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Cyclopalladated Ferrocenyl Amines as Enantioselective Catalysts for the Rearrangement of Allylic Imidates to Allylic Amides

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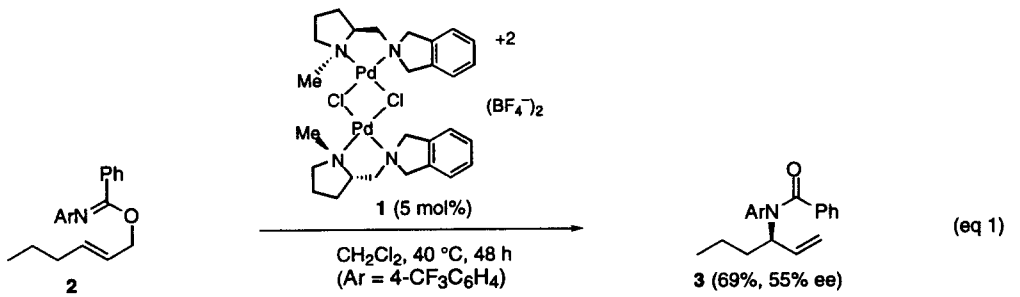
Abstract: The first examples of the use of cyclopalladated complexes in enantioselective catalysis are reported. Cyclopalladated ferrocenyl amine **6f** promotes the rearrangement of some 2-alkenyl imidates to allylically transposed amides in excellent yield and moderate enantioselectivity.

The rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides is a widely used method for the transformation of allylic alcohols to less available allylic amines.[1,2] We recently reported the effectiveness of di-μ-chloro-bis[(*S*)-2-(isoindolinylmethyl)-*N*-methylpyrrolidine]dipalladium(II) bis(tetrafluoroborate), **1**, a palladium diamine chloro-bridged dicationic dimer, as an enantioselective catalyst for the rearrangement of prochiral allylic imidates to allylic amides (eq 1).[3] Although catalyst **1** was the first reported asymmetric catalyst for the rearrangement of allylic imidates, it is not ideal; the rearranged allylic amide **3** was obtained in only moderate yield and enantiomeric purity. A major complication with catalyst **1** is competing ionization of the imidate to form a mixture of hexadienes and 2-hexenyl benzamides (products of 1,3-rearrangement). The formation of these byproducts was only partially mitigated by moderating the basicity of the imidate nitrogen through incorporation of a *para* trifluoromethyl substituent. In this communication, we report that cyclopalladated complexes[4] are improved catalysts for allylic imidate rearrangements furnishing several classes of allylic amides in excellent chemical yield and with the highest enantioselectivities reported to date.

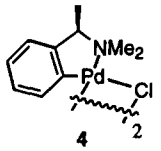


(eq 1)

Our search for an improved catalyst was guided by two considerations. First, in marked contrast to **1**, $PdCl_2(MeCN)_2$ catalyzes the rearrangement of **2** to **3** in near quantitative yield within minutes at room temperature. In a cyclization induced rearrangement (CIR) mechanism,[1,3] activation of the allylic imidate by $PdCl_2(MeCN)_2$ would be initiated by replacement of an acetonitrile ligand with the alkene unit of the imidate to give a neutral Pd-olefin complex. In contrast, the corresponding activated Pd-olefin complex derived from **1** would be cationic.[5] Therefore, we directed our search to Pd complexes containing at least one anionic ligand,

catalysts that would more closely mimic $PdCl_2(MeCN)_2$. Secondly, substitution reactions at square planar Pd occur almost exclusively through an associative process.[6] If olefin coordination is the enantioselective step,[3] ligands that project chirality perpendicular to the Pd square plane might be particularly effective at discriminating prochiral faces of the C–C π-bond of allylic imidates.

We initially evaluated cyclopalladated benzyl amines first reported by Cope and Friedrich.[4a] Enantiopure complex **4**[7] (5 mol%) in CH_2Cl_2 at 40 °C catalyzed the rearrangement of allylic imidate **2** in near quantitative yield, but racemic **3** was obtained (Table 1). Cyclopalladated complex **5**,[8,9] having nitrogen substituents of differing sizes, was also an ineffective asymmetric catalyst (Table 1). Turning to cyclopalladated catalysts with planar chirality, we initially examined the known diastereomerically pure chloride-bridged dimer **6a**.[10,11] This complex catalyzed 3,3-sigmatropic rearrangement of allylic imidate **2** efficiently, without any indication of the formation of byproducts arising from ionization, yielding **3** in 67% ee (Table 1). However, the rate of reaction was not synthetically useful. To improve catalytic turn-over, the bridging ligand was systematically varied by dechlorination of **6a** with various silver salts. After removal of precipitated AgCl, these crude catalysts **6b–6f** were assayed with allylic imidate **2**. The results presented in Table 1 show that trifluoroacetate derivative **6f**[11] is optimal in terms of rate and yield, affording (*R*)-**3** with nearly as high enantioselectivity as does chloride-bridged dimer **6a**. The corresponding acetate bridged dimer **6e** also produced **3** in good enantioselectivity, but in only 25% yield. Catalysts containing weakly coordinating counter-ions (**6b–6d**) produced **3** in low enantioselectivity and at slower rates. The minor diastereomer **7a** obtained from cyclopalladation of (*R*)-(+)-*N*,*N*-dimethylferrocenylethylamine with Na_4PdCl_2[10d] was also dechlorinated with AgO_2CCF_3 to yield catalyst **7b**. To our surprise, this catalyst also provided (*R*)-allylic amide **3**, albeit somewhat slower and in lower enantioselectivity.[12]



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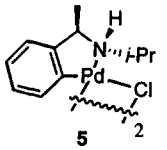

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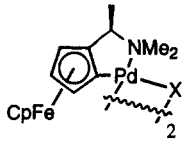

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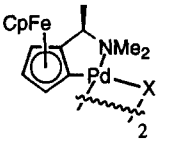
a X = Cl **d** X = BF_4
b X = OTs **e** X = OAc
c X = OTf **f** X = O_2CCF_3



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a X = Cl **b** X = O_2CCF_3

Table 1. Rearrangement of allylic imidate **2** to allylic amide (*R*)-**3** with various cylcopalladated complexes.

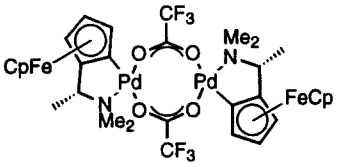
catalyst	rxn. conds.[a]	yield	%ee
4	40 h (40 °C)	97%	0
5	10 d (40 °C)	50%	2
6a	7 d	35%	67
6b	4 d	85%	26
6c	2.5 d	45%	2
6d	21 h	70%	10
6e	21 h	25%	52
6f	21 h	98%	61
7b	40 h	87%	48

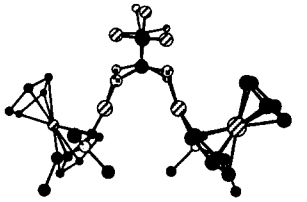
[a] At room temperature in CH_2Cl_2 using 5 mol% of the catalyst, unless noted otherwise.

During our initial trials with trifluoroacetate catalyst **6f** prepared *in situ* by dechlorination of dimer **6a**, enantioselectivity was observed to vary from run to run. After numerous attempts to remove the source of these

deviations were unsuccessful, **6f** was isolated, purified by recrystallization from CH_2Cl_2–hexane and characterized by single crystal X-ray analysis.[11] Similar to other acetate bridged Pd(II) dimers, the square planes of the Pd centers lie in an almost parallel arrangement and the ferrocenyl amine moieties adopt a "trans" orientation across the dimer (Figure 1). Although lacking a crystallographic C_2 axis, the molecular structure of **6f** is pseudo-C_2 symmetric and ^{1}H NMR spectroscopy indicates a C_2 symmetric structure for **6f** on the NMR time scale. While cis-trans isomerization across the dimer occurs slowly in CD_2Cl_2 solution in most instances (2-5%, 24 h), samples were occasionally observed to isomerize in minutes, presumably due to a trace impurity of undetermined origin.[13] A solution of complex **6f** that had isomerized to the extent of 50% produced **3** in somewhat lower enantioselectivity (48% ee) than that observed if catalysis was begun with a solution of the pure trans isomer (60% ee). A catalytic run with pure isolated *trans*-**6f** showed no variation in enantiopurity of **3** (60±2% ee) with time (15–120 min).

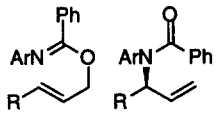
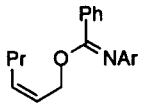
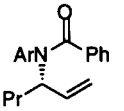
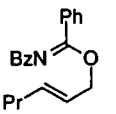
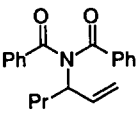
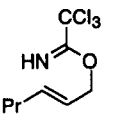
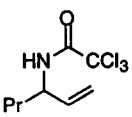
Figure 1. Molecular structure of **6f**.





Results of catalysis[14] with trifluoroacetate **6f** (5 mol% in CH_2Cl_2) of the rearrangement of a variety of imidates are presented in Table 2.[15] For *N*-aryl allylic imidates good rates, good yields, and modest enantioselectivities are realized with catalyst **6f** (Table 2). Variation of the *N*-aryl group of the imidate resulted in little change, contrary to related studies with catalyst **1**. In contrast, the rate of reaction was dramatically slowed by increasing the size of the distal alkene substituent (Table 2, entries 2-6).[16] As expected, changing the geometry of the allylic imidate provided the allylic amide product of opposite absolute configuration. In an attempt to produce rearranged allylic amide products with more readily cleaved nitrogen substituents, *N*-benzoyl-benzimidates[17] and trichloroacetimidates[1] were examined and found to undergo rearrangement only slowly and with low enantioselectivity (Table 2, entries 8 and 9).

Table 2. Rearrangement of allylic imidates (0.1 M) to allylic amides with 5 mol% **6f** in CH_2Cl_2.[a]

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

[a]Room temperature except for entries 6 and 8 (40 °C). [b]Absolute configuration tenatively assigned as *R* in analogy[3] with amide **3** (entries 1 and 7). [c]Ar = 4-$CF_3C_6H_4$. [d]NMR yield.

In summary, ferrocenyl palladacycles are superior to the palladium diamine catalysts we had reported earlier as asymmetric catalysts for the rearrangement of allylic imidates. The marked difference in enantioselectivity observed between benzylpalladacycles **4** and **5** and ferrocenylpalladacycles **6** and **7** is consistent with the enantioselective step being coordination of the C–C π-bond of allylic imidates by an associative pathway. We anticipate that planar chiral palladacycle catalysts will have numerous applications for activating alkenes for asymmetric addition of external nucleophiles. Our ongoing efforts to further optimize this catalyst class will be reported in due course.

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2. Representative examples are cited in reference 3.
3. Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449.
4. (a) Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909. (b) For a recent review with leading references see: Canty, A. J. in *Comprehensive Organometallic Chemistry II* **1995**, *9*, 242-248.
5. We speculate that coordination of the imidate nitrogen with the cationic metal center promotes the competing ionization reaction observed with catalysts such as **1**.
6. Cross, R. J. *Adv. Inorg. Chem.* **1989**, *34*, 219.
7. Purchased from Aldrich Chemical Company.
8. Kuzmina, L. G.; Struchkov, Y. T.; Troitskaya, L. L.; Jokolov, V. I.; Reumov, O. A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1979**, 1528.
9. This complex forms with complete diastereoselectivity at nitrogen.
10. (a) Sokolov, V. I.; Troitskaya, L. L.; Reutov, J. *J. Organomet. Chem.* **1977**, *133*, C28. (b) Sokolov, V. I.; Troitskaya, L. L.; Reutov, J. *Dokl. Akad. Nauk SSSR* **1977**, *236*,371. (c) Lopez, C.; Bosque, R.; Solans, X.; Font-Bardia, M. *Tetrahedron: Asymm.* **1996**, *7*, 2527. (d) This latter paper reports the stereoselective preparation of **6a** by cyclopalladation, in contrast to previous reports[10a] and to our findings. We have independently reproduced the Russian reports[10a,b], and corroborated by reaction with Tl(acac) that the second isomer is that due to activation of the diastereotopic proton on the ferrocene ring.[11]
11. Details of single crystal X-ray structures for **6a**, **6f** and the acac complex derived from **7a** will be reported elsewhere.
12. In attempts to improve enantioselectivity, a number of solvents were screened with catalyst **6f**: hexane (3 d, 65%, 69% ee), Et_2O (3 d, 77%, 69% ee), THF (3 d, 92%, 63% ee), toluene (3 d, 87%, 64% ee), C_6H_6 (3 d, 89%, 64% ee), MeCN (6 d, 13%, 62% ee), MeOH (6 d, 42%, 35% ee), DMF (6 d, 55%, 44% ee), and $MeNO_2$ (6d, 76%, 50% ee). While slight improvement in enantioselectivity was observed with hexane and Et_2O, the rearrangement of **2** to **3** was significantly slower in all solvents evaluated than in CH_2Cl_2. The *N,N*-diethyl analogs of **6a** and **6f** were also prepared[11] and found to be poor catalysts for the rearrangement of **2**, producing **3** in 15% yield (59% ee) after 10 d and 55% yield (20% ee) after 2 d, respectively.
13. Hockless, D. C. R.; Gugger, P. A.; Leung, P.-H.; Mayadunne, R. C.; Pabel, M.; Wild, S. B. *Tetrahedron* **1997**, *53*, 4083.
14. Typical catalysis: (*1S*)-bis-μ-trifluoroacetato-*ab*,*fe*-bis[2-(*1'R*)-(dimethylamino)ethyl)ferrocenyl*C*,*N*]-dipalladium(II),**6f**, (2.0 mg, 0.0021 mmol), (*E*)-2-Hexenyl *N*-phenylbenzimidate (**2**,14.8 mg), and CH_2Cl_2 (0.5 mL) were combined and left to stand for 24 h. The solution was concentrated and the residue was chromatographed on silica gel (4% EtOAc-hexanes) yielding 3-(*N*-Phenyl)-1-hexenylbenzamide (**3**, 14.3 mg, 97%). Enantiopurity was determined by HPLC analysis using a Chiracel AS column (96:4 hexanes–*i*-propanol).
15. Imidates were prepared by standard procedures; see reference 3 for leading references.
16. The *t*-Bu-substituted imidate (Table 2, entry 6) did not rearrange even using $PdCl_2(MeCN)_2$ as catalyst.
17. Overman, L. E.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 2288.

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