Organocatalyzed *Michael* Addition of Aldehydes to Nitro Alkenes – Generally Accepted Mechanism Revisited and Revised

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The amine-catalyzed enantioselective *Michael* addition of aldehydes to nitro alkenes (*Scheme 1*) is known to be acid-catalyzed (*Fig. 1*). A mechanistic investigation of this reaction, catalyzed by diphenylprolinol trimethylsilyl ether is described. Of the 13 acids tested, 4-NO_2–C_6H_4OH turned out to be the most effective additive, with which the amount of catalyst could be reduced to 1 mol-% (*Tables 2–5*). Fast formation of an amino-nitro-cyclobutane **12** was discovered by *in situ* NMR analysis of a reaction mixture. Enamines, preformed from the prolinol ether and aldehydes (benzene/molecular sieves), and nitroolefins underwent a stoichiometric reaction to give single all-*trans*-isomers of cyclobutanes (*Fig. 3*) in a [2+2] cycloaddition. This reaction was shown, in one case, to be acid-catalyzed (*Fig. 4*) and, in another case, to be thermally reversible (*Fig. 5*). Treatment of benzene solutions of the isolated amino-nitro-cyclobutanes with H_2O led to mixtures of 4-nitro aldehydes (the products **7** of overall *Michael* addition) and enamines **13** derived thereof (*Figs. 6–9*). From the results obtained with specific examples, the following tentative, general conclusions are drawn for the mechanism of the reaction (*Schemes 2* and *3*): enamine and cyclobutane formation are fast, as compared to product formation; the zwitterionic primary product **5** of C,C-bond formation is in equilibrium with the product of its collapse (the cyclobutane) and with its precursors (enamine and nitro alkene); when protonated at its nitronate anion moiety the zwitterion gives rise to an iminium ion **6**, which is hydrolyzed to the desired nitro aldehyde **7** or deprotonated to an enamine **13**. While the enantioselectivity of the reaction is generally very high (> 97% ee), the diastereoselectivity depends upon the conditions, under which the reaction is carried out (*Fig. 10* and *Tables 1–5*). Various acid-catalyzed steps have been identified. The cyclobutanes **12** may be considered an off-cycle 'reservoir' of catalyst, and the zwitterions **5** the 'key players' of the process (bottom part of *Scheme 2* and *Scheme 3*).

1. Introduction. – The *Michael* addition is widely recognized as one of the most important C,C-bond-forming transformations in organic synthesis [1]. The reaction of a nucleophile with a *Michael* acceptor can be catalyzed by small organic molecules *via* enamines and iminium ions as reactive intermediates [2–8]. Among such reactions, organocatalyzed *Michael* addition of carbonyl compounds to nitro alkenes, which proceeds *via* an enamine, is particularly important, because it affords synthetically useful γ-nitro carbonyl compounds with excellent diastereoselectivities. In the early 1980s, *Seebach* and co-workers reported the reaction of achiral enamines with β-nitrostyrene yielding the *Michael* adducts in good yields and with excellent diastereoselectivities [9]. The same authors obtained *Michael* adducts in diastereo- and enantiomerically pure form by the stoichiometric reaction of enamines, derived from prolinol methyl ether, with nitro alkenes [10]. In 2001, the first catalytic version of

this transformation was independently developed by *List et al.* [11], and *Betancort* and *Barbas* [12]. Since these initial results, extensive efforts have been devoted to the development of more selective and efficient catalytic systems.

In 2005, *Jørgensen* and co-workers [13], and *Hayashi et al.* [14], independently, discovered that diphenylprolinol silyl ether is an effective organocatalyst [15][16]. *Hayashi et al.* reported its application for the highly enantioselective, catalytic *Michael* addition of aldehydes to nitro alkenes. The 'acid test' of new synthetic methodology is still its applicability in challenging total syntheses of biologically active compounds. *Michael* additions of aldehydes to nitro alkenes catalyzed by diphenylprolinol silyl ether turned out to be a powerful method for the synthesis of compounds such as oseltamivir [17][18] and ABT-341 [19]. During the course of these synthetic studies, we had noticed that an acid additive improves remarkably reactivity and diastereoselectivity of the *Michael* reaction. As this transformation consists of several steps, we have now investigated the effect of acid in detail for each step. Furthermore, *in situ* NMR studies have now revealed the presence of an intermediate cyclobutane formed from the catalyst-derived enamine and nitro alkene by a [2 + 2] cycloaddition. Herein, we discuss the effect(s) of added acid in the diphenylprolinolsilyl ether-catalyzed *Michael* addition of aldehydes to nitro alkenes, and we challenge the generally accepted mechanism.

2. Previous Results. – 2.1. *Effect of Additives.* The beneficial effect of additives, and in particular, of acids, in the organocatalyzed *Michael* reaction of an aldehyde and a nitro alkene is well-known and has been reported in the literature (see *Fig. 1*), but its cause is still unclear. *Alexakis* and *Andrey* reported the use of catalytic amounts of toluenesulfonic acid (TsOH) or HCl in the addition of aliphatic aldehydes (propanal, butanal, pentanal, and isovaleraldehyde) to β-nitrostyrene in the presence of a diamine catalyst [20]: TsOH gives rise to higher diastereoselectivities but lower enantioselectivities, as compared to the reaction without acid additive; with HCl, the enantio- and diastereoselectivity are higher, but reactions are slower than those without acid. The combination chiral-diamine/TFA as catalyst for the *Michael* addition of α,α-disubstituted aldehydes to β-nitrostyrene was reported by *Barbas* and co-workers [21]; there is a small increase of yields and enantioselectivities with concomitant decrease of reaction rate, as compared to the reaction carried out in the absence of acid. *Wennemers* and co-workers [22] also used the CF_3COOH (TFA) salt of their tripeptide catalyst in the *Michael* addition of aliphatic aldehydes (propanal, butanal, pentanal, isovaleraldehyde, and 3-phenylpropanal) to nitro alkenes. *Kotsuki* and co-workers [23] reported *Michael* additions of ketones and an aldehyde to β-nitrostyrenes catalyzed by a pyrrolidine–pyridine conjugate base catalyst and 2,4-dinitrobenzenesulfonic acid as an additive: although excellent results were obtained with this catalyst system in the case of ketones, the product of addition of isovaleraldehyde to β-nitrostyrene was obtained with a very low enantio- but still a good diastereoselectivity. *Moorthy* and co-workers [24] have screened a wide range of conditions, including acid additives, for the *Michael* addition of cyclohexanone to β-nitrostyrene catalyzed by functionalized proline derivatives containing two H-bond donors; the best results were obtained when brine was used as solvent and benzoic acid as additive; only one example of the addition of an aldehyde (propanal) to β-nitrostyrene was reported, and the product was obtained in excellent yield, and diastereo- and enantioselectivity (stereoselectivity).

Finally, *Ni* and co-workers [25] also selected benzoic acid as the best additive for the *Michael* addition of aliphatic aldehydes to nitro alkenes, catalyzed by a diarylprolinol ether; the adducts were obtained in excellent yields and with high stereoselectivities; with other acids, such as TFA, AcOH, or TsOH, only trace amounts of the desired products were formed.

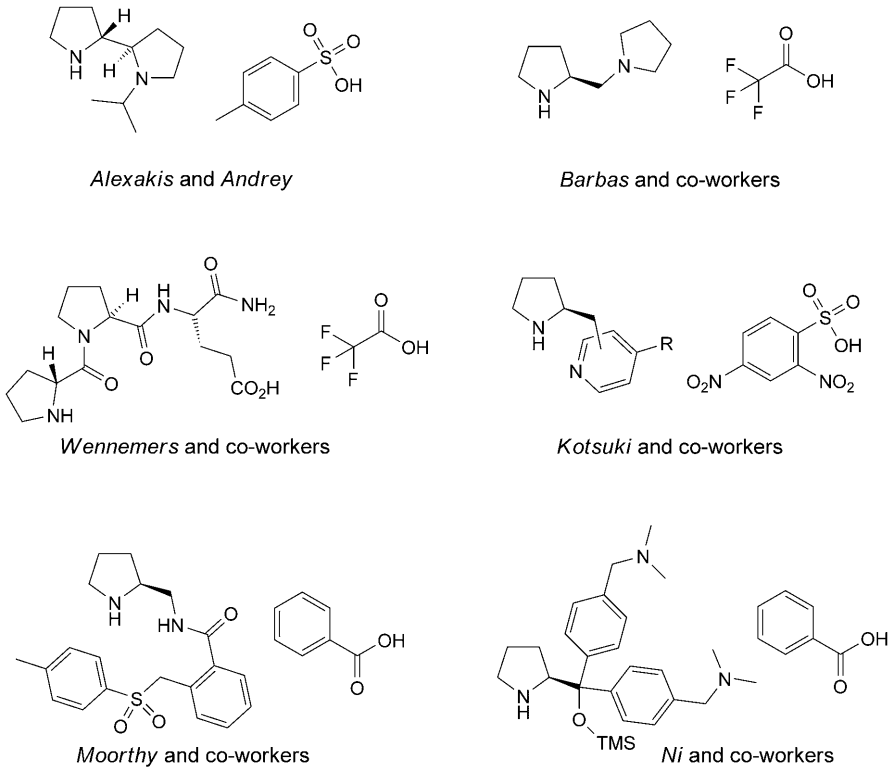


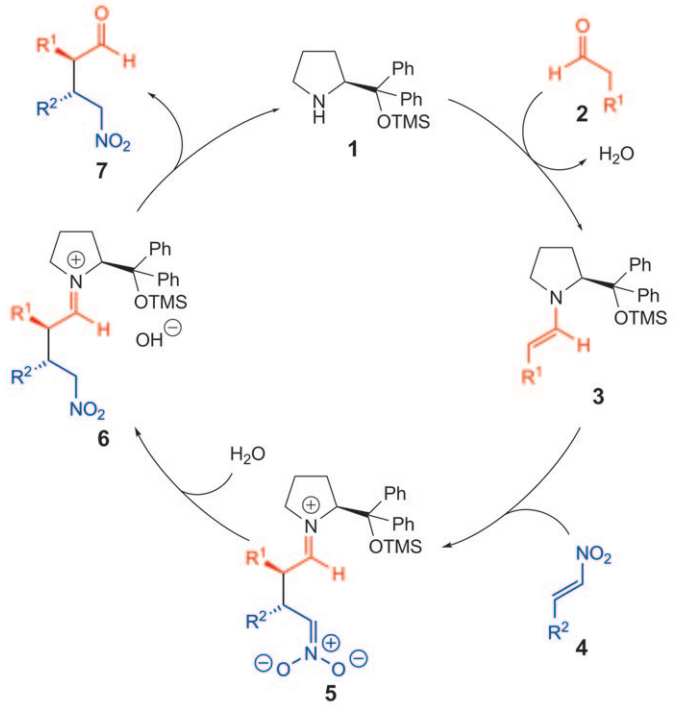
Fig. 1. *Amine-catalysts/acids combinations for aldehyde or ketone additions to nitro olefins, as reported by various research groups.* For details, see accompanying text and references cited therein.

Why do these reactions proceed well in the presence of acid additives? Does the acid effect reactivity, diastereo- and/or enantioselectivity depending upon the particular reaction and amine catalyst used? It is a fact that formation of an enamine from an aldehyde and a *sec.*-amine is catalyzed by – not too strong – acids. However, to the best of our knowledge, there have been no detailed mechanistic investigations to elucidate the role of acid in the context of the entire catalytic cycle involved in the amine-catalyzed conjugate addition of aldehydes to nitro alkenes.

2.2. *Generally Accepted Mechanism.* The generally accepted mechanism (*Scheme 1*) consists of the formation of an enamine **3** by condensation of the chiral amine **1** and an aldehyde **2**. The enamine **3** adds to the nitro alkene **4** to form the zwitterionic intermediate **5**. Protonation of the nitronate C-atom is followed by hydrolysis of the iminium ion **6** to yield the *Michael* product **7** with regeneration of the chiral amine

catalyst **1**. Two roles of acid are proposed: *1*) acid is essential for enamine formation: there is acid-catalyzed addition of the amine **1** to the aldehyde group, followed by likewise acid-catalyzed elimination of H_2O (*vide infra*); *2*) acid protonates the nitronate-anion part of the zwitterionic intermediate **5** to give the iminium ion **6**, thus promoting the conversion to product **7**.

Scheme 1. *Generally Accepted Catalytic Cycle of the Diphenylprolinol Silyl Ether-Catalyzed* Michael *Addition of Aldehydes to Nitro Olefins*. For discussions of this catalytic cycle, see [11][12][14][20–25]; for [2+2] cycloadditions occurring through zwitterionic intermediates, see *Footnotes 5* and *6* below.



3. Results and Discussion. – 3.1. *Preliminary Results.* During our studies on the synthesis of (−)-oseltamivir (**11**), with the aim of limiting the purification steps, an extensive optimization study of the *Michael* addition of 2-(pentan-3-yloxy)acetaldehyde (**8**) to (*E*)-*tert*-butyl 3-nitroacrylate (**9**) was carried out. We found that $ClCH_2COOH$ enhances rate and increases diastereoselectivity of the reaction (*Table 1*[1])) [17][18].

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[1]) The nomenclature *like*/*unlike* [26] is used here:

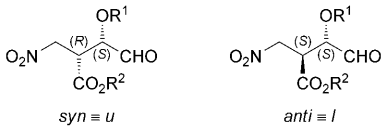
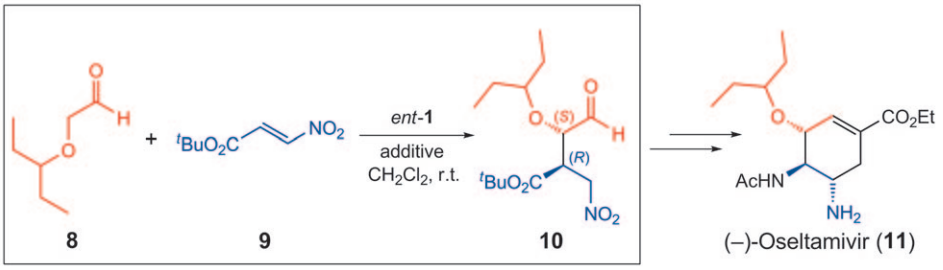


Table 1. *Beneficial Effect of Added Acids to the Reaction Mixture of 2-(Pentan-3-yloxy)acetaldehyde* (**8**) *and Nitro-acrylate* (**9**)



Entry	**1** [mol-%]	Additive	pK_a in H_2O	Time [h]	Yield[a]) [%]	*u*/*l*[b])[1])	ee [%] (*u*, *l*)[c])
1	20	–	–	60	> 99	1.7	nd[d])
2	20	4-NO_2–C_6H_4OH	7.1	24	> 99	1.7	nd
3	5	$ClCH_2CO_2H$	2.86	1	> 99	6.3	96, 87

[a]) Yield of purified product. [b]) *u*/*l* Ratio was determined by NMR analysis of crude product. [c]) Enantiomer excess (ee) was determined by HPLC analysis on chiral column material. [d]) nd = Not determined.

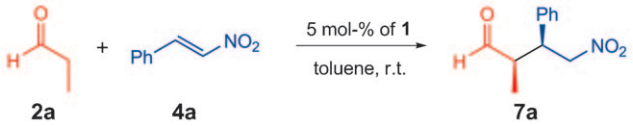
3.2. *Effect of Acid in the Amine-Catalyzed Reaction of Aldehydes with Nitro Alkenes.* Our investigations of the effects of acid began by screening acid additives in the reaction of propanal (**2a**) with *β*-nitrostyrene (**4a**). The reactions were carried out in toluene (1.0M) with 5-mol-% of both 2-[(diphenyl)(trimethylsilyloxy)methyl]pyrrolidine (**1**) and a selection of acids that covered a wide range of pK_a values (*Table 2*).

The results of the screening of acids indicate a direct correlation between the pK_a value of the acid and reaction efficiency. The reaction was complete within 15 min in the presence of 4-nitrophenol (*Entry 10*; pK_a 7.15) with excellent diastereo- and enantioselectivity. Strong acids with pK_a < 3.0 inhibit the reaction, and a decrease of the yields and diastereoselectivities is observed in the presence of chloro-, dichloro- and trichloroacetic acid (*Entries 1–3*; pK_a 0.7–2.85). These results suggest that the optimal acid for *Michael* addition of propanal to *β*-nitrostyrene would have a pK_a value in the range of 6–8. Accordingly, *the acid additive does not affect the enantioselectivity, but increases the reaction rate, allowing the completion of the reaction in a few min compared to 6 h in the absence of the acid additive* (*Entry 14*).

To evaluate the scope of 4-nitrophenol as additive, we investigated a range of aldehydes and nitro alkenes in the presence of 5 mol-% of both chiral amine **1** and 4-nitrophenol (*Tables 3* and *4*). The additive 4-nitrophenol has a significant effect on the rate of the *Michael* addition of propanal (**2a**) to *β*-nitrostyrenes **4a**–**4e** and to aliphatic nitro alkenes **4f**–**4i**. The reaction is complete in less than 1 h[2]), giving access to the desired *Michael* adduct without loss of selectivity, as compared to the transformation carried out in the absence of additive. Nitro alkenes with sterically demanding

[2]) To avoid decrease of the diastereoselectivity, the reaction was quenched as soon as the conversion was complete.

Table 2. *Effect of Various Acids* (5 mol-%) *in the* Michael *Addition of Propanal to β-Nitrostyrene* (**4a**), *Catalyzed by Prolinol Ether* **1**[a])



2a **4a** **7a**

Entry	Acid	pK_a in H_2O[b])	Reaction time	Yield[c]) [%]	*u*/*l*[d])	ee *u*[e]) [%]
1	Cl_3CCO_2H	0.7	10 d	25	2.5	nd[f])
2	Cl_2CHCO_2H	1.29	11 d	70	2.5	nd
3	$ClCH_2CO_2H$	2.85	18 h	85	3	nd
4	HCO_2H	3.75	120 min	88	20	99
5	$CH_2ClCH_2CO_2H$	3.98	80 min	90	6	99
6	$PhCO_2H$	4.19	75 min	90	7	99
7	$EtCO_2H$	4.87	60 min	95	17	98
8	2,4,6-Br_3–C_6H_2OH	5.97	30 min	92	10	98
9	2,4,6-Cl_3–C_6H_2OH	6.21	15 min	88	18	99
10	4-NO_2–C_6H_4OH	7.15	15 min	98	15	99
11	4-Cl–C_6H_4OH	9.18	25 min	90	20	99
12	PhOH	9.89	90 min	89	16	99
13	4-Me–C_6H_4OH	10.2	105 min	90	18	99
14	–	–	6 h	98	14	99

[a]) Propanal (**2a**; 0.51 mmol), *β*-nitrostyrene (**4a**; 0.34 mmol, 100 mol-%), catalyst (0.017 mmol, 5 mol-%), toluene (0.3 ml). [b]) pK_a Values were exported from www.zirchrom.com/organic.htm and the references therein. [c]) Yield of purified product. [d]) *u*/*l* Ratio was determined by NMR analysis of crude product. [e]) ee was determined by HPLC analysis on chiral column material. [f]) nd = Not determined.

substituents in the *β*-position, such as 3,3-dimethyl-1-nitrobut-1-ene (**4j**) did not react even in the presence of acid additive (*Entry 10*, *Table 3*).

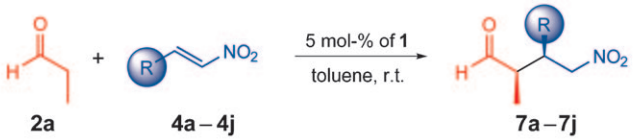
These results demonstrate that 4-nitrophenol acts as a general additive in the addition of propanal (**2a**) to a series of different nitro alkenes, causing rate accelerations, with retention of excellent stereoselectivity.

We next studied the reaction of *β*-nitrostyrene (**4a**) with various *Michael* donors (*Table 4*). Propanal (**2a**), butanal (**2b**), isovaleraldehyde (**2c**), 2-(benzyloxy)acetaldehyde (**2d**) and 3-phenylpropanal (**2e**) led to the desired *γ*-nitro aldehydes **7**.

A clear increase of the rate is observed when reactions are performed in the presence of 4-nitrophenol (*Entries 1–5*). In the case of aldehyde **2f**, with a sterically hindered CHO group, the reaction proceeded neither without nor with additive (*Entry 6*, *Table 4*).

The beneficial effect of the additive on the reaction rate prompted us to examine the possibility of catalyst-loading reduction for the addition of propanal (**2a**) to *β*-nitrostyrene (**4a**) (*Table 5*). The reaction ran efficiently with 5 mol-% (*Entry 1*), 3 mol-% (*Entry 2*), and even with 1 mol-% of catalyst (*Entry 3*, *Table 5*), with slightly extended reaction times. Only when the amount of catalyst was further reduced to 0.1 mol-% did the reaction almost come to a halt (12% conversion after 7 d, *Entry 4*). It

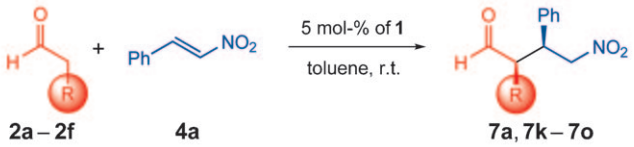
Table 3. Michael *Reaction of Propanal* (**2a**) *with Various Nitro Alkenes with and without 4-Nitrophenol Additive* (5 mol-%)[a])



Entry	Nitro alkene	R	with 4-nitrophenol				without 4-nitrophenol			
			Time	Yield[b]) [%]	ee[c]) [%]	dr[d])	Time	Yield[b]) [%]	ee[c]) [%]	dr[d])
1	**4a**	Ph	15 min	98	99	15	6 h	98	99	15
2	**4b**	4-Br–C_6H_4	35 min	95	99	14	16 h	90	99	10
3	**4c**	4-MeO–C_6H_4	30 min	95	97	4	3 h	95	95	7
4	**4d**	4-CF_3–C_6H_4	15 min	90	99	5	1 h	92	97	9
5	**4e**	3,4-(OCH_2O)C_6H_3	30 min	95	99	15	1.5 h	92	98	15
6	**4f**	Ph(CH_2)$_2$	90 min	92	98	5	12 h	88	97	3
7	**4g**	^{t}BuO_2C	45 min	90	98	9	4 h	92	98	7
8	**4h**	Cyclohexyl	22 h	85	97	2	10 d	43	97	1.5
9	**4i**	^{i}Pr	12 h	90	99	5	7 d	79	99	6.5
10	**4j**[e])	^{t}Bu	–	–	–	–	–	–	–	–

[a]) Nitro alkene (0.30 mmol), aldehyde (0.45 mmol), catalyst (0.015 mmol, 5 mol-%), toluene (0.3 ml). [b]) Yield of purified product. [c]) ee was determined by HPLC analysis on chiral column material. [d]) Diastereoisomer ratio (dr) was determined by NMR analysis of crude product. [e]) No product formed in this case.

Table 4. Michael *Reaction of Various Aldehydes with β-Nitrostyrene* (**4a**) *with or without 4-Nitrophenol Additive* (5 mol-%)[a])

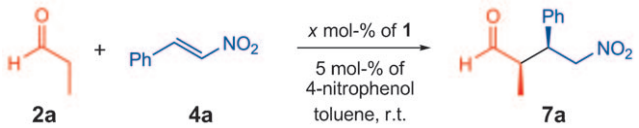


Entry	Aldehyde	R	with 4-nitrophenol				without 4-nitrophenol			
			Time	Yield[b]) [%]	ee[c]) [%]	dr[d])	Time	Yield[b]) [%]	ee[c]) [%]	dr[d])
1	**2a**	Me	15 min	98	99	15	6 h	98	99	15
2	**2b**	Et	45 min	95	96	15	28 h	98	95	8
3	**2c**	^{i}Pr	20 h	95	99	14	14 d	77	nd	15
4	**2d**	BnO	55 h	65	nd	1	13 d	50	nd	1
5	**2e**[e])	Bn	6 h	90	99	11	18 h	90	99	8
6	**2f**[f])	Me(Ph)CH	–	–	–	–	–	–	–	–

[a]) Nitro alkene (0.30 mmol), aldehyde (0.45 mmol), catalyst (0.015 mmol, 5 mol-%), toluene (0.3 ml). [b]) Yield of purified product. [c]) ee was determined by HPLC analysis on chiral column material. [d]) dr was determined by NMR analysis of crude product. [e]) Experimental details not described herein. [f]) No product formed in this case.

is needless to say that it is a great synthetic advantage when such an asymmetric *Michael* addition proceeds in the presence of only 1 mol-% of diphenylprolinol trimethylsilyl ether **1** within a reasonable period of time (95 min) and with excellent stereoselectivity.

Table 5. *Catalyst Loading in the* Michael *Reaction of Propanal* (**2a**) *with β-Nitrostyrene* (**4a**)[a])



2a **4a** **7a**

Entry	Loading cat. **1** [mol-%]	Reaction time	Conversion[b]) [%]	*u*/*l* [b])	ee[c]) [%]
1	5	15 min	98	15	99
2	3	20 min	98	14	97
3	1	95 min	98	19	99
4	0.1[d])	7 d	12	23	99

[a]) **4a** (0.33 mmol), **2a** (0.50 mmol), **1** (x-mol-%), 4-nitrophenol (0.016 mmol), and toluene (0.3 ml). [b]) Determined by ^{1}H-NMR spectroscopy. [c]) ee were determined by HPLC analysis on chiral column material. [d]) Reaction performed on a 2-mmol scale; 0.5 mol-% of additive was used.

3.3. *Studies towards Elucidation of the Reaction Mechanism.* To determine the role of the acid in the *Michael* reaction, which consists of several steps, we decided to investigate the effect of acid in individual steps of the sequence.

a) *Enamine Formation.* The formation of enamine from *equimolar* amounts of aldehyde and amine **1** was examined in C_6D_6. In less than 5 min, *ca.* 30% of an enamine **3** are detected by ^{1}H-NMR analysis. The amount of enamine present in the mixture is unchanged with time, indicating that the reaction had reached an equilibrium. When the reaction was carried out in the presence of molecular sieves, the conversion to enamine **3** was over 90% in 5 min, indicating that the enamine formation is rapid, and that this step is not rate-limiting in the catalytic cycle involving an acid additive.

The effect of acid additives on enamine formation was also studied by ^{1}H-NMR spectroscopy in C_6D_6, with equimolar amounts of butanal (**2b**), catalyst **1**, and four different additives: 4-nitrophenol (pK_a 7.1), propanoic acid (pK_a 4.7), $ClCH_2COOH$ (pK_a 2.8) [17][18], and Cl_3COOH (pK_a 0.8). With the strongest acid, the reaction scarcely proceeded[3]). With the weaker acids ($ClCH_2COOH$ and propionic acid, or 4-nitrophenol), the enamine **3a** is generated in smaller amounts, with simultaneous formation of substantial amounts of self-aldolization product 2-ethylhex-2-enal (*Fig. 2*). The quantitative formation of this self-aldolization product within 6 h in the presence of 4-nitrophenol is compatible with the well-known fact that acid catalyzes enamine formation from an aldehyde and an amine, addition of an enamine to an

[3]) The peaks corresponding to the catalyst are shifted to low field when a strong acid is used, indicating protonation of the amino group with formation of an ammonium salt.

aldehyde (*cf.* (*ii*) in *Footnote 8* below), and dehydration of an aldol adduct to an α,β-unsaturated carbonyl compound[4]).

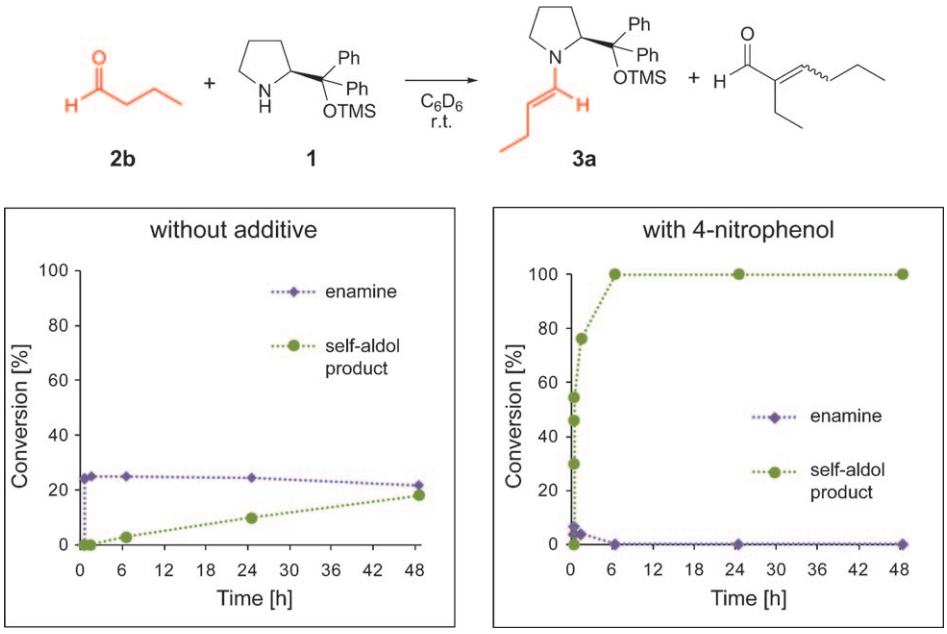


Fig. 2. *NMR Analysis of the effect of acid on the reaction of butanal* (**2b**) *with diphenylprolinol trimethylsilyl ether* (**1**). An 0.1-mmol amount of each component (**2b**, 4-nitrophenol, **1**) was dissolved in 0.6 ml of C_6D_6 in an NMR tube at room temperature. In the absence of 4-nitrophenol, *ca.* 30% enamine is formed, and the amount of self-aldol condensation product slowly increases. In the presence of 4-nitrophenol, the small amount of enamine formed initially disappears quickly, and the unsaturated aldehyde is formed quantitatively.

b) *Discovery of Cyclobutane Formation.* Next, the addition of enamine to β-nitrostyrene was investigated, in the absence of H_2O, *i.e.*, not like in the catalytic reaction where H_2O is being formed (*cf.* enamine formation) and consumed (*cf.* iminium-ion hydrolysis; *vide supra*, *Scheme 1*). β-Nitrostyrene (**4a**) was added to a solution containing a preformed enamine **3** in the presence of molecular sieves. Under these conditions, the spontaneous and very fast formation of cyclobutanes **12** as single isomers was observed, the all-*trans*-configurations of which were deduced from their NMR analysis (see *Fig. 3*). With the NMR spectra of stoichiometrically generated cyclobutanes available, we returned to the reaction under catalytic conditions and searched for the corresponding signals: in every case studied – by catalytic NMR-tube experiments – we were able to detect the tiny peaks stemming from the cyclobutane.

The formation and preparation of cyclobutanes from reactions of isolated enamines, derived from ketones or aldehydes, and alkenes with electron-withdrawing substituents [27–33], *e.g.*, nitro alkenes [27][28][30–32], acrylates [27][29], vinyl

[4]) See textbooks of Organic Chemistry.

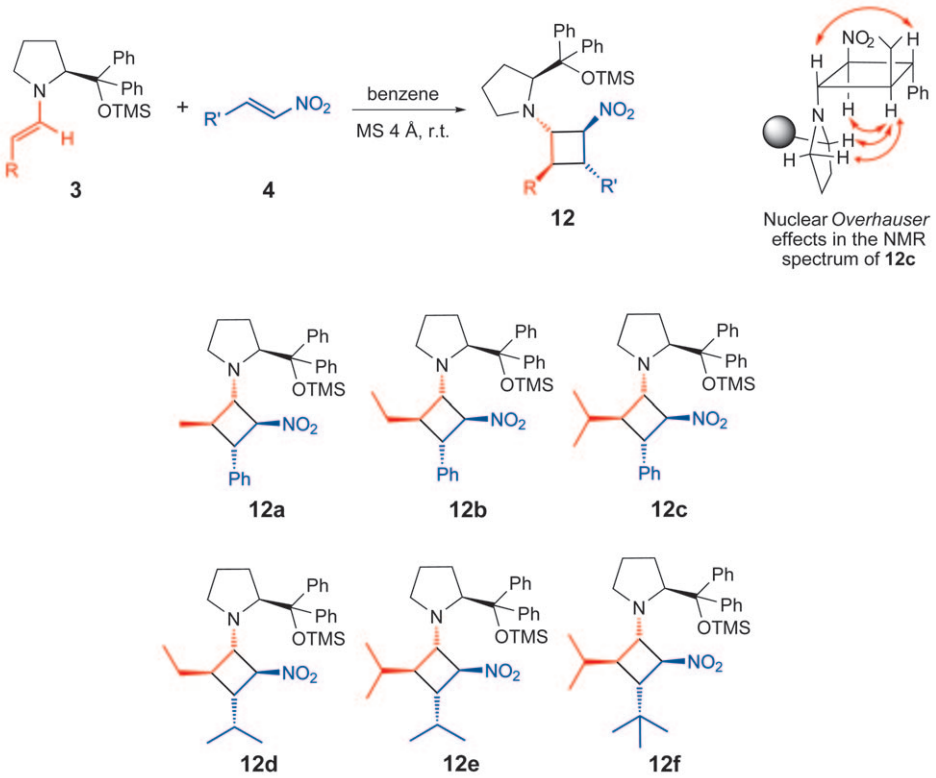


Fig. 3. *Cyclobutanes* **12** *prepared from preformed enamines* **3** *and nitroolefins* **4**, *and assignment of the relative configuration of* **12c** *from NOE in the NMR spectrum*. Note that the cyclobutane **12f** is formed in the stoichiometric reaction of the isovaleraldehyde-derived enamine with the ^{t}Bu-substituted nitroolefin **4j**, while there is no catalytic conversion of propanal and **4j** to the corresponding nitroaldehyde! *Cf. Table 3, Entry 10*.

sulfones [27], and fumarates [27][29][33], has been described a long time ago[5])[6]). However, to the best of our knowledge, a cyclobutane has not been reported as being involved in the *organocatalytic* additions of aldehydes to nitro alkenes or to other *Michael* acceptors, nor has its possible role in the corresponding catalytic cycles been considered.

To find out whether cyclobutanes might be intermediates on the way to the *Michael* adducts in the amine-catalyzed reaction of aldehydes with nitro alkenes, cyclobutane

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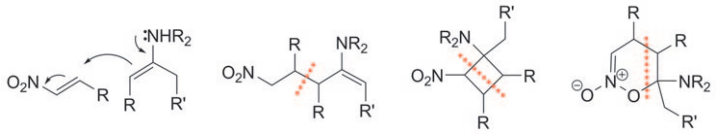
[5]) For masterful discussions by *Huisgen* of [2 + 2] cycloadditions *via* zwitterionic intermediates, see [34].

[6]) The three types of products identified from reactions of enamines with nitro alkenes are a product-derived enamine, a [2 + 2] and a [4 + 2] cycloadduct (see discussion in [9][27][28][30–32]):



formation, and cyclobutane transformation to the products of *Michael* addition, as well as the effect of acid in these two reaction steps were first investigated separately.

c) *[2+2] Cycloaddition of Enamines* **3** *to Nitro Alkenes* **4**. The formation of cyclobutanes by [2+2] cycloaddition of diphenylprolinol silyl ether-derived enamines to nitro alkenes was found to be general (*Fig. 3*): solutions af cyclobutanes **12a**–**12f** were prepared from the propanal-, butanal-, or 3-methylbutanal-derived enamines and β-nitrostyrene, 3-methyl-1-nitrobut-1-ene or 3,3-dimethyl-1-nitrobut-1-ene. The cyclobutanes formed from the substrates with more bulky substituents (*cf.* **12f**) are stable enough for isolation and characterization.

In most cases, cyclobutane formation is a rapid process: *in situ* NMR studies show that the preformed enamine derived from propanal (**2a**) reacts with β-nitrostyrene (**4a**) within 5 min to afford the cyclobutane **12a** almost quantitatively. When the enamine and the nitro alkene carry bulky substituents, however, the cyclobutane formation is slow and can be monitored by ^{1}H-NMR analysis. Thus, we chose the reaction of the enamine (**3b**) derived from 3-methylbutanal with 3-methyl-1-nitrobut-1-ene (**4i**; → **12e**) for a more detailed investigation. Without acid, the reaction was slow, affording the cyclobutane **12e** to the extent of 73% conversion after 80 min at room temperature. On the other hand, 90% of product **12e** was obtained within 12 min in the presence of 1 equiv. of 4-nitrophenol (*Fig. 4*). *These results clearly show that the acid accelerates the cyclobutane formation.*

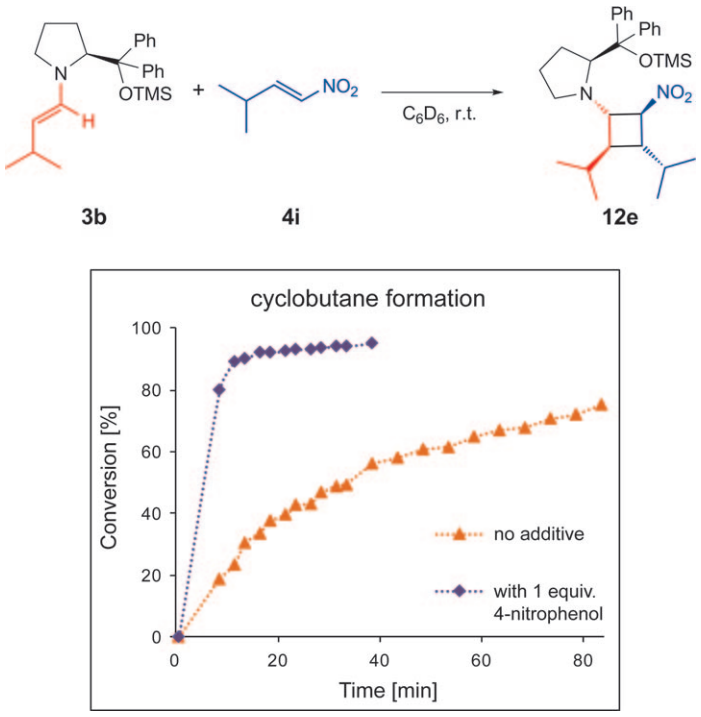


Fig. 4. *Formation cyclobutane* **12e** *without and with 4-nitrophenol.* The reaction was carried out in an NMR tube; an equimolar amount of 4-nitrophenol was added to a 1:1 mixture of preformed enamine and the nitro alkene.

d) *From Cyclobutane to the* Michael *Adduct.* We first determined the thermal stability of an amino-nitro-cyclobutane by ^{1}H-NMR spectroscopy and chose **12c** as a representative example, varying the temperature from 30 to 70° in C_6D_6. At room temperature, a constant 95 : 5 ratio of cyclobutane **12c** and enamine plus β-nitrostyrene, **12c**/(**3b** + **4a**), was observed. The ratio changed gradually from 95 : 5 to 60 : 40 when the reaction mixture was heated to 50° within 1 min, followed by heating to 70° within 1 min and keeping the probe at 70° for 7 min. When the solution was allowed to cool to room temperature, the ratio **12c**/(**3b** + **4a**) returned to 95 : 5 (*Fig. 5*). Thus, the cyclobutane **12c** was in equilibrium with its precursors, and it prevailed at room temperature in benzene. For previous observations of equilibration between amino-nitro-cyclobutanes and their precursors, see [31], and for (*E*/*Z*)-equilibrations in mixtures of enamines and nitroolefins, see [9b].

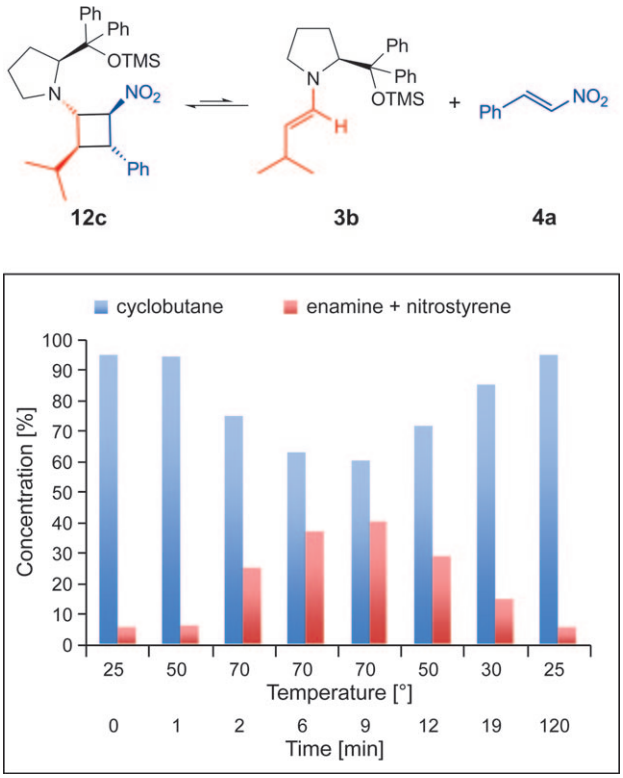


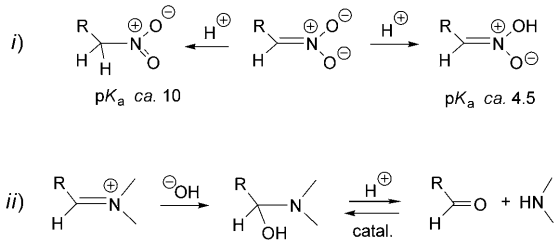
Fig. 5. *A thermal equilibration of an amino-nitro-cyclobutane with its precursors enamine and nitro alkene.* After mixing the aldehyde **2c** and prolinol ether **1** (in C_6D_6, in the presence of molecular sieves) to form the enamine **3b**, an equimolar amount of β-nitrostyrene (**4a**) was added at room temperature; there was 95% conversion to the cyclobutane **12c**; heating in an NMR tube decreased the percentage of cyclobutane; the effect of temperature was completely reversible.

We next studied the reaction of the cyclobutane **12b** with H_2O to see whether this would lead to the *Michael* adduct; addition of an equimolar amount of H_2O in C_6D_6 led

to two compounds, the enamine **13a** and the *Michael* adduct **7k** (*Fig. 6*). The new enamine[7]) is the product of deprotonation of the intermediate iminium ion of type **6** (*Scheme 1*) and, by way of hydrolysis, a possible precursor to the product **7k** of the overall *Michael* addition. This result is compatible with capture of the zwitterion of type **5**, formed upon cyclobutane-ring opening, by H_2O, whereby OH^- would either add as a nucleophile to the iminium C-atom (→ **7k**) or acts as a base to deprotonate the iminium ion (→ **13a**)[8]). The result of the hydrolysis experiment shows that cyclobutane **12b** is converted to the *Michael* adduct **7k** in the presence of H_2O[9]).

The effect of added acid in this reaction of a cyclobutane with H_2O was next examined, using the cyclobutane **12e** with two bulky i-Pr substituents as an example, since the reaction is slow in this case, and can be easily monitored. Without acid, cyclobutane **12e** hardly reacted with H_2O: the starting material was recovered after 12 h. However, the *Michael* adduct **7l** was obtained with 80% conversion in the same period of time in the presence of 1 equiv. of 4-nitrophenol (*Fig. 7*). In this case, the corresponding enamine **13b** was not detected. This indicates that acid accelerates the hydrolytic conversion of cyclobutane **12e** to the product **7l** of *Michael* addition. Neither the zwitterionic intermediate of type **5** nor the iminium-ion intermediate of type **6** (*Scheme 1*) has been detected in any of these ^{1}H-NMR analyses (*vide infra*).

The *in situ* formation of cyclobutane and *Michael* adduct was studied by using *equimolar* amounts of butanal (**2b**), *β*-nitrostyrene (**4a**), and amine **1** in toluene. Three series of reactions were performed: *i*) in the absence of additive, *ii*) in the presence of 10 mol-% propanoic acid, *iii*) in the presence of 10 mol-% 4-nitrophenol. ^{1}H-NMR Experiments (with aliquots withdrawn from the reaction mixture and diluted with C_6D_6) led to the identification of three compounds: cyclobutane **12b**, enamine **13a** of *Michael* adduct, and *Michael* adduct **7k** (*Fig. 8*). We realize that the sampling process for NMR analysis could actually have led to changes of the composition of the reaction mixture[10]), but there were clear-cut differences of results between the three series of



7) Product-derived enamines such as **13a** are commonly observed in the above-mentioned [9][10] stoichiometric reactions of enamines with nitro alkenes under anhydrous conditions.

8) We should keep in mind that H_2O (pK_a *ca.* 15) is not the 'ideal' acid to protonate a nitronate anion (*i*) and that the cleavage of an *α*-amino alcohol to a carbonyl compound and an amine is actually acid catalyzed (*ii*) (*cf. Footnote 4*).

9) The solubility of H_2O in benzene is, of course, very low; the reaction mixture is heterogeneous.

10) Due to the dilution with C_6D_6, due to contact with the atmosphere (moisture) during sampling and diluting, and due to the period of time elapsing between the actual sample withdrawal and the NMR measurement.

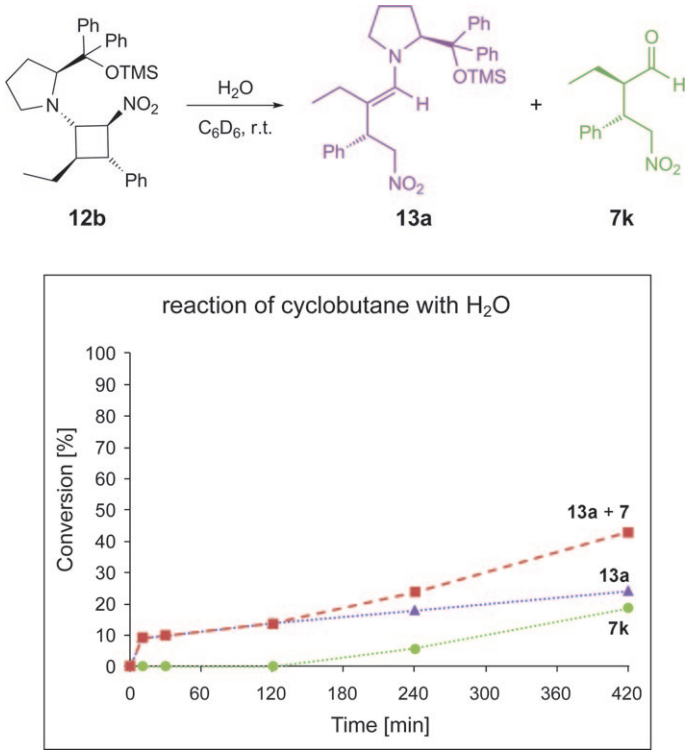


Fig. 6. *NMR Analysis of the reaction of the cyclobutane* **12b** *with H_2O.* To a solution of **12b** in C_6D_6, an equimolar amount of H_2O was added, and withdrawn samples were subjected to NMR analysis. The main product of the sluggish reaction is the enamine **13a** derived from the nitro aldehyde **7k** and **1**. For previous reports on hydrolytic cleavages of 1-amino-2-nitrocyclobutanes to γ-nitro-aldehydes and -ketones, see [27][28][31].

experiments, which we consider significant in view of the role of the acid in the overall process.

In absence of additive, the initial major product formed was the cyclobutane **12b** (40% maximum). The emergence of enamine **13a** and *Michael* adduct **7k** was slow; these two compounds showed similar profiles, indicating they were generated from the same precursor. The curve in *Fig. 8*, *a*, corresponding to 'enamine **13a** + *Michael* product **7k**' indicates that the rate of formation of the *Michael* adduct increases as the reaction progresses, which could be rationalized by considering two different pathways: one would be the *direct* formation of **13a** and **7k** *via Michael* addition of butanal (**2b**) to β-nitrostyrene (**4a**) catalyzed by diphenylprolinol silyl ether **1**, without intervention of the four-membered ring, the other one would be the ring-opening reaction of cyclobutane **12b** generated by prior [2 + 2] cycloaddition (*vide infra*).

When 10 mol-% of propanoic acid was added (*Fig. 8*,*b*), a smaller amount of cyclobutane **12b** was detected, which gradually decreased with time. The rate, at which enamine **13a** plus *Michael* adduct **7k** were formed, was higher than in the absence of the additive (*cf. Fig. 8*,*a* and *b*); the combined yield of **13a** + **7k** was 90% after 3 h.

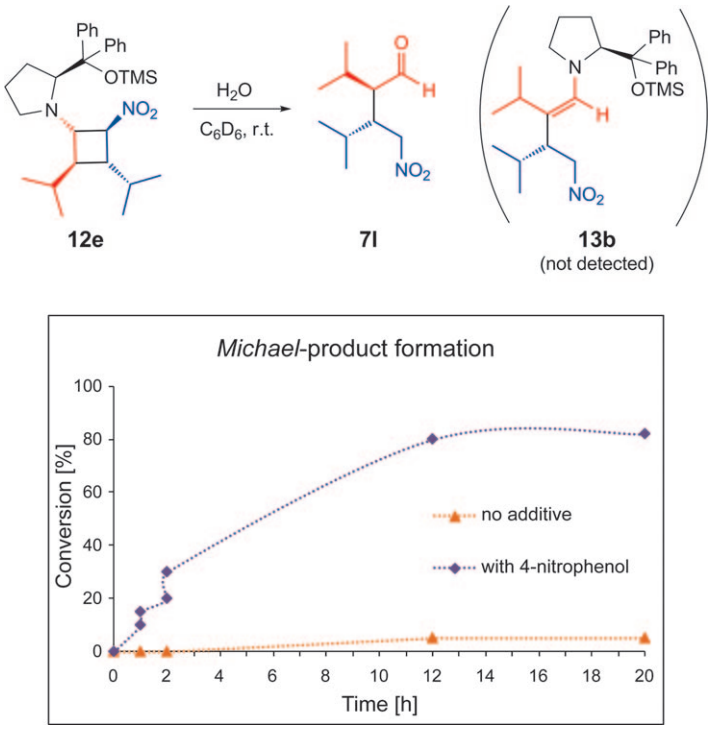


Fig. 7. *Hydrolytic cleavage experiments with the cyclobutane* **12e** *in the absence and in the presence of 4-nitrophenol additive.* With this cyclobutane which carries more bulky substituents than **12b**, there was essentially no reaction in the absence of 4-nitrophenol; in its presence, only the nitro aldehyde **7l** was detected. For previous reports on hydrolytic cleavages of 1-amino-2-nitrocyclobutanes to γ-nitro-aldehydes and -ketones, see [27][28][31].

The reaction in the presence of 4-nitrophenol (*Fig. 8*, *c*) as an additive had a distinctly different profile: the cyclobutane **12b** formed initially was immediately and completely converted to enamine **13a** plus *Michael* adduct **7k**. The formation of these two compounds was fast and reached a stationary stage within 30 min. These results are an indication that the acid additive plays a role in both the formation of cyclobutane **12b** *and* its conversion to the *Michael* product **7k** (*cf. Figs. 4* and *7*).

While the reaction (in benzene) of cyclobutane **12b** with H_2O was shown to be slow in the absence of an acid additive, affording enamine **13a** and *Michael* adduct **7k** in 24% yield within 4 h (*Fig. 6*), cyclobutane **12b** was formed (in toluene) to the extent of 40% in the first 10 min after equimolar amounts of aldehyde, nitro alkene, and amine had been mixed, again without acid additive; the subsequent conversion of the cyclobutane to enamine **13a** and *Michael* adduct **7k** occurred within 3 h (*Fig. 8*, *a*); thus, the conversion of the cyclobutane to open-chain products was much faster in the reaction mixture (*Fig. 8*) than that observed with the cyclobutane alone (*Fig. 6*). To disclose the origin of this difference, the cyclobutane **12b** was treated in C_6D_6 with an equimolar amount of H_2O and butanal. Under these conditions, the ring opening was indeed faster

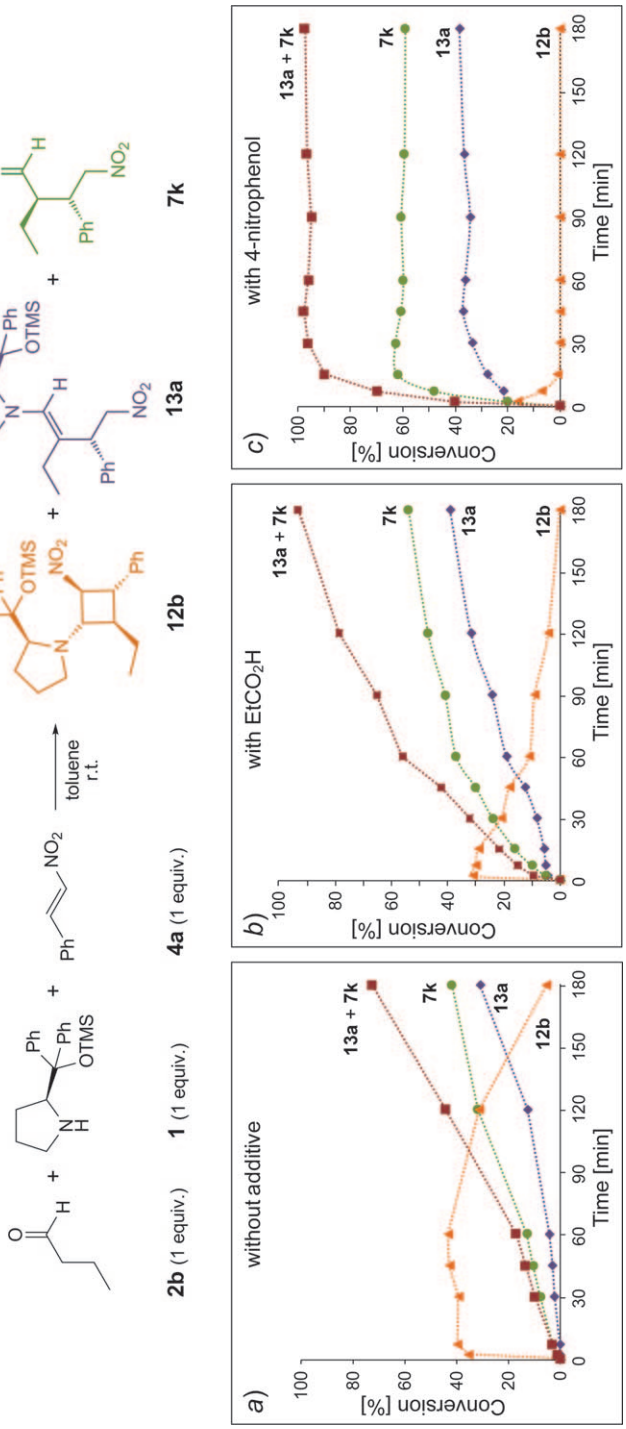


Fig. 8. *Effect of acid on the* Michael *addition of* **2b** *to* **4a** *in the presence of an equimolar amount of prolinol ether* **1** (ratio 1:1:1). The reaction was carried out in toluene; samples were withdrawn at the given points in time and diluted with C_6D_6 for NMR analysis. The formation/disappearance, with time, of the three products, cyclobutane, nitro aldehyde (the actual product of *Michael* addition), and enamine **13a** (derived from **1** and nitro aldehyde), was followed *a*) in the absence of acid additive, *b*) in the presence of an equimolar amount of propanoic acid, and *c*) in the presence of 4-nitrophenol.

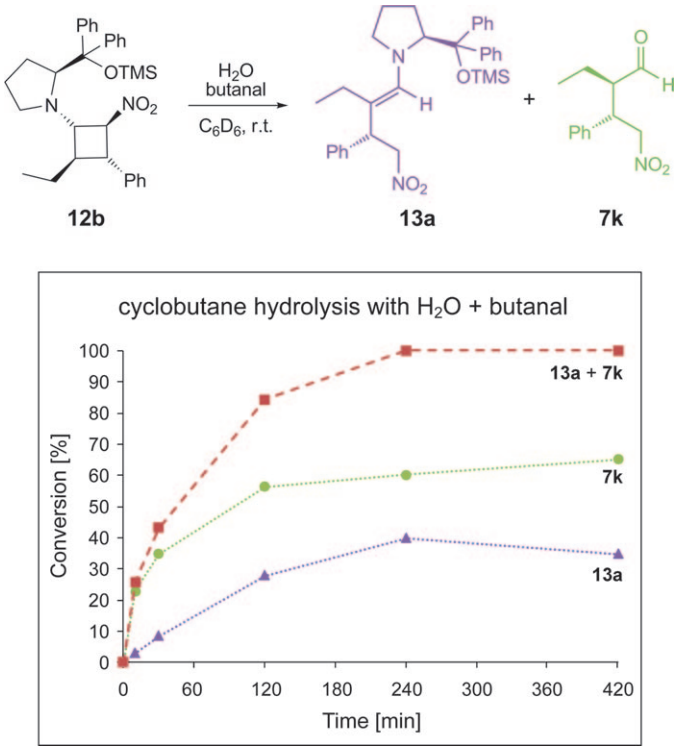


Fig. 9. *Reaction of cyclobutane* **12b** *with* H_2O *in* C_6D_6 *in the presence of butanal.* Equimolar amounts of the three components were used; the reaction was carried out in an NMR tube and followed by peak integrations. The reaction is complete in 6 h, while it has proceeded only to the extent of 25% after the same period of time in the absence of butanal (see *Fig. 6*).

than in the absence of butanal (*cf. Fig. 6* with *Fig. 9*). We could imagine that the hydrate of butanal is involved in this accelerating effect[11]).

e) *Configurational Stability of Product Nitro Aldehydes* **7**. The observed decrease of diastereoselectivity, when the reaction is left 'running' after completion[2]), prompted us to investigate the diastereoisomer ratio of an isolated *Michael* product **7** in the presence of *i*) propanoic acid alone, *ii*) catalyst amine **1** + propanoic acid, and *iii*) amine **1** alone. The results of experiments carried out with the nitro aldehyde **7k** in C_6H_6 showed (*Fig. 10*) that the acid alone does not affect the diastereoisomer ratio (*i.e.* no enolization); however, in the presence of the amine **1**, and even more so when **1** *plus* propanoic acid were present, formation of the enamine **13a** (derived from the aldehyde **7k**) was observed, and the dr value of the recovered nitro aldehyde **7k** decreased significantly (*i.e.*, epimerization in the α-carbonyl position).

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[11]) This hydrate of butanal, C_3H_7–$CH(OH)_2$, could possibly help to carry H_2O into the organic phase (like in a phase-transfer catalysis; *cf. Footnote 9*), or, otherwise, have an accelerating effect similar to that of the weak acid 4-nitrophenol (*cf. Scheme 3*, below); aldehyde hydrates are known to be more acidic than alcohols, the pK_a being close to that of phenol [35].

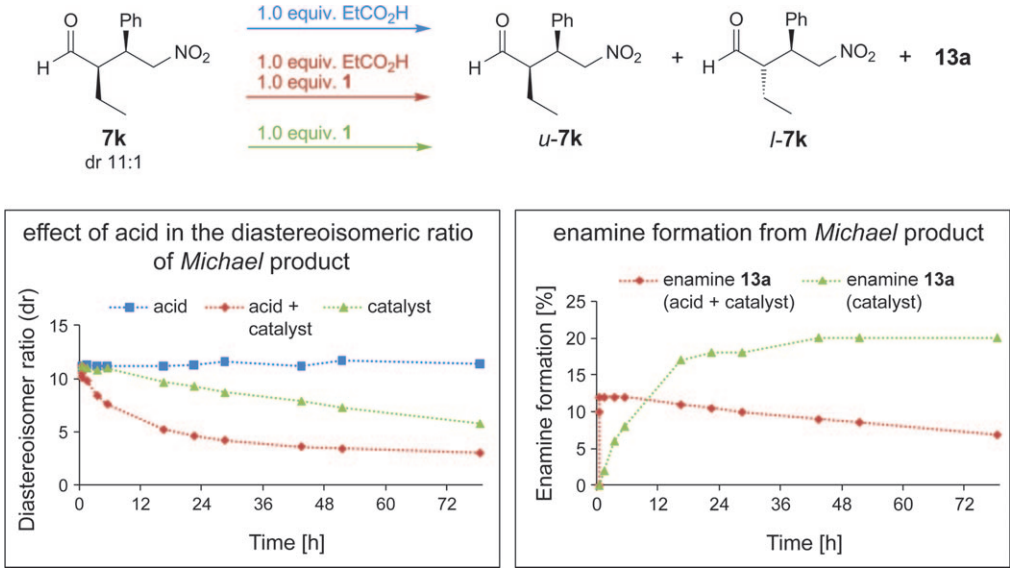


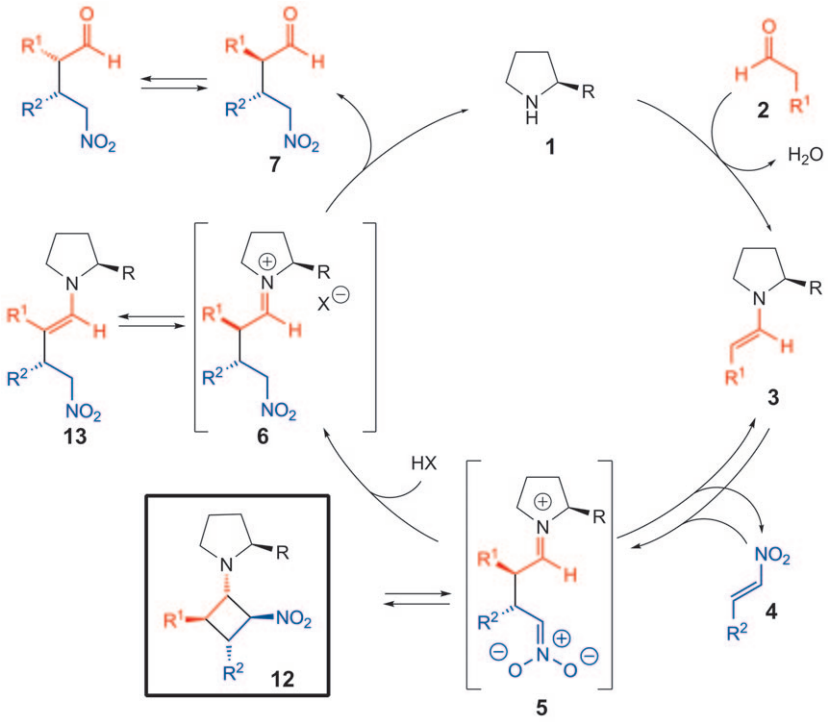
Fig. 10. *Epimerization, monitored by NMR analysis, of the nitro aldehyde* **7k** *under the influence of the catalyst amine* **1** *in* C_6D_6. The configuration is stable in the presence of propanoic acid alone, but decreases especially rapidly when, in addition, the catalyst amine **1** is also present. All components were employed in equimolar amounts.

4. Revised Mechanism of the *Michael* Addition of Aldehydes to Nitro Alkenes Catalyzed by Diphenylprolinol Silyl Ether. The isolation and characterization of intermediates in organic reactions is crucial for discussing reaction mechanisms. The detection of cyclobutane **12** by *in situ* NMR spectroscopy of a reaction mixture containing an aldehyde **2**, a nitro alkene **4**, and the diphenylprolinol silyl ether **1** led us to an investigation with the aim to find out whether these cyclobutane derivatives are reactive intermediates or 'unproductive, parasitic species'[12]). Each reaction step has been investigated separately under non-catalytic conditions. As a result of these investigations, we should like to propose a modified reaction mechanism, which takes into account some of our observations (see *Scheme 2*; compare with *Scheme 1*).

a) *The Modified Mechanism. The catalyst* **1** *reacts with the aldehyde* **2** *to afford the enamine* **3***, which reacts with the nitro alkene* **4** *to generate the zwitterionic intermediate* **5***; two pathways are possible from* **5***:* 1) *cyclization to a cyclobutane derivative* **12***, and* 2) *protonation leading to an iminium ion* **6***, which, in turn, is either hydrolyzed to the product* **7** *of overall-*Michael *addition – with regeneration of the catalyst* **1** *– or deprotonated to an enamine* **13** *of the* Michael *adduct; the cyclobutane* **12** *undergoes ring opening back to the zwitterion* **5***, and thus provides access to the product-forming route, but also to an equilibrium with its precursors, the enamine* **3** *and the nitro alkene* **4**;

[12]) The term 'parasitic' was first used in connection with organocatalysis by *List et al.* [36], when they detected – by *in-situ* NMR measurements – oxazolidinones in proline-catalyzed aldol additions; for recent discussions of the role of oxazolidinones in proline catalysis, see [37–45].

Scheme 2. *Revised Mechanism of the Amine-Catalyzed* Michael *Addition of Aldehydes to Nitro Olefins* (*cf. Scheme 1*). The cyclobutanes **12** are off-cycle species, in which the catalyst is taken out of the catalytic 'traffic'. With the nitrostyrene/3-methylbutanal-derived cyclobutane **12c**, reversibility of the [2+2] cycloaddition was observed (*cf. Fig. 5*). For the observations leading to inclusion of the nitro aldehyde-derived enamine **13** in this scheme and of the epimerization step **7** → *epi*-**7**, see accompanying text.



finally, the product nitro aldehyde **7** *can be epimerized in the α-carbonyl position by the catalyst amine* **1**.

b) *Comments on Particular Steps. i*) The enamine formation is very fast in the presence of a weak acid such as 4-nitrophenol. *ii*) In the catalytic reaction mixture, a cyclobutane **12** is formed in the first minutes of reaction; in the *stoichiometric* reaction under anhydrous conditions, there is complete formation of single isomers of cyclobutanes **12** from enamines **3** and nitro alkenes **4**; this step is especially fast in the presence of an equivalent amount of 4-nitrophenol. *iii*) As documented by one example, amino-nitro-cyclobutanes **12** can be in thermal equilibrium with the corresponding enamines **3** and nitro alkenes **4**, in a reversible [2+2] cycloaddition. *iv*) The transformation of cyclobutanes **12** into the corresponding *Michael* adducts **7** by treatment with equimolar amounts of H_2O in C_6D_6 was studied in two cases; it is a process that is also accelerated by 4-nitrophenol[13]). *v*) The two reactive intermediates **5**

[13]) ... and, surprisingly, also by butanal (see *Footnote 11*)!

and **6** were not detected by ^{1}H-NMR spectroscopy, neither in the catalytic nor in stoichiometric version of the reaction (*i.e.*, they are short-lived species on the NMR time scale). *vi*) As shown in one case, a product **7** of *Michael* addition is configurationally stable in the presence of acid but may epimerize when catalyst base **1** is present.

c) *Discussion of the Role of Acid Additives.* When reactions were performed in the presence of acid additives, several effects of the additive in various steps have been identified – under catalytic and *non-catalytic* conditions. Most of the experiments were performed with 4-nitrophenol (pK_a in H_2O *ca.* 7).

1) Acid accelerates the generation of the enamine **3**, a well-known effect (*cf.* the self-aldolization product, which is formed rapidly in the absence of nitro alkene, *Fig. 2*).

2) Acid accelerates the addition of enamine **3** to nitro olefin **4**. This is demonstrated by the increase of the rate of the [2 + 2] cycloaddition in the presence of an *equimolar* amount of 4-nitrophenol (*Fig. 4*). The low pK_a value of a protonated nitro group (pK_a *ca.* −12) [46] rules out the possibility of protonation of the nitro alkene NO_2 group and, thus, of activation of the nitro alkene, as 4-nitrophenol is too weak an acid (pK_a *ca.* 7). The accelerating effect of 4-nitrophenol in this step might be explained by its ability to interact with an O-atom of the developing nitronate anion in the transition state **A** of C,C-bond formation (**3** + **4** ⇌ **5**; *Scheme 3*)[14])[15])[16]). Thus, decrease in the transition-state energy would cause the acceleration by nitrophenol, and not a ground-state activation of the nitro alkene.

3) The acid additive accelerates the conversion of the cyclobutanes **12** with H_2O to the products of *Michael* addition, the nitro aldehyde of type **7** and its enamine **13** (compare *Figs. 6* and *8*, *a*, with *Figs. 7* and *8*, *c*). As outlined in *Scheme 3*, the ring opening to the zwitterion, **12** → **5**, could profit from interaction with the acid 4-nitrophenol (see transition state **B**[17])); furthermore, the zwitterion must be protonated on the nitronate moiety in the course of the product-forming process.

4) An acid additive does actually not only affect the rate but also the diastereoselectivity of the reaction (see *Tables 1–4*, and *Figs. 6* and *8*), while the enantioselectivity is not affected. The enantiomer-differentiating step is the C,C-bond formation between the β-C-atoms of enamine and nitro alkene (see the trajectory **C**

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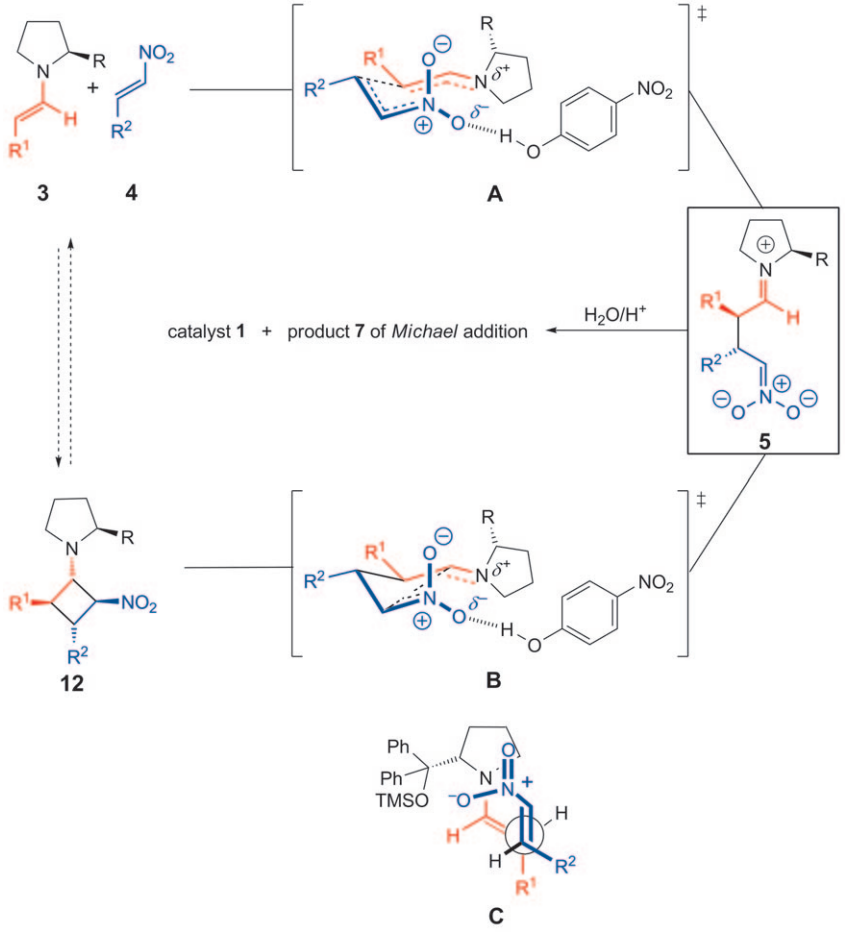
[14]) We expect this kind of H-bonding to be strongest when the pK_a values of the species involved are similar: the pK_a value of nitromethane (H–CH_2–NO_2) is *ca.* 10 and the pK_a value of the tautomeric nitronic acid (H_2C=NO_2–H), the *aci*-nitro form of nitromethane, is *ca.* 4.5 [46]; intriguingly, the pK_a of 7 of what turned out to be the best acid (4-nitrophenol) for the process discussed herein is almost exactly in the middle between these two values.

[15]) The arrangement **A** in *Scheme 3* depicts a transition state of a *ter*molecular reaction, which might occur under the stoichiometric conditions of our experiments (*Fig. 4*), but may not be possible under the catalytic conditions employing as little as 5 mol-% of 4-nitrophenol. The transition state **B**, on the other hand, corresponds to a *bi*molecular reaction.

[16]) This kind of effect of an acid additive has been discussed by *Aggarwal et al.* for the *Baylis–Hillman* reaction [47].

[17]) The drawing **B** in *Scheme 3* may also be considered as a rationale for the observed stabilization of the cyclobutanes **12** by bulky R^1 and R^2 groups. To bring the heteroatom substituents in close proximity (to reduce charge separation in the transition state, an *attractive* effect), the four-membered ring has to attain a so-called roof conformation, which simultaneously leads to a *repulsive* approach of the two R groups. In extreme cases, there appears to be 'no way back' from the cyclobutane (*cf. Entry 10* in *Table 3* and isolation of **4f** (*Fig. 3*)).

Scheme 3. *Transition States* **A** *and* **B** *of C,C-Bond Formation and of Cyclobutane Ring Opening, Respectively, and Intermediate Zwitterion* **5**. The indicated interaction with 4-NO_2–C_6H_4OH is compatible with the observed catalysis by this additive (under stoichiometric conditions). Only when protonated at –CH=NO_2^- does the zwitterion eventually lead to product and catalyst 'recovery'. In **C**, the trajectory of approach of the two trigonal centers is shown (*cf.* **A** and the discussions in [9]).



originally proposed by *Seebach* and *Golinski* [9] in *Scheme 3*). This process occurs from the *Si*-face of the nucleophilic s-*trans*-enamine C-atom, since the bulky (Me_3SiO)Ph_2C moiety covers the *Re*-face, securing essentially exclusive *Si*,*Si*-coupling of the two trigonal centers, and thus excellent enantioselectivity. After the C,C-bond formation, the resulting zwitterionic species undergoes cyclization to the cyclobutane in a fast, intramolecular step (*cf.* the formation of the cyclobutanes **12** as single stereoisomers). The zwitterion can also be protonated (→**6**), followed by hydrolysis (→**7**), or undergo proton shift to the product-derived enamine (→**13**). Whenever this enamine forms, diastereoselectivity is at stake: protonation of the enamine C=C bond, back to the

iminium ion, can lead to diastereoisomers. The acid additive is expected to suppress deprotonation of the iminium ion to the enamine.

5) An effect of acid additive has also been detected in the epimerization in the α-carbonyl position of the final product, the nitro aldehyde **7** (*Fig. 10* and *Footnote 2*).

d) *The Importance of Amino-nitro-cyclobutanes* **12** *and of the Zwitterionic Species* **5** (*Schemes 2* and *3*). The cyclobutane **12** contains the amine catalyst moiety, and it is a kind of a resting state of the catalytic cycle. Thus, its formation and occurrence decrease the effective catalyst concentration, 'inhibiting' *Michael*-adduct formation and catalyst turnover. The cyclobutane is in equilibrium with its precursors, the enamine **3** and the nitro alkene **4**. In this equilibrium, the zwitterion **5** is an intermediate that is constantly formed and consumed. The 'bottle neck' for product formation appears to be the *protonation of the zwitterion* **5** to the iminium ion **6**, *i.e.*, preventing the zwitterion to cyclize to cyclobutane and/or the zwitterion dissociation to the olefinic precursors. Thus, of all the discussed effects of acid, this zwitterion protonation appears to be the most important one.

4. Conclusions. – Optimization of the asymmetric *Michael* addition of aldehydes to nitro alkenes catalyzed by diphenylprolinol silyl ether for application in the synthesis of biologically important molecules was our original goal. We have demonstrated the importance of acid in the reaction mixture and identified 4-nitrophenol as a potent additive for a range of aldehydes and nitro alkenes. In some cases, the reaction times were shortened by a factor of more than 20, without affecting the excellent enantio- and diastereoselectivities of the process. Further, the use of catalytic amounts of 4-nitrophenol allows for reduction of catalyst loading all the way down to 1-mol-% in the case of the propanal-to-β-nitrostyrene addition.

In situ NMR studies led, for the first time, to the identification of cyclobutanes in this amine-catalyzed *Michael* addition of aldehydes to nitro alkenes. The cyclobutanes may be regarded as 'parasitic' components, *i.e.*, an off-cycle resting state of the catalyst, by which the zwitterion intermediate **5** is removed from the catalytic cycle. The acid additive has been shown to influence various steps of the overall process, the most important one of which may be the protonation of the intermediate zwitterion **5**, which, however, our investigation – in the classical organic chemist's way – could not establish.

Much more elaborate kinetic investigations, such as *Blackmond*'s reaction calorimetry[18]), and NMR-exchange spectroscopy (EXSY) and real-time NMR studies of *Gschwind* and co-workers [39] of the actual catalytic reaction will be necessary to determine the rate-determining step of these amine-catalyzed *Michael* additions of aldehydes to nitro alkenes.

It is likely that other organocatalyzed *Michael* additions also involve cyclobutanes, formed from enamines and olefins with electron-withdrawing substituents, and that there may be cases in which the cyclobutanes are so stable [27][29][33] that their formation actually *prevents* catalysis (*cf. Entry 10* in *Table 3* and caption of *Fig. 3*).

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[18]) *Blackmond* and co-workers have studied the reaction of propanal with β-nitrostyrene under diphenylprolinol silyl ether catalysis independently, and their results will be published elsewhere [48].

The results presented herein are yet another demonstration that a 'closer look' at organocatalyzed reactions can provide reasons for revisions of the generally accepted mechanisms[19]).

We thank *D. Blackmond* for a critical discussion of our experimental results and of the conclusions to be drawn for the catalytic cycle of this *Michael* addition. Financial support by the *Japanese Society for the Promotion of Science* (PE 10021) to enable *K. P.-K.*'s work in the *Hayashi* group (May – December 2010) is gratefully acknowledged. We thank *Albert K. Beck* for his invaluable help in preparing the manuscript.

Experimental Part

1. *General. Abbreviations.* MS: molecular sieves, TsOH: *p*-toluenesulfonic acid, TFA: trifluoroacetic acid. Aldehydes were purchased from *TCI,* Japan; nitro alkenes and diphenylprolinol trimethylsilyl ether were prepared in house. All reactions were carried out under Ar and monitored by TLC with *Merck 60 F_{254}* precoated silica-gel plates (0.25 mm thickness). Prep. TLC: *Wakogel B-5F* purchased from *Wako Pure Chemical Industries*, Tokyo, Japan. Flash chromatography (FC): silica gel *60N* of *Kanto Chemical Co. Int.*, Tokyo, Japan. Specific optical rotations: *JASCO P-1020* polarimeter. FT-IR Spectra: *Horiba FT-720* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Brucker AM-400* (400 MHz) instrument; chemical shifts (δ) in ppm rel. to internal standard Me_4Si; coupling constants *J* in Hz; assignments on a routine basis by a combination of 1D and 2D experiments (COSY, HSCQ, HMBC). High-resolution MS: *Bruker* ESI-TOF-MS.

2. *General Procedure* (*GP*) *for* Michael *Addition of Aldehydes to Nitro Alkenes.* To a mixture of nitro alkene **4** (0.3 mmol) and aldehyde **2** (0.45 mmol) in dry toluene (c(nitro alkene) = 1.0M) was added diphenylprolinol trimethylsilyl ether **1** (0.015 mmol, 5 mol-%) and, if applicable, an additive (0.015 mmol, 5 mol-%), and the mixture was stirred at r.t., followed by TLC. After completion, the reaction was quenched by the addition of aq. 1M HCl. The org. material was extracted with AcOEt (3×). The combined org. layers were dried (Na_2SO_4), filtered, concentrated, and purified by prep. TLC (hexane/AcOEt 6:1) to afford the pure *Michael* adduct.

*(2*R*,3*S*)-2-Methyl-4-nitro-3-phenylbutanal* (**7a**). Prepared from *propanal* (**2a**) and *β-nitrostyrene* (= *(2-nitroethenyl)benzene*; **4a**) according to the *GP*. NMR Data correspond to those published in [12]. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.76 (*d*, *J* = 1.2, 1 H); 7.32–7.41 (*m*, 3 H); 7.22 (*d*, *J* = 6.8, 2 H); 4.85 (*dd*, *J* = 5.6, 13.2, 1 H); 4.74 (*dd*, *J* = 10.0, 12.8, 1 H); 3.85 (*ddd*, *J* = 5.6, 9.6, 9.6, 1 H); 2.83 (*m*, 1 H); 1.05 (*d*, *J* = 6.8, 2 H). The enantiomeric excess (ee) was determined by HPLC with *Chiralpak OD-H* column (hexane/^{i}PrOH 10:1; 25°; 1 ml min^{-1}; 212 nm): t_R(*syn* major) 21.1 min, t_R(*syn* minor) 16.5 min.

*(2*R*,3*S*)-3-(4-Bromophenyl)-2-methyl-4-nitrobutanal* (**7b**). Prepared from **2a** and *1-bromo-4-[(*E*)-2-nitroethenyl]benzene* (**4b**) according to *GP*. NMR Data correspond to those published in [14]. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.68 (*s*, 1 H); 7.46 (*d*, *J* = 8.0, 2 H); 7.05 (*d*, *J* = 8.4, 2 H); 4.78 (*dd*, *J* = 5.2, 12.8, 1 H); 4.64 (*dd*, *J* = 9.6, 12.4, 1 H); 3.80–3.75 (*m*, 1 H); 2.78–2.70 (*m*, 1 H); 0.99 (*d*, *J* = 7.2, 3 H). The ee was determined by HPLC with *Chiralpak AD-H* column (hexane/^{i}PrOH 20:1; 25°; 1 ml min^{-1}; 250 nm): t_R(*syn* major) 12.3 min, t_R(*syn* minor) 9.6 min.

*(2*R*,3*S*)-3-(4-Methoxyphenyl)-2-methyl-4-nitrobutanal* (**7c**). Prepared from **2a** and *1-methoxy-4-[(*E*)-2-nitroethenyl]benzene* (**4c**) according to the *GP*. NMR Data correspond to those published in [51]. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.68 (*d*, *J* = 1.6, 1 H); 7.07 (*d*, *J* = 8.4, 2 H); 6.85 (*d*, *J* = 8.8, 2 H); 4.75 (*dd*, *J* = 5.2, 12.8, 1 H); 4.62 (*dd*, *J* = 9.2, 12.4, 1 H); 3.78–3.70 (*m*, 1 H); 3.77 (*s*, 3 H); 2.75–2.68 (*m*, 1 H); 0.98 (*d*, *J* = 7.2, 3 H). The ee was determined by HPLC with *Chiralpak AS-H* column (hexane/^{i}PrOH 20:1; 25°; 1 ml min^{-1}; 231 nm): t_R(*syn* major) 24.5 min, t_R(*syn* minor) 18.9 min.

*(2*R*,3*S*)-2-Methyl-4-nitro-3-[4-(trifluoromethyl)phenyl]butanal* (**7d**). Prepared from **2a** and *1-[(*E*)-2-nitroethenyl]-4-(trifluoromethyl)benzene* (**4d**) according to the *GP*. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.69

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[19]) See also the proline catalysis referred to in *Footnote 12*, above, and the organocatalysis involving iminium ions derived from diarylprolinol ethers and from imidazolidinones as reactive intermediates [49][50].

(*s*, 1 H); 7.60 (*d*, *J* = 7.6, 2 H); 7.32 (*d*, *J* = 7.6, 2 H); 4.84 (*dd*, *J* = 5.6, 13.6, 1 H); 4.70 (*dd*, *J* = 10.0, 12.8, 1 H); 3.94–3.86 (*m*, 1 H); 2.84–2.77 (*m*, 1 H); 1.85–1.81 (*m*, 1 H); 1.00 (*d*, *J* = 7.2, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 202.5; 141.1; 130.8; 128.8; 126.2; 101.6; 77.8; 48.3; 43.9; 12.4. HR-MS: 298.0653 ($C_{12}H_{12}F_3NNaO_3^+$; calc. 298.0661). The ee was determined by HPLC with *Chiralpak AD-H* column (hexane/^{i}PrOH 20 : 1; 25°; 1 ml min^{-1}; 227 nm): t_R(*syn* major) 10.4 min, t_R(*syn* minor) 14.0 min.

*(2*R,*3*S*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-2-methyl-4-nitrobutanal* (**7e**). Prepared from **2a** and *[(*E*)-2-nitroethenyl]benzo[*d*][1,3]dioxole* (**4e**) according to the *GP*. Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.69 (*d*, *J* = 1.6, 1 H); 6.61–6.76 (*m*, 4 H); 5.95 (*s*, 2 H); 4.74 (*dd*, *J* = 6.8, 12.0, 1 H); 4.60 (*dd*, *J* = 9.6, 12.8, 1 H); 3.71 (*m*, 1 H); 2.70 (*m*, 1 H); 1.01 (*d*, *J* = 7.2, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 202.5; 148.6; 130.7; 122.0; 109.0; 108.6; 108.3; 101.6; 78.6; 48.9; 44.2; 12.5. HR-MS: 274.668 ($C_{12}H_{13}NNaO_5^+$; calc. 274.0686). The ee was determined by HPLC with *Chiralpak AS-H* column (hexane/^{i}PrOH 10 : 1; 25°; 1 ml min^{-1}; 206 nm): t_R(*syn* major) 26.2 min, t_R(*syn* minor) 20.6 min.

*(2*R,*3*R*)-2-Methyl-3-(nitromethyl)-5-phenylpentanal* (**7f**). Prepared from **2a** and *[(*E*)-(4-nitrobut-3-en-1-yl]benzene* (**4f**) according to *GP*. NMR Data correspond to those published in [52]. ^{1}H-NMR (400 MHz, $CDCl_3$, 25°): 9.68 (*s*, 1 H); 7.20–7.37 (*m*, 5 H); 4.60 (*dd*, *J* = 6.0, 12.4, 1 H); 4.51 (*dd*, *J* = 7.6, 12.4, 1 H); 2.90–2.79 (*m*, 1 H); 2.79–2.61 (*m*, 3 H); 1.79–1.65 (*m*, 2 H); 1.22 (*d*, *J* = 7.2, 3 H). The ee was determined by HPLC with *Chiralpak OJ-H* column (hexane/^{i}PrOH 10 : 1; 25°; 1 ml min^{-1}; 209 nm): t_R(*syn* major) 28.1 min, t_R(*syn* minor) 35.6 min.

tert-*Butyl (2*R,*3*R*)-3-Methyl-2-(nitromethyl)-4-oxobutanoate* (**7g**). Prepared from **2a** and tert-*butyl 3-nitroprop-2-enoate* (**4g**) according to *GP*. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.68 (*s*, 1 H); 4.85 (*dd*, *J* = 8.8, 14.4, 1 H); 4.41 (*dd*, *J* = 5.6, 14.4, 1 H); 3.69 (*ddd*, *J* = 5.2, 8.8, 10.4, 1 H); 2.71–2.66 (*m*, 1 H); 1.43 (*s*, 3 H); 0.98 (*d*, *J* = 7.4, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 200.6; 169.0; 126.3; 115.9; 83.6; 73.5; 45.7; 43.9; 27.9; 9.9. HR-MS: 254.0974 ($C_{10}H_{17}NNaO_5^+$; calc. 254.0999). The ee was determined by HPLC with *Chiralpak OD-H* column (hexane/^{i}PrOH 100 : 1; 25°; 1 ml min^{-1}; 216 nm): t_R(*syn* major) 29.5 min, t_R(*syn* minor) 31.0 min.

*(2*R,*3*R*)-3-Cyclohexyl-2-methyl-4-nitrobutanal* (**7h**). Prepared from **2a** and *[(*E*)-2-nitroethenyl]cyclohexane* (**4h**) according to *GP*. NMR Data correspond to those published in [51]. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.68 (*s*, 1 H); 4.60 (*dd*, *J* = 5.6, 13.2, 1 H); 4.42 (*dd*, *J* = 6.7, 13.4, 1 H); 2.53–2.62 (*m*, 2 H); 1.53–1.87 (*m*, 5 H); 1.53–1.40 (*m*, 1 H); 1.25–0.84 (*m*, 5 H); 1.22 (*d*, *J* = 7.5, 3 H). The ee was determined by HPLC with *Chiralpak AS-H* column (hexane/^{i}PrOH 40 : 1; 25°; 1 ml min^{-1}; 209 nm): t_R(*syn* major) 9.2 min, t_R(*syn* minor) 8.7 min.

2,4-Dimethyl-3-(nitromethyl)pentanal (**7i**). Prepared from **2a** and *(*E*)-3-methyl-1-nitrobut-1-ene* (**4i**) according to *GP*. NMR Data correspond to those published in [53]. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.76 (*d*, *J* = 1.2, 1 H); 4.85 (*dd*, *J* = 5.6, 13.2, 1 H); 4.72 (*dd*, *J* = 10.0, 12.8, 1 H); 3.90–3.84 (*m*, 1 H); 2.85–2.81 (*m*, 1 H); 1.21 (*d*, *J* = 6.8, 3 H); 0.96 (*d*, *J* = 6.8, 3 H); 0.94 (*d*, *J* = 6.8, 3 H). The ee was determined by HPLC with *Chiralpak AD-H* column (hexane/^{i}PrOH 200 : 1; 25°; 1 ml min^{-1}; 213 nm): t_R(*syn* major) 21.9 min, t_R(*syn* minor) 23.8 min.

*(2*R,*3*S*)-2-Ethyl-4-nitro-3-phenylbutanal* (**7k**). Prepared from *butanal* (**2b**) and **4a** according to *GP*. NMR Data correspond to those published in [12]. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.78 (*d*, *J* = 2.4, 1 H); 7.33–7.43 (*m*, 3 H); 7.25 (*d*, *J* = 7.2, 2 H); 4.78 (*dd*, *J* = 7.6, 12.4, 1 H); 4.70 (*dd*, *J* = 9.6, 12.8, 1 H); 3.87 (*ddd*, *J* = 4.8, 9.6, 9.6, 1 H); 2.72–2.78 (*m*, 1 H); 1.57–1.60 (*m*, 2 H); 0.90 (*t*, *J* = 7.2, 3 H). The ee was determined by HPLC with *Chiralpak OD-H* column (hexane/^{i}PrOH 20 : 1; 25°; 1 ml min^{-1}; 220 nm); t_R(*syn* major) 23.7 min, t_R(*syn* minor) 19.6 min.

*(2*R,*3*S*)-2-Isopropyl-4-nitro-3-phenylbutanal* (**7l**). Prepared from *isovalerylaldehyde* (= *3-methylbutanal*; **2c**) and **4a** according to *GP*. NMR Data correspond to those published in [12]. ^{1}H-NMR (400 MHz, $CDCl_3$): 10.03 (*d*, *J* = 2.4, 1 H); 7.47–7.37 (*m*, 3 H); 7.31–7.29 (*m*, 2 H); 4.77 (*dd*, *J* = 4.4, 12.8, 1 H); 4.68 (*dd*, *J* = 10.0, 12.8, 1 H); 4.01 (*ddd*, *J* = 4.4, 10.4, 10.2, 1 H); 2.90–2.87 (*ddd*, *J* = 2.4, 4.1, 10.7, 1 H); 1.85–1.81 (*m*, 1 H); 1.20 (*d*, *J* = 7.2, 3 H); 0.99 (*d*, *J* = 6.8, 3 H). The ee was determined by HPLC with *Chiralpak AD-H* column (hexane/^{i}PrOH 20 : 1; 25°; 1 ml min^{-1}; 217 nm): t_R(*syn* major) 7.1 min, t_R(*syn* minor) 6.7 min.

*(2*R,*3*S*)-2-Benzyl-4-nitro-3-phenylbutanal* (**7n**). Prepared from *3-phenylpropanal* (**2e**) and **4a** according to *GP*. NMR Data correspond to those published in [54]. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.88 (*d*, *J* = 2.4, 1 H); 7.57–7.29 (*m*, 8 H); 7.20 (*d*, *J* = 7.2, 2 H); 5.05 (*dd*, *J* = 6.4, 13.2, 1 H); 4.97 (*dd*, *J* = 8.8,

12.8, 1 H); 4.0 (*dd*, *J* = 6.0, 8.4, 1 H); 3.27 (*ddd*, *J* = 6.0, 8.4, 14.8, 1 H); 2.93 (*d*, *J* = 5.6, 2 H). The ee was determined by HPLC with *Chiralpak OD-H* column (hexane/^{i}PrOH 10 : 1; 25°; 1 ml min^{-1}; 220 nm): t_R(*syn* major) 32.7 min, t_R(*syn* minor) 30.4 min.

4. *Preparation of Cyclobutane* **12**. *(2*S*)-1-[(1*S*,2*S*,3*S*,4*R*)-3-(*tert*-Butyl)-2-nitro-4-(propan-2-yl)cyclobutyl]-2-{diphenyl[(trimethylsilyl)oxy]methyl}pyrrolidine* (**12f**). To a mixture of **1** (97.5 mg, 0.3 mmol) and **2c** (33 µl, 0.3 mmol) in benzene (0.3 ml) with MS (4 Å) was added *(*E*)-3,3-dimethyl-1-nitrobut-1-ene* (**4j**; 38.75 mg, 0.3 mmol), and the mixture was left to react for 48 h. The material was purified by prep. TLC (hexane/AcOEt, 8 : 1) to afford **12f** (34%). Yellow solid. $[\alpha]_D^{25} = -6.7$ ($c = 19.53$, $CHCl_3$). IR ($CHCl_3$): 3056*w*, 2959*s*, 2871*w*, 2815*w*, 2359*m*, 2337*m*, 1729*w*, 1537*s*, 1468*w*, 1367*m*, 1249*s*, 1092*m*, 1064*s*, 877*m*, 840*s*, 704*s*. ^{1}H-NMR (400 MHz, C_6D_6): 7.55 – 7.49 (*m*, 2 H); 7.45 – 7.40 (*m*, 2 H); 7.33 – 7.25 (*m*, 4 H); 4.86 (*dd*, *J* = 7.2, 8.0, 1 H); 4.06 (*dd*, *J* = 2.8, 9.2, 1 H); 3.90 (*m*, 1 H); 2.62 – 2.54 (*m*, 1 H); 2.54 – 2.47 (*m*, 1 H); 2.20 (*t*, *J* = 9.2, 1 H); 1.94 – 1.72 (*m*, 3 H); 1.71 – 1.59 (*m*, 1 H); 1.24 (*m*, 1 H); 0.84 (*s*, 9 H); 0.78 (*d*, 3 H, *J* = 8.0); 0.67 (br. *d*, 3 H); 0.325 (*m*, 1 H); 0.28 (*s*, 9 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 143.6; 142.9; 130.32; 130.14; 128.6; 78.8; 69.5; 62.7; 49.4; 47.5; 42.3; 31.86; 29.4; 29.1; 23.8; 22.3; 2.23. HR-MS: 521.3160 ($[M-H]^-$, $C_{31}H_{45}N_2O_3Si^-$; calc. 521.32).

*(2*S*)-2-{Diphenyl[(trimethylsilyl]oxy]methyl}-1-[(1*S*,2*S*,3*S*,4*R*)-2-nitro-3-phenyl-4-(propan-2-yl)cyclobutyl]pyrrolidine* (**12c**). To a mixture of **1** (32.5 mg, 0.1 mmol, 1 equiv.) and **2c** (10.8 µl, 0.1 mmol, 1 equiv.) in benzene with MS (4 Å) was added **4a** (38.75 mg, 0.3 mmol, 1 equiv.), and the mixture was stirred at r.t. for 2 h. The crude material was analyzed by NMR; the purification failed due to decomposition towards *Michael* product. ^{1}H-NMR (400 MHz, C_6D_6): 7.67 – 7.61 (*m*, 4 H); 7.22 – 6.95 (*m*, 11 H); 4.96 (*t*, *J* = 7.6, 1 H); 4.50 (*dd*, *J* = 4.4, 8.4, 1 H); 4.26 (br. *m*, 1 H); 3.46 (*t*, *J* = 9.2, 1 H); 2.46 – 2.53 (*m*, 2 H); 1.90 – 1.85 (*m*, 2 H); 1.89 (*m*, 1 H); 1.67 – 1.56 (*m*, 1 H); 1.16 (*m*, 1 H); 0.89 (br. *d*, 3 H); 0.65 (*d*, *J* = 6.8, 3 H); 0.53 (br. *m*, 1 H). ^{13}C-NMR (100 MHz, C_6D_6): 140.69; 140.36; 137.5; 134.9; 128.4; 127.2; 127.0; 126.0; 125.97; 124.3; 81.9; 79.97; 65.75; 63.27; 46.34; 45.01; 40.89; 26.23; 20.90; 17.25; – 0.85.

5. *Catalyst Loading.* To a mixture of **4a** (50 mg, 0.3 mmol, 1 equiv.) and **2a** (36 µl, 0.45 mmol, 1.5 equiv.) in dry toluene (c(**4a**) = 1.0M) were added **1** (*x* mol-%) and 4-nitrophenol (*x* mol-%) at r.t. The reaction was quenched according to *GP*. The product conversion was determined by ^{1}H-NMR of the crude material (*cf. Table 5*).

6. *Studies towards the Elucidation of the Mechanism. Enamine Formation.* Five experiments were performed in ^{1}H-NMR tubes with **1** (0.1 mmol, 1M stock soln. in C_6D_6) and **2b** (0.1 mmol, 1M stock soln. in C_6D_6) in 600 µl of C_6D_6.

Cyclobutane Formation. These experiments were performed using preformed enamine (from equimolar amounts of **1** and **2c** in C_6D_6 with MS (4 Å)) and **4i** in NMR tube. One equiv. of acid (if applicable) was added to the NMR tube.

Thermal Stability. To a mixture of preformed enamine from **1** (32.5 mg, 0.1 mmol, 1 equiv.) and **2c** (10.8 µl, 0.1 mmol, 1 equiv.) in the presence of MS (4 Å) in 1 ml of C_6D_6 was added **4a** (14.9 mg, 0.1 mmol, 1 equiv.) to form **12c**. From this reaction mixture, 0.6 ml were transferred into an NMR tube, and ^{1}H-NMR recordings were performed at the given temp.: starting from 25°, heating up to 50°, and then 70°, followed by cooling down to 25°.

Cyclobutane Hydrolysis. Effect of H_2O and Butanal (**2b**). These experiments were performed using preformed enamine (from equimolar amounts of **1** and **2b** in C_6D_6 with MS (4 Å)) and **4a**. MS were removed, 1 equiv. of H_2O and, if applicable, 1 equiv. of **2b** were added. Aliquots (20 µl) were taken at time *T* and diluted in 500 µl C_6D_6 for ^{1}H-NMR analysis.

Effect of H_2O and Acid Additive. These experiments were performed using preformed enamine (from equimolar amounts of **1** and **2c** in C_6D_6 with MS) and **4i**. The mixture was transferred to an NMR tube, and 1 equiv. of H_2O and, if applicable, 1 equiv. of 4-nitrophenol were added. The evolution of the cyclobutane hydrolysis was followed by ^{1}H-NMR.

Observation of Cyclobutane Formation and Ring Opening under Reaction Conditions. β-Nitrostyrene (**4a**) (0.2 mmol), **2b** (0.2 mmol), and **1** (0.2 mmol) in 200 µl of dry toluene (c = 1.0M). If applicable, additive (propanoic acid or 4-nitrophenol) was added. Aliquots (20 µl) were taken at time *T* and diluted in 500 µl C_6D_6 for ^{1}H-NMR analysis.

Isomerization of Michael *Product. Michael* adduct **7k** of dr ratio 11 : 1 (0.3 mmol) was dissolved in C_6D_6 (1.8 ml) and distributed into three NMR tubes (0.6 ml each). To one NMR tube, 1 equiv. of

propanoic acid (0.1 mmol) was added, to the second one, 1 equiv. of **1** (0.1 mmol) was added, and to third one, 1 equiv. of propanoic acid (0.1 mmol) + 1 equiv. of **1** (0.1 mmol) were added. The dr was determined by integration of the CHO signals of the two diastereoisomers in the ^{1}H-NMR spectrum.

REFERENCES

[1] P. Perlmutter, 'Conjugate Addition Reactions in Organic Synthesis', Oxford Press, Oxford, 1992.
[2] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471 – 5569.
[3] P. M. Pihko, I. Majander, A. Erkkila, in 'Asymmetric Organocatalysis', Springer-Verlag, Berlin, 2010, pp. 29 – 75.
[4] A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416 – 5470.
[5] D. Almasi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299 – 365.
[6] S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701.
[7] S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123.
[8] O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877.
[9] a) D. Seebach, J. Goliński, *Helv. Chim. Acta* **1981**, *64*, 1413; b) D. Seebach, A. K. Beck, J. Goliński, J. N. Hay, T. Laube, *Helv. Chim. Acta* **1985**, *68*, 162.
[10] S. J. Blarer, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 1637.
[11] B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423.
[12] J. M. Betancort, C. F. Barbas, *Org. Lett.* **2001**, *3*, 3737.
[13] J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296.
[14] Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.
[15] C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.
[16] A. Mielgo, C. Palomo, *Chem. – Asian J.* **2008**, *3*, 922.
[17] H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem.* **2009**, *121*, 1330; *Angew. Chem., Int. Ed.* **2009**, *48*, 1304.
[18] H. Ishikawa, T. Suzuki, H. Orita, T. Uchimaru, Y. Hayashi, *Chem. – Eur. J.* **2010**, *16*, 12616.
[19] H. Ishikawa, M. Honma, Y. Hayashi, *Angew. Chem.* **2011**, *123*, 2700; *Angew. Chem., Int. Ed.* **2011**, *50*, 2824.
[20] A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611.
[21] N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas, *Org. Lett.* **2004**, *6*, 2527.
[22] M. Wiesner, G. Upert, G. Angelici, H. Wennemers, *J. Am. Chem. Soc.* **2009**, *132*, 6.
[23] T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558.
[24] S. Saha, S. Seth, J. N. Moorthy, *Tetrahedron Lett.* **2010**, *51*, 5281.
[25] Z. Zheng, B. L. Perkins, B. Ni, *J. Am. Chem. Soc.* **2010**, *132*, 50.
[26] D. Seebach, V. Prelog, *Angew. Chem.* **1982**, *94*, 696; *Angew. Chem., Int. Ed.* **1982**, *21*, 654.
[27] K. C. Brannock, A. Bell, R. D. Burpitt, C. A. Kelly, *J. Org. Chem.* **1964**, *29*, 801.
[28] M. E. Kuehne, L. Foley, *J. Org. Chem.* **1965**, *30*, 4280.
[29] K. C. Brannock, A. Bell, R. D. Burpitt, C. A. Kelly, *J. Org. Chem.* **1961**, *26*, 625.
[30] F. P. Colonna, E. Valentin, G. Pitacco, A. Risaliti, *Tetrahedron* **1973**, *29*, 3011.
[31] F. Felluga, P. Nitti, G. Pitacco, E. Valentin, *Tetrahedron* **1989**, *45*, 5667.
[32] F. Felluga, P. Nitti, G. Pitacco, E. Valentin, *J. Chem. Soc., Perkin Trans. 1* **1992**, 2331.
[33] F. D. Lewis, T.-I. Ho, R. J. DeVoe, *J. Org. Chem.* **1980**, *45*, 5283.
[34] R. Huisgen, *Acc. Chem. Res.* **1977**, *10*, 117, 199.
[35] J. Hine, J. G. Houston, J. H. Jensen, *J. Org. Chem.* **1965**, *30*, 1184.
[36] B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839.
[37] D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425.
[38] C. Isart, J Burés, J. Vilarrasa, *Tetrahedron Lett.* **2008**, *49*, 5414.

[39] M. B. Schmid, K. Zeitler, R. M. Gschwind, *Angew. Chem.* **2010**, *122*, 5117; *Angew. Chem., Int. Ed.* **2010**, *49*, 4997.
[40] A. K. Sharma, R. B. Sunoj, *Angew. Chem.* **2010**, *122*, 6517; *Angew. Chem., Int. Ed.* **2010**, *49*, 6373.
[41] T. Kanzian, S. Lakhdar, H. Mayr, *Angew. Chem.* **2010**, *122*, 9717; *Angew. Chem., Int. Ed.* **2010**, *49*, 9526.
[42] D. Blackmond, A. Moran, M. Hughes, A. Armstrong, *J. Am. Chem. Soc.* **2010**, *132*, 7598.
[43] I. A. Konstantinov, L. J. Broadbelt, *Top. Catal.* **2010**, *53*, 1031.
[44] P. D. de Maria, P. Bracco, L. F. Castelhano, G. Bargeman, *ACS Catal.* **2011**, *1*, 70.
[45] D. A. Bock, C. W. Lehmann, B. List, *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20636.
[46] D. Turnbull, S. H. Maron, *J. Am. Chem. Soc.* **1943**, *65*, 212; I. Erden, J. R. Keeffe, F. P. Xu, J. B. Zheng, *J. Am. Chem. Soc.* **1993**, *115*, 9834; T. R. Kelly, M. H. Kim, *J. Am. Chem. Soc.* **1995**, *116*, 7072; B. R. Linton, M. S. Goodman, A. D. Hamilton, *Chem. – Eur. J.* **2000**, *6*, 2449, and refs. cit. therein.
[47] V. K. Aggarwal, S. Y. Fulford, G. C. Lloyd-Jones, *Angew. Chem.* **2005**, *117*, 1734; *Angew. Chem., Int. Ed.* **2005**, *44*, 1706.
[48] Jordi Burés, Alan Armstrong, Donna G. Blackmond, *J. Am. Chem. Soc.* **2011**, submitted.
[49] D. Seebach, U. Grošelj, D. M. Badine, W. B. Schweizer, A. K. Beck, *Helv. Chim. Acta* **2008**, *91*, 1999; U. Grošelj, W. B. Schweizer, M.-O. Ebert, D. Seebach, *Helv. Chim. Acta* **2009**, *92*, 1; U. Grošelj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi, T. Uchimaru, *Helv. Chim. Acta* **2009**, *92*, 1225; D. Seebach, U. Grošelj, W. B. Schweizer, S. Grimme, C. Mück-Lichtenfeld, *Helv. Chim. Acta* **2010**, *93*, 1.
[50] J. B. Brazier, G. Evans, T. J. K. Gibbs, S. J. Coles, M. B. Hursthouse, J. A. Platts, N. C. O. Tompkinson *Org. Lett.* **2009**, *11*, 133.
[51] O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147.
[52] L. S. Zu, H. Li, J. Wang, X. H. Yu, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 5131.
[53] T. Mandal, C. G. Zhao, *Angew. Chem.* **2008**, *120*, 7828; *Angew. Chem., Int. Ed.* **2008**, *47*, 7714.
[54] P. Kotrusz, S. Toma, H. G. Schmalz, A. Adler, *Eur. J. Org. Chem.* **2004**, 1577.

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