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Nickel-Catalyzed [3+1+1] Cycloaddition Reactions of Alkenyl Fischer Carbene Complexes with Methylenecyclopropanes

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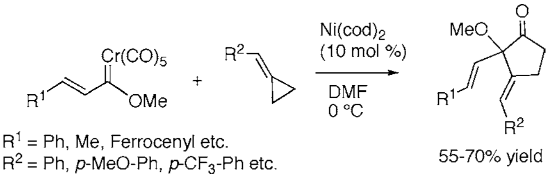
ABSTRACT



Methylenecyclopentanones were synthesized by the nickel-catalyzed [3+1+1] cycloaddition reactions of alkenyl Fischer carbene complexes with methylenecyclopropanes. The methylenecyclopropane was transformed into the C_2-symmetric bis-cyclopentapyridazine derivative by reacting with *p*-toluenesulfonyl hydrazine.

The Fischer carbene complex is one of the most versatile organometallic reagents for organic synthesis, and a number of novel reactions involving this complex have been reported.[1] There is increasing interest in transition metal mediated or catalyzed reactions of Fischer carbene complexes with alkynes,[2] allenes[3] leading to new forms of reactivity. On the other hand, methylenecyclopropanes (MCPs) have been widely utilized as useful building blocks in organic synthesis.[4] In particular, transition metal catalyzed reactions of MCPs have been used for the synthesis of complex organic molecules.[5] Thus, the reactions of Fischer carbene complexes with MCPs *mediated or catalyzed by transition metals* are expected to have great potential for the syntheses of highly functionalized organic molecules. However, so far, the reactions of these reactive species under photochemical and thermal conditions have appeared in only two reports.[6] Recently, de Meijere et al. reported the synthesis of cyclopentenone derivatives via cyclization reactions of MCPs with Fischer carbene complexes in thermal reaction conditions.[6b] As a transition metal is expected to catalyze reactions with MCPs at different reaction sites, we report herein the transition metal catalyzed [3+1+1] cycloaddition reactions of Fischer carbene complexes with MCPs.

Initially, pentacarbonyl[(1-methoxy-(2-phenyl)ethenylcarbene)]chromium(0) (**1**) was treated with phenylmethylenecyclopropane (**2**) in the presence of 1.1 equiv of Ni(cod)$_2$

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(1) (a) Special Issue: Carbene Chemistry: Bertrand, G., Ed. *J. Organomet. Chem.* **2005**, *690*, 5397. (b) Dötz, K. H.; Minatti, A. In *Transition Metals for Organic Synthesis*; Matthias, B., Bolm, C., Eds.; Wiley-VCH: Weiheim, Germany, 2004; p 397. (c) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591. (d) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271.

(2) (a) Barluenga, J.; Vicente, R.; López, L. A.; Rubio, E.; Tomás, M.; Álvarez-Rúa, C. *J. Am. Chem. Soc.* **2004**, *126*, 470. (b) Barluenga, J.; Barrio, P.; López, L. A.; Tomás, M.; García-Granda, S.; Alvarez-Rúa, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3008. (c) Göttker-Schnetmann, I.; Aumann, R. *Organometallics* **2001**, *20*, 346. (d) Göttker-Schnetmann, I.; Aumann, R.; Bergander, K. *Organometallics* **2001**, *20*, 3574.

(3) (a) Barluenga, J.; Vicente, R.; Barrio, P.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2004**, *126*, 5974. (b) Barluenga, J.; Vicente, R.; Barrio, P.; López, L. A.; Tomás, M.; Borge, J. *J. Am. Chem. Soc.* **2004**, *126*, 14354.

(4) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589.

(5) (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (b) Ohta, T.; Takaya, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, UK, 1991; Vol. 5, p 1185. (c) Nakamura, I.; Yamamoto, Y. *Adv. Synth., Catal.* **2002**, *344*, 111. (d) Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430. (e) Kurahashi, T.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7881. (f) Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc.* **2004**, *126*, 10540. (g) Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015. (h) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9597.

(6) (a) Hegedus, L. S.; Bates, R. W.; Söderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923. (b) Kurahashi, T.; Wu, Y.-T.; Meindl, K.; Rühl, S.; de Meijere, A. *Synlett* **2005**, 805.

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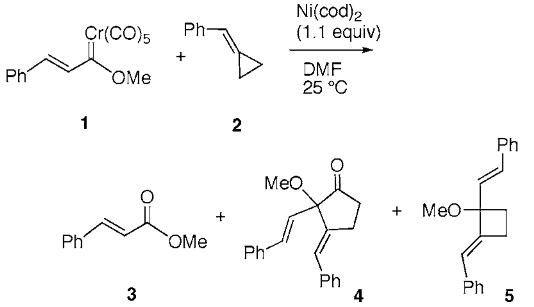
(cod: cyclooctadiene) in MeCN at 0 °C for 20 min. The major product methylcinnamate **3** showed 68% yield, whereas the minor product methylenecyclopentanone **4** was obtained in 15% yield (Table 1, entry 1).

Table 1. [3+1+1] Cycloaddition Reaction of Alkenyl Fischer Carbene Complex with Methylenecyclopropane



entry	solvent	temp (°C)	time (h)	yield of **3** (%)	yield of **4** (%)	yield of **5** (%)
1	MeCN	25	0.3	68	15	
2	toluene	25	2	66		
3	MeOH	25	1	68		
4	THF	25	1	62		21
5	DMF	25	0.3	23	35	
6	DMF	0	0.5	16	40	
7	DMF	−30	12	11	39	
8[a]	DMF	0	1.5	6	57	

[a] 10 mol % Ni(cod)$_2$ was employed.

4 was formed by [3+1+1] cyclization, which had incorporated carbon monoxide and the carbene carbon atom, and its structure was confirmed by the X-ray analysis (Figure 1).[7] As the [3+1+1] cycloaddition reaction was found to proceed, we next optimized the reaction conditions. Initially, we examined suitable solvent for this reaction and found that toluene and methanol are not suitable for this reaction (entries 2 and 3). When the solvent was switched from MeCN to THF, methylenecyclobutene **5**, which was formed by [3+1] cyclization[8] without incorporation of CO, was obtained instead of **4** (entry 4). Optimization revealed DMF to be the solvent of choice and 0 °C was the optimal reaction temperature (entries 5−7). We were pleased to find that the reaction proceeded with 10 mol % of Ni(cod)$_2$ to give the best result (entry 8). On the other hand, we also confirmed that the reaction failed to proceed in the absence of Ni(cod)$_2$ and a stoichiometric or catalytic amount (10 mol %) of Pd$_2$-dba$_3$ in DMF at 25 °C.

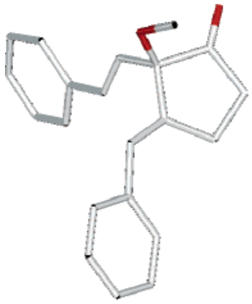
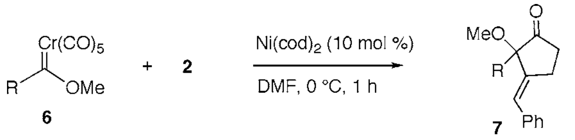
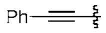
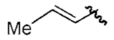
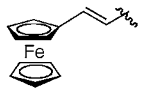
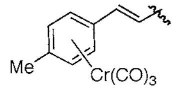


Figure 1. X-ray structure of **4**.

With the optimized catalytic [3+1+1] cycloaddition reaction in hand, we set out to define its generality by employing various Fischer carbene complexes **6** (Table 2).

Table 2. [3+1+1] Cycloaddition Reactions Utilizing Fischer Carbene Complex **6**



entry	R	product	yield (%)
1	PhCH$_2$CH$_2$-	–	No reaction
2		–	No reaction
3		**7a**	55
4		**7b**	51
5		**7c**	58

Since the α,*β*-unsaturated double bond does not participate in the transformation, we expected that the corresponding alkyl or alkynyl Fischer carbene complexes **6** would react with MCP **2** to give methylenecyclopentanone **7** (entries 1 and 2). However, the fact that these carbene complexes did not react under the optimized reaction conditions indicates that the alkenyl group may play a crucial role, such as stabilization of the intermediate of the cycloaddition reaction, although it does not participate in the transformation. On the other hand, when the substituents were switched to the *β*-position of the alkenyl carbene complex, the reaction proceeded in moderate yield regardless of the nature of R (entries 3−5).[9]

We next examined reactions of various types of MCPs (Table 3). MCP **8** with a monoaryl group possessing electron

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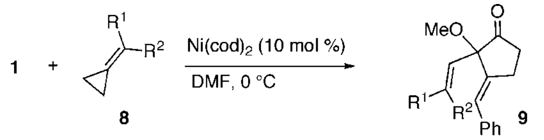
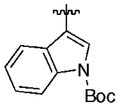
(7) $C_{21}H_{20}O_2$, $M = 304.37$, monoclinic, space group $P2_1$, $a = 9.214(5)$ Å, $b = 10.191(5)$ Å, $c = 9.606(7)$ Å, $\alpha = 90.00°$, $\beta = 111.68(3)°$, $\gamma = 90.00°$, $V = 838.2(9)$ Å^3, $Z = 2$, $\rho_c = 1.206$ g cm^{-3}, μ(Mo Kα) = 0.076 mm^{-1}, $F(000) = 324$, $T = 296.2$ K, colorless needle, 0.3 × 0.1 × 0.1 mm^3. The number of unique reflections was 2025. Data collection was carried out with the RIGAKU RAXIS RAPID, and SHELXL97 programs were used for the structure solution and refinement. R1/wR2 [$I > 2\sigma(I)$] = 0.0542/0.1403, CCDC no. 610945.

(8) [3+1] cyclization utilizing Fischer carbene complexes; see: Zora, M.; Herndon, J. W. *Organometallics* **1994**, *13*, 3370.

(9) α,*β*-Unsaturated methyl esters derived from carbene complexes **6** were obtained in 5−10% yields as the side products.

Table 3. [3+1+1] Cycloaddition Reactions Utilizing Methylenecyclopropanes **8**

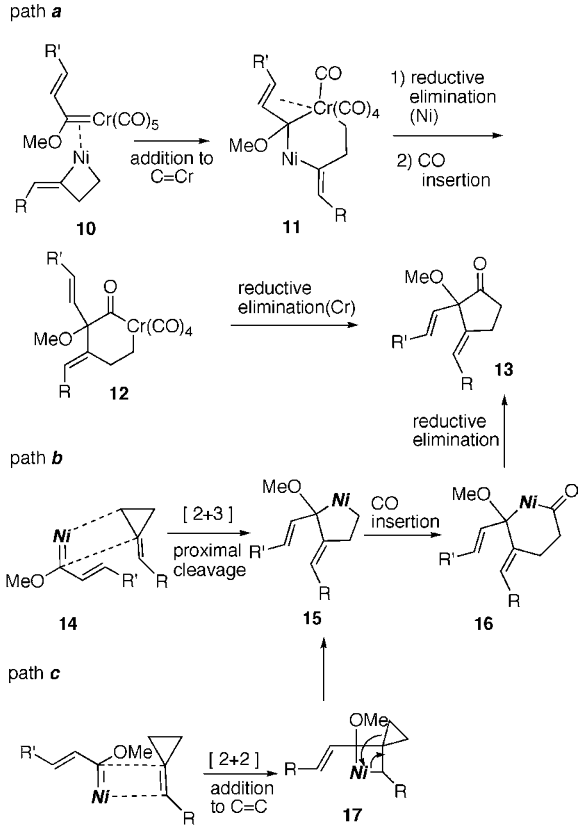


entry	MCPs **8**		product	yield (%)
	R^1	R^2		
1	*p*-tolyl	H	**9a**	69
2	*p*-MeO-phenyl	H	**9b**	71
3	*p*-NMe$_2$-phenyl	H	**9c**	43
4	*p*-chlorophenyl	H	**9d**	51
5	*p*-CF$_3$-phenyl	H	**9e**	43
6	 N Boc	H	**9f**	40
7	CO$_2$Et	H	–	No reaction
8	Ph	Ph	–	No reaction

donating or electron withdrawing substituents at the para position gave moderate to good yields (entries 1–5). The *N*-protected indole can also be utilized for the reaction (entry 6). However, MCPs with an ethoxy carbonyl group or diphenyl groups at the geminal position did not give the desired product (entries 7 and 8).

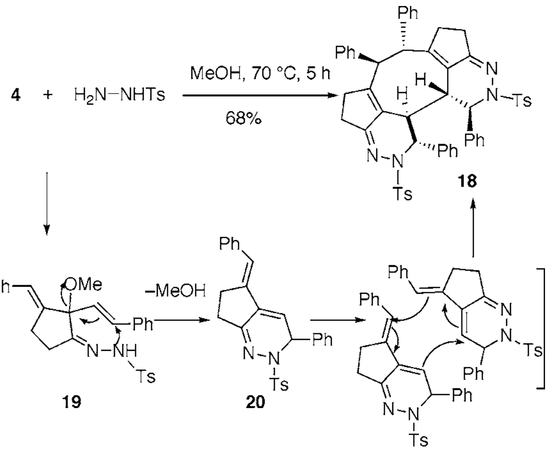
On the basis of these results, we proposed the following reaction mechanisms. Nickelacyclobutane **10**, which is generated by the oxidative addition of methylenecyclopropane to nickel(0), would add regioselectively to the carbon–chromium double bond while avoiding steric repulsion between a methylene group and a chromium pentacarbonyl group (path a). Reductive elimination from the resulting nickel-chromacyclohexane intermediate **11**, which might be stabilized by coordination of the olefin group as an internal ligand and subsequent CO insertion, gave chromacycle intermediate **12**. Reductive elimination from **12** gave product **13**. The second proposed mechanism would involve direct proximal C–C bond cleavage by the addition of nickel carbene complex **14** generated via carbene transfer reaction (Cr to Ni)[10] to form nickelacycle intermediate **15** (path b). Subsequent CO insertion would give intermediate **16**, and reductive elimination would give product **13**. The third proposed mechanism is shown in path c. Initially, the [2+2] addition reaction between the carbene and methylene groups would give nickelacyclobutane intermediate **17**, and subsequent ring expansion would give the same intermediate **15** as in path b. It is still unclear whether Ni(cod)$_2$ reacts primarily with the methylenecyclopropane or with the chromium carbene complex. The carbene dimerization due to the formation of the nickel carbene complex could not be observed even at −30 °C; however, the possibility of the nickel carbene complex cannot be ruled out.

Scheme 1. Proposed Mechanisms



We next examined further organic transformations utilizing the obtained methylenecyclopentanone **4**. **4** was treated with *p*-toluenesulfonyl hydrazine in methanol at 70 °C for 5 h (Scheme 2). Interestingly, C_2-symmetric bis-cyclopentapyridazine derivative **18** was obtained in 68% yield as a single diastereomer whose bonding scheme was confirmed by preliminary X-ray analysis (Figure 2).[11]

Scheme 2. Diastereoselective [4+4] Dimerization Reaction Utilizing Methylenecyclopentanone **4**



C_2-Symmetric bis-cyclopentapyridazine derivative **18** would be obtained by dehydrative condensation followed by internal

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(10) Gómez-Gallego, M.; Mancheño, M. J.; Sierra, M. A. *Acc. Chem. Res.* **2005**, *38*, 44 and references cited therein.

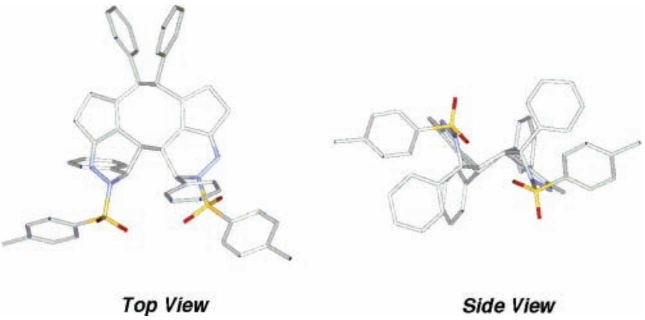

Figure 2. X-ray structure of **18** (two $CHCl_3$ solvent molecules have been omitted for clarity).

S_N2' reaction of the resulting **19** to form methylenecyclopentapyridazine **20**. Subsequent regio- and diastereoselective dimerization via [4+4] cycloaddition[12] of **20** gave **18** with an eight-membered ring as the single diastereomer. Since **18** has both nitrogen atoms and C_2-symmetry, it is expected to be potentially useful for some asymmetric reactions as a ligand.

In conclusion, we have developed the nickel-catalyzed [3+1+1] cycloaddition reaction of alkenyl Fischer carbene complexes with methylenecyclopropanes. Stereoselective synthesis of the quaternary chiral center of the product and application to the asymmetric reaction utilizing C_2-symmetric bis-cyclopentapyridazine derivatives are underway in our laboratory.

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Supporting Information Available: The general procedure for the nickel-catalyzed [3+1+1] cycloaddition reactions, their characterization and NMR spectra, and CIF files of complexes **4** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) $C_{56}H_{50}Cl_6N_4O_4S_2$, $M = 1119.82$, monoclinic, space group $P2_1/n$, $a = 14.894(7)$ Å, $b = 25.242(13)$ Å, $c = 19.300(8)$ Å, $\alpha = 90.00°$, $\beta = 110.11(4)°$, $\gamma = 90.00°$, $V = 6814(6)$ Å^3, $Z = 4$, $\rho_c = 1.092$ g cm^{-3}, μ(Mo Kα) $= 0.353$ mm^{-1}, $F(000) = 2320$, $T = 296.2$ K, colorless block, $0.7 \times 0.3 \times 0.3$ mm^3. The number of unique reflections was 15238. Data collection was carried out using the RIGAKU RAXIS RAPID, and SHELXL97 programs were used for the structure solution and refinement. R1/wR2 [$I > 2\sigma(I)$] = 0.2166/0.5352, CCDC no. 610946.

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