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A comparison of palladium complexes of BINAP and diphenylphosphinooxazoline ligands in the catalytic asymmetric synthesis of *cis*-decalins

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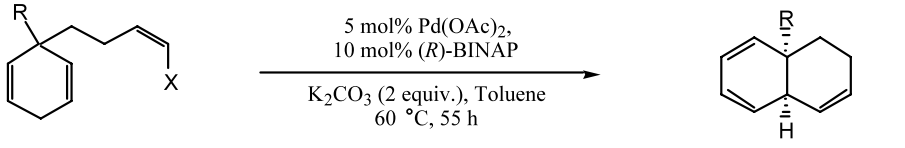
Abstract—BINAP and a range of oxazoline-containing phosphinamine ligands were screened in the palladium-catalysed asymmetric intramolecular Heck cyclisation to form *cis*-decalins. Complexes formed from $Pd_2(dba)_3$ and BINAP gave cyclised products in up to 65% yield and 85% ee. The *t*-leucine-derived diphenylphosphinoferrocenyloxazoline ligand afforded our optimal enantioselectivity of 85% for the range of phosphinamine ligands tested. Variation of solvent and base appears to indicate that this system is sensitive to catalyst deactivation and that a combination of either toluene or *N*-methylpyrrolidine with potassium carbonate as base was required for acceptable catalytic activity. Catalysts prepared from palladium complexes of diphenylphosphinoaryloxazoline ligands were less reactive than the corresponding BINAP catalysts as the optimal yield obtained was 47%.

The palladium-catalysed Heck reaction is an elaboration of substituted alkenes by direct C–C bond formation at a vinylic carbon centre.[1] When employed intramolecularly, the Heck reaction has been used to synthesise a vast array of cyclic products, and has been applied at the strategy level for the synthesis of numerous natural products.[2] The development of the asymmetric Heck reaction using palladium complexes of enantiopure ligands was a significant breakthrough.[3] The first reports on the asymmetric intramolecular Heck reaction were independent contributions from the groups of Shibasaki and Overman in 1989,[4] with the former describing the asymmetric synthesis of *cis*-decalin derivatives **1a–d** (Scheme 1).

These derivatives could be prepared from either the alkenyl triflate **2a**, or the analogous alkenyl iodide **2b** with an added silver salt as halide scavenger. Shibasaki tested a series of chiral bisphosphine ligands, with palladium complexes derived from $Pd(OAc)_2$ and BINAP (**3**) proving to be the most selective catalysts in this system. For the alkenyl triflate **2a**, the optimal ee achieved was 91% in a yield of 54%.[5] Where a variety of ligands have been screened, BINAP has generally proven to be the ligand of choice for a broad range of asymmetric intramolecular Heck reactions. One notable exception was the use of the diphenylphosphinoaryloxazoline ligand **4** by Hallberg, who obtained good regioselectivities and ees up to 99% in an intramolecular



2a: X = OTf
2b: X = I

1a: R = CO_2Me
1b: R = $CH_2OTBDMS$
1c: R = CH_2OAc
1d: R = CH_2OPv

Scheme 1.

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enamide cyclisation.[6] Pfaltz had previously applied ligand **4** in the intermolecular Heck variant and obtained yields up to 87% and ees up to 97% in the phenylation of 2,3-dihydrofuran.[7] We demonstrated the efficacy of heterobidentate P–N systems **4–6** in the intermolecular Heck reaction with both 2,3-dihydrofuran and 2,2-dialkyl-2,3-dihydrofurans as substrates.[8–11] In addition, we recently applied ligands **4–6** to the synthesis of enantioenriched spirooxindoles with excellent regioselectivities and ees up to 85%.[12] More recently, Busacca and co-workers have applied related phosphinoimadazoline ligands to the preparation of analogous spirooxindoles with ees up to 88%.[13]

These previous successes with phosphinamine ligands prompted us to study the applicability of ligands **4–6** in the asymmetric intramolecular Heck reaction with triflate **2a** as the substrate,[14] thus allowing a direct comparison with the analogous reactions using palladium complexes of BINAP (**3**). We now wish to report the initial results of this investigation (Table 1).

Using palladium complexes generated in situ from $Pd_2(dba)_3$ and (*R*)-BINAP (**3**), cyclisation proceeded in reasonable yield (50%), and with good enantioselectivity (82% ee, entry 1). A similar yield (54%), albeit with higher enantioselectivity (91%), was obtained in Shibasaki's study which employed $Pd(OAc)_2$ as the precursor.[5] Increasing the reaction temperature to 110°C resulted in an improved yield (65%) without having an adverse effect on the stereoselectivity of the reaction (entry 2). Using *N*-methylpyrrolidine as solvent resulted in increased activity of the catalyst (80% yield) but also lowered the enantioselectivity (46% ee, entry 3). Using palladium complexes of the *t*-butyl-substituted ferrocenyloxazoline ligand **5** cyclisation proceeded in lower yield (30%) but with an improved enantioselectivity of 85% (entry 4). In an attempt to increase yields, higher reaction temperatures of 80 and 110°C were applied but this led to decreased yields (24 and 23%, respectively) and also decreased enantioselectivies (67 and 42% ee, respectively, entries 5–6). In both cases the mass balance was recovered as unreacted starting triflate **2a**. This, and the precipitation of palla-

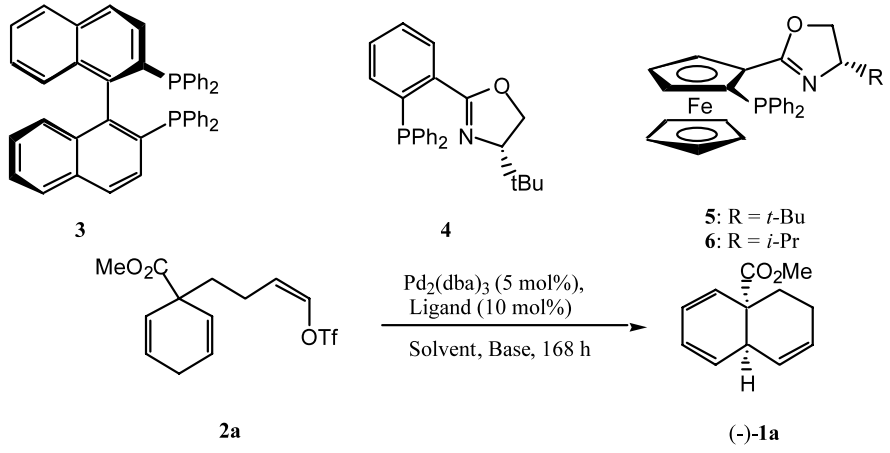

Table 1. Heck cyclisations of alkenyl triflate **2a**[15,16]

Entry	Ligand	Solvent	Base	*T* (°C)	Yield (%)[a]	ee[b,c]
1	**3**	Toluene	K_2CO_3	60	50	82
2	**3**	Toluene	K_2CO_3	110	65	83
3	**3**	NMP	K_2CO_3	60	80	46
4	**5**	Toluene	K_2CO_3	60	30	85
5	**5**	Toluene	K_2CO_3	80	24	67
6	**5**	Toluene	K_2CO_3	110	23	42
7	**5**	Toluene	Na_2CO_3	60	11	67
8	**5**	Toluene	PMP	60	10	74
9	**5**	Toluene	Proton sponge	60	10	28
10	**6**	Toluene	K_2CO_3	60	<5	–
11	**4**	Toluene	K_2CO_3	60	20	47
12	**4**	Toluene	K_2CO_3	110	17	42
13	**5**	Benzene	K_2CO_3	60	11	62
14	**5**	DMA	K_2CO_3	60	<5	–
15	**5**	NMP	K_2CO_3	60	45	58
16	**4**	NMP	K_2CO_3	60	47	43

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

[b] Enantioselectivities were determined by chiral HPLC analysis using a Daicel Chiralpak OJ column (0.46 cm×25 cm), hexane: 100% (t_R = 84.2 (–) and 93.7 (+) min); PMP = 1,2,2,6,6-pentamethylpiperidine, proton sponge = 1,8-bis(dimethylamino)naphthalene.

[c] The specific rotation of the major enantiomer in entries 1–3 was (+) and in entries 4–16 was (–) and the absolute configuration was assigned by comparison with Shibasaki's original work.[4a]

dium black, suggests that higher reaction temperatures lead to catalyst degradation. Alternative bases to potassium carbonate were screened using palladium complexes of ligand **5** (entries 7–9) but low yields of 10–11% were observed. However, there were marked differences in the enantioselectivities obtained as both sodium carbonate and 1,2,2,6,6-pentamethylpiperidine (PMP) gave good enantioselectivies (67 and 74%, respectively), whereas proton sponge gave a poor ee of 28%. A similar trend was observed by Shibasaki when he screened a range of bases in the BINAP-promoted cyclisations of **2a**–**d** and found that the use of tertiary amines as bases led to less reactive systems.[14] Using palladium complexes of the *i*-propyl-substituted ferrocenyloxazoline ligand **6** afforded only trace amounts (<5%) of the cyclised product (entry 10). A similar lowering of reactivity on switching from the *t*-butyl to the *i*-propyl-substituted analogues of ligand **4** was previously noted by Pfaltz in their study of the asymmetric intermolecular Heck reaction.[7]

Palladium complexes of the *t*-butyl-substituted aryloxazoline ligand **4** proved less reactive and less enantioselective than the ferrocene analogue affording a yield of 20% and an enantioselectivity of 47% (compare entries 4 and 11). Increasing the reaction temperature to 110°C again led to both a decrease in yield and enantioselectivity (entry 12), also attributable to catalyst inactivation at elevated temperatures. Using palladium complexes of ligand **5** but switching the solvent to benzene resulted in a significant attenuation of yield to 11%, with an enantioselectivity of 62% (entry 13). Similarly, poor yields were observed in dimethylacetamide (DMA) (entry 14). Reactivity was improved using *N*-methylpyrrolidine (NMP) as solvent, as outlined by a yield of 45% (with palladium complexes of **5**), and with a good enantioselectivity of 58% (entry 15). Improved activity was also seen with catalysts derived from the *t*-butyl-substituted aryloxazoline ligand **4** using NMP as solvent, but only moderate enantioselectivity (43%) was observed (entry 16).

In conclusion, BINAP and a range of phosphinamine ligands were screened in asymmetric Heck reactions of triflate **2a**. Palladium complexes formed from $Pd_2(dba)_3$ and BINAP gave cyclised products in up to 65% yield and 85% ee. The *t*-butyl-substituted ferrocenyloxazoline ligand **5** afforded the optimal enantioselectivity of 85% for the range of phosphinamine ligands tested. Variation of solvent and base appears to indicate that this system is very sensitive to catalyst deactivation and that a combination of either toluene or NMP with potassium carbonate as base was required for acceptable catalytic activity. Catalysts prepared from palladium complexes of the oxazoline ligands (**4**–**6**) were less reactive than the corresponding BINAP catalysts. However, the excellent enantioselectivities obtained (up to 85%) using phosphinamine ligands suggests that there is potential for the application of their palladium complexes in this reaction. Further work on this and related substrates is in progress and will be reported in due course.

Acknowledgements

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15. An oven-dried 10 mL Schlenk flask was flushed with nitrogen for 5 min and then charged with racemic BINAP (9.2 mg, 0.015 mmol), $Pd_2(dba)_3$ (6.7 mg, 0.0075 mmol) and toluene (0.5 mL). The purple suspension thus obtained was stirred for 1 h under a nitrogen atmosphere and had then become an orange solution. Methyl 1-[4-

[(trifluoromethyl)sulfonyl]oxy] - 3(*Z*) - butenyl - 2,5 - cyclohexadiene-1-carboxylate (50 mg, 0.15 mmol) was then added in toluene (1.0 mL) followed by potassium carbonate (41.4 mg, 0.3 mmol). The reaction mixture was degassed by the freeze–thaw–pump method (×3), sealed and heated at 60°C for 72 h. The reaction mixture was allowed to cool to room temperature, then diluted with ether (5 mL), washed with brine (5 mL), dried over magnesium sulfate and concentrated in vacuo. The crude residue was further purified by column chromatography on silica gel (10:1 hexane/ether) to give methyl-3,8a-dihydro-4a-4*H*-naphthalenecarboxylate as a colourless oil (14.0 mg, 51%).

16. NMR data for **1a**: ^{1}H NMR (300 MHz $CDCl_3$): $\delta = 5.94$ (ddd, 1H, $J = 9.5$, 5.1, 0.7 Hz, H_5), 5.79 (m, 1H, H_4), 5.60–5.75 (m, 3H, $H_{4'}$, H_3, H_6), 5.56 (d, 1H, 9.7 Hz, $H_{3'}$), 3.72 (s, 3H, OMe), 3.61 (m, 1H, H_2), 1.93–2.10 (m, 2H, $H_{2'a,b}$), 1.85–1.90 (m, 2H, $H_{1'a,b}$). ^{13}C NMR (75.4 MHz $CDCl_3$): $\delta = 176.1$ (C(O)), 129.7 (CH), 128.9 (CH), 126.7 (CH), 125.7 (CH), 124.0 (CH), 120.6 (CH), 52.3 (OMe), 46.0 (C_1), 36.1 (C_2), 27.4 ($C_{2'}$), 21.7 ($C_{1'}$).