the intermediate zirconocene complex **5**.[6] Zirconacycle **6**, which was observed by ^{1}H NMR, was treated with iodine to give diiodoindoline **7**. Compound **7** can thus be prepared from **4** in a "one-pot" procedure in an isolated yield of 65%. Treatment of **7** with BBr_3[9] afforded phenol **8** in 88% yield, which was used immediately after purification. Treatment of **8** with sodium hydride in THF[3] at 25 °C cleanly gave tetrahydrocycloprop[1,2-*c*]indol-4-one analog **9** in 89% yield as a brownish solid. Although the instability of **9** precluded its purification by chromatography (silica, alumina), it was reasonably pure after filtration of the reaction mixture to remove the sodium salts and removal of the solvent in vacuo (see supplementary material for spectroscopic data). Dienone **9** was found to be stable as a solid for approximately 1 h at room temperature. In solution, however, it proved to be much less stable, affording insoluble material after approximately 30 min in THF at room temperature.

In order to allow for the synthesis of a number of analogs of CC-1065, it is necessary to deprotect the nitrogen in **7**. We found most useful a modification of the method of Olofson,[10] who has demonstrated that tertiary amines can be selectively dealkylated using 1-chloroethyl chloroformate (ACE-Cl). Although aromatic amines have been deprotected using ACE-Cl,[11] the procedures usually require high temperatures and a large excess of the chloroformate. Under these conditions, **7** either decomposed or failed to react with ACE-Cl due to the low nucleophilicity of the nitrogen. We found that if the reaction between **7** and ACE-Cl is conducted in refluxing acetone using 2 equiv of the chloroformate and 3 equiv of sodium iodide (see Scheme II) dealkylation proceeds in good yield. The addition of sodium iodide presumably causes acyl halide exchange to occur to produce a more reactive iodoformate[12] which then reacts with the amine to produce the intermediate carbamate and allyl iodide. Cleavage of the intermediate carbamate was best effected in refluxing methanol with 1,2-dichloroethane as cosolvent. Using these conditions, **7** could be converted to **10** in an overall yield of 67%. It has been demonstrated by Boger and co-workers that indolines such as **10** as can be coupled with a variety of compounds such as phosphodiesterase dimer (PDE-1) to give functional CC-1065 analogs.[3]

The use of this methodology in the synthesis of more substituted pharmacophore analogs is currently being investigated.

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Supplementary Material Available: Experimental details for the preparation and spectroscopic characterization of compounds **2-10**, as well as ^{1}H and ^{13}C NMR spectra for compounds **4, 7, 8, 9, 10** and liquid chromatograms of compounds **8** and **10** (17 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.

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(14) **Note:** Compounds related to **7-10** have been shown to alkylate DNA, and thus they should be handled with caution.[3e]

Salt Effects on a Hydrophobically Accelerated Diels-Alder Reaction Follow the Hofmeister Series

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Summary: The rate of the Diels-Alder reaction between *N*-ethylmaleimide and anthracene-9-carbinol in aqueous sodium salt solutions follows a linear relationship with the size of the anion.

Since the first report of an accelerated Diels-Alder reaction in aqueous media by Rideout and Breslow,[1a] considerable effort has been devoted to determining the source of the rate acceleration.[1-9] It has been suggested that hydrophobic effects are the principal forces responsible for the rate enhancement. In order to reduce their solvent contact with water, organic solutes will tend to aggregate in aqueous solution, and this hydrophobic packing gives rise to the large rate acceleration.[1] Evidence supporting this explanation was found by exploiting the effects of different salts on the aqueous Diels-Alder reaction; since different salts attenuate the magnitude of the hydrophobic effect, such salts are a useful probe.[1b] Some salts, such as LiCl, are salting-out agents which make organics less soluble in water and in doing so enhance the hydrophobic effect. Other salts such as guanidinium chloride are salting-in agents and tend to make organics more soluble in aqueous solution, thus diminishing the hydrophobic effect. Consistent with these ideas are the observations

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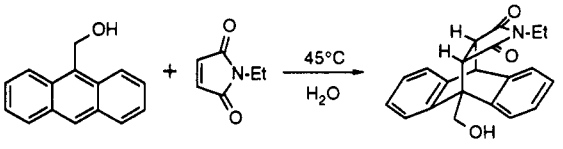
Table I. Effects of Sodium Salts on the Second-Order Rate Constants for the Diels–Alder Reaction of Anthracene-9-carbinol and *N*-Ethylmaleimide at 45 °C[a]

sodium salt (2 M)	$k_2 \times 10^3$, M^{-1} s^{-1}	k_{rel}	ionic radii (Å)
water	230 ± 2	1.00	
Cl^-	308 ± 6	1.34	1.67
Br^-	298 ± 5	1.30	1.82
BF_4^-	224 ± 2	0.98	2.44
ClO_4^-	205 ± 2	0.89	2.64
PF_6^-	190 ± 2	0.83	2.81
AsF_6^-	179 ± 5	0.78	2.89

[a] All data are the average of five runs. Reactions were carried out to at least 7 half-lives.

that LiCl accelerates the aqueous Diels–Alder reaction while guanidinium chloride decreases the rate when compared to water alone. The effects of salts on hydrophobic packing have been previously studied, however in a much different context, on the structure and stability of biopolymers.

The effect of salts on the melting temperature (Tm) of biopolymers has been extensively studied by von Hippel and Jencks.[10] It was observed that some salts tended to stabilize the native structure of proteins and nucleic acids, making them more resistant to thermal denaturation as evidenced by an increase of the Tm. Other salts seemingly promoted denaturation as evidenced by a lowering of the Tm. Moreover, the effects of various salts on the magnitude of the melting temperature generally followed the same order. This order has become known as the Hofmeister series, after Franz Hofmeister who first observed this trend when studying the effects of salts on the solubility of proteins.[11] In general, the effects of the Hofmeister series roughly correlate to the size of the anion and have been found to be valid, with minor variations, to a wide variety of physical measurements.[12]



(eq. 1)

The effects of a series of sodium salts on the rate of an aqueous Diels–Alder reaction between anthracene-9-carbinol and *N*-ethylmaleimide were examined, and the second-order rate constants are given in Table I[13] along with the crystallographic radii of the anion as calculated by the method of Shannon and Prewitt.[14] As can be seen, the rate of the Diels–Alder reaction decreases as the radii of the anion increases, thus approximating a Hofmeister series. Interestingly, when the rate of the Diels–Alder reaction is plotted versus the crystallographic radii of the anion a linear relationship is observed (Figure 1, correlation coefficient $r = 0.9988$). The effect of guanidinium salts on the Diels–Alder reaction were also examined and are summarized in Table II.[13a]

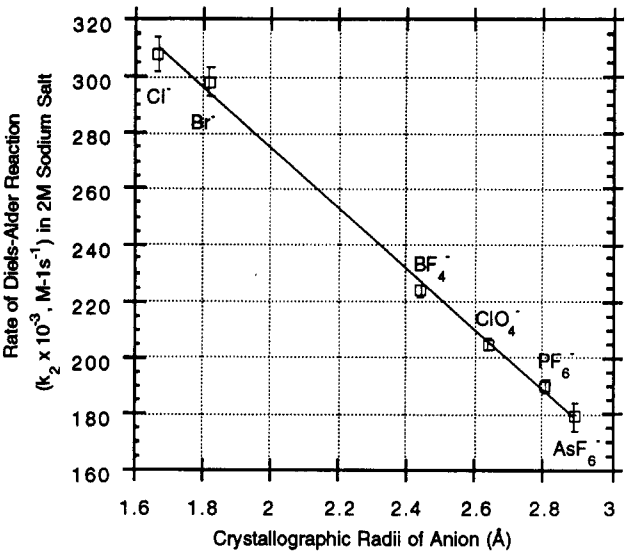


Figure 1. Rate of the Diels–Alder reaction in 2 M sodium salt vs the crystallographic radii of the anions (correlation coefficient $r = 0.9988$).

Table II. Effects of Guanidinium Salts on the Second-Order Rate Constants for the Diels–Alder Reaction of Anthracene-9-carbinol and *N*-Ethylmaleimide at 45 °C[a]

guanidinium salt (2 M)	$k_2 \times 10^3$, M^{-1} s^{-1}	k_{rel}
Cl^-	129 ± 6	0.56
Br^-	116 ± 2	0.50
BF_4^-	92 ± 4	0.40
SCN^-	87 ± 2	0.38
ClO_4^-	86 ± 4	0.37

[a] All data are the average of five runs. Reactions were carried out to at least 7 half-lives. Relative rates are compared to water alone.

Some years ago, Castellino and Barker studied the effects of a series of guanidinium salts on the denaturation and solubility of proteins.[15] These studies revealed that the minimum concentration for complete denaturation always decreased in the order of $Cl^- > Br^- > I^- > SCN^-$ while the solubility increased through this same series. It was concluded from these studies that the effectiveness of the guanidinium salts as protein denaturants is due to their ability to increase the solubility of the hydrophobic portions of the proteins. In the presence of guanidinium salts, the rate of the Diels–Alder reaction decreases as the size of the anion increases, again following the Hofmeister series, and the same linear relationship between rate and crystallographic radii was also observed (correlation coefficient $r = 0.9897$).[16] Furthermore, these results are consistent with the observations of Castellino and Barker and are in accord with the predictions based on the hydrophobic effect.

The present study clearly shows that the effects of salts on a hydrophobically accelerated Diels–Alder reaction between anthracene-9-carbinol and *N*-ethylmaleimide follows a Hofmeister series. The Hofmeister series has been extensively investigated in terms of protein and nucleic acid denaturation, and the trends between those studies and the work presented here appear to be in order. All of the results are completely consistent with predictions based on the hydrophobic effect and the degree to which various salts can help solubilize organic solutes in water.

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(16) Since thiocyanate is not spherical a unique radii cannot be assigned. It was thus omitted from this analysis.

An interesting relationship between the rate of the Diels-Alder reaction and the size of the anion is presented. This relationship indicates that effects of salts on the hydrophobic effects may be due to some surface contact between the electrolyte and the organic solute.[17]

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(17) It should be noted that direct surface contact between electrolyte and solute may not fully account for this correlation, and other explanations are certainly possible. The author gratefully acknowledges thoughtful reviewers for pointing this out.

Supplementary Material Available: Experimental details (1 page). 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.

Stereodivergent Additions of Allylic Chromium(III) Reagents to Aldehydes

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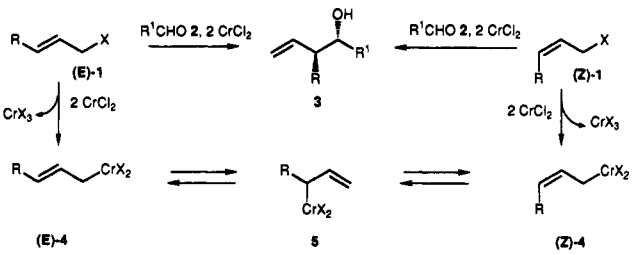
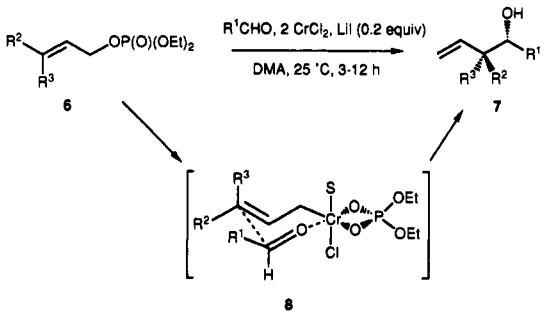
Summary: In contrast to γ-monosubstituted allylic chromium reagents, γ-disubstituted allylic chromium(III) organometallics undergo highly stereoselective stereodivergent additions to aldehydes.

Hiyama[1,2] reported that allylic halides **1** add to aldehydes **2** in the presence of chromium(II) salts. The reaction is highly stereoselective and affords the anti alcohols **3** *regardless* of the stereochemistry of the starting allylic halide.[3] This behavior can be explained by assuming[4] that the intermediate chromium(III) organometallics (*E*)-**4** and (*Z*)-**4** equilibrate rapidly via the chromium(III) species **5** before reacting with an aldehyde **2** (Scheme I).[5] We now report that the reaction of γ-*disubstituted* allylic phosphates **6**[6,7] with aldehydes and $CrCl_2$ in the presence of a catalytic amount of LiI (0.2 equiv)[8] in DMPU[9] is *not*

Scheme I



Scheme II



stereoconvergent and proceeds with high stereoselectivity (Scheme II and Table I). The presence of the two substituents at the γ-position apparently slows down the equilibration process between the intermediate allylic chromium reagents **4** (Scheme I). The use of a phosphate as a leaving group[7] is not responsible for the high stereoselectivity, as the reaction of (*E*)- and (*Z*)-*mono*substituted allylic phosphates such as (*E*)- and (*Z*)-2-hexenyl phosphate with benzaldehyde in the presence of $CrCl_2$ under various reaction conditions always affords the anti alcohol as major diastereoisomer (stereoconvergent reaction). The observed stereochemistry[10] can be rationalized assuming

(1) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.

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(6) Allylic phosphates are readily prepared from the corresponding alcohols ($(EtO)_2P(O)Cl$ (1.05 equiv), Pyr (2 equiv), 0 °C, 4 h, 95% yield) and are considerably more stable and easier to handle than the corresponding mesylates: (a) Poulter, C. D.; Satterwhite, D. M. *Biochemistry* **1977**, *16*, 5470. (b) Poulter, C. D.; King, C.-H. R. *J. Am. Chem. Soc.* **1982**, *104*, 1422. For a recent use of allylic phosphates as electrophiles; (c) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 513.

(7) The insertion of $CrCl_2$ into some allylic phosphates has already been reported: (a) Takai, K.; Nozaki, H. In *Abstracts of the 4th ICOS at Tokyo*, 1982. See also refs 2 and 3c.

(8) Lithium halides react rapidly with allylic phosphates in DMF at 25 °C to afford the corresponding allylic halide with retention of the stereochemistry of the double bond: Araki, S.; Ohmori, K.; Butsugan, Y. *Synthesis* **1984**, 841.

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(10) The relative stereochemistry of compound **7** has been established for **7a** by a detailed stereochemical study performed by: M. Koreeda: Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1982**, 1299. Comparison with these spectral data allowed an unambiguous assignment of the relative stereochemistry of **7a** and **7b**.

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