Development of drug intermediates by using direct organocatalytic multi-component reactions

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Received 22nd February 2006, Accepted 14th March 2006
First published as an Advance Article on the web 23rd March 2006
DOI: 10.1039/b602696f

Novel, economic and environmentally friendly one-pot three-component Knoevenagel/hydrogenation (K/H) and four-component Knoevenagel/hydrogenation/alkylation (K/H/A) reactions of ketones, CH-acids, dihydropyridines and alkyl halides using proline and proline/metal carbonate catalysis, respectively, have been developed. Many of the products of these K/H and K/H/A reactions have direct applications in pharmaceutical chemistry.

A number of pyridine nucleotide-linked dehydrogenases catalyze the reversible hydrogenation–dehydrogenation of the double bond in α,β-unsaturated ketones,[1] and nicotinamide nucleotides play a vital role in biological oxidation–reductions;[2] namely, NAD(P)H reduces carbonyl compounds to alcohols. In certain enzymatic systems, NAD(P)H also reduces carbon–carbon double bonds in α-ketoolefins such as crotonyl-CoA and benzalacetone.[3] Similar biomimetic conjugate reductions of α,β-unsaturated aldehydes and ketones occurs with NAD(P)H models, such as 3,5-dicarboethoxy-2,6-dimethyl-1,4-dihydropyridine (Hantzsch ester).[4] In order to understand mechanisms of biochemical oxidation–reduction reactions and to mimic this completely green approach to synthetic organic chemistry, it is worthwhile to approach the subject from the viewpoint of organic chemistry.

Hydrogenations of double-bond-containing compounds such as carbonyls, imines, and olefins are crucial for living organisms as well as for the industrial production of chemicals. Recently, metal-free catalytic hydrogenations of olefins have been an emerging area in green catalysis.[5] Herein, we disclose a highly efficient and remarkably chemoselective metal-free catalytic transfer hydrogenation of *in situ* generated chemically activated olefins in a tandem approach. The resulting products have direct applications to drug discovery process.

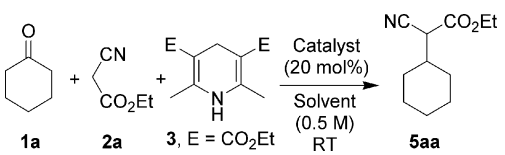
The hydrogenation of activated olefin compounds is a useful but challenging transformation. As both 1,2- and 1,4-reductions readily occur, low selectivity for either of the two pathways is common, and functional groups that are sensitive to hydrogenation conditions such as the ester, nitro, and nitrile groups are usually not tolerated. Clearly, mild, catalytic, one-pot, chemoselective and green variants of this reaction are highly desirable.

Recently, amino acid catalysis has emerged as a powerful green synthetic tool for the development of both achiral and chiral catalysis of condensations and cycloadditions, and the 1,2- and 1,4-additions of enals, enones and ketones with many electrophiles.[6] We reasoned that this catalysis strategy might be applicable to the *in situ* generation and conjugate reduction of highly chemically activated olefin compounds if a suitable hydride donor could be identified. Such a process would constitute a one-pot metal-free green hydrogenation similar to bio-transformations.

As we are interested in the engineering of direct organocatalytic green multi-component reactions,[5a,6f–i,m–o] herein we report the first organocatalytic chemoselective direct tandem Knoevenagel/hydrogenation (K/H) and Knoevenagel/hydrogenation/alkylation (K/H/A) reactions that produce highly substituted tandem products **5** and **8** respectively, from ketones **1a–n**, CH-acids **2a–i**, Hantzsch ester **3**, alkyl halides **7a–f** and amino acids **4a,b**, as shown in Scheme 1.† Tandem products **5** and **8** are attractive intermediates in medicinal chemistry, and analogues thereof have broad utility in pharmaceutical chemistry[7] (as insect repellents, dental adhesives, CRF antagonists, anti-spasmodics, antiulcer agents, drugs for skin diseases, as agents against tuberculosis and leprosy bacteria, and as agents for wound healing *etc.*) and in organic synthesis.

We found that the amino acid proline **4a** readily catalyzes the Knoevenagel condensation of cyclohexanone **1a** with the CH-acid ethyl cyanoacetate **2a** to furnish the active olefin **9aa**, which on treatment with Hantzsch ester **3** produces the hydrogenated product **5aa** with very good yield after 24 h in MeOH at 25 °C (Table 1, entry 1). The same reaction, catalyzed by L-proline **4a** at 25 °C under tandem conditions, furnished the product **5aa** with 90–95% yield in protic solvents (Table 1, entries 1–3). The use of polar aprotic solvents (DMF and DMSO) gave similar yields to

Table 1 Optimization of *in situ* generation and reduction of active olefins[a]



1a 2a 3, E = CO_2Et 5aa

Entry	Catalyst	Solvent	Time/h	Yield (%)[b]
1	**4a**	MeOH	24	90
2	**4a**	EtOH	24	93
3	**4a**	EtOH	36	95
4	**4a**	DMF	24	86
5	**4a**	DMSO	24	86
6	**4a**	$CHCl_3$	24	48
7	**4a**	CH_3CN	24	68
8	—	EtOH	48	80
9	—	DMSO	48	75
10	—	H_2O	48	15
11	**4b**	EtOH	48	72

[a] Experimental conditions: All reactants (**1a**, **2a**, **3**) and catalyst **4** were mixed at the same time in solvent and stirred at room temperature. [b] Yield refers to the column-purified product.

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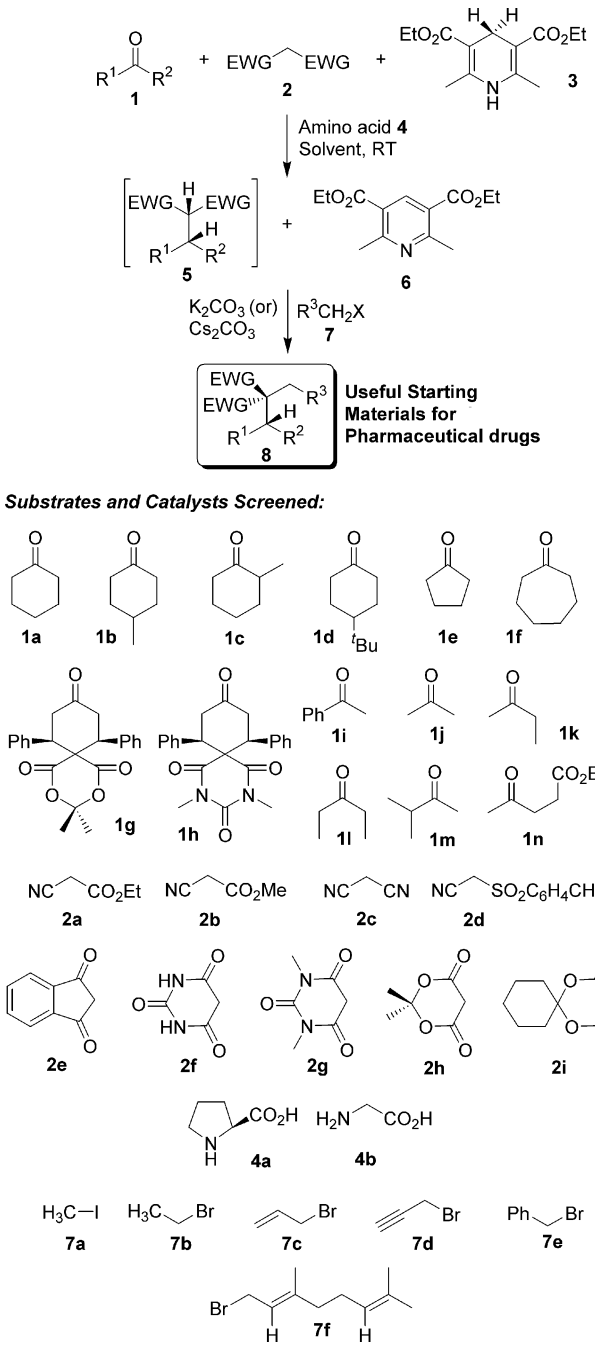
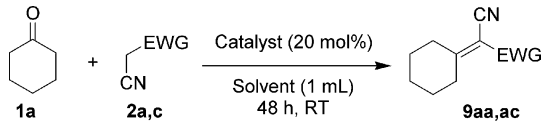


Scheme 1 Direct one-pot organocatalytic K/H and K/H/A reactions.

the reactions in MeOH and EtOH (Table 1, entries 4–7). A simple amino acid, glycine **4b**, also catalyzed the tandem K/H reaction to furnish tandem product **5aa** in 72% yield (Table 1, entry 11). The optimum conditions (entries 3, 4 and 5) involved the use of catalyst **4a** in the tandem K/H reaction of **1a**, **2a** and **3** in EtOH, DMF or DMSO at 25 °C.

Interestingly, the tandem K/H reaction of **1a**, **2a** and **3** in the absence of catalyst at 25 °C furnished, after 48 h, the expected product **5aa** in 80% and 75% yields in EtOH and DMSO, respectively (Table 1, entries 8 and 9). This is best demonstration of the self-catalytic nature of reagents in tandem reactions, and also in mimicking the hydrogenation–dehydrogenation of pyridine

Table 2 Knoevenagel reaction of cyclohexanone **1a** with **2a** and **2c**



Entry	EWG	Catalyst	Solvent	Product	Conversion (%)[a]
1[b]	CO_2Et	**4a**	EtOH	**9aa**	66
2	CO_2Et	**6**	EtOH	**9aa**	<3
3	CO_2Et	**6**	DMSO	**9aa**	<3
4	CO_2Et	—	EtOH	**9aa**	<3
5	CO_2Et	—	DMSO	**9aa**	<3
6	CO_2Et	—	H_2O	**9aa**	<4
7	CN	—	EtOH	**9ac**	70
8	CN	—	DMSO	**9ac**	70
9	CN	—	H_2O	**9ac**	75

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

nucleotide-linked dehydrogenases.[1] The proline-catalyzed Knoevenagel condensation of cyclohexanone **1a** with ethyl cyanoacetate **2a** in the absence of Hantzsch ester **3** furnished the olefin **9aa** with reduced conversion (Table 2, entry 1). Comparison of this result with entry 2 in Table 1 gives support for the self-catalysis of Hantzsch ester **3** in tandem reactions. To understand more about the self-catalysis of **3** in tandem K/H reactions, we performed a Knoevenagel reaction of **1a** with **2a** and **2c** in the presence of **6** (and in the absence of catalysts **3** and **4a**) in EtOH, DMSO and H_2O, as shown in Table 2. Starting from **1a** and **2a**, the Knoevenagel product **9aa** was furnished with very poor conversions after 48 h at 25 °C in EtOH, DMSO and H_2O, both with and without pyridine **6** (Table 2, entries 2–6). Interestingly, Knoevenagel product **9ac** was furnished from **1a** and **2c** in moderate yields under catalyst-free conditions, as shown in Table 2, entries 7–9 .This may be due to the highly acidic nature of malononitrile **2c** compared to ethyl cyanoacetate **2a**. From these results, we have strong support for the self-catalysis of **3** in tandem K/H reactions.

The two possible reaction mechanisms for tandem K/H reactions of **1a**, **2a**, **3** and **4a** are illustrated in Scheme 2. First, reaction of proline **4a** with cyclohexanone **1a** generates the iminium cation **12a**, an excellent electrophile that undergoes Mannich-type reactions with CH-acid **2a** to generate Mannich product **14a**. Retro-Mannich or base-induced elimination reaction of amine **14a** would furnish active olefin **9aa**.[6h] The subsequent hydrogen transfer reactions are dependent upon the electronic nature of the *in situ* generated conjugated system or, more precisely, the HOMO–LUMO gap of the reactants **3** and **9aa**.[5e] Interestingly, Hantzsch ester **3** also catalyzed the simultaneous formation and hydrogenation of active olefin **9aa** *via* key intermediate **16a**, as shown in mechanism 2, and is thus an ideal mimic of the hydrogenation–dehydrogenation of pyridine nucleotide-linked dehydrogenases.[1] We are able to propose mechanism 2 based on the acidic nature of Hantzsch ester **3** ($pK_a = 3.50 \pm 0.70$).[4e]

After this preliminary work, we proceeded to investigate the scope and limitations of the tandem K/H reaction of cyclohexanone **1a** with a range of active CH-acids **2a–i** and Hantzsch ester **3** under proline catalysis in DMSO (Table 3).[8] As shown in Table 3, acyclic CH-acids **2a–d** furnished tandem products **5aa–ad** in lower yields than the cyclic CH-acids **2e–i**. This may be

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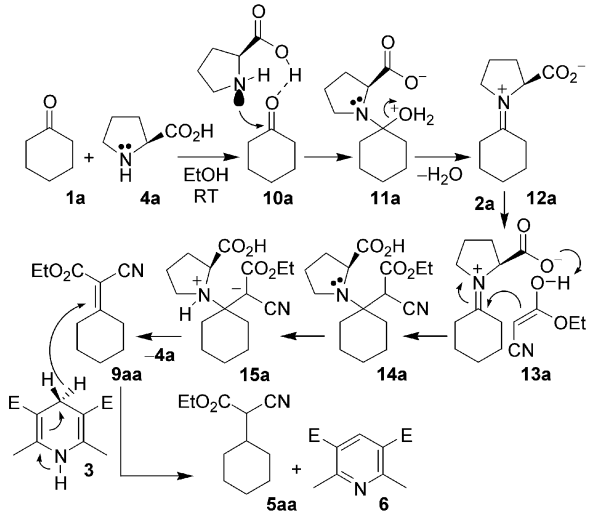
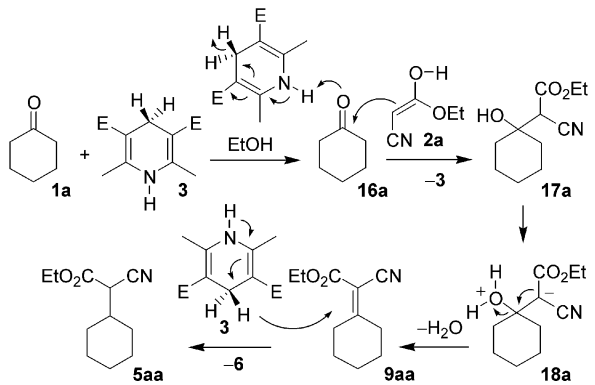
Mechanism 1: Proline-Catalyzed Tandem K/H Reaction of **1a**, **2a** and **3**

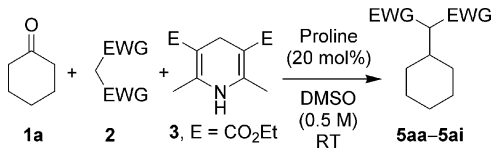


Mechanism 2: Self-Catalyzed Tandem K/H Reaction of **1a**, **2a** and **3**



Scheme 2 Proposed reaction mechanisms.

Table 3 Tandem *in situ* generation and reduction of a variety of activated olefins[a]

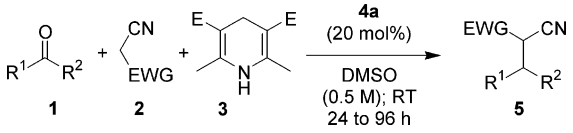


Entry	CH-acid	Time/h	Yield (%)[b]
1	**2a**	24	86
2	**2b**	24	99
3	**2c**	19	90
4	**2d**	60	60
5	**2e**	48	95
6[c]	**2f**	12	90
7	**2g**	24	99
8	**2h**	24	99
9	**2i**	24	93

[a] The reactants (**1a**, **2**, and **3**) and the catalyst **4a** were mixed at the same time in the solvent and stirred at room temperature. [b] Yield refers to the column-purified product. [c] Reaction performed at 70 °C.

due to the difference in acid strength and the HOMO–LUMO gap between Hantzsch ester **3** and the *in situ* generated olefins **9**, respectively. Cyclic CH-acids **2e–i** have a higher acid strength

Table 4 Chemically diverse libraries of tandem K/H products **5**



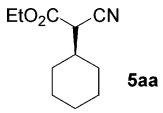
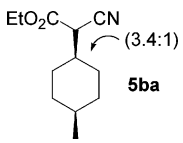
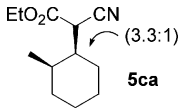
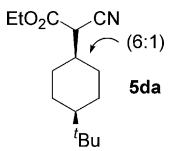
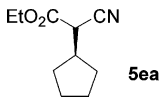
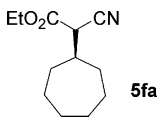
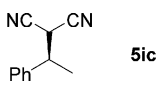
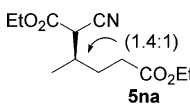
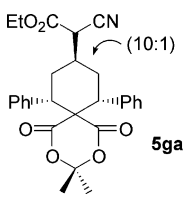
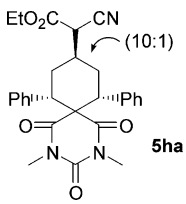
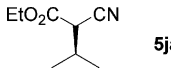
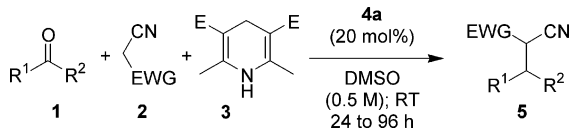
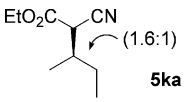
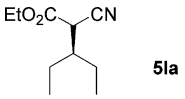
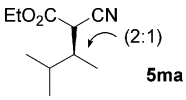
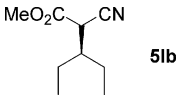
Entry	Product	Yield (%)[a]
1	 **5aa**	95
2[b]	 **5ba**	90
3	 **5ca**	45
4	 **5da**	95
5	 **5ea**	90
6	 **5fa**	90
7	 **5ic**	99
8	 **5na**	85
9	 **5ga**	99
10	 **5ha**	95
11	 **5ja**	93

Table 4 (*Cont.*)



Entry	Product	Yield (%)[a]
12	 **5ka**	92
13	 **5la**	60
14	 **5ma**	61
15	 **5lb**	92

[a] Yield refers to the column-purified product. [b] Ratio determined by ^{1}H and ^{13}C NMR analysis.

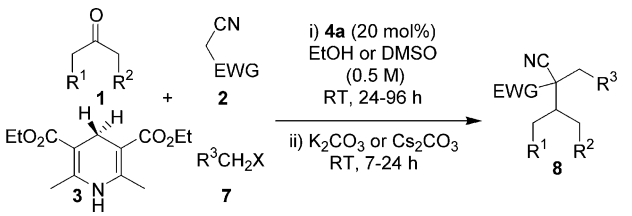
than acyclic CH-acids **2a–d**, and the same acidic property also continues in olefins **9**. Tandem products **5aa–ai** have applications in pharmaceutical chemistry.[7]

We generated a useful library of tandem K/H products **5** under proline catalysis. The results in Table 4 demonstrate the broad scope of this reductive green methodology, covering a structurally diverse group of less reactive ketones **1a–n** and CH-acids **2a–i** with many of the yields obtained being very good, or indeed better, than previously published reactions starting from the corresponding olefins **9** or ketones **1**. The tandem K/H reaction of 4-methylcyclohexanone **1b**, ethyl cyanoacetate **2a** and Hantzsch ester **3** furnished the regioselective hydrogenated ester *cis*-**5ba** in 3.4 : 1 ratio in 90% yield (Table 4, entry 2). Tandem K/H reactions produced hydrogenated products **5ba**, **5ca**, **5da** and **5ma** with good regioselectivities compared to $NaBH_4$ reduction of the corresponding olefins,[9] as shown in Table 4, entries 2–4 and 9–10.[10,11]

Hydrogenated ester **5aa** and analogues are important intermediates for the synthesis of cygerol (a wound treatment ointment),[7e] perfumes, anti-ulcer agents and drugs for skin diseases; tandem ester **5na** is used as intermediate in the synthesis of the ophiobolins (natural products);[7f] tandem products **5ea**, **5ma** and analogues are used in the preparation of active anti-spasmodics;[7d] and tandem hydrogenated product **5lb** is used as a cockroach repellent[7a] in the USA. These applications emphasize the value of this tandem approach.

With pharmaceutical applications in mind, we extended the three-component tandem K/H reactions into a novel proline/Cs_2CO_3- and proline/K_2CO_3-catalyzed one-pot four-component K/H/A reaction of ketones **1**, CH-acids **2** and Hantzsch ester **3** with various alkyl halides **7a–f** (Table 5). Various 2,2-disubstituted ethyl cyanoacetates and malononitriles **8** were synthesized in good yields, as shown in Table 5.[11] We also demonstrated a direct

Table 5 Chemically diverse libraries of tandem K/H/A products **8**



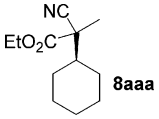
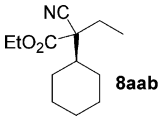
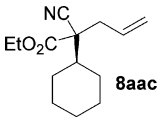
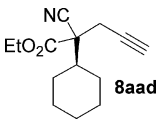
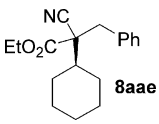
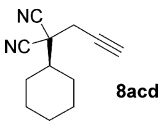
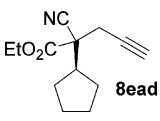
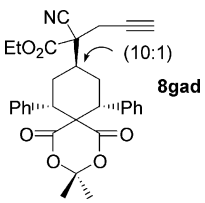
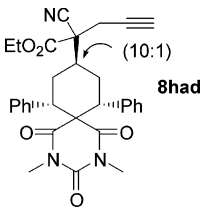
Entry	Base/solvent	Product	Yield (%)[a]
1	K_2CO_3/EtOH	 **8aaa**	65
2	K_2CO_3/EtOH	 **8aab**	65
3	K_2CO_3/EtOH	 **8aac**	80
4	K_2CO_3/EtOH	 **8aad**	80
5	K_2CO_3/EtOH	 **8aae**	99
6	K_2CO_3/DMSO	 **8acd**	80
7	K_2CO_3/DMSO	 **8ead**	90
8[b]	K_2CO_3/DMSO	 **8gad**	85
9[b]	K_2CO_3/DMSO	 **8had**	85

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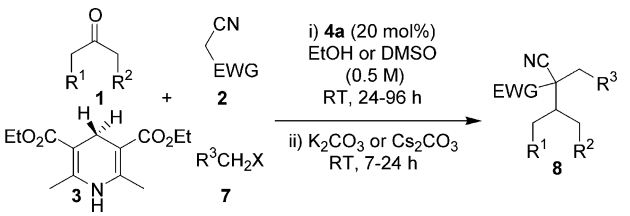
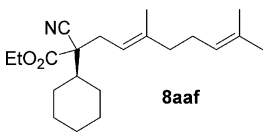
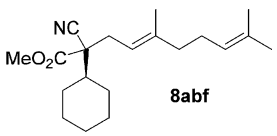
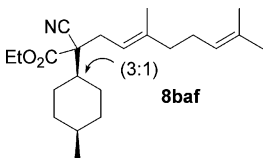
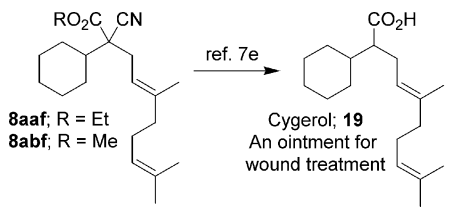
Table 5 (*Cont.*)



Entry	Base/solvent	Product	Yield (%)[a]
10	Cs_2CO_3/DMF	 **8aaf**	75
11	Cs_2CO_3/DMF	 **8abf**	65
12	Cs_2CO_3/DMF	 **8baf**	65

[a] Yield refers to the column-purified product. [b] Ratio determined by ^{1}H and ^{13}C NMR analysis.

organocatalytic approach to the synthesis of key intermediates of the pharmaceutical drug cygerol **19** in a single step (Table 5, entries 10–12). Decyanation followed by hydrolysis of **8aaf** or **8abf** furnished the cyclohexylgeranylacetic acid **19**, useful for wound healing, as demonstrated by Joseph and George in their patent (Scheme 3).[7e]



Scheme 3

In summary, we have developed direct amino acid/metal carbonate-catalyzed tandem K/H and K/H/A reactions which have direct application in drug discovery processes. This experimentally simple and environmentally friendly approach can be used to construct highly substituted hydrogenated products in a regioselective fashion with very good yields. For the first time in organocatalysis, pyridine nucleotide-linked dehydrogenases are mimicked in the laboratory. Further work is in progress to develop an asymmetric version of this tandem process.

We thank DST (New Delhi) for financial support. M. K. and G. B. R. thank CSIR (New Delhi) and UGC (New Delhi) respectively for their research fellowships.

Notes and references

† Representative experimental procedures:
Proline-catalyzed tandem Knoevenagel/hydrogenation reactions: In an ordinary glass vial equipped with a magnetic stirring bar, solvent (1.0 mL) was added to the ketone **1** (0.5 mmol), the CH-acid **2** (0.5 mmol) and the Hantzsch ester **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. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous work-up, and pure tandem products **5** were obtained by column chromatography (silica gel, hexane–ethyl acetate).
Proline/Cs_2CO_3 or K_2CO_3-catalyzed one-pot Knoevenagel/hydrogenation/alkylation reactions: In an ordinary glass vial equipped with a magnetic stirring bar, solvent (1.0 mL) was added to the ketone **1** (0.5 mmol), the CH-acid **2** (0.5 mmol) and the Hantzsch ester **3** (0.5 mmol). The proline catalyst **4a** (0.1 mmol) was added and the reaction mixture stirred at 25 °C for 24–96 h. RCH_2I or RCH_2Br **7** (2.5 mmol) and K_2CO_3 or Cs_2CO_3 (0.4 g) were then added and stirring continued at the same temperature for 7–24 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 **8** were obtained by column chromatography (silica gel, hexane–ethyl acetate).
Many of the tandem products **5** and **8** are commercially available, or have been described previously, and their analytical data match literature values. New compounds were characterized on the basis of IR, ^{1}H and ^{13}C NMR and analytical data.

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