Double cascade reactions based on the Barbas dienamine platform: highly stereoselective synthesis of functionalized cyclohexanes for cardiovascular agents†

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The amino acid proline catalyzed the three- and five-component cascade olefination–Diels–Alder–epimerization and olefination–Diels–Alder–epimerization–olefination–hydrogenation reactions of readily available precursors enones **1a–i**, arylaldehydes **2a–k**, alkyl cyanoacetates **3a–e** and Hantzsch ester **9** to furnish highly substituted prochiral 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **6** and 1-cyano-4-(cyano-alkoxycarbonyl-methyl)-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **10** in a highly diastereoselective fashion with excellent yields. Prochiral *cis*-isomers **6** are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products.

Introduction

The construction of suitably functionalized cyclohexane frameworks plays a central role in many natural product syntheses.[1] Although the Diels–Alder reaction is among the most powerful tools for generating such carbocycles,[2] it is often difficult to form systems that are highly congested or possess substitute arrays that are incompatible with the reaction.[3] A number of alternative methods for synthesizing cyclohexanes have arisen from catalytic approaches, such as the base-catalyzed Michael–aldol, Michael–Mannich and Michael–Michael reactions,[4] transition-metal-catalyzed ring-closing metathesis (RCM)[5] followed by hydrogenation, and cycloisomerization reactions.[6] In contradistinction to the widespread use of these intramolecular processes, intermolecular counterparts for catalytic cyclohexane synthesis are less well developed.[7]

Nucleophilic amine catalysis or organocatalysis has emerged recently as an efficient means of generating carbo- and heterocycles.[8] In particular, Barbas three-component [4 + 2] cycloaddition[9] to form functionalized cyclohexanes from 4-substituted-3-buten-2-ones, aldehydes and Meldrum's acid or 1,3-indandione under proline-catalysis has been applied in the syntheses of several *cis*-spirane products.[9] Nevertheless, proline-catalysis has not been utilized previously for the formation of functionalized cyclohexanes from (*E*)-2-cyano-3-aryl-acrylic acid alkyl esters as dienophiles in Diels–Alder chemistry. Building upon our proline-catalyzed regioselective synthesis of (*E*)-2-cyano-3-aryl-acrylic acid alkyl esters,[10] we reasoned that it might be possible to use as dienophiles in [4 + 2] cycloaddition reaction. Herein, we disclose the facile synthesis of cyclohexanes **5**/**6** and **10** *via* proline-catalyzed cascade annulations from simple substrates (Scheme 1).

As part of our program to engineer novel organocatalytic cascade or multi-component reactions,[10] herein we report the highly regio- and diastereoselective direct organocatalytic cascade olefination–Diels–Alder–epimerization, olefination–Diels–Alder–epimerization–olefination–hydrogenation and olefination–Diels–Alder–epimerization–olefination–hydrogenation–*trans*-esterfication reactions that provide highly substituted prochiral 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **5**/**6** and 1-cyano-4-(cyano-alkoxycarbonyl-methyl)-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **10** from commercially available 4-substituted-3-buten-2-ones **1a–i**, aldehydes **2a–k** and CH-acids, cyano-acetic acid alkyl esters **3a–e** using *in situ* generated (*E*)-2-cyano-3-aryl-acrylic acid alkyl esters **12** as dienophiles and Barbas dienamines **13** (2-amino-1,3-butadienes)[9] as diene sources (Scheme 1). Highly functionalized cyclohexanes **5**/**6** and **10** are attractive intermediates in the synthesis of natural products, and in materials chemistry and are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products.[11]

In our reaction we envisioned that the amino acid proline, **4**, would catalyze the cascade regio-selective olefination reaction of aldehyde **2** with CH-acids (alkyl cyanoacetates) **3** to provide (*E*)-2-cyano-3-aryl-acrylic acid alkyl esters **12** *via* iminium-catalysis, which would then undergo a concerted [4 + 2] cycloaddition with 2-amino-1,3-butadienes **13** (Barbas dienamine) generated *in situ* from enone **1** and proline **4** to form substituted 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **5** and **6** in a diastereoselective manner. Novel epimerization at the β-position to carbonyl of the minor diastereomer *trans*-isomer **5** to the more stable *cis*-isomer **6** could occur under the same reaction conditions as shown in Scheme 1. Further treatment of *cis*-isomer **6** with CH-acids **3** and Hantzsch ester **9** would generate the highly functionalized cyclohexanes **10** in one-pot as shown in Scheme 1. The cascade olefination–Diels–Alder–epimerization, olefination–Diels–Alder–epimerization–olefination–hydrogenation and olefination–Diels–Alder–epimerization–olefination–hydrogenation–*trans*-esterfication reaction sequences would then generate a quaternary center with formation of three new carbon–carbon σ bonds, and four new carbon–carbon σ bonds/two carbon–hydrogen bonds respectively *via* organocatalysis.

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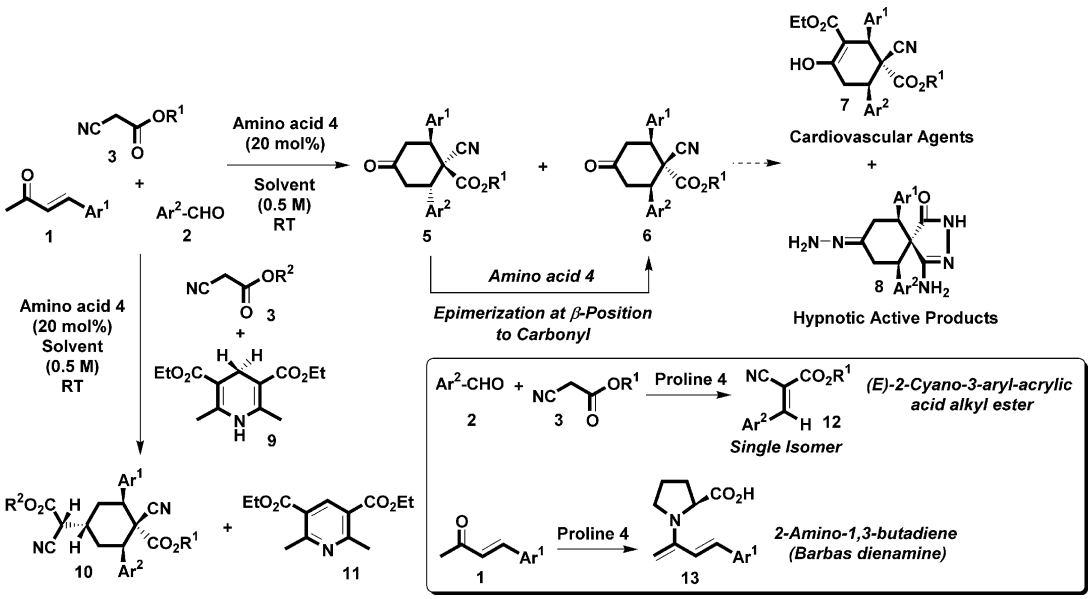
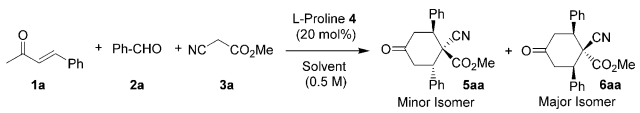


Scheme 1 Development of organocatalytic cascade reactions based on the Barbas dienamine platform.

Results and discussion

We initiated our investigation by seeking a viable proline **4** catalyst for the cascade [4 + 2] annulation of the enone **1a**, benzaldehyde **2a** and methyl cyanoacetate **3a** to provide the cyclohexanone **6aa** (Table 1). We were pleased to find that the three-component reaction of *trans*-4-phenyl-3-buten-2-one **1a**, benzaldehyde **2a** and methyl cyanoacetate **3a** with a catalytic amount of L-proline **4** in methanol at ambient temperature for 30 h furnished Diels–Alder products **5aa** and **6aa** in 76% yield with prochiral *cis*-isomer **6aa** as the major isomer with only 9% de (Table 1, entry 1).[12] The same reaction albeit with an extended reaction time furnished *cis*-isomer **6aa** with 33% de in 78% yield (Table 1, entry 2). The minor diastereomer, *trans*-isomer **5aa**, was effectively epimerized to the thermodynamically stable *cis*-isomer **6aa** under prolonged reaction times *via* proline catalysis. The stereochemistry of products **5aa** and **6aa** was established by NMR analysis.

Table 1 Effect of solvent on the direct amino acid catalyzed cascade O–DA–E reaction of **1a**, **2a** and **3a**[a]



Entry	Solvent (0.5 M)	Temperature (T)/°C	Time/h	Products	Yield[b] (%)	de[c] (%)
1	MeOH	25	30	**5aa**, **6aa**	76	9
2	MeOH	25	96	**5aa**, **6aa**	78	33
3	EtOH	25	96	**5aa**, **6aa**	75	53
4[d]	EtOH	70	72	**6aa**	80	99
5	DMSO	25	6	**5aa**, **6aa**	80	26
6	DMSO	25	72	**6aa**	85	99
7[d]	DMSO	50 → 25	24 → 48	**6aa**	80	99
8	DMF	25	24	**5aa**, **6aa**	77	26
9	DMF	25	72	**5aa**, **6aa**	75	26
10	NMP	25	24	**5aa**, **6aa**	76	−50
11	NMP	25	72	**5aa**, **6aa**	75	−20
12	THF	25	168	**5aa**, **6aa**	≤5	—
13	CH_3CN	25	36	**5aa**, **6aa**	60	0
14	$CHCl_3$	25	72	**5aa**, **6aa**	73	33
15	$C_6H_5CH_3$	25	120	**5aa**, **6aa**	65	0
16	CH_2Cl_2	25	120	**5aa**, **6aa**	68	20
17	[bmim]Br	25	72	**5aa**, **6aa**	80	44
18	[bmim]BF_4	25	72	**5aa**, **6aa**	71	0

[a] Amino acid **4** (0.1 mmol), benzylidene acetone **1a** (1 mmol), benzaldehyde **2a** (0.5 mmol) and CH-acid **3a** (0.5 mmol) in solvent (1 mL) were stirred at ambient temperature for 6 to 120 h. [b] Yield refers to the column purified product. [c] Diastereomeric excesses determined by using ^1H and ^{13}C NMR analysis on isolated products. [d] All reactants (**1a**, **2a** and **3a**) were used in the same equivalents.

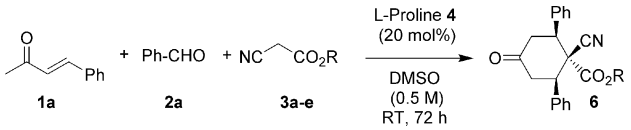
In the three-component cascade olefination–Diels–Alder–epimerization (O–DA–E) reaction of enone **1a**, benzaldehyde **2a** and methyl cyanoacetate **3a** catalyzed directly by L-proline **4**, we found that the solvent (dielectric constant) and temperature had a significant effect on reaction rates, yields and de's (Table 1). Our studies revealed that the cascade O–DA–E reaction catalyzed by L-proline produces products **5aa** and **6aa** in moderate yields and poor selectivity in aprotic non-polar solvents (Table 1, entries 12–16) and with excellent yields and selectivity in protic/polar solvents (Table 1, entries 4–7). But interestingly, the cascade O–DA–E reaction in polar solvents like DMF and NMP looks different compared to DMSO as shown in Table 1, entries 8–11. The same cascade reaction in the ionic liquids [bmim]Br and [bmim]BF_4 catalyzed by L-proline provided the cascade product *cis*-isomer **6aa** with 44% de and 0% de in good yield, respectively (Table 1, entry 17 and 18). Interestingly, under proline catalysis, the cascade O–DA–E reaction worked well in EtOH and DMSO solvents and the optimal conditions involved mixing equimolar amounts of enone **1a**, aldehyde **2a** and CH-acid **3a** in ethanol with heating to 70 °C for 72 h to furnish *cis*-isomer **6aa** as a single diastereomer in 80% yield (Table 1, entry 4) or mixing equimolar amounts of **1a**, **2a** and **3a** in DMSO with heating to 50 °C for 24 h and 25 °C for 48 h to furnish *cis*-isomer **6aa** as a single diastereomer in 80% yield (Table 1, entry 7).

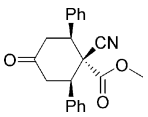
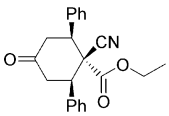
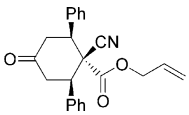
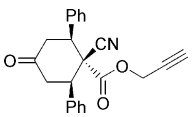
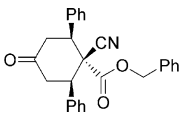
After this preliminary understanding, we proceeded to investigate the scope and limitations of the cascade O–DA–E reaction of **1a** and **2a** with a range of active CH-acids **3a–e** under proline-catalysis in DMSO (Table 2). As shown in Table 2, acyclic CH-acids **3a–e** furnished the expected cascade products **6aa–ae** in good yields with 99% de, but ethyl cyanoacetate **3b** has only furnished cascade product **6ab** in 92% yield with 77% de.

We generated a useful library of cascade O–DA–E products **6** under proline-catalysis. The results in Table 3 demonstrate the broad scope of this green methodology covering a structurally diverse group of less reactive ketones **1a–i**, aldehydes **2a–k** and CH-acids **3a–e** with many of the yields and de's obtained being very good, or indeed better than previously published reactions starting from the divinyl ketones and CH-acids *via* double Michael reactions.[13] Each of the targeted prochiral *cis*-isomers **6** were obtained as single diastereomers in excellent yields. Prochiral *cis*-isomers **6bba–iia** were generated in very good yields with aromatics bearing either electron withdrawing or electron donating groups in the *para* position as shown in Table 3. The prochiral hetero aromatic *cis*-isomer **6iia** was synthesized in 90% yield with 0% de under the reaction conditions (Table 3).

Proline-catalyzed cascade O–DA–E reaction of *trans*-4-(4-nitrophenyl)-3-buten-2-one **1b**, 4-nitrobenzaldehyde **2b** and methyl cyanoacetate **3a** furnished the cascade esters *cis*-**6bba**/*trans*-**5bba** in 80% yield with 50% de of **6bba** (Table 3, entry 1). Interestingly, the cascade reaction of **1c**, **2c** and **3a** furnished the esters **5cca**/**6cca** in 86% yield with 0% de. Cascade O–DA–E reactions produced cyclohexanone products **6dda**, **6eea**, **6ffa**, **6gga**, **6aha** and **6aja** in very good yields with 99% de as shown in Table 3. The proline-catalyzed O–DA–E reaction of **1a**, **2b** and **3b** furnished the non-symmetrical *cis*-isomer **6abb** in 75% yield with 82% de and 14% ee as shown in Table 3. Non-symmetrical *cis*-isomers **6aha**, **6aja** and **6aka** are also generated using cascade O–DA–E reaction in very good yields with good de's as shown in Table 3. Cascade *trans*-isomers of **5bba**, **5cca**, **5hha** and **5iia** were epimerized to the *cis*-isomers **6bba**, **6cca**, **6hha** and **6iia** under proline-catalysis in very good yields with complete conversion at 25 °C for 48 h (Table 4).

Table 2 Effect of CH-acids **3** on the direct amino acid catalyzed cascade O–DA–E reaction of **1a**, **2a** and **3a–e**[a]



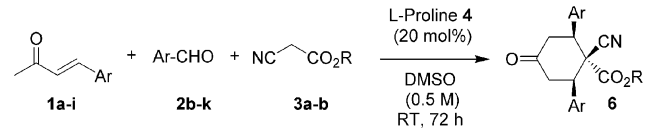
Entry	Products		Yield[b] (%)	de[c] (%)
1		**6aa**	85	99
2		**6ab**	92	77
3		**6ac**	76	99
4		**6ad**	80	99
5		**6ae**	85	99

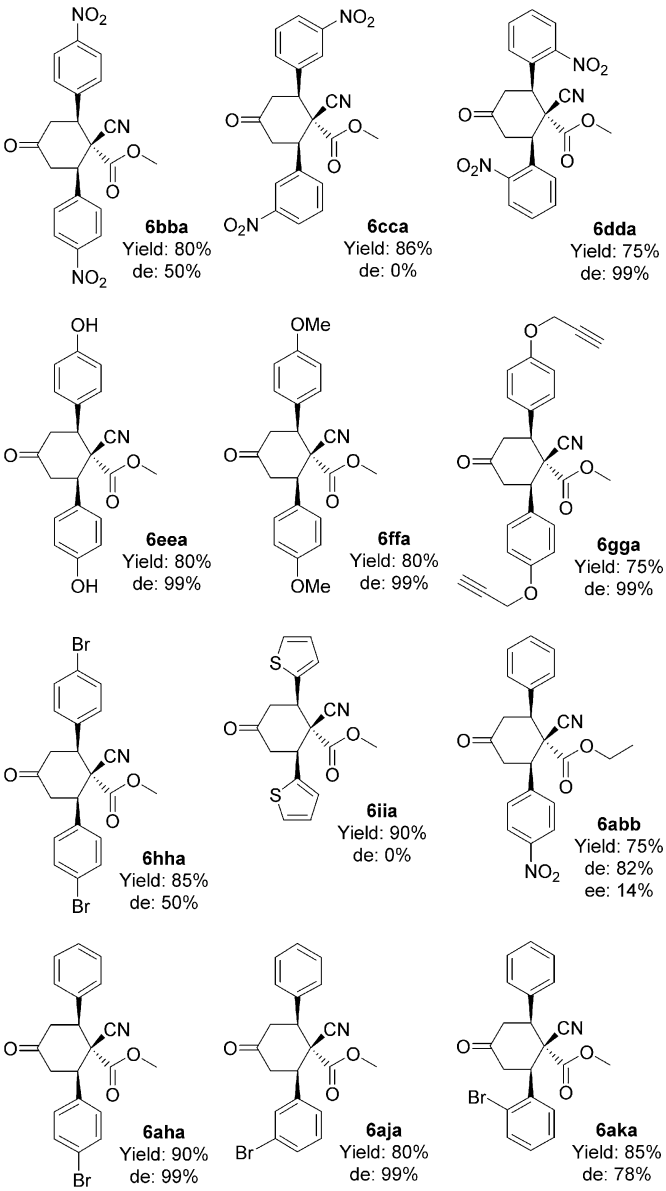
[a] Amino acid **4** (0.1 mmol), benzylidene acetone **1a** (1 mmol), benzaldehyde **2a** (0.5 mmol) and CH-acids **3a–e** (0.5 mmol) in DMSO (1 mL) were stirred at 25 °C for 72 h. [b] Yield refers to the column purified product. [c] Diastereomeric excesses determined by using ^1H and ^{13}C NMR analysis on isolated products.

With pharmaceutical and material applications in mind, we extended the three-component cascade O–DA–E reactions into a novel double cascade proline-catalyzed five-component olefination–Diels–Alder–epimerization–olefination–hydrogenation (O–DA–E–O–H) reaction of enones **1**, aldehydes **2**, CH-acids **3**, and Hantzsch ester **9** with various CH-acids **3a–e** in one-pot (Table 5). A library of double cascade products **10** as shown in Table 5 are furnished in good yields with 99% de under proline-catalysis at 25 °C for 96 h. Interestingly, proline-catalyzed double cascade reaction of **1a**, **2a**, **3a** (2 equiv.) and **9** in EtOH at 70 °C for 96 h furnished the product **10aaab** in 60% yield with 99% de *via* olefination–Diels–Alder–epimerization–olefination–hydrogenation–*trans*-esterfication (O–DA–E–O–H–TE) reaction sequence. The structure and regiochemistry of double cascade products **10** were confirmed by X-ray structural analysis on **10aaee** as shown in Fig. 1.‡

‡ CCDC reference number 664436 for **10aaee**. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b718122a

Table 3 Chemically diverse libraries of cascade O–DA–E products **6**[a,b,c]

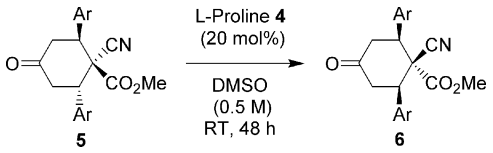


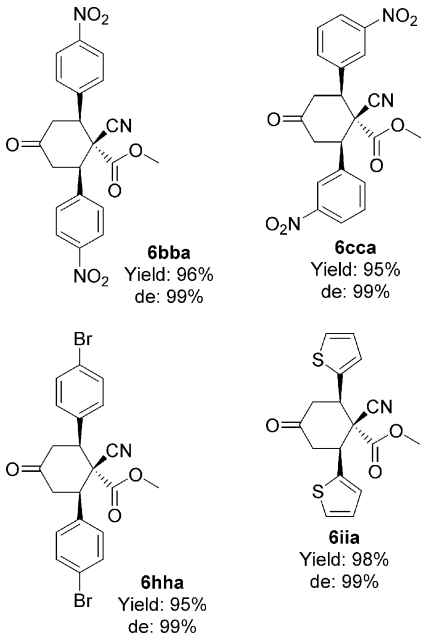


[a] Yield refers to the column purified product. [b] Diastereomeric excesses determined by using ^{1}H and ^{13}C NMR analysis on isolated products. [c] Ee determined by HPLC analysis.

Prochiral *cis*-isomers **6** are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products;[11] and highly functionalized cyclohexanes **10** could serve as suitable synthons for the synthesis of useful materials with different properties.

Table 4 Direct proline-catalyzed epimerization of *trans*-isomers of O–DA products **5**[a,b]





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

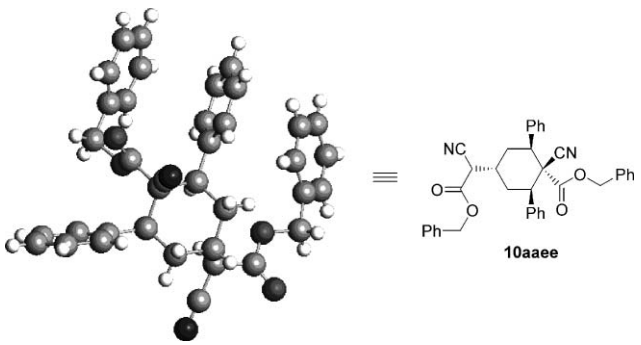
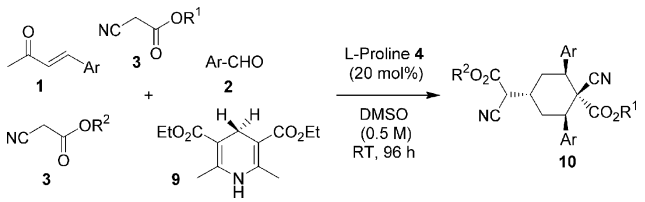


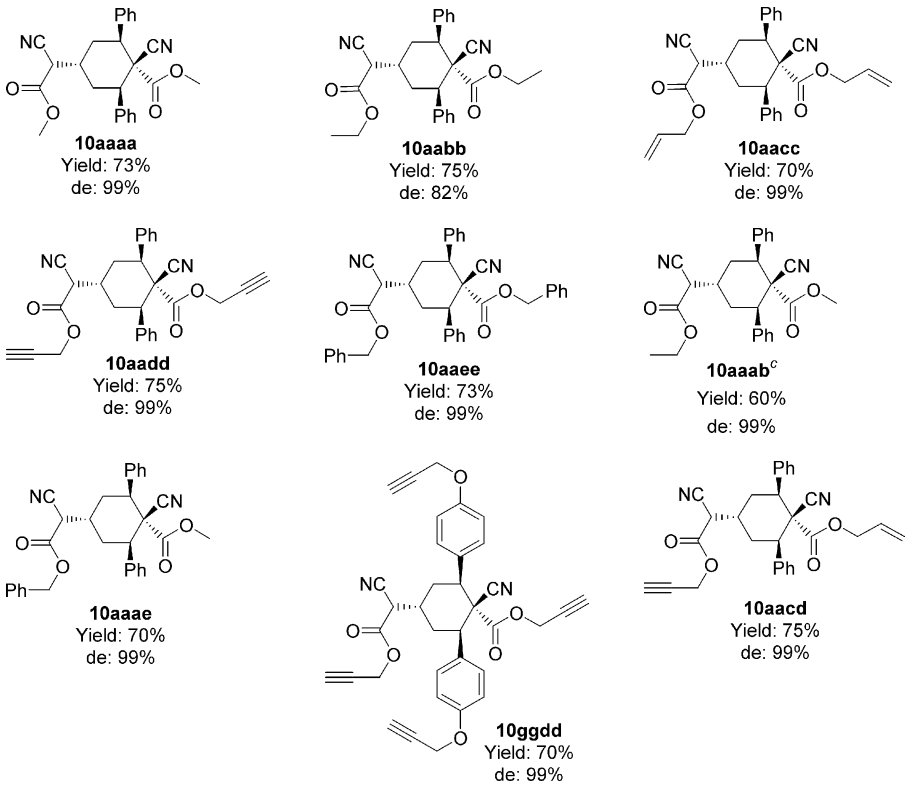
Fig. 1 Crystal structure of 4-(benzyloxycarbonyl-cyano-methyl)-1-cyano-2,6-diphenyl-cyclohexanecarboxylic acid benzyl ester (**10aaee**).

Mechanistic insights

The possible reaction mechanism for L-proline-catalyzed regio- and diastereoselective synthesis of cascade products **6** and **10** through reaction of enone **1**, aldehyde **2**, CH-acid **3** and Hantzsch ester **9** is illustrated in Schemes 2 and 3. This catalytic sequential one-pot, double cascade is a five component reactioncomprising enone **1**, aldehyde **2**, CH-acid **3**, Hantzsch ester **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 2),

Table 5 Chemically diverse libraries of cascade O–DA–E–O–H products **10**[a,b]



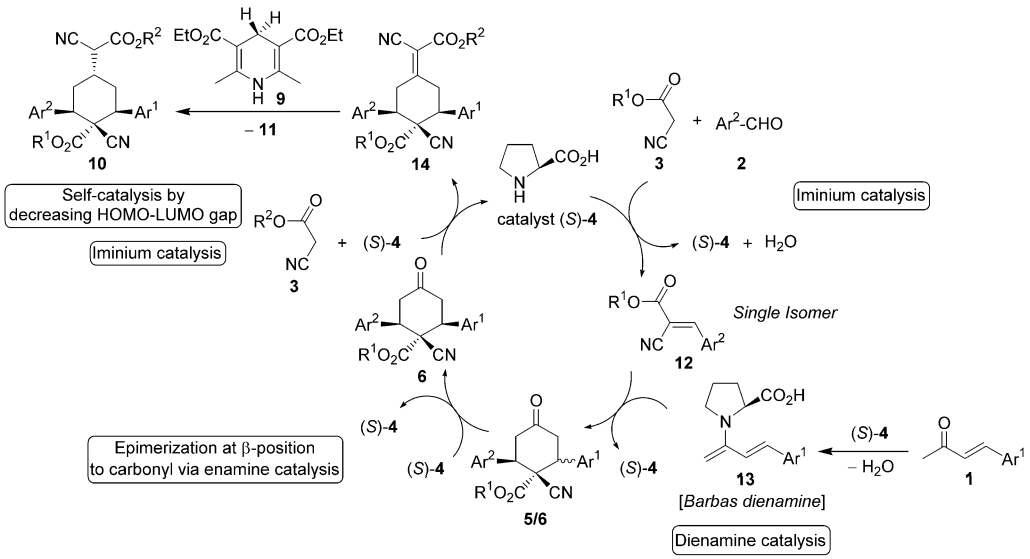


[a] Proline **4** (0.1 mmol), benzylidene acetone **1a** (0.5 mmol), benzaldehyde **2a** (0.5 mmol), and CH-acid **3** (0.5 mmol) in solvent (1 mL) were stirred at ambient temperature for 72 h, and then CH-acid **3** (0.5 mmol) and Hantzsch ester **9** (0.5 mmol) were added (see the Experimental section). [b] Yield refers to the column purified product and diastereomeric excesses determined by using ^{1}H and ^{13}C NMR analysis on isolated products. [c] Product **10aaab** was obtained from the cascade O–DA–E–O–H–TE reaction of **1a**, **2a**, **3a** (2 equiv.), **4** and **9** in EtOH (1.0 mL) at 70 °C for 96 h.

the catalyst (*S*)-**4** activates component **2** by most likely iminium ion formation, which then selectively adds to the CH-acid **3** *via* a Mannich and retro-Mannich type reaction to generate regio-selectively active olefin **12** as dienophile.[10h] The following second step is proline mediated generation of Barbas dienamine **13** (2-amino-1,3-butadiene)[9] as the diene source from enone **1** and proline **4**. In the subsequent third step, Diels–Alder reaction of **12** with *in situ* generated Barbas dienamine **13** *via* most likely concerted [4 + 2] cycloaddition leads to the formation of cascade O–DA products **5**/**6** in good yield with prochiral *cis*-isomer **6** as the major isomer with moderate de. In the fourth step, (*S*)-**4** catalyzes the epimerization at the β-position to carbonyl of *trans*-isomer **5** *via* enamine catalysis and subsequent hydrolysis returns the catalyst (*S*)-**4** for further cycles and releases the desired major *cis*-isomer **6**. In the fifth step, (*S*)-**4** catalyzes the olefination of major isomer **6** with CH-acid **3** to furnish the functionalized olefin **14** *via* most likely iminium catalysis as like the first step. The following sixth step is bio-mimetic hydrogenation of active olefin **14** by Hantzsch ester **9** to produce **10** through self-catalysis by decreasing the HOMO–LUMO energy gap between **14** and **9** respectively.[10]

Taking into account the recent applications of amine-catalyzed olefination reactions[9,10] and based on the different experiments performed (Tables 1–4), we proposed that the most likely reaction course for the organocatalyzed direct epimerization at the β-position to the carbonyl of *trans*-isomer **5** and olefination–hydrogenation of *cis*-isomer **6** is the one outlined through amino acid-catalysis as shown in Scheme 3.

Epimerization of *trans*-isomer **5** or the diastereospecific synthesis of *cis*-isomer **6** in the cascade O–DA–E reaction of enone **1**, aldehyde **2** and CH-acid **3** can be explained as illustrated in Scheme 3. The energy difference (ΔH) between the two isomers **5aa** and **6aa** is 3.085 kcal mol^{-1} based on PM3 calculations. The energy difference (ΔH) between the two isomers **5ab** and **6ab** is 3.081 kcal



Scheme 2 Proposed catalytic cycle for the double cascade reactions.

mol^{-1} based on PM3 calculations. Minimized structures of **5aa**, **6aa**, **5ab**, and **6ab** are depicted in the ESI.† Since the differences in ΔH's between the two isomers of **5aa**/**6aa** and **5ab**/**6ab** are greater than 3 kcal mol^{-1}, the minor kinetic isomers **5aa** and **5ab** are epimerized to the thermodynamically more stable *cis*-isomers **6aa** and **6ab**, respectively, at room temperature under mild organocatalysis. The minor kinetic isomer, *trans*-isomer **5**, was epimerized to the thermodynamically stable *cis*-isomer **6** *via* deprotonation–reprotonation or retro-Michael–Michael reactions catalyzed by amino acid. This is in agreement with the previously proposed retro-Michael–Michael reaction mechanism[9b] at the epimerization step (Scheme 3). As shown in Scheme 3, the amino acid reacts with *trans*-isomer **5** to generate the enamine **15**. The retro-Michael reaction to form the ring-opened imine–enolate **16** should be accelerated by hydrogen bonding with protic/polar solvents. Imine–enolate **16** then undergoes Michael reaction to form the enamine of the thermodynamically stable *cis*-isomer **17**, which undergoes hydrolysis *in situ* to furnish *cis*-isomer **6**.

The possible reaction mechanism for cascade O–H reactions of **6**, **3**, **9** and **4** are illustrated in Scheme 3. First, reaction of proline **4** with *cis*-isomer **6** generates the iminium cation **20**, an excellent electrophile that undergoes Mannich type reactions with CH-acid **3** to generate Mannich product **22**. Retro-Mannich or base induced elimination reaction of amine **22** would furnish active olefin **14**. The next 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 **9** and **14**.[10]

The observed high regio-selectivity in cascade products **10** can be explained by the approach of the hydride source (Hantzsch ester **9**) to olefins **14** being the main controlling factor, rather than thermodynamic stability, of the resulting hydrogenated products **10**. Approach of the Hantzsch ester **9** to olefin **14** through the equatorial position is more favourable than axial position, may be due to the existence of more steric hindrance in an axial approach. Steric strain control (SSC) is main controlling factor than product stability control (PSC) in bio-mimetic cascade reductions, because thermodynamically stable isomer *cis*-**10** is formed as very minor product. This selectivity trend can be easily understood by the approach of bulk hydride source **9** to highly functionalized olefins **14**.

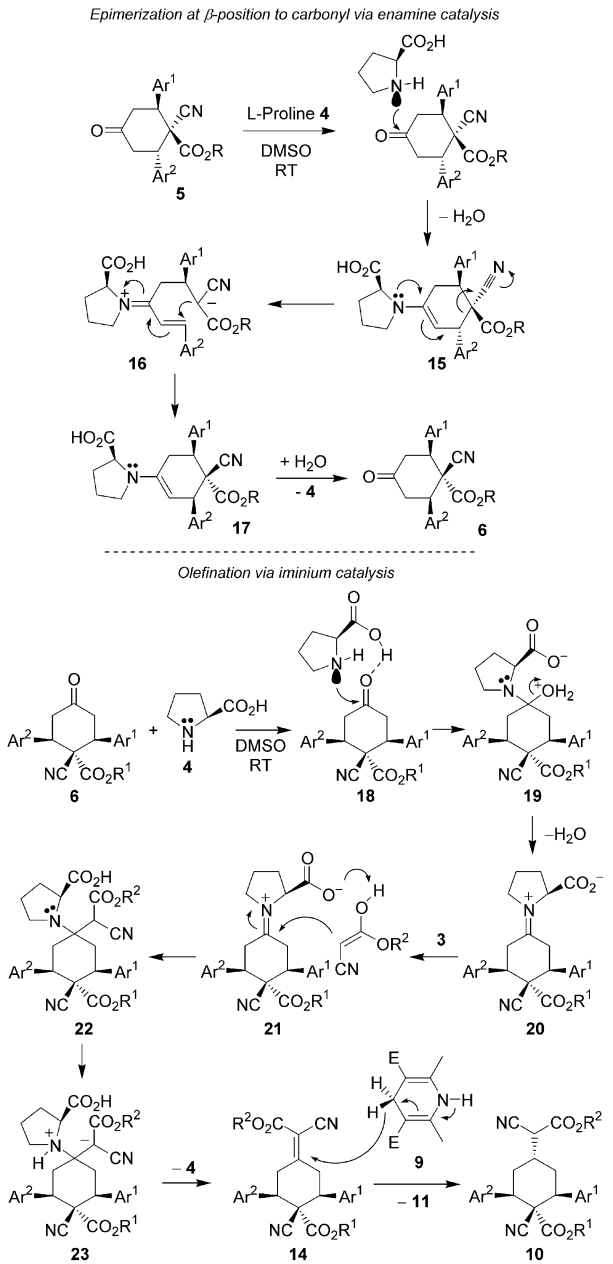
Conclusions

In summary, we have developed the first amino acid catalyzed direct cascade O–DA–E, O–DA–E–O–H and O–DA–E–O–H–TE reactions. This astonishingly simple and atom-economic approach can be used to construct highly functionalized prochiral 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **6** and 1-cyano-4-(cyano-alkoxycarbonyl-methyl)-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters **10** in a diastereospecific fashion. Selective multi-step reactions of this type inspire analogies with biosynthetic pathways and complement traditional multi-component synthetic methodologies. As we have suggested previously, the synthesis of poly-functionalized molecules under amino acid-catalysis provides a unique and under explored perspective on pre-biotic synthesis. A complete understanding of the scope of amino acid-catalysis should not only empower the synthetic chemist but also provide a new perspective on the origin of complex molecular systems.

Experimental

General methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. *In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment, and is given in parentheses.* The coupling constants J are given in Hz. Column chromatography was performed using Acme's silica gel (particle size 0.063–0.200 mm). High-resolution mass spectra were recorded on micromass ESI-TOF MS. GCMS mass spectrometry was performed on Shimadzu GCMS-QP2010 mass



Scheme 3 Proposed mechanisms for the proline-catalyzed epimerization and olefination–hydrogenation reactions.

spectrometer. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. LCMS mass spectra were recorded on either a VG7070H mass spectrometer using the EI technique or a Shimadzu-LCMS-2010A mass spectrometer. IR spectra were recorded on JASCO FT/IR-5300 and Thermo Nicolet FT/IR-5700. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα (λ = 0.71073 Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube (λ = 0.71073 Å). For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating.

Materials

All solvents and commercially available chemicals were used as received.

General experimental procedures for the double cascade reactions

Proline-catalyzed cascade O–DA–E reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of the ketone **1**, 0.5 mmol of aldehyde **2** and 0.5 mmol of CH-acid **3** was added 1.0 mL of solvent, and then the catalyst amino acid **4** (0.1 mmol) was added and the reaction mixture was stirred at 25 °C for the time indicated in Tables 1, 2 and 3. The crude reaction mixture was directly loaded on a silica gel column with or without aqueous work-up and pure cascade products **5/6** were obtained by column chromatography (silica gel, mixture of hexane–ethyl acetate).

Proline-catalyzed O–DA–E–O–H reactions in one-pot. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the ketone **1**, 0.5 mmol of aldehyde **2** and 0.5 mmol of CH-acid **3** was added 1.0 mL of solvent, and then the catalyst proline **4** (0.1 mmol) was added and the reaction mixture was stirred at 25 °C for 72 h then CH-acid **3** (0.5 mmol) and Hantzsch ester **9** (0.5 mmol) was added and stirring continued at the same temperature for 24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure one-pot products **10** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Many of the cascade products **5/6** have been described previously, and their analytical data match literature values; and new compounds were characterized on the basis of IR, ^{1}H and ^{13}C NMR and analytical data (see ESI†).

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