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Organocatalytic Asymmetric Conjugate Addition of Aldehydes to Nitroolefins: Identification of Catalytic Intermediates and the Stereoselectivity-Determining Step by ESI-MS**

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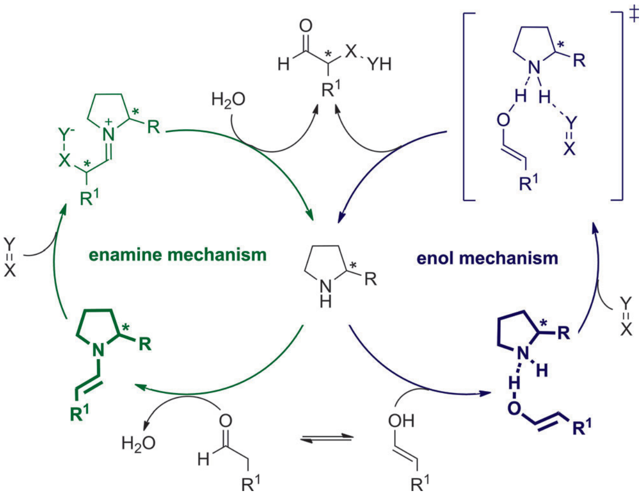
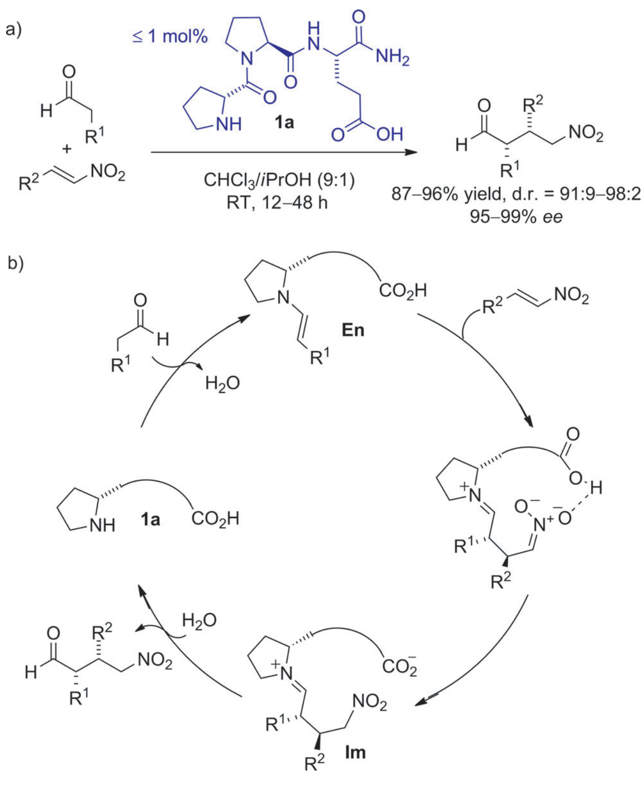
Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 80th birthday

α-Functionalizations of carbonyl compounds are among the most widely used organocatalytic reactions and numerous chiral secondary amine based organocatalysts have been developed for reactions of aldehydes or ketones with electrophiles.[1] A plausible reaction mechanism involves reaction of the catalyst with the carbonyl group of the substrate to form a nucleophilic enamine intermediate which then reacts with the electrophile (Scheme 1, left). An alternative mechanism encompasses noncovalent activation by enol formation and subsequent addition to the electrophile (Scheme 1, right). An enol rather than an enamine mechanism was already proposed by Hajos and Parrish in their pioneering work on proline-catalyzed intramolecular aldol reactions[2] and was also considered by others in recent years.[3] Although an enamine mechanism has been widely accepted it has thus far not been unambiguously validated experimentally.[4,5]



Scheme 1. Enamine versus enol mechanism.

Conjugate addition reactions between aldehydes and nitroolefins to provide chiral γ-nitroaldehydes have been extensively explored and numerous amine-based catalysts have been developed.[6–11] Among the most powerful catalysts for this reaction are tripeptides of the type Pro-Pro-Xaa.[9–11] For example, the tripeptide H-D-Pro-Pro-Glu-NH_2 (**1a**) is a highly efficient catalyst for addition reactions of aldehydes to β-substituted nitroolefins and provides products in excellent yields and stereoselectivities at catalyst loadings lower than 1 mol% (Scheme 2a).[9,10] Mechanistic investigations revealed that the C–C bond-forming step is turnover-limiting and demonstrated that the carboxylic acid moiety within **1a** is critical for optimal stereoselectivity and reactivity.[9c,10] A catalytic cycle involving an enamine (**En**) has been proposed for this reaction (Scheme 2b),[10] however, the available experimental data do not exclude an enol mechanism.



Scheme 2. a) Addition reaction between aldehydes and nitroolefins catalyzed by H-D-Pro-Pro-Glu-NH_2 (**1a**). b) Proposed catalytic cycle.

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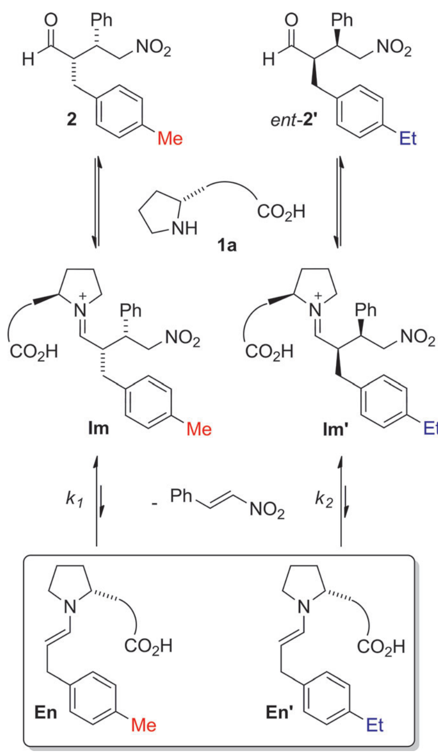
Herein we report the results of a mass spectrometric study of this reaction, which clearly shows that the catalytic cycle proceeds via an enamine intermediate. Moreover, we demonstrate for peptidic catalysts of type **1**, bearing a proton donor on the side chain, that C−C bond formation between the enamine and the nitroolefin is the stereoselectivity-determining step, whereas with catalysts lacking an acidic group the stereoselectivity is determined in a different step.

ESI-MS back-reaction screening using equimolar mixtures of mass-labeled quasienantiomeric substrates is a valuable tool for the rapid determination of the enantioselectivity of chiral catalysts and catalyst mixtures.[12] In contrast to ESI-MS-based mechanistic investigations that solely rely on the detection of reaction intermediates,[5,13] this methodology also provides information on the enantioselectivity-determining step and the intermediates involved therein. It has been successfully used for screening a variety of reactions including palladium-catalyzed allylic substitutions,[12a–e] metal- and organocatalyzed Diels–Alder reactions,[12e,f] and Michael additions.[12g]

We envisioned this method to be ideally suited to examine whether conjugate addition reactions between aldehydes and nitroolefins proceed via an enamine intermediate and whether the C−C bond-forming reaction between this putative enamine and the nitroolefin is the stereoselectivity-determining step. For the back-reaction screening we required a pair of mass-labeled quasienantiomeric conjugate addition products (Scheme 3). Thus, we prepared the substrates (2*S*,3*R*)-**2** and (2*R*,3*S*)-**2′** (*ent*-**2′**) bearing an ethyl and a methyl label, respectively, in the *para*-position of the phenyl ring derived from the aldehyde used in the forward reaction.



Scheme 3. Concept of the back-reaction ESI-MS screening using mass-labeled quasienantiomeric conjugate addition products.

Both **2** and *ent*-**2′** were obtained with the same enantiomeric excess of 97% using the catalyst **1a** and its enantiomer, respectively, thus confirming that the mass labels do not affect the stereoselectivity of the reaction.

In the ESI-MS screening of the back reaction, starting from an equimolar mixture of **2** and *ent*-**2′**, we monitored the signals of the two mass-spectrometrically distinguishable enamines **En** and **En′** which were formed upon reaction with **1a**.[14] The **En**/**En′** ratio, determined from the relative signal intensities, is equivalent to the ratio of the rates by which **2** and *ent*-**2′** are converted into the corresponding enamines **En** and **En′** via the iminium ions **Im** and **Im′** (Scheme 3). If the reaction of the enamine with the nitroolefin is rate-determining in the forward reaction, the stereoselectivity **2**/*ent*-**2′** ($=k_1/k_2$) is determined by the energy difference $\Delta\Delta G^{\pm}$ of the transition states of this step leading to **Im** and **Im′**. In this case, according to the principle of microscopic reversibility, the same transition states would also control the stereoselectivity of the back reaction, which is characterized by a pre-equilibrium between **Im** and **Im′** and a slow rate-determining C−C bond cleavage (Curtin–Hammett conditions). Thus, the **En**/**En′** ratio measured in the back reaction by ESI-MS should be identical to the stereoselectivity determined for the preparative reaction in the forward direction.

Accordingly, a close match between the enantiomeric ratios in the forward reaction and **En**/**En′** measured for the back reaction would provide strong evidence for the involvement of an enamine and not an enol in the stereoselectivity-determining step. In contrast, a **En**/**En′** ratio that deviates from the stereoselectivity of the preparative reaction would not rule out an enamine mechanism but show that C−C bond formation is not the stereoselectivity-determining step.

We started our investigations by reacting an equimolar mixture of the two quasienantiomeric substrates **2** and *ent*-**2′** with **1a** in the protic solvent mixture $CHCl_3$/*i*PrOH as well as the aprotic solvent DMSO, and analyzed the reaction mixture by ESI-MS.[15] $CHCl_3$/*i*PrOH was chosen since it had been found in previous experiments to provide optimum stereoselectivity and reactivity. DMSO was used since enamines are known to be significantly more stable in aprotic compared to protic solvents.[4d,e,16] In addition, the enantioselectivity of **1a** is significantly lower in DMSO (46% *ee*) compared to that in $CHCl_3$/*i*PrOH (97% *ee*). Thus, the signal corresponding to the minor enantiomer of the putative enamines **1a**-**En** and **1a**-**En′** was expected to be more easily detectable in DMSO. In both solvents intense ESI-MS signals corresponding to the iminium ions **1a**-**Im** and **1a**-**Im′** were readily observed (Figure 1a, and see the Supporting Information). Whereas in the protic solvent $CHCl_3$/*i*PrOH the only other visible signals corresponded to the catalyst (see the Supporting Information), signals corresponding to the enamines **1a**-**En** and **1a**-**En′** were clearly identified in DMSO (Figure 1a).[17] The relative intensities of these signals were 73:27, a ratio which correlates perfectly with the enantiomeric ratio observed for the preparative forward reaction. Thus, the intrinsic selectivity of the attack of the enamine onto the nitroolefin determined by ESI-MS matches the stereoselectivity of the preparative reaction.

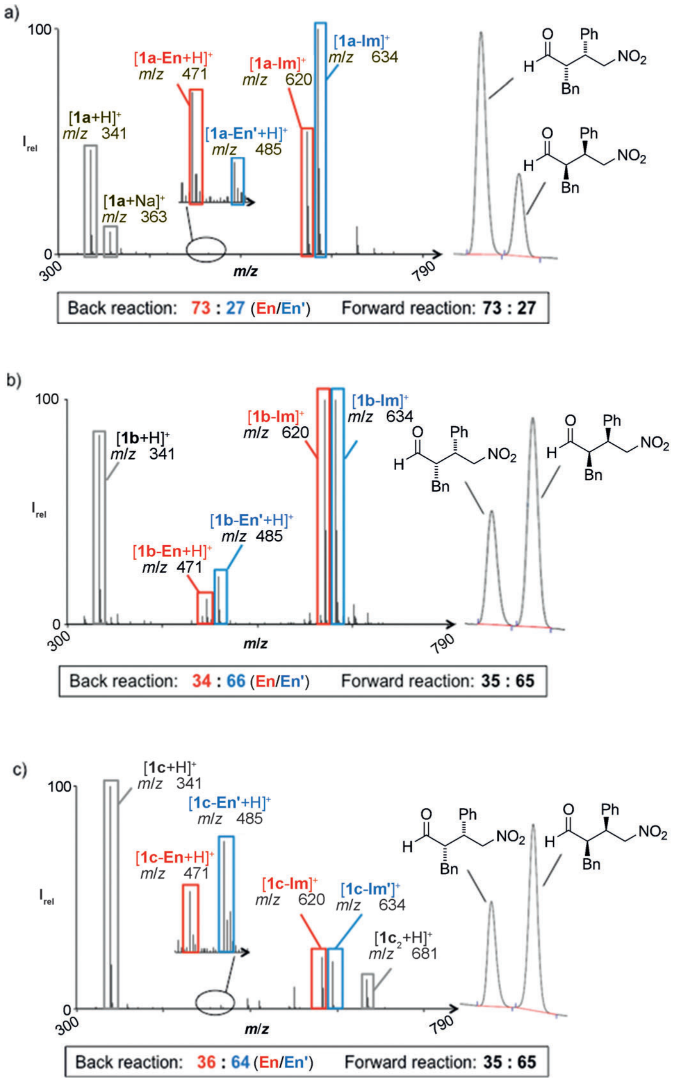


Figure 1. Back-reaction screening and enantioselectivity of the forward reaction in DMSO. a) H-D-Pro-Pro-Glu-NH_2 (**1a**), b) H-Pro-Pro-D-Glu-NH_2 (**1b**), c) H-Pro-Pro-D-Gln-OH (**1c**).

To probe the generality of these observations, back-reaction screening was also performed with the related peptidic catalysts H-Pro-Pro-D-Glu-NH_2 (**1b**) and H-Pro-Pro-D-Gln-OH (**1c**) which had not been evaluated before (Figure 2, top). Based on previous studies these two peptides were not only expected to have lower enantioselectivities compared to **1a** but, since they bear L-Pro instead of D-Pro residues at their N termini, to also provide the opposite enantiomer as the major conjugate addition product compared to **1a**.[9a] Indeed, the protonated enamine species **1b-En** and **1b-En′** as well as **1c-En** and **1c-En′** were detected in ratios of 34:66 and 36:64, respectively (Figure 1b and c). These ratios are in excellent agreement with the enantiomeric ratio of 35:65 in favor of the (2*R*,3*S*)-configured enantiomer of the γ-nitroaldehyde that was observed in the forward reaction with both catalysts under otherwise identical reaction conditions. These results further support a mechanism which involves reaction of the nitroolefin with an enamine formed between the catalyst and the aldehyde as the

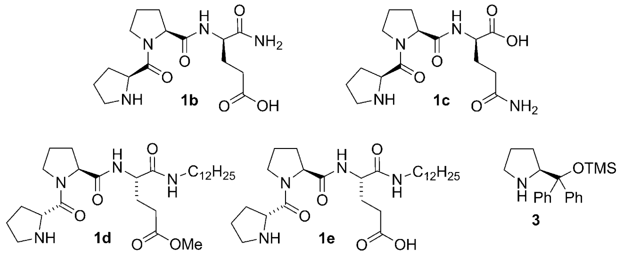


Figure 2. Additional organocatalysts investigated in this study. TMS = trimethylsilyl.

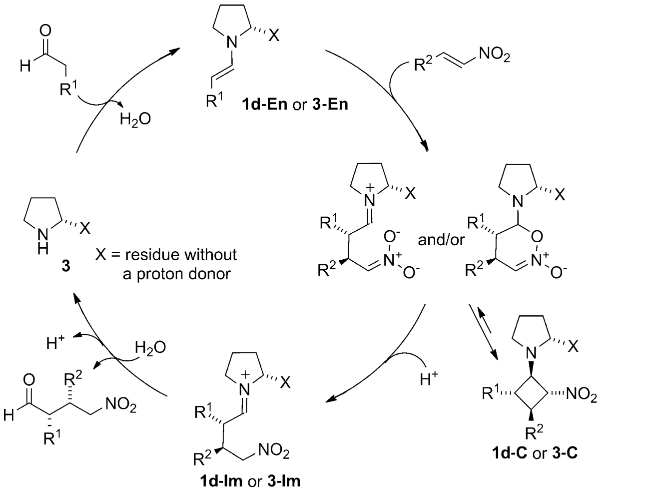
stereoselectivity-determining step for catalysts such as Pro-Pro-Xaa which bear a suitably positioned proton donor.

It should be noted that the iminium ions **1b-Im** and **1b-Im′** as well as **1c-Im** and **1c-Im′** were formed in a ratio of approximately 1:1, and **1a-Im** and **1a-Im′** were present in approximately a 1:2 ratio with the major species corresponding to the minor product enantiomer obtained in the forward reaction. Thus, the stereoselectivity of the reaction is not related to the ratio of the iminium intermediates and is in line with the kinetic regime shown in Scheme 3.

These results, obtained with three different catalysts, provide clear evidence that the reaction proceeds via an enamine intermediate rather than an enol intermediate. In addition they show that the C–C bond-forming reaction is the stereoselectivity-determining step of the reaction.

Next, we wondered how catalysts that lack an intramolecular proton donor, such as the peptide **1d** (bearing a methyl ester instead of a carboxylic acid moiety) and the Hayashi–Jørgensen catalyst (**3**),[8] would perform in back-reaction screening (Figure 2, bottom). Previous studies had led to the conclusion that, in the absence of an appropriately positioned proton donor within the catalyst, the protonation step and not the C–C bond-forming step is rate limiting.[10b,18] While in these cases the reaction rate does not depend on the concentration of the substrates, a significant rate acceleration is observed by an acidic co-catalyst of appropriate strength. Cyclic intermediates such as cyclobutanes and dihydrooxazines form as resting states of the catalysts as depicted in the proposed catalytic cycle which relies on enamine catalysis (Scheme 4).[10b,18] The different rate-determining steps in the catalytic cycles of acidic and nonacidic catalysts suggest that the stereoselectivity-determining steps should differ as well. In fact, Blackmond and co-workers proposed, for reactions catalyzed by the Hayashi–Jørgensen catalyst, that the stereoselectivity depends on the relative stability and reactivity of the diastereomeric cyclobutanes.[19]

Thus, we performed the same back reaction experiments as described above with the peptide **1d**, bearing a methyl ester, its free carboxylic acid analogue **1e**, and the Hayashi–Jørgensen catalyst **3**. Whereas in the presence of **1e** again a good agreement with the preparative reaction was found (**1e-En**/**1e-En′** 76:24 for the back reaction; e.r. 75:25 for the preparative reaction; see the Supporting Information), significant differences were observed with methyl ester **1d** (Figure 3a) and the Hayashi–Jørgensen catalyst **3** (Figure 3b). The enamines derived from the back reaction between **1d** and the quasienantiomers **2** and *ent*-**2′** were



Scheme 4. Proposed mechanism for catalysts lacking an intramolecular proton donor.

formed in a ratio of 84:16, which is considerably different to the ratio of 74:26 for the preparative reaction. Even more dramatically, the enamines **3-En** and **3-En′** of the prolinol silyl ether were formed in a ratio of 88:12 in favor of the quasienantiomer corresponding to the minor product enantiomer of the forward reaction (e.r. 19:81; Figure 3b).[20] This mismatch in the enantioselectivity of the forward reaction with the ratio of the enamines observed in the backward reaction provides strong evidence that C–C bond formation between the enamine and the nitroolefin is not the stereoselectivity-determining step.

The rate acceleration by Brønsted acids, observed in reactions with nonacidic catalysts,[10b,18] led us to examine the effect of *para*-nitrophenol, as an additive,[18a] on the enamine ratio in back-reaction screening with the Hayashi–Jørgensen

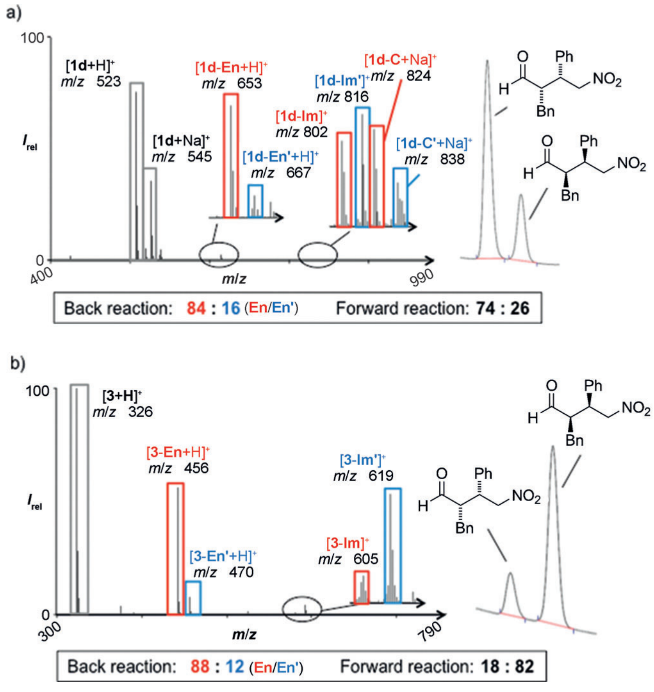


Figure 3. Back-reaction screening with a) the peptide **1d** and b) the Hayashi–Jørgensen catalyst **3** in DMSO.

catalyst **3** (see the Supporting Information). With increasing concentration of *para*-nitrophenol the **3-En**/**3-En′** ratio decreased from 88:12 (no additive) to 67:33 (10 mol%) and 57:43 (100 mol%), while the enantioselectivity in the preparative reaction improved (e.r. 18:82 at 0 mol%; 11:89 at 10 mol%; 3:97 at 100 mol%).[21] Remarkably, in 2,2,2-trifluoroethanol as an acidic solvent the measured enamine ratio of 35:65 was reversed, with the major quasienantiomer now corresponding to the major enantiomer formed in the forward reaction. However, this ratio still deviated strongly from the e.r. value of the preparative reaction (2:98). Thus, acidic additives influence the enantioselectivity of the forward as well as the enamine ratio of the back reaction. But even at relatively high acid concentration, the e.r. value is still not governed by the C–C bond-formation step when catalysts lacking a proton donor are used. Only with an ideally positioned acidic group in the catalyst, does the protonation become so fast that the enantioselectivity is completely determined in the addition between the enamine and the nitroolefin.

In conclusion, starting from quasienantiomeric reaction products, back-reaction screening of Pro-Pro-Xaa catalysts with an acidic group showed that C–C bond formation between an enamine and the nitroolefin is the stereoselectivity-determining step in the reaction of aldehydes with β-nitroolefins. Thus, an enol mechanism can be ruled out for this reaction. In view of these results an enamine mechanism seems also likely for reactions with other electrophiles according to Scheme 1. Screening of nonacidic catalysts such as **1d** or **3** showed that a different step determines the stereoselectivity, which is in line with recent mechanistic studies indicating that protonation occurring after C–C bond formation is the turnover-limiting and stereoselectivity-determining step. The results also demonstrate that ESI-MS back-reaction screening is a valuable tool for probing the mechanism of asymmetric catalytic reactions and for the identification of intermediates involved in the stereoselectivity-determining step.

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[15] The enamine was clearly visible by ESI-MS investigation of the corresponding forward reaction; see the Supporting Information. The reversibility of the conjugate addition reaction was confirmed by crossover experiments: when γ-nitroaldehyde 2-ethyl-3-(4-methoxyphenyl)-4-nitrobutanal was reacted with the catalyst **1a** in the presence of one equivalent of *trans*-β-nitrostyrene in a 9:1 mixture of $CDCl_3$/[D_9]*i*PrOH approximately 20% of *trans*-4-methoxynitrostyrene was released within 2 weeks. This finding demonstrates that the conjugate addition reaction is reversible although the back reaction proceeds only slowly. To ensure that racemization of the quasienantiomers by forward and back reaction was negligible, ESI-MS measurements were performed within the first 2–10 min of the reaction. See the Supporting Information for details.

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[17] Since catalysts **1a-c** and **1e** bear a CO_2H group that destabilizes enamines, low intensities of the enamine signals were expected. When the enantiomeric peptidic catalyst H-D-Pro-D-Pro-Glu-NH_2 (*ent*-**1b**) was used, the expected opposite ratio of *ent*-**1b-En**/*ent*-**1b-En′** was observed. See the Supporting Information for details.

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[20] For catalysts lacking a suitably positioned acidic proton, the enamines are more stable and were observed with a better signal to noise ratio. In addition, the intensities of signals for the adducts formed between the aldehyde, nitroolefin, and either **1d** or **3** are significantly lower compared to those derived from **1a**–**c** and **1e**. Furthermore, for peptide **1d** the sodium adducts of these intermediates were detected. This suggests that the original adducts are neutral which is indicative of the cyclobutanes and/or dihydrooxazine resting states of catalysts lacking a proton donor.

[21] Similar effects on the enamine ratios were observed with acetic acid as additive (**3-En**/**3-En′** 73:27 with 10 mol%; 61:39 with 100 mol%; for the preparative reaction e.r. 14:86 with 10 mol%, 10:90 with 100 mol%).

Communications

Asymmetric Catalysis

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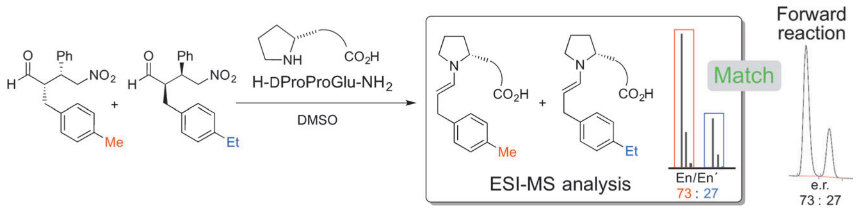
Organocatalytic Asymmetric Conjugate Addition of Aldehydes to Nitroolefins: Identification of Catalytic Intermediates and the Stereoselectivity-Determining Step by ESI-MS



Looking back: The asymmetric organocatalytic 1,4-addition of aldehydes to nitroolefins was studied by ESI-MS. Analysis of the back reaction starting from quasienantiomeric mass-labeled 1,4-adducts (see scheme) provided conclusive evidence for an enamine rather than an enol mechanism, and allowed identification of the enantioselectivity-determining step.

