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Review

Palladium catalyzed enantioselective rearrangement of allylic imidates to allylic amides☆

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Abstract

Recent progress in developing asymmetric Pd(II) catalysts for the [3,3]-sigmatropic rearrangement of allylic imidates to form enantioenriched allylic amides is reviewed. The best catalysts developed to date generate allylic amides in $>90\%$ enantiomeric excess (ee) from some allylic imidate substrates. The most recent catalysts developed in our laboratories are based on cyclopalladated ferrocenes having elements of planar chirality. A mechanistic proposal that enantioselection in Pd(II)-catalyzed allylic imidate rearrangements might derive from axial approach of the alkene to the chiral Pd(II) catalyst has guided our design of improved ligands.

Keywords: Allylic amine; Allylic imidate; Catalysis; Enantioenriched; Enantioselective; Palladium; [3,3]-Sigmatropic rearrangement

1. Introduction

Revolutionary advances in asymmetric catalysis have been recorded during the past 20 years, particularly for oxidations, reductions, and Lewis acid-catalyzed processes [1]. With the exception of alkenes that can be activated by conversion to η^3-allyl complexes, notably underdeveloped are catalytic asymmetric methods for activating carbon–carbon π-bonds for attack by external nucleophiles. The rich electrophilic addition chemistry of alkenes assures that the development of asymmetric methodology for antarafacial functionalization of alkenes would have significant impact on the synthesis of enantiomerically pure organic products [2]. A few years ago, we initiated studies to develop asymmetric catalysts for the addition of external (non-metal bound) nucleophiles to prochiral alkenes [3]. As the first step towards this objective, we have addressed asymmetric catalysis of cyclization-induced [3,3]-sigmatropic rearrangements [4].

[3,3]-Sigmatropic rearrangements are among the premier reactions of synthetic organic chemistry. Classic examples are the Cope (**1**, X = Y = C) and Claisen rearrangements (**1**, X = O, Y = C) which form new C–C σ-bonds. Of growing significance are [3,3]-sigmatropic rearrangements that interchange allylic heteroatoms X and Y [5]. Among this latter group, the rearrangement of allylic imidates (**1**, X = O, Y = N) to allylic amides (**3**, X = O, Y = N) is of notable importance since this rearrangement converts readily-available allylic alcohols to less available allylic amines and derivatives [6]. A particularly useful variant of this transformation is the rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides, a transformation first introduced by the senior author in 1976 [7] that has subsequently been widely exploited in

☆ Dedicated to Professors R.F. Heck and J. Tsuji, two great pioneers of organopalladium chemistry.

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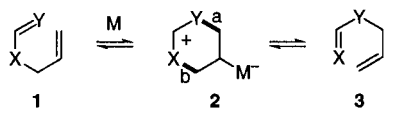


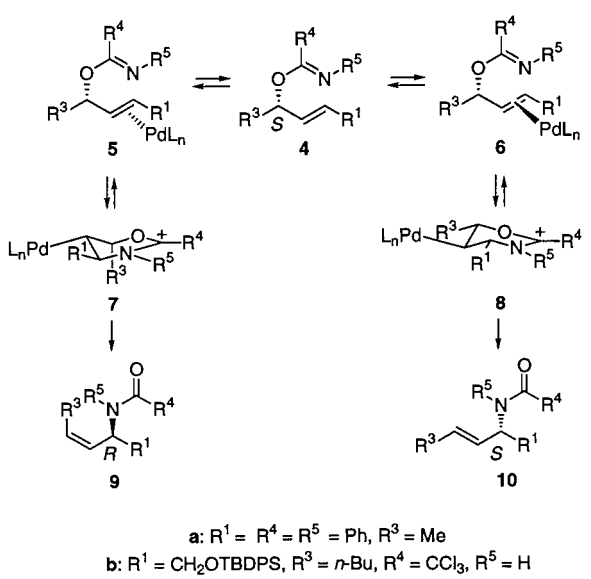
Scheme 1.

the syntheses of nitrogen-containing materials [8]. Since the original reports from our laboratories that [3,3]-rearrangements of allylic trichloroacetimidates could be catalyzed by Hg(II) catalysts [7], Pd(II) complexes have emerged as optimal catalysts for allylic imidate rearrangements and the variety of imidates subject to Pd(II) catalysis has been considerably expanded [9]. The rearrangement of allylic imidates to allylic amides was chosen for our initial asymmetric catalysis studies not only because of the importance of this transformation, but also due to the ca. 14 kcal mol^{-1} exothermicity of the imidate to amide reorganization [10]. This driving force alleviates the problem of reversibility inherent in many sigmatropic rearrangements, and, thus, simplified our initial studies (Scheme 1).

Since our report in 1997 of the first enantioselective catalyst for the rearrangement of allylic imidates to allylic amides [11], we [12–14] along with others [15] have described additional asymmetric catalysts for this reaction. With our most recently developed catalysts [14] producing rearranged amides in $>90\%$ enantiomeric excess (ee) in some cases, an initial review of the field seems appropriate [16].

2. Catalyst design considerations

Pd(II) and Hg(II) catalysis of many [3,3]-sigmatropic rearrangements occurs via a cyclization-induced rearrangement (CIR) mechanism. The evidence in support of the CIR mechanism has been reviewed and will not be discussed further here [4]. This mechanism involves coordination of the metal catalyst (M, Scheme 1) to the alkene of **1** initiating the formation of cyclic intermediate **2**. This intermediate can then follow either of two paths depending on which bond breaks: reversion to starting material **1** (bond a) or conversion to product **3** (bond b).



a: $R^1 = R^4 = R^5 = Ph$, $R^3 = Me$
b: $R^1 = CH_2OTBDPS$, $R^3 = n\text{-}Bu$, $R^4 = CCl_3$, $R^5 = H$

Scheme 2.

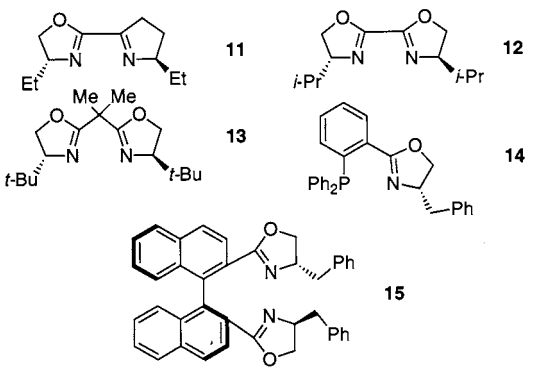
A knowledge of the enantioselective step would be desirable in designing asymmetric Pd(II) catalysts for the allylic imidate rearrangement [17], yet no kinetic information is available about the elementary steps of the catalytic cycle depicted in Scheme 2. However, some insight is available from previous studies of rearrangements of chiral, enantioenriched allylic imidates with $PdCl_2(PhCN)_2$. The key observations are that (*S*)-*N*-phenylbenzimidate **4a** rearranges to yield a 1:4 mixture of *Z*-allylic amide **9a** and *E*-allylic amide **10a** [18], while enantioenriched trichloroacetimidate **4b** yields exclusively *E*-allylic amide **10b** with complete transfer of chirality [19]. A plausible, though not unique, rationalization of these results is the following. If stereochemistry in the catalyzed rearrangement of **4a** were determined in the cyclization step, one would expect **10a** to heavily predominate, since R^3 would be equatorial in cyclic intermediate **8**. Apparently, cyclizations of Pd complexes **5a** and **6a** derived from the *N*-phenylbenzimidate are sufficiently fast that face selectivity in the alkene complexation step at least partially determines product composition. In the case of trichloroacetimidate **4b**, the imidate nitrogen is less nucleophilic and cyclization becomes the first irreversible step. Since it was expected that designing an enantioselective catalyst to preferentially coordinate one prochiral face of an alkene would be easier than designing catalysts to differentiate diastereomeric cyclization transition states, *N*-arylimidates were chosen as the inaugural substrates for our studies. We also assumed at the outset that the asymmetric ligands could not be strongly electron-donating or the ability of the Pd(II) catalyst to activate the alkene toward nucleophilic attack by the imidate nitrogen would be compromised (Scheme 2).

3. Cationic catalysts

3.1. Oxazoline ligands

In our earliest attempts to discover enantioselective catalysts for allylic imidate rearrangements, bis(oxazoline) ligands, which have planar nitrogen atoms coordinated to Pd, were examined [11]. More recently, Hayashi and co-workers have surveyed several additional oxazoline-containing ligands [15]. In our initial study, cationic oxazoline catalysts were generally pre-

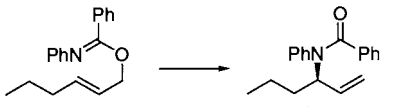
pared without isolation or purification from the reaction of a bis(oxazoline) with a Pd(II) halide followed by partial de-chlorination with $AgBF_4$ (one equivalent) and filtration. The in situ-generated catalysts were then assayed with an allylic imidate. Selected examples from our investigations, and those of Hayashi, are presented in Table 1. It is obvious from this table that catalysts derived from oxazoline ligands **11**–**14** rearrange allylic *N*-phenylbenzimidate **16** to allylic benzamide **17** in moderate yields and with poor to moderate enantiomeric excesses (entries 1–4). Rearrangement of imidate **18** containing an electron-withdrawing *para* substituent on the *N*-aryl ring with catalysts based on ligands **14** and **15** gave improved results (entries 5–6). The best enantioselectivity (81% ee) observed for the cationic oxazoline catalysts was for the rearrangement of imidate **20** to **21** with ligand **14**, however the yield of **21** was only 30% (entry 7) [15]. While these results demonstrated that it was possible to obtain non-racemic allylic amide with an asymmetric Pd(II) catalyst, much room for improvement remained.



3.2. Diamine ligands

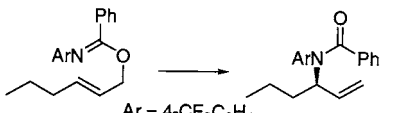
Initial attempts to prepare enantioselective catalysts containing Pd bound to tetrahedral nitrogen atoms of the ligand focused on readily-available complexes of unsymmetrical, chiral diamines. After surveying several diamines, (*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine **22** was selected for further study. Diamine **22** was chosen due to its ease of preparation and the expectation that upon coordination to Pd the *cis*-heterobicyclo[3.3.0]octane ring would be formed due to enhanced ring strain in the *trans*-fused isomer [20]. Upon reacting diamine **22** with either Na_2PdCl_4 or $PdCl_2(MeCN)_2$ kinetic stereoselectivities of 10:1 and 5:1 were obtained for forming *cis*-bicyclo[3.3.0]octane isomer **23**. The *trans* isomer **24** slowly isomerizes to the *cis* isomer **23** in MeCN solution. The moderate kinetic selectivity observed in formation of the *cis*-heterobicyclo[3.3.0]-octane system is likely due to the longer Pd–N bonds (2.05 Å) versus the shorter C–C bonds (1.54 Å), although the thermodynamic equilibrium still lies well toward the *cis* isomer.

Table 1
Rearrangement of allylic imidiates catalyzed by $PdCl_2$(ligand)/$AgBF_4$(one equivalent) in CH_2Cl_2



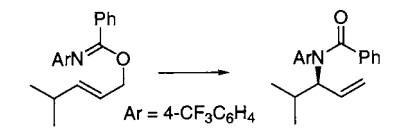
16 17

entry	ligand	yield	%ee	ref.
1	**11**	62%	10	11
2	**12**	24%	0	11
3	**13**	7%	10	11
4	**14**	88%	47	15



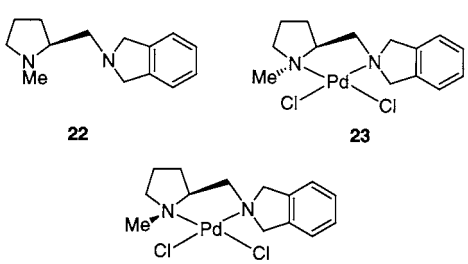
18 19

entry	ligand	yield	%ee	ref.
5	**14**	41%	76	15
6	**15**	44%	17	15



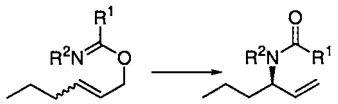
20 21

entry	ligand	yield	%ee	ref.
7	**14**	30%	81	15



Pd(diamine) dichlorides were not found to catalyze allylic imidate rearrangements. To increase the lability of the Pd coordination sphere, diamine complex **23** was reacted with one equivalent of $AgBF_4$ to produce a μ-chloro-bridged dicationic dimer **25**. Dimer **25** was the first enantioselective catalyst reported for the rearrangement of allylic imidates to allylic amides [11]. The results of catalysis of the rearrangement of a variety of allylic imidates with dimer **25** are presented in Table 2. *N*-Phenylbenzimidate **16** yielded only 18% of the desired allylically rearranged benzamide in 41% ee, with the major reaction being elimination of *N*-phenylbenzimidate (entry 1). On the assumption that elimination was promoted by coordination of the imidate nitrogen to Pd (vide infra), *N*-(4-trifluoromethylphenyl)benzimidate **18** was prepared and did rearrange more efficiently in the presence of **25** to produce allylic amide **19**

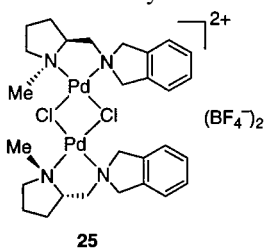
Table 2
Rearrangement of allylic imidates to allylic amides with dimer **25** in CH_2Cl_2



Entry	R^1	R^2	Z/E	Yield (%)	%ee
1	Ph	Ph	*E*	18	41
2	Ph	4-$CF_3C_6H_4$	*E*	69	55
3	Ph	4-$CF_3C_6H_4$	*Z*	86	63[a]
4	H	4-$CF_3C_6H_4$	*E*	<15	37
5	*t*-Bu	4-$CF_3C_6H_4$	*E*	<15	42
6	CCl_3	H	*E*	20	5
7	Ph	Bz	*E*	30	22

[a] Catalyst was dimer **29**.

in a 69% yield and 55% ee (entry 2). Under the conditions of entry 2, all the starting material was consumed with the elimination product **26** and product of [1,3]-rearrangement **27** constituting the remainder of the mass. Variation in substrate structure did not significantly alter enantioselectivity with the exception of the two non-nucleophilic imidates (entries 6 and 7) which were poor substrates for catalyst **25**.



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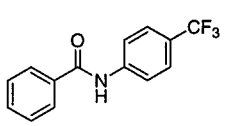

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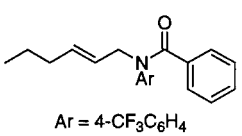


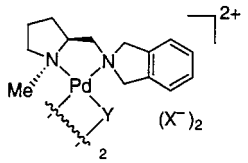
Ar = 4-$CF_3C_6H_4$

27

A number of reaction parameters (catalyst structure, solvent, and additives) were surveyed in attempts to improve enantioselectivity and catalytic rate. The first variable examined was the bridging group and counter-ion of the Pd dimer. Table 3 presents the results of varying the size (Cl, Br, I) and geometry (SCN) of the bridging group, as well as the counter-anions (OTf, PF_6, SbF_6, BF_4). While these variations represent significant differences in bridging distances and geometry of the dimer, and significant differences in size and shape of the counter-anions, no improvements were found.

Changes in the diamine ligand structure were also examined; results are presented in Table 4 where catalysis results with **25** are also included for comparison. The rearrangement of imidate **18** with catalyst **35** gave a 60% yield of amide **19** in 22% ee. While catalyst **36** produced amide **19** in 63% yield and 44% ee. These small variations in diamine ligand structure did not improve the enantioselectivity of the rearrangement, nor was the efficiency of the process improved with elimination remaining a major side reaction.

Table 3
Rearrangement of allylic imidate **18** to allycic amide **19** with various Pd diamine dimers in CH_2Cl_2



Catalyst	X	Y	Time	Yield (%)	%ee
25	BF_4	Cl	2 days	69	55[a]
28	BF_4	Br	18 days	47	51[b]
29	SbF_6	Cl	5 days	68	48[a]
30	PF_6	Cl	5 days	75	50[a]
31	OTf	Cl	3 days	66	56[a]
32	OTf	I	8 days	25	30[a]
33	OTf	SCN	6 days	<20	28[a]
34	SbF_6	O_2CCF_3	11 days	24	23[b]

[a] 40°C.
[b] Room temperature.

Finally, with dimer **25** the rearrangement of allylic imidate **18** to allylic amide **19** in various solvents was examined. The results obtained with solvents of varying coordinating ability and polarity differences are collected in Table 5. Again examination of the data show little change in enantiomeric excess or yield of allylic amide **19**, except for rearrangements in nitrobenzene

Table 4
Rearrangement of allylic imidate **18** to allylic amide **19** with 5 mol% of various diamine dimers in CH_2Cl_2 at 40°C

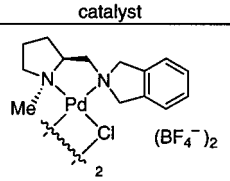
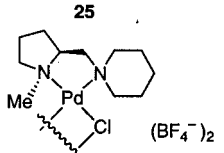
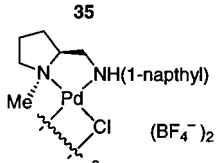
entry	catalyst	yield	%ee
1	 **25**	69%	55
2	 **35**	60%	22
3	 **36**	63%	44

Table 5
Rearrangement of allylic imidate **18** to allylic amide **19** in various solvents

Catalyst	Solvent	%ee
25	CD_2Cl_2	55
25	$CHCl_3$	54
25	DMF	35
25	CD_3NO_2	55
31	$C_6H_5NO_2$	50

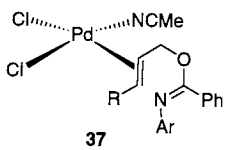
which occurred somewhat faster, requiring only 10 h to produce a 68% yield of amide **19** in 50% ee.

To summarize our investigations of cationic Pd(diamine) catalysts, variations in the bridging group and counter-anion, as well as modifications in the coordination sphere of Pd with additives [21], produced little changes in the observed chemistry. Varying the solvent over a wide range of polarity, dielectric constant, and coordinating ability also did not improve enantioselection, nor did small variations in diamine structure. It was clear from the results of these initial systematic studies of the Pd(diamine) catalysts that changes in catalyst architecture were needed.

4. Neutral catalysts

4.1. Ferrocenyl amine ligands

Two considerations led to the design of an improved catalyst system. The first factor was the experimental observation that unlike the Pd(diamine) catalysts **25** and **28**–**36**, $PdCl_2(MeCN)_2$ rearranges allylic imidate **18** to allylic amide **19** quantitatively in CD_2Cl_2 at room temperature (r.t.) within minutes. Based on the CIR mechanism model, $PdCl_2(MeCN)_2$ activates an allylic imidate by replacement of an acetonitrile ligand with the alkene moiety producing a *neutral* activated complex **37**. In contrast, the activated intermediate produced from the Pd diamine catalysts (**25**, **28**–**36**) is *cationic* (**38**). Further, it is proposed that the cationic complex **39**, where the allylic imidate is coordinated through the imidate nitrogen, is responsible for the competing side reactions which resulted in elimination of amide **26** and formation of the 1,3-rearranged allylic amide **27**. Finding a suitable chiral mono-anionic ligand that would produce a neutral activated complex and would be readily accessible became the focus of our research efforts.



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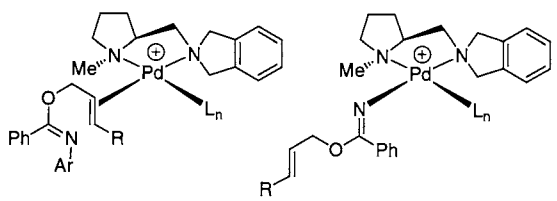

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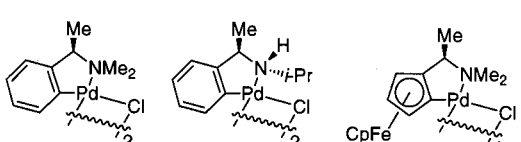
In searching for a suitable mono-anionic ligand, Pd(II) complexes of semicorrins were examined, however, they did not yield improved catalytic results [21]. Turning then to cyclopalladated dimers, achiral versions of which were first reported by Cope [22], a significant improvement was realized. Results of catalyzing the rearrangement of imidate **18** to allylic amide **19** with several cyclopalladated complexes are presented in Table 6. Evaluating commercially available dimer **40** as a catalyst under the same conditions employed for rearrangements conducted with Pd(diamine) catalysts produced allylic amide **19** in quantitative yield, all be it in racemic form. Changing the bridging group in **40** from chloride to trifluoroacetate did not improve enantioselection (entry 2), nor did switching to a cyclopalladated complex **41** [23] having nitrogen substituents of differing sizes. While a significant advance had been made in improving the rate and efficiency of the rearrangement, the enantiomeric excess had dropped precipitously.

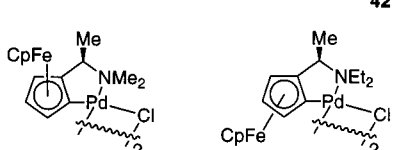
Table 6
Survey of cyclopalladated complexes as catalysts for the rearrangement of allylic imidate **18** to allylic amide **19**

Entry	Catalyst	Time	Yield (%)	%ee
1	**40**	40 h (40°)	97	0
2	**40**/$Ag(O_2CCF_3)$	2 days	6	14
3	**41**	10 days (40°C)	50	2
4	**42**	7 days	35	67 (*R*)
5	**42**/AgOTos	4 days	85	26 (*R*)
6	**42**/AgOTf	2.5 days	45	2
7	**42**/$AgBF_4$	21 h	70	10 (*R*)
8	**42**/AgOAc	21 h	25	10 (*R*)
9	**42**/$Ag(O_2CCF_3)$	21 h	98	61 (*R*)
10	**42**/Tl(acac)[a]	14 days	21	56 (*R*)
11	**42**/$Ag(O_2CCF_3)$	40 h	87	48 (*R*)
12	**44**	10 days	15[b]	59 (*R*)

[a] The isolated acac complex was used.
[b] HPLC yield.

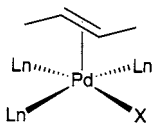


40 41 42



43 44

The second consideration, which eventually led to the design of highly enantioselective catalysts, was the mechanism of substitution at square planar palladium complexes. Cross has reviewed the literature on substitution reactions of square planar transition metal complexes and concluded that, with few exceptions, substitution at square planar palladium is an associative process [24]. Since coordination of the alkene to palladium might be the enantioselective step in the Pd(II)-catalyzed rearrangement of nucleophilic imidates (vide supra), selection of the prochiral alkene faces upon formation of the pentacoordinate square pyramidal intermediate **45** could be crucial[2]. Based upon this analysis, a ligand design was chosen that would project steric bulk above and below the Pd square plane. As will be illustrated below, this design element led to significant improvements in enantioselection.



45

The crystal structures of cyclopalladated benzyl amine complex **41** [24] and cyclopalladated ferrocenyl amine complex **46** [25] were particularly informative. First, an examination of the structure of benzyl amine complex **41** (Fig. 1, one-half of the dimer and the hydrogens have been omitted for clarity) reveals that the isopropyl substituent on nitrogen projects above the Pd square plane. The phenyl ring is essentially co-planar with the Pd square plane leaving the face of Pd opposite the isopropyl group essentially flat, perturbed only by the distant benzylic methyl substituent. Thus, one face of Pd presents a nearly achiral environment with little steric bias to the approaching alkene. It is postulated that this feature is responsible for the low enantioselectivity realized with benzyl amine catalysts **40** and **41**. Insight into improving the ligand design and the enantiodiscrimination of these catalysts is gained from the crystal structure of cyclopalladated ferrocenyl amine complex **46** (Fig. 1, the carbons of the acac ligand and the hydrogens are omitted for clarity). In the structure of complex **46** it is readily noted that the methyl group on nitrogen projects above one face of the Pd square plane and the large FeCp moiety projects

[2] This mechanistic scheme was used for ligand design and is a simplification of the detailed mechanistic possibilities. It is also possible that any of the pseodorotations required for forming the four coordinate square planar Pd(alkene) complex could be the enantioselective step. Also, the possibility exists that the 5-coordinate palladium is in fact the active form of the catalyst and a 4-coordinated alkene complex species is not formed. No experimental evidence pertinent to these issues is extant.

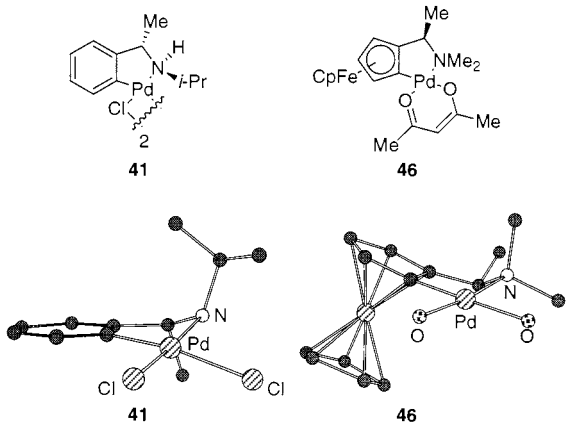
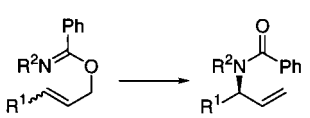


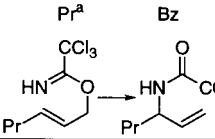
Fig. 1. Chemdraw and crystal structures of cyclopalladated complexes [12,28]. Hydrogens and parts of the structures are omitted for clarity.

on the opposite face. Ferrocenyl amine based ligands display steric elements both above and below the palladium square plane and were expected to provide improved enantioselectivity.

The cyclopalladated ferrocenyl chloro-bridged dimer **42** [23] was readily prepared by cyclopalladation of the commercially available amine and was evaluated as a catalyst for the rearrangement of allylic imidate **18** to allylic amide **19**. The enantiomeric excess obtained for allylic amide **19** was 67%, a significant improvement over that obtained with cyclopalladated dimer **40** (Table 6, entry 4). However, the rate of this reaction was not satisfactory, providing only a 35% yield of **19** after 7 days at r.t., with the remaining mass being recovered **18**. To improve the rate of catalysis a brief survey of counter-ions (entries 4–10) was undertaken and revealed that trifluoroacetate was optimal, providing a nearly quantitative yield of allylic amide **19** at r.t.

Table 7
Rearrangement of allylic imidates to allylic amides with **47** in CH_2Cl_2



entry	R^1	R^2	time	yield	%ee
1	Pr[a]	4-$CF_3C_6H_4$	24 h	97%	57
2	Pr[a]	4-$MeOC_6H_4$	24 h	69%	52
3	Pr[a]	Ph	38 h	84%	61
4	Me[a]	Ph	16 h	94%	54
5	Ph[a]	Ph	27 h	47%	47
6	t-Bu[a]	Ph	48 h		----
7	Pr[b]	4-$CF_3C_6H_4$	6 d	76%	46
8	Pr[a]	Bz	2.5 d	17%[c]	36
9			6 d	39%[c]	8

[a] *E*-alkene geometry. [b] *Z*-alkene geometry. [c] NMR Yield.

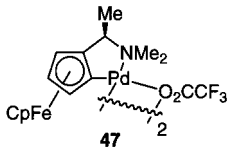
Table 8
Rearrangement of allylic imidate **18** to allylic amide **9** with 5–10 mol% cyclopalladated catalyst in CH_2Cl_2

Catalyst	Time (days)	Yield (%)	%ee
48	2	34	49
48/Ag(O_2CCF_3)	1	47	37
48/Tl(O_2CCF_3)	1	73	40
49	2	0	–
49/Ag(O_2CCF_3)	1	80	17

in an overnight reaction without significant erosion of enantiomeric excess. Diastereomeric complex **43** also was a catalyst for rearrangement of **18** and surprisingly produced allylic amide of the same absolute configuration (Table 6, entry 11).

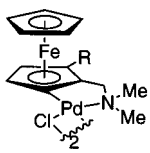
Attempting to improve the observed enantiomeric excess, several *N*-substituted ferrocenyl amine analogs were prepared. Of these only the *N*,*N*-diethyl derivative was successfully cyclopalladated to provide a 9:1 ratio of diastereomeric palladacycles [26]. The major diastereomer **44** proved to be a less efficient catalyst than the *N*,*N*-dimethyl derivative (Table 6, entry 4 versus entry 12); therefore, other analogs were not pursued.

Results obtained from our initial survey of the scope of this catalytic asymmetric method are presented in Table 7. From this compilation it is seen that allylic *N*-arylimidates are excellent substrates providing allylic amides in good rates, good yields and moderate enantioselectivities (entries 1–7). Variation of the electron donating ability of the *N*-aryl group had little effect on the outcome of the reaction (entries 1–3), whereas the rate of reaction decreased dramatically as the size of the substituent on the alkene increased (entries 3–6). The corresponding *Z*-allylic imidate (entry 7) provided the allylic amide product of opposite absolute configuration, with a decrease in reaction rate. An *N*-benzoylbenzimidate (entry 8) and a trichloroacetimidate (entry 9) were examined because the allylic amide product of these precursors would be of broader synthetic interest. Unfortunately, these substrates were found to rearrange only slowly and with low enantioselectivity.



47

In a separate route to cyclopalladated ferrocenyl amine catalysts, Kagan's diastereoselective metalation of ferrocenes [27] and reductive amination were employed to prepare several enantioenriched ferrocenyl amines [13]. Of these only the *N*,*N*-dimethyl derivatives **48** and **49** underwent cyclopalladation under standard conditions. It was found that complexes **48** and **49** decomposed in the presence of Ag(O_2CCF_3), therefore, Tl(O_2CCF_3) was used to dehalogenate these complexes. The results of catalysis with cations derived from cyclopalladated catalysts **48** and **49** are presented in Table 8. It is readily seen that the rearrangement of imidate **18** with these catalysts provided amide **19** with slightly lower stereoselectivity than α-methyl congener **42.**



48 R = Me
49 R = $SiMe_3$

The cyclopalladated ferrocenyl amine complexes were the first catalysts designed on the premise of projecting steric influence both above and below the square plane of a chiral Pd(II) complex. The reported catalysis with **42** represented the first use of an enantioenriched cyclopalladated complex as an enantioselective catalyst.

4.2. Ferrocenyl imine ligands

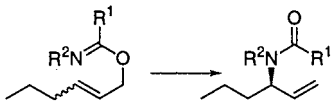
The crystal structure of racemic cyclopalladated ferrocenyl imine **50** reveals that the aryl ring is perpendicular to the Pd square plane [28]. Based on a catalyst design requiring projection of steric bulk above and below the Pd square plane, this class of compounds looked promising for yielding enantioselective catalysts for the rearrangement of allylic imidates. Enantiopure cyclopalladated ferrocenyl imine catalysts **51**–**56** were prepared by reacting enantiopure ferrocenyl iodides [19] with $Pd_2(dba)_3 \cdot CHCl_3$ [13]. The results of the rearrangement of imidate **18** to amide **19** with these catalysts are presented in Table 9. Unlike the chloro-bridged dimers discussed earlier in this review, the iodide-bridged dimer **51** did not catalyze the rearrangement of allylic imidate **18** (entry 1). This observa-

Table 9
Rearrangement of allylic imidate **18** to allylic amide **19** with ferrocenyl imine derived catalysts in CH_2Cl_2/1% MeCN

Entry	Catalyst	Yield (%)	%ee
1	**51**	0	–[a]
2	**51**/Tl(OTf)	80	46
3	**52**/Tl(O_2CCF_3)	60	41
4	**53**/Tl(O_2CCF_3)	100	33
5	**54**/Tl(OTf)	91	49[b]
6	**55**/Tl(OTf)	83	49[b]
7	**56**/Tl(OTf)	87	47[b]

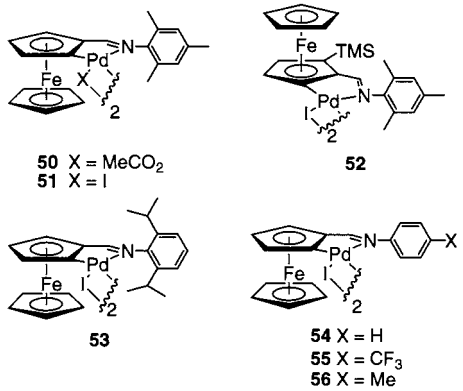
[a] Starting material recovered.
[b] Reaction contained 1% MeCN.

Table 10
Rearrangement of allylic imidates with 10 mol% **51**/Tl(OTf) (four equivalents) in CH_2Cl_2/1% MeCN



Entry	R^1	R^2	Z/E	Yield (%)	%ee
1	Ph	Ph	*E*	57	43
2	Ph	4-$CF_3C_6H_4$	*Z*	45	66
3	Ph	4-$MeOC_6H_4$	*Z*	78	73
4	CCl_3	H	*E*	–[a]	

[a] Complex mixture obtained.



tion reflects a general trend of increased kinetic and thermodynamic stability of palladium(II) iodide-bridged dimers. However, reaction of these complexes with Tl and Ag salts provided catalytically active species. Deiodination of **51** with $Ag(O_2CCF_3)$ led to an active catalyst that produced **19** with moderate enantioselectivity (60–70% ee) but in low yields which varied considerably from run to run. This irreproducibility was attributed to catalyst decomposition due to redox reactions between Ag and Fe. Fortunately, deiodination with thallium salts obviated this problem (entries 2–7). As expected, cationic complexes generated from mesityl imine derivative **51** and the trimethylsilyl congener **52** were found to give opposite enantioselectivity with a similar degree of induction. The *iso*-propyl derivative **53** was a less enantioselective catalyst (entry 4) and surprisingly the triflate analog of **53** produced only elimination.

To pursue potential electronic effects, phenyl imine derivatives **54**–**56** were prepared, activated with Tl(OTf) and assayed as catalysts. While these less-sterically encumbered derivatives provided allylic imidate **19** in the highest enantiomeric excess (49% ee) for this series of catalysts, no electronic effect upon catalytic rate or enantioselectivity was observed (entries 5–7).

Table 11
Rearrangement of *E*-allylic imidate **18** to allylic amide **19** with ferrocenyl oxazoline catalysts in CH_2Cl_2 at 40°C

Entry	Catalyst	Time (days)	Yield (%)	%ee
1	**57**	4	22	37 (*S*)
2	**58**/$Ag(O_2CCF_3)$	2	57	79 (*S*)
3	**59**/$Ag(O_2CCF_3)$	2.5	76	76 (*S*)
4	**60**/$Ag(O_2CCF_3)$	3	95	72 (*R*)

The effect of imidate structure was briefly surveyed. The *N*-aryl substituent of the imidate had little effect on enantioselectivity of the reaction (compare Table 10 entry 1 with Table 9 entry 2). However, *Z*-allylic benzimidates rearranged with slightly higher enantioselectivity to provide allylic benzamide products of the opposite absolute configuration. Unfortunately, an allylic trichloroacetimidate yielded a complex mixture of products when exposed to the catalyst derived from **51**.

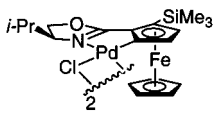
Ferrocenyl imine based catalysts, at least with *Z*-imidate substrates, are promising. Future modifications of this catalyst architecture could yield catalysts capable of rearranging allylic imidates to allylic amides in high ee.

4.3. Ferrocenyl oxazoline ligands

Cyclopalladated ferrocenyl oxazolines are precursors to the most promising catalysts discovered to date [14]. The ferrocenyl oxazoline ligands are readily accessed from ferrocenecarboxylic acid and enantiopure amino alcohols [29], which are then elaborated to the Pd catalyst by an iodination–palladium insertion sequence [14]. Our initial survey in this series involved the *iso*-propyl, *tert*-butyl and 3-methoxy-3-pentyl derivatives **57**–**60**. Results of the rearrangement of allylic imidate **18** to allylic amide **19** with these complexes are summarized in Table 11. The *iso*-propyl-substituted chloride-bridged dimer **57** was examined initially and found to be a poor catalyst providing allylic amide **19** in only 22% yield and 37% ee after 4 days (entry 1). The size of the oxazoline substituent was then increased to *tert*-butyl (**58**, **59**) and 3-methoxy-3-pentyl (**60**) and these iodide-bridged dimers were activated in CH_2Cl_2 by deiodination with $Ag(O_2CCF_3)$. These in situ-generated species catalyzed the rearrangement of *E*-allylic imidate **18** to allylic amide **19** in moderate to good yields with enantioselectivities of 72–79% ee (Table 11). As expected, the catalyst formed from **60** gave the opposite enantiomer of allylic amide **19** than the catalysts generated from **58** or **59**.

Table 12
Rearrangement of *Z*-allylic imidate **61** to allylic amide **19** with ferrocenyl oxazoline catalysts in CH_2Cl_2 at 40°C

Entry	Catalyst	Time (days)	Yield (%)	%ee
1	**58**/Ag(O_2CCF_3)	3	67	91 (*R*)
2	**59**/Ag(O_2CCF_3)	6	89	90 (*R*)
3	**60**/Ag(O_2CCF_3)	6	81	92 (*S*)



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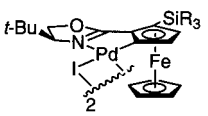
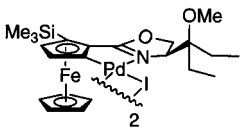
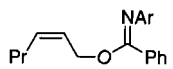


58, R = Me
59, R = Et



60



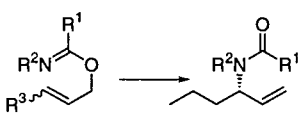
Ar = 4-$CF_3C_6H_4$

61

The 90% ee barrier was finally broken when the rearrangement of *Z*-alkene **61** was surveyed with these catalysts (Table 12). As expected, the opposite enantiomer of the allylic amide product was produced from the *Z* alkene stereoisomer. Whether the oxazoline substituent was *tert*-butyl or 3-methoxy-3-pentyl had no significant effect on the enantiomeric excess of allylic amide **19**. Optimization studies revealed that nitrate and trifluoroacetate counter-ions provided comparable, excellent results. An examination of solvents showed that catalysis in CH_2Cl_2 and toluene yielded similar enantiomeric excesses for allylic amide **19** despite the significant differences in polarity and dielectric constant of these two solvents.

An initial survey of the scope of the allylic imidate rearrangement with ferrocenyl oxazoline catalysts was performed using precatalyst **58** (Table 13). Allylic trichloroacetimidates were once again poor substrates, with the best results being obtained for allylic *N*-arylimidates. In these studies the aryl substituent was *para*-methoxyphenyl, a group which is potentially removable from the amide product. A slight decrease in enantiomeric excess was observed when the alkene substituent R^3 was methyl or phenyl (entries 4 and 6). However, imidates with β-branching in the R^3 substituent (entry 3) produced the rearranged amides with the exceptional enantiomeric excess of 97%, the highest realized to date for catalytic asymmetric rearrangement of an allylic imidate.

Table 13
Rearrangement of allylic imidates to allylic amides with 5 mol% **58**/Ag(O_2CCF_3) in CH_2Cl_2

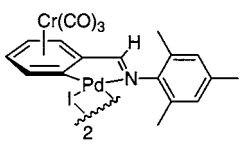


Entry	R^1	R^2	R^3	Time	Yield (%)	%ee
1	CCl_3	H	Pr	6 days	50	43[a]
2	Ph	$MeOC_6H_4$	Pr	21 h	83	90[b]
3	Ph	4-$MeOC_6H_4$	*i*-Bu	27 h	90	97[b]
4	Ph	4-$MeOC_6H_4$	Me	15 h	96	75[b]
5	Ph	4-$MeOC_6H_4$	Bn	3 days	85	88[b]
6	Ph	4-$MeOC_6H_4$	Ph	3 days	11	77[b]

[a] *E*-alkene geometry.
[b] *Z*-alkene geometry.

4.4. Chromium tricarbonyl arylimine ligands

Finally, in an investigation aimed at ascertaining the necessity of the ferrocenyl subunit of these planar chiral catalysts, $Cr(CO)_3$ complex **62** was prepared and demonstrated to be a useful pre-catalyst for allylic imidate rearrangements [30]. Deiodination of chromium tricarbonyl complex **62** with Tl(OTf) in CH_2Cl_2 containing 1% MeCN generated a species that catalyzed the rearrangement of *E*-allylic imidate **18** at r.t. within 24 h to give allylic amide **19** in 75% yield and 80% ee. This promising catalyst is among the best yet discovered for asymmetric rearrangement of *E*-allylic imidates. Results obtained with catalysts derived from **62** clearly demonstrate that the ferrocenyl moiety is not unique to the function of the catalysts we are developing.



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5. Conclusions

In 1997 the first asymmetric catalysts for [3,3]-sigmatropic rearrangement of allylic imidates were reported, however, these cationic Pd(diamine) catalysts were markedly deficient in terms of reaction rate and yield. By changing to mono-anionic ligands we were able to significantly improve the rate of catalysis and eliminate unwanted side reactions. Finally, by turning to catalysts having planar chiral elements enantioselectivity was dramatically improved. The best catalysts discovered to date are cyclopalladated ferrocenyl oxazolines which catalyze the rearrangement of several *Z*-allylic imidates to give rearranged allylic amides in $>90\%$ ee. We anticipate that future developments in this area will lead to improved catalysts for allylic imidate and other [3,3]-sigmatropic rearrangements, as well as new catalysts for promoting antarafacial addition of external nucleophiles to alkenes.

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