Pergamon

Tetrahedron Letters 41 (2000) 7757–7761

TETRAHEDRON LETTERS

Intermolecular asymmetric Heck reactions with 2,2-diethyl-2,3-dihydrofuran

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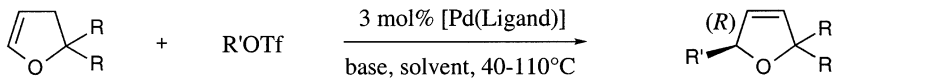
Received 16 June 2000; accepted 1 August 2000

Abstract

Palladium-catalysed intermolecular asymmetric Heck reactions were performed on 2,2-diethyl-2,3-dihydrofuran using chiral diphosphine and phosphinamine ligands. The steric effect of increased bulk at the 2-position was examined for phenylations and cyclohexenylations and lower chemical yields, but similar enantioselectivities were obtained compared to the 2,2-dimethyl analogue. The optimum ee for phenylation was 94% and for cyclohexenylation was 93%, both obtained with the *t*-Bu-substituted diphenylphosphinoaryloxazoline ligand.

The asymmetric intermolecular Heck reaction, a useful palladium(0)-catalysed carbon–carbon bond forming transformation, was first reported by Hayashi in 1991.[1] Their study, as with subsequent investigations by a range of other workers, used 2,3-dihydrofuran **1** as the test substrate to determine and compare the reactivities and enantioselectivities of a range of chiral ligands.[2–4] The possibility of double bond isomerisation for this substrate means that in some cases different ligands lead to predominantly different products and therefore a direct comparison of their selectivity is not possible. We recently reported 2,2-dimethyl-2,3-dihydrofuran **2** as a useful test substrate for the intermolecular asymmetric Heck reaction as it allows for easy and direct comparison of a wide range of ligands as only one regioisomeric product can be formed.[5] Our initial application of this substrate was in the asymmetric phenylation and cyclohexenylation of dihydrofuran **2**, which proceeded in high yields and enantioselectivities of up to 98% of product **3** and 97% of product **4**, Scheme 1.[5,6]



1 R = H R' = Ph **3** R = Me; R' = Ph; up to 98% ee

2 R = Me R' = Cy **4** R = Me; R' = Cy; up to 97% ee

Scheme 1.

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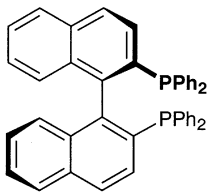
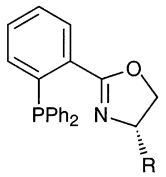
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01325-3

The optimum ee values in our phenylation study with **2** were mostly unchanged when compared to the phenylation of **1** by Hayashi.[1] This was not the case when the cyclohexenylations of **2** were compared with those of **1**,[7] as we observed a significant decrease for palladium complexes of (*R*)-BINAP **5** and for the oxazoline-containing P–N ligands **6**–**9**.[6]

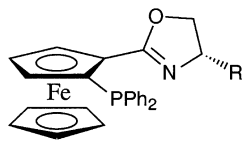
Therefore, in order to investigate the influence of the increased bulk at the 2-position on the ee values obtained, we synthesised 2,2-diethyl-2,3-dihydrofuran **10**, by a modification of literature procedures.[8] In this communication we wish to present our preliminary results on the test reaction of **10** with phenyl trifluoromethanesulfonate and cyclohex-1-en-1-yl trifluoromethanesulfonate, respectively, catalysed by palladium complexes of ligands **5**–**9**.



5

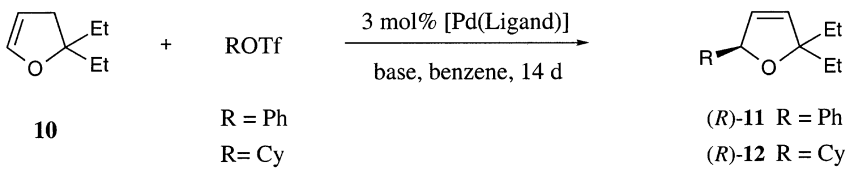


6 R = *i*-Pr
7 R = *t*-Bu



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

The phenylation and cyclohexenylation of **10**, Scheme 2, were carried out using identical reaction conditions to those reported for substrate **2** for comparative purposes and the results obtained are given in Table 1 (note: racemic 2,2-diethyl-5-phenyl-2,5-dihydrofuran **11** and 5-cyclohex-1′-en-1′-yl-2,2-diethyl-2,5-dihydrofuran **12**, required for GC analysis, were prepared using Larock's procedures from dihydrofuran **10** and iodobenzene and 1-iodocyclohexene, respectively).[9,10]



10

R = Ph
R= Cy

(*R*)-**11** R = Ph
(*R*)-**12** R = Cy

Scheme 2.

The yields obtained with palladium complexes of (*R*)-BINAP **5** were low and the enantioselectivities were moderate (54–64%). This compares unfavourably with the yields of 52–100% and ee values of 70–76% obtained in the phenylation of dihydrofuran **2**. The yield using the *i*-Pr-substituted diphenylphosphinoaryloxazoline ligand **6** was low (16%) and only a moderate ee was achieved in contrast to when **2** was used as substrate (44 versus 81%). The yield increased when the *t*-Bu-substituted analogue **7** was tested, as was noted with **2**, and a moderate ee (50%) was achieved with N(*i*-Pr)$_2$Et as base (entry 4). When 1,8-bis(dimethylamino)naphthalene (proton sponge) was used a 74% yield and an optimised ee of 94% was obtained. When the *i*-Pr- or *t*-Bu-substituted diphenylphosphinoferrocenyloxazoline ligands **8** or **9** were tested, low yields (7–17%) were observed and the ee values were also poor (25–43%). This represents a significant lowering of ee compared to that obtained (92–98%) with the less bulky substrate **2**.[5] Therefore, the optimal ee for the phenylation of dihydrofuran **10** was 94%, although in this case it was with the *t*-Bu-substituted diphenylphosphinoaryloxazoline ligand **7**.

Table 1
Asymmetric phenylation and cyclohexenylation of **10**

Entry	Ligand	Base	T/°C	% Yield[a]	Product (% ee)[b,c]
1	**5**[d]	Proton sponge	40	23	**11** (64)
2	**5**[d]	N(*i*-Pr)$_2$Et	40	47	**11** (54)
3	**6**[e]	Proton sponge	80	16	**11** (44)
4	**7**[e]	N(*i*-Pr)$_2$Et	80	33	**11** (50)
5	**7**[e]	Proton sponge	80	74	**11** (94)
6	**8**[e]	Proton sponge	80	7	**11** (25)
7	**9**[e]	Proton sponge	80	17	**11** (43)
8	**5**[d]	Proton sponge	40	32	**12** (14)
9	**5**[d]	N(*i*-Pr)$_2$Et	40	34	**12** (39)
10	**6**[e]	Proton sponge	40	11	**12** (87)
11	**7**[e]	Proton sponge	40	24	**12** (93)
12	**7**[e]	N(*i*-Pr)$_2$Et	40	34	**12** (82)
13	**8**[e]	Proton sponge	40	5	**12** (37)
14	**9**[e]	Proton sponge	40	16	**12** (25)

[a] Yields were calculated by GC (SE-30, 30 m, 11 psi He), 50°C for 4 min, 15°C min^{-1} up to 170°C, $t_R = 13.7$ min for product **11**, $t_R = 13.5$ min for product **12** and $t_R = 14.1$ min for tridecane.

[b] Enantiomeric excesses were determined by GC on a Chiraldex™ γ-cyclodextrin TFA capillary column (30 m × 0.25 m, 15 psi He); 80°C, 0.3°C min^{-1} up to 92°C, 5°C min^{-1} up to 130°C, ($t_R = 52.0$ (*R*) and 52.4 (*S* min) for **11**; 65°C, 0.3°C min^{-1} up to 95°C, 5°C min^{-1}, 95°C, 0.3°C min^{-1} up to 105°C, 1°C min^{-1}, 5°C min^{-1} up to 130°C ($t_R = 79.3$ (*R*) and 79.9 (*S*) min) for **12**.

[c] The absolute configuration was determined to be (*R*) by comparison of the chiral GC retention times and optical rotations of **11** and **12** with optically pure samples of (*R*)-2-phenyl-2,5-dihydrofuran and (*R*)-2-cyclohex-1′-en-1′-yl-2,5-dihydrofuran, respectively.

[d] Pd^0 complexes formed in situ from Pd(OAc)$_2$ and **6**.

[e] Pd^0 complexes formed in situ from Pd$_2$(dba)$_3$ and phosphinamines **7**–**10**.

When palladium complexes of (*R*)-BINAP **5** were tested in the cyclohexenylation of **10**, the ee values (14–39%) and the yields (32–34%) were low, but similar to those obtained with dihydrofuran **2**. The *i*-Pr-substituted diphenylphosphinoaryloxazoline ligand **6** also gave a low yield (11%), but with a good ee of 87%, again a similar result to that obtained with dihydrofuran **2** (23% yield, 83% ee).[6] With the *t*-Bu-substituted analogue **7**, somewhat higher yields were obtained (24–34%), although these were lower than with **2** (26–68%).[6]

Good ee values of 82–93% were obtained with this ligand and proton sponge as base afforded our optimal result in this series (93%, entry 11), whilst the use of N(*i*-Pr)$_2$Et gave a slightly lowered ee of 82% (entry 12). The yield obtained when the *i*-Pr-substituted diphenylphosphinoferrocenyloxazoline ligand **8** was used was extremely poor (5%) and the ee decreased from when the less bulky dihydrofuran **2** was used (37 versus 76%). The yield for the *t*-Bu-substituted analogue **9** was only slightly higher (16%) and the ee was even lower (25%), which represents a large decrease when the same catalyst system was used for the cyclohexenylation of **2** (88% yield, 73% ee).

To conclude, we have seen that the increased bulk at the 2-position of 2,2-disubstituted-2,3-dihydrofurans does affect both the yields and ee values of the asymmetric Heck reactions conducted upon them. In general, a decline in chemical yield was noted for reactions using the diethyl substituted substrate **10** compared with those using the dimethyl-substituted substrate **2**.

This may be due to increased ligand–reactant steric interactions in the migratory insertion transition state caused by the bulkier alkene (**10** versus **2**). Overall, the ee values decreased slightly when complexes of ligand **5** were employed, remained reasonably constant for complexes of ligands **6** and **7**, but surprisingly fell dramatically for complexes of the diphenylphosphinoferrocenyloxazolines **8** and **9**. The reason for the oxazoline-containing ligands **6**–**7** and **8**–**9** to behave so differently must lie in their subtle steric and electronic differences. This work again highlights the difficulty in finding a ligand suitable for a wide spectrum of substrates and the need for a tailoring of ligands to each substrate used. Further studies on related substrates are in progress and will be reported in due course.[11]

Acknowledgements

This Asymmetric Heck project and A.J.H. have been supported by an Enterprise Ireland Basic Research Award (SC/96/435) and a President's Research Award (RP100) to P.J.G. Y.M.M. and D.J.C. received financial support from Enterprise Ireland Research Scholarships BR/94/024 and BR/99/238, respectively. The award of the BOC Gases Postgraduate Bursary to Y.M.M. and A.J.H. in 1997 and 1998, respectively, is gratefully acknowledged. We thank Merck Sharpe & Dohme (Ireland Ltd) for their support of and interest in our Heck research, Schering Corporation (USA) for their support of D.J.C. and Johnson Matthey for a loan of Pd salts.

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10. Selected data for **11**: ^{1}H NMR (270 MHz): δ ($CDCl_3$) 0.88–0.97 (6H, m, 2×CH_3), 1.59–1.81 (4H, m, 2×H_2C), 5.78–5.83 (2H, m, *H*C(3), HC(5)), 5.88 (1H, dd, *J* 5.91, 1.69, *H*C(4)) and 7.24–7.37 (5H, m, Ph); ^{13}C NMR (67.5 MHz): δ ($CDCl_3$) 8.94 (CH_3), 9.56 (CH_3), 31.88 (H_2C-C(2)), 33.00 (H_2C-C(2)), 87.99 (H*C*(5)), 94.71 (*C*(2)), 128.11 (27×*m*-Ph), 128.89 (2×*o*-Ph), 130.15 (H*C*(3)) and 133.54 (H*C*(4)), 142.51 (*ipso*-Ph); ν_{max} (CH_2Cl_2) 1640 (w) (C=C) cm^{-1}; *m*/*z* (eims 70 eV) 202 (M^+, 1%), 201(8), 173(33), 115(18), 105(44), 57(47) and 29(100). Selected data for **12**: ^{1}H NMR (270 MHz): δ ($CDCl_3$) 0.84–0.92 (6H, m, 2×CH_3), 1.47–1.72 (8H, m, 2×CH_2, H_2C(4′), H_2C(5′)),

1.82–2.02 (4H, m, H_2C(3′), H_2C(6′)), 5.09 (1H, m, HC(2′)) and 5.67–5.74 (3H, m, HC(3), HC(4), HC(5)); ^{13}C NMR (67.5 MHz): δ ($CDCl_3$) 8.39 (CH_3), 8.97 (CH_3), 22.61 (H_2C(4′)), 22.69 (H2C(5′)), 24.24 (H_2C(3′)), 25.19 (H_2C(6′)), 30.93 (H_2C-C(2)), 32.45 (H_2C-C(2)), 90.42 (HC(5)), 93.14 (C(2)), 124.59 (HC(2′)), 128.92 (HC(3)), 133.19 (HC(4)) and 137.83 (C(1′)); ν_{max} (CH_2Cl_2) 1620 (w) (C=C) cm^{-1}; m/z (eims 70 eV) 206 (M^+, 5%), 205(4), 178(17) and 177(100).

11. Hennessy, A. J.; Kilroy, T.; Malone, Y. M.; Guiry, P. J., unpublished results.