

# Chiral Induction in Intramolecular Rhodium-Catalyzed [2+2+2] Cycloadditions of Optically Active Allene-ene/yne-allene Substrates

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**Abstract.** Allene-yne-allene and allene-ene-allene *N*-tosyl-linked substrates with two chiral centres in the  $\alpha$ -position of the allene moiety were satisfactorily prepared starting both from racemic and chiral propargylic alcohols. The Wilkinson's complex-catalyzed [2+2+2] cycloaddition reaction of these substrates was evaluated. In the case of enantiomerically pure bisallenes, perfect stereoselectivity was observed, giving a diastereomerically pure cycloadduct. The chirality of starting bisallene substrates can be completely transferred to the cycloadducts, representing an atom-economical and enantiospecific process for the construction of fused polycycles. However, when reacting an oxygen-linked allene-ene-allene substrate, the stereoselectivity decreased and two diastereoisomers were formed. A detailed characterization study of the resulting cycloadducts allows us to identify the enantioisomer generated in the cycloaddition.

**Keywords:** Allenes; Chiral induction; Cycloaddition; Polycycle; Rhodium

The transition-metal catalyzed [2+2+2] cycloaddition reaction is a powerful tool for one-step construction in an atom-economical process of highly functionalized polycyclic compounds.<sup>[1]</sup> An attractive feature of this transformation is that it can lead to optically active derivatives.<sup>[2]</sup> When the reaction involves only triple carbon-carbon bonds  $C_{sp}$  hybridized unsaturations, axial, planar, or helical chirality can be built up on cycloaddition. In the specific case in which at least one unsaturation with a containing a  $C_{sp^2}$  is involved, central chirality can also be constructed. As the number of  $C_{sp^2}$  – containing unsaturations increases, the number of stereogenic centres generated can also increase,

generally complicating the control of the stereoselectivity.

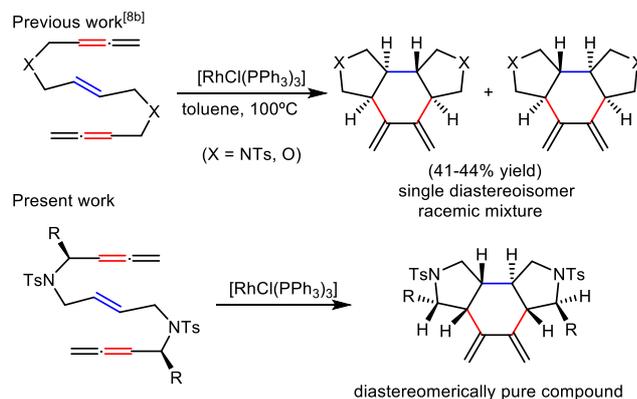
Although the use of chiral catalysts has been the preferred option to induce chirality in most of the [2+2+2] cycloaddition reactions reported so far, a few studies based on diastereoselective reactions of easily accessible chiral substrates have also been reported. Hapke et al.<sup>[3]</sup> synthesized axially chiral naphthyl tetrahydroisoquinolines through a cobalt-catalyzed [2+2+2] cycloaddition of chiral proline-based naphthyl diynes with nitriles. No large selectivity effects were observed, presumably due to the distance of the proline moiety from the reaction centre. However, this is a good strategy to access these compounds without the need for chiral catalysts since both diastereoisomeric atropoisomers could be easily separated by column chromatography. Tanaka et al.<sup>[4]</sup> reported the rhodium(I)-catalyzed diastereoselective [2+2+2] cycloaddition of tetraynes containing chiral centres with monoynes to achieve  $C_2$ -symmetric enantiopure biaryls with axial chirality. The authors demonstrated that the substrate determines the diastereoselectivity of the process even when a chiral ligand was used in the catalytic system. Central-to-helical chirality induction was also demonstrated in several papers by the group of Stará and Stary.<sup>[5]</sup> They developed stereoselective [2+2+2] cycloadditions mediated by a cobalt/phosphine catalytic system to obtain functionalized penta-, hexa-, hepta- and undecacyclic helicene scaffolds as well as [5]-, [6]-, and [7]heterohelicenes in non-racemic form starting from optically pure triynes. Finally, Carbery et al.<sup>[6]</sup> reported the synthesis of heliceneoidal-4-dimethyl-amino pyridine derivatives upon diastereoselective  $[RhCl(PPh_3)_3]$ -catalyzed [2+2+2] cycloisomerization of an optically pure triyne that

already contained a pyridine ring and had a stereogenic centre, which controls the helical orientation the helicity of the product.

Apart from these examples involving only triple bonds unsaturations and, hence, with chiral induction taking place from central to either axial or helical chirality, Malacria et al.<sup>[7]</sup> studied chirality transfer using axially chiral allenes as unsaturated substrates in [2+2+2] cycloadditions, reporting that optically active allenediynes underwent intramolecular cobalt-mediated [2+2+2] cycloaddition to afford cyclohexadiene-cobalt complexes containing one stereocentre as a single enantiomer. without any erosion of the enantiomeric excess.

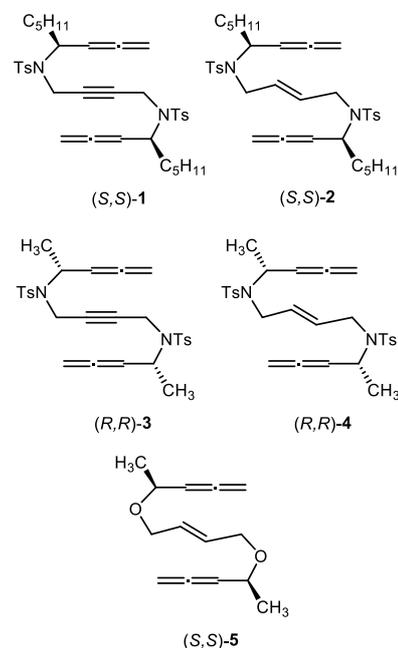
As part of our continuing interest in the use of allenes as unsaturated substrates for the construction of polycyclic scaffolds by Rh-catalyzed cycloaddition reactions,<sup>[8]</sup> we have recently described the cycloaddition of linear allene-ene-allene (shown in Scheme 1) and allene-yne-allene substrates promoted by the Wilkinson complex to afford tricyclic scaffolds featuring exocyclic dienes. The process was diastereoselective, furnishing cycloadducts with four or two stereocentres, respectively, as a single diastereoisomer. Cycloadducts were formed by a chemoselective reaction of the inner allene double bond and, therefore, featured an exocyclic diene motif<sup>[8b]</sup> (Scheme 1). Given that new stereocentres were generated in the cycloadducts, we tried to obtain optically pure polycycles using combinations of a cationic rhodium source and chiral biphosphine ligands. However, the diastereoselectivity of the reaction dramatically decreased making the process inefficient.

Here, we report a different approach to chiral polycycles that consists of inducing chirality from easily accessible starting chiral substrates. Enantiomerically pure allene-ene/yne-allene substrates, readily synthesized from commercially available optically active propargylic alcohols, have been cycloisomerized under [RhCl(PPh<sub>3</sub>)<sub>3</sub>] catalysis to determine whether or not it is possible to induce chirality in control the configuration of the two or four stereogenic centres generated in the [2+2+2] cycloaddition reaction by the influence of two chiral centres already present in the substrate. In other words, if successful, central chirality would be induced, which, unlike the induction of axial and helical chirality, has not been previously reported.



**Scheme 1.** [RhCl(PPh<sub>3</sub>)<sub>3</sub>]-catalyzed [2+2+2] cycloaddition reactions of achiral and chiral allene-ene-allene substrates.

In order to perform the study of the stereoselective [2+2+2] cycloaddition reaction with chiral bisallene substrates, five model compounds bearing N-tosyl (NTs) and oxygen (O) linkage were prepared (see SI for their synthesis). Two chiral centres were situated in the  $\alpha$ -position to the allene functionality, a long alkyl chain C<sub>5</sub>H<sub>11</sub> [(*S,S*)-1, (*S,S*)-2] and a methyl group [(*R,R*)-3, (*R,R*)-4 and (*S,S*)-5]. The bisallene compounds with the methyl group and a NTs linker have the opposite configuration to that of C<sub>5</sub>H<sub>11</sub>. The substrates have either an alkyne (**1** and **3**) or an alkene (**2**, **4** and **5**) unit in the centre of the chain (Figure 1).



**Figure 1.** Stereopure bis-allene substrates used in this study.

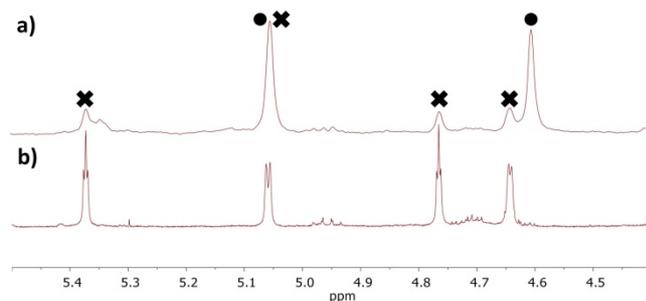
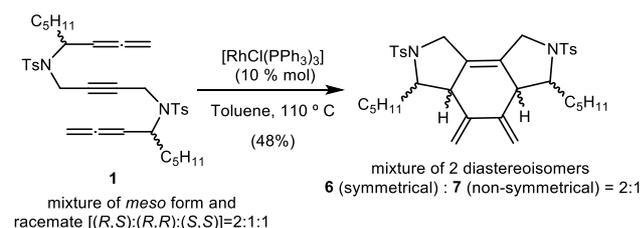
We prepared **1-5** from commercially available racemic and/or enantiopure propargylic alcohols. Throughout the whole synthetic process, the products obtained with the chiral enantiopure alcohol were

analysed by **chiral HPLC** to prove that the **chirality had not been erased their optical purity**. In all cases, when the synthesis was started with racemic propargylic alcohols, inseparable **1:1** mixtures of *meso* form and a **racemic mixture of two enantiomers racemate** of the bisallene derivatives were obtained.

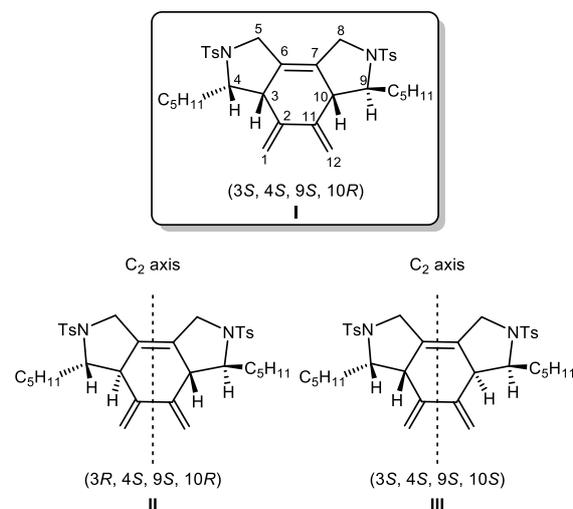
After the preparation of the model substrates, their reactivity in the [2+2+2] cycloaddition reaction was evaluated. The use of Wilkinson's catalyst and toluene as the solvent at 110°C was chosen as reaction conditions based on our previous results.<sup>[8b]</sup>

We first investigated the reaction of allene-yne-allene **1** prepared from racemic propargylic alcohol. In this case, only two new stereogenic centres were generated. **instead of four in the cases of ene-bisallenes 2 and 3**. In the cycloaddition of **1**, two diastereoisomers were formed. A detailed NMR analysis of the olefinic part of the spectrum revealed that one symmetrical (**6**) (dots) and one non-symmetrical cycloadduct (**7**) (crosses) were formed in a 2:1 ratio (Scheme 2). **This indicates that the *meso* form is more reactive than the racemate.**

The cycloaddition of the enantiomerically pure bisallene (*S,S*)-**1** showed a single non-symmetric enantiomer **in 46% yield**, which happened to correspond to the minor diastereoisomer **7** obtained in the previous reaction (Scheme 2). To determine the absolute configuration of the enantiopure cycloadduct, we studied the stereoisomers that might be generated. The cycloadduct has four stereocentres. Two of them are new stereogenic centres generated in the cycloaddition whereas the other two are transferred from the substrate, maintaining their (*S*) absolute configuration. Figure 2 shows the three stereoisomers that could be derived from the relative position of the two hydrogens on the carbon C(3) and C(10). However, we can discard structures **II** and **III** with C<sub>2</sub> symmetry axis, since a non-symmetric compound arises from the NMR spectra analysis.

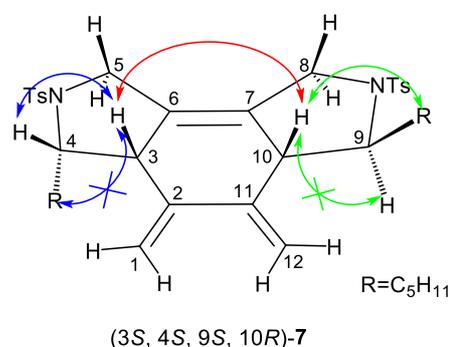


**Scheme 2.** [2+2+2] Cycloaddition reaction of substrate **1**. a) <sup>1</sup>H-NMR of olefinic part of the cycloadduct mixture from **1** and b) from optically pure (*S,S*)-**1**.



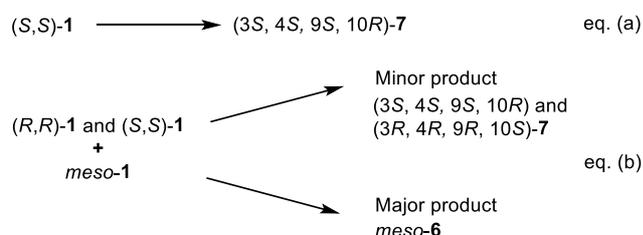
**Figure 2.** Three possible stereoisomers that could be formed upon cycloaddition of (*S,S*)-**1**.

In order to confirm that the cycloadduct obtained corresponded to structure **I**, bidimensional NMR studies were undertaken. NOESY correlations showed strong dipolar couplings between H(3) and H(4) together with the absence of NOE contact between H(3) and the protons on the pentyl chain on C(4) (blue arrows in Figure 3), indicating a *cis* relationship between H(3) and H(4). The presence in the NOESY spectrum of NOE cross-peaks between H(10) and the protons of the aliphatic groups in C(9) together with the lack of dipolar coupling between H(10) and H(9) revealed a *trans* relative configuration in the other half of the cycloadduct (green arrows in Figure 3). A NOE cross-peaks observed between H(3) and H(10) confirmed their *cis* relationship excluding possible structures **II** and **III** (red arrow in Figure 3).



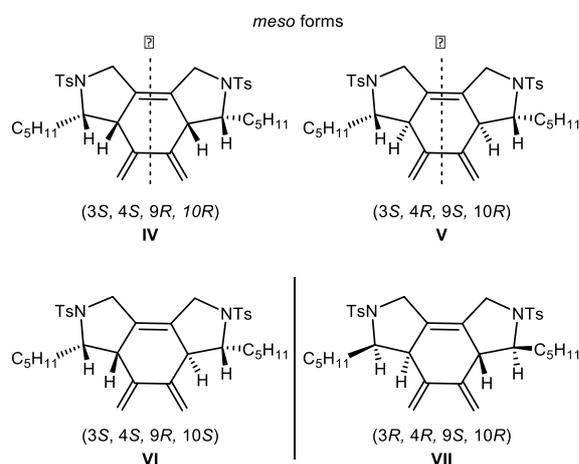
**Figure 3.** Main observed NOESY correlations in good agreement with the proposed structure of **7**.

We then turned our attention to the major diastereoisomer **6** formed in the cycloaddition of **1**, as a mixture of stereoisomers. The minor diastereoisomer corresponds to a racemic mixture of **7**, one of the enantiomers of which was obtained in the cycloaddition of the optically pure substrate (*S,S*)-**1** as has previously been stated. Thus, we assumed that cycloadduct **6** was formed from the *meso* compound present in the mixture of substrate **1** (Scheme 3).



**Scheme 3.** Stereochemical correlations in the cycloaddition of **1**.

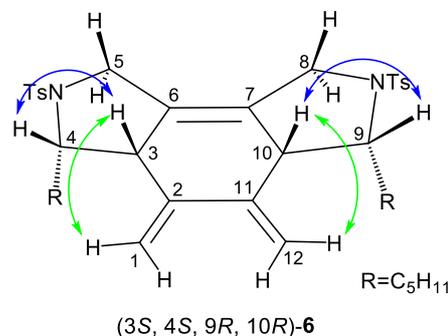
Taking into account that the structure of **6** must have an (*R,S*) configuration at the C(4) and C(9) position, and, due to the symmetry of the molecule, the number of possible stereoisomers was reduced to four (Figure 4). Structures **IV** and **V** are *meso* forms whereas structures **VI** and **VII** are a pair of enantiomers. Since the major product is symmetrical, the enantiomeric pair can be discarded.



**Figure 4.** Possible stereoisomers of **6**

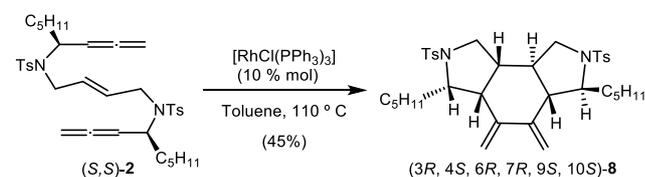
After a complete chemical shift assignment of the signals, the dipolar couplings observed in the NOESY spectrum were analysed (Figure 5). The main difference between structure **IV** and **V** is that protons H(3) and H(10) are in a *cis* relative configuration with the protons H(4) and H(9) respectively (for structure **IV**, Figure 4) or in a *trans* relative configuration (for structure **V**, Figure 4). The olefinic proton signals on C(1) and C(12) show

dipolar coupling with the protons H(3) and H(10), respectively (green arrows). The strong NOE cross-peak between H(3) and H(4), and between H(9) and H(10) (blue arrows) fully confirm that the configuration of cycloadduct **6** matches with structure **IV**.



**Figure 5.** Main observed NOESY correlations of cycloadduct **6** supporting the proposed structure.

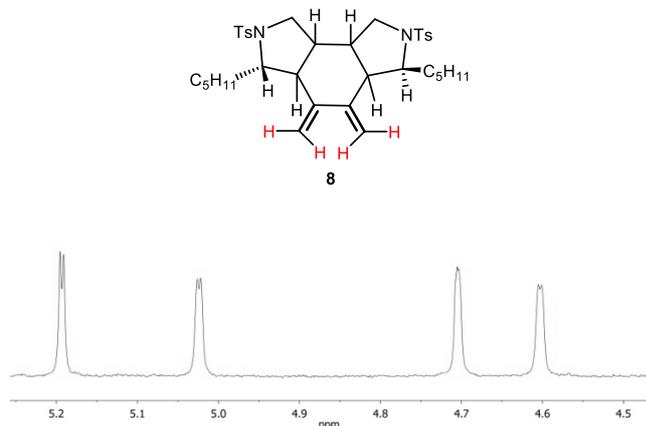
In a next step we wanted to study more challenging substrates. We have demonstrated that a chiral centre in the  $\alpha$ -position of the allene moiety induces chirality in stereogenic centres C(3) and C(10). Now we wish to introduce a *E* double bond in the bisallene (**2**) in order to generate two more stereogenic centres in the cycloaddition and explore the chiral induction due to these two more distant chiral centres. The cycloaddition of allene-ene-allene substrate **2** was evaluated following the same methodology as for case **1**. The cycloaddition of both **2** (derived from racemic propargylic alcohols) and enantiopure (*S,S*)-**2** was analysed (Scheme 4). It is known that [2+2+2] cycloaddition is completely stereospecific with respect to the stereochemistry of the original double bond. Thus, these two protons should be in a relative *anti* position in the resulting cycloadduct.



**Scheme 4.** [RhCl(PPh<sub>3</sub>)<sub>3</sub>]-catalyzed [2+2+2] cycloaddition reactions of allene-ene-allene **2**

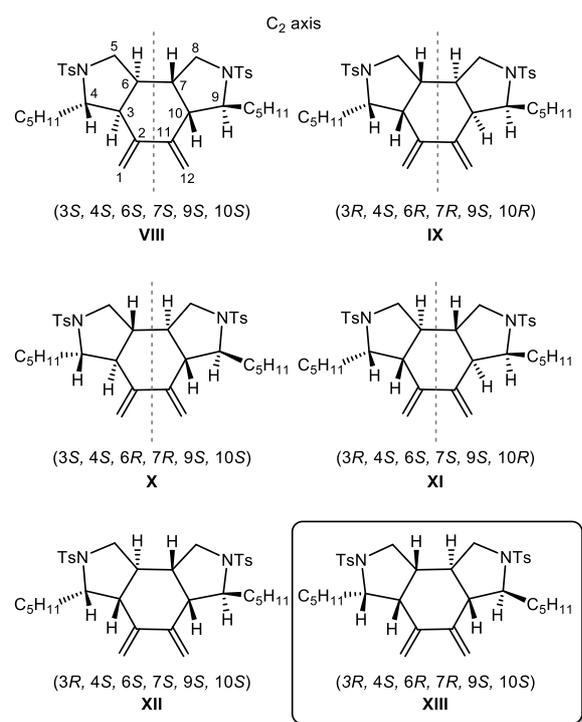
In practice, the Rh-catalyzed cycloaddition of enantiopure (*S,S*)-**2**, showed a complete stereoselectivity, demonstrating that stereogenic centres play a total control. Thus, analysis of the NMR spectra showed that only stereoisomer **8** was formed with four different olefinic protons, indicating a non-symmetrical structure (Figure 6). In addition, HPLC analysis of the product showed a single peak, at a retention time of 9.75 minutes, corresponding to

one of the stereoisomers arising from the cycloaddition of **2** (mixture of a pair of enantiomers and a *meso* form).



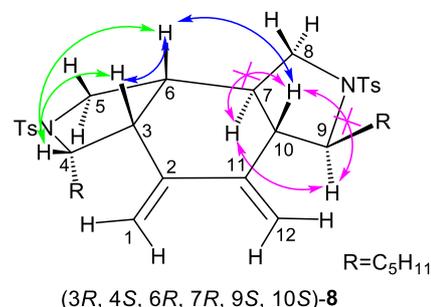
**Figure 6.** Olefinic segment of the  $^1\text{H-NMR}$  spectra of cycloadduct **8**.

In order to determine the absolute relative configuration of the newly formed stereogenic centres in cycloadduct **8** derived from (*S,S*)-**2**, some points need to be taken into account. Cycloadduct **8** bears six stereocentres: four are new stereogenic centres that are formed in the reaction whereas two are transferred from the substrate, maintaining the (*S*) absolute configuration. Taking into account the fact that the [2+2+2] cycloaddition is stereospecific in respect of the *trans* alkene, only six stereoisomers can be formed upon the cycloaddition of (*S,S*)-**2**. These six possible stereoisomers are shown in Figure 7.



**Figure 7.** Six possible stereoisomers that could be formed upon cycloaddition of (*S,S*)-**2**.

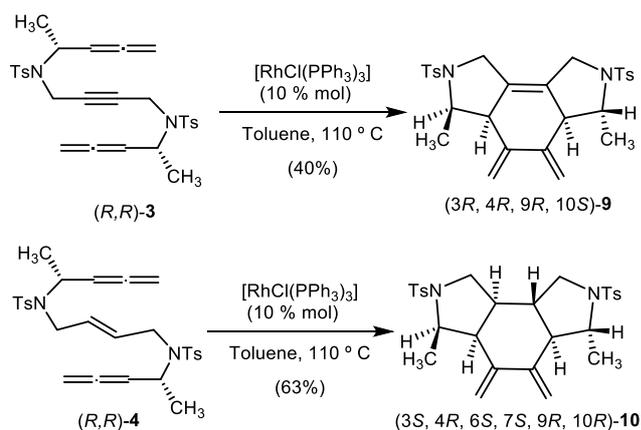
Stereoisomers **VIII** and **IX**, which have the two *cis* 5,6-ring fusions, and stereoisomers **X** and **XI**, which have two *trans* 5,6-ring fusions, should be discarded as they bear a  $C_2$  axis of symmetry and, as seen in Figure 6, the cycloadduct is non-symmetrical. The two remaining stereoisomers, **XII** and **XIII**, both have a *cis* and a *trans* 5,6-ring fusion that could match the configuration of the product. A careful analysis of the 1D and 2D NMR spectroscopic data of cycloadduct **8** was undertaken to establish its structure. After a complete assignment of the  $^1\text{H-NMR}$  signals, the dipolar couplings observed in the NOESY spectrum of **8** were analyzed (Figure 8). Strong NOE cross-peaks were observed between H(4) and both H(3) and H(6) protons, confirming the *cis* ring fusion and the *cis* configuration of H(4) with the two protons on the ring junction (green arrows in Figure 8). An intense dipolar coupling was also observed between the proton H(9) and H(7) which, together with the absence of NOE contacts between H(10) and either H(9) or H(7), clearly indicate their *anti* configuration (pink arrows in Figure 8). On the other hand, the H(6) proton shows strong NOE with the H(3) and H(10), indicating their relative *cis* relationship (blue arrows in Figure 8). Therefore, the configuration of the cycloadduct **8** coincides with structure **XIII** of Figure 7.



**Figure 8.** Main NOESY correlations observed, supporting the structure of the enantiopure cycloadduct **8**.

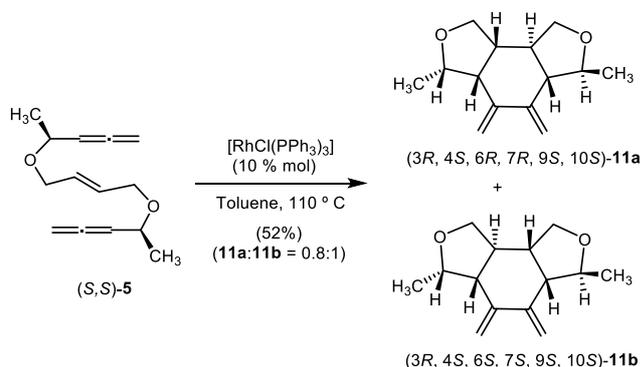
Bisallenes (*R,R*)-**3** and (*R,R*)-**4** (Figure 1) underwent [2+2+2] cycloaddition reactions, giving cycloadducts in a 40% and 63% yield, respectively, demonstrating that the length of the alkyl chain in the substrate has no influence on little relevance to the diastereoselectivity of the reaction (Scheme 5). The same structural characterization was performed for cycloadducts **9** and **10**. As expected, the configuration of **9** was determined as (3*R*, 4*R*, 9*R*, 10*S*) and the configuration of **10** as (3*S*, 4*R*, 6*S*, 7*S*, 9*R*, 10*R*), showing that the inversion of the configuration of the inducing stereocentre results in the inversion of the configuration of the stereocentres generated upon cycloaddition to give access to both

enantiomers of tricyclic scaffolds with total stereoselectivity.



**Scheme 5.** [RhCl(PPh<sub>3</sub>)<sub>3</sub>]-catalyzed [2+2+2] cycloaddition reactions of allene-ene-allene (R,R)-3 and (R,R)-4

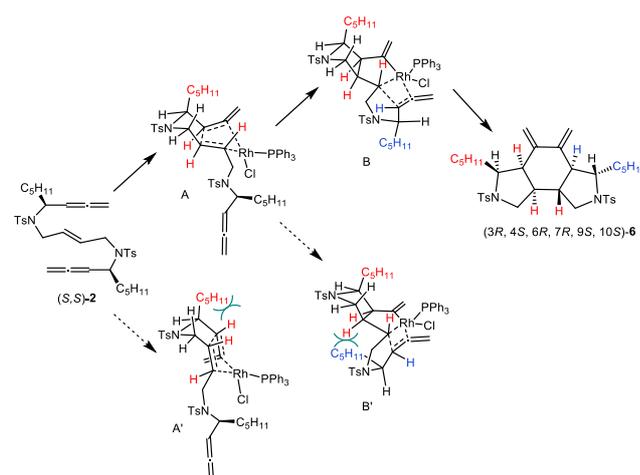
Finally, we turned our attention to wanted to test the influence of the tether on the process. We prepared compound (S,S)-5 with an oxygen-tether was introduced between the unsaturations instead of NTs linkers. Compound (S,S)-5 This compound has a double bond in the middle of the chain and two methyl groups with an (S) configuration. After treatment of 5 with [RhCl(PPh<sub>3</sub>)<sub>3</sub>] in toluene at reflux, an inseparable mixture of two cycloadducts, 11a and 11b, was obtained with a 52% global yield and with a 0.8:1 ratio<sup>[9]</sup> (Scheme 6). After a careful NMR analysis, we were able to determine that out of the six possible stereoisomers that can be formed (Figure 7), only the two featuring a *trans/cis* ring fusion were obtained (XII for 11b and XIII for 11a). Therefore the tether has a strong influence on the overall stereoselectivity of the process.



**Scheme 6.** [RhCl(PPh<sub>3</sub>)<sub>3</sub>]-catalyzed [2+2+2] cycloaddition reaction of oxygen-tethered allene-ene-allene (S,S)-5

Scheme 7 depicts (shows?) a possible mechanism for the diastereoselective formation of (3R, 4S, 6R, 7R, 9S, 10S)-6 by using the Wilkinson's complex as the

catalyst. In our previous study<sup>[8b]</sup> based on the stereoselective rhodium-catalyzed [2+2+2] cycloaddition of linear allene-ene-allene substrates, DFT calculations were carried out in order to rationalize the order in which the unsaturations take part in the catalytic cycle, the reactivity of the two double bonds of the allene towards the cycloaddition, and the diastereoselectivity of the reaction. Based on these previous studies, we interpret assume that the initial oxidative addition takes as taking place between the ene and the internal double bond of one of the allene groups giving a first *cis* ring fusion. Taking into account Of the two possible intermediates A and A' that could be generated, we can discard A' due to the steric repulsion between the alkyl group (C<sub>5</sub>H<sub>11</sub>) and one of the H of the ring fusion. Therefore, in the first carbon-carbon bond formation step, the alkyl group is located on the opposite side of the two *cis* hydrogens of the ring. Subsequent In the subsequent insertion of the second allene takes place also with the internal double bond, two possible intermediates can arise: intermediate B, in which the hydrogen atom on the allene points inside the rhodacyclopentane, and intermediate B', in which the same hydrogen points outside the rhodacyclopentane A. Steric interactions between the alkyl group and one of the hydrogens of the ring fusion again favour the course of the process through intermediate B, discarding intermediate B'. Finally, reductive elimination affords the diastereomerically pure cycloadduct 6. In the case of the oxygen tethered substrates, the reduced steric hindrance at the tether level might account for a higher fluxionality of the ring and reduces the difference in energy barriers of the intermediates A and A', giving thus a mixture of the two possible *cis/trans* products.



**Scheme 7.** Possible mechanism for the selective formation of (3R, 4S, 6R, 7R, 9S, 10S)-6

## Conclusions

In conclusion, the Wilkinson's complex catalyzed the [2+2+2] cycloaddition reaction of allene-yne/ene-allene substrates bearing chiral centres in the  $\alpha$ -position of the allene functionality. The enantiomerically pure bisallenes gave a completely diastereoselective reaction and the product was isolated as a single optically pure enantiomer. The built-in chirality present in the allene-yne/ene-allene starting substrates was preserved and used to generate two or four more chiral centres employing the [2+2+2] cycloaddition reaction. Steric effects allow us to propose a mechanistic hypothesis justifying the diastereoselectivity of the overall process.

## Experimental Section

### Cycloaddition reaction of (*S,S*)-1. General procedure

In a 10 mL 2-necked round bottom flask, a mixture of compound (*S,S*)-1 (0.020 g, 0.031 mmols) and tris(triphenylphosphine)rhodium(I)chloride (0.003 g, 0.003 mmols) was purged with nitrogen and dissolved in anhydrous toluene (3 mL). The mixture was stirred at reflux for 2h (TLC monitoring). The solvent was removed and the crude was purified by column chromatography using a mixture of hexane:ethyl acetate (90:10) as the eluent to give cycloadduct **5** (0.009 g, 45%) as a colourless solid.

## Acknowledgements

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