Towards organo-click reactions: development of pharmaceutical ingredients by using direct organocatalytic bio-mimetic reductions†

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Economic and environmentally friendly bio-mimetic one-pot three and four-component Knoevenagel–hydrogenation (K–H), five-component Knoevenagel–hydrogenation–alkylation (K–H–A) and six-component Knoevenagel–hydrogenation–alkylation–Huisgen cycloaddition (K–H–A–HC) reactions of aldehydes, CH-acids, *o*-phenylenediamine, alkyl halides and azides using proline, proline–metal carbonate and proline–metal carbonate–Cu^{I}-catalysis, respectively have been developed. Many of K–H and K–H–A compounds have direct application in pharmaceutical chemistry.

Introduction

The reduction chemistry of flavines and dihydropyridines has been extensively studied in conjunction with the enzymic processes mediated by these types of cofactors.[1] Although not as extensively explored, it is also well established that heterocyclic compounds having a hydrogen-donating ability, such as dihydrobenzazoles[2] or 1,4-dihydropyridines[3] are useful as such selective bio-mimetic reducing agents. Recently, we[4] and others[5] have been developing the organocatalytic bio-mimetic chemoselective reduction of olefinic double bonds in α,β-unsaturated carbonyls by using 1,4-dihydropyridine derivatives (so-called NADPH model compounds) such as 3,5-bis(ethoxycarbonyl)-1,4-dihydro-2,6-dimethyl-pyridine (Hantzsch ester) as reducing agent. The main drawback in these useful reactions is removal of by-product pyridine from the reaction mixture. In this regard, we are interested to develop novel bio-mimetic reductions by utilizing *in situ* generation of both hydrogen source and olefins *via* amino acid-catalysis and separation of by-products through simple filtration.

Herein we disclose a highly efficient and remarkably chemoselective metal-free catalytic transfer hydrogenation process for *in situ* generation of both hydrogen-donating heterocyclic benzimidazoline and chemically activated olefins in a cascade approach *via* amino acid-catalysis and both the resulting hydrogenated products and by-products are showed to have direct application in pharmaceutical chemistry.

Taking inspiration from nature's approach, we address here the development of a set of powerful, highly reliable, and selective cascade reactions for the rapid synthesis of useful pharmaceutical intermediates and ingredients through proline, metal carbonate and Cu^{I}-catalyzed Knoevenagel, hydrogenation, alkylation and Huisgen cycloaddition reactions, an approach we call "organo-click reactions". Recently, Sharpless and co-workers introduced the concept of click chemistry.[6] Later on Ramachary and Barbas combined organocatalytic reactions with click chemistry (organo-click chemistry).[7] Ideally, organocatalytic cascade reactions can also fulfil all aspects of click reaction conditions, such as the reactions must be modular, wide in scope, high yielding, generate only inoffensive by-products, and be stereospecific.

As we are interested in the engineering of direct organocatalytic cascade reactions,[8] herein we report the direct organocatalytic chemoselective cascade Knoevenagel–hydrogenation (K–H), Knoevenagel–hydrogenation–alkylation (K–H–A) and Knoevenagel–hydrogenation–alkylation–Huisgen cycloaddition (K–H–A–HC) reactions that produce highly substituted cascade products **7**, **8**, **10**, **11** and **12** respectively, from aldehydes **1a–u**, CH-acids **2a–j**, *o*-phenylenediamine **3**, alkyl halides **9a–d**, benzyl azide, catalysts **4a–b**, potassium carbonate, copper and copper sulfate as shown in Scheme 1. Cascade products **7**, **8**, **10** and **11** are attractive intermediates and ingredients in medicinal chemistry, and analogues thereof have broad utility in pharmaceutical chemistry[9,10] (herbicidal, anti-diabetic, analgesic, anti-inflammatory, anti-thrombotics, anti-ulcers, anti-hypertensives, anti-virals, anti-fungals, anti-cancers, and anti-histaminics) and in organic synthesis.

Results and discussion

We found that cascade K–H reaction of two equivalents of aldehyde **1a**, CH-acid **2a**, *o*-phenylenediamine **3** and catalyst **4a** furnished the products **7aa** and **8a** with very good yields in MeOH at 25 °C for 1 h (Table 1, entry 1), which are purified by using simple filtration followed by flash column chromatography. The same reaction, catalyzed by proline **4a** at 25 °C under cascade conditions furnished the product **7aa** with 80% yield and by-product **8a** with 80% yield in aprotic polar solvents for 24 h (Table 1, entries 3–4); and in water gave products **7aa** and **8a** in moderate yields (Table 1, entry 7). The optimum conditions (entry 2) involved the use of catalyst **4a** in cascade K–H reaction of **1a**, **2a** and **3** in EtOH at 25 °C to furnish **7aa** and **8a** in very good yields. To see the effect of chiral amino acid, L-proline **4a** for asymmetric induction in cascade K–H reactions, we measured the optical rotation of cascade product **7aa** obtained from optimum conditions (Table 1, entry 2). But unfortunately we have not seen enantioselectivity in this reaction ($\alpha = 0$).

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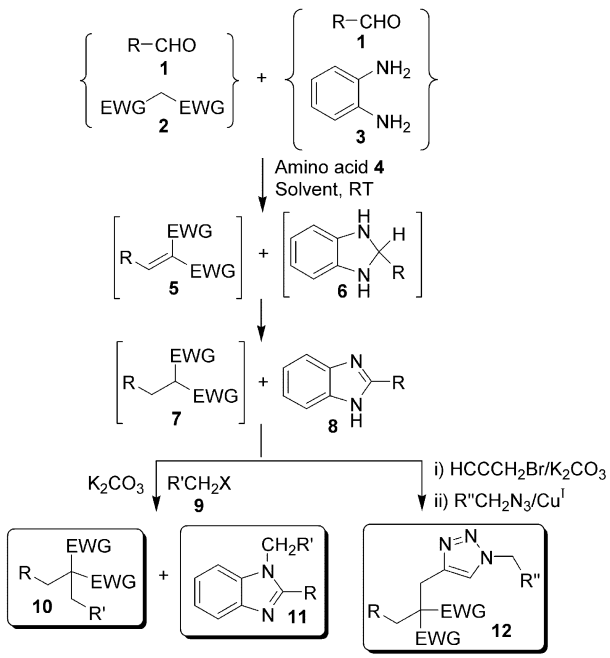
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. See DOI: 10.1039/b612611a



Substrates and Catalysts Screened:

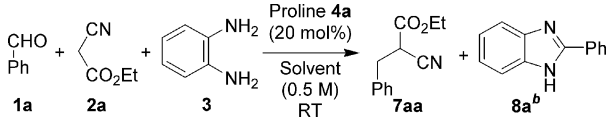
1a R = C_6H_5
1b R = 2-ClC_6H_4
1c R = 3-ClC_6H_4
1d R = 4-ClC_6H_4
1e R = 2-BrC_6H_4
1f R = 3-BrC_6H_4
1g R = 4-BrC_6H_4
1h R = 2-FC_6H_4
1i R = 4-FC_6H_4
1j R = 4-CNC_6H_4
1k R = 4-$OMeC_6H_4$
1l R = 4-$CHOC_6H_4$
1m R = 2,4,6-$(CH_3)_3C_6H_2$
1n R = 4-$HCCCH_2OC_6H_4$
1o R = 4-$H_2CCHCH_2OC_6H_4$
1p R = 2-Thiophenyl
1q R = 3,4-$(OCH_2O)C_6H_3$
1r R = $(CH_3)_2CHCH_2$
1s R = $CH_3(CH_2)_2CH_2$
1t R = $CH_3(CH_2)_4CH_2$
1u R = $PhCH_2CH_2$
2a Ethyl cyanoacetate
2b Methyl cyanoacetate
2c Ethyl nitroacetate
2d Malononitrile
2e (Toluene-4-sulfonyl)-acetonitrile
2f *N,N*-Dimethylbarbituric acid
2g Meldrum's acid
2h Indandione
2i 1,5-Dioxa-spiro[5.5]undecane-2,4-dione
2j Dimethyl malonate
4a Proline
4b Aniline
9a CH_3I
9b CH_3CH_2Br
9c $H_2C{=}CHCH_2Br$
9d $HCCCH_2Br$

Scheme 1 Towards organo-click reactions in one-pot.

Interestingly, cascade K–H reaction of **1a**, **2a** and **3** in the absence of catalyst at 25 °C for 2 h furnished the expected products **7aa** and **8a** in 81% and 85% yields in EtOH respectively (Table 1, entry 9). This is the best demonstration of the self and auto-catalytic nature of reagents in cascade reactions.[4] The catalyst effect on proline-catalyzed Knoevenagel condensation of aldehydes **1a** and **1d** with ethyl cyanoacetate **2a** were revealed in Table 2. Simple amine, aniline **4b** also catalyzed the Knoevenagel condensation of **1a** with **2a** to produce **5aa** with reduced conversion (entry 2), which gives support for the self-catalytic nature of **3**. Interestingly, cascade by-product 2-phenyl-benzimidazole **8a** also catalyzed Knoevenagel reaction (entry 3), which gives strong support for the auto-catalysis in cascade K–H reactions. Catalyst loading revealed that 20% of **4a** was required to increase the rate of reaction (entries 4–6). From these results we have strong support for the useful self and auto-catalysis in organocatalytic cascade K–H reactions.

After these interesting results, we decided to investigate the scope and limitations of the cascade K–H reaction with a range

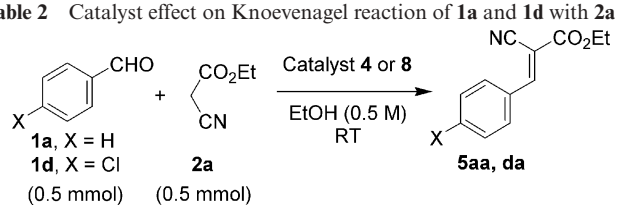
Table 1 Optimization of bio-mimetic reductions[a]



Entry	Solvent	Time/h	Conversion (%)[c]	Yield (%)[d] **7aa**
1	MeOH	1	99	90
2	EtOH	1	99	93
3	DMSO	24	90	80
4	DMF	24	90	80
5	CH_3CN	24	90	75
6	$CHCl_3$	24	40	30
7	H_2O	6	90	60
8	[bmim]BF_4	24	90	53
9[e]	EtOH	2	99	81

[a] All reactants [**1a** (2 equivalents), **2a**, **3**] and catalyst **4a** were mixed at the same time in solvent and stirred at room temperature. [b] 80–95% of **8a** was isolated. [c] Conversion based on TLC analysis. [d] Yield refers to the filtration followed by column purified product. [e] Without catalyst.

Table 2 Catalyst effect on Knoevenagel reaction of **1a** and **1d** with **2a**



Entry	Aldehyde	Catalyst	Time/h	Product	Conv. (%)[a]
1	**1a**	**4a** (20 mol%)	1	**5aa**	95
2	**1a**	**4b** (20 mol%)	1	**5aa**	85
3	**1a**	**8a** (20 mol%)	20	**5aa**	99
4	**1d**	**4a** (5 mol%)	4	**5da**	99
5	**1d**	**4a** (10 mol%)	3	**5da**	99
6	**1d**	**4a** (20 mol%)	2	**5da**	99

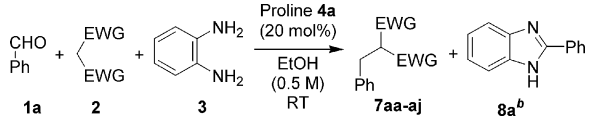
[a] Determined by ^{1}H NMR analysis.

of aldehydes **1a–u**, active CH-acids **2a–j** and *o*-phenylenediamine **3** under proline-catalysis in EtOH (Tables 3 and 4). As shown in Table 3, acyclic CH-acids ethyl nitroacetate **2c** and toluene-4-sulfonyl-acetonitrile **2e** furnished cascade products **7ac** and **7ae** in lower yields than the other CH-acids **2**. CH-Acid, dimethyl malonate **2j** did not furnish the expected cascade product **7aj** and gave only Knoevenagel product **5aj** (entry 10). This may be due to the difference in acid strength and HOMO–LUMO gap between *in situ* generated both 2-phenyl-benzimidazoline **6a** and olefins **5** respectively.

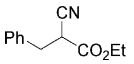
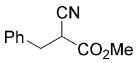
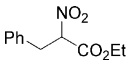
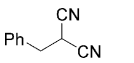
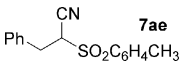
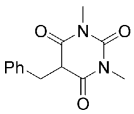
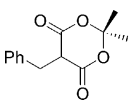
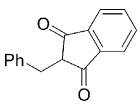
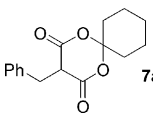
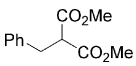
As shown in Table 4, we studied the effect of aldehydes **1** in proline-catalyzed cascade K–H reactions of **1**, **2a** and **3**. Aromatic aldehydes **1b–d** and **1j–k** furnished the expected hydrogenated **7ba–da** and **7ja–ka** and heterocyclic 2-aryl-benzimidazole **8b–d** and **8j–k** products in good yields without being affected by electronic factors. But cascade K–H reaction with aliphatic aldehydes **1r–u** furnished the expected products **7ra–ua** and **8r–u** in moderate yields due to the self-aldol reactions of aldehydes **1r–u** under proline-catalysis.

We generated a useful library of four-component, one-pot K–H products **7** under proline-catalysis. The results in Table 5 demonstrate the broad scope of this *in situ* reductive green

Table 3 Cascade *in situ* reduction with a variety of CH-acids **2a–j**[a]



1a 2 3 7aa-aj 8a[b]

Entry	CH-Acid	Time/h	Product	Conv. (%)[c]	Yield (%)[d] 7
1	**2a**	1	 **7aa**	>99	93
2	**2b**	1	 **7ab**	>99	99
3	**2c**	6	 **7ac**	90	73
4	**2d**	1	 **7ad**	99	92
5	**2e**	3	 **7ae**	85	75
6	**2f**	1	 **7af**	99	92
7	**2g**	1	 **7ag**	99	90
8	**2h**	1	 **7ah**	>99	99
9	**2i**	1	 **7ai**	>99	95
10[e]	**2j**	20	 **7aj**	—	—

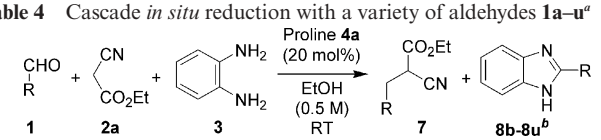
[a] All reactants [**1a** (2 equivalents), **2**, **3**] and catalyst **4a** were mixed at the same time in solvent and stirred at room temperature. [b] 80–95% of **8a** were isolated in all reactions. [c] Conversion based on TLC analysis. [d] Yield refers to the filtration followed by column purified product. [e] 75% of Knoevenagel product **5aj** were isolated.

methodology covering a structurally diverse group of less reactive aldehydes **1a–u** and CH-acids **2a–j** with many of the yields obtained being very good, or indeed better, than previously published reactions starting from the corresponding olefins **5**. One-pot, proline-catalyzed K–H reaction of **1q**, **2a** or **2b**, **1a** and **3** did not furnished the expected products **7qa**, **7qb** and **8a** at RT but furnished the hydrogenated products with moderate yields at 50 °C for 8 h (see Table 5).

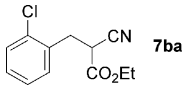
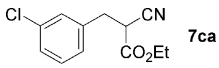
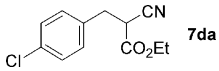
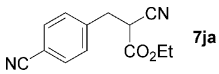
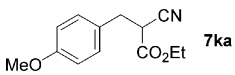
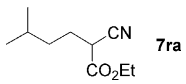
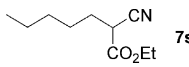
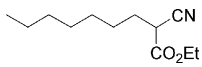
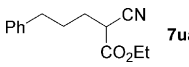
Hydrogenated product **7ia** is important intermediate for the synthesis of methyl 3-(4-fluorobenzyl)-1-methylpiperidine-3-carboxylate as ingredient for chemokine receptor antagonists;[9e] K–H product **7pa** is a useful intermediate for the synthesis of anthelmintic and pesticidal compositions;[9f] one-pot products **7qa** and **7qb** are useful intermediates for the synthesis of anti-malarial and cardiovascular products;[9g,9h] heterocyclic by-products **8a–8u**[10] are useful intermediates for the preparation of estrogen agonists/antagonists, anti-bacterial, anti-fungal, muscarinic agonists, inhibitors of HIV-1 reverse transcriptase, preventing sleep apnea and for treating physiological disorders emphasizing the value of this cascade K–H approach.

To show direct applications in pharmaceutical chemistry, we extended the three and four-component cascade K–H reactions into a novel one-pot five-component proline–K_2CO_3-catalyzed K–H–A reaction of aldehydes **1**, CH-acid **2a**, *o*-phenylenediamine **3** and benzaldehyde **1a** with various alkyl halides **9a–d** (Table 6). 2,2-Disubstituted ethyl cyanoacetates **10** and 1-alkyl-2-phenylbenzimidazoles **11aa–ad** were constructed in good to moderate yields with various substitutes as shown in Table 6. One-pot

Table 4 Cascade *in situ* reduction with a variety of aldehydes **1a–u**[a]

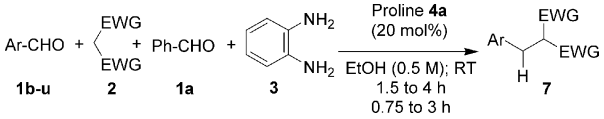


1 2a 3 7 8b-8u[b]

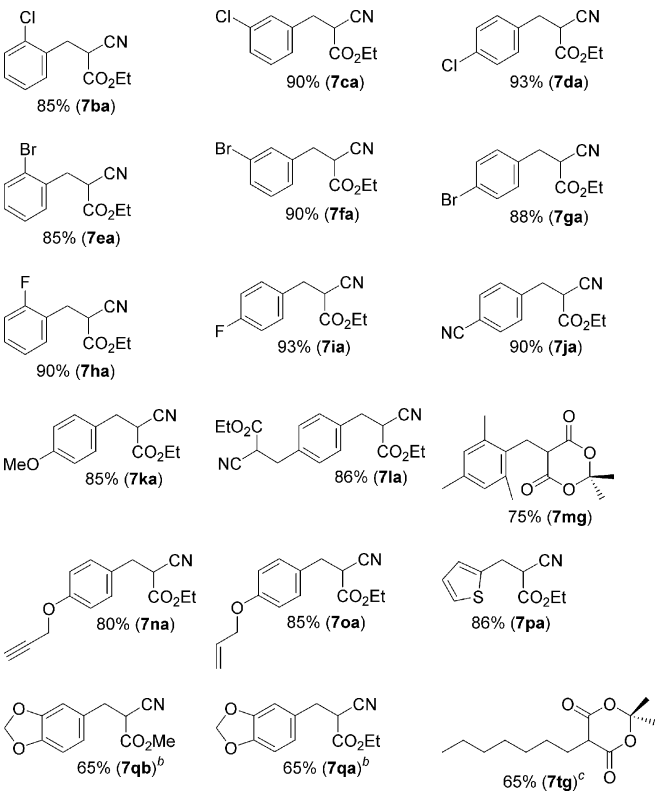
Entry	R	Time/h	Product	Yield (%)[c]
1	**1b**	2.5	 **7ba**	80
2	**1c**	2.5	 **7ca**	85
3	**1d**	2.5	 **7da**	90
4	**1j**	5	 **7ja**	88
5	**1k**	5	 **7ka**	82
6	**1r**	3	 **7ra**	50
7	**1s**	3	 **7sa**	60
8	**1t**	3	 **7ta**	62
9	**1u**	3	 **7ua**	70

[a] All reactants [**1** (2 equivalents), **2a**, **3**] and catalyst **4a** were mixed at the same time in solvent and stirred at room temperature. [b] 80–95% of **8b–d**, **8j–k** and 50–70% of **8r–u** were isolated. [c] Yield refers to the filtration followed by column purified product.

Table 5 Chemically diverse libraries of cascade K–H products **7**[a]



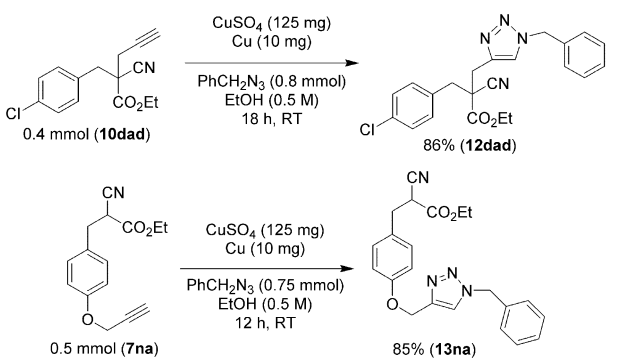
1b-u 2 1a 3 7



[a] Yield refers to the filtration followed by column purified product. [b] Reaction performed at 50 °C for 8 h. [c] Aldehyde **1t** were taken as two equivalents.

products **10** are useful as analgesics, antidepressants, and anti-inflammatories;[9b] and products **11** have many applications in pharmaceutical chemistry as ingredients for example active anthelmintic agents, treatment for anti-obesity, fungicides and anti-microbial action.[10]

Here we demonstrated the two, five and six-component Cu^{I}-catalyzed regiospecific [3 + 2] cycloaddition of one-pot products **10** and **7** with benzyl azide to produce highly functionalized 1,2,3-triazoles **12** and **13** as shown in Scheme 2. 1,2,3-Triazoles **12dad** and **13na** were furnished with same yields in both two and five or six-component strategy but the purity of the product is good in two-component reactions.

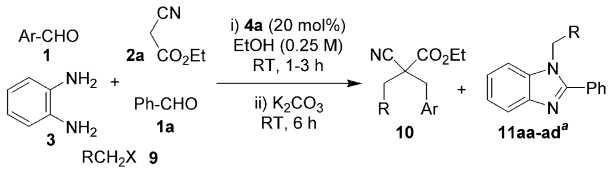


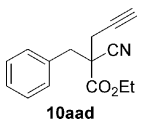
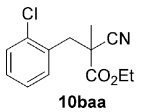
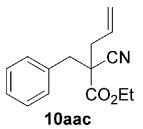
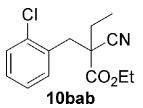
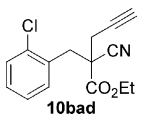
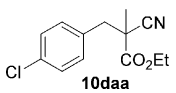
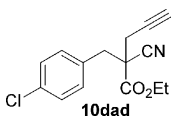
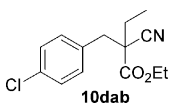
Scheme 2 Cu^{I}-catalyzed click reaction on cascade products **7na** and **10dad**.

Conclusions

In summary, we have developed the direct proline, proline–metal carbonate, proline–metal carbonate–Cu^{I}-catalyzed cascade K–H, K–H–A and K–H–A–HC reactions through formation of two C–H, two C–C and five C–N bonds in a single step. This experimentally simple, environmentally and economically friendly green approach can be used to construct highly substituted cyano-esters **7**, **10**, **12** and 1,2-substituted benzimidazoles **8** and **11** in a regioselective fashion with very good yields. Many of these products are showed to have direct application in pharmaceutical chemistry. Further work is in progress to utilize synthetic application of this cascade process.

Table 6 Chemically diverse libraries of cascade K–H–A products **10**



Entry	Product	Yield[b]
1	 **10aad**	76
2	 **10baa**	75
3	 **10aac**	78
4	 **10bab**	65
5	 **10bad**	85
6	 **10daa**	70
7	 **10dad**	88
8	 **10dab**	66

[a] 25–35% of 1-alkyl-2-phenylbenzimidazole **11aa–ad** and 55–65% of unreacted 2-phenylbenzimidazole **8a** were isolated. [b] Yield refers to the column purified product.

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 to 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 recording the 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 MS. GCMS mass spectrometry 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 on either a VG7070H mass spectrometer using EI technique or a Shimadzu-LCMS-2010A mass spectrometer. IR spectra were recorded on a JASCO FT/IR-5300. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 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.

General experimental procedures for the organo-click reductions

Proline-catalyzed cascade Knoevenagel–hydrogenation reactions. In an ordinary glass vial equipped with a magnetic stirring bar, solvent (1.0 mL) was added to the aldehyde **1** (1.0 mmol), the CH-acid **2** (0.5 mmol) and the *o*-phenylenediamine **3** (0.5 mmol). The amino acid catalyst **4** (0.1 mmol) was then added and the reaction mixture stirred at 25 °C for the time indicated in Tables 1, 3 and 4. Pure cascade products **7** and **8** were obtained by simple filtration of crude product through a sintered funnel with dichloromethane to produce 85–90% purity. High purity products were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Proline–K_2CO_3-catalyzed one-pot Knoevenagel–hydrogenation–alkylation reactions. In an ordinary glass vial equipped with a magnetic stirring bar, solvent (2.0 mL) was added to the aldehyde **1** (0.5 mmol) and the CH-acid **2** (0.5 mmol). The proline catalyst **4a** (0.1 mmol) was added and the reaction mixture was stirred at 25 °C for 1.5–4 h. *o*-Phenylenediamine **3** (0.5 mmol) and benzaldehyde **1a** (0.5 mmol) were then added and stirring continued at the same temperature for 1–3 h. RCH_2I (4.0 mmol) or RCH_2Br **9** (2.5 mmol) and K_2CO_3 (4.0 mmol) were then added and stirring continued at the same temperature for 6 h. The crude reaction mixture was worked up with aqueous NH_4Cl and the aqueous layer extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **10** and **11** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Proline–K_2CO_3–Cu^I-catalyzed one-pot Knoevenagel–hydrogenation–alkylation–Huisgen cycloaddition reactions. In an ordinary glass vial equipped with a magnetic stirring bar, solvent (2.0 mL) was added to the aldehyde **1** (0.5 mmol) and the CH-acid **2** (0.5 mmol). The proline catalyst **4a** (0.1 mmol) was added and the reaction mixture was stirred at 25 °C for 1–4 h. *o*-Phenylenediamine **3** (0.5 mmol) and benzaldehyde **1a** (0.5 mmol) were then added and stirring continued at the same temperature for 1–3 h. $HCCCH_2Br$ **9d** (2.5 mmol) and K_2CO_3 (4.0 mmol) were then added and stirring continued at the same temperature for 6 h. Excess propargyl bromide **9d** was removed

by vacuum pump then $CuSO_4$ (0.75 mmol), Cu wire (10 mg) and benzyl azide (0.75 mmol) were added and stirring continued at the same temperature for 18 h. The crude reaction mixture was worked up with aqueous NH_4Cl and the aqueous layer extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products **12** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Many of the cascade products **7**, **8**, **10** and **11** are commercially available, or have been described previously, and their analytical data match literature values. New compounds were characterized on the basis of IR, ^1H and ^{13}C NMR and analytical data (see supporting information†).

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