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Synthesis of Polyheterocyclic Tropones by [2 + 2 + 2 + 1] Carbonylative Cycloaddition of Triynes

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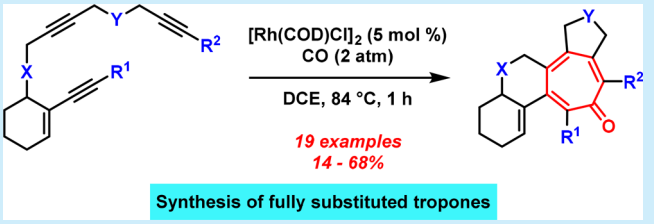
Supporting Information

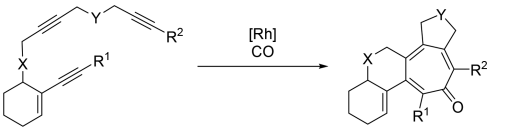
ABSTRACT: A direct synthesis of tropones (2,4,6-cycloheptatrienes) from simple preorganized triynes has been elaborated. This simple rhodium-catalyzed domino strategy allows one-pot access to fully substituted tropones in a 6−6−7−5 tetracyclic core in average to high yields.



Gaining access to medium-sized carbocycles has been a long-standing challenge for synthetic chemists, and it is well established that the formation of these cycles poses a hardship due to entropic and enthalpic factors and transannular interactions. In the past decades, many new methodologies have been developed in order to bypass these difficulties. One approach that has given good results is the use of carbonylative cycloaddition.[1] Through the presence of a carbonyl function, medium-sized carbocycles formed by carbonylative cycloaddition grant access to a wide panel of functionalities, thereby allowing access to new scaffolds.

The synthesis of fused medium-sized carbocycles by metal-catalyzed domino reactions to access high molecular complexity has been a continued interest in our group.[2−5] Part of our efforts has been employed toward the synthesis of cycloheptatrienes, which we recently achieved using palladium catalysis, albeit with moderate results.[6] With the idea to further investigate the possibilities in the field of seven-membered rings, we have become interested in a different type of compounds: 2,4,6-cycloheptatrieneones. These compounds, more commonly referred to as tropones, are nonbenzenoid aromatic seven-membered rings that have attracted considerable interest due to original electronic properties[7] and their presence in several natural products.[8] Moreover, tropones have often been used as building blocks in cycloadditions.[9−16] With this in mind, a number of syntheses of the tropone ring have been devised, and among those, cycloaddition reactions such as [5 + 2],[17−19] [3 + 2],[20] and [4 + 3][21−23] cycloadditions are well represented. However, these syntheses require one or several transformations following the key step to access the desired tropone ring. Moreover, surprisingly, these strategies did not make use of the presence of the carbonyl function in tropones for their synthesis. Attracted by the scarcity of efficient carbonylative strategies to access tropones, we have imagined that three alkyne moieties in the presence of carbon monoxide and a suitable catalyst could allow the formation of tropones via a [2 + 2 + 2 + 1] cycloaddition reaction. The [2 + 2 + 2 + 1] carbocyclization of enediynes has given remarkable results in the synthesis of 1,3-cycloheptatrienes from enediynes,[24−26] but led to ambivalent results with modest documentation in the case of triynes.[27] We have therefore endeavored to devise an efficient method to synthesize tropones from triynes and carbon monoxide in the presence of a rhodium catalyst. In order to increase yields as well as molecular complexity, we have chosen to use a cyclohexene core bearing tethered alkynes. By the strategic placement of the triynes around the core and the tethers, we could impose the preorganization of the system in order to facilitate the successive cyclization reactions. Herein, we report a mild [2 + 2 + 2 + 1] carbonylative cycloaddition, giving access to unprecedented polyheterocyclic scaffolds of high molecular complexity containing a fully substituted tropone ring through the closure of three cycles in a single step (Scheme 1).

Scheme 1. [2 + 2 + 2 + 1] Synthesis of Tropones



The major challenge for the formation of carbonylated compounds with the [2 + 2 + 2 + 1] carbonylative cycloaddition from triynes is the competition with the well-established rhodium-catalyzed [2 + 2 + 2] cycloaddition of triynes, which leads to the stable aromatic benzenoid compound.[28] The main goal for our optimization process was therefore to find conditions which allowed the synthesis of the tropone as a major product. Based on preliminary results in our group, we decided to optimize the reaction using model substrate **1a**.

Triyne **1a** was obtained from 2-cyclohexenone using a six-step synthesis with 35% overall yield (Scheme 2). 2-Iodocyclohex-2-enone **4** was obtained from 2-cyclohexenone using a described procedure.[29] It then underwent a Sonogashira reaction to yield

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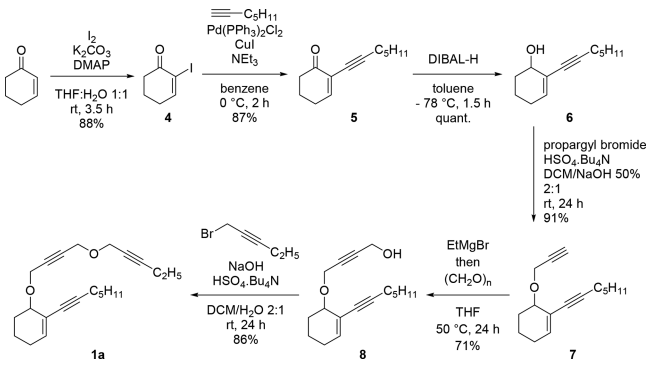
Scheme 2. Typical Synthesis of Substrates 1



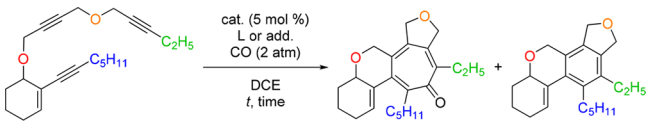
enyne **5**. The ketone was reduced using dibutylaluminum hydride to yield enynol **6**. The alcohol was subsequently propargylated in biphasic media using concentrated sodium hydroxide and propargyl bromide. The terminal alkyne thus obtained was then converted to propargyl alcohol **8** by deprotonating the terminal alkyne using ethylmagnesium bromide and allowing the formed species to react with paraformaldehyde at 50 °C over 1 day. Triyne **1a** was then obtained by performing a second propargylation in the same conditions as previously described. With this substrate in hand, we undertook the process of optimizing the reaction conditions for the synthesis of tropone **2a** (see Supporting Information).

We were pleased to find that, under 2 atm of CO in the presence of $[Rh(COD)Cl]_2$, the triyne **1a** underwent cyclization at room temperature with definite selectivity in favor of the carbonylated product **2a** (Table 1, entry 1), whereas using $[RhCl(CO)_2]_2$ lowered the selectivity of the reaction slightly (entry 2). As the cyclization was very sluggish at room temperature with both catalysts, and long reaction times afforded only poor conversion, we increased the temperature to reflux of DCE, which afforded complete conversion within 3 h and yielded 68% of the desired isolated tropone (entry 3). Seminal experiments in our group and data in the literature[30] indicated that increasing the pressure of carbon monoxide too much (10 atm) seemed to hinder the catalysis, leading us to conduct this study preferably using low pressures. However, when the reaction was conducted under atmospheric pressure of CO, the isolated yield of tropone decreased (entry 4), but no notable effect was observed when the pressure was increased from 2 to 4 atm (entry 5). Further shortening of the reaction time to 1 h maintained both conversion and selectivity, allowing us to obtain the fully substituted tropone in 68% yield (entry 6).

The influence of the metal ligands was then studied. Using a bidentate phosphine ligand not only slowed the reaction considerably but also lowered the ratio of carbonyl insertion (entry 7). When a monodentate phosphine ligand was used in the shape of Wilkinson's catalyst, the major product was benzenoid compound **3a**, and the conversion only attained 24% (entry 8). This can be slightly improved by the use of a cationic catalyst, i.e. adding silver triflate to the mixture, affording an 87% conversion. However, selectivity remained less favorable than that obtained with our original catalyst (entry 9).[31,32] Ruthenium and cobalt are other metals that are associated with carbonylative cycloaddition reactions, but control experiments using their carbonyl complexes gave low to no conversion (entries 10 and 11).[33,34] Noteworthy, we observed during this study that the triyne substrates **1** are poorly stable and needed to be freshly purified prior to cycloaddition experiments to avoid yield depletion.

We have proposed a mechanism based on the results of a theoretical study of the rhodium-catalyzed [2 + 2 + 2 + 1] carbonylative cycloaddition of enediynes (Scheme 3).[35] We propose that the cyclooctadiene ligand is easily decoordinated and replaced by carbon monoxide. The L′ ligand, on the other hand, can either be μ-Cl[Rh(COD)] or be replaced by CO. L′ is then displaced by the alkynes that are ideally preorganized due to the presence of the cyclohexene ring, to obtain intermediate **A**. A [2 + 2 + M] cycloaddition occurs toward five-membered rhodacycle **B**. Henceforth, two pathways are possible, the limiting factor being the kinetics of the chelation of the third alkyne. If this step is slow with respect to the migratory insertion of carbon monoxide from the rhodium to the C−Rh bond, the carbonylated six-membered rhodacyclic intermediate **C** is obtained. Here, the triple bond chelates the rhodium and is inserted in the cycle to obtain eight-membered intermediate **D**. The reductive elimination of rhodium gives tropone **2**. However, to some extent, the chelation of the rhodium by the third alkyne

Table 1. Optimization Reaction



1a 2a 3a

	cat./L or add.	time (h)	t (°C)	conv (%)[b]	2a/3a[b]	2a (%)[a]	3a (%)[a]
1	$[Rh(COD)Cl]_2$/−	40	rt	65	70/30	40	18
2	$[Rh(CO)_2Cl]_2$/−	23	rt	35	60/40	nd	nd
3	$[Rh(COD)Cl]_2$/−	3	84	100	67/33	68	30
4	$[Rh(COD)Cl]_2$/−[c]	3	84	100	65/35	58	35
5	$[Rh(COD)Cl]_2$/−[d]	3	84	100	68/32	66	34
6	$[Rh(COD)Cl]_2$/−	1	84	100	68/32	68	30
7	$[Rh(COD)Cl]_2$ /dppp	3.5	84	90	60/40	46	27
8	$RhCl(PPh_3)_3$/−[e]	1	84	24	41/59	nd	nd
9	$RhCl(PPh_3)$/AgOTf[e]	1	84	87	55/45	nd	nd
10	$Co_2(CO)_8$/−	1	84	78	45/55	nd	nd
11	$Ru_3(CO)_{12}$/−	1	84	<10	0/100	−	nd

[a]Isolated yields. [b]^{1}H NMR ratio. [c]P_{CO} = 1 atm. [d]P_{CO} = 4 atm. [e]10 mol % cat. was used.

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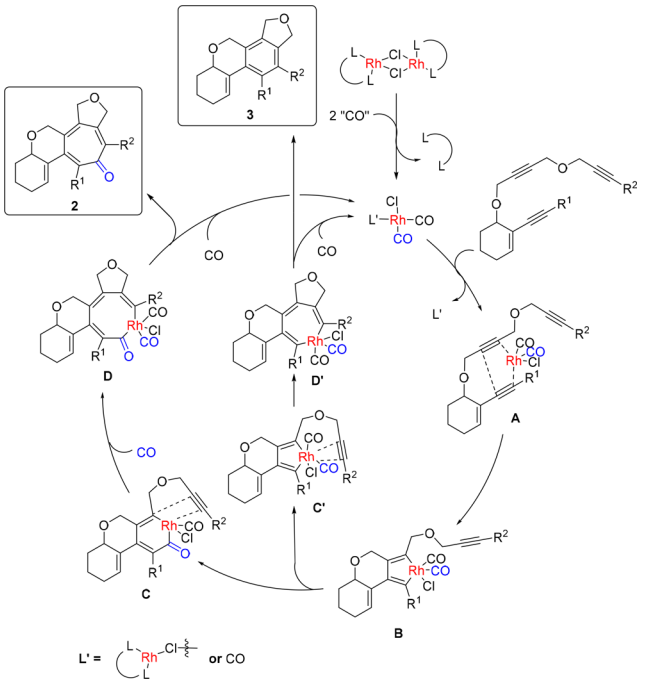
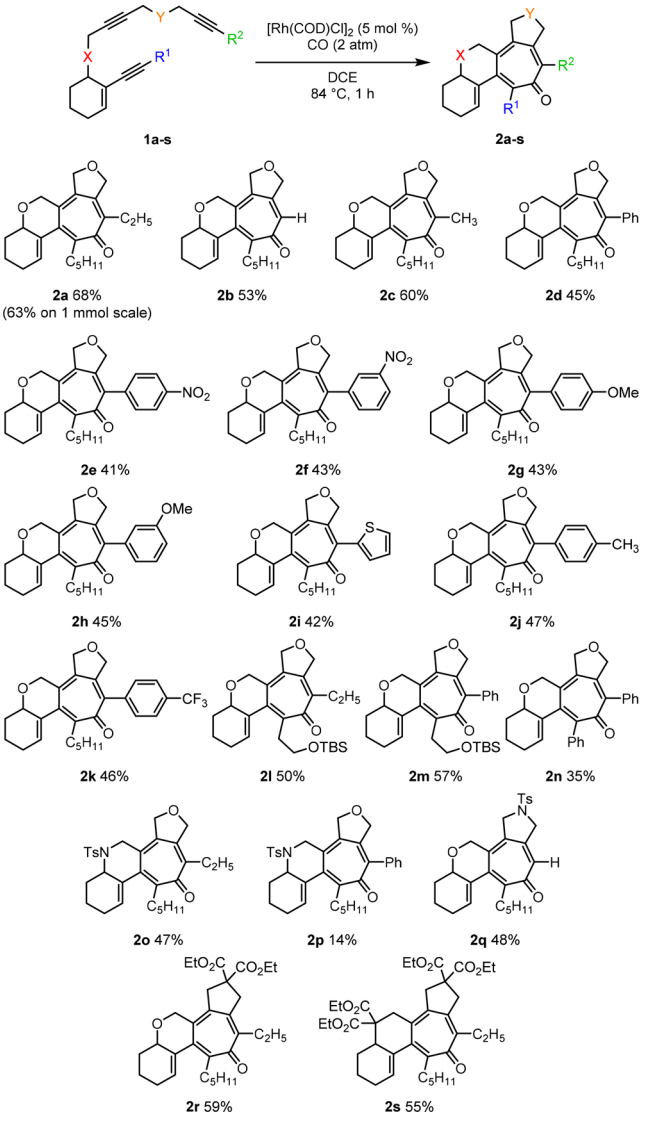
Scheme 3. Possible Mechanism



Scheme 4. Scope of the Reaction



can be faster than the migratory insertion. In this case, from **B** we obtain chelated intermediate **C′**, followed by insertion of the triple bond yielding seven-membered rhodacyclic intermediate **D′**. Final reductive elimination then produces benzenoid compound **3**.

With this proposed mechanism in hand, we have investigated the scope of the reaction (Scheme 4). When R^2 is a different alkyl chain, the yields are similar (**2a**/**2c**); however, in the presence of a terminal alkyne the yield lowers to 53% (**2b**). In order to investigate the consequences of electronic effects on the triple bond, we synthesized a number of substrates possessing differently substituted aryls using a Sonogashira reaction on **1b** (**1e**−**1k**). We hoped that a visible effect on the selectivity would be seen depending on the donating or withdrawing quality of the aryl substituent, which would favor or disfavor the rapid chelation of the third alkyne. However, when substrates **1e**−**1k** were exposed to the reaction conditions, the efficiency of the desired [2 + 2 + 2 + 1] reaction lowered. Moreover, no definite effect of the substituent could be observed. We hypothesize that rather than the electronic effects of the substituents, it is the steric hindrance of aryl groups at this position which has the strongest repercussions and interferes with the migratory insertion of carbon monoxide during the catalytic cycle (**B** to **C** or **C′**). Our efforts to synthesize a substrate possessing an ester as an electron-withdrawing group at the R^2 position to withdraw the steric factor have unfortunately been unsuccessful. Surprisingly, in the presence of a siloxyalkyl R^1 chain, an aryl at the R^2 position gave higher conversion and yield than an alkyl (**2l**/**2m**). However, the carbonylative cycloaddition of the diphenyl substrate **1n** was again disfavored by the high steric hindrance. This goes to confirm that steric hindrance, rather than favoring the formation of the least hindered species (nonbenzenoid compound **2**), inhibits the CO insertion and consequently the formation of the desired tropone, leading to an increased amount of benzenoid compound **3**. To study the possibility of enriching the heterocyclic scaffolds, we have substituted the ether tethers by various atoms. When X = NTs, the reaction produces **2o** as a major compound in 47% yield with an alkyl R^2 chain, but with a phenyl terminal group, the formation of tropone remarkably decreases and the desired compound becomes a minority product (**2p**). Inversely, when the nitrogen was in the Y position, full conversion was achieved, and the yield was restored to a reasonable 48% (**2q**).

Good results were also obtained when a geminal diester was used either as Y or both X and Y tethers, in which case full conversion was achieved and good yields were obtained for the formation of tropones **2r** and **2s**. In all cases the sole byproducts were the benzenoid compounds **3**, and full conversion was achieved in 1 h for a vast majority of the substrates (see Supporting Information for the yields and structures of the byproducts).

When the tether was extended by one carbon, however, conversion was extremely low and no tropone was observed (Scheme 5), and most of the starting material could be recovered. Such results have already been observed, notably in our group during cyclocarbopalladation reactions.[36] This indicates that the extended distance between the rhodium in intermediate **B** or **C** and the third alkyne likely hampers the chelation of the latter to the metal, leading to a very sluggish

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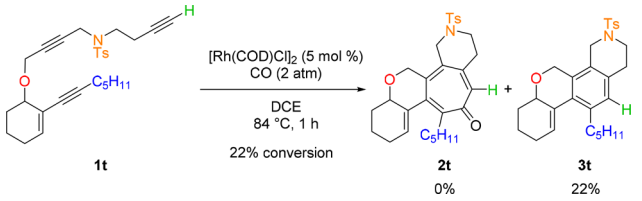
Scheme 5. Effect of a Six-Membered Tether



reaction. As both **2t** and **3t** compounds are aromatic, we can speculate that they have a similar stability, making it complicated to rationalize the sole formation of the benzenoid compound without extensive calculations.

In summary, we have devised a new method for the one-pot synthesis of fully substituted polyheterocyclic tropones via the rhodium-catalyzed [2 + 2 + 2 + 1] carbonylative cycloaddition. The use of preorganized triynes allows reaching good yields with respect to the high molecular complexity of the formed compounds. Indeed, in a single step, four C−C bonds and three cycles are formed. It is, to the best of our knowledge, one of the first syntheses of highly substituted tropones using a one-pot reaction.[18,37−39] The heteroatoms can be modified, and many functionalities are tolerated by the reaction conditions, which are mild and require only a low pressure of carbon monoxide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01496.

Procedures for the synthesis of substrates and final products and characterization, ^{1}H and ^{13}C NMR spectras of isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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