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Rh(II) catalysts with 4-hydroxyproline-derived ligands

Hanne Therese Bonge, Massoud Kaboli, Tore Hansen *

Department of Chemistry, University of Oslo, Sem Sælands vei 26, N-0315 Oslo, Norway

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ABSTRACT

Three new chiral Rh(II) catalysts with 4-hydroxyproline-derived ligands have been synthesised through a short and efficient synthetic route. The catalysts give good yields and ees in C–H insertion and cyclopropanation reactions, and their properties indicate an all-up reactive conformation of proline- and 4-hydroxyproline-derived Rh(II) catalysts.

Carbenoid C–H insertion and cyclopropanation reactions catalysed by chiral dirhodium(II) catalysts represent extremely powerful methods in asymmetric synthesis, often giving high chemo-, regio- and diastereoselectivity along with excellent enantioselectivity.[1] The development of new chiral Rh(II) catalysts, and the understanding of their mode of asymmetric induction, is therefore of great importance.

Proline-derived Rh(II) carboxylates, in particular $Rh_2(DOSP)_4$ (**4**, Fig. 1), are catalysts that have found widespread use in carbenoid reactions.[2] The merits of **4** include excellent enantioselectivities in C–H insertion and cyclopropanation reactions with Davies' aryl- and vinyl-substituted diazo compounds. Our group has recently developed methodology for selective O-acylation of 4-hydroxyproline with acyl chlorides.[3] This methodology offers a short and practical route to chiral, 4-hydroxyproline-based ligands (HYP-ligands) for new Rh(II) catalysts. While proline is a well-known chiral component in Rh(II) ligands, HYP-ligands are, to the best of our knowledge, yet to be used. They do, however, offer certain advantages over proline-derived ligands, such as a second stereogenic centre, and a side-chain that can be used for tuning properties such as solubility and steric bulk. Additional factors that make 4-hydroxyproline a highly appealing building block for new chiral ligands are those of economy and availability: *trans*-4-hydroxyproline is commercially available at a low cost and can, in a facile manner,[3,4] be cleanly converted into the more costly *cis*-isomer.

Herein, we report the synthesis of three new Rh(II)-HYP catalysts (**1**–**3**, Fig. 1) through a short, convenient synthetic route (Scheme 1) in good overall yields.

Following the previously described method,[3] *trans*- and *cis*-4-hydroxyprolines were O-acylated with lauroyl chloride or cyclohexylcarbonyl chloride in good to excellent yields without the need for chromatography. N-Sulfonation with 4-*t*-butylphenylsulfonyl chloride, in good yields, completed the synthesis of the ligands. Coordination of the ligands to dirhodium was accomplished through high temperature ligand exchange[5] with commercially available $Rh_2(OAc)_2$, giving catalysts **1**–**3** in good to excellent yields.

The Rh(II)-HYP catalysts have advantageous solubility in organic solvents. With the sizeable hydrophobic side-chains of the HYP-ligands, the 4-dodecylphenyl substituent used to aid solubility in $Rh_2(DOSP)_4$ (**4**) is no longer necessary. For instance, the commercially available $Rh_2(TBSP)_4$ (**5**) is a catalyst that displays near identical reactivity and selectivity to **4**,[6] but with a 4-*t*-butylphenyl group instead of 4-dodecylphenyl, it is less soluble in organic solvents and has therefore found little use. However, the 4-*t*-butyl-phenyl group works well in the Rh(II)-HYP catalysts, showing how the range of possible aryl groups is broadened compared to the catalysts with proline-derived ligands.

The three new catalysts **1**–**3** were tested in cyclopropanation reactions with styrene and C–H insertion reactions with adamantane (Table 1). As methyl aryldiazoacetate is known to give good results in reactions catalysed by $Rh_2(DOSP)_4$,[7] this diazo compound became our test substrate. In order to lower the ee compared to the optimal results, thus facilitating comparison of the different catalysts, the reactions were performed at room temperature, a higher reaction temperature than is optimal for **4**.[6] The Rh(II)-HYP

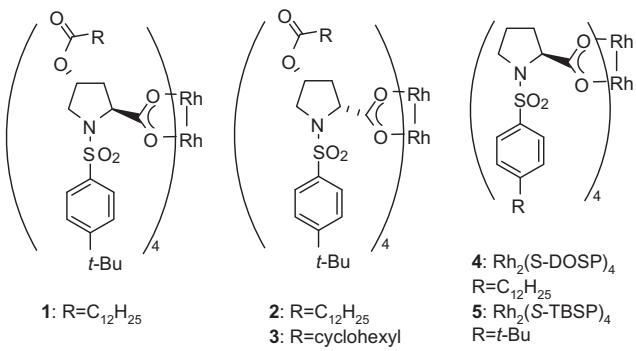

Figure 1. New catalysts **1**–**3** and catalysts with proline-derived ligands **4** and **5**.

* Corresponding author. Tel.: +47 22 85 53 86; fax: +47 22 85 54 41.
E-mail address: t.hansen@kjemi.uio.no (T. Hansen).

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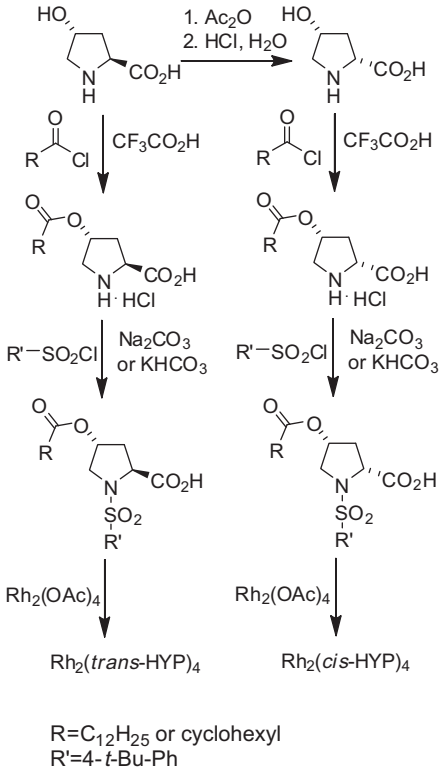
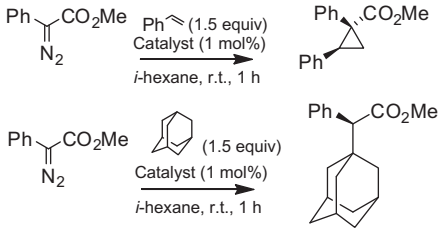


Scheme 1. General synthesis of Rh(II)-HYP catalysts.

Table 1
Cyclopropanation and C–H insertion reactions with catalysts **1**–**5**



Entry	Substrate	Catalyst	Yield (%)	ee
1	Styrene	**4**	80	80
2	Styrene	**1**	76	84[a]
3	Styrene	**2**	78	90[b]
4	Styrene	**3**	74	80[b]
5	Adamantane	**4**	56	86
6	Adamantane	**5**	55	85[a]
7	Adamantane	**1**	56	92[a]
8	Adamantane	**2**	65	90[b]
9	Adamantane	**3**	67	93[b]

The ee was measured by chiral HPLC, directly for entries 5–9, and after $LiAlH_4$ reduction of the ester group to the corresponding alcohol for entries 1–4.

[a] Same absolute configuration as with **4**.

[b] Opposite absolute configuration to that with **4**. The de in the cyclopropanation reactions, measured by ^1H NMR spectroscopy of crude product, was in all instances ~20:1.

catalysts gave very good results in both the cyclopropanation reaction and the C–H insertion reaction. The yields with catalysts **1**–**3** in all the reactions were very similar to those obtained with **4** and **5**. The level of enantiocontrol with the new catalysts also matched that observed with the proline-derived catalysts; the ees obtained with **1**–**3** were similar to the ees with **4** and **5**. As expected, catalysts **1** and **2** displayed opposite enantioselectivity to each other. It is known from results with Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-DOSP)$_4$ that the enantioselectivities of proline-derived catalysts are governed by the stereochemistry at C2 of proline, and as a starting material *cis*-4-hydroxyproline is generated from *trans*-4-hydroxyproline through inversion at C2, catalysts **1** and **2** have opposite stereochemistry at this centre.[3,4]

The Rh(II)-HYP catalysts are also useful tools in the ongoing pursuit for understanding the mode of asymmetric induction in the chiral Rh(II) catalysts. The exact nature of the stereochemical induction achieved using the proline-based carboxylate ligands in catalysts **4** and **5** has yet to be explored. The prevalent hypothesis is that the ligands in chiral Rh(II) catalysts possess 'blocking groups' that, pointing either up or down in a total of four possible catalyst conformations (Fig. 2), favour one enantiotopic trajectory of the substrate towards the carbenoid over the other.[2,6] Davies et al. have postulated a D_2-symmetric (up, down, up, down) orientation of the aryl groups in **4** and similar catalysts, resulting in two equivalent catalyst faces.[2] This has its basis in that catalysts with two different faces should be ineffective, as the less sterically encumbered face appears achiral. Recently, however, Fox and coworkers performed a computational study of Rh_2(*S*-PTTL)$_4$, another frequently employed chiral Rh(II) catalyst, with results indicating an all-up, 'chiral crown' conformation with C_4-symmetry.[8] The proposition that the catalyst has a reactive chiral face and an unreactive achiral face represents a novel way of perceiving these catalysts, and has sparked a renewed interest in understanding their mode of chiral induction. The group of Charette has further investigated this theory, finding strong experimental evidence in favour of a reactive all-up conformation for certain catalysts similar to Rh_2(*S*-PTTL)$_4$.[9] An important question which then arises is if this conformation is specific only for the catalysts studied by Charette and Fox, or if an all-up orientation of the ligands is in fact the active conformation of other chiral Rh(II) catalysts as well, such as Rh_2(DOSP)$_4$ (**4**) and its analogues.

The observed high level of similarities between the Rh(II)-HYP catalysts and the proline-derived catalysts in the C–H insertion and cyclopropanation reactions, both in yields and enantioselectivity, has interesting implications for understanding of the mode of stereoselectivity for proline- and hydroxyproline-derived catalysts. Our findings show that the outcome of the C–H insertion and cyclopropanation reactions is not affected by the presence of a large substituent on C4 of the proline ring. Both yields and ee remain largely unchanged in going from unsubstituted **4** and **5** to lauroyl-substituted **1** and **2** or cyclohexylcarboxyl-substituted **3**, and changing the relative stereochemistry of the ligands from *trans* in **1** to *cis* in **2** also has minor effects. Two implications follow from these results: (i) the active conformation of the catalysts must have the ligands oriented in such a way that the side-chains are remote from the reactive site of the carbenoid, so that they do not

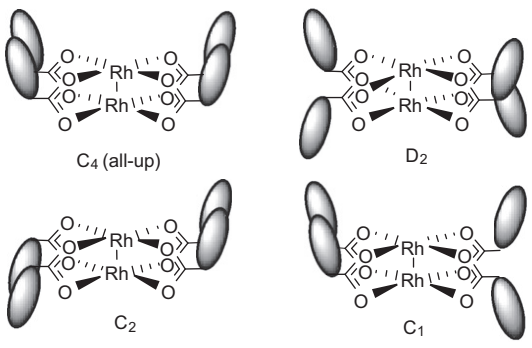


Figure 2. Four possible conformations of the chiral Rh(II) catalysts. The spheres represent arylsulfonyl groups.

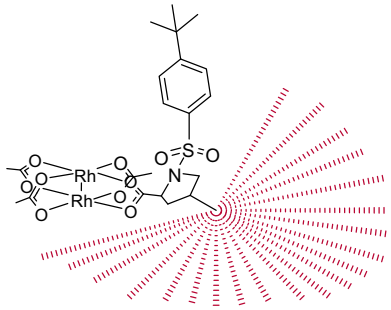


Figure 3. Illustration of the wide range of movement of acyl substituents (red). Only one substituent is drawn for clarity. The orientations of the proline and aryl rings are based on computational optimisation of a simplified DOSP-ligand.[10]

influence the reaction and (ii) this orientation of the ligands must be the same for all catalysts **1**–**5**, as indicated by their very similar enantioselectivities. Of the four catalyst conformations shown in Figure 2, the only one that clearly fits these criteria is the all-up, C_4-symmetric conformation. Only if the reaction takes place at the top face of a catalyst with all the arylsulfonyl groups pointing up can the side-chains, at all times, be sufficiently far away from the reaction site not to be expected to influence the reaction. The large acyl substituents have a wide range of movement, as illustrated in Figure 3, and if either of the ligands were to have the arylsulfonyl group pointing down, the side-chain could come into proximity to the carbenoid.

An all-up conformation gives rise to two different catalyst faces: a bottom face which is not expected to induce stereocontrol, and which in the case of **4** and **5** is completely unshielded, and a sterically congested chiral top face, where the reaction must take place. We hypothesise, along the lines of Charette and co-workers,[9] that π-stacking interactions between the arylsulfonyl groups and the carbenoid substituents may be the reason why formation of the most sterically hindered carbenoid is favoured. The scope of **4** gives credence to this theory: catalyst **4** induces high ee in reactions with aryl- and vinyldiazoacetates,[2,7] which have substituents capable of π-stacking, but gives poor enantiocontrol with others such as ethyl diazoacetate[11] and halodiazoacetates.[12] Thus, our findings indicate that the arylsulfonyl groups are not merely blocking groups, but take part in a dynamic process in coordination of a carbenoid to the catalyst, giving rise to an induced fit with a chiral pocket around the carbenoid, the arylsulfonyl groups blocking one of the enantiotopic faces of the carbenoid.

In summary, we have developed a facile protocol for the synthesis of new 4-hydroxyproline-derived chiral Rh(II) catalysts. The Rh(II)-HYP catalysts possess a side-chain that aids solubility in organic solvents, and they have been shown to give similar yields and enantioselectivities in cyclopropanation and C–H insertion reactions in comparison to the widely used $Rh_2(DOSP)_4$ and its analogues. Studies on the Rh(II)-HYP catalysts imply an all-up conformation with a reactive chiral face and an unreactive achiral face for Rh(II) catalysts with proline-derived ligands such as $Rh_2(DOSP)_4$ and $Rh_2(TBSP)_4$, along with the new Rh(II)-HYP catalysts. Further studies will be reported in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.115.

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