First Stereoselective Synthesis of Arene Chromium Tricarbonyl Complexes via the Benzannulation Reaction

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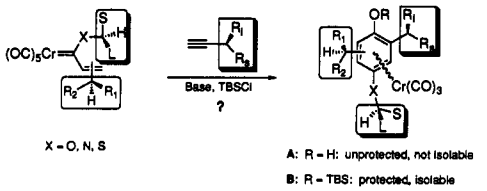
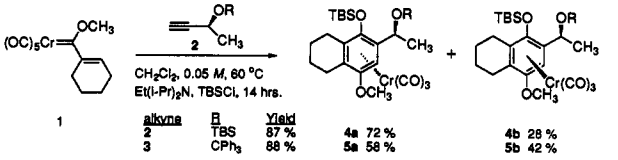
It would appear that the integral issue in current studies of the chemistry of arene chromium tricarbonyl complexes[2] is the synthetic utility of chiral complexes[3] in either stoichiometric or catalytic processes. The benzannulation reaction[4-6] produces arene chromium tricarbonyl complexes in a process where the arene ring is constructed from three different ligands (carbene, carbon monoxide, and alkyne) in the coordination sphere of the metal. Since the arene ring is synthesized at the metal center, there is the potential that an asymmetric induction could occur from an existing chiral center in one of the pieces, resulting in a facial selectivity of the coordination of the chromium to the newly formed arene, but, as of yet, this has not been realized. As outlined in Scheme 1, there are three potential sources of induction for an asymmetric benzannulation reaction. While we have been pursuing all three approaches, we report here our first success in achieving high asymmetric induction in the formation of arene chromium tricarbonyl complexes from the benzannulation reactions with chiral propargylic ethers.

Our initial efforts were with the benzannulation reactions of the cyclohexenyl methoxy chromium carbene complex **1** with chiral alkynes **2** and **3**.[7] These reactions were carried out in CH_2Cl_2 at 60 °C in the presence of Hunig's base and TBSCl (the concurrent condition[6a]) and gave the isomeric arene chromium tricarbonyl complexes **4** and **5** with diastereomeric ratios of 72:28 and 58:42, respectively (Scheme 2).[8] The ratio of the isomers of **4** is not affected by the reactions conditions. A sample of **4** enriched in the minor isomer **4b** (5.2:1) was resubmitted to the exact reaction conditions (including all reagents except **1**) and was recovered in 98% yield as a 6.3:1 mixture of **4b:4a**. The stereochemistry of the products of these reactions was unambiguously determined by an X-ray diffraction analysis of the arene chromium tricarbonyl complex **4b**.[9,10]

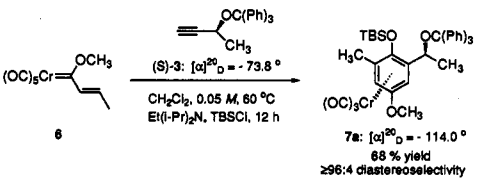
Scheme 1



Scheme 2



Scheme 3



In contrast to the benzannulation of the cyclohexenyl complex **1**, very high asymmetric induction was observed in the benzannulation of the *trans*-propenyl complex **6** with alkyne **3**. With the optically pure *S*-enantiomer of **3**,[7] the benzannulation with carbene complex **6** gave arene chromium tricarbonyl complex **7a** in 68% yield as a single diastereomer, as determined by ^1H and ^{13}C NMR (Scheme 3).[12] As can be seen from the first five entries in Table 1, the induction in this reaction does depend on the size of the acetylenic oxygen substituent (R_5). Whereas the trityl-protected propargyl ether **3** gives only one diastereomeric arene chromium tricarbonyl complex, smaller protecting groups give both isomers. For derivatives of 1-butyn-3-ol, the ratio decreases for silyl ethers with decreasing size of the silyl group, and the lowest selectivity is seen with the methyl ether, where an 85:15 ratio of isomers was produced. Thus it appears that the high selectivity is not the result of chelation of the propargylic oxygen to the metal.

(1) American Chemical Society Organic Division R. W. Johnson Fellow, 1993–1994.

(2) For recent reviews, see: (a) Davies, S. G.; Donohoe, T. J. *Synlett* **1993**, 323. (b) Davies, S. G.; Coote, S. J.; Goodfellow, C. L. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc.: Greenwich, CT, 1991; Vol. 2. (c) Uemura, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc.: Greenwich, CT, 1991; Vol. 2. (d) Semmelhack, M. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol 4, pp 517–549. (e) Solladie-Cavallo, A. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc.: Greenwich, CT, 1989; Vol. 1. (f) Kündig, E. P. *Pure Appl. Chem.* **1985**, *57*, 1855.

(3) For recent examples, see: (a) Schmalz, H.-G.; Arnold, M.; Hollander, J.; Bats, J. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 109. (b) Baldoli, C.; Buttero, P. D.; Licandro, E.; Maiorana, S.; Papagni, A. *Synlett* **1994**, 183. (c) Price, D. A.; Simpkins, N. S.; MacLeod, A. M.; Watt, A. P. *J. Org. Chem.* **1994**, *59*, 1961. (d) Uemura, M.; Nishimura, H.; Kamikawa, K.; Kankayama, K.; Hayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 1909. (e) Mukai, C.; Kim, I. J.; Furu, E. *Tetrahedron Lett.* **1993**, *49*, 8323. (f) Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* **1993**, *58*, 6182. (g) Kündig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett.* **1993**, *34*, 7049. (h) Brocard, J.; Pelinski, L.; Goetghelnik, S.; Maciejewski, L. *J. Organomet. Chem.* **1993**, *456*, C24. (i) Laschat, S.; Noe, R.; Riedel, M., *Organometallics* **1993**, *12*, 3738. (j) Perez-Encabo, A.; Perrio, S.; Slawin, A. M. Z.; Thomas, S. E.; Wierzchleyski, A. T.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1059. (k) Ganesh, S.; Sathe, K. M.; Nandi, M.; Chakrabarti, P.; Sarkar, A. *J. Chem. Soc., Chem. Commun.* **1993**, 224.

(4) For reviews, see: (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (b) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press LTD: Greenwich, CT, 1989; Vol. 1, pp 209–393. (c) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.: Pergamon Press: New York, 1991, Vol. 5, pp 1065–1113.

(5) For citations to applications in natural product synthesis, see: Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102.

(6) (a) Chamberlin, S.; Wulff, W. D.; Bax, B. M. *Tetrahedron*, **1993**, *49*, 5531. (b) Chamberlin, S.; Wulff, W. D. *J. Am. Chem. Soc.* **1992**, *114*, 10667.

(7) The details for the preparation of all the chiral alkynes in this work can be found in the supplementary material. The optically pure (*S*)-3 was prepared from (*S*)-3-butyn-2-ol, which was generously supplied by Abbott Laboratories.

(8) The high chemical yields of these reactions were somewhat unexpected given recent reports on the benzannulations of α-oxygenated alkynes with arylchromium carbene complexes: (a) Semmelhack, M. F.; Jeong, N. *Tetrahedron Lett.* **1990**, *31*, 605. (b) Semmelhack, M. F.; Jeong, N.; Lee, G. R. *Tetrahedron Lett.* **1990**, *31*, 609. Other differerences in the reactions of alkenyl and aryl complexes have been documented.[5]

(9) For details see Supplementary Material.

(10) (a) The minor diastereomers from the benzannulations in this work are usually more crystalline than the major ones. Although in some cases we were able to painstakingly separate out the major isomers (lower R_f with higher dipole moment[10b]) from the minor ones (higher R_f with lower dipole moment[10b]) via silica gel column chromatography, fractional recrystallization proved to be a rather useful separation technique. (b) Gracey, D. E. F.; Jackson, W. R.; McMullen, C. H. Thompson, N. *J. Chem. Soc. (B)* **1969**, 1197.

(11) (a) Hofmann, P.; Hämmerle, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 908. (b) Hofmann, P.; Hämmerle, M.; Unfried, G. *New. J. Chem.* **1991**, *15*, 769.

(12) The stereochemical assignments for the arene complexes shown in Table I were made by a combination of chemical and ^1H NMR correlations to **4a** and **4b**, which were assigned by X-ray diffraction analysis.[9]

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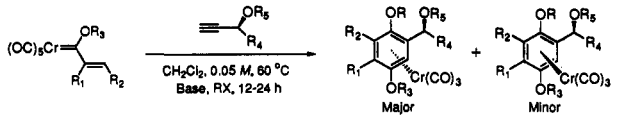
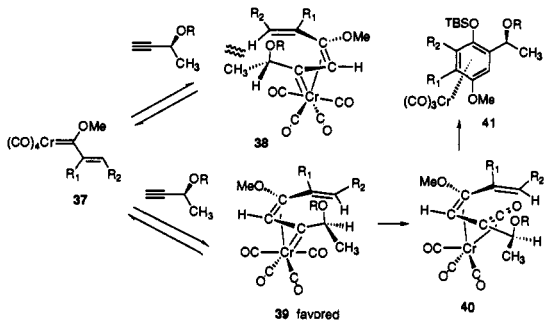
Table 1. Asymmetric Induction in the Benzannulation of Alkenyl Carbene Complexes[a]



entry	complex	alkyne	R_1	R_2	R_3	R_4	R_5	product	yield[b]	diastereomeric ratio[c]
1	**6**	**12**	H	CH_3	CH_3	CH_3	CH_3	**21**	82	85:15
2	**6**	**13**	H	CH_3	CH_3	CH_3	TMS	**22**	75	90:10
3	**6**	**2**	H	CH_3	CH_3	CH_3	TBS	**23**	70[d]	91:9
4	**6**	**14**	H	CH_3	CH_3	CH_3	TIPS	**24**	87	95:5
5	**6**	**3**	H	CH_3	CH_3	CH_3	$C(Ph)_3$	**7**	68	≥96:4
6	**6**	**15**[e]	H	CH_3	CH_3	*n*-Pr	TIPS	**26**	68	93:7
7	**6**	**16**	H	CH_3	CH_3	*n*-Pr	$C(Ph)_3$	**27**	72[f]	≥96:4
8	**8**	**2**	H	CH_3	*i*-Pr	CH_3	TBS	**28**	80	91:9
9	**9**	**2**	H	*t*-Bu	CH_3	CH_3	TBS	**29**	74[g]	91:9
10	**10**	**3**	H	TBS	CH_3	CH_3	$C(Ph)_3$	**30**	65	69:31
11	**6**	**17**	H	CH_3	CH_3	CH_3	$SiMe_2$(*p*-MeOPh)	**31**	56	88:12
12	**6**	**18**	H	CH_3	CH_3	CH_3	$SiMe_2Ph$	**32**	40	85:15
13	**6**	**19**	H	CH_3	CH_3	CH_3	$SiMe_2C_6F_5$	**33**	32	62:38
14	**11**	**3**	CH_3	H	CH_3	CH_3	$C(Ph)_3$	**34**	89	55:45
15	**11**	**2**	CH_3	H	CH_3	CH_3	TBS	**35**	41[h]	57:43
16	**11**	**20**	CH_3	H	CH_3	Ph	TBS	**36**	81	71:29

[a] All reactions were carried out with 1.9 equiv of alkyne, 5–6 equiv of Hunig's base, and 3–5 equiv of *t*-$BuMe_2SiCl$ (RX) except for entry 1, where 2,6-lutidine was the base and RX = *t*-$BuMe_2SiOTf$, entries 4 and 6, where RX = *i*-Pr_3SiCl, and entry 10, where no base or RX was needed. For entry 12, RX = $Me_2PhSiCl$. [b] All yields are isolated yields. [c] Ratios were determined by ^1H and/or ^{13}C NMR. [d] The corresponding free arene was isolated in <3% yield. [e] This alkyne was generated in situ with Hunig's base and *i*-Pr_3SiCl just prior to the benzannulation reaction (see supplementary material). [f] Also isolated was a 13% yield of the corresponding unprotected free phenol. [g] These complexes were isolated as their free phenol complexes (R = H), which were unusually stable to air and silica gel and which could not be silylated. [h] Also isolated was a 6% yield of the corresponding free arene.

Scheme 4



The evidence suggests that the propargylic oxygen plays a stereoelectronic role in determining the stereoselectivity which underlies and dominates the steric effects of the propargyl ether protecting groups. Indications of this can be seen in entries 11–13 where the stereoselectivty falls from 7.3 to 1 with a (*p*-methoxyphenyl)dimethylsilyl group to 1.6 to 1 with a (pentafluorophenyl)dimethylsiloxy group, although the lower yields for these reactions should be noted. Clear-cut evidence for a stereoelectronic influence of the propargylic oxygen substituent is revealed in the reactions of the complex **6** with 3,4,4-trimethyl-1-pentyne and 3-phenyl-1-butyne, where the arene chromium tricarbonyl complexes from each reaction are produced as a 1.2:1 mixtures of diastereomers in 79 and 74% total yield, respectively (not shown in Table 1). In addition to the strong influence of the propargylic oxygen a dramatic dependence in the selectivity on the substitution pattern of the alkenyl carbene complex is noted (entries 3, 5, 14, and 15). The reaction of the isopropenyl complex **11** with alkyne **3** is essentially stereorandom.

A working model to account for the stereoselection observed in these reactions is presented in Scheme 4 and is based on the assumption, which has been suggested in recent theoretical studies,[11] that the η^1,η^3-vinyl carbene complexed intermediates **38** and **39** are in equilibrium, and on the assumption that the more stable intermediate proceeds to product. From the stereoselection observed, the reaction must proceed through the intermediate **39**, and an investigation of models reveals that allylic strain would be the most likely source for a greater stability of **39** over **38**. If this is true, then there must be a stereoelectronic preference for an alignment of the propargylic oxygen in a direction approximately anti to the chromium. This positions the methyl group on the propargyl carbon inside and toward the alkenyl substituent in **38** and outside and away from the alkenyl group in the more stable intermediate **39**. The difference in selectivities between the *trans*-propenyl complex **6** and the isopropenyl complex **11** (and also complex **1**) can then be accounted for by anticipated conformational preferences about the bond which attaches the alkenyl group to the η^1,η^3-vinyl carbene unit. Relative to the *trans*-propenyl group, the isopropenyl group would be expected to populate conformers in which the methyl group at R_1 does not eclipse the methoxyl group at the original carbene carbon. Thus, when the plane containing the isopropenyl group is perpendicular to the plane containing the three carbons of the η^1,η^3-vinyl carbene unit, the allylic strain in **38** is greatly diminished, as is the energy difference between **38** and **39**. Consistent with this model are the observations that the selectivity is not changed by the presence of a *trans-tert*-butyl group in the alkenyl complex relative to methyl (entries 3 and 9) but that the selectivity for the reactions of the isopropenyl complex **11** is enhanced when R_4 of the alkyne is changed from methyl to phenyl (entries 15 and 16).

Given the current status of our understanding of the mechanism of the benzannulation reaction[4,11] and given the various possibilities for asymmetric induction for this reaction (Scheme 1), the high selectivities observed for the benzannulation of propargyl ethers was surprising and would have been difficult to predict. The synthetic applications and mechanistic implications raised by this work are being pursued.

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Supplementary Material Available: Procedures and spectral data for all new compounds and tables of X-ray data for compound **4b**, including fractional coordinates, isotropic and anisotropic thermal parameters, and bond distances and bond angles (31 pages); listing of observed and calculated structure factors (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.