS-2** respectively (Scheme 7). Inter- and intra-molecular hydrolysis of in situ generated cascade O/H product **8ha** with solvents like EtOH or H_2O gives the cascade O/H/H intermediates as shown in **TS-1** and **TS-2** respectively. These two different types of hydrolysis can be possible due to the nucleophilic nature of alcoholic solvents and possibility of hydrogen bonding interactions with water.

MCC products **13aa** and analogues are important intermediates for the synthesis of glucocorticoid receptor modulator (**E**),[1b] HIV-1 and HIV-2 protease inhibitors (**G** and **H**),[1d,e] anti-ulcer and anti-diabetic agents (**J**),[1g] and ligands for the neuromodulatory receptors (**K**)[1h] and chiral MCC products **13e′b** and **13f′b** are useful intermediates for the total synthesis of female sex pheromone of the German cockroach (**D**).[1a] MCC products **13ga** and **13gi** are important intermediates for the total synthesis of fasidotril, a potent dual ACE/NEP inhibitor (**I**);[1f] and products **13c′a**, **13d′a** and their analogues are key intermediates for the synthesis of peptide deformylase inhibitors (**F**) and for the prostaglandin-H synthase inhibitors,[1c,j] products **13h′a** and **13h′i** are key intermediates for the synthesis of prostaglandin analogues,[1m] and blood clotting factor inhibitors[1n] emphasizing the value of this MCC approach to the pharmaceuticals.

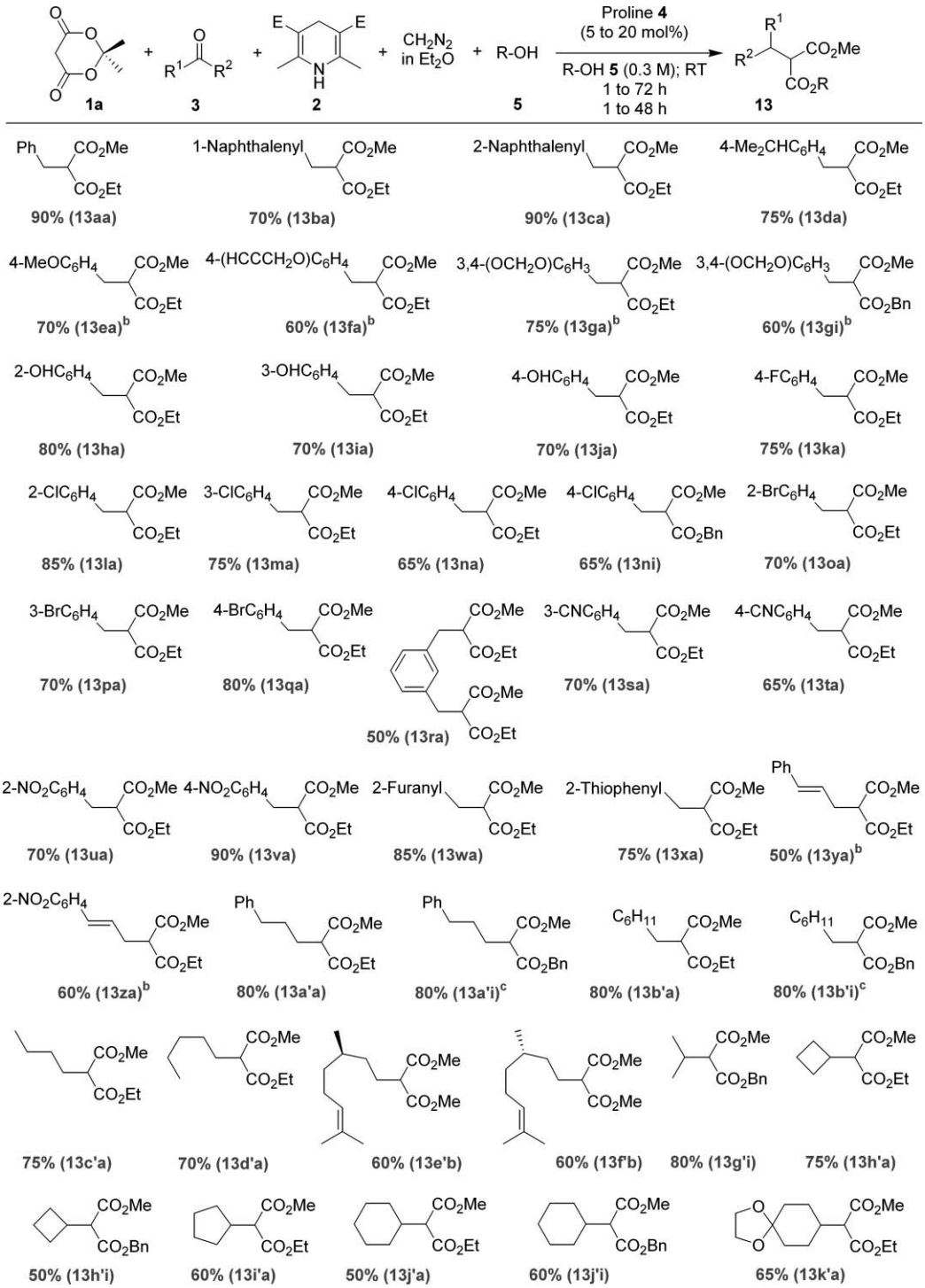


Scheme 5 Applications of one-pot product-specific MCC reactions.

Development of the MCC reaction for the one-pot generation of quaternary carbon centres

As part of our program to engineer direct one-pot MCC reactions to deliver highly functionalized molecules with quaternary carbons relevant to pharmaceutical applications, we extended the five-component cascade O/H/A/K/E reactions into a novel proline-/self-/HMPT-catalyzed six-component one-pot O/H/A/K/E/A reaction of benzaldehyde **3a**, Meldrum's acid **1a**, Hantzsch ester **2**, diazomethane and ethanol **5a** with various active olefins and acetylenes **14a–e** (Scheme 8). MCC products **16** were constructed in very good yields with high selectivity, and this method should be useful in the synthesis of functionalized small molecules. Highly substituted non-symmetrical 2,2-dialkylated malonates

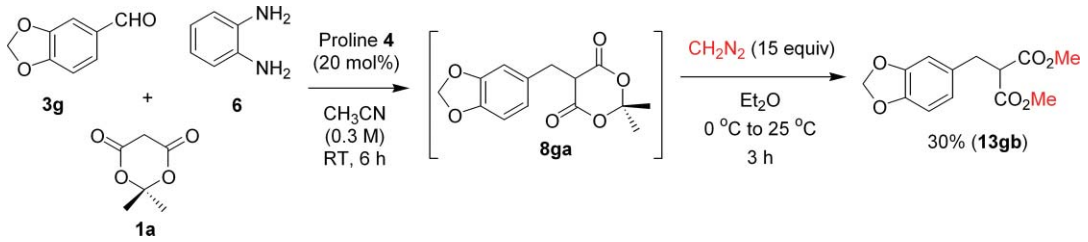
Table 3 Chemically diverse libraries of MCC products **13** [a]



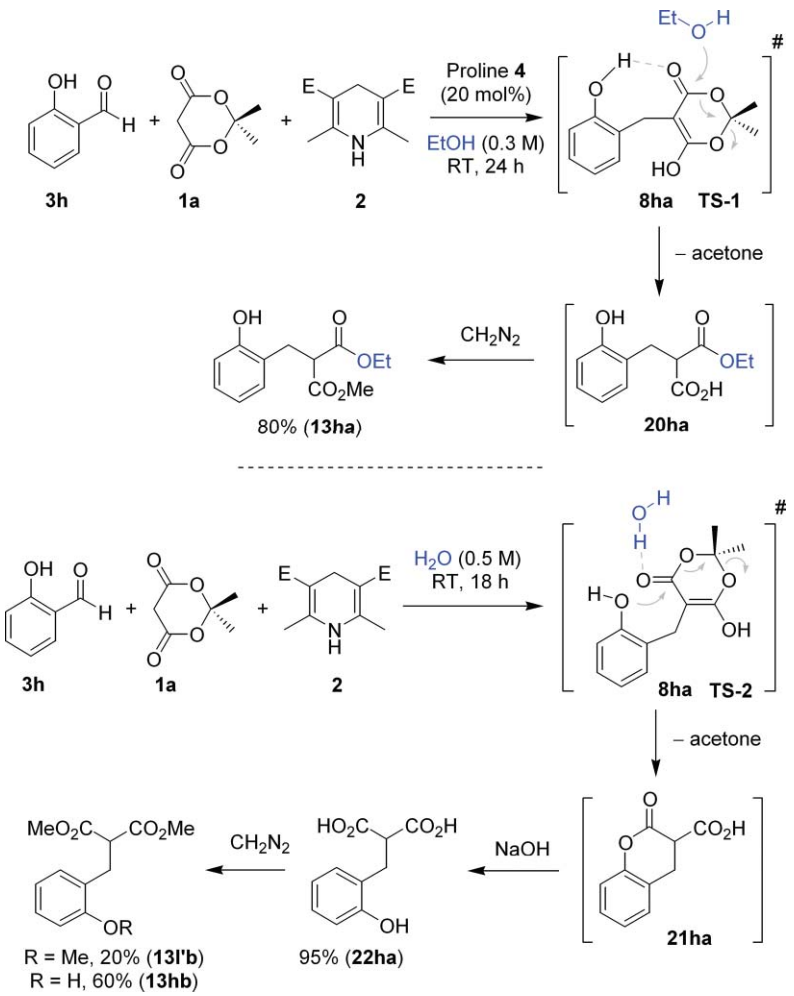
[a] Yield refers to the column-purified product. [b] *In situ*-generated benzimidazolines **6′e**–**z** used as organic hydrides. [c] Compounds **13a′i**/**13a′b** and **13b′i**/**13b′b** were furnished in a 6:1 ratio.

16 have gained importance in recent years as starting materials and intermediates for the synthesis of biologically active compounds – for example, new M_2-selective muscarinic receptor antagonists and isozyme-selective glutathione *S*-transferase inhibitors.[1i–k]

The O/H cascade reaction of **1a**, **2**, **3a** and **5a** under catalysis by 20 mol% of proline furnished the substituted 5-benzyl-2,2-dimethyl-[1,3]dioxane-4,6-dione **8aa** in good conversion. This, on *in situ* treatment with ethereal diazomethane at 0–25 °C for 2 h, furnished ethyl methyl 2-benzylmalonate **13aa** in good



Scheme 6 Applications of one-pot product-specific MCC reactions.

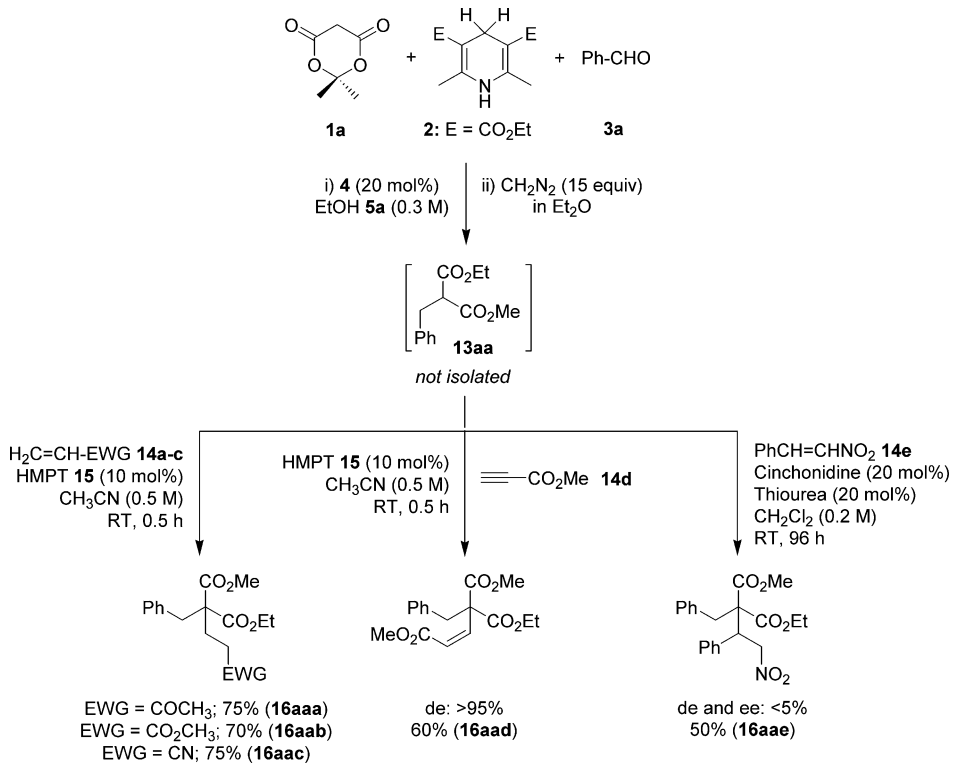


Scheme 7 Applications of MCC reactions with 2-hydroxy-benzaldehyde in one-pot.

conversion, which on treatment with catalytic HMPT and methyl vinyl ketone **14a** in CH_3CN at 25 °C for 0.5 h furnished the O/H/A/K/E/A product **16aaa** with 75% yield, as shown in Scheme 8. The generality of the proline-/self-/HMPT-catalyzed chemoselective one-pot O/H/A/K/E/A reaction was further confirmed by three more examples using methyl acrylate **14b**, acrylonitrile **14c** and methyl propiolate **14d** to furnish the expected products **16aab** (70%), **16aac** (75%) and **16aad** (60%) with >95% de, respectively (Scheme 8). Interestingly, alkylation reaction of *in situ*-generated cascade O/H/A/K/E product **13aa** with β-nitrostyrene **14e** under catalysis by HMPT did not furnish the expected compound **16aae**, but the same reaction under catalysis by chiral cinchonidine/thiourea did give **16aae**, albeit in 50% yield with ≤5% de and ≤5% ee (Scheme 8). To achieve high ee, it will be necessary to optimise the catalyst conditions.

Conclusions

In summary, we have developed direct amino acid-/self-/self-/self-/self-/HMPT-catalyzed cascade olefination/hydrogenation/alkylation/ketenization/esterification and olefination/hydrogenation/alkylation/ketenization/esterification/alkylation reactions, which have been shown to have direct application in the drug discovery process. For the first time we have demonstrated that multi-component coupling can be a product-specific reaction, furnishing a single product out of many possible compounds. This



Scheme 8 Applications of MCC for the one-pot generation of quaternary carbon centres.

experimentally simple and environmentally friendly approach can be used to construct highly functionalized products in a selective fashion with very good yields. For the first time in organocatalysis, methoxycarbonylketenes **12** have been generated *in situ* and their application in organic synthesis has been demonstrated. Further work is now in progress to further utilize the active species **12** in cascade chemistry.

Experimental

General methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield of TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by a DEPT-135 experiment, and is given in parentheses. The coupling constants J are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063–0.200 mm). High-resolution mass spectra were recorded on a Micromass ESI-TOF mass spectrometer. GCMS was performed on a Shimadzu GCMS-QP2010 mass spectrometer. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. LCMS mass spectra were recorded either on a VG7070H mass spectrometer using the EI technique or a Shimadzu-LCMS-2010A mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700 instruments. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite-monochromated, Mo-Kα ($\lambda = 0.71073$ Å) radiation with CAD4 software. X-Ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube ($\lambda = 0.71073$ Å). For thin-layer chromatography (TLC), Merck 60 F254 silica gel plates were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. All solvents and commercially available chemicals were used as received.

General experimental procedures for the MCC reactions

Proline-catalyzed one-pot cascade O/H/A/K/E reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the aldehyde/ketone **3**, 0.5 mmol of CH-acid **1** and 0.5 mmol of Hantzsch ester **2** was added 1.7 mL of solvent. The catalyst amino acid **4** (0.1 mmol) was then added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1–3. To the crude reaction mixture was added 15 equivalents of an ethereal solution of diazomethane, and the reaction mixture was stirred at room temperature for the time indicated in Tables 1–3. After complete evaporation of the solvent and excess diazomethane in a fumehood, the crude reaction mixture was worked up with water if necessary, and then loaded onto a silica gel column, giving pure one-pot products **13** after chromatography (solvent: hexane/ethyl acetate).

Proline/HMPT-catalyzed one-pot cascade O/H/A/K/E/A reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the aldehyde/ketone **3**, 0.5 mmol of CH-acid **1** and 0.5 mmol of Hantzsch ester **2** was added 1.7 mL of solvent. The amino acid catalyst **4** (0.1 mmol) was

then added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1–3. To the crude reaction mixture was added 15 equivalents of an ethereal solution of diazomethane, and the reaction mixture was stirred at room temperature for the time indicated in Tables 1–3. After complete evaporation of the solvent and excess diazomethane in a fumehood, active olefins/acetylenes **14a–d**, hexamethylphosphorous triamide (HMPT) **15** (10 mol%) and CH_3CN (1.0 mL) were added to the crude reaction mixture, and the mixture stirred at 25 °C for 0.5 h. The crude reaction mixture was worked up with water if necessary, and then loaded onto a silica gel column, giving pure one-pot products **16** after chromatography (solvent: hexane/ethyl acetate).

Many of the MCC products **13** and **16** are commercially available or have been described previously, and their analytical data match literature values; new compounds were characterized on the basis of IR, ^{1}H and ^{13}C NMR and analytical data (see ESI†).

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