High Enantioselection in the Rearrangement of Allylic Imidates with Ferrocenyl Oxazoline Catalysts

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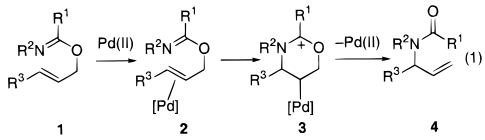
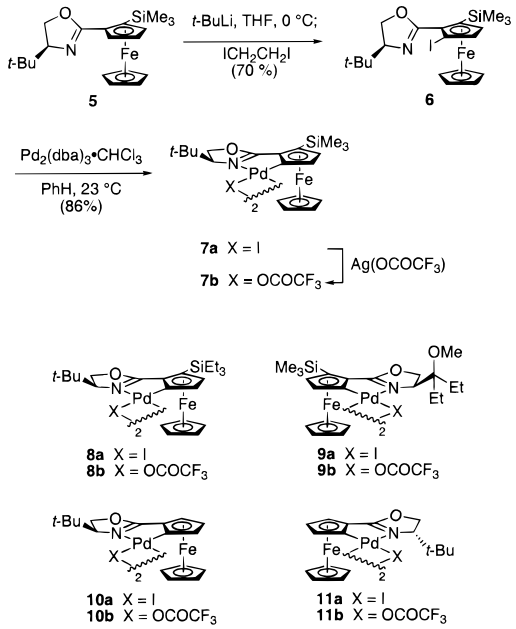
Current investigations in these laboratories focus on the development of asymmetric catalysts for the addition of external (nonmetal bound) nucleophiles to prochiral alkenes. As an entry point to this area, we have been investigating the Pd(II)-catalyzed rearrangement of allylic imidates to allylic amides (eq 1).[1] Substantial evidence points to a cyclization-induced rearrangement mechanism for this reaction in which a pivotal step is attack of the imidate nitrogen onto a palladium-complexed alkene **2**.[2] Subsequent deoxypalladation of **3** yields the rearranged amide **4** and regenerates the Pd(II) catalyst.

The first asymmetric catalysts described for this synthetically important rearrangement were cationic Pd(diamine) and Pd(bis-oxazoline) complexes[1a] that, like cationic complexes containing phosphine and oxazoline ligands,[3] gave the rearranged amides in moderate yield and enantioselectivity. The major competing reaction was ionization of the allylic imidate, presumably promoted by coordination of the imidate nitrogen to the cationic palladium catalyst. Our most recent work has demonstrated the potential of asymmetric Pd(II) catalysts having anionic ferrocenyl ligands.[1b,c] These neutral catalysts promoted the rearrangement of allylic *N*-arylbenzimidates in high yield within hours at room temperature, although enantioselectivity was still moderate. In this paper, we report a new family of cyclopalladated catalysts bearing ferrocenyl-oxazoline ligands which catalyze the rearrangement of allylic imidates in high efficiency at convenient rates and with the highest enantioselectivities (up to 96% ee) reported to date.



The synthesis of the ferrocenyl oxazoline palladacycles relies on the high-yielding oxidative addition of Pd(0) to the corresponding iodide as the key step and is exemplified in the synthesis of complex **7a** (Scheme 1).[4] Thus, ortholithiation of the known enantioenriched oxazoline complex **5**, a 30:1 mixture of diastereoisomers,[5] followed by reaction with diiodoethane provided iodide **6** as a single stereoisomer in 70% yield after recrystallization. A deficiency of *tert*-butyllithium was employed to minimize side products resulting from dilithiation of **5**.[6] Treatment of **6** with $Pd_2(dba)_3$•$CHCl_3$ then provided the iodide-bridged dimer **7a** in 86% yield. Ferrocenyl oxazoline complexes **8a**−**11a** were

Scheme 1



prepared in a similar fashion.[7] Complexes **7a**−**11a** were stable, highly crystalline solids which could be chromatographed on silica gel or florisil. The sequence illustrated in Scheme 1 is sufficiently efficient to conveniently provide these complexes in multigram quantities. Moreover, the presence of crystalline intermediates along this route allowed for easy diastereomer separation at various stages. Alternate approaches to this family of catalysts involving cyclopalladation or transmetalation were much less successful, presumably because the Pd(II) salts employed in these procedures promoted oxidative decomposition of the ferrocene unit.[8] The structures of complexes **7a** and **9a** were confirmed by X-ray crystallography.[9]

These novel palladacycle catalysts were initially evaluated for the rearrangement of (*E*)- and (*Z*)-2-hexenyl-*N*-(4-trifluoromethylphenyl)benzimidates (**12** → **13**, eq 2). Although iodide-bridged complex **7a** was inactive, 5 mol % of the trifluoroacetate complexes **7b**−**11b**, generated in situ by reaction of the corresponding iodide-bridged dimer with 2 equiv of $Ag(OCOCF_3)$, promoted the rearrangement of **12** in CH_2Cl_2 at room temperature.[10] Several trends are evident in Table 1. All catalysts except **10b** show higher enantioselectivity for rearrangement of the *Z* stereoisomer of **12**. With the silyl-containing catalysts **7b**−**9b**, benzamide **13** is produced in 90% ee or greater from (*Z*)-**12**. Catalyst **9b** gives the opposite enantiomer of **13** to that produced by the "pseudo" enantiomeric catalysts **7b** or **8b**. For both imidate stereoisomers, increasing the size of the oxazoline substituent from *tert*-butyl to 3-methoxy-3-pentyl had no discernible effect on enantioselectivity, although reaction rate was somewhat decreased.

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(3) Uozumi, Y.; Kato, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1065.

(4) For other examples of the use of oxidative addition for the synthesis of palladacycles, see: (a) Denmark, S. E.; Stavenger, R. A.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375. (b) Mateo, C.; Cardenas, D. J.; Fernandez-Rivas, C.; Echavarren, A. M. *Chem.—Eur. J.* **1996**, *2*, 1596.

(5) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10.

(6) These conditions are adapted from the following: Rebiere, F.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1990**, *31*, 3121.

(7) Experimental details for preparing these catalysts and their characterization data are provided in the Supporting Information.

(8) For a review of palladacycle synthesis, see: Canty, A. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 9, pp 242−248.

(9) The authors have deposited coordinates for these compounds with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(10) The trifluoroacetate complexes generated in this way were much less stable than the iodide-bridged dimers and consequently were directly employed without purification. ^{1}H NMR data for **7b**: (300 MHz, CD_2Cl_2) δ 5.14 (d, J = 1.9 Hz 1 H), 4.76 (dd, J = 8.9, 2.9, 1 H), 4.60 (app t, J = 8.9 Hz, 1 H), 4.36 (s, 5 H), 4.24 (br m, 1 H), 3.69 (dd, J = 8.5, 2.9 Hz, 1 H), 0.95 (s, 9 H), 0.22 (s, 9 H).

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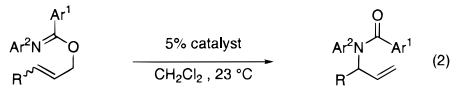
Table 1. Enantioselective Formation of Amide **13** from Imidate **12**[a]

entry	catalyst	imidate	time	yield,%	ee,%[b]/conf.
1	**7b**	*E*	2 d	57	79/*S*
2	**7b**	*Z*	3 d	67	91/*R*
3	**8b**	*E*	63 h	76	76/*S*
4	**8b**	*Z*	6 d	89	90/*R*
5	**9b**	*E*	3 d	95	72/*R*
6	**9b**	*Z*	6 d	81	92/*S*
7	**10b**	*E*	2 d	77	69/*S*
8	**10b**	*Z*	2 d	15	49/*R*
9	**11b**	*E*	2 d	86	8/*S*
10	**11b**	*Z*	3 d	28	53/*R*
11[c]	**7** (X = Cl)	*E*	3 d	<10	79/*S*

[a] Reaction conditions are shown in eq 2. [b] Determined by HPLC analysis (see ref 1a). [c] This reaction was run in MeCN at 40 °C.

Changing the ferrocenyl silyl substituent from $SiMe_3$ to $SiEt_3$ also did not significantly affect enantioselectivity. However, catalyst stability[11] and enantioselectivity were markedly eroded when this substituent was not present as in **10b** (compare entries 1−6 to 7 and 8). Enantioselectivity was also poor with catalyst **11b** in which the oxazoline substituent has an endo orientation with respect to the CpFe unit. It is interesting to note that the chloride-bridged dimer analogue of **7a**,[12] although a poor catalyst in terms of rate, gave **13** with the same enantioselectivity as the trifluoroacetate derivative **7b**.



(2)

12 Ar^1 = Ph, Ar^2 = 4-$CF_3C_6H_4$, R = *n*-Pr **13**

14 Ar^2 = 4-$MeOC_6H_4$, Ar^1 and R (Table 2) **15**

In searching for imidate substrates that would give amide products having potentially removable substituents on nitrogen, (*E*)-3-hexenyl trichloroacetimidate and the corresponding (*Z*)-3-hexenyl *N*-benzoylbenzimidate were investigated. The former gave the allylically transposed trichloroacetamide in only 43% ee and at an impractical rate with 5% **7b** (50% conversion after 6 d at 40 °C), whereas rearrangement of the latter substrate was not catalyzed by 5% of **9b**.

Changing the nitrogen substituent to 4-methoxyphenyl was more successful as this modification increased the rearrangement rate without loss in enantioselectivity. Our initial investigations of the scope of the rearrangement of allylic *N*-(4-methoxyphenyl)-arylimidates (**14** → **15**, eq 2) with catalyst **7b** are summarized in Table 2.[13] In all cases, the *Z* stereoisomer of the imidate rearranges with higher enantioselection than the *E* stereoisomer. The rearranged allylic amide **15** was produced with excellent enantioselectivity (86−96% ee) from (*Z*)-imidates **14** having a variety of 3-alkyl substituents (entries 2, 4, and 6−11). Changing the imidoyl substituent from Ph to *o*-tolyl resulted in a decrease in rate; however, enantioselection was unaffected (entries 6 and 7). Enantioselection is lowest (75% ee) when the 3-substituent is Me (entry 3) and highest (up to 96% ee) when the 3-substituent is primary and β-branched (entries 6−11). Although increasing the size of the 3-substituent to neopentyl or *iso*-propyl caused a reduction in rate, enantioselectivity remained high (entries 9−11).

Table 2. Enantioselective Formation of Amides **15** from Imidates **14** with Catalyst **7b**[a]

entry	imidate	R	Ar^1	time, h	yield,%	ee,%[b]/conf.[c]
1	*E*	*n*-Pr	Ph	18	93	83/*S*
2	*Z*	*n*-Pr	Ph	21	83	91/*R*
3	*Z*	Me	Ph	15	96	75/*R*
4	*Z*	Bn	Ph	23	85	88/*R*
5	*E*	*i*-Bu	Ph	25	97	84/*S*
6	*Z*	*i*-Bu	Ph	25	89	96/*R*
7	*Z*	*i*-Bu	*o*-Tol	38[d]	97	96/*R*
8	*Z*	$CH_2C_6H_{11}$[e]	Ph	26	87	90/*R*
9	*Z*	neopentyl	Ph	89	35	92/*R*
10[f]	*Z*	neopentyl	Ph	47	77	87/*R*
11[f]	*Z*	*i*-Pr	Ph	72	59	86/*R*
12	*E*	Ph	Ph	26	59	63/*R*
13	*Z*	Ph	Ph	20	11	77/*S*

[a] Reaction conditions are shown in eq 2. [b] Determined by HPLC analysis (see Supporting Information). [c] Absolute configuration was assigned in analogy to entry 3. [d] This reaction was run for 19 h at 23 °C and 19 h at 40 °C. [e] C_6H_{11} = cyclohexyl. [f] This reaction was run in toluene at 75 °C.

To obtain practical rates in these latter cases, the reaction was best run at 75 °C in toluene, which resulted in a slight diminution of enantioselectivity (entries 10 and 11). The cinnamyl derivatives were poor substrates, rearranging slowly and with low ee (entries 12 and 13). In all cases where direct comparisons can be made, (*E*)- and (*Z*)-imidates gave amides **15** of opposite configuration. The absolute configuration of **15** (R = Me, Ar^1 = Ph) produced in entry 3 was established by chemical correlation with (*R*)-*N*-benzoylalanine methyl ester;[14] absolute configurations of the other products reported in Table 2 were assigned by analogy.

In summary, the novel ferrocenyl oxazoline palladacycles described here are the best asymmetric catalysts discovered to date for the rearrangement of allylic imidates to allylic amides. With (*Z*)-allylic *N*-(4-methoxyphenyl)benzimidates, enantioselectivities of >90% ee can be realized in many cases. The usefulness of this route to enantioenriched amines would be markedly increased if the nitrogen substituents of the product allylic amide were more easily removed than benzoyl and 4-methoxyphenyl. Studies to address this deficiency as well as to extend this structurally novel family of Pd(II) catalysts to other reactions involving the addition of nucleophiles to prochiral alkenes are in progress.

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Supporting Information Available: Experimental procedures for preparing **6**, **7a**−**11a** and for catalytic rearrangements and analytical data for new imidates **14** and amides **15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Catalysts **10b** and **11b** were markedly less stable than catalysts **7b**−**9b** as signaled by the deposit of a black solid during the catalytic reactions reported in Table 1, entries 7−10.

(12) This chloride-bridged dimer was prepared in low yield by treatment of the corresponding (chlormercuric)ferrocene with $PdCl_2(CH_3CN)_2$.

(13) Analogues of **7b** having tosylate, *p*-nitrophenylsulfonate, and nitrate counterions performed similarly. Iodide **7a** was a poor catalyst rearranging (*Z*)-**14** (R = *n*-Pr, Ar^1 = Ph) to **15** (R = *n*-Pr, Ar^1 = Ph) in 20% yield and 41% ee after 5 days in CH_2Cl_2. Attempted formation of a triflate catalyst by treatment of **7a** with AgOTf resulted in apparent catalyst decomposition. Toluene was also a suitable reaction solvent, although reaction times were somewhat longer.

(14) This conversion was accomplished by ozonolysis,[15] to give *N*-benzoyl−*N*-(4-methoxyphenyl)alanine methyl ester in 65% yield, followed by cleavage of the 4−methoxyphenyl group (10% yield) by treatment with ceric ammonium nitrate:[16] $[\alpha]^{26}_D$ −22.6 (*c* 0.16, $CHCl_3$); ref 17, (S)-enantiomer (54% ee): $[\alpha]^{20}_D$ +20.9 (*c* 1.0, $CHCl_3$).

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