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Diphosphites as a promising new class of ligands in Pd-catalysed asymmetric allylic alkylation

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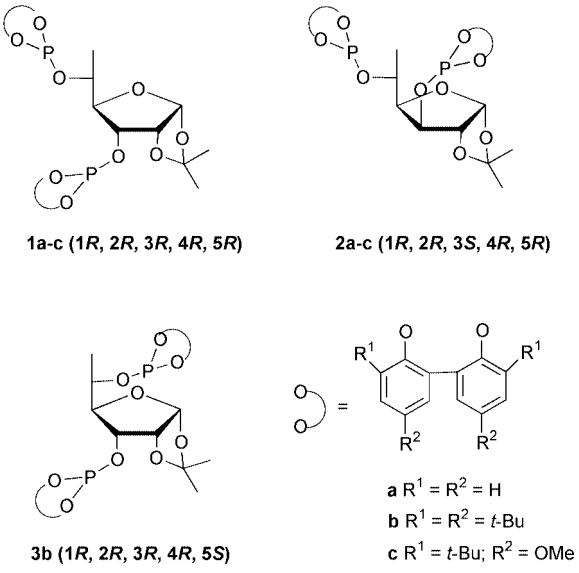
A series of diphosphite ligands, derived from readily available D-(+)-glucose, have been used for the first time in the palladium-catalysed allylic alkylation reaction with high enantioselectivity (ee up to 95%) and activity in standard conditions.

One of the main objectives in modern synthetic organic chemistry is the catalytic enantioselective formation of C–C bonds.[1] In this respect, Pd-catalysed allylic alkylation is a powerful and highly versatile procedure. In recent years, the asymmetric version of this reaction has been reported with various C_2- and C_1-symmetric bidentate chiral ligands providing excellent enantiomeric excesses.[2] However, one drawback of using these ligands is that they are often synthesised from expensive chiral sources and in tedious synthetic steps. Therefore it is important to develop new chiral ligands derived from readily available simple starting materials and to show their applicability in C–C bond formation. In this context, carbohydrates, which have been widely used in organic synthesis as inexpensive starting materials or as chiral auxiliaries,[3] have only recently shown their huge potential as a source of highly effective chiral ligands.[4]

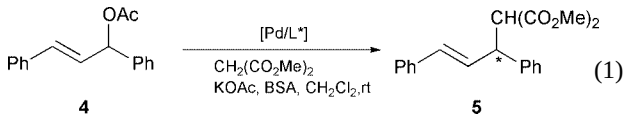
In this context, we have recently described the synthesis of a new class of furanoside diphosphite ligands (Scheme 1), prepared in a few steps from readily available D-(+)-glucose, and their successful use in the rhodium catalysed asymmetric hydroformylation of vinyl arenes (ee values up to 91%).[5]

The advantage of these ligands is that their modular nature allows a facile systematic variation in the configuration of the stereocenters (C-3, C-5) at the ligand bridge and in the biphenyl substituents, allowing the optimum configuration for maximum stereoselectivity to be determined. In this paper we report on the use of this new class of sugar diphosphite ligands in enantioselective Pd-catalysed allylic alkylation. We also examined the effect of the configuration of the stereogenic centers C-3 and C-5 since this was expected to be important for the catalytic reaction because of the proximity of these centers to the metal. The influence of the substituents on the biphenyl moieties was also studied. Although the combination of mixed phosphite–oxazoline,[6] phosphite–thioether[7] functionalities and phosphite–phosphine[8] ligands has already been successfully used in Pd-catalysed allylic alkylation, to the best of our knowledge this is the first example of diphosphite ligands being applied to this type of reaction.



Scheme 1

For initial evaluation of the new ligands we chose the palladium(0)-catalysed addition of dimethyl malonate to *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (**4**) [eqn. (1)] because this



4 **5** (1)

reaction has been carried out with a wide variety of ligands carrying different donor groups, enabling direct comparison of the efficacy of different ligand systems. In addition, many successful ligands developed for this reaction have been found to have broader applicability in other related reactions.[2]

Asymmetric allylic substitution of **4** was carried out with the palladium complex generated *in situ* by mixing the corresponding chiral ligand and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, under basic Trost conditions.[9] Results are given in Table 1.

Table 1 Palladium-catalysed asymmetric allylic alkylation with chiral ligands **1**–**3**[a]

Entry	L*	Time/min	% Conv.[b]	% ee[c]
1	**1a**	1440	50	2 (*R*)
2	**1b**	15	100	64 (*R*)
3	**1c**	19	100	45 (*R*)
4	**2c**	35	60	9 (*S*)
5	**2b**	5	100	84 (*S*)
6	**2c**	10	100	95 (*S*)
7	**3b**	3600	100	52 (*S*)
8	**6**	71	100	61 (*S*)
9	**7**	65	100	59 (*S*)
10[d]	**8**	1440	100	61 (*S*)

[a] Reaction conditions: 1 mmol of substrate, 3 mmol of dimethyl malonate, 3 mmol of *N*,*O*-bis(trimethylsilyl)acetamide (BSA), 1 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 2.5 mol% of L* and 2 mol % of KOAc, in 4 cm^3 of CH_2Cl_2 at room temperature. [b] Conversion percentage based on the substrate determined by ^{1}H NMR spectroscopy. [c] Enantiomeric excesses determined by HPLC on a Chiralcel-OD column. Absolute configuration, in parentheses, determined by optical rotation.[10] [d] Data from reference 11.

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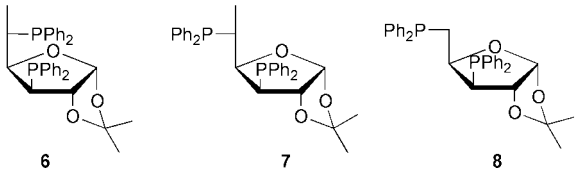

6 7 8

Scheme 2

The reaction at room temperature using ligand **1a** with two unsubstituted biphenol moieties provided (*R*)-**5** with an ee value of only 2% (entry 1). The presence of bulky *tert*-butyl groups in the *ortho*-positions of the biphenyl moiety (ligands **1b** and **1c**) had a positive effect on the enantioselectivity (ee values up to 64%, entries 2 and 3). Furthermore, the presence of *tert*-butyl groups also had an extremely positive effect on the activity (entry 1 *vs.* entries 2 and 3).

The use of ligands **2a**–**c**, in which the configuration of carbon atom C-3 is opposite to those of ligands **1a**–**c** (Scheme 1), produced improved enantioselectivities and activities (entries 1–3 *vs.* entries 4–6). Thus, ligand **2b** showed not only higher asymmetric induction (84%) but also very high catalytic activity (5 minutes for total conversion of substrate, entry 5). Such remarkably high activity, which can be explained by the large π-acceptor ability of the diphospite ligands, contrasts with the low activity reported for other homo-donor ligands.[2,4k,12] The enantioselectivity was increased to 95% (*S*)-**5** when ligand **2c**, with methoxy groups instead of *tert*-butyl groups in the *para* positions of the biphenyl moieties, was used (entry 5 *vs*. entry 6).

The use of ligand **3b**, which resulted from changing the configuration of C-5 from (*R*) to (*S*) in ligands **1**, leads to lower activity and slightly lower enantioselectivity than the catalytic system Pd/**1** (entry 2 *vs.* entry 7). Moreover, comparison of entries 2, 5 and 7 clearly shows that the enantiomeric excesses are strongly dependent on the absolute configuration of the carbon C-3 stereocenter of the carbohydrate backbone. The best enantioselectivities were obtained using ligands **2b** and **2c** with (*S*) configuration at C-3. The presence of methoxy groups in the biphenyl moieties significantly improved the enantioselectivity (ee up to 95%).

Note that these diphosphite ligands showed higher enantioselectivity and reaction rates than their corresponding diphosphines **6** and **7**[13] (entries 8 and 9) and the *xylo*-furanoside diphosphine **8**[11] analogue (entry 10) under the same reaction conditions (Scheme 2). The similar enantioselectivities obtained with ligands **6** and **7** confirms that the configuration of C-5 has no relevant influence on the enantiodiscrimination as observed for the diphosphite ligands.

In summary, we have described the first application of diphosphite ligands in asymmetric allylic alkylation reactions. These ligands can be prepared in a few steps from commercial D-(+)-glucose as an inexpensive natural chiral source. The combination of high enantioselectivities (ee up to 95%) and high activities in simple unoptimized reactions and the low cost of the ligands makes these catalyst systems very attractive for further research. These results also open up a new class of ligands for enantioselective Pd-catalysed allylic alkylation, which will be of great practical interest. For example, phosphites are less sensitive to oxidation than phosphines. Moreover, because of the modular construction of diphosphites, structural diversity is easy to achieve, so enantioselectivity can be maximised for each new substrate as required. Studies of this kind, as well as mechanistic studies, are currently under way.

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