Rhodium N-Heterocyclic Carbene Complexes as Effective Catalysts for [2+2+2]-Cycloaddition Reactions

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Abstract: Rhodium complexes of N-heterocyclic carbenes (NHC) [RhCl(cod)(NHC)], [cod = 1,5-cyclooctadiene, NHC = 1,3-diisopropylimidazolin-2-ylidene, and NHC = 1,3-dimesitylimidazolin-2-ylidene] are tested for intra- and partially intramolecular [2+2+2]-cycloaddition reactions demonstrating their effectiveness in this kind of process. This is the first use of a rhodium-NHC complex in a [2+2+2]-cycloaddition reaction of three alkynes. ESI-MS has been used to detect oxidative addition intermediates using rhodium NHC as the catalytic system.

Key words: cycloadditions, rhodium, carbenes, homogenous catalysis, polycycles

The development of efficient methods for transition-metal-catalyzed [2+2+2]-cycloaddition reactions of unsaturated substrates has attracted considerable attention in recent decades.[1] A number of excellent procedures have been published using various transition metals. Among the metals able to promote this atom-economical transformation, rhodium has been widely used due to its efficient performance in catalytic conditions.

Phosphane-stabilized rhodium complexes, whether the Wilkinson catalyst or a combination of $[Rh(cod)_2]BF_4$ and bidentate diphosphine ligands (i.e., BINAP), constitute the most common source of rhodium for these transformations. Rhodium complexes stabilized by N-heterocyclic carbene (NHC) ligands show great electronic versatility, are easy to handle, readily synthesized, and have applications in other rhodium-catalyzed transformations (C–H activation, hydroborylation, hydrosililation, etc.).[2] However, they have been little used in cycloaddition reactions, and only a few studies have described the use of Rh–NHC complexes in this kind of process. Evans et al. described a diastereoselective [4+2+2] cycloaddition[3] of 1,6-enynes and 1,3-butadiene, Chung et al. developed [4+2] and [5+2] cycloadditions of dienynes and alkyne vinylcyclopropanes, respectively, in their intra- and intermolecular versions,[4] and Webster and Li used a quinoline-tethered NHC to assist rhodium to catalyze a [3+2] cycloaddition of diphenylcyclopropenone and internal alkynes.[5]

The use of transition-metal catalysts of metals other than rhodium stabilized with NHC for [2+2+2]-cycloaddition reactions has also been reported by some groups in the last decade. Louie et al. used Ni–NHC complexes with great success in [2+2+2] cycloadditions of two alkynes and aldehydes and ketones,[6] isocyanates,[7] nitriles,[8] and carbon dioxide.[9] Okamoto et al. described the intramolecular cyclotrimerization of triynes catalyzed by NHC cobalt and iron complexes,[10] and more recently Aubert, Gandon et al. reported a straightforward [2+2+2] cycloaddition of enediynes mediated by cobalt and an N-heterocyclic carbene in the presence of manganese.[11]

Phosphane ligands, mainly used to stabilize rhodium catalysts in [2+2+2]-cycloaddition reactions, are prone to oxidation and so the reactions need to be run in anaerobic conditions. Furthermore, the corresponding phosphane oxides formed at the end of the process often hamper product purification. Therefore, the aim of the present study was to test the ability of readily available [RhCl(IPr)(cod)] and [RhCl(IMes)(cod)] complexes towards [2+2+2] carbocyclization of macrocyclic triynes and enediynes, as well as in intramolecular and partially intramolecular versions in order to circumvent the drawbacks of phosphane use.

[RhCl(IPr)(cod)][12] (**1**) and [RhCl(IMes)(cod)][13] (**2**) [cod = 1,5-cyclooctadiene, IPr = 1,3-diisopropylimidazolin-2-ylidene, and IMes = 1,3-dimesitylimidazolin-2-ylidene] (Figure 1) were prepared by deprotonation of the corresponding imidazolium salt with potassium *tert*-butoxide followed by transmetalation with $[RhCl(cod)]_2$, as already described in the literature.

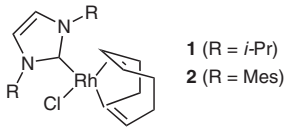

Figure 1 Rhodium–NHC complexes used in the study

Macrocyclic ligands, cycloisomerized in the group using the Wilkinson catalyst,[14] were the first substrates to be tested. The [2+2+2]-cycloaddition reaction was studied both on the triyne macrocycle **3a** and enediyne macrocycle **3b** (Table 1). Remarkably, although it took seven days, it was possible to accomplish the reaction of macrocycle **3a** using catalyst **1** at room temperature in dichloromethane media (entry 1, Table 1). The reaction time was considerably decreased by switching to toluene and heating to 50 °C (entry 2, Table 1). IMes catalyst **2** was also able to promote the cycloisomerization but needed more vigorous heating (90 °C, entry 3, Table 1). Enediyne macrocycle **3b** was also cycloisomerized with excellent yields using catalyst **1** at 50 °C (entry 4, Table 1). The more vigorous conditions needed for Rh–NHC catalyst **2**

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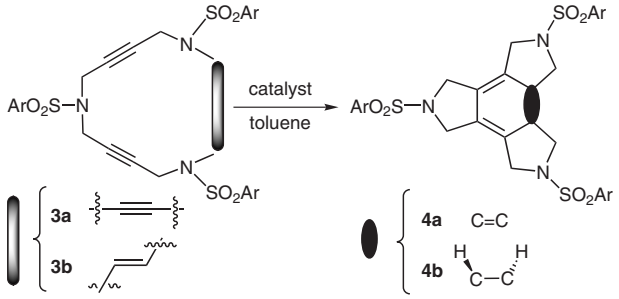
to accomplish the cycloisomerization of the triyne macrocycle may possibly be explained by the greater steric hindrance introduced by the mesityl substituents in the NHC.

Table 1 [2+2+2] Cycloisomerization of Triyne Macrocycle **3a** and Enediyne Macrocycle **3b**

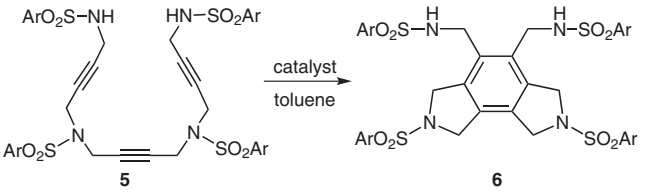


Entry	Substrate[a]	Catalyst (mol%)	Temp (°C)	Time (d)	Product	Yield (%)
1[b]	**3a**	**1** (5)	r.t.	7	**4a**	90
2	**3a**	**1** (5)	50	2	**4a**	98
3	**3a**	**2** (5)	90	1	**4a**	97
4	**3b**	**1** (5)	50	3	**4b**	98

[a] Ar = 2,4,6-triisopropylphenyl.
[b] CH_2Cl_2 was used as the reaction media.

A completely intramolecular version in open-chain analogues of the macrocycles **3** was also tested (Table 2). Triyne **5** was treated with 5 mol% of the catalyst in toluene at 90 °C. Using the two NHC catalysts **1** and **2**, a good yield of the cyclotrimerized product **6** was obtained after one day of reaction (entries 1 and 2, Table 2).

Table 2 [2+2+2] Cycloisomerization of Triyne **5**[a]



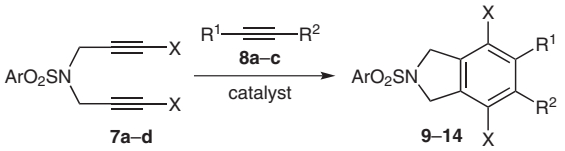
Entry	Catalyst (mol%)	Temp (°C)	Time (d)	Product	Yield (%)
1	**1** (5)	90	1	**6**	66
2	**2** (4)	90	1	**6**	76

[a] Ar = 4-methylphenyl.

The activity of the Rh–NHC complexes was also examined in the partially intramolecular version of the [2+2+2] cycloaddition. Several N-tethered diynes were reacted with 2-butyne-1,4-diol, propargyl alcohol, or phenylacetylene under rhodium catalysis using either toluene or ethanol as the solvent (Table 3).

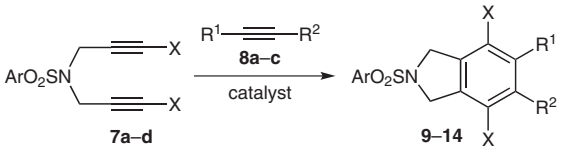
The hindered diyne **7a** was reacted with 2-butyne-1,4-diol **8a** in toluene with Rh–NHC catalysts. In all cases, the desired benzene product **9** was obtained in moderate yields, with slightly higher yields being obtained when IPr was used as the ligand for rhodium (entries 1 and 2, Table 3). The reaction was then tested in the less hindered 1,6-diyne **7b**, resulting from dialkylation of *p*-methylphenylsulfonamide with 1-bromo-2-butyne. The reaction conditions for the cycloaddition of diyne **7b** were optimized to minimize homocoupling of the starting diyne. By conducting the reaction in refluxing ethanol it was possible to isolate cycloaddition product **10** with a 65% yield when using a 10 mol% of catalyst **2** (entry 3, Table 3).

Table 3 [2+2+2] Cycloaddition of Azatethered Diynes **7** with Various Monoynes **8**[a]



Entry	**7** X	**8** R^1/R^2 (equiv)	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Product	Yield (%)
1[b]	**7a** CH_2NHSO_2Ar	**8a** CH_2OH (1.2)	**2** (5)	toluene	65	48	**9**	46
2[b]	**7a** CH_2NHSO_2Ar	**8a** CH_2OH (1.2)	**1** (5)	toluene	90	24	**9**	61
3	**7b** Me	**8a** CH_2OH (1.2)	**2** (10)	EtOH	reflux	30	**10**	65
4	**7b** Me	**8a** CH_2OH (5)	**2** (10)	EtOH	reflux	72	**10**	85
5	**7b** Me	**8a** CH_2OH (5)	**2** (5)	EtOH	reflux	45	**10**	68
6[c]	**7b** Me	**8a** CH_2OH (5)	**2** (5)	EtOH	reflux	48	**10**	78
7	**7c** H	**8a** CH_2OH (5)	**2** (5)	EtOH	reflux	24	**11**	42
8	**7c** H	**8a** CH_2OH (5)	**2** (10)	EtOH	reflux	24	**11**	59
9	**7b** Me	**8b** H/Ph (5)	**2** (5)	EtOH	reflux	48	**12**	64

Table 3 [2+2+2] Cycloaddition of Azatethered Diynes **7** with Various Monoynes **8**[a] (continued)



Entry	**7** X	**8** R^1/R^2 (equiv)	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Product	Yield (%)
10	**7d** Me/H	**8c** H/CH_2OH (5)	**2** (5)	EtOH	reflux	24	**13**	68 (*m/o* = 1.27)
11[c]	**7d** Me/H	**8b** H/Ph (5)	**2** (5)	EtOH	reflux	24	**14**	82 (*m/o* = 1.84)

[a] Unless otherwise noted, Ar = 4-methylphenyl.
[b] Ar = 2,4,6-triisopropylphenyl.
[c] Solvent was taken directly from the bottle without any degassing or drying.

This yield was considerably increased when the number of equivalents of the monoyne was increased from 1.2 to 5 (compare entries 3 and 4, Table 3). When the catalyst load was decreased to 5 mol%, the yield fell to 68% (entry 5, Table 3). Interestingly, when the reaction was carried out with absolute ethanol taken straight from the bottle without any additional drying or degassing[15] it was found that the yield increased to 78% (entry 6, Table 3). This procedure has clear advantages over the use of a phosphane-based catalyst, which requires care to avoid oxidation of the phosphanes. The reaction was then tested with terminal diyne **7c**. A moderate 42% yield of **11** was obtained after 24 hours at reflux which became 59% when the amount of catalyst was increased from 5 to 10% mol (entries 7 and 8, Table 3). Phenylacetylene **8b** was also checked as a monoyne partner in the Rh–NHC-catalyzed cycloaddition. A 64% yield of the corresponding biphenyl product **12** was obtained after 48 hours at reflux. Asymmetric 1,6-diyne **7d** was reacted with either propargyl alcohol **8c** or phenylacetylene **8b** in order to evaluate the regiochemical control of NHC catalyst **2**. Good yields of cycloaddition products **13** and **14** were achieved but only a poor regioisomeric ratio was obtained for each of the two acetylenes. In the two cases, the less sterically hindered regioisomer with the two substituents in a relative *meta* position is the main compound (entries 10 and 11, Table 3).

In order to gain further mechanistic information about the [2+2+2] cycloaddition of alkynes catalyzed by the Rh–NHC complexes, an electrospray ionization mass spectrometry (ESI-MS)[16] study was conducted. This technique has become increasingly popular as a mechanistic tool for the study of transient intermediates involved in organometallic catalytic reactions.[17] The partially intramolecular cycloaddition reaction between diyne **7b** and alkyne **8a** was chosen as the reaction model. First, Rh–NHC complex **2** was dissolved in ethanol and injected into the mass spectrometer for analysis. A peak corresponding to the catalyst which is ionized by the loss of the chlorine atom appeared at *m/z* = 515.2 {[Rh(IMes)(cod)]$^+$} together with a smaller peak corresponding to the protonated carbene ligand at *m/z* = 305.1 {[IMes + H]$^+$}. Diyne **7b** was then added to the former solution and, after 30 minutes of stirring at reflux, a sample was injected into the mass spectrometer. A new cluster corresponding to the oxidative addition intermediate could be detected centered at *m/z* = 790.2 {[Rh(IMes)(cod)(**7b**)]$^+$}, which retains both the NHC and cod ligands in the rhodium metal (Figure 2). The oxidative coupling of the two alkynes in the diyne to generate a rhoda(III)cyclopentadiene is supported by the isolation and characterization of several derivatives[18] and is a common intermediate postulated in these Rh-catalyzed cycloaddition reactions. An excess of 2-butyne-1,4-diol **8a** was then added to the reaction mixture. However, no further intermediate could be observed involving the monoyne reacting partner although a small cluster at *m/z* = 384.1 corresponding to [**10** + Na]$^+$ was observed after 1.5 hours of stirring at reflux, showing that the reaction does take place (as is also seen by TLC monitoring). Interestingly, a peak at *m/z* = 1065.2 was observed (Figure 3) which is assigned to the most advanced intermediate involving the third alkyne of another diyne molecule {[Rh(IMes)(cod)(**7b**)$_2$]$^+$}. This intermediate evolves

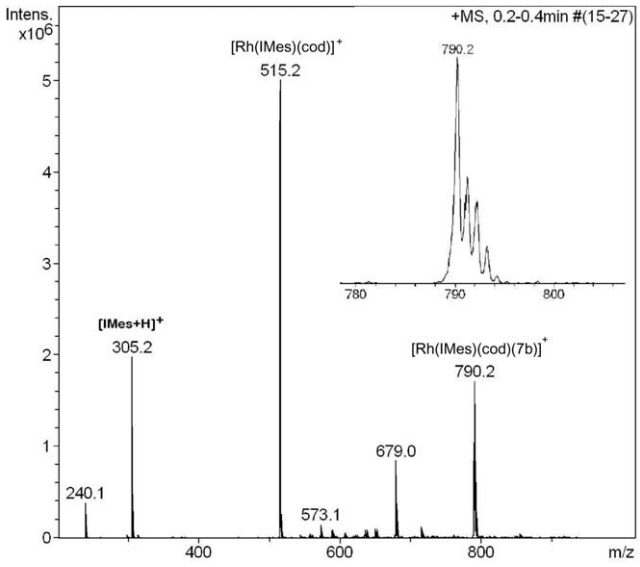


Figure 2 ESI(+)-MS spectrum of the reaction mixture: **7b** (1 equiv) and **2** (0.5 equiv) in EtOH at reflux after 0.5 h of reaction

to the homocoupled product observed in traces in these reactions.

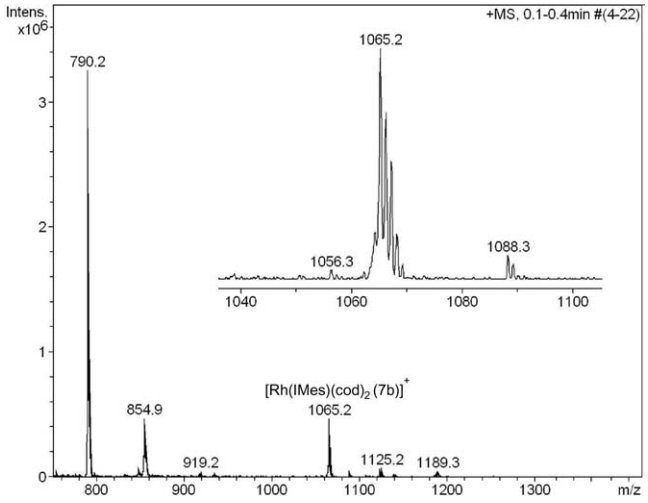


Figure 3 ESI(+)-MS spectrum of the reaction mixture: **7b** (1 equiv), **2** (0.5 equiv), and **8a** (excess) in EtOH at reflux after 1.5 h of reaction

It can be concluded from the results obtained that N-heterocyclic carbene rhodium complexes **1** and **2** are efficient catalysts for the [2+2+2]-cycloaddition reaction. They are able to promote the cycloisomerization of both triyne and enediyne azamacrocycles as well as the cycloisomerization of open-chain triyne substrates. Furthermore, the partially intramolecular version of the [2+2+2] cycloaddition of three alkynes can be achieved with readily available Rh–NHC catalysts. It has also been shown that the robust Rh–NHC catalysts studied here can be run under aerobic conditions with solvent taken straight from the bottle. ESI-MS was used to detect the oxidative addition intermediate generated from diyne **7b** and Rh complex **2**.

[2+2+2] Cycloaddition of Compound 5 with [RhCl(IPr)(cod)] (1, Entry 1, Table 2) –General Method

A degassed solution of 1,6,11,16-tetrakis[(4-methylphenyl)sulfonyl]-1,6,11,16-tetraazahexadeca-3,8,13-triyne (**5**, 0.082 g, 0.098 mmol) and [RhCl(IPr)(cod)] (0.0020 g, 0.0050 mmol) in anhydrous toluene (15 mL) was heated at 90 °C for 1 d (TLC monitoring). The solvent was then evaporated, and the residue was purified by column chromatography on silica gel with mixtures of CH_2Cl_2 and EtOAc (polarity from 20:1 to 10:1) to afford **6** (0.054 g, 66%) as a colorless solid.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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