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Preparation of bis[palladacycles] and application to asymmetric aza-Claisen rearrangement of allylic imidates

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Abstract—A variety of optically active bis[palladacycles] **1**–**3** were prepared from ferrocene. The synthetic application of these chiral catalysts in asymmetric aza-Claisen rearrangement of allylic imidates was carried out with high enantioselectivity. © 2002 Elsevier Science Ltd. All rights reserved.

Bimetallic species are potentially bidentate Lewis acids,[1] and they can bring the Lewis-basic reactants together into the reaction center if certain requirements are met. Herein is reported a synthesis of several bis(palladacycles). Palladacycles **1**–**3** (Fig. 1) were designed for stabilization by tri-coordination[2] to the ligand backbone of varying degrees of ligating power, and they were applied to a catalytic asymmetric reaction.

These palladacycles **1**–**3** (X = I) were prepared by reacting $Pd_2(dba)_3$–$CHCl_3$ with the corresponding iodides. The preparation process is detailed below. The known diamine **4**[3] was metalated and iodinated with iodine to give the diiodide **5** in 67% yield. Subsequent quarternization with MeI followed by substitution with *N*,*N*,*N*′-trimethylenediamine provided the tetraamine **6** in 65% yield (acetoxylation of **5**, instead of quarternization, followed by amination gave similar yields). Finally, formation of the palladacycle **1** through double oxidative addition of $Pd_2(dba)_3$–$CHCl_3$ (1.2 equiv.) to the diiodide **6** in benzene at rt for 18 h was achieved in 25% yield after usual work-up and recrystallization (Scheme 1).

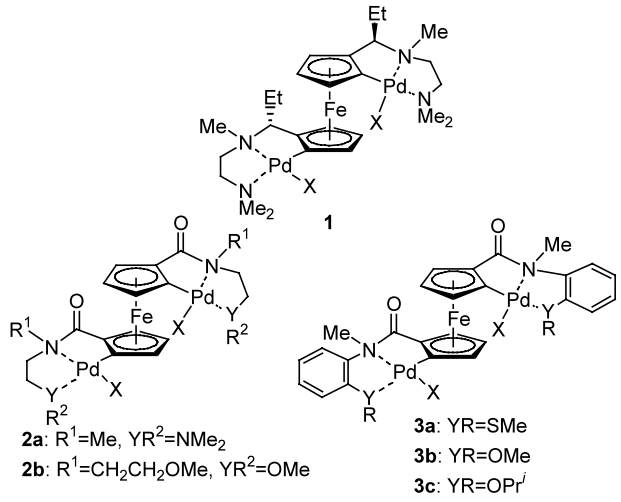
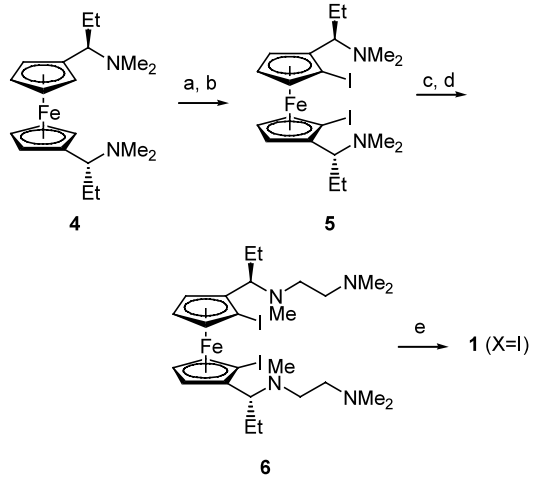


Figure 1. Bis(palladacycle) catalysts examined.



Scheme 1. Preparation of palladacycle **1**. *Reagents and conditions*: (a) *n*-BuLi (3 equiv.), ether, rt, 12 h; (b) I_2 (3 equiv.), THF, −78°C to rt (67%); (c) CH_3I (9 equiv.), acetone, 0°C, 30 min (99%); (d) $MeNHCH_2CH_2NMe_2$ (12 equiv.), CH_3CN, 50°C, 18 h (65%); (e) $Pd_2(dba)_3$–$CHCl_3$ (1.2 equiv.), PhH, rt, 18 h (25%).

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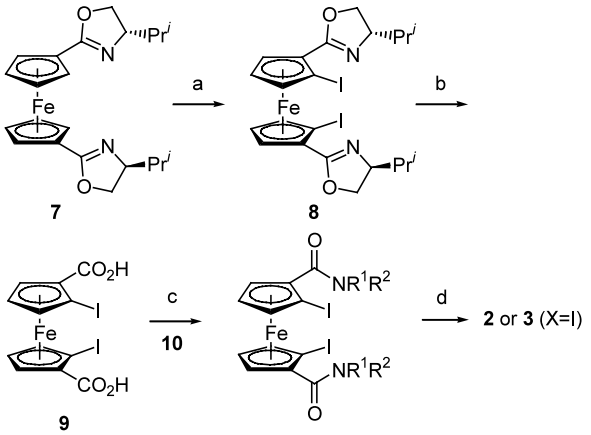
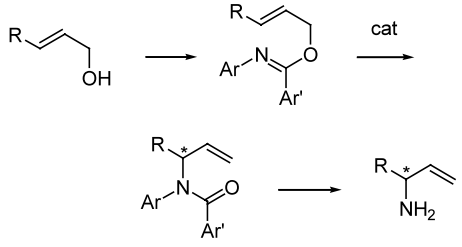
Amidopalladacycles, **2** and **3**,[†] were prepared as shown in Scheme 2. Thus, the chiral 1,1′-bis(oxazolinyl)-ferrocene **7** was metalated with *sec*-BuLi, and the resulting lithio species was iodinated with ethylene diiodide to give the diiodide **8** in 55% isolated yield, following the known procedure.[4] The undesired diastereoisomeric diiodide formed in ca. 15% yield could be easily removed by silica gel column chromatography and recrystallization. In a three-step sequence (first, hydrolysis with TFA and sodium sulfate, second, acetylation of the resulting crude amine with acetic anhydride, and, finally, saponification with NaOH in aqueous methanol at rt for 12 h),[5] the oxazoline moiety in the diiodide **8** was converted to the corresponding diacid **9** in 90% yield. Subsequently, it was treated with oxalyl chloride followed by treatment of the resulting acid chloride with various amines **10** afforded the corresponding tertiary amides **11** in excellent yields. The palladacycle **2** and **3** were obtained as a brown solid by oxidative additionof $Pd(dba)_3$–$CHCl_3$ with amide **11** in benzene at room temperature and were purified by recrystallization with ethyl acetate.



Scheme 2. Preparation of palladacycles **2** and **3**. *Reagents and conditions*: (a) (1) *sec*-BuLi (3 equiv.), THF, −78°C, 3 h, (2) ICH_2CH_2I (6 equiv.), THF, −78°C to rt (55%); (b) (1) TFA (10 equiv.), Na_2SO_4 (100 equiv.), THF/H_2O, 30°C, 24 h, (2) Ac_2O (80 equiv.), pyridine (152 equiv.), CH_2Cl_2, rt, 20 h, (3) NaOH (40 equiv.), CH_3OH/H_2O, rt, 12 h (84% for three steps from **8**); (c) (1) $(COCl)_2$ (5 equiv.), DMF(cat), CH_2Cl_2, rt, 1 h, (2) amine [$MeNHCH_2CH_2NMe_2$ (**10a**) (67%), $HN(CH_2CH_2OMe)_2$ (**10b**) (98%), *N*-methyl-*o*-methylthioaniline (**10c**) (96%), *N*-methyl-*o*-methoxyaniline (**10d**) (99%) or *N*-methyl-*o*-isopropoxyaniline (**10e**) (80%)], THF, 0°C to rt, 12 h; (d) $Pd_2(dba)_3$–$CHCl_3$ (1.2 equiv.), PhH, rt (**2a** 77%; **2b** 58%; **3a** 50%; **3b** 54%; **3c** 72%).

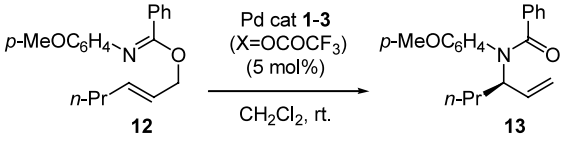
With these catalysts in hands, catalytic [3,3]-sigmatropic rearrangements of allylic imidates[6] (Scheme 3) were attempted to benchmark our catalysts among many reactions catalyzed by palladacycles.[7]

As noted earlier,[6] the iodides **1**–**3** (X = I) were not effective at all for the rearrangements. More importantly, even the tri-coordinated nature of our catalysts did not tolerate appropriate stability of 'free' cation, which was generated from the iodides **1**–**3** (X = I) and Ag(I) salts such as $AgBF_4$, $AgPF_6$, etc. Accordingly, trifluoroacetate salts **1**–**3** ($X = OCOCF_3$) were generated in situ by stirring the corresponding iodide species with an excess of silver trifluoroacetate in dichloromethane at rt.



Scheme 3.

Table 1. Enantioselective rearrangements of allylic imidate **12** with various catalysts

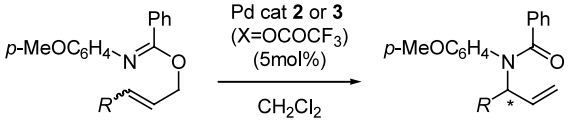


Entry	Pd cat. ($X = OCOCF_3$)	Time (h)	Yield[a] (%)	% ee[b] (conf.[c])
1	**1**		NR	
2	**2a**	60	30	49 (*R*)
3	**2b**	12	74	67 (*R*)
4	**3a**	40	27	64 (*R*)
5	**3b**[d]	12	83	87 (*R*)
6	**3c**	0.5	91	92 (*R*)

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] Determined by optical rotation.[6b]
[d] 3.5 mol%.

[†] Spectroscopic data for the key catalyst **3c** and its precusor **11e**.
Compound **11e** : brown oil; $[\alpha]_D^{25} = +42.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.20–1.50 (m, 12H, *i*-Pr), 3.61 (d, 6H, $J = 18.0$ Hz, NCH_3), 3.33 (bs, 2H, $CH(CH_3)_2$), 3.80–4.40 (m, 6H, FcH), 6.55–7.50 (m, 8H, Ph); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 22.1 (t, $J = 31.1$ Hz), 37.6, 69.6, 70.6, 71.9, 75.2, 80.3, 82.2 (t, $J = 77.5$ Hz), 112.8 (d, $J = 13.4$ Hz), 113.6, 120.3 (t, $J = 28.1$ Hz), 128.4 (m), 129.1, 129.9, 152.6, 167.2. Anal. calcd for $C_{32}H_{34}FeI_2N_2O_4$: C, 46.86; H, 4.18; N, 3.42. Found: C, 47.39; H, 4.31; N, 3.47%.
Compound **3c** : brown solid; mp 229–231°C (dec.); $[\alpha]_D^{25} = +380.6$ (*c* 0.036, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 1.34–1.44 (m, 6H), 1.50–1.58 (m, 6H), 2.41–2.58 (m, 2H), 3.42–3.52 (m, 6H), 3.62–3.72 (m, 4H), 4.77 (bs, 2H), 6.80–7.22 (m, 8H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 21.82, 22.11, 22.61, 22.83, 38.36, 67.16, 67.96, 69.30, 70.99, 81.54, 114.13, 120.35, 128.38, 128.95, 130.49, 143.32, 153.07, 153.97, 179.11. Anal. calcd for $C_{32}H_{34}FeI_2N_2O_4Pd_2$: C, 37.20; H, 3.32; N, 2.71. Found: C, 37.27; H, 3.29; N, 2.53%.

Table 2. Enantioselective rearrangements of allylic imidates with palladacycles **2a**, **3b** and **3c**



Entry	R	Pd cat.	Temp. (°C)	Time (h)	Yield[a] (%)	% ee[b] (conf.[c])
1	Pr^n (*E*)	**2b**	rt	12	74	67 (*R*)
2	Pr^n (*Z*)	**2b**	0	120	43	68 (*S*)
3	Ph (*E*)	**2b**	0	113	69	40 (*S*)
4	Pr^n (*E*)	**3b**[d]	rt	12	83	87 (*R*)
5	Pr^n (*Z*)	**3b**[d]	rt	13	73	82 (*S*)
6	Bu^i (*E*)	**3b**[d]	rt	41	65	89 (*R*)
7	Bu^i (*Z*)	**3b**[d]	rt	13	54	72 (*S*)
8	Ph (*E*)	**3b**[d]	rt	13	63	67 (*S*)
9	Pr^n (*E*)	**3c**	rt	0.5	91	92 (*R*)
10	Pr^n (*Z*)	**3c**	rt	12	85	90 (*S*)
11	Bu^i (*E*)	**3c**	rt	10	74	95 (*R*)
12	Bu^i (*Z*)	**3c**	rt	10	70	86 (*S*)
13	Ph (*E*)	**3c**	rt	1	90	87 (*S*)
14	Me (*E*)	**3c**	rt	12	68	90 (*R*)

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] Determined by optical rotation.[6b]
[d] 3.5 mol%.

With the chiral trifluoroacetate palladacycle catalysts, the rearrangement was carried out at room temperature (Table 1). The stereochemical outcome of the reaction was uniform. And more importantly, the reactivity and enantioselectivity with catalysts were low, as expected, with amine and thioether functional groups, which contain strong ligating atoms. Noteworthy were the outcomes from the ether amide catalysts, **2b** and **3c**, in that bulkier isopropyl ether catalyst **3c** gave the highest reactivity and enantioselectivity (Table 1).

Various allylic imidates were subjected to the asymmetric rearrangement in the presence of a palladacycle catalyst, **2a**, **3b** or **3c**, and the results are summarized in Table 2. As seen in the previous table, the catalyst **3c** gave the best rate and enantioselection. And surprisingly, though, a very short reaction time was required, and no side reaction occurred as in the entries 9 and 13. Besides, the high enantioselectivity was not much affected by *E*/*Z* configuration of substrates, which is also in good contrast to the Overman's report in terms of reactivity and enantioselectivity.[6b]

Presumably, the relatively bulkier isopropoxy group together with the conformational rigidity of the *o*-phenylene tether created a more chiral environment, and, thus, induced the higher enantioselectivity.

But, as noted above, the bis(palladacycle) **3c** is better than the mono(palladacycles), such as **14** and **15**[9] (Fig. 2); Overman's mono(palladacycle) catalyst **14** was much better than the tridentate mono(palladacycle) **15** (Table 3). Additionally, the tridentate mono(palladacycle) **15** was unstable during the reaction, decomposing to a black precipitate and also giving a relatively lower yield and enantioselection.

As for the mechanism of this reaction, we believe that the cyclization-induced rearrangement (CIR) mechanism (Scheme 4) proposed by Overman[6,8] still operates although the minute details may be different.

Based on the above results, the stereochemical consequences of the reaction can be explained by the following working model in which 1) one of the Pd atoms present in the bis[palladacycle] **3c** coordinates to alkene

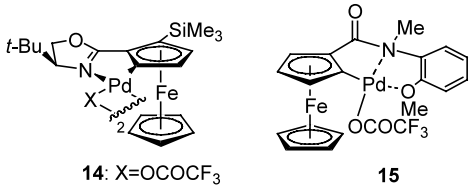
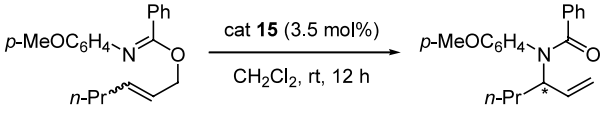


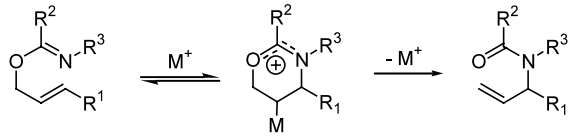
Figure 2.

Table 3. Enantioselective rearrangements of allylic imidates with mono-palladacycle **15**

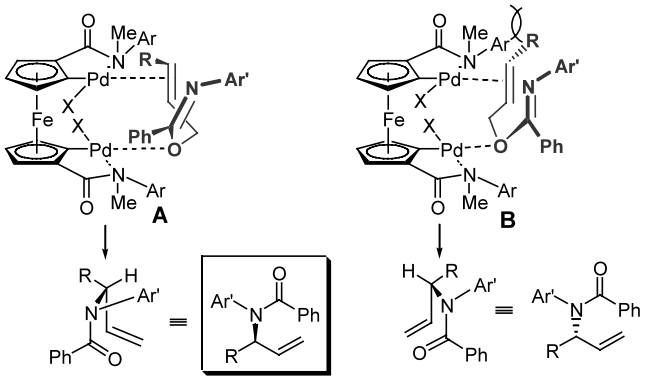


Entry	Stereochem. (imidate)	Yield[a] (%)	% ee[b] (conf.[c])
1	*E*	32	30 (*R*)
2	*Z*	10	34 (*S*)

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] Determined by optical rotation.[6b]



Scheme 4. CIR mechanism of rearrangement of allylic imidates.



Scheme 5.

moiety, 2) the remaining second Pd atom is bound to the oxygen in the imidate moiety, 3) finally, out of the two possible transition states, the reaction proceeds to furnish R isomers through the adduct **A** in which there is no serious steric interaction is present whereas there is serious steric repulsions between the alkyl group in the imidate and *N*-alkyl groups of the amide may be present in the alternative form **B**. Although one should await for concrete evidence to support this, the bis[palladacycle] is designed to be a bidentate Lewis acid and thus behaves as a template to bring the reacting centers together. Additionally, the isopropoxy group stabilizes the complex and then becomes a spectator during the catalytic cycle (Scheme 5).

In conclusion, we have prepared a series of optically active homogeneous bis[palladacycles] and discovered that the isopropoxy compound **3c** is an excellent catalyst in the catalytic asymmetric rearrangement of allylic imidates.

Acknowledgements

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References

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9. Compound **15** was prepared in the same manner as the bis-(palladacycle) **3b** with diastereoselective *ortho*-lithiation and subsequent iodination by the known method[10] as a key step (a diastereomeric ratio of up to 100:1 as determined by ^{1}H NMR and HPLC).
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