The Application of HETPHOX Ligands to the Asymmetric Intermolecular Heck Reaction of 2,3-Dihydrofuran and 2,2-Disubstituted-2,3-Dihydrofurans

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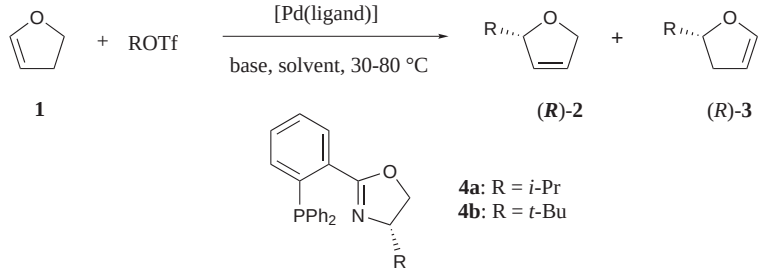
Abstract: A series of thiophene- and benzothiophene-oxazoline containing ligands, were applied in the intermolecular asymmetric phenylation and cyclohexenylation of 2,3-dihydrofuran **1**. Phenylation proceeded in moderate to high chemical yields, with good regioselectivities and in up to 95% ee. Cyclohexenylations gave similarly high chemical yields and regioselectivities with the optimal result being a 96% yield of the major product in 97% ee. 2,2-Dialkyl-2,3-dihydrofurans were also tested as substrates and the phenylation and cyclohexenylation of 2,2-dimethyl-2,3-dihydrofuran proceeded in high yields and ee's up to 91% and 89%, respectively. The phenylation and cyclohexenylation of the 2,2-diethyl analogue proceeded in excellent yields and ee's up to 99% and 87%, respectively. For each substrate, palladium complexes formed from the *t*-butyl-substituted ligand **10** gave the highest yields, regioselectivities, and enantioselectivities over the broad range of reaction conditions studied. 2,2-Diisopropyl-2,3-dihydrofuran was prepared but was found to be unreactive in the intermolecular Heck reaction thus providing insight into to the steric limits for 2,3-dihydrofuran substrates.

Key words: P,N ligands, oxazoline, asymmetric catalysis, intermolecular Heck reaction, palladium

Introduction

The Heck reaction, the palladium(0)-catalysed substitution of a vinylic hydrogen by an aryl, vinyl or benzyl group, is a highly versatile procedure for C–C bond formation.[1] The potential of both intramolecular and intermolecular Heck reactions has been exploited in the key steps of many total syntheses and a better understanding of the reaction mechanism continues to emerge.[2–4] The asymmetric variant has been extensively studied and applied in natural product total synthesis.[5,6] Since the first enantioselective intermolecular Heck reactions by Hayashi using the diphosphine ligand BINAP,[7] there has been a recent emphasis on the application of new classes of chiral ligands. The first use of P,N ligands in this reaction was reported by Pfaltz who described the arylation and cyclohexenylation of 2,3-dihydrofuran (**1**, Scheme 1).[8] In contrast to the regioisomer problem encountered by Hayashi who formed both the kinetic and thermodynamic products (**2** and **3**), the application of palladium complexes of diphenylphosphinooxazoline ligands **4** produced only (*R*)-**2** in 97% ee.

Since that study a range of oxazoline-containing ligands have been applied to this reaction by the groups of Gilbertson, Hashimoto, and Hou with similar high levels of regioselectivity and enantioselectivities.[9] We also reported the application of diphenylphosphinoferrocenyloxazoline ligands which gave (*R*)-**2** in moderate to good yields of up to 72% with good regioselectivity for phenylations with consistently high ee's of up to 99%, while cyclohexenylations gave the related cyclohexenylated kinetic isomer in moderate to good yields of up to 75% and good ee's up to 85%.[10] We recently extended the application of diphenylphosphinoaryloxazolines to the asymmetric intramolecular Heck reaction.[11] Related (phosphinophenyl)benzoxazine ligands from Kündig and Meier and *iso*-PINPHOS ligands from Kocovsky followed the same pat-



Scheme 1

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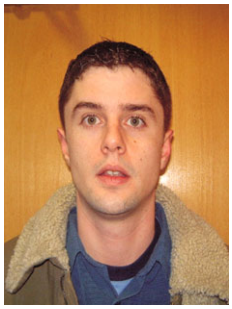
Biographical Sketches



Tim Kilroy was awarded a BSc in Hons. Chemistry from University College Dublin. He graduated with a PhD in Organic Chemistry in November 2003 from U.C.D. Tim studied the intermolecular asymmetric Heck reaction under the supervision of Professor Patrick Guiry. He recently joined Pfizer Little Island, Cork in February 2004 as a development chemist in the technical services department.

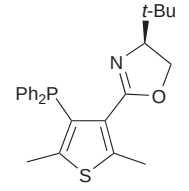
Pier Giorgio Cozzi was born in Legnano (Milan) in 1963. He studied chemistry at the University of Milan where he received his Laurea degree in 1989 working with Professor Cesare Gennari. After spending four years as research associate in Lausanne (Switzerland) with Professor Carlo Floriani he was appointed assistant (1994) and then associate professor (2000) at the University of Bologna. The development of new, enantioselective catalytic reactions, the design of new chiral ligands, and the formations of quaternary stereocenters with new synthetic methodologies are his preeminent interests. Professor Pier Giorgio Cozzi has been visiting professor in the University of Aachen (Germany), Neuchâtel (Switzerland), Ottawa (Canada), Basel (Switzerland), Aarhus (Denmark) and he is participating in two European Networks in the Sixth Framework Program Priority: the European LigBank, and the IBA_2C projects.

Nicole End was born in Zurich, Switzerland in 1967. She studied chemistry at the University of Basel where she received her diploma in 1993 under the guidance of Carsten Bolm. Subsequently she joined the group of Andreas Pfaltz and began working on enantioselective ruthenium-catalyzed epoxidations – both in Basel and at the Max-Planck-Institut für Kohleforschung in Mühlheim, Germany. After finishing her PhD in 1997 she turned on to an industrial career, starting with postdoctoral studies on epothilone at the Novartis Pharma Division, Basel. In 1999 she entered the former Life Science Molecules group of Ciba Speciality Chemicals Inc., conducting research related to the design of novel synthetic concepts for API's. Presently, she holds a position as a research chemist in Ciba's corporate technology group. Her work covers the development of new catalytic and biocatalytic processes with a particular focus on catalytic oxidation reactions. Nicole End is the co-author of several publications, including patents and reviews.

Pat Guiry graduated from University College Dublin with an Honours BSc degree in Chemistry and a PhD under the supervision of Professor Dervilla Donnelly on the application of aryl-lead triacetates to the synthesis of natural products. He moved to the group of Dr John Brown FRS at the Dyson Perrins Laboratory, Oxford University for postdoctoral studies in the area of asymmetric catalysis. He returned to the University College Dublin as a College Lecturer in 1993 where he started his independent research. His research interests are: the design and preparation of chiral ligands and their application in asymmetric catalysis, total synthesis, chemistry/biology of amphetamines. To date he has graduated 15 PhD students and currently has 10 PhD students and 5 postdoctoral researchers in his research group. He has been a Visiting Professor in the group of Professor Andreas Pfaltz at the Max-Planck-Institut für Kohleforschung at Mülheim in 1996 and in the group of Professor Mark Lautens at the University of Toronto in 2004. He was the recipient of a President's Research Award in 1996 and a President's Teaching Award in 2000 from University College Dublin. He was promoted to Senior Lecturer in 2002 and to Professor of Synthetic Organic Chemistry in 2003. He was appointed as Chief Executive of the Conway Institute of Biomolecular and Biomedical Research at University College Dublin in June 2004. A keen tennis player, he represented Ireland in the Italia Cup (ITF World Team Competition) in Berlin and in the Home Nations Series in Glasgow, both in 2003.

tern of both high regioselectivity and enantioselectivity in the intermolecular Heck reaction.[12,13]

Tietze reported the synthesis of novel chiral thiophene-, benzothiophene- and benzofuran-oxazoline ligands **5**–**10** and their application to palladium-catalysed allylic allylations.[14] We have independently prepared the HETPHOX ligands (**8**–**10**) and recently applied them to the iridium-catalysed asymmetric hydrogenation of olefins and imines.[15] These ligands differ in the substitution pattern of the oxazoline unit and diphenylphosphino substituent on the heterocyclic ring. This, coupled with the electronic effect of the sulfur atom, provided an interesting combination of factors whose effects we were interested in studying in the intermolecular Heck reaction and we outlined in preliminary form the application of these ligands in the asymmetric phenylation and cyclohexenylation of 2,3-dihydrofuran (**1**).[16] In this article, we wish to report in full on the synthesis of HETPHOX ligands (**10**, **12**), the application of the thiophene- and benzothiopheneoxazoline-containing ligands **8**–**12** in the asymmetric Heck reactions employing 2,3-dihydrofuran (**1**) and 2,2-dialkyl-2,3-dihydrofurans.



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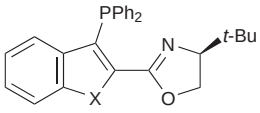
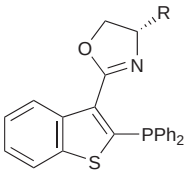
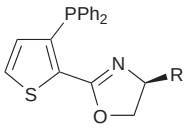


6: X = S
7: X = O



8: R = *i*-Pr
9: R = *t*-Bu
11: R = Ph

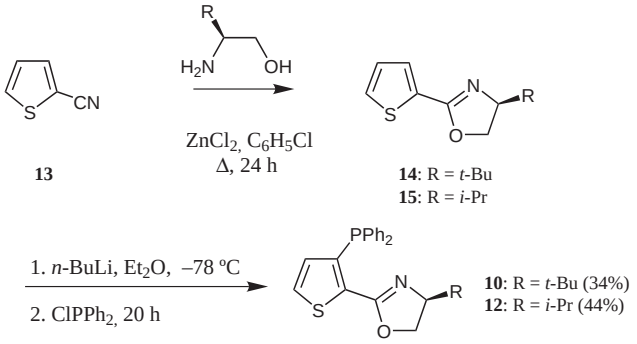


10: R = *t*-Bu
12: R = *i*-Pr

Figure 1

Synthesis of Ligands

The approach taken to prepare ligands **10** and **12** was to use the oxazoline unit to direct metallation followed by reaction with chlorodiphenylphosphine for the introduction of the diphenylphosphine group (Scheme 2). Following Williams's procedure the thiopheneoxazolines **14**, **15** were prepared from 2-cyanothiophene (**13**) in 83% and 85% yields, respectively, after chromatographic purification (CH_2Cl_2–Et_2O, 1:1).[17] Although the procedure gives complete conversion and almost pure products, it is better to perform chromatographic purification in order to facilitate the subsequent metallation step. The choice of Et_2O as solvent is crucial as performing the reaction in THF leads to the introduction of the diphenylphosphine group at the 5-position in low to moderate yields. Selective 3-metallation followed by the addition of chlorodiphenylphosphine afforded the desired ligands **10** and **12** in moderate yields of 34% and 44%, respectively. This is a different route to that reported by Tietze, who formed 3-bromo-2-thiopheneoxazoline from 3-bromo-2-thiophenecarboxylic acid and then introduced the diphenylphosphino group by direct bromo-lithium exchange.[14] The preparation of the benzothiophene ligands and their application in palladium-catalysed allylic substitution and ruthenium-catalysed transfer hydrogenation of ketones has recently been reported by us.[18]



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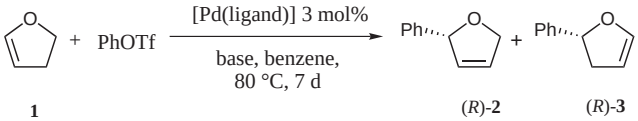
14: R = *t*-Bu
15: R = *i*-Pr

10: R = *t*-Bu (34%)
12: R = *i*-Pr (44%)

Scheme 2

Asymmetric Phenylation of 2,3-Dihydrofuran

Using 3 mol% palladium(0) complexes formed in situ from $Pd_2(dba)_3$ and ligands **8** to **12**, the initial phenylations were carried out in toluene at reflux, conditions which previously afforded our optimal results using diphenylphosphinoferrocenyloxazolines ligands.[10] These reaction conditions generally gave (*R*)-phenyl-2,5-dihydrofuran (**2**) and (*R*)-phenyl-2,3-dihydrofuran (**3**) in low yields with poor regioselectivities and moderate enantioselectivities. It was found that the catalyst systems were more reactive in benzene in which shorter reaction times of seven days were required and therefore benzene was the solvent employed in our further studies (Scheme 3, Table 1).



1

(*R*)-**2** (*R*)-**3**

Scheme 3

The catalyst derived from ligand **11**, containing the phenyl-substituted oxazoline ring, gave consistently good yields ranging from 48–66% of the kinetic isomer **2**. The enantioselectivities were also good ranging from 68–77% (entries 1–3). The *i*-Pr-substituted ligand **8** was found to give lower yields (23–46%), although with higher ee's of 70–89% (entries 4–6). The use of diisopropylamine as

Table 1 Phenylation of 2,3-Dihydrofuran (**1**) with Palladium Complexes of Ligands (**8**–**12**)

Entry	Ligand	Base	Yield (%)[a] **2** (**3**)	ee (%)[b] (*R*)-**2** ((*R*)-**3**)
1	**11**	*i*-Pr_2NH	66 (8)	77 (nd)[c]
2	**11**	Proton sponge[d]	62 (2)	68 (nd)
3	**11**	Et_3N	48 (7)	75 (nd)
4	**8**	Et_3N	46 (7)	70 (nd)
5	**8**	Proton sponge	23 (6)	89 (nd)
6	**8**	*i*-Pr_2NH	33 (7)	87 (nd)
7	**9**	Et_3N	8 (19)	43 (16)
8	**9**	Proton sponge	8 (30)	27 (13)
9	**9**	*i*-Pr_2NH	7 (11)	33 (21)
10	**12**	Et_3N	17 (1)	81 (nd)
11	**12**	Proton sponge	18 (2)	82 (nd)
12	**12**	*i*-Pr_2NH	57 (6)	78 (nd)
13	**10**	Et_3N	90 (9)	95 (nd)
14	**10**	Proton sponge	72 (8)	91 (nd)
15	**10**	*i*-Pr_2NH	97 (2)	95 (nd)

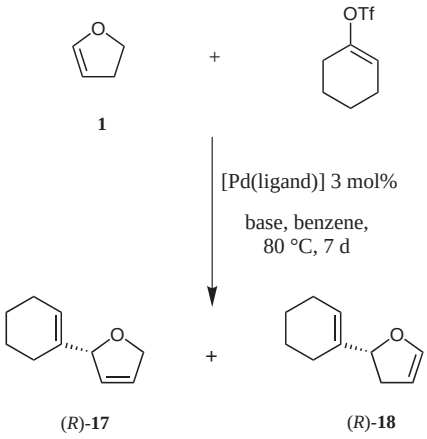
[a] Conversions by GC (SE-30, 30 m, 11 psi He).
[b] Enantiomeric excesses were determined by GC on a Chiraldex γ-cyclodextrin TFA capillary column (30 m × 0.25 m, 15 psi He); 80 °C, 0.3 °C min^{-1} up to 90 °C, 5 °C min^{-1} up to 120 °C, [t_R = 31.80 (*S*) and 34.0 (*R*) min for **2** and t_R = 23.30 (*S*) and 24.6 (*R*) min for **3**].
[c] Enantiomeric excess not detected.
[d] Proton sponge = 1,8-bis(dimethylamino)naphthalene.

base gave the optimum result of 33% yield and 87% ee although proton sponge gave a slightly higher ee of 89% but a considerably lower yield of 23%. The bulky *t*-butyl-substituted benzothiophene analogue **9** gave opposite regioselectivity in all cases, with the thermodynamic isomer **3** being favoured over **2** and the highest yield of the thermodynamic isomer **3** reaching 30%. Moderate ee's of regioisomer (*R*)-**3** were also obtained ranging from 13–21% (entries 7–9). Interestingly, although lower yields of the kinetic isomer **2** were seen, higher ee's of 27–43% were obtained. These results are in contrast to those reported by Pfaltz, which showed increased reactivity and enantioselectivities with the ligand possessing the more bulky substituent. The thiophene-containing ligands **12** and **10** were also tested for their enantiodifferentiating ability in the phenylation of 2,3-dihydrofuran. Ligand **12**, containing a thiophene ring and an *i*-Pr-substituted oxazoline ring, provided a catalyst which gave moderate yields but quite high enantioselectivities of between 78–82% (entries 10–12). The use of diisopropylamine as base again gave the best yield (57%) for ligand **12** and a reasonable ee of 78%. The other bases tested, triethylamine and proton sponge gave slightly higher ee's of 81% and 82%, but considerably lower yields (17% and 18%), respectively. Reactions using ligand **10** gave both good to excellent yields (up to 97%) and high ee's irrespective of base employed (up to 95%) in all cases (entries 13–15). Our optimal result used diisopropylamine as the base with a palladium complex of ligand **10** in benzene, providing (*R*)-**2** in 97% yield with excellent regioselectivity and in 95% ee within seven days (entry 15).

Of the benzothiopheneoxazoline-containing ligands **8**, **9**, **11**, reactions with ligand **11** were found to give the optimum results with both good ee's and yields, unlike those with ligand **8**, which, despite found to give slightly higher ee's, gave poorer yields. Complexes derived from ligand **9**, however, although expected to give higher enantioselectivities, a feature noted from our work with diphenylphosphinoferrocenyloxazoline ligands and Pfaltz in his work with ligands **4**, gave both poor yields and ee's in the intermolecular asymmetric Heck reaction. Of the thiopheneoxazoline-containing ligands **10** and **12**, ligand **12** gave good yields and high ee's but was out-performed by ligand **10**, the optimal ligand overall, in all cases.

Asymmetric Cyclohexenylation of 2,3-Dihydrofuran

The asymmetric cyclohexenylation of 2,3-dihydrofuran (**1**) was also tested using palladium complexes of ligands **9**–**12** (Scheme 4, Table 2).



Scheme 4

Complexes derived from ligand **11** gave quite high yields (78% and 89%) in the cases where diisopropylamine and triethylamine were used as base, respectively, although the ee's obtained were reasonable (54–76%). An unexpected result was obtained in the case where proton sponge was used as base in that the major regioisomer formed was that of the thermodynamic isomer **18** in 29% yield as opposed to 20% of the kinetic isomer **17** formed. The ee of the major thermodynamic isomer **18** was found to be quite low (20%) although interestingly a higher ee of the minor regioisomer **17** was observed (34%, entry 2). Application of ligand **9** proved again to give low yields ranging from 26–49% of the thermodynamic regioisomer

Table 2 Cyclohexenylation of 2,3-Dihydrofuran (**1**) with Palladium Complexes of Ligands (**9**–**12**)

Entry	Ligand	Base	Yield (%)[a] **17** (**18**)	ee (%)[b] (*R*)-**17** ((*R*)-**18**)
1	**11**	*i*-Pr_2NH	78 (10)	76 (nd)[c]
2	**11**	Proton sponge	20 (29)	34 (20)
3	**11**	Et_3N	89 (5)	54 (nd)
4	**9**	Et_3N	3 (49)	nd (61)
5	**9**	Proton sponge	21 (26)	61 (40)
6	**9**	*i*-Pr_2NH	30 (41)	55 (51)
7	**12**	Et_3N	36 (9)	55 (nd)
8	**12**	Proton sponge	49 (4)	47 (nd)
9	**12**	*i*-Pr_2NH	13 (5)	50 (nd)
10	**10**	Et_3N	96 (4)	97 (nd)
11	**10**	Proton sponge	97 (3)	95 (nd)
12	**10**	*i*-Pr_2NH	69 (3)	89 (nd)

[a] Conversions by GC (SE-30, 30 m, 11 psi He).
[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 90 °C, 5 °C min^{-1} up to 120 °C, [t_R = 22.20 (*S*) and 24.9 (*R*) min for **17** and t_R = 18.0 (*S*) and 18.3 (*R*) min for **18**].
[c] Enantiomeric excess not detected.

18 but gave higher ee's than for the corresponding phenylations in all cases (entries 4–6). Triethylamine was found to be the base of choice, giving the highest ee and yield with this particular ligand (49% yield of **18** and 61% ee, entry 4).

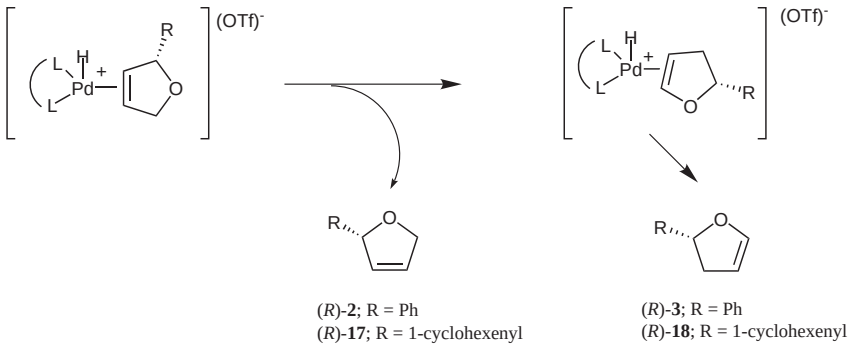
Using ligand **12**, the highest yield of the major regioisomer **17** was obtained with proton sponge as base (49%, entry 8) but the highest ee obtained was using triethylamine as base (55%, entry 7). A substantial drop in yield to 13% of **17** was observed when diisopropylamine was used as base, although little effect was seen with the ee (entry 9). Once again ligand **10** gave the best results with ee's in the range of 89–97% and yields of 69–96% (entries 10–12). The optimum result with this ligand was using triethylamine as base and this gave (*R*)-2-cyclohex-1′-en-1′-yl-2,5-dihydrofuran (**17**) in 96% yield and 97% ee after seven days (entry 10).

The regioselectivities obtained above for both phenylation and cyclohexenylation of 2,3-dihydrofuran with these HETPHOX ligands are further evidence for the preference of palladium phosphinamine complexes for the formation of the kinetic product. One explanation for the difference in product distribution between catalyst systems derived from diphosphines and phosphinamines is that the initial olefin-bound complex, formed after migratory insertion and β-elimination, is more prone to dissociation to give **2**/**17** in the 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 **3**/**18** (Scheme 5).

Mechanistically it is clear that the thermodynamic products **3**/**18** can only be formed when there is a H substituent at C-2. A dihydrofuran disubstituted at this position would be a substrate that would provide a true comparative test of reactivity and enantioselectivity for a range of Pd(0) complexes. This is not the case using substrate **1** as the final isomer ratio and enantioselectivities are complicated by kinetic resolution processes.[19] Therefore, 2,2-dimethyl-2,3-dihydrofuran (**19**) and its 2,2-diethyl analogue **20** were developed by us as substrates for the intermolecular asymmetric Heck reaction as they allow for a simple and direct comparison of various ligands in this reaction as only one regioisomeric product can be formed.[10,20] The Heck product of 2,2-dimethyl-2,3-dihydrofuran (**19**) is a useful synthetic intermediate as it can be viewed as a masked isoprene unit as exemplified in the cycloshikonin natural product class **21** and its conversion to shikonin **22** and alkannin **23**.[21,22] We had previously tested a range of phosphinamine ligands with substrates **19** and **20** and it was of interest to determine the efficacy of the new HETPHOX ligands.

Asymmetric Heck Reactions with 2,2-Dimethyl-2,3-dihydrofuran

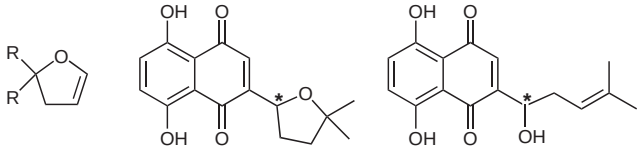
We tested the full range of ligands previously applied in reactions with 2,3-dihydrofuran in the phenylation of 2,2-



(*R*)-**2**; R = Ph
(*R*)-**17**; R = 1-cyclohexenyl

(*R*)-**3**; R = Ph
(*R*)-**18**; R = 1-cyclohexenyl

Scheme 5



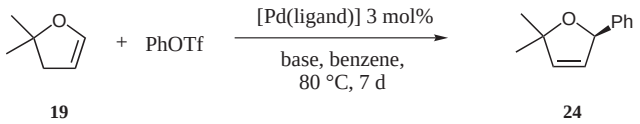
19: R = Me
20: R = Et

21

22: * = (*R*)
23: * = (*S*)

Figure 2

dimethyl-2,3-dihydrofuran (Scheme 6). Complexes derived from ligand **8** were quite unreactive giving very low yields (1–7%). Ligand **11**, when applied, fared little better, giving a yield of only 10%. These results are in marked contrast to those obtained with 2,3-dihydrofuran where complexes derived from ligand **11** gave good yields up to 66% and ee's up to 77% while palladium complexes of ligand **8** also gave moderate yields (23–46%) and ee's (70–89%). Reactions with ligand **12** afforded good yields ranging from 60–74% and good to high enantioselectivities of 64–84% (Table 3, entries 1–3). These results compare favourably with the phenylation of 2,3-dihydrofuran where yields up to 57% and enantioselectivities of up to 82% were observed. However, as in our phenylation studies with 2,3-dihydrofuran, the use of palladium complexes derived from ligand **10** afforded excellent yields with high enantioseletivities (entries 4–6). The use of triethylamine as base was optimal in terms of enantioselectivity (91%) whereas employment of proton sponge and diisopropylamine led to higher yields (91% and 98%) although with lowered enantioselectivities (75% and 77%), respectively.



19 **24**

Scheme 6

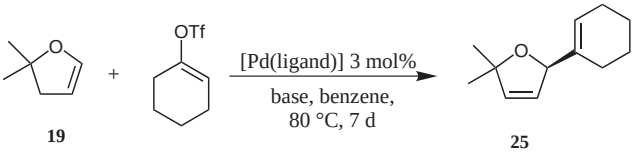
Table 3 Phenylation of 2,2-Dimethyl-2,3-dihydrofuran **19** with Palladium Complexes of Ligands **10**, **12**

Entry	Ligand	Base	Yield (%)[a] **24**	ee (%)[b] (*R*)-**24**
1	**12**	*i*-Pr_2NH	60	64
2	**12**	Proton sponge	66	68
3	**12**	Et_3N	74	84
4	**10**	*i*-Pr_2NH	98	77
5	**10**	Proton sponge	91	75
6	**10**	Et_3N	80	91

[a] Conversions by GC (SE-30, 30 m, 11 psi He).
[b] Enantiomeric excesses were determined by GC on a Chiraldex γ-cyclodextrin TFA capillary column (30 m × 0.25 m, 15 psi He); {80–95 °C, 0.3 °C, 95–120 °C, 1.5 °C min^{-1}, 120 °C, 10 min, [t_R = 40.28 (*S*) and 41.24 (*R*) min for **24**]}.

As asymmetric phenylation had been successfully performed for 2,2-dimethyl-2,3-dihydrofuran (**19**), it was of interest to determine whether the trends observed with these ligands would continue in the corresponding cyclohexenylation. In view of the poor results obtained with ligands **8** and **11** for the phenylation of 2,2-dimethyl-2,3-dihydrofuran (**19**), cyclohexenylations were investigated with only the best performing ligands from the previous studies, ligands **10** and **12** (Scheme 7, Table 4).

Complexes derived from ligand **12** afforded product **25** in moderate to high yields (46–79%) but in poor to moderate enantioselectivities (25–54%, entries 1–3). However, complexes formed from ligand **10** gave **25** in excellent yields (88–100%) and in enantioselectivities of up to 89% (entries 4–6). For both ligands the enantioselectivities obtained were lower than those obtained in the corresponding cyclohexenylation of 2,3-dihydrofuran, e.g. for ligand **10** (66–89% versus 89–95%, respectively). In general, the yields obtained were similar demonstrating that the increased steric bulk at the 2-position did not have a marked effect on yields.



19 **25**

Scheme 7

Table 4 Cyclohexenylation of 2,2-Dimethyl-2,3-dihydrofuran (**19**) with Palladium Complexes of Ligands **10**, **12**

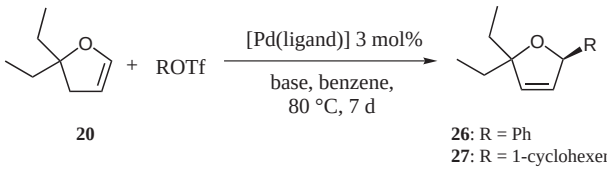
Entry	Ligand	Base	Yield (%)[a] **24**	ee (%)[b] (*R*)-**24**
1	**12**	*i*-Pr_2NH	60	64
2	**12**	Proton sponge	66	68
3	**12**	Et_3N	74	84
4	**10**	*i*-Pr_2NH	98	77
5	**10**	Proton sponge	91	75
6	**10**	Et_3N	80	91

[a] Conversions by GC (SE-30, 30 m, 11 psi He).
[b] Enantiomeric excesses were determined by GC on a Chiraldex γ-cyclodextrin TFA capillary column (30 m × 0.25 m, 15 psi He); {65–95 °C, 0.3 °C, 95–120 °C, 5 °C min^{-1}, 120 °C, 10 min, [t_R = 52.13 (*S*) and 53.33 (*R*) min] for **25**}.

Asymmetric Heck Reactions with 2,2-Diethyl-2,3-dihydrofuran

We have previously investigated 2,2-diethyl-2,3-dihydrofuran (**20**) as a substrate for intermolecular asymmetric Heck reactions catalysed by palladium complexes of BINAP and a range of diphenylphosphinoaryloxazoline ligands.[20c] We tested complexes formed from ligands **10**,

12 in the phenylation and cyclohexenylation of dihydrofuran **20** (Scheme 8) and the results of that investigation are given in Table 5.



20

26: R = Ph
27: R = 1-cyclohexenyl

Scheme 8

Table 5 Phenylation and Cyclohexenylation of 2,2-Diethyl-2,3-dihydrofuran (**20**)

Entry	Ligand	Base	Yield (%)[a] **24**	ee (%)[b] (*R*)-**24**
1	**12**	*i*-Pr_2NH	60	64
2	**12**	Proton sponge	66	68
3	**12**	Et_3N	74	84
4	**10**	*i*-Pr_2NH	98	77
5	**10**	Proton sponge	91	75
6	**10**	Et_3N	80	91

[a] Conversions by GC (SE-30, 30 m, 11 psi He).
[b] Enantiomeric excesses were determined by GC on a Chiraldex γ-cyclodextrin TFA capillary column (30 m × 0.25 m, 15 psi He); {80–92 °C, 0.3 °C min^{-1}, 92–130 °C, 5 °C min^{-1}, [t_R = 52.0 (*S*) and 52.4 (*R*) min for **26]** and 65–95 °C, 0.3 °C min^{-1}, 95–105 °C, 1 °C min^{-1}, 105–130 °C, 5 °C min^{-1}, 10 min, [t_R = 79.3 (*S*) and 79.9 (*R*) min) for **27**]}.

The yields obtained in the reaction with phenyl triflate were poor for complexes derived from ligand **12** (16–23%) and the enantioselectivities were modest (51–61%, entries 1–3). We were pleased to see that catalysts formed from ligand **10** were highly active and enantioselective with our optimal result being the formation of (*R*)-**26** in 98% yield and with 99% ee when triethylamine was used as base (entry 6). In our previous study employing dihydrofuran **20** as substrate our best result was a 74% yield of (*R*)-**26** in 94% ee using the palladium complex formed from ligand **4b**. We observed similar trends in the cyclohexenylation of dihydrofuran **20** with poor yields (9% and 18%) and modest enantioselectivities (38% and 47%) when ligand **12** was employed and far superior yields (59% and 93%) and enantioselectivities (76% and 87%) for complexes derived from ligand **10** (entries 7–10). Again our best result here compares favourably with our previous study of the cyclohexenylation of **20**, in which, with a catalyst formed from ligand **4b**, we obtained (*R*)-**27** in 93% ee but in 24% yield. It is also worth noting that the reaction time here is seven days compared to fourteen days in our previous study. We had previously attributed the decline in chemical yields in Heck reactions on changing substrates from 2,2-dimethyl-2,3-dihydrofuran (**19**) to 2,2-diethyl-2,3-dihydrofuran (**20**) to the increased bulk at the 2-position and a consequential increase in ligand-reactant steric interactions in the migratory insertion step. This does not appear to be a factor for complexes derived from ligand **12** and it was therefore of interest to probe the substrate scope for this ligand by preparing and testing 2,2-diisopropyl-2,3-dihydrofuran (**28**, Figure 3) in the intermolecular asymmetric Heck reaction.

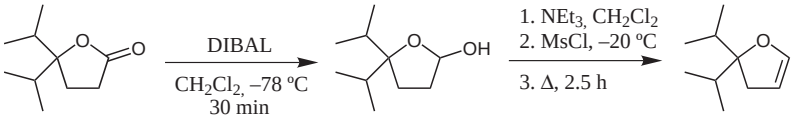
28: R = *i*-Pr

Figure 3

Synthesis of 2,2-Diisopropyl-2,3-dihydrofuran

We initially chose to investigate the same synthetic route which had proven successful for the preparation of the 2,2-dialkylated-2,3-dihydrofurans **19** and **20**.[10] However, the first step in that route, the base-promoted addition of propargylic alcohol to the appropriately substituted ketone, 2,4-dimethyl-3-pentanone, was unsuccessful. After investigating a variety of other pathways we noted that Katritzky had reported the preparation of 2,2-diisopropyl-dihydrofuran-2-one (**29**) which we had envisaged could be transformed to 2,2-diisopropyl-2,3-dihydrofuran (**28**) after reduction and dehydration.[23] We prepared 2,2-diisopropyl-dihydro-furan-2-one (**29**) according to Katritzky's procedure and reduced it to the corresponding lactol **30** in 76% yield by reduction with DIBAL (Scheme 9). Subsequent reaction with methanesulfonyl chloride in the presence of triethylamine promoted elimination to give the required 2,3-dihydrofuran **29** in 56% yield.

We then tested 2,2-diisopropyl-2,3-dihydrofuran (**28**) for its suitability as a substrate in the intermolecular Heck reaction, initially in a racemic sense so that we could determine the conditions for obtaining yields and enantiomeric excesses by GC analysis. We subjected **28** to our standard phenylation and cyclohexenylation conditions using palladium complexes of racemic BINAP. However, this



29 **30** **28**

Scheme 9

failed to yield any of the desired products even after reaction times of 14 days in either toluene or benzene and variation of the base employed. As the palladium complex derived from BINAP may be too bulky for association of a sterically hindered alkene such as 2,2-diisopropyl-2,3-dihydrofuran (**28**) we then tested palladium complexes derived from the less bulky ligands **10** and **12**. However, we again failed to form any of the desired Heck products. The possible explanations for the inactivity of this substrate are that the alkene association step is being retarded due to the bulk of the isopropyl groups or that migratory insertion is prevented if alkene association had indeed occurred.

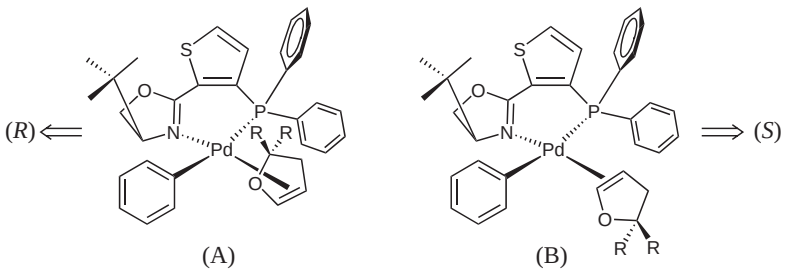
Mechanistic Considerations

For the phenylation of 2,3-dihydrofurans **1**, **19** and **20** the possible intermediates prior to migratory insertion in the palladium catalyst derived from ligand **10** are shown in Schemes 10 and 11. The alkene can be bound to palladium by either of its faces and can bind in a *trans*-fashion to the nitrogen atom, Scheme 10, or the phosphorous atom, Scheme 11. Similar intermediates have been proposed by Hallberg for an intramolecular Heck reaction with ligand **4b**.[24]

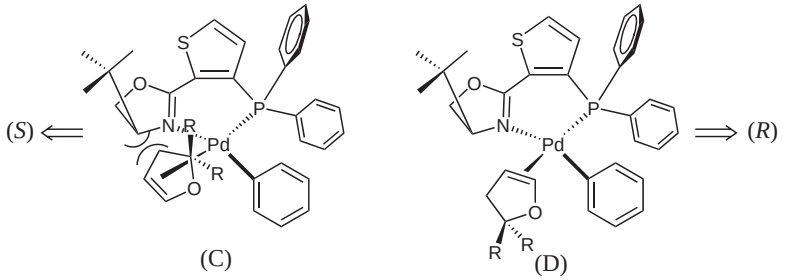
When the alkene approaches *trans* to nitrogen there seems to be little steric repulsion in binding either face of the alkene. Intermediate (A) would lead to the (*R*)-configured product while intermediate (B) would lead to the (*S*) product. If there were little energy difference between either intermediate a low ee would be expected if migratory insertion occurred in this way. When the approach is *trans* to phosphorous, intermediate (C) suffers steric repulsion but intermediate (D) does not. This route for migratory insertion would lead to a high ee of the (*R*) product and this is what is seen experimentally in the study completed herein. The coordination of groups after oxidative addition to Pd complexes containing P,N ligands has received some study by the groups of van Leeuwen and Vrieze.[25]

Conclusions

We have prepared two new HETPHOX ligands (**10** and **12**) and applied them and a series of thiophene- and benzothiopheneoxazoline-containing ligands in the intermolecular asymmetric phenylation and cyclohexenylation of 2,3-dihydrofuran (**1**). Phenylation proceeded in moderate to high chemical yields, with good regioselectivity and in up to 95% ee. Cyclohexenylations gave similarly high chemical yields and regioselectivities with the optimal result being a 96% yield of the major product in 97% ee. 2,2-Dialkyl-2,3-dihydrofurans were tested as substrates and the phenylation and cyclohexenylation of 2,2-dimethyl-2,3-dihydrofuran (**19**) proceeded in high yields and ee's up to 91% and 89%, respectively. The phenylation and cyclohexenylation of the 2,2-diethyl analogue **20** proceeded in excellent yields and ee's up to 99% and 87%, respectively. For each substrate palladium complexes formed from the *t*-butyl-substituted ligand **10** gave the highest yields, regioselectivities and enantioselectivities. 2,2-Diisopropyl-2,3-dihydrofuran (**28**) was prepared but was found to be unreactive in the intermolecular Heck reaction thus providing insight into to the steric limits for 2,3-dihydrofuran substrates.



Scheme 10 Alkene approaches *trans* to nitrogen



Scheme 11 Alkene approaches *trans* to phosphorous

^{1}H and ^{13}C spectra were recorded at 270 (67.5) MHz or 500 (125) MHz at ambient temperature on JOEL JNM-PMX-270 MHz or Varian-Unity 500 MHz spectrometers with tetramethylsilane as the internal standard. Peak assignments were aided by ^{1}H–^{1}H correlation experiments. Coupling constants are given as absolute values. ^{31}P spectra were recorded at 121 MHz on a Bruker 300 MHz spectrometer. Unless otherwise stated, NMR spectra were recorded in $CDCl_3$. Low resolution electron-impact mass spectra were measured on a VG Analytical spectrometer with attached INCOS 2400 data system at an ionization potential of 70 eV. Isomers were assumed to have the same response factors. Elemental analyses were performed by Ms Anne Connolly, Department of Chemistry, University College Dublin. Infra-red spectra were recorded on a Perkin-Elmer Paragon 1000 Infra-red FT spectrometer. Optical rotation values were measured on a Perkin Elmer 241 polarimeter. Melting points were determined in open capillary tubes in a Gallenkamp melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on aluminum sheets pre-coated with silica gel 60 F_{254} (0.25 mm, Macherey-Nagel). Column chromatography separations were performed using Merck Kieselgel 60 (Art. 7734), Merck Alumina (Art. 1097) or Merck Alumina (Art. 1104) as stated. Solvents were dried immediately prior to use by distillation from standard drying agents. Oxazolines **14**, **15** and 2,2-diisopropyl-dihydrofuran-2-one (**29**) were prepared according to literature procedures.[17,23] The products of the asymmetric Heck reactions, 2-phenyl-2,5-dihydrofuran (**2**), 2-phenyl-2,3-dihydrofuran (**3**), 2-cyclohex-1′-en-1′-yl-2,5-dihydrofuran (**17**), 2-cyclohex-1′-en-1′-yl-2,3-dihydrofuran (**18**), 2,2-dimethyl-5-phenyl-2,5-dihydrofuran (**24**), 5-cyclohex-1′-en-1′-yl-2,2-dimethyl-2,5-dihydrofuran **25**, 2,2-diethyl-5-phenyl-2,5-dihydrofuran (**26**), 5-cyclohex-1′-en-1′-yl-2,2-diethyl-2,5-dihydrofuran (**27**) have been reported previously.[10]

4-*tert*-Butyl-2-[3-(diphenylphosphino)-2-thienyl]-4,5-dihydro-1,3-oxazole (10)

Oxazoline **14** (0.418 g, 2 mmol) was dissolved in Et_2O (5 mL) and the solution was cooled at –78 °C. *n*-Butyllithium (1.6 mL, 2.5 M in hexane, 4 mmol) was added dropwise and the yellow solution was stirred at –78 °C for 30 min. The reaction was warmed to 0 °C and stirred at this temperature for 30 min. The yellow-green solution was finally cooled to –78 °C, then $ClPPh_2$ (0.720 mL, 4 mmol) was added to the solution. The reaction was allowed to warm to r.t. during 20 h and then quenched with water. The phases were separated and the aqueous phase was extracted with Et_2O (2 × 5 mL). The organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The resulting yellow-brown oil was purified by chromatography (cyclohexane–Et_2O, 9:1) to afford **10** (0.35 g, 34%) as a clear oil that slowly turned into a waxy white solid.

$[\alpha]_D$ –135.8 (*c* 0.53, $CHCl_3$).

^{1}H NMR (270 MHz): δ = 0.62 (s, 9 H), 3.91–4.13 (m, 3 H), 6.31 (d, 1 H, *J* = 4.6 Hz), 7.23–7.30 (m, 11 H).

^{13}C NMR (50 MHz): δ = 25.59, 33.82, 66.82, 76.35, 127.38, 128.26 (d, *J* = 4 Hz), 128.31, 128.61, 131.60 (d, *J* = 22.1 Hz), 132.94, 133.40, 133.50 (d, *J* = 11 Hz), 133.83 (d, *J* = 21 Hz), 137.28 (d, *J* = 9 Hz), 138.40 (d, *J* = 12 Hz), 141.23, (d, *J* = 27 Hz), 158.00 (d, *J* = 4Hz).

^{31}P NMR (124 MHz): δ = –13.14.

MS (EI, 70 eV): *m*/*z* (%) = 378 (M^+ – Me, 6), 336 (57), 308 (100), 281 (3), 258 (10), 234 (10), 189 (27), 152 (10), 133 (3), 107 (8), 77 (10), 57(6).

Anal. Calcd for $C_{23}H_{24}NOPS$: C, 70.21; H, 6.15; N, 3.56. Found: C, 70.11; H, 6.12; N, 3.55.

2-[3-(Diphenylphosphino)-2-thienyl]-4-isopropyl-4,5-dihydro-1,3-oxazole (12)

Oxazoline **15** (200 mg, 1.025 mmol) was dissolved in Et_2O (3 mL), then the solution was cooled at –78 °C. *n*-Butyllithium (0.82 mL, 2.5 M in hexane, 2.05.mmol) was added dropwise and the yellow solution was stirred at –78 °C for 30 min. The reaction was warmed to 0 °C and stirred at this temperature for 30 min. The yellow-green solution was finally cooled to –78 °C then $ClPPh_2$ (0.370 mL, 2.05 mmol) was added to the solution. The reaction was allowed to warm to r.t. over 20 h and then quenched with water. The phases were separated and the aqueous phase was extracted with Et_2O (2 × 5 mL). The organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The resulting yellow-brown oil was purified by chromatography (cyclohexane–Et_2O, 9:1) to afford a clear oil that slowly turned into a waxy white solid (0.17 g, 44%).

$[\alpha]_D$ –99 (*c* 0.9, $CHCl_3$).

^{1}H NMR (270 MHz): δ = 0.62 (d, 3 H, *J* = 6.7 Hz), 0.67 (d, 3 H, *J* = 6.7 Hz), 1.5 (sept, 1 H, *J* = 6.7 Hz), 3.83 (dd, 1 H, *J* = 7.3, 7.6 Hz), 3.85–4.00 (m, 1 H), 4.12 (dd, 1 H, *J* = 8.8, 7.3 Hz), 6.27 (dd, 1 H, *J* = 5.28, 1.1 Hz), 7.16–7.40 (m, 10 H), 7.6–7.7 (m, 1 H).

^{13}C NMR (50 MHz): δ = 18.15, 18.44, 32.77, 70.38, 73.02, 127.41, 128.32 (d, *J* = 12 Hz), 128.38, 128.60, 133.30 (d, *J* = 22 Hz), 133.48, 133.52, 133.50 (d, *J* = 11 Hz), 133.62 (d, *J* = 21 Hz), 137.23 (d, *J* = 10 Hz), 138.04 (d, *J* = 12 Hz), 141.04, (d, *J* = 27 Hz), 158.18.

^{31}P NMR (124 MHz): δ = –13.10.

MS (EI, 70 eV): *m*/*z* (%) = 378 (M^+, 4), 364 (6), 336 (18), 308 (100), 288 (55), 246 (16), 234 (10), 152 (4), 139 (3), 107 (3), 77 (10), 63(4).

Anal. Calcd for $C_{22}H_{22}NOPS$: C, 69.64; H, 5.84; N, 3.69. Found: C, 69.60; H, 5.80; N, 3.68.

Asymmetric Heck Reactions; General Procedure

A solution of the appropriate trifluoromethanesulfonate (0.13 mmol) and *n*-tridecane (10.0 mg, 0.054 mmol) in benzene (0.5 mL) was added to a Schlenk tube containing $Pd_2(dba)_3$ (2.3 mg, 0.004 mmol) and ligand (0.008 mmol) under nitrogen. To this solution was then added the 2,3-dihydrofuran (0.65 mmol) and base (0.39 mmol). The resulting solution was then degassed by three freeze-thaw cycles at 0.01 mbar and left to stir under nitrogen at 80 °C for 7 d 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 Et_2O (10 mL). This solution was then concentrated and the yield calculated using GC (Se-30, 11 psi, 50 °C, 4 min, 15 °C/min, 170 °C, 10 min) by the internal standard method. Further purification by TLC (a normal sized TLC plate was run and a strip cut off and visualised with $KMnO_4$, the silica of the remainder of the plate at the same R_f as the product was then scraped off and extracted with CH_2Cl_2) to give the product. Its enantiomeric excess was determined by chiral GC.

5,5-Diisopropyltetrahydrofuran-2-ol (30)

Diisobutylaluminium hydride (1.84 mL, 1 M in toluene, 2.3 mmol) was added to a solution of 5,5-diisopropyldihydrofuran-2(3*H*)-one (0.3 g, 1.76 mmol) in anhyd CH_2Cl_2 (5 mL) and cooled to –78 °C under nitrogen and the solution was stirred for 30 min. The reaction mixture was then poured into 0.2 M HCl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with $NaHCO_3$, dried (Na_2SO_4) and concentrated in vacuo to give an oil which was purified by column chromatography (CH_2Cl_2–pentane, 2:1) affording **30** (0.23 g, 76%) as a yellow oil.[26]

IR (film): 3418 (-OH), 2966, 2916, 2896, 1475, 1384, 1196, 997, 618 cm^{-1}.

^{1}H NMR (500 MHz): δ = 0.83 (d, 6 H, *J* = 7 Hz), 0.91 (d, 6 H, *J* = 7 Hz,), 1.90 (hept, 2 H, *J* = 7 Hz), 1.81 (t, 2 H, *J* = 4 Hz), 2.0 (m, 2 H), 5.46 (dd, 1 H, *J* = 1, 6 Hz).

^{13}C NMR (75 MHz): δ = 17.9, 18.4, 19.4, 19.8, 26.4, 33.4, 34.6, 34.9, 93.0, 102.0.

MS (EI, 70 eV): *m*/*z* (%) = 154 (M^+ – 18, 16), 129 (19), 111 (45), 93 (100), 83 (22).

2,2-Diisopropyl-2,3-dihydrofuran (28)

5,5-Diisopropyltetrahydrofuran-2-ol (160 mg, 0.93 mmol) was dissolved in anhyd CH_2Cl_2 (5 mL), cooled to –20 °C under nitrogen, and treated with NEt_3 (0.39 mL, 2.79 mmol) followed by trifluoromethanesulfonyl chloride (0.1 mL, 1.21 mmol). The resultant white suspension was stirred at –20 °C for 30 min and then refluxed for 2.5 h. The mixture was then diluted with CH_2Cl_2, washed with H_2O, dried (Na_2SO_4) and concentrated affording a red oil which was purified by column chromatography (pentane–CH_2Cl_2, 4:1; R_f = 0.5) to afford **28** (86 mg, 60%) as a colourless oil.

IR (film): 3081, 2965, 2933, 2877, 2305, 1623 (C=C), 1473, 1265, 1061, 748 cm^{-1}.

^{1}H NMR (500 MHz): δ = 0.87 (dd, 12 H, *J* = 6.7 Hz), 1.90 (m, 2 H), 2.33 (app t, 2 H, 2.4 Hz), 4.71 (m, 1 H), 6.24 (m, 1 H).

^{13}C NMR (75 MHz): δ = 15.18, 15.39 (2 × CH_3), 31.33 (CH), 32.83 (C3), 92.05 (C2), 97.81 (C4), 144.70 (C5).

MS (EI, 70 eV): *m*/*z* (%) = 154 (M^+, 12), 129 (14), 111 (36), 93 (100), 83 (18).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.52; H, 11.56.

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