Asymmetric Catalysis

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A Highly Enantioselective Overman Rearrangement through Asymmetric Counteranion-Directed Palladium Catalysis**

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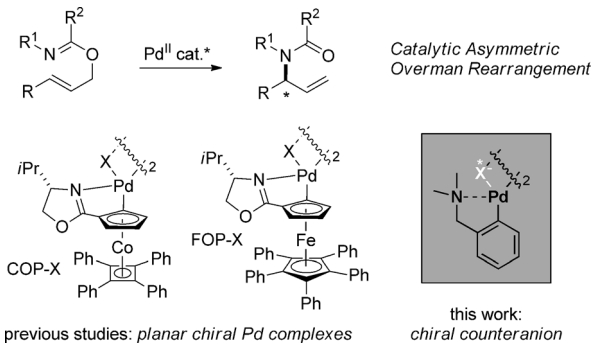
The Overman rearrangement is an important method for the construction of allylic amine derivatives from allylic imidates and has found widespread application in organic synthesis.[1] Since the first enantioselective version of this Pd^{II}-catalyzed aza-Claisen-type rearrangement appeared in 1997,[2] significant progress has been marked by the introduction of the oxazoline-based palladacycle catalysts COP-X[3] and FOP-X[4] (Scheme 1). The success of these catalysts is based on



Scheme 1. The ACDC approach for the Overman rearrangement.

their planar chiral sandwich motif, a drawback of which is their required multistep synthesis. Considering the well-established Pd^{II}-π-Lewis acid mediated cyclization-induced mechanism,[3,4] we were quickly attracted to extending and capitalizing on the potential of our asymmetric counteranion-directed catalysis (ACDC) concept.[5–10] We have recently applied this approach to Pd-catalyzed Tsuji–Trost-type reactions that bear some mechanistic resemblance.[8] Potentially, an ACDC strategy could ultimately be used to develop simplified and yet highly enantioselective catalysts. Here we report significant progress towards this goal with the development of a simple palladacyle catalyst that incorporates our chiral TRIP counteranion and catalyzes the Overman rearrangement with high enantioselectivity.

We anticipated that an ACDC strategy for the Overman rearrangement could take advantage of the fact that a chiral soft Pd–π-Lewis acid complex may be easily generable in situ from an achiral Pd halide through anion metathesis with readily available chiral C_2-symmetric phosphate anions. Such an approach would provide a complementary strategy to the existing ligand-dependent protocols based on planar chiral cobalt and iron sandwich complexes.

Indeed, our initial studies focused on identifying a palladium species capable of catalyzing the desired enantioselective rearrangement using the chiral TRIP counteranion, which is easily introduced by reacting its silver salt with a Pd–Cl species. As a model, we looked at the reaction of *N*-(*p*-methoxyphenyl)trifluoroacetimidate (**1a**), which was previously shown to undergo facile Overmann rearrangements by Overman et al.[3b,4a] and Peters et al.[4c,d] Indeed, when **1a** was treated with 1 mol% of $[PdCl_2(CH_3CN)_2]$ (**Pd1**) and 2 mol% of (*S*)-TRIP-Ag in $CHCl_3$ at 35°C for 40 h, the rearranged allylic amide **2a** was obtained in low yield (20%) but with non-negligible enantioselectivity (53:47 e.r.) (Table 1, entry 1).

While far from satisfactory, this initial result nonetheless indicated that our chiral counteranion strategy may indeed be feasible. Encouraged, we screened several simple palladacycles. Using oxazoline-containing palladacycle **Pd2**, efficient rearrangement can be achieved, albeit in still moderate enantioselectivity (Table 1, entry 2). Further investigations led to the discovery that cyclopalladated benzyl amines **Pd3**–**Pd5** are efficient and highly enantioselective catalysts (Table 1, entries 3–6).

Compared to **Pd3** and **Pd4**, the commercially available palladacycle (*S*)-**Pd5** gave excellent results in terms of reactivity and enantioselectivity (Table 1, entry 5). The corresponding mismatched complex generated from (*R*)-**Pd5** gave product **2a** in 94:6 e.r. (Table 1, entry 6). In the absence of TRIP-Ag, (*S*)-**Pd5** accelerated the rearrangement of **1a** to give racemic **2a** in near-quantitative yield, similar to the previous result reported by Overman and co-workers[11] (Table 1, entry 7). As expected, (*S*)-TRIP-Ag alone is completely inactive for the rearrangement (Table 1, entry 8). These results suggest that the Pd^{II} complex is indeed responsible for promoting the reaction, and more importantly, that the enantioselectivity is induced mostly by the chiral phosphate counteranion.

We next explored other substrates. As summarized in Table 2, the present method is particularly suited for *n*-alkyl-substituted allylic imidates. For instance, imidates **1b–g** underwent efficient rearrangement in high yields and enantioselectivities (Table 2, entries 1–6). Even with branched substituents, the rearrangement proceeded readily in high yields and enantioselectivity with only slightly higher catalyst loadings (Table 2, entries 7 and 8).

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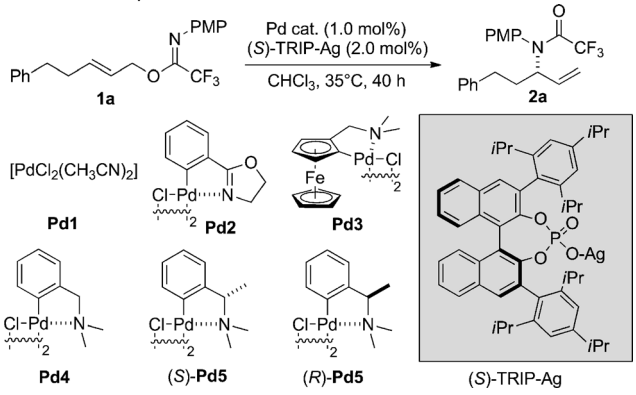
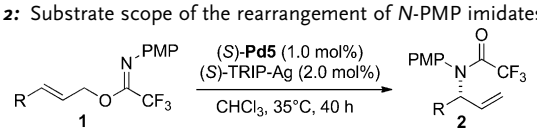
Table 1: Development of suitable reaction conditions.[a]

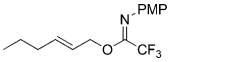
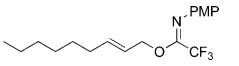
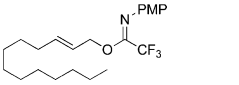
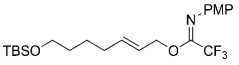
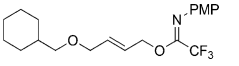
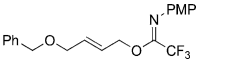
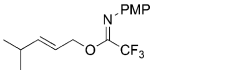
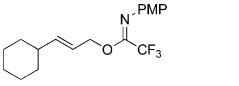
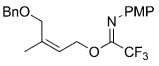
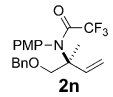


Entry	Cat.	Yield [%][b]	e.r.[c]
1	**Pd1**	20	53:47
2	**Pd2**	94	68:32
3	**Pd3**	93	93:7
4	**Pd4**	94	97:3
5	(*S*)-**Pd5**	93	99:1
6	(*R*)-**Pd5**	96	94:6
7[d]	(*S*)-**Pd5**	99	50:50
8[e]	–	n.r.[f]	–

[a] Reactions performed on 0.3 mmol scale. [b] Yield of isolated product. [c] Determined by HPLC after hydrolysis of **2a** to the corresponding amine (see the Supporting Information). [d] No Ag salt used. [e] Only Ag salt used. [f] No reaction.

Table 2: Substrate scope of the rearrangement of *N*-PMP imidates.[a]

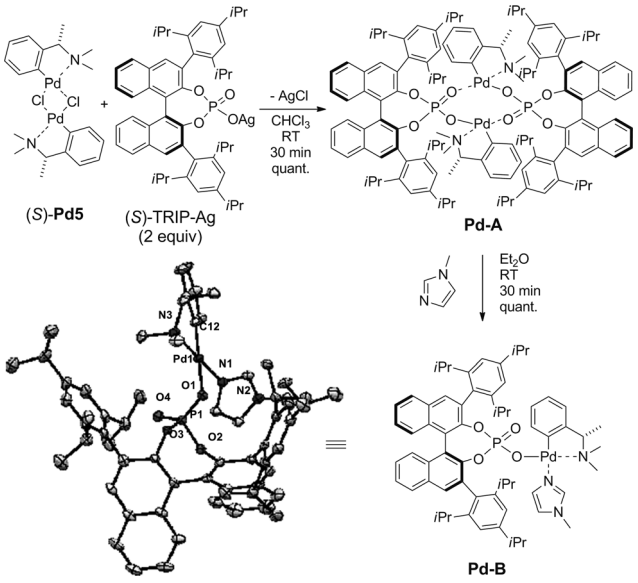


Entry	Substrate	Product	Yield [%][b]	e.r.[c]
1		**2b**	92	96.5:3.5
2		**2c**	96	98:2
3		**2d**	92	98:2
4		**2e**	97	94.5:5.5
5		**2f**	92	98.5:1.5
6[d]		**2g**	93	98:2
7[d]		**2h**	91	92:8
8[d]		**2i**	90	92:8
9	X = H	**2j**	92	95:5
10	X = F	**2k**	90	96:4
11	X = Cl	**2l**	93	99:1
12	X = Me	**2m**	97	92:8
13[d]		 **2n**	91	90:10

[a] Reactions performed on 0.3 mmol scale. [b] Yield of isolated product. [c] Determined by HPLC or GC with a chiral stationary phase (see the Supporting Information). [d] 2.0 mol% of (*S*)-**Pd5**, 4.0 mol% of (*S*)-TRIP-Ag, reaction time 60 h.

Importantly, we were pleased to find that in the case of challenging aryl-substituted trifluoroacetimidates, our new catalyst system gave significantly higher enantioselectivities than those obtained with FOP-X. Excellent enantioselectivities were achieved with all four cinnamyl alcohol derivatives **1j**–**m** studied (Table 2, entries 9–12).[4c] With these substrates we observe electronic effects on the enantioselectivity. For example, the introduction of electron-withdrawing groups such as *p*-F and *p*-Cl to the parent phenyl-substituted imidate leads to an increase in enantioselectivity. A mildly electron-donating group such as *p*-Me has a small negative effect on the enantioselectivity. The lower enantioselectivity previously obtained with such aryl-substituted trifluoroacetimidates has been explained with a non-enantioselective thermal background rearrangement.[4h] The high catalytic activity of our catalyst system may effectively outperform this uncatalyzed process. A β,β-disubstituted imidate was also investigated; it smoothly provided the allylic amide product **2n**, which has a quaternary stereogenic center, in high yield and with reasonably good enantioselectivity (Table 2, entry 13).

Finally, attempts were made towards isolating and structurally characterizing our proposed ion-pair catalyst. Accordingly, treating the (*S*)-**Pd5** dimer with 2.0 equivalents of (*S*)-TRIP-Ag in $CHCl_3$ at room temperature led to the rapid formation of a AgCl precipitate. After filtration and evaporation, a yellow foam was obtained in quantitative yield. The ^{31}P NMR spectrum of this compound shows a singlet resonance at 6.88 ppm in [D_6]DMSO (Scheme 2). This assignment is supported by the mass spectrum, which displays a signal corresponding to a fragmentation product that has lost one of the two bridging phosphates. Similar fragmentation patterns are also observed with the analogous acetate- and chloride-bridged dimers.[4i] Complex **Pd-A** indeed catalyzes the rearrangement of imidate **1b** to product **2b** and also that of substrate **1g** to amide **2g**; the yields and enantioselectivities are identical to those obtained with the in situ procedure. After many unsuccessful attempts to obtain single crystals of **Pd-A** suitable for X-ray structure determination, we found that when *N*-methylimidazole in Et_2O was added, an air-stable colorless precipitate formed rapidly and quantitatively. This material could be characterized as the monomeric Pd complex **Pd-B**; it displays a singlet at 8.19 ppm in [D_6]DMSO in the ^{31}P NMR spectrum and a $[M]^+$ signal at m/z 1087 in its mass spectrum. Moreover, suitable single crystals of **Pd-B** could be obtained and analyzed (Scheme 2). In the corresponding X-ray structure, it is noteworthy that the Pd1–N1 bond (2.034(4) Å) is slightly shorter than the Pd1–N3 bond , which suggests a stronger complexation between Pd and the imidazole ligand.[12] It is also apparent that the phosphate acts as an anionic Pd ligand (Pd1—O1 2.149(3) Å) rather than a



Scheme 2. Preparation of **Pd-A** and its derivative **Pd-B**. ORTEP representation of **Pd-B** (hydrogen atoms are omitted for clarity; ellipsoids are set at 30% probability).

"true" counteranion. As expected, **Pd-B** is catalytically inactive for the rearrangement of **1a** to **2a** as it lacks a vacant coordination site for the activation of the C=C bond of the substrate.

On the basis of the obtained structural information, we have devised models to rationalize the observed enantioselectivity. Accordingly, replacing the *N*-methylimidazole ligand with the olefin portion of the two enantiomeric precyclization conformations of substrate **1a** provides two diastereomeric transition states leading to the corresponding product enantiomers (Figure 1). Unfavorable steric interactions between the substituent of the coordinated olefin, and to a lesser extent of the N substituent, with the bulky substituent at the 3,3′-position of the phosphate moiety disfavor the pathway leading towards the *R* enantiomer (Figure 1, left). Similar destabilizing interactions are absent in the transition-state model leading to the corresponding *S* product, which is also experimentally the preferred product (Figure 1, right).

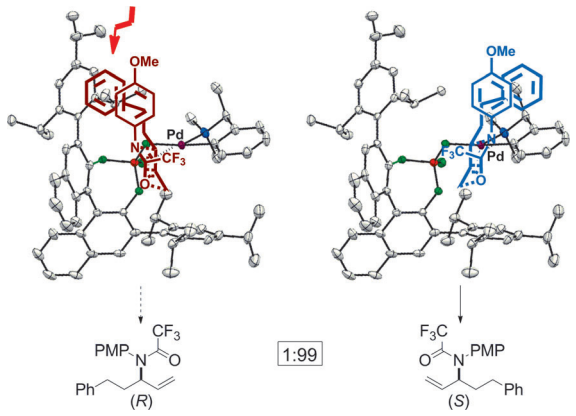


Figure 1. Reaction models rationalizing the observed enantioselectivity.

Obviously, our X-ray-structure-based model is speculative. Nonetheless, it qualitatively explains the observed stereoselectivity.

In summary, we have successfully extended the asymmetric counteranion-directed catalysis (ACDC) concept to the Pd catalysis of the asymmetric Overman rearrangement. Interestingly, the enantioselectivity was induced by the chiral phosphate anion even though the catalyst incorporates a chiral palladacycle. The X-ray structure of **Pd-B** can be used to create reasonable transition-state models that explain the origin of enantioselectivity. Further studies on the potential applications of this unique Pd complex are in progress.

Experimental Section

Under argon, (*S*)-**Pd5** (1.74 mg, 1.0 mol%) and (*S*)-TRIP-Ag (5.16 mg, 2.0 mol%) were stirred and dissolved in $CHCl_3$ (0.30 mL) in the absence of light. The mixture was stirred vigorously for 1 h at room temperature, then a solution of **1a** (109.0 mg, 0.30 mmol) in $CHCl_3$ (0.30 mL) was added at room temperature by syringe. The reaction flask was sealed under argon, protected from light, and maintained at 35 °C. After 40 h, the residue was diluted with CH_2Cl_2, filtered through a short Celite column, and concentrated. Purification of the residue by column chromatography on silica gel (hexane/EtOAc 10:1) afforded **2a** (101.3 mg; 93% yield) with 99:1 e.r. as determined by HPLC analysis after hydrolysis to the corresponding secondary amine.

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[12] Selected distances [Å] and angles [°]: Pd1–O1 2.149(3), Pd1–N1 2.034(4), Pd1–N3 2.075(4), Pd1–C12 1.968(4); N1-Pd1-O1 90.06(13), N1-Pd1-N3 176.96(15), N3-Pd1-O1 92.91(13), C12-Pd1-O1 174.72(15), C12-Pd1-N1 94.54(15), C12-Pd1-N3 82.54(16). For more crystallographic data, see the Supporting Information.

