Transition Metal-Catalyzed [5 + 2] Cycloadditions of Allenes and Vinylcyclopropanes: First Studies of Endo−Exo Selectivity, Chemoselectivity, Relative Stereochemistry, and Chirality Transfer

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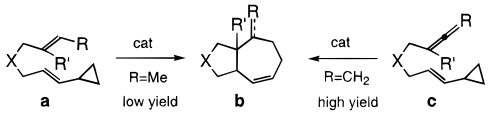
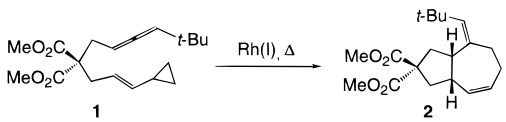
As part of our continuing studies of transition metal-catalyzed [$m + n$] cycloadditions,[1] we reported in 1995 the first examples of metal-catalyzed [5 + 2] cycloadditions between vinylcyclopropanes and alkynes.[2] More recently, this new class of reactions for seven-membered ring synthesis has been shown to proceed with high stereoselectivity and efficiency when mono- (**a**: R = R′ = H) and 1,1-disubstituted (**a**: R = H, R′ = Me) alkenes are used in place of alkynes.[3] In contrast, the use of 1,2-disubstituted alkenes (**a**: R = Me, R′ = H) resulted in complex mixtures,



putatively arising through competitive β-hydride elimination involving the intermediate metallacycles.[4] This is a major synthetic limitation since it precludes synthetic access to the carbocyclic cores of some of the largest natural product families (e.g., guaianes, pseudoguaianes, and tiglianes) and biologically most potent compounds known (e.g., phorbol esters[5] and resiniferatoxin[6]). We now report a general and efficient solution to this problem. Described herein are the first examples of the metal-catalyzed [5 + 2] cycloadditions[7] of vinylcyclopropanes and allenes[8] (**c** → **b**), the initial study of the stereoselectivity of these cycloadditions, and the first study of chirality transfer with a chiral allene.

Table 1. Cycloaddition of Allene−Vinylcyclopropane **1**



entry	catalyst	mol % Rh	solv	concn[a]	yield[b]
1	$RhCl(PPh_3)_3$	1	$PhCH_3$	0.1 M	96%
2	$RhCl(PPh_3)_3$	0.2	$PhCH_3$	1.0 M	90%
3	$[Rh(CO)_2Cl]_2$	1	DCE[c]	0.1 M	89%

[a] Concentration of **1**. [b] Isolated yield of **2**. [c] DCE = $ClCH_2CH_2Cl$.

Allene **1** was used as a reference substrate for the systematic investigation of reaction conditions (Table 1).[9] In the presence of 0.2 mol % $RhCl(PPh_3)_3$, allene−vinylcyclopropane **1** (0.1 M in toluene) gave after 5 h at 110 °C cycloadduct **2** in remarkably high *isolated* yield (96%). Importantly, only a *single* diastereomer was obtained with addition proceeding to the proximate alkene, away from the *tert*-butyl group, and with the formation of a cis-ring fusion.[10] The stereochemistry of cycloadduct **2** was assigned on the basis of an X-ray crystal structure of the diol derived from LAH reduction of **2**.[11] The cycloaddition of **1** proceeds efficiently with substrate concentrations ranging from 0.1 to 1.0 M and catalyst loads from 0.2−1 mol % (Table 1). At concentrations higher than 1.0 M, competing oligomerization processes begin to dominate. For this system, both $RhCl(PPh_3)_3$ and $[Rh(CO)_2Cl]_2$[12] work comparably well.

The scope of this new cycloaddition reaction was explored with a complete set of mono-, di-, and trisubstituted allenes (Table 2). In the presence of a catalyst system derived from 5 mol % $RhCl(PPh_3)_3$ and 5 mol % AgOTf, monosubstituted allene **3a** (entry 2) was converted to cycloadducts **4a** and **5a** (1.1:1, resp.) in 68% isolated yield.[13] Silver triflate is not a required additive, but in this and several other cases it is found to facilitate the reaction, putatively by opening a coordination site on the rhodium through precipitation of the chloride ligand. While these conditions provide the first example of a trans-fused 5,7-system arising in such [5 + 2] cycloadditions, *it is noteworthy that the ring fusion selectivity can be controlled by changing the catalyst system.* Thus, when substrate **3a** was slowly added to 10 mol % $[Rh(CO)_2Cl]_2$ in toluene/dichloroethane (6.5:1), only the cis-fused cycloadduct was obtained (entry 3). Substrate **3b** also underwent efficient cyclo-

(1) [4 + 4] Cycloadditions: Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678−4678. Wender, P. A.; Correia, C. R. D.; Ihle, N. C. *J. Am. Chem. Soc.* **1988**, *110*, 5904−5906. Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089−1094. [4 + 2] Cycloadditions: Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432−6434. Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843−1844. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962−2963. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824−825. Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255−1275.

(2) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721.

(3) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.. *J. Am. Chem. Soc.* **1998**, *120*, 1940−1941. Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. Pleuss, N. *Tetrahedron* **1998**, *54*, 7203−7220.

(4) For additional information pertaining to possible mechanistic pathways, see refs 2 and 3.

(5) For lead references and total synthesis, see: Evans, F. J., Ed. *Naturally Occurring Phorbol Esters*; CRC Press: Boca Raton, FL, 1986. Hecker, E.; Schmidt, R. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 377. Wender, P. A.; Kogen, H.; Lee, H-Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957−8958. Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897−7898.

(6) For lead references and total synthesis, see: Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976−12977.

(7) For general references to metal-catalyzed cycloadditions and seven-membered ring synthesis, see: refs 1−3. Nola, E.; Dzwiniel, T. L.; Schweibert, K. E.; Stryker, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 9702−9703. Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609. Wender, P. A.; Love, J. A. *Adv. Cycloaddit.*, **1999**, 1−45.

(8) For recent examples of metal-catalyzed reactions of allenes, see: Murakami, M.; Itami, K.; Ubukata, M.; Tsuji, I.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 4−5. Xiao, W. J.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1998**, *63*, 2609−2612. Brummond, K. M.; Wan, H. *Tetrahedron Lett.* **1998**, *39*, 931−934. Hashmi, A.; Ruppert, T. L.; Knofel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295−7304. Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843−1844.

(9) Substrate **1** is prepared in 81% yield by alkylation of dimethyl 2-(3′-cyclopropyl-2′-propen-1′-yl)-malonate with methanesulfonic acid 5,5-dimethyl-hexa-2,3-dienyl ester. The mesylate is derived from 5,5-dimethyl-hexa-2,3-dien-1-ol, which is prepared by the method of Lang and Hansen: Lang, R. W.; Hansen, H-J. *Org. Synth.* **1984**, 202. Details are provided in the Supporting Information.

(10) In a representative procedure, tris(triphenylphosphine)rhodium(I) chloride (0.1mol %) is added in one batch to a base-washed, oven-dried Schlenk flask under an argon atmosphere and is dissolved in freshly distilled, oxygen-free toluene (1.0 mL). The solution is stirred for 5 min at room temperature, after which ene-vinylcyclopropane **1** (42.3 mg, 0.132 mmol in 0.3 mL of toluene) is added over 10 s, and the solution is heated to 110 °C for 5 h. After cooling, the reaction mixture is filtered through a plug of alumina and concentrated. HPLC analysis of this mixture indicates that **2** is formed with >99% selectivity. Flash chromatography (silica gel, 10% ethyl acetate in hexane) gives cycloadduct **2** in 96% yield as a colorless oil.

(11) Details of the X-ray data for **2** are provided in the Supporting Information.

(12) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164−4165.

(13) The stereochemistry of **4a** was assigned on the basis of the nOe exhibited between the ring junction hydrogens. The stereochemistry of ring fusion isomer **4b** follows from this assignment.

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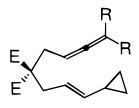
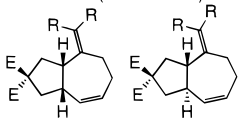
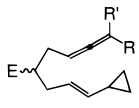
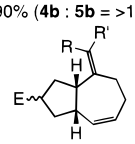
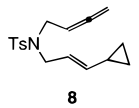
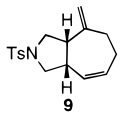
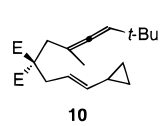
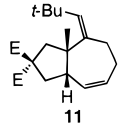
Table 2. Transition Metal-Catalyzed Intramolecular [5 + 2] Cycloadditions of Vinylcyclopropanes and Allenes

	Vinylcyclopropane-Allene[a]	Cycloadduct(s), Yield	Conditions, Time
	1	**2**	
1.	 **3**	89-96% (See Table 1)  **4** **5**	A, 5 h
2.	**a**: R = H	68% (**4a** : **5a** = 1.1 : 1)	B, 10 h
3.	**a**: R = H	83% (**4a** : **5a** = >20 : 1)	C, 3.5 h
4.	**b**: R = Me	92% (**4b** : **5b** = 2 : 1)	D, 1 h
5.	**b**: R = Me	90% (**4b** : **5b** = >10 : 1)	E, 0.75 h
	 **6**	 **7**	
6.	**a**: R = R' = Me	93%	F, 2 h
7.	**b**: R = *t*-Bu, R' = H	91%	F, 1 h
8.	**b**: R = *t*-Bu, R' = H	88%	D, 1 h
	 **8**	 **9**	
9.		85%	D, 0.5 h
10.		90%	F, 0.75 h
	 **10**	 **11**	
11.		70%	G, 16 h

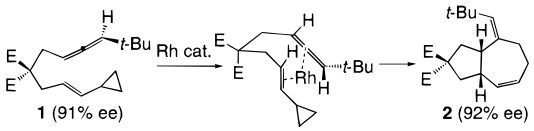
[a] E = CO_2Me. A; 0.2 mol % $RhCl(PPh_3)_3$, $PhCH_3$, 100 °C, 1.0 M. B: 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, $PhCH_3$, 100 °C, 0.01 M. C: 5 mol % $[Rh(CO)_2Cl]_2$, DCE, 90 °C, 0.003−0.01 M. D: 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, $PhCH_3$, 0.01 M. E. 10 mol % $Rh(CO)_2Cl$, $PhCH_3$, 110 °C, 0.01 M. F: 5 mol % $[Rh(CO)_2Cl]_2$, $PhCH_3$, 100 °C, 0.01 M. G: 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, $PhCH_3$, 100 °C, 0.01 M.

addition in the presence of $RhCl(PPh_3)_3$, providing cycloadducts **4b** and **5b** in a 2:1 ratio and in 92% yield (entry 4). As observed for **3a**, the use of $[Rh(CO)_2Cl]_2$ as the catalyst gave a marked improvement in the stereoselectivity of the cycloaddition.

Substrates **6a**, **6b**, and **8** (entries 6−10) were designed to determine whether a geminal-diester moiety in the tether is necessary for cycloaddition. As indicated, both **6a** and **6b** underwent efficient cycloaddition, providing cycloadducts **7a** and **7b** in high yield (>88%) as single ring junction isomers with a 1:1 ratios of ester epimers.[14] Likewise, a substrate bearing a nitrogen atom (**8**) in the tether is efficiently cyclized in the presence of $RhCl(PPh_3)_3$ to provide **9** in 85% isolated yield with >25:1 selectivity (entry 9).[15] This already high selectivity is further enhanced by the use of $[Rh(CO)_2Cl]_2$, which provides **9** in 90% yield as a single isomer (entry 10).

To explore access to naturally occurring bicyclo[5.3.0]decanes containing angular substituents, the cycloaddition of substrate **10** (entry 11) was examined. Notwithstanding the attendant development of a quaternary center, this substrate reacted to provide cis-fused cycloadduct **11** in good yield.[16]

A final point of both synthetic and mechanistic importance bearing on the selectivity of this cycloaddition pertains to whether the chirality of the allene can be transferred to the cycloadduct. To examine this point, allene **1**[17] was prepared in enantiomerically enriched form (91%ee). When treated with 1 mol % $RhCl(PPh_3)_3$ in toluene at 100 °C, *allene **1** was converted to **2** with complete retention of stereochemistry*.[18]



In summary, the rhodium-catalyzed intramolecular [5 + 2] cycloaddition of allenes and vinylcyclopropanes is shown to provide a general and efficient method for the synthesis of seven-membered rings. Reduction of or addition to the resultant exocyclic alkene provides products that cannot otherwise be accessed through the corresponding cycloaddition of alkenes. This reaction works with mono-, di-, and trisubstituted allenes and proceeds in good to excellent yields (68−96%) even when quaternary centers are formed. The reaction also works well with high substrate concentrations and low catalyst loads. The exo−endo selectivity of the process favors the formation of a cis-ring fusion. The level of selectivity can be controlled and amplified by the catalyst used. The cycloaddition is found to preferentially occur at the internal alkene of the allenyl system as would be expected from entropic considerations. In the case of the chiral allene studied, chirality is completely conserved in the course of the cycloaddition. Further studies on the development of this new reaction and its application in synthesis are in progress.

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Supporting Information Available: IR, NMR, and mass spectroscopy data for compounds **1**−**11** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The stereochemistries of **7a** and **7b** were determined by correlation with the monodecarboxylation products of **4b** and **2**, respectively.

(15) The cis-ring fusion stereochemistry of **9** was assigned by analogy to **2**, **4a**, **5a**, **7a**, and **7b**.

(16) The stereochemistry of **11** was assigned on the basis of the nOe exhibited between the angular methyl and the ring junction hydrogen.

(17) Chiral **1** was prepared as described in ref 8 using a chiral mesylate prepared by the method of Carreira: Carreira, E. M.; Hastings, C. A.; Shephard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622−6630.

(18) The enantiomeric excesses of **1** and **2** were determined using chiral HPLC analysis (CHIRALPAK-AD column). Details are provided in the Supporting Information.