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An investigation into the diastereoselective palladation of oxazoline appended cobalt metallocenes

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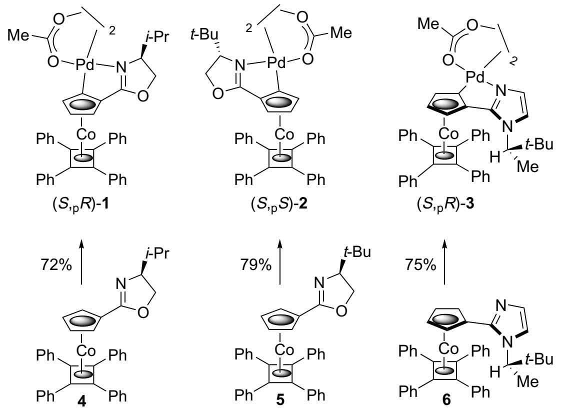
Abstract—The diastereoselective reactions of palladium acetate with (η^5-(*S*)-2-(4-methylethyl)oxazolinylcyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt, which gives a planar chiral palladacycle with ($_{p}R$) configuration, and (η^5-(*S*)-2-(4-dimethylethyl)oxazolinylcyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt, which results in the opposite ($_{p}S$) configuration, are shown to be a consequence of these reactions displaying thermodynamic and kinetic control, respectively.

1. Introduction

Over the past decade or so, there has been a great deal of interest in the application of palladacycles as catalysts for organic synthesis.[1] As part of a programme exploring the synthesis and application of metallocene-based palladacycles, we have described the diastereoselective synthesis of complexes **1**,[2] **2**[3] and **3**.[4] Of these planar chiral palladacycles, **1** and its chloride-bridged derivative (COP-Cl) have been applied extensively as highly enantioselective catalysts for the synthesis of chiral allylic amides[5] and related compounds.[6] In addition, both **1** and **2** have been utilised as reagents for enantioselective transcyclopalladation.[7] In each case, the diastereomerically pure palladacycles **1**–**3** were obtained as crystalline products after heating the precursor heterocycle appended metallocenes **4**–**6** for thirty minutes with palladium acetate in acetic acid at 95 °C (Scheme 1). Of particular interest is the sense of diastereoselection observed with the *i*-Pr substituted oxazoline **4**, compared to the *t*-Bu derivative **5**. Herein we report on further investigations into these palladation reactions, and provide an explanation for the striking reversal of diastereoselectivity observed with **4** and **5**.



Scheme 1. Synthesis of palladacycles **1**–**3** (Pd(OAc)$_2$, AcOH, 95 °C, 30 min).

Oxazoline **4** and an equimolar quantity of palladium acetate[8] were combined in glacial acetic acid and the reaction vessel placed in an oil bath preheated to 95 °C.[9] Aliquots of the vigorously stirred reaction mixture were removed at specified time intervals and immediately diluted with $CDCl_3$ prior to examination by ^1H NMR. In the first few minutes of the reaction a set of diastereotopic *i*-Pr doublets were observed, similar to but distinct from the corresponding doublets of **1**, and corresponding to the (*S*,$_{p}S$)-diastereoisomer **7** (Scheme 2, Table 1, entries 1–5). At the end of the standard 30 min reaction time, the ratio of the major to minor diastereoisomers was unchanged at >20:1 and an orange precipitate was observed, as previously described.[10]

Repetition of this protocol at 70 °C revealed diastereoisomer **7** to be the major palladacycle formed in the first few

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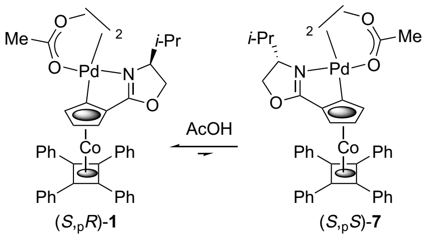


Scheme 2. Palladacycle epimerisation.

Table 1. Palladation of oxazoline **4**[a] with $Pd(OAc)_2$

Entry	Temperature (°C)	Time	Conversion to palladacycles[b] (%)	Ratio **1**[c]:**7**[d]
1	95	1 min	8	~1:2
2	95	5 min	58	3.2:1
3	95	10 min	74	>20:1
4	95	20 min	64	>20:1
5	95	30 min	60	>20:1[e]
6	70	5 min	19	1:2.5
7	70	10 min	39	1:1.1
8	70	20 min	51	1.4:1
9	70	30 min	66	1.8:1
10	70	1 h	63	2.3:1
11	70	2 h	56	3:1
12	70	5 h	52	5.5:1
13	70	27 h	27	13:1

[a] Selected ^{1}H NMR data for **4**: 0.77 (3H, d, *J* 7, $-CH_3$), 0.97 (3H, d, *J* 7, $-CH_3$).

[b] Determined by ^{1}H NMR and a figure corresponding to the percentage integration of the methyl doublets of **1** and **7** relative to the total methyl integral (−0.10 to 1.10 ppm).

[c] Selected ^{1}H NMR data for **1**: −0.01 (6H, d, *J* 7, $-CH_3$), 0.45 (6H, d, *J* 7, $-CH_3$).

[d] Selected ^{1}H NMR data for **7**: 0.14 (6H, d, *J* 7, $-CH_3$), 0.57 (6H, d, *J* 7, $-CH_3$).

[e] Approximately 22:1.

minutes of the reaction (Table 1, entries 6 and 7, Fig. 1a and b). Further heating resulted in a reversal of this selectivity to again provide **1** as the major diastereoisomer (Table 1, entries 8–13, Fig. 1c–e). This reveals a kinetic and thermodynamic selectivity for diastereoisomers **7** and **1**, respectively, the latter lower energy isomer containing the oxazoline *i*-Pr substituent orientated away from the bulky tetraphenylcyclobutadiene moiety.[11] The reversibility of the reaction is a consequence of the protonolysis of the palladacycle carbon-palladium bond by acetic acid, reforming the starting metallocene and palladium acetate.[12] A notable feature of the reaction at 70 °C is the reduction in the overall percentage of the two palladacycles **1** and **7** when the reaction mixture is heated for longer than 30 min. This is likely due to the removal of 'active' palladium from the reaction mixture, due to the formation of the observed palladium black.

In an attempt to determine the fate of the oxazoline that was not converted into a palladacycle, **4** was heated in acetic acid at 95 °C for 41 h in the absence of palladium acetate. This resulted in the essentially quantitative formation of ring-opened product **8**,[13] the identity of which was confirmed by the independent synthesis from the known amido-alcohol **9**[2] (Scheme 3). In contrast to other acid promoted oxazoline ring opening reactions, the oxazoline of **1** is transformed into an amide rather than an ester functionality.[14] This is likely due to the operation of an alternative ring opening mechanism involving nucleophilic attack by acetic acid on a protonated oxazoline. At the end of the palladation reactions at 95 °C and 70 °C, only trace amounts of **8** were present, and no other metallocene derivatives were observed by ^{1}H NMR spectroscopy.

The palladation reaction of the *t*-Bu substituted derivative **5** was also examined in detail by ^{1}H NMR (Table 2). In this instance, only **2** was observed in the early and late stages of the reaction. By comparison with the reaction of the *i*-Pr substituted oxazoline **4**, the expected thermodynamic product would be the (*S*,p*R*)-diastereoisomer in which the *t*-Bu group is pointing away from the metallocene. This was not observed even after prolonged heating in acetic acid at 95 °C or on heating **2** in 5% AcOH/toluene at 70 °C for 65 h. In both instances, the palladacycle reverts to the starting oxazoline **5** accompanied by the formation of palladium black. Thus only the kinetic product, the (*S*,p*S*)-diastereoisomer, is formed, and the energy barrier to the alternative thermodynamic diastereoisomer is too high to be accessed.

A possible explanation for this kinetic selectivity is illustrated in Scheme 4 based upon an electrophilic aromatic substitution pathway for palladation,[15] involving the *exo* attack of a nitrogen coordinated palladium.[16,17] Compared to the down–up–down transition state model **A**, which results in the observed (p*S*) configuration, model **B** highlights the unfavourable proximity of ligated palladium to the oxazoline *t*-Bu substituent as a consequence of the alternative up–up–down arrangement of large groups. With the *i*-Pr substituted oxazoline, orientation of the isopropyl methine towards the metal results in the corresponding transition state to **B** being significantly lower in energy, and thus more accessible. Models **A** and **B** are similar to those used to account for the diastereoselective lithiation of chiral ferrocenyloxazolines, such as (*S*)-2-(4-methylethyl)oxazolinylferrocene, which also proceeds with the same sense of kinetic stereoselectivity.[18]

Finally, palladation of the imidazole derivative **6** at 70 °C was also examined by ^{1}H NMR (Table 3). In this instance, the relatively rapid formation of **3** was observed with none of the other possible diastereoisomer detected. As the conformational preferences that were invoked to explain the selective formation of **3**[4] also result in orientation of the *t*-Bu group away from the metallocene,[19] it would seem likely that in this instance the kinetic and thermodynamic products are one and the same.

2. Conclusion

In conclusion, the *ortho*- (or α) heteroatom-directed diastereoselective palladation of bulky cobalt metallocenes under protic conditions can be rationalised by consideration of the relative energies of the two possible product stereoiso-

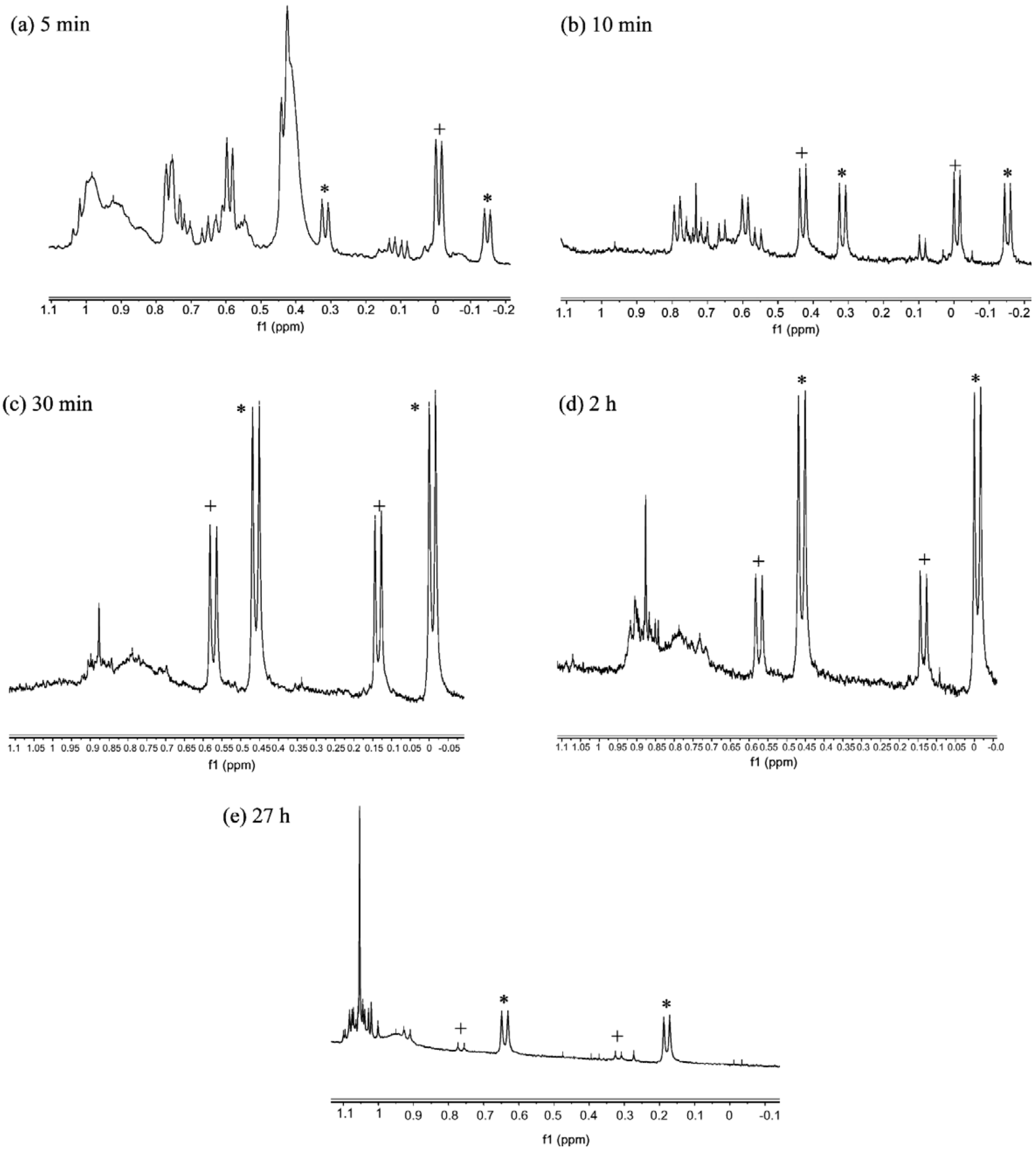
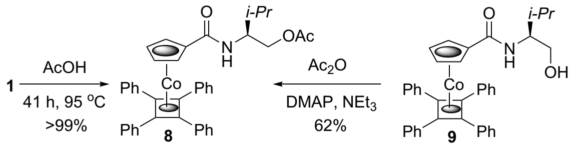


Figure 1. ^{1}H NMR spectra of the palladation of **4** with Pd(OAc)$_2$ at 70 °C after (a) 5 min, (b) 10 min, (c) 30 min, (d) 2 h and (e) 27 h ($* =$ **1**, $+ =$ **7**).



Scheme 3. Identification of an oxazoline ring-opened by-product.

mers. As a consequence of the bulky tetraphenylcyclobutadiene moiety, these differences are sufficiently large enough to result in the selective formation of a predominant diastereoisomer. The only exception arises where the transition state leading to the anticipated

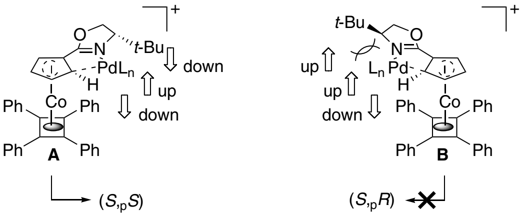
Table 2. Palladation of oxazoline **5**[a] with Pd(OAc)$_2$

Entry	Temperature (°C)	Time	Conversion to palladacycles **2**[b,c] (%)
1	70	5 min	0
2	70	10 min	0.7
3	70	30 min	4
4	70	2 h	11
5	70	5 h	14
6	70	27 h	33

[a] Selected ^{1}H NMR data for **5**: 0.81 (9H, s, –(CH_3)$_3$).

[b] Selected ^{1}H NMR data for **2**: 0.37 (18H, s, –(CH_3)$_3$).

[c] Determined by ^{1}H NMR and a figure corresponding to the percentage of **2** relative to **2** + **5** (*t*-Bu).



Scheme 4. Origin of kinetic selectivity in the palladation of **5**.

Table 3. Palladation of imidazole **6**[a] with Pd(OAc)$_2$

Entry	Temperature (°C)	Time	Conversion to palladacycles **3**[b,c] (%)
1	70	5 min	59
2	70	30 min	70
3	70	1 h	61
4	70	24 h	40

[a] Selected ^{1}H NMR data for **6**: 0.71 (9H, s, –(C*H*$_3$)$_3$), 0.73 (3H, d, *J* 7, CHC*H*$_3$).

[b] Selected ^{1}H NMR data for **3**: 0.49 (24H, m, –(C*H*$_3$)$_3$ + CHC*H*$_3$).

[c] Determined by ^{1}H NMR and a figure corresponding to the percentage integration of **3** relative to **3** + **5** (*t*-Bu/Me).

thermodynamic product is kinetically inaccessible, but significantly the palladation reaction remains highly diastereoselective. It is anticipated that this analysis will aid the selective synthesis of alternative planar chiral palladacycles based upon bulky cobalt metallocenes and related systems.

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10. This >20:1 ratio was obtained following evaporation of the whole reaction mixture and examination by ^{1}H NMR spectroscopy. The precipitate itself was composed of only a single diastereoisomer, (*S*,$_p$*R*)-**1**.
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19. The minimal energy conformation with respect to the N(1)–C(α) bond is that with the hydrogen attached to the stereogenic centre pointing to the metallocene. Although not specifically studied in solution, this is observed by X-ray crystallography in the solid state, see Ref. 4.