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Development of Pharmaceutical Drugs, Drug Intermediates and Ingredients by Using Direct Organo-Click Reactions

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Here we report on our studies of the use of combinations of amino acids, amines, K_2CO_3 or Cs_2CO_3 and $CuSO_4$/Cu for catalysing green cascade reactions. We aimed to prepare the highly reactive and substituted olefin species **7** and **8**, under very mild and environmentally friendly conditions, thus giving the hydrogenated products **10** and **12** through the action of Hantzsch ester (**4**) by self-catalysis through decreasing the HOMO–LUMO energy gaps between olefins **7**/**8** and Hantzsch ester (**4**) through biomimetic reductions. Highly useful compounds **10** to **14** were assembled from simple substrates such as aldehydes **1**, ketones **2**, CH acids **3**, Hantzsch ester (**4**) and alkyl halides **5** by diversity-oriented green synthesis involving cascade olefination/hydrogenation (O/H), olefination/hydrogenation/alkylation (O/H/A) and hydrogenation/olefination/hydrogenation (H/O/H) reaction sequences in one-pot fashion with stereospecific organo- and organo-/metal-carbonate catalysis. Highly functionalized diverse compounds such as **10** to **14** are biologically active products and have found wide applications as pharmaceutical drugs, drug intermediates and drug ingredients. For the first time in organocatalysis, we report the O/H/A/TE reaction to furnish high yields of transesterification products **11** by simply mixing the reactants under proline/K_2CO_3 catalysis conditions. Additionally, a novel organocatalytic H/O/H reaction sequence for the synthesis of alkyl-substituted aromatics has been developed. Furthermore, for the first time we have developed organocatalysed cascade olefination/hydrogenation/hydrolysis (O/H/H) reactions to furnish highly useful materials such as 2-oxochroman-3-carboxylic acid (**14kc**) and 2-amino-4*H*-chromene-3-carbonitrile (**14kj**) in good yields. Experimentally simple and environmentally friendly organocatalytic two-carbon homologation through cascade O/H/H reactions of aldehydes **1**, Meldrum's acid (**3c**), Hantzsch ester (**4**) and acetic acid/triethylamine in ethanol has been demonstrated. Additionally, we have developed a green synthesis of the highly substituted 1,2,3-triazole **17** from simple substrates through a two-step combination of olefination/hydrogenation/alkylation and Huisgen cycloaddition reaction sequences under stereospecific organocopper catalysis conditions. In this paper we have found strong support for our hypothesis that, "decreasing the HOMO–LUMO energy gap between olefins **7**/**8** and Hantzsch ester (**4**) will drive the biomimetic hydrogenation reaction by self-catalysis". This self-catalysis was further confirmed with many varieties of examples.

Introduction

Development of drug-like small molecules from simple substrates through cascade reactions is one of the emerging areas in modern synthetic chemistry, even though there are already many common organic reactions and reaction strategies for the construction of C–C, C–N, C–O, C–S and C–X (X = halogen) bonds in structurally diverse natural and non-natural products by conventional methods. More typically, these reactions and reaction strategies are not ideal in comparison with biochemical reactions in terms of selectivity (chemo-, regio-, diastereo- and enantioselectivity) or in the ecology and economy of chemical reactions. From the organic chemist's point of view, ideal reaction strategies for the preparation of structurally diverse substances would involve sequences in which stereocontrolled formation of multiple carbon–carbon and carbon–heteroatom bonds occur in a single step from simple, readily available starting materials. As a result, great attention has been paid to the development of cascade or domino reactions, because of their high degrees of atom economy and their applications in combinatorial chemistry as well as diversity-oriented synthesis.[1] Despite the intense interest, there are only a few reports of organocatalysed cascade reactions for the synthesis of stereochemically complex compounds.[1n–1ee] A key to many interesting cascade reactions is the incorporation of biomimetic olefination, hydrogenation and alkylation reaction sequences to enable construction of structurally diverse compounds in a completely stereoselective manner.[2]

Recent studies in our laboratory have led to the development of novel organocatalytic cascade or domino reactions of simple substrates in one-pot fashion, such as organocata-

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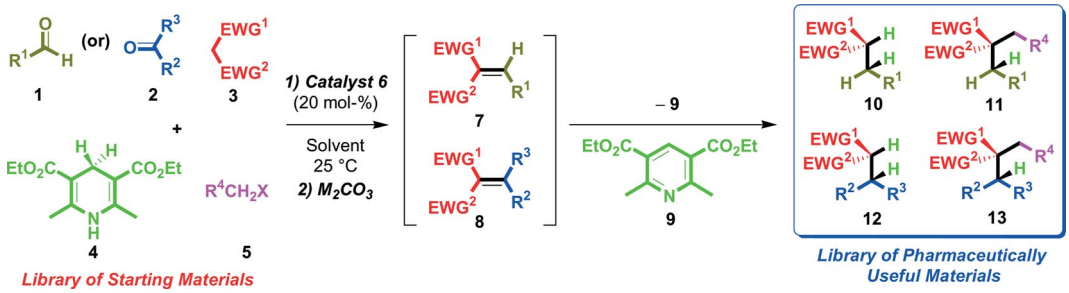
lytic Claisen–Schmidt/isoaromatization,[1dd] Knoevenagel/hydrogenation,[2a,2b] Knoevenagel/hydrogenation/alkylation,[2a,2b] Knoevenagel/Michael/aldol condensation/decarboxylation,[1ee] enamine amination/isoaromatization,[1ee] enamine amination/isoaromatization/alkylation,[1ee] and Knoevenagel/hydrogenation/Robinson annulation[2d] reaction sequences. These reaction conditions use less solvent and less toxic solvents than previously developed schemes and are thus significantly more environmentally friendly.

Taking our cue from nature, here we address the development of a set of powerful, reliable and selective cascade reactions for the rapid synthesis of combinatorial libraries for use as pharmaceutical drugs, drug intermediates and ingredients through organo-/metal carbonate- and organo-/Cu^{I}-catalysed cascade olefination/hydrogenation, olefination/hydrogenation/alkylation, hydrogenation/olefination/hydrogenation, olefination/hydrogenation/hydrolysis and olefination/hydrogenation/alkylation/Huisgen cycloaddition reaction sequences, an approach we call "organo-click reactions". K. B. Sharpless and co-workers recently provided guidelines for click chemistry,[3] while Ramachary and Barbas later combined organocatalytic reactions with click chemistry (organo-click chemistry).[1r,2c] Ideally, organocatalytic cascade reactions can also fulfil all aspects of click



Scheme 1. Direct organometal carbonate-catalysed cascade reactions.

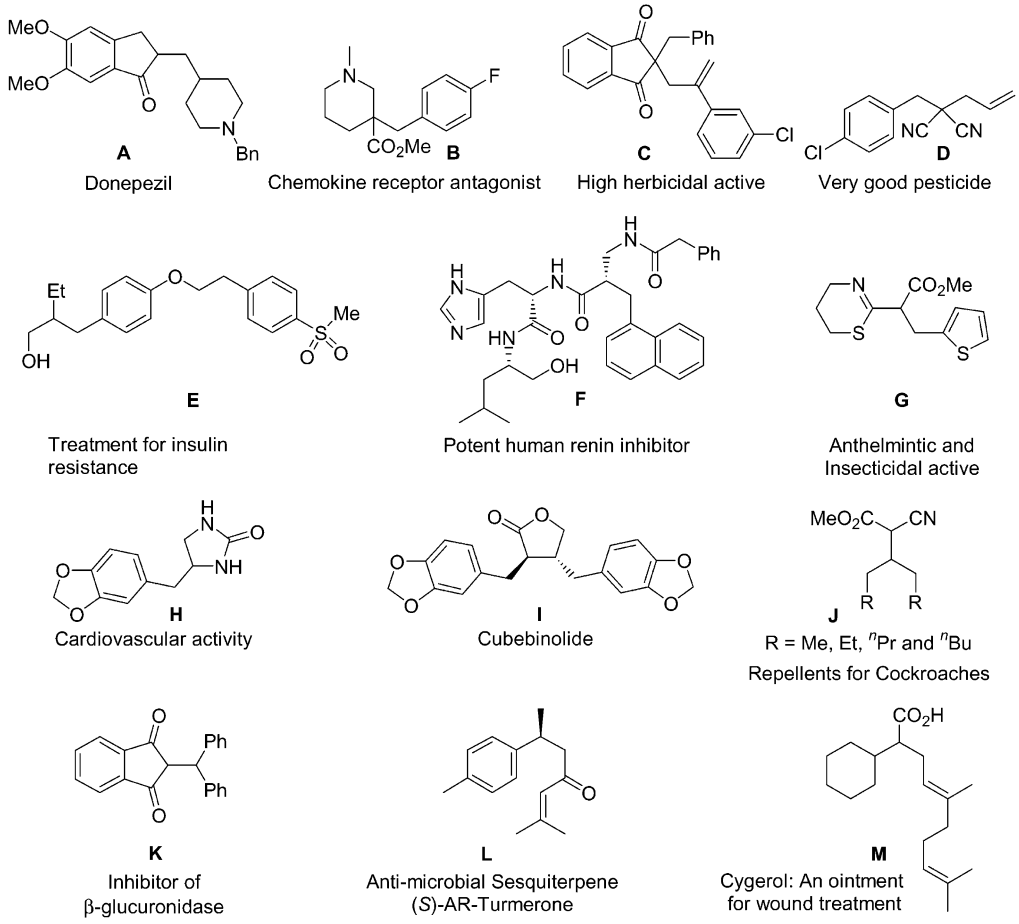


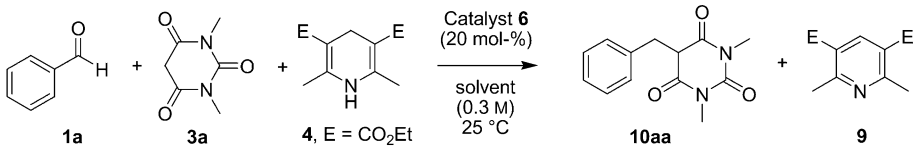
Figure 1. Natural and unnatural products library generated from cascade olefination/hydrogenation and olefination/hydrogenation/alkylation products.

reaction conditions. Among these, the reactions must be modular, wide in scope and high-yielding, generate only inoffensive by-products, and must also be stereospecific (Scheme 1).

As part of our program to engineer direct organocatalytic cascade or domino reactions, and in an extension of our previous work,[2a,2b] here we report one-pot organo- and organometal carbonate-catalysed chemoselective direct cascade olefination/hydrogenation, olefination/hydrogenation/alkylation, hydrogenation/olefination/hydrogenation and olefination/hydrogenation/hydrolysis reaction sequences that produce very useful pharmaceutical drugs, drug intermediates and ingredients of types **10**, **11**, **12**, **13** and **14** from commercially available aldehydes **1**, ketones **2**, CH acids **3**, Hantzsch ester (**4**), alkyl halides **5**, amino acids or amines **6**, K_2CO_3 and Cs_2CO_3 as shown in Scheme 1. Structurally diverse compounds **10**–**13** are attractive intermediates in the synthesis of natural products and in medicinal chemistry, while compounds **10** and **11** have broad utility in pharmaceutical chemistry and are excellent starting materials in natural product synthesis as shown in Figure 1.[4] Hence, their preparation has continued to attract considerable synthetic interest in the form of the development of new methods for their syntheses.

In our reactions we envisioned that amino acids and amines would catalyse the cascade olefination of CH acids **3** with aldehydes **1** or ketones **2** to form substituted 2-alkylidene CH acids **7** and **8**, respectively. These are very reactive intermediates and further undergo chemoselective biomimetic reductions with Hantzsch ester (**4**) to produce hydrogenated products **10** and **12**, respectively, under appropriate reaction conditions. Metal carbonate-catalysed alkylation of the in situ generated products **10** and **12** with alkyl halides **5** furnishes the useful products **11** and **13** in very good yields with interesting selectivity as shown in Scheme 1. Organocatalytic two-carbon homologation

Table 1. Optimization of the direct organocatalytic cascade olefination/hydrogenation reactions of **1a**, **3a** and **4**.[a]



1a + **3a** + **4**, E = CO_2Et → **10aa** + **9**

Entry	Catalyst	Solvent	Ester **4** [equiv.]	Time [h]	% Conv.[b]
1	proline **6a**	EtOH	1.06	2 → 14	99
2	proline **6a**	MeOH	1.06	4 → 6	82
3	proline **6a**	DMF	1.06	3 → 6	99
4	proline **6a**	DMSO	1.06	4 → 6	90
5	proline **6a**	$CHCl_3$	1.06	3 → 6	98
6	proline **6a**	CH_3CN	1.06	2 → 14	99
7	**proline 6a**	**EtOH**	**1.00**	**2**	**98**
8[c]	**proline 6a**	**EtOH**	**1.00**	**8**	**98**
9	proline **6a**	CH_3CN	1.00	2	97
10	proline **6a**	[bmim]BF_4	1.00	2	98
11	proline **6a**	CH_2Cl_2	1.00	8	98
12	proline **6a**	THF	1.00	2	98
13	proline **6a**	Et_2O	1.00	8	98
14[d]	glycine **6b**	EtOH	1.00	3	99
15	pyrrolidine **6c**	EtOH	1.00	6	98
16	piperidine **6d**	EtOH	1.00	2	98
17	morpholine **6e**	EtOH	1.00	6	98
18	benzylamine **6f**	EtOH	1.00	6	98
19	–	**CH_3CN**	**1.00**	**5**	**99**
20[e]	–	CH_3CN	–	48	–
21	–	**H_2O**	**1.00**	**0.25 → 2**	**99**

[a] Experimental conditions: Method **A**: A mixture of **1a** (0.3 mmol), **3a** (0.3 mmol) and catalyst **6** (20 mol-%) were stirred at 25 °C for 2 to 4 h then **4** was added and stirring continued at the same temperature. Method **B**: All reactants **1a**, **3a**, **4** and catalyst **6** were mixed at the same time and stirred at 25 °C. [b] Determined by ^1H NMR spectroscopy. [c] Proline **6a** were taken as 5 mol-%. [d] Product **10aa** were isolated as a 1:1 mixture of keto and enol forms. [e] Knoevenagel product **7aa** did not form.

through cascade olefination/hydrogenation/hydrolysis reactions of aldehydes **1**, Meldrum's acid **3c**, Hantzsch ester (**4**) and acetic acid/triethylamine in ethanol was demonstrated. Additionally we have developed a green synthesis of the highly substituted 1,2,3-triazole **17** through organo-click reactions.

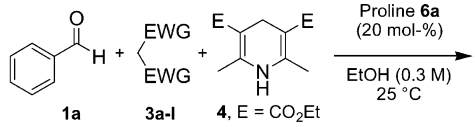
Results and Discussion

Cascade Olefination/Hydrogenation Reactions of Aldehydes 1 with 3 and 4 – Reaction Optimization

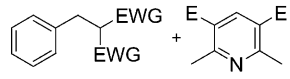
We were pleased to find that the one-pot reaction of benzaldehyde (**1a**), *N*,*N*-dimethylbarbituric acid (**3a**) and Hantzsch ester (**4**) in the presence of a catalytic amount of proline (**6a**) in EtOH at 25 °C for 2 to 14 h furnished the hydrogenated product 5-benzyl-1,3-dimethylpyrimidine-2,4,6-trione (**10aa**)‡ as a single isomer, with 99% conversion (Table 1, Entry 1) [‡ In all compounds denoted **7xy**, **8xy**, **10xy**, **11xyz**, **12xy**, **13xyz** and **14xy**, **x** is incorporated from reactant aldehydes **1** or ketones **2**, **y** is incorporated from the reactant CH acids **3**, and **z** is incorporated from the reactant alkyl halides **5**]. The same reaction, catalysed by proline (**6a**) in EtOH at 25 °C under cascade conditions furnished the product **10aa** with 98% conversion in a shorter reaction time (Table 1, Entry 7), perhaps due to the catalytic nature of the Hantzsch ester (**4**) in the cascade olefination/hydrogenation (O/H) reaction. Interestingly, there is little solvent effect on the proline-catalysed cascade O/H reaction of **1a**, **3a** and **4** in three different type of solvents (protic polar, aprotic polar and aprotic nonpolar) as shown in Table 1, Entries 1–13. The simple amino acid glycine (**6b**) also catalysed the cascade O/H reaction to furnish hydrogenated product **10aa** with 99% conversion as a 1:1 ratio of keto/enol forms (Table 1, Entry 14). The simple amines pyrrolidine (**6c**), piperidine (**6d**), morpholine (**6e**) and benzylamine (**6f**) also catalysed the cascade O/H reaction to furnish hydrogenated product **10aa** with 98–99% conversion as shown in Table 1, Entries 15–18. Interestingly, the cascade O/H reaction of **1a**, **3a** and **4** without catalyst at 25 °C for 5 h also furnished the expected product **10aa** with 99% conversion (Table 1, Entry 19), which is the best demonstration of the catalytic nature of the reagent in cascade reactions. The solvent-promoted one-pot O/H reaction of **1a**, **3a** and **4** in H_2O without catalyst furnished the expected hydrogenated product **10aa** 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 21). The optimized conditions for the cascade O/H reaction of **1a**, **3a** and **4** in CH_3CN, EtOH or H_2O at 25 °C to furnish **10aa** with excellent conversions required the presence of catalytic amounts of amino acid **6a** or piperidine (**6d**) (Entries 7–8 and 16), but not in the cases of Entries 19 and 21.

Following these promising results, we proceeded to investigate the scope and limitations of the cascade O/H reaction with a range of CH acids **3a**–**l** and Hantzsch ester (**4**) with and without catalyst (Table 2 and Table 3). Proline-catalysed (**6a**-catalysed) cascade O/H reactions of benzaldehyde (**1a**) and Hantzsch ester (**4**) with a variety of CH acids **3a**–**k** in EtOH at 25 °C for 2–27 h furnished the expected cascade reductive alkylation products, the 2-benzyl-CH acids **10aa**–**ak**, in very good yields, as shown in Table 2, Entries 1–11.

Table 2. Direct organocatalytic cascade olefination/hydrogenation reactions of **1a** and **4** with a variety of CH acids **3a**–**l**.[a]



1a **3a-l** **4**, E = CO_2Et



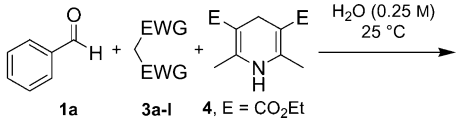
10aa-al **9**

Entry	CH acid **3**	Time [h]	Product	% Yield **10**[b]
1	**3a**	2	**10aa**	98
2	**3b**	5	**10ab**	95
3	**3c**	4	**10ac**	90
4	**3d**	26	**10ad**	88
5	**3e**	5	**10ae**	95
6	**3f**	16	**10af**	85
7	**3g**	12	**10ag**	91
8	**3h**	24	**10ah**	85
9	**3i**	24	**10ai**	85
10	**3j**	7	**10aj**	95
11	**3k**	27	**10ak**	65
12	**3l**	24	**10al**	5

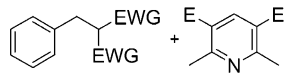
[a] See Experimental Section. [b] Yield refers to the column purified product.

Interestingly, diethyl malonate (**3l**) did not furnish the expected reductive alkylation product **10al** in the proline-catalysed cascade O/H reaction with **1a** and **4** in EtOH, and we also found that **3l** did not undergo olefination reaction either (Table 2, Entry 12). The same reaction in DMSO under proline catalysis conditions furnished only the olefination product **7al** without the expected hydrogenated product **10al** (result not shown in Table 2).

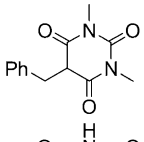
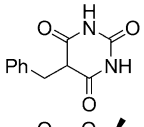
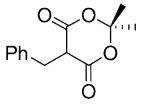
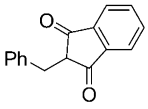
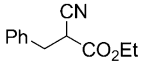
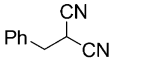
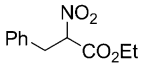
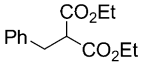
Table 3. Direct water-promoted cascade olefination/hydrogenation reactions of **1a** and **4** with a variety of CH acids **3a**–**l**.[a]



1a **3a-l** **4**, E = CO_2Et



10aa-al **9**

Entry	CH acid **3**	Time [h]	Product	% Conv. **10**[b]
1	**3a**	0.25 → 2		**10aa** 99
2	**3b**	0.5 → 4		**10ab** 99
3	**3c**	1 → 16		**10ac** 85
4	**3d**	3 → 25		**10ad** 40
5[c]	**3f**	3 → 54		**10af** 40
6	**3j**	2 → 25		**10aj** 60
7[c]	**3k**	48		**10ak** <25
8[c]	**3l**	5 → 40		**10al** –

[a] A mixture of **1a** (0.5 mmol) and **3** (0.5 mmol) were stirred at room temperature for 0.25 to 5 h then **4** was added and stirring continued at the same temperature. [b] Determined by ^1H NMR analysis. [c] Olefin formation was very poor.

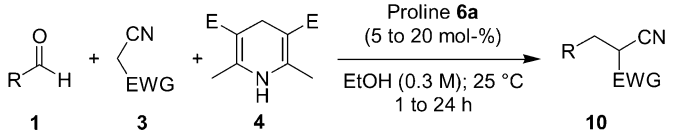
After successful demonstration of one of the sets of optimized reaction conditions (Table 1, Entry 7) for the cascade O/H reaction with a variety of CH acids **3a**–**l**, we decided to investigate the same with other two optimized sets of conditions (cascade reactions promoted by H_2O and Hantzsch ester (**4**)). The selective solvent-promoted one-pot O/H reaction of benzaldehyde (**1a**) and Hantzsch ester (**4**) with a variety of CH acids **3a**–**l** was screened in H_2O at 25 °C without catalysis, which furnished the expected hydrogenated products **10aa**–**ak** in yields ranging from very good to poor as shown in Table 3. Cascade O/H reactions with various CH acids **3** and aldehydes **1** promoted by Hantzsch ester (**4**) furnished the expected cascade products **10** with poor to moderate yields (discussion of the results is in the next section). After testing the autocatalytic nature of the reactions promoted by Hantzsch ester (**4**) and H_2O in one-pot O/H reactions with different CH acids **3** and aldehydes **1** as shown in Table 3, we decided to generate a pharmaceutically useful library of cascade products **10** under proline or piperidine catalysis conditions.

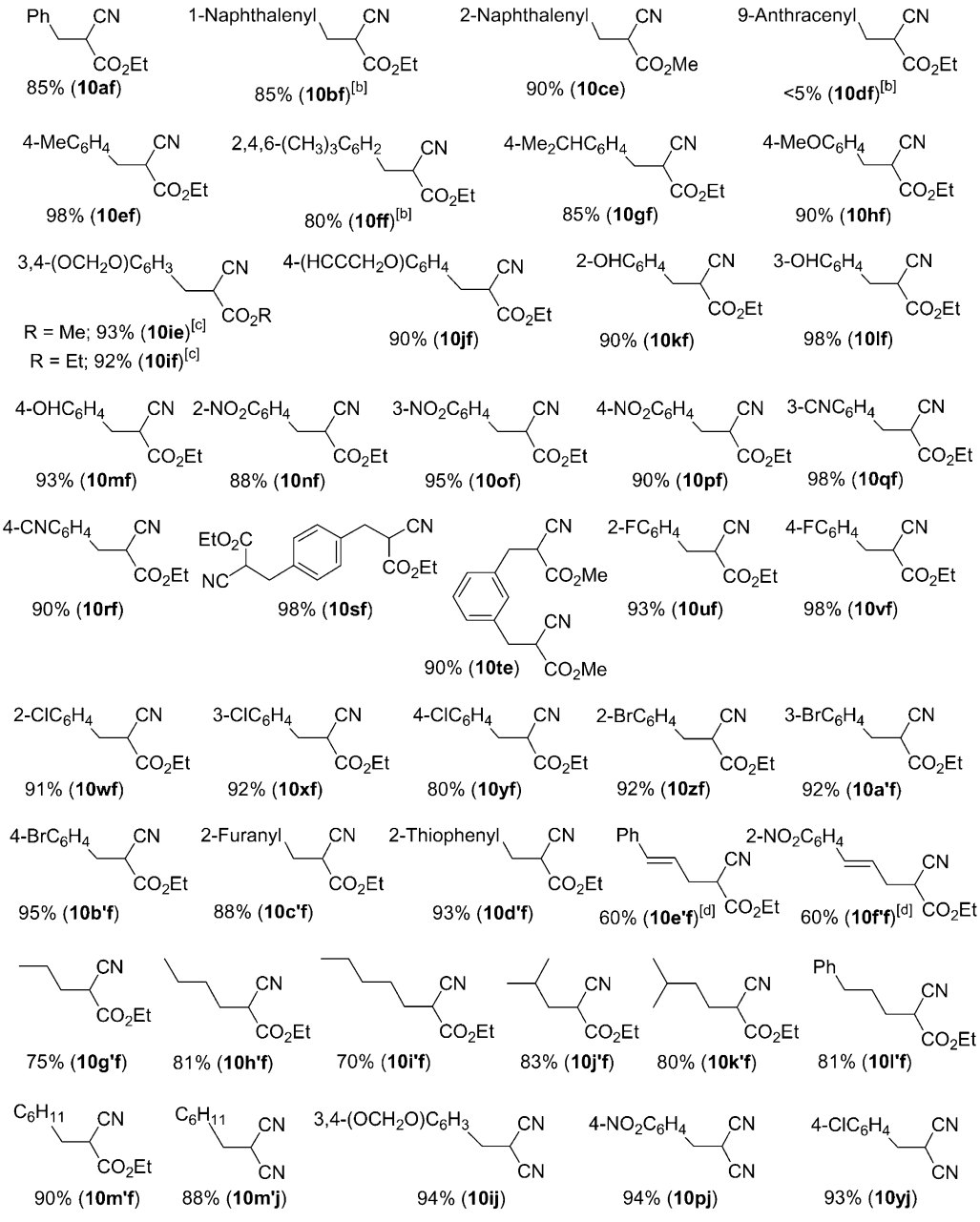
Diversity-Oriented Green Synthesis of Reductive Alkylation Products 10af–10m′f

With an efficient organocatalytic cascade reductive alkylation protocol to hand, the scope of the proline-catalysed cascade O/H reactions was investigated with various aldehydes **1a**–**z**, **1a′**–**m′** and CH acids **3e**–**j** through the generation of a highly useful diversity-oriented library. A series of substituted aromatic, heteroaromatic and aliphatic aldehydes **1a**–**m′** were treated with 1.0 equiv. of methyl cyanoacetate (**3e**), ethyl cyanoacetate (**3f**) or malononitrile (**3j**) and Hantzsch ester (**4**) (1.0 equiv.), with catalysis by 5 to 20 mol-% of proline (**6a**) at 25 °C in EtOH (Table 4). The 2-aryl-2-cyanoacetic acid ethyl esters **10af**–**d′f**, ethyl 2-alkyl-2-cyanoacetates **10e′f**–**m′f** and 2-alkylmalononitriles **10ij**–**m′j** were obtained as single isomers in excellent yields. Catalyst loading for the cascade O/H reactions can be taken from 5 to 20 mol-% without affecting reaction yields, but reaction times vary from 1 to 24 h. Interestingly, both proline- and piperidine-catalysed cascade O/H reactions of ethyl cyanoacetate (**3f**) with naphthalene-1-carbaldehyde (**1b**) at 25 °C in EtOH furnished the reductive alkylation product **10bf** in poor to moderate yields (not shown in Table 4), but the same reaction under DMAP (10 mol-%) catalysis conditions in EtOH at 80 °C furnished the reductive alkylation product **10bf** in a very good yield (Table 4). A similar reaction trend was observed for the synthesis of ethyl 2-cyano-2-(2,4,6-trimethylbenzyl)acetate (**10ff**) from a cascade O/H reaction as shown in Table 4. This may be due to the generation of more steric hindrance in the transition state of the olefin's formation from aldehydes **1b** or **1f** with CH acid **3f** through enamine/iminium catalysis.

The results in Table 4[4a–4p] demonstrate the broad scope of this reductive methodology, covering a structurally diverse group of activated aldehydes **1a**–**m′** and CH acids **3e**–**f** and **3j**, with many of the yields obtained being very good, or indeed better than those of previously published alkylation reactions starting from the corresponding olefins **7** or aldehydes **1**. Cascade O/H reactions of (*E*)-cinnamaldehyde (**1e′**) and 3-(2-nitrophenyl)propenal (**1f′**) with **3f** and

Table 4. Synthesis of chemically diverse libraries of alkyl 2-alkyl-2-cyanoacetates **10** through organocatalysed cascade olefination/hydrogenation reactions.[a]





[a] Yield refers to the column purified product. [b] Reaction stirred at 80 °C for 5-24 h under DMAP-catalysis in EtOH. [c] Reaction stirred at 50 °C for 12 h. [d] Nearly 10-15% of completely reduced products were isolated.

Hantzsch ester (**4**) chemoselectively furnished the hydrogenated esters **10e′f** and **10f′f**, respectively, in good yields (Table 4). The hydrogenated esters ethyl 2-cyano-3-(1-naphthyl)propionate (**10bf**) and ethyl 2-cyano-3-(2-naphthyl)propionate (**10cf**) are important intermediates for the synthesis of potent human renin inhibitors **F**,[4j] while cascade esters ethyl 2-cyano-3-(2-fluorophenyl)propionate (**10uf**) and ethyl 2-cyano-3-(4-fluorophenyl)propionate (**10vf**) are important intermediates for the synthesis of chemokine receptor antagonists **B**,[4h] and ethyl and methyl 3-(benzo-1,3-dioxol-5-

yl)-2-cyanopropionates **10ie** and **10if** are useful synthons for the synthesis of cardiovascular active products **H**[4m] and for the synthesis of cubebinolide **I**.[4n] In addition, ethyl 2-cyano-3-(thiophen-2-yl)propionate (**10d′f**) and its corresponding methyl ester are important intermediates for the synthesis of anthelmintic and insecticidal active products **G**,[4k] while ethyl 2-cyano-3-(4-hydroxyphenyl)propionate (**10mf**) is a useful material for the synthesis of insulin resistance products **E**,[4i] emphasizing the value of this cascade approach.

Diversity-Oriented Green Synthesis of Reductive Alkylation Products 10ac–10n′c

After successful demonstration of the cascade O/H reaction for the library generation of ethyl 2-aryl-2-cyanoacetates **10af**–**d′f** and ethyl 2-alkyl-2-cyanoacetates **10e′f**–**m′f**, we then decided to apply the same synthetic strategy to the green synthesis of 5-aryl-2,2-dimethyl-1,3-dioxane-4,6-diones **10ac**–**d′c** and 5-alkyl-2,2-dimethyl-1,3-dioxane-4,6-diones **10e′c**–**n′c**, which are highly useful materials in chemistry. One of the major application of 5-aryl-2,2-dimethyl-1,3-dioxane-4,6-diones **10ac**–**d′c** and 5-alkyl-2,2-dimethyl-1,3-dioxane-4,6-diones **10e′c**–**n′c** is in the two-carbon homologation of the corresponding aldehydes **1a**–**n′**. Two-carbon homologation is a very important transformation in synthetic organic chemistry, and numerous methods are available, although most involve redox functional group transformations rather than carbon–carbon bond formation.[5] In this regard, the development of two-carbon homologation through carbon–carbon bond formation by the organocatalytic cascade reductive methodology might provide an expedient access to homologated products **10ac**–**n′c** from simple starting materials. Homologated esters **10ac**–**n′c** are attractive intermediates in medicinal chemistry, and their analogues have broad utility in pharmaceutical chemistry[4a–4p] (herbicidal, antidiabetic, analgesic, antiinflammatory and antithrombotics) and in organic synthesis. Hence, new methods for their syntheses have continued to attract considerable interest.

The results given in Table 5 demonstrate the broad scope of this reductive green homologation, covering a structurally diverse group of aldehydes **1a**–**n′** and CH acids **3a**–**c**, with many of the yields obtained being very good, or indeed better than those of previously published homologation reactions starting from the corresponding aldehydes **1a**–**n′** or olefins **7**.[5] A series of substituted aromatic, heteroaromatic and aliphatic aldehydes **1a**–**n′** were treated with 1.0 equiv. of Meldrum's acid (**3c**), *N*,*N*-dimethylbarbituric acid (**3b**) or barbituric acid (**3a**) and Hantzsch ester (**4**) (1.0 equiv.), with catalysis by 5 to 20 mol-% of proline (**6a**) at 25 °C in EtOH or CH_3CN (Table 5). The 5-aryl-2,2-dimethyl-1,3-dioxane-4,6-diones **10ac**–**d′c**, 5-alkyl-2,2-dimethyl-1,3-dioxane-4,6-diones **10e′c**–**n′c** and 5-alkylpyrimidine-2,4,6-triones **10m′b** were obtained as single isomers in excellent yields. Interestingly, the proline-catalysed cascade O/H reaction of Meldrum's acid (**3c**) with 2-hydroxybenzaldehyde (**1k**) and Hantzsch ester (**4**) at 25 °C in EtOH furnished the unexpected cascade olefination/hydrogenation/hydrolysis (O/H/H) product – monoethyl 2-(2-hydroxybenzyl)malonate (**10kn**) – in a very good yield [Table 5 and Eq. (1)]. The same reaction in MeOH also furnished the unexpected cascade O/H/H product monomethyl 2-(2-hydroxybenzyl)malonate (**10km**) in a very good yield as shown in Table 5 and Eq. (1), though the same proline-catalysed cascade O/H reaction of Meldrum's acid (**3c**) with 3-hydroxybenzaldehyde (**1l**) or 4-

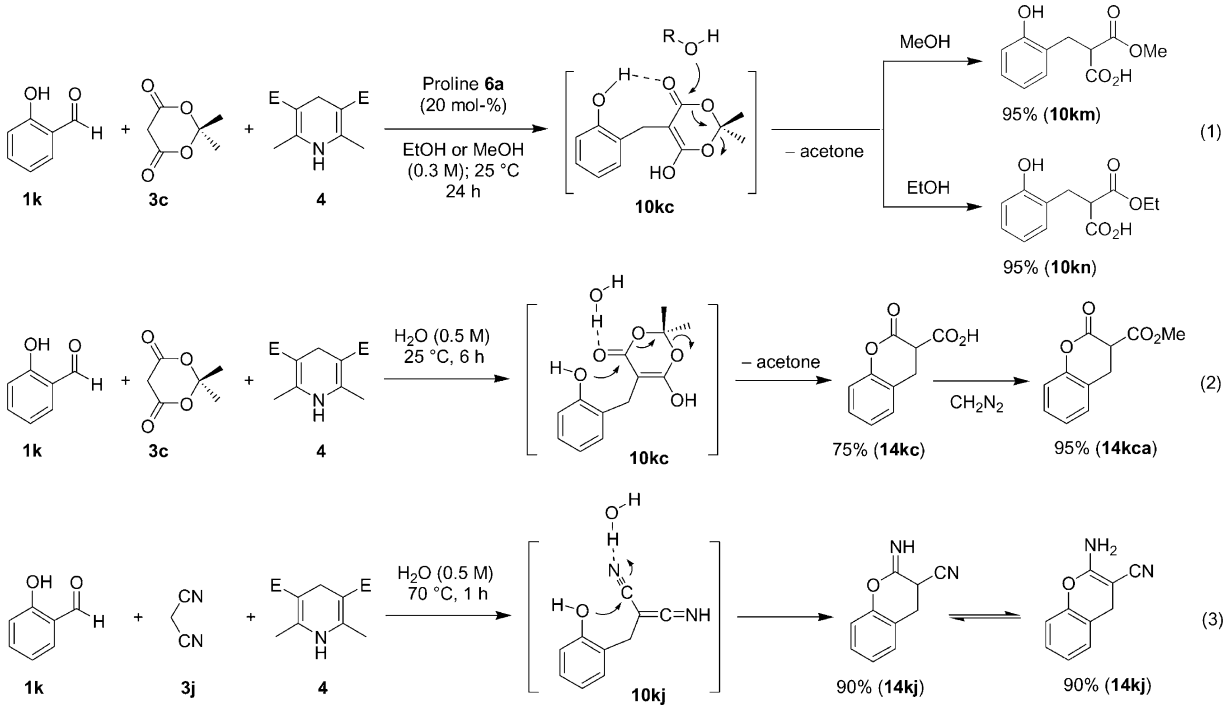
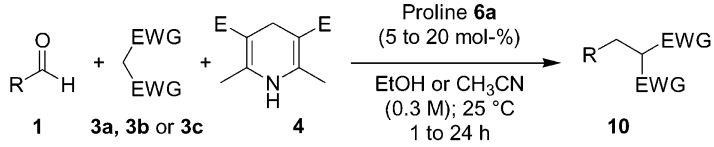
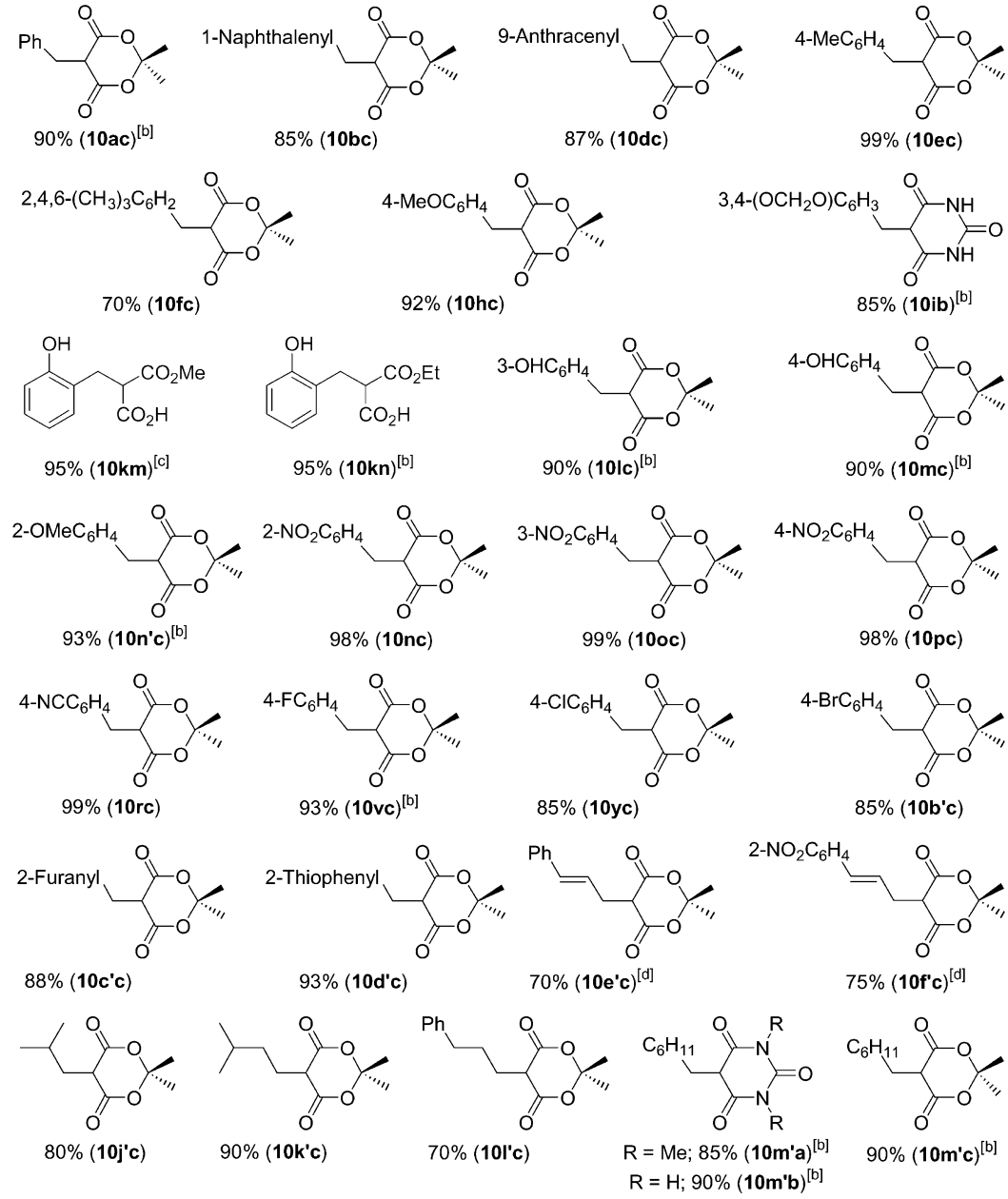


Table 5. Synthesis of chemically diverse libraries of 5-alkyl-2,2-dimethyl-1,3-dioxane-4,6-diones **10** through organocatalysed cascade olefination/hydrogenation reactions.[a]





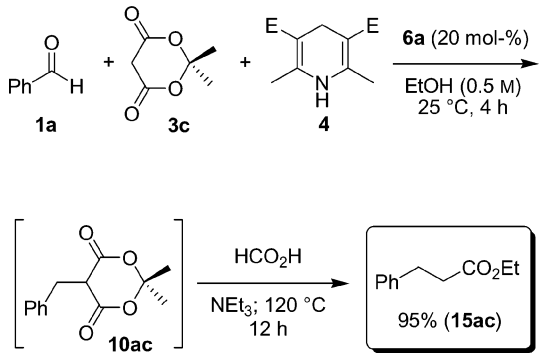
[a] Yield refers to the column purified product. [b] EtOH used as solvent. [c] MeOH used as solvent. [d] Reaction performed in CH_2Cl_2 and nearly 15% of completely reduced products were isolated.

hydroxybenzaldehyde (**1m**) and Hantzsch ester (**4**) at 25 °C in EtOH furnished the expected cascade O/H products **10lc** and **10mc**, respectively, in very good yields as shown in Table 5.

Interestingly, the water-promoted cascade O/H reaction of Meldrum's acid (**3c**) with 2-hydroxybenzaldehyde (**1k**) and Hantzsch ester (**4**) at 25 °C in water furnished the unexpected cascade O/H/H product 2-oxochroman-3-carboxylic acid (**14kc**) in a good yield [Eq. (2)]. In addition, the water-promoted cascade O/H reaction of malononitrile (**3j**) with 2-hydroxybenzaldehyde (**1k**) and Hantzsch ester (**4**) at 70 °C in water furnished the unexpected cascade O/H/H product

2-amino-4*H*-chromene-3-carbonitrile (**14kj**) in a very good yield [Eq. (3)]. Formation of the unexpected cascade O/H/H products **10km**, **10kn**, **14kc** and **14kj** from **1k**, **3c**, **3j** and **4** with and without proline catalysis in MeOH, EtOH and H_2O, respectively, can be explained as shown in Eq. (1)–(3). Inter- and intramolecular hydrolysis of the cascade O/H products **10kc** and **10kj** generated in situ by solvents such as MeOH/EtOH or H_2O gives the cascade O/H/H products **10km**, **10kn**, **14kc** and **14kj**, respectively. These two different types of hydrolysis might possibly be due to the nucleophilic natures of the alcoholic solvents and the possibility of additional weak interactions in water [see Eq. (1)–(3)].

5-(4-Cyanobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**10rc**) is an important intermediate for herbicidal and antithrombotic[4c] chemicals and the cascade ester 5-[(anthracen-9-yl)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**10dc**) is a very useful intermediate for the preparation of dienophile scavengers,[4d] while 5-(cyclohexylmethyl)pyrimidine-2,4,6-trione (**10m′b**) shows narcotizing properties,[4p] emphasizing the value of this reductive homologation approach. Interestingly, the cascade O/H product 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (**10ac**) was converted into the two-carbon homologated ester ethyl 3-phenylpropionate (**15ac**) by a cascade O/H/H sequence in good yield with HCO_2H/NEt_3 in one-pot fashion as shown in Scheme 2.



Scheme 2. Direct organocatalytic two-carbon homologation through a one-pot cascade olefination/hydrogenation/hydrolysis reaction.

Diversity-Oriented Green Synthesis of Reductive Alkylation Products 11

In view of the results of the proline-catalysed three- and four-component O/H and O/H/H reactions with various aldehydes **1a**–**n′** and CH acids **3a**–**l**, we also engineered a novel proline/K_2CO_3-catalysed, one-pot, four-component O/H/A reaction of aldehydes **1**, ethyl cyanoacetate (**3f**), or malononitrile (**3j**), Hantzsch ester (**4**) and alkyl halides **5a**–**e** (Table 6). Highly substituted cyano esters **11**, each containing a quaternary carbon, were constructed in good yields with various substituents as shown in Table 6, this process being the first example of the utility of the proline/K_2CO_3 combination in green catalysis.

Here we have demonstrated a direct organo/K_2CO_3-catalytic double-alkylation approach to the synthesis of highly substituted cyano esters **11kfc**–**mfc** in good yields in a single step (Table 6, Entries 7–9). We have also demonstrated the double-cascade O/H/A reaction with benzene-1,3-dicarbaldehyde (**1t**) with **3f**, **4** and **5e** under proline/K_2CO_3 catalysis conditions as shown in Table 6, Entry 15. The one-pot cyano ester products **11** have direct applications in pharmaceutical and agricultural chemistry.[4a–4p] As examples, among the cascade O/H/A generated products, ethyl 2-(4-chlorobenzyl)-2-cyanopropionate (**11yfa**) is antiinflammatorily active,[4b] ethyl 2-(2-chlorobenzyl)-2-cyanobutyrate (**11wfb**) is analgesically active,[4b] and 2-allyl-2-(4-chlorobenzyl)malononitrile (**11yjc**, **D**) is very good pesticide, which showed 100% control against *Musca domestica* (German cockroach).[4o]

Observation of Transesterification in Cascade O/H/A Reactions

As shown in Table 6, Entries 13 and 14, cascade O/H/A reactions of **1a**, **3g**, **4** and **5c**/**5d** in DMSO solvent under proline/K_2CO_3 catalysis conditions furnished the expected one-pot products **11agc** and **11agd** in good yields. Interestingly, the same procedure in EtOH as solvent furnished the one-pot transesterification products **11afc** and **11afd** in good yields, as shown in Scheme 3. This is the best demonstration of the biomimetic transesterification[6] of highly functionalized allyl esters **11agc** and **11agd** under mild basic conditions and is also first observation in organocatalysis.

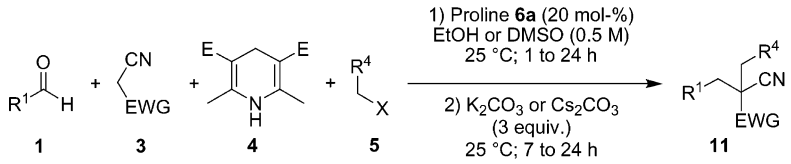
One-Pot Synthesis of Highly Active Herbicidal Products from Direct Cascade O/H/A Reactions

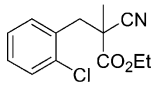
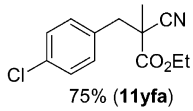
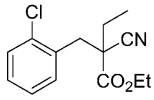
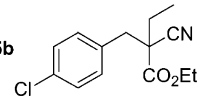
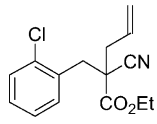
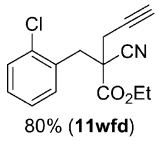
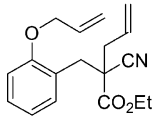
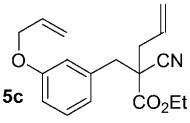
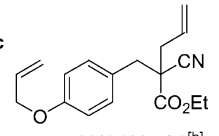
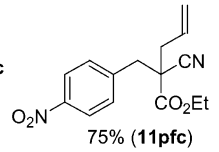
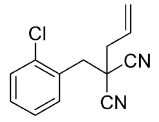
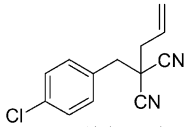
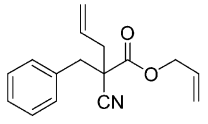
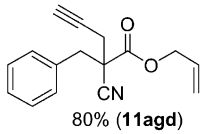
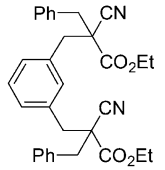
To show more direct applications of cascade O/H/A reactions to pharmaceutical chemistry, here we present the direct one-step synthesis of highly active herbicidal products **11adf** and **11o′df** in very good yields from simple starting materials (**1a** or **1o′**, **3d**, **4** and **5f**) under proline/K_2CO_3 catalysis conditions at room temperature as shown in Scheme 4. The developed cascade O/H/A methodology can be utilized to develop the diversity-oriented library of analogues of herbicidal products **11adf** in very good yields in comparison with the two-step synthesis demonstrated by Mitsubishi Kasei Corporation, Japan in their patent.[4a,4f]

Organocatalytic Cascade Hydrogenation/Olefination/Hydrogenation Reactions

List et al. recently demonstrated the amine/acid-catalysed hydrogenation of α,β-unsaturated aldehydes **1e′** and **1f′** with Hantzsch ester (**4**) to furnish the saturated aldehydes **1l′** and **1p′**, respectively, in good yields.[7] Here we utilized the List technique to obtain the saturated aldehydes **1l′** and **1p′** in situ from α,β-unsaturated aldehydes **1e′** and **1f′**, and further allowed them to react with CH acid **3** and Hantzsch ester (**4**) to generate the highly functionalized CH acids **10** in good yields in one-pot fashion. Morpholine/CF_3CO_2H-catalysed hydrogenation of *trans*-cinnamaldehyde (**1e′**) in

Table 6. Synthesis of chemically diverse libraries of analgesic and antiinflammatory cyano esters **11** through organo/metal carbonate-catalysed cascade olefination/hydrogenation/alkylation reactions.[a]



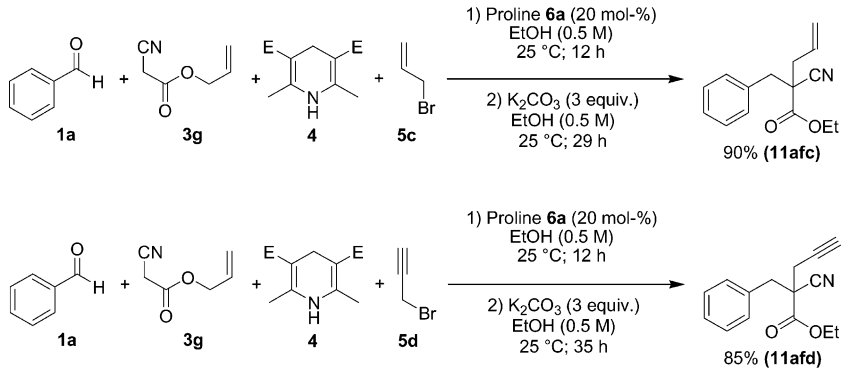
Entry	Solvent/M_2CO_3	R^4CH_2X **5**	Product **11**
1	EtOH/K_2CO_3	CH_3I **5a**	 65% (**11wfa**)
2	EtOH/K_2CO_3	CH_3I **5a**	 75% (**11yfa**)
3	EtOH/K_2CO_3	CH_3CH_2Br **5b**	 65% (**11wfb**)
4	EtOH/K_2CO_3	CH_3CH_2Br **5b**	 60% (**11yfb**)
5	EtOH/K_2CO_3	$H_2C{=}CHCH_2Br$ **5c**	 80% (**11wfc**)
6	EtOH/K_2CO_3	$HCCCH_2Br$ **5d**	 80% (**11wfd**)
7	EtOH/K_2CO_3	$H_2C{=}CHCH_2Br$ **5c**	 80% (**11kfc**)[b]
8	EtOH/K_2CO_3	$H_2C{=}CHCH_2Br$ **5c**	 85% (**11lfc**)[b]
9	EtOH/K_2CO_3	**5c**	 83% (**11mfc**)[b]
10	EtOH/K_2CO_3	**5c**	 75% (**11pfc**)
11	EtOH/K_2CO_3	**5c**	 95% (**11wjc**)
12	DMF/Cs_2CO_3	**5c**	 93% (**11yjc**)
13	DMSO/K_2CO_3	**5c**	 90% (**11agc**)
14	DMSO/K_2CO_3	**5d**	 80% (**11agd**)
15	EtOH/K_2CO_3	$PhCH_2Br$ **5e**	 60% (**11tfe**)

[a] See Experimental Section and yield refers to the column purified product. [b] Product obtained from olefination/hydrogenation/*C*-alkylation/*O*-alkylation sequence.

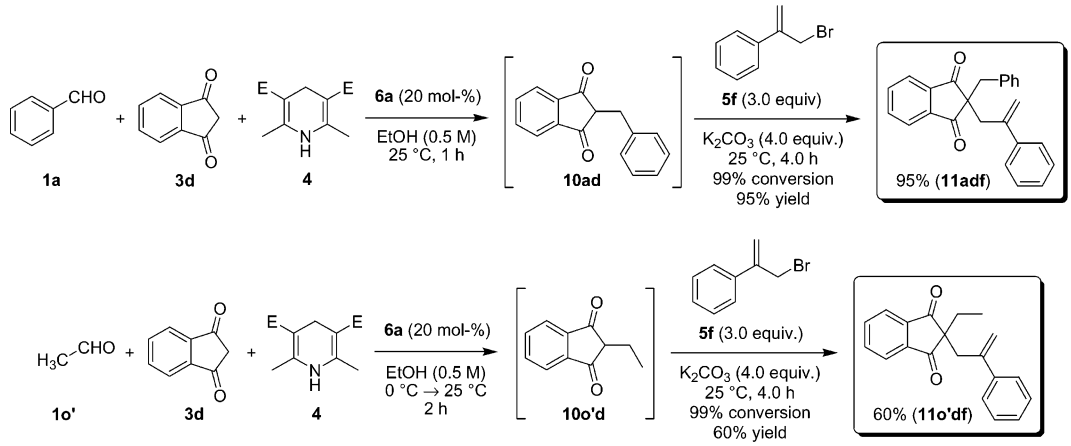
the presence of 1.0 equiv. of Hantzsch ester (**4**) in THF at 25 °C furnished 3-phenylpropionaldehyde (**1l′**), which on treatment with 1.0 equiv. each of Meldrum's acid (**3c**) and Hantzsch ester (**4**) at 25 °C in the same solvent furnished the cascade H/O/H product **10l′c** in 50% yield as shown in Scheme 5. The same reaction sequence with *trans*-2-nitrocinnamaldehyde (**1f′**) also furnished the cascade H/O/H product **10p′c** in 70% yield as shown in Scheme 5. Combination of amine/acid- and self-catalysed cascade hydrogenation reactions will surely have much impact on synthetic sequences utilized in the total synthesis of natural products.

Cascade Olefination/Hydrogenation Reactions of Ketones 2 with 3 and 4 – Reaction Optimization

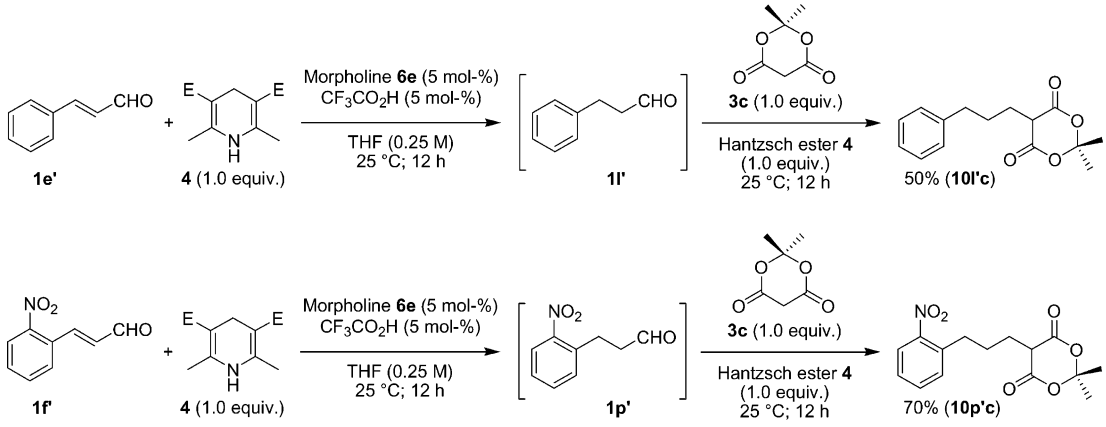
After successful demonstration of the amino acid- and metal carbonate-promoted cascade O/H, O/H/A, O/H/A/



Scheme 3. Observation of transesterification in organo-/metal carbonate-catalysed cascade olefination/hydrogenation/alkylation reactions.



Scheme 4. Synthesis of highly active herbicidal products through direct one-pot organo-/metal carbonate-catalysed cascade olefination/hydrogenation/alkylation reactions.



Scheme 5. Direct organocatalysed one-pot cascade hydrogenation/olefination/hydrogenation reactions.

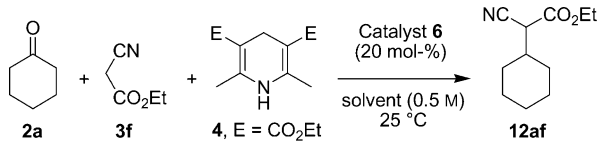
TE, H/O/H and O/H/H reactions for the library generation of highly useful products **10** and **11** from aldehydes **1**, CH acids **3**, Hantzsch ester (**4**) and alkyl halides **5**, we then decided to apply the same cascade strategy for the generation of cascade products **12** and **13**, which are highly useful materials in medicinal chemistry, from the less reactive ketones **2**, CH acids **3**, Hantzsch ester (**4**) and alkyl halides **5**. Cascade products **12** and **13** are attractive intermediates in medicinal chemistry, and their analogues have broad utility both in pharmaceutical chemistry[4q–4z] (insect repellents, dental adhesives, CRF antagonists, antispasmodics, antiulcer agents, drugs for skin diseases, against tuberculosis and leprosy bacteria, and wound healing etc.) and in organic synthesis.

We found that the amino acid proline (**6a**) readily catalyses the olefination of cyclohexanone (**2a**) with the CH acid ethyl cyanoacetate (**3f**) to furnish the active olefin **8af**, which on treatment with Hantzsch ester (**4**) in MeOH at

25 °C for 24 h produced the hydrogenated product **12af** in very good yield (Table 7, Entry 1). The same reaction catalysed by L-proline (**6a**) in protic solvents at 25 °C under cascade conditions furnished the product **12af** in 90 to 95% yields (Table 7, Entries 1–3). The use of polar aprotic solvents (DMF and DMSO) gave yields similar to those obtained in the reactions in MeOH and EtOH (Table 7, Entries 4–7). Interestingly, proline-catalysed cascade O/H reactions with ketones **2** are solvent-dependent (Table 7), unlike the same reactions with aldehydes **1** (see Tables 1, 2, 3, 4, 5, and 6), which may be due to the less reactive nature of ketones **2**. The simple amino acid glycine (**6b**) also catalysed the cascade O/H reaction to furnish cascade product **12af** in 72% yield (Table 7, Entry 10). The simple amines pyrrolidine (**6c**), piperidine (**6d**), morpholine (**6e**) and benzylamine (**6f**) also catalysed the cascade O/H reaction at 25 °C for 48 h to furnish the hydrogenated product **12af** in 90% yield as shown in Table 7, Entries 11–14. Interestingly, the cascade O/H reaction of **2a**, **3f** and **4** in the absence of catalyst at 25 °C for 48 h furnished the expected product **12af** in 80% and 75% yields in EtOH and DMSO solvents, respectively (Table 7, Entries 15 and 16). This is an excellent demonstration of the self-catalytic nature of reagents in cascade reactions, and also of mimicking of the hydrogenation/dehydrogenation of pyridine nucleotide-linked dehydrogenases.[8] The optimum conditions (Entries 3–5 and 11–14) involved the use of catalyst, amino acid **6a** or amines **6c**–**f** in cascade O/H reactions of **2a**, **3f** and **4** in EtOH, DMF or DMSO at 25 °C to furnish **12af** in very good yields.

Having obtained this preliminary understanding, we proceeded to investigate the scope and limitations of the cascade O/H reaction of cyclohexanone **2a** with a range of active CH acids **3a**–**o** and Hantzsch ester (**4**) under proline catalysis conditions in DMSO (Table 8). Even though cascade O/H reactions gave good yields in EtOH (Table 7), here we used DMSO or DMF as solvent because of the poorer solubilities of the reactants in EtOH. As shown in

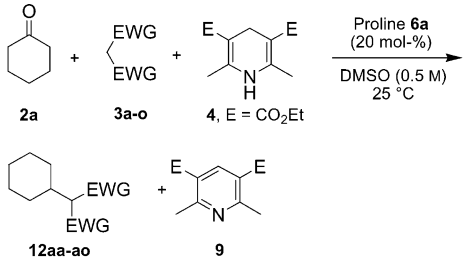
Table 7. Optimization of the direct organocatalytic cascade olefination/hydrogenation reactions of **2a**, **3f** and **4**.[a]



Entry	Catalyst	Solvent	Time [h]	% Yield[b]
1	proline **6a**	MeOH	24	90
2	proline **6a**	EtOH	24	93
3	proline **6a**	EtOH	36	95
4	proline **6a**	DMF	24	86
5	proline **6a**	DMSO	24	86
6	proline **6a**	$CHCl_3$	24	48
7	proline **6a**	CH_3CN	24	68
8	proline **6a**	[bmim]BF_4	48	50
9	proline **6a**	THF	48	–
10	glycine **6b**	EtOH	48	72
11	pyrrolidine **6c**	EtOH	48	90
12	piperidine **6d**	EtOH	48	90
13	morpholine **6e**	EtOH	48	90
14	benzylamine **6f**	EtOH	48	90
15	–	EtOH	48	80
16	–	DMSO	48	75
17	–	H_2O	48	15

[a] Experimental conditions: All reactants (**2a**, **3f**, **4**) and catalyst **6** were mixed at the same time in solvent and stirred at room temperature. [b] Yield refers to the column purified product.

Table 8. Direct organocatalytic cascade olefination/hydrogenation reactions of **2a** and **4** with a variety of CH acids **3a**–**o**.[a]



Entry	CH acid **3**	Time [h]	Product	% Yield **12**[b]
1	**3a**	24	**12aa**	99
2	**3b**	12	**12ab**	90
3	**3c**	24	**12ac**	99
4	**3d**	48	**12ad**	95
5	**3e**	24	**12ae**	99
6	**3f**	24	**12af**	86
7	**3i**	60	**12ai**	60
8	**3j**	19	**12aj**	90
9	**3o**	24	**12ao**	93

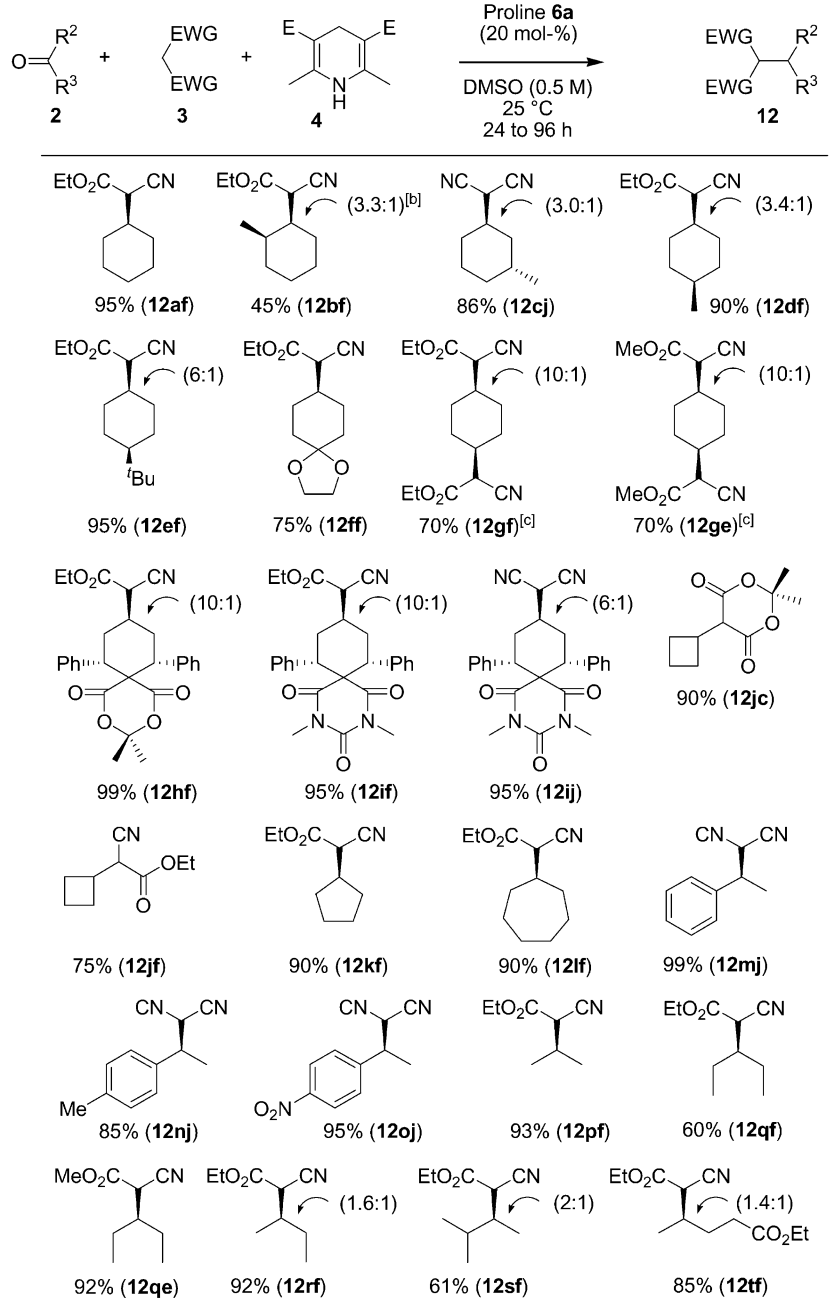
[a] See Experimental Section. [b] Yield refers to the column purified product.

Table 8, acyclic CH acids **3e**–**j** furnished cascade products **12ae**–**aj** in smaller yields than cyclic CH acids **3a**–**d** and **3o** in cascade O/H reactions, possibly due to the difference in acid strength and HOMO–LUMO energy gap between Hantzsch ester (**4**) and the olefins **8** generated in situ. Cyclic CH acids **3a**–**d** and **3o** have higher acid strengths than acyclic CH acids **3e**–**j**, and the same acidic property also continues in olefins **8**. Cascade products **12aa**–**ao** have many applications in pharmaceutical chemistry.[4q–4z]

Diversity-Oriented Green Synthesis of Reductive Alkylation Products 12af–12tf

With an ideal cascade reductive alkylation protocol to hand, the scope of the proline-catalysed cascade O/H reactions was investigated with various ketones **2a**–**t** and CH acids **3e**–**j** in the generation of the highly useful diversity-oriented library **12**. The results in Table 9 demonstrate the broad scope of this reductive green methodology, covering

Table 9. Synthesis of chemically diverse libraries of **12** through organocatalysed cascade olefination/hydrogenation reactions of **2**, **3** and **4**.[a]



[a] Yield refers to the column purified product. [b] Ratio determined by ^{1}H and ^{13}C NMR analysis. [c] Cyclohexane-1,4-dione **2g** is starting material for these products.

a structurally diverse group of less reactive ketones **2a**–**t** and CH acids **3e**–**j**, with many of the yields obtained being very good, or indeed better than those of previously published reactions starting from the corresponding olefins **8** or ketones **2**. The cascade O/H reaction of (*R*)-3-methylcyclohexanone (**2c**), malononitrile (**3j**) and Hantzsch ester (**4**) furnished the regioselective chiral hydrogenated ester (1*R*,3*R*)-2-(3-methylcyclohexyl)malononitrile (**12cj**) in 3.0:1 ratio in 86% yield, the cascade O/H reaction of 4-methylcyclohexanone (**2d**), ethyl cyanoacetate (**3f**) and Hantzsch ester (**4**) furnished the regioselective hydrogenated ester *cis*-**12df** in 3.4:1 ratio in 90% yield (Table 9, Entry 4), the cascade O/H reaction of cyclohexane-1,4-dione (**2g**) with CH acids **3e** or **3f** and Hantzsch ester (**4**) under proline catalysis conditions furnished the double cascade products **12ge** and **12gf** in good yields with high selectivity as shown in Table 9, and the cascade O/H reactions of highly substituted cyclohexanones **2h** or **2i** with CH acids **3f** or **3j** and Hantzsch ester (**4**) under proline catalysis conditions furnished the cascade products **12hf**, **12if** and **12ij** in good yields and with high selectivity as shown in Table 9. The structures and regiochemistry of cascade O/H products **12bf**–**ij** were confirmed by X-ray structure analysis on **12if** as shown in Figure 2.[9]

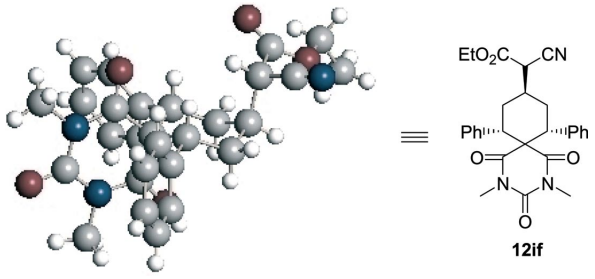


Figure 2. Crystal structure of ethyl cyano-(2,4-dimethyl-1,3,5-trioxo-7,11-diphenyl-2,4-diazaspiro[5.5]undec-9-yl)acetate (**12if**).

The observed high regioselectivity in cascade **12bf**–**ij** products can be explained as shown in Figure 3. Here, the approach of the hydride source [Hantzsch ester (**4**)] to olefin **8bf**–**ij** is the main controlling factor, rather than thermodynamic stability of the resulting hydrogenated products **12bf**–**ij**. The approach of the Hantzsch ester (**4**) towards olefin **8if** through the equatorial position is more favourable than through the axial position, perhaps due to the existence of more steric hindrance in an axial approach. As shown in Figure 3, steric strain control (SSC) is the main controlling factor rather than product stability control (PSC) in biomimetic cascade reductions, as the thermodynamically stable isomer *cis*-**12if** is formed as a minor product. This selectivity trend can be easily understood in terms of the approach of bulk hydride source **4** to olefins **8**.

Simple cyclic ketones cyclobutanone (**2j**), cyclopentanone (**2k**) and cycloheptanone (**2l**) reacted with **3** and **4** under amino acid catalysis conditions to furnish the expected cascade O/H products **12jc**, **12jf**, **12kf** and **12lf** in very good yields as shown in Table 9. Acyclic ketones **2m**–**t** also participated in the three-component cascade O/H reaction with **3** and **4** to furnish the cascade products **12mj**–**12tf** in very good yields as shown in Table 9. The cascade O/H reactions produced hydrogenated products **12bf**, **12cj**, **12df**, **12ef** and **12sf** with good regioselectivities in comparison with $NaBH_4$ reduction of corresponding olefins,[10] as shown in Table 9.

The hydrogenated ester **12af** and its analogues are important intermediates for the synthesis of cygerol (wound treatment ointment),[4u] perfumes, anti-ulcer agents and drugs for skin diseases, cascade esters **12ge** and **12gf** are useful materials for the synthesis of alignment films for liquid crystal displays,[4y] cascade esters **12jc** and **12jf** are useful intermediates for the synthesis of prostaglandin analogues,[4z] cascade products **12mj**–**oj** are useful intermediates for the synthesis of the antimicrobial sesquiterpene (*S*)-arturmerone (**L**) and analogues,[4w] cascade ester **12tf** has been used as an intermediate in the synthesis of ophiobolin natural products,[4v] cascade products **12kf**, **12sf** and analogues have been used for the preparation of active antispasmodics,[4t] and cascade hydrogenated product **12qe** has been used in the USA as a repellent for cockroaches[4q], emphasizing the value of this cascade approach.

Diversity-Oriented Green Synthesis of Reductive Alkylation Products 13

With pharmaceutical applications in mind, we extended the three-component cascade O/H reactions to provide a novel proline/Cs_2CO_3- and proline/K_2CO_3-catalysed four-

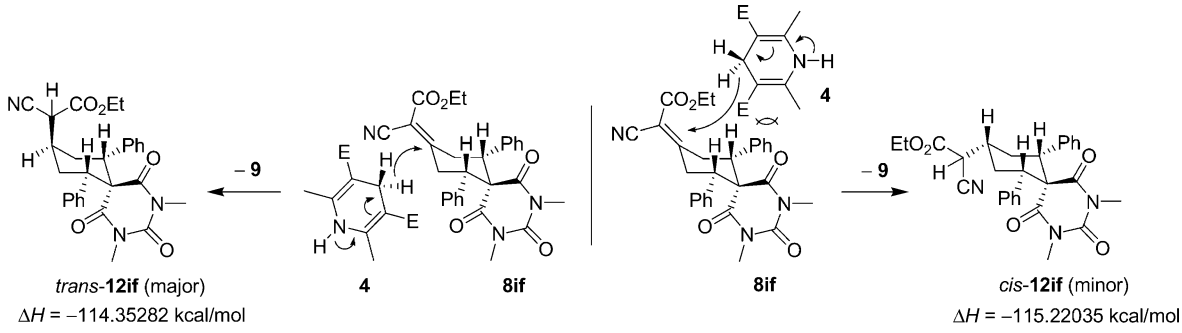
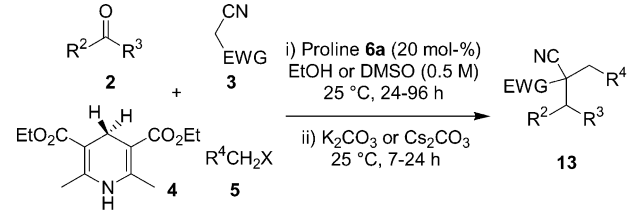


Figure 3. Observation of steric strain control (SSC) as dominating factor rather than product stability control (PSC) in biomimetic cascade reductions.

component one-pot O/H/A reaction of ketones **2**, CH acids **3** and Hantzsch ester (**4**) with various alkyl halides **5a**–**g** (Table 10). 2,2-Disubstituted ethyl cyanoacetates and malononitriles **13** were constructed in good yields with various substituents as shown in Table 10. Here we have demonstrated a direct organocatalytic approach to the synthesis of key intermediates of the pharmaceutical drug cygerol (**M**; see Figure 1) in a single step (Table 10, Entries 10–12). Decyanation followed by hydrolysis of **13aeg** or **13afg** furnished the cyclohexylgeranylacetic acid (**M**), useful for wound healing as demonstrated by Joseph and George in their patent.[4u]

Table 10. Synthesis of chemically diverse libraries of **13** through organocatalysed cascade olefination/hydrogenation/alkylation reactions of **2**, **3**, **4** and **5**.[a]

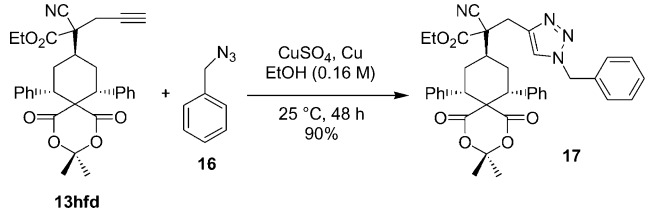


Entry	Product	Entry	Product
1[c]	65% (**13afa**)	8[d]	(10:1)[b] 85% (**13hfd**)
2[c]	65% (**13afb**)	9[d]	(10:1)[b] 85% (**13ifd**)
3[c]	80% (**13afc**)	10[e]	75% (**13afg**)
4[c]	80% (**13afd**)	11[e]	65% (**13aeg**)
5[c]	99% (**13afe**)	12[e]	(3:1) 65% (**13dfg**)
6[d]	80% (**13ajd**)		
7[d]	90% (**13kfd**)		

[a] Yield refers to the column purified product. [b] Ratio determined by ^{1}H and ^{13}C NMR analysis. [c] Alkylation performed under K_2CO_3/EtOH conditions. [d] Alkylation performed under K_2CO_3/DMSO conditions. [e] Alkylation performed under Cs_2CO_3/DMF conditions.

Huisgen Cycloaddition Reactions on Cascade O/H/A Products

Huisgen's 1,3-dipolar cycloadditions[11a] are important ring-fusion processes, the most useful member of this class arguably being the cycloaddition of azides and alkynes to give triazoles. The Huisgen cycloaddition of the propargyl-substituted cascade product **13hfd** with benzyl azide **16** under $CuSO_4$/Cu catalysis conditions furnished the regiospecifically 1,4-disubstituted 1,2,3-triazole **17** in very good yield as shown in Scheme 6. 1,2,3-Triazoles have found wide applications in biology, chemistry and materials science,[11b–11d] so it is important to develop new and more efficient cascade approaches to develop a diverse array of starting materials **13** and **16** for the library generation of 1,2,3-triazoles **17**, which can be tested for pharmaceutical applications. In this respect our cascade O/H/A reactions can deliver a diversity-oriented library of click-chemistry precursors.

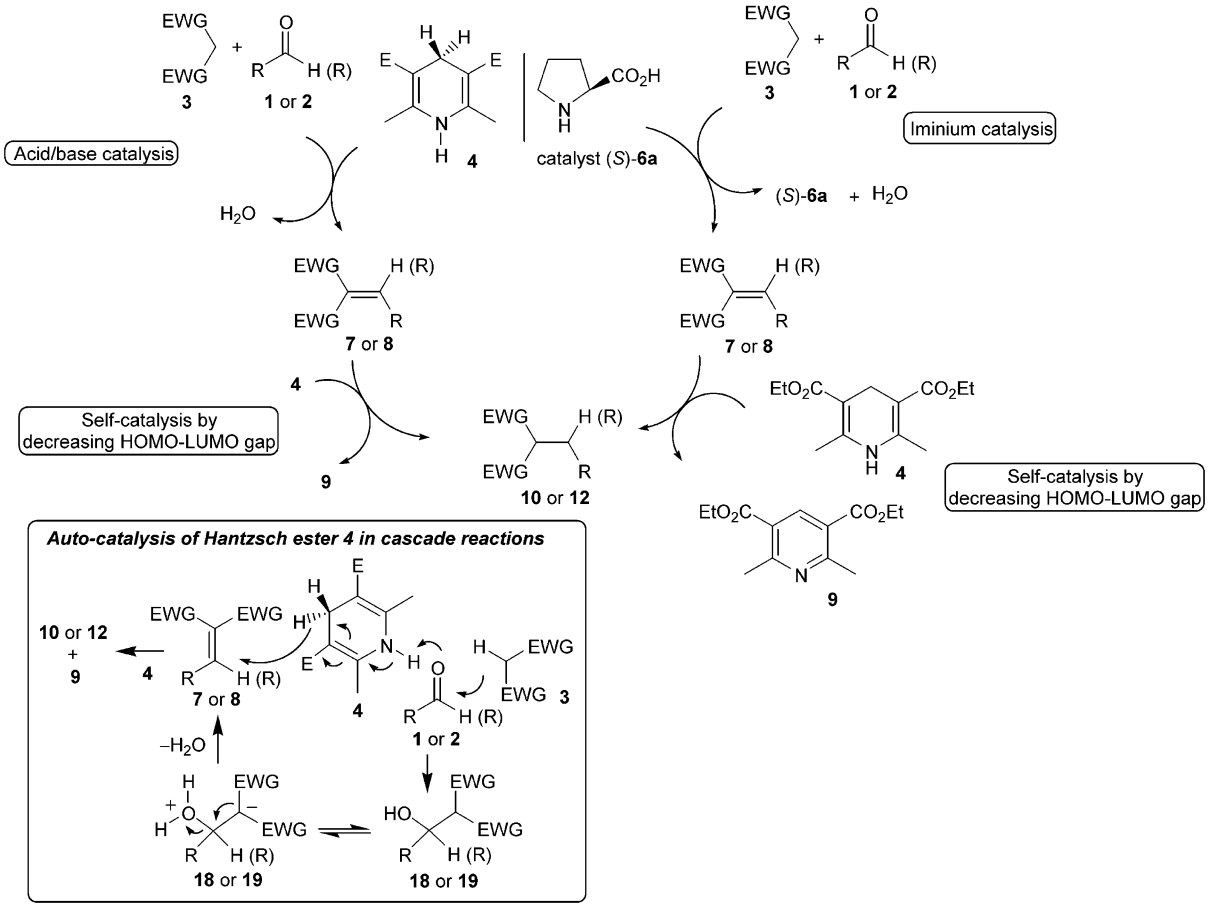


Scheme 6. Regiospecific synthesis of highly functionalized 1,4-disubstituted 1,2,3-triazole **17**.

Mechanistic Insights

The possible reaction mechanism for proline-, self- and auto-catalysed regio- and chemoselective synthesis of cascade products **10** and **12** through reactions of aldehyde **1** or ketone **2**, CH acid **3**, and Hantzsch ester (**4**) is illustrated in Scheme 7. This double catalytic cascade reaction is a three-component reaction involving aldehyde **1** or ketone **2**, CH acid **3**, Hantzsch ester (**4**) and a simple catalyst amine or amino acid **6a**, which is capable of catalysing each step of this double catalytic cascade reaction. In the first step (Scheme 7), the catalyst **6a** activates component **1/2**, most probably by iminium ion formation, and this then selectively adds to the CH acid **3** through a Mannich- and a retro-Mannich-type reaction to generate active olefin **7/8**.[2] The following second step is a biomimetic hydrogenation of active olefin **7/8** by Hantzsch ester (**4**) to produce **10/12** through self-catalysis by decreasing the HOMO–LUMO energy gaps between **4** and **7/8**.[2d]

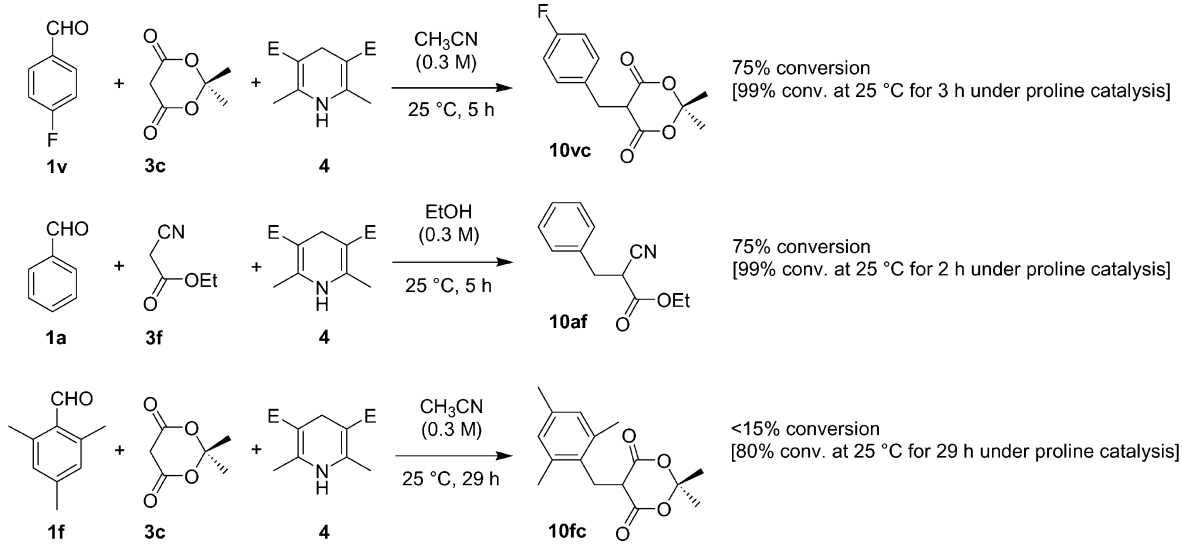
Interestingly, one of the reagents in the cascade reaction also catalyses the cascade sequence to furnish the products **10/12** in good yields. In the first step (Scheme 7), the Hantzsch ester (**4**) activates components **1/2**, most probably by acid/base catalysis, and these then selectively add to the CH acid **3** in a aldol-type reaction to generate active olefins **7/8**.[2] The following second step is biomimetic hydrogenation of active olefins **7/8** by Hantzsch ester (**4**) to produce **10/12** through self-catalysis. As shown in Scheme 7,



Scheme 7. Proposed catalytic cycle for the organocatalytic olefination/hydrogenation reactions of **1**, **2**, **3** and **4**.

Hantzsch ester (**4**) simultaneously catalyses the activation of carbonyls **1/2** to form olefins **7/8** and the reduction of active olefins **7/8** to generate cascade products **10/12** in a single step.

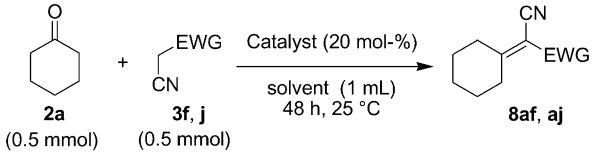
The dual role of Hantzsch ester (**4**) as a catalyst and reagent in the cascade O/H reactions was further confirmed by conducting controlled experiments on various substrates as shown in Scheme 8 and Table 11. Cascade O/H reactions of 4-fluorobenzaldehyde (**1v**), Meldrum's acid (**3c**) and Hantzsch ester (**4**) in CH_3CN at 25 °C for 5 h and of benzaldehyde (**1a**), ethyl cyanoacetate (**3f**) and Hantzsch ester (**4**) in EtOH at 25 °C for 5 h furnished the cascade prod-



Scheme 8. Dual role of Hantzsch ester (**4**) as both catalyst and reagent in the cascade olefination/hydrogenation reactions.

ucts 5-(4-fluorobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**10vc**) and ethyl 2-cyano-2-phenylpropionate (**10af**), respectively, with 75% conversions. However, the same reactions under proline catalysis conditions furnished the expected products **10vc** and **10af** with 99% conversions and in shorter times (Scheme 8). To understand more about the self-catalysis of **4** in cascade O/H reactions, we performed olefination reaction of **2a** with **3f** and **3j** in the presence of **9** and in the absence of catalyst **6a** and **4** in EtOH, DMSO and H_2O solvents as shown in Table 11. Olefin product **8af** was furnished in very poor conversions after 48 h at 25 °C, with and without pyridine (**9**) catalysis in EtOH, DMSO and H_2O solvents starting from **2a** and **3f** (Table 11, Entries 2–6). Interestingly, olefin product **8aj** was furnished from **2a** and **3j** in moderate yields under catalyst-free conditions, as shown in Table 11, Entries 7–9; this may be due to the highly acidic nature of malononitrile (**3j**) in relation to ethyl cyanoacetate (**3f**). From these results we have strong support for the self-catalysis of **4** in cascade O/H reactions.

Table 11. Olefination of cyclohexanone **2a** with **3f** and **3j** under organo- and self-catalysis conditions.



Entry	EWG	Catalyst	Solvent	% Conv.[a]
1[b]	CO_2Et	**6a**	EtOH	**8af** (66)
2	CO_2Et	**9**	EtOH	**8af** (<3)
3	CO_2Et	**9**	DMSO	**8af** (<3)
4	CO_2Et	–	EtOH	**8af** (<3)
5	CO_2Et	–	DMSO	**8af** (<3)
6	CO_2Et	–	H_2O	**8af** (<4)
7	CN	–	EtOH	**8aj** (70)
8	CN	–	DMSO	**8aj** (70)
9	CN	–	H_2O	**8aj** (75)

[a] Determined by ^{1}H NMR analysis. [b] Reaction time was 24 h.

Taking the recent applications of amine-catalysed Knoevenagel reactions[1q,1r] into account, and in view of the different experiments performed (Scheme 8 and Table 11), we propose that this cascade reaction is a double catalytic cascade reaction: catalysis by a combination of amine **4** and amino acid as shown in Scheme 7.

Conclusions

In conclusion, we have demonstrated the organo-, organo-/metal carbonate- and organo-/Cu^I-catalysed enzyme-like assembly of cascade products **10**, **11**, **12**, **13**, **14**, **15** and **17** from readily available precursors through O/H, O/H/A, O/H/A/TE, H/O/H, O/H/H and O/H/A/HC reaction sequences. The combination of proline/M_2CO_3 and proline/Cu^I ions proved to be the optimal organo-/metal catalysts for the one-pot cascade reactions. This simple one-pot procedure provides direct access to functionalized diversity-oriented products **10** to **17**, shown to be pharmaceutical drugs, drug intermediates and ingredients in medicinal chemistry. For the first time in organocatalysis, we have reported the O/H/A/TE reaction, furnishing high yields of transesterification products **11** simply on mixing of the reactants under proline/K_2CO_3 catalysis conditions. Additionally, a novel organocatalytic H/O/H reaction sequence for the synthesis of alkyl-substituted aromatics has been developed. Furthermore, we have for the first time developed organocatalysed cascade O/H/H reactions to furnish highly useful materials such as 2-oxochroman-3-carboxylic acid (**14kc**) and 2-amino-4*H*-chromene-3-carbonitrile (**14kj**) in good yields. We have also demonstrated one-pot two-carbon homologation of aldehydes in high yields through organocatalysed O/H/H reactions. Simple amines **6c**–**f** and amino acids **6a**–**b** were used as organocatalysts for catalysis of olefin formation in cascade reactions.

Cascade reactions catalysed by combinations of primitive biomolecules and metal ions should open new doors for biomimetic strategies in organic synthesis, and should also give possible reaction mechanisms in the prebiotic evolution of the molecular world.[1n–1s,12] These reactions can be performed on multigram scales under operationally simple and environmentally safe conditions. Further studies aimed at exploring the scope of cascade reactions of these types are ongoing.

Experimental Section

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 from TMS (δ = 0 ppm) for ^{1}H NMR spectra and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectra. Coupling constants in ^{1}H NMR measurements are given in Hz. In the ^{13}C NMR spectra, the different signals of the carbon atoms (for C, CH, CH_2 or CH_3) were assigned by recording the DEPT-135 experiment, and are given in parentheses. Column chromatography was performed on Acme's silica gel (particle size 0.063–0.200 mm). High-resolution mass spectra were recorded on a Micromass ESI-TOF MS instrument. GCMS mass spectrometry was performed on a Shimadzu GCMS-QP2010 mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700 instruments. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded either on a VG7070H mass spectrometer by the EI technique or on a Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf–Nonius MACH 3 diffractometer with use of graphite-monochromated Mo-K_α (λ = 0.71073 Å) radiation and CAD4 software, or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system fitted with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å). For thin-layer chromatography (TLC), silica gel plates (Merck 60 F_25_4) 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.

Materials: All solvents and commercially available chemicals were used as received. CH-Acids **3g**–**h**[13a] and **3o**,[1r] spiro ketones **2h**,[1q]

and **2i**[1r] were prepared according to literature procedures. (1-Bromomethyl-vinyl)benzene (**5f**) was synthesized by a literature procedure.[13b]

General Experimental Procedures for Organo-Click Reactions

Amine- or Amino Acid-Catalysed Cascade Olefination/Hydrogenation Reactions: In an ordinary glass vial containing a magnetic stirring bar, solvent (1.0 mL) was added to the aldehyde **1** or ketone **2** (0.5 mmol), CH acid **3** (0.5 mmol) and Hantzsch ester (**4**, 0.5 mmol). The catalyst amine or amino acid **6** (0.025 mmol to 0.1 mmol) was then added, and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1, 2, 3, 4, 5, 7, 8 or 9. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade products **10** and **12** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Proline/Cs_2CO_3- or K_2CO_3-Catalysed One-Pot Olefination/Hydrogenation/Alkylation Reactions: In an ordinary glass vial containing a magnetic stirring bar, solvent (1.0 mL) was added to the aldehyde **1** or ketone **2** (0.5 mmol), CH acid **3** (0.5 mmol) and Hantzsch ester **4** (0.5 mmol). The catalyst proline (**6a**, 0.1 mmol) was then added, and the reaction mixture was stirred at 25 °C for 1–96 h. R^4CH_2I or R^4CH_2Br **5** (2.5 mmol) and K_2CO_3 or Cs_2CO_3 (0.4 g) were then added, and stirring was 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 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot products **11** and **13** were obtained by column chromatography (silica gel, mixtures of hexane/ethyl acetate).

Amine/Acid-Catalysed One-Pot Hydrogenation/Olefination/Hydrogenation Reactions: Morpholine (**6e**, 0.05 mmol, 5 mol-%) and trifluoroacetic acid (0.05 mmol, 5 mol-%) were placed in an ordinary glass vial containing a magnetic stirring bar, and the system was stirred at 25 °C for 10 minutes. THF solvent (4.0 mL), *trans*-cinnamaldehyde (**1e′**) or *o*-nitrocinnamaldehyde (**1f′**) (1.0 mmol) and Hantzsch ester (**4**) (1.0 mmol) were then added, and stirring was continued at the same temperature for the time indicated in Scheme 5. After completion of the hydrogenation, Meldrum's acid (**3c**, 1.0 equiv.) and Hantzsch ester (**4**, 1.0 equiv.) were added to the crude reaction mixture, and stirring was continued at the same temperature for the time indicated in Scheme 5. The crude reaction mixture was worked up with aqueous $NaHCO_3$ and NH_4Cl solutions and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot products **10** were obtained by column chromatography (silica gel, mixtures of hexane/ethyl acetate).

Amino Acid-Catalysed One-Pot Olefination/Hydrogenation/Hydrolysis Reactions: In an ordinary glass vial containing a magnetic stirring bar, EtOH (1.0 mL) was added to the aldehyde **1a** (0.5 mmol), Meldrum's acid (**3c**, 0.5 mmol) and Hantzsch ester (**4**, 0.5 mmol). The catalyst amino acid **6a** (0.1 mmol) was then added, and the reaction mixture was stirred at 25 °C for the time indicated in Scheme 2. HCO_2H (0.5 mL) and NEt_3 (1.8 mL) were added to the crude reaction mixture, which was stirred 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 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot product **15ac** was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

$CuSO_4$/Cu-Catalysed Huisgen Cycloaddition Reaction: For the synthesis of highly functionalized triazole **17**, O/H/A cascade product **13hfd** (0.22 mmol), benzyl azide **16** (0.44 mmol), $CuSO_4$ (0.22 mmol, 35 mg) and Cu wire (23 mg) in ethanol (1.0 mL) were placed in an ordinary glass vial containing a magnetic stirring bar and stirred at 25 °C for the time indicated in Scheme 6. The crude reaction mixture was directly loaded onto a silica gel column without aqueous workup, and pure triazole **17** was obtained by flash column chromatography (silica gel, mixture of hexane/ethyl acetate).

Many of the cascade products **10** to **17** are commercially available or have been described previously; their analytical data match literature values. New compounds were characterized by IR, ^1H and ^{13}C NMR and analytical data (see electronic supporting information).

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, compound characterization, and analytical data (^1H NMR, ^{13}C NMR and HRMS) for all new compounds.

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