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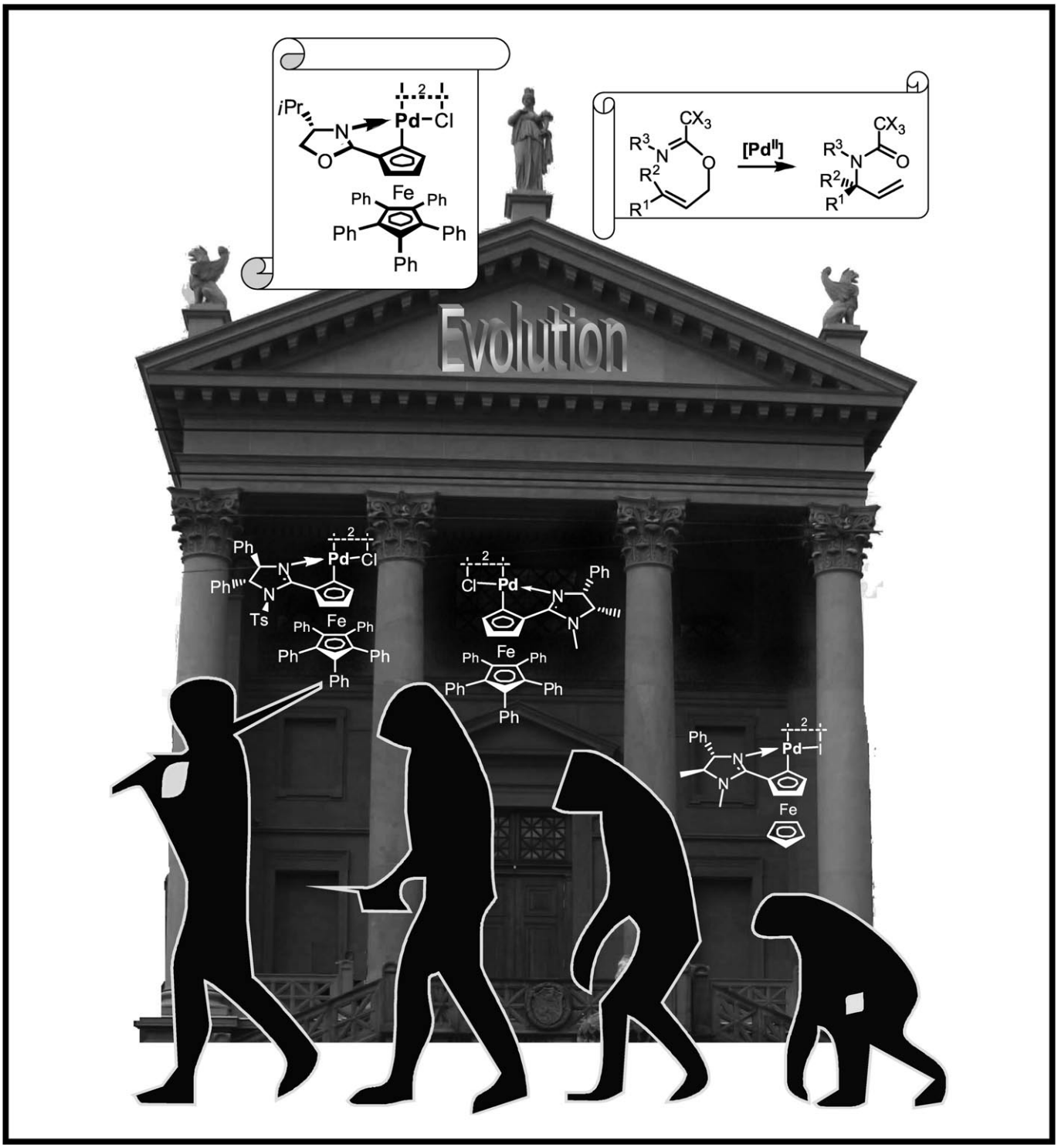
The Asymmetric Aza-Claisen Rearrangement: Development of Widely Applicable Pentaphenylferrocenyl Palladacycle Catalysts

Daniel F. Fischer,[b] Assem Barakat,[a, b] Zhuo-qun Xin,[a, b] Matthias E. Weiss,[b] and René Peters*[a]



Abstract: Systematic studies have been performed to develop highly efficient catalysts for the asymmetric aza-Claisen rearrangement of trihaloacetimidates. Herein, we describe the stepwise development of these catalyst systems involving four different catalyst generations finally resulting in the development of a planar chiral pentaphenylferrocenyl oxazoline palladacycle. This complex is more reactive and has a broader substrate tolerance than all previously known catalyst systems for asymmetric aza-Claisen rearrangements. Our investigations also reveal that subtle changes can have a big impact on the activity. With the enhanced catalyst activity, the asymmetric aza-Claisen rearrangement has a very broad scope: the methodology not only allows the formation of highly enantioenriched primary allylic amines, but also secondary and tertiary amines; allylic amines with N-substituted quaternary stereocenters are conveniently accessible as well. The reaction conditions tolerate many important functional groups, thus providing stereoselective access to valuable functionalized building blocks, for example, for the synthesis of unnatural amino acids. Our results suggest that face-selective olefin coordination is the enantioselectivity-determining step, which is almost exclusively controlled by the element of planar chirality.

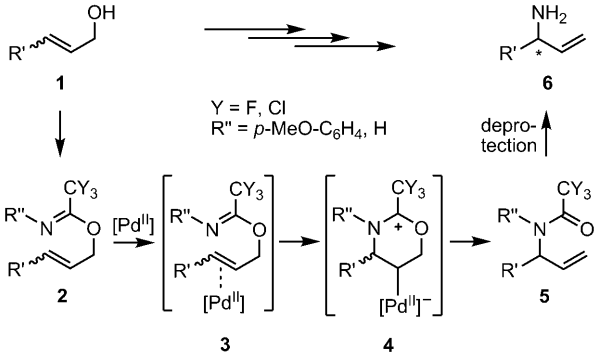
Keywords: allylic compounds · amines · aza-Claisen rearrangement · cyclopalladation · palladium

Introduction

Soft Lewis acids such as Pd^{II}, Pt^{II}, or Au^{I} have become more and more important for organic synthesis, because coordination of these carbophilic late-transition-metal cations to olefins or alkynes results in a net transfer of electron density to the metal center, thus activating the unsaturated system for the attack by nucleophiles.[1] The soft Lewis acid can therefore be regarded as a chemoselective (owing to its low oxophilicity) and possibly chiral proton substitute.

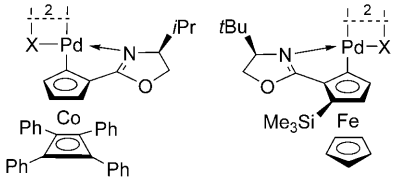
For example, the Pd^{II}-catalyzed aza-Claisen rearrangement[2] of allylic trichloro-[3] and trifluoroacetimidates[4] enables the transformation of achiral allylic imidates **2**, readily prepared in a single step from allylic alcohols **1**, to chiral enantioenriched allylic amides **5** (Scheme 1). Since the trihaloacetamide-protecting groups can be readily removed, the overall transformation leads to valuable allylic amine building blocks **6**. There is ample evidence that these reactions proceed by means of a cyclization-induced rearrangement mechanism, in which the olefin moiety of **2** coordinates to the Pd^{II} complex and is thereby activated in **3** for a nucleophilic attack by the imidate N atom.[5] In 1974, 37 years after the first description of the thermal aza-Claisen rearrangement of allylic benzimidates by Mumm and Möller,[6] Overman reported the first application of trichloroacetimidate substrates and demonstrated that the rearrangement can be catalyzed by soft Lewis acids such as Hg^{II}.[7]

In 2003, Overman, Richards, and co-workers disclosed an additional breakthrough: the first highly enantioselective



Scheme 1. The aza-Claisen (Overman) rearrangement of trihaloacetimidates **2**.

catalyst for the rearrangement of trihaloacetimidates, the planar chiral oxazoline-based palladacycle COP-X (**7**, X = Cl).[3a,4a] This catalyst was found to be superior to its ferrocene analogue FOP-X (**8**)[4c] in a number of aspects such as preparation (i.e., FOP-X could not be prepared by direct cyclopalladation due to oxidative decomposition by Pd^{II}, but required two low-temperature lithiations), catalyst stability, catalytic activity, and substrate scope.[8]



COP-X (**7**) FOP (**8**)

Unfortunately, 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,

[a] A. Barakat, Z.-q. Xin, Prof. Dr. R. Peters
Institut für Organische Chemie, Universität Stuttgart
Pfaffenwaldring 55, 70569 Stuttgart (Germany)
Fax: (+49) 711-685-64321
E-mail: rene.peters@oc.uni-stuttgart.de

[b] Dr. D. F. Fischer, A. Barakat, Z.-q. Xin, M. E. Weiss
ETH Zürich, Hönggerberg, Laboratory of Organic Chemistry
Wolfgang-Pauli-Strasse 10, 8093 Zürich (Switzerland)

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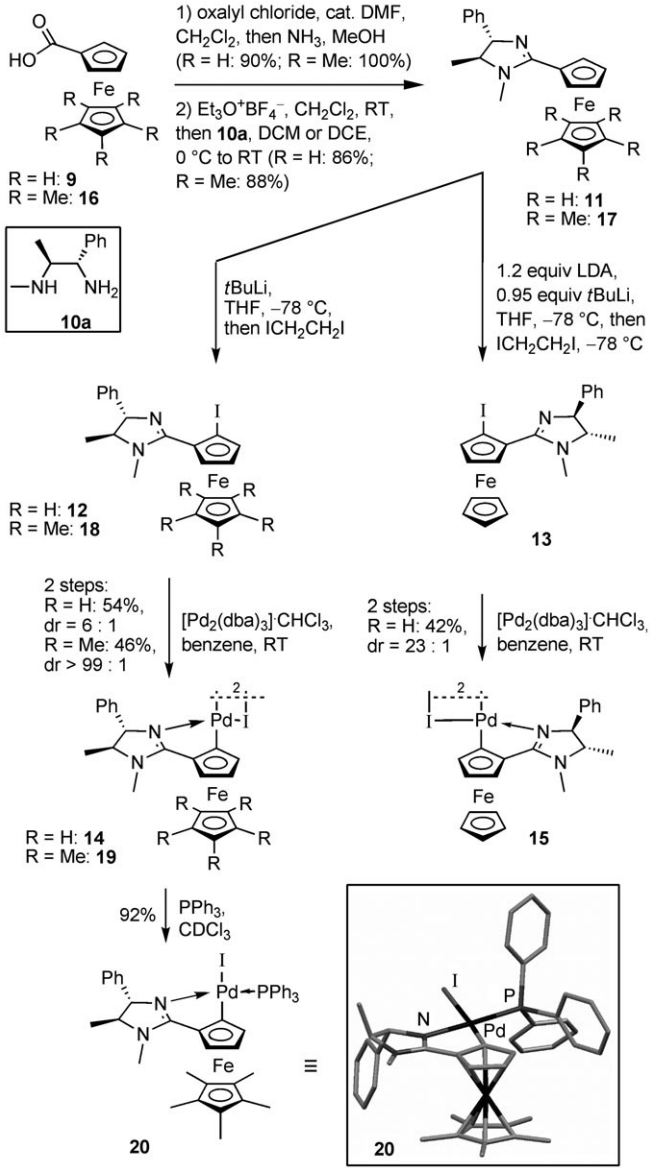
COP-Cl still required loadings that are not attractive for large-scale applications ($\geq$10 mol% Pd^{II}) and long reaction times were necessary for high conversion. Moreover, the scope was limited to substrates bearing α-unbranched alkyl substituents (R′) at the 3-position of the allylic imidate.

To fully capitalize on the potential of the synthetically attractive allylic imidate rearrangement concept, we have systematically addressed the issues of catalytic activity and scope, ultimately resulting in the development of highly active chiral catalysts for the rearrangement of trifluoro- and trichloroacetimidates, thereby providing allylic trihaloacetamides with excellent enantioselectivities. In this full paper, we describe the stepwise development of these catalyst systems involving four different catalyst generations.

Results and Discussion

The previous investigations pioneered by the Overman group had shown that planar chirality is in principle an effective means of achieving high enantioselectivities. Our investigations were based upon the assumption that a highly modular design of a carbophilic Lewis acid system would arguably allow for an adjustment of electronic and steric properties over a wide range but also for a final fine-tuning for ultimate optimization. Although all ferrocene-based catalysts such as FOP-X were previously not as efficient as COP-X, in the present study ferrocene moieties were chosen as the backbone for planar chiral catalyst systems for two main reasons: 1) the cobalt-based sandwich complexes proved to be very sensitive with regard to the cyclopalladation outcome depending on their substitution pattern in terms of reactivity and stereochemistry, thus limiting the number of accessible catalyst structures;[4b] 2) for the cobalt-based sandwich backbone the electron density could not be extensively variegated, in contrast to ferrocenes, for which, for example, the oxidation potentials are strongly dependent upon the substitution pattern. Along these lines, imidazoline rather than oxazoline coordination sites fit better into a modular concept to understand how the electronic properties ideally should be, since electron density can be readily adjusted by the choice of the amino-N substituent.



Scheme 2. Synthesis of *N*-methyl 2-ferrocenyl imidazoline palladacycles **14** and **15**, **19** and **20**.

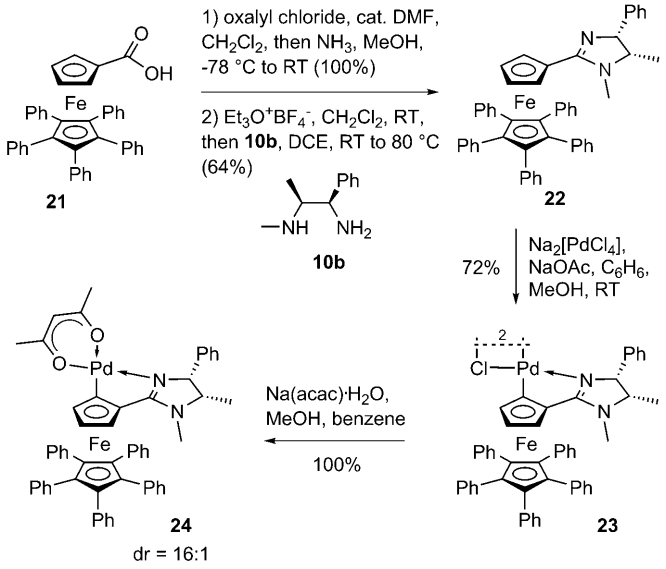
First- and second-generation catalysts: The investigations started with catalyst systems closely related to FOP-X so as to study the effect of an electron-rich donor system in *N*-methyl 2-ferrocenyl imidazolines. Since, analogously to FOP, all attempts failed to obtain the corresponding palladacycles by direct cyclometallation with Pd^{II} salts as both $Na_2[PdCl_4]$ and $Pd(OAc)_2$ gave practically no diastereoselectivity, palladacycles **14** and **15** were prepared by a two-step procedure (Scheme 2). *t*BuLi and a combination of *t*BuLi and lithium diisopropylamide (LDA) allowed for diastereoselective *ortho*-lithiations,[9] and subsequent reaction with 1,2-diiodoethane as iodinating agent provided selective access to both planar chiral diastereomers **12** and **13** in the form of air- and light-sensitive solids that had to be purified by using a silica gel column under the exclusion of light. Oxidative addition of $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) provided iodide-bridged palladacycles **14** and **15** in 54 and 42% overall yield, respectively.

Unfortunately, activating **14** and **15** with silver salts such as silver trifluoroacetate (AgTFA) for the rearrangement of *N*-PMP (*p*-methoxyphenyl)-trifluoroacetimidates resulted in low enantioselectivities and poor reproducibility, which was ascribed to insufficient catalyst stability (formation of Pd black), whereas the iodide bridged dimers were catalytically almost inactive without activation.

The sterically more demanding pentamethylferrocenyl (Fc*) imidazoline palladacycle **19** was not only expected to allow for a more pronounced steric discrimination of the space above and below the Pd square plane, but also to pro-

vide a relatively stable ferrocenium ion generated by the silver-activating agent (kinetic stability due to shielding of Fe^{III} by C_5Me_5 (Cp*) and thermodynamic stability due to the electron-donating effect of the five methyl groups). As Pd^{II} salts oxidatively decomposed Fc* imidazoline ligand **17** or resulted in low diastereoselectivity for cyclopalladations, **19** was also prepared by means of a lithiation procedure (Scheme 2).[4d] The diastereomeric ratio (dr) of 19:1 for iodo derivative **18** was improved to >99:1 in the iodide-bridged palladacycle complex. Treatment of **19** with PPh_3 led to the diastereomerically pure monomeric species **20**, the structure of which was determined by X-ray crystallography (Scheme 2), thereby revealing the S_p configuration with regard to the planar chirality.[10,11] The observed configuration is in harmony with a mechanistic model presented by Richards et al. for *ortho*-lithiations of ferrocenyl oxazolines.[12] The Pd center adopts a distorted square-planar coordination geometry, and the PPh_3 ligand is exclusively positioned *trans* to the imino-type nitrogen atom.

In addition, we were interested in sterically even more demanding, yet less electron-rich pentaphenylferrocenyl (Fc^{Φ}) systems like **23** (Scheme 3), which should be more resistant

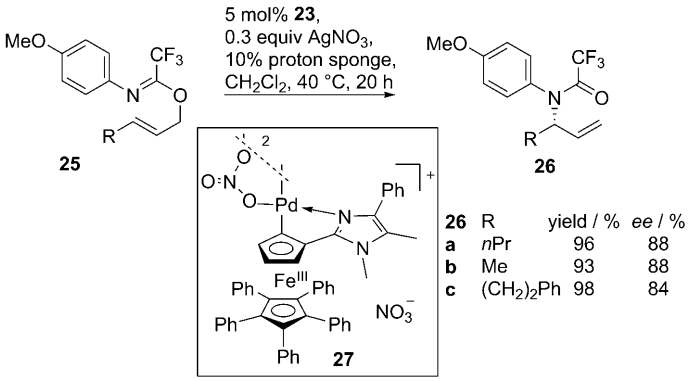


Scheme 3. Synthesis of *N*-methyl 2-(pentaphenyl)ferrocenyl imidazoline palladacycles **23** and **24** by direct diastereoselective cyclopalladation.

towards oxidative decomposition. All attempts to *ortho*-lithiate **22** failed and the starting material was always recovered unchanged. However, unlike Fc* derivative **17**, **22** could be directly and diastereoselectively *ortho*-palladated with $Na_2[PdCl_4]$/NaOAc furnishing the air-stable palladacycle **23** as a dimeric chloride-bridged complex. To determine the diastereoselectivity of the cyclopalladation, **23** was treated with an excess of Na(acac) (acac = acetylacetonate), thereby leading to the monomeric complex **24** (dr = 16:1).[13,14]

The absolute configuration was assigned by NOESY experiments of **24** (see the Supporting Information) because suitable crystals could not be obtained. Like lithiations of the Fc* imidazolines **17**,[4d] the cyclopalladation reaction occurs in a way that the phenyl group at the imidazoline 4-position points toward the spectator Cp ligand (*endo*).

Complexes **19** and **23** were examined in the aza-Claisen rearrangement of allylic trifluoroacetimidates **25** (Scheme 4) after activation with AgTFA or $AgNO_3$ in the presence of



26	R	yield / %	*ee* / %
a	*n*Pr	96	88
b	Me	93	88
c	$(CH_2)_2Ph$	98	84

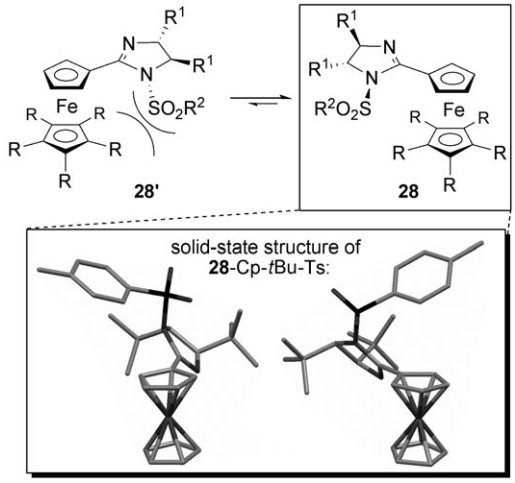
Scheme 4. Aza-Claisen rearrangement of trifluoroacetimidates **25** using **23** as precatalyst, which presumably generates **27** as the catalytically active species.

substoichiometric amounts of proton sponge (PS, *N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene) to prevent decomposition of the substrate by traces of acid.[4c] $AgNO_3$ generally provided a more active species than AgTFA, and 6 equiv Ag^I per palladacycle dimer gave the best results. Whereas Fc* derivative **19** (10 mol%, reaction time 20 h at 40°C in CH_2Cl_2) gave at best only 50% yield and a moderate *ee* value of 70% for model substrate **25a** (R = *n*Pr), 5 mol% of Fc^{Φ} derivative **23** provided good enantioselectivities and excellent yields under the same conditions.[15]

Activation of the precatalyst dimer by $AgNO_3$ is assumed to take place as follows: 2 equiv per dimer are necessary to exchange both of the strongly binding Cl anions by weakly binding nitrate. Another 2 equiv oxidize the two Fe centers from Fe^{II} to Fe^{III}, thus leading to a far less electron-rich (paramagnetic) ligand and resulting in a stronger Lewis acid. The remaining Ag ions might partly oxidize the imidazoline moieties to form imidazoles as donor (as in **27** in Scheme 4), which renders the Pd centers even less electron-rich.

Despite the fact that the diastereomeric ratio of the precatalyst was only 16:1 (i.e., diastereomeric excess (*de*) = 88%), enantioselectivity is only slightly lower than that for COP-Cl.[4a] However, the catalyst has two main technical disadvantages: 1) it could not be generated in diastereomerically pure form by a more selective metalation or by crystallization or chromatography to obtain very high enantioselectivities; 2) the diamines **10a**/**b** used for imidazoline formation are not commercially available.

Third-generation catalysts: Because these initial two catalyst generations had shown that reduced electron density of the ligand results in higher stability, activity, and enantioselectivity, a third-generation catalyst was targeted in which a strongly electron-withdrawing *N*-sulfonyl residue is the structural key element. The Pd center consequently displays a higher Lewis acidity while the ferrocene body is more stable toward oxidative decomposition. In addition, the sulfonyl group permits a diastereoselective direct cyclopalladation of ligand systems **28**: steric repulsion between the residue R^1 at the imidazoline 5-position and the sulfonyl group effects a transfer of chirality by transmitting stereoinformation to the sulfonylated nitrogen atom (Scheme 5), which

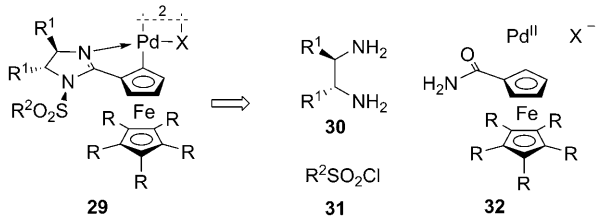


Scheme 5. Top: Conformational equilibrium for **28** caused by chirality transfer to the sulfonylated N atom and steric repulsion between the sulfonyl residue and the Cp spectator ligand. Bottom: Confirmation by X-ray crystal structure analysis. Due to crystal packing effects, two N–S rotamers are formed, in which the C–S bond is either *syn*- (left) or *anti*-periplanar (right) to the N-atom lone pair. Both species adopt a similar conformation around the C(imidazoline)–Cp bond.

adopts a significantly pyramidalized geometry and results in a preferred conformation in which the sulfonyl group points away from the ferrocenyl floor and, as a result, allows for a diastereoselective cyclopalladation. In contrast to the direct cyclopalladation of Fc^{Φ} imidazoline **22**, the stereochemical outcome can thus be explained by the reaction of the thermodynamically most stable conformer.

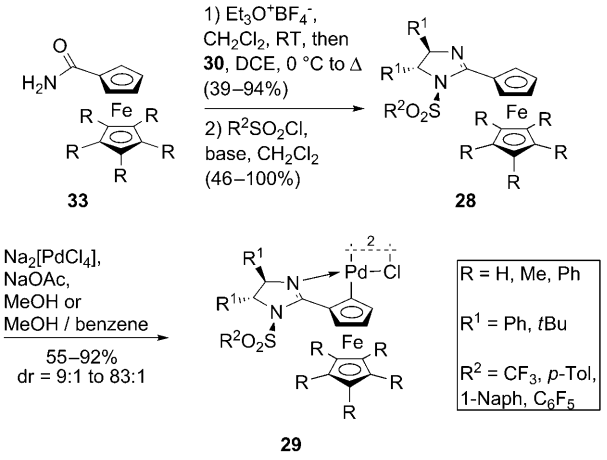
The hypothesis of chirality transfer to the *N*-sulfonyl group was confirmed by X-ray crystal structure analysis (Scheme 5) of imidazoline **28**-Cp-*t*Bu-Ts (numbering system: **28**-(C_5R_5)-R^1-(SO_2R^2); Ts = tosyl).[16] The sulfonylated N atom is significantly pyramidalized, thus minimizing unfavorable steric interactions with the neighboring substituents.

The third-generation palladacycles **29** are created based on a modular design that allows adjustment of both the steric and the electronic properties of the Lewis acid by five different modules (Scheme 6):[4e] 1) the Cp′ spectator ligand C_5R_5 (C_5H_5 = Cp, C_5Me_5 = Cp*, C_5Ph_5 = Cp^{Φ}), 2) the imidazoline part synthesized from an enantiomerically pure C_2-symmetric diamine **30**, 3) the sulfonyl residue, 4) the counteranion X^-, and 5) the oxidation state of the Fe ion (ferrocene versus ferrocenium).



Scheme 6. Modular concept of *N*-sulfonyl 2-ferrocenyl imidazoline palladacycles **29**.

The air-stable and crystalline imidazolines **28** were prepared in good yield from carbamides **33**[4d] by activation by means of the corresponding iminium ether intermediate and a subsequent sulfonylation with various commercially available sulfonyl chlorides (Scheme 7, Table 1).



Scheme 7. Synthesis of *N*-sulfonyl ferrocenyl imidazoline palladacycles **29** by direct diastereoselective cyclopalladation (*p*-Tol = *p*-toluene; 1-Naph = 1-naphthyl).

Yields for the formation of ligands **28** were comparable for all imidazolines based on 1,2-diphenylethylenediamine regardless of the size of the Cp′ spectator ligand (Table 1, entries 1–3 and 5–8), whereas the more bulky 1,2-di-*tert*-butylethylenediamine resulted in a poor yield (Table 1, entry 4).

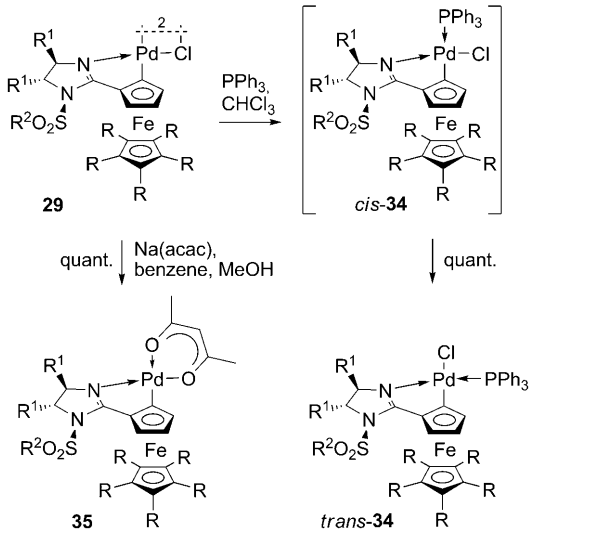
Cyclopalladation at RT with $Na_2[PdCl_4]$/NaOAc in MeOH (plus benzene if the solubility of the imidazoline is insufficient in MeOH) provided the air-stable dimeric complexes **29** in good yield and with high diastereoselectivity with regard to the planar chirality (dr = 7:1–20:1 and 9:1–83:1 before and after chromatography, respectively). The cyclopalladations usually proceeded best for Cp′-unsubstituted imidazolines (Table 1, entries 9–11), thereby providing high yields with the exception of **28**-Cp-*t*Bu-Ts carrying two *t*Bu substituents on the imidazoline backbone (Table 1,

Table 1. Preparation of imidazolines **28** and palladacycles **29**.

Entry	Product	C_5R_5	R^1	R^2	Yield[a] [%]	dr[b]	dr[c]
1	**28**	Cp	Ph	CF_3	72[d]	–	–
2	**28**	Cp	Ph	*p*-Tol	73[d]	–	–
3	**28**	Cp	Ph	1-Naph	73[d]	–	–
4	**28**	Cp	*t*Bu	*p*-Tol	18[d]	–	–
5	**28**	Cp*	Ph	CF_3	71[d]	–	–
6	**28**	Cp*	Ph	*p*-Tol	81[d]	–	–
7	**28**	Cp*	Ph	C_6F_5	65[d]	–	–
8	**28**	Cp^{Φ}	Ph	*p*-Tol	77[d]	–	–
9	**29**	Cp	Ph	CF_3	92	9:1	9:1
10	**29**	Cp	Ph	*p*-Tol	93	18:1	18:1
11	**29**	Cp	Ph	1-Naph	91	12:1	12:1
12	**29**	Cp	*t*Bu	*p*-Tol	55	20:1	72:1
13	**29**	Cp*	Ph	CF_3	69	15:1	83:1
14	**29**	Cp*	Ph	*p*-Tol	85	20:1	20:1
15	**29**	Cp*	Ph	C_6F_5	60	7:1	14:1
16	**29**	Cp^{Φ}	Ph	*p*-Tol	50	20:1	38:1

[a] Isolated yield after chromatography. [b] The dr values of the crude product as determined by ^{1}H NMR spectroscopy of complex **34** or **35**. [c] The dr values of the isolated product as determined by ^{1}H NMR spectroscopy of complex **34** or **35**. [d] Yield over 2 steps from **33**.

entry 12). For reactions with incomplete conversion, most of the unreacted ligands **28** can be readily recovered after the reaction. To determine the ratio of diastereomers with regard to the introduced planar chirality, the dimers **29** were transformed into monomeric complexes **34** and **35** by treatment with PPh_3 or Na(acac) (Scheme 8).



Scheme 8. Synthesis of the monomeric complexes **34** and **35** with PPh_3 or Na(acac) to determine the diastereomeric ratio of **29** with regard to the planar chirality.

Determination of the diastereomeric ratio is complicated at the dimer stage by the existence of geometrical isomers around the Pd–Cl square planes resulting in up to 6 signal sets in NMR spectroscopy ((*S*$_p$/*S*$_p$)-*cis*, (*S*$_p$/*S*$_p$)-*trans*, (*S*$_p$/*R*$_p$)-*cis*, (*S*$_p$/*R*$_p$)-*trans*, (*R*$_p$/*R*$_p$)-*cis*, (*R*$_p$/*R*$_p$)-*trans*).

Interestingly, upon addition of PPh_3 in $CDCl_3$, Fc*- and Fc^{Φ}-complexes **29** rapidly provided a mixture of monomeric isomers with the phosphine in a *cis* and *trans* position to the N-donor atom (Scheme 8), but completely isomerized after several hours at RT to yield, as expected from comparable complexes, the *trans* isomers as a result of the so-called *trans* effect.[17] Using a less bulky phosphine ($MePPh_2$), or working with Cp′-unsubstituted complexes **29**, only one isomer was detected directly after addition. These findings can be rationalized by the better (thus kinetically favored) steric accessibility of the position *cis* to N, which is, however, thermodynamically less favored for π-acidic ligands.

The structures of **35**-Cp^{Φ}-Ph-Ts and **34**-Cp*-Ph-Ts were determined by X-ray crystal structure analysis (Figure 1),[18] thus confirming the predicted S_p configuration for the major diastereomer.[19,20] The same configuration was confirmed

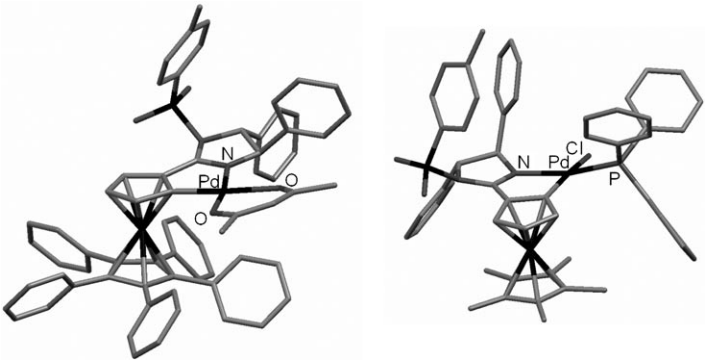


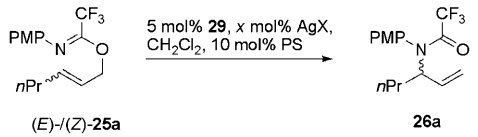
Figure 1. X-ray crystal structures of the monomeric complexes **35**-Cp^{Φ}-Ph-Ts and **34**-Cp*-Ph-Ts.

for **35**-Cp-Ph-Ts and **35**-Cp^{Φ}-Ph-Ts, as determined by NOESY experiments (see the Supporting Information).

Complexes **29** were then investigated in the aza-Claisen rearrangement of *N*-PMP-trifluoroacetimidate model-substrate **25a** (Table 2). All five modules of the catalyst, the solvent, and different additives were examined to find the best conditions. The Cl-bridged dimeric palladacycle **29**-Cp-Ph-Ts was found to be nearly unreactive as catalyst (Table 2, entry 1). Therefore, different silver salts AgX (X = TFA, OTf, OTs, BF_4, NO_3; entries 2–9 in Table 2; OTf = trifluoromethanesulfonate) were evaluated for their catalyst-activating properties by exchanging chloride with a more labile coordinating ligand.

Although AgTFA is the most general activating reagent of those investigated (Table 2, entries 3, 6), AgOTf proved to be superior in the case of **29**-Cp catalyst precursors for *Z*-configured imidates **25** (Table 2, entry 8). Treatment of **29**-Cp-Ph-Ts with 2 equiv AgTFA led to the formation of the corresponding TFA complex, of which an ^{1}H NMR spectrum could be recorded displaying a single set of signals (one geometric isomer around the Pd square plane), whereas addition of another 2 equiv of AgTFA led to a color change from dark red to brown and the complete disappear-

Table 2. Investigation of the silver salt for precatalyst activation.



(*E*)-/(*Z*)-**25a** **26a**

Entry	**25a**	**29**	AgX (*x* [mol%])	*t* [h]	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1	*E*	**29**-Cp-Ph-Ts	–	120	20	0	–
2	*E*	**29**-Cp-Ph-Ts	AgTFA (10)	48	20	5	n.d.[c]
3	*E*	**29**-Cp-Ph-Ts	AgTFA (20)	48	20	88	67
4	*E*	**29**-Cp-Ph-Ts	AgOTf (20)	24	20	95	56
5	*E*	**29**-Cp-Ph-Ts	$AgBF_4$ (20)	24	40	66	56
6	*Z*	**29**-Cp-Ph-Tf	AgTFA (20)	24	40	100	73
7	*Z*	**29**-Cp-Ph-Tf	AgOTs (20)	48	20	76	81
8	*Z*	**29**-Cp-Ph-Ts	AgOTf (20)	24	20	90	91
9	*E*	**29**-Cp-Ph-Ts	$AgNO_3$ (20)	48	20	92	69

[a] Yield determined by ^{1}H NMR spectroscopy. [b] The *ee* values determined by HPLC after hydrolysis of **26a** to the secondary amine (see the Supporting Information). [c] n.d. = not determined.

ance of the ^{1}H NMR spectroscopic signals, indicating the complete oxidation of Fe^{II} to Fe^{III}. A paramagnetic ferrocenium species is thus formed, which is also the catalytically active species as the rearrangement proceeds only very slowly employing 2 equiv of the silver salt per dimer **29**.[21] Whereas 5 mol% of **29**-Cp-Ph-Ts, activated by 2 equiv of AgTFA, catalyzed the reaction of **25a** to **26a** with only 5% yield after 48 h (Table 2, entry 2), activation with 4 equiv AgTFA led to a complex that performed the same reaction with 88% yield (Table 2, entry 3). Similar results were obtained with $AgNO_3$ (Table 2, entry 9). Alternatively, thallium(I) triflate, which is a less potent oxidizing agent as compared to AgOTf, was investigated as halide scavenger. As expected, the precatalyst treated with TlOTf was not active.

Generally speaking, the counterion should not transfer too much electron density to the Pd center, it should also prevent formation of kinetically inert dimers like in the case of halide counterions. Furthermore, it should selectively block one defined position—most likely the *cis* position to the N donor—in the square-planar complex so as to achieve selective coordination of the substrate molecules at the same defined coordination site, most likely the *trans* position to the N donor.[22] On the other side, a coordinatively unsaturated Pd^{II} center, as presumably formed with noncoordinating counterions like BF_4^- (Table 2, entry 5), may not only lead to an unstable Pd complex, but also to a less regioselective coordination mode.

After a solvent screening, the noncoordinating CH_2Cl_2 was selected for further catalyst optimization since it allowed for the highest enantioselectivities and a promising catalytic activity (general trend: 1) catalyst activity: 1,2-dichloroethane (DCE) > CH_2Cl_2 > $CHCl_3$ > PhH > CH_2Cl_2 and DMF (1%) > MeCN > Et_2O (catalyst not soluble); 2) enantioselectivity: CH_2Cl_2, CH_2Cl_2 and DMF (1%) > PhH > DCE, MeCN > $CHCl_3$). The catalyst activation is also best performed in CH_2Cl_2. The active catalyst solution is subsequently added to neat substrate and most of the solvent is then removed to enhance the reaction rate by a higher concentration of catalyst. Gratifyingly, the activated catalyst stays in solution even in neat substrate.

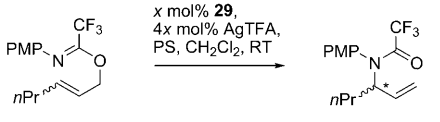
As mentioned for the first- and second-generation precatalysts, the rearrangements were performed in the presence of the noncoordinating, non-nucleophilic base proton sponge (1–2 equiv/dimer **5**) to prevent elimination of *N*-PMP-trifluoroacetamide triggered by traces of acid that are possibly formed by the hydrolysis of AgTFA with moisture to give small amounts of trifluoroacetic acid. The use of PS also results in higher *ee* values (higher catalyst stability) at the expense of somewhat decreased conversion rates, which might be ascribed to a weak coordination to the catalytically active center or a partial reduction of the ferrocenium core, but allowing for significantly cleaner reaction outcomes. In addition, prior to use the activated catalyst solution is usually filtered over CaH_2 to trap traces of acid.

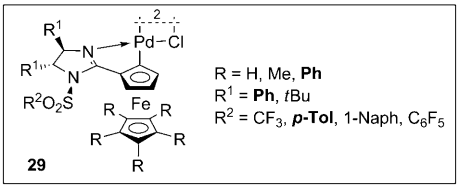
During the investigation of the sulfonyl module, the *p*-toluenesulfonyl group emerged as the best residue of those investigated (Table 3, entries 2, 5, 9, 11, 12). Larger groups like 1-naphthylsulfonyl lowered the reaction rate significantly (Table 3, entries 3 and 6), whereas groups with a stronger electron-withdrawing character did not result in considerably higher yields or *ee* values (Table 3, entries 1, 4, and 10), but in some cases (**29**-Cp*-Ph-Tf) led either to decomposition of the catalyst and thus a racemic rearrangement product (Table 3, entry 8), or even impeded the cyclopalladation. For instance, **28**-Cp^{Φ}-Ph-Tf ($R^2 = CF_3$) did not undergo a cyclopalladation at all with either $Na_2[PdCl_4]$/NaOAc in methanol (50°C, 16 h), $Pd(OAc)_2$ in benzene at 60°C, or $Pd(OAc)_2$ (24 h) in acetic acid at 70°C (8 h).

No significant difference in enantioselectivity and yield of **26a** was found for the residue R^1 being either Ph or *t*Bu (Table 3, entries 2 and 7). Because the imidazolines with R^1 = Ph are prepared in much higher yields and the required diamine is commercially available at a reasonable price for larger amounts,[23] they were selected for the investigation of the influence of the cyclopentadienyl spectator ligand module, which has the highest impact on the rearrangement outcome.

Whereas catalysts possessing an unsubstituted Cp′ ring did not provide useful *ee* levels for the *E*-configured model substrate **25a** (Table 3, entries 1–3, 7), the rearrangement of (*Z*)-**25a** enabled formation of amide **26a**, reaching the 90% *ee* benchmark (Table 3, entries 4, 5). By contrast, with a more bulky, yet more electron-rich Cp* spectator ligand, both (*E*)- and (*Z*)-**25a** gave about 90% *ee* (Table 3, entries 9, 11) although the reaction mixtures had to be heated to 40°C to obtain useful conversion rates with a precatalyst

Table 3. Catalyst screening with model substrate (*E*)-/(*Z*)-**25a**.

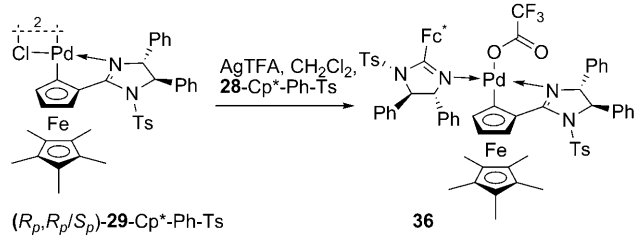




Entry	**25a**	C_5R_5	R^1	R^2	*x*	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1	*E*	Cp	Ph	CF_3	5	20	96[c]	64 (*R*)
2	*E*	Cp	Ph	*p*-Tol	5	20	88[c]	67 (*R*)
3	*E*	Cp	Ph	1-Naph	5	20	54[c]	65 (*R*)
4[d]	*Z*	Cp	Ph	CF_3	5	20	90[e]	91 (*S*)
5[d]	*Z*	Cp	Ph	*p*-Tol	5	20	75[c]	89 (*S*)
6[d]	*Z*	Cp	Ph	1-Naph	5	20	19[c]	72 (*S*)
7	*E*	Cp	*t*Bu	*p*-Tol	5	20	76[c]	66 (*R*)
8[f]	*E*	Cp*	Ph	CF_3	5	40	80[g]	0
9[f]	*E*	Cp*	Ph	*p*-Tol	5	40	91[e]	89 (*R*)
10[f]	*E*	Cp*	Ph	C_6F_5	5	40	88[e]	74 (*R*)
11	*Z*	Cp*	Ph	*p*-Tol	5	40	72[e]	93 (*S*)
12	*E*	Cp^{Φ}	Ph	*p*-Tol	1.0	20	96[e]	97 (*R*)
13	*E*	Cp^{Φ}	Ph	*p*-Tol	0.5	20	95[e]	98 (*R*)
14	*E*	Cp^{Φ}	Ph	*p*-Tol	0.1	20	94[e]	97 (*R*)
15	*E*	Cp^{Φ}	Ph	*p*-Tol	0.05	40	95[h]	95 (*R*)
16	*Z*	Cp^{Φ}	Ph	*p*-Tol	5	40	36[e]	85 (*S*)

[a] Yield determined by ^{1}H NMR spectroscopy. [b] The *ee* values determined by HPLC after hydrolysis of **26a** to the secondary amine (see the Supporting Information). [c] Reaction time 2 d. [d] AgOTf was used for activation. [e] Reaction time 1 d. [f] Catalyst precursor doped with 10% **28**-Cp*-Ph. [g] Reaction time 5 h. [h] Reaction time 3 d.

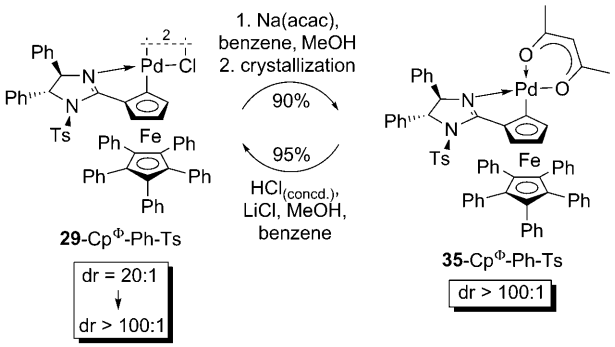
loading of 5 mol%. Interestingly, to obtain these high levels of asymmetric induction for (*E*)-**25a**, the catalyst precursor **29**-Cp*-Ph-Ts (dr = 20:1) had to be doped with 10% **28**-Cp*-Ph-Ts (i.e., 0.5 mol% with regard to (*E*)-**25a**). In the absence of **28**-Cp*-Ph-Ts, the *ee* decreased significantly to 73%. We assume that the R_p-configured catalyst (the minor palladacycle isomer) is preferentially deactivated by the formation of a monomeric complex with the imidazoline imino N atom of **28**-Cp*-Ph-Ts (Scheme 9).[24]



Scheme 9. Proposed deactivation of the R_p-configured isomer of **29**-Cp*-Ph-Ts by imidazolines **28**-Cp*-Ph-Ts.

A breakthrough was achieved with the less electron-rich and even more bulky Cp^{Φ} spectator ligand, which resulted not only in significantly higher enantioselectivity for (*E*)-**25a** (*ee* = 97%, entry 12 in Table 3) but also in a highly active catalyst, thus allowing for a reduction of the precatalyst amount to an unprecedented 0.5 to 0.05 mol% without largely effecting the enantioenrichment yet still providing useful reaction rates (Table 3, entries 13–15). In contrast, **29**-Cp^{Φ}-Ph-Ts is not a useful catalyst for (*Z*)-**25a**, which was converted in only 36% yield and 85% *ee* using high catalyst loadings (Table 3, entry 16).

Having identified the most active and selective catalyst of this series, attempts were made to synthesize the complex in a diastereomerically pure form. Crystallization was not successful since two main isomers (the geometrical isomers of the S_p,S_p diastereomer around the Pd–Cl squares, ca. 2:1) plus four minor isomers are present (see above). However, it was found that the acac monomer **35**-Cp^{Φ}-Ph-Ts can be conveniently crystallized on a preparative scale, thereby leading to diastereomerically pure material in the form of purple-red needles (Scheme 10). Treatment with a mixture of benzene (to dissolve the complex), MeOH (to get miscibility with the aqueous phase), LiCl (as Cl source), and concentrated aqueous HCl (to protonate $[acac]^-$) then leads within minutes to the regeneration of **29**-Cp^{Φ}-Ph-Ts in a diastereomerically pure form with respect to planar chirality. Only minor decomplexation of Pd^{II} was observed (<5%), which means that the Pd–C σ bond is remarkably stable, even to strong acids.

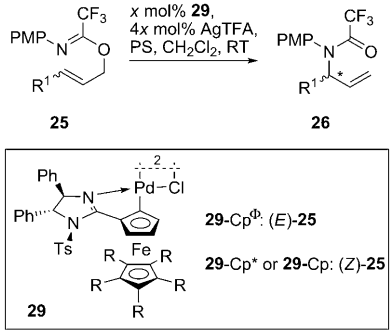


Scheme 10. Formation of geometrically pure **29**-Cp^{Φ}-Ph-Ts.

The diastereomerically pure catalyst precursor leads only to a negligible further improvement of the *ee* of the rearrangement product, since the minor diastereomer is arguably less catalytically active. The scope of the rearrangement of imidates **25** was then studied in detail using **29**-Cp-Ph-Ts and **29**-Cp*-Ph-Ts for *Z*- and **29**-Cp^{Φ}-Ph-Ts for *E*-substrates **25** (Table 4).

Whereas the former two catalyst precursors provide good conversions and yields only for α-unbranched allylic substrates (*Z*)-**25** requiring a precatalyst loading of 5 mol% (Table 4, entries 1–6), the latter has a broad applicability even at low catalyst loadings. The rate of the rearrangement depends primarily on the steric bulk of the residue R′. With unbranched alkyl substituents (R^1 = Me, *n*Pr, $(CH_2)_2$Ph,

Table 4. Screening of substrates **25** bearing different groups R^1 with **29**-Cp-Ph-Ts/**29**-Cp*-Ph-Ts (*Z*-substrates) and **29**-Cp^{Φ}-Ph-Ts (*E* substrates).



Entry	**25**	R^1	C_5R_5	*x*	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1[c]	(*Z*)-**25a**	*n*Pr	Cp	5	20	75	89 (*S*)
2[c]	(*Z*)-**25c**	$(CH_2)_2$Ph	Cp	5	20	70	90 (*S*)
3[c]	(*Z*)-**25d**	*i*Bu	Cp	5	20	69	96 (*S*)
4[c]	(*Z*)-**25a**	*n*Pr	Cp*	5	40	72	93 (*S*)
5[c]	(*Z*)-**25c**	$(CH_2)_2$Ph	Cp*	5	40	95	95 (*S*)
6[c]	(*Z*)-**25d**	*i*Bu	Cp*	5	40	82	96 (*S*)
7[c]	(*E*)-**25a**	*n*Pr	Cp^{Φ}	0.5	20	95	98 (*R*)
8[c]	(*E*)-**25a**	*n*Pr	Cp^{Φ}	0.1	40	89	97 (*R*)
9[d]	(*E*)-**25a**	*n*Pr	Cp^{Φ}	0.05	40	95	95 (*R*)
10[d]	(*E*)-**25b**	Me	Cp^{Φ}	0.1	20	91	95 (*R*)
11[d]	(*E*)-**25b**	Me	Cp^{Φ}	0.05	40	98	92 (*R*)
12[c]	(*E*)-**25c**	$(CH_2)_2$Ph	Cp^{Φ}	1.0	20	94	99.7 (*R*)
13[d]	(*E*)-**25c**	$(CH_2)_2$Ph	Cp^{Φ}	0.05	40	99	98 (*R*)
14[c]	(*E*)-**25d**	*i*Bu	Cp^{Φ}	0.2	40	96	98 (*R*)
15[c]	(*E*)-**25d**	*i*Bu	Cp^{Φ}	0.1	40	95	98 (*R*)
16[c]	(*E*)-**25e**	*i*Pr	Cp^{Φ}	0.5	40	75	96 (*R*)
17[d]	(*E*)-**25e**	*i*Pr	Cp^{Φ}	0.1	40	81	93 (*R*)
18[d]	(*E*)-**25f**	*c*-Hex	Cp^{Φ}	1.0	40	96	99 (*S*)
19[d]	(*E*)-**25f**	*c*-Hex	Cp^{Φ}	0.5	40	82	97 (*S*)
20[d]	(*E*)-**25g**	$(CH_2)_2CO_2Et$	Cp^{Φ}	0.35	40	96	97 (*R*)
21[c]	(*E*)-**25h**	Ph	Cp^{Φ}	1.0	40	99	88 (*S*)
22[c]	(*E*)-**25h**	Ph	Cp^{Φ}	0.5	40	97	84 (*S*)

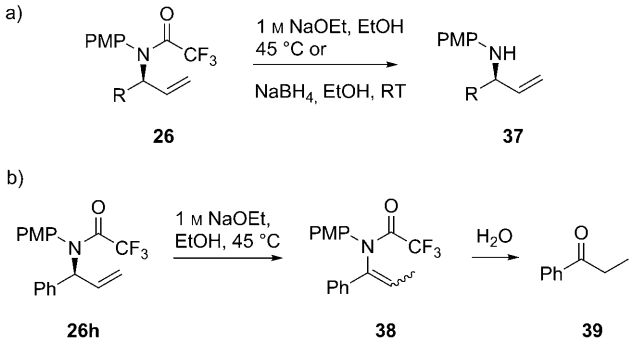
[a] Isolated yield. [b] The *ee* values determined by HPLC after hydrolysis of **26** to the secondary amines (see the Supporting Information). [c] Reaction time 1 d. [d] Reaction time 3 d.

*i*Bu), (*R*)-**26** is formed in excellent yield with 0.05 to 0.1 mol% catalyst loading, providing very high enantioselectivities (Table 4, entries 7–15). The most difficult aliphatic substrate in terms of the enantioselectivity prepared from crotonylic alcohol (i.e., R^1 = Me) furnished (*R*)-**26b** with 95% *ee* (Table 4, entry 10). Even in the case of the branched *i*Pr or cyclohexyl (*c*-Hex) substituents, a case that has not been described so far, the rearrangement proceeds with acceptable rates with 0.1 to 1.0 mol% catalyst precursor (Table 4, entries 16–19). An ester functionality somewhat lowered the reaction rate but still permitted good *ee* values and yields with 0.35 mol% precatalyst (Table 4, entry 20). Also, the aromatic Ph substituent (best reported results:[4b] yield: 72%; *ee* = 81% with 5 mol% COP-TFA) is well tolerated (Table 4, entries 21 and 22). The comparatively lower *ee* values of 84–88% obtained with **25h** using precatalyst loadings of 0.5–1.0 mol% are the consequence of a relatively rapid noncatalyzed, thermal rearrangement (vide infra), which was not observed for 3-alkyl-substituted substrates and that might also be the reason for the low enantioselectivity obtained with previous less active catalysts.

Using the deprotection protocol from the literature, that is, treatment with 1 M NaOEt in EtOH at 45 to 50 °C overnight (Scheme 11),[4a] allylic trifluoroacetamides **26** could be generally deacylated with good yields, except for **26h**. In that case complete decomposition to phenylethylketone (**39**) was found, probably through base-catalyzed tautomerization to form an enamine. However, amide **26h** could be deacylated in 88% yield by reaction with $NaBH_4$ in EtOH at RT.[25] This method could also be applied as an alternative method to all other allylic amides **26**.

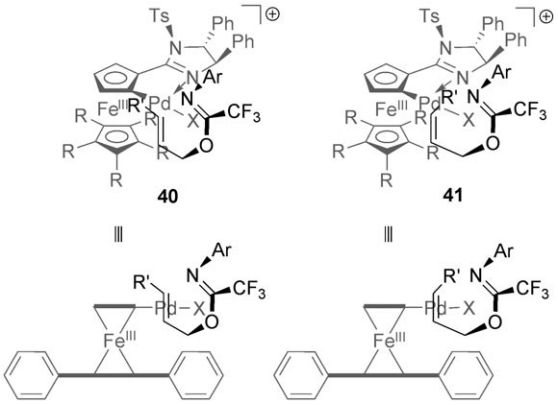
Opposite absolute configurations were obtained for the major enantiomers of rearrangement products **26** starting from either (*E*)- or (*Z*)-**25**. This is accounted for by the working model depicted in Scheme 12.

Assuming that the olefin as π-acidic ligand will preferentially coordinate *trans* to the imidazoline N atom due to the *trans* effect,[17] and that the *cis* position is blocked by the negatively charged counterion,[22] the imidate N atom, which is not



Scheme 11. a) Procedures for the cleavage of the trifluoroacetamide group; b) phenylethylketone formation from **26h** by cleavage attempts with NaOEt.

coordinated to the Pd center, will approach the olefin by means of an outer-sphere attack (remote to the Pd center). Increased steric interactions of the coordinated olefin with bulky substituted Cp′ spectator ligands presumably results in a better face selectivity of the olefin coordination, thus ex-



Scheme 12. An explanation of the stereospecific outcome of the rearrangement of **25**.

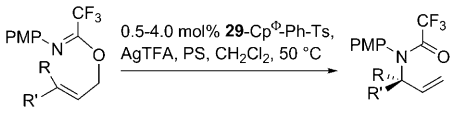
plaining the higher enantioselectivity as compared to derivatives bearing the unsubstituted Cp. The exceptionally high catalytic activity is mainly attributed to five factors: 1) the possibility to apply almost solvent-free reaction conditions, 2) the robustness of the active catalyst under the reaction conditions even at enhanced temperatures, 3) the bulk of the Cp^{Φ} ligand, which might lead to a facilitated monomer formation of the active species, but also in less product inhibition due to destabilization of the corresponding olefin complex, 4) the formation of a ferrocenium system as catalytically active species by oxidation of the ferrocene core by the silver salt, and 5) the electron-withdrawing nature of the five phenyl substituents on the Cp^{Φ} spectator ligand.[26,27] The last two factors enhance the Lewis acidity of the Pd center in **29**-Cp^{Φ}.

Prior to this work, a longstanding problem has been the catalytic enantioselective formation of N-substituted quaternary stereocenters by aza-Claisen rearrangement or allylic substitution reactions.[28] In the former case, this can be attributed to insufficient catalyst activity, as the formation of a quaternary center is slowed for steric reasons. Previously, the aza-Claisen rearrangement forming quaternary carbon centers has only been reported in a nonenantioselective way.[29] Since quaternary carbon atoms bearing a nitrogen substituent are a widespread structural motif for bioactive natural and unnatural compounds,[30] the asymmetric construction of those stereocenters by means of asymmetric catalysis is an important challenge. A key application of enantiopure allylic amines might become the formation of quaternary amino acids and derivatives, of which many can be found in biologically active natural products and pharmaceuticals.[31] These targets are attractive due to their ability to, for example, induce helical peptide structures,[32] and also owing to the fact that peptides incorporating quaternary amino acid residues possess enhanced stability to proteases.[33] To this end, various methods have been developed in the past for the formation of quaternary amino acids, some of them also utilizing asymmetric catalysis, while the large majority of reactions is still relying on stoichiometric concepts.[31a]

The enhanced catalyst activity of **29**-Cp^{Φ} in combination with the stereospecific reaction outcome explained by the working model shown in Scheme 12 led to the investigation of the enantioselective formation of N-substituted quaternary stereocenters by means of the aza-Claisen rearrangement using 3,3-disubstituted allylic trifluoroacetimidates **42**.

2.0 mol% of the catalyst precursor **29**-Cp^{Φ}-Ph-Ts activated in situ with 3.75 equiv of AgTFA[34] (relative to **29**) were generally sufficient to give high conversion after 2.5 days at 50 °C with substrates in which one of the substituents R or R′ is a methyl group (Table 5).[4e] The allylic trifluoroacetamides **43** were formed with high to excellent *ee* values and in good yield (Table 5, entries 1–10). As expected, the rearrangement of 3,3-disubstituted substrates **42** is significantly slower relative to substrates in which R = H.[4e] The lower turnover frequency is attributed to the additional double-bond substituent hampering the attack of the imidate nitrogen atom on the sterically more hindered olefin. It is possible, though, to lower the catalyst loading to 0.5 mol% (Table 5, entry 2), albeit at the price of a prolonged reaction time of 10 d, but still attaining an excellent *ee* (97% for substrate **42a** with R = Me, R′ = $(CH_2)_2$Ph). This implies that the thermal rearrangement at 50 °C is at most 3% within 10 d.

Table 5. Highly enantioselective rearrangement of 3,3-disubstituted allylic imidates **42**.[a]



42 **43**

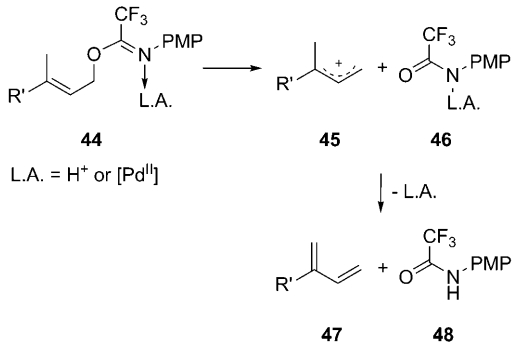
#	**42**	R′	R	Cat. [mol%]	Yield[b] [%]	*ee*[c] [%]
1	**a**	$(CH_2)_2$Ph	Me	2	94[d]	99.6 (*R*)
2	**a**	$(CH_2)_2$Ph	Me	0.5	79[e,f]	97 (*R*)
3	**b**	*n*Bu	Me	2	63	93 (*R*)
4	**c**	$(CH_2)_2CH{=}CMe_2$	Me	2	74	98 (*R*)
5	**d**	$(CH_2)_3OSi(iPr)_3$	Me	2	73	96 (*R*)
6	**e**	$(CH_2)_3O(CO)OBn$	Me	2	84	98 (*R*)
7	**f**	$(CH_2)_3NBnBoc$	Me	2	64	93 (*R*)
8	**g**	$(CH_2)_2CO_2Et$	Me	2	50	96 (*R*)
9	**h**	Me	$(CH_2)_3OSi(iPr)_3$	2	74	98 (*S*)
10	**i**	Me	CH_2OBn	2	84	99 (*R*)
11	**j**	Et	CH_2OBn	4	81	98 (*R*)
12	**k**	*n*Pr	CH_2OBn	4	63[g]	>99.5 (*R*)
13	**l**	*n*Bu	CH_2OBn	4	61[g]	98 (*R*)
14	**m**	$(CH_2)_3OSi(iPr)_3$	CH_2OBn	4	51[g]	97 (*R*)

[a] The reactions were performed on a 0.03–0.08 mmol scale (reaction time 2.5 d) unless otherwise noted. [b] Yield of isolated **43**. [c] The *ee* values determined by HPLC. [d] 0.3 mmol scale. [e] Reaction time 10 d. [f] 1.0 mmol scale. [g] Reaction time 3.5 d.

Whereas in previous experiments with **29**-Cp^{Φ}-Ph-Ts, *Z*-configured 3-monosubstituted imidates had given significantly lower reaction rates as compared to *E*-configured substrates (see above), this difference vanishes if both R and R′ are larger than H.[4e] For example, both the *E*- and *Z*-configured substrates **42d** and **42h** bearing a bulky

$(CH_2)_3OTIPS$ (TIPS = triisopropylsilyl) moiety gave practically the same yield and conversion. In both cases the product was formed under identical conditions with very high *ee* values (96 and 98% respectively; Table 5, entries 5 and 9), but with the opposite configuration.

Substrates **42** were in general found to be much more sensitive towards (Brönsted or Lewis) acid-catalyzed elimination of trifluoroacetamide than 3-monosubstituted imidates **25**, since the additional 3-substituent can stabilize an intermediary allylic cation **45** (Scheme 13). Acid-catalyzed elimination of PMP-trifluoroacetamide **48** is thus a significant side reaction.[35] However, by the use of proton sponge as Brönsted acid scavenger, this competitive reaction pathway can be suppressed to a large degree (Table 5).



Scheme 13. Acid-triggered elimination of trifluoroacetamide **48**.

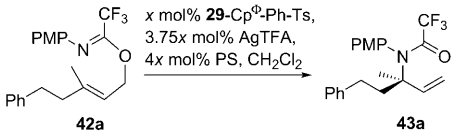
If both substituents R and R′ are larger than a methyl group, 4.0 mol% of **29**-Cp^{Φ}-Ph-Ts was employed to obtain synthetically useful yields and the reaction time was prolonged to 3.5 d. In that case, one of the substituents should display an electron-withdrawing character, since otherwise decomposition is becoming predominant. The attack by the imidate N is retarded with increasing size of the substituents and cannot compete with the formation of an allylic cation, whereas destabilization of the allylic cation by electron-withdrawing groups can overcome this problem.

With R′ = CH_2OBn, R was varied from Me to Et, *n*Pr, *n*Bu, and $(CH_2)_3OTIPS$, showing practically no difference in enantioselectivity (Table 5, entries 10–14). Excellent enantioselectivities were attained even in those cases in which R and R′ have a similar size (Table 5, entries 12–14). Gratifyingly, the rearrangement is compatible with important functional groups such as olefin, ester, carbonate, silyl ether, benzyl ether, or Boc-protected secondary amino moieties. An azide-functionalized substrate (R = Me, R′ = $(CH_2)_3N_3$) gave only very little conversion, probably owing to catalyst poisoning by the azide functionality.

If one of the two substituents at C-3 is Me, branches in the other residue are tolerated only starting from the 6-position. Substrates bearing isobutyl or benzyl residues thus did not react to the desired product. An *i*Bu group mainly resulted in decomposition, whereas the substrate with a Bn moiety simply did not react (the phenyl substituent might be already sufficiently electron-withdrawing to prevent the facile formation of an allylic carbocation **45**).

Raising the reaction temperature above 50 °C was investigated in the case of substrate **42a** to enhance the rearrangement rate (Table 6). Whereas at 50 °C a reaction time of 48 h with 2 mol% catalyst precursor was necessary (Table 6, entry 1), 1 mol% at 70 °C is sufficient for full conversion with a reduced reaction time of 30 h (Table 6, entry 2). Increasing the reaction temperature further is not useful since the enantioselectivity is dropping and side reactions like elimination and [1,3] shift, possibly due to catalyst decomposition, are observed (Table 6, entry 3).

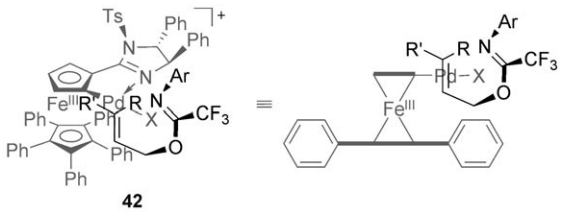
Table 6. Temperature dependence for the enantioselective rearrangement of 3,3-disubstituted allylic imidate **42a**.



Entry	T [°C]	x	t [h]	Yield[a] [%]	*ee*[b] [%]
1	50	2.0	48	94	>99
2	70	1.0	30	82	96
3	80	1.0	30	76	93

[a] Yield of isolated **43a**. [b] The *ee* values determined by HPLC.

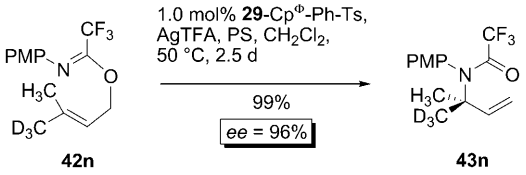
Since the enantioselectivity of the rearrangement is apparently largely independent from the steric discrimination of the two residues R and R′ at the imidate 3-position and since the rearrangement proceeds in a stereospecific fashion (opposite enantiomers are formed from geometric isomers, see Table 5, entries 5 and 9), the enantioselectivity-determining step should be the face-selective coordination of the olefin moiety to the Pd^{II} center (Scheme 14).[36] Again, the olefin is assumed to coordinate *trans* to the imidazoline N atom in **49**, thereby triggering an attack of the imidate N atom at the olefin from the face remote to the Pd center. In the stereoelectronically preferred orientation of the olefin part parallel to the ferrocene axis, that is, perpendicular to the Pd square plane, the sterically undemanding C-1 methylene moiety should point towards the bulky Cp^{Φ} spectator ligand to minimize unfavorable steric interactions, while the bulky imidate moiety is avoiding the ferrocene core. Coordination of the enantiotopic olefin face is less favorable again owing to steric arguments. As a consequence of these as-



Scheme 14. Assumed coordination mode of the olefinic moiety of allylic imidates **42**.

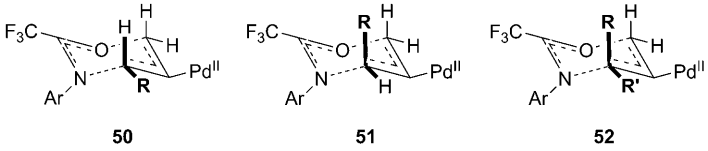
sumptions, it was expected that even substrates in which R and R′ have an identical size should provide almost perfect enantioselectivities.

To verify this hypothesis, the use of the geometrically pure allylic imidate **42n** in which R and R′ have practically the same size, namely, CH_3 and CD_3 (Scheme 15), was investigated. Also in this case the product **43n** is formed with an *ee* value of 96%, thus confirming the mechanistic hypothesis.[37]



Scheme 15. Highly enantioselective formation of CH_3/CD_3-substituted allylic amide **43n** (200 mg scale), a substrate with practically no steric difference between both of its 3-substituents.

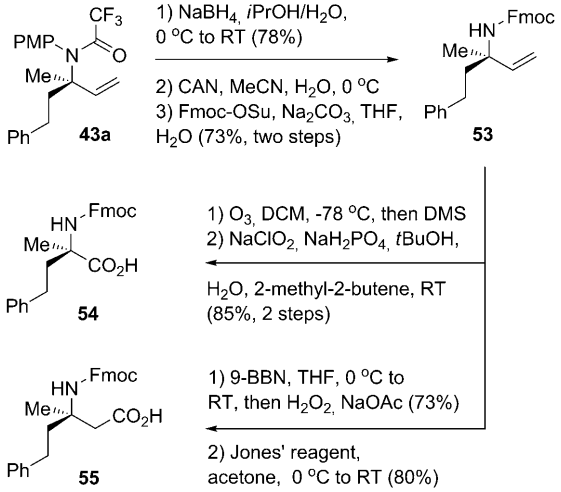
As mentioned above, **29**-Cp$^{\Phi}$-Ph-Ts provides a highly efficient catalyst for *E*-configured 3-monosubstituted substrates **25**, but it is comparatively slow for the *Z*-configured counterparts, whereas if both R and R′ in **42** are larger than H, there is no clear difference in rate between *E*- and *Z*-configured substrates. This finding can be rationalized by the assumed six-membered cyclic transition state (Scheme 16):[2a]



Scheme 16. Transition states for *E*- and *Z*-configured substrates. If both 3-substituents are larger than H, the energetic difference for positioning the more bulky one in an axial position is much lower than if one substituent is H.

in the case of an *E*-configured 3-monosubstituted substrate, the substituent R is in an equatorial position whereas H adopts an axial position in **50**. In the case of a *Z*-configuration, R is axially and H equatorially oriented in **51** (energetically less favored). If, however, both R and R′ are larger than H, the difference in energy of the two transition states is considerably lower, resulting in similar reaction rates for *E* as well as *Z* configuration (see **52**).

To showcase the utility of the rearrangement products, allylic amide **43a** was employed to synthesize 9-fluorenylmethoxycarbonyl (Fmoc)-protected α,α-disubstituted α-amino acid **54** and β,β-disubstituted β-amino acid **55** (Scheme 17). The PMP group in amides **43** could not be directly removed, since the oxidation by ceric ammonium nitrate (CAN) requires sufficient electron density of the aromatic system. Hence, the trifluoroacetyl group was first removed by $NaBH_4$ in *i*PrOH/H_2O (10:1), followed by oxidative cleavage of the PMP group with CAN in MeCN/H_2O (1:1). Due to limited stability of the free amine, the crude reaction mixture was directly used for Fmoc protection. Alternatively, the amine could be purified as hydrochloride.



Scheme 17. Use of allylic amide **43a** for the preparation of α,α-disubstituted α-amino acid **54** and β,β-disubstituted β-amino acid **55** (Fmoc-OSu = *N*-(9-fluorenylmethyloxycarbonyloxy)succinimide; DMS = dimethyl sulfide).

The vinyl system was cleaved by ozonolysis, followed by oxidation with $NaClO_2$ to form α-amino acid **54** in 85% yield. Alternatively, hydroboration with 9-borabicyclo-[3.3.1]nonane (9-BBN) and oxidative workup with H_2O_2 and NaOAc gave the corresponding amino alcohol in 73% yield; it was subsequently converted to β-amino acid **55** in 80% yield by CrO_3 in 6 N H_2SO_4.

The absolute configuration of α-amino acid **54** was determined after removal of the Fmoc group with tetrabutylammonium fluoride (TBAF) by comparison with the reported specific optical rotation[38] and found to correspond to the expected configuration. Since a uniform mechanism for the stereospecific rearrangement step can be expected, the absolute configuration of all compounds in Table 5 can be assigned.

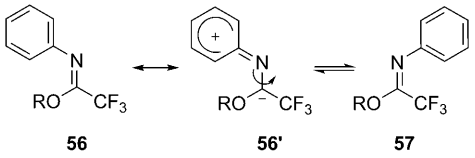
The approaches described above and in previous publications were limited to trifluoroacetimidate substrates in which the N atom is protected by a PMP moiety that can be oxidatively removed to furnish free primary allylic amines. A variation of the imidate N substituent would allow for the direct formation of chiral secondary allylic amines without the need for a protecting group and a subsequent alkylation step. To our knowledge, the N substituent was previously always considered to be a protecting group. Moreover, even in the case of the more reactive benzimidate substrates (aryl instead of CY_3 in **2** in Scheme 1) providing the synthetically less useful benzoylamides, only a small number of examples has been described. In those cases the N substituent was restricted to either a carbobenzyloxy (Cbz) group (no enantioselectivity)[4c] or to a few phenyl residues.[39] Since hydrolysis

of the resulting benzamides is very difficult, no examples for secondary amines were reported. For the application of *N*-alkyl substituents, there was previously no example in the literature, which can be attributed to a reduced reactivity of these substrates as our results below reveal. **29**-Cp$^{\Phi}$-Ph-Ts allowed for the first catalytic asymmetric preparation of unprotected secondary allylic amines by aza-Claisen rearrangement of *N*-aryl- or *N*-alkyl-substituted trifluoroacetimidates.[4i]

The imidate substrates **60** were prepared in good yield by condensation of iminochlorides **58** with geometrically pure allylic alcohols **59** after deprotonation of the hydroxy group with NaH or lithium hexamethyl disilazide (LHMDS) in THF (Table 7). The iminochlorides **58** were readily available by a modified literature procedure.[40]

Allylic trifluoroacetimidates bearing an aromatic residue on nitrogen generally exhibit a very broad ^{19}F NMR spectroscopic signal at RT for the CF_3 group and broad signals in ^{1}H NMR spectroscopy for all protons in close proximity to the imidate functionality. *N*-Alkyl-substituted imidates, in contrast, often have two separated, rather sharp signals for the CF_3 group and protons in proximity, pointing to the coexistence of two geometric isomers. Attempts to determine the geometry of the C=N double bond in *N*-aryl imidates by NOE experiments failed, whereas for imidate **60l** (*N*-$CH_2CH_2CO_2Et$), an NOE between the NCH_2 protons and the CF_3 group was observed, thus suggesting that the major isomer is *E*-configured (see the Supporting Information).

The line broadening in the case of *N*-aryl-substituted imidates can be explained by a fast isomerization that is slow on the NMR spectroscopic timescale for *N*-alkyl imidates. This finding can be explained by the resonance structure **56′** (Scheme 18), which results in a facilitated rotation around



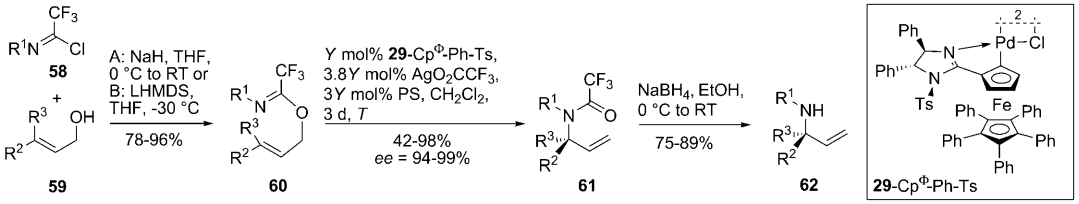
Scheme 18. Explanation of line broadening in NMR spectra of imidates bearing aromatic residues on nitrogen.

the C=N bond. In contrast, with aliphatic residues, such a resonance structure is not possible and as a consequence the C=N bond is configurationally more stable.

To find the lowest catalyst loadings that still provide good yields for most of the rearrangement products **61** within a reaction time of 3 d (Table 7), various substrates were investigated at 50 and 70 °C using 0.05, 0.1, 0.2, 0.5, 1.0, 2.0, or 5.0 mol % of precatalyst **29**-Cp$^{\Phi}$-Ph-Ts.

The $E_{(C=C)}$-configured allylic imidates **60a–e** carrying *N*-aryl residues with different electronic or steric properties such as 4-F-C_6H_4, 4-I-C_6H_4, 1-naphthyl, 2,4-dimethoxyphenyl, or 3,4-dimethoxyphenyl require similar precatalyst loadings (0.05–0.2 mol %; Table 7, entries 1–5) as substrates bearing the *N*-PMP moiety. Interestingly, the nonenantioselective $[PdCl_2(NCMe)_2]$-catalyzed rearrangement was not feasible for dimethoxyphenyl-substituted imidates **60d/e**: In all cases, a complete decomposition was observed, probably by Pd^{II}-promoted oxidation of the electron-rich aromatic systems. Such a decomposition was not observed using chiral palladacycle **29**-Cp$^{\Phi}$-Ph-Ts. Racemic samples for HPLC analysis were thus prepared through a thermal rearrangement (2 h at 160 °C, neat or in mesitylene 1:1 w/w). Gratifyingly, *N*-alkyl-substituted imidates also undergo the aza-

Table 7. Synthesis of imidates **60**, enantioenriched trifluoroacetamides **61**, and the free secondary allylic amines **62**.



Entry	R^1	R^2	R^3	**60**	Yield [%][a]	**61**	*T* [°C]	Y[b]	Yield [%][c]	*ee* [%]	**62**	Yield [%][c]
1	4-I-C_6H_4	*n*Pr	H	**60a**	87 (A)	**61a**	70	0.2	85	96[d]	**62a**	90[e]
2	4-F-C_6H_4	*n*Pr	H	**60b**	68 (A)	**61b**	50	0.1	91	96[d]	**62b**	82
3	1-naphthyl	*n*Pr	H	**60c**	85 (A)	**61c**	70	0.05	90	97[d]	**62c**	86
4	2,4-OMe-C_6H_3	*n*Pr	H	**60d**	87 (B)	**61d**	50	0.05	96[f]	98	**62d**	91[g]
5	3,4-OMe-C_6H_3	*n*Pr	H	**60e**	89 (B)	**61e**	50	0.1	97[f]	98	**62e**	89[g]
6	$(CH_2)_2$Ph	Me	H	**60f**	80 (A)	**61f**	50	2.0	98	94[h]	**62f**	77
7	$(CH_2)_2$Ph	*i*Pr	H	**60g**	85 (A)	**61g**	70	2.0	51	97[h]	**62g**	75
8	*n*Hex	$(CH_2)_2$Ph	H	**60h**	74 (A)	**61h**	50	0.2	91	99[d]	**62h**	89
9	$(CH_2)_2$*i*Pr	$(CH_2)_2$Ph	H	**60i**	77 (A)	**61i**	50	1.0	99	98[d]	**62i**	84
10	$(CH_2)_2$OTIPS	$(CH_2)_2$Ph	H	**60k**	67 (A)	**61k**	70	1.0	92	98[h]	**62k**	78
11	$(CH_2)_2CO_2Et$	$(CH_2)_2$Ph	H	**60l**	58 (B)	**61l**	70	1.0	84	99[h]	**62l**	80
12	*n*Hex	$(CH_2)_2$Ph	Me	**60m**	70 (A)	**61m**	70	2.0	42	98[h]	**62m**	76

[a] Isolated yield (in brackets the method which was used is given, see graphic). [b] Precatalyst loading (see Scheme 3). [c] Isolated yield. [d] The *ee* values determined by HPLC after hydrolysis of **61** to **62**. [e] Amide cleavage with NaOEt. [f] Reaction time 48 h. [g] Amide cleavage with MeLi, THF, −78 °C to RT. [h] The *ee* values determined by HPLC.

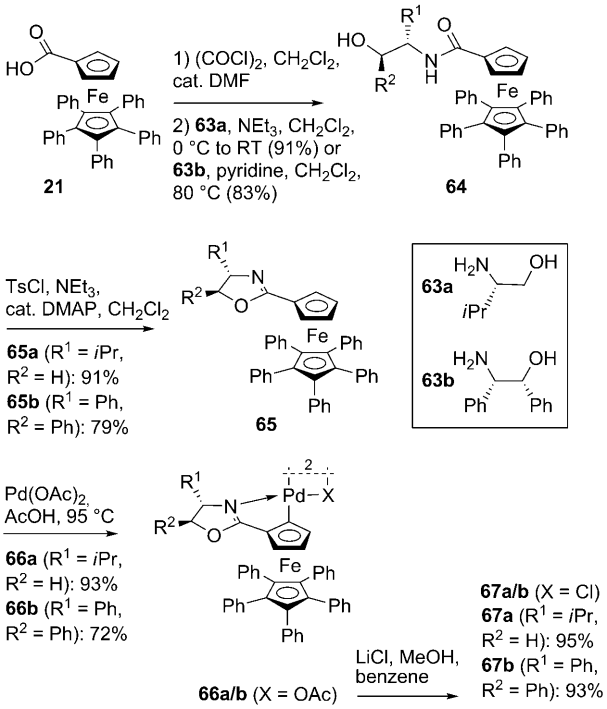
Claisen rearrangement with excellent enantioselectivity and in most cases with high yield. The required catalyst loadings depend largely upon the steric bulk of the alkyl substituent R^1; whereas only 0.2 mol% precatalyst were required for the case of the unbranched alkyl residue *n*-hexyl (Table 7, entry 8), with branched or functionalized *N*-alkyl groups precatalyst loadings of 1.0 to 2.0 mol% were needed. Nevertheless, also in those cases the products were formed in high yield and with almost perfect stereocontrol (Table 7, entries 6, 9–11). A moderate yield was obtained for the combination of an alkyl residue R^1 with an α-branched residue R^2 (Table 7, entry 7). No product was formed employing α-branched alkyl substituents R^1. In contrast to catalytic allylic substitutions, secondary allylic amines with a quaternary N-substituted stereocenter can also be generated highly enantioselectively (Table 7, entry 12), albeit in only moderate yield.

The clearly lower reaction rate of *N*-aliphatic imidates as compared to *N*-aryl-substituted substrates is most likely caused by electronic effects. One possible explanation might be that an imidate nitrogen bearing an aliphatic residue is more electron-rich and thus a better competing ligand for Pd^{II}, thereby lowering the concentration of active, accessible catalyst. An alternative explanation is the resonance stabilization of the positive charge on the N atom in the benzylic position in the cyclic intermediate **4** (Scheme 1), although using classical resonance structures, a transfer of electron density from the *N*-aryl substituent to N cannot be achieved without charge separation.

Reductive removal of the trifluoroacetamide protecting group releasing the free secondary allylic amines was usually achieved in high yield with $NaBH_4$ (Table 7). The reductive cleavage has the general advantage of shorter reaction times as compared to hydrolytic procedures utilizing, for example, NaOEt in EtOH (4 h versus 1–2 d). For **61a** though (Table 7, entry 1), the iodo atom was partially removed under reductive conditions and therefore basic hydrolysis (K_2CO_3, MeOH/H_2O (10:1)) was preferred for this example.[41] Alternatively, MeLi in THF at −78 °C leads to a smooth deprotection if there are no other functional groups sensitive to this reagent (Table 7, entries 4, 5).

The absolute configuration was determined by chemical correlation. The *R*-configured compounds **62h** and **62m** were independently prepared by aza-Claisen rearrangement of the corresponding PMP-substituted allylic trifluoroacetimidates **25c** and **42a** (R^1 = PMP, $R^2 = (CH_2)_2Ph$, R^3 = H or Me), with full deprotection yielding the free primary amine and subsequent reductive monoalkylation with hexanal/$NaBH_4$. Comparison of HPLC retention times revealed that this material had the same configuration as the material reported in Table 7, entries 8 and 12, respectively. Since we have shown that the aza-Claisen rearrangement of allylic trifluoroacetimidates catalyzed by **29**-Cp^{Φ}-Ph-Ts is a stereospecific reaction and a uniform reaction mechanism can be assumed, the configuration has been assigned to all allylic amines **62a**–**m**.

Fourth-generation catalysts: To understand if the higher catalytic activity and selectivity of Fc^{Φ} imidazoline palladacycle **29**-Cp^{Φ}-Ph-Ts as compared with the COP-Cl system **7** is mainly caused by the imidazoline or by the pentaphenyl ferrocenium moiety, Fc^{Φ} oxazolines **65a** (R^1 = *i*Pr, R^2 = H) and **65b** ($R^1 = R^2$ = Ph) were prepared according to Scheme 19 in 83 and 66% yield (over two steps), respectively, starting from carboxylic acid **21** and (*S*)-valinol (**63a**) or (1*R*,2*S*)-1,2-diphenylethanolamine (**63b**).



Scheme 19. Synthesis of Fc^{Φ} palladacycles **66**/**67** by diastereoselective cyclopalladation.

Upon heating oxazolines **65** with $Pd(OAc)_2$ in HOAc, palladacycles **66a** and **66b** precipitated in diastereomerically pure form and could be isolated by filtration, whereas byproducts and possibly also the minor diastereomer stayed in solution. Further purification was carried out by recrystallization, thus delivering pure **66a** and **66b** in 93 and 72% yield, respectively. Conversion of the acetate-bridged palladacycles to the Cl-bridged complexes **67a/b** took place in 95 and 93% yield, respectively, by stirring a suspension of **66** and LiCl in MeOH/benzene. Whereas the acetate-bridged dimers exist as a single diastereomer relative to the Pd–acetate square planes, the chloride-bridged complexes were formed as approximately 2:1 mixtures of geometrical isomers. Alternative conditions for the cyclopalladation, notably $Na_2[PdCl_4]$ in combination with NaOAc in MeOH/benzene or CH_2Cl_2, as well as $Pd(OAc)_2$ in CH_2Cl_2 or benzene, failed to give any cyclopalladated product. Instead of cyclopalladation, a complete decomposition was found to take place within less than 30 min.

The absolute configuration of palladacycle **66a** was determined by X-ray crystal structure analysis (Figure 2).[42,43] In contrast to COP-OAc (OAc = X in **7**), the isopropyl group is pointing towards the sandwich core.

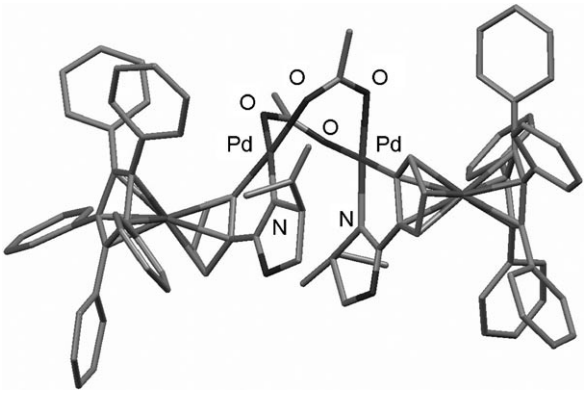


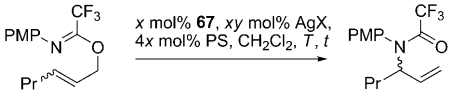
Figure 2. X-ray crystal structure of the acetate-bridged dimeric complex **66a**.

The absolute configuration of palladacycle **66b** was tentatively assigned by the known absolute configuration of the aza-Claisen rearrangement product of imidate **25a**. The same major enantiomer as with complex **66a** and **29**-Cp^{Φ}-Ph-Ts was obtained, suggesting an S_p-configuration, since mainly the element of planar chirality is decisive for the configuration of the catalysis product. This assumption was confirmed by ^{1}H NOESY experiments (see the Supporting Information).

Utilizing the optimized conditions for activating imidazoline catalyst **29**-Cp^{Φ}-Ph-Ts, that is, 3.75 equiv of AgTFA per precatalyst dimer, oxazoline **66a** (0.5 mol%) rearranged the 3-monosubstituted model substrate **25a** with only 44% yield and 90% *ee* (Table 8, entry 1) at 40°C for 24 h (83% conversion after 72 h), whereas **29**-Cp^{Φ}-Ph-Ts had given practically full conversion and 95% *ee* with $^1/_{10}$ of the catalyst amount (Table 4, entry 9). As the nature of the Ag salt has a large impact on the reaction rate and selectivity, further Ag salts were examined. It was found that $AgNO_3$ generates a highly active and selective catalyst (Table 8, entry 2), whereas AgOTs allows for high activity (Table 8, entry 3) but considerably lower enantioselectivity. Further studies were thus carried out with $AgNO_3$.

By use of 2 equiv of $AgNO_3$ per Cl-bridged dimer **67a**, full conversion and 96% *ee* were obtained with 0.5 mol% precatalyst, whereas 0.2 mol% led to only 45% conversion (Table 8, entries 4, 5). Part of this catalytic activity might be explained by oxidation of **67a** to the corresponding active ferrocenium system on the surface of precipitated AgCl. However, nonactivated **66a** also has some, yet low, catalytic activity (6% conversion with 1 mol% catalyst at 40°C for 24 h; Table 8, entry 6). Complete oxidation to the corresponding ferrocenium species is accomplished with 4 equiv of $AgNO_3$ per Cl-bridged dimer resulting in the best reactivity.

Table 8. Optimization of the rearrangement of model substrates (*E*)-/(*Z*)-**25a** catalyzed by **67**.



25a **25b**

Entry	**67**	*x*	AgX (*y*)	*E*/*Z*	*t* [h]	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1	**a**	0.5	AgTFA (3.8)	*E*	24	40	44	90
2	**a**	0.5	$AgNO_3$ (3.8)	*E*	24	40	>99	97
3	**a**	0.5	AgOTs (3.8)	*E*	24	40	98	77
4	**a**	0.5	$AgNO_3$ (2.0)	*E*	24	40	99	96
5	**a**	0.2	$AgNO_3$ (2.0)	*E*	24	40	45	n.d.
6[c]	**a**	1.0	–	*E*	24	40	6	n.d.
7	**a**	0.2	$AgNO_3$ (3.8)	*E*	24	40	>99	97
8	**b**	0.2	$AgNO_3$ (3.8)	*E*	24	40	>99	97
9	**b**	0.1	$AgNO_3$ (3.8)	*E*	24	40	70	n.d.
10	**a**	0.1	$AgNO_3$ (3.8)	*E*	24	RT	99	97
11	**a**	0.05	$AgNO_3$ (3.8)	*E*	24	40	99	97
12	**a**	2	$AgNO_3$ (3.8)	*Z*	24	40	97	88
13	**a**	1	$AgNO_3$ (3.8)	*Z*	24	40	87	88

[a] Yield determined by NMR spectroscopy. [b] The *ee* values determined by HPLC after hydrolysis to the corresponding amine (see the Supporting Information). [c] **66a** was used.

In addition to *i*Pr-substituted complex **67a**, the 4,5-diphenyl-substituted oxazoline palladacycle **67b** was examined. While there is practically no difference in enantioselectivity, the catalytic activity slightly decreases (Table 8, entries 7–10). Whereas 0.1 mol% **67a** completely convert the test substrate within 24 h at RT (Table 8, entry 10), the same amount of **67b** at 40°C resulted in only 70% yield due to incomplete conversion (Table 8, entry 9). Since complex **67b** was prepared in lower yields and from a more expensive amino alcohol than **67a**, all further investigations were carried out with **67a**.

A screening of the catalyst amount was performed for both the *E*- and the *Z*-configured test substrates (*E*)-/(*Z*)-**25a**. Like for the imidazoline palladacycle **29**-Cp^{Φ}-Ph-Ts, the *E*-configured substrate not only reacts considerably faster than its *Z*-configured counterpart, it also provides significantly higher *ee* values. Although (*E*)-**25a** reacts completely within 1 d at 40°C using only 0.05 mol% precatalyst (Table 8, entry 11), full conversion for (*Z*)-**25a** requires 2 mol% (Table 8, entry 12). Ferrocenyl bisimidazoline bispalladacycle complexes thus remain the catalysts of choice for *Z*-configured substrates.[4f,h]

The enantioselectivity obtained for (*E*)-**25a** did not significantly change within the investigated temperature range. Catalyst loadings below 0.05 mol% were studied as well, but the results were not reliable, which is most probably explained by a partial catalyst deactivation by trace impurities of the substrate. A certain threshold of catalyst is thus necessary on laboratory scale. The same was found with **29**-Cp^{Φ}-Ph-Ts, in which catalyst loadings below 0.05 mol% had resulted in low conversions even at prolonged reaction times.

The rearrangement could be scaled up without any problem. Using 10.0 mmol of substrate (*E*)-**25a** (3.01 g) in combination with 0.1 mol% **67a** (0.4 mol% $AgNO_3$, 40°C) resulted in complete conversion and an isolated yield of 98% with 97.5% *ee*.[44]

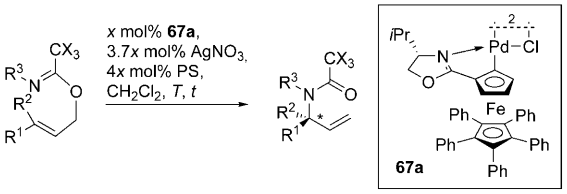
Oxazoline **67a** activated by $AgNO_3$ is in general more reactive than imidazoline **29**-Cp$^{\Phi}$-Ph-Ts (Table 9, entries 2–15). For instance, with the (*E*)-3-Ph-substituted substrate **26h**, a temperature of 40°C was necessary using **29**-Cp$^{\Phi}$-Ph-Ts, whereas **67a** is effective already at RT (Table 9, entry 2). Also, the 3,3-disubstituted substrate **42m** (R′ = $(CH_2)_3$OTIPS, R = CH_2OBn), which required 4 mol% **29**-Cp$^{\Phi}$-Ph-Ts and a reaction time of 3.5 d to give a yield of 51%, reacted within 2 d in a nearly quantitative yield (or within 3 d with 2 mol% catalyst; Table 9, entries 12, 13). Like with **29**-Cp$^{\Phi}$-Ph-Ts, N-substituted quaternary stereocenters can be generated with almost perfect stereocontrol (Table 9, entries 8–13).

Due to the enhanced catalytic activity, substrates that could not be processed with **29**-Cp$^{\Phi}$-Ph-Ts or any other reported chiral catalyst were investigated: whereas allylic trifluoroacetimdates bearing a *t*Bu or a Bn moiety as R^1 still did not react at useful rates (Table 9, entries 6, 7) although mono-α-branched aliphatic residues R^1 such as *i*Pr or *c*-Hex are well tolerated (Table 9, entries 4, 5), this catalyst is for the first time able to rearrange substrates bearing an α-branched aliphatic N-substituent R^3 (Table 9, entries 14, 15): the *N*-cyclohexyl-substituted imidate **60n** rearranged with reasonable catalyst loadings (1.0 or 4.0 mol%) and excellent enantioselectivities, thus yielding the protected secondary allylic amine **61n**.

The formation of a tertiary allylic amine bearing three different N substituents would require even more steps with the traditional protecting group/alkylation strategy (vide supra). Rearrangement of an allylic imidate already containing the complete carbon skeleton would only entail a reduction of the amide functionality, for example, with $LiAlH_4$, to provide the tertiary amine. To establish proof of principle, allylic imidate **70** (Scheme 20) was prepared in a one-pot reaction from acetanilide **68** to study if enolizable imidates bearing α-acidic hydrogen atoms can be employed. Imidate **70** was found to be in equilibrium with its tautomer, the ketene *N*,*O*-acetal **71** (ratio **70**/**71** = ca. 3:1). With 0.2 mol% **67a** activated by $AgNO_3$ the rearrangement product was formed in high yield and with excellent enantioselectivity (Table 9, entry 16). A Claisen rearrangement product was not detected.

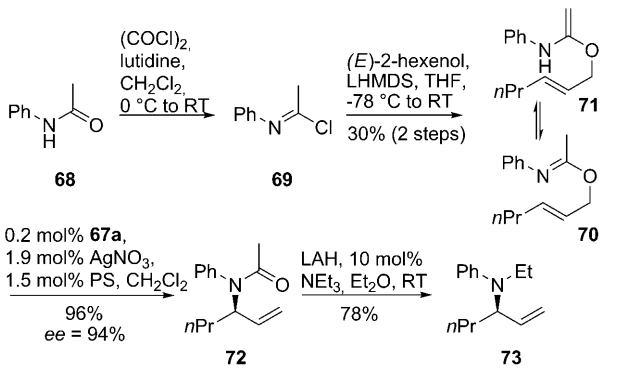
29-Cp$^{\Phi}$-Ph-Ts is not able to rearrange allylic trichloroacetimidates with a free NH, the substrates of the original Overman rearrangement, presumably since it is deactivated by coordination with the free NH group. In contrast, **67a** was found to be a highly active catalyst for these compounds (Table 9, entries 17, 18), producing

Table 9. Investigation of the substrate scope of the rearrangement of trifluoroacetimidates with **67a**.



Entry	R^1	R^2	R^3	CX_3	Product	*x*	*t* [h]	*T* [°C]	Yield[a] [%]	*ee* [%]
1	*n*Pr	H	PMP	CF_3	**26a**	0.05	24	40	99	97[b]
2	Ph	H	PMP	CF_3	**26h**	0.5	24	20	98	98[b]
3	Ph	H	PMP	CF_3	**26h**	0.2	24	40	96	90[b]
4	*i*Pr	H	PMP	CF_3	**26e**	0.5	24	20	76	99[b]
5	*c*-Hex	H	PMP	CF_3	**26f**	0.5	24	40	99	99[b]
6	*t*Bu	H	PMP	CF_3	**26i**	2.0	24	50	2	n.d.
7	CH_2Ph	Me	PMP	CF_3	**43o**	2.0	24	50	12	n.d.
8	$(CH_2)_2$Ph	CH_3	PMP	CF_3	**43a**	2.0	24	50	71	98[c]
9	$(CH_2)_2$Ph	CH_3	PMP	CF_3	**43a**	2.0	72	50	90	99[c]
10	CH_3	CH_2OBn	PMP	CF_3	**43i**	1.0	24	50	98	97[c]
11	CH_3	CH_2OBn	PMP	CF_3	**43i**	0.5	24	70	74	96[c]
12	$(CH_2)_3$OTIPS	CH_2OBn	PMP	CF_3	**43m**	4.0	48	50	95	97[d]
13	$(CH_2)_3$OTIPS	CH_2OBn	PMP	CF_3	**43m**	2.0	72	50	95	97[d]
14	$(CH_2)_2$Ph	H	*c*-Hex	CF_3	**61n**	4.0	48	50	90	99[b]
15	$(CH_2)_2$Ph	H	*c*-Hex	CF_3	**61n**	1.0	72	70	91	98[b]
16	*n*Pr	H	Ph	CH_3	**72**	0.2	48	50	96	94[c]
17	$(CH_2)_2$Ph	H	H	CCl_3	**74**	0.25	24	60	99	95[c]
18	$(CH_2)_2$Ph	H	H	CCl_3	**74**	0.5	24	50	85	97[c]

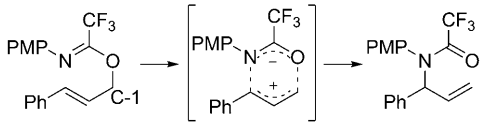
[a] Isolated yield. [b] *ee* determined by HPLC after hydrolysis to the corresponding amine (see the Supporting Information). [c] *ee* determined by HPLC. [d] *ee* determined by HPLC after cleavage of TIPS with excess TBAF (see the Supporting Information).



Scheme 20. Synthesis of the enolizable acetimidate **70** and its use for the catalytic asymmetric formation of tertiary amine **73** (LAH = lithium aluminum hydride).

trichloroacetamide **74** in 24 h at 60 °C with a quantitative yield and 95 % *ee* using 0.25 mol % of precatalyst.

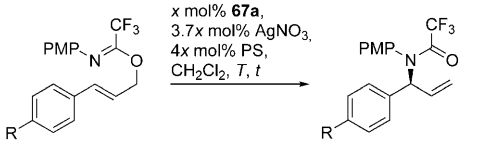
Furthermore, problematic trifluoroacetimidate substrates were investigated, which react already to a considerable degree in the absence of a soft transition-metal ion by thermal rearrangement. Allylic trifluoroacetimidates tend to undergo a thermal rearrangement at ambient temperature if the O–allyl bond is reactive due to formation of a particularly stabilized allylic carbocation as result of a terminal aromatic substituent (Scheme 21).



Scheme 21. Acceleration of the thermal rearrangement of 3-aryl-substituted allylic imidates by stabilization of the positive charge in transition state **75**.

Phenyl-substituted imidate **25h** thus rearranged in 72 % yield and only 81 % *ee* employing 5 mol % of COP-Cl **7** (Cl = X),[4b] whereas **29**-Cp$^{\Phi}$-Ph-Ts (1 mol %) was able to improve these values to 99 % yield and 88 % *ee*. Better enantioselectivities were not possible without increased catalyst loadings because a temperature of 40 °C was necessary to obtain reasonable conversion rates. On the other hand, **67a** is already able to rearrange **25h** at RT, thereby producing **26h** with an *ee* value of 98 % (Table 10, entry 1). To investigate the electronic influence of the aryl substituents, a series of 3-aryl-substituted imidates **25j–m** was applied with varying substituents (Table 10, entries 3–8). Substrates bearing electron-donating (*p*-Me) or -withdrawing substituents (*p*-Cl, *p*-CF_3) display an intrinsic thermal rearrangement rate constant low enough to allow for a successful asymmetrically catalyzed reaction at RT, whereas **25m**, bearing a *p*-methoxyphenyl group, reacts simply too quickly, even at 4 °C (Table 10, entry 8).

Table 10. Rearrangement of 3-aryl-substituted imidates with **67a**.



Entry	**25**	X (*x* [mol %])	R	*t* [h]	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1	**h**	0.5	H	24	20	98	98
2	**h**	0.2	H	24	40	96	90
3	**j**	1.0	CF_3	48	20	99	92
4	**k**	1.0	Cl	24	20	95	98
5	**k**	0.2	Cl	24	40	80	87
6	**l**	1.0	Me	48	20	99	98
7	**m**	1.0	OMe	24	20	93	28
8	**m**	1.0	OMe	48	4	52	34

[a] Isolated yield. [b] The *ee* values determined by HPLC.

A kinetic study (Figure 3) of the thermal rearrangement at 40 °C in $CDCl_3$ for the three 3-aryl-substituted imidates **25h/k/l** allowed the determination of rate constants for the first-order kinetics, which fit well with the Hammet σ^+ values ($\rho = -0.47$; see the Supporting Information).

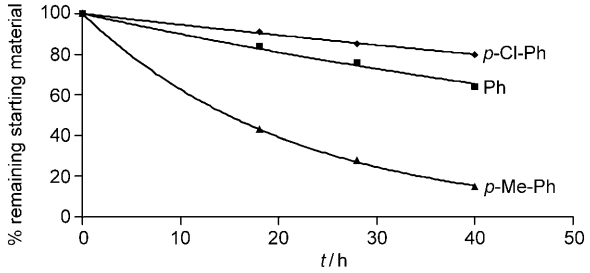
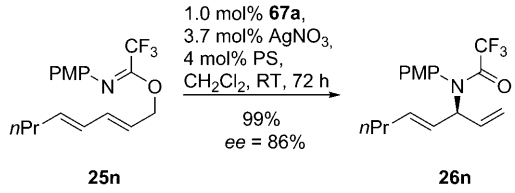


Figure 3. Thermal rearrangement of three aryl-substituted imidates **25h/k/l** at 40 °C in $CDCl_3$. Conversions were determined by ^{19}F NMR spectroscopy.

Similar to the 3-aryl-substituted substrates, pentadienylic imidates such as **25n**, which possess a conjugated diene system, are able to form particularly stabilized cations. Nevertheless, a synthetically useful 86 % *ee* value was attained under the conditions depicted in Scheme 22.



Scheme 22. Regioselective rearrangement of diene substrate **25n**.

The steric environment of COP-X **7** and **29**-Cp$^{\Phi}$-Ph-Ts around the catalytic palladium site mainly differs in a phenyl (**29**-Cp$^{\Phi}$-Ph-Ts) and an *i*Pr group (**7**) next to the coordinating N site and the type and distance of the spectator ligand (Cp$^{\Phi}$ for **29**-Cp$^{\Phi}$-Ph-Ts, tetraphenylcyclobutadiene for COP). Although the distance between the two sandwich ligands differs only marginally between COP and **29**-Cp$^{\Phi}$-Ph-Ts (3.4 vs. 3.3 Å), oxidation of the ferrocene to the ferrocenium species is expected to shorten this distance further. Overall, the steric hindrance to access the Pd center is more distinct for **29**-Cp$^{\Phi}$-Ph-Ts. These steric effects can be used to explain the higher *ee* value obtained with **29**-Cp$^{\Phi}$-Ph-Ts, but not necessarily the higher rearrangement rate. One would have to assume that the rate-determining step, if accelerated by steric bulk, is either the collapse of the anticipated cyclic intermediate **4** (Scheme 1), which might also be a transition state, or the decomplexation of the resulting vinyl group from the catalyst. Since turnover frequencies are in the range of approximately 1–40 per h, one of these intermedi-

ates should be detectable, which was not the case in these studies. However, the sterically overcrowded dimeric Fc^{Φ} complexes might more readily form the catalytically active monomeric species.

From an electronic point of view, the differences are more pronounced since the type of N donor (oxazoline versus *N*-Ts-imidazoline) as well as the overall charge of the ligand (−1 for COP, 0 for **29**-Cp^{Φ}-Ph-Ts after oxidation to the ferrocenium species) change. As Pd^{II} most likely acts as a carbophilic Lewis acid coordinating to an olefin, the lower electron density in **29**-Cp^{Φ}-Ph-Ts is suitable to explain the higher reactivity found for this complex. This is supported by the solubility: **29**-Cp^{Φ}-Ph-Ts is soluble in practically neat substrate, thus allowing the reaction to be run at the highest possible concentration.

Comparing COP-X **7** to Fc^{Φ} oxazoline **67a**, there are two major differences: 1) the isopropyl residue on the oxazoline moiety in **67a** is pointing towards to the Cp′-spectator ligand, thereby leaving the space unhindered above the Cp–oxazoline–Pd plane, whereas in COP, the substituent is pointing away from the sandwich core; 2) **67a** can be oxidized to a ferrocenium species, again providing a less electron-rich ligand.

Because a Fc^{Φ} oxazoline complex with an identical configuration as in COP could not be prepared so far, a direct comparison is not possible. However, Overman and Richards reported a *tert*-butyl-substituted COP derivative in which the substituent points towards the spectator ligand.[4b] By using AgTFA for activation, significantly lower yields and enantioselectivities were obtained relative to the analogous complex with the *i*Pr pointing away from the sandwich core. However, a different catalyst-activation method might lead to different results.

The origin of the higher rate of **67a** as compared to **29**-Cp^{Φ}-Ph-Ts might be explained by the better accessibility of the Pd^{II} center in the former, as the *exo* face above the Pd square plane is open, thus resulting in a facilitated olefin coordination by means of an associative mechanism. Since the *ee* values obtained with **67a** are practically identical to those obtained with **29**-Cp^{Φ}-Ph-Ts, enantioselectivity originates nearly exclusively from the planar chiral Fc^{Φ} backbone.

According to the previously accepted hypothesis about the ideal catalyst design represented by **76** (Figure 4, left side), the residue (1) next to the N-binding site should point away from the sandwich complex core (2), and all previously highly enantioselective sandwich complexes used for the aza-Claisen rearrangement fulfilled this model. However, the excellent *ee* values and activities obtained with **67a** show that at least the position of block (1) is not necessarily relevant. Apparently, much more important is the choice of (2) and (3) to completely shield the bottom, as in **77**, to achieve a face-selective olefin coordination.

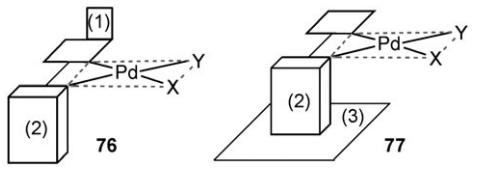


Figure 4. Schematic representation of Overman's original model **76** (left side) for the ideal catalyst geometry and the revised version **77** (right side) after the present studies.

Conclusion

The systematic studies presented herein have enabled us to attain a more detailed understanding of the mode of action of the catalytic asymmetric aza-Claisen rearrangement, thereby resulting in the development of highly efficient catalysts. Compound **67a**, a hybrid system between Overman's/Richards' COP-Cl and our Fc^{Φ} imidazoline system **29**-Cp^{Φ}-Ph-Ts, is more reactive than both systems and has a broader substrate tolerance. However, one should be aware that Fc^{Φ} oxazoline palladacycle **67a** and Fc^{Φ} imidazoline palladacycle **29**-Cp^{Φ}-Ph-Ts are not directly comparable for two main reasons: the stereocenter next to the N-donor atom has the opposite configuration and with the current technology directly comparable compounds with identical configurations cannot be accessed. Moreover, subtle changes can have a big impact: using the same mode of activation for **29**-Cp^{Φ}-Ph-Ts and **67a** by virtue of the properties of AgTFA, imidazoline palladacycle **29**-Cp^{Φ}-Ph-Ts seemed to be superior and only an additional screening of activation agents disclosed the excellent activity of **67a**.

With the enhanced reactivity of **29**-Cp^{Φ}-Ph-Ts and **67a**, the catalytic asymmetric aza-Claisen rearrangement has a very broad scope. Now, the methodology not only allows for the formation of highly enantioenriched primary allylic amines, but also secondary and tertiary amines. Allylic amines with quaternary N-substituted stereocenters are also conveniently accessible. The reaction conditions tolerate many important functional groups, thus providing stereoselective access to valuable functionalized building blocks, for example, for the synthesis of unnatural amino acids. Our studies suggest that face-selective olefin coordination is the enantioselectivity-determining step, which is almost exclusively controlled by the element of planar chirality.

Experimental Section

General procedure

Precatalyst activation: A solution of the dimeric precatalyst (1 equiv) in dry CH_2Cl_2 (1 mL/3 μmol) was added to the corresponding silver salt (3.75 equiv if nothing else is specified) in a dry, pear-shaped flask under N_2, sealed, shielded from light, and stirred for 3 h (Cp- and Cp*-based complexes) or overnight (Cp^{Φ}-based complexes) at RT. The resulting suspension was filtered under an N_2 atmosphere through Celite/CaH_2 (≈1:1, ca. 5 mm thickness) and the filter cake was washed with dry CH_2Cl_2 (1 mL/3 μmol). Proton sponge (as 0.1 M solution in CH_2Cl_2, 2 to 4 equiv) was added.

Catalysis: The calculated amount of activated catalyst as stem solution in CH_2Cl_2 was transferred to a flask containing the imidate (1 equiv, for

most experiments 60 μmol). A stream of N_2 was passed through the flask until the solvent volume reached 0.2 mL or less (for a 60 μmol experiment). The flask was sealed with a plastic cap and stirred for the indicated time at the indicated temperature. After the reaction, the residue was purified by filtration over silica gel (CyH/EtOAc 9:1 or pentane/EtOAc 9:1).

Di-μ-acetatobis[{η^5-(*S*)-(*S$_p$*)-2-[2′-(4′-methylethyl)oxazolinyl]cyclopentadienyl,1-*C*,3′-*N*}-(η^5-pentaphenylcyclopentadiene)ferrocene]dipalladium (66a): A solution of oxazoline **65a** (400 mg, 0.59 mmol) and $Pd(OAc)_2$ (132 mg, 0.59 mmol, 1 equiv) in glacial acetic acid (2 mL) was heated in a preheated oil bath to 95 °C for 30 min, furnishing a red precipitate. The mixture was cooled to room temperature and the solid product was separated by filtration and washed with further glacial acetic acid (2 mL), showing only one diastereomer in ^{1}H NMR spectroscopy. For further purification, **66a** was dissolved in a minimum of DCE (ca. 2 mL for 0.5 g of crude complex) and transferred into a crystallization beaker (ca. 3 mm height of the solution, 5 cm diameter), which was placed into a desiccator containing *n*-pentane (height ca. 2 cm, ca. 25 cm diameter). After generally 1 d, dark red crystals of chemically and diastereomerically pure **66a** had formed. The supernatant was decanted and the crystals were dried in vacuo (460 mg, 0.27 mmol, 93 %). $C_{96}H_{82}Fe_2N_2O_6Pd_2$; M_r = 1684.14 g mol^{-1}; m.p. 230.0–231.3 °C (decomp); $[\alpha]_D^{23.4} = -1018.5$ (c = 0.274 g dL^{-1} in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.25–7.01 (m, 25H; arom. *H*), 4.25 (d, J = 2.1 Hz, 1H; *m*-$C_5H_3R_3$), 4.24 (d, J = 2.1 Hz, 1H; *o*-$C_5H_3R_3$), 3.95 (d, J = 1.5 Hz, 1H; *o*-$C_5H_3R_3$), 3.84–3.69 (m, 2H; OCH_2), 2.90–2.83 (m, 1H; NC*H*), 2.06 (s, 3H; CH_3COO), 2.00–1.95 (m, 1H; C*H*$(CH_3)_2$), 0.61 (d, J = 7.2 Hz; CH_3CHCH$_3$), 0.03 ppm (d, J = 6.9 Hz; CH_3CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 181.1, 177.1, 135.4, 132.7, 132.4, 126.9, 126.2, 90.8, 88.5, 77.8, 77.7, 75.8, 71.2, 70.8, 66.8, 28.2, 24.2, 20.7, 14.5 ppm; IR (film): $\tilde{\nu}$ = 3057, 2961, 1576, 1503, 1413, 909, 738, 699 cm^{-1}; MS (MALDI): *m*/*z* (%): 782 (100) $[M+H]^+$; HRMS (MALDI): *m*/*z*: calcd for $C_{46}H_{39}FeNOPd$ (loss of bridging OAc ligand): 782.1350; found: 782.1365; elemental analysis calcd (%) for $C_{96}H_{82}Fe_2N_2O_6Pd_2$: C 67.45, H 5.17, N 1.71; found: C 67.73, H 5.14, N 1.67.

Di-μ-chlorobis[{η^5-(*S*)-(*S$_p$*)-2-[2′-(4′-methylethyl)oxazolinyl]cyclopentadienyl,1-*C*,3′-*N*}(η^5-pentaphenylcyclopentadiene)ferrocene]dipalladium (67a): To a suspension of acetate bridged complex **66a** (145 mg, 0.086 mmol) in MeOH (20 mL), benzene (5 mL) and LiCl (250 mg) were added. The reaction mixture was stirred at RT for 1 h, then diluted with water and the phases were separated. The organic phase was washed with brine and dried over $MgSO_4$. All volatiles were removed under reduced pressure to yield the title product **67a** as dark red solid (138 mg, 0.082 mmol, 95 %), which did not require further purification. $C_{92}H_{76}Fe_2N_2O_2Cl_2Pd_2$; M_r = 1636.36 g mol^{-1}; m.p. 204.5–205.5 °C (decomp); $[\alpha]_D^{22.7} = -1129.4$ (c = 0.275 g dL^{-1} in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.36–7.24 and 7.09–6.99 (m, 25H; arom. *H*), 4.46–4.10 (m, 5H; *o*-$C_5H_3R_3$, *m*-$C_5H_3R_3$, OCH_2), 3.87–3.84 (m, 1H; NC*H*), 2.41 (m, 1H; C*H*$(CH_3)_2$), 0.81–0.75 (m, 3H; CH_3CHCH$_3$), 0.08–0.05 ppm (m, 3H; CH_3CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 178.0, 135.0, 134.8, 132.6, 126.7, 126.2, 125.9, 94.8, 88.8, 88.7, 76.5, 75.8, 71.4, 71.1, 67.9, 28.8, 20.7, 14.1 ppm; IR (film): $\tilde{\nu}$ = 3057, 2960, 2365, 1602, 1505, 1444, 1372, 1185, 1028, 909, 737, 700 cm^{-1}; MS (MALDI): *m*/*z* (%): 1636.3 (100) $[M+H]^+$; HRMS (MALDI): *m*/*z* calcd for $C_{92}H_{76}Fe_2N_2O_2Cl_2Pd_2$: 1636.3646; found: 1636.2240; elemental analysis calcd (%) for $C_{92}H_{76}Fe_2N_2O_2Cl_2Pd_2$: C 67.42, H 4.80, N 1.71; found: C 67.23, H 5.04, N 1.79.

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