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A comparative study of diphosphine and phosphinamine palladium complexes on a new substrate for the intramolecular asymmetric Heck reaction

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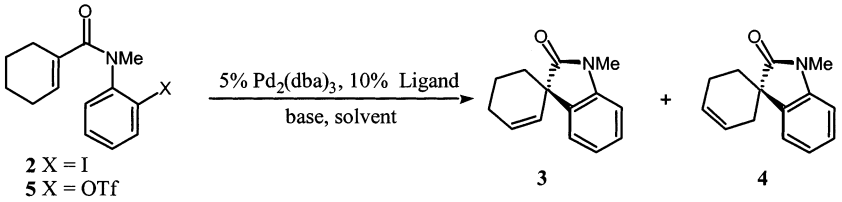
Abstract—Palladium-catalysed intramolecular asymmetric Heck reactions were performed on triflate **5** using complexes derived from BINAP and a range of oxazoline-containing phosphinamine ligands. The optimum ee obtained was 85% employing the *t*-butyl-substituted ferrocenyloxazoline ligand **6**. The isomer distribution of the product spirooxindoles was dependent on the ligand chosen, with the oxazoline-containing ligands showing an increased selectivity (up to 99:1) for the $\Delta^{2,3}$-isomer **3** compared to BINAP (optimum 75:25).

The asymmetric intramolecular Heck reaction was initially reported independently by Shibasaki and Overman in 1989.[1] Since then it has emerged as one of the most useful catalytic methods of enantioselective C–C bond formation.[2,3] The vast majority of asymmetric Heck cyclizations reported to date have utilised palladium complexes of BINAP **1**. In cases where a variety of homobidentate and heterobidentate ligands have been screened, BINAP has generally proven to be the ligand of choice for a range of substrates. One notable exception is the use of diphenylphosphinoaryloxaxoline ligands by Hallberg where he obtained excellent enantioselectivities and good regioselectivities in his enamide synthesis.[4] More recently, we have demonstrated the efficacy of heterobidentate P–N systems in the intermolecular variant with both 2,3-dihydrofuran and 2,2-dialkyl-2,3-dihydrofurans as substrates.[5–8]

The aryl iodide **2** had previously been tested by Overman,[9] with enantioselectivities of up to 95% being realised using (*R*)-BINAP with PMP (1,2,2,6,6-pentamethylpiperidine) as base, with approximately a 50:50 mixture of spirooxindole double bond isomers **3** and **4** being formed. A range of phosphinamine ligands applied in that study were unsuccessful. The excellent enantioselectivities obtained were rationalised by a neutral Heck reaction mechanism, which is accessible from halide substrates in the absence of silver salts. The alternative Heck reaction mechanism is one which proceeds via a cationic square-planar palladium intermediate which is accessible from halide substrates in the presence of halide scavengers such as silver salts, or from the corresponding aryl triflates. Therefore, we have chosen the novel triflate **5**, which was readily prepared in five steps from 1-cyclohexene-1-carboxylic



2 X = I
5 X = OTf

3 **4**

Scheme 1.

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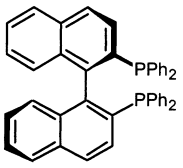
acid,[10] as substrate for our study, as it should provide a useful comparison with the neutral pathway.[11]

In this report we describe cyclisations of **5** using Pd complexes generated from (*R*)-BINAP (**1**) and the phosphinamine ligands **6**–**9** (Scheme 1).



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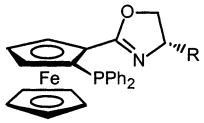
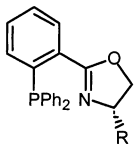


6 R = *t*-Bu
7 R = *i*-Pr



8 R = *t*-Bu
9 R = *i*-Pr

The results of our preliminary investigations on this intramolecular Heck reaction are given in Table 1 (racemic samples of both **3** and **4**, required for HPLC analysis, were prepared using racemic BINAP).[12] Using palladium complexes generated in situ from (*R*)-BINAP (**1**) and $Pd_2(dba)_3$, cyclisation occurred in a good yield of 90% employing dimethylacetamide (DMA) as solvent and PMP as base (entry 1). However, a mixture of spirooxindole double bond isomers **3** and **4** was obtained in a ratio of 25:75 in which the enantiomeric excess for **3** was 74%, whereas **4** was formed with a much decreased stereoselectivity of 27% ee. Under similar reaction conditions palladium complexes of the *t*-butyl-derived ferroceneoxazoline ligand **6** induced cyclisation with almost complete regioselectivity for **3** with a good enantioselectivity of 65% (entry 2). The minor isomer **4** was formed as a racemate in this and all other reactions employing palladium complexes of ligands **6**–**9**. A possible explanation for the different product distributions is that the olefin bound product formed after migratory insertion is more susceptible to dissociation to give **3** in Pd(P–N) catalyst systems, whereas in Pd(P–P) systems a reverse β-elimination may occur leading to the formation of **4**. A change of base to proton sponge (PS) led to an increase in enantioselectivity of 85% for the palladium catalyst system derived from ligand **6** (entry 3). Use of the *i*-propyl-substituted analogue **7** in DMA with PMP as base gave poorer yield (13%), regioselectivity (71:29) and significantly lowered enantioselectivity of 37%. Similar lowering of reactivity and asymmetric induction in going from *t*-butyl- to *i*-propyl-substituted analogues was previously noted by Pfaltz in their study of the intermolecular asymmetric Heck reaction.[13] The *t*-butyl-substituted diphenylphosphinoaryloxazoline ligand **8** was not as active, regio- or enantioselective as its ferrocene analogue (compare entries 5 and 2). However, a change of base to proton sponge was again beneficial as the regioselectivity increased to 99:1 and the ee improved to 71% (entry 6). The less sterically demanding *i*-propyl-substituted ligand **9** again was less reactive (7% yield) and selective (72:28 and 33% ee) (entry 7).

A switch of solvent to toluene, previously found by Shibasaki to lead to improved reactivity for triflate substrates,[16] caused the regioselectivity for isomer **3**/**4** to be reversed in the case of BINAP **1**, which suggests a significant role for coordinating versus non-coordinating solvents in the cationic pathway (entry 8). The yield in toluene using the *t*-butyl-derived ferroceneoxazoline ligand **6** improved to 70% albeit with slightly poorer regioselectivity and enantioselectivity (compare entries 2 and 9). Lowering the reaction temperature from reflux to 80°C led to a small increase in regio- and enantioselectivity (entry 10). Keeping the same reaction temperature and changing the base to proton sponge gave a significantly lower yield of 15% although with excellent regioselectivity (99:1) and with high enantioselectivity of 82% (entry 11). A similar pattern of lowered reactivity and enantioselectivity was observed in toluene using the *i*-propyl-derived ferroceneoxazoline

Table 1. Intramolecular Heck reaction of triflate **5**[14]

Entry	Ligand	Solvent	*T* (°C)	Base	Time (h)	Yield[a]	**3**/**4**[b]	ee **3**[c] (config.)[d]
1	1	DMA	110	PMP	48	90	25:75	74 (*S*)
2	6	DMA	110	PMP	228	36	99:1	65 (*R*)
3	6	DMA	110	PS	168	30	99:1	85 (*R*)
4	7	DMA	110	PMP	228	13	71:29	37 (*R*)
5	8	DMA	110	PMP	228	20	76:24	57 (*R*)
6	8	DMA	110	PS	168	20	99:1	71 (*R*)
7	9	DMA	110	PMP	228	7	72:28	33 (*R*)
8	1	Toluene	110	PMP	48	90	75:25	71 (*S*)
9	6	Toluene	110	PMP	168	70	94:6	51 (*R*)
10	6	Toluene	80	PMP	168	70	99:1	53 (*R*)
11	6	Toluene	80	PS	168	15	99:1	82 (*R*)
12	7	Toluene	110	PMP	168	35	93:7	12 (*R*)
13	7	Toluene	80	PMP	168	5	90:10	30 (*R*)
14	8	Toluene	110	PMP	168	20	90:10	19 (*R*)
15	6	Benzene	80	PMP	168	5	98:2	63 (*R*)

[a] Yields were determined by ^{1}H NMR analysis of the reaction mixture.[15]

[b] Isomeric ratio determined by HPLC analysis.

[c] Enantioselectivities were determined by chiral HPLC analysis using a Daicel Chiralpak OJ column (0.46×25 cm), hexane:2-propanol 99.5:0.5 (t_R = 38.9 (*S*) and 52.3 (*R*) min) for alkene isomer **3**; (t_R = 26.6 (*S*) and 29.6 (*R*) min) for alkene isomer **4**; PMP = 1,2,2,6,6-pentamethyl-piperidine, PS = proton sponge).

[d] Absolute configuration assignment is based on the sign of the optical rotation and comparison with Overman's work.[9]

ligand **7** (entries 12 and 13). Again the *t*-butyl-substituted diphenylphosphinoaryloxazoline ligand **8** performed poorly in toluene compared to its ferrocene analogue (compare entries 14 and 10). Finally, use of benzene as solvent did not lead to increased reactivity as a poor yield of only 5% was obtained with the catalyst system which was superior in either DMA or toluene.

In conclusion, we have a tested a range of Pd-complexes in the Heck cyclisation of triflate **5** and have achieved ees of up to 85% with the *t*-butyl-substituted ferrocenyloxazoline ligand **6**. These results suggest that palladium complexes of phosphinamine ligands may be applied successfully in enantioselective Heck reactions, via the cationic Heck mechanism, which is accessible from aryl or alkenyl triflates, thus increasing the scope of this reaction. Reactivity is optimal with catalysts incorporating the BINAP ligand system, however, regioselectivity is much improved using the phosphinamine ligands. Further work on this and related substrates is in progress and will be reported in due course from these laboratories.

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12. Spectral data for compounds **3** and **4**: $\Delta^{2,3}$ (**3**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.20 (m, 2H, $H_{5',6'}$), 7.0 (m, 1H, $H_{4'}$), 6.83 (d, 1H, $J = 7.6$ Hz, $H_{3'}$), 6.13 (dt, 1H, $J = 9.8$, 4.0 Hz, H_2), 5.28 (d, 1H, $J = 9.9$ Hz, H_3), 3.21 (s, 3H, NMe), 2.25–2.20 (m, 2H, $H_{4a,b}$), 2.05–2.00 (m, 2H, $H_{6a,b}$), 1.65–1.95 (m, 2H, $H_{5a,b}$). $\Delta^{3,4}$ (**4**): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.31$ (t, 1H, $J = 7.3$ Hz, $H_{6'}$) 7.27–7.25 (m, 1H, $H_{5'}$), 7.04 (t, 1H, $J = 7.5$ Hz, $H_{4'}$), 6.86 (d, 1H, $J = 7.7$ Hz, $H_{3'}$), 5.84–5.95 (m, 2H, $H_{3,4}$), 3.23 (s, 3H, NMe), 2.61–2.70 (m, 1H, H_{2a}), 2.30–2.36 (m, 2H, $H_{5a,b}$), 1.91–2.00 (m, 2H, H_6), 1.49–1.58 (m, 1H, H_{2b}).
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14. Typical experimental procedure: An oven-dried 10 mL Schlenk flask was charged with $Pd_2(dba)_3$ (0.002 mmol), ligand (0.008 mmol) and purged with nitrogen for 5 min. Solvent (0.5 mL) was added and the suspension stirred for 1 h until a solution was apparent. A dimethylacetamide (0.5 mL) solution of the triflate (0.08 mmol) was added followed by PMP (0.4 mmol). The reaction mixture was degassed by the pump freeze thaw method (×3). The reaction vessel was then sealed and heated to 110°C for 168 h. The reaction was then quenched with saturated aqueous sodium bicarbonate (5 mL), diluted with water (5 mL) and ethyl acetate (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2×5mL). The combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate and concentrated in vacuo. The crude product was further purified by preparative chromatography on silica gel (5:1 Pet spirits 40:60/ethyl acetate).
15. Relative integration of *N*-methyl singlets, 3.21 ppm in product **3**, 3.34 ppm in the triflate.
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