Examining the factors that govern the regioselectivity in rhodium-catalysed alkyne cyclotrimerisation

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ABSTRACT: The electronic and steric factors that favour the formation of 1,2,4- and 1,3,5-regioisomers in the intermolecular [2+2+2] cyclotrimerisation of terminal alkynes are not well understood. In this work, this problem was analysed from a theoretical and experimental point of view. Density functional theory (DFT) calculations of the [2+2+2] cyclotrimerisation of p-X-substituted phenylacetylenes (X = H, NO₂, and NH₂) catalysed by [Rh(BIPHEP)]⁺ were carried out to determine the reaction mechanism in each case and analyse the effect that the electronic character of the substituents has on the regioselectivity. For the rate-determining step corresponding to the oxidative coupling leading to the rhodacyclopentadiene intermediate, we have taken into account two reaction pathways: the reaction pathway with the lowest energy barrier and the reaction pathway through the most stable transition state (Curtin-Hammett pathway). Our results show that the theoretical results conform experimental outcomes for different p-X-substituted phenylacetylenes (X = NO₂, F, H, Me, ‘Bu, OMe, NMe₂) only when the Curtin-Hammett reaction pathway is considered. A fairly good correlation has been obtained between the electronic nature of the substituents (as expressed by the Hammett σ para constant values) and the regioisomeric ratios experimentally obtained and computationally predicted.

INTRODUCTION

Polysubstituted benzenes are extremely useful compounds that are widely used both in industry and in academia. Since Reppe et al. discovered in 1948 that nickel catalysed the [2+2+2] cyclotrimerisation of three alkynes, this process has evolved into an elegant preparative route to polysubstituted benzenes.⁵

A simplified picture of the most generally accepted mechanism of the [2+2+2] cyclotrimerisation, supported by experimental evidences³ and computational studies,⁴ is shown in Scheme 1. The reaction begins via a pair of ligand-alkyne substitution reactions. The oxidative coupling of the two alkylene ligands then generates a metallacyclopentadiene IIIa or a metallacyclopentatriene IIIb with a biscarbene structure. Subsequent coordination of a third alkylene ligand to IIIa or IIIb intermediates is followed by either alkylene insertion to form a metallacycloheptatriene V (the so-called Schore’s mechanism)⁹ or metal-mediated [4+2] cycloaddition to yield the metallanorbornadiene VI or [2+2] cycloaddition to give a metallabicyclo[3.2.0]heptatriene VII. Finally, the arenne VIII is formed by reductive elimination of the metal.

A successful control of the regioselectivity in the intramolecular version of the [2+2+2] cycloaddition reactions is generally accomplished by altering the positions of the alkynes in the linear substrate and/or by modulating the strain in the intermediates or products. On the other hand, successful regiocontrol in a fully intermolecular reaction is much more challenging.⁶ In the intermolecular [2+2+2] cyclotrimerisation of three identical monosubstituted alkynes, there is no chemoselectivity but regioselectivity remains a problem. Scheme 2 shows the two possible regioisomers, 1,2,4-trisubstituted benzene and 1,3,5-trisubstituted benzene, that can be formed in the cycloaddition process.

The formation of the two regioisomers of Scheme 2 can be understood following the postulated general mechanism for this reaction. In the case of the rhodium(I)-catalysed cyclotrimerisation reactions, in the formation of the rhodacyclopentadiene III, the two alkynes can be coupled oxidatively to the rhodium(I) in three or four (depending on the symmetry of the catalyst) different ways, namely, head-to-head, tail-to-tail, tail-to-head, and head-to-tail giving the 1,4, 2,3, and 1,3/2,4 regioisomeric metallacyclopentadiens (Scheme 2). In this notation, we consider the phenyl group as the tail of the phenylacetylene molecule. In the subsequent insertion of the third alkylene and posterior reductive elimination, intermediates 1,4 and 2,3 only afford regioisomer 1,2,4-, and only intermediates 1,3/2,4...
can give regioisomers 1,2,4- or 1,3,5-. As can be seen in Scheme 2, it is more likely to form regioisomer 1,2,4- than regioisomer 1,3,5-, if we suppose similar energy barriers for the formation of all intermediates. It can be concluded that there are two crucial steps in obtaining high selectivity in the formation of one of the regioisomers: i) the selective formation of metallacyclopentadiene intermediate and ii) in the case of intermediate 1,3/2,4 the regioselective insertion of the third alkyne. This second aspect is crucial for the formation of the 1,3,5-regioisomer.

**Scheme 1.** Generally accepted mechanism for the [2+2+2] cyclotrimerisation reaction of three alkynes. [M] = transition metal.

**Scheme 2.** Possible regioisomers in the [2+2+2] cyclotrimerisation of three identical terminal alkynes and their mechanism of formation.

Substantial research efforts have been devoted to the development of reaction conditions and catalytic systems that allow the regioselective synthesis of polysubstituted benzenes. The regioselectivity ratios obtained have been rationalised mainly based on steric grounds but also on the basis of electronic effects in some examples, but there is not a clear consensus on how the steric and electronic effects govern the process, so there is a lack for predictive criteria.

To gain insight into the factors that govern the regioselectivity in the [2+2+2] cycloaddition reactions we decided to study the cyclotrimerisation of differently p-X-substituted phenylacetylenes both experimentally and by means of density functional theory (DFT) calculations. We selected the cases X = H, NO₂, and NR₂ (R = H in the computational study and R = CH₃ in experiments) with the aim to discuss electronic effects in this cyclotrimerisation. Rhodium has been chosen as transition-metal in the catalytic system since is one of the most often used catalyst. In particular, we considered the cationic [Rh(BIPHEP)]⁺ catalyst, (BIPHEP=2,2-bis(diphenylphosphino)-1,1-biphenyl), as it has been widely used for these [2+2+2] cycloaddition reactions.

**RESULTS AND DISCUSSION**

Let us start the discussion by analyzing the [2+2+2] cyclotrimerisation of unsubstituted phenylacetylene to yield 1,2,4- and 1,3,5-triphenylbenzene. The phenyl group has a weak π-donor and inductive withdrawing character that makes phenylacetylene a mild electron deficient alkyne. The Gibbs energy profile obtained for the [2+2+2] cyclotrimerisation of phenylacetylene catalysed by [Rh(BIPHEP)]⁺ is shown in Scheme 3. There is a preactivation scenario that transforms A₀ to A₂ in an exergonic process by ca. 40 to 50 kcal/mol. On the other hand, the catalytic cycle that involves A₂ to A₆ species is very exergonic by about 130 to 145 kcal/mol. This huge thermodynamic driving force is generated by the formation of three new C-C σ bonds and the gain of aromatic stabilisation energy. Somewhat unexpectedly, 1,3,5-triphenylbenzene is 1.6 kcal/mol less stable than 1,2,4-triphenylbenzene. π-π stacking interactions between adjacent phenyl groups in 1,2,4-triphenylbenzene makes this compound more stable than its 1,3,5-regioisomer. Formation of 1,3,5-triphenylbenzene is, therefore, statistically (only 25% of the possible reaction paths leads to its formation, Scheme 2) and thermodynamically disfavoured.

To discuss the kinetic preferences of the two isomers, we have to analyse the entire reaction mechanism. In the first step, the interaction of one phenylacetylene with the [Rh(BIPHEP)]⁺ catalyst yields 14-electron intermediate A₁ and stabilizes the system by 31.3 kcal/mol. In the second step, a second phenylacetylene molecule coordinates to the metal center to form A₂. This interaction can occur in four different ways, namely, tail-to-tail (A₂, 2,3), head-to-head (A₂, 1,4), tail-to-head (A₂, 1,3), and head-to-tail (A₂, 2,4, see Scheme 3). Depending on the orientation of the two phenylacetylenes, the stabilisation energy of A₂ with respect to A₁ and a free phenylacetylene ranges from 10.0 to 19.0 kcal/mol, the most stable A₂ intermediates being the head-to-head A₂, 1,4 and the head-to-tail A₂, 2,4 isomers. Unsurprisingly, for steric reasons, the tail-to-tail A₂, 2,3 disposition of the two ligands leads to the less stable A₂ intermediate. On the other hand, the tail-to-head
the [2+2+2] cyclotrimerisation catalysed by [Rh(BIPHEP)]+ of phenylacetylene with that of acetylene. The latter can be found in the Supporting Information. The energy barrier of the oxidative coupling of two acetylenes is 3.1 kcal/mol lower than that found for the 1,3-oxidative coupling of two phenylacetylenes. This result is somewhat unexpected, since it has been reported that electron-withdrawing groups facilitate the oxidative coupling by lowering the LUMO of the π-bond. It is likely that steric effects are responsible for the increase in the energy barrier when going from acetylene to phenylacetylene.

Coming back to the [2+2+2] cyclotrimerisation of phenylacetylene catalysed by [Rh(BIPHEP)]+, let us discuss first the evolution of the intermediate coming from the lowest barrier in the oxidative coupling. Once the 1,3-di-phenylrhodacyclopentadiene intermediate \(A_3\) is formed, another phenylacetylene molecule coordinates to Rh to yield the 16-electron intermediate \(A_4\) and releasing about 18 kcal/mol. The molecular structure of the resulting complex is similar to the only reported example of a metallacyclopentadiene(alkyne) species. Interestingly, in this case, the addition of the new coordinated phenylacetylene molecule to the 1,3-diphenylrhodacyclopentadiene occurs through an insertion on to the Rh-C bond (Schore’s mechanism). We tried to locate the rhodanorbornadiene and rhodabicyclo[3.2.0]heptatriene intermediates but all our attempts failed, and, consequently, presence of these intermediates in the reaction mechanism was ruled out. The insertion through the Schore’s mechanism does not generate the expected rhodacyclopentatriene or the four- and five-membered bicyclic intermediate. Instead of that, the reaction evolves directly to the formation of \(A_5\), i.e., the product \(7^\alpha\)-coordinated to the Rh[BIPHEP]+ with Rh-C distances ranging from 2.26 to 2.47 Å. For the insertion process, we have analysed all four possible insertions of the phenylacetylene molecule to the rhodacyclopentadiene complex (Scheme 4, first row). The two attacks in which the phenylacetylene is inserted into the Rh-C bond of the rhodacyclopentadiene complex with the C, being attached to a hydrogen (types I and II) were found to lead to \(A_5\) intermediate with low Gibbs energy barriers. The insertions onto the Rh-C bond in which the C is attached to the phenyl (types III and IV) were found to have barriers higher by at least 9.3 kcal/mol. Type I insertions are usually preferred for electrostatic reasons. The unsubstituted C atoms in phenylacetylene and rhodacyclopentadiene are more negatively charged than the C atoms with Ph substituents having electron withdrawing character. Based on electrostatic grounds, the more negatively charged unsubstituted C atom in phenylacetylene interacts better with the metal and the less negatively charged C atom in phenylacetylene prefers the unsubstituted C of the rhodacyclopentadiene.
Scheme 3. Gibbs energy profile (in kcal/mol) for the [2+2+2] cycloaddition reaction of three phenylacetylenes catalysed by [Rh(BIPHEP)]+*. Four possible oxidative coupling pathways have been explored but from A3 only two paths have been followed, the lowest energy barrier path (in green) leading to the 1,3,5 isomer and the Curtin-Hammett favoured path (in grey) leading to the 1,2,4 isomer.

Table 1. Gibbs energy barriers (in kcal/mol) for the oxidative coupling step in the [2+2+2] cyclotrimerisation reaction of p-X-substituted phenylacetylenes catalysed by Rh[BIPHEP]+ (TS(A2, A3)).

<table>
<thead>
<tr>
<th>Coupling</th>
<th>X =</th>
<th>X =</th>
<th>X =</th>
<th>Regioisomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,4</td>
<td>23.4</td>
<td>16.6</td>
<td>18.8</td>
<td>1,2,4-</td>
</tr>
<tr>
<td>2,4</td>
<td>19.5</td>
<td>17.4</td>
<td>16.8</td>
<td>1,2,4-</td>
</tr>
<tr>
<td>2,3</td>
<td>19.2</td>
<td>21.5</td>
<td>18.5</td>
<td>1,2,4-</td>
</tr>
<tr>
<td>1,3</td>
<td>17.4</td>
<td>21.9</td>
<td>13.9</td>
<td>1,2,4-</td>
</tr>
</tbody>
</table>

As for the oxidative coupling process, in the insertion step, we also considered the possibility that the different metallacyclopentadiene(alkyne) complexes A4 were in equilibrium. However, the barriers for the insertion are lower than those for the conversion of A4 into A3, so the Curtin-Hammett conditions are not fulfilled in this insertion process.

Now, let us move to the evolution of the intermediate A3_2,4, that comes from the Curtin-Hammett path in the oxidative coupling reaction (in grey in Scheme 3). We have again analysed all four possible insertions of the phenylacetylene molecule to the rhodacyclopentadiene complex (Scheme 4, second row). In this case, the insertion with the lowest barrier (6.7 kcal/mol) takes place onto the Rh-Cα bond in which the Cα is attached to the phenyl (type III) and leads to the 1,2,4-regioisomer. The preference for this insertion as compared to type I seems to arise from a better π-π interaction in the transition state of the type III insertion. A type IV insertion from A3_2,4 yields the 1,3,5-regioisomer with a barrier of 10.4 kcal/mol. Using the transition state theory, one predicts a 99:1 (1,2,4:1,3,5-) regioisomeric ratio.

As a whole, whereas the path with the lowest energy barrier for the oxidative coupling generates preferentially the 1,3,5-triphenylbenzene (with a predicted 1:99 1,2,4-1,3,5-regioisomeric ratio using the transition state theory), the pathway that is followed under Curtin-Hammett conditions leads preferentially to the 1,2,4-triphenylbenzene (99:1 ratio). If the two pathways were operative and equally favoured, we would predict the formation of a ca. 50:50
Scheme 4. Gibbs energy barriers (in kcal/mol) for the insertion of phenylacetylene in the 1,3- or 2,4-diphenylrhodacyclopentadiene (TS(A4,A5)). A green tick indicates the preferred pathway (insertion with the lowest barrier). [a] Despite many attempts to fully optimize the TS for this approach, this TS was optimised only for the forces but not for the displacements due to very flat potential energy surface. Therefore, the reported Gibbs energy barrier represents an estimation that we think should be close to the exact value.

<table>
<thead>
<tr>
<th>Insertion products from A3_1,3</th>
<th>Lowest energy barrier path</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>type I insertion (TS(A4A5_1,3_I)</td>
</tr>
<tr>
<td></td>
<td>type II insertion (TS(A4A5_1,3_II))</td>
</tr>
<tr>
<td></td>
<td>type III insertion (TS(A4A5_1,3_III))</td>
</tr>
<tr>
<td></td>
<td>type IV insertion (TS(A4A5_1,3_IV))</td>
</tr>
<tr>
<td>Gibbs energy barrier (kcal/mol)</td>
<td>6.5</td>
</tr>
<tr>
<td>Regioisomer obtained</td>
<td>1,3,5-</td>
</tr>
</tbody>
</table>

Scheme 5. Gibbs energy barriers (in kcal/mol) for the insertion of p-NO₂-phenylacetylene in the 1,4-dinitrophenylrhodacyclopentadiene (TS(A4,A5)). A green tick indicates the preferred pathway (insertion with the lowest barrier). [a] Despite many attempts to fully optimize the TS for this approach, this TS was optimised only for the forces but not for the displacements due to very flat potential energy surface. Therefore, the reported Gibbs energy barrier represents an estimation that we think should be close to the exact value.

<table>
<thead>
<tr>
<th>Insertion products from A3_2,4</th>
<th>Curtin-Hammett favored path</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>type I insertion (TS(A4A5_2,4_I))</td>
</tr>
<tr>
<td></td>
<td>type II insertion (TS(A4A5_2,4_II))</td>
</tr>
<tr>
<td></td>
<td>type III insertion (TS(A4A5_2,4_III))</td>
</tr>
<tr>
<td></td>
<td>type IV insertion (TS(A4A5_2,4_IV))</td>
</tr>
<tr>
<td>Gibbs energy barrier (kcal/mol)</td>
<td>13.1</td>
</tr>
<tr>
<td>Regioisomer obtained</td>
<td>1,3,5-</td>
</tr>
</tbody>
</table>

mixtures of 1,2,4- and 1,3,5-triphenylbenzene as a result of competing paths of similar energy barriers. However, experimental (theoretical) results found a 96:4 (99:1) ratio of the two regioisomers (vide infra), the 1,2,4-triphenylbenzene being clearly favoured. This result indicates that the Curtin-Hammett pathway is the preferred one in the Rh-catalysed alkyne cyclotrimerisation.

Final release of the product from A5 is assisted by the addition of two phenylacetylene molecules directly regenerating intermediate A2.

Next, we increased the electron-withdrawing character of the phenyl group by adding a nitro substituent in the para position of phenyl group, i.e., we studied the cyclotrimerisation of p-nitrophenylacetylene catalysed by [Rh(BIPHEP)]⁺. The Gibbs energy profile for this [2+2+2] cyclotrimerisation is given in the Supporting Information (Scheme S1). Electron-withdrawing effects of p-nitrophenyl group are now enhanced and, as a result, the barrier for the 2,3-attack increases and that of the 1,4-oxidative coupling decreases (Table 1). Therefore, this 1,4-transition state is now the most stable and also it is the oxidative coupling with the lowest energy barrier. Consequently, calculations predict the formation of only the 1,2,4-regioisomer. For the 1,4-di-p-nitrophosphorhabodyclopentadiene, the type V insertion (Scheme 5) has the lowest energy barrier (4.0 kcal/mol) and the lowest in energy transition state. We name type V to VIII insertions because, at variance with insertions in 1,3- and 2,4-diphenylrhodacyclopentadienes, in 1,4-diphenyldihydridclopentadienes, the two possible Rh-C₆ insertions have C₆ atoms with Ph substituents. The insertion reaction is more favourable for the p-nitrophosphorhabodyclopentadiene molecules than for the phenylacetylenes. The insertion leads to intermediate A5 (the product η⁶ coordinated to [Rh(BIPHEP)]⁺) that subsequently releases...
Scheme 6. Gibbs energy barriers (in kcal/mol) for the insertion of \(p\)-aminophenylacetylene in the 1,3-, 2,4- or 1,4-diaminophenylrhodacyclopentadiene (TS\(A_4,A_5\)). A green tick indicates the preferred pathway (insertion with the lowest barrier).

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The 1,2,4-tri-\(p\)-nitrophenylbenzene in the final reductive elimination process. As a whole, the route followed in the \([2+2+2]\) cyclotrimerisation of \(p\)-nitrophenylacetylene is the one corresponding to the 1,4-oxidative coupling always leading exclusively to the 1,2,4-tri-\(p\)-nitrophenylbenzene.

Finally, we reduced the electron-withdrawing character of the phenyl group by adding an amino substituent in the para position of phenyl group, i.e., we studied the cycloaddition of \(p\)-aminophenylacetylene catalysed by [Rh(BIPHEP)]\(\text{+}\). The Gibbs energy profile for this \([2+2+2]\) cyclotrimerisation is given in the Supporting Information (Scheme S2). Electron-donating effects of the amino group result in a decrease of the barrier for the 2,3-attack and in an increase of the 1,4-oxidative coupling when compared to those of the \(p\)-nitrophenylacetylene (Table 1). For steric reasons, the tail-to-head (\(A_2,1,3\)) disposition of the two ligands leads to the less stable \(A_2\) intermediate. This intermediate is connected to the TS\(A_2,A_3\) of the 1,3-oxidative coupling that has the lowest Gibbs energy barrier (13.9 kcal/mol). The Gibbs energy barriers of the rest of possible oxidative couplings are, at least, 2.9 kcal/mol higher in energy. We also considered the pathways that start with the head-to-head (\(A_2,1,4\)) and head-to-tail (\(A_2,2,4\)) dispositions of the two \(p\)-aminophenylacetylenes that correspond to the transition states lowest in energy (Curtin-Hammett pathways). These two transition states differ by only 0.1 kcal/mol, and for this reason we analysed two Curtin-Hammett paths for this cyclotrimerisation. This 0.1 kcal/mol energy difference corresponds to a product ratio of 54:46 in favour of the 1,2,4-regioisomer (considering that \(A_2,1,4\) leads to 1,2,4-regioisomer and that \(A_2,2,4\) evolves to 1,3,5-regioisomer, vide infra). Once the 1,3-, 1,4-, or 2,4-di-\(p\)-aminophenylrhodacyclopentadiene intermediate \(A_3\) is formed, another \(p\)-aminophenylacetylene molecule coordinates to Rh to yield the 16-electron intermediate \(A_4\) and releasing about 20 kcal/mol depending on the orientation of the incoming molecule. As for the path through the lowest energy barrier for the phenylacetylene, type I insertions onto 1,3- and 2,4-di-\(p\)-aminophenylrhodacyclopentadiene intermediates, in which the \(p\)-aminophenylacetylene is inserted into the Rh-C\(o\) bond of the rhodacyclopentadiene complex with the unsubstituted C\(o\) were found to lead to \(A_5\) intermediate with low Gibbs energy barriers (Scheme 6). For 1,4-di-\(p\)-aminophenylrhodacyclopentadiene, type V
insertion is preferred, as in the case of \( p \)-nitrophénylacetylene. The Gibbs energy barrier for the transformation of \( \text{A}_4 \) into \( \text{A}_5 \) are 4.4 kcal/mol for the type I insertion in \( \text{A}_4 \text{-1,3} \) leading to the 1,3,5-isomer, 4.9 for the type V insertion in \( \text{A}_4 \text{-1,4} \) producing the 1,2,4-isomer, whereas the type I insertion in \( \text{A}_4 \text{-2,4} \) is barrierless and yields the 1,3,5-regioisomer (see Schemes 6 and S2). In all cases, these paths represent the insertion with both the lowest transition state and the lowest energy barrier. Although, formation of the 1,3,5-isomer is slightly favoured thermodynamically (by 1.5 kcal/mol), from a kinetic point of view and given the existence of multiple paths with relatively low Gibbs energy barriers, it is likely that, experimentally, a mixture of 1,3,5- and 1,2,4-tri-\( p \)-aminophénylacetylene benzene will be formed. In particular, the Curtin-Hammett pathway, which is found to be the preferred one in the Rh-catalysed alkyne cyclotrimerisation of phenylacetylene, produces a mixture of the 1,2,4-isomer coming from the \( \text{A}_4 \text{-1,4} \) intermediate via type V insertion and the 1,3,5-regioisomer generated from type I insertion in \( \text{A}_4 \text{-2,4} \).

To check experimentally the conclusions from the theoretical results, we conducted the rhodium-catalysed \([2+2+2]\) cyclotrimerisation of a series of commercially available \( p \)-substituted phenylacetylenes 1 (Table 2) with different electronic demand (\( X = H, X = \text{NO}_2 \) and \( X = \text{NH}_2 \) that has been replaced by \( X = \text{NMe}_3 \)) including the substrates studied theoretically.\(^{20}\) A combination of cationic rhodium complex [Rh(COD)\(_2\)]BF\(_4\) and BIPHEP as the biphosphine was selected as the catalytic system. Using a 5 mol\% of the catalytic system [Rh(COD)\(_2\)]BF\(_4\)/BIPHEP in dichloroethane as the solvent, the reaction was carried out under reflux. The results obtained are shown in Table 2 together with the Hammett substituent \( \sigma_{\text{para}} \) constants of the different substrates.\(^{21}\) Every reaction was run twice in the same reaction conditions to check the reproducibility of the method, especially in the case of the ratio between regioisomers. The low yields of the \( \text{NO}_2 \), \( F \) and \( \text{NMe}_3 \) cases is due to the polymerization of the \( para \)-substituted phenylacetylenes and formation of decomposition products.

The correlation between the ratio of 1,2,4(2):1,3,5(3) regioisomers formed and the Hammett substituent \( \sigma_{\text{para}} \) constants is fairly good. The highly electronwithdrawing nitro group yielded the 1,2,4-regioisomer 2 exclusively and no traces of the 1,3,5-regioisomer 3 were detected (entry 1, Table 2), as was predicted with our DFT calculations. On the other extreme, when the reaction was run with \( p \)-dimethylaminoacetylene (entry 7, Table 2), the cyclotrimerisation gave a mixture of the two regioisomers in a 59:41 ratio (as compared to theoretical 54:46 prediction). When \( p \)-aminophénylacetylene was calculated, two possible insertions (\( \text{A}_3 \text{-2,4} \) and \( \text{A}_3 \text{-1,4} \)) were possible, each one leading to the formation of one different isomer, and so a mixture of both isomers could be expected which is what is observed experimentally. The remaining substrates, comprising substituents with \( \sigma_{\text{para}} \) values ranging from 0.06 to -0.27 (entries 2-6, Table 2) led to regioisomeric mixtures ranging from 96:04 to 81:19, highly enriched with the 1,2,4-regioisomer. In the cyclotrimerisation of phenylacetylene following the Curtin-Hammett calculated path, the type III insertion from \( \text{A}_3 \text{-2,4} \) is the most favoured explaining why the 1,2,4 isomer was the one obtained predominantly in the experiments, a result which we think can be extrapolated to all this set of substituents.

### Table 2. \([\text{Rh(COD)}\text{BF}_4]/\text{BIPHEP}\)-catalysed \([2+2+2]\) cyclotrimerisation of phenylacetylene derivatives 1.\(^{4}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>( X )</th>
<th>( \sigma_{\text{para}} )</th>
<th>Yield(^b) (%) (2:3)</th>
<th>Ratio(^c) (2:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{NO}_2 )</td>
<td>0.78</td>
<td>38</td>
<td>100:00</td>
</tr>
<tr>
<td>2</td>
<td>( F )</td>
<td>0.06</td>
<td>36</td>
<td>92:08</td>
</tr>
<tr>
<td>3</td>
<td>( H )</td>
<td>0</td>
<td>62</td>
<td>96:04</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Me} )</td>
<td>-0.17</td>
<td>96</td>
<td>95:05</td>
</tr>
<tr>
<td>5</td>
<td>( \text{t}Bu )</td>
<td>-0.20</td>
<td>92</td>
<td>81:19</td>
</tr>
<tr>
<td>6</td>
<td>( \text{OMe} )</td>
<td>-0.27</td>
<td>65</td>
<td>94:06</td>
</tr>
<tr>
<td>7</td>
<td>( \text{NMe}_3 )</td>
<td>-0.83</td>
<td>33</td>
<td>59:41</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: [Rh(COD)\(_2\)]BF\(_4\) (0.025 mmol), BIPHEP (0.025 mmol), alkyne (0.5 mmol), DCE (3 mL) at reflux for 3 hours (\( X = \text{H and NO}_2 \)) or reflux for 23 hours (\( X = F, \text{Me}, \text{t}Bu, \text{OMe, NMe}_3 \)). \(^b\) Isolated yield. \(^c\) Ratio was determined by \( ^1H \) NMR of the crude mixture except in the case of \( p \)-fluorophénylacetylene in which \( ^19F \) NMR was used.

### CONCLUSIONS

We performed density functional theory (DFT) calculations of three \( p \)-\( X \)-substituted phenylacetylenes (\( X = \text{H, NO}_2 \) and \( \text{NH}_2 \)) and experimental studies of seven \( p \)-\( X \)-substituted phenylacetylenes (\( X = \text{NO}_2 , F, H, \text{Me}, \text{t}Bu, \text{OMe, NMe}_3 \) in the \([2+2+2]\) cyclotrimerisation catalysed by [Rh(BIPHEP)]\(^+\) to analyse the effect of the electronic character of the substituents on the regioselectivity of the reaction. Our theoretical and experimental results show that \( p \)-nitrophénylacetylene, which have the most electron withdrawing substituent, yields exclusively the 1,2,4-regioisomer by favouring the head-to-head oxidative coupling. On the other hand, when \( X = \text{H} \), the 1,2,4-regioisomer is formed preferentially, whereas when \( X = \text{NMe}_3 \), a 59:41 mixture of both isomers is obtained. These experimental results provide evidence that, from the two possible reactions pathways analysed computationally (lowest in energy barrier and Curtin-Hammett paths), the Curtin-Hammett
EXPERIMENTAL SECTION

Representative methods

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Reactions requiring anhydrous conditions were conducted in oven-dried glassware under a dry nitrogen atmosphere. Dichloromethane was degassed and dried under a nitrogen atmosphere by passing through solvent purification columns (MBraun, SPS-800). Solvents were removed under reduced pressure with a rotary evaporator. Reaction mixtures were chromatographed on a silica gel column (230–400 mesh) by using a gradient solvent system as the eluent.

General procedure for [2+2+2] cycloaddition reactions of p-substituted phenylacetylenes: In a 10 mL flask, a mixture of [Rh(COD)]_2BF_4 (0.025 mmol) and BIPHEP (0.025 mmol) was dissolved in CH_2Cl_2 (3 mL) Hydrogen gas was introduced to the catalyst solution and stirred for 30 min. The resulting mixture was then concentrated to dryness. Dichloroethane (2 mL) was added and the solution was stirred under a N_2 atmosphere and heated at 80 ºC. A solution of phenylacetylene (1.05 mmol) in dichloroethane (1 mL) was then added to the pre-heated catalytic mixture. The reaction mixture was then stirred at reflux until completion (TLC and GC monitoring). The solvent was evaporated and the residue was purified by column chromatography on silica gel.

Computational details

Geometries of the reactants, intermediates, transition states (TSs), and products were optimised using the DFT B3LYP method with a similar double-

polarised functions has been recently recommended to predict structures. In all calculations the D3 Grimme energy correction for dispersion was included. The all-electron cc-pVDZ basis set was employed for Rh. The same method (B3LYP-D3) with a similar double-

pp basis set containing an effective core relativistic pseudopotential was used for Rh. Results reported are limited to the singlet state potential energy surfaces. However, we calculated the triplet state for all reactants, intermediates, transition states, and products and we found that triplet states were higher in energy in all cases and, therefore, were not considered in the reaction path. The electronic energy was improved by performing single point calculations with the aug-cc-pVTZ (cc-pVTZ-PP for Rh) basis set. Analytical Hessians were computed to determine the nature of stationary points (one and zero imaginary frequencies for TSs and minima, respectively) and to calculate unscaled zero-point energies (ZPEs) as well as thermal corrections and entropy effects using the standard statistical-mechanics relationships for an ideal gas. These two latter terms were computed at 353.15 K (temperature of experiments) and 1 atm to provide the reported relative Gibbs energies (ΔG). Entropy corrections were divided by a factor of 2 to correct for the overestimation suffered by gas-phase entropies when used to determine entropies for reactions in solution. Finally, solvation Gibbs energies in dichloroethane were calculated with the B3LYP-D3/cc-pVDZ-PP method using the PCM continuum solvation model at the gas-phase geometries. The resulting solvation Gibbs energies were added to the final Gibbs energies in gas-phase to obtain Gibbs energies in solution. Standard Gibbs energies in solution refer to a 1 M standard-state concentration for all species. The change of conventional 1 atm standard state for gas-phase calculations to a standard-state gas-phase concentration of 1 M requires the introduction of a concentration change energy term of 2.36 kcal/mol at 353.15 K. As a summary, the hereafter reported Gibbs energies contain electronic energies calculated at the B3LYP-D3/aug-cc-pVTZ-PP//B3LYP-D3/cc-pVDZ-PP level together with gas phase thermal corrections and entropic contributions (the latter divided by two) at 353.15 K as well as the 2.36 kcal/mol term of changing the standard states from 1 atm to 1 M and the solvation energies computed with the B3LYP-D3/cc-pVDZ-PP method. Furthermore, the connectivity between stationary points was unambiguously established by intrinsic reaction path calculations. The Cartesian coordinates of all minima and TSs located can be found in the Supporting information.

ASSOCIATED CONTENT

Supporting Information

Characterization data for the cyclotrimerized products, Gibbs energy profiles (in kcal/mol) for the [2+2+2] cyclotrimerisation reaction calculated by Rh[BIPHEP] of three 4-nitrophenylacetylenes, three 4-amino phenylacetylenes, and three acetylenes (pdf file) together with Cartesian coordinates of all minima and transition states (text file). The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support from the Spanish Ministry of Economy and Competitiveness (MINECO) (Project No. CTQ2017-85341-P) and the DUE of the Generalitat de Catalunya (Project No. 2017SGR39 and ICREA Academia 2014 to M. S.) are acknowledged. Thanks are due to the Generalitat de Catalunya for FI predoctoral grants to O.T., M.F. and À.D.-J. The EU under the FEDER grant UNG10-4E-801 has also funded this research.

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(20) A blank experiment was run in the case of the cycloptimerisation of phenylacetylene using [Rh(COD)],BF₄ without BIPHEP but only decomposition of the starting acetylene was observed demonstrating the need of the ligand in such a process.


Graphic entry for the Table of Contents (TOC):