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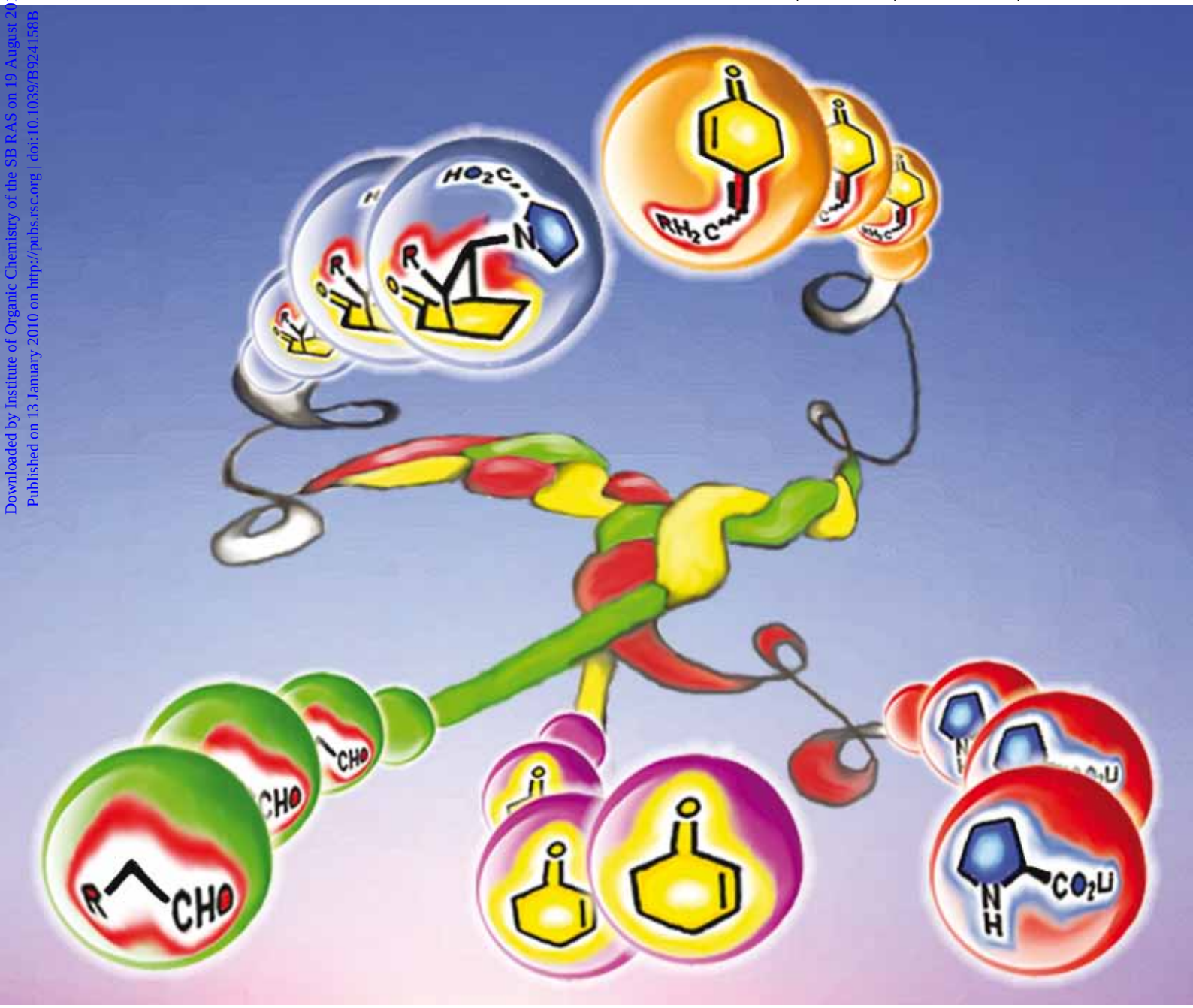

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Multicomponent asymmetric reactions mediated by proline lithium salt†

Polyssena Renzi, Jacob Overgaard‡ and Marco Bella*

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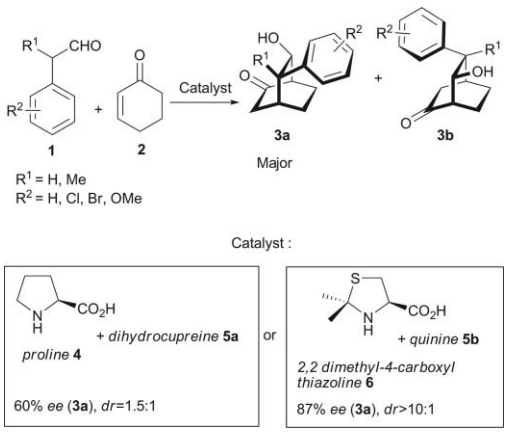
The multicomponent reaction between proline lithium salt, 2-cyclohexen-1-one and aliphatic aldehydes affords the 4-alkylidene-2-cyclohexen-1-ones, which are interesting fragrances, and bicyclic amino acids that bear four additional stereocenters, obtained as single stereoisomer.

Organic synthesis has witnessed a major revolution since the year 2000 when two landmark papers, reporting on the discovery of the proline-catalyzed intermolecular aldol reaction authored by List, Barbas and Lerner,[1] and on the first organocatalyzed high enantioselective Diels–Alder reaction disclosed by MacMillan and co-workers,[2] opened a new horizon for asymmetric catalyzed transformations. Since then, the growing interest of the scientific community has been witnessed by the exponential increase of publications in this field, and new privileged structures, such as Jørgensen–Hayashi trimethylsilyl prolinol[3] or Yamamoto–Ley tetrazole[4] have shown excellent efficacy in a multitude of asymmetric transformations, including those where complex molecular frameworks are accessed and several stereocenters are cast at once.[5]

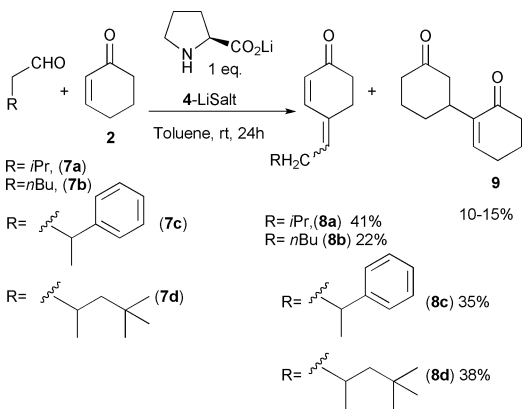
A recurring feature in the catalysts employed in these processes can be identified: the presence of a secondary amine together with a source of protons, within the same molecule, such as in proline or in the combination of TMS diarylprolinol and MacMillan imidazolidinone[6] catalyst with organic acids.[7] Examples where the catalytic system is instead a combination of secondary amines, such as proline and base, are seldom encountered. It should be noted that in 1996 Yamaguchi had already shown the synthetic potential of alkaline metal salts of proline in the asymmetric conjugate addition of malonates[8] and nitroalkanes[9] to cyclic enones. In 2000 Hanessian optimized the addition of nitroalkanes to enones exploiting a combination of proline and amines.[10] We recently proved that the combination of proline **4** or 2,2-dimethyl-4-carboxyl thiazolidine **6** with *Cinchona* alkaloids such as **5a, b** shows a strong synergistic effect in the reaction affording compounds **3**. These elaborated molecular frameworks bear four asymmetric carbons and are obtained with excellent stereochemical control. We defined this particular kind of catalysis SAOc, or Synergic Asymmetric Organocatalysis (Scheme 1).[11] Notably, the cycloadducts **3** are generated only if a particular class



Scheme 1 Addition of arylacetaldehydes **1** to 2-cyclohexen-1-one **2** mediated by SAOc.

of aldehydes is employed, such as the *aryl* acetaldehydes **1**; the usage of *aliphatic* acetaldehydes **7** leads to a completely different reaction pathway, and these intriguing results of our investigation are presented here.

When 1 eq of 2-cyclohexen-1-one **2** is reacted in toluene with 1 eq of proline **4** and an aldehyde such as isovaleraldehyde **7a** or capronaldehyde **7b**, consumption of the α,β-unsaturated reactant is observed within one or two days. Water is added and the reaction mixture is then extracted with ethyl acetate; evaporation and purification (Flash Chromatography) of the organic phase affords the cyclohexenone derivatives **8**, together with the autocondensation product of the aldehyde and dimerization product **9** derived from 2-cyclohexen-1-one **2** (Scheme 2).



Scheme 2 Synthesis of 4-alkylidene-2-cyclohexen-1-ones **8**.

Albeit in moderate yield, the formation of the 2-cyclohexen-1-one derivatives **8** represents, to the best of our knowledge, the first example of dienamine catalysis[12] where an α,β-unsaturated ketone

Dipartimento di Chimica, Università" Sapienza" di Roma, and Istituto di Chimica Biomolecolare del CNR, P.le Aldo Moro 5, 00185, Roma, Italy. E-mail: marco.bella@uniroma1.it

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‡ To whom correspondence regarding X-ray should be addressed. Department of Chemistry, Aarhus Universitet, Langelandsgade 140, 8000 C Aarhus, Denmark; E-mail: jacobo@chem.au.dk

is employed instead of an aldehyde. Compounds **8a–d**, which are formed as a mixture of geometric isomers, are unknown in the literature, and they present an intense and characteristic scent.[13] The 4-alkylidene-2-cyclohexen-1-one moiety is a recurring feature in several fragrances and natural substances, such as in the aroma of tobacco and honey.[14] The cyclohexenone dimer **9**, which has already been prepared by us[15] with 92% *ee* by chiral PTC,[16] is the major product if no aldehyde is added.

The mass balance of the crude reaction after aqueous workup, in no case accounted for the initial amount of 2-cyclohexen-1-one **2**, suggesting the formation of a water-soluble adduct derived from **2**. To the crude reaction mixture was added DCM avoiding aqueous workup. The mixture was then filtered in order to remove any unreacted salt of proline, over a pad of celite, the solvent removed *in vacuo* and crude product directly purified by FC. The ^{1}H-NMR spectra of a fraction eluted by methanol : ethyl acetate in the ratio 1 : 10 showed the presence of i) the aliphatic chains derived from aldehydes **7a, b**, ii) the cyclohexenone ring and iii) the proline moiety. The material isolated was a thick yellow oil, which could be purified either by dissolving most of it into D_2O when the reaction is performed with aldehyde **7a** or by crystallization from ethanol in the case of aldehyde **7b** affording a white solid, which ^{13}C-NMR spectra clearly indicated in both cases the presence of only a single diastereoisomer.[17]

In order to elucidate the structure of this compound, a single crystal X-ray analysis was performed, which indicated the formation of the three component adduct **10a** (Fig. 1), where the original stereocenter of proline **4** had been able to control the configuration of four additional carbon atoms.[18,19]

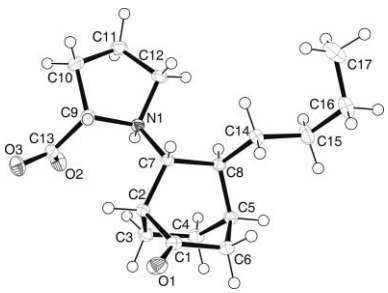
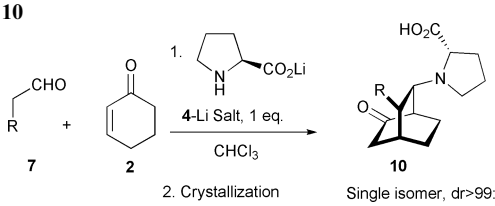


Fig. 1 ORTEP drawing of compound **10a** showing 50% thermal ellipsoids.[20]

Several attempts were performed in order to optimize the reaction yield; chloroform employed as the solvent rather than toluene favored the formation of the aminoacid **10** over the cyclohexenenone derivative **8**, together with an improvement in the yield, which, however, remained not high (Table 1, entry 1 and 2). The reaction was then tested on more aldehydes (Table 1, entries 3–5) and the bicyclic adduct **10** was isolated in all cases.[21] We cannot rule out the formation of more stereoisomers of compounds **10**, however, neither in the crude material obtained after chromatography nor after crystallization, can any of these diastereoisomers can be detected.

In any case, it should be noted that i) the reaction can be performed on gram scale, ii) the bicyclic systems **10**, which are obtained as single stereoisomers, can be purified to a high degree and iii) in this process three different substrates are combined, forming two new carbon-carbon bonds and four new stereocenters

Table 1 Cascade three-component reaction for the synthesis of bicyclic adducts **10**



Entry[a]	Aldehyde, R	Time, days	Yield, [b]%
1[c]	**7b**, *n*-Bu	2	**10a**, 22 (12)[d]
2	**7b**, *n*-Bu	2	**10a**, 37 (21)[d]
3	**7a**, *i*-Pr	4	**10b**, 32(20)[e]
4	**7e**, *n*-Octyl	5	**10c**, 38 (22)[d]
5	**7f**, Bn	3	**10d**, 35 (21)[d]

[a] Reactions performed on 1 g of 2-cyclohexen-1-one **2** (10.4 mmol), 20.8 mmol of aldehyde **7** (2 eq) and 1.26 g of proline **4**-lithuim salt (10.4 mmol, 1 eq) in 20 mL of solvent. [b] Isolated yield after chromatographic purification. [c] Toluene as the solvent. [d] Yield after crystallization. [e] Purified by extraction in water, see SI for details.†

with excellent control of their absolute configuration. A possible mechanism, which can rationalize the formation of reaction products **8** and **10**, is presented in Scheme 3. A "classic" catalytic cycle operates when 2-cyclohexen-1-one **2** and proline **4** lithium salt react to give iminium ion **I** which is in equilibrium with enamine **II**. This vinylogous enamine **II** then condenses with aldehydes **7** to give, through iminium ion **III**, the cyclohexenone derivatives **8** and releases the organocatalyst, which initiates a new catalytic cycle (*reaction path 1*).

Proline **4** lithium salt is consumed *via* the concurrent *reaction path 2*: its enamine **V**, formed with aldehydes **7**, deprotonates the 2-cyclohexen-1-one **2** giving rise to the formation of an activate diene. The cycloaddition reaction occurs then through transition state **VI** to trap in an irreversible manner the organocatalyst into the bicyclic adducts **10**.

The different stability of the conjugated enamine **Va** derived from aryl acetaldehydes **1** (Fig. 2) with respect to the ones formed from alkyl acetaldehydes **7** (**Vb**, R = alkyl) is probably involved in the different kind of products observed when the two classes of aldehydes are reacted with 2-cyclohexen-1-one **2**.

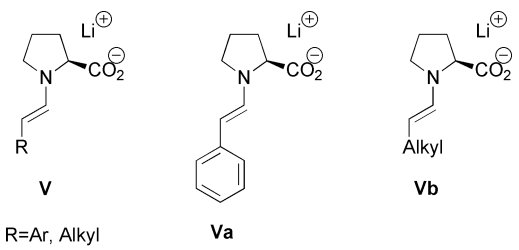
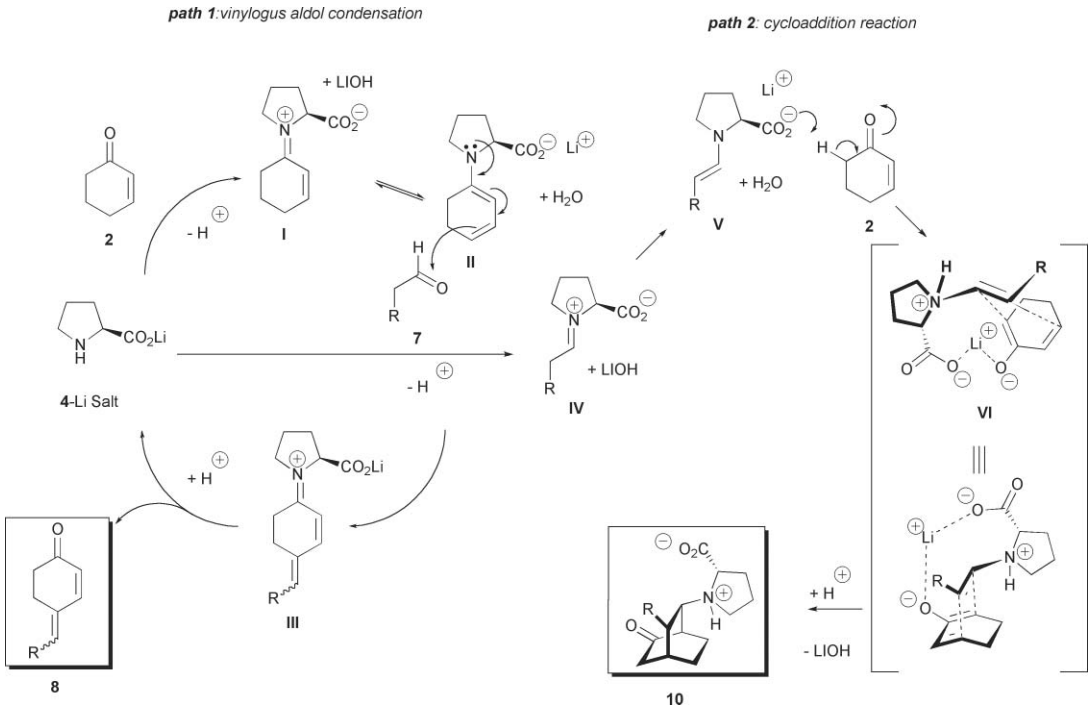


Fig. 2 Conjugated and non-conjugated enamine **Va, b**.

In the organocatalyzed reactions by proline and derivatives generally the catalyst loading is significantly high (up to 30%); investigations have been conducted in order to identify the byproducts arising from the organocatalyst responsible for such high loading. We believe that similar processes to the cycloadditions of enamines as described in Scheme 3 with the formation of water



Scheme 3 Proposed mechanism for the formation of cyclohexenone derivative **8** and the cycloaddition reaction leading to bicycles **10**.

soluble adducts could account for material loss also in several other reactions.[22]

In conclusion, in this paper we present two new reaction types: i) the organocatalytic vinylogous aldol condensation to afford 4-alkylidene 1-cyclohexen-2-one derivatives **8**, which are analogues of well known odorous molecules and interesting fragrances, and ii) the three component reaction of 2-cyclohexen-1-one **2**, proline **4** lithium salt and aldehydes **7** to access the aminoacid derivatives **10** bearing four additional stereocenters as a single stereoisomer. While the products are obtained in moderate yields, it should be noted that complex molecular frameworks are prepared in a single step on multigram quantities, employing inexpensive and commercially available reactants.

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