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Unprecedented preparation of pincer bis(oxazolinyl)phenyl ligands on solid support and their use in the first heterogeneously-catalyzed enantioselective allylation of aldehydes†

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Unprecedented solid-phase synthesis of bis(oxazolinyl)phenyl (Phebox) ligands *via* an efficient five-step sequence led to the demonstration of the first heterogeneously-catalysed enantioselective allylation of aldehydes.

Supported catalysts, based on well-defined catalytic units tethered to polymeric support, attract considerable attention as heterogeneous substitutes to homogeneous analogues.[1] In addition to economic and environmental benefits, the interest in supported catalysis is dictated by the rapidly expanding field of solution-phase combinatorial synthesis, based on immobilized reagents, catalysts and scavengers.[2] One of the frequently observed problems in supported organometallic catalysis is metal leaching which obstructs catalyst recycling and may promote competing reactions. In order to avoid such a course of events, an extremely stable ligating environment is required.

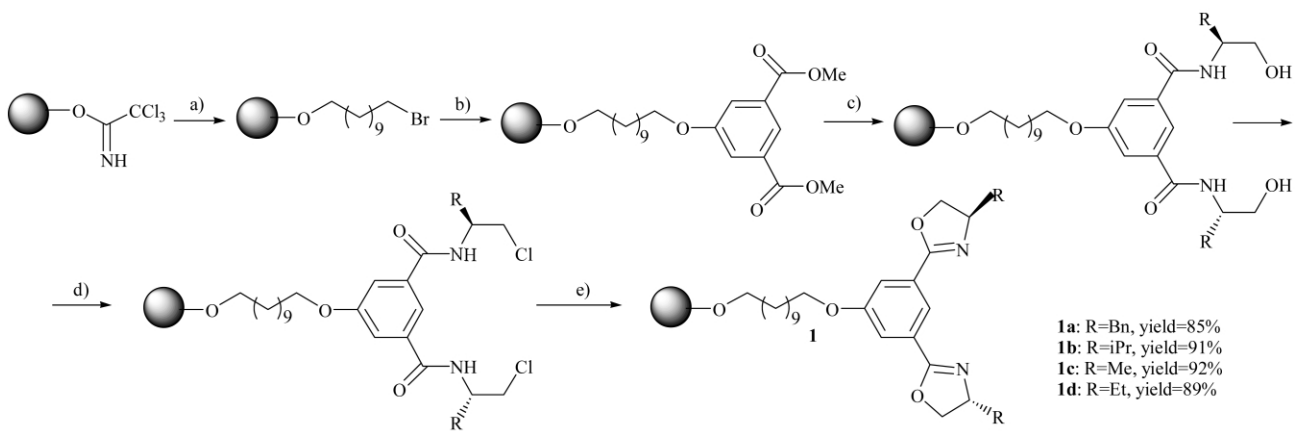
Development of enantioselective catalytic reactions is currently one of the core subjects of synthetic organic chemistry. Herein we report the preparation of an extraordinary stable enantioselective supported organometallic catalyst for the allylation of aldehydes, based on the polymer-bound tridentate pincer-type ligand Phebox. The reaction reported herein is the first example of enantioselective aldehyde allylation promoted by supported catalysts.[3,4]

Pincer-type ligands, demonstrating versatility and high metal affinity, have attracted increased attention in recent years.[5] The interest in these systems was inspired by a number of remarkable catalytic processes, reported with complexes of pincer ligands.[6] Among the few chiral pincer ligands, Phebox ligand (**1**), including two oxazoline moieties, was introduced a few years ago.[7] The deprotonated ligand is isoelectronic and isostructural to the well-known neutral Pybox ligand.[8] Phebox complexes catalyzed, in solution, a number of enantioselective processes.[9]

Oxazoline-containing ligands, in general, and bis(oxazolinyl) ligands, in particular, are highly successful in promoting high enantiomeric excesses in such reactions as Diels–Alder, aldol addition and cyclopropanation.[10] Since, in most of these applications, a relatively high ratio of catalyst to substrate should be used,[11] the development of heterogeneous bis(oxazolinyl) ligand systems is the subject of intensive research. Although a number of such systems have been prepared in recent years, all of these efforts focused on bis(oxazoline) (Box) ligands.[11,12] Box ligands, covalently immobilized on organic supports, were prepared *via* grafting or polymerization of soluble ligands, possessing a suitable functional or polymerizable unit.[13,14] Stepwise solid-phase synthesis of Box ligands, an alternative approach we recently presented,[15] is based on base-induced aminolysis of esters with β-aminoalcohols and bears potential advantages over existing methods (*e.g.* technical simplicity and more easily attainable diversity). This synthetic methodology was recently extended to the synthesis of Phebox ligands as we report herein.

The synthetic procedure (Scheme 1) starts with the immobilization of 11-bromo-1-undecanol (spacer) on Wang resin (trichloroacetimidate precursor). Highly efficient substitution of bromide by the 5-hydroxyisophthalate diester is followed by steps previously reported for Box synthesis.[15] The aminolysis step is more efficient and clean than in the synthesis of Box derivatives, probably due to the reduced steric hindrance. The oxazoline formation, following the chlorodehydroxylation step, also proceeds with higher purity than the case of Box ligands. The acidolytic cleavage of the ligands, followed by ^{1}H NMR, reveals high yields and purity. Although the oxazolines do not survive the acidic conditions, formation of the protonated bis(aminoester) hydrolysis product clearly demonstrates the existence of oxazolines prior to the cleavage.[16] Effective oxazoline formation in the last synthetic step is also confirmed

† Electronic supplementary information (ESI) available: general procedures for the preparation of resins **1** and **2** and the catalysis and characterisation data of resins **1**. See http://www.rsc.org/suppdata/cc/b3/b301308a/



Scheme 1 *Reagents and conditions:* a) 11-Bromoundecan-1-ol, $BF_3{\cdot}OEt_2$, cyclohexane/DCM, r.t., 15 min, quantitative. b) dimethyl 5-hydroxyisophthalate, LiH, TBAI, DMF, 60 °C, 36 h, quantitative. c) β-amino alcohol, LDA, DMF, 60 °C, 12 h. d) PPh_3, C_2Cl_6, THF, r.t., 12 h, quantitative. e) DBU, THF, 60 °C, 2 d.

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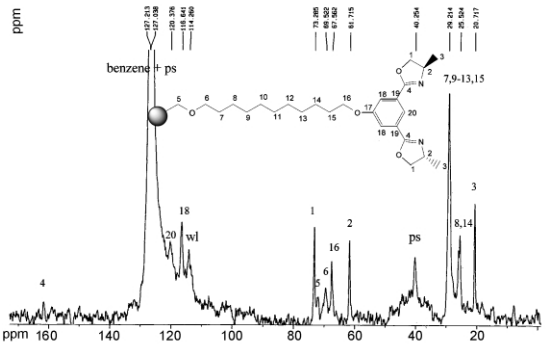
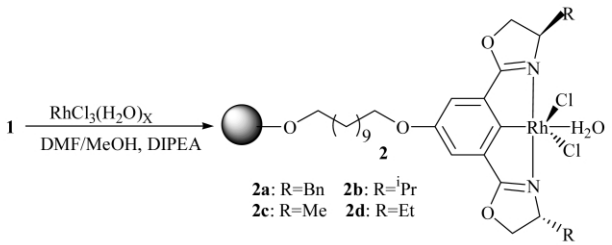


Fig. 1 Gel-phase ^{13}C NMR of **1c**. ps = polystyrene; wl = Wang linker.

by gel-phase ^{13}C NMR. For instance, in the gel-phase ^{13}C NMR of **1c** (Fig. 1) the characteristic peaks at 61.7 and 73.3 ppm prove the formation of the oxazoline heterocycles.[9b]

Following the successful preparation of ligands **1a–1d**, the attempts to complex the ligand with $RhCl_3 \cdot H_2O$ were performed. Although Phebox complexes of a number of transition metals were prepared, only for Rh was a direct metallation method reported.[7] Eventually, complexation was achieved using a DMF:MeOH (10:1) mixture of solvents (Scheme 2). The presence of a base is essential in order to avoid the cleavage of the compound from the support by HCl released during the complexation. The extent of complexation can be measured by the decrease in the intensity of the signal of the aromatic proton, positioned *ortho* to both oxazolines, in the ^1H NMR of the cleavage solution.

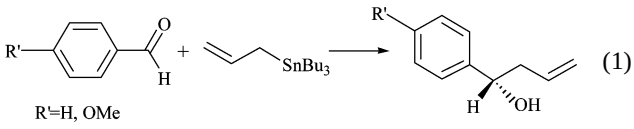


Scheme 2 Complexation of **1**.

We decided to test the supported complexes **2a–2d** in the enantioselective allylation of aldehydes. This synthetically useful reaction has never been catalyzed by a heterogeneous catalyst. Moreover, effectiveness of Phebox rhodium complex in catalysis of this reaction was demonstrated by Nishayama and coworkers.[9a,b] To our delight, we discovered that 3% of complexes **2a–2d** catalyze enantioselectively the allylation of benzaldehyde (eqn. 1, R = H, Table 1).[17] Moreover, while the reaction rate is rather slow, prolonged reaction times result in high yields. The enantioselectivity was surprisingly low for **2a** (R = Bn). (In solution, its analogue was the most selective ligand.[9a,b]) However, the selectivity improved for **2b** (R = ^{i}Pr) and further for **2c** (R = Me). The best outcome was obtained for **2d** (R = Et) with ee = 48%. Similar results were obtained for anisaldehyde.

Remarkably, the catalyst can easily be recycled without substantial loss in conversion and enantioselectivity. Two to three cycles were examined for most ligands, each demonstrating the highly reproducible ee and yield.

In conclusion, we demonstrated for the first time immobilization of Phebox ligands on solid support as well as the first heterogeneously-catalyzed enantioselective aldehyde allylation. Although only modest ee can be obtained at this stage, these results are an excellent starting point for optimization studies. This effective preparation of a complex enantioselective catalyst further demonstrates the potential of the stepwise synthesis of ligands on solid support.



(1)

Table 1 Allylation of aldehydes with catalyst **2**

R′	Catalyst	Cycle	Yield(%)[a]	ee(%)[b]
H	**2a**[c]	1	72	8[d]
H	**2a**[c]	2	76	9[d]
H	**2a**[e]	1	75	10[f]
H	**2b**[c]	1	72	18[d]
H	**2b**[c]	2	69	18[d]
H	**2c**[e]	1	86	29[f]
H	**2c**[e]	2	93	30[f]
H	**2c**[e]	3	93	30[f]
H	**2d**[e]	1	88	48[f]
H	**2d**[e]	2	84	48[f]
OMe	**2a**[c]	1	64	10[d]
OMe	**2b**[c]	1	76	20[d]
OMe	**2c**[e]	1	86	26[f]
OMe	**2c**[e]	2	84	25[f]
OMe	**2d**[e]	1	88	44[f]

[a] Determined using ^1H NMR. [b] Determined using HPLC. [c] *S,S*-ligand. [d] *S*-isomer. [e] *R,R*-ligand. [f] *R*-isomer.

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