JOC Article

Organocatalytic Sequential One-Pot Double Cascade Asymmetric Synthesis of Wieland−Miescher Ketone Analogues from a Knoevenagel/Hydrogenation/Robinson Annulation Sequence: Scope and Applications of Organocatalytic Biomimetic Reductions

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A practical and novel organocatalytic chemo- and enantioselective process for the cascade synthesis of highly substituted 2-alkyl-cyclohexane-1,3-diones and Wieland−Miescher (W−M) ketone analogs is presented via reductive alkylation as a key step. First time, we developed the one-step alkylation of dimedone and 1,3-cyclohexanedione with aldehydes and Hantzsch ester through an organocatalytic reductive alkylation strategy. Direct combination of L-proline-catalyzed cascade Knoevenagel/hydrogenation and cascade Robinson annulation of CH acids (dimedone and 1,3-cyclohexanedione), aldehydes, Hantzsch ester, and methyl vinyl ketone furnished the highly functionalized W−M ketone analogues in good to high yields and with excellent enantioselectivities. Many of the reductive alkylation products show a direct application in pharmaceutical chemistry.

Introduction

Critical objectives in modern organic chemistry include the improvement of reaction efficiency, the avoidance of toxic reagents, the reduction of waste, and the responsible utilization of our resources. Organocatalytic cascade reactions, which consist of several bond-forming reactions, address many of these objectives.[1] Organocatalytic cascade reactions involve two or more bond-forming transformations that take place under the same reaction conditions from simple starting materials catalyzed by small molecular units of antibodies or enzymes.[1] One of the ultimate goals in organic synthesis is the catalytic asymmetric assembly of simple and readily available precursor molecules into bioactive products, a process that ultimately mimics biological synthesis. Cascade reactions have gained wide acceptance because they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used.[2] Thus, these reactions can facilitate ecologically and economically favorable syntheses such as in vitro biological reactions.[2]

We are in the "golden age of organocatalysis", and organocatalytic reactions have in the past few years emerged as a powerful synthetic tool for the construction of highly functionalized and optically active compounds.[3] Especially, organocatalytic cascade or tandem reactions have emerged as ideal synthetic strategies for the synthesis of highly functionalized compounds and drug-like small molecules in one-pot syntheses, mimicking biological reactions.[4]

The use of natural and unnatural amino acids and chiral secondary amines as catalysts for the α-functionalization of

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aldehydes and ketones via iminium and enamine formation represents an important breakthrough in modern asymmetric synthesis, and a large variety of functionalizations, such as C−C,[5] C−N,[6] C−O,[7] C−S,[8] and C−X (X = halogen)[9] bond-forming reactions among others, has been developed. The combination of two or more organocatalytic reactions with a proper synthetic plan utilizing one or more organocatalysts in a one-pot synthesis delivers complex products, which is presently being developed as a new strategy in cascade reactions.

A natural amino acid, proline, is certainly part of this noble catalyst club, and in the recent past, it has been defined as a universal catalyst and a simple enzyme because of its high utility especially in enantioselective aldol,[10] Mannich,[11] amination,[6] and α-aminoxylation reactions.[7]

As part of our program to engineer direct organocatalytic cascade or multicomponent reactions,[4a−e] herein we report the first organocatalytic asymmetric chemoselective direct cascade Knoevenagel/hydrogenation (K/H) and Knoevenagel/hydrogenation/Robinson annulation (K/H/RA) reactions that produce very useful drug synthons, 2-alkyl-cyclohexane-1,3-diones **7** and Wieland−Miescher (W−M) ketone analogues **10** from commercially available cyclohexane-1,3-diones **1**, aldehydes **2**, Hantzsch ester **3**, methyl vinyl ketone **9**, and amino acid **4** as shown in Scheme 1. 2-Alkyl-cyclohexane-1,3-diones **7** and W−M ketone analogues **10** are attractive intermediates in the synthesis of natural products and in medicinal chemistry,[12] while 2-alkyl-cyclohexane-1,3-diones **7** have a broad utility in pharmaceutical chemistry[13] and are excellent starting materials in the natural product synthesis as shown in Chart 1. Hence, their preparation has continued to attract considerable synthetic interest in developing new methods for their syntheses.[14]

Surprisingly, there is no direct method for the synthesis of useful 2-alkyl-cyclohexane-1,3-diones **7**, and only two-step methods are known to prepare them.[14] Recently, Paquette et al. developed the two-step synthesis of 2-alkyl-cyclohexane-1,3-diones **7** in moderate to good yields via an in situ protection and deprotection sequence on 2-alkylidene-1,3-diones **5** with

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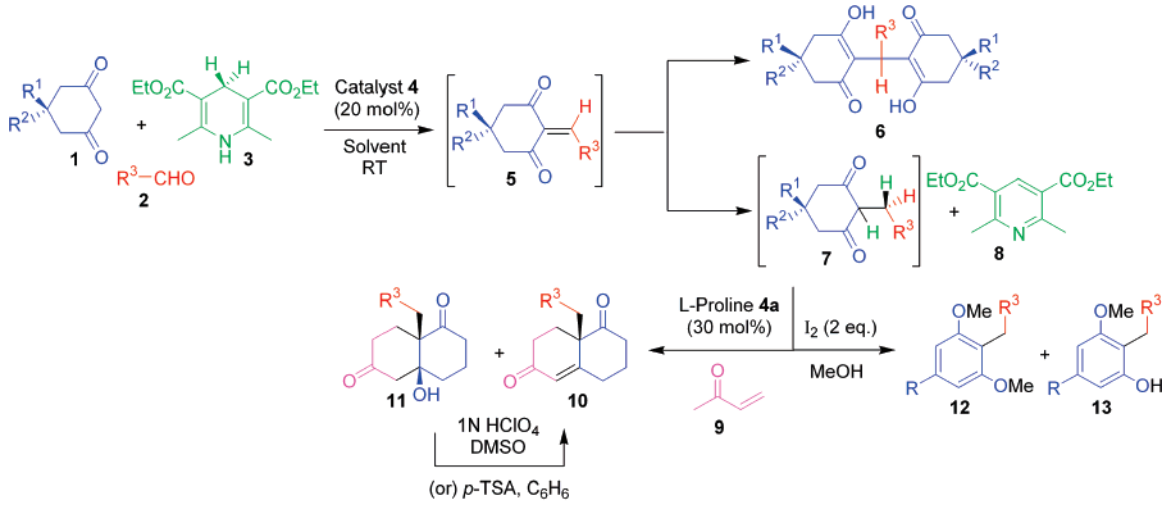
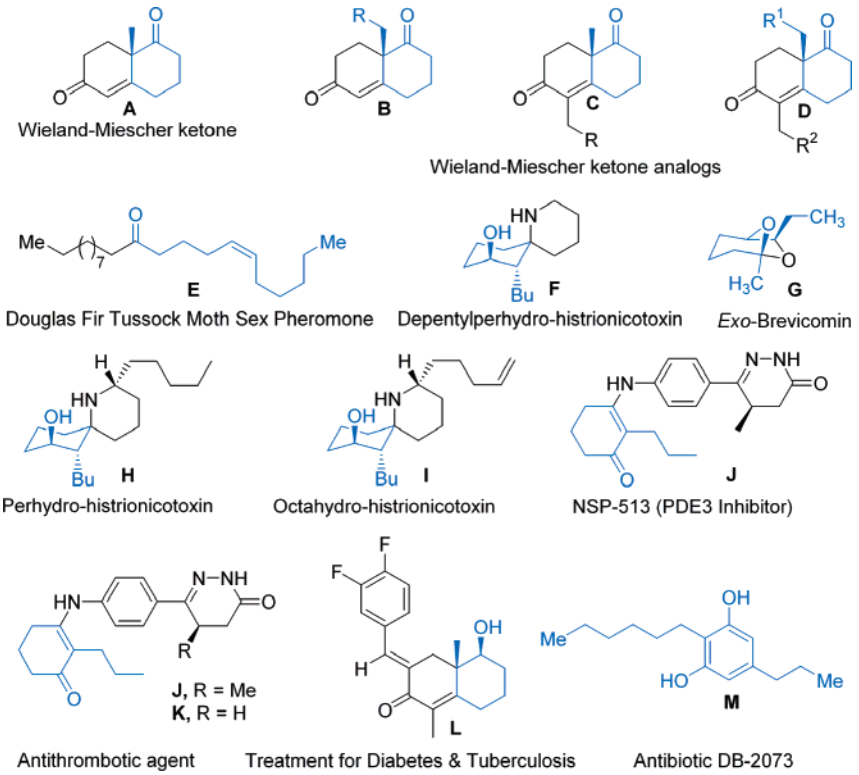
SCHEME 1. Direct Organocatalytic Asymmetric Cascade K/H and K/H/RA Reactions



Substrates and Catalysts Screened:

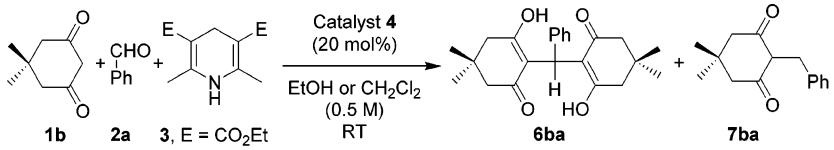
1a: $R^1 = R^2 = H$
1b: $R^1 = R^2 = Me$
1c: $R^1 = H$, $R^2 = Ph$
2a: $R^3 = C_6H_5$
2b: R^3 = 1-Naphthalenyl
2c: $R^3 = 3,4\text{-}(OCH_2O)C_6H_3$
2d: $R^3 = 4\text{-}CNC_6H_4$
2e: $R^3 = 4\text{-}NO_2C_6H_4$
2f: $R^3 = 4\text{-}FC_6H_4$
2g: $R^3 = 4\text{-}ClC_6H_4$
2h: $R^3 = 3\text{-}ClC_6H_4$
2i: $R^3 = 4\text{-}BrC_6H_4$
2j: $R^3 = trans\text{-}C_6H_5CH{=}CH$
2k: $R^3 = trans\text{-}2\text{-}NO_2C_6H_4CH{=}CH$
2l: $R^3 = CH_3$
2m: $R^3 = CH_3CH_2$
2n: $R^3 = CH_3CH_2CH_2$
2o: $R^3 = CH_3CH_2CH_2CH_2$
2p: $R^3 = CH_3CH_2CH_2CH_2CH_2$
2q: $R^3 = C_6H_{11}$
4a: L-Proline
4b: D-Proline
4c: Triethyl amine
4d: Quinine
4e: Acetic acid

CHART 1. Natural and Unnatural Products Library Generated from 2-Alkyl-cyclohexane-1,3-diones



thiophenol and Raney nickel, respectively.[14f,g] As shown in Scheme 1, the well-recognized fact is the inability to arrest Knoevenagel reactions involving CH acids **1** (dimedone and 1,3-cyclohexanedione) and aliphatic or aromatic aldehydes **2** at the monoaddition stage.[15] Very few adducts such as **5** have been isolated.[16] This is because these Knoevenagel products **5** are highly reactive Michael acceptors capable of engaging the unreacted CH acid reagent in kinetically rapid 1,4-addition to

TABLE 1. Preliminary Studies on Reductive In Situ Trapping of 2-Alkylidene-cyclohexane-1,3-diones[a]



entry	catalyst **4** (20 mol %)	aldehyde **2a** (equiv)	H. ester **3** (equiv)	time (h)	products **6ba**	yield (%)[b] **7ba**
1		5.0		2	>95	
2	proline **4a**	5.0		1	>95	
3		2.0	1.0	24	50	50
4		3.0	1.0	24	17	83
5	proline **4a**	3.0	1.0	12	10	90
6[c]	proline **4a**	3.0	1.0	3	10	90
7[c]	triethyl amine **4c**	3.0	1.0	3	95	5
8[c]	quinine **4d**	3.0	1.0	3	95	5
9[c]	acetic acid **4e**	3.0	1.0	20	33	67
10[c]	pyridine **8**	3.0	1.0	24	20	80
11[c]		3.0	1.0	24	20	80

[a] Reactions were carried out in EtOH or CH_2Cl_2 (0.5 M) with 2.0−5.0 equiv of **2a** and 1.0 equiv of **3** relative to **1b** (0.5 mmol) in the presence of 20 mol % of catalyst **4**. [b] Yield refers to the column purified product. [c] CH_2Cl_2 (0.5 M) used as solvent.

give bis-adducts such as **6**. Also, there is no report on the asymmetric synthesis of higher alkyl substituted W−M ketone analogues **10**. This has prompted us to investigate the cascade synthesis of very useful 2-alkyl-cyclohexane-1,3-diones **7** and W−M ketone analogs **10** in a single step through mild amino acid-catalysis.

We therefore set out to develop an amino acid-catalyzed asymmetric cascade synthesis of W−M ketones **10** from simple starting materials, which have not been prepared in the past. In this article, we present the development and application of the proline-catalyzed reductive alkylation of CH acids through the cascade K/H reaction of reactive CH acids **1** (dimedone and 1,3-cyclohexanedione), aldehydes **2**, and Hantzsch ester **3**. Furthermore, we will present mechanistic insight into the reaction course, applying a new concept of self-catalysis leading to an understanding of the cascade K/H reaction.

We envisioned that an amino acid would catalyze the cascade Knoevenagel condensation of CH acid **1** with an aldehyde **2** to form substituted 2-alkylidene-cyclohexane-1,3-diones **5**, which are very reactive intermediates and further undergo chemoselective reactions with both CH acids **1** and Hantzsch ester **3** to produce bis-adducts **6** and hydrogenated 2-alkyl-cyclohexane-1,3-diones **7**, respectively, based on reaction conditions. Proline-catalyzed Robinson annulation of products **7** with methyl vinyl ketone **9** furnishes the W−M ketones **10** and alcohols **11** in good yield with interesting enantioselectivity, and alcohol **11** could be converted into ketone **10** without losing enantioselectivity as shown in Scheme 1.

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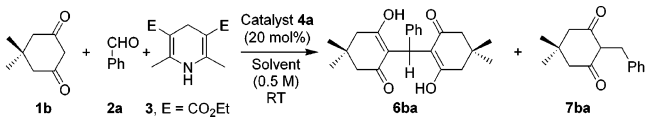
TABLE 2. Effect of Solvent on Direct Amino Acid-Catalyzed Reductive Alkylation of Dimedone 1b with 2a and 3[a]



entry	solvent (0.5 M)	aldehyde **2a** (equiv)	time (h)	products **6ba**	yield (%)[b] **7ba**
1	EtOH	5.0	12	5	95
2	EtOH	3.0	12	10	90
3	MeOH	3.0	24	10	90
4	H_2O	3.0	24	13	87
5	DMSO	3.0	24	20	80
6	DMF	3.0	24	15	85
7	CH_3CN	3.0	24	10	90
8	CH_2Cl_2	3.0	12	3	97
9	CH_2Cl_2	1.0	12	5	95

[a] Reactions were carried out in solvent (0.5 M) with 1.0−5.0 equiv of **2a** and 1.0 equiv of **3** relative to **1b** (0.5 mmol) in the presence of 20 mol % of proline **4a**. [b] Yield refers to the column purified product.

Results and Discussion

Preliminary Studies on Reductive in Situ Trapping of 2-Alkylidene-cyclohexane-1,3-diones. On the basis of our recent discovery of biomimetic reduction of novel active olefins with Hantzsch ester **3** through self-catalysis by decreasing the HOMO−LUMO energy gap between olefins and Hantzsch ester **3**,[4b−d] we initiated our preliminary studies of the reductive in situ trapping of 2-benzylidene-5,5-dimethyl-cyclohexane-1,3-dione **5ba** as shown in Table 1. (In all compounds denoted **5xy**, **6xy**, **7xy**, **10xy**, **11xy**, **12xy**, **13xy**, and **14xy**, **x** is incorporated from reactant CH acids **1**, and **y** is incorporated from the reactant aldehydes **2**.)

The self-catalyzed reaction of dimedone **1b** with 5 equiv of benzaldehyde **2a** furnished the only unexpected bis-adduct **6ba** without the expected Knoevenagel product **5ba** (Table 1, entry 1). The same reaction under proline catalysis also furnished the only bis-adduct **6ba** without product **5ba** with reduced reaction time (Table 1, entry 2). Interestingly, the self-catalyzed reaction of dimedone **1b** and 2 equiv of benzaldehyde **2a** with Hantzsch

ester **3** furnished the bis-adduct **6ba** and the expected reductive alkylation product **7ba** in a 1:1 ratio with 99% yield after 24 h at 25 °C (Table 1, entry 3). The self-catalyzed reductive alkylation reaction with 3 equiv of benzaldehyde **2a** furnished the product **7ba** in 83% yield (Table 1, entry 4). Interestingly, the same reaction under proline catalysis furnished the expected reductive alkylation product **7ba** with 90% yield after 12 h at 25 °C in EtOH as shown in Table 1, entry 5. The same reaction under proline catalysis in CH_2Cl_2 furnished the expected product **7ba** in 90% yield with a reduced reaction time (Table 1, entry 6). The reductive alkylation reaction under base catalysis in CH_2Cl_2 furnished the bis-adduct **6ba** as a major product (Table 1, entries 7 and 8). The same reaction under acid catalysis in CH_2Cl_2 furnished the bis-adduct **6ba** and reductive alkylation product **7ba** in a 1:2 ratio with 99% yield after 20 h at 25 °C (Table 1, entry 9). There is not much effect of the byproduct pyridine **8** on the reductive alkylation reaction as shown Table 1, entries 10 and 11. These preliminary results prompted us to investigate the solvent effect on in situ trapping of the Knoevenagel product of dimedone **1b** with benzaldehyde **2a** through biomimetic hydrogenation as shown in Table 2.

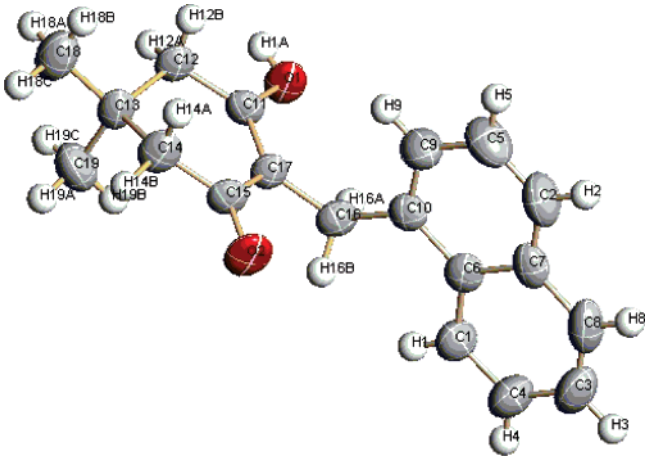


FIGURE 1. Crystal structure of 3-hydroxy-5,5-dimethyl-2-naphthalen-1-ylmethyl-cyclohex-2-enone (**7bb**).

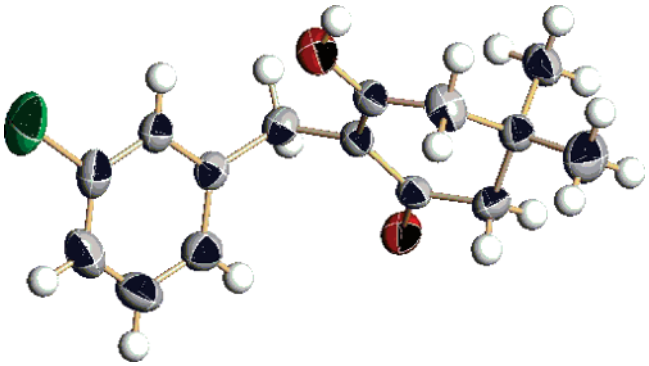


FIGURE 2. Crystal structure of 2-(3-chloro-benzyl)-3-hydroxy-5,5-dimethyl-cyclohex-2-enone (**7bh**).

Direct Organocatalyzed Cascade Reductive Alkylation of Dimedone: Reaction Optimization. We were pleased to find that proline-catalyzed reductive alkylation or the cascade K/H reaction of dimedone **1b** and benzaldehyde **2a** (5 equiv) with Hantzsch ester **3** furnished the expected product **7ba** in 95% yield after 12 h at 25 °C (Table 2, entry 1). Interestingly, there is little solvent effect on the direct proline-catalyzed reductive alkylation or cascade K/H reaction of **1b**, **2a**, and **3** as shown in Table 2. The proline-catalyzed cascade K/H reaction can be performed in three types of solvents (protic polar, aprotic polar, and aprotic nonpolar) with good yields as shown in Table 2. Surprisingly, the cascade K/H reaction of **1b**, **2a**, and **3** in H_2O also furnished the expected hydrogenated product **7ba** in 87% yield after 24 h at 25 °C (Table 2, entry 4). We envisioned the optimized condition to be mixing the equivalent molar ratios

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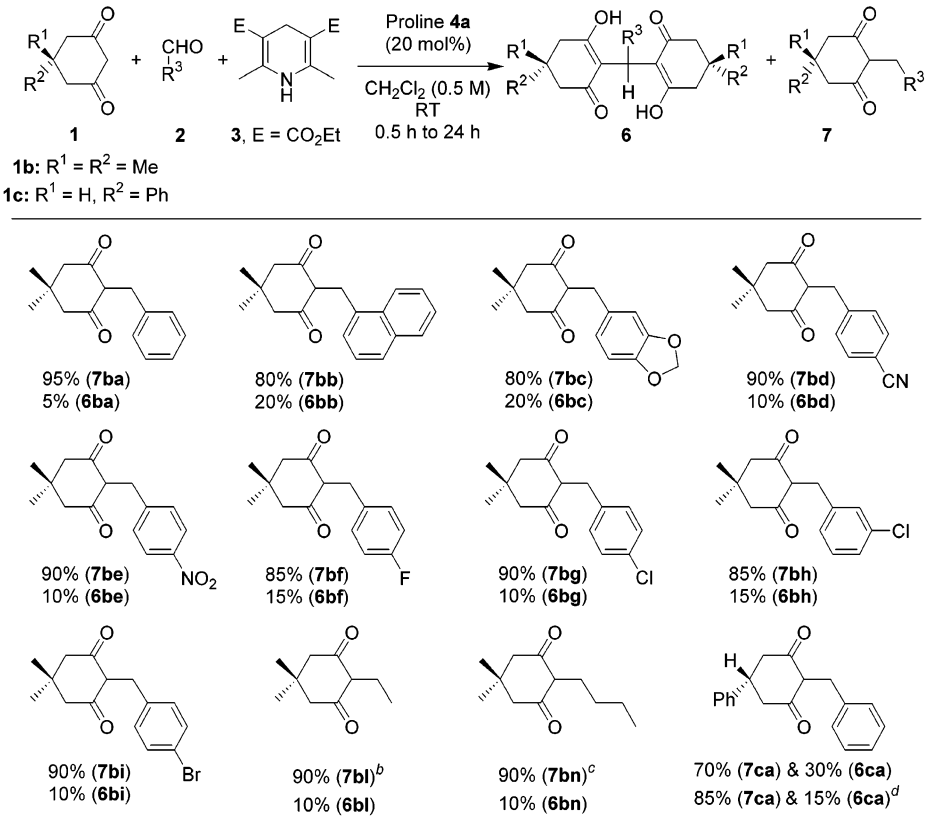
TABLE 3. Synthesis of Reductive Alkylation Library via Cascade K/H Reactions from Dimedone 1 and Aldehydes 2[a]



[a] Yield refers to the column purified product. [b] Acetaldehyde **2l** was taken as 5 equiv, and reaction time was 1 h. [c] Butyraldehyde **2n** was taken as 2 equiv, and reaction time was 0.5 h. [d] Benzaldehyde **2a** was taken as 3 equiv.

of starting materials at 25 °C in CH_2Cl_2 under 20 mol % of proline catalysis to furnish hydrogenated product **7ba** in 95% yield (Table 2, entry 9).

Diversity-Oriented Synthesis of Reductive Alkylation Products 7ba−7bn. With an efficient organocatalytic cascade reductive alkylation protocol in hand, the scope of the proline-catalyzed cascade K/H reactions was investigated with various aldehydes **2a**−**n** and CH acids **1b**,**c**. A series of aromatic and aliphatic aldehydes **2a**−**n** was reacted with 1.0 equiv of dimedone **1b** or 5-phenyl-cyclohexane-1,3-dione **1c** catalyzed by 20 mol % of proline at 25 °C in CH_2Cl_2 (Table 3). The 2-alkyl-5,5-dimethyl-cyclohexane-1,3-diones **7ba**−**7bn** and 2-alkyl-5-phenyl-cyclohexane-1,3-diones **7ca** were obtained as single isomers with excellent yields. The reaction of dimedone **1b** with naphthalene-1-carbaldehyde **2b** furnished the reductive alkylation product **7bb** as a single isomer, in good yield (Table 3). The synthesis of 2-arylmethyl-5,5-dimethyl-cyclohexane-1,3-diones **7ba**−**7bi** from **1b**, **2a**−**i**, and **3** at 25 °C under proline catalysis has a longer reaction time (24 h), as compared to aliphatic aldehydes **2l**−**n** (Table 3). Both aliphatic aldehydes **2l**−**n** generated expected 2-alkyl-5,5-dimethyl-cyclohexane-1,3-diones **7bl**−**7bn** with dimedone **1b** in excellent yields (Table 3). The results in Table 3 demonstrate the broad scope of this reductive cascade methodology covering a structurally diverse group of aldehydes **2a**−**n** and CH acids **1b**,**c** with many of the yields obtained being very good, or indeed better, than previously published two-step alkylation reactions.[14] Structure and regiochemistry of 2-alkyl-5,5-dimethyl-cyclohexane-1,3-diones **7ba**−**7bn** were confirmed by X-ray structure analysis on **7bb** and **7bh** as shown in Figures 1 and 2.[17]

Direct Organocatalyzed Cascade Reductive Alkylation of Cyclohexane-1,3-Dione: Reaction Optimization. Because of the more pharmaceutical applications of 2-alkyl-cyclohexane-1,3-diones **7**, we further extended the application of the organocatalyzed cascade reductive alkylation methodology to cyclohexane-1,3-dione **1a** and various aldehydes **2a**−**q** as shown in Tables 4 and 5. Surprisingly, the reactivity pattern of

(14) For two-step synthesis of 2-alkyl-cyclohexane-1,3-diones, see: (a) Karl Wilhelm, R.; Hartwig, B. *Chem. Ber.* **1961**, *94*, 2394−2400. (b) Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977**, *42*, 3755−3757. (c) Wheeler, T. N. *J. Org. Chem.* **1979**, *44*, 4906−4912. (d) Sardina, F. J.; Johnston, A. D.; Mourino, A.; Okamura, W. H. *J. Org. Chem.* **1982**, *47*, 1576−1578. (e) Bassetti, M.; Cerichelli, G.; Floris, B. *Gazz. Chim. Ital.* **1986**, *116*, 583−585. (f) Fuchs, K.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 528−532. (g) Paquette, L. A.; Backhaus, D.; Braun, R.; Underiner, T. L.; Fuchs, K. *J. Am. Chem. Soc.* **1997**, *119*, 9662−9671. (h) Pashkovsky, F. S.; Lokot, I. P.; Lakhvich, F. A. *Synlett* **2001**, 1391−1394.

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(17) CCDC-633527 for **7aa**, CCDC-633528 for **7bb**, CCDC-633529 for **7bh**, and CCDC-633530 for **10aa** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; fax: (+44)1223-336-033; or mail: deposit@ccdc.cam.ac.uk.

TABLE 4. Effect of Solvent on Direct Amino Acid-Catalyzed Reductive Alkylation of Cyclohexane-1,3-dione 1a with 2a and 3[a]

entry	solvent (0.5 M)	aldehyde **2a** (equiv)	time (h)	products **6aa**	yield (%)[b] **7aa**
1	EtOH	3.0	20	40	60
2	THF	3.0	24	65	35
3	CH_3CN	3.0	20	40	60
4	CH_2Cl_2	1.0	24	30	70
5	CH_2Cl_2	2.0	24	25	75
6	CH_2Cl_2	3.0	24	10	90

[a] Reactions were carried out in solvent (0.5 M) with 1.0−3.0 equiv of **2a** and 1.0 equiv of **3** relative to **1a** (0.5 mmol) in the presence of 20 mol % of proline **4a**. [b] Yield refers to the column purified product.

cyclohexane-1,3-dione **1a** looks different as compared to dimedone **1b** in the proline-catalyzed cascade reductive alkylation reaction with benzaldehyde **2a** and Hantzsch ester **3** as shown in Table 4. Unexpectedly, the proline-catalyzed reductive alkylation of cyclohexane-1,3-dione **1a**, benzaldehyde **2a** (3 equiv), and Hantzsch ester **3** furnished the expected product **7aa** in only 60% yield, accompanied by 40% yield of the bis-adduct **6aa** at 25 °C for 20 h (Table 4, entry 1). Interestingly, there is a large solvent effect on the direct proline-catalyzed reductive alkylation or cascade K/H reaction of **1a**, **2a**, and **3** as shown in Table 4 as compared to dimedone **1b** (see Tables 1 and 2). Proline-catalyzed cascade K/H reactions are performed in three types of solvents (protic polar, aprotic polar, and aprotic nonpolar) and furnished the expected product **7aa** in good to moderate yields as shown in Table 4 (some of the solvents are not shown). Surprisingly, the cascade K/H reaction of **1a**, **2a**, and **3** in THF furnished the expected hydrogenated product **7aa** in 35% yield accompanied by 65% yield of the bis-adduct **6aa** at 25 °C for 24 h (Table 4, entry 2). We envisioned the optimized condition to be mixing the 3 equiv of benzaldehyde **2a** with cyclohexane-1,3-dione **1a** and Hantzsch ester **3** at 25 °C in CH_2Cl_2 under 20 mol % of proline catalysis to furnish the hydrogenated product **7aa** in 90% yield (Table 4, entry 6). The structure and regiochemistry of 2-benzyl-cyclohexane-1,3-dione **7aa** were confirmed by X-ray structure analysis as shown in Figure 3.[17] Interestingly, the cascade product **7aa** was obtained in a completely enolic form in crystals as compared to in solution.

Diversity-Oriented Synthesis of Reductive Alkylation Products 7aa−7aq. With the optimized reaction conditions in hand, the scope of the proline-catalyzed K/H cascade reactions was investigated with cyclohexane-1,3-dione **1a**, various aldehydes **2a−q**, and Hantzsch ester **3** as shown in Table 5. A series of aromatic and aliphatic aldehydes **2a−q** (3 equiv) was reacted with cyclohexane-1,3-dione **1a** and Hantzsch ester **3** catalyzed by 20 mol % of proline at 25 °C in CH_2Cl_2 (Table 5). The 2-arylmethyl-cyclohexane-1,3-diones **7aa−7ai** and 2-alkyl-cyclohexane-1,3-diones **7aj−7aq** were obtained as single isomers with excellent yields. The reaction of cyclohexane-1,3-dione **1a** with piperonal **2c** and Hantzsch ester **3** under proline catalysis furnished the reductive alkylation product **7ac** in 70% yield at 70 °C, and there was no reaction at 25 °C (Table 5). The synthesis of 2-arylmethyl-cyclohexane-1,3-diones **7aa−7ai** from **1a**, **2a−i**, and **3** at 25 °C under proline catalysis took a longer reaction time (24−48 h), as compared to aliphatic aldehydes **2j−q** as shown in Table 5. Interestingly, the proline-catalyzed reductive alkylation reaction of cyclohexane-1,3-dione **1a**, α,β-unsaturated aldehydes **2j**,**k**, and Hantzsch ester **3** generated the expected 2-alkyl-cyclohexane-1,3-diones **7aj−7ak** in excellent yields with high regioselectivity (Table 5). The

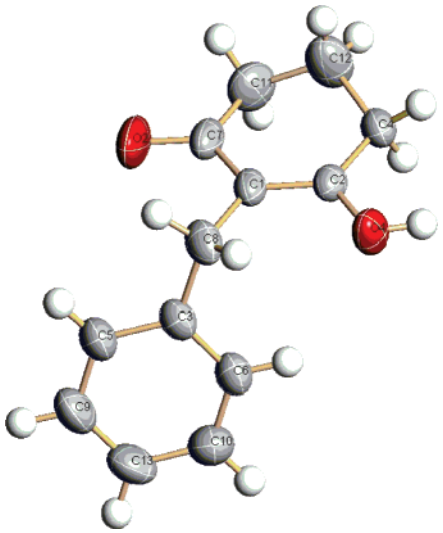


FIGURE 3. Crystal structure of 2-benzyl-3-hydroxy-cyclohex-2-enone (**7aa**).

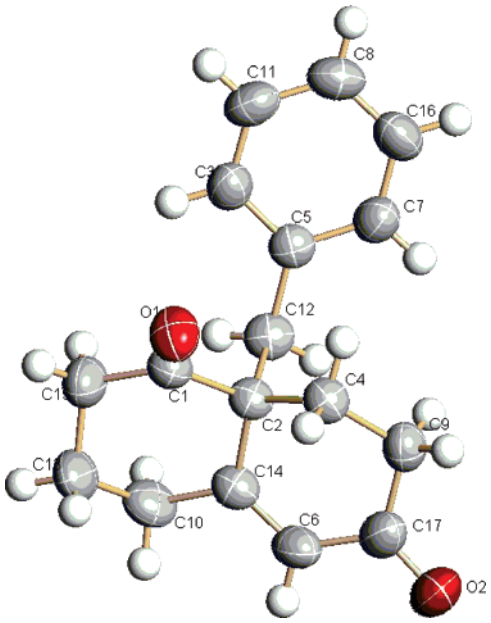
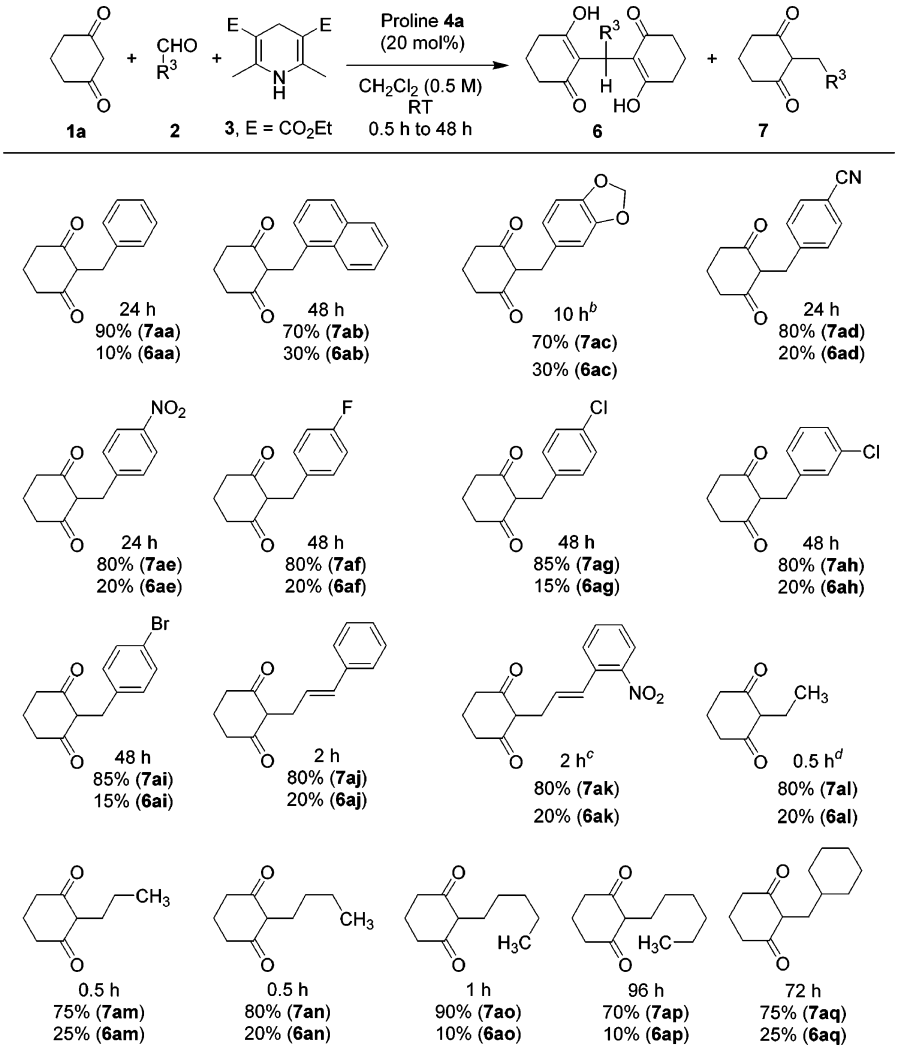


FIGURE 4. Crystal structure of (+)-(*R*)-8a-benzyl-3,4,8,8a-tetrahydro-2*H*,7*H*-naphthalene-1,6-dione (**10aa**).

results in Table 5 demonstrate the broad scope of this reductive cascade methodology covering a structurally diverse group of aldehydes **2a−q** with many of the yields obtained being very good, or indeed better, than the previously published two-step alkylation reactions.[14] The structure and regiochemistry of 2-alkyl-cyclohexane-1,3-diones **7aa−7aq** were confirmed by X-ray structure analysis on **7aa** as shown in Figure 3.[17]

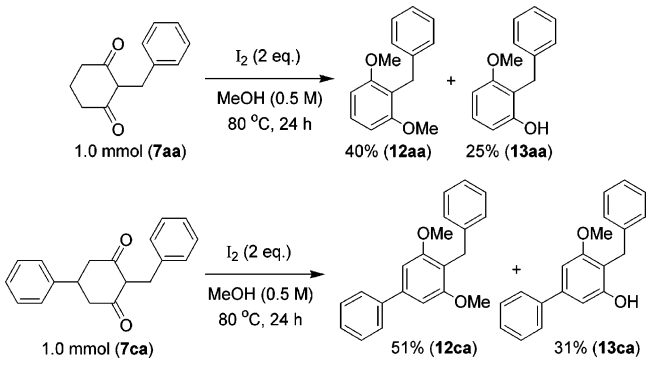
Applications of Reductive Alkylation Products 7. (A) Aromatization of 2-Alkyl-cyclohexane-1,3-diones. 2-Alkyl-cyclohexane-1,3-diones **7** were readily transformed into substituted monomethyl and dimethyl resorcinols with iodine and methanol as shown in Scheme 2.[13e] The substituted resorcinol unit is a basic building block of a large number of valuable naturally occurring polyketide metabolites.[18a−c] Highly substituted resorcinols have gained importance in recent years as starting materials and intermediates for the synthesis of cannabinoids and benzochroman derivatives, which possess a wide

TABLE 5. Synthesis of Reductive Alkylation Library via Cascade K/H Reactions from Cyclohexane-1,3-dione 1a and Aldehydes 2[a]



[a] Yield refers to the column purified product. [b] Reaction performed at 70 °C. [c] 3-(2-Nitrophenyl)-propenal **2k** was taken as 1 equiv. [d] Acetaldehyde **2l** was taken as 5 equiv.

SCHEME 2. Synthesis of 2,5-Dialkylresorcinols from Reductive Alkylation Products 7



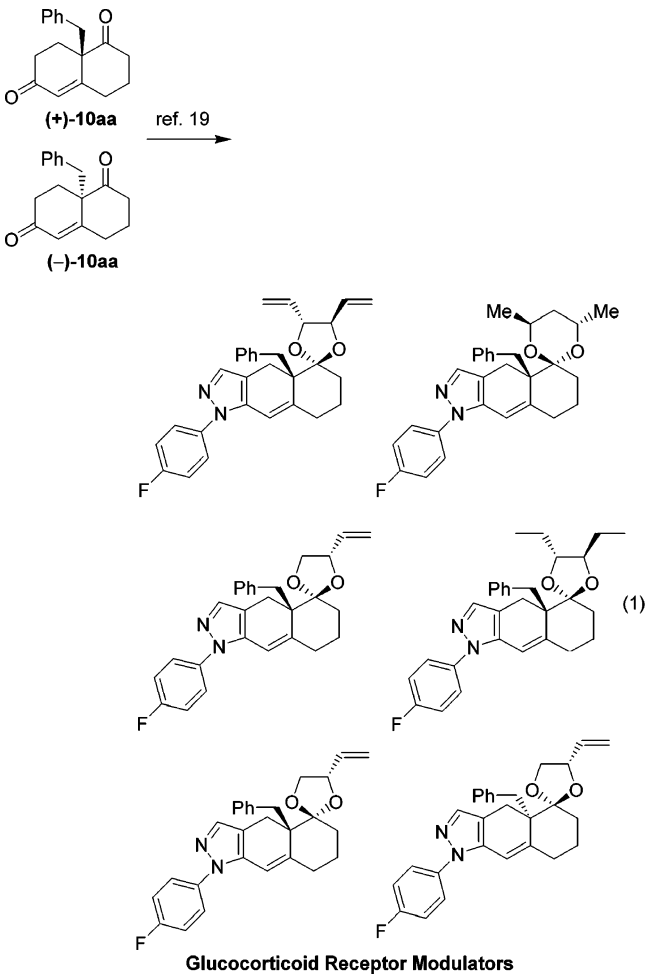
range of physiological and pharmacological properties.[18d−i] Long chain 5-alkyl resorcinols have been successfully utilized as ideal models for sequence-selective DNA strand scissions and as leukotriene antagonists for the treatment or prevention of Alzheimer's disease.[18j−m]

I_2/MeOH mediated aromatization of highly substituted cyclohexane-1,3-diones **7** gave good yields of medicinally important dimethyl and monomethyl resorcinols **12** and **13** as shown in Scheme 2.[13e] For the pharmaceutical applications, the

(18) (a) Sammes, P. G.; Kennewell, P. D.; Jaxa-Chamiec, A. A. *J. Chem. Soc., Perkin Trans 1* **1980**, 170−175. (b) Barrett, A. G. M.; Morris, T. M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans 1* **1980**, 2272−2277. (c) Mann, J. *Secondary Metabolism*; Oxford University Press: New York, 1980. (d) Razdan, R. K.; Gordon, P. M.; Siegel, C. *J. Org. Chem.* **1989**, *54*, 5428−5430. (e) Tius, M. A.; Kerr, M. A.; Gu, X. *J. Chem. Soc., Chem. Commun.* **1989**, 62−63. (f) Chan, T. H.; Chaly, T. *Tetrahedron Lett.* **1982**, *23*, 2935−2938. (g) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 3693−3695. (h) Razdan, R. K.; Dalzell, H. C. *J. Med. Chem.* **1976**, *19*, 719−721. (i) Razdan, R. K.; Pars, H. G.; Granchelli, F. E.; Keller, J. K.; Teiger, D. G.; Rosenbeg, F. J.; Harris, L. S. *J. Med. Chem.* **1976**, *19*, 445−454. (j) Hecht, S. M.; Reddy, K. S.; Murty, V. S.; Barr, J. R.; Scannell, R. T. *J. Am. Chem. Soc.* **1988**, *110*, 3650−3651. (k) Hecht, S. M.; Chrisey, L. A.; Bonjar, G. H. S. *J. Am. Chem. Soc.* **1988**, *110*, 644−646. (l) Tyman, J. H. P.; Durrani, A. A. *J. Chem. Soc., Perkin Trans 1* **1980**, 1658−1666. (m) Altstiel, L. D.; Fleisch, J. H. *Eur. Pat. Appl.* **1996**, CODEN: EPXXDW EP 743064 A1 19961120, CAN 126:74591 (in English; 124 pp).

(19) Ali, A.; Balkovec, J. M.; Beresis, R.; Colletti, S. L.; Graham, D. W.; Patel, G. F.; Smith, C. J. *PCT Int. Appl.* **2004**, CODEN: PIXXD2 WO 2004093805 A2 20041104, CAN 141:395547 (in English; 201 pp).

diversity-oriented library of resorcinols **12** and **13** could be generated by using our amino acid-catalyzed diversity-oriented library of highly substituted cyclohexane-1,3-diones **7** through a simple I_2/MeOH reaction.

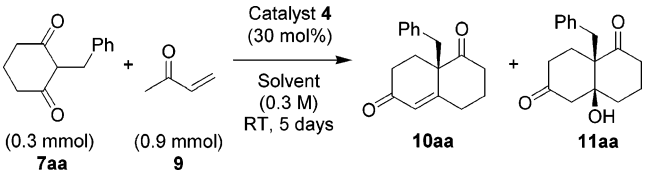


(B) Amino Acid-Catalyzed Asymmetric Robinson Annulations. W−M ketone analogues **10** are very good intermediates for the synthesis of steroids,[12] and also recently, Ali et al. reported in their patent[19] that W−M ketone analogue **10aa** is a very good intermediate for the synthesis of pharmaceutically acceptable salts or hydrates of spiro-heterocycles, which are disclosed as selective glucocorticoid receptor modulators for treating a variety of autoimmune and inflammatory diseases or conditions (see eq 1). Surprisingly, to the best of our knowledge, there is no report on the asymmetric synthesis of useful W−M ketone analogues **10**. In this article, we are presenting the asymmetric synthesis of W−M ketone analogues **10** with interesting ee and yields via amino acid-catalyzed asymmetric RA of 2-alkyl-cyclohexane-1,3-diones **7** with methyl vinyl ketone **9** as shown in Tables 6 and 7 and Scheme 3.

We were pleased to find that the L-proline-catalyzed RA reaction of 2-benzyl-cyclohexane-1,3-dione **7aa** with 3 equiv of methyl vinyl ketone **9** in THF furnished the expected product **10aa** in 70% yield with 33% ee and alcohol **11aa** in 10−15% yield at 25 °C for 5 days (Table 6, entry 1). Solvent screening on the direct L-proline-catalyzed RA reaction of **7aa** with **9** revealed that DMF and DMSO solvents were suitable to achieve high ee values as shown in Table 6. Interestingly, the freshly distilled methyl vinyl ketone **9** showed a large effect on the proline-catalyzed RA reaction of **7aa** and **9** with respect to yield and ee values as shown in Table 6. We envisioned the optimized condition to be mixing the CH acid **7aa** and 3 equiv of freshly distilled methyl vinyl ketone **9** at 25 °C in DMF under 30 mol % of L-proline catalysis to furnish W−M ketone analogue **10aa** in 50% yield with 72% ee and alcohol **11aa** in 30−45% yield (Table 6, entry 6). The D-proline-catalyzed RA reaction of **7aa** with **9** furnished the opposite enantiomer of the W−M ketone analogue **10aa** in 50% yield with 74% ee and alcohol **11aa** in 30−45% yield (Table 6, entry 7).

The hydrolysis of bicyclic alcohols (+)/(−)-**11aa** obtained from L/D-proline catalysis with 1 N $HClO_4$ in DMSO at 90 °C

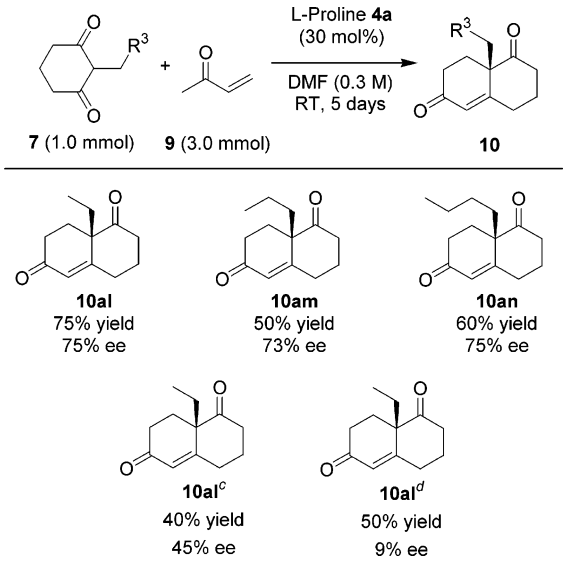
TABLE 6. Direct Amino Acid-Catalyzed Robinson Annulation of 7aa with 9[a]



entry	solvent (0.3 M)	catalyst **4** (30 mol %)	yield (%)[b] **10aa**	ee (%)[c] **10aa**
1[d]	THF	**4a**	70	33
2[d]	CH_3CN	**4a**	85	51
3[d]	DMSO	**4a**	50	64
4[d]	DMF	**4a**	65	65
5[d]	DMF	**4b**	65	−50
6[e]	DMF	**4a**	50	72
7[e]	DMF	**4b**	50	−74

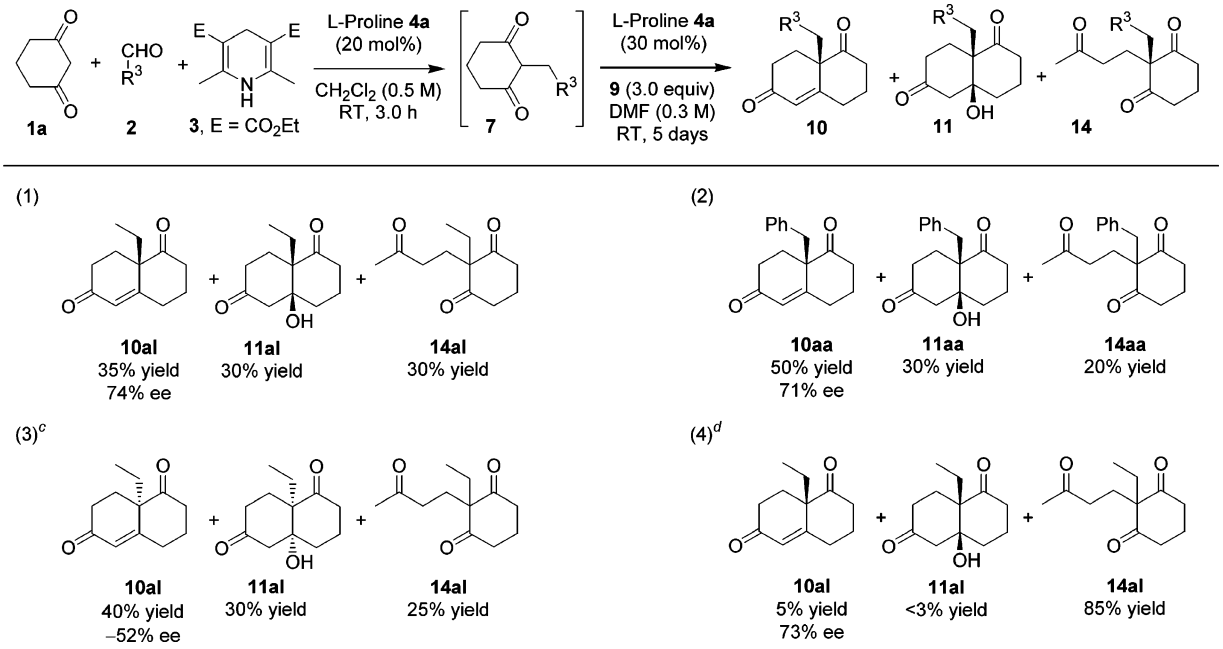
[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv of **9** in the presence of 30 mol % of proline **4**. [b] Yield refers to the column purified product. [c] ee was determined by HPLC analysis. [d] Product **11aa** was isolated in 10−15% yield. [e] Freshly distilled methyl vinyl ketone **9** was used, and product **11aa** was isolated in 30−45% yield.

TABLE 7. Organocatalytic Asymmetric Synthesis of W−M Ketone Analogues 10[a,b]



[a] See Experimental Section. [b] Yield refers to the column purified product, and ee was determined by HPLC analysis. [c] Reaction was carried out without solvent. [d] Reaction was carried out without solvent with 1.0 equiv of **4a** and 2.0 equiv of **9** relative to **7al**.

TABLE 8. Direct Organocatalytic One-Pot Double Cascade Asymmetric Synthesis of W−M Ketone Analogues 10[a,b]

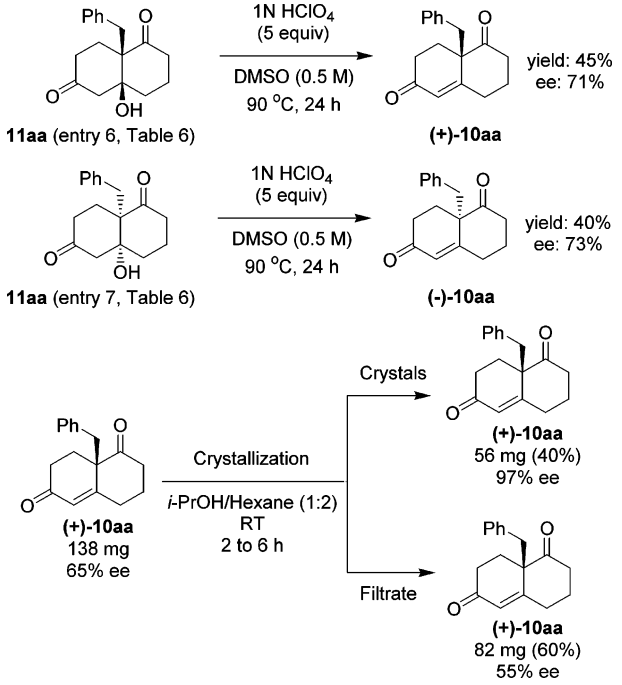


[a] See Experimental Section. [b] Yield refers to the column purified product, and ee was determined by HPLC analysis. [c] D-Proline **4b** (20 mol %) was used for the Robinson annulation step. [d] One-pot reaction was carried out without addition of second catalyst **4**.

for 24 h furnished the expected bicyclic ketones (+)/(−)-**10aa** in good yields with 71−73% ee as shown in Scheme 3. The crystallization of the 65% ee W−M ketone analogue (+)-**10aa** in a 2:1 mixture of hexane and isopropyl alcohol at 25 °C for 2−6 h furnished the brown block-shaped crystals in 40% yield with an enriched ee value of 97% (Scheme 3). The absolute configuration of product (+)-**10aa** prepared under L-proline catalysis was established by using X-ray crystallography and also by comparison with the proline-catalyzed Hajos−Parrish−Eder−Sauer−Wiechert reaction.[20] The crystal structure of product (+)-**10aa** is depicted in Figure 4.[17]

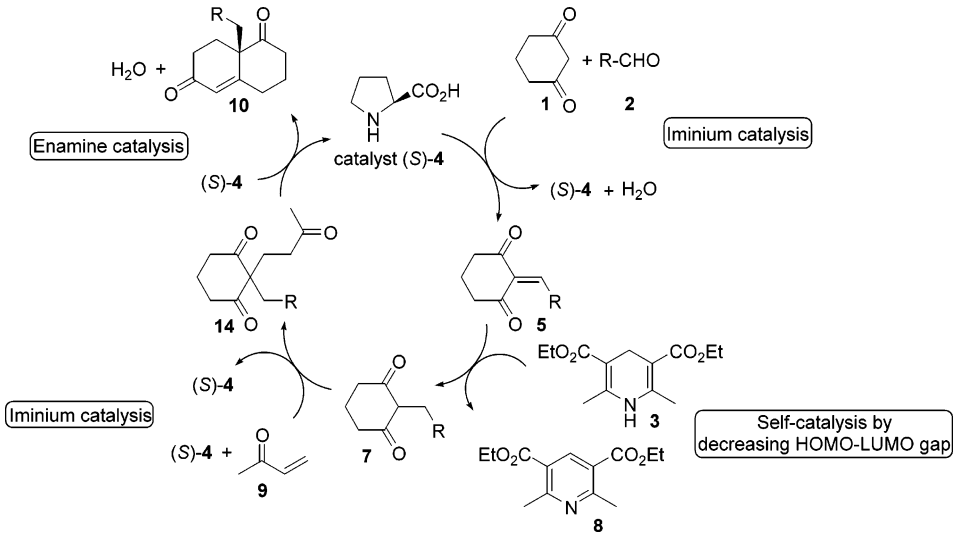
With an efficient organocatalytic asymmetric cascade RA protocol in hand, the scope of the proline-catalyzed cascade asymmetric RA reactions was investigated with various 2-alkyl-cyclohexane-1,3-diones **7** and methyl vinyl ketone **9**. A series of 2-alkyl-cyclohexane-1,3-diones **7al**−**7an** was reacted with 3.0 equiv of methyl vinyl ketone **9** catalyzed by 30 mol % of L-proline at 25 °C in DMF for 5 days (Table 7). All expected W−M ketone analogues **10al**−**10an** were obtained in good yields with 73−75% ee as shown in Table 7. Interestingly, in these reactions, only trace amount of bicyclic alcohols **11al**−**11an** were isolated. L-Proline-catalyzed asymmetric RA reactions of **7al** with **9** were effected by solvent and catalyst loading on ee as shown in Table 7. Interestingly, ee values of product **10al** were drastically smaller when the reaction was performed under neat and L-proline **4a** as compared to 1.0 equiv of **7al**.

SCHEME 3. Hydrolysis of Alcohol 11aa and Enantioenrichment of W−M Ketone Analogue 10aa by Crystallization



(20) (a) Hajos, Z. G.; Parrish, D. R. *Ger. Offen.* **1971**, CODEN: GWXXBX DE 2102623 19710729, CAN 76:59072 (in German: 42 pp). (b) Eder, U.; Wiechert, R.; Sauer, G. *Ger. Offen.* **1971**, CODEN: GWXXBX DE 2014757 19711007, CAN 76:14180 (in German: 20 pp). (c) Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1997**, *119*, 8131−8132. (d) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273−11283. (e) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911−12912. (f) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16−17. (g) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475−2479. (h) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839−5842. (i) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558−569. (j) Cheong, P. H-Y.; Houk, K. N. *Synthesis* **2005**, 1533−1537.

SCHEME 4. Proposed Catalytic Cycle for Double Cascade Reactions



The same results were observed by Swaminathan et al. in their attempt to synthesize the asymmetric W−M ketone analogue **10al**.[12k]

(C) Amino Acid-Catalyzed Asymmetric Double Cascade One-Pot Robinson Annulations. After successful demonstration of the L-proline-catalyzed cascade asymmetric K/H and RA reactions, we decided to investigate the combination of these two cascade reactions in one pot. The reaction of 5 equiv of acetaldehyde **2l** with CH acid **1a** and Hantzsch ester **3** under l-proline catalysis in CH_2Cl_2 at 25 °C for 3.0 h furnished the expected 2-ethyl-cyclohexane-1,3-dione **7al** in good yield. Removing the solvent CH_2Cl_2 by vacuum pump and adding solvent DMF and 30 mol % of L-proline **4a** and methyl vinyl ketone **9** to the reaction mixture of cascade asymmetric K/H/RA furnished the expected W−M ketone analogue **10al** in 35% yield with 74% ee accompanied by bicyclic alcohol **11al** in 30% yield and the Michael adduct **14al** in 30% yield as shown in Table 8. In L-proline-catalyzed sequential one-pot double cascade asymmetric K/H/RA reactions, the ee values were not effected by the reaction byproduct 2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester **8**, but a rate of the RA reaction was affected, and the requirement came to add another 30 mol % of catalyst to the one-pot reaction as shown in Table 8, entries 3− and 4. The successful combination of two cascade K/H and RA reactions under L-proline catalysis was demonstrated by two more examples as shown in Table 8, and this one-pot synthetic strategy shows a large impact on the asymmetric synthesis of functionalized small molecules.

Mechanistic Insights. The possible reaction mechanism for L-proline-catalyzed regio- and chemoselective and enantioselective synthesis of cascade products **7** and **10** through reaction of CH acid **1**, aldehyde **2**, and Hantzsch ester **3** is illustrated in Scheme 4. This catalytic sequential one-pot double cascade is a four component reaction comprised of CH acid **1**, aldehyde **2**, Hantzsch ester **3**, methyl vinyl ketone **9**, and a simple chiral amino acid **4**, which is capable of catalyzing each step of this double cascade reaction. In the first step (Scheme 4), the catalyst (*S*)-**4** activated component **2** by most likely iminium ion formation, which then selectively added to the CH acid **1** via a Mannich and retro-Mannich-type reaction to generate active olefin **5**.[4c,k] The following second step was biomimetic hydrogenation[4b−d] of active olefin **5** by Hantzsch ester **3** to produce **7** through self-catalysis by decreasing HOMO−LUMO energy gap between **3** and **5**, respectively.[21] In the subsequent third step, the Michael addition of **7** to methyl vinyl ketone **9** via most likely iminium ion activation led to the formation of Michael adduct **14**.[20] In the fourth step, (*S*)-**4** catalyzed the asymmetric intramolecular aldol condensation of **14** via enamine catalysis,[20] and subsequent hydrolysis returned the catalyst (*S*)-**4** for further cycles and released the desired W−M ketone analogue **10**.

Taking into account the recent applications of amine-catalyzed Knoevenagel reactions[4k,22] and based on the different experiments performed (Table 1), we proposed that the most likely reaction course for the organocatalyzed direct addition of CH acids **1** to aldehydes **2** is the one outlined through amino acid catalysis in Scheme 5. Self- and acid-catalyzed olefin formation is slow reaction, but base and amino acid-catalyzed olefin formation is a very fast reaction and may be due to their high activation effect. The formation of active olefins **5** through proline catalysis by means of Mannich and retro-Mannich reactions support our hypothesis that aldol products **15** did not form in these reactions. This hypothesis is also supported by the recent discovery of organoclick reactions[4k] and the mechanistic investigation of pyrrolidine-catalyzed enal formation through aldehyde self-condensation reported by Saito et al.[22b]

Our proposal of the Michael addition of **7** to methyl vinyl ketone **9** via iminium ion activation or base catalysis is supported by results presented in Table 9. The values for the simultaneous proline-catalyzed Michael reaction followed by aldol reaction of **7aa** with **9** is shown in Table 9, entry 1. Triethyl amine **4c** and quinine **4d** catalyzed the only Michael addition of **7aa** to **9** (Table 9, entries 2 and 3), but there is not much product formation on acidic and uncatalyzed conditions as shown in Table 9. On the basis of the previous results, we proposed that the most likely activation for the proline-catalyzed Michael reaction is iminium ion activation.[5h]

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SCHEME 5. Proposed Mechanisms for Olefin Formation

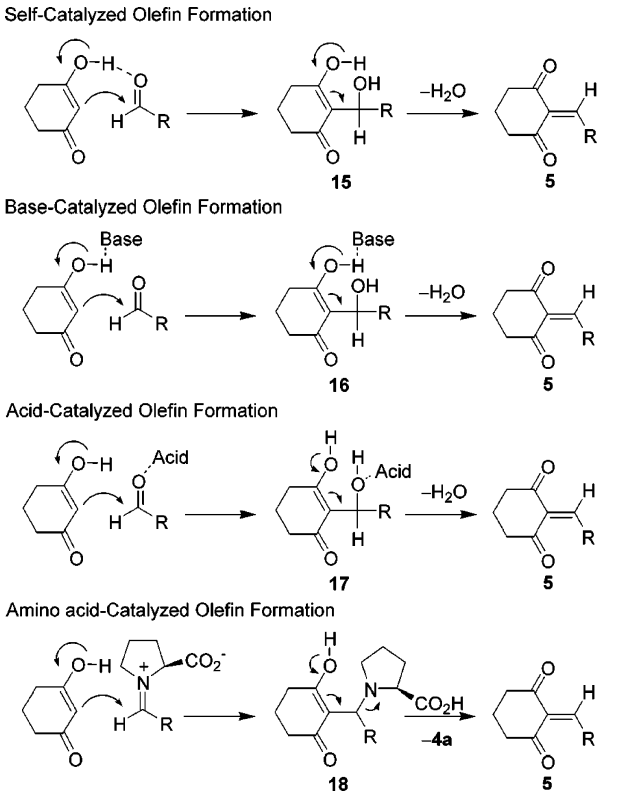
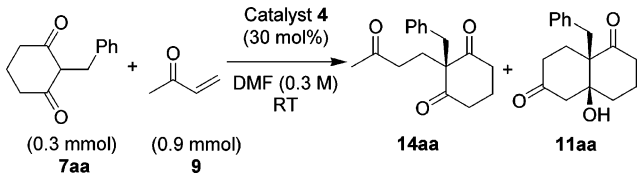


TABLE 9. Effect of Catalyst on Robinson Annulation of 7aa with 9[a]



entry	catalyst **4** (30 mol %)	time (h)	conversion (%)[b]	yield (%)[c] **14aa**	yield (%)[c] **11aa**
1	**4a**	11	99	50	24
2	**4c**	8	99	90	
3	**4d**	11	99	90	
4	**4e**	24	<10	5	
5		24	<10	5	

[a] Reactions were carried out in solvent (0.3 M) with 3.0 equiv of **9** in the presence of 30 mol % of catalyst **4**. [b] Conversion based on TLC analysis. [c] Yield refers to the column purified product.

Conclusion

In summary, we have developed a metal-free one-pot cascade synthesis of highly substituted 2-alkyl-cyclohexane-1,3-diones **7** and chiral W−M ketone analogues **10** from simple starting materials via cascade K/H, RA, and K/H/RA reactions under amino acid catalysis. First time, we have reported the reductive alkylation of highly reactive CH acids (cyclohexane-1,3-dione and dimedone) with aldehydes and Hantzsch ester under amino acid catalysis. The reductive alkylation's strategy or cascade K/H reaction proceeds in good yield with high chemo- and regioselectivity using amino acids as the catalysts. In this article, we demonstrated the concept of self-catalysis by decreasing the HOMO−LUMO energy gap between in situ generated olefins **5** and Hantzsch ester **3**. Furthermore, we have demonstrated the synthetic application of reductive alkylation products **7**. Further work is in progress to utilize novel K/H and K/H/RA reactions in synthetic chemistry.

Experimental Section

General Experimental Procedures for the Cascade Reactions: Amino Acid-Catalyzed Cascade Knoevenagel/Hydrogenation Reactions with Dimedone. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the aldehyde **2**, 0.5 mmol of CH acid **1b**, and 0.5 mmol of Hantzsch ester **3** was added 1.0 mL of solvent, and then the catalyst amino acid **4** (0.10 mmol) was added, and the reaction mixture was 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 workup, and pure cascade products **7** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Amino Acid-Catalyzed Cascade Knoevenagel/Hydrogenation Reactions with Cyclohexane-1,3-diones. In an ordinary glass vial equipped with a magnetic stirring bar, to 1.5 mmol of the aldehyde **2**, 0.5 mmol of CH- acid **1a** or **1c**, and 0.5 mmol of Hantzsch ester **3** was added 1.0 mL of solvent, and then the catalyst amino acid **4** (0.10 mmol) was added, and the reaction mixture was stirred at 25 °C for the time indicated in Tables 4 and 5. The crude reaction mixture was directly loaded onto a silica gel column with or without aqueous workup, and pure cascade products **7** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Amino Acid-Catalyzed Robinson Annulation Reaction. In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of 2-alkyl-cyclohexane-1,3-diones **7** and 3.0 mmol of methyl vinyl ketone **9** was added 3.0 mL of DMF solvent, and then the catalyst proline **4a** (0.3 mmol) was added, and the reaction mixture was stirred at 25 °C for 5 days. 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 products **10** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Amino Acid-Catalyzed One-Pot Double Cascade Knoevenagel/Hydrogenation/Robinson Annulation Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 5.0 mmol of the aldehyde **2**, 1.0 mmol of CH acid **1a**, and 1.0 mmol of Hantzsch ester **3** was added 2.0 mL of dichloromethane, and then the catalyst amino acid **4** (0.2 mmol) was added, and the reaction mixture was stirred at 25 °C for the time indicated in Table 8. After evaporation of the solvent completely, to the crude reaction mixture was added 3.0 mmol of methyl vinyl ketone **9**, 3.0 mL of DMF solvent, and 0.30 mmol of L-proline **4a**, and the reaction mixture was stirred at 25 °C for 5 days. 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 **10**, **11**, and **14** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for Aromatization of 2-Alkyl-cyclohexane-1,3-dione Compounds. A solution of 2-alkyl-cyclohexane-1,3-dione compound **7** (1.0 mmol) and iodine (2.0 mmol) in methanol was refluxed for 24 h. After cooling, the reaction mixture was washed with aqueous sodium thiosulphate and brine 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 products **12** and **13** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

General Procedure for Dehydration of 8a-Alkyl-4a-hydroxy-hexahydro-naphthalene-1,6-diones 11. Method (1). A solution of alcohol compound **11** (0.5 mmol) and 1 N $HClO_4$ (1.5 mmol) in

DMSO (1.5 mL) was stirred at 90 °C for 24 h. After cooling, the reaction mixture was washed with water, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **10** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Method (2). A solution of alcohol compound **11** (0.5 mmol) and *p*-TSA (0.15 mmol) in benzene (1.5 mL) was stirred at 80 °C for 2 h. After cooling, the reaction mixture was washed with aqueous sodium bicarbonate 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 products **10** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Acknowledgment. This work was made possible by a grant from the Department of Science and Technology (DST), New Delhi. M.K. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for his research fellowship. We thank Prof. M. V. Rajasekharan, A. R. Biju, and P. Raghavaiah for their help in X-ray structural analysis.

Supporting Information Available: Complete experimental procedures, compound characterization, X-ray crystal structures, and analytical data (^{1}H NMR, ^{13}C NMR, HRMS, and elemental analysis) for all new compounds. Copies of ^{13}C NMR spectrum of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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