Simultaneous control of regioselectivity and enantioselectivity in the hydroxycarbonylation and methoxycarbonylation of vinyl arenes†

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Using a family of novel mononuclear and dinuclear palladium complexes of phanephos ligands, the simultaneous control of regioselectivity and enantioselectivity in the hydroxycarbonylation and alkoxycarbonylation of styrene derivatives has been realised for the first time.

Chiral carboxylic acids are key building blocks for the synthesis of chiral drugs and natural products. To be viable at larger scale, a synthesis of enantiomerically enriched small molecules needs to use cheap reagents. Hydroxycarbonylation is a reaction that converts a generally cheap class of starting material (an alkene) into an acid, using two of the cheapest chemicals known: water and carbon monoxide; in an idealised case there are no by-products.1,2 There are several processes to produce achiral or racemic acids (or esters by alkoxycarbonylation) at large scale.

Since the birth of asymmetric catalysis, attempts have been made to realise alkene carbonylation enantioselectively. Although some excellent research has helped understand the nature of this reaction, until recently enantioselective hydroxycarbonylation of the model substrate styrene always gave near racemic products, often with no control of regioselectivity and unfavourable reaction conditions.3 Enantioselective methoxy-carbonylation of styrene has recorded better results, but none are really synthetically useful and the use of high temperatures with >1 equivalents of acid cocatalyst is common.4 In general monophosphines do control regioselectivity, but give low ee, while diphosphines give mainly linear products. A few papers report on branched-selective alkoxycarbonylation of styrene with diphosphine species with electron deficient or bulky phosphorus centres;1b,c,h,4a these show that this type of modification can improve branched selectivity. However, the only chiral catalysts in these studies gave 30% ee or less with a b : l of 2 : 1 (or less) in methoxycarbonylation of styrene.4a

We recently discovered that Pd complexes of the Phanephos ligands gave high enantioselectivity in these reactions (up to 95% ee for norbornene; 80% ee for styrene).5 None-the-less, even these catalysts did not control regioselectivity in the hydroxycarbonylation of styrene. Since this class of reaction and the Phanephos ligands6 have been proven to be adaptable to commercial production, we have initiated a project aiming to transform these promising initial findings into a synthetically useful catalyst. Here we show that new phanephos ligands generate catalysts that display exquisite control of regioselectivity while maintaining good levels of enantioselectivity in both hydroxycarbonylation and methoxycarbonylation of styrenes.

Before embarking on a programme of making new catalysts, a range of other reaction variables were investigated for the hydroxycarbonylation of styrene using the Xyl-Phanephos–Pd system. These results are archived in the ESI† and can be simply summarised; the dipalladium species outperforms the monomeric catalysts significantly in terms of productivity, an acid at least as strong as trifluoroacetic acid is needed, and chloride is required for the higher enantioselectivity. Under any conditions examined, the regioselectivity is quite close to 1 : 1. A range of new Phanephos–Pd catalysts were therefore prepared (Scheme 1 and ESI†).

The ligands were either prepared using commercially available chlorophosphines or from the known precursor bis-dichlorophosphate paracyclophane6e The choice of meta-substitution patterns stemmed from repeatedly finding better results with meta-xyl-Phanephos relative to Ph-Phanephos in our prior studies. The procedures reported reproducibly gave crude ligands of high purity, that were then fully purified in workable yields. The monomeric complexes are readily prepared in pure form. If these are treated with one further equivalent of [PdCl2(PhCN)2]4, then immediate formation of the dipalladium species was observed, or the dipalladium complexes are more conveniently prepared from two equivalents of [PdCl2(PhCN)2]. Some of the dipalladium complexes have sparing solubility, and complex 3di was completely insoluble in common solvents,

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possibly influencing its performance in catalysis. A family of 14 Phanephos-derived catalysts were available to test in the alkoxycarbonylation of alkenes. The alkoxycarbonylation of alkenes is also a potentially important reaction, since it produces esters in a single step without coupling agents. All the new catalysts were examined in methoxycarbonylation of styrene as a model reaction. A full table showing all the pre-catalysts under a variety of conditions can be found in the ESI.† Scheme 2 shows the most useful results. We were delighted to find that 6di delivers high yields

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The results strongly suggest that steric bulk and electronegative substituents both have a separate positive effect on the branched regioselectivity. The most regioselective catalyst, which gave essentially a single regiosomer, was the dipalladium complex derived from the most electron withdrawing ligand, 6di. This catalyst achieves this by analogy.

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of an essentially regiochemically pure branched ester with similarly good enantioselectivity as it does in hydroxycarbonylation, providing methanol is used as a reagent (2.5 equiv.), rather than solvent. The catalysts derived from ligand L4 also show very different behaviour in neat methanol to using a small excess (ESI†), with quite respectable 93% regioselectivity and 4:1 ratio of enantiomers (Scheme 2). The bulky ligand L3, which gave very poor catalysts in styrene hydroxycarbonylation, gives good reactivity near room temperature using 0.5% catalyst, reasonable control of regioselectivity (80%) and over 20:1 ratio of enantiomers. In this case, the more soluble monomeric catalyst is slightly more active than the (less soluble) dimer and the performance of the former is shown in Scheme 2.

A range of mono- and dinuclear palladium complexes of a family of Phaneos ligands have been prepared. Investigating this group of catalysts in the hydroxycarbonylation and methoxycarbonylation of styrene and a few of its derivatives has uncovered a remarkable improvement in regioselectivity from around 1:1 in the parent Ph-substituted system to over 100:1. While the results referred to in the literature enabled us to predict some increase in branched selectivity using the fluorinated ligands, the ability to tune from 1:1 to essentially perfect regioselectivity, whilst retaining decent levels of enantioselectivity is completely unexpected. The parent system, 2di while giving good enantioselectivity delivers less than 50% yield of the desired enantiomer once conversion, regioselectivity and ee are taken into account, but 6di produces around 90% ee enantiomer yield in these reactions, not too dissimilar from the best examples of enantioselective hydroformylation. It is therefore hoped that asymmetric hydro- and methoxy-carbonylation of alkenes may be capable of becoming a practical reaction for scaleable asymmetric synthesis. Mechanistic studies, catalyst recycling, further optimisation of catalysts, and new synthetic applications seem to be the most pressing topics to be dealt with and investigations are underway.

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Notes and references


