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Synthesis of Nearly Enantiopure Allylic Amines by Aza-Claisen Rearrangement of *Z*-Configured Allylic Trifluoroacetimidates Catalyzed by Highly Active Ferrocenylbispalladacycles

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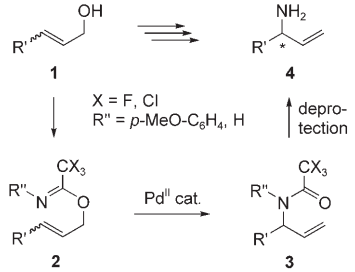
Abstract: The development of the first highly active enantioselective catalyst for the aza-Claisen rearrangement of *Z*-configured allylic trifluoroacetimidates generating valuable almost enantiopure protected allylic amines is described. Usually *Z*-configured allylic imidates react significantly slower than their *E*-configured counterparts, but in the present study the opposite effect was observed. *Z*-Configured olefins have the principal practical advantage that a geometrically pure C=C double bond can be readily obtained, for example, by semihydrogenations of alkynes. Our catalyst, a C_2-symmetric planar chiral bispalladacycle complex, is rapidly prepared from ferrocene in four simple steps. Key step of this protocol is an unprecedented highly diastereoselective biscyclopalladation providing dimeric macrocyclic complexes of fascinating structure. In the present study as little as 0.1 mol% of catalyst precursor were sufficient for most of the alkyl substituted substrates to give in general almost quantitative yields. NMR investigations revealed a monomeric structure for the active catalyst species. The bispalladacycle can also be used for the formation of almost enantiomerically pure allylic amines ($ee \geq 96\%$) substituted with important functional groups such as ester, ketone, ether, silyl ether, acetal or protected amino moieties providing high-added-value allylic amine building blocks in excellent yield ($\geq 94\%$). The preparative advantages should render this methodology highly appealing as a practical and valuable tool for the formation of allylic amines in target oriented synthesis.

Keywords: allylic amines · aza-Claisen rearrangement · cyclopalladation · ferrocene · imidazoline

Introduction

The asymmetric aza-Claisen rearrangement[1] of allylic trichloro-[2] and trifluoroacetimidates[3] is a useful synthetic tool for the formation of allylic trihaloacetamides **3** starting from readily available allylic alcohols **1** (Scheme 1). In 1974, 37 years after the first description of the thermal aza-Claisen rearrangement of allylic benzimidates by Mumm and Möller,[4] Overman reported the first application of trichloroacetimidate substrates and demonstrated that the rearrangement can be catalyzed by soft Lewis acids such as mercury trifluoroacetate.[5] The trihaloacetamide protecting groups can be readily removed from the N atom of the initial rearrangement products **3** and therefore the overall transformation leads to primary allylic amines **4**. Those are valuable building blocks due to the presence of two highly versatile functional groups: the amino and the olefin moiety.

Due to its conceptual attractiveness this approach[6] has been frequently applied in organic synthesis: more than 180 publications report the use of the thermal or non-enantiose-



Scheme 1. Aza-Claisen (Overman) rearrangement of trihaloacetimidates.

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X-Ray crystal structure analysis.

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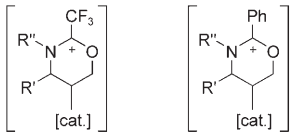
lective Lewis acid catalyzed aza-Claisen rearrangement to prepare allylic amines.[2b]

In 1997 a chiral Pd^{II} complex was reported—again by Overman et al.—acting as the first enantioselective catalyst for the rearrangement of allylic imidates.[7] The subsequent development of catalysts with increasing enantioselectivity concentrated on the rearrangement of allylic benzimidates yielding benzoylamides as products, which are of limited synthetic value though, since the hydrolytic cleavage of the benzoyl amide group proceeds typically with very low yield. In 2003, the Overman group disclosed the first highly enantioselective catalyst for the rearrangement of the less reactive trihaloacetimidates providing the allylic trihaloacetamides **3** in synthetically useful yields.[2a,3a] However, for trifluoroacetimidates high catalyst loadings were usually required (10 mol% of Pd^{II}) owing to the electron withdrawing nature of the trihalomethyl group, which diminishes the nucleophilicity of the imidate N atom since it destabilizes the positive charge in the cationic reaction intermediate **5**,



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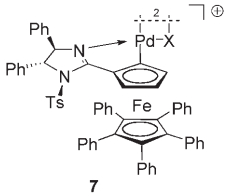
whereas in the case of benzimidates the generated positive charge is in a benzylic position thus stabilizing the transition state leading to intermediate **6**.

Even with these high catalyst loadings long reaction times were generally required for high conversion. In the case of trifluoroacetimidate substrates, which appear to be synthetically slightly more attractive than the corresponding trichloro derivatives due to milder deprotection conditions for the resulting amide, the scope was limited to substrates bearing α-unbranched alkyl substituents R′ at the 3-position of the allylic imidate. These limitations are the reason why the catalytic asymmetric aza-Claisen rearrangement of trifluoroacetimidates—despite its conceptual potential—has found almost no application in target oriented synthesis, in particular on a technical scale. To develop a practical catalyst system of synthetic impact, the issues of catalytic activity and scope were recently addressed by us with the development of the first highly active chiral catalyst (catalyst loadings are usually at 0.05–0.1 mol%) for the rearrangement of *E*-configured trifluoroacetimidates providing allylic trifluoroacetamides **3** with excellent enantioselectivities while tolerating a broad substrate scope: for the first time α-branched alkyl groups as well as aromatic substituents were well tolerated as substituent R′ in the 3-position.[3e] The catalyst **7**, a planar chiral ferrocenium imidazoline palladacycle (FIP),[8] is the result of a highly modular catalyst design and the optimization of the catalyst structure in which both the steric and the electronic properties of the Pd^{II} center could be adjusted by five different modules: the counteranion X, the bottom Cp spectator ligand (here $Cp^{\Phi} = C_5Ph_5$), the oxidation state of the Fe atom (ferrocene vs. ferrocenium), the imidazoline backbone and the residue on the amino N atom (here a tosyl group).



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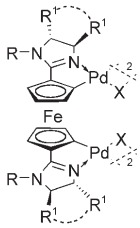
The exceptionally high catalytic activity is mainly attributed to four factors: the possibility to apply almost solvent-free reaction conditions, the robustness of the active catalyst under the reaction conditions, the formation of a ferrocenium system as catalytically active species by oxidation of the ferrocene core with a silver salt and the electron withdrawing nature of the five phenyl substituents on the Cp^{Φ} spectator ligand. The last two factors enhance the Lewis acidity of the Pd center in **7**.[9,10] However, complex **7** showed a much lower catalytic activity for the rearrangement of *Z*-configured substrates **2** which is a practical disadvantage, since high enantioselectivities are only achieved with isomerically pure substrates and *Z*-configured olefins are in principal more readily accessible in isomerically pure form, for example, by semihydrogenation of a triple bond. For this reason our goal was to develop a highly enantioselective catalyst with an extraordinary catalytic activity for *Z*-configured allylic trifluoroacetimidates. In addition, to be attractive as synthetic tool, the catalyst should be readily accessible to allow also large-scale applications.

Results and Discussion

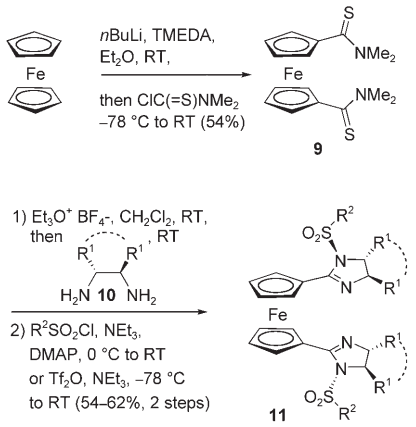
To further decrease the electron density of the Pd^{II}-centers, we have designed 1,1′-ferrocenyl-bisimidazoline palladacycle systems **8** (FBIP) which could be prepared by the first direct diastereoselective biscyclopalladation of an enantiomerically pure sandwich complex as the key step.[11]



FBIP (**8**)

The ligand preparation takes advantage of the ensuing C_2-symmetry reducing the number of required steps starting from parent ferrocene.[12] The initial plan to adopt the conditions used for the synthesis of ferrocenyl monoimidazolines, namely to make use of a primary amide functionality for the imidazoline formation by first activating the amide group via alkylation and subsequent condensation of the in situ generated iminium ether with a diamine, was given up, since ferrocenyl-1,1′-diamide is almost insoluble in aprotic non-nucleophilic solvents such as CH_2Cl_2, DCE or $CHCl_3$ thus suppressing the alkylation step. Bisthioamide **9** was therefore utilized, which is highly soluble in chlorinated solvents and which was formed by dilithiation of ferrocene at room temperature in Et_2O and subsequent trapping of the biscarbanion with *N*,*N*-dimethyl-

aminothiocarbamoyl chloride using a modified literature procedure (Scheme 2).[13]



Scheme 2. Synthesis of the C_2-symmetric ligands **11**.

The reactivity of the thioamide functionality was not yet sufficient for a direct condensation with primary 1,2-diamines even under Lewis acid activation. However, activation of the thioamide moieties by S-alkylation using Meerwein's salt followed by treatment of the solution of the resulting iminium thioether with (*R*,*R*)-1,2-diphenylethane-1,2-diamine (**10a**) or (*S*,*S*)-cyclohexane-1,2-diamine (**10b**) provided the corresponding bisimidazolines, which could not be obtained in analytically pure form by column chromatography on silica gel or alumina owing to an increased basicity as compared to ferrocenyl monoimidazolines. For these reasons the crude material was directly subjected to sulfonylation yielding the less electron rich and bench stable ligands **11a–f** (Table 1).

Table 1. Preparation of bisimidazoline ligands **11a–f**.

Entry	Product	R^1	R^2	Yield[a] [%]
1	**11a**	Ph	*p*-Tol	57
2	**11b**	Ph	C_6F_5	54
3	**11c**	Ph	mesityl	60
4	**11d**	Ph	*p*-Ph-C_6H_4	41
5	**11e**	Ph	CF_3	62
6	**11f**[b]	$(CH_2)_4$	*p*-Tol	62

[a] Isolated yield over 2 steps starting from **9**. [b] (*S*,*S*)-Cyclohexane-1,2-diamine (**10b**) was used for the imidazoline formation. The absolute configuration of **11f** is thus opposite to the one depicted in Scheme 2.

The key structural design element to achieve high diastereoselectivity for the subsequent biscyclopalladation is the strong pyramidalization of the two sulfonylated N atoms which is confirmed by X-ray crystal structure analysis (Figure 1):[14,15] steric repulsion between the residue R^1 at the imidazoline 5-position and the sulfonyl group effects a transfer of chirality to the N atom.

The consequence is a preferred conformation in which the sulfonyl residue and therefore the substituent at the imidazoline 4-position point away from the ferrocenyl core to minimize unfavorable steric interactions with the metallocene core (Figure 2).

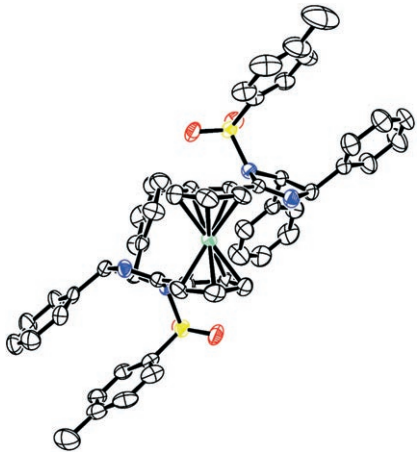


Figure 1. ORTEP representation of ligand **11a** (R^2 = *p*-Tol). The 30% probability ellipsoids have the following color code: C (black); N (blue); O (red); S (yellow); Fe (aquamarine). H atoms are omitted for clarity.

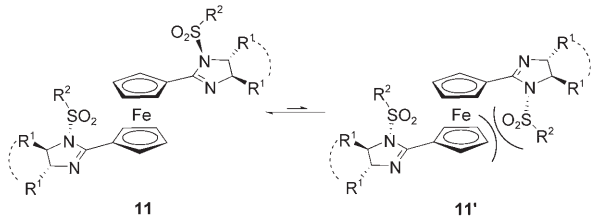
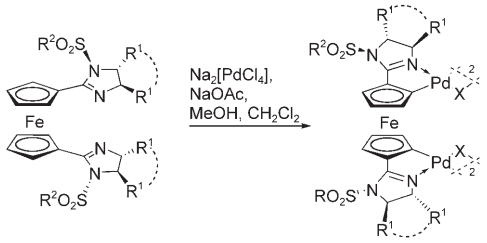


Figure 2. Chirality transfer to the sulfonylated N-atoms as major ligand design principle resulting in a preferred equilibrium conformation of **11** to allow for a highly diastereoselective biscyclopalladation.

Due to this preferred conformation, the attacking Pd^{II} electrophile is directed by the coordinating imino type N-atom to only one of the two possible *ortho*-positions. For that reason the direct biscyclopalladation proceeds with excellent diastereoselectivity using various aromatic or non-aromatic sulfonyl residues (Table 2, entries 1–6). CH_2Cl_2 was employed as a cosolvent to increase the solubility of the ligand systems in the biscyclopalladation step, while MeOH is required to dissolve the Pd^{II} source. To our knowledge these are the first and only examples for direct diastereoselective biscyclopalladations of enantiomerically pure sandwich complexes reported in literature.[16] Previous syntheses of non-racemic ferrocenyl bispalladacycles relied on double *ortho*-lithiation, iodination and subsequent oxidative addition of Pd^0 to the corresponding bisiodoferrocenes.[17]

At the outset of this project we were expecting that the bispalladacycles would mainly form polymeric linear chains in which the monomers would be connected via chloride bridges. However, the ^{1}H NMR spectra for **12a–f** show only a single set of sharp signals indicating the formation of a C_2-

Table 2. Preparation of bispalladacycles **12**.



11 **12**

Entry	Product	R^1	R^2	Yield[a] [%]	dr[b]
1	**12a**	Ph	*p*-Tol	56	>100:1
2	**12b**	Ph	C_6F_5	34	>100:1
3	**12c**	Ph	mesityl	40	>100:1
4	**12d**	Ph	*p*-Ph-C_6H_4	40	>100:1
5	**12e**	Ph	CF_3	35	>100:1
6	**12f**[c]	$(CH_2)_4$	*p*-Tol	5–25	>100:1

[a] Isolated yield after purification by silica gel filtration. [b] dr referring to a single Cp unit of the product after silica gel filtration as determined by ^{1}H NMR.[33] [c] The absolute configuration of **11f** and **12f** is opposite to the one depicted in Table 2.

symmetric species. An X-ray crystal structure analysis of **12a** revealed that the bispalladacycles are C_2-symmetric dimers with an (S_p,S'_p,S^*_p,$S^{*\prime}_p$)-configuration[18] (Figure 3).[15] The formation of a single dimeric isomer is remarkable in the sense, that in principle seven different diastereomeric dimers with regard to the planar chirality could have been formed.[19] Due to the theoretical stereochemical complexity, the dr values provided in Table 2 refer to a single Cp unit per complex. The complexes **12** can also be regarded as macrocyclic systems comprising two ferrocenyl units and four chloride bridged palladium ions (see bottom view in Figure 3). The dimeric nature of **12** forces two chloride bridged palladium square planes to be arranged in an almost co-planar fashion which is otherwise unusual. Moreover, halide bridged ferrocenyl monoimidazoline palladacycle complexes and other conventional halide bridged palladacycles usually form geometric isomers about the Pd^{II} centers. In contrast, in the present case the planar chirality dictates for geometric reasons the coordination sphere about the Pd^{II} square planes in a sense that the all-(S_p)-configured complexes **12** exist exclusively as all-*trans*-configured isomers, that is, the imidazoline N-atoms, which are positioned in the same $(PdCl)_2$ plane, are always arranged *trans* to each other.

The moderate but reproducible yields for the biscyclopalladation step (best yield: 56% for R^1=Ph, R^2=*p*-Tol) is the consequence of the formation of a side product, which is most likely the expected oligomeric/polymeric material. This assumption is supported by extremely complex ^{1}H NMR spectra. Attempts to transform this side-product into the Cl-bridged dimer were not successful. Moreover, attempts to form monomeric acac complexes or PPh_3 adducts to simplify the stereochemical analysis and to allow the unambiguous identification of the side product remained fruitless. In fact we cannot rule out the possibility that diastereomers pos-

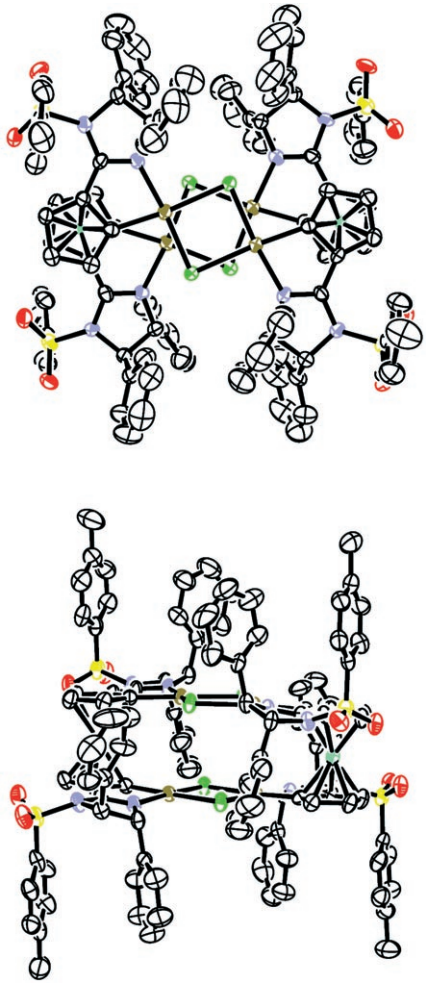
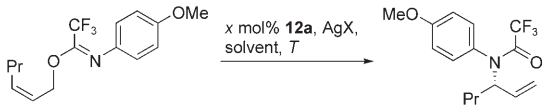


Figure 3. Ortep-representations of the dimeric bispalladacycle **12a**. The 30% probability ellipsoids have the following color code: C (black); N (blue); O (red); S (yellow); Fe (aquamarine); Pd (bronze); Cl (green). H atoms are omitted for clarity. At the top: view along the ferrocene axis; below: view perpendicular to the ferrocene axis.

sessing one (R_p)- and one (S_p)-configured Cp unit per ferrocene moiety are consumed by polymerization since no stable dimeric geometry might be found for such a system. The isolation of the pure dimeric complexes **12** is nevertheless readily achieved by a simple filtration over silica gel using dichloromethane as eluent, since the side products have significantly different R_f values and require a more polar eluent such as pure EtOAc. While in the case of imidazoline systems **11a–e** derived from (*R*,*R*)-1,2-diphenylethane-1,2-diamine (**10a**), no oxidative decomposition was observed during the biscyclopalladation, with ligand **11f** derived from (*R*,*R*)-cyclohexane-1,2-diamine (**10b**), the product was formed in low and irreproducible yield (ranging from 5–25%) presumably as a result of a significantly lower stability of both the ligand and the generated Pd complex (Table 2, entry 6).

The diastereomerically pure bispalladacycle **12a** was then examined in the aza-Claisen rearrangement of the *Z*-configured trifluoroacetimidate model substrate **13a** bearing an

Table 3. Screening of conditions for the rearrangement of model substrate **13a**.



13a **14a**

Entry	*x* mol% **12a**	AgX (mol%)	*T* [°C]	Solvent	Activation time [h]	*t* [h]	Yield[a] [%]	*ee*[b] [%]
1[d]	5	AgTFA (10)	20	CH_2Cl_2	3	91	87	91
2[d]	5	AgTFA (20)	20	CH_2Cl_2	3	44	80	89
3[d]	5	AgTFA (30)	20	CH_2Cl_2	3	20	94	89
4[c,d]	5	AgTFA (30)	20	CH_2Cl_2	3	89	87	91
5[d]	5	AgOTs (30)	20	CH_2Cl_2	3	18	95	94
6[e]	5	AgOTs (30)	20	$CHCl_3$	3	24	18	94
7[e]	5	AgOTs (30)	20	$CHCl_3$	22	24	76	96
8[e]	5	AgOTs (30)	20	$CHCl_3$	46	24	83	95
9[e,g]	5	AgOTs (30)	20	$CHCl_3$	3	24	77	95
10[f]	0.5	AgOTs (3)	20	$CHCl_3$	45	24	72	97
11[f]	0.1	AgOTs (0.6)	20	$CHCl_3$	45	24	14	96
12[f]	0.1	AgOTs (0.6)	40	$CHCl_3$	46	72	80	94
13[f]	0.1	AgOTs (0.6)	55	$CHCl_3$	46	72	98	95

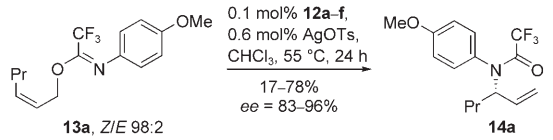
[a] The reactions were performed on 8 mg scale and the yields were determined by ^{1}H NMR after filtration over silica gel. The remaining material is starting material (<2% decomposition). **13a** contained 2% of the *E* isomer. [b] *ee* determined by HPLC on a chiral stationary phase (Daicel OD-H) after hydrolysis of **14a** to the corresponding secondary amine. [c] Reaction in the presence of 20 mol% proton sponge. [d] 200 μL of solvent were used. [e] 50 μL of solvent were used. [f] 10 μL of solvent were used. [g] The catalyst was activated at 40°C.

*n*Pr substituent at the imidate 3-position.[20] The chloride bridged dimer displayed no catalytic activity at all, presumably since in the dimeric rigid cage-like structure an olefin moiety of the substrate is not able to substitute one of the strongly binding bridging chloride anions. Consequently, the chloride counteranion was exchanged by the more labile trifluoroacetate ligand using silver trifluoroacetate (AgTFA) as a chloride trap. The rearrangement of **13a** proceeded still very sluggishly in CH_2Cl_2 using 2 equiv of AgTFA/dimer **12a** even in the presence of 5 mol% of the bispalladacycle yet provided (*S*)-**14a** in high yield and with 91% *ee* (Table 3, entry 1). An increased amount of the silver salt (4 or 6 equiv) improved the reaction rate significantly while the high enantioselectivity was maintained (entries 2–3). Proton sponge (1,8-bis(dimethylamino)naphthalene), which has been used as an additive with several catalysts to suppress elimination reactions and which often has a positive impact on the enantioselectivity of the aza-Claisen rearrangement reactions, had in the present case no beneficial effect with regard to the enantioselectivity, but considerably slowed down the reaction (entry 4). Compared to AgTFA, AgOTs slightly increased the catalyst activity and since product (*S*)-**14a** was also formed with enhanced enantioselectivity (94% *ee*, entry 5), AgOTs was selected as the preferred catalyst activating agent. To further improve both catalytic activity and enantioselectivity, the influence of various solvents was investigated. For the solvent screening and all following experiments, the activation of the precatalyst was still performed in CH_2Cl_2. Coordinating solvents such as acetonitrile, acetone or dioxane resulted in significantly slower conversion and reduced enantioselectivities. Using $CHCl_3$ as solvent for the rearrangement, a marked influence of the activation time was found (entries 6–9) which is presumably best explained by the fact that the chloride bridged dimeric bispalladacycles **12** are kinetically much more inert than standard halide bridged monopalladacycle dimers owing to the rigid cage-like structure containing two almost parallel $(PdCl)_2$ planes. The best turnover numbers were accomplished with a catalyst activation time of two days at room temperature (entry 8) or of 3 h at 40°C (entry 9). With the optimized catalyst activation procedure the catalyst amount could be reduced to 0.5 mol% (entry 10) while still obtaining reasonable conversions at room temperature. In contrast the reaction became very slow with only 0.1 mol% precatalyst activated by 0.6 mol% AgOTs (entry 11). However, the excellent thermal robustness and the high solubility of the catalyst allowed us to perform the rearrangement at elevated temperatures and at higher concentrations (entries 12–13): at 55°C, the product was formed with 95% *ee* in almost quantitative yield after three days, although the model substrate **13a** was not isomerically pure (*Z*/*E* 98:2).

After optimization of the model reaction conditions, the diastereomerically pure bispalladacycles **12a–f** which differ in the residue R^2 connected to the sulfonyl moiety and in the imidazoline backbone (Table 4) were investigated under identical conditions (0.1 mol% **12**, 0.6 mol% AgOTs, catalyst activation time: 46 h at room temperature, $CHCl_3$, 55°C). The reactions were stopped after 24 h to directly compare the catalytic activity. While **12a** and **12b** gave similar activities and enantioselectivities demonstrating that the electronic influence of an aromatic residue R^2 is almost negligible (entries 1–2), the bulkier mesityl- and biphenylsulfonyl groups reduced the catalyst activity considerably while still maintaining high enantioselectivities (entries 3–4). With the non-aromatic and strongly electron withdrawing SO_2CF_3 residue, the catalytic activity was surprisingly reduced to a large degree, while the *ee* was still excellent (entry 5). The influence of the imidazoline backbone was demonstrated by catalyst precursor **12f** derived from cyclohexane-1,2-diamine. This system had the lowest catalytic activity and resulted in a considerably lower enantioselectivity (entry 6) which might be a direct consequence of the catalyst stability.

To achieve a high reproducibility of the catalytic procedure, stem solutions of the hygroscopic silver salt in acetonitrile were prepared in a glove box under nitrogen atmos-

Table 4. Catalyst screening with model substrate **13a**.



13a, *Z*/*E* 98:2 **14a**

Entry	**12**	R^1	R^2	Reaction time [h]	Yield[a] [%]	*ee*[b] [%]
1	**a**	Ph	*p*-Tol	24	78	96
2	**b**	Ph	C_6F_5	24	77	92
3	**c**	Ph	mesityl	24	37	90
4	**d**	Ph	*p*-Ph-C_6H_4	24	21	92
5	**e**	Ph	CF_3	24	54	95
6	**f**	$(CH_2)_4$	*p*-Tol	24	17	83[c]

[a] The reactions were performed on 8 mg scale (use of 10 μL of $CHCl_3$) and the yields were determined by ^{1}H NMR after filtration over silica gel. The remaining material is starting material (<2% decomposition). [b] *ee* determined by HPLC on a chiral stationary phase (Daicel OD-H) after hydrolysis of **14a** to the corresponding secondary amine. [c] The *R* enantiomer was formed in excess.

phere. After the precatalyst activation in CH_2Cl_2, the heterogeneous mixture is filtrated over a small pad of Celite/CaH_2 (1:1) to remove the AgCl precipitate and unreacted AgOTs and to remove traces of acid which might cause decomposition of the acid labile substrates. To acquire more information about the nature and structure of the catalytically active species formed from the best precatalyst **12a**, ^{1}H NMR investigations were performed showing the presence of a structurally well defined C_2-symmetric major species which is formed in large excess and which is in equilibrium with a complex mixture.[21] Although the solvent of the AgOTs stem solution is removed in vacuum prior to the catalyst activation, one acetonitrile molecule is coordinated to each Pd center in the major species **15** of the activated catalyst (Figures 4 and 5, spectrum 1).

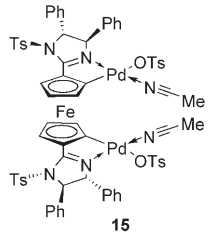


Figure 4. Proposed structure of the activated catalyst as revealed by ^{1}H NMR analysis.

If the activated catalyst is subjected to vacuum for extended periods of time, the amount of the complex side product(s) is significantly increased. Repetitive dissolution of the activated catalyst in $CDCl_3$ and subsequent removal of the solvent has the same effect (see Figure 5, spectra 2–5). This effect is dramatically enhanced by evaporation from a toluene/$CDCl_3$ mixture (spectrum 6). However, addition of acetonitrile regenerates **15** (spectrum 7). The minor species of the activated catalyst is thus formed by removal of acetonitrile as coordinating ligand presumably resulting in the formation of dimeric and oligomeric complexes. This process is reversible and the coordinated acetonitrile can rapidly exchange with free acetonitrile as revealed by the use of free CD_3CN (10 equiv). After 2 min, ca. 60% of the coordinated CH_3CN were already replaced at room temperature in $CDCl_3$ (catalyst concentration: 10 μmol mL^{-1}).

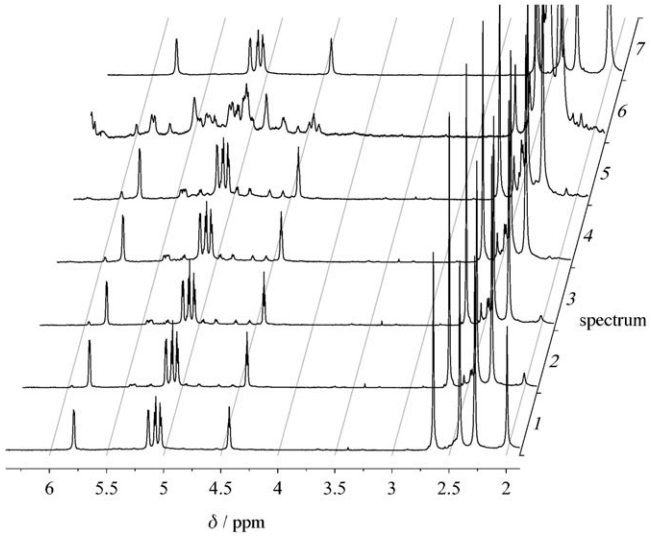


Figure 5. NMR investigations of the activated catalyst (in $CDCl_3$ at 21 °C) generated from **12a** in CH_2Cl_2 and a stem solution of AgOTs in MeCN. Spectrum *1* shows the freshly activated catalyst species (after 15 min at high vacuum), which consists largely of the monomeric symmetric complex **15**. Free MeCN is detected at 1.99 ppm. Spectra *2*–*5* were recorded after repetitive dissolution in $CDCl_3$ and subsequent evaporation of the solvent. Spectrum *6* was obtained after dissolution in a mixture of $CDCl_3$ and toluene and subsequent removal of the solvent (repeated twice). Treatment of the resulting material with acetonitrile regenerated complex **15** as revealed by spectrum *7*.

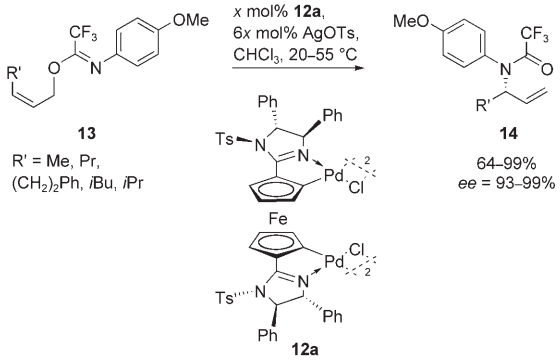
Although we have no direct proof, since attempts to crystallize the activated catalyst for an X-ray crystal structure analysis failed and ^{1}H NMR NOE analysis was without explanatory power in that case, it is very likely that acetonitrile coordinates in the major species *trans* to the imidazoline N-atom as a result of the *trans* effect[22] in analogy to the structures of the large majority of palladacycle complexes bearing an additional monodentate N-ligand such as pyridine or N-methylimidazole.[23] The second coordination site, which should therefore be *cis* to the imidazoline unit, is occupied by tosylate.[24] Even with an excess of free acetonitrile, the tosylate is not replaced by the neutral ligand meaning that a cationic Lewis acid is not formed.

Identical spectra for the activated catalyst were obtained whether by treatment of **12a** with 4, 5 or 6 equiv of AgOTs. No paramagnetic species was observed even with an excess of the silver salt indicating that there is almost no oxidation of the ferrocenyl core providing a ferrocenium salt. This stands in contrast to previous reports which have shown that ferrocenyl oxazoline and ferrocenyl imidazoline monopalladacycles are oxidized by silver salts to the corresponding ferrocenium species which are the catalytically active spe-

cies.[3c,e,25] Even so, 6 equiv of AgOTs per palladacycle dimer were generally utilized to ensure a complete chloride exchange.

Employing the best catalyst precursor **12a**, the scope of *Z*-configured imidates **13** was studied (Table 5). The rate of the rearrangement depends primarily on the steric bulk of the residue R′. With α-unbranched substituents (R′ = Me, *n*Pr, $(CH_2)_2$Ph, *i*Bu), (*S*)-**14** is formed in excellent yield and enantioselectivity with 1.0 mol% precatalyst at room temperature (entries 1, 4, 6, 9). By decreasing the precatalyst amount to 0.1 to 0.2 mol% and increasing the reaction temperature to 55 °C, yields and enantioselectivities were only marginally affected due to the high robustness of the catalyst against decomposition (entries 2, 5, 7, 10). The rearrangements were performed using 25 mg of substrates **13**, yet, working on larger scale (2.6 to 11.6 mmol) provided similar results (entries 3, 8, 11).

Table 5. Screening of substrates **13** bearing different groups R′.



Entry	**13**	R′	*x* mol% **12a**	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1[c]	**a**	*n*Pr	1.0	20	96	98
2[c]	**a**	*n*Pr	0.1	55	94	97
3[c,d]	**a**	*n*Pr	0.1	55	97	97
4[e]	**b**	Me	1.0	20	94	96
5[f]	**b**	Me	0.1	55	97	94
6[c]	**c**	$(CH_2)_2$Ph	1.0	20	99	96
7[c]	**c**	$(CH_2)_2$Ph	0.2	55	90	95
8[g]	**c**	$(CH_2)_2$Ph	0.2	55	92	97
9[c]	**d**	*i*Bu	1.0	20	87	98
10[c]	**d**	*i*Bu	0.1	55	86	98
11[h]	**d**	*i*Bu	0.1	55	93	99
12[c]	**e**	*i*Pr	1.0	55	64	93

[a] Isolated yield. The reactions were unless otherwise noted performed on 25 mg scale. [b] *ee* determined by HPLC on a chiral stationary phase (Daicel OD-H) after hydrolysis of **14** to the corresponding secondary amine. [c] Reaction time 3 d. [d] 3.5 g of substrate **13a** (11.6 mmol) were used. [e] Reaction time 1.5 d. [f] Reaction time 1 d. [g] 0.94 g (2.59 mmol) of substrate **13c** were used. [h] 1.21 g of substrate **13d** (3.83 mmol) were used.

Particularly noteworthy in this series are the excellent *ee* values obtained with the most difficult 3-alkyl substituted substrate in terms of enantioselectivity, imidate **13b** bearing the small methyl substituent (94–96% *ee*, entries 4–5). The highest literature value so far was 86% for this specific example.[3a]

For the first time even *Z*-configured trifluoroacetimidates bearing an α-branched alkyl moiety were well tolerated as substrates as exemplified for **13e** (R′ = *i*Pr, entry 13) providing **14e** in a yield of 64% and with 93% *ee*. 1 mol% of precatalyst and a temperature of 55 °C were employed in this case to obtain preparatively useful conversions. The lower yield as compared to the use of substrates bearing α-unbranched alkyl groups is a direct consequence of the lower reaction rate.[26]

Similar arguments as those used for our FIP catalyst **7** bearing the Cp^{Φ} spectator ligand can be used to rationalize the high enantioselectivity and the absolute configuration of the rearrangement product. The enantioselectivity determining step is expected to be the enantioface selective coordination of the olefin moiety to one Pd^{II} center (Figure 5).[27] Assuming that the olefin will coordinate *trans* to one imidazoline N atom due to the *trans* effect thus replacing the neutral acetonitrile ligand,[23] the imidate N atom will attack the olefin at the face remote to the Pd atom (Figure 6). In the preferred orientation of the olefin part parallel to the ferrocene axis, the sterically undemanding allylic C(1) methylene moiety should point towards the bulky metallocene core to minimize unfavorable steric interactions. Coordination of the enantiotopic olefin face should be less favorable again owing to steric arguments.[28]

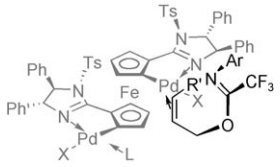
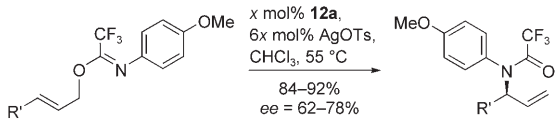


Figure 6. Explanation of the enantioselectivity and absolute configuration by enantioface selective olefin coordination.

However, using 3-monosubstituted substrates with *E*-configuration under the above-described reaction conditions optimized for the *Z*-configured systems gave significantly lower and synthetically unattractive enantioselectivities (Table 6, *ee* = 62–78%) while the catalytic activities are slightly reduced with the exception of substrate (*E*)-**13e** bearing the α-branched *i*Pr group (entry 4). The major enantiomers formed from (*E*)-**13** have, as expected and in accordance with our model, the opposite absolute configuration as those derived from (*Z*)-**13**. We can only speculate about the origin of the reduced selectivity. One of many possible explanations would, for example, be that the *E*-configured substrates partially undergo a two-point-binding to Pd^{II} thus replacing both MeCN and the tosylate counterion by the olefin moiety and the imidate N atom. This would mean that the nucleophilic attack of the imidate on the olefin could proceed via the expected *anti*-aminopalladation, but in competition with a *syn*-aminopalladation thus lowering the enantioselectivity. The two-point-binding mode would also explain the reduced reactivity of the *E* sub-

Table 6. Investigation of *E*-configured substrates.



(*E*)-**13** **14**

Entry	(*E*)-**10**	R′	mol % **12a**	Yield[a] [%]	*ee*[b] [%]
1	**a**	*n*Pr	0.2	84	70
2	**b**	Me	0.1	91	62
3	**d**	*i*Bu	0.5	92	78
4	**e**	*i*Pr	1.0	87	63

[a] The reactions were performed on 25 mg scale for 72 h. The yields were determined after column chromatography. The remaining material is mostly starting material. [b] *ee* determined by HPLC on a chiral stationary phase (Daicel OD-H) after hydrolysis of **14a** to the corresponding secondary amine.

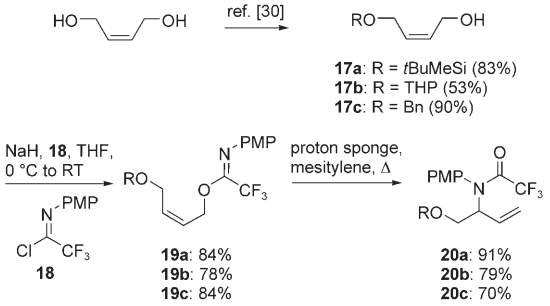
strates, since the catalyst might be partially blocked by the chelating substrate.

The observed reaction rate tendency is quite unusual, since in general *E*-configured 3-monosubstituted allylic imidates are known to rearrange significantly faster than their *Z*-configured counterparts. This is attributed to the fact that the 3-substituent adopts in the former case a pseudoequatorial position in the six-membered cyclic transition state leading to a cationic intermediate like **5**, whereas in the latter case the substituent is expected to be in the less favorable pseudoaxial position.

The results for *Z*-configured substrates presented in Table 5 are restricted to unfunctionalized trifluoroacetimidate substrates. However, a prerequisite for the use of the easily accessible FBIP in target-oriented synthesis would be next to high catalyst activities and enantioselectivities its tolerance to synthetically important functional groups.[29] The commercially available *Z*-configured but-2-en-1,4-diol served as starting material to synthesize functionalized substrates. Imidates **19a–c** containing a silyl ether, benzyl ether or THP acetal moiety were prepared in two steps by monoprotection[30] followed by imidate formation (Scheme 3).

Attempts to synthesize the racemic rearrangement products **20a–c** as reference samples using achiral Pd^{II} catalysts such as $[Cl_2Pd(NCCH_3)_2]$ were unsuccessful and resulted either in no conversion or in decomposition. The racemic samples had to be prepared via thermally induced [3,3]-sigmatropic rearrangements in the presence of catalytic amounts of proton sponge to trap traces of acid in order to avoid substrate decomposition (Scheme 3).

Additional imidate substrates were prepared via alkylation of dimethylmalonate with allylic chloride **21** and subsequent Krapcho decarboxylation providing THP acetal **23**,[30a,31] which was used to prepare various functionalized derivatives (Scheme 4). Acidic hydrolysis of the acetal moiety and ensuing imidate formation gave access to **24** containing a methyl ester group. A methyl ketone derivative was prepared by formation of morpholine amide **25** and monoaddition of MeLi to the amide moiety,[32] while benzyl ether **29** was obtained via reduction of **23** and Williamson



Scheme 3. Preparation of functionalized substrates **19a–c**.

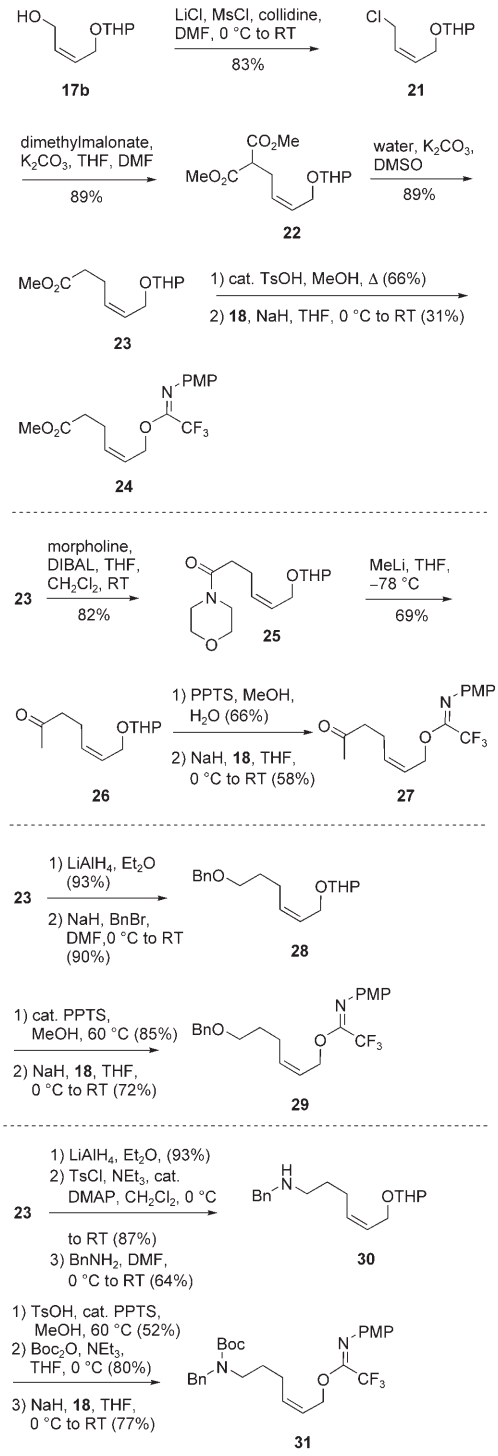
etherification. Boc-protected benzyl amine **31** was synthesized by monoalkylation of benzyl amine, THP cleavage and carbamate formation.

All of the imidate substrates prepared through intermediate **23** could be rearranged by the action of a catalytic amount of $[Cl_2Pd(NCCH_3)_2]$ (10 mol %) providing racemic amides **32a–d** (Scheme 5).

For the enantioselective rearrangement of functionalized substrates, FBIP precatalyst **12a** was again activated by AgOTs. Experiments on 8 mg scale at 55 °C using 0.05, 0.1, 0.2, or 0.5 mol % were performed to find the lowest catalyst loading which still provides complete conversion within 72 h. The best conditions were subsequently applied on 250 mg scale (Table 7). For most of the investigated substrates the required catalyst amount was slightly higher than for the non-functionalized substrates. This outcome is attributed to the competitive reversible binding of the heteroatom substituents to the catalyst. For the TBS protected alcohol **19a** as little as 0.05 mol % resulted in a yield of 94–96 % on 250 mg and 4 g scale, respectively (entries 5 and 6), since the TBS protected oxygen atom is not an efficient Lewis base. Ester, ketone, ether, silyl ether, acetal and Boc protected amino groups are all well tolerated and the optimized reaction conditions provided the protected, functionalized allylic amines in nearly quantitative isolated yield for each example with the catalyst loading generally not exceeding 0.2–0.5 mol %. All of these high-added-value building blocks were produced with excellent enantioselectivity (*ee* = 96–98 %). The value of the presented methodology is further enhanced by the operational simplicity. The solution of the activated catalyst is added to neat substrate, the reaction vessel is subsequently sealed and heated for three days to 55 °C. After cooling to room temperature, a mixture of cyclohexane/ethyl acetate is added causing a precipitation of the Pd complex. The product is subsequently isolated in analytically pure form by a simple filtration.

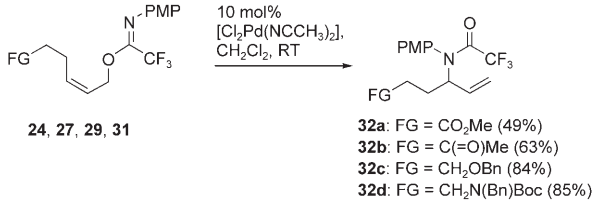
Conclusion

We have developed the first highly active enantioselective catalyst for the aza-Claisen rearrangement of *Z*-configured trifluoroacetimidates requiring as little as 0.1 mol % of catalyst precursor for most of the alkyl substituted substrates.



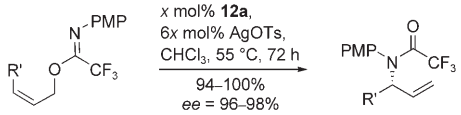
Scheme 4. Preparation of functionalized substrates **24**, **27**, **29** and **31**.

Key step of the catalyst formation is an unprecedented highly diastereoselective biscyclopalladation providing dimeric macrocyclic complexes of fascinating structure. This novel catalyst type also allowed for the formation of almost enantiomerically pure allylic amines ($ee \geq 96\,\%$) substituted with important functional groups (esters, ketones, ethers, silyl ethers, acetals, protected amines) providing high-added-value building blocks in excellent yield ($\geq 94\,\%$; 0.05–0.5 mol% of catalyst precursor). These results—the simple and rapid ligand and catalyst preparation, the unprecedented catalytic activity for *Z*-configured allylic trifluoroacetimidate substrates, the excellent enantioselectivity, scalability and functional group compatibility as well as the operational simplicity—should render this methodology highly appealing as a practical and valuable tool for target oriented synthesis.



Scheme 5. Synthesis of racemic functionalized allylic amine derivatives **32a–d**.

Table 7. Catalytic asymmetric synthesis of functionalized allylic amine building blocks.



Entry	Product	R′	*x* mol%	Yield[a] [%]	*ee*[b] [%]
1	**32a**	$(CH_2)_2CO_2Me$	0.5	98	98
2	**32b**	$(CH_2)_2C(=O)Me$	0.5	97	97
3	**32c**	$(CH_2)_3OBn$	0.2	100	97
4	**32d**	$(CH_2)_3N(Bn)Boc$	0.2	99	98
5	**20a**	CH_2OTBS	0.05	94	97
6[c]	**20a**	CH_2OTBS	0.05	96	97
7[d]	**20b**	CH_2OTHP	0.2	94	98
8	**20c**	CH_2OBn	0.2	99	96

[a] The reactions were unless otherwise noted performed on 250 mg scale. Isolated yield after filtration over silica gel. [b] Determined by HPLC on a chiral stationary phase (Daicel OD-H). [c] The reaction was performed on 4.0 g scale. [d] The reaction was performed on 25 mg scale. Proton sponge (0.2 mol%) was required to avoid decomposition of the acetal moiety.

Experimental Section

General methods and additional selected experimental procedures are given in the Supporting Information.

Ferrocene-1,1′-bis-*N*,*N*-dimethylthioamide (9):[13] Ferrocene (13.36 g, 71.8 mmol) was dissolved in diethyl ether (300 mL) and *n*BuLi (99 mL, 158.4 mmol, 2.2 equiv, 1.6 mol L^{-1} in *n*-hexane) and TMEDA (26 mL, 180 mmol, 2.4 equiv) were added successively. After 19.5 h the reaction mixture was cooled down to −78 °C and a solution of *N*,*N*-dimethylthiocarbamate chloride (19.5 g, 160 mmol, 2.20 equiv) in Et_2O (170 mL) was added. After 5 min the cooling bath was removed and stirring was continued for additional 120 min. The reaction mixture was filtered, the filter cake was extracted with $CHCl_3$ and the solvent was removed. The remaining solid residue was washed with Et_2O. The product was obtained as a dark red crystalline solid (13.9 g, 38.8 mmol, 54%). M.p. 163–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): $\delta = 4.78$ (t, $J = 1.8$ Hz, 4H, *o*-C_5H_4R),

4.43 (t, $J=1.8$ Hz, 4H, *m*-C_5H_4R), 3.49 (s, 6H, NCH_3), 3.32 ppm (s, 6H, NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): $\delta=198.3$, 88.9, 76.2, 72.4, 45.2, 44.7 ppm; IR (film): $\tilde{\nu}=3074$, 2925, 1510, 1505, 1434, 1386, 1333, 1273, 1133, 1057, 990, 913 cm^{-1}; HRMS (MALDI): *m/z*: calcd for $C_{16}H_{21}N_2S_2Fe$: 361.0490 $[M+H]^+$; found: 361.0482; elemental analysis calcd (%) for $C_{16}H_{20}N_2S_2Fe$ (360.32): C 53.33, H 5.59, N 7.77; found: C 53.44, H 5.58, N 7.81.

(4″*R*,5″*R*)-1,1′-Bis-(2″-4″,5″-dihydro-4″,5″-diphenyl-1″-H-imidazolyl) ferrocene (33a): A solution of Meerwein's salt (579 mg, 3.05 mmol, 2.05 equiv) in CH_2Cl_2 (7 mL) was added to thioamide **6** (536 mg, 1.48 mmol) in CH_2Cl_2 (10 mL). After 3.5 h (*R*,*R*)-1,2-diphenylethane-1,2-diamine (**10a**) (663 mg, 2.10 equiv, 3.12 mmol) dissolved in CH_2Cl_2 (7 mL) was added rapidly. After 17 h at room temperature, ca. 75% of the solvent were removed and diisopropyl ether (40 mL) was added causing precipitation. The supernatant was removed by decantation and the solid residue was taken up in CH_2Cl_2 and washed with 2 N NaOH. The organic phase was dried with Na_2CO_3 and the solvent was removed after filtration. The crude product (988 mg) was directly used for the sulfonylation reactions. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): $\delta=7.30$–7.15 (m, 20H, arom. *H*), 6.31 (br, 2H, N*H*), 4.78–4.63 (br, 4H, C*H*Ph) 4.74 (br, 2H, *o*-C_5H_4R), 4.68 (br, 2H, *o*-C_5H_4R), 4.58 (br, 2H, *m*-C_5H_4R), 4.43 ppm (br, 2H, *m*-C_5H_4R); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): $\delta=$ 164.6, 143.2, 128.5, 127.2, 126.7, 74.5, 73.0, 71.1, 70.6, 69.1 ppm; HRMS (MALDI): *m/z*: calcd for $C_{40}H_{35}N_4Fe$: 627.2206 $[M+H]^+$; found: 627.2195.

General procedure (GP 1) for the sulfonylation of bisimidazolines 33: Bisimidazolines **33** were dissolved in CH_2Cl_2 and NEt_3. Subsequently, DMAP and the sulfonylating agent were successively added at 0 °C. The reaction mixture was slowly warmed to room temperature. After 3–18 h additional CH_2Cl_2 was added and the mixture was washed with saturated aqueous Na_2CO_3 solution. The aqueous phase was extracted once with CH_2Cl_2 and the combined organic phases were dried over $NaHCO_3$. The crude products were purified by flash column chromatography.

(4″*R*,5″*R*)-1,1′-Bis-(2″-4″,5″-dihydro-4″,5″-diphenyl-1″-tosyl-imidazolyl) ferrocene (11a): According to GP 1, crude **33a** (395 mg, < 0.630 mmol) was treated with NEt_3 (351 μL, 2.52 mmol, > 4.0 equiv), DMAP (14 mg, 0.11 mmol, > 0.18 equiv) and TsCl (480 mg, 2.52 mmol, > 4.0 equiv) for 3 h in CH_2Cl_2 (10 mL). After flash chromatography (cyclohexane/EtOAc 4:1, 3% NEt_3) **11a** was obtained as a red crystalline solid (334 mg, 0.357 mmol, 57% starting from **9**). M.p. 225 °C (decomp); $[\alpha]_D^{25}=(c=0.110$ g dL^{-1}, $CHCl_3)=-578.1$; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): $\delta=$ 7.53–7.37 (m, 8H, arom. *H*), 7.36 (t, $J=7.2$ Hz, 2H, *p-H* of Ph), 7.24–7.16 (m, 6H, arom. *H*), 7.11 (t, $J=7.2$ Hz, 4H, *m-H* of Ph), 7.03 (d, $J=7.8$ Hz, 4H, arom. *H*), 6.70 (d, $J=6.9$ Hz, 4H, *arom. H*), 5.29 (t, $J=1.5$ Hz, 2H, *o*-C_5H_4R), 5.08 (d, $J=3.9$ Hz, 2H, C*H*Ph), 5.06 (t, $J=1.2$ Hz, 2H, *o*-C_5H_4R), 5.02 (d, $J=3.6$ Hz, 2H, C*H*Ph), 4.51 (m, 2H, *m*-C_5H_4R), 4.43 (m, 2H, *m*-C_5H_4R), 2.37 ppm (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): $\delta=158.9$, 144.1, 142.2, 141.7, 134.6, 129.4, 129.2, 128.4, 128.0, 127.6, 127.0, 125.8, 77.3, 74.5, 74.1, 73.6, 73.5, 73.2, 72.6, 21.6 ppm; IR (film): $\tilde{\nu}=2924$, 1620, 1494, 1454, 1366, 1282, 1172, 1090, 1022 cm^{-1}; HRMS (MALDI): *m/z*: calcd for $C_{54}H_{47}N_4O_4S_2Fe$: 935.2383 $[M+H]^+$; found: 935.2366; elemental analysis calcd (%) for $C_{54}H_{46}N_4O_4S_2Fe$ (934.94): C 69.37, H 4.96, N 5.99; found: C 69.38, H 4.79, N 5.99.

General procedure (GP 2) for the biscyclopalladation of bisimidazolines 11: A solution of bisimidazolines **11** in a 1:1 mixture of CH_2Cl_2/methanol was cooled to 0 °C. Na_2PdCl_4 and NaOAc were added and the reaction was allowed to slowly warm to room temperature. After stirring for the indicated time at this temperature, the solvent was completely removed in vacuo at 40 °C and the crude product was subjected to a filtration over silica gel with CH_2Cl_2 as eluent.

Bis(di-μ-chloro-μ-{[bis-η^5-(4′*R*,5′*R*)-(S_p)-2-(2′-4′,5′-dihydro-4′,5′-diphenyl-1′-tosyl-imidazolyl)cyclopentadienyl)] iron(II) 1-*C*,3′-*N*} dipalladium (II)) (12a): According to GP 2, **11a** (224 mg, 0.240 mmol) was treated with Na_2PdCl_4 (166 mg, 0.563 mmol, 2.35 equiv) and NaOAc (55 mg, 0.67 mmol, 2.8 equiv) in 18 mL of solvent for 18 h. **12a** was isolated as a dark red crystalline substance (162 mg, 0.133 mmol, 56%). M.p. > 230 °C; $[\alpha]_D^{25}=(c=0.0215$ g dL^{-1}, $CHCl_3)=-305.4$; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): $\delta=7.63$ (d, $J=7.5$ Hz, 8H, arom. *H*), 7.35 (t, $J=7.5$ Hz, 4H, *p-H* of ph), 7.21 (m, 20H, arom. *H*), 7.02 (t, $J=7.5$ Hz, 8H, *m-H*), 6.95 (d, $J=8.4$ Hz, 8H, arom. *H*), 6.60 (d, $J=7.5$ Hz, 8H, arom. *H*), 5.06 (dd, $J_1=2.4$, $J_2=0.9$ Hz, 4H, *o*-C_5H_3RR′), 4.94 (d, $J=2.4$ Hz, 4H, C*H*Ph), 4.80 (d, $J=2.4$ Hz, 4H, C*H*Ph), 4.56 (dd, $J_1=2.4$, $J_2=0.9$ Hz, 4H, *o*-C_5H_3RR′), 4.41 (t, $J=2.4$ Hz, 4H, *m*-C_5H_3RR′), 2.36 ppm (s, 12H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): $\delta=169.9$, 144.9, 140.7, 139.9, 134.3, 129.8, 129.5, 128.7, 128.5, 127.3, 127.0, 126.8, 125.4, 96.6, 77.1, 75.9, 75.2, 71.6, 69.6 (2C), 21.5 ppm; IR (film): $\tilde{\nu}=3029$, 1596, 1555, 1454, 1360, 1168, 1095, 1028, 969 cm^{-1}; HRMS (MALDI): *m/z*: calcd for $C_{108}H_{88}N_8O_8S_4Cl_4Fe_2Pd_4$: 2432.9232 $[M]^+$; found: 2432.9192; elemental analysis calcd (%) for $C_{108}H_{88}N_8O_8S_4Cl_4Fe_2Pd_4$ (2433.34): C 53.31, H 3.64, N 4.60.; found: C 53.59, H 3.42, N 4.52.

General procedure (GP 3) for the catalyst activation (Table 5): A solution of AgOTs (37.4 mg, 0.134 mmol, 6.0 equiv) in MeCN (0.155 mL) was evaporated to dryness and a solution of **12a** (54.4 mg, 0.0224 mmol) in CH_2Cl_2 (2 mL) was added to the silver salt. The reaction mixture was subsequently diluted under nitrogen atmosphere with CH_2Cl_2 (14 mL) and stirred in the absence of light. After 46 h the mixture was filtered over CaH_2/Celite (1:1; vol: 1 cm^3). The filter cake was extracted with CH_2Cl_2 until the organic solution was colorless. The solvent was removed with a steady flow of N_2 and finally by using high vacuum (15 min). A stem solution of activated catalyst **15** was prepared by dissolving the solid in dry $CHCl_3$ (1.05 mL; accounts for 20.0 mmol L^{-1} of dimer **12a** in its activated form). ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): $\delta=7.63$–7.12 (m, 48H, *arom. H*), 7.01 (t, $J=7.8$ Hz, 8H, *arom. H*), 6.92 (d, $J=7.6$ Hz, 8H, *arom. H*), 6.54 (d, $J=7.2$ Hz, 8H, *arom.* H), 5.78 (d, $J=2.1$ Hz, 4H, C_5H_3RR), 5.29 (d, $J=2.1$ Hz, 4H, C_5H_3RR), 5.07 (d, $J=3.3$ Hz, 4H, C*H*Ph), 5.02 (d, $J=3.3$ Hz, 4H, C*H*Ph), 2.64 (s, 12H, CH_3CN→Pd), 2.41 (s, 12H, N-Ts(CH_3)), 2.27 (s, 12H, Pd-O-Ts(CH_3)), 1.99 ppm (s, 12H, free CH_3CN); MS (MALDI): *m/z*: calcd for $C_{61}H_{51}FeN_4O_7Pd_2S_3$: 1316.96 $[M]^+$; found: 1316.96.

General procedure (GP 4) for the rearrangement of *Z*-configured substrates 13 using 12a as catalyst precursor (Table 5): To substrates **13** (25 mg) a solution of the activated catalyst (see GP 3) in $CHCl_3$ (entry 1: 39.0 μL; entry 4: 43.0 μL; entry 6: 32.3 μL; entry 9: 37.3 μL; entry 12: 39.0 μL; for entries 2, 5, 7 and 10 the catalyst stem solution was further diluted to a concentration of 4.47 mmol L^{-1}; amount used of the diluted stem solution: entry 2: 18.5 μL; entry 5: 20.5 μL; entry 7: 30.8 μL; entry 10: 17.8 μL) was added and the reactions were stirred in the absence of light under nitrogen atmosphere for the indicated time at the indicated temperature in a sealed and shielded flask. The remaining solvent was removed *in vacuo* at room temperature, the residue was suspended in cyclohexane/EtOAc 9:1 and subsequently purified by filtration over silica gel (for **14a–d**) or column chromatography (**14e**; cyclohexane/EtOAc 9:1).

(*S*)-2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-(1-propylallyl)acetamide [(*S*)-14a]: GP 4: Catalyst amount: 1.0 mol%; reaction time: 3 d; reaction temperature: 20 °C, yield: 96%. Catalyst amount: 0.1 mol%; reaction time: 3 d; reaction temperature: 55 °C, yield: 94%. The analytical data were in accordance with the literature.[3a,e]

Large-scale rearrangement of 13a (Table 5, entry 3): A solution of AgOTs (22.4 mg, 0.0801 mmol, 6.0 equiv) in MeCN (0.655 mL) was evaporated to dryness and a solution of **12a** (32.5 mg, 0.0134 mmol) in CH_2Cl_2 (9.5 mL) was added in the absence of light under nitrogen atmosphere to the silver salt. After 46 h the mixture was filtered over CaH_2/Celite (1:1; vol: 1.5 cm^3). The filter cake was extracted with CH_2Cl_2 until the organic solution was colorless. The solvent was removed with a steady flow of N_2 and finally by using high vacuum. A stem solution of the activated catalyst was prepared by dissolving the solid in dry $CHCl_3$ (1.00 mL; accounts for 13.3 mmol L^{-1} of the dimer **12a** in its activated form). 0.86 mL of the solution were added to neat **13a** (3.500 g, 11.62 mmol) and the solution was stirred in a sealed and shielded flask for 3 d at 55 °C in the absence of light under nitrogen atmosphere. The residue was suspended in cyclohexane/EtOAc 9:1 and subsequently purified by filtration over silica gel (cyclohexane/EtOAc 9:1) to obtain **14a** (3.404 g, 11.29 mmol, 97%, *ee* = 97%).

(*S*)-2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-(1-methylallyl)acetamide [(*S*)-14b]: GP 4: Catalyst amount: 1.0 mol%; reaction time: 40 h; reac-

tion temperature: 20 °C, yield: 94 %. Catalyst amount: 0.1 mol %; reaction time: 1 d; reaction temperature: 55 °C, yield: 97 %. The analytical data were in accordance with the literature.[3a,e]

(*S*)-2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-(1-phenethylallyl)acetamide [(*S*)-14c): GP 4: Catalyst amount: 1.0 mol %; reaction time: 3 d; reaction temperature: 20 °C, yield: 99 %. Catalyst amount: 0.2 mol %; reaction time: 3 d; reaction temperature: 55 °C, yield: 90 %. The analytical data were in accordance with the literature.[3a,e]

Large-scale rearrangement of 13c (Table 5, entry 8): A solution of AgOTs (22.9 mg, 0.08020 mmol, 6.0 equiv) in MeCN (0.260 mL) was evaporated to dryness and a solution of **12a** (33.8 mg, 0.0139 mmol) in CH_2Cl_2 (9.6 mL) was added to the silver salt in the absence of light under nitrogen atmosphere. After 46 h the mixture was filtered over CaH_2/Celite (1:1; vol: 1.5 cm^3). The filter cake was extracted with CH_2Cl_2 until the organic solution was colorless. The solvent was removed with a steady flow of N_2 and finally by using high vacuum. A stem solution of the activated catalyst was prepared by dissolving the solid in dry $CHCl_3$ (1.00 mL; accounts for 13.3 mmol L^{-1} of the dimer **12a** in its activated form). 0.378 mL of the solution were added to neat **13c** (0.940 g, 2.59 mmol) and the solution was stirred in a sealed and shielded flask for 3 d at 55 °C in the absence of light under nitrogen atmosphere. The residue was suspended in cyclohexane/EtOAc 9:1 and subsequently purified by filtration over silica gel (cyclohexane/EtOAc 9:1) to obtain **14c** (0.862 g, 2.37 mmol, 92 %, *ee* = 97 %).

(*S*)-2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-(1-isobutylallyl)acetamide [(*S*)-14d]: GP 4: Catalyst amount: 1.0 mol %; reaction time: 3 d; reaction temperature: 20 °C, yield: 87 %. Catalyst amount: 0.1 mol %; reaction time: 3 d; reaction temperature: 55 °C, yield: 86 %. The analytical data were in accordance with the literature.[3a,e]

Large-scale rearrangement of 13d (Table 5, entry 11): A solution of AgOTs (22.9 mg, 0.08020 mmol, 6.0 equiv) in MeCN (0.260 mL) was evaporated to dryness and a solution of **12a** (33.8 mg, 0.0139 mmol) in CH_2Cl_2 (9.6 mL) was added to the silver salt in the absence of light under nitrogen atmosphere. After 46 h the mixture was filtered over CaH_2/Celite (1:1, vol: 1.5 cm^3). The filter cake was extracted with CH_2Cl_2 until the organic solution was colorless. The solvent was removed with a steady flow of N_2 and finally by using high vacuum. A stem solution of the activated catalyst was prepared by dissolving the solid in dry $CHCl_3$ (1.00 mL; accounts for 13.3 mmol L^{-1} of the dimer **12a** in its activated form). 0.279 mL of the solution were added to neat **13d** (1.207 g, 3.828 mmol) and the solution was stirred in a sealed and shielded flask for 3 d. The residue was suspended in cyclohexane/EtOAc 9:1 and subsequently purified by filtration over silica gel (cyclohexane/EtOAc 9:1) to obtain **14d** (1.117 g, 3.542 mmol, 93 %, *ee* 99 %).

(*S*)-2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-(1-isopropylallyl)acetamide [(*S*)-14e]: GP 4: Catalyst amount: 1.0 mol %; reaction time: 3 d; reaction temperature: 55 °C, yield: 65 %. The analytical data were in accordance with the literature.[3e]

(*S*)-*N*-(4-Methoxyphenyl)-3-amino-1-hexene from allylic amide [(*S*)-14a]: Application of the hydrolysis procedure developed by Overman et al.[3a] gave the deacylated product in 98/97 % *ee* (1.0 (Table 5, entry 1)/ 0.1 mol % (entries 2, 3) precatalyst) for the formation of (*S*)-**14a**) (Chiralcel OD-H, 99.8:0.2 *n*-hexane/*i*PrOH, 0.8 mL min^{-1}) with *S* configuration. The other analytical data were in accordance with the literature.[3a]

(*S*)-*N*-(4-Methoxyphenyl)-3-amino-1-butane from allylic amide [(*S*)-14b]: Application of the hydrolysis procedure developed by Overman et al.[3a] gave the deacylated product in 96/94 % *ee* (1.0 (Table 5, entry 4)/ 0.1 mol % (entry 5) precatalyst) for the formation of (*S*)-**14b**) (Chiralcel OD-H, 99.8:0.2 *n*-hexane/*i*PrOH, 0.8 mL min^{-1}) with *S* configuration. The other analytical data were in accordance with the literature.[3a]

(*S*)-*N*-(4-Methoxyphenyl)-3-amino-5-phenyl-1-pentene from allylic amide [(*S*)-14c]: Application of the hydrolysis procedure developed by Overman et al.[3a] gave the deacylated product in 96/95/97 % *ee* (1.0 (Table 5, entry 6)/0.2 (entry 7)/0.2 mol % (entry 8) precatalyst) for the formation of (*S*)-**14c**) (Chiralcel OD-H, 98.2:1.8 *n*-hexane/*i*PrOH, 0.8 mL min^{-1}) with *S* configuration. The other analytical data were in accordance with the literature.[3a]

(*S*)-*N*-(4-Methoxyphenyl)-3-amino-5-methyl-1-hexene from allylic amide [(*S*)-14d]: Application of the hydrolysis procedure developed by Overman et al.[3a] gave the deacylated product in 98/98/99 % *ee* (1.0 (Table 5, entry 9)/0.1 (entry 10)/0.1 mol % (entry 11) precatalyst) for the formation of (*S*)-**14d**) (Chiralcel OD-H, 99.8:0.2 *n*-hexane/*i*PrOH, 0.8 mL min^{-1}) with *S* configuration. The other analytical data were in accordance with the literature.[3a,e]

(*S*)-*N*-(4-Methoxyphenyl)-3-amino-4-methyl-1-pentene from allylic amide [(*S*)-14e]: Application of the hydrolysis procedure developed by Overman et al.[3a] gave the deacylated product in 93 % *ee* (1.0 mol % precatalyst for the formation of **14e**, Table 5, entry 12) (Chiralcel OD-H, 99.8:0.2 *n*-hexane/*i*PrOH, 0.8 mL min^{-1}) with (*S*)-configuration. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 6.77–6.73 (m, 2H, *arom-H*), 6.59–6.55 (m, 2H, *arom-H*), 5.71 (ddd, J = 17.1, 10.2, 6.6 Hz, 1H, CH_2=C*H*), 5.14 (m, 2H, CH_2=CH), 3.73 (s, 3H, OCH_3), 3.56 (dd, J = 6,3, 5.1 Hz, NC*H*), 1.86 (m, C*H*$(CH_3)_2$), 0.99 (d, J = 6.9 Hz, CH(CH_3)$_2$), 0.95 ppm (d, J = 6.9 Hz, CH(CH_3)$_2$). The other analytical data were accordance with the literature data for the *R* isomer.[3e]

General procedure (Gp 5) for the aza-Claisen rearrangement of *Z*-configured functionalized substrates (Table 7): A solution of AgOTs (27.5 mg, 0.0986 mmol, 6.0 equiv/**12a**) in MeCN (0.214 mL) was evaporated to dryness and a solution of FBIP-Cl (**12a**, 40.0 mg, 0.0164 mmol) in CH_2Cl_2 (12.0 mL) was added to the silver salt. The reaction mixture was stirred in the absence of light. After 46 h the mixture was filtrated over CaH_2/Celite (1:1, vol: 1 cm^3). The filter cake was extracted with CH_2Cl_2 until the filtrate was colorless. The solvent was removed with a steady flow of N_2 and finally by high vacuum. A stem solution of the activated catalyst was prepared by dissolving the solid in dry $CHCl_3$ (1.0 mL for entries 1, 2, 3, 4, 8 $\approx$ 16.4 mmol L^{-1} of dimer **12a** in its activated form; 3.0 mL for entries 5, 7 $\approx$ 5.4 mmol L^{-1} of dimer **12a** in its activated form). To substrates **24**, **27**, **29**, **31** or **19a** (250 mg, entries 1–5), **19c** (210 mg, entry 8) and **19b** (25.0 mg, entry 7) a solution of the activated catalyst in $CHCl_3$ [entry 1: 225 μL (0.5 mol %); entry 2: 236 μL (0.5 mol %); entry 3: 76 μL (0.2 mol %); entry 4: 61 μL (0.2 mol %); entry 5: 57.0 μL (0.05 mol %); entry 7: 24.6 μL (0.5 mol %); entry 8: 69 μL (0.5 mol %)] was added. In case of **19b** (entry 7) a solution of proton sponge (0.03 mg, 0.2 mol %) in $CHCl_3$ (15.1 μL) was previously added. The reactions were stirred for 72 h at 55 °C in a sealed flask in the absence of light and under nitrogen atmosphere. The residue was subsequently suspended in cyclohexane/EtOAc 9:1 and filtrated over a patch of silica gel (cyclohexane/EtOAc 9:1). Since a uniform reaction pathway can be assumed,[3e] the absolute configuration has been assigned based on the configurations determined for unfunctionalized rearrangement products prepared by the action of the (S_p)-configured FBIP catalyst.

***rac*-*N*-(1-(*tert*-Butyldimethylsilyloxy)but-3-en-2-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (20a)**: A solution of **19a** (142 mg, 0.352 mmol) and proton sponge (14 mg, 0.070 mmol, 0.20 equiv) in mesitylene (10 mL) was heated to 160 °C for 43 h. After solvent removal the crude product was submitted to column chromatography (pentane/EtOAc 200:1) to provide racemic **20a** as a colorless oil (129 mg, 0.320 mmol, 91 %). ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.32–7.29 (m, 1H, *arom. H*), 7.11–7.07 (m, 1H, *arom. H*), 6.88–6.85 (m, 2H, *arom. H*), 5.69–5.57 (m, 1H, CH_2=C*H*), 5.31–5.22 (m, 2H, CH_2=CH), 5.08 (q, J = 7.2 Hz, 1H, C*H*-N), 3.82 (s, 3H, OCH_3), 3.64 (d, J = 7.2 Hz, 2H, CH_2-O), 0.90 (s, 9H, *t*Bu), 0.07 ppm (s, 6H, Si-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 159.7, 156.8 (q, J = 34.8 Hz, *C*-CF_3), 132.0, 131.6, 131.3, 127.9, 120.2, 116.3 (q, J = 286.5 Hz, *C*F_3), 113.6, 62.9, 61.6, 25.9, 18.2, −5.3 ppm; ^{19}F NMR (282 MHz, $CDCl_3$, 21 °C): δ = −67.2 ppm; IR (film): $\tilde{\nu}$ = 2957, 2932, 2860, 1699, 1610, 1513, 1466, 1301, 1254, 1207, 1154, 1108, 1035 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{15}H_{19}F_3NO_3Si$: 346.1081 $[M-C_4H_9]^+$; found: 346.1080; elemental analysis calcd (%) for $C_{19}H_{28}F_3NO_3Si$ (403.51): C 56.56, H 6.99, N 3.47. Found: C 56.79, H 6.91, N 3.46.

(*R*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)but-3-en-2-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide (20a): GP 5 (Table 7, entry 5): colorless oil, yield: 94 %, *ee*: 97 %. The *ee* value was determined by chiral column HPLC after hydrolysis of the amide and TBS group (see below) to give 2-(4-methoxyphenylamino)but-3-en-1-ol: Chiralcel OD-H, *n*-hexane/ *i*PrOH 90:10, 0.8 mL min^{-1}, detection at 210 nm. $[\alpha]_D^{25}$ = (c = 0.902 g L^{-1},

$CHCl_3$) = −4.8; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.32–7.29 (m, 1H, *arom. H*), 7.11–7.07 (m, 1H, *arom. H*), 6.88–6.85 (m, 2H, *arom. H*), 5.69–5.57 (m, 1H, CH_2=C*H*), 5.31–5.22 (m, 2H, CH_2=CH), 5.08 (q, *J* = 7.2 Hz, 1H, C*H*-N), 3.82 (s, 3H, Ar-OCH_3), 3.64 (d, *J* = 7.2 Hz, 2H, CH_2-O), 0.90 (s, 9H, *t*Bu), 0.07 ppm (s, 6H, Si-CH_3). The other analytical data were in accordance with the racemate (see above).

Large-scale rearrangement of 19a (Table 7, entry 6): A solution of AgOTs (24.9 mg, 0.0893 mmol, 6.0 equiv) in MeCN (0.478 mL) was evaporated to dryness and a solution of **12a** (36.5 mg, 0.0149 mmol) in CH_2Cl_2 (10.5 mL) was added in the absence of light under nitrogen atmosphere to the silver salt. After 46 h the mixture was filtered over CaH_2/Celite (1:1; vol: 1.5 cm^3). The filter cake was extracted with CH_2Cl_2 until the organic solution was colorless. The solvent was removed with a steady flow of N_2 and finally by using high vacuum. A stem solution of the activated catalyst was prepared by dissolving the solid in dry $CHCl_3$ (1.00 mL; accounts for 14.9 mmol L^{-1} of the dimer **12a** in its activated form). 0.334 mL of the solution were added to neat **19a** (4.008 g, 9.945 mmol) and the solution was stirred in a sealed and shielded flask for 3 d at 55 °C in the absence of light under nitrogen atmosphere. The residue was suspended in cyclohexane/EtOAc 9:1 and subsequently purified by filtration over silica gel (cyclohexane/EtOAc 9:1) to obtain **20a** (3.844 g, 9.540 mmol, 96%, *ee* = 97%).

***rac*-2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-(1-(tetrahydro-2*H*-pyran-2-yloxy)but-3-en-2-yl)acetamide (20b)**: A solution of **19b** (221 mg, 0.592 mmol) and proton sponge (25 mg, 0.12 mmol, 0.20 equiv) in mesitylene (15 mL) was heated to 160 °C for 22 h. After solvent removal the crude product was submitted to column chromatography (cyclohexane/EtOAc 9:1) to provide racemic **20b** as a colorless oil (174 mg, 0.466 mmol, 79%, 1:1 diastereomeric mixture). Analytical data are provided for the diastereomeric mixture: ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.46–7.31 (m, 1H, *arom. H*), 7.22–7.05 (m, 3H, *arom. H*), 6.92–6.84 (m, 4H, *arom. H*), 5.80–5.58 (m, 2H, CH_2=C*H*), 5.33–5.14 (m, 6H, CH_2=CH, C*H*-N), 4.68 (t, *J* = 3.3 Hz, 1H, O-C*H*-O), 4.53 (t, *J* = 3.3 Hz, 1H, O-C*H*-O), 3.87–3.37 (m, 14H, Ar-OCH_3, N-CH-CH_2, OCH_2-CH_2), 1.90–1.51 ppm (m, 12H, CH-CH_2-CH_2-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 159.8, 157.1 (q, *J* = 34.6 Hz, *C*-CF_3), 157.0 (q, *J* = 34.6 Hz, *C*-CF_3), 132.0, 131.9, 131.7, 131.5, 131.4, 131.0, 128.3, 127.8, 120.3, 120.0, 116.4 (q, *J* = 286.5 Hz, *C*F_3), 116.3 (q, *J* = 286.5 Hz, *C*F_3), 113.7, 98.6, 98.2, 65.4, 65.0, 62.4, 62.0, 61.2, 59.5, 30.6, 25.5, 19.5, 19.2 ppm; ^{19}F NMR (282 MHz, $CDCl_3$, 21 °C): δ = −67.7, −67.8 ppm; IR (film): $\tilde{\nu}$ = 2945, 2873, 1694, 1609, 1514, 1467, 1444, 1418, 1354, 1300, 1252, 1203, 1152, 1076, 1035, 975 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{18}H_{22}F_3NO$: 373.1496 $[M]^+$; found: 373.1497; elemental analysis calcd (%) for $C_{18}H_{22}F_3NO_4$ (373.37): C 57.90, H 5.94, N 3.75. Found: C 57.63, H 6.03, N 3.85.

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((2*R*)-1-(tetrahydro-2*H*-pyran-2-yloxy)but-3-en-2-yl)acetamide (20b): GP 5 (Table 7, entry 7): colorless oil, yield: 94%, *ee*: 98%, dr 1:1. The *ee* value was determined by chiral column HPLC after hydrolysis of the amide and THP group (see below) to give 2-(4-methoxyphenylamino)but-3-en-1-ol: Chiralcel OD-H, *n*-hexane/*i*PrOH 90:10, 0.8 mL min^{-1}, detection at 210 nm. $[\alpha]_D^{25}$: not determined since mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.46–7.31 (m, 1H, *arom. H*), 7.22–7.05 (m, 3H, *arom. H*), 6.92–6.84 (m, 4H, *arom. H*), 5.80–5.58 (m, 2H, CH_2=C*H*), 5.33–5.14 (m, 6H, CH_2=CH, C*H*-N), 4.68 (t, *J* = 3.3 Hz, 1H, O-C*H*-O), 4.53 (t, *J* = 3.3 Hz, 1H, O-C*H*-O), 3.87–3.37 (m, 14H, Ar-OCH_3, N-CH-CH_2, OCH_2-CH_2), 1.90–1.51 ppm (m, 12H, CH-CH_2-CH_2-CH_2). The other analytical data were in accordance with the racemate (see above).

(*R*)-2-(4-Methoxyphenylamino)but-3-en-1-ol

Method A: TBAF (1 M in THF, 0.12 mmol, 1.1 equiv, 122 mL) was added to a solution of **20a** (45.1 mg, 0.112 mmol) in THF (2 mL). After stirring for 45 min the reaction mixture was quenched by the addition of water, extracted with CH_2Cl_2 and dried over Na_2SO_4. Column chromatography (cyclohexane/EtOAc 4:1, 3% NEt_3 → cyclohexane/EtOAc 2:1, 3% NEt_3) gave 2-(4-methoxyphenylamino)but-3-en-1-ol as a slightly brown oil (12.1 mg, 0.0418 mmol, 37%).

Method B: A solution of **20b** (51 mg, 0.140 mmol) and $TsOH_*H_2O$ (5 mg, 0.03 mmol, 0.2 equiv) in MeOH (5 mL) was heated to 55 °C for 2.5 h and the solvent was subsequently removed at reduced pressure. Column chromatography (cyclohexane/EtOAc 4:1, 3% NEt_3 → cyclohexane/EtOAc 2:1, 3% NEt_3) of the residue gave 2-(4-methoxyphenylamino)but-3-en-1-ol as a brown oil (18 mg, 0.093 mmol, 67%). $[\alpha]_D^{25}$ = (*c* = 0.835 g dL^{-1}, $CHCl_3$) = −25.0; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 6.78 (dt, *J* = 9.0, 2.4 Hz, 2H, *arom. H*), 6.65 (dt, *J* = 9.0, 2.4 Hz, 2H, *arom. H*), 5.79 (ddd, *J* = 17.1, 10.5, *J* = 5.4 Hz, 1H, CH_2=C*H*), 5.30 (dt, *J* = 17.4, 1.5 Hz, 1H, CH_2=CH), 5.24 (dt, *J* = 10.5, 1.5 Hz, 1H, CH_2=CH), 3.98–3.92 (m, 1H, C*H*-N), 3.81–3.75 (m, 1H, O*H* or N*H*), 3.75 (s, 3H, Ar-OCH_3), 3.64–3.57 (m, 2H, CH_2-O), 1.94 ppm (b, 1H, O*H* or N*H*); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 152.6, 141.0, 136.5, 117.3, 115.6, 114.7, 64.8, 58.8, 55.6 ppm; IR (film): $\tilde{\nu}$ = 3381, 2935, 2833, 1618, 1513, 1465, 1239, 1180, 1037, 993 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{11}H_{15}NO_2$: 193.1098 $[M]^+$; found: 193.1098; elemental analysis calcd (%) for $C_{11}H_{15}NO_2$ (193.24): C 68.37, H 7.82, N 7.25. Found: C 68.13, H 7.61, N 7.07.

***rac*-*N*-(1-(Benzyloxy)but-3-en-2-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)-acetamide (20c)**: A solution of **19c** (149 mg, 0.393 mmol) and proton sponge in mesitylene (13 mL) was heated to 160 °C for 18 h. After solvent removal the crude product was submitted to column chromatography (pentane/EtOAc 9:1) to provide racemic **20c** as a colorless oil (104 mg, 0.274 mmol, 70%). ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.39–7.28 (m, 2H, *arom. H*), 7.22–7.19 (m, 1H, *arom. H*), 7.10–7.07 (m, 1H, *arom. H*), 6.88–6.81 (m, 2H, *arom. H*), 5.71–5.60 (m, 1H, CH_2=C*H*), 5.39–5.25 (m, 2H, CH_2=CH, C*H*-N), 4.53 (q, *J* = 15.0 Hz, 2H, CH_2Ph), 3.83 (s, 3H, Ar-OCH_3), 3.50 ppm (d, *J* = 7.2 Hz, 2H, BnO-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 159.8, 157.2 (q, *J* = 34.6 Hz, *C*-CF_3), 137.6, 131.9, 131.6, 131.4, 128.4, 127.7, 120.3, 116.4 (q, *J* = 286.5 Hz, *C*F_3), 113.7, 113.6, 72.9, 68.2, 59.8, 55.5 ppm; ^{19}F NMR (282 MHz, $CDCl_3$, 21 °C): δ = −67.2 ppm; IR (film): $\tilde{\nu}$ = 3066, 3032, 2939, 2864, 1694, 1608, 1513, 1455, 1420, 1300, 1252, 1192, 1152, 1108, 1031, 995 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{20}H_{20}F_3NO_3$: 379.1390 $[M]^+$; found: 379.1393; elemental analysis calcd (%) for $C_{20}H_{20}F_3NO_3$ (379.37): C 63.32, H 5.31, N 3.69. Found: C 63.60, H 5.36, N 3.77.

(*R*)-*N*-(1-(Benzyloxy)but-3-en-2-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)-acetamide (20c): GP 5 (Table 7, entry 8): colorless oil, yield: 99%, *ee*: 96%. The *ee* value was determined by chiral column HPLC: Chiralcel OD-H, *n*-hexane/*i*PrOH 99:1, 0.8 mL min^{-1}, detection at 210 nm. $[\alpha]_D^{25}$ = (*c* = 1.89 g dL^{-1}, $CHCl_3$) = −32.3; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.39–7.28 (m, 5H, *arom. H*), 7.22–7.19 (m, 1H, *arom. H*), 7.10–7.07 (m, 1H, *arom. H*), 6.88–6.81 (m, 2H, *arom. H*), 5.71–5.60 (m, 1H, CH_2=C*H*), 5.39–5.25 (m, 2H, CH_2=CH, C*H*-N), 4.57 (d, *J* = 12.0, 1H, CH*H*Ph), 4.48 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 3.83 (s, 3H, Ar-OCH_3), 3.50 ppm (d, *J* = 7.2 Hz, 2H, BnO-CH_2). The other analytical data were in accordance with the racemate (see above).

***rac*-Methyl 4-(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)hex-5-enoate (32a)**: A solution of **24** (109 mg, 0.303 mmol) and $PdCl_2(CH_3CN)_2$ (8 mg, 0.03 mmol, 0.1 equiv) in CH_2Cl_2 (2 mL) was stirred for 75 min. The solvent was removed and the residue was purified by column chromatography (cyclohexane/EtOAc 9:1) giving **32a** as a colorless oil (53 mg, 0.15 mmol, 49%). ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.12–7.03 (m, 2H, *arom. H*), 6.90–6.86 (m, 2H, *arom. H*), 5.62–5.50 (m, 1H, CH_2=C*H*), 5.31–5.22 (m, 2H, CH_2=CH), 4.98 (t, *J* = 6.9 Hz, 1H, C*H*-N), 3.83 (s, 3H, Ar-OCH_3), 3.67 (s, 3H, COOCH_3), 2.36 (t, *J* = 7.5 Hz, 2H, CH_2-COOMe), 2.05–1.93 (m, 1H, NCH-CH_2-CH$_2$), 1.90–1.77 ppm (m, 1H, NCH-CH_2-CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 172.9, 159.9, 156.8 (q, *J* = 34.8 Hz, *C*-CF_3), 134.3, 131.7 and 130.9, 127.7, 120.2, 116.3 (q, *J* = 288.1 Hz, *C*F_3), 114.0 and 113.8 (hindered rotation of the amide bond), 60.5, 55.5, 51.8, 30.9, 26.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$, 21 °C): δ = −67.2 ppm; IR (film): $\tilde{\nu}$ = 2955, 2843, 1739, 1694, 1514, 1439, 1421, 1358, 1299, 1254, 1205, 1152, 1034, 997, 940 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{16}H_{18}F_3NO_4$: 345.1182 $[M]^+$; found: 345.1184; elemental analysis calcd (%) for $C_{16}H_{18}F_3NO_4$ (345.31): C 55.65, H 5.25, N 4.06; found: C 55.56, H 5.62, N 4.06.

(*S*)-Methyl 4-(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)hex-5-enoate (32a): GP 5 (Table 7, entry 1): colorless oil, yield: 98%, *ee*: 98%. The *ee* value was determined by chiral column HPLC: Chiralcel OD-H, *n*-hexane/*i*PrOH 99.5:0.5, 0.8 mL min^{-1}, detection at 210 nm. $[\alpha]_D^{25}$ = (*c* = 0.885 g dL^{-1}, $CHCl_3$) = −1.7; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.12–

7.03 (m, 2H, *arom. H*), 6.90–6.86 (m, 2H, *arom. H*), 5.62–5.50 (m, 1H, CH_2=C*H*), 5.31–5.22 (m, 2H, CH_2=CH), 4.98 (t, J=6.9 Hz, 1H, C*H*-N), 3.83 (s, 3H, Ar-OCH_3), 3.67 (s, 3H, COOCH_3), 2.36 (t, J=7.5 Hz, 2H, CH_2-COOMe), 2.05–1.93 (m, 1H, NCH-CH_2-CH_2), 1.90–1.77 ppm (m, 1H, NCH-CH_2-CH_2). The other analytical data were in accordance with the racemate (see above).

***rac*-2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-(6-oxohept-1-en-3-yl)acetamide (32b)**: A solution of **27** (196 mg, 0.595 mmol) and $PdCl_2(CH_3CN)_2$ (15 mg, 0.060 mmol, 0.10 equiv) in CH_2Cl_2 (2 mL) was stirred for 30 min. The solvent was removed at 40 °C and the residue was submitted to column chromatography (pentane/EOAc 9:1 → 4:1) giving **32b** as a colorless oil (124 mg, 0.376 mmol, 63 %). ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ=7.10–7.00 (m, 2H, *arom. H*), 6.88–6.84 (m, 2H, *arom. H*), 5.50 (ddd, J=15.0, 9.9, 7.8 Hz, 1H, CH_2=C*H*), 5.27–5.17 (m, 2H, CH_2=CH), 4.94 (t, J=7.8 Hz, 1H, NC*H*) 3.80 (s, 3H, OCH_3), 2.46 (t, J=7.2 Hz, 2H, O=C-CH_2), 2.12 (s, 3H, CH_3), 1.94–1.71 ppm (m, 2H, CH_2-CH_2-CH); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ=207.0, 159.8, 156.9 (q, J=34.8, *C*-CF_3), 134.6, 131.8, 130.9, 127.5, 120.0, 116.3 (q, J=288.1 Hz, *C*F_3), 60.3, 55.5, 40.1, 30.2, 25.5 ppm; ^{19}F NMR (282 MHz, $CDCl_3$, 21 °C): δ=−67.1 ppm; IR (film): $\tilde{\nu}$=1694, 1513, 1419, 1361, 1300, 1254, 1204, 1152, 1034, 999, 937 cm^{-1}; HRMS (MALDI): *m*/*z*: calcd for $C_{16}H_{18}F_3NO_3Na$: 529.2285 $[M+Na]^+$; found: 529.2284; elemental analysis calcd (%) for $C_{16}H_{18}F_3NO_3$ (329.31): C 58.36, H 5.51, N 4.25; found: C 58.45, H 5.70, N 4.26.

(*S*)-2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-(6-oxohept-1-en-3-yl)acetamide (32b): GP 5 (Table 7, entry 2): colorless oil, yield: 97 %, *ee*: 97 %. The *ee* value was determined by chiral column HPLC: Chiralcel OD-H, *n*-hexane/EtOH 98.2:1.8, 0.8 mL min^{-1}, detection at 210 nm. $[\alpha]$=(*c*=1.00 g dL^{-1}, $CHCl_3$)=−2.4; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ=7.10–7.00 (m, 2H, *arom. H*), 6.88–6.84 (m, 2H, *arom. H*), 5.50 (ddd, J=15.0, 9.9, 7.8 Hz, 1H, CH_2=C*H*), 5.27–5.17 (m, 2H, CH_2=CH), 4.94 (t, J=7.8 Hz, 1H, NC*H*) 3.80 (s, 3H, OCH_3), 2.46 (t, J=7.2 Hz, 2H, O=C-CH_2), 2.12 (s, 3H, CH_3), 1.94–1.71 ppm (m, 2H, CH_2-CH_2-CH). The other analytical data were in accordance with the racemate (see above).

***rac*-*N*-(6-(Benzyloxy)hex-1-en-3-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)-acetamide (32c)**: A solution of **29** (283 mg, 0.695 mmol) and $PdCl_2(CH_3CN)_2$ (16 mg, 0.70 mmol, 0.10 equiv) in CH_2Cl_2 (3 mL) was stirred for 60 min. The solvent was removed at 40 °C and the residue was submitted to column chromatography (pentane/EtOAc 9:1) giving **32c** as a colorless oil (238 mg, 0.584 mmol, 84 %). ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ=7.37–7.25 (m, 5H, *Ph*), 7.13–7.03 (m, 2H, *arom. H*), 6.88–6.81 (m, 2H, *arom. H*), 5.63–5.51 (m, 1H, CH_2=C*H*), 5.29–5.19 (m, 2H, CH_2=CH), 5.04 (q, J=7.5 Hz, 1H, N-C*H*), 4.49 (s, 2H, Ph-CH_2), 3.82 (s, 3H, CH_3), 3.49 (t, J=5.7 Hz, 2H, CH_2-OBn), 1.77–1.53 ppm (m, 4H, CH-CH_2-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ=160.0, 156.8 (q, J=34.7 Hz, *C*-CF_3), 138.4, 135.1, 131.8, 131.1, 128.3, 127.5, 119.4, 116.4 (q, J=288.8 Hz, *C*F_3), 113.7, 113.6, 72.8, 69.5, 60.4, 55.3, 28.2, 26.4 ppm; ^{19}F NMR (282 MHz, $CDCl_3$, 21 °C): δ=−67.1 ppm; IR (film): $\tilde{\nu}$=3065, 3031, 2938, 2860, 1694, 1608, 1513, 1455, 1418, 1361, 1299, 1253, 1204, 1187, 1151, 1109, 1034, 996, 936 cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{22}H_{24}F_3NO_3$: 407.1703 $[M]^+$; found: 407.1703; elemental analysis calcd (%) for $C_{22}H_{24}F_3NO_3$ (407.43): C 64.85, H 5.94, N 3.44; found: C 64.85, H 5.91, N 3.46.

(*S*)-*N*-(6-(Benzyloxy)hex-1-en-3-yl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)-acetamide (32c): GP 5 (Table 7, entry 3): colorless oil, yield: 100 %, *ee*: 97 %. The *ee* value was determined by chiral column HPLC: Chiralcel OD-H, *n*-hexane/*i*PrOH 99:1, 0.8 mL min^{-1}, detection at 210 nm. $[\alpha]_D^{25}$=(*c*=0.910 g dL^{-1}, $CHCl_3$)=−27.2; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ=7.37–7.25 (m, 5H, *Ph*), 7.13–7.03 (m, 2H, *arom. H*), 6.88–6.81 (m, 2H, *arom. H*), 5.63–5.51 (m, 1H, CH_2=C*H*), 5.29–5.19 (m, 2H, CH_2=CH), 5.04 (q, J=7.5 Hz, 1H, N-C*H*), 4.49 (s, 2H, Ph-CH_2), 3.82 (s, 3H, CH_3), 3.49 (t, J=5.7 Hz, 2H, CH_2-OBn), 1.77–1.53 ppm (m, 4H, CH-CH_2-CH_2). The other analytical data were in accordance with the racemate (see above).

***rac*-*tert*-Butyl benzyl(4-(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)-hex-5-enyl)carbamate (32d)**: A solution of **31** (188 mg, 0.371 mmol) and $PdCl_2(CH_3CN)_2$ (9 mg, 0.04 mmol, 0.1 equiv) in CH_2Cl_2 (2 mL) was stirred for 60 min. The solvent was removed at 40 °C and the residue was submitted to column chromatography (cyclohexane/EtOAc 9:1) giving **32d** as a colorless, highly viscous oil (160 mg, 0.316 mmol, 85 %). ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ=7.33–7.20 (m, 5H, *Ph*), 7.01 (d, J=8.7 Hz, 2H, *arom. H*), 6.86 (d, J=8.7 Hz, 2H, *arom. H*), 5.58–5.46 (m, 1H, CH_2=C*H*), 5.25–5.17 (m, 2H, CH=CH_2), 5.00–4.93 (m, 1H, N-C*H*), 4.39 (b, 2H, Ph-CH_2), 3.83 (s, 3H, O-CH_3), 3.15 (b, 2H, N-CH_2-CH_2), 1.52 (b, 2H, CH_2-CH_2-CH_2), 1.46 ppm (b, 9H, C-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ=159.8, 156.8 (q, J=34.8, *C*-CF_3), 155.9 and 155.5 (hindered rotation of the amide bond), 138.4, 135.0, 131.7, 130.9, 128.4, 127.6, 127.1, 119.5, 116.4 (q, J=288.0 Hz, *C*F_3), 113.8 and 113.7 (hindered rotation of the amide bond), 79.8, 60.6, 55.5, 50.6 and 50.1 (hindered rotation of the amide bond), 46.2, 28.8, 28.5, 24.9. ^{19}F NMR (282 MHz, $CDCl_3$, 21 °C): δ=−67.1 ppm; IR (film): $\tilde{\nu}$=2976, 2936, 1694, 1513, 1464, 1417, 1367, 1298, 1252, 1154, 1034, 935 cm^{-1}; HRMS (MALDI): *m*/*z*: calcd for $C_{27}H_{33}F_3N_2O_4Na$: 529.2285 $[M+Na]^+$; found: 529.2284; elemental analysis calcd (%) for $C_{18}H_{27}NO_3$ (506.56): C 64.01, H 6.71, N 5.57. Found: C 64.02, H 6.75, N 5.52.

(*S*)-*tert*-Butyl benzyl(4-(2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamido)-hex-5-enyl)carbamate (32d): GP 5 (Table 7, entry 4): colorless oil, yield: 99 %, *ee*: 98 %. The *ee* value was determined by chiral column HPLC: Chiralcel OD-H, *n*-hexane/*i*PrOH 99:1, 0.8 mL min^{-1}, detection at 210 nm. $[\alpha]_D^{25}$=(c=1.07 g dL^{-1}, $CHCl_3$)=−8.7; ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ=7.33–7.20 (m, 5H, *Ph*), 7.01 (d, J=8.7 Hz, 2H, *arom. H*), 6.86 (d, J=8.7 Hz, 2H, *arom. H*), 5.58–5.46 (m, 1H, CH_2=C*H*), 5.25–5.17 (m, 2H, CH=CH_2), 5.00–4.93 (m, 1H, N-C*H*), 4.39 (b, 2H, Ph-CH_2), 3.83 (s, 3H, O-CH_3), 3.15 (b, 2H, N-CH_2-CH_2), 1.52 (b, 2H, CH_2-CH_2-CH_2), 1.46 ppm (b, 9H, C-CH_3). The other analytical data were in accordance with the racemate (see above).

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[15] X-Ray crystal structure analyses. Bruker-Nonius Kappa-CCD diffractometer, $Mo_{K\alpha}$ radiation, $\lambda = 0.7107$ Å, The structures were solved by direct methods (SIR-97; A. Altomare, M. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119) and refined by full-matrix least-squares analysis (SHELXL-97; G. M. Sheldrick, SHELXL-97, Program for the Refinement of Crystal Structures, University of Göttingen (Germany), **1997**), using an isotropic extinction correction. All non-H atoms were refined anisotropically, H atoms isotropically, whereby H-positions are based on stereochemical considerations. X-ray crystal structure of **11a**. Crystal data at 220(2) K for $C_{54}H_{46}FeN_4O_4S_2$, $M_w = 934.92$; orthorhombic space group $P2_12_12_1$ (no. 19), $\rho_{calcd} = 1.386\ g\,cm^{-3}$, $Z = 4$, $a = 11.1108(2)$, $b = 11.3676(2)$, $c = 35.4662(7)$ Å, $V = 4479.49(14)$ Å^3. Linear crystal dimensions ca. $0.21 \times 0.19 \times 0.17$ mm, $\mu = 0.483\ mm^{-1}$. Final $R(F) = 0.042$, $wR(F^2) = 0.097$ for 635 parameters and 6264 reflections with $I > 2\sigma(I)$ and $2.49 < \theta < 26.01°$ (corresponding R values based on all 7194 reflections are 0.054 and 0.105, respectively). CCDC 617968 contains 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. X-ray crystal structure of **12a**. Crystal data at 220(2) K for $C_{108}H_{88}Cl_4Fe_2N_8O_8Pd_4S_4 \cdot 7\,CHCl_3$, $M_w = 3268.91$; orthorhombic space group $P2_1$ (no. 4), $\rho_{calcd} = 1.392\ g\,cm^{-3}$, $Z = 2$, $a = 15.5124(3)$, $b = 30.3423(9)$, $c = 15.8007(3)$ Å, $\beta = 118.956(1)$, $V = 6507.4(3)$ Å^3. Linear crystal dimensions ca. $0.14 \times 0.12 \times 0.10$ mm, $\mu = 1.392\ mm^{-1}$. Final $R(F) = 0.049$, $wR(F^2) = 0.115$ for 1499 parameters, 1 restraint, and 21058 reflections with $I > 2\sigma(I)$ and $2.95 < \theta < 26.02°$ (corresponding R values based on all 23932 reflections are 0.059 and 0.122, respectively). CCDC 617969 contains 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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[20] Using the same enantiomerically pure catalyst, *E*- and *Z*-configured substrates generally give the opposite major enantiomers. For that reason it is important to have isomerically pure substrates to get maximum *ee* values. **13a** used for the catalyst screening experiments contained 2% of the *E*-configured isomer.

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