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Addition of the *ortho*-C–H bonds of phenol across an olefin catalysed by a chiral iridium(I) diphosphine complex

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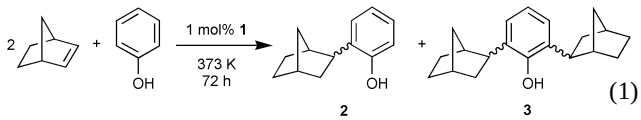
A chiral iridium(I) diphosphine complex efficiently catalyses the unprecedented *ortho*-alkylation of phenol with norbornene in the absence of solvent leading to the formation of one and two C–C bonds.

Arenes such as benzenes, phenols, and anilines are important commodity chemicals. Catalytically efficient activation of aromatic C–H bonds leading to new C–C bond formation is thus a highly desirable goal and would provide a clean and economic method for adding value to such compounds. Although there are numerous examples of stoichiometric reactions of aromatic C–H bonds with transition metal compounds, catalytic systems for addition to C–C multiple bonds are rare.[1] Brunet *et al.* demonstrated the feasability of rhodium catalysed *ortho*-alkylations of anilines by norbornene.[2] Ruthenium[3a,b] and rhodium[3c] complexes were shown to catalyse *ortho*-alkylations of aromatic ketones by olefins. A protocol for the reaction of phenols with alkynoates catalysed by electrophilic palladium complexes in acidic media appeared recently.[4] One of us has reported the first example of a direct, asymmetric hydroarylation of norbornene with benzamide catalysed by electron-rich Ir(I) complexes.[5]

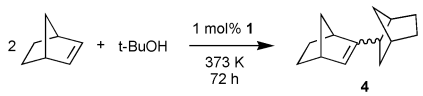
We present here first results on the Ir-catalysed, enantioselective (although marginally) *ortho*-norbornylation of phenol. To the best of our knowledge, this reaction represents the first example of a coupling of a non-functionalised olefin with phenol catalysed by a transition-metal complex. Furthermore, it proceeds under mild conditions, does not require any solvent and can be conducted in nearly stoichiometric amounts of reactants. We also present an efficient Ir-catalysed dimerisation of norbornene.

The dinuclear Ir complex [IrCl{(*R*)-(*S*)-PPFPPh$_2$}]$_2$ (**1**, Fig. 1, (*R*)-(*S*)-PPFPPh$_2$ = (*R*)-1-{(*S*)-2-(diphenylphosphino)ferrocenyl}ethyldiphenylphosphine) is isolable in high yield as a *ca.* 60 : 40 *cis*/*trans* mixture by reaction of a benzene solution of (*R*)-(*S*)-PPFPPh$_2$ with a benzene slurry of [IrCl(COE)$_2$]$_2$ (COE = cyclooctene).[6]

Complex **1** was used as catalyst precursor in the model reaction of norbornene with phenol. All the reactions were performed without solvent under anaerobic and anhydrous conditions. Heating a solution of 2 equiv. of norbornene, 1 equiv. of phenol, and 1 mol% of complex **1** at 373 K for 72 h resulted in the formation of a viscous oil (eqn. 1).† A TLC analysis of the reaction mixture revealed three reaction products and no starting material. Upon separation by flash chromatography **2** was isolated in 69% yield as an oil and **3** in 13% yield as fine yellowish needles. Both products were analytically pure and characterised by GC-MS and NMR.† Compound **3** arises from the reaction of the monoalkylated phenol **2** with a second equiv. of norbornene and shows that the same reactivity is obtained with *ortho*-substituted phenols such as **2**. The third product was the dimer of norbornene, *exo*-norbornyl-norbornene **4** (see eqn. 2). Although we do not yet know whether the addition of the sp^2 C–H bonds across the double bond of norbornene in **2** and **3** occurs in an *endo* or *exo* fashion, the selectivity for either one of the two possibilities is complete. Based on numerous precedents and preliminary NMR data we clearly favor *exo*-addition.[7]



(1)



(2)

The optical rotations of **2** (−2.5, *c* 1.55, $CHCl_3$) and **3** (− 6.5, *c* 1.34, $CHCl_3$) indicated some degree of enantioselectivity. The enantiomeric excess (ee) of **2** was 4.5% (determined by chiral HPLC, see Experimental footnote†). Unfortunately, the three possible *exo*-(or *endo*-)isomers of **3** (*R,R*, *S,S*, and *meso*) could not be completely separated on a chiral column (best results obtained with Chiracel OD-H, 1% i-PrOH–hexane, 0.5 mL min^{-1}, λ = 214 nm).

A plausible reaction mechanism is outlined in Scheme 1 and involves initial coordination of phenol cleaving the chloro-bridges in dimer **1** leading to the monomeric square-planar species **A**. This electron-rich species then undergoes selective *ortho*-metallation of phenol, which is probably the rate-determining step.[8] This is followed by insertion of the double bond of norbornene giving species **C**. Reductive elimination of **2** leads to the regeneration of **1**. We have shown that complexes

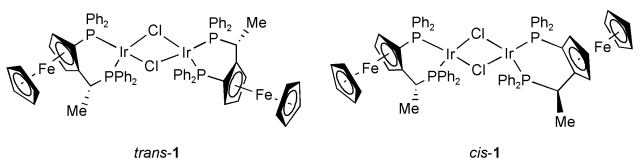
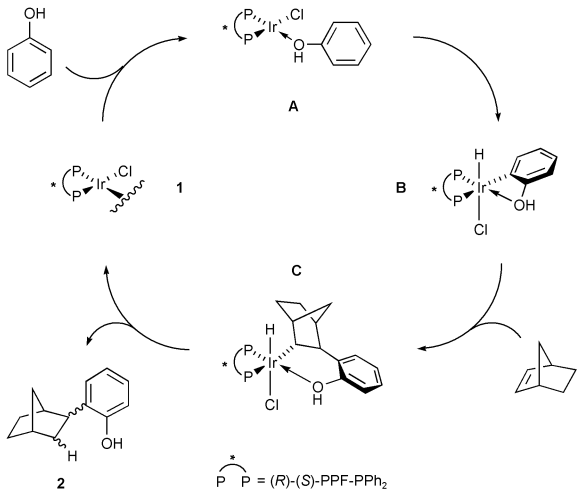


Fig. 1



Scheme 1

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of the type $[IrCl(PP)^*]_2$ undergo smooth and reversible C–H bond activation,[9] and catalyse the addition of benzamide to norbornene *via* C–H activation.[5] Furthermore, an example of an iridium complex utilising the halogen of haloarenes as a directing group for the selective *ortho*-C–H activation of such compounds will appear soon.[10]

Different control experiments underline the validity of such a catalytic cycle. Experiments at lower temperature (348 K) resulted in poorer yields. The presence of water, which was shown to oxidatively add to complex **1** at room temperature, significantly lowered the yields.[11] Using the hydroxo-bridged Ir(III) hydride complex $[\{(R)\text{-}(S)\text{-}PPFPPh_2\}(H)IrCl(\mu\text{-}OH)_2(H)IrCl\{(R)\text{-}(S)\text{-}PPFPPh_2\}]$, which is the reaction product of **1** with water, as catalyst precurser resulted in *ca*. 35% lower yields. Addition of co-catalysts such as 'naked' fluoride (phosphazenium fluoride-P_2), TlF, or $ZnCl_2$ had no or detrimental effects on the activity. Furthermore, the more challenging sp^3 C–H activation was not observed. Indeed, stirring a mixture of 2 equiv. of norbornene, 1 equiv. of t-BuOH, and 1 mol% of **1** at 373 K for 72 h afforded *exo*-norbornyl-norbornene **4** in 76% isolated yield as the only reaction product along with unreacted t-BuOH (eqn. 2).[12]† Moreover, this surprising catalytic dimerisation of norbornene does not proceed in absence of t-BuOH, indicating that initial coordination of t-BuOH to complex **1** is crucial insofar as it enhances the nucleophilicity of the iridium centre and allows the following olefin sp^2 C–H activation step. Finally, control experiments without the use of catalyst **1** did not show any reaction between norbornene and phenol or t-BuOH.

In summary we have demonstrated the feasibility of an enantioselective, atom-economical *ortho*-alkylation of phenols without the need of a solvent. We propose a catalytic cycle that features an sp^2 C–H bond activation with subsequent coupling to the double bond of norbornene. These first results show that not only phenol, but also *ortho*-alkylated phenols (in this case compound **2**) undergo such a reaction. Alkylation of t-BuOH by norbornene is not observed, but instead we observe selective dimerisation of norbornene *via* olefin sp^2 C–H activation and subsequent C–C coupling with a second olefin.

We are currently working on the full stereochemical characterisation and separation of the isomers of compounds **2**–**4**. Future studies on the reaction will include (a) exploring the effect of different donor/acceptor groups on the phenol ring, (b) expanding the reaction to other olefin substrates,[13] and (c) investigating the steric and/or electronic effects of different chiral (PP)* ligands on the performance of the catalyst precursor (of general formula $[IrCl(PP)^*]_2$) described herein.[14]

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Notes and references

† **Catalytic condensation of phenol with norbornene.** Norbornene (1136 mg, 12.06 mmol) was gently warmed in the presence of phenol (568 mg, 6.04 mmol) affording a solution which was added to $[IrCl\{(R)\text{-}(S)\text{-}PPFPPh_2\}]_2{\cdot}0.2C_5H_{12}$ (**1**, 98.5 mg, 0.0603 mmol). The resulting limpid orange solution was stirred at 373 K for 72 h. The viscous reaction mixture was quenched by adding CH_2Cl_2 in air. Drying *in vacuo* afforded 1555 mg of a brownish oil. FLASH chromatography (hexane : ethylacetate = 10) allowed us to separate the reaction products: 2-norbornylphenol (**2**, 782 mg, yellowish oil), 2,5-bis-norbornylphenol (**3**, 217 mg, yellowish needles), and norbornyl-norbornene (**4**, 330 mg, colourless oil).

Catalytic dimerisation of norbornene. A mixture of norbornene (1101 mg, 11.69 mmol) and t-BuOH (433 mg, 5.84 mmol) was added to **1** (95.5 mg, 0.0585 mmol) resulting in a yellow slurry which was heated at 373 K for 72 h. During the course of the reaction the mixture turned limpid orange and small amounts of a black deposit were observed. Purification through a silica plug and drying *in vacuo* afforded a colorless oil (**4**, 834 mg, 76%).

Characterisation of 2-norbornyl-phenol (2). Anal. calc. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.94; H, 8.80%. ^{1}H NMR ($CDCl_3$, 250.13 MHz): δ 1.25–1.45 (m, 3H), 1.45–1.70 (m, 4H), 1.75–1.90 (m, 1H), 2.37 (m, 1H), 2.45 (m, 1H), 2.86 (m, 1H), 4.74 (s, 1H), 6.75–6.85 (m, 1H), 6.85–6.95 (m, 1H), 7.00–7.15 (m, 1H), 7.15–7.25 (m, 1H). R_f = 0.42 (hexane : ethylacetate = 10). $[\alpha]_D^{20}$ = −2.5 (*c* = 1.5525 in $CHCl_3$). The enantiomers were separated by HPLC using Daicel's Chiracel OD-H column (eluent: i-PrOH–hexane 4:96 v/v, 0.5 mL min^{-1}, 298 K) with retention times of 13.8 and 15.4 min.

Characterisation of bis-2,5-norbornyl-phenol (3). Anal. calc. for $C_{20}H_{26}O$: C, 85.06; H, 9.28. Found: C, 85.27; H, 9.31%. ^{1}H NMR ($CDCl_3$, 250.13 MHz): δ 1.15–1.45 (m, 6H), 1.45–1.70 (m, 8H), 1.70–1.90 (m, 2H), 2.37 (m, 2H), 2.44 (m, 2H), 2.83 (m, 2H), 4.78 (s, 1H), 6.86 (t, 1H), 7.06 (m, 2H). $[\alpha]_D^{20}$ = −6.5 (*c* = 1.3405 in $CHCl_3$). R_f = 0.61 (hexane : ethylacetate = 10).

Characterisation of norbornyl-norbornene (4). Anal. calc. for $C_{14}H_{20}$: C, 89.30; H, 10.70. Found: C, 89.36; H, 10.68. ^{1}H NMR (C_6D_6, 250.13 MHz): δ 1.10–1.30 (m, 6H), 1.35–1.80 (m, 8H), 2.20 (m, 1H), 2.29 (m, 2H), 2.71 (m, 1H), 2.86 (m, 1H), 5.60 (m, 1H). R_f = 0.88 (hexane : ethylacetate = 10).

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8 In fact, prolonged heating at 373 K of **1** in a benzene or toluene solution does neither alter the *cis*/*trans* ratio of **1**, nor is any C–H activation of the solvents detected.

9 R. Dorta and A. Togni, *Organometallics*, 1998, **17**, 3423. Note that also in this case, C–H activation is achieved after initial coordination of an amine group to the metal centre. Future efforts will be directed at isolating the proposed intermediates **A** and **B**.

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11 Separate experiments showed that **1** does not mediate any reaction between water and norbornene at 373 K.

12 It appears that diastereomeric control in the C–C bond forming step is complete as determined by GC-MS and ^{13}C-NMR. Theoretically, two diastereomeric pairs of enantiomers of the *exo*-product are possible.

13 Norbornene belongs to a rather special class of strained cyclic olefins and the question of whether C–H activation or olefin insertion are rate-limiting may depend in part on the olefin used.

14 In the closely related olefin hydroamination protocol (*cf.* ref. 6), employing complex **1** gave low yields (27%, compared to a maximum of 81% with $[IrCl\{(R)\text{-}(S)\text{-Josiphos}\}]_2$) and low ee values (9%, compared to a maximum value of 95% with $[IrCl\{(S)\text{-BINAP}\}]_2$).