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An efficient Rh-catalyst system for the intramolecular [4+2] and [5+2] cycloaddition reactions

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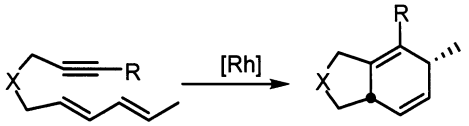
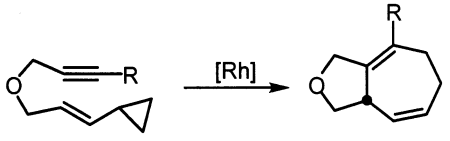
Abstract

A new Rh-catalyst system has been developed for the [4+2] and [5+2] cycloaddition reactions. This new system shows high reactivity at room temperature and the Rh-center bears tunable phosphine ligands. Up to 1000 turnovers have been obtained for the [4+2] cycloaddition reaction at room temperature. © 2000 Elsevier Science Ltd. All rights reserved.

Intramolecular cycloaddition of unactivated dieneynes or vincylcyclopropanes and alkynes by transition metals provides convenient access to 6,5 or 7,5-fused ring systems (Eqs. (1) and (2)). The resulting bicyclic structures are commonly encountered in a variety of designed and natural molecules and some of these products are difficult to construct without the aid of a transition metal complex.[1,2] An advantage of transition metal-catalyzed reactions is the potential to make new ring systems with multiple stereogenic centers in a single synthetic operation under mild reaction conditions. Recent advances in developing these types of reactions are quite impressive. Wender, Livinghouse, Trost and others have used different transition metals such as Ni,[3] Rh,[4,5] Ru[6] and Pd[7] to catalyze these reactions. Despite such significant progress, there is still a need to discover more efficient catalyst systems. For examples, the Rh-catalyzed cycloaddition sometimes requires high temperatures (e.g. 55°C for [4+2],[4a] 55–110°C for [5+2][5] cycloaddition with the Wilkinson compound as the catalyst), and some side products are formed depending on reaction conditions.[4d]



(1)



(2)

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An important advance in this area is the observation by Gilbertson[4d,f] that the catalyst system [Rh(DIPHOS)(CH_2Cl_2)n]SbF_6, generated by hydrogenation of a [Rh(NBD)(DIPHOS)]SbF_6 precursor in CH_2Cl_2, promotes [4+2] cycloaddition under mild conditions. Recently, we developed a more active Rh-catalyst, [Rh(bisphosphine)(substrate)]$^+$, to promote the Alder–ene reaction.[8] In this reaction, we found that the Rh-complex prepared by the Gilbertson's protocol gave no desired ene product.[8] We envisioned that the protocol developed by us for the Rh-catalyzed Alder–ene reaction may be efficient for promoting [4+2] and [5+2] cycloaddition reactions under mild conditions. This extension is based on the recognition that the [4+2],[4a] [5+2][5a] cycloaddition and the Alder–ene reaction[8] share in common with the cyclometallapentane intermediate III. Bosnich[9] has demonstrated the similar strategy for enhancing the reaction rate in the Rh-catalyzed hydroacylation reactions (Fig. 1).

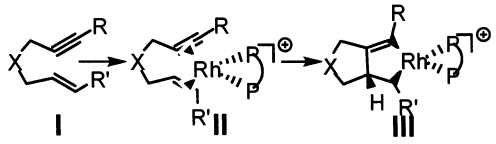
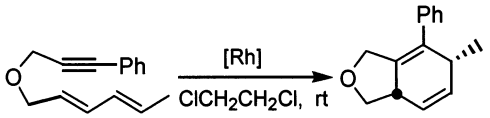


Figure 1. Mechanism of Rh-catalyzed [4+2] and [5+2] cycloaddition reaction

In an initial experiment, reaction of the dieneyne **3d** with 2.5% of [Rh(dppb)Cl]$_2$ was done in the presence of $AgSbF_6$ in 1,2-dichloroethane (DCE) at room temperature. After 10 minutes, cycloadduct **4d** was obtained in 99% yield as a single diastereomer.[10] Based on this finding, a number of phosphines were tested for the [4+2] cycloaddition reaction. Some experimental results are shown in Table 1. Interestingly, Rh complexes with a variety of electronically and sterically different phosphine ligands all had high reactivity and gave excellent yields (entries 1, 2, 5, 6). It is also noteworthy to point out that the cycloaddition occurs with a catalyst loading as low as 0.1 mol% at room temperature (entry 7). Such high turnovers (up to 1000) are useful for this type transformation. However, the reactivity decreased significantly with dppe and dppp

Table 1
Effect of phosphine ligands on the Rh-catalyzed intramolecular [4+2] cycloaddition reactions[a]



Entry	[Rh][c]	Time	Yield (%)	Entry	[Rh][c]	Time	Yield (%)
1	[Rh(dppm)]$^+$	10 min	98	5	[Rh(dppb)]$^+$	10 min	99
2	[Rh(dmpe)]$^+$	15 min	97	6	[Rh(dppbo)]$^+$	10 min	99
3	[Rh(dppe)]$^+$	4 h	86	7[b]	[Rh(dppb)]$^+$	4 h	93
4	[Rh(dppp)]$^+$	7 h	81	8	[Rh(dppb)(NBD)]$^+$	10 h	0

[a] The reaction was run in DCE with substrate (0.25 mmol, 0.1 M)/[Rh(bisphosphine)Cl]$_2$/$AgSbF_6$ = 1:0.0125:0.025 at room temperature. [Rh(I)(bisphosphine)]$^+$ was generated by adding $AgSbF_6$ to [Rh(bisphosphine)Cl]$_2$ in the presence of dieneyne substrate.

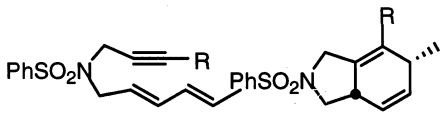
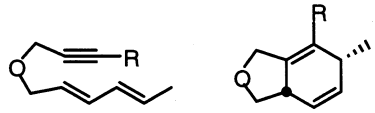
[b] The reaction was run using 0.1 mol% catalyst in 0.2 M DCE solution.

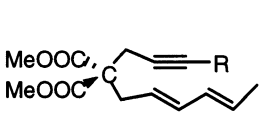
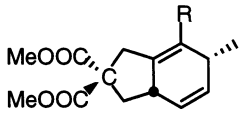
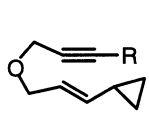
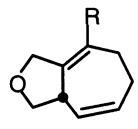
[c] dppm: bis-diphenylphosphinomethane; dmpe: 1, 2-bis-dimethylphosphinoethane; dppe: 1, 2-bis-diphenylphosphinoethane; dppb: 1, 4-bis-diphenylphosphinobutane; dppbo: 1,4-bis-diphenylphosphinyoxybutane.

and reaction required a longer time to reach good conversion. In the presence of 2,5-norbornadiene (NBD), the Rh(I) complex is not active for the reaction due to the competition between the NBD and substrate (entry 8).

By preparing a variety of substrates, the reaction scope was explored to establish the generality of the process and its applicability for synthetic problems. A variety of dieneyne substrates were converted to the corresponding cycloadducts in excellent yields at room temperature using the Rh–dppb catalyst. Our results show that this catalyst system can accept the oxygen, nitrogen or carbon tether in the substrate. Change of terminal substituents in the alkyne (entries 1–4, 6–10, 12–15) has little effect on the efficiency of the cycloaddition. Importantly, the catalyst loading can be decreased to 1 mol% and reaction still gave high yields in the short period of time due to the high reactivity of the catalyst (entry 5, 11, 16). To explore the utility of our catalyst system, we have investigated the Wender [5+2] cycloaddition reaction.[5] An important observation is that the new protocol permits Rh-catalyzed [5+2] cycloaddition to occur smoothly at room temperature. With the exception of the volatile product **8a**, cycloadditions proceeded in excellent isolated yield and products are clean. The catalyst is active and low catalyst loading (1 mol%) can be used (entry 23, Table 2).

Table 2
Rh-Catalyzed intramolecular [4+2] and [5+2] cycloaddition reactions[a]

Entry	Substrate	Product, Yield(%)	Time
			
	1	**4**	
1	a: R=H	95	1 hr
2	b: R=CH_3	95	1 hr
3	c: R=C_2H_5	93	1 hr
4	d: R=Ph	94	1 hr
5[b]	c: R=C_2H_5	99	1 hr
			
	3	**4**	
6	a: R=H	75[c]	10 min
7	b: R=CH_3	90	10 min
8	c: R=C_2H_5	89	10 min
9	d: R=Ph	99	10 min
10	e: R=$SiMe_3$	96	2 hr
11[b]	b: R=CH_3	92	1 hr

Entry	Substrate	Product, Yield(%)	Time
			
	5	**6**	
12	a: R=H	98	3 hr
13	b: R=CH_3	99	3 hr
14	c: R=C_2H_5	98	3 hr
15	d: R=Ph	98	3 hr
16[b]	d: R=Ph	98	5 hr
			
	7	**8**	
17	a: R=H	52[c]	2 hr
18	b: R=CH_3	91	1.5 hr
19	c: R=C_2H_5	92	1.5 hr
20	d: R=Ph	91	2 hr
21	e: R=$SiMe_3$	96	2 hr
22	f: R=COOMe	93	2 hr
23[b]	e: R=$SiMe_3$	97	3 hr

[a] The reaction was run in DCE with substrate (0.50 mmol, 0.1 M)/[Rh(bisphosphine)Cl]$_2$/$AgSbF_6$=1: 0.0125: 0.025 at room temperature. [Rh(I)(dppb)]$^+$ was generated by adding $AgSbF_6$ to [Rh(dppb)Cl]$_2$ in the presence of substrate. [b] The reaction was run using 1.0 mol% catalyst in 0.1 M DCE solution. [c] Low yield in this case due to product volatility.

In summary, we have developed a new Rh-catalyst system for the intramoleculer [4+2] and [5+2] cycloaddition reactions by generating coordinatively unsaturated Rh catalysts with substrates. The following attractive features of this system are: (1) easy variation of the bisphosphine ligand in $[Rh(bisphosphine)Cl]_2$ which allows fine-tuning of the Rh-catalyst to meet steric and electronic requirements of substrate; (2) high reactivity for both the [4+2] and [5+2] cycloadditions at room temperature (a turnover of up to 1000 has been achieved in one case); (3) excellent isolated yields were obtained with no detectable amount of side-products. Work toward developing an asymmetric variant of the [4+2] and [5+2] reactions is underway.

Acknowledgements

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References

1. For reviews and lead references on six-membered-ring natural products: (a) Devon, T. K.; Scott, A. *Handbook of Naturally Occurring Compounds*; Terpenes. Academic Press: New York, 1972; Vol. 2; (b) Fallis, A. G. *Acc. Chem. Res.* **1999**, *32*, 464.
2. For reviews and lead references on seven-membered-ring natural products: (a) Heathcock, C. M.; Graham, S. L.; Pirrung, M. C.; Paroac, F. In *Total Synthesis of Natural Products*; Apsimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5, p. 333; (b) Rigby, J. H. In *Studies in Natural Products Chemistry*; Atta-Ur-Rahman, Ed.; Elsevier Science Publishers B. V.: Amsterdan, 1988; Vol. 12, p. 233; (c) Fraga, B. M. *Nat. Prod. Rep.* **1996**, *13*, 307; (d) Wender, P. A.; Love, J. A. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Stamford, CT, 1999; p. 1; For Reviews of Transition Metal Catalyzed Cycloaddition Reactions: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49; (b) Dell, C. P. Comtem. *Org. Syn.* **1997**, *4*, 87.
3. **[4+2]**: (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432; (b) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843; (c) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824; (d) Wender, P. A.; Smith, T. E. *Tetrahedron* **1998**, *54*, 1255.
4. **[4+2]**: (a) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965; (b) Makinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145; (c) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843; (d) Gilberson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075; (e) O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, *443*; (f) Gilberson, S. R.; Hoge, G. S.; Genov, D. G. *J. Org. Chem.* **1998**, *63*, 10077.
5. **[5+2]**: (a) Wender, P. A. Takahashi, H.; Witulski, B. *J. Am. Chem Soc.* **1995**, *117*, 4720; (b) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940; (c) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203; (d) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164; (e) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348; (f) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442.
6. **[5+2]**: Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379.
7. **[4+2]**: Kumar, K.; Jolly, R. S. *Tetrahedron Lett.* **1998**, *39*, 3047.
8. Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490.
9. Fairle, D.; Bosnich, B. *Organometallics* **1988**, *7*, 936.
10. General procedure for the [4+2] and [5+2] cycloaddition reactions: In a glovebox, a dry 25 ml Schlenk tube is charged with **3d** (106 mg, 0.5 mmol), $[Rh(dppb)Cl]_2$ (7 mg, 0.0062 mmol) and DCE (5 ml). The reaction mixture was stirred for 1 min and followed by addition of $AgSbF_6$ (4.3 mg, 0.0124 mmol) at room temperature. The resulting orange solution was stirred at room temperature under nitrogen for 10 min. The reaction mixture was diluted with ether (5 ml) and fitered through celite to remove silver chloride, then conconcentrated and purified by flash chromatography (silical gel, 5% ether in hexane) to give a cycloadduct **4d** in 99% yield as a colorless oil.