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LETTERS

# 2,2-Dimethyl-2,3-dihydrofuran, a new substrate for intermolecular asymmetric Heck reactions

Alan J. Hennessy, Yvonne M. Malone and Patrick J. Guiry *
*Department of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland*

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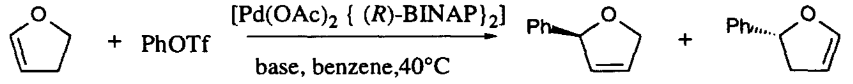
**Abstract**

2,2-Dimethyl-2,3-dihydrofuran is tested as a new substrate for the intermolecular asymmetric Heck reaction. Phenylation proceeded in enantioselectivities of up to 98% ee with $Pd^0$ complexes of diphenylphosphinoferrocenyloxazoline ligands. © 1999 Elsevier Science Ltd. All rights reserved.

The Heck reaction is a Pd-catalysed elaboration of substituted alkenes by direct C–C bond formation at a vinylic carbon centre.[1] It has evolved into a synthetic transformation whose potential has only recently been exploited in the key steps of many total syntheses[2] and a better understanding of the reaction mechanism continues to emerge.[3] Both intramolecular and intermolecular asymmetric variants have been extensively studied.[4] The cyclic olefin investigated by Hayashi in asymmetric intermolecular arylation studies was 2,3-dihydrofuran **1**.[5] The asymmetric induction obtained was due to Pd complexes of (*R*)-BINAP **2** and a mixture of regioisomers **3** and **4** were obtained, with isomer **4** being formed in 96% ee, favoured over **3** in a 71:29 ratio when 1,8-bis(dimethylamino)naphthalene [proton sponge] was used as the base (Scheme 1).



**1** **(*S*)-3** **(*R*)-4**

Scheme 1.

In an important extension to this work, Pfaltz has described the application of diphenylphosphinooxazoline ligands to the arylation and alkenylation of substrate **1** with complexes of diphenylphosphinooxazoline **5b** affording both the best enantioselectivities and catalyst activity.[6] In contrast to the regioisomer problem observed by Hayashi, the phenylation of dihydrofuran **1** produced only (*R*)-**3** in 97% ee.

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* Corresponding author.

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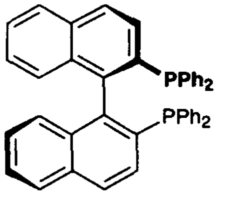
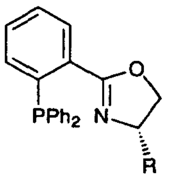
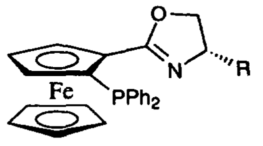


**2**

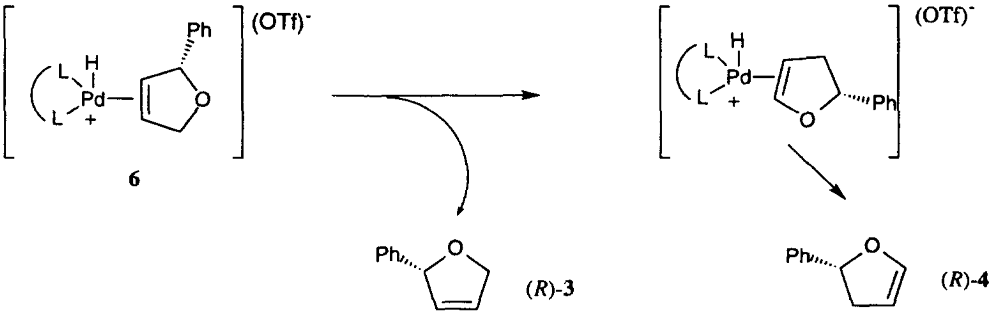


**5a**: R = *i*-Pr
**5b**: R = *t*-Bu



**8a**: R = *i*-Pr
**8b**: R = *t*-Bu

One explanation for the difference in product distribution between these catalyst systems is that the olefin-bound complex **6**, formed after migratory insertion and β-elimination, is more prone to dissociation to give **3** in Pd{P–N} catalyst systems than in the Pd{P–P} catalyst system, where a reverse β-elimination followed by β-elimination and dissociation affords **4** (Scheme 2).[7]



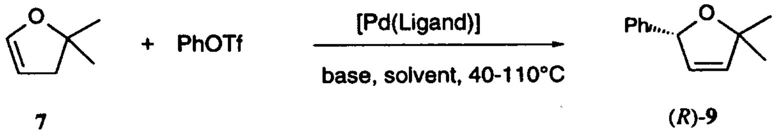
Scheme 2.

Mechanistically it is clear that isomer **4** can only be formed when there is an H-substituent at C-2. A dihydrofuran disubstituted at this position would be a substrate which would provide a true comparative test of reactivity and enantioselectivity for a range of $Pd^0$ complexes. This is not the case when using substrate **1** as the final isomer ratio and enantioselectivities are complicated by kinetic resolution processes.[8]

Therefore, 2,2-dimethyl-2,3-dihydrofuran **7** was prepared by a four-step route from propargyl alcohol and acetone, by modifying procedures reported for related compounds.[9] Herein we now report our initial findings on the phenylation of **7** with palladium complexes derived from a range of chiral ligands, from diphosphine **2**, to the diphenylphosphinoaryloxazolines **5** and diphenylphosphinoferrocenyloxazolines **8**. The latter class of ligands were independently prepared by our group[10] and have been successfully applied in asymmetric catalysis.[11]

The results of our initial investigations on the phenylation of dihydrofuran **7** are given in Table 1.

Using $Pd^0$ complexes (3 mol%) formed in situ from $Pd(OAc)_2$ and (*R*)-BINAP **2**, phenylation gave (*R*)-2,2-dimethyl-5-phenyl-2,5-dihydrofuran **9**[12] (Scheme 3) in consistently good ees and in good yield, except when proton sponge was used as base. The chemical yields observed using catalysts prepared in situ from $Pd_2(dba)_3$ and diphenylphosphinoaryloxazoline ligand **5a** were poor although the ees improved to 81%. As in the Pfaltz work[6] the more sterically demanding *tert*-butyl substituted ligand **5b** afforded a more reactive catalyst and ees in the range of 89–92% were obtained with benzene being the best solvent. A change to diphenylphosphinoferrocenyloxazoline ligand **8a** gave similar ees and chemical yields to that of **5a**. Our best results were obtained using ligand **8b** although the chemical yields were highly dependent on the base employed. Proton sponge gave poor chemical yields but consistently high ees, whereas Hünig's base gave 98% ee in 68% yield and triethylamine gave our optimal result of 98% ee



7

(*R*)-9

Scheme 3.

Table 1
Asymmetric phenylation of furan 7[13]

| Entry | Ligand | Solvent | Base | *T*/ °C | Yield (%)[a] | Ee (%)[b] (config.)[c] |
|---|---|---|---|---|---|---|
| 1 | **2**[d] | Benzene | Proton Sponge | 40 | 52 | 76 (*R*) |
| 2 | **2**[d] | Benzene | *i*-$Pr_2NEt$ | 40 | 100 | 76 (*R*) |
| 3 | **2**[d] | Benzene | $Et_3N$ | 40 | 95 | 70 (*R*) |
| 4 | **5a**[e] | Toluene | Proton Sponge | 110 | 13 | 76 (*R*) |
| 5 | **5a**[e] | Benzene | Proton Sponge | 80 | 23 | 81 (*R*) |
| 6 | **5b**[e] | Toluene | Proton Sponge | 110 | 37 | 89 (*R*) |
| 7 | **5b**[e] | Benzene | Proton Sponge | 80 | 100 | 92 (*R*) |
| 8 | **8a**[e] | Toluene | Proton Sponge | 110 | 34 | 78 (*R*) |
| 9 | **8a**[e] | Benzene | Proton Sponge | 80 | 42 | 79 (*R*) |
| 10 | **8b**[e] | Benzene | Proton Sponge | 80 | 27 | 95 (*R*) |
| 11 | **8b**[e] | Benzene | *i*-$Pr_2NEt$ | 80 | 68 | 98 (*R*) |
| 12 | **8b**[e] | Benzene | $Et_3N$ | 80 | 90 | 98 (*R*) |
| 13 | **8b**[e] | Toluene | Proton Sponge | 110 | 57 | 92 (*R*) |
| 14 | **8b**[e] | Toluene | *i*-$Pr_2NEt$ | 110 | 45 | 92 (*R*) |

[a] Conversions by GC (SE-30, 30 m, 11 psi He), 50 °C for 4 min, 15 °C $min^{-1}$ up to 170°C, $t_R$ = 13.5 min for for product **9** 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 x 0.25 m, 15 psi He); 80 °C, 0.3 °C $min^{-1}$ up to 90°C, 5 °C $min^{-1}$ up to 110°C, ($t_R$=29.6 (*S*) and 30.9 (*R*) min) for **9**.[14] [d] Absolute configuration shown assumes the same sense of asymmetric induction as with 2,3-dihydrofuran as the optical rotation was also (+) and the (*R*)-isomer had the longer retention time.[6a] [d]$Pd^0$ complexes formed *in situ*. from $Pd(OAc)_2$ and (*R*)-BINAP. [e]$Pd^0$ complexes formed *in situ*. from $Pd_2(dba)_3$ and phosphinamines **5**, **8**.

in 90% yield. This contrasts with Hayashi's work where proton sponge gave the highest ee and Hünig's base and triethylamine afforded lower ee values (82 and 75%, respectively).[5]

In conclusion, we have tested a range of Pd-complexes in the intermolecular phenylation of 2,2-dimethyl-2,3-dihydrofuran and have obtained upto 98% ee with diphenylphosphinoferrocenyloxazoline ligands, the first time this class has been applied in this reaction. This work highlights 2,2-dimethyl-2,3-dihydrofuran as a new and useful substrate for the asymmetric Heck reaction which allows easy and direct comparison of a wide range of ligands. Further studies on this and related substrates are in progress and will be reported in due course.[15]

## Acknowledgements

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7. One intermediate **6** is shown for clarity and (*S*)-**3** and (*S*)-**4** are formed in a similar manner from the C2-epimer of **6**.
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12. Selected data for **9**: Found: HRMS, $M^+$, 174.0958. $C_{12}H_{14}O$ requires $M^+$: 174.1045; $\delta_H$ (500 MHz) 1.40 (3H, s, $CH_3$), 1.46 (3H, s, $CH_3$), 5.74 (1H, dd, $J$=1.5 and 5.9 Hz, *H*C(3)), 5.80 (1H, dd, $J$=1.7 and 2.38 Hz, *H*C(5)), 5.89 (1H, dd, $J$=2.4 and 5.9 Hz, *H*C(4), 7.25–7.36 (5H, m, Ph); $\delta_C$ (125.7 MHz) 27.89, 28.86, 86.89, 126.67, 126.93, 127.89, 128.32, 128.64, 135.71, and 141.98; $\nu_{max}$ ($CH_2Cl_2$)/cm$^{-1}$: 3124 (s), 3070 (s), 2992 (s), 1445 (m), 1260 (s), 895 (m), and 728 (s); *m/z* (EI, 70 eV) 174 (10%, $M^+$), 159 (26), 123 (47), 105 (100), 91(10), 77 (39), and 55 (15). $[\alpha]^{21}_{D}$=+152.4 [98% ee] (*c* 0.1, $CH_2Cl_2$).
13. Typical procedure: A solution of phenyl trifluoromethanesulfonate (30 mg, 0.13 mmol) and tridecane (10 mg, 0.054 mmol) in benzene (0.5 ml) was added to a Schlenk containing $Pd_2(dba)_3$ (2.3 mg, 0.004 mmol) and ligand (0.008 mmol) under $N_2$. To this was added 2,2-dimethyl-2,3-dihydrofuran (63.7 mg, 0.65 mmol) and base (0.39 mmol). The resulting red solution was then degassed by three freeze-thaw cycles at 0.01 mbar and then left to stir under $N_2$ at 80°C for 14 days giving a red solution with precipitation of base·HOTf. Pentane (10 ml) was then added to the reaction mixture and the resulting suspension was filtered through 2 cm of silica with further elution using diethyl ether (10 ml). This solution was concentrated and the yield calculated using GC. Further purification by preparative TLC gives 2,2-dimethyl-5-phenyl-2,5-dihydrofuran **9**.
14. Racemic 2,2-dimethyl-5-phenyl-2,5-dihydrofuran required for GC analysis was prepared from furan **7** and iodobenzene using literature procedures: Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603.
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