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Novel Thermal Reaction of Fischer Carbene Complexes with Imines: Synthesis of *β*-Methoxy Allylic Amine Derivatives

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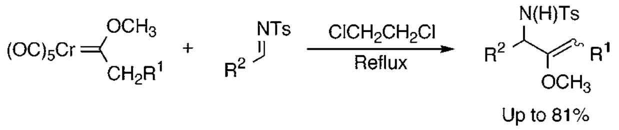
ABSTRACT



Alkyl-substituted chromium Fischer carbene complexes were found to react with various *N*-tosylimines to give *β*-methoxy allylic amine derivatives under thermal conditions. This result is essentially distinct from the photochemical outcome in which *β*-lactam derivatives are obtained.

From their first synthesis by E. O. Fischer and A. Maasböl,[1] Fischer carbene complexes of group six metals have attracted the interest of organic chemists, as well as of organometallic chemists. Due to their unique reactivities, a large number of carbon−carbon bond-forming reactions have been developed[2] and have been applied to total synthesis of natural products.[3] The Fischer carbene complexes thus have been established as useful tools for organic synthesis.

Our interest in the reaction of the carbene complexes with imines resulted in the development of novel [3 + 2] cycloaddition reactions. Treatment of alkenyl carbene complexes with imines in the presence of 20 mol % GaCl$_3$ afforded trans-2,5-disubstituted 3-pyrroline derivatives in good yields.[4,5]

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(1) Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 580.

(2) For reviews, see: (a) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, Chapter 5, p 1065. (b) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999; Chapter 2, p 13. (c) Brown, F. J. *Prog. Inorg. Chem.* **1980**, *27*, 1. (d) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (e) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 5.3, p 469. (f) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271. (g) Hegedus, L. S. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 5.4, p 549. (h) Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105.

(3) For example, benzannulation (refs 2e,f) and photochemical formation of ketene−chromium complex (refs 2g,h) were utilized for synthesis of dihydrovitamin $K_{1(20)}$ and (+)-tetrahydrocerulenin, respectively. For the dihydrovitamin $K_{1(20)}$ synthesis, see: (a) Dötz, K. H.; Pruskil, I. *J. Organomet. Chem.* **1981**, *209*, C4. (b) Dötz, K. H.; Pruskil, I.; Mühlemeier, J. *Chem. Ber.* **1982**, *115*, 1278. For the (+)-tetrahydrocerulenin synthesis, see: (c) Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779.

(4) (a) Kagoshima, H.; Akiyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 11741. (b) Kagoshima, H.; Okamura, T.; Akiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 7182.

(5) Thermal reactions of carbene complexes with imines have been examined by other groups. For reactions of acyloxy and alkoxy carbene complexes with imines, see: (a) Murray, C. K.; Warner, B. P.; Dragisich, V.; Wulff, W. D. *Organometallics* **1990**, *9*, 3142. For cyclizations of the carbene complexes with α,*β*-unsaturated imines, see: (b) Danks, T. N.; Velo-Rego, D. *Tetrahedron Lett.* **1994**, *35*, 9443. (c) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; López-Ortiz, F. *J. Chem. Soc., Chem. Commun.* **1994**, 321. (d) Barluenga, J.; Tomás, M.; López-Pelegrín, J. A.; Rubio, E. *J. Chem. Soc., Chem. Commun.* **1995**, 665. (e) Barluenga, J.; Tomás, M.; Rubio, E.; López-Pelegrín, J. A.; García-Granda, S.; Pertierra, P. *J. Am. Chem. Soc.* **1996**, *118*, 695. (f) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Carbajo, R. J.; López-Ortiz, F.; García-Granda, S.; Pertierra, P. *Chem. Eur. J.* **1996**, *2*, 88. (g) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Suárez-Sobrino, A. *J. Org. Chem.* **1997**, *62*, 9229. (h) Barluenga, J.; Tomás, M.; Rubio, E.; López-Pelegrín, J. A.; García-Granda, S.; Priede, M. P. *J. Am. Chem. Soc.* **1999**, *121*, 3065 and references therein.

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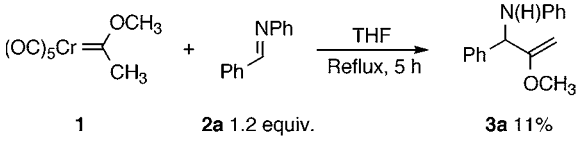
We further investigated reactions of Fischer carbene complexes with imines and have recently found that alkyl-substituted carbene complexes of chromium react with imines to give β-methoxy allylic amine derivatives.

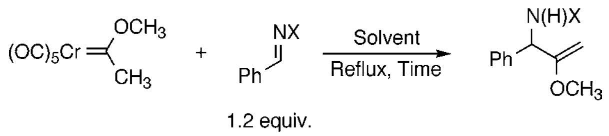
At first, we examined reaction of methyl carbene complex **1** with *N*-benzylideneaniline **2a** (Scheme 1); complex **1** was treated with 1.2 equiv of **2a** in THF, and the solvent was refluxed under a nitrogen atmosphere. After confirmation that the starting complex had disappeared by TLC analysis, the reaction mixture was filtered through a small pad of silica gel. Purification of the crude product by preparative TLC showed that β-methoxy allylic amine derivative **3a** was generated, albeit in 11% yield.[6]

Scheme 1



We next examined *N*-substituents and solvents (Table 1). Use of an *N*-tosylimine **4a** increased the yield of the corresponding allylic amine derivative **5a** (32%, entry 2), although use of an *N*-(*p*-methoxyphenyl)imine **6a** gave no identifiable products (entry 3). Among the solvents examined, 1,2-dichloroethane gave the best result,[7] whose yield reached up to 73% (entry 7).[8]

Table 1. Examination of *N*-Substituent and Solvent

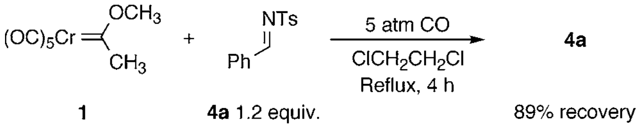


entry	X (imine)	solvent, time	yield (product)
1	Ph (**2a**)	THF, 5 h	11% (**3a**)
2	Ts[a] (**4a**)	THF, 6.5 h	32% (**5a**)
3	C_6H_4(*p*-OMe) (**6a**)	THF, 9 h	–
4	Ts (**4a**)	CH_3CH_2CN, 0.5 h	–
5	Ts (**4a**)	1,4-dioxane, 1 h	44% (**5a**)
6	Ts (**4a**)	toluene, 1 h	60% (**5a**)
7	Ts (**4a**)	$ClCH_2CH_2Cl$, 4 h	73% (**5a**)

[a] Ts = *p*-toluenesulfonyl.

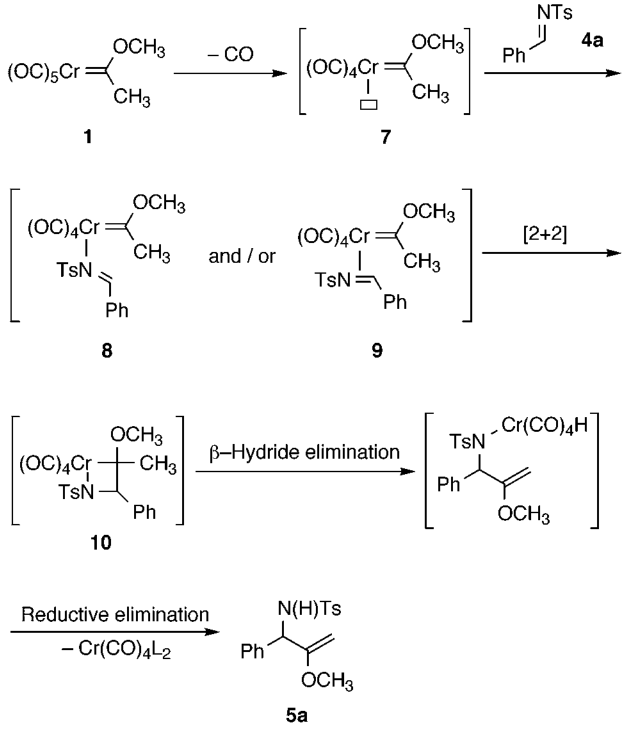
This reaction was found to be significantly affected by a CO atmosphere (Scheme 2). When the reaction of complex **1** and imine **4a** was carried out under 5 atm of CO pressure, the starting imine **4a** was recovered in 89% yield.[9] This fact strongly suggests that dissociation of carbonyl ligand is essential.[10]

Scheme 2



Taking this result into consideration, we now suppose that the reaction proceeds as follows (Scheme 3): thermal dissociation of carbonyl ligand from the starting complex **1** gives coordinatively unsaturated species **7**. Species **7** forms σ-complex **8** and/or π-complex **9** with imine **4a**,[11] which undergo(es) [2 + 2] cyclization to give azachromacyclobutane intermediate **10**. Intermediate **10** undergoes β-hydride elimination followed by reductive elimination to give the product **5a**.[12,13]

Scheme 3



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(6) No identifiable products besides **3a** were isolated.

(7) *N*-Benzylideneaniline gave unsatisfactory results even in 1,2-dichloroethane solvent. Reaction of complex **1** and imine **2a** in 1,2-dichloroethane took as much as 32 h to complete, and the yield of the product **3a** was less than 10%.

(8) In all of the cases listed in Table 1, the starting complex **1** had disappeared completely. No identifiable products other than the allylic amine products were isolated.

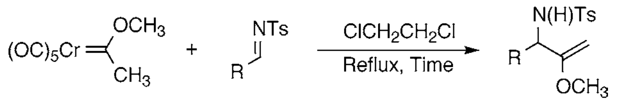
(9) We were unable to recover the starting complex **1**.

(10) Reaction of the tungsten complex corresponding to **1** with **4a** also resulted in failure, i.e., no conversion of the starting complex (TLC analysis). This result also suggests that carbonyl dissociation is necessary for the reaction. The bond energy of M−CO is 179 kJ/mol for $W(CO)_6$ but only 107 kJ/mol for $Cr(CO)_6$.

(11) We suppose that the *N*-sulfonyl group promotes this coordination step because an electron-withdrawing group makes back-donation from metal to imine more facile.

This reaction could be applied to various *N*-tosylimines (Table 2).[14] Both aromatic and aliphatic imines afforded the corresponding products in good yields.[15]

Table 2. Reaction of Various Imines with Methyl Carbene Complex **1**

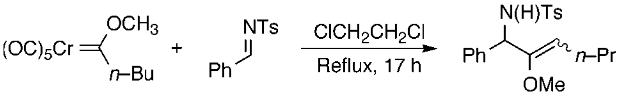


1 **4** 1.2 equiv. **5**

entry	R (**4**)	time	yield of **5**
1	Ph (**4a**)	4 h	73% (**5a**)
2	1-Naphthyl (**4b**)	6 h	80% (**5b**)
3	C_6H_4(*p*-Cl) (**4c**)	4 h	76% (**5c**)
4	C_6H_4(*p*-CN) (**4d**)	5 h	72% (**5d**)
5	*p*-Tolyl (**4e**)	7 h	69% (**5e**)
6	*n*-Bu (**4f**)	12 h	73% (**5f**)
7	*i*-Pr (**4g**)	9 h	81% (**5g**)
8	*c*-Hex (**4h**)	11 h	63% (**5h**)

We could also obtain a γ-substituted allylic amine derivative by using butyl carbene complex **11** (Scheme 4). When **11** was treated with **4a** under the same conditions as those for complex **1**, the corresponding allylic amine derivative **12** was obtained in 46% yield as a 58:42 diastereomeric mixture.[16]

Scheme 4



11 **4a** 1.2 equiv. **12** 46%, dr = 58:42

It is well-established that Fischer carbene complexes of chromium react with imines to give β-lactam derivatives under photochemical conditions.[2g,h] This reaction is supposed to proceed via ketene−chromium complexes. On the other hand, as described above, the carbene complexes thermally undergo carbonyl dissociation to give coordinatively unsaturated species, which react with imines to give β-methoxy allylic amine derivatives. That is, it is revealed that distinct reactive species were generated according to the reaction conditions.[17]

In contrast to photochemical reactions, thermal reaction of the carbene complexes with imines has not been fully established. The reaction described in this manuscript is, indeed, a novel example of thermal reaction of the chromium carbene complexes.

In conclusion, we could develop a novel synthesis of β-methoxy allylic amine derivatives utilizing thermal reaction of chromium carbene complexes with *N*-tosylimines.

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Supporting Information Available: Spectral data (^{1}H NMR, ^{13}C NMR, IR, and elemental analysis) for all of the products listed in Table 2 and Scheme 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) We cannot exclude the following alternative mechanism: **10** undergoes reductive elimination to give an aziridine intermediate. The aziridine intermediate affords the β-methoxy allylic amine product by ring-opening reaction.

(13) H. -U. Reissig and his co-worker described the same kind of mechanism for their insertion reaction of a carbene ligand into an olefinic C−H bond. See: Wienand, A.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1129.

(14) **Typical Procedure:** A 1,2-dichloroethane solution (2 mL) containing the carbene complex **1** (25 mg, 0.10 mmol) and imine **4a** (31 mg, 0.12 mmol) was refluxed for 4 h. After confirmation that complex **1** was consumed completely by TLC analysis, the reaction mixture was filtered through a small pad of silica gel using dichloromethane as an eluent. The filtrate was concentrated and purified by preparative TLC (silica gel, 30:1:3 toluene/AcOEt/NEt_3) to afford the β-methoxy allylic amine product **5a** (23 mg, 73%).

(15) We suppose that the products are stable under the reaction conditions. For example, when *p*-tolylimine **4e** was heated with complex **1** for 24 h, the allylic amine derivative **5e** was obtained in 68% yield.

(16) Geometry of the carbon−carbon double bond was not determined.

(17) It is supposed that irradiation of carbene complexes causes metal-to-ligand charge transfer, which promotes formation of ketene−chromium complexes (See ref 2h). On the other hand, we suppose that thermal dissociation of the carbonyl ligand takes place when the carbene complex is heated.