Diastereoselective metal-catalyzed [4 + 2 + 2] carbocyclization reactions utilizing a rhodium *N*-heterocyclic carbene (NHC) complex: the first example of a rhodium NHC-catalyzed [*m* + *n* + *o*] carbocyclization†

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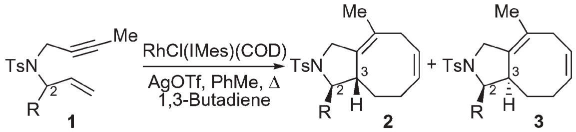
The air and moisture stable rhodium *N*-heterocyclic carbene (NHC) complex, RhCl(IMes)(COD) (IMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazole-2-ylidine; COD = 1,5-cyclooctadiene), facilitates a diastereoselective metal-catalyzed [4 + 2 + 2] carbocyclization of 1,6-enynes in the presence of silver triflate and 1,3-butadiene.

We recently reported a series of *inter*molecular rhodium-catalyzed [4 + 2 + 2] carbocyclization reactions of heteroatom-tethered 1,6-enynes with 1,3-butadiene, using silver triflate *modified* Wilkinson's catalyst for the construction of bicyclic cyclooctanoids.[1–3] In the course of these studies, we demonstrated that this reaction was highly efficient and diastereoselective with the C-2 napthyl substituted 1,6-enyne **1** (R = Np). Surprisingly, the extension of this methodology to other C-2 substituted 1,6-enynes, particularly alkyl derivatives, afforded only trace amounts of the product thus indicating that the original catalyst was highly substrate dependent. Herein, we now report a highly efficient and diastereoselective metal-catalyzed [4 + 2 + 2] carbocyclization reaction utilizing the recently reported rhodium *N*-heterocyclic carbene (NHC) complex, RhCl(IMes)(COD),[4–6] which provides a general solution to this problem over a broad range of C-2 substituted 1,6-enynes. Moreover, this represents the first example, as far as we can determine, of a rhodium NHC-catalyzed [*m* + *n* + *o*] type carbocyclization.[7]



(1)

In the course of extending the scope of the diastereoselective rhodium-catalyzed [4 + 2 + 2] carbocyclization with C-2 substituted 1,6-enynes, we determined the original silver triflate *modified* Wilkinson's catalyst to be substrate specific. For example, treatment of the enyne **1a** (R = Me) with this catalyst in the presence of 1,3-butadiene, afforded only trace amounts of the carbocycle **2a** (eqn. (1); <5%). Table 1 summarizes the examination of various precatalysts and ligands in an attempt to develop a more general reaction. Bidentate phosphine ligands were initially explored (Entries 1–3) which, with the exception of ethane-1,2-diylbis(diphenylphosphine) (dppe) (Entry 1), provided analogous results to Wilkinson's catalyst. Various monodentate trialkyl phosphines were also examined, as exemplified by tri-*n*-butylphosphine and tricyclohexylphosphine (Entries 4 and 5), which afforded the desired product as a single diastereoisomer, with improved yield. Based on the improved efficiency demonstrated with the electron-rich monodentate ligands, we speculated that strong σ-donation might be a crucial component for catalytic turnover in this particular reaction.

Table 1 Precatalyst/ligand screening for the diastereoselective [4 + 2 + 2] carbocyclization (eqn. (1); R = Me)[a]

Entry	Precatalyst[b,c]	Ligand	Ratio of **2** : **3**[d]	Yield (%)[e]
1	$[RhCl(COE)_2]_2$	dppe	>19 : 1	34
2	″	dppp	—	<5
3	″	dppb	—	<5
4	″	$P(^nBu)_3$	>19 : 1	45
5	″	$P(^cHex)_3$	>19 : 1	30
6	***RhCl(IMes)(COD)***	—	***>19 : 1***	***75***

[a] All reactions (0.25 mmol) were carried out in toluene (0.08 M) at 110 °C. [b] 10 mol% of monomer and 5 mol% of dimer were employed. [c] 2 equivalents of AgOTf relative to the metal were utilized. [d] Ratios determined by 400 MHz ^{1}H NMR on crude reaction mixtures. [e] GLC yields (COE = cyclooctene).

N-heterocyclic carbene ligands are known phosphine surrogates, which fulfill the criterion for strong σ-donation. Indeed, since the first independent reports of *N*-heterocylic carbene complexes by Wanzlick[8] and Öfele[9] and the isolation of the first crystalline NHC by Arduengo,[10] these carbenes have gained considerable prominence as important ligands in organometallic chemistry. This may be attributed to the fact that these singlet carbenes behave in an analogous manner to amines, ethers, and phosphines as classical $2e^-$ donors,[11] in which the NHC's serve as better donors than some of the best phosphines. Furthermore, NHC's are often more resistant to dissociation from the metal center in many systems.[12] As a result, NHC–metal complexes have been successfully utilized as catalysts or precatalysts for a variety of transition metal-catalyzed transformations.[11,13] Despite the myriad of transformations utilizing NHC–metal complexes, there are relatively few examples of their use in [*m* + *n* + *o*] carbocyclization reactions.[14]

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† Electronic supplementary information (ESI) available: experimental procedures, X-ray crystallographic analysis of the 3,5-dinitrobenzoates of **2f** and **5**, and spectral data (IR, ^{1}H and ^{13}C NMR) including high resolution MS for **1a–l**, **2a–l** and **5**. See http://www.rsc.org/suppdata/cc/b4/b413438a/

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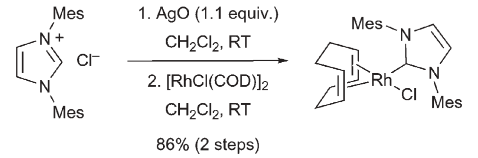


(2)

The rhodium–NHC complex, RhCl(IMes)(COD), was prepared in good yield *via* transmetallation of $[RhCl(COD)]_2$ with a silver carbene complex (eqn. (2)).[12c,15] The intermediate Ag–NHC complex, which was prepared *in situ* through the treatment of the imidazolium salt with silver oxide, was added directly into a solution of $[RhCl(COD)]_2$ in methylene chloride to afford the desired metal complex. The air and moisture stable complex was then purified by column chromatography to remove any residual salts and $[RhCl(COD)]_2$. While spectroscopic data for this complex have been reported,[4] a definitive structure was not forthcoming. We were able to obtain crystals suitable for X-ray crystallographic analysis, and thereby prove the structure of this complex (Fig. 1).§

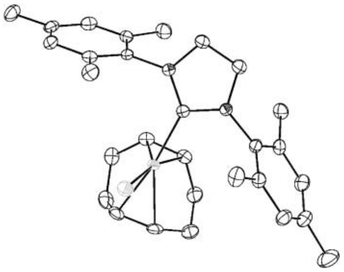


Fig. 1 Thermal ellipsoid plot of RhCl(IMes)(COD) (50% probability thermal ellipsoids).

Gratifyingly, the utilization of the rhodium–NHC complex, RhCl(IMes)(COD), provided a remarkable improvement in the overall efficiency of the reaction, in which the cyclooctanoid **2a** was obtained in 75% yield, as a single diastereoisomer (Entry 6). In light of this result, we decided to examine the substrate scope of this catalyst for a variety of C-2 substituted 1,6-enynes, since it demonstrated considerable promise as a potential solution to the [4 + 2 + 2] reaction and also represents a novel catalyst for carbocyclization reactions.

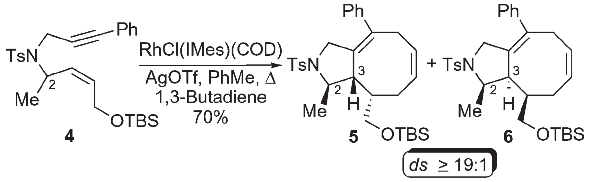
Table 2 summarizes the reactions of various enynes **1a–l** with silver triflate *modified* RhCl(IMes)(COD) in the presence of excess 1,3-butadiene. In all cases the rhodium-catalyzed [4 + 2 + 2] carbocyclization reaction proceeds with excellent diastereocontrol affording the desired carbocycles **2a–l** in high yield.¶ This catalytic system works efficiently with various linear and branched alkyl and benzyl substituents at the C-2 position (Entries 1-5). Interestingly, the reaction is also tolerant of a free hydroxyl group, albeit resulting in lower yield (Entry 6). Presumably, the free hydroxyl group's ability to coordinate the metal center hinders the efficiency of the reaction. In line with this reasoning, protection of the hydroxyl substituent allowed for improved efficiencies (Entry 7–8). Likewise, the catalytic system is tolerant of functional groups such as ethers, esters, other olefins, and aryl groups (Entries 9–12).

Table 2 Scope of the diastereoselective [4 + 2 + 2] carbocyclization using RhCl(IMes)(COD)†

Entry	1,6-Enyne **1**^{a} R =		Ratio of **2** : **3**^{b}	Yield (%)^c
1	Me	**a**	$\geqslant$19 : 1	84
2	Bn	**b**	$\geqslant$19 : 1	79
3	$Ph(CH_2)_2$	**c**	$\geqslant$19 : 1	83
4	^{i}Pr	**d**	$\geqslant$19 : 1	84
5	^{c}Hex	**e**	$\geqslant$19 : 1	75
6	$HOCH_2$	**f**	$\geqslant$19 : 1	55
7	$BnOCH_2$	**g**	$\geqslant$19 : 1	77
8	$TBSOCH_2$	**h**	$\geqslant$19 : 1	83
9	CO_2Me	**i**	$\geqslant$19 : 1	71
10	$CH_2{=}CH$	**j**	$\geqslant$19 : 1	81
11	$CH_2{=}CHCH_2$	**k**	$\geqslant$19 : 1	79
12	Ph	**l**	$\geqslant$19 : 1	89

^{a} All reactions (0.25 mmol) were carried out using 10 mol% of the catalyst and 20 mol% AgOTf in toluene (0.08 M) at 110 °C. ^{b} Ratios determined by 400 MHz ^{1}H NMR on crude reaction mixtures. ^{c} Isolated yields.

We envisioned that the application of this methodology to substituted alkenes would further highlight the synthetic utility of this catalyst through the introduction of an additional stereogenic center. Moreover, alkene substitution is often poorly tolerated, given that these substrates are prone to enyne cycloisomerization.[16,17] Treatment of the enyne **4** under the standard [4 + 2 + 2] carbocyclization conditions, using the RhCl(IMes)(COD) catalyst, furnished the carbocycle **5** in 70% yield, with $\geqslant$19 : 1 diastereoselectivity (eqn. (3)).



(3)

In conclusion, we have demonstrated that the air and moisture stable complex RhCl(IMes)(COD) is a suitable catalyst for the diastereoselective [4 + 2 + 2] carbocyclization and thus provides the first example of a rhodium–NHC-catalyzed carbocyclization. Additionally, the utilization of the carbene catalysts allows for the construction of three contiguous stereocenters in a single transformation from a substituted 1,6-enyne.

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Notes and references

§ Crystal structure data for RhCl(IMes)(COD), $C_{29}H_{36}ClN_2Rh$, yellow block, tetragonal, $I4_1/a$, a = 32.464(2) Å c = 9.9286(7) Å V = 10463.7(10) Å^3, Z = 16, T= 113(2) K, ρ_{calc} = 1.399 Mg m^{-3}, μ = 0.774 mm^{-1}, GOF = 1.033, $R(F)$ = 0.0276 and $wR(F2)$ = 0.0635 for 6359 observed reflections $I > 2\sigma(I)$, $4.28° \leqslant 2\theta \leqslant 60.16°$. CCDC 249419. See http://www.rsc.org/suppdata/cc/b4/b413438a/ for crystallographic data in .cif or other electronic format.

¶ The relative configuration of the major diastereoisomer **2f** was confirmed by X-ray crystallographic analysis after conversion to the corresponding 3,5-dinitrobenzoate. The relative configuration was then relayed to that of deprotected **2g–h**. The alkyl substituted product **2a**, was confirmed *via* reduction of the tosylate of **2f**.

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