Asymmetric Rearrangement

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Practical, Highly Active, and Enantioselective Ferrocenyl–Imidazoline Palladacycle Catalysts (FIPs) for the Aza-Claisen Rearrangement of *N-para*-Methoxyphenyl Trifluoroacetimidates**

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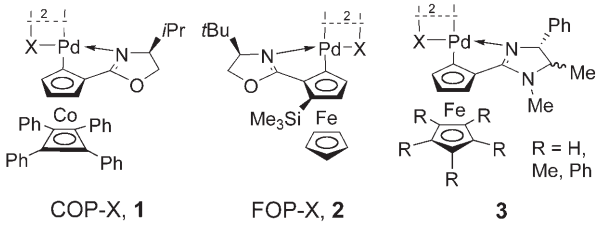
Dedicated to Professor Dieter Enders on the occasion of his 60th birthday

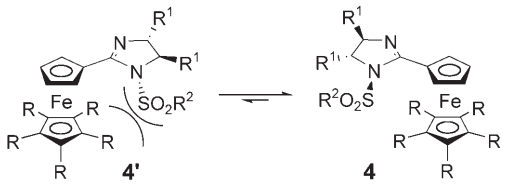
[3,3]-Sigmatropic rearrangements rank among the most fundamental reactions in organic chemistry.[1] Particularly attractive is the Pd^{II}-catalyzed aza-Claisen rearrangement, also known as the Overman rearrangement, which allows for the formation of chiral enantioenriched protected allylic amines starting from achiral allylic imidates, which are easily synthesized from allylic alcohols in a single high-yielding step.[2] The resulting allylic amine derivatives are valuable building blocks for the synthesis of important compound classes such as unnatural amino acids.[3] However, most of the catalytic asymmetric aza-Claisen rearrangements that have been investigated have been limited to *N*-aryl benzimidates, which are of little practical value since cleavage of the amide protecting group is typically very low-yielding. Notable exceptions are the use of allylic trichloroacetimidates[4] and *N-para*-methoxyphenyl trifluoroacetimidates[5] since the protecting groups can generally be removed in preparatively useful yields. Only a few studies have been devoted to these practical, but less reactive substrates, and the planar chiral oxazoline-based palladacycle complexes **1** (COP-X) and **2** (FOP-X) have emerged as the most versatile catalyst systems.[4,5] Their design is based upon the premise that steric bulk has to be projected above and below the Pd square plane in order to allow for a face-selective coordination of the substrate olefin to the Pd^{II} complex.[2] FOP catalysts **2** are not accessible by direct cyclopalladation of the ferrocene moiety;



their preparation requires two *ortho* lithiations. Moreover, in the case of *N-para*-methoxyphenyl trifluoroacetimidates, the catalyst loading had to be as high as 5–7.5 mol% (that is, 10–15 mol% Pd^{II}) for both **1** and **2**, while long reaction times were still required in order to obtain preparatively useful conversions.

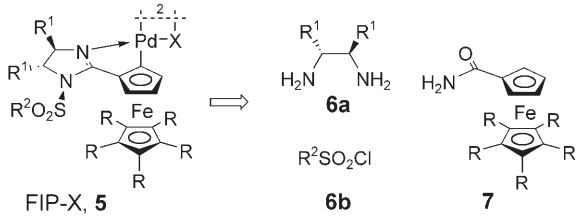
Our goal was to develop a practical, highly active catalyst for the asymmetric rearrangement of *N-para*-methoxyphenyl trifluoroacetimidates as a means to produce chiral primary allylic amines. Ideally the catalyst should be easily accessible without the necessity of low-temperature lithiations.

Recently, we described the first preparation of optically pure 2-ferrocenyl-1-alkyl imidazolines and their pentamethyl- as well as pentaphenylferrocenyl derivatives.[6,7] The direct cyclopalladations of these systems are diastereoselective only in the case of the pentaphenylferrocenyl derivative (R = Ph in **3**).[7] This Pd complex gave up to 88% *ee* for the aza-Claisen rearrangement of trifluoroacetimidates with 5 mol% catalyst loading at 40 °C after activation with Ag^{I}.[8] Based on these results, we have designed a less electron-rich catalyst system in which a bulky *N*-sulfonyl residue is the key constituent to permit a direct diastereoselective cyclopalladation of **4**. Steric



repulsion in **4** between the residue R^1 at the 5-position of the imidazoline and the sulfonyl group effects a transfer of chirality to the sulfonylated nitrogen atom, thus resulting in a preferred equilibrium conformation in which the sulfonyl group is oriented away from the ferrocenyl moiety, thereby allowing for a diastereoselective cyclopalladation.

The modular design allowed us to create catalysts **5** in which the steric demand and the electronic properties could be adjusted by each single module (Scheme 1), the modules



Scheme 1. Modular design of catalysts **5**.

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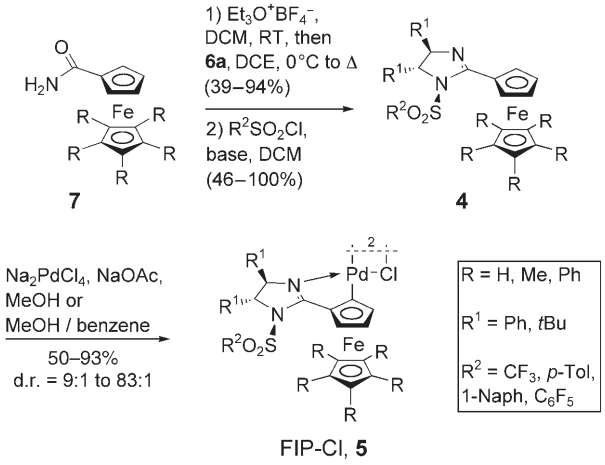
being a) a ferrocenyl,[9] pentamethylferrocenyl, or pentaphenylferrocenyl moiety, b) an imidazoline constituent that is synthesized from an enantiomerically pure C_2-symmetric diamine, and c) a sulfonyl residue.

The air-stable and crystalline imidazolines **4** were prepared in good yield from the amides **7**[6,7] by activation via the corresponding iminium ether intermediate and a subsequent sulfonylation (Scheme 2, Table 1).



Scheme 2. Synthesis of ferrocenyl–imidazoline palladacycles **5**. DCM = dichloromethane, DCE = 1,2-dichloroethane.

Table 1: Preparation of imidazolines **4** and palladacycles **5**.

Entry	Prod.	C_5R_5[a]	R^1	R^2	Yield[b] [%]	d.r.[d]	d.r.[e]
1	**4**	Cp	Ph	CF_3	72[c]	–	–
2	**4**	Cp	Ph	*p*-Tol	73[c]	–	–
3	**4**	Cp	Ph	1-Naph	73[c]	–	–
4	**4**	Cp	*t*Bu	*p*-Tol	18[c]	–	–
5	**4**	Cp*	Ph	CF_3	71[c]	–	–
6	**4**	Cp*	Ph	*p*-Tol	81[c]	–	–
7	**4**	Cp*	Ph	C_6F_5	65[c]	–	–
8	**4**	Cp^Φ	Ph	*p*-Tol	77[c]	–	–
9	**5**	Cp	Ph	CF_3	92	9:1	9:1
10	**5**	Cp	Ph	*p*-Tol	93	18:1	18:1
11	**5**	Cp	Ph	1-Naph	91	12:1	12:1
12	**5**	Cp	*t*Bu	*p*-Tol	55	20:1	72:1
13	**5**	Cp*	Ph	CF_3	69	15:1	83:1
14	**5**	Cp*	Ph	*p*-Tol	85	20:1	20:1
15	**5**	Cp*	Ph	C_6F_5	60	7:1	14:1
16	**5**	Cp^Φ	Ph	*p*-Tol	50	20:1	38:1

[a] Cp* = C_5Me_5, Cp^Φ = C_5Ph_5. [b] Yield of isolated product after chromatography. [c] Yield over two steps from **7**. [d] Diastereomeric ratio of the crude product as determined by ^{1}H NMR of complex **8** or **9**. [e] Diastereomeric ratio of the isolated product as determined by ^{1}H NMR of complex **8** or **9**.

The hypothesis of chirality transfer to the *N*-sulfonyl group was confirmed by X-ray analysis of imidazoline **4**-Cp-*t*Bu-Ts (labeling system: **4**-C_5R_5-R^1-R^2),[10] in which the sulfonylated N atom is significantly pyramidalized, thus minimizing unfavorable steric interactions with the neighboring substituents (Figure 1).

Cyclopalladation under standard conditions at room temperature with Na_2PdCl_4/NaOAc in MeOH (with or without benzene) proved to be a very reliable method for preparing the air-stable dimeric complexes FIP-Cl (**5**) as geometrical isomers about the Pd^{II} square planes in good yield and with moderate to high diastereoselectivity with regard to the planar chirality (d.r. = 7:1 to 20:1 and 9:1 to 83:1 before and after chromatography).[11] To determine the diastereoselectivity, the dimeric species **5** were treated with PPh_3 or Na(acac) to furnish the monomeric complexes **8** and **9** (Scheme 3).[12]

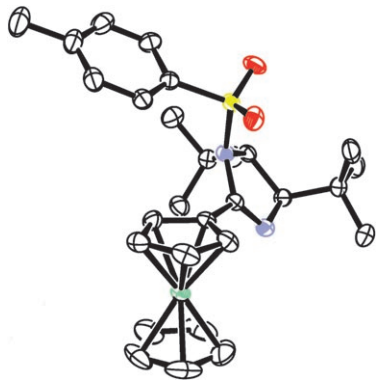
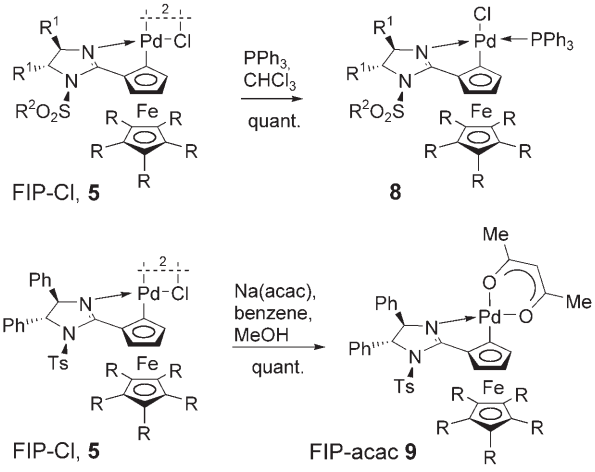


Figure 1. ORTEP representation of **4**-Cp-*t*Bu-Ts with eclipsed Cp rings (the unit cell contains two different conformers). Ellipsoids are set at 50% probability (C black, N blue, O red, S yellow, Fe green); H atoms are omitted for clarity.



Scheme 3. Synthesis of the monomeric complexes **8** and **9**. acac = acetylacetonate.

The crystal structures of **9**-Cp^Φ-Ph-Ts (Figure 2)[13] and **8**-Cp*-Ph-Ts as well as nOesy experiments on **9**-Cp-Ph-Ts and **9**-Cp^Φ-Ph-Ts (see the Supporting Information) confirmed the predicted S_p configuration.[14,15]

The dimeric complexes **5** were then investigated in the aza-Claisen rearrangement of *N*-*para*-methoxyphenyl trifluoroacetimidates **10** (Scheme 4). With (*E*)- and (*Z*)-**10a** as model substrates, various silver salts AgX (X = O_2CCF_3 (TFA), OTf, OTs, BF_4) were evaluated for their catalyst-activating properties since the dimeric palladacycles **5** alone proved to be unreactive as catalysts. While silver trifluoroacetate is the most general activating reagent of those

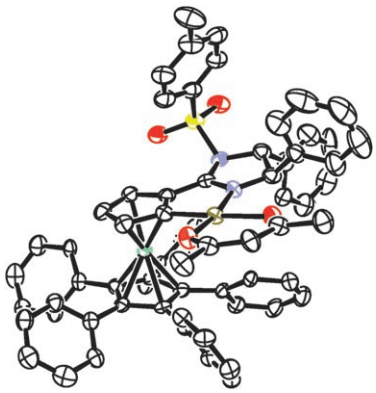
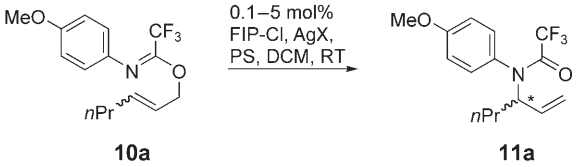
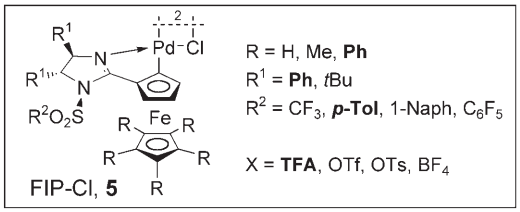


Figure 2. ORTEP representation of **9**-Cp$^{\Phi}$-Ph-Ts with staggered conformation of the Cp rings (the unit cell contains two different conformers). Ellipsoids are set at 50% probability (C black, N blue, O red, S yellow, Fe green, Pd bronze); H atoms are omitted for clarity.





Scheme 4. Screening of catalysts with model substrates (*E*)- and (*Z*)-**10a**.

investigated, AgOTf proved to be superior in the case of **5**-Cp catalyst precursors for *Z*-configured imidates **10**. The silver salts presumably not only lead to an exchange of Cl for X in the active catalyst species, but also oxidize the ferrocene moiety to provide a ferrocenium cation since the rearrangement proceeds extremely slowly with only two equivalents of AgX per dimer **5**. This assumption is supported by the fact that the ^{1}H NMR spectrum of the catalyst disappears as a result of the formation of a paramagnetic species after addition of four equivalents of AgTFA, whereas with two equivalents the NMR signals are still sharp. In analogy to the work published by Overman et al., the rearrangements were performed in the presence of proton sponge (PS, two equivalents per dimer **5**), which resulted in higher *ee* values at the expense of somewhat decreased conversion rates, but led to significantly cleaner reactions. In all experiments described, only traces of side products were detected in the presence of PS.

After an extensive solvent screening,[16] CH_2Cl_2 was selected for further experiments, in which the influence of the different modules was investigated (Table 2). The comparison of different sulfonyl groups revealed that increasing the steric bulk of the sulfonyl group does not necessarily lead to higher enantioselectivities (Table 2, entries 1–6) but results

Table 2: Catalyst screening with model substrates (*E*)- and (*Z*)-**10a**.

Entry	(*E*/*Z*)-**10a**	mol% **5**	*T* [°C]	C_5R_5	R^1	R^2	Yield[a] [%]	*ee*[b] [%]
1	***E***	5	20	Cp	Ph	CF_3	96[f]	64 (*R*)
2	***E***	5	20	Cp	Ph	*p*-Tol	88[f]	67 (*R*)
3	***E***	5	20	Cp	Ph	1-Naph	54[f]	65 (*R*)
4[c]	***Z***	5	20	Cp	Ph	CF_3	90[e]	91 (*S*)
5[c]	***Z***	5	20	Cp	Ph	*p*-Tol	75[f]	89 (*S*)
6[c]	***Z***	5	20	Cp	Ph	1-Naph	19[f]	72 (*S*)
7	***E***	5	20	Cp	*t*Bu	*p*-Tol	76[f]	66 (*R*)
8[h]	***E***	5	40	Cp*	Ph	CF_3	80[d]	0
9[h]	***E***	5	40	Cp*	Ph	*p*-Tol	91[e]	89 (*R*)
10[h]	***E***	5	40	Cp*	Ph	C_6F_5	88[e]	74 (*R*)
11	***Z***	5	40	Cp*	Ph	*p*-Tol	72[e]	93 (*S*)
12	***E***	1.0	20	Cp$^{\Phi}$	Ph	*p*-Tol	96[e]	97 (*R*)
13	***E***	0.5	20	Cp$^{\Phi}$	Ph	*p*-Tol	95[e]	98 (*R*)
14	***E***	0.1	20	Cp$^{\Phi}$	Ph	*p*-Tol	94[e]	97 (*R*)
15	***E***	0.05	40	Cp$^{\Phi}$	Ph	*p*-Tol	95[g]	95 (*R*)
16	***Z***	5	40	Cp$^{\Phi}$	Ph	*p*-Tol	36[e]	85 (*S*)

[a] Yield determined by ^{1}H NMR. [b] Enantiomeric excess determined by chiral HPLC (Daicel OD-H) after hydrolysis of **11a** to the secondary amine (see the Supporting Information). [c] AgOTf was used for activation. [d] Reaction time 5 h. [e] Reaction time 1 day. [f] Reaction time 2 days. [g] Reaction time 3 days. [h] Catalyst precursor **5** doped with 10% **4**-Cp*-Ph-Ts.

in prolonged reaction times. Since catalysts bearing the small and strongly electron-withdrawing trifluoromethylsulfonyl moiety led in some cases to catalyst decomposition (Table 2, entry 8), the tosyl group emerged as the sulfonyl moiety of choice.

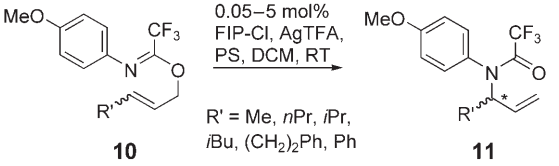
With regard to the imidazoline backbone, no significant difference in enantioselectivity and yield of **11a** was found for R^1 = Ph or *t*Bu (Table 2, entries 2 and 7).[17] Since the imidazolines **4** with R^1 = Ph are prepared in much higher yields (Table 1), they were selected for the investigation of the influence of the ferrocenyl spectator ligand module, which has the highest impact on the rearrangement outcome. While catalysts possessing an unsubstituted Cp ring did not provide useful *ee* values for (*E*)-**10a** (Table 2, entries 1–3, 7), the rearrangement of (*Z*)-**10a** enabled amide **11a** to be prepared with 90% *ee* (Table 2, entries 4, 5). By contrast, with a bulkier yet electron-richer Cp* spectator ligand, both (*E*)- and (*Z*)-**10a** gave about 90% *ee* (Table 2, entries 9, 11) although the reaction mixtures had to be heated to 40°C to obtain useful conversion rates with a precatalyst loading of 5 mol%. Interestingly, in order to obtain these high levels of asymmetric induction for (*E*)-**10a**, the catalyst precursor **5**-Cp*-Ph-Ts had to be doped with 10% **4**-Cp*-Ph-Ts (that is, 0.5 mol% with regard to (*E*)-**10a**). In the absence of **4**-Cp*-Ph-Ts, the *ee* value decreased significantly to 73%. At present, we can only speculate about the origin of this effect and further studies will be required, but we hypothesize that the R_p-configured catalyst (the minor palladacycle isomer) is preferentially deactivated by the formation of a monomeric complex with the imidazoline N atom.[18]

Gratifyingly, the electron-poorer and even bulkier Cp$^{\Phi}$ spectator ligand (Cp$^{\Phi}$ = C_5Ph_5) resulted not only in significantly higher enantioselectivity for (*E*)-**10a** (97% *ee*, Table 2, entry 12) but also in a highly active catalyst, thus allowing the

amount of the precatalyst to be reduced to unprecedented levels of 0.05 to 1.0 mol% without largely affecting the enantioenrichment whilst still providing useful reaction rates (Table 2, entries 12–15).[19] Compound **5**-Cp$^{\Phi}$-Ph-Ts is however not a useful catalyst for (*Z*)-**10a** (Table 2, entry 16).

After the optimization of the reaction conditions, the scope of the rearrangement of imidates **10** was studied in detail by using **5**-Cp-Ph-Ts and **5**-Cp*-Ph-Ts for substrates (*Z*)-**10** and **5**-Cp$^{\Phi}$-Ph-Ts for substrates (*E*)-**10** (Table 3).

Table 3: Screening of substrates **10** with different groups R^1 in the presence of **5**-Cp or **5**-Cp* [*Z* substrates] or **5**-Cp$^{\Phi}$ [*E* substrates].



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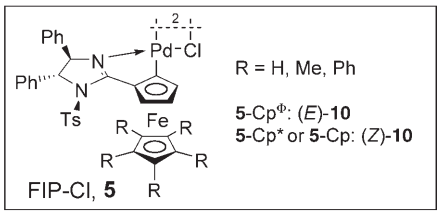

Entry	(*E*/*Z*)-**10**	R′	C_5R_5	mol% **5**	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1[c,e]	(*Z*)-**10a**	*n*Pr	Cp	5	20	75	89 (*S*)
2[c,e]	(*Z*)-**10b**	$(CH_2)_2$Ph	Cp	5	20	70	90 (*S*)
3[c,e]	(*Z*)-**10c**	*i*Bu	Cp	5	20	69	96 (*S*)
4[c]	(*Z*)-**10a**	*n*Pr	Cp*	5	40	72	93 (*S*)
5[c]	(*Z*)-**10b**	$(CH_2)_2$Ph	Cp*	5	40	95	95 (*S*)
6[c]	(*Z*)-**10c**	*i*Bu	Cp*	5	40	82	96 (*S*)
7[c]	(*E*)-**10a**	*n*Pr	Cp$^{\Phi}$	0.5	20	95	98 (*R*)
8[c]	(*E*)-**10a**	*n*Pr	Cp$^{\Phi}$	0.1	40	89	97 (*R*)
9[d]	(*E*)-**10a**	*n*Pr	Cp$^{\Phi}$	0.05	40	95	95 (*R*)
10[d]	(*E*)-**10f**	Me	Cp$^{\Phi}$	0.1	20	91	95 (*R*)
11[d]	(*E*)-**10f**	Me	Cp$^{\Phi}$	0.05	40	98	92 (*R*)
12[c]	(*E*)-**10b**	$(CH_2)_2$Ph	Cp$^{\Phi}$	1.0	20	94	99.7 (*R*)
13[d]	(*E*)-**10b**	$(CH_2)_2$Ph	Cp$^{\Phi}$	0.05	40	99	98 (*R*)
14[c]	(*E*)-**10c**	*i*Bu	Cp$^{\Phi}$	0.2	40	96	98 (*R*)
15[c]	(*E*)-**10c**	*i*Bu	Cp$^{\Phi}$	0.1	40	95	98 (*R*)
16[c]	(*E*)-**10d**	*i*Pr	Cp$^{\Phi}$	0.5	40	75	96 (*R*)
17[d]	(*E*)-**10d**	*i*Pr	Cp$^{\Phi}$	0.1	40	81	93 (*R*)
18[c]	(*E*)-**10e**	Ph	Cp$^{\Phi}$	1.0	40	99	88 (*S*)
19[c]	(*E*)-**10e**	Ph	Cp$^{\Phi}$	0.5	40	97	84 (*S*)

[a] Yield of isolated product. [b] Enantiomeric excess determined by chiral HPLC (Daicel OD-H) after hydrolysis of **11** to the secondary amine (see the Supporting Information). [c] Reaction time 1 day. [d] Reaction time 3 days. [e] AgOTf was used for catalyst activation.

Whereas the former two catalyst precursors provide good conversions and yields only for α-unbranched allylic substrates (*Z*)-**10** and require a catalyst loading of 5 mol% (Table 3, entries 1–6), the Cp$^{\Phi}$ derivative has a broad applicability even at very low catalyst loadings. The rate of the rearrangement depends primarily on the steric bulk of the residue R′. With unbranched substituents (R′ = Me, *n*Pr, $(CH_2)_2$Ph, *i*Bu), (*R*)-**11** was formed in excellent yield with 0.05 to 0.1 mol% catalyst loading, and the highest enantioselectivities obtained so far for substrates **10** were exhibited (Table 3, entries 7–15; highest *ee* values previously reported: Me 88%, *n*Pr 95%, $(CH_2)_2$Ph 97%, *i*Bu 97%).[5a,7] The most difficult aliphatic substrate in terms of the enantioselectivity, prepared from crotonylic alcohol, furnished (*R*)-**11f** with 95% *ee* (Table 3, entry 10). Even in the case of the α-branched *i*Pr substituent, a case which has not been described so far, the rearrangement proceeded with acceptable rates with 0.1 to 0.5 mol% catalyst precursor (Table 3, entries 16 and 17). Also the aromatic Ph substituent, which has not provided useful yields and enantioselectivities so far (best reported results: 46% yield, 45% *ee*),[5c] is well-tolerated (Table 3, entries 18 and 19).

The opposite absolute configurations of the major enantiomers of rearrangement products **11** starting from either (*E*)- or (*Z*)-**10** may be accounted for by the working model depicted in Figure 3. Assuming that the olefin coordinates (in analogy to PPh_3) *trans* to the imidazoline N atom as a result of the *trans* effect,[20] the imidate N atom attacks the olefin at the face remote to the Pd atom. Increased steric interactions of the coordinated olefin with the Cp* and Cp$^{\Phi}$ ligands presumably results in a better face selectivity for the olefin coordination at the Pd^{II} center, which thus explains the higher enantioselectivity as compared to derivatives that bear the unsubstituted Cp ligand. The very high activity of the catalyst derived from **5**-Cp$^{\Phi}$-Ph-Ts may be accounted for by the electron-withdrawing influence of the Cp$^{\Phi}$ ligand, but also by a higher tendency to form a monomeric, catalytically active species.

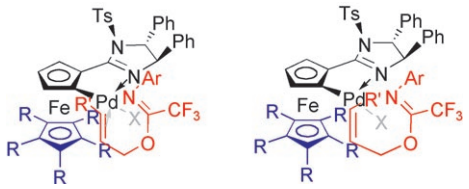

Figure 3. Proposed explanation for the stereochemistry of the catalysis product.

In conclusion, we have developed practical, highly efficient ferrocenyl–imidazoline palladacycles (FIPs) as catalysts for the aza-Claisen rearrangement of *N*-*para*-methoxyphenyl trifluoroacetimidates, which are versatile substrates for the formation of protected chiral primary allylic amines. The catalysts are not only easily prepared but also exhibit unprecedented activity, enantioselectivity, and tolerance toward a broad spectrum of substrates. This methodology compares favorably to existing enantioselective approaches to protected chiral primary allylic amines.

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[8] For other applications of imidazolines in asymmetric catalysis, see for example: a) F. Menges, M. Neuburger, A. Pfaltz, *Org. Lett.* **2002**, *4*, 4713; b) C. A. Busacca, D. Grossbach, R. C. So, E. M. O'Brien, E. M. Spinelli, *Org. Lett.* **2003**, *5*, 595; c) S. Bhor, G. Anilkumar, M. K. Tse, M. Klawonn, C. Dobler, B. Bitterlich, A. Grotevendt, M. Beller, *Org. Lett.* **2005**, *7*, 3393.

[9] a) *Ferrocenes* (Eds.: T. Hayashi, A. Togni), VCH, Weinheim, **1995**; b) C. J. Richards, A. J. Locke, *Tetrahedron: Asymmetry* **1998**, *9*, 2377; c) R. C. J. Atkinson, V. C. Gibson, N. J. Long, *Chem. Soc. Rev.* **2004**, *33*, 313.

[10] CCDC-606393 (**4**-Cp-*t*Bu-Ts) 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.

[11] Only very few direct diastereoselective cyclopalladations of chiral ferrocene derivatives are known; see reference [7] and references therein.

[12] Note that six different dimeric isomers are possible for **5** and thus lead to complex NMR spectra.

[13] CCDC-604468 (**9**-Cp^{Φ}-Ph-Ts) and CCDC-606392 (**8**-Cp*-Ph-Ts) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] The stereodescriptors with regard to the planar chirality are used according to: K. Schlögl, *Top. Stereochem.* **1967**, *1*, 39.

[15] The crystal structures of **4**-Cp-*t*Bu-Ts and **9**-Cp^{Φ}-Ph-Ts show two symmetrically independent molecules with different conformations of the Cp ring from almost eclipsed to staggered. Despite the different degree of bulkiness of the substituents on the Cp rings, the distance of the ring centers are nearly constant in all molecules (3.30–3.34 Å).

[16] General trends: a) catalyst activity: DCE > DCM > $CHCl_3$ > C_6H_6 > DCM/1% DMF > MeCN ≫ Et_2O (catalyst not soluble); b) enantioselectivity: DCM ≈ DCM/1% DMF ≫ C_6H_6 > DCE ≈ MeCN > $CHCl_3$.

[17] The (1*R*,2*R*)-cyclohexyldiamine backbone resulted in much lower *ee* values.

[18] *N*-Methylimidazole is, for example, known to cleave palladacycle dimers: C. López, R. Bosque, X. Solans, M. Font-Bardía, D. Tramuns, G. Fern, J. Silver, *J. Chem. Soc. Dalton Trans.* **1994**, 3039.

[19] **5**-Cp^{Φ}-Ph-Ts as well as **7**-Cp^{Φ} will soon be commercially available from Sigma–Aldrich.

[20] F. R. Hartley, *Chem. Soc. Rev.* **1973**, *2*, 163.

