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The asymmetric cyclohexenylation of 2,2-dimethyl-2,3-dihydrofuran

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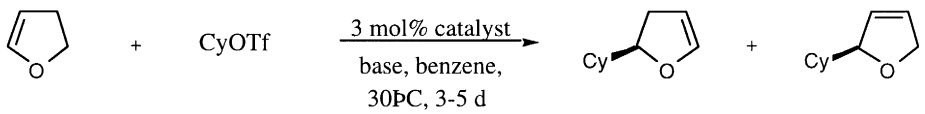
Abstract

The palladium catalysed asymmetric cyclohexenylation of 2,2-dimethyl-2,3-dihydrofuran is described. Use of this substrate allowed for an easy and direct comparison of a range of ligands in this reaction. The ligands employed included BINAP and phosphinamines and enantioselectivities of up to 97% were obtained with *tert*-leucinol-derived diphenylphosphinoaryloxazolines.

Enantioselective Heck reactions were first reported in 1989 and since then several catalyst systems have been shown to give good reactivities and moderate to excellent control over the regio- and stereochemistry of the products obtained. The asymmetric intramolecular Heck reaction has been developed to the extent that it has been applied in the synthesis of a wide range of complex natural products.[1] The asymmetric intermolecular Heck reaction has been mainly applied to test substrates as a means of developing this asymmetric methodology.[2]

The standard olefinic test substrate used has been 2,3-dihydrofuran **1**.[3] The alkenylation of this substrate by a variety of vinyl triflates was first reported by Hayashi with palladium complexes of (*R*)-BINAP **2** in the presence of 1,8-bis(dimethylamino)naphthalene (proton sponge) as base giving high enantioselectivities (87%) of product **3**.[4] Using palladium complexes of ligand **5**, Pfaltz obtained excellent yields and enantioselectivities (99%) of product **4**.[5] As ligands **2** and **5** lead to different products, when 2,3-dihydrofuran is used as substrate, a direct comparison of their selectivity is not possible, Scheme 1.



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

Scheme 1.

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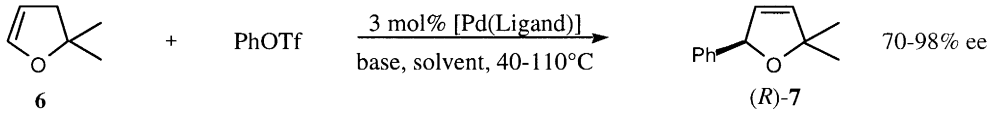
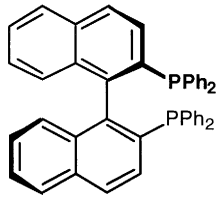
We recently reported 2,2-dimethyl-2,3-dihydrofuran **6** as a new test substrate for the intermolecular Heck reaction as it allows for easy and direct comparison of a wide range of ligands due to the fact that only one regioisomer can be formed.[6] Our initial application of this substrate was in the asymmetric phenylation of dihydrofuran **6**, which proceeded in high yield and enantioselectivities of up to 98% of product **7**, Scheme 2.



6 (*R*)-**7**

Scheme 2.

We now wish to report our preliminary work on the asymmetric, intermolecular Heck alkenylation of dihydrofuran **6**.[7] The ligands which we screened were (*R*)-BINAP **2**, the diphenylphosphinoaryloxazolines **5** and **8** and the diphenylphosphinoferrocenyloxazolines **9** and **10**. The results obtained using these ligands in the test reaction of **6** with cyclohex-1-en-1-yl trifluoromethanesulfonate **11**, Scheme 3, are given in Table 1.



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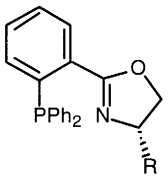
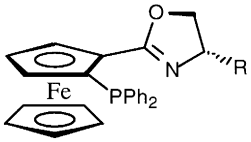


5: R = *t*-Bu
8: R = *i*-Pr

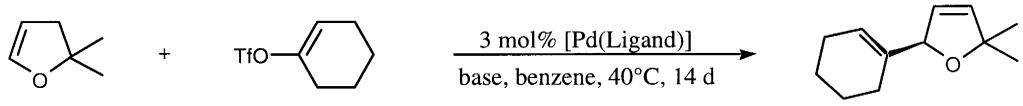


9: R = *i*-Pr
10: R = *t*-Bu

The first experiments used palladium complexes of (*R*)-BINAP **2** generated in situ from $Pd(OAc)_2$ and **2**. The yields of (*R*)-5-cyclohex-1′-en-1′-yl-2,2-dimethyl-2,5-dihydrofuran **12**[8] were moderate (34-52%, entries 1–3) and the ees obtained were poor (optimized to 37% using $N(i\text{-}Pr)_2Et$ as base). With the preformed Pd(0)-BINAP catalyst[9] yields were even lower (12–15%, entries 3–6) and an optimal ee of 35% was attained using proton sponge as base. These results compare poorly with those obtained by Hayashi using 2,3-dihydrofuran **1** as substrate, vide infra.[4] This lowered enantioselectivity was not observed in the phenylation of 2,2-dimethyl-2,3-dihydrofuran **6** as similar ees in the range 70–76% were observed.[6] This may be due to increased ligand-reactant steric interactions in the migratory insertion transition state caused by both a bulkier alkene (**6** versus **1**) and a bulkier nucleophilic component (cyclohexenyl versus phenyl) when BINAP is the ligand.

The next catalysts tested were generated in situ from $Pd_2(dba)_3 \cdot dba$ and the diphenylphosphinooxazolines **5**, **8**, **9** and **10**, respectively. The catalyst derived from the *i*-Pr substituted ligand **8** exhibited low reactivity (13–33% yield, entries 7–9) but a marked improvement in enantioselectivity of up to 83% when proton sponge was the base (entry 7). With the *t*-Bu substituted ligand **5** a more reactive catalyst was formed and the chemical yield increased to 68% with an optimal ee of 97% (entry 10). For complexes derived from **5** and **8**, proton sponge gave both higher chemical yields and enantioselectivities compared to the trialkylamines tested. These results contrast with the work of Pfaltz who reported excellent ees (>98%) and yields (>92%) with a variety of amine bases in the cyclohexenylation of 2,3-dihydrofuran **1**.[5b]

We have reported that palladium complexes of the analogous diphenylphosphinoferrocenyloxazoline ligands **9** and **10**,[10] gave ees of up to 98% in the phenylation of dihydrofuran **6**.[6] Complexes derived from the *i*-Pr substituted ligand **9** once again gave poor yields (17–19%, entries 13 and 14) and an optimum enantioselectivity of 76% when proton sponge was used as base (entry 13). The palladium catalyst prepared from the *t*-Bu substituted ligand **10** gave improved yields (73–88%) and high ees (73–87%),



6 **11** (*R*)-**12**

Scheme 3.

Table 1
Asymmetric cyclohexenylation of **6**

Entry	Ligand	Base	Yield (%)[a]	Ee (%)[b] (config.)[c]
1	**2**[d]	Proton Sponge	34	19 (*R*)
2	**2**[d]	*i*-Pr_2NEt	44	37 (*R*)
3	**2**[d]	Et_3N	52	18 (*R*)
4	**2**[e]	Proton Sponge	12	35 (*R*)
5	**2**[e]	*i*-Pr_2NEt	15	16 (*R*)
6	**2**[e]	Et_3N	13	18 (*R*)
7	**8**[f]	Proton Sponge	33	83 (*R*)
8	**8**[f]	*i*-Pr_2NEt	13	22 (*R*)
9	**8**[f]	Et_3N	23	22 (*R*)
10	**5**[f]	Proton Sponge	68	97 (*R*)
11	**5**[f]	*i*-Pr_2NEt	60	40 (*R*)
12	**5**[f]	Et_3N	26	38 (*R*)
13	**9**[f]	Proton Sponge	19	76 (*R*)
14	**9**[f]	*i*-Pr_2NEt	17	22 (*R*)
15	**10**[f]	Proton Sponge	88	73 (*R*)
16	**10**[f]	*i*-Pr_2NEt	73	87 (*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 = 13.2 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 x 0.25 m, 15 psi He); 80 •C, 0.3 •C min^{-1} up to 90•C, 5 •C min^{-1} up to 130•C, (t_R=22.0 (*S*) and 22.6 (*R*) min) for **12**.[11] [c] Absolute configuration shown assumes the same sense of asymmetric induction as with 2,3-dihydrofuran by comparison of the optical rotations of **12** and an enantiopure sample of (*R*)-**4**.[5b] [d] Pd^0 complexes formed *in situ* from $Pd(OAc)_2$ and (*R*)-BINAP. [e] Pd^0 BINAP complexes pre-formed.[8] [f] Pd^0 complexes formed *in situ* from $Pd_2(dba)_3$ and phosphinamines **5**, **8**.

which were not as dependent upon the choice of base as complexes made from **5**, **8** or **9** were. The highest ee was still lower than that observed when ligand **5** was employed (87 versus 97%). In addition, the catalyst derived from **10**, which gave our best ee in the corresponding phenylation of dihydrofuran **6**, was not as successful in the corresponding cyclohexenylation of the same substrate (98 versus 87%).

The reasons why complexes derived from ligand **10** are superior to those from ligand **5** for the

phenylation and not the cyclohexenylation of **6** and the greater reactivity and selectivity of the palladium complexes from *i*-Pr substituted ligands (**8**, **9**) compared to the *t*-Bu substituted ligands (**5**, **10**) underline how the electronic and steric properties of ligands must be finely tuned for individual substrates. To date a ligand which provides the maximum reactivity and selectivity across a wide range of substrates remains elusive.

In conclusion, catalysts derived from a range of ligands have been directly compared in the asymmetric cyclohexenylation of 2,2-dimethyl-2,3-dihydrofuran **6**. The diphosphine (*R*)-BINAP **2** gave poor results in comparison to use of 2,3-dihydrofuran **1** as substrate, regardless of whether it was made in situ or preformed. More reactive and more enantioselective catalysts were derived from phosphinamine ligands and our highest enantioselectivity of 97% was obtained using complexes derived from the *t*-Bu substituted diphenylphosphinoaryloxazoline ligand **5**. The choice of amine base was also crucial for both diphosphine and phosphinamine chelating ligands with proton sponge giving better results than trialkylamines. Further studies on the application of substrate **6** and related substrates in the asymmetric intermolecular Heck reaction will be described in future publications from these laboratories.[12]

Acknowledgements

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8. Selected data for **12**: found: C, 80.6; H, 10.3. $C_{14}H_{22}O$ requires C, 80.9; H, 10.2. ^{1}H NMR (270 MHz): δ ($CDCl_3$) 1.30 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.50–1.67 (m, 4H, H_2C(4′), H_2C(5′)), 1.83–2.08 (m, 4H, H_2C(3′), H_2C(6′)), 5.14 (1H, m, *H*C(2′), 5.56 (1H, dd, *J* 1.46, 6.04, *H*C(3)), 5.73 (1H, m, *H*C(5)) and 5.77 (1H, dd, *J* 2.44, 5.86, *H*C(4)); ^{13}C NMR (67.5 MHz): δ ($CDCl_3$) 22.61 (H_2C(4′)), 22.64 (H_2C(5′)), 23.65 (H_2C(3′)), 25.20 (H_2C(6′)), 27.91 (*C*H_3), 28.41 (*C*H_3), 87.27 (*C*(2)), 89.80 (H*C*(5)), 124.93 (H*C*(2′)), 127.39 (H*C*(3)), 136.16 (H*C*(4)) and 137.90 (*C*(1′)); ν_{max} (CH_2Cl_2) 1620 (w) (C=C) cm^{-1}; *m/z* (eims, 70 eV) 178 (M^+, 3%), 167 (7), 151 (10), 109 (35), 97 (60) and 57 (100).
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