Metal-Catalyzed Reactions

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Regiodivergent Ligand-Controlled Rhodium-Catalyzed [(2+2)+2] Carbocyclization Reactions with Alkyl Substituted Methyl Propiolates**

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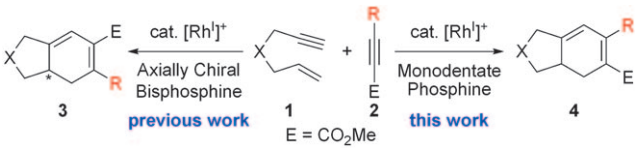
Dedicated to Professor Jack R. Norton on the occasion of his 65th birthday

The importance of transition metal-catalyzed reactions may be attributed, at least in part, to the manner in which they can control the formation of a specific product using ancillary ligands on the metal center.[1] In this context, metal-catalyzed [2+2+2] carbocyclization reactions present a formidable challenge with respect to controlling chemo-, regio-, and various aspects of stereoselectivity.[2–4] A fundamental objective in this area is the ability to predict and control the outcome of a specific transformation without recourse to extensive experimentation.[5] In a program directed towards the development and understanding of this type of transformation, we described the first regio- and enantioselective rhodium-catalyzed [(2+2)+2] carbocyclization of 1,6-enynes **1** with aryl substituted methyl propiolates **2** for the construction of bicyclohexa-1,3-dienes **3** (Scheme 1).[4,6] As a consequence of this study, we were intrigued by the factors that control regioselectivity and whether the ancillary ligands could be modified to switch the regioselective outcome to provide selective access to both regioisomers.[7]



Scheme 1. Regiodivergent rhodium-catalyzed [(2+2)+2] carbocyclization reactions.

Herein, we now describe the regiodivergent rhodium-catalyzed [(2+2)+2] carbocyclization of 1,6-enynes **1** with alkyl substituted methyl propiolates **2** for the construction of the bicyclohexa-1,3-dienes **3** and **4** (Scheme 1).[8,9] Furthermore, these studies provide another example of the detrimental role that silver salts have on selectivity in a metal-catalyzed reaction, which has important implications for development and rationalization of related higher-order carbocyclization reactions.[10]

Table 1 outlines the preliminary studies to probe the feasibility of the regiodivergent carbocyclization reaction. Treatment of the 1,6-enyne **1a** (X = NTs) and methyl 2-butynoate **2a** (R = Me, E = CO_2Me) with silver triflate modified Wilkinson's catalyst in benzene, furnished the bicyclohexa-1,3-dienes **4a** and **3a** in 90% yield, with 7:1 regioselectivity favoring **4a** (Table 1, entry 1). Although the selectivity was modest, the reaction provides the opposite regioselectivity to that obtained with an axially chiral phosphine ligand (see below).[4b] In order to further improve the selectivity we elected to examine the reaction under *salt-free* conditions using the cationic rhodium complex, [Rh-

Table 1: Optimization of the regioselective rhodium-catalyzed [(2+2)+2] carbocyclization reaction (Scheme 1; **1a** X = NTs, **2a** R = Me, E = CO_2Me).[a]

Entry	Rhodium complex	Ligand	Ratio of Rh:L	AgX[b]	Yield [%][c]	Ratio of **4a**:**3a**[d]
1	[Rh(PPh$_3$)$_3$Cl]	–	–	OTf	90	7:1
2	[Rh(cod)$_2$]OTf	PPh$_3$	1:1	–	57	1:1
3	[Rh(cod)$_2$]OTf	PPh$_3$	1:2	–	63	15:1
4	**[Rh(cod)$_2$]OTf**	**PPh$_3$**	**1:3**	**–**	**75**	**≥19:1**
5	[Rh(PPh$_3$)$_3$Cl]	–	–	OTf[e]	90	7:1
6	[Rh(PPh$_3$)$_3$Cl]	cod	1:2	OTf	42	5:1
7	[Rh(cod)$_2$]OTf	PPh$_3$	1:3	Cl	60	6:1
8	[Rh(cod)$_2$]OTf	PPh$_3$	1:3	OTf	45	7:1
9[f]	**[Rh(cod)$_2$]OTf**	**Xyl-binap**	**1:1.5**	**–**	**91**	**≤1:19**

[a] All reactions were carried out on a 0.25 mmol reaction scale utilizing 5 mol% of the rhodium catalyst in benzene at 60°C. [b] 5 mol%. [c] Yields of isolated products. [d] Ratios determined by 500 MHz ^{1}H NMR on the crude reaction mixture. [e] The insoluble silver salts were filtered through a 13 mm syringe filter with a 0.2 μm PTFE membrane prior to the introduction of **1a** and **2a**. [f] Reaction performed in tetrahydrofuran for solubility of the ligand.[13]

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$(cod)_2$]OTf (cod = cyclooctadiene), which obviates the need for the counterion exchange and thereby allows the reconstitution of the cationic version of Wilkinson's catalyst in the absence of silver salts.[10] Interestingly, this study clearly demonstrated the importance of the ligand stoichiometry (Table 1, entries 2–4) and the detrimental effect of the silver salts on regioselectivity. For example, the optimal reaction conditions provide the bicyclohexa-1,3-diene **4a** in 75% yield with ≥19:1 regioselectivity (Table 1, entry 4 vs. 1).[11] Although these conditions should provide the same active pre-catalyst, the absence of the residual silver salt clearly has an impact on the level of regiocontrol. Additional control experiments indicate that the partial solubility of both silver chloride and triflate are sufficient to provide lower selectivity (Table 1, entries 5–8).[10] Having established optimal reaction conditions for the formation of **4a**, we elected to reexamine the axially chiral phosphine ligands for the formation of **3a**, which had previously proven suboptimal.[4b,6] Gratifyingly, Xyl-binap (2,2′-bis[di(3,5-xylyl)phosphanyl]-1,1′-binaphthyl) proved to be the optimal ligand for the formation of bicyclohexa-1,3-diene **3a**, which was obtained in 91% yield with ≥19:1 regioselectivity (Table 1, entry 9), to provide a selective protocol for the more challenging alkyl substituted methyl propiolates.[12]

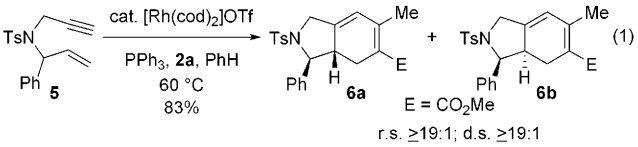
Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 4) to various tethers and substituted methyl propiolates to determine the scope and limitations of this transformation. This study demonstrates that nitrogen, carbon, and oxygen containing tethered enynes **1a–c** undergo the carbocyclization with exquisite regiocontrol with an array of straight chain and branched alkyl, including benzyl-protected hydroxymethyl-substituted methyl propiolates **2a–d**, to furnish the corresponding bicyclohexa-1,3-dienes **4a–l** in good to excellent yield. X-ray crystallographic analysis of the cycloadducts **4a** and **4d** allowed the correlation of the NMR spectra to confirm the regiochemical assignment in each case. *Overall, this work provides the first regiodivergent metal-catalyzed [(2+2)+2] carbocyclization reaction for the construction of novel bicyclohexa-1,3-dienes, which provide useful synthons for target directed synthesis.*[2–4]

Table 2: Scope of the intermolecular rhodium-catalyzed [(2+2)+2] carbocyclization reaction (Scheme 1; E = CO_2Me).[a]

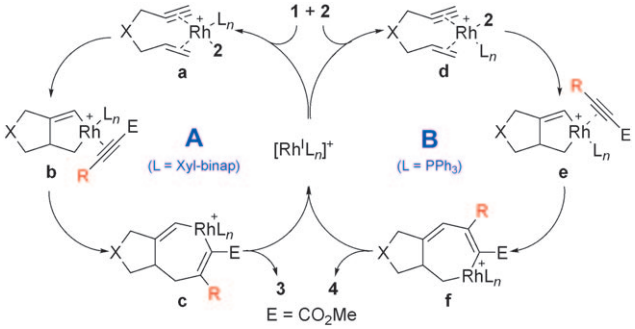
Entry	1,6-Enyne **1** X =		Alkyne **2** R =		Yield of **4** [%][b]		Ratio of **4**:**3**[c]
1	NTs	**a**	Me	**a**	75	**a**	≥19:1
2	NTs	**a**	*i*Pr	**b**	79	**b**	≥19:1
3	NTs	**a**	c-Pr	**c**	82	**c**	≥19:1
4	NTs	**a**	CH_2OBn	**d**	83	**d**	≥19:1
5	$C(CO_2Me)_2$	**b**	Me	**a**	77	**e**	≥19:1
6	$C(CO_2Me)_2$	**b**	*i*Pr	**b**	74	**f**	≥19:1
7	$C(CO_2Me)_2$	**b**	c-Pr	**c**	71	**g**	≥19:1
8	$C(CO_2Me)_2$	**b**	CH_2OBn	**d**	78	**h**	≥19:1
9	O	**c**	Me	**a**	71	**i**	≥19:1
10	O	**c**	*i*Pr	**b**	84	**j**	≥19:1
11	O	**c**	c-Pr	**c**	69	**k**	≥19:1
12	O	**c**	CH_2OBn	**d**	69	**l**	≥19:1

[a] All reactions were carried out on a 0.25 mmol reaction scale using 5 mol% of [Rh(cod)$_2$]OTf, modified with 15 mol% PPh_3 in benzene at 60°C under argon. [b] Yields of isolated products. [c] Ratios determined by 400 MHz ^{1}H NMR on crude reaction mixtures.

Additional studies focused on further enhancing the scope through the examination of the combined regio- and diastereoselective reaction. The phenyl-substituted 1,6-enyne **5** was selected to facilitate the direct comparison with prior investigations in related higher-order carbocyclization reactions. Whereas the silver salt modified Wilkinson's catalyst furnished the bicyclohexa-1,3-dienes **6a** and **6b** with poor regio- and stereocontrol, the salt-free conditions afforded **6a** in 83% yield with ≥19:1 regio- and diastereoselectivity [Eq. (1)].[14] X-ray crystallographic analysis of **6a** confirmed the regio- and stereochemical assignment, which is consistent with our related studies.



Outlined in Scheme 2 is a plausible mechanistic hypothesis for the regiodivergent behavior, which occurs as the result of switching the ancillary ligands. As illustrated, the first step in each of these processes is the formation of the metallabicyclopentene **b** and **e** from the oxidative addition of the metal into the 1,6-enyne **1**.[15] The divergence occurs for the preferential migratory insertion of the metal–alkyl bond in **b** to provide metallabicycloheptadiene **c** (cycle A), versus the metal–vinyl bond in **e** to provide the metallabicycloheptadiene **f** (cycle B).[16,17] Reductive elimination of the isomeric metallacycles provides the bicyclohexa-1,3-dienes **3** and **4**, respectively. The preferential migration of the metal–alkyl versus metal–vinyl bond is presumably the consequence of the axially chiral bidentate ligand preventing the necessary *cis*-alignment with the vinyl group in **b**, which promotes the generally less-favorable alkyl migration.[16,18]



Scheme 2. Proposed catalytic cycles for the regiodivergent rhodium-catalyzed [(2+2)+2] carbocyclization reaction.

In conclusion, we have described the regio- and diastereoselective intermolecular rhodium-catalyzed [(2+2)+2]

carbocyclization of carbon- and heteroatom tethered terminal 1,6-enyne derivatives with a range of alkyl substituted methyl propiolates. A key feature of this study is an intriguing mechanistic dichotomy that provides the ability to control the formation of either regioisomer through the judicious choice of the ancillary ligand. Central to this accomplishment was the realization that residual silver salts from the salt metathesis of the neutral complex have a detrimental effect on regio- and diastereoselectivity. We anticipate the ability to reverse the regiocontrol in this manner in conjunction with the elimination of unnecessary silver salts, provide fundamentally important considerations for future developments in this important area.

Experimental Section

$[Rh(cod)_2]OTf$ (5.9 mg, 0.0125 mmol) and triphenylphosphine (9.8 mg, 0.0375 mmol) were suspended in benzene (5 mL) under an atmosphere of argon. The catalyst mixture was warmed to 60 °C using a preheated oil bath and the mixture stirred for approximately 30 min to afford a homogeneous solution. Methyl-2-butynoate (**2a**; 73.5 mg, 0.75 mmol) was added through a tared microliter syringe, followed by the syringe pump addition of the 1,6-enyne **1a** (62.3 mg, 0.25 mmol) in benzene (1 mL) over approximately 2 h. The reaction was allowed to stir at 60 °C for an additional approximately 2 h (t.l.c. control), cooled to room temperature, and evaporated in vacuo to afford a crude oil. Purification by flash chromatography (eluting with a gradient of 10–30 % ethyl acetate/hexanes) furnished the bicyclohexa-1,3-diene **4a** (65.4 mg, 75 %) as a white crystalline solid.

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[1] a) P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741; b) P. W. N. M. van Leeuwen in *Homogeneous Catalysis: Understanding the Art*, Kluwer, Dordrecht, **2004**, pp. 10–25.

[2] For excellent reviews on metal-catalyzed [2+2+2] carbocyclizations involving 1,6-enynes, see: a) M. Malacria, C. Aubert, J. L. Renaud in *Science of Synthesis: Houben-Weyl Methods for Molecular Transformations*, *Vol. 1* (Eds.: M. Lautens, B. M. Trost), Thieme, New York, **2001**, pp. 439–530; b) P. A. Inglesby, P. A. Evans, *Chem. Soc. Rev.* **2010**, *39*, DOI: 10.1039/b913110h.

[3] For examples of metal-catalyzed and metal-mediated intermolecular [(2+2)+2] carbocyclizations of tethered 1,6-enynes with alkynes, see: a) **Co**: C.-A. Chang, J. A. King, Jr., K. P. C. Vollhardt, *J. Chem. Soc. Chem. Commun.* **1981**, 53; b) **Ir**: S. Kezuka, T. Okado, E. Niou, R. Takeuchi, *Org. Lett.* **2005**, *7*, 1711; c) **Pd**: B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1987**, *109*, 4753; Y. Yamamoto, S. Kuwabara, Y. Ando, H. Nagata, H. Nishiyama, K. Itoh, *J. Org. Chem.* **2004**, *69*, 6697; d) **Rh**: R. Grigg, R. Scott, P. Stevenson, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1365; C. H. Oh, H. R. Sung, S. H. Jung, Y. M. Lim, *Tetrahedron Lett.* **2001**, *42*, 5493; T. Shibata, Y. Arai, Y.-k. Tahara, *Org. Lett.* **2005**, *7*, 4955.

[4] a) P. A. Evans, J. R. Sawyer, K. W. Lai, J. C. Huffman, *Chem. Commun.* **2005**, 3971; b) P. A. Evans, K. W. Lai, J. R. Sawyer, *J. Am. Chem. Soc.* **2005**, *127*, 12466.

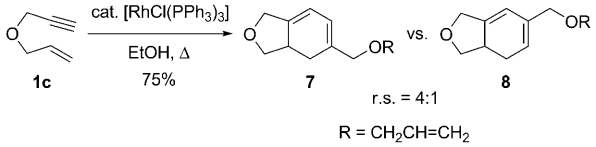
[5] For recent examples of DFT predicted metal-catalyzed carbocyclization reactions, see: a) Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 10060; b) H. Wang, J. R. Sawyer, P. A. Evans, M.-H. Baik, *Angew. Chem.* **2008**, *120*, 348; *Angew. Chem. Int. Ed.* **2008**, *47*, 342.

[6] Although the aryl substituted methyl propiolates undergo selective carbocyclization with axially chiral bidentate phosphines, the alkyl-substituted derivatives only proceed with modest regiocontrol. For example, the analogous enantioselective carbocyclization of **1a** with **2a** using the chiral complex derived from $[\{Rh(cod)Cl\}_2]$ and (*S*)-Xyl-P-Phos modified with $AgBF_4$, afforded **3a**/**4a** with 4:1 regioselectivity favoring **3a** with excellent enantioselectivity (90 % *ee*).[4b]

[7] For a recent example of ligand-controlled carbocyclization reactions, see: P. Mauleón, R. M. Zeldin, A. Z. González, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 6348.

[8] The term *regiodivergent*, adapted from Nógrádi's definition of *stereoconvergence*, refers to the formation of two isomeric products from the same starting material(s). M. Nógrádi in *Stereoselective Synthesis*, VCH, New York, **1996**.

[9] Although Oh et al. have reported the ability to switch the regiochemistry in the rhodium-catalyzed dimerization of 1,6-enynes, we have recently demonstrated that these reaction conditions provide the same regioisomer as originally reported by Grigg and co-workers, namely the formation of **7**. This misassignment by Oh is presumably the result of the analysis of the cycloadducts in $[D_1]$chloroform rather than $[D_6]$benzene.[3d]



[10] For other transition metal-catalyzed reactions that have implicated the silver salt for poor selectivity, see: a) F. Miyazaki, K. Uotsu, M. Shibasaki, *Tetrahedron* **1998**, *54*, 13073; b) T. M. Schmid, G. Consiglio, *Chem. Commun.* **2004**, 2318; c) K. C. Nicolaou, A. Li, D. J. Edmonds, G. S. Tria, S. P. Ellery, *J. Am. Chem. Soc.* **2009**, *131*, 16905.

[11] The monodentate ligands also switch the regioselectivity for the aryl-substituted methyl propiolates that were originally investigated.[4b] For example, treatment of enyne **1b** with methyl phenyl propiolate **2e** (R = Ph) under the optimal conditions, furnished the bicyclohexa-1,3-diene **4m** in 52 % yield and with ≥19:1 regioselectivity.

[12] Interestingly, the salt-free conditions dramatically improve the regioselective formation of the bicyclohexa-1,3-diene **3a** (X = NTs, R = Me), which is significantly lower in the presence of silver salts (r.s. = 4:1).[4b,6]

[13] The analogous carbocyclization reaction (Table 1, entry 1) in tetrahydrofuran furnished the bicyclohexa-1,3-diene **4a** in 76 % yield as the major regioisomer (r.s. = 4:1), which indicates the solvent is not playing a major role on the reversal of the regioselection.

[14] The origin of diastereocontrol is consistent with our previous studies and a related iridium-catalyzed [(2+2)+2] carbocyclization with a symmetrical alkyne.[2b,3b]

[15] For examples of selective formation of metallacyclopentenes in the presence of both alkynes and alkenes, see: M. Jeganmohan, C.-H. Cheng, *Chem. Eur. J.* **2008**, *14*, 10876.

[16] For selected examples of metal–vinyl versus metal–alkyl migratory insertion, see: a) Y. Wakatsuki, K. Aoki, H. Yamazaki, *J. Am. Chem. Soc.* **1979**, *101*, 1123; b) K. M. Doxsee, J. K. M.

Mouser, *Organometallics* **1990**, *9*, 3012; c) T. Shibata, Y.-k. Tahara, K. Tamura, K. Endo, *J. Am. Chem. Soc.* **2008**, *130*, 3451.

[17] For a recent example of the regioselective insertion of polarized alkynes to form metallacycles in which the electron-withdrawing group is adjacent to the metal, see: M. Paneque, C. M. Posadas, M. L. Poveda, N. Rendón, E. Álvarez, K. Mereiter, *Chem. Eur. J.* **2007**, *13*, 5160.

[18] For the rationalization of the geometry of metallacycles analogous to **b** and **e**, see: a) **cycle A**: C. E. Dean, R. D. W. Kemmitt, D. R. Russell, M. D. Schilling, *J. Organomet. Chem.* **1980**, *187*, C1; b) **cycle B**: J. B. Bleeke, W.-J. Peng, Y.-F. Xie, M. Y. Chiang, *Organometallics* **1990**, *9*, 1113, and references therein.

