Multicomponent Reactions

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Dynamic One-Pot Three-Component Catalytic Asymmetric Transformation by Combination of Hydrogen-Bond-Donating and Amine Catalysts**

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Substituted chiral pyrrolidine and proline derivatives are very important pharmaceuticals, natural products, organocatalysts, and building blocks in organic and diversity-oriented synthesis.[1] In this context, biologically active highly substituted pyrrolidine derivatives containing a quaternary stereocenter (e.g. **1**–**4**; Figure 1) are found in, and form the core of many pharmaceutical candidates and natural products.[2]

Multicomponent reactions that involve the formation of multiple carbon–carbon and carbon–heteroatom bonds, and multiple stereocenters in one pot, is a rapidly growing area of research for the synthesis of small molecules that have complex molecular architectures.[3] Multicomponent transformations reduce the synthetic steps, amount of waste produced, and amount of solvents required, which are important factors in "green" chemistry.[4]

The catalytic enantioselective [3+2] cycloaddition of azomethine ylides with electron-deficient olefins is a powerful method for creating structural diversity and for the formation of chiral pyrrolidine and proline derivatives that contain four stereocenters.[1a–f,5] The catalytic asymmetric transformations are mostly carried out using preformed dipolar precursors as substrates.[6–8] However, there are only a few reports on the catalytic enantioselective synthesis of polysubstituted proline derivatives containing a chiral quaternary α stereocenter.[9] According to retrosynthetic analysis, the dynamic one-pot reaction between aldehydes **5**,[10a] protected α-cyanoglycine esters **6b**, and enals **7** should give access to chiral proline derivatives **8**, which have chiral quaternary α stereocenters, through a [2+3] cycloaddition catalyzed by chiral amine **9** (Scheme 1).[10,11]

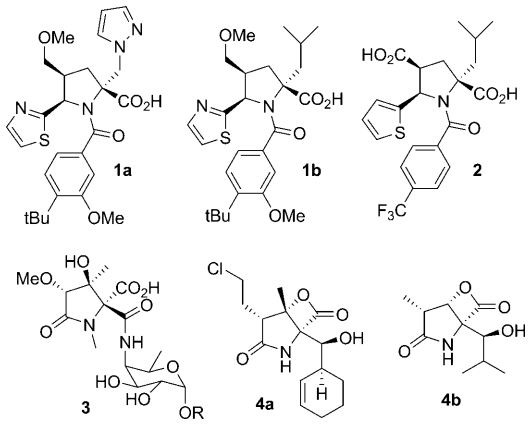

Figure 1. Natural products and biologically active proline derivatives **1**–**4**, which contain a quaternary stereocenter in the α position.

However, such transformations can be plagued by Michael reactions between α-cyanoglycine ester **6** and enal **7** as well as low diastereo- and *endo*/*exo* selectivities.[12] Thus, it is crucial to direct the chemoselectivity (dipolar addition versus Michael addition) of the dynamic process towards an in situ imine formation with a subsequent predominant formation of dipole **A** over dipole **B**, and achieve stereoselective [2+3] cycloaddition with an in situ generated catalytic iminium intermediate (Scheme 1).

Supramolecular interactions (e.g. hydrogen bonding) are highly useful for controlling the reaction outcome and the selectivity of dynamic multicomponent processes in synthetic chemistry.[13] These interactions are also a powerful means of activation in asymmetric catalysis.[14–16] Hydrogen-bond-donating networks in combination with a co-catalyst should have all the essentials for directing and achieving highly selective reactions under both thermodynamic and kinetic control. Thus, we envisioned that by adding a hydrogen-bond-donating co-catalyst to the dynamic three-component system the equilibrium could be pushed towards imine formation and subsequent [2+3] cycloaddition (Scheme 1). Moreover, we predicted that this would favor the formation of intermediate **A** over **B** by locking its conformation by hydrogen bonding, and thereby increase the chance of making the transformation highly diastereoselective.

Herein, we report that the dynamic one-pot three-component reaction between aldehydes **5**, protected α-

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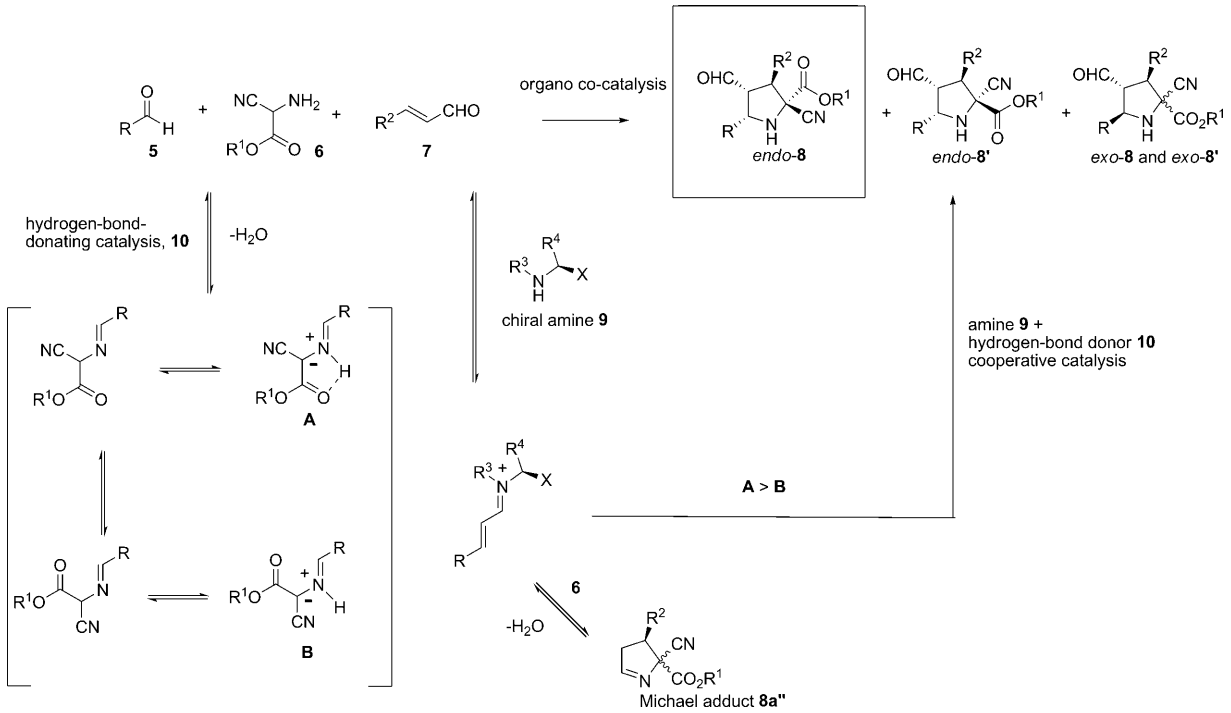
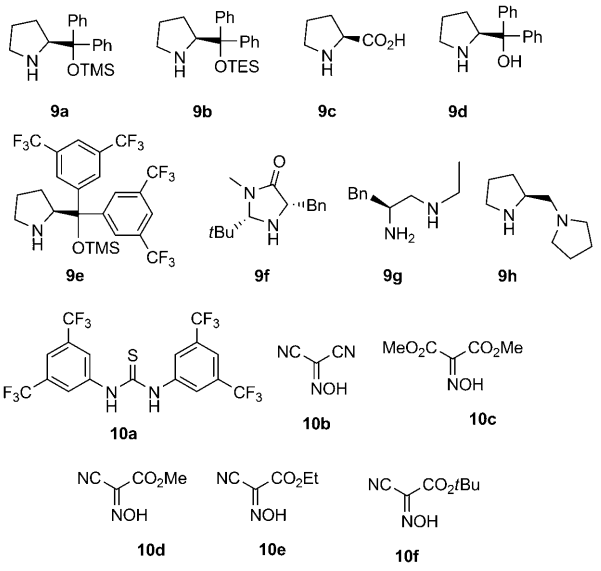


Scheme 1. Possible pathways for the one-pot reaction between aldehyde **5**, amine **6**, and enal **7** to form proline derivatives **8**.

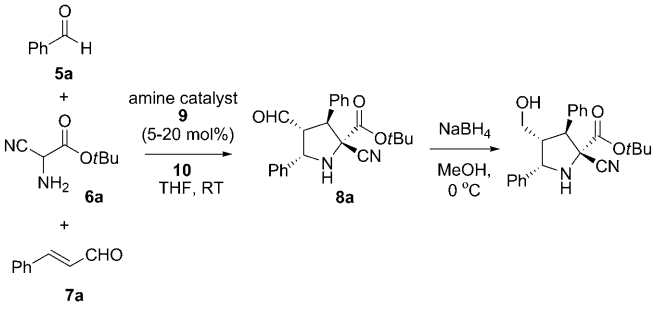
cyanoglycine esters **6**, and enals **7** can be catalyzed with a chiral pyrrolidine catalyst **9**, provided that an appropriate hydrogen-bond-donating co-catalyst **10** is employed, to give proline derivatives **8**, which contain a quaternary α stereocenter, with high *endo*-, diastereo-, and enantioselectivities. The choice of the co-catalyst is critical for the chemoselectivity (dipolar addition versus Michael addition), stereoselectivity, and for acceleration of the rates of both the imine formation and the cycloaddition.

We began by investigating the reaction between benzaldehyde **5a**, α-cyanoglycine esters **6**, and cinnamic aldehyde **7a** catalyzed by chiral amine **9a**. However, the reactions gave only the corresponding Michael adduct **8a″** (Scheme 1) in high conversion but with no diastereoselectivity, even when the enal component (**7a**) was added sequentially after 2 hours of stirring (Scheme 1). The reaction between **5a**, α-cyanoglycine ester **6a**, and **7a** gave predominantly the Michael adduct **8aa″**, but a small amount of the polysubstituted chiral pyrrolidine **8a** was also formed with high *endo*- and diastereoselectivity, and good enantioselectivity in DMF (Table 1, entry 1). With this result in hand, extensive screening for suitable chiral amines **9**, hydrogen-bond-donating molecules **10**, and reaction conditions could be accomplished. The key results are shown in Table 1. In all cases the aldehyde moiety of pyrrolidine **8a** was subsequently reduced to give the alcohol in the yield presented in Table 1.



Pleasingly, the dynamic one-pot process can be completely directed towards cycloaddition in THF or DMF, and no Michael adducts were formed. Thus, the reaction became chemospecific in the presence of hydrogen-bond-donating compounds **10**. For example, we observed a significant rate acceleration when the thiourea reported by Schreiner and Zhang (**10a**)[14c] or phenol was added as a co-catalyst and the reactions were completed within 6 hours and 4 hours, respectively (Table 1, entries 2 and 5).[17] Moreover, the small amount of water released from the imine formation co-mediated the dynamic process towards cycloaddition, but the reaction time increased significantly (Table 1, entry 3).[18] The addition of organic acids (e.g. benzoic acid) as co-catalysts resulted in excellent stereoselectivity, but the reaction was slower compared to the reactions that employed **10a** and phenol (Table 1, entry 4 versus entries 2 and 5).[19] Thus, hydrogen-bond-donating molecules were favorable for the acceleration of the dynamic process and for directing it towards the cycloaddition pathway. Notably, we found that

Table 1: Screen of catalysts and reaction conditions for the one-pot three-component reaction between **5a**, amine **2a**, and enal **7a**.[a]

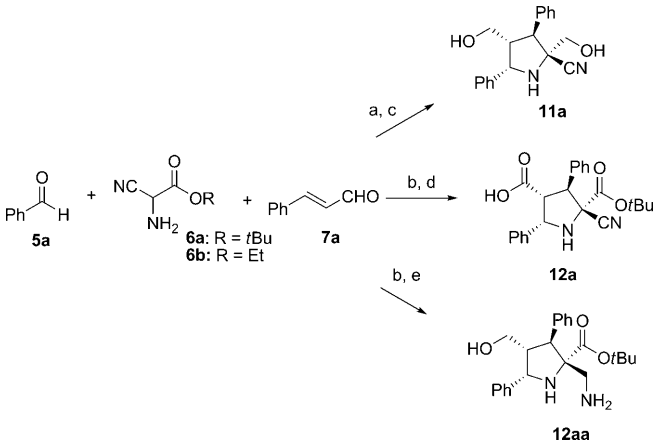


Entry	Amine **9**	Cat. **10**	*t* [h]	Yield [%][b]	*endo*/*exo*[c]	d.r.[c]	*ee* [%][d]
1	**9a**[e,f]	–	6[e]	15[e]	7:1	19:1	73
2	**9a**	**10a**	6	76	3:1	9:1	95
3	**9a**	–	25	64	3:1	9:1	97
4	**9a**	benzoic acid	26	57	9:1	8:1	99
5	**9a**	phenol	4	51	3:1	7:1	76
6	**9a**	**10b**	4	29	10:1	10:1	98
7	**9a**	**10c**	26	74	4:1	14:1	99
8	**9a**	**10d**	4	77	9:1	19:1	98
9	**9a**	**10e**	3.5	74	9:1	19:1	98
10	**9a**	**10f**	3	78	8:1	18:1	97
11	**9b**	**10d**	5	77	11:1	19:1	97
12	**9c**	**10d**	4	63	7:1	6:1	30
13	**9d**	**10d**	4.5	67	11:1	15:1	94
14	**9e**	**10d**	4	74	4:1	19:1	94
15	**9f**	**10d**	52	34	15:1	8:1	27
16	**9g**	**10d**	4	76	10:1	9:1	17
17	**9h**	**10d**	4	94	11:1	8:1	10
18	**9b**[g]	**10d**	5	80	11:1	19:1	97
19	**9b**[h]	**10d**	7	79	11:1	19:1	97
20	**9a**[i,j]	**10f**	3.5	41	4:1	15:1	94
21	**9a**[k,j]	**10f**	4	11	4:1	14:1	97
22	**9a**[l,j]	**10f**	3	42	6:1	15:1	97
23	**9a**[f]	**10f**	4	77	8:1	14:1	81

[a] A mixture of **5a** (0.50 mmol), **6a** (0.375 mmol), enal **7a** (0.25 mmol; added after 2 h), **10** (0.188 mmol), and catalyst **9** (0.05 mmol) in 0.5 mL of solvent was stirred at RT. [b] The yield of the isolated pure alcohol, which was synthesized by the reduction of the aldehyde moiety of **8a** (two steps), after column chromatography on silica gel. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined after reduction of the aldehyde moiety of **8a** by HPLC analysis on a chiral stationary phase. [e] Michael adduct **8a″** was isolated in 55% yield, 1:1 d.r., 92% *ee*, and 96% *ee*. [f] Reaction was performed in DMF. [g] Used 10 mol% of **9b**. [h] Used 5 mol% of **9b** at 4°C. [i] Reaction was performed in $CHCl_3$. [j] The imine that was generated in situ from **5a** and **6a** oligomerized, thus resulting in a reduced yield. [k] Reaction was performed in toluene. [l] Reaction was performed in CH_3CN. DMF = dimethylformamide, THF = tetrahydrofuran, TES = triethylsilyl, TMS = trimethylsilyl.

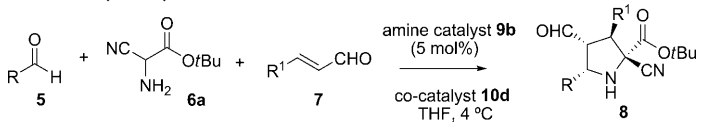
oximes derived from malonate and cyanoacetate esters (**10b**–**f**) also can co-catalyze the reaction. They were chosen since we believed that their intramolecular hydrogen bonding and similarity with the amine component **6a** would have a beneficial effect. For example, the oxime derived from malononitrile **10b** [$pK_a = 5.6$ (DMSO)][20] accelerated the reaction but unwanted side reactions and decomposition occurred and reduced the formation of **8a** (Table 1, entry 6). The one-pot reaction with malonate-derived oxime **10c** [$pK_a = 7.2$ (DMSO)] exhibited lower activity and the reaction required 26 hours for completion; however, **8a** was formed with excellent enantioselectivity (Table 1, entry 7). In comparison, the oximes that were derived from cyanoacetate esters [**10d**: $pK_a = 4.9$ (DMSO)] had the right acidity for achieving both dramatic rate acceleration and high stereoselectivity (Table 1, entries 8–19). To the best of our knowledge, these types of oximes have never previously been used as catalysts for organic asymmetric reactions involving carbonyl compounds. The catalyst screen showed that both protected and unprotected chiral diarylprolinols **9** co-catalyzed the reaction with the highest stereoselectivity (Table 1, entries 8, 11, 13, and 14).[21] We were also able to reduce the catalyst loading of **9** without significantly affecting the reaction times (Table 1, entries 18 and 19). Based on these results, we decided to investigate the enantioselective dynamic multicomponent cycloaddition process between aldehydes **5**, α-cyanoglycine ester **6a**, and enals **7** by using chiral amine **9b** and oxime **10d** as co-catalysts in THF (Table 2).[22]

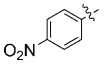
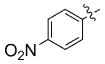
The organo-co-catalytic asymmetric three-component reactions gave the corresponding highly substituted α-quaternary proline derivatives **8a**–**8n** as the predominant diastereoisomer in good to high yields (Table 2, 56–87%); this diastereomer was the only one isolated by column chromatography on silica gel. The enantioselectivity of the reaction was excellent (93–99% *ee*). Thus, the one-pot procedure allows for the construction of four contiguous stereocenters, including a quaternary stereocenter, with high stereocontrol. We did not observe any dipolar addition products from the possible reaction between amine **6a** and two molecules of enal **7**. In fact, mixing just enal **7a** (0.75 mmol) and **6a** (0.375 mmol) in the presence of **9b** and **10d** gave the corresponding imine, but no dipolar addition occurred. We also investigated the use of aliphatic aldehyde components **5** (e.g. isobutyraldehyde, pivalaldehyde, *n*-butanal), however only traces of products **8** were formed. To demonstrate the synthetic utility of the transformation and the possibility of employing it in diversity-oriented synthesis,[23] we further modified the proline derivatives **8** (Scheme 2). Consequently,



Scheme 2. a) **6b**, **9b**, **10d**, THF, 4°C, 70%; b) **6a**, **9b**, **10d**, THF, 4°C, 79%; c) $NaBH_4$ (3 equiv), MeOH, 0°C, 75%; d) $NaClO_2$, KH_2PO_4, $(CH_3)_2C{=}CHCH_3$, *t*BuOH:H_2O (5:1), 96%; e) $NaBH_4$, $CoCl_2{\cdot}6H_2O$, MeOH, 0°C→RT, 34%.

Table 2: Catalytic asymmetric domino reactions between enal **1** and ester **2**.[a]



Entry	R	R^1	8	Yield [%][b]	*endo*/*exo*[c]	d.r.[c]	*ee* [%][d]
1			**8a**	79[e]	11:1	19:1	97
2			**8b**	75	6:1	>19:1	98
3			**8c**	83	9:1	>19:1	97
4			**8d**	87[f]	7:1	>19:1	95
5			**8e**	73	10:1	14:1	96
6			**8f**	71[e,f]	12:1	10:1	97
7			**8g**	85	16:1	17:1	96
8			**8h**	79	13:1	14:1	96
9			**8i**	87	11:1	15:1	97
10			**8j**	83	10:1	11:1	95
11			**8k**	88[f]	8:1	>19:1	97
12			**8l**	62[e,g]	>19:1	>19:1	98
13			**8m**	80	14:1	15:1	93
14			**8n**	56[e,g]	>19:1	>19:1	96

[a] A mixture of **5** (0.50 mmol), **6** (0.375 mmol), and enal **7** (0.25 mmol, added after 2 h), **10d** (0.188 mmol) and catalyst **9b** (12.5 μmol) in 0.5 mL THF was stirred for 6 h at 4 °C. [b] Yield of isolated pure **8** after column chromatography on silica gel. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. [e] The yield of the isolated pure alcohol, which was synthesized by the reduction of the aldehyde moiety of **8** (two steps), after column chromatography on silica gel. [f] Used 20 mol% of **9b**. [g] Used 0.125 mmol of **10d** and stirred reaction mixture for 6 h.

either reduction or oxidation gave the corresponding chiral pyrrolidine **11a**, acid **12a**, and diamine **12aa**. Reduction of the cyano group is possible and gives access to chiral diamines containing both a secondary and primary amine structural motif (**12aa**), which is a useful combination both in organocatalysis as well as medicinal chemistry.[1] The absolute stereochemistry of the highly substituted quaternary proline derivatives **8** was confirmed by the X-ray crystallographic analysis of **8c** (2*S*, 3*R*, 4*R*, 5*S*; Figure 2).[24]

As shown above, the employment of hydrogen-bond-donating additives **10** has a dramatic effect on the reaction outcome and the rate of the dynamic multicomponent process. It significantly accelerated the iminium formation, as determined by ^{1}H NMR analysis. We also separately investigated the hydrogen-bond-donating effect of **10d** for the [2+3] cycloaddition step by using preformed imines as substrates. The cycloaddition between the imine derived from **5a** and **6a**, and enal **7a** without co-catalyst was finished after 17 hours and gave the corresponding proline **8a** in 77% yield with 9:1 d.r. (4:1 *endo*/*exo*) and 97% *ee*. In comparison, the same reaction using oxime **10d** as an additive was much faster; it was complete within 2 hours to give **8a** in 78% yield with 19:1 d.r. (11:1 *endo*/*exo*) and 97% *ee*. These results demonstrate that the hydrogen-bond donation of **10d** significantly accelerates the rate and improves the diastereoselectivity of the cycloaddition reaction. Based on our experimental results, X-ray crystallographic, ^{1}H NMR, and HRMS analyses, we propose the following mechanistic pathway to account for the observed chemoselectivity and stereochemistry of the dynamic multicomponent transformation (Scheme 1 and Scheme 3).

The hydrogen-bond-donating molecule is crucial for the fast formation of the imine and thus pushes the equilibrium of the reaction towards the imine formation. Most likely this occurs by activation of the carbonyl group of aldehyde **5**.[14] Next, the intramolecular hydrogen-bonding network, which can be created by **10**, will activate the imine and lock its conformation to **C** (Scheme 3). The imine will now undergo proton shifts to form intermediates **A1**–**A3**, which are stabilized by the hydrogen-bonding network. In parallel, chiral amine **9** will form the iminium intermediate **I**, which is efficiently shielded at the *Si* face by the bulky aryl groups. Next, the activated species **A**, for which the conformation is locked by hydrogen bonding with co-catalyst, approaches the opposite face, and stereoselective C–C bond formation occurs from the *Re* face of intermediate **II** either by a concerted *endo*-selective mechanism (cycloaddition) or a stepwise (Michael/Mannich) mechanism to give iminium intermediate **III**.[25] Subsequent hydrolysis regenerates catalyst **9** and gives the polysubstituted proline derivative **8**. It is known that the [2+3] dipolar cycloaddition can proceed by a stepwise mechanism.[7o] However, we did not observe any Michael adduct intermediates by ^{1}H NMR analysis. A stepwise mechanism cannot be excluded since DFT calculations of the transition states of the transformation, reported in reference [10], indicate a stepwise mechanism (Prof. Jose Vicario personal communication).

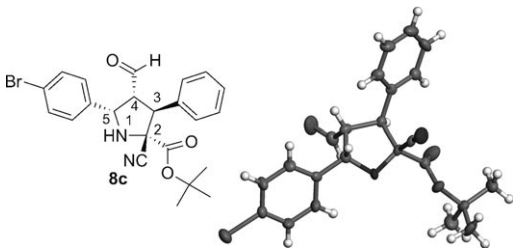
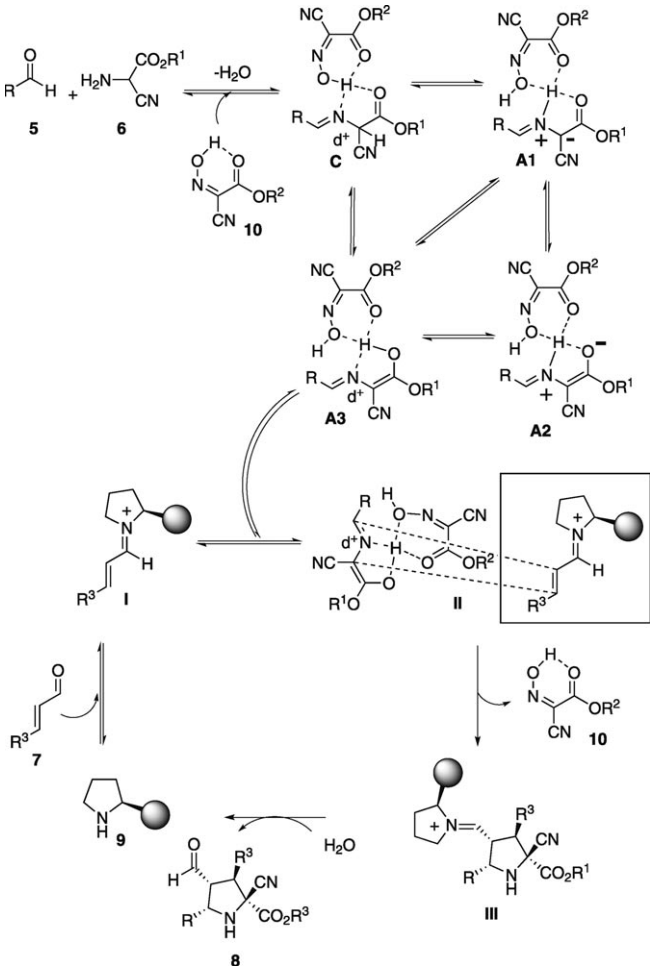


Figure 2. ORTEP picture of the crystalline compound **8c**.



Scheme 3. Proposed reaction pathway (R^3 = aliphatic or aryl group, gray circle = bulky aryl groups).

In summary, we have developed the first highly diastereo- and enantioselective organo-co-catalytic dynamic one-pot asymmetric transformation between, aldehydes, protected α-cyanoglycine esters, and enals. The catalytic dynamic three-component process affords cyano-, formyl-, and ester-functionalized α-quaternary proline derivatives with four contiguous stereocenters (93–99% *ee*). The biomimetic cooperative combination of hydrogen-bond and iminium activation of the carbonyl components was essential to achieve chemo- and stereoselective cycloaddition under kinetic control. The application of simple oximes, which were derived from cyanoacetate esters, as hydrogen-bond-donating molecules gave significant rate acceleration. Further applications of hydrogen-bond donation in combination with amino catalysis for controlling dynamic processes (e.g. dynamic multicomponent combinatorial synthesis), pathways, and C–C bond-forming transformations as well as mechanistic studies are ongoing in our laboratories.

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[25] The importance of the intramolecular hydrogen bond of **10d** was further shown when the O-acetylated **10d** was used instead. This change resulted in a significantly decreased reaction rate for the **9a**-mediated transformation and **8a** was isolated in 37% yield with 19:1 d.r. (3.1 *endo*/*exo*) and 96% *ee*. For the exact comparison see Table 1, entry 8.

