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Unusual reactivity of rhodium carbenes with allenes: an efficient asymmetric synthesis of methylenetetrahydropyran scaffolds†

Òscar Torres, , Miquel Solà, , Anna Roglans  and Anna Pla-Quintana *

A Rh^I/(S)-BINAP catalytic system is able to promote carbene alkyne metathesis and cascade this elemental step with an stereoselective reaction with allenes. An unusual carbene/allene reactivity is discovered that, through a formal addition of *p*-toluenesulfonic acid to a Rh-bound trimethylenemethane intermediate, affords 4-methylenetetrahydropyran compounds in good yields and excellent enantioselectivities.

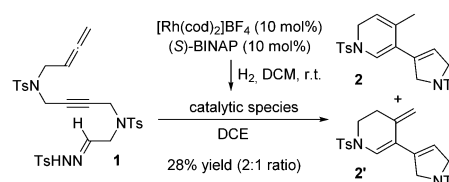
Metal carbenes are versatile reaction intermediates that can react with a wide variety of functional groups to synthesize complex organic molecules with high levels of chemo-, diastereo-, and enantioselectivity.¹ The reaction of metal carbenes with alkenes to afford cyclopropanes has been extensively and systematically studied.² In contrast, their reaction with allenes has received much less attention. In these latter reactions, alkylidenecyclopropanes are normally formed through a formal [2+1] cycloaddition.³ However, formal [3+2] cycloadditions, which afford cyclopentenes containing an exocyclic double bond, are observed when vinyl carbenes are reacted.⁴

We recently reported that Rh^I/BINAP is an efficient catalytic system for base-free generation of rhodium carbenes from *N*-tosylhydrazones and their subsequent carbene/alkyne metathesis.^{1*h*,5} This reaction provides rhodium vinylcarbenes that can react further in an enantioselective manner. When an alkyne is present in the molecule, a double carbene alkyne metathesis⁶ takes place, providing enantiomerically pure sulfones.^{5*a*} On the other hand, when there is an alkene in the molecule, an intramolecular cyclopropanation takes place, efficiently affording chiral vinylcyclopropanes.^{5*b*} Continuing with our interest in the cascade cyclization reactions involving rhodium vinylcarbenes, we report that *N*-tosylhydrazone/alkyne/allene substrates generate a rhodium vinylcarbene that

reacts with an allene. Unexpectedly the reaction does not follow any of the already reported reaction modes but rather generates a rhodium trimethylenemethane intermediate that formally adds arylsulfonic acid to allow for stereoselective construction of methylenetetrahydropyran scaffolds.

At the outset of this study, linear substrate **1** with NTs tethers (Scheme 1) was synthesized. Under the conditions previously optimized in our earlier studies,⁵ a 28% yield of an inseparable mixture of two trienic isomers **2** and **2'** in a 2 : 1 ratio was isolated (see Scheme S1 in the ESI† for the mechanistic proposal).

As attempts to improve the reaction conditions, either by decreasing the temperature or by adding a base, were unsuccessful, we decided to place an oxygen tether between the alkyne and the allene. The resulting compound, **3a** (R = *p*-C₆H₄CH₃), was then synthesized and its reactivity was evaluated under the previously described reaction conditions. After one hour of reaction, two products were isolated that, upon complete characterization including X-ray diffraction,⁷ were identified as the 4-methylenetetrahydropyran derivative (*R,R*)-**4a** and the cyclopentenone derivative **5** (Scheme 2). Although **4a** was obtained with excellent enantioselectivity, the reaction showed a low selectivity since the two products were isolated in equal quantities. Due to the relevance of chiral functionalized tetrahydropyran rings in natural products and their use as fragrances and pharmaceuticals,⁸ we sought to develop an efficient synthesis of the methylenetetrahydropyran core taking advantage of the unusual rhodium carbene/allene reactivity that we had discovered.

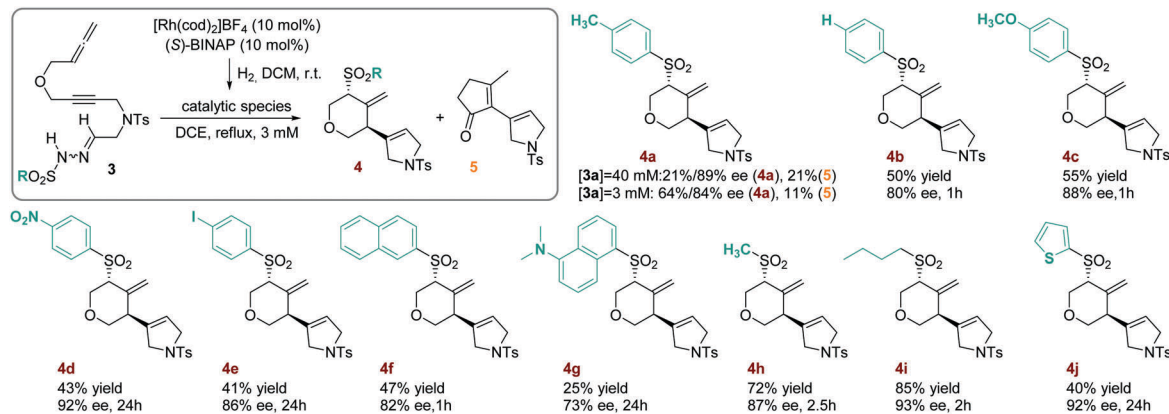


Scheme 1 Cyclization of NTs-tethered substrate **1**.

Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química, Facultat de Ciències, C/Maria Aurèlia Capmany, 69, E-17003-Girona, Catalunya, Spain. E-mail: anna.plaq@udg.edu

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Scheme 2 Rhodium-catalyzed asymmetric cyclization of **3**. Reaction conditions: 0.21 mmol of substrate **3** in 70 mL of dichloroethane (DCE). Cited yields are of isolated products. The stereochemistry of products **4** is assigned with analogy to **4a**. Traces of cyclopentenone derivative **5** were obtained in the formation of **4f** and **4g**.

We therefore proceeded to optimize the reaction conditions, finally finding that the most critical parameter for selectivity was the concentration (see Table S2 in the ESI† for the optimization). When the reaction was carried out for one hour in lower concentrations (3 mM *versus* 40 mM in our first test), the 4-methylenetetrahydropyran derivative **4a** was obtained in 64% yield whilst excellent enantioselectivity and a decrease in cyclopentenone derivative **5** formation were obtained (Scheme 2). We postulate that the cyclopentenone derivative **5** is formed from a product analogous to **2** (Scheme 1) from which an allyl Claisen rearrangement, followed by a Rh^{I} -catalyzed alkene hydroacylation, gives the cyclopentenone derivative **5** (see Scheme S1 in the ESI† for the detailed mechanistic proposal).

The scope of the process was then evaluated (Scheme 2). First, a series of substrates with several substituents in the phenyl ring of the sulfonyl hydrazone were reacted to give the corresponding 4-methylenetetrahydropyran derivatives (**4b–4e**). In all cases the reaction occurred with high enantioselectivity and the sulfonyl group migration was regioselective.⁹ However, when an electron-withdrawing substituent such as nitro (**4d**) or iodine (**4e**) was present, the yield dropped and there was a considerable increase in the reaction time. It is noteworthy that a *p*- $\text{C}_6\text{H}_4\text{I}$ -sulfonyl group is efficiently involved in the reaction (**4e**), opening the possibility of further transformations of the cyclized compound.

More sterically hindered products, containing either a 2-naphthylsulfonyl (**4f**) or dansyl (**4g**) group, were also efficiently obtained although the yields were lower, especially in the case of dansyl. In these two examples, traces of derivative **5** were detected, indicating that the less favorable attack of a more sterically hindered sulfinate favors the formation of cyclopentenone derivative **5**. Two aliphatic sulfonylhydrazones were also reacted under the optimized conditions. Cyclized products **4h** and **4i** were enantioselectively obtained in high yields. Finally, a 2-thiophenylsulfonylhydrazone-yne-allene substrate **3j** was reacted affording the heteroaromatic derivative **4j** after 24 hours of reaction.

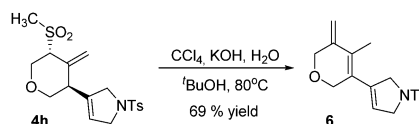
The Ramberg–Bäcklund rearrangement, a base-mediated conversion of α -halosulfones, is an excellent option to synthesize

regiodefined alkenes. Having synthesized aliphatic sulfones we decided to test their conversion to alkenes. Methylsulfone **4h** was reacted under the Ramberg–Bäcklund rearrangement conditions, by forming *in situ* the α -halosulfones, to generate conjugated triene **6** in 69% yield (Scheme 3).

To get further insight into the reaction mechanism of the transformation of **3a** to **4a**, we performed B3LYP/aug-cc-pVDZ-PP//B3LYP/cc-pVDZ-PP calculations using reasonable models of the Rh^{I} /BINAP catalyst and reactant **3a** to reduce the computational cost (see Scheme 4 and Computational methods in the ESI† for more detailed information). The reported energies are Gibbs energies that incorporate the effect of dichloroethane solution.

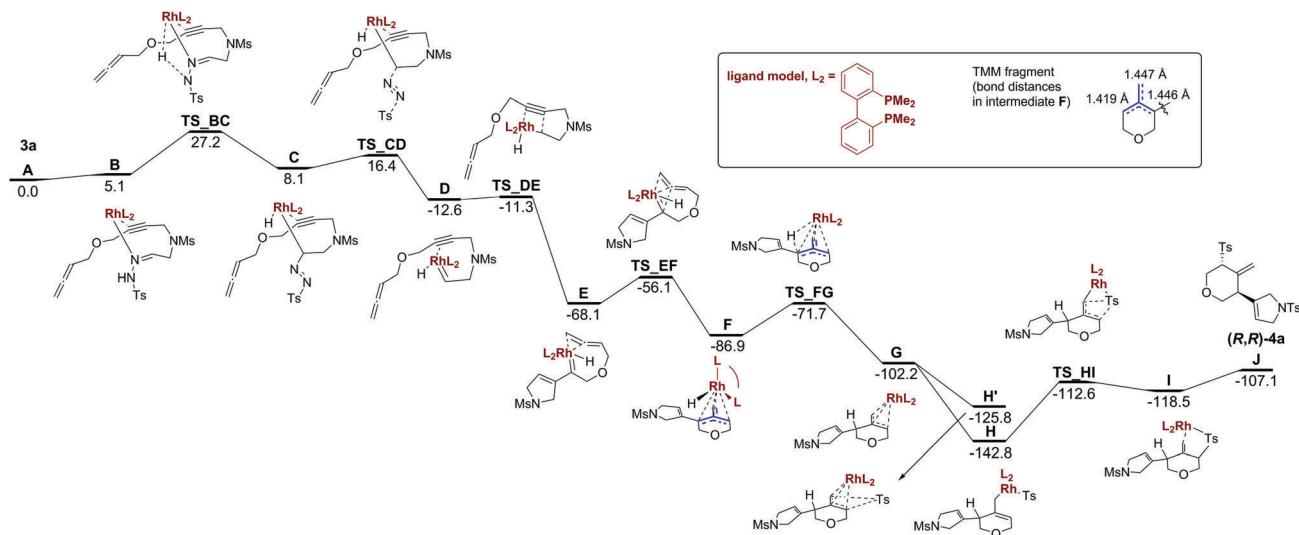
Scheme 4 shows the Gibbs energy profile for the transformation of the reactant **3a** into the final product (*R,R*)-**4a**. In the first step, the Rh^{I} /BINAP catalyst coordinates to **3a** through the N electron pair and η^2 with the π -system of the alkyne group to form intermediate **B** in an endergonic process ($5.1 \text{ kcal mol}^{-1}$). **B** evolves to **C** by means of a H transfer combined with the breaking of the Rh–N initial coordination and the formation of a N=N double bond and a Rh–C bond. The Gibbs energy barrier for the conversion of **3a** to **C** is $27.2 \text{ kcal mol}^{-1}$ (see Fig. S70 in the ESI† for the molecular structure of **TS_{BC}**). **C** yields **D** through **TS_{CD}** with a barrier of $8.3 \text{ kcal mol}^{-1}$ in a complex process that involves the release of N_2 , the generation of the Ts^- group, and the formation of a Rh=C bond. Then, an almost barrierless carbene/alkyne metathesis of **D** leads to intermediate **E**.

The relative Gibbs energy of **E** with respect to our model of **3a** and Rh^{I} /BINAP is $-68.1 \text{ kcal mol}^{-1}$ in dichloroethane. **E** is a rhodium(i) species in a square pyramidal coordination geometry



Scheme 3 Ramberg–Bäcklund rearrangement of **4h**.





Scheme 4 Gibbs energy profile (kcal mol^{-1}) for the Rh^{I} catalyzed transformation of **3a** into (R,R) -**4a**. Intermediates and TS from **B** to **TS_CD** and from **H** and **H'** to **I** have +1 charge. Intermediates and TS from **D** to **G** have +2 charge.

in which the π -system of the external double bond of the allene group interacts with the d orbitals of the metal in a basal position and the hydride occupies the apical position. Ring closure through a [2+2] cycloaddition of the double bond of the external allene and the rhodium-carbene double bond develops a strained rhodacyclobutane that is not stable and rearranges to form intermediate **F** in an exergonic process ($18.8 \text{ kcal mol}^{-1}$) that takes place through a barrier of $8.0 \text{ kcal mol}^{-1}$ (see Fig. S73 in the ESI† for the molecular structure of **TS_EF**). Intermediate **F** had an electronic structure resembling that of trimethylenemethane (fragment in blue in Scheme 4). The biradical π -system of the 4-methylenetrihydropyran ring is stabilized by a facial η^3 -coordination to the metal so that the intermediate **F** formed has a closed-shell electronic ground state. The binding is essentially symmetric with respect to the three C-C bonds (see the C-C bond distances in the inset of Scheme 4) with the rhodium located in a central position.¹⁰ Moreover, the similar Rh-C bond distances of 2.17, 2.21, and 2.29 Å confirm this almost symmetric arrangement.

Trimethylenemethane (TMM) diyl intermediates have been invoked in the tandem cycloaddition reaction of allenyl diazo compounds forming triquinane structures.¹¹ In this metal-free process, the TMM diyl, constrained as a part of a ring, intramolecularly reacts with a tethered alkene in a formal [3+2] cycloaddition. The TMM reactivity can also be exploited in synthetic applications when complexed to a metal centre.¹² Rhodium-bound TMM has also been invoked by Sarpong *et al.* in the synthesis of 3,4-fused pyrroles by the reaction of an imino rhodium carbene – generated by the decomposition of *N*-sulfonyl-1,2,3-triazoles – and a tethered allene.^{4a} The rhodium-bound TMM again reacts in a formal [3+2] cycloaddition. An intermolecular variation has also been reported by Murakami *et al.* using nickel as the catalyst.^{4b} In the reaction under study, the rhodium-bound trimethylenemethane **F** evolves through a reverse β -H-elimination *via* **TS_FG** that transfers the H atom from

Rh to the C atom attached to the 2,5-dihydropyrrole substituent to yield **G**. This process is exergonic by $15.3 \text{ kcal mol}^{-1}$ and has to surpass a barrier of $15.2 \text{ kcal mol}^{-1}$. In the next step, the Ts^- group coordinates to Rh to yield intermediate **H**, which has a square pyramidal geometry with the diphosphine ligand and the Ts^- group, coordinating in a bidentate fashion, occupying the basal positions. This process is exergonic by $40.6 \text{ kcal mol}^{-1}$. An alternative pathway through **H'** (Scheme 4) in which the Ts^- group directly attacks the other side of the 4-methylenetrihydropyran ring of intermediate **G** without prior coordination to Rh is also possible, although this alternative is energetically less favourable. From **H**, an intramolecular nucleophilic attack of the Ts^- group to C5 of the dihydropyran ring takes place to yield **I**, in which the final *trans*-disubstituted product (R,R) -**4a** coordinated to the metal has already been formed. This attack is endergonic by $24.3 \text{ kcal mol}^{-1}$ and has to surmount a barrier of $30.2 \text{ kcal mol}^{-1}$ (see Fig. S79 in the ESI† for the molecular structure of **TS_HI**). This, therefore, is the rate-determining step (rds) of the reaction mechanism. It would be expected that this step would have higher barriers for systems with electron-withdrawing substituents such as **4d** or **4e** or sterically hindered sulfonates such as **4f** or **4g**. The final release of **4a** costs an additional energy of $11.4 \text{ kcal mol}^{-1}$. However, it is likely that the release of **4a** would be assisted by the addition of **3a** to reduce or even remove this energetic cost. The transformation of reactants **3a** to the product (S,S) -**4a** (the enantiomer of the experimentally obtained product (R,R) -**4a**) *via* an alternative diastereomeric route is also possible (see Section S.14 and Scheme S2 in the ESI†). However, the route that leads to (S,S) -**4a** has an rds with a barrier that is $2.7 \text{ kcal mol}^{-1}$ higher in energy than that of the pathway shown in Scheme 4. This energy difference in the barrier of the rds justifies the experimental formation of only (R,R) -**4a**.¹³

Further evidence supporting the postulated mechanism was gained by carrying out a deuterium-labelling experiment. The treatment of substrate **3e** with deuterated water afforded the



deuterium-labelled compound **3e-D**. Upon cyclization, NMR characterization confirmed that the deuterium was selectively incorporated into the 5-position of the tetrahydropyran ring (see ESI†).

In conclusion, we have developed an enantioselective synthesis of 4-methylenetetrahydropyran derivatives that rely on the reaction of rhodium vinyl carbenes and allenes as a key step. This cyclization reaction represents an efficient synthesis of *trans*-disubstituted methylenetetrahydropyrans that has revealed a highly unusual reactivity pattern in carbene/allene chemistry. DFT calculations show that a rhodium-bound trimethylene-methane intermediate is involved which has formally added arylsulfonic acid in an enantioselective manner. It is important to highlight that asymmetric variants of the transition-metal catalyzed [3+2] cycloaddition involving TMM remained elusive for a long period of time¹⁴ and that enantioselective additions of pronucleophiles are even rarer. The rate-determining step is the nucleophilic intramolecular attack of the Ts⁻ group to the tetrahydropyran ring.

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Conflicts of interest

There are no conflicts to declare.

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