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Catalytic Asymmetric Synthesis of Spirocyclic Azlactones by a Double Michael-Addition Approach

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Abstract: Spirocyclic azlactones are shown to be useful precursors of cyclic quaternary amino acids, such as the constrained cyclohexane analogues of phenylalanine. These compounds are of interest as building blocks for the synthesis of artificial peptide analogues with controlled folds in the peptide backbone. They were prepared in the present study by a step- and atom-economic catalytic asymmetric tandem approach, requiring two steps starting from *N*-benzoyl glycine and divinylketones. The key of this protocol is the enantioselective formation of the azlactone spirocycles, which involves a Pd^{II}-catalyzed double 1,4-addition of an in situ generated azlactone intermediate to the dienone (a formal [5+1] cycloaddition). As the catalyst, a planar chiral ferrocene bispalladacycle was used. Mechanistic studies suggest a monometallic reaction pathway. Although the diastereoselectivity was found to be moderate, the enantioselectivity is usually high for the formation of the azlactone spirocycles, which contain up to three contiguous stereocenters. Spectroscopic studies have shown that the spirocycles often prefer a twist over a chair conformation of the cyclohexanone moiety.

Keywords: asymmetric catalysis · [5+1] cycloaddition · domino reactions · palladacycle · spiro compounds · twist conformation

Introduction

Spirocycles represent a frequently found structural motif in natural products and pharmacologically interesting compounds. Their stereoselective access has therefore been intensively investigated by exploring a variety of different strategies.[1] In 2010 we reported the first example to obtain a chiral highly enantioenriched spirocycle by a catalytic asymmetric double 1,4-addition of a cyclic methylene-containing pronucleophile (in our case a glycine-derived azlactone) to a divinylketone.[2] After our initial report, a number of complementary catalytic asymmetric double 1,4-additions providing enantioselective access to various cyclohexanone systems have been reported.[3,4] Although these catalytic asymmetric methodologies have only very recently been available, nonenantioselective versions for these stepwise formal [5+1] cycloadditions have been known for a long time, the first example apparently dating back to 1924 for the formation of functionalized cyclohexanones (although in that case, lacking a spirocyclic motif).[5,6]

In this paper, we give a detailed account on the development of the catalytic asymmetric tandem reaction[7] to prepare highly enantioenriched azlactone/cyclohexanone spirocycles (3-oxa-1-azaspiro[4.5]dec-1-ene-4,8-diones), which proceeds through a double Michael addition of an achiral glycine-derived azlactone to symmetric and unsymmetric divinylketones. In this approach, which generates up to three contiguous stereocenters (one of which is quaternary),[8] the azlactone pronucleophile can be formed in situ from *N*-benzoyl glycine. Furthermore, we demonstrate the synthetic utility of the reaction products for the formation of cyclic quaternary amino acids.

Azlactones have found frequent applications as substrates in asymmetric catalysis[9,10] for a diversity-oriented entrance to α,α-disubstituted α-amino acid derivatives, owing to the presence of orthogonal nucleophilic and electrophilic reactive sites in the heterocyclic systems.[9] Catalytic asymmetric 1,4-additions[11] of azlactones to various classes of Michael acceptors, which proceed with high levels of enantioselectivity, have recently been reported.[12] We have recently described the first catalytic asymmetric conjugate additions of azlactones to enones.[13] In this context we have also reported the first catalytic asymmetric examples, in which the azlactone substrates have been formed in situ from racemic acylated or unprotected amino acids.[13]

Results and Discussion

Catalytic investigations: As part of our program to study cooperative effects in asymmetric catalysis,[14] we have investigated a planar chiral ferrocene bisimidazoline bispalladacycle (FBIP, prepared in four steps from ferrocene), which has recently been developed and studied in our research group for various bimetal-catalyzed applications.[15–18] For catalytic

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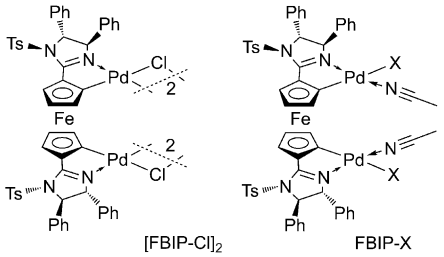
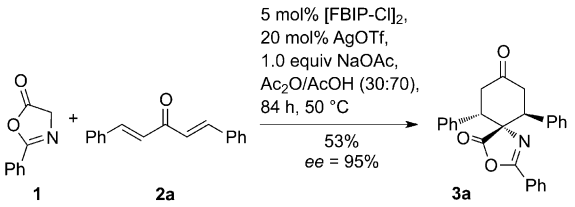


Figure 1. The dimeric precatalyst [FBIP−Cl]$_2$ and the monomeric activated catalyst species FBIP−X generated by treatment of the precatalyst with AgX/MeCN.

activity the dimeric precatalyst [FBIP−Cl]$_2$ (Figure 1) usually has to be activated by replacing the bridging chloride ligands. This is achieved by utilizing acetonitrile complexes of silver salts AgX to generate monomeric catalyst species FBIP−X (X^- = anionic ligand).[15b,d]

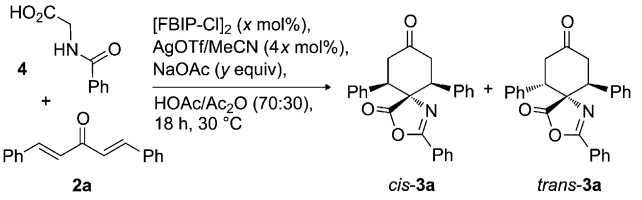
To establish a proof of principle for the formation of spirocyclic azlactones through a formal [5+1] cycloaddition, we initially treated the isolated glycine-derived azlactone **1** with dibenzylidene acetone (**2a**, dba). By using conditions similar to those used in the 1,4-addition reactions with simple enones (AcOH/Ac$_2$O (70:30) as the solvent mixture, NaOAc as a base), product **3a** was formed in a promising yield and with excellent enantioselectivity (Scheme 1).



Scheme 1. Tandem double Michael addition to form the spirocyclic product **3a**.

To increase the step economy and operational simplicity, we were then interested to form the azlactone substrate **1** in situ by starting from N-benzoylated glycine **4** (Table 1). The conditions developed for N-benzoylated tertiary amino acids[2] (i.e., 2 mol% [FBIP−Cl]$_2$, 8 mol% AgOTf/MeCN, 10 mol% NaOAc) gave the chiral *trans* diastereomer with a good enantiomeric excess (*ee*) of 83%, yet in a moderate yield of only 36% (Table 1, entry 1). In the absence of NaOAc, *trans*-**3a** was formed with a comparable yield, but the enantioselectivity was somewhat reduced (Table 1, entry 2). By using stoichiometric or excess amounts of NaOAc the undesired achiral *cis*-**3a** product was also formed in significant amounts (Table 1, entries 4–6), but on the other hand, both the yield and enantiomeric excess of *trans*-**3a** also increased with higher NaOAc loadings. In general, relatively high concentrations have been required for sufficiently fast product formation. Higher precatalyst loadings than 2 mol% revealed only a small influence on both yield and enantioselectivity (Table 1, entries 8 and 9). In the

Table 1. Optimization of the model reaction to form **3a** by using a double 1,4-addition of azlactone **1** generated in situ from N-benzoylated glycine **4** to dienone **2a**.



Entry	x	y	Yield *cis*-**3a** [%][a]	Yield *trans*-**3a** [%][a]	*ee* *trans*-**3a** [%][b]
1	2	0.1	1	36	83
2	2	–	4	42	78
3	2	0.5	6	44	86
4	2	1.0	11	58	91
5	2	1.5	14	73	91
6	2	2	18	82	94
7	–	2	1	10	–
8	4	2	18	82	96
9	6	2	17	82	97

[a] Determined by using ^{1}H NMR spectroscopy with mesitylene as the internal standard. [b] Determined by using HPLC analysis.

absence of the Pd^{II} catalyst, only a small product amount was formed (Table 1, entry 7) favoring the *trans* isomer.

The optimized reaction conditions were then applied to various symmetric and unsymmetric dienones on a preparative scale (Table 2).[19] With model dienone **2a** ($R^1 = R^2 =$ Ph), the *trans* isomer was isolated in good yield (85%) and in a highly enantiomerically enriched form (95% *ee*, Table 2, entry 1). Electron donors in the *para* position of the aromatic substituents (methyl, methoxy) resulted in good *trans* selectivity and the *trans* isomers were again formed in good yields with high enantioselectivity (entries 2 and 3). *para*-Bromo and *ortho*-chloro substituents resulted in lower product yields (entries 4 and 5). In case of the *p*-Br substituents, the *trans*/*cis* diastereoselectivity was considerably reduced, whereas the enantioselectivity was maintained to a high level. In contrast, the *ortho*-chloro substituents in **2e** resulted in excellent *trans* selectivity as only the *trans* isomer could be detected, but the enantioselectivity was only moderate in that case. The dialkyl-substituted substrate **2f** was not well-tolerated (entry 6), since both the *trans*/*cis* ratio and the product yield were poor, whereas at least the enantioselectivity was useful.

With unsymmetrical dienones, the stereochemical situation is further complicated, because eight stereoisomers can in principal be formed: enantiomeric pairs of two different *trans* diastereomers and of two different *cis* diastereomers. In all investigated cases the *trans* diastereomers were formed in excess, sometimes almost exclusively (Table 2, entry 10). Regarding the two possible *cis* diastereomers, only one of them has been detected in nearly all cases,[20] whereas the other one is obviously not formed in significant amounts. In those reactions employing an unsymmetrical dienone, in which a *cis* diastereomer has been detected, it has been formed in nearly racemic form. In contrast, both possible *trans*-diastereomers have been formed in similar quanti-

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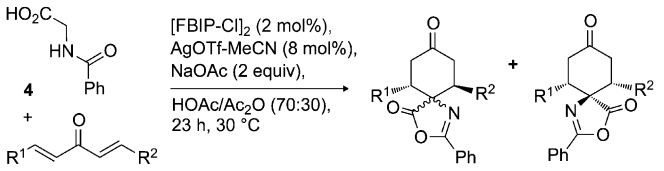
Table 2. Tandem approach featuring two consecutive Michael additions as key steps to form spirocyclic products **3**.



Entry	**2**	**3**	R^1	R^2	*trans*/*cis*	Yield *trans*-**3** [%][a]	d.r. *trans*-**3**[b]	*ee* *trans*-**3**[c]
1	**a**	**a**	Ph	Ph	89:11	85	–[d]	95
2[e,f]	**b**	**b**	4-MeO-C_6H_4	4-MeO-C_6H_4	92:8	89	–[d]	91
3[e]	**c**	**c**	4-Me-C_6H_4	4-Me-C_6H_4	93:7	78	–[d]	96
4[f]	**d**	**d**	4-Br-C_6H_4	4-Br-C_6H_4	75:25	43	–[d]	91
5[f]	**e**	**e**	2-Cl-C_6H_4	2-Cl-C_6H_4	> 100:1	44	–[d]	63
6	**f**	**f**	Me	Me	62:38	23	–[d]	81
7	**g**	**g**	Ph	4-MeO-C_6H_4	83:17	73	57:43	77/> 98[g]
8	**h**	**h**	Ph	4-Me-C_6H_4	91:9	82	57:43	99/93[g]
9[f]	**i**	**i**	Ph	4-Br-C_6H_4	88:12	73	50:50	92/93[g]
10	**j**	**j**	Ph	2-Cl-C_6H_4	> 100:1	78	60:40	81/47[g]
11[f]	**k**	**k**	Ph	4-NC-C_6H_4	n.d.	13	73:27	88/86[g]
12[f]	**l**	**l**	Ph	4-O_2N-C_6H_4	76:24	52	67:33	94/91[g]
13	**m**	**m**	Ph	2-furyl	88:12	79	65:35	98/95[g]

[a] Yield of the isolated product. [b] Diastereomeric ratio of two *trans* isomers determined by ^{1}H NMR spectroscopic analysis of the isolated product. [c] Determined by HPLC analysis. [d] Only one *trans* diastereomer is possible with symmetric dienone substrates **2**. [e] Reaction at 55 °C. [f] One equivalent of the dienone was used. [g] *ee* values of the major and minor *trans* isomers, respectively.

ties with unsymmetrical dienones and the enantioselectivity is usually high for both of them. Good yields of the *trans* isomers have been obtained for unsymmetrical dienones carrying a σ donor (entry 8), a π donor (entry 7), a σ acceptor (entries 9 and 10), or an electron-rich heterocycle (entry 13). Moderate or poor yields were obtained for dienone substrates equipped with a π acceptor (entries 11 and 12).

Stereochemistry: Compared with the major products obtained from simple enones (see ref. [13]), the configuration is surprisingly inverted at the β-positions to the keto group, as revealed by the X-ray single-crystal structure analysis of *trans*-**3j** (major diastereomer and enantiomer), which possesses an *S*,*S*,*S* configuration (Figure 2, top).[21,22] Additional X-ray crystal structure analyses of *trans*-**3a**, *trans*-**3d**, *trans*-**3e**, and *trans*-**3l** (major isomer) confirm the preferred *trans* configuration of the cyclohexanone rings with regard to the two dienone β-substituents (Figure 2). The *S* configuration of the stereocenters in the β-position to the keto group has also been confirmed by chemical correlation for *trans*-**3a** (see below in the subchapter "azlactone derivatization"). A stereochemical consequence of the symmetric constitution of *trans*-**3a** is that the spirocenter is not a stereocenter in that case.

Different conformers are preferred in the solid state depending on the dienone substitution patterns. In *trans*-**3a** and the major diastereomer of *trans*-**3j**, a twist conformation of the cyclohexanone core is found that accommodates both aryl rings in equatorial positions.

On the contrary, the major isomer of *trans*-**3l** carrying one phenyl group plus a *para*-nitro-substituted phenyl ring adopts a chairlike conformation (Figure 2, bottom, left), in which the phenyl substituent and the azlactone N atom adopt a *trans*-diaxial position. The alternative chair conformer with an axial azlactone carbonyl moiety (after ring inversion) is expected to be energetically less-favorable due to a more severe 1,3-diaxial interaction as a consequence of the enhanced steric demand of the carbonyl group relative to the azlactone N atom. Chairlike conformers were also noticed for *trans*-**3d** and -**3e** (Figure 2).

The absolute configuration of the minor diastereomer of *trans*-**3l** could also be determined (Figure 3).[23] The 5*R*,6*S*,10*S* configuration reveals that only the configuration at the spirocenter is inverted relative to (5*S*,6*S*,10*S*)-**3j**. By using an unsymmetrical dienone, the catalyst system used is thus not capable of setting up the configuration of the spirocenter with a high level of stereocontrol.

The conformational behavior in solution was studied by ^{1}H NMR spectroscopy for compounds **3**. In a chairlike conformation of a *trans*-1,3-disubstituted cyclohexanone moiety only one 1,3-*trans*-diaxial proton–proton coupling can be observed, whereas in a twistlike conformation two of them are present. The average coupling constants for 1,3-*trans*-diaxial couplings usually range from $^3J = 10$ to 15 Hz, whereas the other vicinal ^3J couplings are usually between 2 to 5 Hz, both depending on the dihedral angle.[24] It should be noted that in NMR spectroscopic experiments, usually only the average of these couplings can be measured for equilibrium mixtures of conformers, meaning that "mixed" coupling constants are observed. For the preference of a chairlike conformation of *trans*-1,3-disubstituted cyclohexanones in solution, the observed coupling constants for the vicinal couplings are consequently lower than for the preference of a twistlike conformation. For the proton on C10 of *trans*-**3a** (see Figure 4 with $R^1 = R^2 = Ph$), ^3J couplings of 8.5 and 5.1 Hz are observed, whereas for the proton on C6 ^3J values of 12.3 and 4.4 Hz are measured. That means there is arguably one 1,3-*trans*-diaxial interaction and one "mixed" coupling, pointing to a mixture of both chair and twist conformers. The existence of significant amounts of the twist conformer in solution is also supported by a relatively strong nuclear Overhauser effect (NOE) signal between the proton on C10 and the axial proton on C7, for which the distance is considerably shorter in the twist conformation (2.64 Å in the crystal structure of *trans*-**3a** (R = Ph, twist conformer) versus

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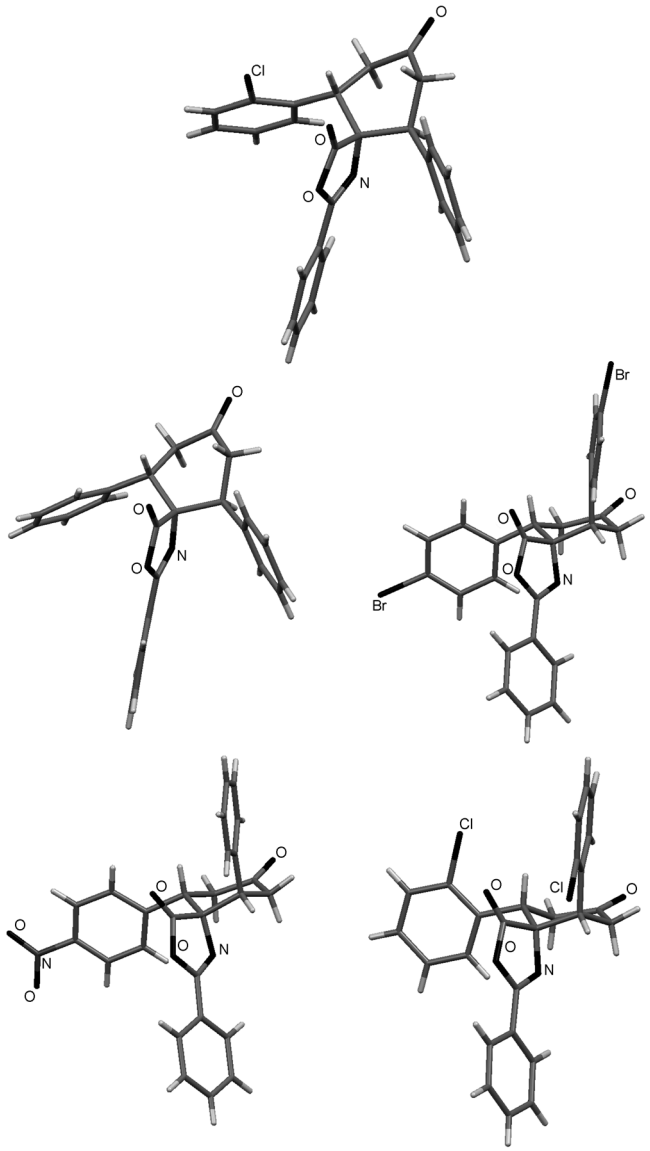

Figure 2. X-ray crystal structure analyses of spirocyclic azlactones **3**. Determination of the *S*,*S*,*S* configuration of *trans*-**3j** (major isomer, top, twist conformation) and the relative configuration of *trans*-**3a** (middle, left, twist conformation), *trans*-**3d** (middle right, chair conformation), *trans*-**3l** (major isomer, bottom, left, chair conformation), and *trans*-**3e** (bottom right, chair conformation).

4.11 Å in the crystal structure of *trans*-**3l** (R = 4-O_2N−C_6H_4, chair conformer)). However, as judged by the relatively low coupling constant (^3J = 8.5 Hz) both conformers are arguably present in comparable amounts in this mixture. Similar observations have also been made for most *trans*-**3**-derivatives, in which no signal overlaying hampered the analysis.

Typically, twist conformations are about 5 kcal mol^{-1} higher in energy than the corresponding chair conformations,[25] but the possibility in a twist conformation to accommodate both cyclohexanone residues R^1 and R^2 of compounds *trans*-**3** in the favorable equatorial positions apparently lowers the relative energy of the twist conformers, because in the chair conformation one substituent needs to adopt an axial position. In contrast, for compounds *cis*-**3**, the chairlike conformation (see also Figure 6) is strongly preferred, because both substituents can be accommodated in equatorial positions.

For the *ortho*-chlorophenyl-substituted derivative *trans*-**3j**, the coupling constants have been determined at temperatures from 243 to 313 K. The couplings of the proton on C10 vary relatively strongly with the temperature, whereas the couplings of the proton on C6 are relatively uniform (Figure 5). The H^{C10}–H^{C9b} coupling constant steadily rises with increasing temperature, whereas the H^{C10}–H^{C9a} coupling constant decreases. Based on the Karplus curve, this indicates that the dihedral angle decreases between H^{C10} and H^{C9a} and also between H^{C10} and H^{C9b}. In the X-ray crystal structure of *trans*-**3a**, adopting the twist conformation, dihedral angles of 177.0 (H^{C10}–H^{C9a}) and 65.0° (H^{C10}–H^{C9b}) have been determined. In the chair conformation of **3l**, dihedral angles of 74.6 (H^{C10}–H^{C9a}) and 41.7° (H^{C10}–H^{C9b}) have been determined. Upon warming, both dihedral angles of the H^{C10}/H^{C9} protons decrease, thus indicating an increasing amount of the chairlike conformation at higher temperatures. The free enthalpy of the twist conform-

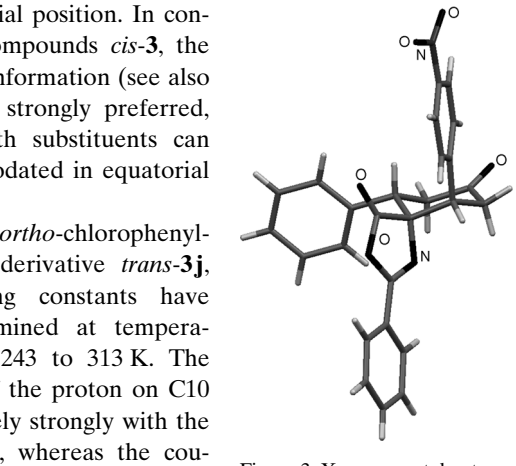

Figure 3. X-ray crystal structure analysis of the minor diastereomer of *trans*-**3l** revealing a 5*R*,6*S*,10*S* configuration.

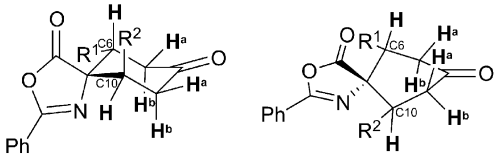

Figure 4. Schematic representation of the chair and the twist conformation of the spirocycles *trans*-**3**.

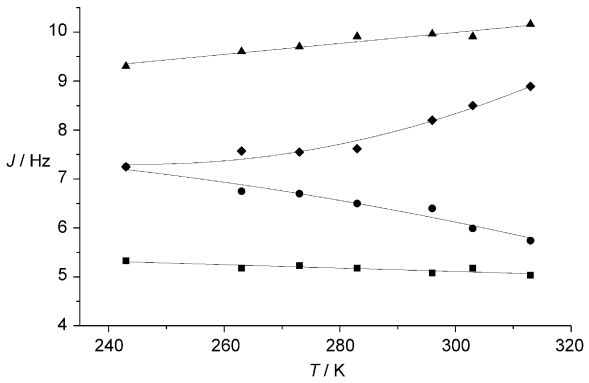

Figure 5. Temperature dependence for selected coupling constants in the spirocycle *trans*-**3j**. H^{C6}–H^{C7b} (▲), H^{C10}–H^{C9b} (◆), H^{C10}–H^{C9a} (●), H^{C6}–H^{C7a} (■).

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er should thus be lower in the investigated case of *trans*-**3j**.[26,27]

As mentioned above, for *meso*-configured- and thus achiral *cis* isomers derived from symmetric dienones **2** only one of two possible *cis* stereoisomers is formed. Either the azlactone carbonyl moiety or the N atom could, in principal, be in the *cis* position to the residues R^1/R^2. The spirocarbon is thus a center of pseudoasymmetry.[28] Notably, also for unsymmetrical dienones only one of the possible two *cis* diastereomers is formed. X-ray crystal structure analyses of *cis*-**3a**, *cis*-**3b**, *cis*-**3h**, *cis*-**3i**, and *cis*-**3m** show that in the *cis* diastereomers the azlactone carbonyl moiety always adopts the axial position (Figure 6).[29]

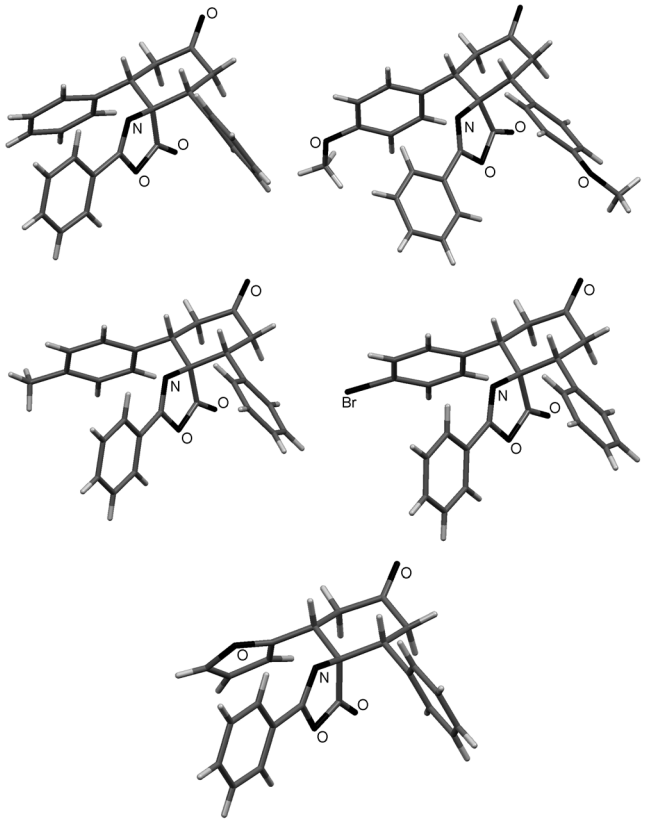
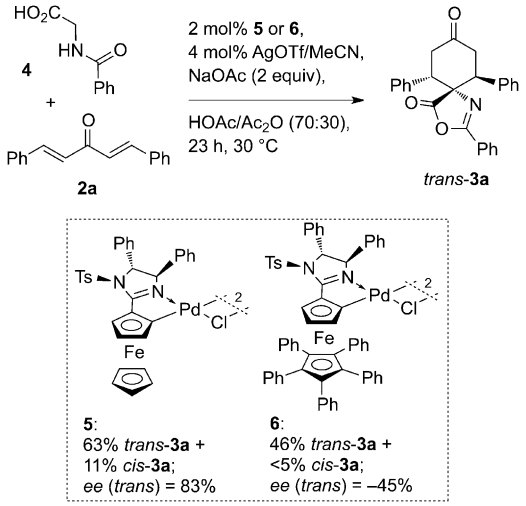


Figure 6. X-ray crystal structure analyses of the *cis*-configured spirocyclic azlactones *cis*-**3a** (top left), *cis*-**3b** (top right), *cis*-**3h** (middle left), *cis*-**3i** (middle right), and *cis*-**3m** (bottom) to determine the relative configuration.

Mechanistic considerations: In the 1,4-addition of 2-Ph-substituted azlactones to give simple enones we have previously found that a bimetallic mechanism is likely to be preferred, because significantly lower product yields were obtained with related monopalladacycles.[13] Moreover, the product was formed with only low-to-moderate enantioselectivity with monopalladacycles. We have explained the preference for a bimetallic catalyst by a simultaneous activation of the enone substrate and the azlactone through a bimetallic coordination mode.[13c,d] To clarify if an intramolecular bimetallic activation mode is also likely in the title reaction with divinylketones, control experiments have been performed with



Scheme 2. Control experiments with related monopalladacycle catalysts.

monopalladacycles **5** and **6** (Scheme 2), which are structurally related to $[FBIP{-}Cl]_2$.[30] Monopalladacycles **5** and **6** both provided the spirocyclic product *trans*-**3a** in significant amounts, with a higher activity and good enantioselectivity for the sterically less-encumbered palladacycle **5**.

These results indicate that a bimetallic intramolecular mechanism is not essential in the double 1,4-addition approach using dienone substrates **2**. The energetically lower LUMOs of the dienones with their extended cross-conjugated π-systems might more readily allow for a monometallic pathway, in which the dienone is not activated by a Pd^{II} center.

The higher electrophilicity of the divinylketones has been confirmed by quantum mechanical computations. By using the DFT/B3LYP/6-31G* method, the LUMOs of dibenzylidene acetone (**2a**) and chalcone were compared. In a vacuum, the LUMO of **2a** was found to be 14.7 kJ mol^{-1} lower in energy than the LUMO of chalcone. In acetic acid the energy difference was calculated to be 16.3 kJ mol^{-1}, again with a lower LUMO energy for **2a**.

Both *trans* diastereomers of the spirocyclic products **3** are generated with high enantioselectivity in most cases. Notably, compared to the major products obtained from simple enones,[13] the configuration is inverted at the β-positions to the keto group hence preferring the *S* configuration. The facial differentiation of the Michael acceptor moieties is thus different for enones and dienones. In our previous studies with enones, we have explained the preference for the *R* configuration at the β-position to the keto group of product (*R*,*R*)-**8** by coordination of the carbonyl moiety of the enone in the assumed catalytic intermediate **7** (Scheme 3), whereas the *S* configuration in the β-position to the keto group of product (*R*,*S*)-**8** would have been expected by face-selective olefin coordination in **9**.[13c]

As discussed above, the higher electrophilicity of dienones most likely also allows for a rapid monometallic reaction pathway, in which the dienone is not further activated by a Pd^{II} center. In this mechanism, only the azlactone would be

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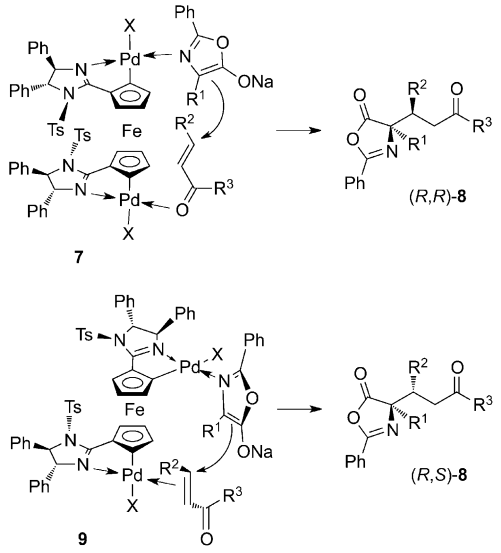
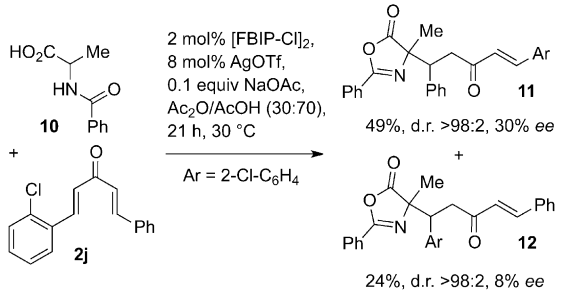


Scheme 3. Top: Possible dual-activation mode to rationalize 1) the reactivity of FBIP in the 1,4-addition of 2-Ph-azlactones and enones and 2) the absolute and relative configuration of the reaction products (*R*,*R*)-**8**. Bottom: Initially assumed bimetallic activation mode, in which the enone is activated by face-selective coordination of the C=C double bond in **9** (minimizing repulsive interactions between the ferrocene core and the enone residues). This mechanism would provide an *S* configuration at the β-position to the carbonyl moiety, which is not observed.[13c]

activated as nucleophilic species in the intermolecular Michael-addition step by coordination to a Pd^{II} center. Compared with the bimetallic mechanism with enones, this single-point activation might result in a lower facial differentiation with the dienone substrates in the initial 1,4-addition step, because the latter substrate would not be pre-organized by interaction with the catalyst. A moderate stereoselectivity would be the stereochemical consequence.

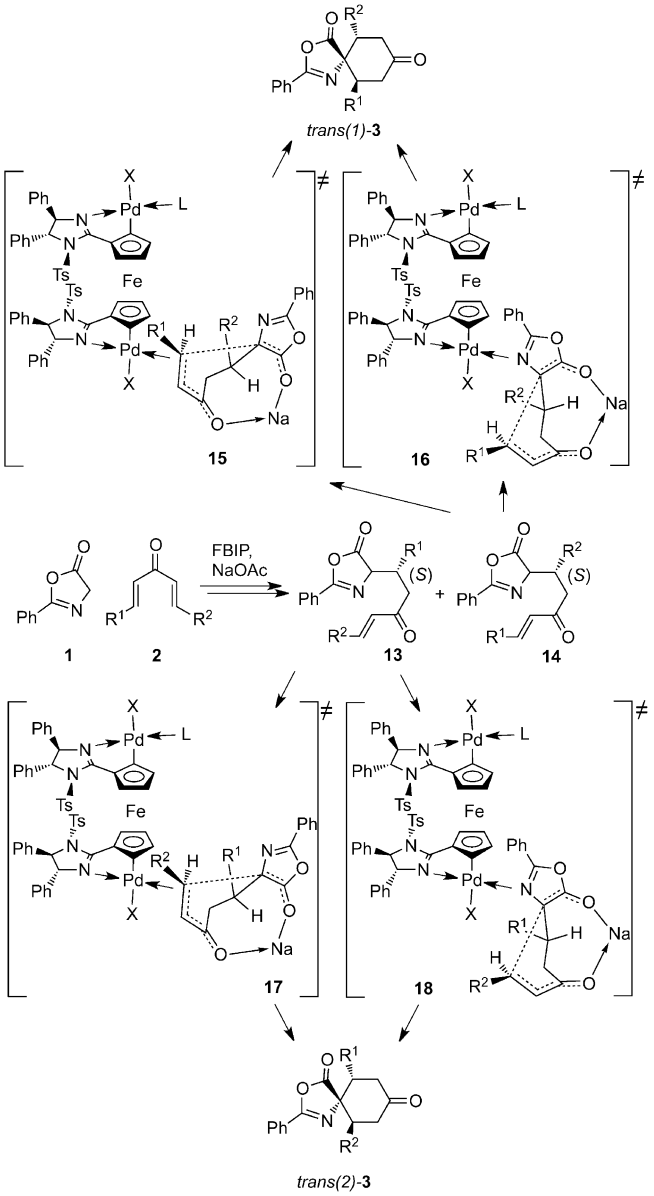
Unfortunately, despite considerable efforts we were not able to isolate or detect the initial 1,4-addition monoadducts to determine the enantioselectivity of the initial Michael-addition step. Evidently, the intramolecular 1,4-addition proceeds much faster than the intermolecular one. As a model reaction, we have therefore investigated the 1,4-addition of the azlactone, which is formed in situ from racemic *N*-benzoyl alanine **10**, to the unsymmetrical enone **2j** (Scheme 4). In contrast to the enantioselective addition of the same



Scheme 4. Model reaction of the intermolecular 1,4-addition with dienones.

azlactone to simple enones,[13c] this reaction provided two almost racemic regioisomeric 1,4-addition products **11** and **12** (ratio of 2:1). Due to this observation it is likely that the initial intermolecular Michael additions of the glycine-derived azlactone **1** to dienones **2** also proceed with moderate enantio- and regioselectivity.

The observation that the FBIP catalyst is not capable of setting up the configuration of the spirocenters of *trans*-**3** with a high level of stereocontrol, might be the result of this low regioselectivity for the initial 1,4-addition step.[31] The configuration of the spirocenters is defined in the subsequent intramolecular 1,4-addition step (Scheme 5).[32] At least two scenarios are possible for each of the initial regioisomeric 1,4-addition products **13** and **14**: the enone double



Scheme 5. Possible explanation for the formation of two *trans* diastereomers and the generation of the *S* configuration at the former enone β-carbon atom in the cyclization step. Only the *S*-configured initial 1,4-addition products **13** and **14** are shown for simplicity.

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bond could, for example, be activated in a face-selective manner by coordination to a Pd^{II} center. An *S* configuration for the emerging stereocenter at the former enone β carbon atom would be expected in that case, because 1) repulsive interactions between the catalyst core and the coordinated dienone are minimized in the suggested coordination mode[33,34] and 2) the azlactone enolate is expected to attack from the outer-sphere (see transition states **15** and **17**). Alternatively, the azlactone N atom could coordinate to a Pd center to facilitate the enolate formation triggering the subsequent cyclization step (see transition states **16** and **18**). Irrespective of which of these two activation pathways might be preferred, the ratio of the *trans* diastereomers would be predetermined by the regioselectivity of the initial intramolecular 1,4-addition step.

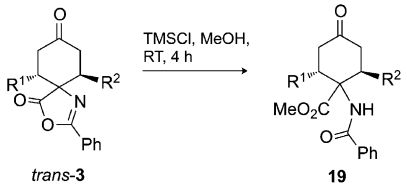
The coordination of acetonitrile in the activated catalyst FBIP−X (Figure 1) should be *trans* to the N donor, in agreement with the solution structure of FBIP catalysts carrying an aromatic sulfonate counterion.[15d] In addition, there seems to be a general preference in ferrocene-based palladacycles for coordination of neutral ligands *trans* to the N donors and of anionic ligands *trans* to the C donors.[16c,30e,35,36] We thus assume that substitution of acetonitrile by the substrate molecules should take place at the position *trans* to the N donors leading to the reaction pathways depicted in Scheme 5,[37] but a substrate coordination *cis* to the N donors cannot be completely excluded.

As mentioned above, the *cis* diastereomers of **3** are nearly racemic using unsymmetrical dienones. The amount of *cis*-**3** is considerably increased in the presence of stoichiometric or excess amounts of NaOAc (see Table 1). On the other hand, in the absence of catalyst, almost no *cis* product is formed and the *trans* isomer is the major product (Table 1, entry 7). It is thus likely that the catalyst is also involved in the formation of the *cis*-configured side product. Only one of two possible *cis* isomers has been detected in nearly all cases.[20] Notably, the *cis* isomer that has been formed should be the thermodynamically less-favorable one, as the azlactone carbonyl group (and not the sterically less-demanding N atom) adopts the axial position thereby resulting in stronger 1,3-diaxial interactions in the chairlike conformers (Figure 6). This has been confirmed by DFT calculations (B3LYP/6-31G* method), which suggest that the observed isomer is by about 3.7 kJ mol^{-1} higher in energy than the alternative isomer.

Formation of the *cis*-configured side product should thus be kinetically controlled. It might be that the *R*-configured monoadducts (*R*)-**13** and (*R*)-**14** mainly react to *cis*-**3**, that is, 6*R*,10*S*/6*S*,10*R*-configured products, as a result of the above described preference of the catalyst for the generation of the *S*-configured stereocenters at the β-position to the keto moiety in the cyclization step. Nearly racemic products would again be the consequence of a low regioselectivity in the initial intermolecular 1,4-addition step.

Azlactone derivatization: α,α-Disubstituted α-amino acids (quaternary amino acids) are of biological and pharmacological interest.[38] They 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.[38,39] The spirocyclic azlactones *trans*-**3** were therefore studied for the formation of protected constrained cyclohexane analogues **19** of phenylalanine (Table 3).[40] These compounds

Table 3. Synthesis of constrained cyclohexane analogues **19** of phenylalanine through nucleophilic azlactone ring-opening with methanol.



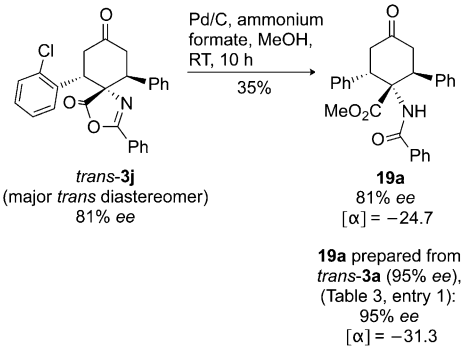
trans-**3** **19**

Entry	**3**	**19**	R^1	R^2	**19** [%][a]
1	**a**	**a**	Ph	Ph	90
2	**b**	**b**	4-MeO-C_6H_4	4-MeO-C_6H_4	86
3	**c**	**c**	4-Me-C_6H_4	4-Me-C_6H_4	100
4	**g**	**g**	Ph	4-MeO-C_6H_4	80
5	**h**	**h**	Ph	4-Me-C_6H_4	81
6	**i**	**i**	Ph	4-Br-C_6H_4	83
7	**m**	**m**	Ph	2-furyl	93

[a] Yield of the isolated product.

are of interest as building blocks for the synthesis of artificial peptide analogues with controlled folds in the peptide backbone, since they are able to restrict the χ^1 torsion angle.[41] Moreover they are important in peptide receptor recognition processes.[41] Treatment of *trans*-**3a** with MeOH and TMSCl at ambient temperature gave access to diastereomerically pure methyl ester **19a** in high yield and with an unchanged *ee* value of 95% (Table 3, entry 1).

Compound **19a** was also obtained from the major diastereomer of *trans*-**3j** (for which the absolute configuration has been determined by X-ray crystal structure analysis (see Figure 2, top, major enantiomer)) by reductive removal of the Cl atom in MeOH (Scheme 6). *Trans*-**3j** and *trans*-**3a** have formed the same enantiomer of **19a**, thus confirming the *S*,*S* configuration for *trans*-**3a**.



trans-**3j**
(major *trans* diastereomer)
81% *ee*

19a
81% *ee*
[α] = −24.7

19a prepared from
trans-**3a** (95% *ee*),
(Table 3, entry 1):
95% *ee*
[α] = −31.3

Scheme 6. Reductive removal of the Cl substituent in *trans*-**3j** plus azlactone ring opening to confirm the absolute configuration of *trans*-**3a**.

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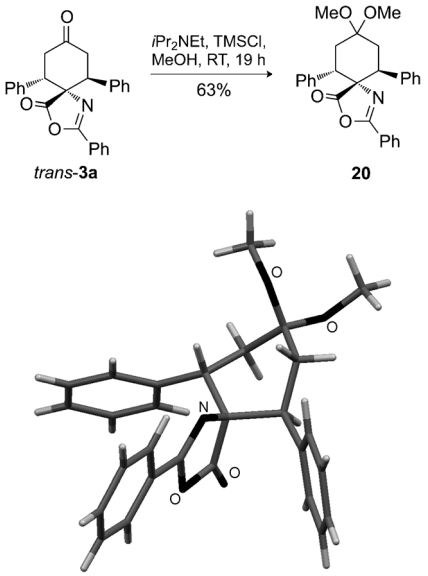
Methanolysis of several other spirocyclic azlactones proceeded with similar efficiency (Table 3). In entries 4–7 the diastereomeric ratios of the two *trans* isomers were identical in the starting material and the corresponding product. If the reaction mixture was buffered by using iPr$_2$NEt, the azlactone ring-opening by MeOH was decelerated and dimethylketal **20** was formed. The X-ray crystal structure analysis of this compound again confirmed the *S*,*S* configuration of *trans*-**3a** (Scheme 7).[42] Also, in this case a twist conformer was found in the solid state.



Scheme 7. Synthesis and X-ray crystal structure analysis of dimethylketal **20**.

Conclusion

We have described a catalytic asymmetric tandem reaction to prepare highly enantioenriched azlactone/cyclohexanone spirocycles through a double Michael-addition approach (a formal [5+1] cycloaddition) in which an achiral glycine-derived azlactone pronucleophile is generated in situ from N-benzoylated glycine and acetic anhydride. Both symmetrical and unsymmetrical divinylketones have been investigated in the title reaction, which generates up to three contiguous stereocenters, one of which is quaternary. X-ray crystal structure analyses have revealed the preferred *trans* configuration of the cyclohexanone rings with regard to the two dienone substituents and the absolute configuration. Unfortunately, the catalyst system is not capable of setting up the configuration of the spirocenter with a high level of stereocontrol in the *trans* products and therefore two *trans* diastereomers are formed in similar quantities by using unsymmetrical dienones. Nevertheless, both *trans* diastereomers are formed with high enantioselectivity in most cases. Control experiments with related monopalladacycles suggest that a bimetallic mechanism is not necessarily required for enantioselective product formation. The comparatively high electrophilicity of dienones presumably allows for a monometallic reaction pathway, in which the catalyst only activates the pronucleophile for the initial, slower intermolecular 1,4-addition. Depending on the substitution pattern of the dienones, the *trans* isomers can prefer a twist- rather than a chair conformer, both in the solid state and in solution, to minimize 1,3-diaxial interactions. Only one *cis* diastereomer, which is either achiral or nearly racemic, has been detected as a side product. We have shown that the spirocyclic reaction products can, for example, serve as precursors for the formation of cyclic quaternary amino acids by azlactone ring opening.

Experimental Section

General procedure for the activation of precatalyst [FBIP−Cl]$_2$: The precatalyst [FBIP−Cl]$_2$ (1 equiv) and silver triflate (4 equiv) were dissolved in acetonitrile (1 mL per 5 mg [FBIP−Cl]$_2$) and stirred at room temperature overnight. Afterwards, the mixture was filtered through Celite and free acetonitrile was removed under reduced pressure (ca. 5 min at 15 mbar and RT). A stock solution of the activated catalyst in a mixture of acetic acid and acetic anhydride (70:30) was subsequently prepared (typically 1 μmol precatalyst per 150 μL solvent).

General procedure for the catalytic asymmetric synthesis of spirocyclic azlactones: *N*-Benzoyl glycine (1 equiv, 0.60 mmol, 108 mg), sodium acetate (2 equiv, 1.20 mmol, 98.4 mg), and the corresponding dienone (1 or 2 equiv, 0.60 or 1.20 mmol) were charged to a vial. The activated catalyst (prepared from [FBIP−Cl]$_2$ (0.02 equiv, 12.0 μmol, 29.2 mg) and silver triflate (0.08 equiv, 48.0 μmol, 12.3 mg) as described in the general procedure) was added as a stock solution (1.80 mL, AcOH/Ac$_2$O, 70:30). The resulting mixture was warmed to 30 °C for 24 h or to 55 °C for 20 h. After cooling to room temperature, the mixture was taken up in CH_2Cl_2 (ca. 40 mL) and was washed with sat. aq. $NaHCO_3$ and was then dried over Na_2SO_4. The targeted product was isolated by using silica gel chromatography. Nearly racemic reference samples were synthesized in the same manner by use of approximately a 1:1 mixture of both catalyst enantiomers on a 50 μmol scale.

General procedure for the azlactone ring-opening esterification: A mixture of the corresponding spirocyclic azlactone **3** (1 equiv), TMSCl (4 equiv), and methanol was heated to 40 °C for 4 h. After removal of the volatiles, the crude product was purified by silica gel chromatography.

Acknowledgements

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

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[19] Pure precatalyst could be recovered in 46–56% yield after a catalytic run (see the Supporting Information). Catalyst recycling is also possible by catalyst precipitation after a catalytic run, but the enantioselectivity and the catalytic activity both decrease after the first run (see the Supporting Information).

[20] The only exception is the 2-furyl substituted product **3m**, for which a diastereomeric ratio (d.r.) of 93:7 was determined for two *cis* isomers.

[21] CCDC-918517 (*trans*-**3j**, major diastereomer and enantiomer), CCDC-918519 (*trans*-**3a**), CCDC-918526 (*trans*-**3d**), CCDC-918518 (*trans*-**31**, major diastereomer), and CCDC-918524 (*trans*-**3e**) contain the supplementary crystallographic data for this paper. These

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data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[22] The absolute configuration previously tentatively assigned to *trans*-**3a** in ref. [2] is not correct. The authors wish to apologize for any inconvenience caused by the initial misassignment.

[23] CCDC 918527 (*trans*-**3l**, minor diastereomer) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[24] M. Karplus, *J. Am. Chem. Soc.* **1963**, *85*, 2870.

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[26] Preferences for a twist conformer have also been reported for other 1,3-*trans*-disubstituted six-membered rings: a) H. Kessler, V. Gusowski, M. Hanack, *Tetrahedron Lett.* **1968**, *9*, 4665; b) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, F. A. Van-Catledge, *J. Am. Chem. Soc.* **1968**, *90*, 1199; c) G. Gill, D. M. Pawar, E. A. Noe, *J. Org. Chem.* **2005**, *70*, 10726.

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[29] CCDC-918522 (*cis*-**3a**), CCDC-918523 (*cis*-**3b**), CCDC-918528 (*cis*-**3h**), CCDC-918525 (*cis*-**3i**) and CCDC-918521 (*cis*-**3m**) contains the supplementary crystallographic data. 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] Recently, the important role of dynamic kinetic resolution on the outcome of organocatalyzed double Michael-addition reactions has been described: a) J. Wang, H. Xie, H. Li, L. Zu, W. Wang, *Angew. Chem.* **2008**, *120*, 4245; *Angew. Chem. Int. Ed.* **2008**, *47*, 4177; b) C. Yu, Y. Zhang, A. Song, Y. Ji, W. Wang, *Chem. Eur. J.* **2011**, *17*, 770. To investigate if dynamic kinetic resolution might also play a role in our study, we have examined if the formation of **11** and **12** is reversible. The isolated compounds **11** and **12** were thus treated with the usual reaction conditions of the catalysis. Regioisomeric mixtures have indeed been obtained by using the single regioisomers. However, the equilibration is rather slow (see the Supporting Information). In contrast, the formation of the *S*,*S*-configured spirocyclic product *trans*-**3a** was found to be irreversible (see the Supporting Information). Treating the isolated diastereomerically pure material under the usual reaction conditions does not form any *R*,*S*-configured isomer and *trans*-**3a** was reisolated in quantitative yield with an unchanged *ee* value of 95%. Based on the slow retro-Michael reaction of the initial 1,4-addition product in combination with the very rapid and irreversible intramolecular Michael addition, a dynamic kinetic resolution is unlikely to have a large impact in the present case.

[32] Alternatively, the facial selectivity of the azlactone-enolate faces might be low in transition states similar to **15**–**18**, but lacking the suggested chelation by Na^+.

[33] Note that in square-planar Pd^{II} complexes, the olefin axis is usually perpendicular to the olefin square plane. See: P. M. Henry, *Handbook of Organopalladium Chemistry for Organic Synthesis Vol. 2*, Wiley-Interscience, New York, **2002**, p. 2119 and cited references.

[34] By coordination of the alternative olefin face either the olefin substituent R^1/R^2 or the carbonyl moiety plus the neighboring α-CH_2 would point to the ferrocene bulk of the catalyst thus resulting in stronger repulsive interactions.

[35] C. J. Richards, in *Chiral Ferrocenes in Asymmetric Catalysis*, (Eds.: L.-X. Dai and X.-L. Hou,), Wiley-VCH, Weinheim, **2010**, pp. 337–368.

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[42] CCDC-918520 (**20**) contains the supplementary crystallographic data. This 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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