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REGIOSELECTIVITY OF THE REACTION OF A CHROMIUM-CARBENE COMPLEX WITH ALKYNES: EXAMINATION OF STERIC AND ELECTRONIC FACTORS

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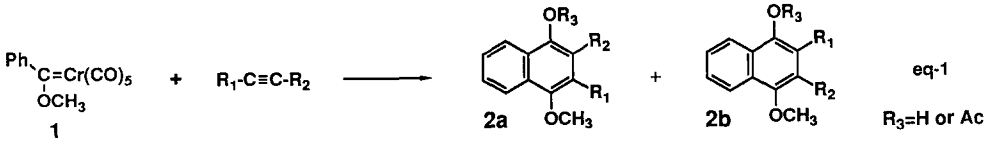
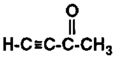
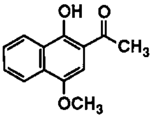
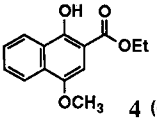
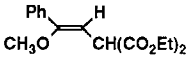
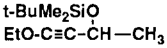
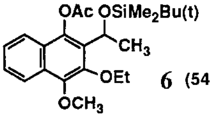
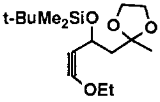
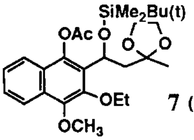
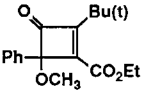
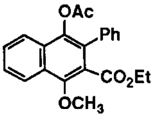
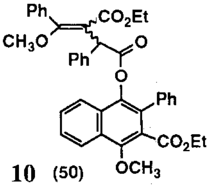
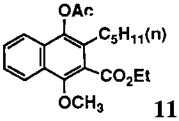
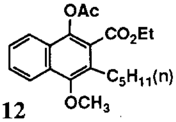
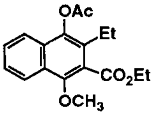
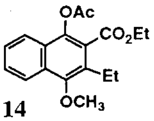
Abstract: Examination of a steric and electronic factor of alkyne in regioselectivity in the reaction of a phenyl chromium carbene complex with unsymmetrical alkynes is described.

The reaction between a phenyl chromium carbene complex (1) and alkyne is a direct method for preparation of substituted hydronaphthoquinones,[1] and has begun to be applied in natural product synthesis.[2] Although regioselectivity of this reaction appears to be strongly influenced by the steric effects of alkyne substituents in earlier observations with dialkyl and arylalkyl alkynes,[3] question of regioselectivity with unsymmetrical alkynes which bear both different steric and electronic parameters remains to be of fundamental concern for application of this reaction in complex synthesis. We reported the first example of an electron-rich alkoxyalkyne participating in the alkyne-carbene reaction process observing a domination steric effect.[4] In this paper, we report the results from examination of a steric and electronic effect of alkyne substituents in regioselectivity of this reaction process (eq. 1, Table I).



In order to avoid handling a labile phenol which is readily oxidized to form a quinone, we carried out the reaction with an *in situ* protection method.[5] The complex (1) was heated at 65°C (bath temperature) under argon with alkyne (1.5 mol eq) in tetrahydrofuran (THF, 30 ml/mmole) in the presence of acetic anhydride (Ac_2O, 1.1-2.5 mol eq) and triethylamine (NEt_3, 1.1-2.5 mol eq). TLC analysis indicated that the reaction was complete in 3 to 6 hrs. The products were isolated by flash column chromatography and characterized by ir, mass, UV, and ^1H and ^{13}C-NMR spectra. we examined alkynes bearing the sterically hindered, electron-rich, and electron-withdrawing substituents for their influences on regioselectivity, and Table I presents the results.[6]

Table-I:Reaction of **1** with unsymmetrical alkynes, $R_1\text{-}C{\equiv}C\text{-}R_2$

Entry	$R_1\text{-}C{\equiv}C\text{-}R_2$	Ac_2O/NEt_3 (mol.eq.)	Time(hr)	Products(%,ratio) *a
1	 $\mathrm{H\text{-}C{\equiv}C\text{-}\overset{\overset{O}{\Vert}}{C}\text{-}CH_3}$	0/0	5	 **3** (42)
2	$H\text{-}C{\equiv}C\text{-}CO_2Et$	0/0	5	 **4** (41) +  **5** (9.0)
3	 $\mathrm{EtO\text{-}C{\equiv}C\text{-}\overset{t\text{-}BuMe_2SiO}{CH}\text{—}CH_3}$	1.5/1.5	3	 **6** (54)
4		1.5/1.5	7	 **7** (45)
5	$t\text{-}Bu\text{-}C{\equiv}C\text{-}CO_2Et$	0/0	6	 **8** (93)
6	$Ph\text{-}C{\equiv}C\text{-}CO_2Et$	1.2/1.3	6	 +  **9** (22) **10** (50)
7	$n\text{-}C_5H_{11}\text{-}C{\equiv}C\text{-}CO_2Et$	2.5/2.0	5	 +  **11** **12** (60; **11**:**12** =1.6:1.0) *b
8	$Et\text{-}C{\equiv}C\text{-}CO_2Et$	2.5/2.0	5	 +  **13** **14** (38, **13**:**14** =1.1:1.0) *b

*a Isolated yield

*b Combined yield of two isomers, which ratio was determined by H-NMR spectrum and analytical HPLC analysis

Terminal alkynes (entries 1, 2) showed a 100% regioselectivity regardless of a steric and an electronic effect on alkyne substituents.[7,11] An electron-rich alkoxyalkyne (entry 3, 4) provided a single product (**6**, 54%, and **7**, 45%).[8] Ethyl 3,3-dimethylbutynolate (entry 5) underwent 1,4-cycloaddition, forming the cyclobutenone **8** in a 91% yield.[9] Ethyl 3-phenylpropiolate (entry 6) produced the naphthol (**9**, 22%) and the vinyl ether derivative (**10**, 50%).[10,11] The structures **8**, **9**, and **10** require that the carbene carbon attached the ester bearing carbon with 100% regioselectivity. The reactions of **1** with ethyl octynolate (entry 7) and ethyl pentynolate (entry 8) provided both mixture of two regioisomers in a 1.6:1 (**11**:**12**) and a 1.1:1(**13**:**14**) ratio, respectively.[11] The results from Table I together with earlier observations[3] strongly claim that regioselectivity in the carbene-alkyne reaction is dominated only by the steric effects on alkyne substituents, and that electronic effects of substituents are unimportant in determining the selectivity. Furthermore, absolute regioselectivity can be predicted by comparing the A-values ($-\Delta G_x^\circ$ kcal/mol)[12] of two substituents.[13] Table II summarizes the A-value difference ($\Delta G_{R1} - \Delta G_{R2}$) between two alkyne substituents and the ratio of two regioisomers. This observation extends the general trend that 100% regioselectivity can be expected in the carbene-alkyne reaction when the difference of A-values of substituents on alkyne is greater than 1.4.

Table II: A-value differences of alkyne substituents and selectivity

R_2-C≡C-R_1	**ΔG_{R1}-ΔG_{R2}**	**Ratio**	**R_2-C≡C-R_1**	**ΔG_{R1}-ΔG_{R2}**	**Ratio**
t-Bu-C≡C-CO_2Et	4.5	100%	n-C_5H_{11}-C≡C-CO_2Et	1.0	1.6:1
Ph-C≡C-CO_2Et	2.0	100	Et-C≡C-CO_2Et	0.7	1.1:1
Ph-C≡C-Me	1.4	100[3b]	i-Pr-C≡C-Me	1.0-0.5	4.9:1[3b]
Me-CH-C≡C-OEt OSiMe_2Bu(t)	1.4	100	n-Pr-C≡C-Me	0.4	2.9:1[3b]
			Et-C≡C-Me	0.1	1.5:1[3b]

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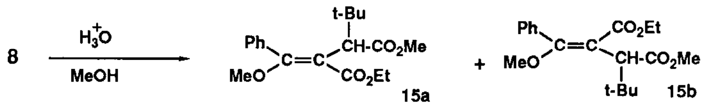
1. (a) K. H. Dötz, *Agnew. Chem. Int. Ed.*, **14** 644 (1975); (b) K.H.Dötz, B. Fügen-Döser, *Chem.Ber.*, **113**, 1449 (1980); (c) K.H.Dötz, I. Pruskil, *J. Oragnomet. Chem.*, **209**, C4 and references therein (1984).
2. (a) M.F. Semmelhack, J.J. Bozell, T. Sato, W.D. Wulff, E. Spiess, A. Zask, *J. Amer. Chem. Soc.*, **104**, 5850 (1982); (b) W.D. Wulff, P.C. Tang, *J. Amer. Soc.*, **106**, 434 (1984); (c) A. Yamashita, *J. Amer. Chem. Soc.*, **107** 5823 (1985).
3. (a) W.D. Wulff, P.C. Tang, J.S. McCallum, *J. Amer. Chem. Soc.*, **103**, 7677 (1981); (b) W.D. Wulff, K.S. Chan, P.C. Tang, *J. Org. Chem.*, **49**, 2293 (1984) and references therein.
4. A. Yamashita, T.A. Scahill, C.G. Chidester, *Tet. Lett.*, **26** 1159 (1985).
5. A. Yamashita, T.A. Scahill, A.Toy, *Tet Lett.*, **26**, 2969 (1985).

6. All new compounds (**3**, **4**, **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, and **14**) have been characterized by satisfactory combustion and spectral (high resolution mass, IR, UV, ^{1}H and ^{13}C-NMR) analysis.

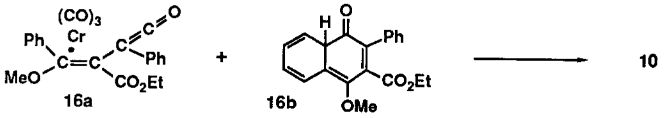
7. This was also supported by the result from the reaction of **1** with ethylpropiolate in the presence of EtOH, providing an 83% yield of **5** as a 6:1 mixture of E and Z isomers; A. Yamashita, T.A. Scahill, *Tet. Lett.*, **23** 3765 (1982).

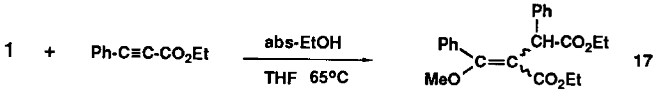
8. The stereochemistry of **6** and **7** was determined based upon earlier observations; see ref. 4.

9. To confirm the regiochemistry of **8**, **8** was treated with 1N HCl and MeOH at 25°C, yielding the vinyl ether derivatives of succinate, **15a** and **15b**, in a quantitative yield. (**15a**>>**15b**)



10. The structure **10** can be understood in terms of a nucleophilic attack of **16b** to the vinyl ketene intermediate (**16a**). This result was also supported by formation of the vinyl ether derivatives of the succinate (**17**; an 85% yield) from the reaction of **1** with phenylpropiolate in the presence of abs-EtOH.





11. In order to determine the stereochemistry of **9**, **11**, **12**, **13**, **14**, the acetate was removed by treatment with aq $NaHCO_3$-MeOH. The phenols from **12** and **14** showed the hydrogen-bonding phenol peaks at δ 12.41, respectively. On the other hand, the phenols from **9**, **11**, and **13** failed to show this downfield peak.

12. (a) E.L. Eliel, N.L. Allinger "Conformational Analysis", John Wiley & Sons, Inc.: New York, 1965; (b) S. Winstein, N.J. Holness, *J. Amer. Chem. Soc.*, **77** 5562 (1955).

13. While the authors recognize that there is not necessarily any relationship between the steric interactions responsible for the derivation of A value and the steric interactions responsible for the regioselectivity of the carbene-alkyne cycloadditions, the difference in the substituent A-values (ΔΔG°) provides a useful empirical guide to predict the outcome.

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