

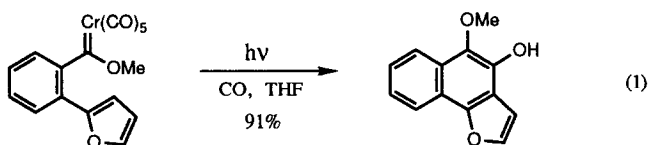
Regioselectivity of Photochemical Annulations of Chromium Carbene Complexes

Craig A. Merlic* and W. Michael Roberts

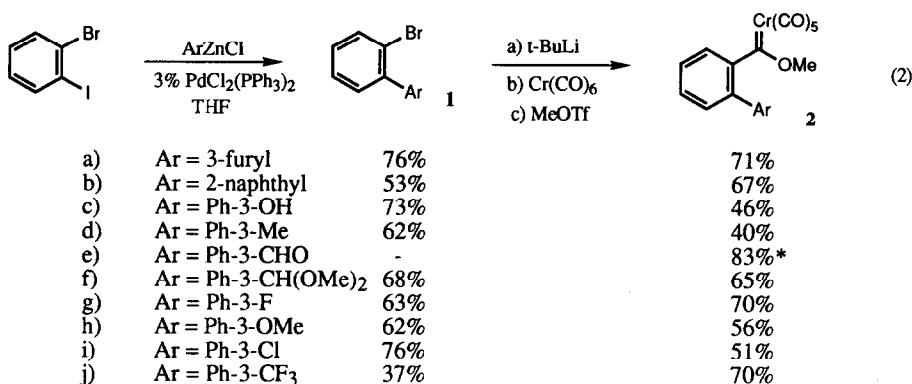
Department of Chemistry and Biochemistry
University of California, Los Angeles, California 90024-1569

Abstract: The regioselectivity of photochemical benzannulation reactions of chromium biarylcarbene complexes is reported. Excellent selectivity is observed in furyl- and naphthyl-substituted substrates. Interesting *ortho* versus *para* selectivity is found in *meta* substituted (biphenyl)carbene substrates.

Recently, we reported photochemical benzannulation reactions of chromium dienylcarbene complexes.^{1,2} These reactions efficiently produced *ortho* alkoxy- and (amino)phenols via electrocyclicization of intermediate photogenerated chromium complexed ketenes (e.g. eq 1). This chemistry provides products complementary to the well established chromium carbene plus alkyne annulation (Dötz reaction) which yields *para* alkoxy phenols.³ Expanding the scope of our initial reports, we describe herein studies on the regioselectivity of the photochemical benzannulation reaction.



A series of biarylcarbene substrates **2** containing a common benzene ring, but variously substituted aromatic rings *ortho* to the carbene moiety, were prepared for investigation of the regiochemistry of cyclization. The substrates were prepared as shown in equation 2. A selective palladium catalyzed coupling reaction⁴ of 1-bromo-2-iodobenzene with arylzinc chlorides produced the biaryls **1**.^{5,6} After initial difficulties, we found that a highly active catalyst was required for efficient cross coupling reactions. Preparation of PdCl₂(PPh₃)₂ by a modification⁷ of the standard procedure⁸ provided a reproducibly active catalyst⁹ that yielded the biaryls in high yield at room temperature, usually in a matter of minutes. The carbene complexes **2** were then prepared from the biaryls in the standard manner via metal-halogen exchange, addition of the resultant carbanions to chromium hexacarbonyl, followed by alkylation with methyl triflate.^{6,10,11}



*) Prepared from carbene complex **2f** via hydrolysis.

The photoinduced benzannulation reactions of carbene complexes **2** were performed in THF or toluene solvent using a 450 watt medium pressure mercury lamp and the results are shown in the Table.¹² Product ratios were determined by GC and ¹H NMR analyses on crude reaction mixtures and the yields shown are for purified isolated products.⁶ Differentiation of products **6** from **7** was based on the ¹H NMR coupling constants. In particular, the hydrogens at C-4 in products **7** were observed as very deshielded singlets. The regioselectivity is excellent for the furyl (**2a**), naphthyl (**2b**), and certain biphenyl substrates. The biphenyl substrates present an interesting mode of regioselectivity resulting from a competition between cyclization at the *ortho* and *para* positions relative to the unique remote substituent.

The selectivity observed with the furyl- and naphthyl-substituted substrates is readily understood by consideration of the frontier molecular orbitals. Reactions at the furyl C-2 and naphthyl C-1 positions are expected since the HOMO and LUMO coefficients are largest there. The selectivity seen with the biphenyl substrates **2c-j** is more difficult to explain. The *ortho* vs *para* selectivity is principally dependent on electronic and steric effects, but there can be additional factors to consider such as coordination to the substituent, hydrogen bonding and solvent effects.¹³ The data for THF solvent (entries 3-10) in the Table roughly correlate with σ^+ values,^{13,14} but there is significant scatter in a log(*o/p* ratio) vs σ^+ plot, indicative of steric effects superimposed on the fundamental electronic effects. Overall, synthetically useful levels of regiocontrol are found with strongly electron withdrawing or sterically demanding *meta* substituents. Thus, electrocyclozation of the ketene intermediate is principally charge controlled with reactions occurring *para* to electron withdrawing substituents. Similar levels of regioselectivity have been reported in chromium¹⁵ and iron¹⁶ carbene plus alkyne annulation reactions.

A strong solvent effect is seen in the photochemical benzannulation (entries 11-16 vs 3-7,9). Use of toluene provides higher levels of selectivity in both the *ortho*-selective and *para*-selective directions. It is possible that the transition states leading to products **6** and **7** are polar; thus, toluene would enhance the difference in energies compared with THF. Another possibility is that cyclization occurs via the chromium-complexed ketene in toluene while in THF, demetallation of the ketene occurs before cyclization. A final possibility is that the electrocyclozation is reversible, potentially facilitated by chromium complexation, and the rate and product determining step is tautomerization. Incipient *peri* interactions and solvent effects on tautomerization would control product ratios. Experiments are currently underway to address these questions.

Table. Photochemical Benzannulation Reactions of Carbene Complexes

Entry	Carbene	Products
1		 65%
2		 11 : 1 83%
3	c) X = OH	1.2 : 1 65%*
4	d) X = Me	1.2 : 1 71%
5	e) X = CHO	1 : 1.3 71%
6	f) X = CH(OMe) ₂	1 : 1.5 74%
7	g) X = F	1 : 5 66%
8	h) X = OMe	1 : 7 70%
9	i) X = Cl	1 : 14 89%
10	j) X = CF ₃	<1 : >25** 69%
11	c) X = OH	5.4 : 1 75%
12	d) X = Me	1 : 12 96%
13	e) X = CHO	1 : 3 88%
14	f) X = CH(OMe) ₂	<1 : >25** 92%
15	g) X = F	<1 : >25** 58%
16	i) X = Cl	<1 : >25** 89%

*) Isolated as the diacetate.

**) Minor isomer not detected.

Acknowledgement: We thank the National Institutes of Health (GM46509) for support of this research.

References and Notes:

- Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 7418.
- Merlic, C. A.; Xu, D.; Gladstone, B. G. *J. Org. Chem.* **1993**, *58*, 538.
- For reviews on Fischer carbene complexes, see: (a) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1990; Vol. 5. (b) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press Inc.: Greenwich, CT, 1989; Vol. 1. (c) *Advances in Metal Carbene Chemistry*; Schubert, U., Ed.; Kluwer Academic Publishers: Hingham, MA, 1989. (d) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissel, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1983.
- Potter, G. A.; McCague, R. *J. Org. Chem.* **1990**, *55*, 6184.
- Procedure for **1i**: t-BuLi (8.5 mL, 14.4 mmol, 1.7 M) was added over 5 min to a solution of 1-chloro-3-iodobenzene (1.633 g, 6.85 mmol) in THF (7 mL) at -65°C and the solution was stirred for 1.5 h. ZnCl₂ (9.85 mL, 6.85 mmol, 0.695 M in THF) was added and the solution was stirred for 2 h at room temperature. PdCl₂(PPh₃)₂ (81 mg, 0.12 mmol) in THF (20 mL) was reduced with PhLi (0.13 mL, 0.23 mmol, 1.8 M) (addition of 2 eq NaI can facilitate this step), then 1-bromo-2-iodobenzene (867 mg, 3.06 mmol) was added followed by the zinc solution via cannula and the solution was stirred for 10 h. Deposition of the reaction mixture on silica gel and purification by flash chromatography (hexane) provided 621 mg (76%) of **1i** as a colorless oil.
- All new compounds were fully characterized by ¹H NMR, ¹³C NMR and IR spectroscopy and elemental composition was established by combustion analysis and / or high-resolution mass spectroscopy.
- PdCl₂, extracted with CHCl₃ to remove the β-form,^a was mortar-ground with PPh₃ and heated at 110°C. After stirring for 45 min at this temperature, the crude solid was washed with hot ether, then dissolved in hot CHCl₃. The catalyst crystallized at room temperature from the CHCl₃ solution. Yields were high, depending on initial integrity of the PdCl₂. a) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*; John Wiley and Sons: New York, 1988; pp. 877-878.
- a) Hartley, F. R. *Organomet. Chem. Rev., A* **1970**, *6*, 119. b) Chatt, J.; Mann, F. G. *J. Chem. Soc.* **1939**, 1622.
- See also: Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513.
- Procedure for **2a**: t-BuLi (3.5 mL, 5.9 mmol, 1.7 M) was added over 5 min to a solution of **1a** (535 mg, 2.4 mmol) in ether (25 mL) at -78°C. The solution was stirred for 1.3 h and added by cannula to a solution of Cr(CO)₆ (528 mg, 2.4 mmol) in ether (15 mL) at room temperature. After 45 min, MeOTf (0.7 mL, 6.2 mmol) was added to the dark amber solution and the resultant red solution was stirred for 3 h. Purification by flash chromatography (hexane) provided 640 mg (71%) of **2a** as a red solid.
- For a recent study on the alkylation of lithium acylchromates, see: Hoyer, T. R.; Chen, K.; Vyvyan, J. R. *Organometallics* **1993**, *12*, 2806.
- Procedure for **6d** and **7d**: Photolysis (15 min) of carbene **2d** (200 mg, 0.498 mmol) in CO-sparged THF (125 mL) in a quartz photoreactor equipped with a 450 watt medium pressure mercury lamp and a pyrex filter at room temperature yielded a bronze solution. Filtration through a plug of silica gel and concentration gave a yellow oil shown by GC and ¹H NMR to be a 1.2 : 1 mixture of **6d** and **7d**. Purification by flash chromatography (9 : 1 hexanes : ethyl acetate) yielded **6d** (35 mg, 30%) and **7d** (49 mg, 41%) as yellow solids. **6d**: ¹H NMR (CDCl₃, 360 MHz) δ: 3.01 (s, 3H), 3.97 (s, 3H), 6.43 (s, 1H), 7.36 (d, *J* = 7.1 Hz, 1H), 7.42-7.52 (m, 2H), 7.59 (m, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.51 (d, *J* = 8.3 Hz, 1H), 8.61 (d, *J* = 8.3 Hz, 1H). **7d**: ¹H NMR (CDCl₃, 500 MHz) δ: 2.62 (s, 3H), 3.99 (s, 3H), 6.12 (s, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.49-7.53 (m, 1H), 7.58-7.63 (m, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.42 (s, 1H), 8.62 (d, *J* = 8.2 Hz, 1H).
- Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley and Sons: New York, 1990; pp. 483-490.
- Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1963**, *1*, 35.
- Wulff, W. D.; Tang, P.-C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677.
- ur-Rehman, A.-; Schnatter, W. F. K.; Manolache, N. *J. Am. Chem. Soc.*, in press.