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On the enantioselective hydrogenation of isomeric β-acylamido β-alkylacrylates with chiral Rh(I) complexes—comparison of phosphine ligands and substrates

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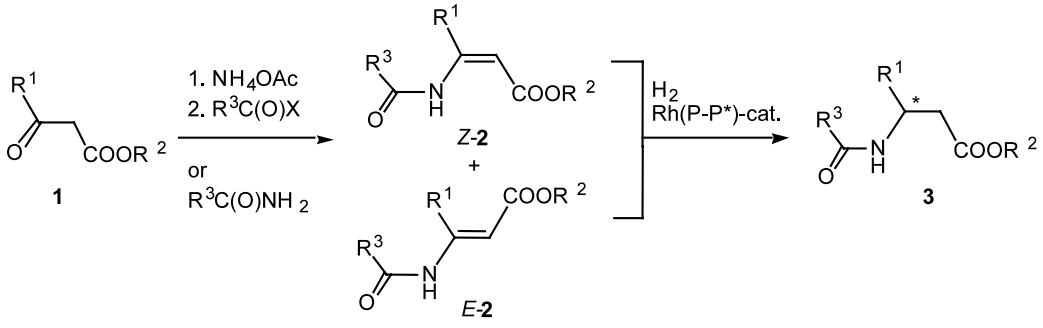
Abstract—The rhodium(I)-catalyzed enantioselective hydrogenation of *E*- and *Z*-configured β-acylamido β-alkylacrylates as well as of isomeric mixtures has been investigated. As ligands 1,2-bisphospholanes like DuPHOS, BPE and Me_4-BASPHOS have been tested, but also diphosphines forming seven-membered chelates such as DIOP. The effect of additional oxy groups in the diphosphine ligand on rate and enantioselectivity was likewise elucidated. In general, with all catalysts screened the hydrogenation is strongly sensitive to the *E*/*Z*-geometry of the substrate. *E*-Substrates are converted with good or excellent enantioselectivites into the desired β-amino acid derivatives. The hydrogenation of *Z*-substrates showed the known H_2-pressure dependency of the ee.

1. Introduction

The synthesis of enantiopure β-amino acids is of considerable importance for the pharmaceutical industry.[1] Over the last few years broad entry to these compounds has been established, at least at laboratory scale, by application of the common methodologies of enantioselective synthesis, such as chiral pool syntheses or the employment of chiral auxiliaries in stoichiometric or catalytic amounts.[2] One of the most attractive methods for the preparation of protected β-amino acids **3**, even on a large scale, seems to be the enantioselective hydrogenation of prochiral β-acylamido acrylates **2** with Rh(I) catalysts bearing chiral phosphorus ligands (Scheme 1).[3]

The requisite substrates can be easily synthesized starting from a broad range of commercially available β-



Scheme 1.

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keto esters **1**. One of the main challenges of this hydrogenation approach consists of the highly enantioselective reduction of the *E*- as well of the *Z*-substrate (*E*-/*Z*-**2**) as both are formed during synthesis, the *Z*-isomer being predominant.

Recently, we have shown that the hydrogenation of *E*-methyl β-*N*-acetylamido butenoate as well as its *Z*-analogue can proceed very fast and with high enantioselectivity when the reaction is run in the presence of a cationic Rh(I)-DuPHOS catalyst in polar solvents at 1 bar hydrogen pressure.[3d] These findings opened up the opportunity to reduce efficiently mixtures of isomeric substrates with good enantioselectivity. An additional kinetic study revealed that with both isomeric substrates highest enantioselectivities can be achieved at room temperature and below, whereas highest activity is at 30–50°C.[4] Interestingly, the enantioselectivity of the hydrogenation of the *Z*-substrate was strongly dependent on the H_2 pressure. High pressure dramatically diminished the ee.

Apparently, the efficiency of the hydrogenation is also strongly dependent on the ligand used. Thus, with the exceptions of a few Rh(I)[3b,e,g] and Ru(II) catalysts[5] sometimes dramatic differences in the enantioface-discriminating abilities were noted in the reduction of *E*- and *Z*-isomeric substrates.[3d,6]

In order to show which structural motifs are capable of providing high enantioselectivities for both substrate isomers we report here on the Rh-catalyzed hydrogenation of isomeric β-*N*-acylamido acrylates **2** by application of ligands like DuPHOS[7] or DIOP[8] forming five- or seven-membered chelate rings, respectively, with the metal. Moreover, we also tested diphosphines such as HO-DIOP[9] and Me_4-BASPHOS[10] bearing additional HO- and MeO-groups. From the related enantioselective hydrogenation of α-*N*-acetylamido acrylates it is known, that such additional ligating groups may exert a pronounced influence on the hydrogenation in terms of reactivity and enantioselectivity.[11,12] In the past particularly valuable conclusions could be derived from a comparison of the effect of HO- and MeO-groups. Therefore, appropriate ligands bearing a conformationally flexible backbone equipped with such oxy groups were also considered in our investigations. In order to broaden the scope of the hydrogenation approach some other prochiral substrates were also tested.

2. Results and discussion

In general, hydrogenations discussed have been carried out in MeOH at 25°C with a substrate:catalyst ratio of 100:1. Kinetic curves depicted are derived from hydrogenation measurements employing catalysts of the type [Rh(diphosphine)$(MeOH)_2$]$^+$, which were generated prior to the addition of the prochiral substrate by prehydrogenation of the relevant COD- or NBD-precatalysts.[13]

2.1. Variation of the ligand

As shown in Fig. 1 (see also Table 1) the Et-DuPHOS-catalyst reduces *Z*-methyl β-acetylamino butenoate *Z*-**2a** at room temperature ca. three fold faster than the corresponding isomer *E*-**2a**. Interestingly, the functionalization of the four ethyl groups of Et–DuPHOS by four MeO-groups giving rise to the ligand Me_4-BASPHOS changed this order. Now, the *E*-substrate is converted faster than the *Z*-substrate.

The nature of the bridge linking both phospholane units in DuPHOS-type ligands does not dramatically influence the rate of the hydrogenation of *Z*-**2a** as shown in the hydrogenation with catalysts based on Me-DuPHOS and Me-BPE (Fig. 2).

Replacement of the Me groups (Me-DuPHOS) by Et-groups (Et-DuPHOS) only slightly diminished the rate. The particular effect of the oxy-functionalization becomes again obvious, when the activities of the rele-

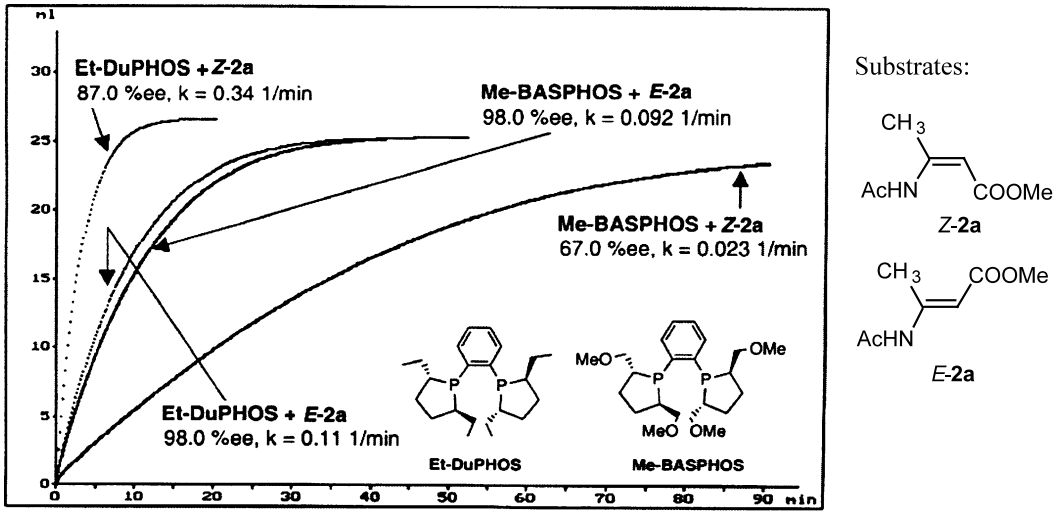
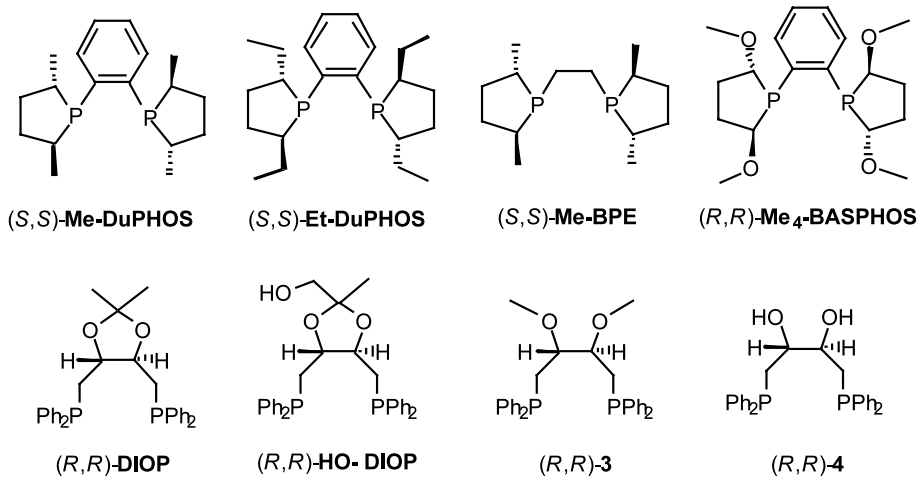


Figure 1. Hydrogenation of *Z*-**2a** and *E*-**2a** with cationic [Rh(bisphospholane)$(MeOH)_2$]$^+$catalysts.

Table 1. First order rate constants and enantioselectivities observed in the hydrogenation of *Z*-**2a** and *E*-**2a** with (Rh-(ligand)$(MeOH_2)]^+$ in MeOH (normal pressure)



Ligand	*Z*-**2a**		*E*-**2a**	
	$k_{1st\ order}$ (1/min)	ee (%)	$k_{1st\ order}$ (1/min)	ee (%)
(*S*,*S*)-**Me-DuPHOS**	1.3	88	–	99
(*S*,*S*)-**Et-DuPHOS**	0.3	87	0.1	98
(*S*,*S*)-**Me-BPE**	1.0	68	–	98
(*R*,*R*)-**Me_4-BASPHOS**	0.02	67	0.09	98
(*R*,*R*)-**DIOP**	0.25	17	0.1	71
(*R*,*R*)-**HO-DIOP**	0.1	36	0.04	71
(*R*,*R*)-**3**	3 h: 100% conversion	rac	3.8 h: 86% conversion	rac
(*R*,*R*)-**4**	80 h: 72% conversion	37[a]	40 h: 55% conversion	57[a]

[a] Reaction was stopped due to slow conversion.

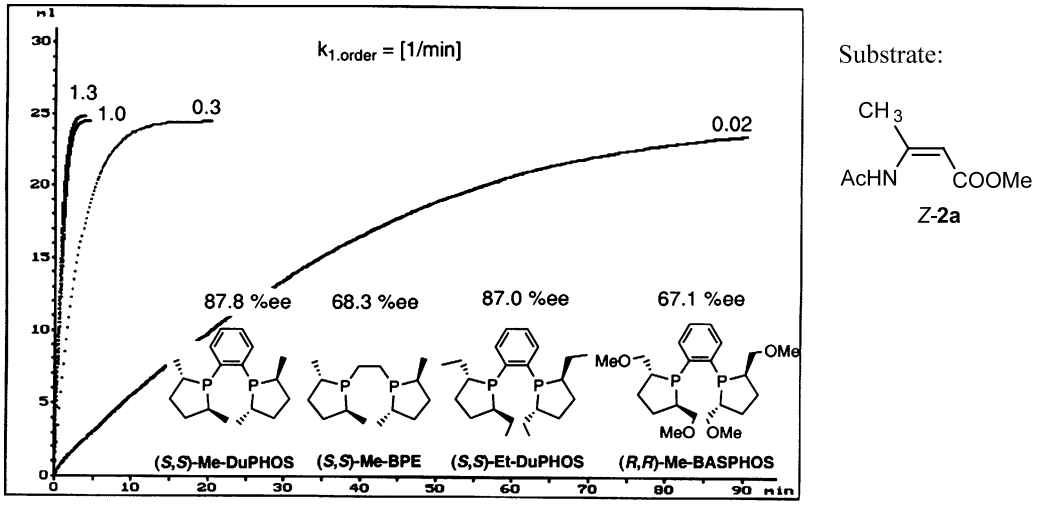


Figure 2. Comparison of activity and enantioselectivity of cationic $[Rh(bisphospholane)(MeOH)_2]^+$ catalyst (with the exception of the catalyst of Me-BPE, where OTf^- has been used as counterion, other ligands were incorporated in BF_4 complexes; standard conditions).

vant catalysts are compared. Thus, Me_4-BASPHOS formed a catalyst, operating much more slowly than its nonfunctionalized counter-part. In general, under these conditions both DuPHOS catalysts gave significantly higher enantioselectivities than complexes derived from BPE or Me_4-BASPHOS.

Fig. 3 shows the typical hydrogen consumption curves obtained by application of a DIOP catalyst. Similarly, as seen for five-membered Rh(I) chelates of DuPHOS or BPE the hydrogenation of the *Z*-**2a** also occurs faster than the reaction with *E*-**2a** applying this seven-membered chelate.

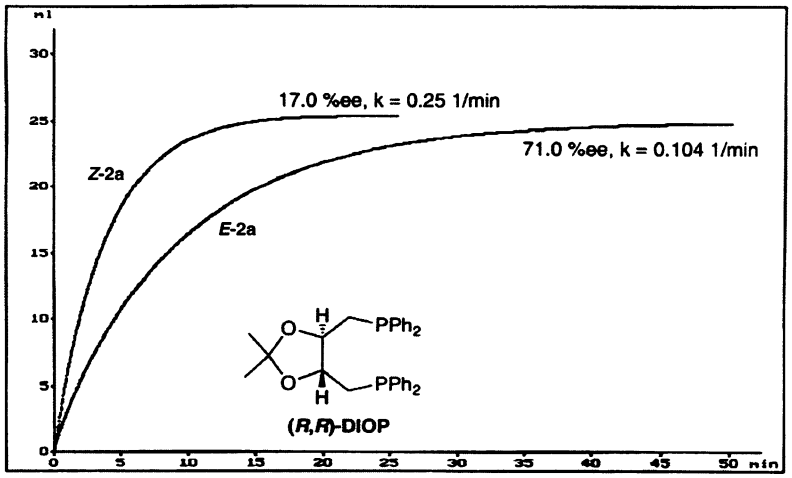


Figure 3. Comparison of activity and enantioselectivity achieved in the hydrogenation of *E*-**2a** and *Z*-**2a** with $[Rh(DIOP)(MeOH)_2]BF_4$; standard conditions.

Catalytic features observed by using different ligands for the hydrogenation of isomeric substrate **2a** are summarized in Table 1.

Some trends become obvious. Thus, as already shown in Fig. 2 among catalysts based on five-membered chelates Me-DuPHOS and BPE complexes are more active than a catalyst based on Et-DuPHOS. The latter has similar activity to DIOP, which forms a seven-membered chelate ring with the metal. Highest ee's were achieved by employment of DuPHOS-type ligands (Me- and Et-DuPHOS). Incorporation of a remote HO-group in DIOP (HO-DIOP) affected the ee of the hydrogenation of the *Z*-substrate, whereas when *E*-**2a** was subjected to the hydrogenation no pressure effect on the enantioselectivity was observed. Particular noteworthy is the dramatic increase by 57% ee due to the replacement of the MeO groups in ligand **3**[14] by hydroxy groups (ligand **4**).[14] The increase is more pronounced in the hydrogenation of *E*-**2a** than with *Z*-**2a**. In general, when hydroxy phosphines were employed instead of their parent ligands or MeO counterparts significant lower rates were found. The enantioselectivity enhancing effect caused by hydroxy groups accompanied by the activity diminishing effect is well-known from the related enantioselective hydrogenation of α-acetamido acrylates and itaconates and conforms with the results presented here.[11]

2.2. Influence of the H_2 pressure

Our recent investigation on the pressure dependency of the ee revealed that with DuPHOS-type catalysts the lowering of the pressure improved dramatically the ee in the hydrogenation of *Z*-**2a**, while the ee in the hydrogenation of *E*-**2a** is independent of the pressure and constantly high.[3d] Surprisingly this pressure dependency was less pronounced when a catalyst based on Me_4-BASPHOS was used.[10] Thus, at 35 bar the BASPHOS catalysts gave higher ee's than the DUPHOS complex, whereas at 1 bar the latter was superior. In Table 2 results employing also other ligands are listed.

Table 2. Dependency of the enantioselectivity upon the H_2 pressure[a]

Ligand	pH_2 (bar)	*Z*-**2a** ee (%)	*E*-**2a** ee (%)
(*S*,*S*)-**Et-DuPHOS**[b]	45	35	96
	30	47	96
	1	87	98
(*S*,*S*)-**Me-BASPHOS**	45	57	96
	30	56	98
	1	67	98
(*R*,*R*)-**DIOP**	30	26	70
	1	17	71
(*R*,*R*)-**HO-DIOP**	30	32	70
	1	36	71
(*R*,*R*)-**3**	30	rac	rac
	1	rac	rac
(*R*,*R*)-**4**	30	17	38
	1	37	57

[a] Conditions: For the structures of the ligands, see Table 1. For hydrogenation under elevated pressure complexes of the type [Rh(ligand)(COD)]BF_4 and at 1 bar of the type [Rh(ligand)$(MeOH)_2$]BF_4 were used. The ee was not influenced by the type of the catalysts.
[b] See Ref. 3d.

Similar as was found with the Et-DUPHOS complexes other catalysts also give higher ee's in the hydrogenation of *Z*-**2a** at lower pressure. A remarkable exception is found with the DIOP-catalyst which affords lower enantioselectivity at 1 bar than at 30 bar.

In general, the hydrogenation of *E*-**2a** with other catalysts is in accordance with the results obtained with Et-DuPHOS, e.g. less sensitivity to the hydrogen pressure. The only exception is the catalyst based on the hydroxy-phosphine **4**, where the hydrogenation of *E*-**2a** benefits from a lowering of the hydrogen pressure.

2.3. Hydrogenation of *Z*/*E*-2a mixtures

As shown in our preliminary communication, with a DuPHOS-catalyst under uniform conditions for the

Table 3. Comparison of enantioselectivities obtained in the individual hydrogenation and hydrogenations of 1/1 mixtures of *Z*-**2a** and *E*-**2a** with (Rh(ligand)($MeOH_2$)]BF_4

Ligand	H_2 (bar)	*Z*-**2a**	*E*-**2a**	*Z*-**2a**/*E*-**2a**	
		ee (%)	ee (%)	ee (%) found	ee (%) mean value
(*S*,*S*)-**Et-DuPHOS**[a]	35	44	96	67	70
	1	87	97	92	89
(*S*,*S*)-**Me-BasPHOS**	35	56	97	76	76.5
	1	67	98	83	82.5
(*R*,*R*)-**DIOP**	35	26	70	48	48

[a] See Ref. 3d.

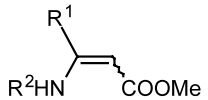
hydrogenation of *Z*-**2a** and *E*-**2b**, and the formation of the product with the same configuration the hydrogenation of substrate mixtures with high ee is possible.[3d] Table 3 displays a comparison of the enantioselectivities achieved under varying H_2-pressure when Et-DuPHOS, Me_4-BASPHOS and DIOP were employed as ligands. The ee corresponds in all cases to the mean values of the individual hydrogenations.

2.4. Other substrates

As illustrated above the most effective catalysts for the hydrogenation of *E*- and *Z*-**2a** are Rh-complexes based on DuPHOS-type ligands. In order to broaden the scope of this approach we have also tested other prochiral β-acylamido acrylates. The results are summarized in Table 4.

As shown already with *E*-**2a** as substrate the enantioselectivities of related *E*-configured substrates are independent upon the H_2 pressure. In general excellent ee's were observed. The increase of the steric bulk of the β-alkyl group (R^1) has a beneficial effect. Thus, in the hydrogenation of *i*-propyl derivative *E*-**2c** >99% ee was achieved. The reaction with *Z*-isomeric substrates is strongly dependent on the hydrogen pressure. In all cases an increase of the pressure decreased the ee. This behavior with substrates *Z*-**2b** and *Z*-**2c**, which gave moderate or poor ee at low pressure, led to an inversion of the configuration with increasing pressure. In other words, with these substrates after passing 0% ee an increase of the pressure improves the enantioselectivity of the product; however, in this case the product with the opposite configuration is formed. Unfortunately, beyond 30 bar no further increase of the ee was observed. The feature of changing configuration in the product in dependency on the pressure has to be carefully considered when mixtures of isomeric substrates are hydrogenated! Typical *N*-protecting groups of amino acid chemistry like Boc and Cbz disadvantageously affected the rate and enantioselectivity.

Table 4. Hydrogenations of substrates **2a**–**e** with the [Rh((*S*,*S*)-Et-DuPHOS)(COD)]BF_4 in MeOH at 25°C



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	Substrate				
	R^1	R^2	Config.	*p* (bar)	ee (%)
2a[a]	Me	Ac	*Z*	1	87 (*S*)
				35	44 (*S*)
			E	1	97 (*S*)
				30	96 (*S*)
2b	Et	Ac	*Z*	1	68 (*S*)
				30	28 (*R*)
			E	1	98.5 (*S*)
				30	97.5 (*S*)
2c	*i*-Pr	Ac	*Z*	1	31 (*R*)
				30	72 (*S*)
				100	71 (*S*)
			E	1	>99 (*R*)
				30	99 (*R*)
2d	Me	BnO-CO	*Z*	1	80[b] (*S*)
				30	38 (*S*)
			E[c]	–	–
2e	Me	*t*-Bu-CO	*Z*	1	79[b] (*S*)
				30	66 (*S*)
			E[c]	–	–

[a] See Ref. 3d.
[b] The ee could only be roughly determined due to poor conversion.
[c] *E*-Isomers were not formed in the synthesis.

3. Summary and conclusions

A range of chiral diphosphine ligands such as (*S*,*S*)-DuPHOS, (*S*,*S*)-BPE, (*R*,*R*)-Me_4-BASPHOS, (*R*,*R*)-DIOP and (*R*,*R*)-HO-DIOP have been tested for the enantioselective hydrogenation of prochiral isomeric β-acylamido β-alkylacrylates. As already found for DuPHOS complexes the hydrogenation is strongly sensitive to the *E*/*Z*-geometry of the substrates. In general, *E*-substrates are converted with good or excellent enantioselectivities into the desired β-amino acid derivatives. *Z*-Substrates showed the known H_2-pressure dependency of the ee. In several instances the lowering of the hydrogen pressure has a beneficial effect on the ee. Principally, each catalytic system displays its individual behavior in terms of H_2-pressure dependency, rate and enantioselectivity depending on the isomerism of the substrate.

4. Experimental

4.1. General

Solvents were dried and freshly distilled under argon before use. The syntheses of β-acylamido acrylates **2a–c** used as substrates were carried out following known protocols.[3b] Flash chromatography was carried out with silica gel 60 (particle size 0.040–0.063 mm, Merck). NMR spectra were recorded at the following frequencies: 400.13 MHz (^{1}H) and 100.63 MHz (^{13}C). Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm downfield from TMS as internal standard. Signals are quoted as s (singlet), br (broad) and m (multiplet).

Hydrogenation experiments have been carried out under normal pressure and isobaric conditions with an automatically registering gas measuring device (1.0 atm overall pressure over the solution). The experiments were performed with 0.01 mmol precatalyst, 1.0 mmol of prochiral olefin in 15.0 mL MeOH at 25.0°C. The conversion of the prochiral dehydroamino acids and the %ee were determined by GC or HPLC: methyl 3-acetamido butenoate (**2a**): 50 m Chiraldex β-PH, 130°C; methyl 3-acetamido-2-pentenoate (**2b**): 25 m Lipodex E, 130°C; methyl 4-methyl-3-acetamido-2-pentenoate (**2c**): 25 m Lipodex E, 130°C; methyl 3-benzoyloxycarbonylamido butenoate (**2d**): Chiralpak OD, *n*-hexane: EtOH = 97:3; methyl 3-*t*-butyloxycarbonylamido butenoate (**2e**): Chiralpak OD, *n*-hexane: EtOH = 95:5.

4.2. General procedure for the preparation of Boc- and Cbz-protected enamides 2d,e

To ethyl acetoacetate (20 mM, 2.32 g) *t*-butyl carbamate (40 mM, 4.68 g) and benzyl carbamate (40 mM, 6.04 g), respectively, dissolved in toluene (100 mL), *p*-toluene sulfonic acid (2 mM, 360 mg) was added. The mixture was heated under reflux for 24 h. After cooling to rt the solution was washed with aq. $NaHCO_3$ solution (1N, 100 mL) and water (100 mL). After drying (Na_2SO_4) and filtration the solvent was evaporated. The products were purified by flash chromatography (*n*-hexane: AcOEt = 9:1).

4.2.1. *Z*-Methyl 3-benzyloxycarbonylamido-2-butenoate (*Z*-2d). The raw product was first purified by bulb-to-bulb distillation. Under these conditions the corresponding benzoate was also formed as a side product. Colorless syrup, 2.20 g (44%), $bp_{0.2} = 150$°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 4.90 (1H, s, =CH), 5.13 (2H, s, CH_2Ph), 7.33–7.39 (5H, m, arom. H), 10.69 (1H, s(br), NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 50.9 (OCH_3), 67.0 (CH_2Ph), 95.0 (=CH), 128.1, 128.3, 128.5, 135.6 (arom. C), 152.6, 154.7 (-C=, N-C=O), 169.3 (C=O). Calcd for $C_{13}H_{15}O_4N$ (249.27): C, 62.64; H, 6.07; N, 5.62; found: C, 63.04; H, 6.22; N, 5.45.

4.2.2. *Z*-Methyl 3-*t*-butyloxycarbonylamido-2-butenoate (*Z*-2e). Colorless syrup, 2.40 g (56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (9H, s, CH_3), 2.29 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 4.82 (1H, s, =CH), 10.38 (1H, s(br), NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 28.1 ($C(CH_3)_3$), 50.8 (OCH_3), 81.0 (O-C), 94.0 (=CH), 151.8, 155.5 (=C-, N-C=O), 169.5 (C=O). Calcd for $C_{10}H_{17}O_4N$ (215.25) C, 55.80; H, 7.96; N 6.51; found: C, 56.06; H, 7.92; N, 6.53.

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