CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201202455

Bispalladacycle-Catalyzed Michael Addition of In Situ Formed Azlactones to Enones

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Abstract: The development and further evolution of the first catalytic asymmetric conjugate additions of azlactones as activated amino acid derivatives to enones is described. Whereas the first-generation approach started from isolated azlactones, in the second-generation approach the azlactones could be generated in situ starting from racemic *N*-benzoylated amino acids. The third evolution stage could make use of racemic unprotected α-amino acids to directly form highly enantioenriched and diastereomerically pure masked quaternary amino acid products bearing an additional tertiary stereocenter. The step-economic transformations were accomplished by cooperative activation by using a robust planar chiral bis-Pd catalyst, a Brønsted acid (HOAc or BzOH; Ac = acetyl, Bz = benzoyl), and a Brønsted base (NaOAc). In particular the second- and third-generation approaches provide a rapid and divergent access to biologically interesting unnatural quaternary amino acid derivatives from inexpensive bulk chemicals. In that way highly enantioenriched acyclic α-amino acids, α-alkyl proline, and α-alkyl pyroglutamic acid derivatives could be prepared in diastereomerically pure form. In addition, a unique way is presented to prepare diastereomerically pure bicyclic dipeptides in just two steps from unprotected tertiary α-amino acids.

Keywords: catalysis · domino processes · dynamic kinetic resolution · peptides · quaternary amino acids

Introduction

From a biological and pharmacological point of view α,α-disubstituted (quaternary) α-amino acids constitute an important compound class.[1] Quaternary amino acids often restrict the conformational flexibility of peptides and induce a unique peptide folding, whereas at the same time the hydrophobicity and stability against peptide degradation are noticeably increased.[1,2] Mainly for these two reasons the development of divergent, rapid, and operationally simple approaches to access quaternary α-amino acids are important tasks.

Oxazol-5-(4*H*)-ones, commonly called azlactones, are masked and activated α-amino acid derivatives, which are usually available in 2–4 steps from α-amino acids and which have lately been repeatedly employed for the catalytic asymmetric construction of quaternary α-amino acid derivatives.[3] The use of azlactones is particularly attractive for a diversity-oriented access to α,α-disubstituted α-amino acid derivatives owing to the presence of orthogonal nucleophilic and electrophilic reactive sites in the heterocyclic systems.[3] The reported methodologies explore the marked tendency of azlactones to enolize ($pK_A = \pm 9$), which is caused by the aromatic character of the corresponding enol tautomers. The nucleophilic C-4 position of an azlactone has, for example, been employed for catalytic asymmetric substitutions,[4] rearrangements,[5] cycloadditions,[6] and 1,2-addition reactions[7] to form quaternary stereocenters[8] with high levels of enantioselectivity. 1,4-Additions of azlactones to enals have recently been reported to proceed with moderate to good diastereoselectivity and high enantioselectivity by using proline-derived organocatalysts.[9,10] Afterwards, organocatalytic protocols have been described for other highly reactive Michael acceptors.[11–15]

Being part of our program to study cooperative effects in asymmetric catalysis,[16] we report herein the first catalytic asymmetric conjugate additions of azlactones to enones[17–19] and describe the first catalytic asymmetric examples in which the azlactone substrates are formed in situ, starting either from racemic *N*-benzoyl α-amino acids or even from unprotected racemic amino acids.

Results and Discussion

1,4-Additions with isolated azlactones: Recently, we have reported the asymmetric Michael addition of α-cyanoacetates[18e] to vinylketones catalyzed by a readily accessible planar chiral ferrocene bisimidazoline bispalladacycle (FBIP, prepared in four steps from ferrocene)[20–22] generating quaternary stereocenters with a high level of enantiocontrol.[23] A bimetallic activation mode[24] has received validation by spectroscopic and kinetic investigations. For catalytic activity

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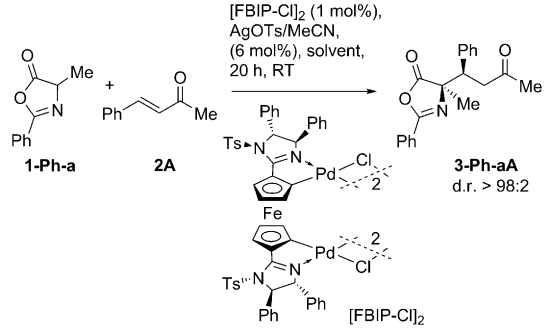
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201202455.

the dimeric precatalyst $[FBIP\text{-}Cl]_2$ had to be activated by replacing the chloride ions utilizing acetonitrile complexes of silver sulfonates to generate the monomeric active catalyst species. Under similar reaction conditions as used in this previous study (diglyme, RT, catalyst activation with AgOTs, OTs = tosylate) the addition of azlactone **1-Ph-a** to the β-substituted enone **2A** gave the product **3-Ph-aA** in very poor yield (Table 1, entry 1).[25] Other ethereal solvents

Table 1. Investigation of the solvent effect for the conjugate addition of azlactone **1-Ph-a** derived from (±)-alanine to enone **2A**.



	Solvent	Conv. [%][a]	Yield [%][a]	*ee* [%][b]
1	diglyme	16	3	39
2	glyme	56	5	34
3	THF	45	5	29
4	CH_2Cl_2	56	25	17
5	$ClCH_2CH_2Cl$	79	13	38
6	$CHCl_3$	81	25	25
7	CH_2Cl_2 + 0.3 equiv HOAc[c]	64	21	39
8	CH_2Cl_2 + 1.0 equiv HOAc	62	14	49
9	HOAc	83	47	73
10	HOAc + 30 vol % Ac_2O	90	46	79

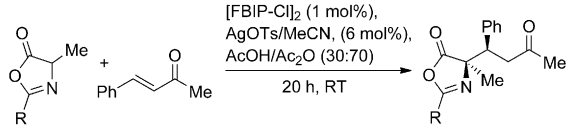
[a] Determined by ^1H NMR spectroscopy by using mesitylene as internal standard. [b] Determined by HPLC. [c] Ac = acetyl.

(Table 1, entries 2 and 3) or chlorinated solvents (Table 1, entries 4–6) resulted in low enantioselectivities. Inert reaction conditions were found to be necessary to avoid the hydrolysis of the azlactone by moisture.

Acetic acid as an additive slightly improved the enantioseletivity (Table 1, entries 7 and 8) and a considerably higher enantioselectivity was attained in pure acetic acid, which also had a positive impact on the product yield (Table 1, entry 9). To trap traces of moisture acetic anhydride was examined as a cosolvent (30 vol %), which further increased the enantioselectivity (Table 1, entry 10). Notably, under all conditions shown in Table 1, **3-Ph-aA** was formed in nearly diastereomerically pure form (d.r. > 98:2)

The role of the C-2 substituent R of the 1,3-oxazolin-5-one was subsequently examined (Table 2), but none of the alternative aromatic substituents investigated allowed for higher enantioselectivity than Ph, regardless of the aryl substitution pattern. There is no clear tendency in terms of electronic substituent effects on the reaction outcome. Exceedingly bulky substituents impede the product formation (Table 2, entries 6–7 and 15).

Table 2. Investigation of the influence of the C-2 substituent R.



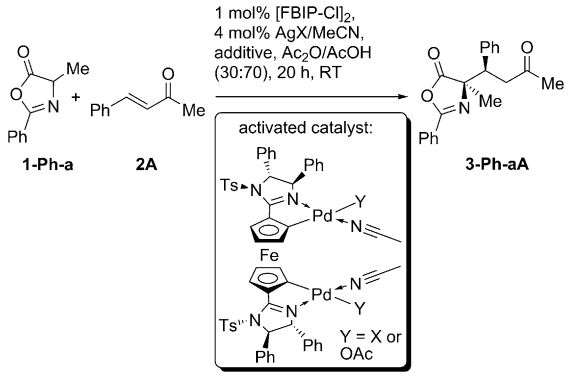
	R	Yield [%][a]	*ee* [%][b]
1	4-MeO-C_6H_4	20	71
2	3,4,5-$(MeO)_3$-C_6H_2	58	45
3	4-Me-C_6H_4	75	75
4	4-*t*Bu-C_6H_4	89	50
5	3,5-$(Me)_2$-C_6H_3	70	64
6	2,4,6-$(i\text{Pr})_3$-C_6H_2	0	–
7	2,4,6-$(Me)_3$-C_6H_2	0	–
8	1-naphthyl	29	58
9	2-naphthyl	34	61
10	biphenyl	34	59
11	4-Cl-C_6H_4	79	62
12	4-F-C_6H_4	40	69
13	4-F_3C-C_6H_4	52	44
14	4-O_2N-C_6H_4	86	52
15	*t*Bu	0	–

[a] Determined by ^1H NMR spectroscopy by using mesitylene as internal standard. [b] Determined by HPLC.

Various silver salts were subsequently examined for the catalyst activation (Table 3). Although silver 1- and 2-naphthylsulfonate permitted high yields (Table 3, entries 2 and 3), the enantioselectivity was lower than with AgOTs (Table 3, entry 1). AgOTf (OTf = triflate) gave similar results as the latter (enantiomeric excess (*ee*) = 78 %, Table 3, entry 5). Silver carboxylates or nitrate performed in general inferior in terms of the enantioselectivity (Table 3, entries 6–9), whereas with the non-coordinating BF_4^- ion a good enantioselectivity was attained (Table 3, entry 10) at the expense of a low reactivity. A major improvement of the product yield was achieved in case of silver sulfonates or acetate by addition of catalytic or stoichiometric amounts of NaOAc (Table 3, entries 11–16). To further accelerate the conjugate addition the model reaction was conducted at 30 °C by using 2 mol % of the precatalyst and two equivalents of enone **2A**. This change resulted in an almost quantitative yield with nearly unchanged enantioselectivity (Table 3, entry 18). In contrast, poor results were obtained in the presence of NaOAc, when the catalyst was not activated by a silver salt (Table 3, entry 17).

The optimized conditions were then applied to a variety of azlactones and enones (Table 4). Gratifyingly, changing to substituents R^1 at the enolizable C-4 atom with a larger steric demand than Me resulted in general in higher enantioselectivity (Table 4, entries 2–16) with up to 99 % *ee* (Table 4, entry 11). For the enone substituents R^2 and R^3 the combinations of aryl/alkyl (Table 4, entries 1–5, 8–13, and 16), alkyl/alkyl (Table 4, entries 6–7 and 15), and aryl/aryl (Table 4, entry 14) were all well tolerated, giving useful yields as well as high enantio- and diastereoselectivity. A number of functional groups on R^2 was examined revealing that electronic effects play only a minor role. Substrates

Table 3. Investigation of the catalyst activation by various silver salts and the role of NaOAc.



	AgX	Additive ([mol%])	Conv. [%][a]	Yield [%][a]	d.r.	*ee* [%][b]
1[c]	AgOTs	–	90	46	>98:2	79
2[c]	AgO_3S-1-naphthyl	–	100	quant.	>98:2	72
3[c]	AgO_3S-2-naphthyl	–	100	88	>98:2	73
4	AgOMs[e]	–	65	28	>98:2	68
5	AgOTf	–	72	37	96:4	78
6[c]	AgOAc	–	50	44	>98:2	70
7[c]	AgO_2CCF_3	–	58	50	>98:2	72
8	$AgO_2C_7F_{15}$	–	63	32	95:5	69
9	$AgNO_3$	–	59	19	>98:2	31
10	$AgBF_4$	–	60	26	>98:2	74
11	AgOTs	NaOAc (4)	94	83	>98:2	78
12	AgOMs	NaOAc (4)	71	55	>98:2	75
13	AgOTf	NaOAc (4)	89	85	>98:2	78
14[c]	AgOAc	NaOAc (4)	100	73	>98:2	78
15	AgOTf	NaOAc (100)	92	87	>98:2	78
16	AgOTf	NaOAc (10)	88	87	>98:2	78
17	–	NaOAc (4)	40	8	>98:2	31
18[d]	AgOTf	NaOAc (10)	100	98	>98:2	79

[a] Determined by ^{1}H NMR spectroscopy by using mesitylene as internal standard. [b] Determined by HPLC. [c] 6 mol% of AgX were used. [d] The reaction was performed by using 2 mol% of $[FBIP-Cl]_2$, 8 mol% of AgOTf, and 2 equiv of **2A** at 30°C. [e] OMs = mesylate.

equipped with a π-donor substituent such as *p*-OMe (Table 4, entries 3 and 9), π-acceptor substituents such as *p*-NO_2 (Table 4, entry 12), σ-acceptor substituents such as *o*- or *p*-Cl (Table 4, entries 10 and 11), or substrates with electron-rich heterocycles like 2-furyl (Table 4, entry 13) gave similar results regarding the yield and the enantioselectivity.[26] Arylbromides can also be used in the presence of the Pd catalyst (Table 4, entry 5), because the catalyst system is relatively inert towards the formation of Pd^0 by catalyst decomposition under the acidic reaction conditions.

The absolute configuration of the 1,4-addition products was determined by X-ray single-crystal structure analysis of **3-Ph-dA** and **3-Ph-cM** (Figure 1).[27]

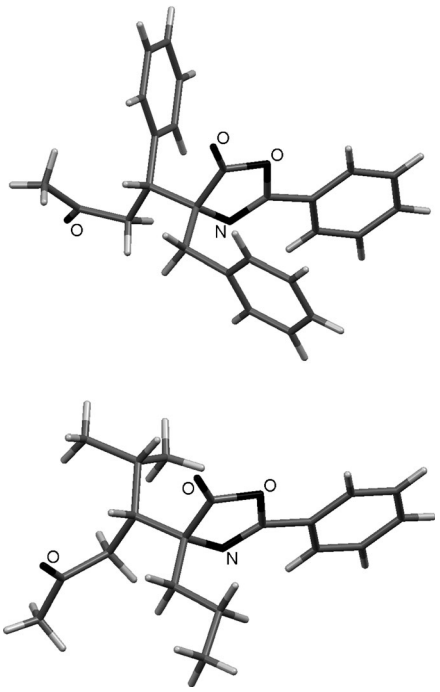


Figure 1. Single-crystal structures of **3-Ph-dA** (left) and **3-Ph-cM** (right).

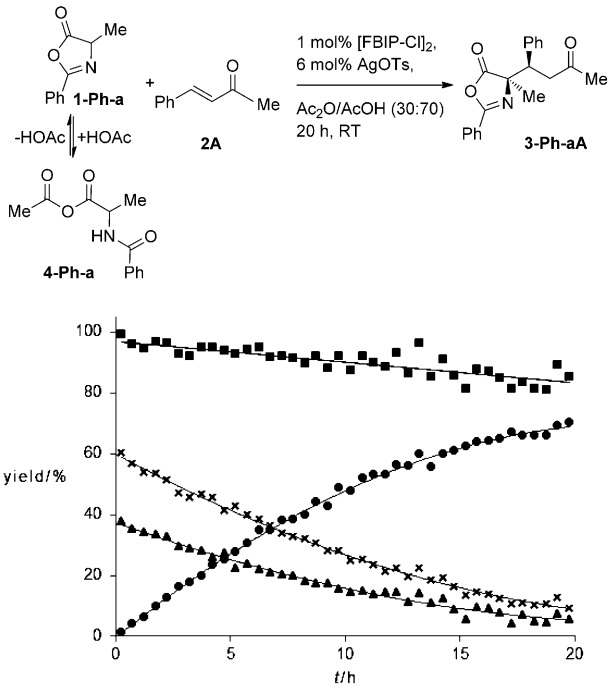
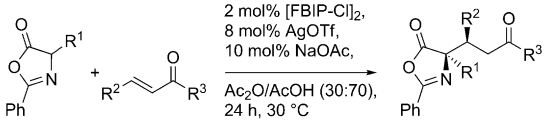


Figure 2. Monitoring of the model reaction of **1-Ph-a** and **2A** by ^{1}H NMR spectroscopy (▲ = **4-Ph-a**, × = **1-Ph-a**, ● = **3-Pha-A**, ■ = sum of the yields).

1,4-Additions starting from *N*-benzoylated amino acids: Monitoring of the model reaction by ^{1}H NMR spectroscopy over 20 h (Figure 2) revealed that azlactone **1-Ph-a** is ring-openend by acetic acid in a rapid equilibrium with a constant ratio of **1-Ph-a**/**4-Ph-a** of approximately 1.7:1. This ring-opening apparently occurs considerably faster than the Michael addition of **1-Ph-a** to **2A**.[28]

Because the mixed anhydride **4-Ph-a** is thus in rapid equilibrium with the azlactone and because the activated bispalladacycle catalyst was found to be remarkably stable to-

Table 4. Scope of the conjugate addition of the racemic azlactones **1-Ph** to the enones **2**.



1-Ph 2 3-Ph

	3	R^1	R^2	R^3	Yield[a] [%]	d.r.[b]	*ee* [%][c]
1	**3-Ph-aA**	Me	Ph	Me	96	>98:2	75
2	**3-Ph-bA**	Et	Ph	Me	95	>98:2	96
3	**3-Ph-bB**	Et	3,4-$(MeO)_2$-C_6H_3	Me	89	>98:2	91
4	**3-Ph-bC**	Et	4-HO-C_6H_4[d]	Me	42	>98:2	84
5	**3-Ph-bD**	Et	4-Br-C_6H_4	Me	86	>98:2	91
6	**3-Ph-bE**	Et	Me	Et	94	>98:2	88
7	**3-Ph-bF**	Et	*n*Pr	Me	93	>98:2	90
8	**3-Ph-cA**	*n*Pr	Ph	Me	86	>98:2	98
9	**3-Ph-cG**	*n*Pr	4-MeO-C_6H_4	Me	80	>98:2	95
10	**3-Ph-cH**	*n*Pr	4-Cl-C_6H_4	Me	80	>98:2	97
11	**3-Ph-cI**	*n*Pr	2-Cl-C_6H_4	Me	94	>98:2	99
12	**3-Ph-cJ**	*n*Pr	4-O_2N-C_6H_4	Me	80	>98:2	97
13	**3-Ph-cK**	*n*Pr	2-furyl	Me	96	>98:2	96
14[e]	**3-Ph-cL**	*n*Pr	Ph	Ph	92	>98:2	90
15	**3-Ph-cM**	*n*Pr	*i*Pr	Me	65	>98:2	>97
16[e]	**3-Ph-dA**	Bn[f]	Ph	Me	73	>98:2	82

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy of the isolated product. [c] Determined by HPLC. [d] The OH group is acylated during the reaction. [e] 5 mol% of $[FBIP-Cl]_2$, 20 mol% of AgOTf, and 25 mol% of NaOAc were used. [f] Bn = benzyl.

wards acetic anhydride, the option was investigated to directly start from the racemic *N*-benzoylated α-amino acids **5-Ph** to develop a tandem reaction protocol.[29] The α-amino acids **5-Ph** should be *O*-acylated under the optimized reaction conditions to generate the mixed anhydrides **4-Ph** in equilibrium with the azlactones **1-Ph**. The conditions optimized for the reaction by using the isolated azlactones were thus exploited for the domino azlactone formation/Michael addition (Table 5). Under these conditions the products **3-Ph** were usually formed in high yield and with good to excellent enantioselectivity.

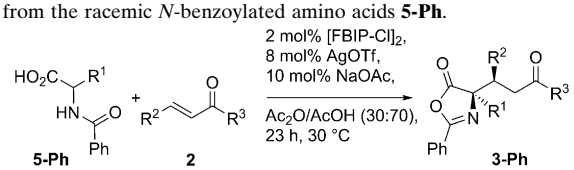
Again, increasing the steric bulk of the substituent R^1 at the enolizable C-4 atom from Me to a larger alkyl group resulted in general in high enantioselectivity (Table 5, entries 2–16) providing up to 99% *ee* with R^1 = *n*Pr (Table 5, entry 11). The enone substrate scope was found to be very similar in terms of steric and electronic effects as compared to the use of isolated azlactones as substrates.

Catalyst recycling: The recycling of the catalysts containing noble metals is very desirable for ecological and economic reasons. An operationally simple protocol for the recycling of the bis-Pd catalyst FBIP is presented in Table 6, in which the 1,4-addition of the azlactone generated from *N*-benzoylated ethylglycine (**5-Ph-b**) to enone **2A** was investigated. After the indicated time all volatiles were removed and the residue was extracted with *n*-hexane. The remaining residue containing the catalyst and the base was subsequently treated again with the solvent mixture and the reactants for the next run. This procedure allows the efficient use of the same activated catalyst up to seven times with good yield and high stereoselectivity. Unfortunately starting with the 8th run the product yield dropped below 50%.

1,4-Additions by using unprotected racemic amino acids: Because the reactions described above were performed under acylating reaction condition, a one-pot procedure was envisaged employing the unprotected racemic α-amino acids **6** as cost-efficient alternative starting material. The tandem sequence should imply *N*- and *O*-amino acid acylations, a cyclization to form an azlactone, the enolization, and the catalytic asymmetric addition to the Michael acceptor.

Attempts to utilize the reaction conditions optimized for the *N*-benzoylated amino acids

Table 5. Asymmetric domino azlactone formation/Michael addition starting from the racemic *N*-benzoylated amino acids **5-Ph**.



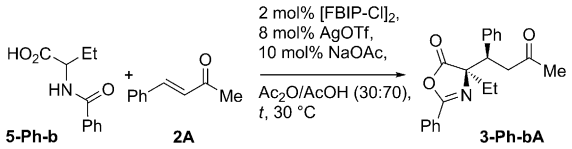
5-Ph 2 3-Ph

	3-Ph	R^1	R^2	R^3	Yield[a] [%]	d.r.[b]	*ee* [%][c]
1	**3-Ph-aA**	Me	Ph	Me	95	>98:2	76
2	**3-Ph-bA**	Et	Ph	Me	92	>98:2	93
3	**3-Ph-bB**	Et	3,4-$(MeO)_2$-C_6H_3	Me	81	>98:2	91
4	**3-Ph-bC**	Et	4-HO-C_6H_4[d]	Me	43	>98:2	88
5	**3-Ph-bD**	Et	4-Br-C_6H_4	Me	88	>98:2	92
6	**3-Ph-bE**	Et	Me	Et	92	>98:2	87
7	**3-Ph-bF**	Et	*n*Pr	Me	90	>98:2	90
8	**3-Ph-cA**	*n*Pr	Ph	Me	89	>98:2	98
9	**3-Ph-cG**	*n*Pr	4-MeO-C_6H_4	Me	81	>98:2	96
10	**3-Ph-cH**	*n*Pr	4-Cl-C_6H_4	Me	85	>98:2	98
11	**3-Ph-cI**	*n*Pr	2-Cl-C_6H_4	Me	82	>98:2	99
12	**3-Ph-cJ**	*n*Pr	4-O_2N-C_6H_4	Me	76	>98:2	98
13	**3-Ph-cK**	*n*Pr	2-furyl	Me	88	>98:2	96
14[e]	**3-Ph-cL**	*n*Pr	Ph	Ph	87	98:2	90
15	**3-Ph-cM**	*n*Pr	*i*Pr	Me	64	>98:2	>97
16[e]	**3-Ph-dA**	Bn	Ph	Me	41	>98:2	81

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy of the isolated product. [c] Determined by HPLC. [d] The OH group is acylated during the reaction. [e] 5 mol% of $[FBIP-Cl]_2$, 20 mol% of AgOTf, and 25 mol% of NaOAc were used.

(i.e., 2 mol% of $[FBIP-Cl]_2$, 8 mol% of AgOTf, 10 mol% of NaOAc in AcOH/Ac_2O at RT) in the model reaction of racemic unprotected norvaline (**6c**) with enone **2A** gave the desired tandem reaction product **3-Me-cA** with an excellent

Table 6. Catalyst recycling study.



5-Ph-b 2A 3-Ph-bA

Run	*t* [h]	Conv. [%][a]	Yield [%][a]	d.r. [%][a]	*ee* [%][b]
1	22	100	88	>98:2	98
2	24	100	86	>98:2	97
3	24	100	89	>98:2	97
4	23	100	87	>98:2	97
5	24	100	86	>98:2	96
6	23	96	80	>98:2	95
7	23	89	70	>98:2	93
8	23	67	45	>98:2	90

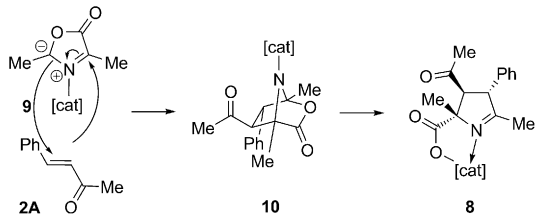
[a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] Determined by HPLC.

enantiomeric excess of 96% (Table 7, entry 1), yet in poor yield mainly due to a low conversion arguably as a result of a lower enolization tendency of the azlactone substrate carrying a non-aromatic C-2 residue. By performing the model reaction at higher temperatures (up to 70°C) the product was still formed in relatively low yield, primarily because of the competing formation of the regioisomeric C-2 addition product **7-Me-cA** (Table 7, entries 2 and 3), which is generated as a diastereomeric mixture, whereas the targeted regioisomer **3-Me-cA** is nearly diastereomerically pure.

A kinetic investigation at 70°C by ^{1}H NMR spectroscopy revealed that *N*-acetylnorvaline and the corresponding azlactone **1-Me-c** are rapidly formed in comparable amounts, which gradually decrease after 20 min due to the formation of both Michael addition regioisomers. The latter are initially formed with similar rates (Figure 3, top), but the ratio **3-Me-cA**/**7-Me-cA** steadily increases due to decomposition of **7-Me-cA**.

Attempts to isolate the catalyst after the reaction led to the identification of another side product obviously inhibiting the catalyst by the formation of the C_2-symmetric complex **8**, according to Figure 4, which was identified by X-ray crystal structure analysis (Figure 4).[30] Complex **8** is the almost exclusively found bispalladium species at the end of the reaction in acetic acid/acetic anhydride. The inhibiting side product, a dehydroproline derivative with a quaternary stereocenter at C-2 and two adjacent tertiary stereocenters at C-3 and C-4, chelates each Pd center of the bimetallic catalyst.[31]

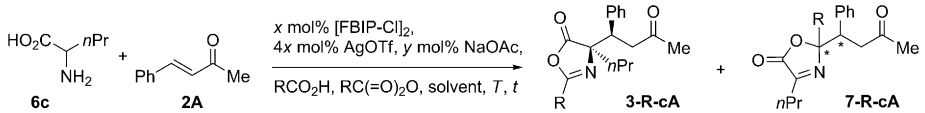
The 3,4-dihydropyrrole might either be formed through a 1,3-dipolar cycloaddition pathway[6e,f] of compounds **9** and **2A** or, alternatively, by the undesired Michael addition at the C-2 of the azlactone followed by an intramolecular Mannich addition, initially generating the bicyclic proline intermediate **10** (Scheme 1). The latter could subsequently undergo a ring-opening of the *N*,*O*-acetal moiety giving complex **8**.



Scheme 1. Mechanistic proposal for the formation of the inhibited catalyst **8**.

The fact that both Pd centers of the FBIP system bind almost exclusively to the dehydroproline side product demonstrates that the corresponding binding constants are much higher than those of the targeted product **3-Me-cA**, most likely due to the presence of the carboxylate moiety as anionic donor, whereas **3-Me-cA** contains only neutral

Table 7. Elaboration of the reaction conditions with unprotected norvaline (**6c**) and enone **2A**.[a]



6c 2A 3-R-cA 7-R-cA

	R	*x*	*y*	Solvent	*T* [°C]	*t* [h]	**3-R-cA**/**7-R-cA**	Yield **7-R-cA** [%][b]	Yield **3-R-cA** [%][b]	d.r. **3-R-cA**[b]	*ee* **3-R-cA** [%][c]
1	Me	2	10	–	23	30	2.7:1	6	17	>98:2	96
2	Me	2	10	–	50	18	1.7:1	27	45	>98:2	97
3	Me	3	25	–	70	5	2.0:1	22	43	>98:2	95
4	Et	3	25	–	70	5	2.4:1	20	48	>98:2	95
5	*i*Bu	3	25	–	70	5	4.3:1	10	43	>98:2	72
6	*t*Bu	3	25	–	70	5	n.d.[f]	<4	<4	n.d.	n.d.
7	H[d]	3	25	–	70	5	n.d.	<2	<2	–	–
8	Ph	3	25	–	70	5	>34:1	<2	69	>98:2	90
9[e]	Ph	3	25	–	70	5	>31:1	<2	62	>98:2	66
10	Ph	3	25	THF/PhMe (10:1)	70	5	>36:1	<2	73	>98:2	92
11[e]	Ph	3	25	THF	70	5	>26:1	<2	52	>98:2	75

[a] Reactions were performed in a parallel synthesizer heated by a metal block. [b] Determined by ^{1}H NMR spectroscopy of the crude product by using mesitylene as internal standard. [c] Determined by HPLC. [d] A mixture of formic acid and acetic anhydride was used. [e] No benzoic acid was added. [f] n.d. = not determined.

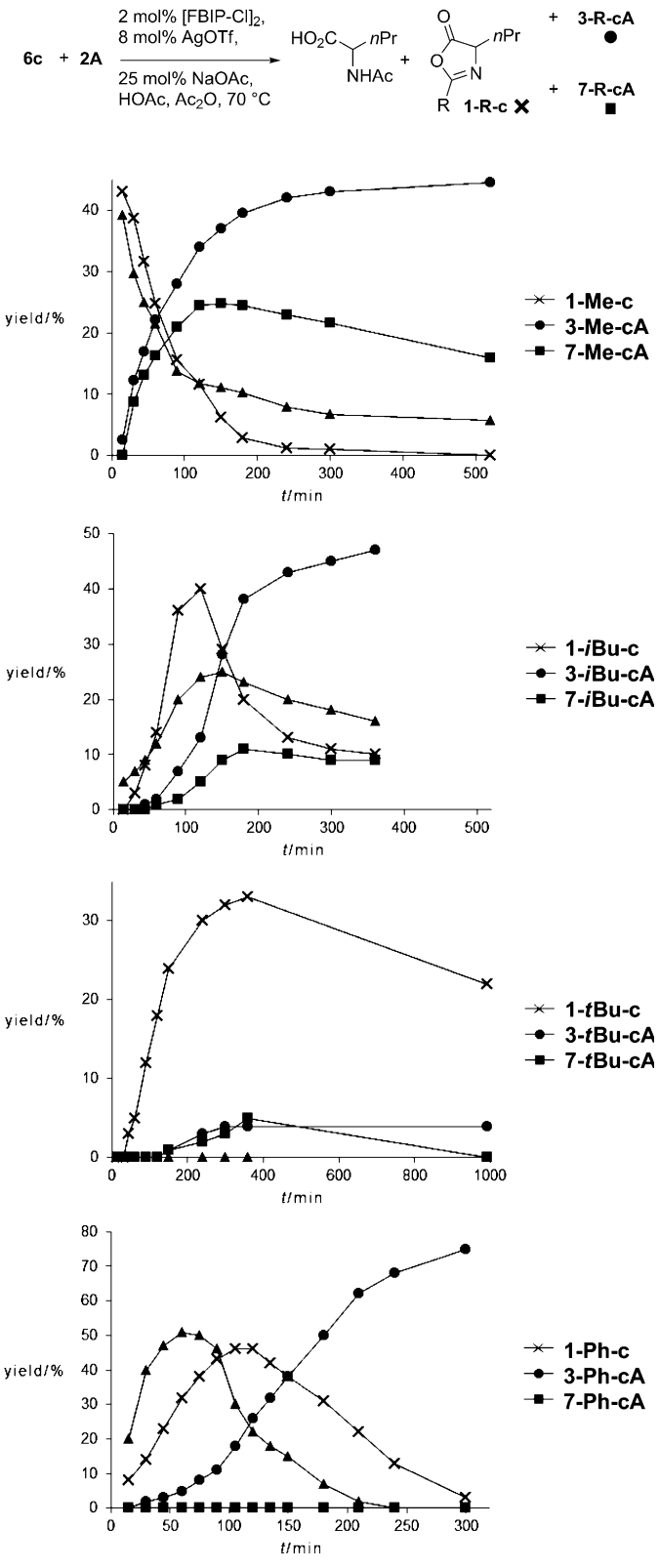


Figure 3. Kinetic control of the model reaction described in Table 7 (entries 3, 5, 6, and 10).

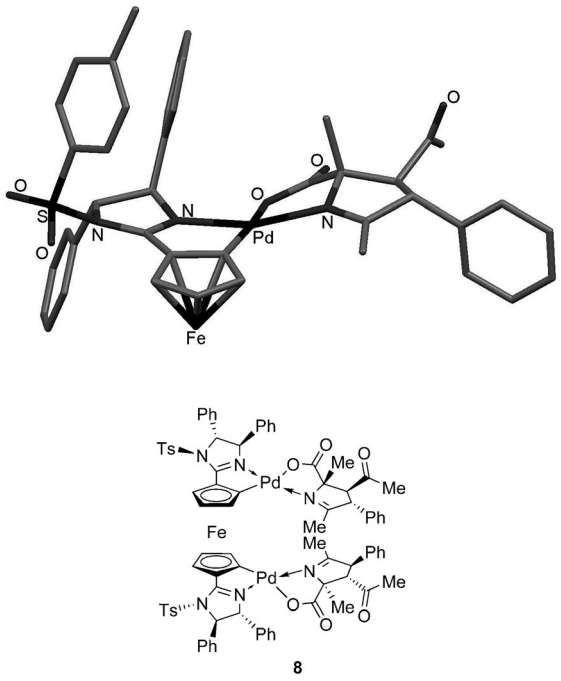


Figure 4. X-ray crystal structure analysis of the C_2-symmetric complex **8**, which is formed during the catalysis event in AcOH/Ac_2O. Hydrogen atoms are omitted and only one half of the C_2-symmetric **8** is shown for clarity.

donor atoms. The anionic donor in compound **8** (i.e., the carboxylate group) binds *cis*, and the neutral donor (i.e., the imino group) binds *trans* to the imidazoline moiety as a result of a *trans* effect,[32] in agreement with our previous findings for ferrocene bisimidazoline bispalladacycles.[20b] If the formation of **3-Me-cA** follows a bimetallic reaction pathway (see below), the coordination of one dehydroproline would already be deleterious for the catalyst performance.

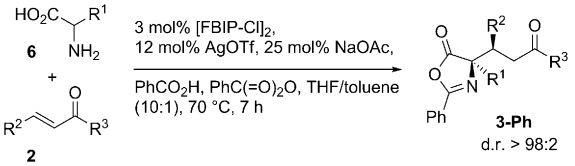
Various combinations of carboxylic acids and anhydrides ($(RCO)_2O$) were then surveyed (Figure 3) in order to decrease the nucleophilicity at the C-2 position thus minimizing the formation of the undesired regioisomer **7** or the (formal) 1,3-dipolar cycloaddition product blocking the catalyst. More bulky alkyl groups R (Table 7, entries 4–6) resulted in general in a lower reactivity, but unfortunately not only at the C-2 atom (Figure 3). For R = *i*Bu or *t*Bu, the in-situ formation of the corresponding azlactones **1** is considerably retarded. Although for R = *i*Bu the initial ratio of the C-4/C-2 addition products is improved compared to R = Me, yet at the cost of reduced enantioselectivity (Table 7, entry 5), for R = *t*Bu both regioisomeric products are initially generated with similarly low rates and only traces of **3-*t*Bu-cA** were formed. On the other hand, for R = H (formic acid, Table 7, entry 7), no product was formed as a consequence of catalyst decomposition (formation of Pd black).

In contrast, R = Ph (benzoic acid/anhydride) shifted the reactivity to the C-4 position and the undesired Michael addition regioisomer was not detected anymore (Figure 3, bottom).[33] The targeted product **3-Ph-cA** was formed in considerably better yield regardless of a heterogeneous reaction mixture in that case (Table 7, entry 8). Addition of various co-solvents gave homogeneous mixtures and thus al-

lowed for a better reproducibility, whereas there was almost no impact on the stereoselectivity.[34] The best data were obtained with a mixture of THF/toluene (10:1, Table 7, entry 10).[35] The presence of benzoic acid is essential for a high enantioselectivity as the experiments in Table 7, entries 9 and 11 reveal, in which the reaction was performed without addition of benzoic acid. In that case formation of Pd black was observed.[36]

With the optimized reaction conditions from the initial screening, preparative experiments were conducted for various enones and unprotected racemic amino acids (alanine (**6a**), ethylglycine (**6b**), norvaline (**6c**), phenylalanine (**6d**), norleucine (**6e**), leucine (**6f**) and glutamic acid 5-methyl ester (**6g**), Table 8). In contrast to the use of isolated azlactones or *N*-benzoylated amino acids, the third-generation approach did not provide useful *ee* values for R^1=Me and also in the case of R^1=Et the enantioselectivity was found to be considerably lower as compared to the first- and second-generation approach. A certain steric demand of the substituent R^1 at the enolizable C-4 atom is again advantageous resulting in up to 96% *ee* with R^1=*n*Bu (Table 8, entry 17). As a general trend the amino acid reactivity towards reaction with the same enone increased with a decreasing steric bulk of the amino acid side chain R^1 (compare Table 8, entries 1, 2, 7, 16, 17, 22, and 23) and the best yields were thus found for sterically less-demanding unbranched alkyl substituents R^1 allowing for product formation in up to 90% yield for the one-pot procedure (Table 8, entry 2), whereas the β-branched isobutyl residue R^1 (leucine (**6f**), Table 8, entry 22) or a benzyl group (phenylalanine (**6d**), Table 8, entry 16) led to product formation in moderate yields (52 and 66%, respectively).

Table 8. Application of the optimized reaction conditions to different unprotected racemic amino acids **6** and Michael acceptors **2**.[a]



	3-Ph	R^1	R^2	R^3	Yield[b] [%]	*ee* [%][c]
1	**3-Ph-aA**	Me	Ph	Me	79	47
2	**3-Ph-bA**	Et	Ph	Me	90	78
3	**3-Ph-bB**	Et	3,4-$(MeO)_2$-C_6H_3	Me	70	72
4	**3-Ph-bD**	Et	4-Br-C_6H_4	Me	90	71
5[d]	**3-Ph-bE**	Et	Me	Et	81	66
6	**3-Ph-bF**	Et	*n*Pr	Me	81	65
7	**3-Ph-cA**	*n*Pr	Ph	Me	87	90
8	**3-Ph-cG**	*n*Pr	4-MeO-C_6H_4	Me	75	82
9	**3-Ph-cH**	*n*Pr	4-Cl-C_6H_4	Me	73	84
10	**3-Ph-cI**	*n*Pr	2-Cl-C_6H_4	Me	76	85
11	**3-Ph-cJ**	*n*Pr	4-O_2N-C_6H_4	Me	58	80
12	**3-Ph-cK**	*n*Pr	2-furyl	Me	76	82
13[e]	**3-Ph-cL**	*n*Pr	Ph	Ph	41	78
14	**3-Ph-cM**	*n*Pr	*i*Pr	Me	62	81
15[f]	**3-Ph-cN**	*n*Pr	Ph	*i*Pr	52	94
16[e]	**3-Ph-dA**	Bn	Ph	Me	66	74
17	**3-Ph-eA**	*n*Bu	Ph	Me	72	96
18	**3-Ph-eD**	*n*Bu	4-Br-C_6H_4	Me	71	88
19	**3-Ph-eF**	*n*Bu	*n*Pr	Me	77	90
20	**3-Ph-eH**	*n*Bu	4-Cl-C_6H_4	Me	72	87
21	**3-Ph-eI**	*n*Bu	2-Cl-C_6H_4	Me	72	90
22[d]	**3-Ph-fA**	*i*Bu	Ph	Me	52	73
23[g]	**3-Ph-gA**	$(CH_2)_2E$	Ph	Me	73	87
24[g]	**3-Ph-gB**	$(CH_2)_2E$	3,4-$(MeO)_2$-C_6H_3	Me	65	75

[a] Reactions were performed in Schlenk tubes heated by an oil bath. [b] Yield of isolated product. [c] Determined by HPLC. [d] 7.5 mol% of $[FBIP-Cl]_2$, 30 mol% of AgOTf, and 62.5 mol% of NaOAc were used. [e] 10 mol% of $[FBIP-Cl]_2$, 40 mol% of AgOTf, and 62.5 mol% of NaOAc were used. [f] 5 mol% of $[FBIP-Cl]_2$ and 20 mol% of AgOTf were used. [g] E=CO_2Me.

This methodology is also attractive for a rapid access to unnatural glutamic acid derivatives. Natural glutamic acid acts as an essential neurotransmitter in the mammalian central nervous system and is playing a key role in the pathogenesis of neuronal damage that causes various neuronal diseases by interaction with glutamate membrane receptors.[37] Investigation of unnatural glutamic acid derivatives is considered to be a useful tool to study the role of these receptors as well as their modulation mechanism in the central nervous system.[38] An operationally simple and rapid catalytic asymmetric access might contribute to accelerate the progress in this field. Entries 23 and 24 in Table 8 demonstrate that α-alkyl-glutamic acid derivatives are accessible in diastereomerically pure form starting from racemic glutamic acid 5-methyl ester (**6g**) in good yields and with good to high enantioselectivity.

Again a broad variety of enones with R^2/R^3=(het)aryl/alkyl (Table 8, entries 1–4, 7–12, 15–18, and 20–24), alkyl/alkyl (Table 8, entries 5, 6, 14, and 19), or aryl/aryl (Table 8, entry 13) was accommodated under the reaction conditions. The reactivity and diastereoselectivity was found to be lower in the aryl/aryl case. The alkyl/alkyl case suffered from moderate enantioselectivity in the case of ethylglycine as azlactone precursor. Otherwise, steric and electronic enone substituent effects were again found to play only a minor role and very similar results were obtained as starting from *N*-benzoylated azlactones.

Mechanistic considerations: A sulfonate ion exchange at the catalyst during the reaction by acetate was verified by ^{1}H NMR spectroscopy. In addition, the precatalyst activated by AgOAc was found to provide a very similar activity and identical stereoselectivity as the catalysts activated by silver sulfonates, if the reactions were performed in the presence of NaOAc (compare Table 3, entries 11–15).

The inherent diastereoselectivity might be explained be a transition state adopting a staggered conformation around the developing C–C-bond in which the energy is minimized by π interaction of the electron-poor enone and the electron-rich enol(ate) possessing nucleophilic positions at the C-4/C-2 atoms (Figure 5).

The frontier molecular orbitals were therefore calculated for enone **2A** (LUMO) and the enolate form of azlactone **1-Ph-a** (HOMO) by DFT computations (B3LYP6-31G*) in vacuum (Figure 6) and indicate a maximum molecular orbital overlap in a transition state leading to the observed dia-

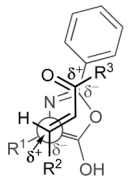


Figure 5. Possible explanation of the inherent diastereoselectivity outcome.

stereomer. The arrow in Figure 6 pointing to the azlactone C-4 atom highlights the interaction resulting in the C–C bond formation, the other arrow pointing to the azlactone C-2 atom indicates a secondary molecular orbital interaction. This additional interaction might explain the inherent diastereoselectivity of the title reaction.

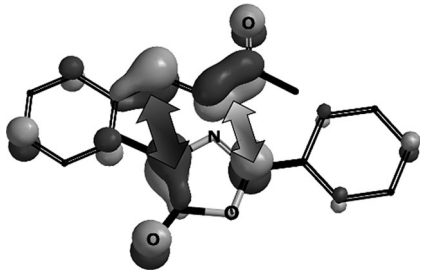


Figure 6. Calculated frontier molecular orbitals for enone **2A** (LUMO) and the enolate form of azlactone **1-Ph-a** (HOMO). Protons are omitted for clarity.

Initially, we speculated that the soft bimetallic catalyst would allow for a highly ordered transition state in which the azlactone should be activated by enolization promoted by N-coordination, whereas the enone should be simultaneously activated as an electrophile by face-selective coordination of the C=C double bond (Figure 7), similar to our previous investigations with vinylketones and α-cyanoacetates.[23] The expected *Re*-face selectivity (nomenclature based on the β-C atom of the enone) for coordination of (*E*)-configured olefins to minimize repulsive interactions between the enone substituent R^2 and the ferrocene core should lead to a *Si*-face outer-sphere attack at the enone.[20] However, this is not in agreement with the relative configuration of the products, because the epimeric product is almost exclusively formed.

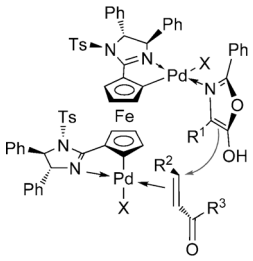


Figure 7. Initially assumed bimetallic activation mode.

At least three alternative scenarios could rationalize the reaction outcome. One of them involves coordination of the bidentate azlactone to both Pd centers of the same catalyst molecule thereby strongly activating the azlactone for enolization (Figure 8).[39]

NaOAc acts as a base and deprotonates the acidified α position to form enolate **11**, in which the *Si*-face is blocked by the ferrocene core, whereas the *Re*-face is accessible for attack by the enone, which itself might be activated by acetic acid.

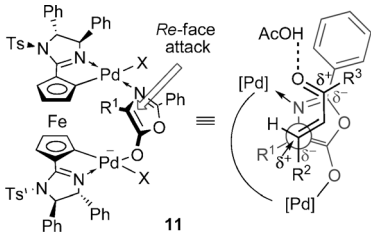
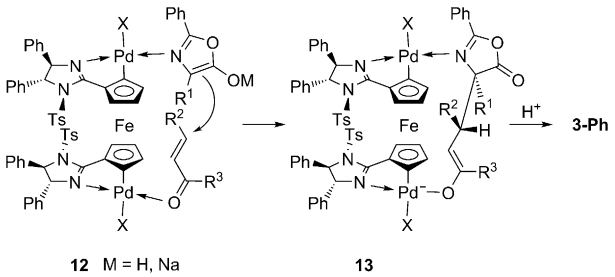


Figure 8. Possible bimetallic activation pathway of the azlactone substrate.

A second option involves simultaneous activation of both substrates, but in contrast to our initial mechanistic assumptions the carbonyl moiety might coordinate to one metal center (Scheme 2). In that case interaction of the substrates with the activating metal centers organizes both reactants in the "chiral space" explaining the high stereoselectivity and facilitates the HOMO/LUMO overlap of the reacting substrates in complex **12** by spatial proximity and cooperative dual electronic activation. Acetic acid might be crucial to accelerate the protonolysis of the incipient enolate **13**, which is formed, thus avoiding a retro-Michael addition or a β-hydride elimination. Moreover, it might also partly protonate or form a hydrogen bond with the catalyst counterion X^-, which would provide a more potent Lewis acid. NaOAc might be necessary to generate an enolate or to pick-up the enol proton upon or after the C–C bond formation.



Scheme 2. Possible dual activation mode and rationalization of the absolute and relative configuration of products **3-Ph**.

A third scenario proceeding through complex **14** might involve both the bidentate azlactone coordination plus the enone coordination of the carbonyl group (Figure 9).

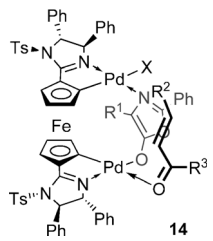
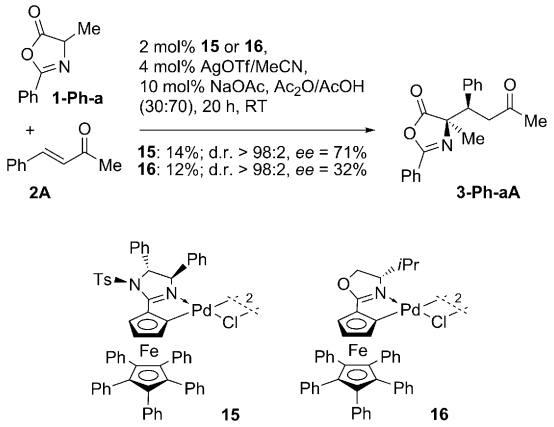


Figure 9. Possible bimetallic activation of both substrates through bidentate azlactone and monodentate enone coordination.

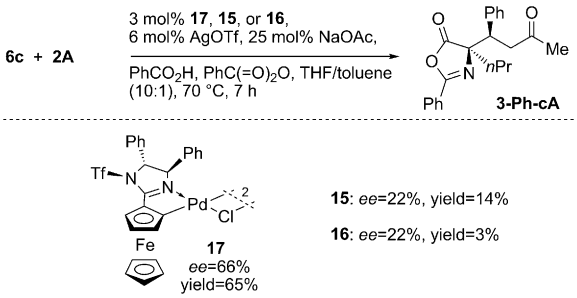
Bimetallic activation pathways are supported by control experiments with structurally related ferrocene imidazoline and oxazoline monopalladacycles (Scheme 3).[40] Although a conversion of azlactone **1a** of 78 and 42% was noticed in the addition to enone **2A** employing precatalysts **15**[40b–g] and



Scheme 3. Control experiments with the related ferrocene imidazoline and oxazoline monopalladacycles **15** and **16**.

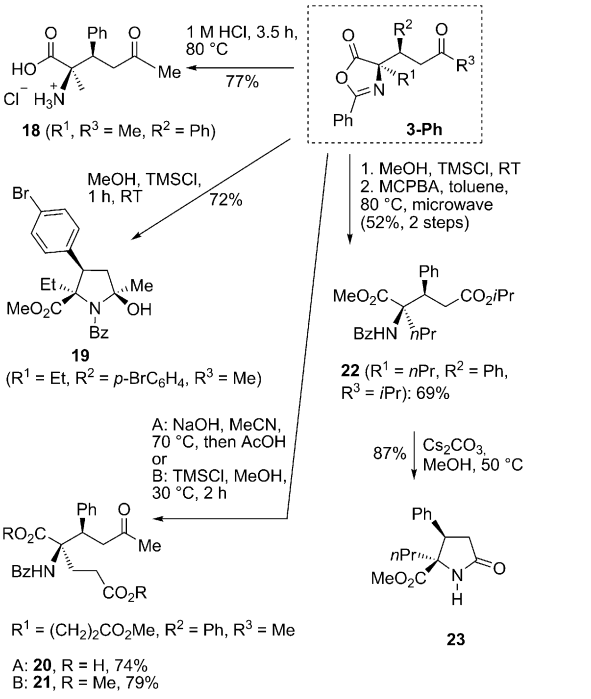
16,[40e–g] respectively, the yield of the conjugate addition product **3-Ph-aA** was very low.

Similar results were obtained starting from unprotected norvaline (**6c**, Scheme 4). In the model reaction with **2A** a moderate enantioselectivity was for instance attained with precatalyst **17**[40b,e] whereas the sterically more demanding pentaphenylferrocene derivatives **15** and **16** resulted in very poor yields and nearly racemic products. These data point to a cooperation of both metal centers in the 1,4-addition event by using FBIP, but cannot exclude one of the above-presented mechanistic scenarios.



Scheme 4. Investigation of structurally related ferrocene monopalladacycle catalysts in comparison to $[FBIP\text{-}Cl]_2$ (Table 8, entry 7, **3-Ph-Aa**: 90% *ee*, yield = 87%).

Synthetic access to quaternary amino acid derivatives: Due to the synthetic versatility of the functional groups present in the conjugate addition products **3**, they can be utilized for a rich and divergent follow-up chemistry to access unnatural quaternary amino acid derivatives. Owing to their anhydride-type structures, azlactones undergo facile nucleophilic ring-opening reactions.[3] Treatment of **3-Ph-aA**, for example, with 1 M HCl for 3.5 h at 80 °C thus provided the quaternary amino acid **18** as a hydrochloride salt in good yield and almost diastereomerically pure form (Scheme 5). Treatment of **3-Ph-bD** derived from ethylglycine with MeOH/TMSCl furnished the cyclic quaternary amino acid derivative **19** as a

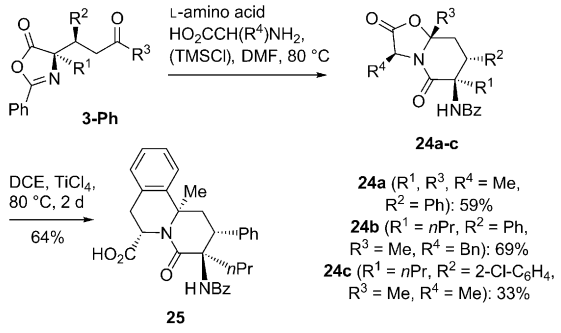


Scheme 5. Synthesis of the unnatural quaternary amino acid derivatives **18**–**23**. TMS = trimethylsilyl, MCPBA = *m*-chloroperbenzoic acid, Bz = benzoyl.

single diastereomer. In contrast, under very similar reaction conditions **3-Ph-gA** derived from glutamic acid provided the acyclic ketone **21**. The corresponding free glutamic acid **20** was obtained by ring-opening of **3-Ph-gA** with NaOH. Compounds **20** and **21** are thus accessible from racemic glutamic acid 5-methyl ester in just two steps in 54 and 58% overall yield, respectively. A complementary route to the above-highlighted class of quaternary α-alkyl-glutamic acid derivatives is provided by regioselective Baeyer–Villiger oxidation of an *i*Pr ketone moiety like in **3-Ph-cN** after nucleophilic ring-opening with MeOH/TMSCl providing the α-alkyl-glutamic acid derivative **22**. By means of asymmetric catalysis this type of 2,3-disubstituted glutamic acid derivatives was previously only accessible in single cases, by using the 1,4-addition of isolated azlactones to acylphosphonates mainly due to the C-2/C-4 regioselectivity issue. In addition, these products were only accessible with moderate enantiomeric excess (up to 55% *ee*).[13c] Compound **22** was also shown to serve as a direct precursor to the *N*-unprotected pyroglutamic acid derivative **23** with an adjacent quaternary and tertiary stereocenter by treatment with Cs_2CO_3 in MeOH.

Nucleophilic azlactone ring-opening with the unprotected α-amino acids L-alanine and L-phenylalanine provided the bicyclic diastereomerically pure dipeptides **24** (Scheme 6).[41] The overall protocol thus enables the formation of dipeptides in two steps starting from two unprotected amino acids.

The absolute configuration of the dipeptide **24c** was determined by X-ray crystal structure analysis (Figure 10, top left) confirming the stereochemical assignment for the Michael addition products.[42]



Scheme 6. Synthesis of the bicyclic dipeptides **24a–c** and the conformationally rigid phenylalanine dipeptidomimeticum **25**. DCE = 1,2-dichloroethane.

The relative configurations were also determined for **24a** (Figure 10, top, right) and **24b** (Figure 10, bottom, left). Because in all cases L-configured amino acids were used for the azlactone-opening (**3-Ph**→**24**), the relative configuration implicates the absolute configuration as well. Treatment of *ent*-**3-Ph-aA** with L-phenylalanine provided the diastereomeric dipeptide **26** also depicted in Figure 10 (bottom, right). In all cases, the δ-lactam ring adopts a (distorted) half-chair-like conformation. Moreover, the α-amino acid residue R^4 in the five-membered lactone and the substituent R^2 in the six-membered ring always adopt an equatorial position in the solid-state structure.

Dipeptide **24b** was applied to an intramolecular electrophilic aromatic substitution to give the conformationally rigid phenylalanine dipeptidomimeticum **25** (Scheme 6), whose structure was confirmed by X-ray analysis as displayed in Figure 11.[43] Compounds of this type have been recently reported to be of biological interest, but the synthetic access required multistep syntheses and gave the products in overall yields lower than 1%.[44] In comparison, compound **25** was formed in three steps from racemic norvaline in 38% overall yield.

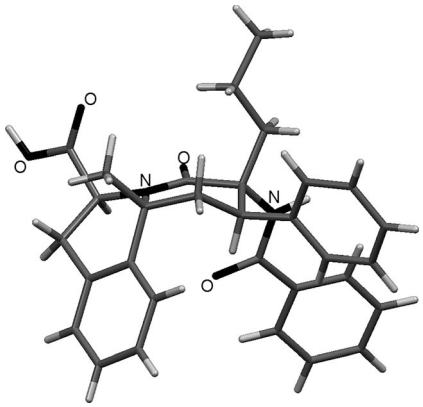


Figure 11. X-ray crystal structure analysis of the tricyclic dipeptidomimeticum **25**.

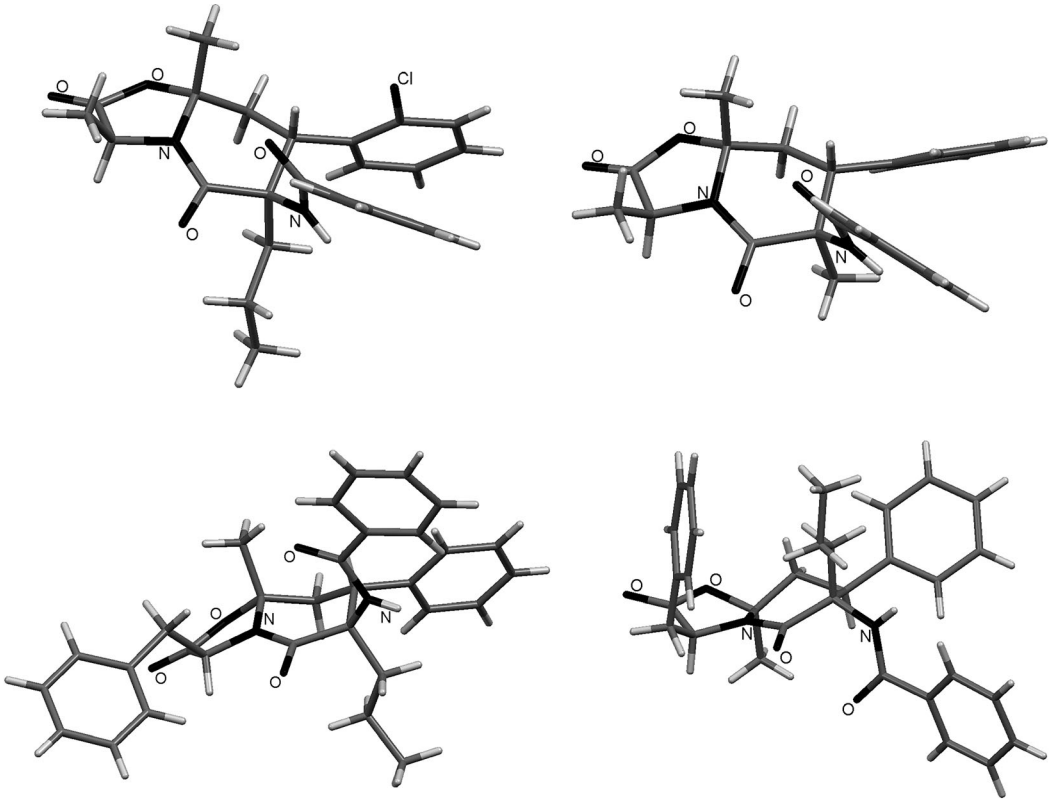


Figure 10. X-ray crystal structure analyses of the bicyclic dipeptides. Determination of the absolute configuration of **24c** (top, left) and the relative configuration of **24a** (top, right), **24b** (bottom, left), and **26** (bottom, right).

Conclusion

In conclusion, we have reported the first catalytic asymmetric conjugate additions of azlactones to enones. This task was accomplished by the cooperative activation by a bis-Pd catalyst, a Brønsted acid (acetic or benzoic acid), and a Brønsted base (NaOAc). Kinetic studies revealed that the azlactone is in a rapid equilibrium with the corresponding acyclic mixed anhydride by ring-opening with acetic acid. Due to the remarkable robustness of the bis-Pd catalyst towards acetic anhydride, this equilibrium could be explored to develop a tandem azlactone formation/Michael addition process starting from racemic *N*-benzoylated tertiary amino acids. The next evolution stage involved a tandem process, which is capable to directly transform unprotected racemic α-amino acids into the masked and activated highly enantioenriched quaternary amino acid products bearing an additional tertiary stereocenter. This sequence implies both an *N*- and *O*-amino acid acylation, a cyclization to form racemic azlactones, an enolization, and the asymmetric addition to the enone. The methodology offers a broad variability and provides rapid access to biologically interesting unnatural quaternary amino acid derivatives in a single step from inexpensive bulk chemicals. The synthetic utility of the conjugate addition products was showcased by the rapid and divergent formation of various quaternary amino acid derivatives like an acyclic unmasked α-amino acid, α-alkyl proline, and pyroglutamic acid derivatives. Moreover two complementary routes to biologically interesting α-alkyl glutamic acid derivatives have been developed and we have demonstrated that diastereomerically pure bicyclic dipeptides are accessible in just two steps from unprotected tertiary α-amino acids.

Experimental Section

Activation of the precatalyst [FBIP-Cl]$_2$: [FBIP-Cl]$_2$ (1 equiv) and the corresponding silver salt (4 equiv) were suspended/dissolved in acetonitrile (1 mL per 5 mg [FBIP-Cl]$_2$) and stirred for 6 h at room temperature. The reaction flask was covered with aluminum foil to shield it from light during that period. Subsequently, the mixture was filtered through celite and free acetonitrile was removed under reduced pressure (ca. 5 min at 15 mbar and room temperature). A stock solution was subsequently prepared.

General procedure for the catalytic asymmetric synthesis of α,α-disubstituted amino acid derivatives starting from isolated azlactones: Stock solutions of NaOAc (0.1 equiv, 270 μmol, 2.21 mg in 500 μL AcOH/Ac_2O (70:30)) and the activated catalyst [FBIP-Cl]$_2$ (0.02 equiv, 5.40 μmol, 13.1 mg in 310 μL AcOH/Ac_2O (70:30)) were added to the corresponding racemic azlactone **1-Ph** (1.0 equiv, 0.27 mmol), followed by the addition of the corresponding enone **2** (2.0 equiv, 0.54 mmol). The resulting mixture was warmed to 30 °C for 23 h. After cooling to room temperature, the crude product was directly used for silica gel chromatography.

General procedure for the catalytic asymmetric synthesis of α,α-disubstituted amino acid derivatives starting from *N*-benzoyl amino acids: The corresponding enone **2** (2 equiv, 0.54 mmol) was added to the corresponding racemic *N*-benzoyl amino acid **5-Ph** (1 equiv, 0.27 mmol) at 8 °C. Stock solutions of NaOAc (0.1 equiv, 27.0 μmol, 2.21 mg in 125 μL AcOH/Ac_2O (70:30)) and the activated catalyst [FBIP-Cl]$_2$ (0.02 equiv, 5.40 μmol, 13.1 mg in 200 μL HOAc/Ac_2O (70:30)) were successively added to this mixture The resulting slurry was heated to 30 °C. After 23 h the reaction mixture was cooled to room temperature and was directly used for silica gel column chromatography.

General procedure for the catalytic asymmetric synthesis of α,α-disubstituted amino acid derivatives by using unprotected amino acids: The corresponding racemic amino acid **6** (1.00 equiv, 0.20 mmol), the corresponding enone **2** (6.00 equiv, 1.20 mmol), NaOAc (0.25 equiv, 50.0 μmol, 4.10 mg), benzoic acid (35 equiv, 7.00 mmol, 855 mg), and benzoic anhydride (20 equiv, 4.00 mmol, 905 mg) were successively charged into a flask. The activated catalyst [FBIP-Cl]$_2$ was added to this mixture as a stock solution in THF/PhMe (0.03 equiv, 6.00 μmol, 14.6 mg in 440 μL THF/PhMe (10:1)). The resulting slurry was heated to 70 °C under vigorous stirring for 7 h. After this time, the mixture was cooled to room temperature. The solidified crude product was taken up in CH_2Cl_2 (≈20 mL) and was washed once with saturated aqueous $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. The targeted amino acid derivative was purified by silica gel column chromatography. To completely remove benzoic anhydride, the fractions containing the target product were concentrated and subjected to another silica gel column. Remaining benzoic acid was removed by washing the fractions containing the target product with saturated aqueous solution of $NaHCO_3$, and then Na_2SO_4 was used for drying.

General procedure for the recycling of the FBIP catalyst: The activated catalyst (2 mol%, 1 μmol, 2.43 mg) was added as stock solution in acetic acid/acetic anhydride (7:3, 150 μL) to *N*-benzoyl norvaline (**5-Ph-c**) (1.0 equiv, 50.0 μmol, 11.1 mg), *trans*-4-phenyl-but-3-en-2-one (**2A**) (2.0 equiv, 100 μmol, 14.6 mg), and sodium acetate (10 mol%, 5.0 μmol, 0.4 mg). The resulting mixture was warmed to 30 °C for the indicated time and then cooled to room temperature. After removal of the volatiles, *n*-hexane was added (15×5 mL) to extract the residue. The liquid was concentrated and the crude product was used for the determination of conversion and yield (^{1}H NMR spectroscopic analysis by using mesitylene (7.22 equiv, 0.36 mmol, 43.4 mg, 50 μL) as internal standard) and was purified by silica gel chromatography (petrol ether/ethyl acetate 7:3). The isolated product was used to determine the enantiomeric excess of **3-Ph-cA** by chiral HPLC (Chiracel AD-H, *n*-hexane/*i*PrOH (98:2), 0.7 mL min^{-1}, detection at 245 nm (14.0 min minor enantiomer, 20.2 min major enantiomer)). For the next catalytic run, the flask containing the catalyst was then directly charged with *N*-benzoyl norvaline (**5-Ph-c**) (1.0 equiv, 50.0 μmol, 11.1 mg) and *trans*-4-phenyl-but-3-en-2-one (**2A**) (2.0 equiv, 100 μmol, 14.6 mg). Acetic acid/acetic anhydride (7:3, 150 μL) was added to this mixture and the resulting solution was heated to 30 °C. All following manipulations were performed as described above.

Acknowledgements

This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG, PE 818/4-1).

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[27] CCDC-887979 (**3-Ph-dA**) and 887978 (**3-Ph-cM**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[31] The isolated compound **8** was also investigated as a catalyst. With 5 mol% of **8** at 70 °C, 15% of the C-4 addition product **3-Me-aA** (87% *ee*) and 8% of the C-2 addition product **6-Me-aA** were formed confirming the reduced catalyst activity by formation of **8**.

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[34] Conditions of Table 1, entry 7, 0.25 M in **1A**; yield/*ee* **3-Ph-Aa** (%): $CHCl_3$: 54/87; $ClCH_2CH_2Cl$: 63/94, THF: 68/87; glyme: 56/88; diglyme: 64/87; benzene: 53/87; toluene 53/88.

[35] Changing sodium acetate to benzoate resulted in almost no change.

[36] This points to the formation of a Pd–alkyl intermediate, which can undergo an undesired β-hydride elimination rather than a productive protonolysis. The latter is accelerating by addition of benzoic acid. A similar effect was observed by us in a previous study, in which a bimetallic activation mechanism by using an FBIP catalyst was strongly supported by detailed kinetic investigations (see Ref. [14]).

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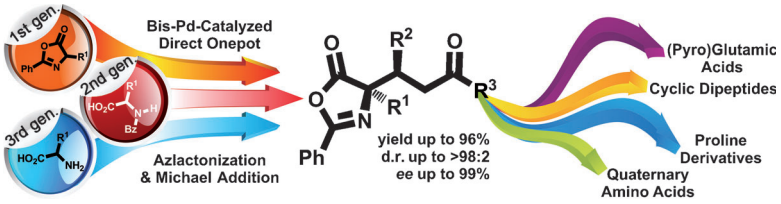
Received: July 10, 2012
Published online: ■■ ▮▮, 0000

Asymmetric Catalysis

*M. Weber, S. Jautze, W. Frey, R. Peters** ..... ▮▮▮▮–▮▮▮▮

Bispalladacycle-Catalyzed Michael Addition of In Situ Formed Azlactones to Enones



Flourishing step economy: The evolution of the catalytic asymmetric addition of azlactones to enones is described. The first-generation approach started from isolated azlactones. In the second-generation approach azlactones could be generated in situ from racemic *N*-benzoylated amino acids. The third evolution stage could directly use racemic unprotected α-amino acids to form a large number of highly enantioenriched quaternary amino acids derivatives (see figure).

