Combining multi-catalysis and multi-component systems for the development of one-pot asymmetric reactions: stereoselective synthesis of highly functionalized bicyclo[4.4.0]decane-1,6-diones†

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We have developed a direct amine/acid-catalyzed stereoselective hydrogenation of a variety of Wieland–Miescher (W–M) ketones, Hajos–Parrish (H–P) ketones and their analogs with organic hydrides (Hantzsch esters) as the hydrogen source. This astonishingly simple and biomimetic approach was used to construct highly functionalized chiral bicyclo[4.4.0]decane-1,6-diones 6 in a diastereoselective fashion. This is an example of the development of a new technology by the combination of multiple catalysts and components in one pot to deliver highly functionalized chiral molecules.

Intense efforts have been made by the organic chemistry community in the synthesis of complex molecules, but lengthy processing times, wasteful and expensive routes are often required. Thus, targets of practical use (for example, pharmaceutical drugs and drug intermediates) can be challenging to produce even if they are only moderately complex. We believe that organic synthesis can be made much more efficient by designing processes in which multiple catalysts operate sequentially in one pot with multiple components. Ultimately, this approach should reduce the cost and waste associated with pharmaceutical synthesis.

The increasing demands for environmentally friendly and economic synthetic processes have promoted the development of the one-pot combination of multiple catalysts and multiple components to provide the desired products in the most efficient way.[1] It can be anticipated that this strategy could minimize processing times and the production of waste. The understanding and practice of this concept may be taken from cellular reactions, in which numerous enzymes function with the cooperation of two or more active sites derived from each enzyme to result in a "one-pot" transformation.[2]

Interestingly, an instructive example was demonstrated by A. Ian Scott and co-workers in 1994, in which corrin was synthesized *in vitro* from 5-aminolevulinic acid using 12 enzymes with an overall yield of 20% in a total of 17 steps in a single flask.[3] Mimicking of this type of bio-catalysis in artificial chemical catalysis would be of great interest to chemists. In this regard, extensive studies have been conducted on the preparation and utilization of multi-functional catalyst systems in organic synthesis. For example, catalysts that contain both Lewis-acidic and -basic sites have been elegantly utilized for the simultaneous activation of substrates and reagents, making possible multiple cascade reactions in a one-pot reaction.[4] Despite the significant developments recently achieved, increasing the number of starting components, accurately predicting the binding mode and the interaction between substrates and catalysts is still in its early stages, and thus a more systematic design and synthesis of multi-functional catalysts is still under development.[5]

Recent developments in amino acid-catalyzed cascade and multi-component reactions[6] give promise that this kind of catalysis is suitable for combining multi-catalysis and multi-component reactions in one pot to deliver highly functionalized molecules. Herein we report a highly chemo-, regio- and diastereoselective cascade Robinson annulation/hydrogenation reaction catalyzed by amines, amino acids, and Brønsted acids, providing highly substituted chiral hydrogenated Wieland–Miescher (W–M) ketones, Hajos–Parrish (H–P) ketones and their analogs **6**, starting from commercially available 2-alkylcyclohexane-1,3-diones or 2-alkylcyclopentane-1,3-diones **1a–g**, Hantzsch esters **2** and methyl vinyl ketones **3** (Scheme 1). The products **6** are attractive intermediates in natural product synthesis and materials chemistry, and are excellent starting materials for the synthesis of steroids.[7]

Most of the hydrogenated W–M and H–P ketones contain *trans*-fused decalin systems. As a result, there is a substantial amount of literature on the synthesis and reactivity of enone **5**, some of its simple derivatives, and its *trans*-fused reduction products.[8] In contrast, there is less information on the reactivity of the corresponding *cis*-fused decalones, perhaps because *trans*-fused decalins are more common features in terpenoids and steroids than the corresponding *cis*-fused systems. With our own interest in the development of diversity-oriented synthesis of functionalized chiral products that incorporate a *cis*-fused decalin ring prompted us to investigate *cis*-fused decalin synthesis.

In our multi-catalysis/multi-component reaction we envisioned that simple amines, triethylamine or amino acids, *e.g.* proline **4**, would catalyze the regioselective cascade Michael reaction of **1** with methyl vinyl ketone **3** to provide Michael adduct *via* base or iminium catalysis, which would then undergo a Robinson annulation through amino acid/Brønsted acid catalysis to furnish the chiral W–M/H–P ketones **5** and their analogs as shown in Scheme 1. Further treatment of products **5** with Hantzsch ester **2** and catalyst diamine **4** would generate the highly functionalized hydrogenated W–M/H–P ketones and their analogs **6** in one pot as shown in Scheme 1. The cascade Robinson annulation–hydrogenation reaction sequence would then generate a quaternary center with formation of two new carbon–carbon σ-bonds, and two carbon–hydrogen bonds respectively, *via* amine/amino acid/bifunctional amine acid catalysis.

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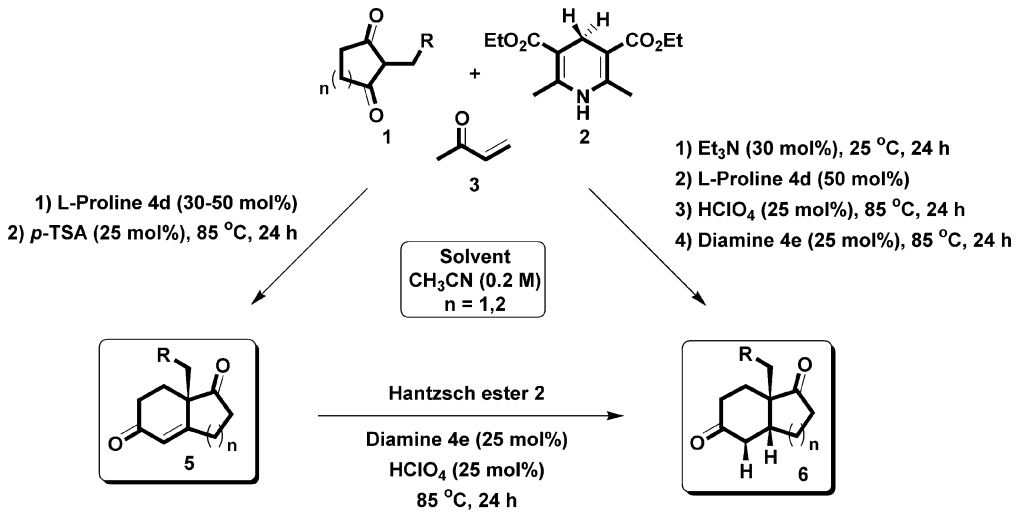
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds; crystal structure data for **6a**. See DOI: 10.1039/b806243a



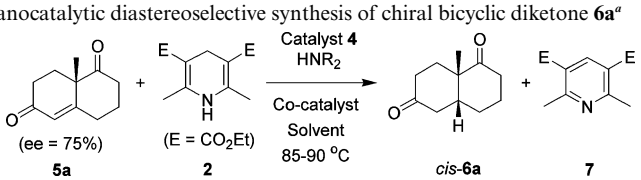
Scheme 1 Combining multi-catalysis and multi-component systems for one-pot asymmetric reactions.

First, we initiated our studies for the optimization of chemo-, regio- and diastereoselective biomimetic hydrogenation of W–M ketone **5a** *via* direct organocatalysis, and then applied this to the diversity-oriented synthesis of hydrogenated products **6** in stereoselective manner. Then we utilized the optimized biomimetic hydrogenation conditions to the development of a multi-catalysis/multi-component synthesis of hydrogenated W–M and H–P ketones **6** in one pot with good yields and selectivities.‡

During our investigations on amino acid-catalyzed double cascade synthesis of W–M ketone analogs **5**,[6w] we envisioned that W–M ketone and their analogs **5** can undergo biomimetic stereoselective hydrogenation with **2** under amine or amino acid catalysis. Here we chose chiral W–M ketone **5a** for the optimization of hydrogenation with **2** *via* organocatalysis as shown in Table 1. Interestingly, reaction of W–M ketone **5a** and Hantzsch ester **2** with one equiv. of L-proline **4d** in CH_3CN at 85–90 °C for 14 h furnished the hydrogenated product **6a** in only 20% yield with *cis*-fused isomer **6a** as the major isomer with >99% de (Table 1, entry 4).

A number of organic amines and amine/acid combinations were tested as catalysts using the hydrogenation of W–M ketone **5a** as a benchmark, at 85–90 °C in various solvents (Table 1). (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine **4e** and $HClO_4$ (Table 1, entry 6) were the best catalysts for hydrogenation of W–M ketone **5a** compared to amines **4d–e** (Table 1, entries 4 and 12), acids $HClO_4$, AcOH, $(PhO)_2PO_2H$ (entry 13) and (*R*)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (entry 14) and other amine/acid bi-functional catalysts (entries 1–11). When the loading of organic hydride **2** was changed from 1 equiv. to 2 equiv. for the hydrogenation of enone **5a** under **4e**/$HClO_4$-catalysis in CH_3CN at 90 °C for 8 h, the product yield increased from 50% to 80% (entries 5 and 6). Interestingly, there is no reaction in other solvents like DMSO

Table 1 Optimization of the direct organocatalytic diastereoselective synthesis of chiral bicyclic diketone **6a**[a]



Entry	Catalyst (25 mol%)	Co-catalyst (25 mol%)	Hantzsch ester **2** (equiv.)	Solvent (0.2 M)	Time/h	Yield (%)[b]	de[c]
1[d]	Pyrrolidine **4a**	$HClO_4$	1.0	CH_3CN	20	33	>99
2[d]	Piperidine **4b**	$HClO_4$	1.0	CH_3CN	30	50	>99
3[d]	Morpholine **4c**	$HClO_4$	1.0	CH_3CN	3	40	>99
4[d]	Proline **4d**	—	1.0	CH_3CN	14	20	>99
5[e]	Diamine **4e**	$HClO_4$	1.0	CH_3CN	8	50	>99
6	**Diamine 4e**	**$HClO_4$**	**2.0**	**CH_3CN**	**8**	**80**	**>99**
7	Diamine **4e**	CH_3CO_2H	2.0	CH_3CN	16	72	>99
8[f]	Diamine **4e**	$HClO_4$	2.0	DMSO	45	<5	—
9[f]	Diamine **4e**	$HClO_4$	2.0	DMF	45	<5	—
10	Diamine **4e**	$HClO_4$	2.0	$CHCl_3$	12	70	>99
11	Diamine **4e**	$HClO_4$	2.0	EtOH	15	55	>99
12[f]	Diamine **4e**	—	2.0	CH_3CN	24	—	—
13[f]	—	$(PhO)_2PO_2H$	2.0	CH_3CN	24	—	—
14[f]	—	(*R*)-BNDHP[g]	2.0	CH_3CN	36	—	—

[a] Reactions were carried out in solvent (0.2 M) with 1.0 to 2.0 equiv. of **2** relative to **5a** in the presence of 25 mol% of catalyst **4** and 25 mol% of co-catalyst. [b] Yield refers to the column-purified product. [c] Diastereomeric excess was determined by NMR analysis. [d] 100 mol% of catalyst **4a–d** and 100 mol% of co-catalyst were used. [e] (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine **4e**. [f] 80 to 95% of starting material **5a** was isolated. [g] (*R*)-1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate.

and DMF (entries 8 and 9). Amines or acids did not catalyze the biomimetic hydrogenation reaction of **5a** with **2** directly, but certain amine/acid combinations could catalyze it (entry 6) and this is a good support for the iminium ion catalysis rather than acid/base catalysis. Interestingly, using 25 mol% of **4e**/$HClO_4$ as a catalyst, the hydrogenation reaction worked well in CH_3CN and $CHCl_3$. The optimal conditions involved mixing W–M ketone **5a**, 2 equiv. of Hantzsch ester **2**, 25 mol% of diamine **4e** and 25 mol% of $HClO_4$ in CH_3CN with heating to 90 °C for 8 h to furnish *cis*-isomer **6a** as a single diastereomer in 80% yield (entry 6). The structure and regiochemistry of hydrogenated product **6a** were confirmed by NMR analysis and also by X-ray structure analysis, as shown in Fig. 1.

With an efficient **4e**/$HClO_4$-catalyzed stereoselective hydrogenation protocol in hand, the scope of the reaction was investigated with various chiral W–M ketones, H–P ketones and their analogs **5** with Hantzsch ester **2**. A series of 9-alkyl W–M ketone analogs **5b–e** were reacted with 2.0 equiv. of Hantzsch ester **2** catalyzed by 25 mol% of **4e**/$HClO_4$ at 85–90 °C in CH_3CN for 24–36 h (Table 2, entries 1–5). All expected hydrogenated W–M ketone

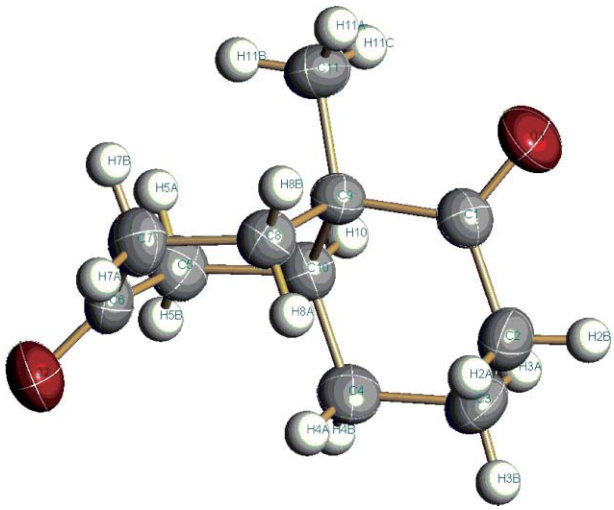
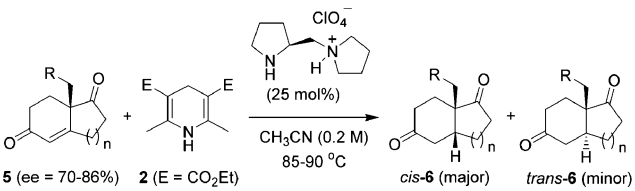
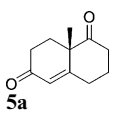
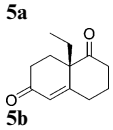
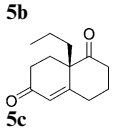
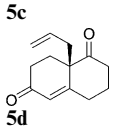
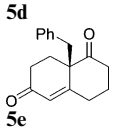
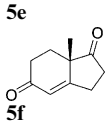
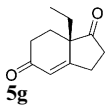


Fig. 1 Crystal structure of (9*R*,10*S*)-9-methylbicyclo[4.4.0]decane-1,6-dione (**6a**). CCDC reference number 684132. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b806243a

Table 2 Direct organocatalytic diastereoselective synthesis of chiral bicyclic diketones **6**[a]



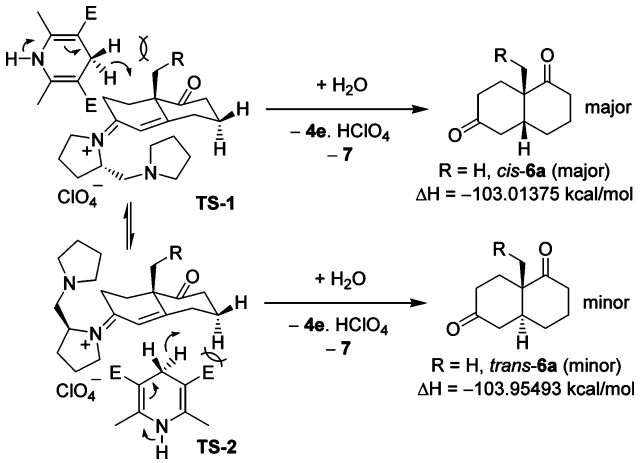
Entry	Chiral enone **5**	ee of chiral enone **5**[b]	Time/h	Yield (%)[c] **6a–g**	de[d] *cis*-**6a–g**
1	 **5a**	75	8	80	>99
2	 **5b**	75	24	70	60
3	 **5c**	73	32	70	60
4[e]	 **5d**	73	36	55	82
5	 **5e**	70	33	75	50
6	 **5f**	86	38	73	>99
7[e]	 **5g**	85	50	45	70

[a] Reactions were carried out in CH_3CN (0.2 M) with 2.0 equiv. of **2** relative to the **5a–g** in the presence of 25 mol% of catalyst **4e** and 25 mol% of co-catalyst. [b] Enantiomeric excesses were determined by HPLC analysis. [c] Yield refers to the column purified product. [d] Diastereomeric excesses were determined by NMR analysis. [e] 30 to 50% of starting materials **5d** and **5g** were isolated.

analogs *cis*-**6b–e** were obtained in good yields with 50 to 82% de. Interestingly, in these reactions the diastereoselectivities of the 9-alkyl-substituted W–M ketone analogs **6b–e** decreased to 50–82% de, in contrast to 9-methyl substitution. The mechanistic aspect of this selectivity is discussed below. The biomimetic **4e**/$HClO_4$-catalyzed hydrogenation reaction of H–P ketone **5f** with 2 equiv. of **2** at 85–90 °C in CH_3CN for 38 h furnished the expected hydrogenated product *cis*-**6f** in 73% yield with >99% de (entry 6). Interestingly, the same reaction with 8-ethyl-substituted H–P ketone analog **5g** furnished the expected hydrogenated product *cis*-**6g** in 45% yield with only 70% de (entry 7).

After this successful demonstration of biomimetic hydrogenation of W–M ketones, H–P ketones and their analogs, we decided to investigate the one-pot asymmetric synthesis of hydrogenated W–M and H–P ketones *cis*-**6a** and *cis*-**6f** (see Scheme 2). Reaction of three equiv. of methyl vinyl ketone **3** with 2-methylcyclohexane-1,3-dione **1a** under Et_3N catalysis in CH_3CN at 25 °C for 24 h furnished the expected Michael adduct, 2-methyl-2-(3-oxobutyl)cyclohexane-1,3-dione in good yield. 50 mol% of L-proline **4d** and 25 mol% of $HClO_4$ were added to the crude reaction mixture and stirring continued at 85 °C for 24 h to furnish the expected W–M ketone **5a** in good yield with 75% ee. This, on treatment with two equiv. of Hantzsch ester **2** and 25 mol% of (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **4e** at 85 °C for 24 h, furnished the expected hydrogenated W–M ketone *cis*-**6a** in 45% yield with >99% de (Scheme 2). Interestingly, for the synthesis of *cis*-**6a**, our strategy did not show much difference in terms of enantioselectivity compared to the two-component reaction catalyzed by L-proline **4d**. However, there was a difference in the synthesis of hydrogenated H–P ketone *cis*-**6f**, for which the ee drastically decreased from 86% to 20%, as shown in Scheme 2. This may be because of the involvement of Et_3N in the transition state of the proline-mediated asymmetric intra-molecular aldol reaction.

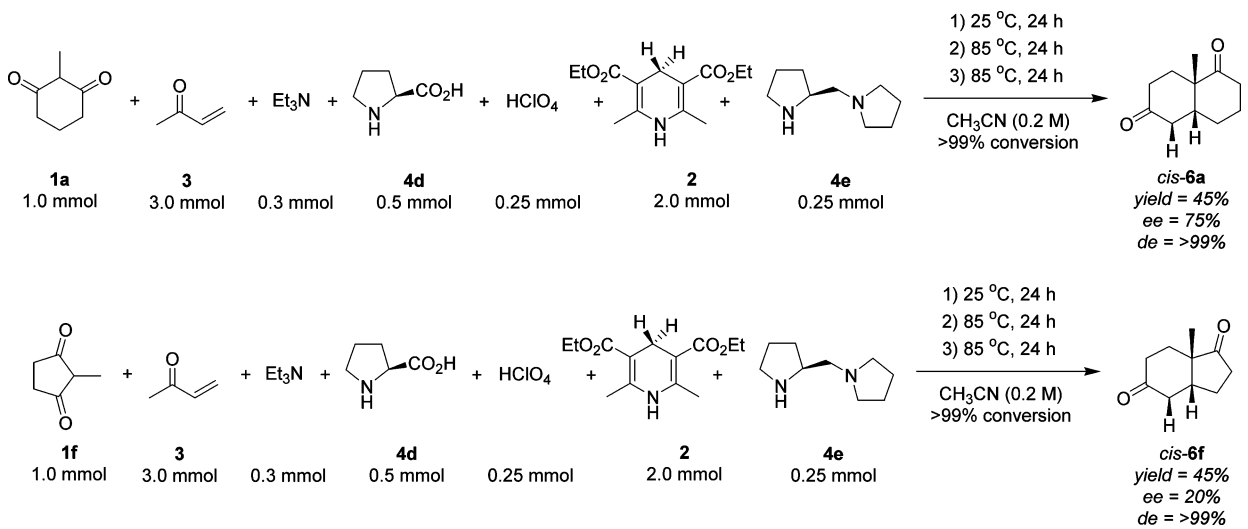
The observed high regio- and diastereoselectivities of the one-pot-hydrogenated products **6a–g** can be explained as shown in Scheme 3. The approach of the organic hydride source (Hantzsch ester **2**) to iminium ions generated *in situ* is the main controlling factor apart from the thermodynamic stability of the resulting



Scheme 3 Proposed mechanism for the **4e**-catalyzed *syn*-selective hydrogenation reactions.

hydrogenated products *cis*-**6a–g**/*trans*-**6a–g**. Approach of the Hantzsch ester **2** to the *exo*-face of the iminium ion (the same side as the alkyl group), **TS-1**, is more favourable than through the *endo*-face (opposite to the alkyl group), **TS-2**. This may be due to the existence of more steric hindrance in an *endo* approach. As shown in Scheme 3, steric strain control is the main controlling factor, not product stability control, because the thermodynamically stable isomers *trans*-**6a–g** are formed as the *minor* products. Also, as shown in Table 2 and Scheme 3, the bulkiness of the alkyl group decreases the amount of *cis*-attack and increases the *trans*-attack of hydride source to imines. This type of selectivity trend can be easily understood by the approach of bulk organic hydride source **2** to active imines generated *in situ*.

In summary, we have developed the direct amine/acid-catalyzed stereoselective hydrogenation of variety of W–M ketones, H–P ketones and their analogs with organic hydride as the hydrogen source. This astonishingly simple and biomimetic approach can be used to construct highly functionalized chiral bicyclo[4.4.0]decane-1,6-diones **6** in a diastereoselective fashion. In this paper, we have developed a new concept by combining



Scheme 2 Combining multi-catalysis and multi-component systems for one-pot asymmetric reactions.

multiple catalysts and multiple components in one pot to deliver highly functionalized molecules. Reactions of this type inspire analogies with cellular reactions and compliment traditional organic reactions. As we have suggested previously, the synthesis of poly-functionalized molecules using amino acid catalysis provides a unique and under-explored perspective on prebiotic synthesis.

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Notes and references

‡ **Representative experimental procedures: General procedure for the reduction of unsaturated cyclic enones:** (*S*)-(+)-1-(2-Pyrrolidinylmethyl)-pyrrolidine **4e** (0.019 g, 0.125 mmol) and 70% $HClO_4$ (8 μL, 0.125 mmol) in dry CH_3CN (1.0 mL) were stirred at 25 °C for 10 minutes, and then of chiral enone **5** (0.5 mmol) in CH_3CN (1.0 mL) were added slowly and stirring was continued at the same temperature for 5 min. To the reaction mixture was added Hantzsch ester **2** (0.253 g, 1 mmol), and the mixture refluxed for 8 h. The crude reaction mixture was worked up with aqueous NH_4Cl or $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure hydrogenated products **6** were obtained by column chromatography (silica gel, hexane–ethyl acetate). **Amine/amino acid/acid/amine-catalyzed one-pot Michael–Robinson annulation–hydrogenation reactions:** In an ordinary glass vial equipped with a magnetic stirring bar, to CH-acid **1** (1.0 mmol) and triethylamine (0.30 mmol) was added of CH_3CN (3.0 mL), and then freshly distilled methyl vinyl ketone (0.25 mL, 3.0 mmol) was added and the reaction mixture was stirred at 25 °C for 24 h. To the reaction mixture was added L-proline **4a** (58 mg, 0.5 mmol) and 70% $HClO_4$ (15 μL, 0.25 mmol), and the mixture refluxed for 24 h. After confirmation of complete conversion of the Michael adduct into the enone **5** by TLC, (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine **4e** (38 mg, 0.25 mmol) and Hantzsch ester **2** (506 mg, 2.0 mmol) were added and refluxing continued for 24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot products **6** were obtained by column chromatography (silica gel, hexane–ethyl acetate). Many of the cascade products **6** 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 ESI).

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