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Reactions of Zirconacyclopentadienes with C═O, C═N, and N═N Moieties with Electron-Withdrawing Groups: Formation of Six-Membered Heterocycles

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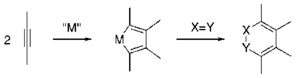
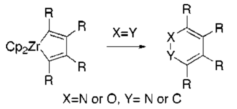
Formation of six-membered heterocycles by the reaction of metallacyclopentadienes prepared from two alkynes or diynes with unsaturated compounds −X═Y− is an attractive methodology in organic synthesis. However, only several examples have been reported for Co, Ni, and Rh.[1,2]



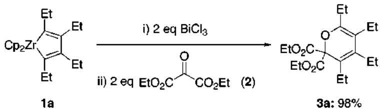
(1)

Zirconacyclopentadienes are very useful intermediates in organic synthesis, and they can be conveniently prepared from two different alkynes with high selectivity.[3] However, there is no example of six-membered heterocyclic compound formation from zirconacyclopentadienes, although five-membered heterocycles have been prepared by the reaction with dihalohetero compounds such as $RPCl_2$, R_2SnX_2, R_2GeX_2, $SOCl_2$, and BiX_3.[4] In this paper we would like to report the selective reaction of zirconacyclopentadienes with C═O, C═N, and N═N with electron-withdrawing groups for the formation of six-membered heterocycles such as pyran, pyridine, and dihydropyridazine derivatives.



(2)

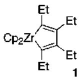
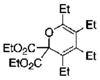
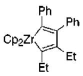
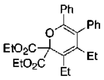
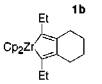
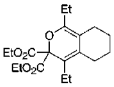
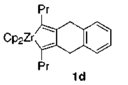
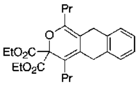
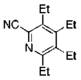
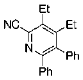
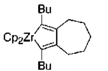
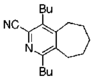
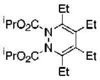
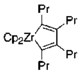
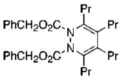
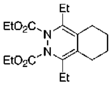
Reaction of zirconacyclopentadienes **1** with diethyl ketomalonate **2** gave α-pyrans in excellent yields in the presence of $BiCl_3$ as shown in eq 3. A typical procedure is as follows. To a THF solution of **1a** (1 mmol) was added $BiCl_3$ (2 mmol), and the solution was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C. To the mixture was added diethyl ketomalonate (2 mmol), and the mixture was stirred at the same temperature for 1 h. Pyran **3a** was formed in 98% (GC) yield. Zirconacyclopentadiene **1a** was completely consumed.



(3)

In the absence of $BiCl_3$, zirconacyclopentadienes did not react with diethyl ketomalonate. Zirconacyclopentadienes remained unreacted. In the presence of 2 equiv of CuCl, **3a** was formed in a lower yield (40%). Using other metal halides such as $NiCl_2(PPh_3)_2$, Me_2SnCl_2, $ZnCl_2$, or $AlCl_3$ did not produce the desired products. For the carbon−carbon bond formation reactions of zirconacyclopentadienes, transmetalation of zirconacyclopentadienes with metal salts is an effective protocol. We have recently reported that the transmetalation of zirconacyclopentadienes to Cu, Li, and Ni[5−7] is very useful for selective carbon−carbon bond formation in organic synthesis. For the α-pyran formation, we found the best metal salt to achieve excellent results was $BiCl_3$.

Table 1. One-Pot Preparation of Six-Membered Heterocycles from Zirconacyclopentadienes[a]

Zirconacyclopentadiene	Substrate	Metal salt	Product		Yield/%[b]
 **1a**	**2**	$BiCl_3$		**3a**	98(80)
 **1b**	**2**	$BiCl_3$		**3b**	93(72)
 **1c**	**2**	$BiCl_3$		**3c**	72(53)
 **1d**	**2**	$BiCl_3$		**3d**	76(53)
1a	**7**	—		**8a**	95 (85)
1b	**7**	—		**8b**	63 (51)
 **1e**	**7**	—		**8c**	86 (70)
1a	**10a**	CuCl		**11a**	(67)
 **1f**	**10b**	CuCl		**11b**	(51)
1c	**10c**	CuCl		**11c**	(65)

[a] Reactions were carried out at 0 °C for pyran formation and at −78 °C for pyridine and pyridazine formation. [b] GC or NMR yields. Isolated yields are given in parentheses.

The results are shown in Table 1. Unsymmetrical zirconacyclopentadiene **1b** prepared in situ from two different alkynes and Cp_2ZrEt_2 afforded **3b** as one regioisomer in 93% yield. The structure of **3b** was characterized by X-ray analysis. This structure clearly shows the regioselective formation of pyrans by the reaction of **1b** with **2**. Interestingly, bicyclic or tricyclic α-pyran derivatives **3c** and **3d** could be efficiently prepared by this procedure. 2,3-Diethyl-

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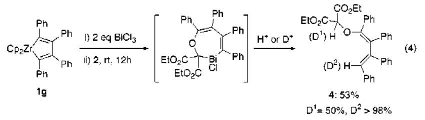
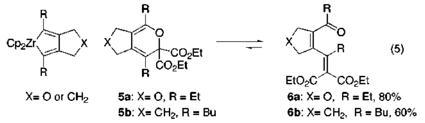
4,5-dithienylzirconacyclopentadiene also afforded the corresponding pyran in 45% isolated yield.

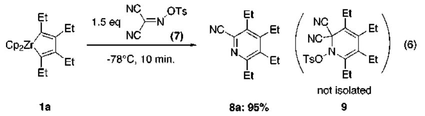
It is known that zirconacyclopentadienes react with $BiCl_3$ to give chlorobismole, which can be converted into phenylbismole.[4i] In fact, when $BiCl_3$ was added to 2,3,4,5-tetramethylzirconacyclopentadiene, the quantitative formation of Cp_2ZrCl_2 was observed. To check the formation of unstable chlorobismole in the reaction mixture, PhLi was added to it, and the formation of the phenylbismole was detected. Monitoring of the reaction of the chlorobismole with **2** showed the direct formation of the free pyran. The formation of oxabismacycles was not detected. The reaction of **1g** with **2** did not give a pyran product; instead, a dienolic ether **4** was obtained in 53% isolated yield. The reaction of **1g** with **2** followed by deuteriolysis with 20% DCl in D_2O afforded, after workup, a dideuterated compound with deuterium incorporation $D^1 = 50\%$, $D^2 > 98\%$ (eq 4). This result suggested the formation of an intermediate of seven-membered oxabismacycle via insertion of the C═O double bond and also indicated the sense of this novel insertion is such that the C−O bond was formed rather than the Bi−O bond. The structure of **4** was confirmed by X-ray analysis.



It was known that an α-pyran ring which bears a dienolic ether structure may undergo electrocyclic ring-opening to a dienone. When zirconacyclopentadiene fused with five-membered oxa or carbocycles was employed, the dienone tautomers **6a** and **6b** were obtained in 80% and 60% yields, respectively. This isomerization strongly depended on the structure and substituents of the α-pyran ring.

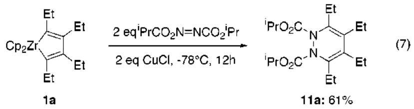


When 1.5 equiv of oximinosulfonate **7** was added to zirconacyclopentadiene **1a** in THF at −78 °C, the reaction proceeded smoothly to give **8a** in 95% GC yield within 10 min, and no cycloadduct of **9** was isolated (eq 6). A similar result was obtained even at −100 °C. Unlike the copper- or nickel-catalyzed or -mediated cycloaddition of zirconacyclopentadiene,[5,7] this reaction does not need any metal salt as a transmetalation reagent to increase the reactivity of zirconacycles.



The results are shown in Table 1. The corresponding pyridine compounds **8a**−**c** were obtained in good to high yields. Interestingly, bicyclic zirconacycle **1e** afforded cyclohepta[d]pyridine **8c** in 86% yield. Unsymmetrical zirconacycle **1b** reacted with oximinosulfonate regioselectively to give exclusively **8b** in 63% yield without formation of the 3,4-diphenyl-5,6-diethyl substituted regioisomer. Similar regioselectivity was obtained for the formation of pyridines from azazirconacyclopentadienes.[7c] The structure of **8b** was characterized by X-ray analysis.

The cycloaddition was also applied to the formation of substituted dihydropyridazines by the reaction of **1** with azodicarboxylate **10**. When **1a** was treated with 2 equiv of azodicarboxylate and 2 equiv of CuCl at −78 °C and stirred for 12 h, dihydropyridazine **11a** was formed in 61% yield (eq 7). The structure of **11c** was determined by X-ray analysis.



Supporting Information Available: Experimental details and spectroscopic characterization of new compounds, and structures, tables of crystallographic data, atomic coordinates, thermal parameters, bond lengths and angles for **3b**, **4**, **8b**, and **11c** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 753−770. (b) Shore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1152−1162.

(2) For cobalt-catalyzed cycloaddition, see: (a) Hong, P.; Yamazaki, H. *Synthesis* **1977**, 50−52. (b) Hong, P.; Yamazaki, H. *Tetrahedron Lett.* **1977**, *15*, 1333−1336. (c) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786−4800. (d) Wakatsuki, Y.; Yamazaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2715−2716. (e) Schulz, W.; Pracejus, H.; Oehme, G. *Tetrahedron Lett.* **1989**, *30*, 1229−1232. (f) Jerome, K. S.; Parsons, E. J. *Organometallics* **1993**, *12*, 2991−2993. (g) Saa, C.; Crotts, D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487−489. (h) Heller, B.; Oehme, G. *J. Chem. Soc., Chem. Commun.* **1995**, 179−180. For Ni: (i) Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 324−325. (j) Tsuda, T.; Kiyoi, T.; Miyane, T.; Saegusa, T. *J. Am. Chem. Soc.* **1988**, *110*, 8570−8572. (k) Tsuda, T.; Morikawa, S.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1989**, 9−10. (l) Tsuda, T.; Morikawa, S.; Hasegawa, N., Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2978−2981. For Rh: (m) Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P. *J. Mol. Catal.* **1987**, *40*, 337−357. (n) Diversi, P.; Ingrosso, G.; Lucherini, A.; Minutillo, A. *J. Mol. Catal.* **1987**, *40*, 359−377.

(3) For intermolecular cross-coupling reactions of alkynes with zirconocene, see: (a) Takahashi, T.; Swanson, R. D.; Negishi, E. *Chem. Lett.* **1987**, 623−626. (b) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870−2874. (c) Wagenen, B. C. V.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495−3498. (d) Xi, Z.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, *60*, 4444−4448.

(4) (a) Fagan, P. J.; Nugent, W. A. *J. Am. Chem. Soc.* **1988**, *110*, 2310−2312. (b) Buchwald, S. L.; Qun, F. *J. Org. Chem.* **1989**, *54*, 2793−2797. (c) Dufour, P.; Dubac, J.; Dartiguenave, Y. *Organometallics* **1990**, *9*, 3001−3003. (d) Buchwald, S. L.; Fisher, R. A.; Foxman, R. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 771−772. (e) Tour, J. M.; Wu, R. L.; Schumm, J. S. *J. Am. Chem. Soc.* **1990**, *112*, 5662−5663. (f) Mohamadi, F.; Spees, M. M. *Organometallics* **1992**, *11*, 1398−1400. (g) Spence, R. E. V. H.; Hsu, D. P.; Buchwald, S. L. *Organometallics* **1992**, *11*, 3492−3493. (h) Ashe, A. J., III; Kampf, J. W.; Al-Taweel, S. M. *J. Am. Chem. Soc.* **1992**, *114*, 372−374. (i) Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 1880−1889. (j) Ura, Y.; Li, Y.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1998**, *39*, 2787−2790. (k) Ura, Y.; Li, Y.; Tsai, F.; Nakajima, K.; Kotora, M.; Takahashi, T. *Heterocycles* **2000**, *52*, 1171−1189.

(5) For the reaction of zirconacyclopentadienes with organocopper, see: (a) Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672−1680. (b) Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N.; Nakajima, K. *Organometallics* **1994**, *13*, 4183−4185. (c) Takahashi, T.; Hara, R.; Nishihara, Y.; Kotora, M. *J. Am. Chem. Soc.* **1996**, *118*, 5154−5155. (d) Hara, R.; Liu, Y.; Sun, W.-H.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 4103−4106.

(6) For the reaction of zirconacyclopentadienes with organolithium, see: (a) Takahashi, T.; Huo, S.; Hara, R.; Noguchi, Y.; Nakajima, K.; Sun, W.-H. *J. Am. Chem. Soc.* **1999**, *121*, 1094−1095.

(7) For the reaction of zirconacyclopentadienes with nickel salts, see: (a) Takahashi, T.; Tsai, F. Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093−11100. (b) Wang, H.; Tsai, F. Y.; Takahashi, T. *Chem. Lett.* **2000**, 1410−1411. See also: (c) Takahashi, T.; Tsai, F. Y.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994−4995.

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