DOI: 10.1002/adsc.201200085

Catalytic Asymmetric Synthesis of Functionalized α,α-Disubstituted α-Amino Acid Derivatives from Racemic Unprotected α-Amino Acids *via in-situ* Generated Azlactones

Manuel Weber,[a] Wolfgang Frey,[a] and René Peters[a,*]

[a] Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany
Fax: (+49)-(0)711-685-54330; e-mail: rene.peters@oc.uni-stuttgart.de

Received: December 24, 2012; Revised: March 2, 2012; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200085.

Abstract: Masked and activated highly enantioenriched α,α-disubstituted α-amino acids with an additional adjacent stereocenter were formed by a tandem reaction involving five steps using racemic unprotected amino acid substrates. Key step is the 1,4-addition of *in-situ* generated azlactones to a broad number of enones. The products of this step-economic route can, e.g., be useful for a divergent and rapid access to biologically interesting unnatural glutamic acid derivatives.

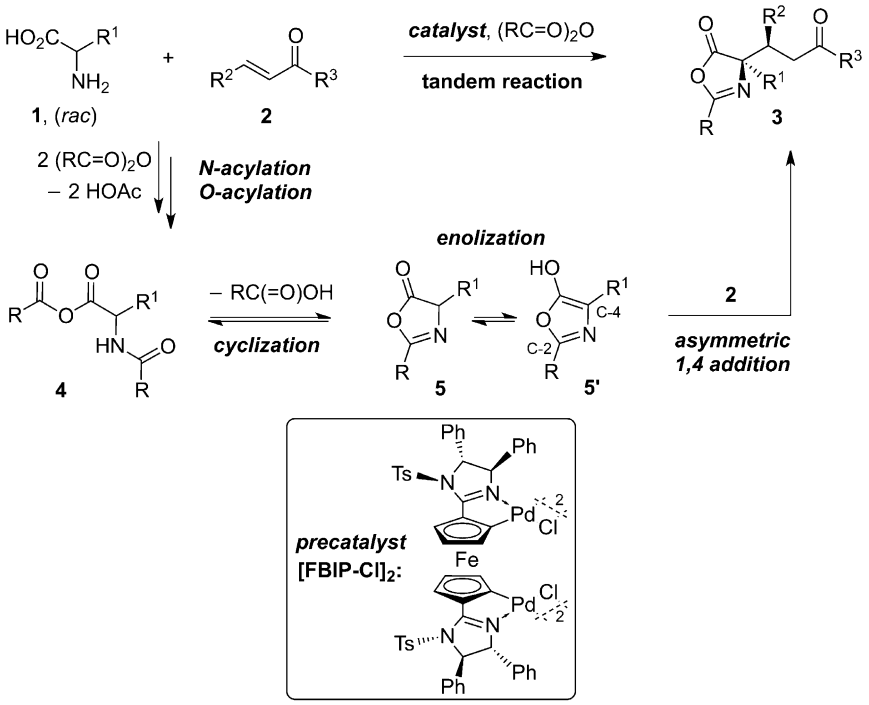
Keywords: azlactones; bimetallic catalysis; domino process; dynamic kinetic resolution; glutamic acid derivatives

Scalemic α,α-disubstituted α-amino acids are currently receiving large interest for a number of reasons.[1] A large part of the high motivation to intensively study α,α-disubstituted α-amino acids is based on their ability to restrict the conformational flexibility of peptides and to induce a unique peptide folding, while at the same time hydrophobicity and stability against peptide degradation are increased.[1,2]

Azlactones **5** [systematic name: oxazol-5-(4*H*)-ones] are masked and activated amino acid derivatives that have recently been employed for the catalytic asymmetric construction of α,α-disubstituted α-amino acids taking advantage of the pronounced tendency of the heterocycles to enolize ($pK_a = \pm 9$) due to the aromatic character of the enol tautomer **5′** (see Scheme 1).[3] The nucleophilic azlactone C-4 position could, e.g., be employed for catalytic asymmetric substitutions,[4] additions,[5,6] and rearrangements[7] to form tetrasubstituted stereocenters[8] with a high level of enantioselectivity. The use of azlactones **5**, which are usually accessible in 2–4 steps from amino acids, is particularly attractive for the diversity oriented synthesis of α,α-disubstituted α-amino acids owing to the presence of orthogonal nucleophilic and electrophilic reactive sites in the heterocyclic systems.[3]

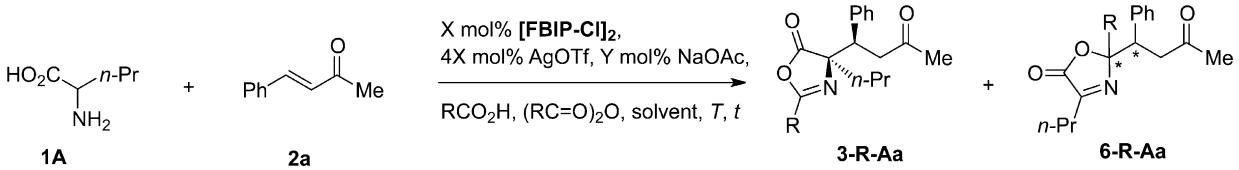
Recently, we have reported the first catalytic asymmetric 1,4-addition of azlactones to enones.[6e] In that study we observed that under the reported reaction conditions the azlactone formed an equilibrium with a mixed anhydride by azlactone ring opening/closing with the solvent acetic acid. Herein, we describe a one-pot procedure for the catalytic asymmetric construction of functionalized amino acid derivatives **3** from inexpensive *un*protected racemic α-amino acids **1** (Scheme 1). The tandem sequence[9] involves both an *N*- and *O*-amino acid acylation, a cyclization to form racemic azlactones **5**, an enolization to **5′** and the catalytic asymmetric addition to the Michael acceptor.[10] Product formation is catalyzed by the readily accessible planar chiral ferrocene bispalladacycle **[FBIP-Cl]$_2$** (4 steps from ferrocene) after activation with a silver salt.[11,12] This catalyst has recently emerged as a powerful π-acid to stereospecifically activate olefins[13] and to promote bimetallic reaction pathways by intramolecular cooperation of the two Pd centers.[6e,14,15]

Attempts to utilize the reaction conditions of our previous study (i.e., 2 mol% **[FBIP-Cl]$_2$**, 8 mol% AgOTf, 10 mol% NaOAc in AcOH/Ac_2O at room temperature) in the model reaction of racemic unprotected norvaline (**1A**) with enone **2a** gave the desired tandem reaction product with an excellent enantiomeric excess (*ee*) of 96% (Table 1, entry 1), yet in poor yield mainly due to a low conversion. Since **[FBIP-Cl]$_2$** itself shows almost no catalytic activity as a result of the relatively strongly coordinating chloride counterions,[13b] it was activated with AgOTf leading to a counterion exchange with precipitation of AgCl which is removed by filtration. The model reaction was then conducted at temperatures up to 70 °C, but the product was still formed in low yield, mainly because of the competing formation of the regioiso-



Scheme 1. One-pot tandem reaction sequence to form the masked and activated α,α-disubstituted α-amino acid derivatves **3** bearing an additional stereocenter in the β-position.

Table 1. Elaboration of the reaction conditions with norvaline (**1A**) and enone **2a**.[a]



#	R	X	Y	Solvent	*T* [°C]	*t* [h]	**3-R-Aa/6-R-Aa**	Yield [%][b] **6-R-Aa**	Yield [%][b] **3-R-Aa**	*dr* **3-R-Aa**[b]	*ee* [%][c] **3-R-Aa**
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.	<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 of the crude product using mesitylene as internal standard (n.d.: not determined).
[c] Determined by HPLC.
[d] A mixture of formic acid and acetic anhydride was used.
[e] No benzoic acid was added.

meric C-2 addition product **6-Me-Aa** (entries 2 and 3) which is generated as a diastereomeric mixture, whereas the targeted regioisomer **3-Me-Aa** is nearly diastereomerically pure.

A kinetic investigation at 70 °C by ^{1}H NMR then revealed that *N*-acetylnorvaline and azlactone **5-Me-A** are rapidly formed in comparable amounts, which gradually decrease due to the formation of both Mi-

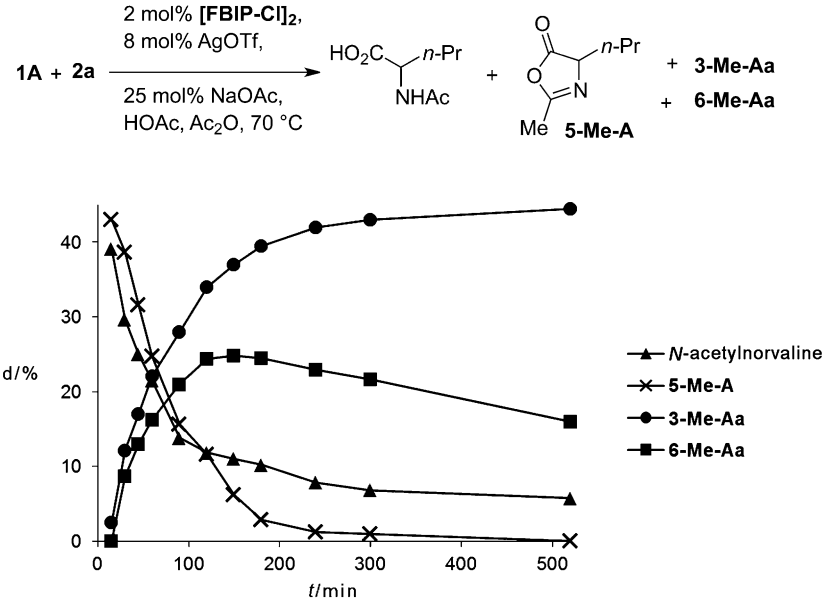


Figure 1. Kinetic control of the model reaction (Table 1, entry 3).

chael addition regiosiomers. The latter are initially formed with similar rates (Figure 1), but the ratio **3-Me-Aa**/**6-Me-Aa** steadily increases due to decomposition of **6-Me-Aa**.

Attempts to isolate the catalyst after the reaction led to the identification of a second side product obviously inhibiting the catalyst by the formation of the C_2-symmetrical complex **7** which was identified by an X-ray crystal structure analysis (Figure 2).[16] Complex **7** 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 tetrasubstituted carbon at C-2 and two additional stereocenters at C-3 and C-4, chelates each Pd-center of the bimetallic catalyst. The 3,4-dihydropyrrole might either be formed *via* a 1,3-dipolar cycloaddition pathway,[17] or alternatively by the undesired Michael addition at C-2 of the azlactone followed by an intramolecular Mannich addition, initially generating the bicyclic proline intermediate **8** (Scheme 2). The latter could subsequently undergo a ring opening of the *N*,*O*-acetal moiety giving **7**.

The fact that both Pd centers of the **FBIP** system bind almost exclusively to a dehydroproline molecule demonstrates that the corresponding binding constants are arguably much higher than those of the targeted product **3-Me-Aa**, most likely due to the presence of the carboxylate moiety as anionic donor, whereas **3-Me-Aa** contains only neutral donors. The anionic donor in **7** (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,[18] in agreement with our previous findings for ferrocene imidazoline palladacycles.[13b,19] If the formation of **3-Me-Aa** follows a bimetallic reaction pathway, the coordination of one dehydroproline would already be deleterious for the catalyst activity.

Various combinations of carboxylic acids and anhydrides $(RC{=}O)_2O$ were then surveyed in order to decrease the nucleophilicity of C-2, thus minimizing the

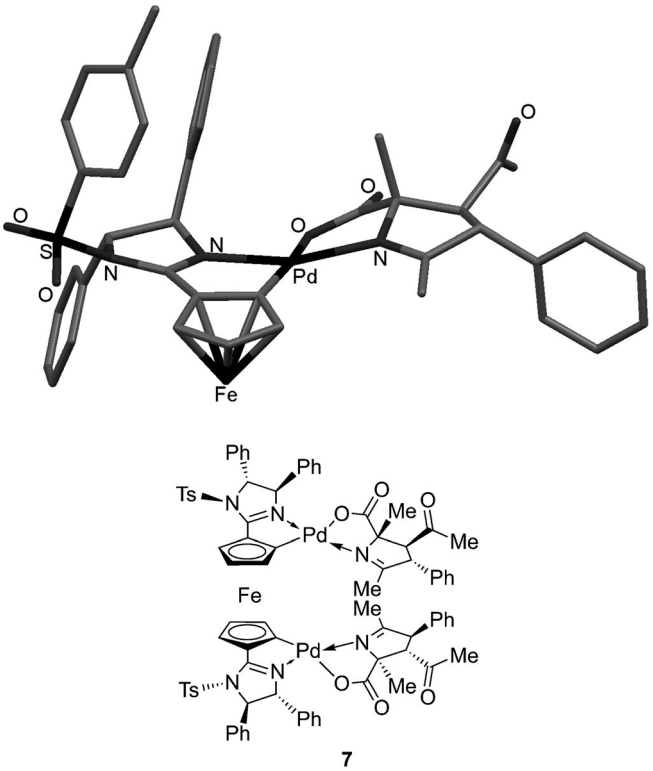
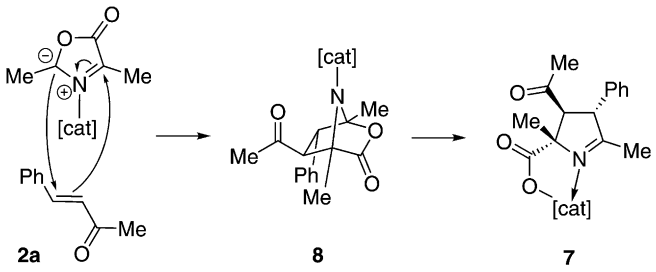


Figure 2. X-ray crystal structure analysis of the C_2-symmetric complex **7**, which is formed during the catalysis event in $AcOH/Ac_2O$. H atoms are omitted and only one half of the C_2-symmetrical **7** is shown for clarity.

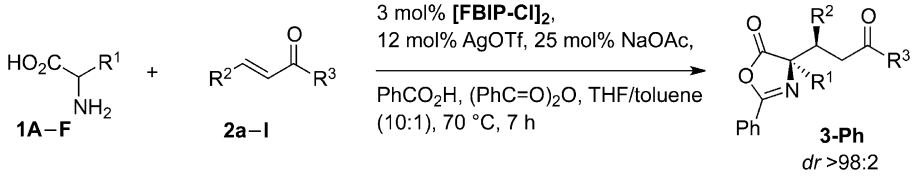


Scheme 2. Mechanistic proposal for the formation of the inhibited catalyst **7**.

formation of the undesired regioisomer **6** and the 1,3-dipolar cycloaddition product blocking the catalyst.[20] More bulky alkyl groups R resulted, in general, in a lower reactivity (Table 1, entries 4–6), but unfortunately not only at C-2. For R = H (formic acid, entry 7), no product was formed as a consequence of catalyst decomposition (formation of Pd black). In contrast, R = Ph (benzoic acid/anhydride) sheparded the reactivity to the C-4-position and the undesired Michael addition regioisomer was not detected anymore.[21] The targeted product **3-Ph-Aa** was formed in considerably better yield despite a heterogeneous reaction mixture in that case (entry 8). Addition of various co-solvents gave homogeneous mixtures and thus allowed for a better reproducibility, while there was almost no impact on the stereoselectivity.[22] The best data were obtained with a mixture of THF/toluene (10:1, entry 10).[23] The presence of benzoic acid is essential for high enantioselectivity as the experiments in 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.[24]

With the optimized reaction conditions from the initial screening, which was performed in a parallel synthesizer, preparative experiments were conducted for various enones and unprotected racemic amino acids (ethylglycine, norvaline, norleucine, leucine, phenylalanine, glutamic acid 5-methyl ester) using a conventional reaction set-up (Table 2). As a general trend the amino acid reactivity towards reaction with the same enone increased with decreasing steric bulk of the amino acid side chain R^1 (compare entries 1, 3,

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



#	3-Ph	R^1	R^2	R^3	Yield[b] [%]	*ee* [%][c]
1	**3-Ph-Ba**	Et	Ph	Me	90	78
2	**3-Ph-Bb**	Et	4-Br-C_6H_4	Me	90	71
3	**3-Ph-Aa**	*n*-Pr	Ph	Me	87	90
4	**3-Ph-Ac**	*n*-Pr	4-MeO-C_6H_4	Me	75	82
5	**3-Ph-Ad**	*n*-Pr	4-Cl-C_6H_4	Me	73	84
6	**3-Ph-Ae**	*n*-Pr	2-Cl-C_6H_4	Me	76	85
7	**3-Ph-Af**	*n*-Pr	4-O_2N-C_6H_4	Me	58	80
8	**3-Ph-Ag**	*n*-Pr	2-furyl	Me	76	82
9	**3-Ph-Ah**	*n*-Pr	*i*-Pr	Me	62	81
10	**3-Ph-Ai**	*n*-Pr	Ph	*i*Pr	49	91
11[d]	**3-Ph-Aj**	*n*-Pr	Ph	Ph	41	78
12	**3-Ph-Ca**	*n*-Bu	Ph	Me	72	96
13	**3-Ph-Cb**	*n*-Bu	4-Br-C_6H_4	Me	71	88
14	**3-Ph-Cd**	*n*-Bu	4-Cl-C_6H_4	Me	72	87
15	**3-Ph-Ce**	*n*-Bu	2-Cl-C_6H_4	Me	72	90
16	**3-Ph-Ck**	*n*-Bu	*n*-Pr	Me	77	90
17[e]	**3-Ph-Da**	*i*-Bu	Ph	Me	52	73
18[d]	**3-Ph-Ea**	Bn	Ph	Me	66	74
19	**3-Ph-Fa**	$(CH_2)_2CO_2Me$	Ph	Me	73	87
20	**3-Ph-Fl**	$(CH_2)_2CO_2Me$	3,4-$(MeO)_2C_6H_3$	Me	65	75

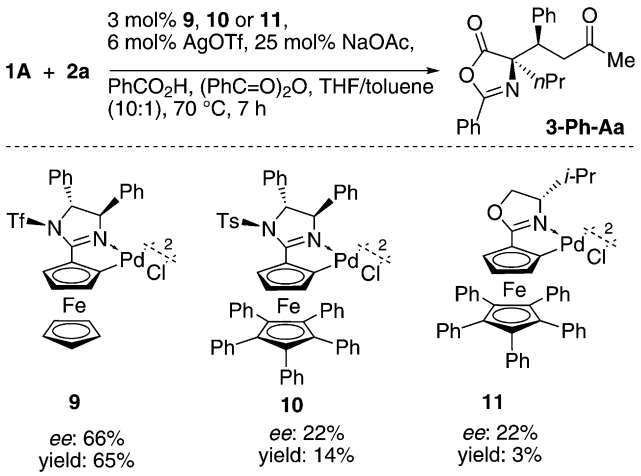
[a] Reactions were performed in Schlenk tubes heated by an oil bath.
[b] Yield of isolated product.
[c] Determined by HPLC.
[d] 10 mol% **[FBIP-Cl]$_2$**, 40 mol% AgOTf and 62.5 mol% NaOAc were used.
[e] 7.5 mol% **[FBIP-Cl]$_2$**, 30 mol% AgOTf and 62.5 mol% NaOAc were used.

12, 17–19) 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, five-step procedure (average yield per step in entry 1: 98%), whereas the β-branched isobutyl residue R^1 [leucine (**1D**), entry 17] or a benzyl group [phenylalanine (**1E**), entry 18] led to product formation in moderate yields (52% and 66%, respectively; average yield per step 88% and 92%).

The reported methodology is also useful 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.[25] 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.[26] An operationally simple and rapid catalytic asymmetric access might contribute to accelerate the progress in this field. Entries 19 and 20 in Table 2 demonstrate that α-alkylglutamic acid derivatives are accesible in diastereomerically pure form from racemic glutamic acid 5-methyl ester (**1F**) in good yields and with good to high enantioselectivity.

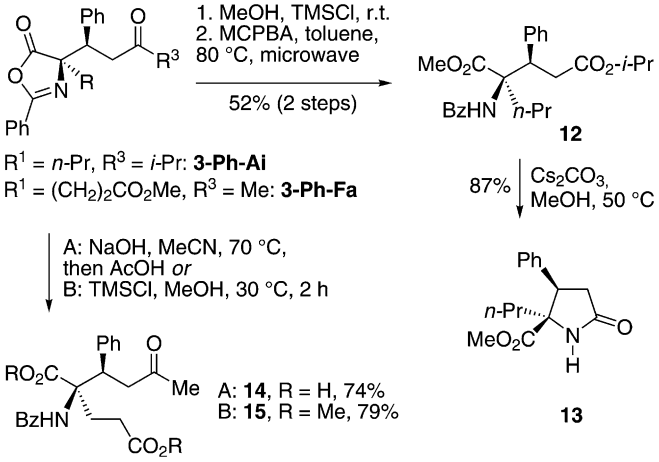
Moreover, a broad variety of enones with R^2/R^3 = (het)aryl/alkyl (entries 1–8, 10, 12–15, 17–20), alkyl/alkyl (entries 9 and 16) or aryl/aryl (entry 11) is accomodated under the reaction conditions, albeit reactivity and diastereoselectivity are lower in the latter case. Remarkably, for alkyl/alkyl combinations, an *i*-Pr moiety as R^2 is also well tolerated (entry 9) despite the presence of three vicinal branched sp^3-C atoms in **3-Ph-Ah**. Investigation of various functional groups on aryl moieties R^2 confirmed that electronic and steric effects play only a minor role with regard to the enone. Substrates equipped with a strong π-donor substituent such as *p*-OMe (entries 4 and 20), π-acceptor substituents such as *p*-NO_2 (entry 7), σ-acceptor substituents such as *o*-Cl (entries 6 and 15) or *p*-Cl (entries 5 and 14) or substrates bearing electron-rich heterocycles like 2-furyl (entry 8) gave useful results in terms of yield and enantioselectivity. Aryl bromides can be used in the presence of the Pd catalyst (entries 2 and 13), since **FBIP** is relatively inert against formation of Pd(0) by catalyst decomposition under the acidic reaction conditions.

Structurally related ferrocene monopalladacycles performed significantly less enantioselective than **FBIP** (Scheme 3). Moderate enantioselectivity was, for instance, attained in the model reaction of **1A** and **2a** with precatalyst **9**[19b,c] whereas the sterically more demanding pentaphenylferrocene derivatives **10**[19b,c,27] and **11**[19c] resulted in low yields and nearly racemic product. These data might point to a cooperation of both metal centers in the 1,4-addition event using **FBIP**.



Scheme 3. Investigation of structurally related ferrocene mono-palladacycle catalysts for comparison to **[FBIP-Cl]$_2$** (Table 2, entry 3, *ee* **3-Ph-Aa**: 90%, yield **3-Ph-Aa**: 87%).

Due to the synthetic versatility of the functional groups present in the tandem reaction products **3**, a rich follow-up chemistry can be envisaged. This is showcased by two complementary routes to the above mentioned class of α-alkylglutamic acid derivatives (Scheme 4). Nucleophilic ring opening of **3-Ph-Fa** with NaOH gave access to the α-alkyl *N*-benzoylglutamic acid **14**, whereas MeOH/TMSCl provided the corresponding dimethyl ester **15**. Compounds **14** and **15** are thus accessible from racemic glutamic acid 5-methyl ester in just two steps in 54% and 58% overall yields, respectively. Alternatively, regioselective Baeyer–Villiger oxidation of the *i*-Pr-ketone moiety in **3-Ph-Ai** after nucleophilic ring opening with MeOH/TMSCl provided the α-alkylglutamic acid derivative **12**. By means of asymmetric catalysis 2,3-di-



Scheme 4. Synthesis of unnatural α-alkyl (pyro)glutamic acid derivatives **12**–**15**.

substituted glutamic acid derivatives were previously only accessible in single cases, using the 1,4-addition of isolated azlactones to acylphosphonates due to the C-2/C-4 regioselectivity issue. In addition, these products were only accessible with moderate enantiomeric excess (up to 55% *ee*).[6c]

Compound **12** was also shown to serve as a direct precursor to the *N*-unprotected pyroglutamic acid derivative **13** with adjacent tetra- and trisubstituted stereocenters. Treatment of **12** with Cs_2CO_3 in MeOH provided the scalemic heterocycle in high yield.

In conclusion, we have developed a tandem process that is able to directly transform unprotected racemic amino acids by a single operation into masked and activated scalemic α,α-disubstituted α-amino acids. The tandem sequence involves an *N*- and *O*-amino acid acylation, a cyclization to form racemic azlactones, an enolization and the asymmetric addition to the enone. Key for a high efficiency is the choice of the carboxylic anhydride required for the *in-situ* formation of the azlactone. With aliphatic anhydrides like Ac_2O the formation of larger quantities of an undesired regioisomeric Michael addition side product was observed, whereas with benzoic anhydride addition of the azlactone C-4 atom is almost exclusively favored. It was also found that the bis-Pd-catalyst is inhibited by a strongly binding dehydroproline side product which is generated *via* a (formal) 1,3-dipolar cycloaddition, also caused by the nucleophilic character of the azlactone C-2 atom when acetic anhydride was used. This dehydroproline side product is less prominent with benzoic anhydride due to a lower reactivity of C-2. The methodology allows for a broad variability and thus provides rapid access to biologically interesting unnatural α,α-disubstituted α-amino acid derivatives in a single step from inexpensive bulk chemicals. In particular, the possibility to divergently and rapidly synthesize unnatural glutamic acid derivatives should be of biological interest.

Experimental Section

General Procedure for the Activation of the Pre-Catalyst [FBIP-Cl]$_2$

[FBIP-Cl]$_2$ (1 equiv., 8.22 μmol, 20 mg) and silver triflate (4 equiv., 32.9 μmol, 8.45 mg) were suspended/dissolved in acetonitrile (4 mL) and stirred for 6 h at room temperature. The reaction flask was covered with aluminum foil to shield it from light during that period. After activation was complete the mixture was filtered through celite and free acetonitrile was removed under reduced pressure (*ca.* 5 min at 15 mbar and room temperature).

General Procedure for the Catalytic Asymmetric Synthesis of α,α-Disubstituted Amino Acid Derivatives

The corresponding racemic amino acid (**1**, 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. To this mixture was added the activated catalyst (see above) as a stem solution in THF/PhMe (0.03 equiv., 6.00 μmol, prepared from 14.6 mg **[FBIP-Cl]$_2$** 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 dichloromethane (*ca.* 20 mL) and was washed once with saturated aqueous $NaHCO_3$. The organic layer was separated, then 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 $NaHCO_3$ solution, then Na_2SO_4 was used for drying.

Acknowledgements

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

References

[1] a) J. Venkatraman, S. C. Shankaramma, P. Balaram, *Chem. Rev.* **2001**, *101*, 3131; b) H. Vogt, S. Bräse, *Org. Biomol. Chem.* **2007**, *5*, 406; c) C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry* **2007**, *18*, 569.

[2] a) M. Tanaka, *Chem. Pharm. Bull.* **2007**, *55*, 349; b) A. Giannis, T. Kolter, *Angew. Chem.* **1993**, *105*, 1303; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244; c) M. C. Khosla, K. Stachowiak, R. R. Smeby, F. M. Bumpus, F. Piriou, K. Lintner, S. Fermandjian, *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 757.

[3] Reviews: a) R. A. Mosey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008**, *19*, 2755; b) Z. Rodriguez-Docampo, S. J. Connon, *ChemCatChem* **2012**, *4*, 151; c) A.-N. R. Alba, R. Rios, *Chem. Asian J.* **2011**, *6*, 720.

[4] Selected examples: a) B. M. Trost, X. Ariza, *J. Am. Chem. Soc.* **1999**, *121*, 10727; b) D. Uraguchi, Y. Asai, T. Ooi, *Angew. Chem.* **2009**, *121*, 747; *Angew. Chem. Int. Ed.* **2009**, *48*, 733.

[5] Selected examples: a) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 14088; b) M Terada, H. Tanaka, K. Sorimachi, *J. Am. Chem. Soc.* **2009**, *131*, 3430; c) T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286.

[6] Selected 1,4 additions a) S. Cabrera, E. Reyes, J. Alemán, A. Milelli, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, *130*, 12031; b) Y. Hayashi, K. Obi, Y. Ohta, D. Okamura, H. Ishikawa, *Chem. Asian J.* **2009**, *4*, 246; c) H. Jiang, M. W. Paixão, D. Monge, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, *132*, 2775; d) D. Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, *326*, 120; e) M. Weber, S. Jautze, W. Frey, R. Peters, *J. Am. Chem. Soc.* **2010**, *132*, 12222; f) T. Tsubogo, Y. Kano, K. Ikemoto, Y. Yamashita, S. Kobayashi, *Tetrahedron: Asymmetry* **2010**, *21*, 1221.

[7] Selected examples: a) J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 11532; b) S. A. Shaw, P. Alemán, J. Christy, J. W. Kampf, P. Va, E. Vedejs, *J. Am. Chem. Soc.* **2006**, *128*, 925; c) H. V. Nguyen, D. C. D. Butler, C. J. Richards, *Org. Lett.* **2006**, *8*, 769; d) C. Joannesse, C. P. Johnston, C. Concellón, C. Simal, D. Philp, A. D. Smith, *Angew. Chem.* **2009**, *121*, 9076; *Angew. Chem. Int. Ed.* **2009**, *48*, 8914; e) C. Kanta De, N. Mittal, D. Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 16802.

[8] Recent review about the asymmetric synthesis of tetrasubstituted C-atoms: *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, Germany, **2005**.

[9] Reviews on catalytic asymmetric domino reactions: a) D. Enders, C. Grondal, M. R. M. Huettl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; b) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1.

[10] Selected recent reviews about asymmetric conjugate additions: a) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279; b) A. Alexakis, J.-E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796; c) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824; d) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058; e) S. Jautze, R. Peters, *Synthesis* **2010**, 365.

[11] Preparation: S. Jautze, S. Diethelm, W. Frey, R. Peters, *Organometallics* **2009**, *28*, 2001.

[12] Recent reviews about palladacycles: a) J.-P. Djukic, A. Hijazi, H. D. Flack, G. Bernardinelli, *Chem. Soc. Rev.* **2008**, *37*, 406; b) J. Dupont, M. Pfeffer, *Palladacycles*, Wiley-VCH, Weinheim, Germany, **2008**.

[13] a) S. Jautze, P. Seiler, R. Peters, *Angew. Chem.* **2007**, *119*, 1282; *Angew. Chem. Int. Ed.* **2007**, *46*, 1260; b) S. Jautze, P. Seiler, R. Peters, *Chem. Eur. J.* **2008**, *14*, 1430.

[14] S. Jautze, R. Peters, *Angew. Chem.* **2008**, *120*, 9424; *Angew. Chem. Int. Ed.* **2008**, *47*, 9284.

[15] Review about the application of imidazolines in asymmetric catalysis: a) H. Liu, D.-M. Du, *Adv. Synth. Catal.* **2009**, *351*, 489; selected recent applications of bisimidazoline ligands: b) H. Huang, R. Peters, *Angew. Chem.* **2009**, *121*, 612; *Angew. Chem. Int. Ed.* **2009**, *48*, 604; c) H. Liu, D.-M. Du, *Adv. Synth. Catal.* **2010**, *352*, 1113; d) M. Ohara, S. Nakamura, N. Shibata, *Adv. Synth. Catal.* **2011**, *353*, 3285; e) K. Hyodo, S. Nakamura, K. Tsuji, T. Ogawa, Y. Funahashi, N. Shibata, *Adv. Synth. Catal.* **2011**, *353*, 3385.

[16] CCDC 864567 contains the supplementary crystallographic data for **7**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[17] a) A. D. Melhado, G. W. Amarante, Z. J. Wang, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 3517; b) M. Martín-Rodríguez, C. Nájera, J. M. Sansano, *Synlett* **2012**, 62.

[18] a) R. Hartley, *Chem. Soc. Rev.* **1973**, *2*, 163; b) F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, 5th edn., John Wiley, New York, **1988**, pp 1299–1300.

[19] a) R. Peters, Z.-q. Xin, D. F. Fischer, W. B. Schweizer, *Organometallics* **2006**, *25*, 2917; b) M. E. Weiss, D. F. Fischer, Z.-q. Xin, S. Jautze, W. B. Schweizer, R. Peters, *Angew. Chem.* **2006**, *118*, 5823; *Angew. Chem. Int. Ed.* **2006**, *45*, 5694; c) D. F. Fischer, A. Barakat, Z.-q. Xin, M. E. Weiss, R. Peters, *Chem. Eur. J.* **2009**, *15*, 8722.

[20] Kinetic control of each combination is shown in the Supporting Information.

[21] Nevertheless, a catalyst species binding to the formal 1,3-diploar cycloaddition product was also detected by ^{1}H NMR and ESI-MS, but could not be isolated.

[22] 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.

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

[24] 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 accelerated by addition of benzoic acid. A similar effect was observed by us in a previous study, in which a bimetallic activation mechanism using an FBIP catalyst was strongly supported by detailed kinetic investigations (see ref.[14]).

[25] a) S. Nakanishi, *Science* **1992**, *258*, 597; b) H. S. Parthasarathy (Ed.), *Nature* **1999**, *399*, A1–A47; c) A. D. Blasi, P. J. Conn, J. P. Pin, F. Nicoletti, *Trends Pharmacol. Sci.* **2001**, *22*, 114.

[26] Selected examples: a) C. G. Wermuth, A. Mann, A. Schoenfelder, R. A. Wright, B. G. Johnson, J. P. Burnett, N. G. Mayne, D. D. Schoepp, *J. Med. Chem.* **1996**, *39*, 814; b) J. A. Monn, M. J. Valli, S. M. Masset, R. A. Wright, C. R. Salhoff, B. G. Johnson, T. Howe, C. A. Alt, G. A. Rhodes, R. L. Robey, K. R. Griffey, J. P. Tizzano, M. J. Kallman, D. R. Helton, D. D. Schoepp, *J. Med. Chem.* **1997**, *40*, 528; c) F. C. Acher, F. J. Tellier, R. Azerad, I. N. Brabet, L. Fagni, J.-P. R. Pin, *J. Med. Chem.* **1997**, *40*, 3119; d) A. P. Kozikowski, D. Steensma, G. L. Araldi, S. Pshenichikin, S. Surina, J. T. Wroblewski, *J. Med. Chem.* **1998**, *41*, 1641.

[27] a) D. F. Fischer, Z.-q. Xin, R. Peters, *Angew. Chem.* **2007**, *119*, 7848; *Angew. Chem. Int. Ed.* **2007**, *46*, 7704; b) Z.-q. Xin, D. F. Fischer, R. Peters, *Synlett* **2008**, 1495; c) R. Peters, Z.-q. Xin, F. Maier, *Chem. Asian J.* **2010**, *5*, 1770; d) S. H. Eitel, M. Bauer, D. Schweinfurth, N. Deibel, B. Sarkar, H. Kelm, H.-J. Krüger, W. Frey, R. Peters, *J. Am. Chem. Soc.* **2012**, *134*, 4683.