Straightforward approach to norbornene core based chiral ligands by tandem cross dehydrogenative coupling reactions

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ABSTRACT

The first synthesis of rigid pentacyclic NORPHOS derivatives by a tandem cross-coupling/cross-dehydrogenative-coupling according to the Catellani reaction protocol is reported. Mediated by palladium complexes of C,P-chelating monophosphine ligands, the readily available enantiopure NORPHOS oxide underwent a stereo- and regio-selective cyclocondensation reaction with arylhalides involving the activation of two unreactive C–H bonds.

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Introduction

Chiral phosphines play a prominent role as ligands in transition metal mediated enantioselective catalysis.[1] Chiral ligands should assure the significant energetic differentiation between the possible key transition states and intermediates of catalysed asymmetric reactions.[2,3] It is also important to limit the number of possible alternative reaction pathways and restrict the conformational interconversion of the intermediates. For this reason chelating, rigid, bisphosphines are the ligands of choice in the majority of catalytic asymmetric syntheses.[4] One such highly efficient chiral bisphosphine ligands is NORPHOS developed by Brunner et al. (Fig. 1).[5]

Thanks to its strained bicyclic core the efficiency of rhodium complexes with NORPHOS in asymmetric hydrogenations has proved to be significant. The presence of the strained carbon–carbon double bond in the norbornene core of NORPHOS provides the unique opportunity to prepare structurally diversified derivatives with special properties and complete retention of the electronic and geometric features of the bis(diphenylphosphino) ethane moiety.

The most challenging and at the same time most promising as well as desirable, palladium catalysed carbon–carbon bond forming reactions proceed via two-fold activation of non-reactive C–H bonds according to dehydrogenative Heck reaction or cross dehy-

Figure 1. The chemical and single crystal X-Ray structures of (*S,S*)-NORPHOS.[14]

drogenative coupling reaction protocols.[6,7] Such reactions, run under mild conditions and with utilisation of simple substrates, allow the achievement of a high level of structural complexity in a single reaction step with excellent atom economy.

In 1985 Catellani et al. reported adducts of arylpalladium species with norbornene serving as new intermediates for further catalytic transformations.[8,9] These early examples provided the background for modern approaches to polyfunctionalised (hetero)aromatics of enormous practical interest.[9d,10–12] In the original work by Catellani and Lautens, norbornene was used only as a "vehicle" transferring palladium from one carbon to another (C–H). Nevertheless, in some rare cases the studies were also focused on the functionalisation of norbornene.[9,13]

Results and discussion

Herein, we report the synthesis of novel, more spatially extended, rigid, pentacyclic NORPHOS derivatives **3** (Scheme 1) by a tandem cross-coupling/cross dehydrogenative coupling reaction according to the Catellani reaction protocol.
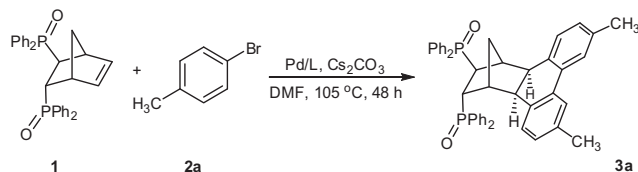
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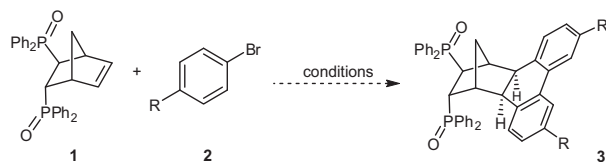
Scheme 1. Approach to novel NORPHOS derivatives **3**.

Table 1

Reaction of NORPHOS-O_2 with 4-bromotoluene in the presence of a palladium phosphine ligand complex

Entry	Ligand	Time (h)	Yield[a] (%)
1	PPh$_3$	72	—[c]
2	S-Phos (**L3**)	48	70
3	*Sym*-Phos (**L1**)	18	65
4	*Sym*-Phos (**L1**)	48	30[b]
5	MeO*Sym*-Phos (**L2**)	48	33
6	MeO*Sym*-Phos (**L2**)	72	62
7	P(fur-2-yl)$_3$ (**L4**)	48	58

[a] All reactions were carried out using NORPHOS-O_2 (0.2 mmol), aryl bromide (0.6 mmol), Cs$_2$CO$_3$ (0.6 mmol), Pd(OAc)$_2$ (4 mol %), ligand (8 mol %) and DMF (4 mL) at 105 °C.
[b] K$_2$CO$_3$ was used instead of Cs$_2$CO$_3$.
[c] Some of product C$_{38}$H$_{34}$O$_2$P$_2$ was formed instead of **3a**.

In preliminary experiments for the arylation of racemic NOR-PHOS bisoxide (NORPHOS-O_2, **1**) we tested several ligands and conditions (Table 1). A three-fold excess of *p*-bromotoluene **2a** was used. Considering the known superior activity of electron rich and bulky C,P-chelating monophosphine ligands of *Sym*-Phos (**L1**) type[15] in different types of cross-coupling reactions, we decided to use the palladium complexes of our new ligand MeO*Sym*-Phos (**L2**),[16] commercially available *Sym*-Phos,[15] as well as well recognised ligands S-Phos (**L3**)[17] and P(fur-2-yl)$_3$ (**L4**) (Fig. 2). The catalysts were formed in situ by premixing Pd(OAc)$_2$ and the corresponding ligands, or prepared separately from Pd(Me$_3$CCN)$_2$-Cl$_2$ and the ligands.

In a control experiment, use of the palladium acetate complex with PPh$_3$ did not form the expected 1,2,3,4,4a,12b-hexahydro-1,4-methanotriphenylene-2,3-diylbis(diphenylphosphane) dioxide (**3a**). However, in the presence of 4 mol % of Pd(OAc)$_2$, 8 mol % of S-Phos and 3 equiv of caesium carbonate in DMF at 105 °C, the product **3a** was isolated in 70% yield after 48 h. The *Sym*-Phos ligand was also efficient and **3a** was isolated in 65% yield after a shorter reaction time (18 h). Utilisation of MeO*Sym*-Phos and P(fur-2-yl)$_3$ furnished product **3a** in 62% and 58% yields, respectively.
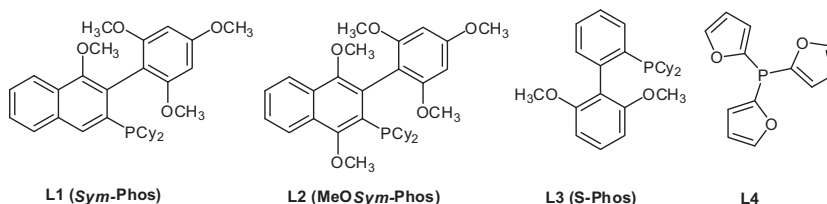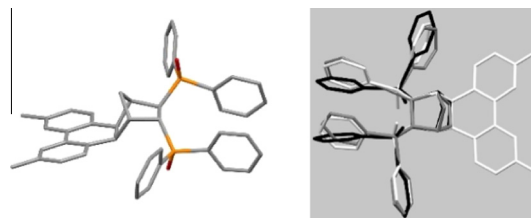

Figure 3. Single crystal X-Ray structure of (*R,R*)-**3a** and superposition of molecule (*R,R*)-**3a** (white), NORPHOS (grey) and NORPHOS-O_2 (black).

The structure of novel phosphine oxide **3a** (Fig. 3) was unam-biguously confirmed by single crystal X-ray diffraction, NMR spec-troscopy and mass spectroscopic methods (ESI). Depending on whether racemic **1**, or its (*R,R*)- or (*S,S*)-isomers were used in the reaction, the obtained products were rac-**3a**, (*R,R*)-**3a** or (*S,S*)-**3a**. Rac-**3a**, crystallised from non-anhydrous acetonitrile, formed a crystalline solvate in the monoclinic *P*2$_1$/*c* space group with both enantiomers in the asymmetric unit together with additional molecules of water and acetonitrile. At the same time, the sample of (*R,R*)-**3a**, obtained from enantiomeric NORPHOS-O_2 and crys-tallised from hexane-dichloromethane, formed homochiral crystals in the orthorhombic *P*22$_1$2$_1$ space group with two molecules in the asymmetric unit of the same configuration but with different crys-tal environment and 5 *n*-hexane solvent molecules disordered along the crystal channels along the *b* crystallographic axis (see ESI: CCDC-1431123 for rac-**3a** and CCDC-1451377 for (*R,R*)-**3a**).

The geometry of molecules **3a** in both crystals is similar to the previously reported structures of NORPHOS[14] and NORPHOS-O_2.[18] The structure overlay of molecule (*R,R*)-**3a** (extracted from the crystal structure of rac-**3a**) with inverted structure of NORPHOS[14] and NORPHOS-O_2 (extracted from the crystal structure of NOR-PHOS-O_2·DBTA complex)[18] is presented in Figure 2. The superposi-tion was made for the rigid bicyclic core substituted with two P atoms. The root mean square optimal superposition distance (RMSD) calculated for both pairs was 0.083 Å and 0.116 Å, respec-tively, which suggests close similarity of these molecular frag-ments.[19] Some differences were observed in the region of phenyl rings, which may rotate freely. Further crystallographic details are given in the ESI.

To define the limitations of the reaction, several EWG- and EDG-substituted aromatic bromides were tested. The results indicate that the reaction is compatible with a wide range of functional groups with different electronic properties (Table 2). The catalysts were prepared in situ from the free ligand and Pd(OAc)$_2$ as well as separately from bis(acetonitrile)dichloropalladium(II) or bis(pival-onitrile) dichloropalladium(II) complexes. Ligands **L1**–**L3** were tested in the coupling reactions leading to products **3**. Utilisation of Pd(OAc)$_2$ derived catalysts led to better yields of **3**. In the pres-ence of palladium dichloride complexes PdCl$_2$L and PdCl$_2$L$_2$ the yields of the product did not exceed 20%.

In the cases of aryl bromides bearing strongly coordinating sub-stituents such as unprotected hydroxyl or amino groups, the reac-tions gave a mixture of undefined compounds and products **3** were

L1 (*Sym*-Phos)　　　　　**L2 (MeO*Sym*-Phos)**　　　　　**L3 (S-Phos)**　　　　　**L4**

Figure 2. Monophosphine ligands applied to the Heck-Catellani reaction.