Intermolecular rhodium-catalyzed [2 + 2 + 2] carbocyclization reactions of 1,6-enynes with symmetrical and unsymmetrical alkynes†

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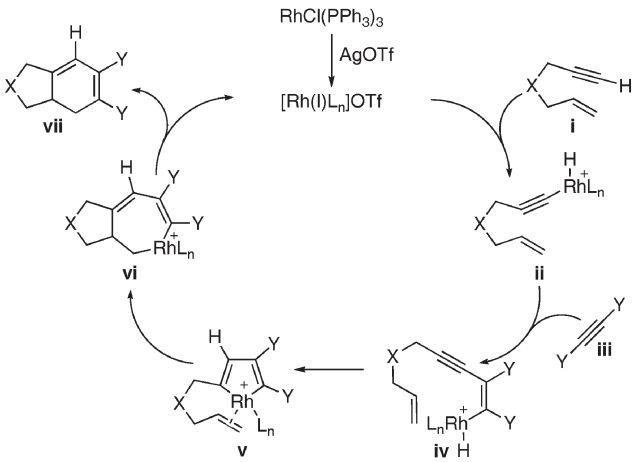
The *crossed inter*molecular rhodium-catalyzed [2 + 2 + 2] carbocyclization of carbon and heteroatom tethered 1,6-enynes can be accomplished with symmetrical and unsymmetrical alkynes, to afford the corresponding bicyclohexadienes in an efficient and highly selective manner.

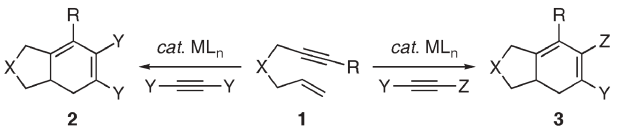
Transition metal-catalyzed carbocyclization reactions provide powerful and expeditious methods for the construction of complex polycyclic systems, which are generally not accessible *via* classical pericyclic reactions.[1] The metal-catalyzed [2 + 2 + 2] reaction of a tethered 1,6-diyne is representative of this class of transformations, and has been employed extensively as a tactic for the construction of various natural product skeletons.[2] Despite the myriad studies with 1,6-diynes,[3,4] the *crossed inter*molecular rhodium-catalyzed [2 + 2 + 2] carbocyclization with 1,6-enynes has not been forthcoming.[5–7] We envisioned that this type of carbocyclization would facilitate the rapid increase in molecular complexity, through the ability to introduce stereoelectronically orthogonal alkynes in a selective fashion. Herein, we now describe the rhodium-catalyzed *inter*molecular [2 + 2 + 2] carbocyclization of carbon and heteroatom tethered 1,6-enynes **1** with symmetrical and unsymmetrical alkynes, to afford the corresponding bicyclohexadienes **2** and **3** in a highly efficient and regioselective manner, respectively (Scheme 1).

The mechanistic hypothesis for the desired carbocyclization outlined in Scheme 2, draws from the seminal studies of others.[2–5] It was anticipated the terminal acetylenic C–H bond of the tethered enyne **i** should undergo an oxidative insertion to afford **ii**. Coordination of the free alkyne **iii** followed by hydrometallation should lead to the formation of **iv**, *en route* to the key metallacyclopentadiene **v**.[8] Intramolecular migratory insertion across the tethered alkene, followed by a reductive elimination of metallacycle **vi**, should then afford the [2 + 2 + 2] carbocyclization adduct **vii**. We reasoned that selective intermolecular [2 + 2 + 2] carbocyclization would be feasible, since alkyne **iii** should preferentially undergo hydrometallation with **ii**, provided the concentration of alkyne **iii** was such that it would avoid competition with the *intra*molecular migratory insertion of the alkene in **v**.



Scheme 2 Proposed catalytic cycle for the rhodium-catalyzed [2 + 2 + 2] carbocyclization reaction.

Preliminary studies tested this hypothesis by screening various reaction conditions, as outlined in Table 1. Treatment of the enyne **1a** (X = NTs, R = H) with silver triflate *modified* Wilkinson's catalyst in the presence of excess dimethyl acetylenedicarboxylate



Scheme 1 Crossed *inter*molecular metal-catalyzed [2 + 2 + 2] carbocyclization of 1,6-enynes with symmetrical and unsymmetrical alkynes.

Table 1 Development of the rhodium-catalyzed [2 + 2 + 2] carbocyclization reaction (Scheme 1; **1a** where X = NTs, R = H and Y/Y = CO_2Me)[a]

Entry	Conc. (mol/L)	Solvent	Temp. (°C)	Yield (%)[b]
1	0.10	EtOH	60	17
2	”	MeCN	”	42
3	”	PhH	”	80
4	0.50	”	”	57
5	0.05	PhH	60	95
6	”	”	40	48
7	”	”	80	82

[a] All reactions were carried out on a 0.25 mmol reaction scale utilizing 10 mol% of Wilkinson's catalyst [$RhCl(PPh_3)_3$] modified with 20 mol% of silver triflate with dimethyl acetylenedicarboxylate (3 equiv.) under an atmosphere of argon. [b] HPLC yield.

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† Electronic supplementary information (ESI) available: experimental procedures, X-ray crystallographic analysis of **3a**, and spectral data (IR, ^1H and ^{13}C-NMR) including High Resolution MS for **2a–i** and **3a**. See http://www.rsc.org/suppdata/cc/b5/b505383h/index.sht

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(Y/Y = CO_2Me) in ethanol at 60 °C, furnished the bicyclohexadiene **2a** in 17% yield (Entry 1). Additional studies examined the effect of solvent (Entries 1–3), concentration (Entries 3–5), and temperature (Entries 5–7), in an attempt to optimize for the desired carbocyclization reaction. Gratifyingly, the non-coordinating solvent benzene (0.05 M) at 60 °C proved optimum, affording **2a** in 95% yield (Entry 5).[9] Interestingly, the homodimerization adduct was not observed, whereas the product resulting from the competitive trapping of the metallacyclopentadiene **v** with a second equivalent of dimethyl acetylenedicarboxylate was produced in varying amounts, depending upon the concentration. Furthermore, the terminal acetylenic proton of the 1,6-enyne **1a** proved to be crucial for catalytic activity, since the corresponding substituted derivatives, where R = Me, Ph or TMS, did not afford any of the carbocyclization adduct.[3–5,7]

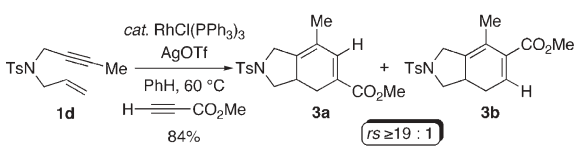
Table 2 Scope of the *inter*molecular rhodium-catalyzed [2 + 2 + 2] carbocyclization reaction (Scheme 1; where R = H)

Entry	1,6-Enyne **1**[a] X =		5,6-Bicyclohexadiene **2** Y/Y =		Yield (%)[b]
1	TsN	**a**	CO_2Me	**a**	92
2	”	”	COPh	**b**	84
3	”	”	$CONMe_2$	**c**	61
4	$C(CO_2Me)_2$	**b**	CO_2Me	**d**	85
5	”	”	COPh	**e**	74
6	”	”	$CONMe_2$	**f**	54
7	O	**c**	CO_2Me	**g**	84
8	”	”	COPh	**h**	81
9	”	”	$CONMe_2$	**i**	55

[a] All reactions were carried out on a 0.25 mmol reaction scale utilizing 10 mol% of Wilkinson's catalyst [$RhCl(PPh_3)_3$] modified with 20 mol% of silver triflate with the requisite 1,2-disubstituted alkyne (3 equiv.) under an atmosphere of argon.[9] [b] Isolated yield.

Table 2 outlines the examination of the influence of various tethers and the scope of alkyne substituents that are tolerated. This study demonstrated that nitrogen, carbon, and oxygen containing tethered enynes furnish the corresponding bicyclohexadienes **2a–i** in good to excellent yield. Examination of the alkyne scope revealed that the reaction was optimal for the 1,2-disubstituted alkynes bearing electron withdrawing groups, *i.e.* dimethyl acetylenedicarboxylate, *bis*-phenyl ketone and *bis*-dimethylamide, albeit slightly less efficient in the latter case. Interestingly, diphenylacetylene (Y/Y = Ph) furnished only a trace amount of the carbocyclization product, thereby confirming the necessity for a strongly electron withdrawing group on the alkyne.

In order to further demonstrate the potential synthetic utility of this transformation and the importance of a terminal alkyne, we elected to examine the regioselective version utilizing an unsymmetrical alkyne (eqn. 1).[10] Treatment of the 1,6-enyne **1d** with methyl propiolate in the presence of Wilkinson's catalyst *modified* with silver triflate, furnished the azabicycles **3a/3b** in 84% yield, in a highly regioselective manner (≥ 19 : 1 by NMR).[11] The regioselective outcome for this transformation was confirmed by X-ray crystallographic analysis of **3a**.§



(1)

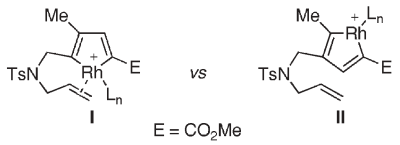


Fig. 1 Analysis of the plausible regioisomeric metallacycle intermediates.

The origin of the excellent regioselectivity can be rationalized by considering the putative metallacycle intermediates, as outlined in Fig. 1. We assume that provided the metallacycle intermediates are formed in an analogous manner outlined in Scheme 2, the 1,6-enyne **1d** with methyl 2-propiolate should lead to the formation of **I** and **II**, in which **II** would be unable to undergo the *intra*molecular carbocyclization due to geometrical constraints.[12] The efficiency of the carbocyclization and absence of homodimerization products are consistent with the notion that either the metallacycle formation is reversible, allowing the equilibration of **I** and **II**, or that **I** is formed exclusively. Additional studies are now underway to elucidate the origin of the regioselectivity.

In conclusion, we have developed a *crossed inter*molecular rhodium(I)-catalyzed [2 + 2 + 2] carbocyclization reaction with carbon and heteroatom tethered 1,6-enynes using symmetrical 1,2-disubstituted alkynes. This study demonstrates that a terminal alkyne is crucial for good reactivity, and the nature of the *bis*-carbonyl 1,2-substituted alkyne impacts on the overall efficiency of this transformation. Moreover, this study also illustrates that analysis of the putative metallacycle provides insight into controlling the regioselective *inter*molecular rhodium-catalyzed [2 + 2 + 2] carbocyclization with terminal alkynes. Finally, this work provides novel and exciting possibilities for the synthesis of bicyclohexadiene derivatives that are applicable to target directed synthesis.

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Notes and references

§ Crystal structure data for **3a**: $C_{18}H_{21}NO_4S$, colorless, monoclinic, $P2_1/c$, a = 5.9474(8) Å, b = 19.586(2) Å, c = 14.4749(18) Å, β = 97.260(4)°, V = 1672.6(4) Å^3, Z = 4, T = 119(2) K, ρ_{calc} = 1.380 Mg/m^3, μ = 0.216 mm^{-1}, GOF = 0.864, $R(F)$ = 0.0496 and $wR(F2)$ = 0.1169 for 2166 observed reflections $I > 4\sigma$, $2.5° \leqslant 2\theta \leqslant 27.5°$. CCDC 269096. See http://www.rsc.org/suppdata/cc/b5/b505383h/index.sht for crystallographic data in CIF or other electronic format.

1 For a recent review on metal-catalyzed carbocyclization reactions involving 1,*n*-enynes, see: C. Aubert, O. Buisine and M. Malacria, *Chem. Rev.*, 2002, **102**, 813 and pertinent references cited therein.

2 For recent reviews on metal-mediated [2 + 2 + 2] cyclizations, see: (*a*) M. Malacria, C. Aubert and J. L. Renaud, in *Science of Synthesis: Houben-Weyl Methods for Molecular Transformations*; M. Lautens and B. M. Trost, Eds.; Georg Thieme Verlag: New York, 2001; Vol. 1, pp. 439–530; (*b*) J. Varela and C. Saá, *Chem. Rev.*, 2003, **103**, 3787; (*c*) M. Fujiwara and I. Ojima, in *Modern Rhodium-Catalyzed Organic Reactions*; P. A. Evans, Ed.; 2005, Ch. 7, pp. 129–150 and pertinent references cited therein.

3 For pioneering work on the rhodium-catalyzed intermolecular [2 + 2 + 2] carbocyclization using tethered 1,6-diynes and 1,6-enynes, see: (*a*) R. Grigg, R. Scott and P. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1357; (*b*) R. Grigg, R. Scott and P. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1365.

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4 For some recent examples of intermolecular rhodium-catalyzed [2 + 2 + 2] carbocyclizations of tethered 1,6-diynes, see: (*a*) F. E. McDonald, H. Y. H. Zhu and C. R. Holmquist, *J. Am. Chem. Soc.*, 1995, **117**, 6605; (*b*) B. Witulski and T. Stengel, *Angew. Chem., Int. Ed.*, 1999, **38**, 2426; (*c*) H. Nishiyama, E. Niwa, T. Inoue, Y. Ishima and K. Aoki, *Organometallics*, 2002, **21**, 2572; (*d*) H. Kinoshita, H. Shinokubo and K. Oshima, *J. Am. Chem. Soc.*, 2003, **125**, 7784 and pertinent references cited therein.
5 For a recent example of a rhodium-catalyzed [2 + 2 + 2] dimerization of 1,6-enynes, see: C. H. Oh, H. R. Sung, S. H. Jung and Y. M. Lim, *Tetrahedron Lett.*, 2001, **42**, 5493.
6 For examples of an *inter*molecular metal-catalyzed [2 + 2 + 2] carbocyclization with various 1,6-enynes using symmetrical alkynes, see: (*a*) *Pd*: B. M. Trost and G. J. Tanoury, *J. Am. Chem. Soc.*, 1987, **109**, 4753; (*b*) *Ir*: S. Kezuka, T. Okado, E. Niou and R. Takeuchi, *Org. Lett.*, 2005, **7**, 1711.
7 (*a*) J. Ohshita, K. Furumori, A. Matsuguchi and M. Ishikawa, *J. Org. Chem.*, 1990, **55**, 3277; (*b*) L. D. Field, A. J. Ward and P. Turner, *Aust. J. Chem.*, 1999, **52**, 1085.
8 For a trans-hydrometalation with rhodium, see: (*a*) K. Tanaka and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 11492; (*b*) K. Tanaka and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 1607.
9 *Representative procedure for the rhodium-catalyzed [2 + 2 + 2] carbocyclization:* Wilkinson's catalyst (23.1 mg, 10 mol%) and silver triflate (12.8 mg, 20 mol%) were suspended in anhydrous benzene (4.0 mL) under an atmosphere of argon. The catalyst was then placed in a preheated oil bath at 60 °C for *ca.* 5 minutes, before dimethyl acetylenedicarboxylate (100.6 mg, 0.75 mmol) was added *via* a tared microliter syringe. In a separate flask, enyne **1a** (62.3 mg, 0.25 mmol) was dissolved in anhydrous benzene (0.5 mL), and placed in the 60 °C bath for *ca.* 5 minutes, before being transferred *via* Teflon® cannula to the preformed catalyst solution (2 × 0.25 mL rinse). The reaction mixture was allowed to stir at 60 °C for *ca.* 12 hours under an inert atmosphere of argon (t.l.c. control), before being concentrated *in vacuo* to afford the crude product as a brown solid. Purification by flash chromatography (gradient elution 20–40% ethyl acetate/hexanes) furnished the azabicycle **2a** (90 mg, 92%) as a white crystalline solid (mp 139–148 °C, dec.).
10 For an example of an *inter*molecular cobalt-mediated [2 + 2 + 2] carbocyclization with various 1,6-enynes using an unsymmetrical alkyne, see: C.-A. Chang, J. A. King, Jr. and K. P. C. Vollhardt, *J. Chem. Soc., Chem. Commun.*, 1981, 53.
11 The alkyne was added *via* syringe pump to avoid competitive dimerization of the enyne **1d**, which proved problematic for this particular carbocyclization.
12 For an example of complementary regiochemistry in metallacycle formation, see: K. Tanaka and K. Shriasaka, *Org. Lett.*, 2003, **5**, 4697.