Fused tetracycles with a benzene or cyclohexadiene core: [2 + 2 + 2] cycloadditions on macrocyclic systems†

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A series of fused tetracycles with a benzene or cyclohexadiene core (2a–h) is satisfactorily prepared by intramolecular [2 + 2 + 2] cycloadditions of triynic and enediynic macrocycles (1a–h) under $RhCl(PPh_3)_3$ catalysis; the enantioselective cycloaddition of macrocycles 1b and 1e gives chiral tetracycles with moderate enantiomeric excess.

The transition-metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes is an interesting method for synthesizing polysubstituted benzene derivatives.[1] When running this reaction intramolecularly, three fused rings are formed in one synthetic operation. Furthermore, when it is performed in a closed system, *i.e*. a macrocycle, the reaction leads to fused tetracycles, which is a highly attractive synthetic strategy.

There are some well-known fused tetracycles with benzene cores such as trindane which has applications in organometallic complex stabilization.[2] The radioactive technetium complexes of trindane have also been tested as myocardial imaging agents in rats.[3] Analogous fused tetracycles with a benzene core have been prepared using routes that afford only symmetrical products.[4] Ma *et al*. accomplished the synthesis of asymmetrically substituted tetrafused benzenes by triple Mizoroki–Heck[5] or Suzuki–Miyaura[6] reactions on hexasubstituted benzenes although the processes of synthesis are quite laborious. Triannulated benzenes with attached nitrogen functional groups are also known compounds, particularly benzotripyrrolium cations, which are used in the synthesis of a number of zeolites,[7] and the mellitic triimides, which are used as C_3-symmetric supramolecular building blocks.[8] To the best of our knowledge, fused tetracycles with a cyclohexadiene core have not been previously described, even though it is likely that they may be useful as substrates for Diels–Alder reactions.

We have previously reported the [2 + 2 + 2] cycloisomerization of 15-membered macrocyclic triynes catalyzed by different transition metals.[9,10] Wilkinson catalyst [$RhCl(PPh)_3)_3$] was found to give the best results and the same catalytic system was applied to a series of macrocyclic triynes and *cis* and *trans* enediynes bearing different aryl substituents on the sulfonamide moieties. The same reaction was also efficiently run in non-conventional media such as molten TBAB.[11]

Given that the [2 + 2 + 2] cycloisomerization reaction inside macrocyclic systems to yield fused tetracycles is an interesting reaction which is still quite unexplored, we describe here the synthesis of triynic and enediynic triazamacrocycles and its cycloisomerization reactions. Preliminary results of the enantioselective versions of the reaction will also be presented.

Macrocycles **1a–h** (Fig. 1) were synthesized and completely characterized by spectroscopic methods[12] (see ESI). They all have a common 1,6,11-tris(arilsulfonyl)-1,6,11-triazaundeca-3,8-diyne part but have different chains closing the macrocyclic rings. The macrocycles differ from each other in the ring size (15-, 16-, 17-membered), the number and sort of unsaturation (three triple bonds or two triple bonds and one double bond), and also the substituents present in the double bond or in the α-position relative to the triple bond. **1a** also has different aryl units compared to the rest of the compounds.[13] We then proceeded to study the various intramolecular cycloisomerization reactions. Wilkinson's catalyst ($RhCl(PPh_3)_3$) was selected as it had formerly given the best results.[10] In all cases, cycloisomerized products (Table 1) were obtained in high yields (from 71% to 99%).[14] The [2 + 2 + 2] cycloaddition of enediynic macrocycles **1b–g** proceeds with total stereoselectivity (Table 1, entries 2–7), and the relative *syn*/*anti* stereochemistry of cycloisomerized compounds **2b–g** was determined from NOE data and from correlated ^1H and ^{13}C chemical shifts (see ESI†). In order to study the scope of the methodology, we chose different macrocycles (**1b–e**) whose later cycloisomerization led to various fused tetracycles such as 5,5,5-, 5,5,6- and 5,6,6-. As a general trend for enediynic macrocycles (Table 1, entries 2–5), the formation of 5,6,6-membered rings fused to a cyclohexadienic core (product **2d**) is much faster than the formation of 5,5,6-ring system (products **2b** and **2c**), which at the same time is faster than the formation of the 5,5,5-tetrafused structure (product **2e**). Although there is a certain tendency to the formation of bigger rings giving faster reactions, all the macrocycles gave fused tetracycles unlike in other methods of synthesis, where the failure to construct 5,5,5- is attributed to ring constraint.[5] We have also made an initial study into the effects of including substituents at different positions of the ring. The incorporation of a methyl group at the propargylic position (**1h**) does not seem to encumber the reaction. Indeed, the yield, reaction time, and temperature for both the methyl containing and the non-methyl-containing[10] 15-membered macrocycles are

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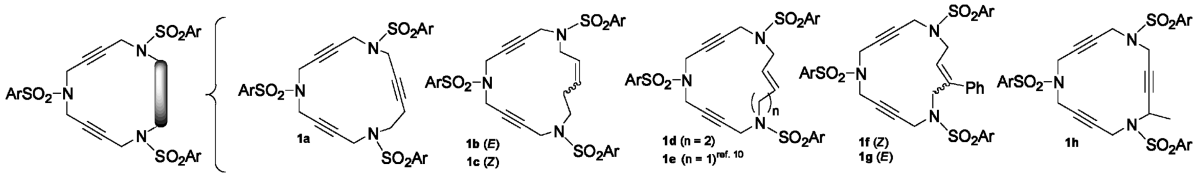
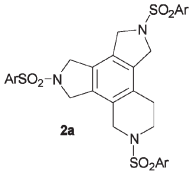
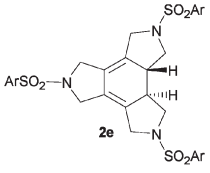
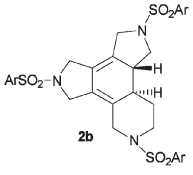
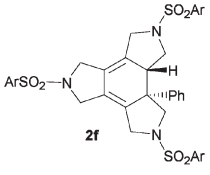
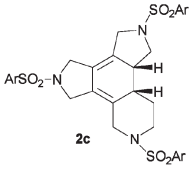
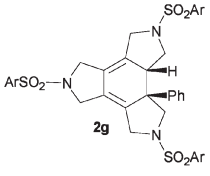
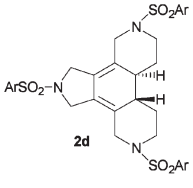
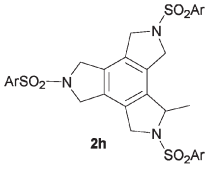


Fig. 1 Macrocycles **1** prepared with their differential chains.

Table 1 [2 + 2 + 2] Cycloaddition reactions of triynic and enediynic macrocycles **1**

Entry	Substrate	T/°C	t/h	Product	Yield (%)	Entry	Substrate	T/°C	t/h	Product	Yield (%)
1[a]	**1a**	90	28		81	5[ac]	**1e**	90	24		98
2[b]	**1b**	80	5		90	6[a]	**1f**	Reflux	24		95
3[b]	**1c**	80	5		87	7[a]	**1g**	Reflux	24		71
4[b]	**1d**	60	4		98	8[b]	**1h**	60	24		99

[a] 5 mol% $RhCl(PPh_3)_3$ catalyst used. [b] 10 mol% $RhCl(PPh_3)_3$ catalyst used. [c] Reaction published elsewhere (see ref. 10).

almost equivalent. Hence, the cycloaddition reaction does not seem to be affected by the steric hindrance introduced in the propargylic position. The situation is slightly different for substituents introduced at the double bond of the enediynic macrocycles (**1f**, **1g**). If we compare entries 5–7 (Table 1), it is observed that harsher conditions were required to cycloisomerize enediynes containing a phenyl substituent on the double bond (reflux toluene, entries 6 and 7) as compared to the non-substituted macrocycle **1e** (90 °C, entry 5). In conclusion, the success of the cycloisomerization reaction may be attributed to the macrocyclic nature of the reagent, which brings the unsaturated bonds close together with an orientation that is favourable to the process.

The [2 + 2 + 2] intramolecular cycloaddition reactions studied, with the exception of macrocycle **1a**, led to tetracyclic products containing one (**2h**) or two asymmetric carbons. Therefore, the enantioselective version of this reaction was the next aspect to be evaluated. The intramolecular enantioselective cycloaddition of triynes has been reported in just three cases using Ni,[15] Ir,[16] and Rh[17] catalysts. Furthermore, two examples of enantioselective intramolecular cycloaddition of enediynes have been reported,[18] one of them including a case involving macrocycle **1e**.[10] The study of the enantioselective version of the cycloaddition reaction was undertaken starting with macrocycle **1e** (Table 2). None of the reactions using $[RhCl(COD)]_2$ and chiral phosphanes with different steric hindrances [(*S*)-BINAP (L^1), (*S*)-(+)-neomenthyldiphenylphosphane (L^2) or (2*S*,3*S*)-(−)-2,3-bis(diphenylphosphino)butane (L^3), Table 2, entries 1–3] led to chirality induction, but the use of a cationic catalyst $[Rh(hpd)L^3]ClO_4$ (hpd = bicyclo[2.2.1]hepta-2,5-diene) with the chiral ligand already coordinated (*i.e.* not formed *in situ*) induced up to a 44% ee, whether or not activated by hydrogen gas (entries 4 and 5). Using the cationic complex and changing toluene for

Table 2 Enantioselective [2 + 2 + 2] cycloaddition reactions[a]

Entry	Substrate	Catalyst/ligand	Product	Yield (%)	ee[b] (%)
1[c]	**1e**	$[Rh(COD)Cl]_2/L^1$	**2e**	96	0
2[c]	**1e**	$[Rh(COD)Cl]_2/L^2$	**2e**	96	0
3[c]	**1e**	$[Rh(COD)Cl]_2/L^3$	**2e**	98	0
4	**1e**	$[Rh(hpd)L^3]ClO_4$	**2e**	95	44
5[c]	**1e**	$[Rh(hpd)L^3]ClO_4$	**2e**	98	43
6[d]	**1e**	$[Rh(hpd)L^3]ClO_4$	**2e**	97	26
7	**1e**	$[Rh(COD)_2]BF_4/L^3$	**2e**	96	10
8[d]	**1e**	$[Rh(COD)_2]BF_4/L^3$	**2e**	35	12
9	**1b**	$[Rh(hpd)L^3]ClO_4$	**2b**	46	41
10[e]	**1b**	$[Rh(hpd)L^3]ClO_4$	**2b**	24	33

[a] All reactions were performed with 10 mol% of catalyst loading using toluene as the solvent at 65 °C for 24 h. [b] Determined by chiral phase HPLC (Kromasil TBB; heptane–THF (80 : 20)). [c] Hydrogen gas was introduced to the catalyst solution prior to substrate introduction. [d] The reaction was performed with CH_2Cl_2 heated to reflux. [e] Reaction time 60 h.

CH_2Cl_2 in order to reduce the temperature gave lower ee (entry 6). On observing that the cationic catalyst gave better ee results, we tested $[Rh(COD)_2]BF_4$ with one of the three chiral phosphanes, specifically (2*S*,3*S*)-(−)-2,3-bis(diphenylphosphino)butane (L^3). The best reaction conditions with the new catalytic system (toluene at 65 °C) gave only 10% of ee (entry 7). When we used CH_2Cl_2 as the solvent, a 35% of yield of **2e** with a 12% of ee was obtained after heating to reflux (entry 8). We then tested macrocycle **1b** in the conditions which were successful for **1e**. The cycloisomerized product **2b** was obtained with a 41% ee, similar to that obtained for **2e**, but in only a 46% yield (entry 9). In an attempt to increase the yield, the same reaction was run for a longer reaction time (60 h instead of 24 h), but more decomposition was obtained giving a reduced 24% yield and 33% ee (entry 10).

In conclusion, a series of fused tetracycles with benzene cores (5,5,5- and 5,5,6-) and cyclohexadiene cores (5,5,5-, 5,5,6- 5,6,6-) can be conveniently prepared by Rh(I)-catalyzed [2 + 2 + 2] cycloadditions of macrocyclic systems. When the reaction was run with a chiral Rh(I) complex, the tetracycles were obtained in high yields and moderate ee's.

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14 *General procedure*: In a 50 mL flask, macrocycle **1** (1 equiv) and $RhCl(PPh_3)_3$ (0.1 equiv) were introduced and degassed, and anhydrous toluene (10 cm^3) was added. The mixture was heated and stirred under N_2 until completion. The solvent was removed and the residue was purified by column chromatography on silica gel.

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