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The effect of face-blocking in the enantioselective aza-Claisen rearrangement of allylic imidates

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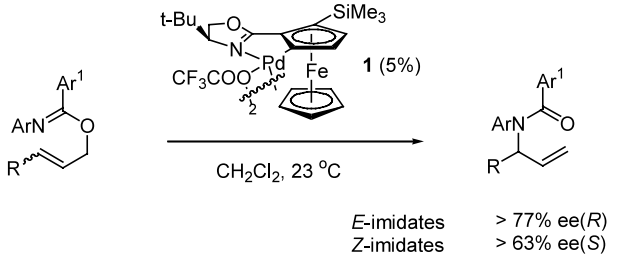
Abstract—A new cobaltocenyl oxazoline palladacycle compound was prepared for the enantioselective aza-Claisen rearrangement of allylic imidates. Studies on the effect of face-blocking and the mechanism of the reaction were carried out.

Asymmetric aza-Claisen rearrangements of allylic imidates provide enantiopure *N*-allylic amides with clean 1,3-transposition of the alkene moiety. Overman reported the first asymmetric catalysts for this useful reaction using cationic Pd(diamine) and Pd(bis-oxazoline) complexes, which gave moderate yields and enantioselectivities.[1] This was followed by development of cationic complexes containing phosphine and oxazoline Pd-catalysts[2] and more refined cyclopalladated catalysts bearing ferrocenyl-oxazoline ligands such as **1**.[3]

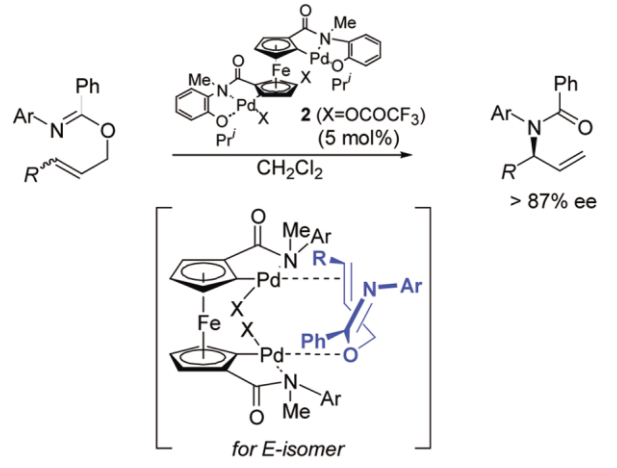
The stereochemical outcome of the reaction (Scheme 1) seem to be influenced chiefly by face-blocking of the unsubstituted lower Cp ring and the unsymmetrical environment of the coordination sphere around the Pd atom.

To test the first effect from the opposite direction, we have recently developed bis(palladacycle)s such as **2** as bidentate Lewis acid catalysts (which necessitate bidentate coordination, and thus minimize the effect of face-blocking) in asymmetric aza-Claisen rearrangements of allylic imidates.[4] This modification led to a considerable reduction in the reaction time, while the enantioselectivity increased significantly with (*E*)-allylic imidates but remained almost the same for (*Z*)-allylic imidates (Scheme 2).[4]

Herein, we report our further studies into the effect of face-blocking on the enantioselectivity of the reaction using a new readily available catalyst **3** which blocks the lower face completely.



Scheme 1.



Scheme 2.

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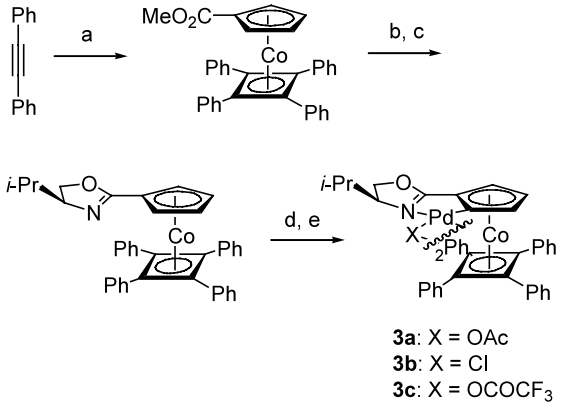
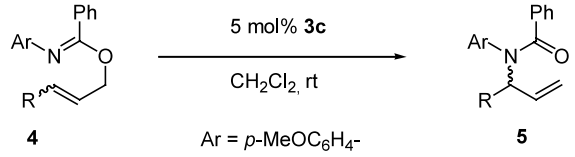
The known 2-(η^5-cyclopentadienyl)(η^4-tetraphenylcyclo-butadiene)cobalt oxazoline palladacycle catalyst **3a**, readily prepared in six steps from diphenylacetylene following the method of Richards,[5] was subjected to anion exchange by treatment with LiCl (LiCl, acetone, rt, 3 d)[6] to give the palladium chloride dimer **3b** in 88% yield (Scheme 3).[7]



Scheme 3. Preparation of cobaltocenyl oxazoline palladium catalyst. *Reagents and conditions*: (a) $[(Ph_3P)_3CoCl, Na^+[C_5H_4CO_2Me]^-$, toluene, reflux, 5 h (38%); (b) *t*-BuOK, DMSO, rt, 8 h, 83%; (c) i. oxalyl chloride, CH_2Cl_2, rt, 1 h; ii. (*S*)-Valinol, Et_3N, CH_2Cl_2, rt, 1 h (82% for 2 steps); iii. *p*-TsCl, Et_3N, CH_2Cl_2, rt, 12 h, 80%; (d) $Pd(OAc)_2$, AcOH, 95°C, 0.5 h, 61% (X = OAc); (e) LiCl, acetone, rt, 3 d, 88% (X = Cl).

Complexes **3a** and **3b** were inactive as catalysts. On the other hand, 5 mol% of the trifluoroacetate complex **3c**, generated in situ by reaction of the corresponding chloride-bridged dimer **3b** with 2 equivalents of $Ag(OCOCF_3)$ in dichloromethane, promoted the rearrangement of imidate **4** in CH_2Cl_2 at room temperature (Scheme 4).

The (*Z*)-allylic imidates examined with catalyst **3c** underwent very fast reaction to give more than 94% ee.



Scheme 4.

The results with the other two catalysts are summarized in Table 1.

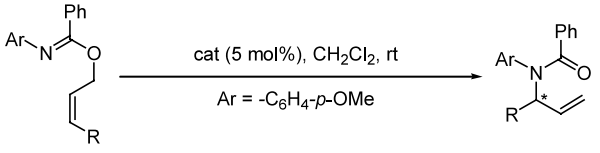
On the other hand, the rearrangements of (*E*)-allylic imidates with catalyst **3c** were very slow (even after 12 h, the reaction was incomplete) and the enantioselectivity was again low in every case. For this type of substrate **2** remains the catalyst of choice. The results with the other two catalysts are summarized in Table 2.

The stereochemical outcome can be explained by cyclization-induced rearrangement protocol.[3] Thus, the '*trans* influence'[8] of the Cp ring would place the alkene moiety *trans* to it because the bond strength between Cp and palladium is expected to be stronger than that between the nitrogen atom of the oxazoline and the palladium centre.

One of the two possible transition states is shown in Fig. 1: The model **7** of the *Z*-substrate, in which the R group of the substrate is located far away from the isopropyl group in the oxazoline ring, would be more stable than the alternative **6** in which there would be a severe steric interaction between the R and *i*-Pr group. Subsequent nucleophilic attack of the imidate nitrogen in **7** from the *Re* face would lead to the formation of the *R* product (Fig. 1).

In the case of the *E* isomer (Fig. 2), the conformer **9**, in which the R group is placed far away from the isopropyl group in the oxazoline ring, would be slightly more stable than the alternative conformer **8**, even though the severe steric interaction of the R group with the lower tetraphenylcyclobutadienyl ring is unavoidable in

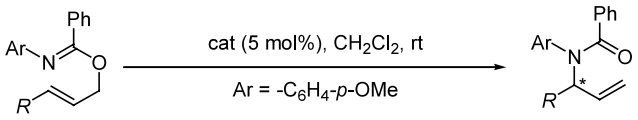
Table 1. The rearrangement of (*Z*)-allylic imidate **4** to *N*-allylic amide **5**



R	Catalyst	Time (h)	Yield (%)[a]	Ee (%)/configuration[b]	Ref.
Pr^n	**1**	21	83	91/*R*	3
	2	12	85	90/*S*	4
	3c	3	92	94/*R*	Present work
Bu^i	**1**	25	89	96/*R*	3
	2	10	70	86/*S*	4
	3c	7	72	95/*R*	Present work

[a] Isolated yield.
[b] Determined from the specific rotation value.[3]

Table 2. The rearrangement of (*E*)-allylic imidate **4** to *N*-allylic amide **5**



R	Catalyst	Time (h)	Yield (%)[a]	Ee (%)/configuration[b]	Ref.
Pr^n	**1**	18	93	83/*S*	3
	2	0.5	91	92/*R*	4
	3c	13	82	45/*S*	Present work
Bu^i	**1**	25	97	84/*S*	3
	2	10	74	95/*R*	4
	3c	12	82	50/*S*	Present work
Ph	**1**	26	59	63/*R*	3
	2	1	97	87/*S*	4
	3c	13	70	68/*R*	Present work

[a] Isolated yield.
[b] Determined from the specific rotation value.[3]

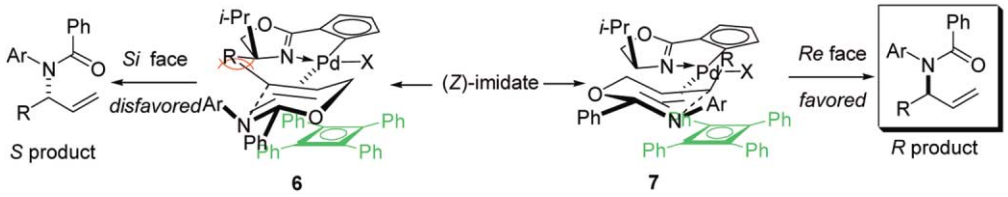


Figure 1. Consideration of the transition state of *Z*-imidate.

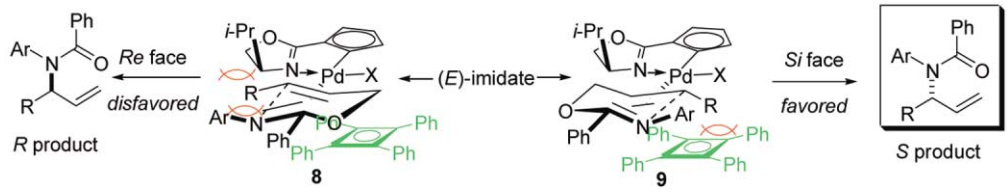


Figure 2. Consideration of the transition state of *E*-imidate.

both cases. This may be the reason why the reactions of (*E*)-imidates were slow but intramolecular attack to the *Si* face by the imidate nitrogen was still preferred by a small margin.

In conclusion, we have determined factors affecting the enantioselectivity of the catalytic asymmetric rearrangement of allylic imidates. A severe blocking of one face increased reaction rates and enantioselectivities for (*Z*)-allylic imidates but at the cost of decreased reaction rates and enantioselectivity for (*E*)-allylic imidates. Consequently, the CpCbCo compound **3c** is an excellent catalyst for the catalytic asymmetric rearrangement of (*Z*)-allylic imidates.

General procedure for rearrangement of allylic imidates to *N*-allylic amides: A solution of palladium catalyst **3b** (5 mol%) and CF_3CO_2Ag (10 mol%) in dichloromethane was stirred for 1 h at room temperature. The reaction mixture was filtered through Celite under nitrogen atmosphere directly into a round-bottom flask containing imidate substrate. The reaction mixture was stirred at room temperature for an appropriate period, monitoring the progress of the reaction by ^1H NMR, the reaction mixture was concentrated at reduced pressure and the resulting crude product was purified by column chromatography to afford the corresponding amide. The enantiomeric purity was determined by HPLC analysis[9] and the configuration of the product was determined from the specific rotation value.[3]

Acknowledgements

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7. **Compound 3b:** The starting palladium acetate dimer (250 mg, 0.331 mmol) was dissolved in acetone (5.0 mL) and LiCl (35 mg, 0.827 mmol) was added to the reaction mixture at room temperature. After stirring for 3 days at ambient temperature, the mixture was concentrated under reduced pressure. The resultant crude product was purified by flash column chromatography to give an orange solid (213 mg, 88% yield). $R_f = 0.39$ (20% EA/*n*-hexane); M.p. = 192–196°C (sublimation); $[\alpha]_D^{23} = +1064$ (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.71–0.81 (m, 12H), 2.20–2.30 (m, 2H), 3.01–3.15 (m, 2H), 3.33 (t, 1H, $J = 9$ Hz), 3.43 (t, 1H, $J = 9$ Hz), 4.17–4.20 (m, 2H), 4.27 (t, 1H, $J = 2$ Hz), 4.39 (t, 1H, $J = 2$ Hz), 4.69–4.73 (m, 2H), 4.97–4.99 (m, 2H), 7.16–7.26 (m, 24H), 7.58–7.69 (m, 16H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.1, 18.7, 28.8, 65.5, 71.1, 76.4, 77.4, 80.5, 84.5, 85.4, 86.8, 98.4, 126.2, 128.0, 129.2, 135.2; Anal. calcd for $C_{78}H_{66}Co_2N_2O_2Cl_2Pd_2$: C, 61.9; H, 4.54; N, 1.91; Found: C, 60.3; H, 4.11; N, 1.67%.
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9. **Compound 5:** (a) R = Ph; slightly yellow oil; $R_f = 0.29$ (20% EA/*n*-hexane); HPLC (Chiralcel AS, 20% IPA/*n*-Hex, 0.5 mL/min) 24.0 min (*R*), 43.8 min (*S*); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 3H), 5.36 (d, 1H), 5.47 (d, 1H), 6.10 (ddd, 1H), 6.56–6.66 (m, 5H), 7.10–7.30 (m, 10H); (b) R = *n*-Pr; slightly yellow oil; $R_f = 0.31$ (20% EA/*n*-Hexane); HPLC (Chiralcel AS, 10% IPA/*n*-Hex, 0.8 mL/min) 18.8 min (*S*), 33.4 min (*R*); ^1H-NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H), 1.43-1.70 (m, 4H), 3.73 (s, 3H), 5.20 (d, 1H), 5.28-5.30 (m, 1H), 5.75–5.82 (m, 1H), 6.69 (d, 2H), 6.91 (d, 2H), 7.15–7.26 (m, 5H); (c) R = *i*-Bu; slightly yellow oil; $R_f = 0.28$ (20% EA/*n*-Hexane); HPLC (Chiralcel AS, 10% IPA/*n*-Hex, 0.4 mL/min) 20.9 min (*S*), 25.4 min (*R*); ^1H-NMR ($CDCl_3$, 300 MHz) δ 0.90–1.10 (m, 6H), 1.40–1.70 (m, 3H), 3.72 (s, 3H), 5.17 (d, 1H), 5.29 (br d, 1H), 5.42 (br s, 1H), 5.70–5.80 (m, 1H), 6.69 (d, 2H), 6.91 (d, 2H), 7.10–7.20 (m, 5H).