Mixed-Ligand Arenechromium Carbonyl Complexes as Electronic Modulators

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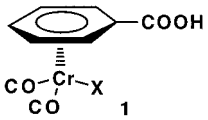
A number of mixed ligand η^6 arenechromium carbonyl complexes have been prepared and investigated for their ability to effect electronic modulation of arene chemistry. In the case of an aniline-derived system, the arenechromium carbonyl complex is able to modulate the inductive capacity of the aniline nitrogen atom and thus, regulate its anchimeric ability. In the case of 8-phenylmenthol and benzyloxazolidinone derivatives, modulation of arene π basicity is achieved, and results suggest that important vinylarene $\pi-\pi$ interactions exist in acrylate derivatives of these chiral auxiliary systems.

Introduction

Arenechromium(0) carbonyl complexes are versatile components of the synthetic arsenal, a consequence of the broad range of chemical and stereochemical properties they possess.[1] On complexation to an arene ring, significant changes to its chemistry occur, including increased susceptibility to nucleophilic attack,[2] increase in acidity of ring protons,[3] and enhanced solvolytic properties,[4] in addition to introduction of the stereodirective capacity of the metal carbonyl tripod.[5] We recently developed a family of enantioselective catalysts that incorporate the arenechromium tricarbonyl group as a stereodirective element[6−8] and have applied these systems in the preparation of enantiomerically enriched synthons for natural product synthesis.[9−11] With the objective of expanding the scope of this emerging class of new catalysts, we became interested in exploiting the *electronic* properties of arenechromium carbonyl complexes, specifically the ability to tune electronic parameters of the arene by selection of appropriate tripod ligands.[12,13] Modulation of the orbital density of arenechromium carbonyl complexes was originally demonstrated by Jaouen in elegant studies involving the ionization of mixed ligand chromium-complexed benzoic acids **1**.[14] As expected, carboxylate acidity was strongly influenced by donor/acceptor contributions of the arenemetal carbonyl system, and the observed pK_a of the tricarbonylchromium derivative (X = CO) reflects the potent withdrawing ability of this subgroup.



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X	pKa **1**
PPh_3	6.15
(benzoic acid	5.68)
$POEt_3$	5.62
$POMe_3$	5.52
CO	4.77

The corresponding dicarbonyl monophosphites, approximately isoelectronic with the uncomplexed arene carboxylate, are notably less acidic, and the dicarbonyl monophosphine complex is more resistant to ionization than the parent carboxylate itself, a consequence of the donor ability of the phosphine group.[14] MO theory of arenechromium carbonyl complexes suggests major changes in both the σ and π bonding occur on complexation, with the principal interactions between $Cr(CO)_3$ and arene being via the $1e-e_{2u}$ and $2e-e_{1g}$ fragment orbitals.[15,16] Ring substituents also interact with the π orbitals of arene complexes, and traditional π-donor substituents (e.g., NEt_2, NH_2, OMe, F, Me) induce π-symmetry interactions with the complex, which can be

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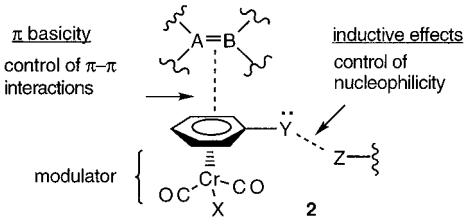
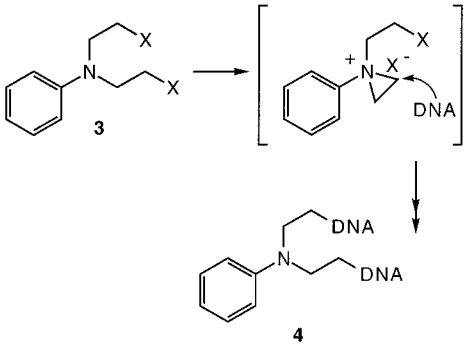


monitored by concomitant lowering of the (CO) infrared carbonyl stretching frequencies.[17] Due to the ability of arenechromium carbonyl complexes to influence the electronic properties of both ring substituents and the π orbitals of the arene, we became interested in developing systems that harness these effects, as depicted in **2**. Modulation of electronic parameters via ligand substitution would be a key feature of such systems, with the metal carbonyl tripod functioning either as a regulator of intermolecular arene−substrate π association by variation of arene π basicity or controlling the nucleophilicity of ring substituents of the system via inductive effects.

Scheme 1

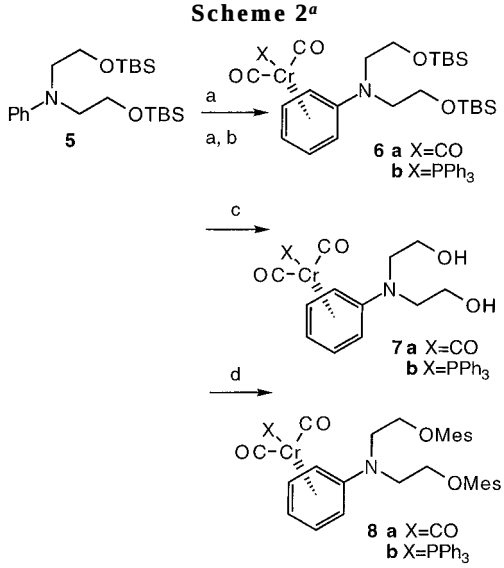


Such a design would offer the potential for *incremental* control of electronic effects and provide a means to match desired electronic properties of the system with the appropriate ligand combinations. We elected to provide proof of principal for this strategy with selected model systems and identified appropriate candidates.

Results and Discussion

1. Inductive Effects: Aniline Mustard Agents. Nitrogen mustard agents that have the capacity to cross-link DNA have proven clinically useful as antineoplastics.[18] Among the simplest of this class are the aniline mustards **3**, typified by the investigational agents NSC18429 (X = Cl) and NSC71035 (X = OMes).[19] Their alkylative ability is principally derived from formation of the intermediate aziridinium ion, which is then attacked by a nucleophilic site of a target macromolecule. In the case of DNA, this predominantly involves guanine at position N-7, ultimately resulting in doubly alkylated species **4** that include interstrand cross-linked adducts (Scheme 1).[20] The alkylative capacity of β-(chloroethyl) or β-(methanesulfonyl)aniline mustards is known to be influenced by electronic parameters on the arene ring,

Scheme 2[a]



[a] Reagents: (a) $Cr(CO)_6$, Δ, Bu_2O:THF; (b) *hν*, PPh_3, PhH; (c) DIBAL-H; (d) MesCl.

an effect that has been exploited effectively in the design of bioreductively activated prodrug systems.[21,22] By increasing the nucleophilicity of the aniline nitrogen atom, increased propensity for formation of aziridinium ions results, leading to a greater potential for alkylative events, including cross-linking.

The significance of inductive electronic control of this process prompted us to investigate the η^6 arenemetal carbonyl group as a modulating device. Direct complexation of *N*,*N*-dialkylaniline derivatives is possible, and due to the thermal instability of the desired alkylating species (**8**), we elected to install the arenechromium carbonyl complex at an early stage. Thus, common precursor **5** was first formed by addition of 2-chloroethanol to aniline, followed by subsequent silylation with *tert*-butyldimethylsilyl triflate (Scheme 2). The silyl ether was then subjected to standard complexation conditions using hexacarbonylchromium, giving the desired chromium complex **6a** in nearly quantitative yield.[12] Using appropriate stoichiometry, photolytic ligand exchange could then carried out to give monophosphine **6b**. Liberation of the hydroxyl groups of these analogues to give diols **7** was eventually accomplished using DIBAL-H,[23] since deprotection using hydrogen fluoride−pyridine resulted in partial decomplexation. Finally, the methanesulfonyl derivatives **8** were prepared, using methanesulfonyl chloride in the presence of triethylamine. The mesyl group was chosen in favor of the chloro group due to both its hydrophilicity (π = −0.88 vs 0.71 Cl) and leaving group ability (L = 1.57 vs −1.61 Cl),[24] important considerations for projected in vitro analysis.

To highlight the importance of the aziridinium ion intermediate on alkylation, control substrate **11** and noncomplexed analogue **12** were also prepared using a similar strategy (Scheme 3). Such agents, being inca-

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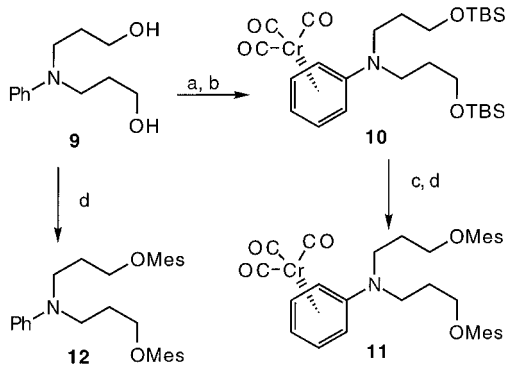
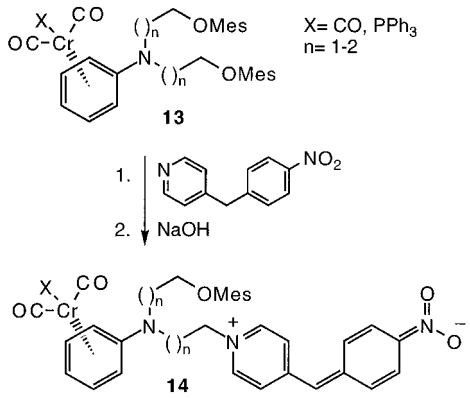
Scheme 3[a]



[a] Reagents: (a) TBSOTf; (b) $Cr(CO)_6$, Δ, Bu_2O/THF; (c) DIBAL-H; (d) Mes-Cl.

Scheme 4



pable of aziridinium ion formation, would be expected to undergo sluggish S_N2 and S_N1 reactions, independent of the electronic environment of the arene.

With the requisite substrates available, aziridinium ion formation was probed using the established 4-(4′-nitrobenzyl)pyridine (NBP) method, which has proven a sensitive assay for the quantitative determination of various alkylating agents (Scheme 4).[25] Thus, nucleophilic addition of 4-NBP to agents **8**, **11**, uncomplexed mustard NSC71035, and agent **12** were carried out, and the formation of adduct **14** (following basification) was assessed as a function of time via colorimetric analysis (Scheme 4).

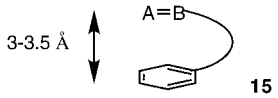
The results, shown in Figure 1 demonstrate clearly the retardative effect of the tricarbonylchromium group in the addition to the complex **8a** relative to NSC71035, a presumed consequence of sluggish formation of the derived aziridinium ion. The mixed ligand complex **8b**, on the other hand, forms the adduct more readily, in agreement with a trend based on the electron-donor capacity of mixed-arenechromium carbonyl complexes (**1**). The involvement of aziridinium ion intermediates was further supported by the failure of complex **11** or analogue **12** to form appreciable quantities of NBP adducts under the conditions employed.

To assess the relevance of alkylative ability in a biological context, the antitumoral activity (growth inhibition) of these agents was then examined using the sensitive human colon tumor cell line HCT-116 (Table 1).[26] Though complexed mustard **8b** was more active than NSC71035, tricarbonyl complex **8a** and related controls also showed high growth inhibition, suggesting cytotoxicity reflects a combination of alkylative ability and independent pathways involving the metal carbonyl appendage. Similar findings were observed against the human breast cancer cell line MCF-7, albeit attenuated due to the decreased sensitivity of these cells to cytotoxic agents.

In addition to the arenemetal carbonyl group itself, decomplexation products could also contribute to independent cytotoxicity. Since a variety of biological agents may, in principle, initiate decomplexation, we assessed conversion of **8a** and **8b** to NSC71035 using suitable mimics (Table 2). As can be seen, peroxides and quinols initiate rapid decomplexation, making it entirely likely that the decomplexed species could be formed to some extent during bioassay. Decomposition of the phosphine complex occurs more rapidly than the tricarbonyl, and this may also be reflected in its comparative cytotoxicity.

On the basis of the alkylation experiments, the metal carbonyl group is clearly functioning as intended in this family of agents—as an electronic modulator able to control aziridinium ion formation via inductive effects through the aniline nitrogen atom. Though intriguing, the therapeutic value of these agents would presumably be overshadowed by independent cytotoxicity of the metal carbonyl group itself. However, it is interesting to note that a number of arenemetal carbonyl complexes have recently been examined as probes for biological receptors.[27,28] On the basis of the results obtained herein, another potential use of such systems may be in the form of tunable molecular probes, in circumstances where (ligand) arene π-receptor interactions are dominant and variation is desirable.[29]

2. π Basicity: Control of π–π Stacking Interactions. In recent years, interest in the attractive interaction generally referred to as "π stacking" has grown immensely.[30] The basic criteria for two molecules to engage in a π stack are satisfied when π clouds interact through space at a distance of between 3 and 3.5 Å, with optimal overlap at approximately 3.4 Å viz. **15**. Applica-



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tions of this stabilizing phenomenon have been demonstrated in areas as diverse as asymmetric synthesis,[31–33] synthetic receptor design,[34] small molecule–DNA inter-

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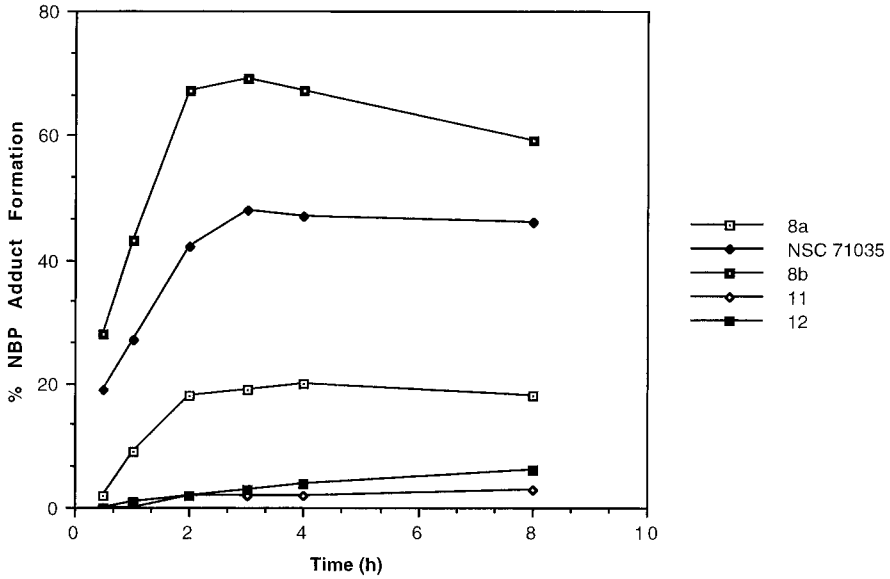


Figure 1. Substrates (0.2 μmol/mL) in EtOH, treated with NBP (1 mL of 5% w/v in pyridine) and potassium hydrogen phthalate buffer (1 mL, 0.05 M), incubated at 80 °C for a fixed period, and then KOH (0.5 mL, 0.1 N) in EtOH (80% v/v) added and colorimetry performed.

Table 1. Growth-Inhibiting Activity (IC_{50}) against HCT-116 and MCF-7 Tumor Cells[a]

entry	compd	HCT-116	MCF-7
1	**8b**	1.4×10^{-9}	1.1×10^{-7}
2	**3** (X = Mes)	2.5×10^{-8}	1.5×10^{-5}
3	**8a**	1.9×10^{-9}	6.6×10^{-6}
4	**5**	1.9×10^{-6}	8.5×10^{-4}
5	**6a**	1.7×10^{-8}	4.1×10^{-5}
6	**11**	1.5×10^{-8}	
7	**12**	9.9×10^{-8}	

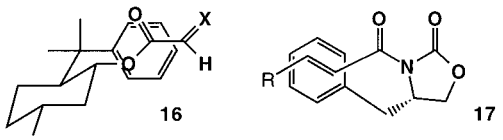
[a] Cells were split, grown to 50% confluence, and then treated with candidate compounds (in triplicate, with concentrations of 10^{-3}–10^{-11} M) and [^{3}H]thymidine. Cell growth was determined by the relative rates of thymidine incorporation into DNA. Cells were maintained in phenol red-free medium containing charcoal-stripped serum to mitigate endogenous estrogenic effects.

Table 2. Decomplexation of 8 to NSC71035 Using External Agents[a]

		% decomplexation			
entry	agent	**8a**:	1 h/12 h	**8b**:	1 h/12 h
1	H_2O_2	55[b]	95[b]	73[b]	99[b]
2	hydroquinone	21	59	33	84
3	$h\nu$[c]	40	99	59	99
4	AIBN	35	75	43	95
5	$HSCH_2CH_2OH$	17[b]	64[b]	29[b]	81[b]
6	control	0	<5	2	14

[a] Compounds (2 mmol) were exposed to excess (2 equiv) decomplexing agent in the dark at 37 °C in degassed DMF solution. [b] Accompanied by mesylate hydrolysis. [c] 450 W Hg lamp.

actions,[35] and photoconductive materials.[36] Of these fields, asymmetric induction has witnessed a recent surge in application in this phenomenon, yet the only direct attempts at *tuning* π-attractive interactions have involved direct replacement of the arene portion of a chiral controller and subsequent comparison of the arene–substrate stacking.[31,32,37] This is a difficult strategy to implement in most cases, with resynthesis of the modified catalyst or chiral controller being required. Since ligand substitution of arene complexes is a trivial process, we envisioned the benefits of a tuned η^6 arenechromium carbonyl system would be clear. Accordingly, we selected two established model compounds, acrylate esters of the 8-phenylmenthol-derived chiral auxiliary system **16** and the (*S*)-phenylalanine-derived benzyloxazolidinone family **17**, both of which have been suggested to facilitate some form of aryl π-substrate π-attractive interactions.[30]



(i) 8-Phenylmenthol Derivatives. Since its introduction in 1975, the 8-phenylmenthol chiral auxiliary **18** has been used to mediate a plethora of asymmetric transformations.[38] The observed asymmetric induction to acrylate derivatives is believed to benefit from π-attractive interactions between the arene moiety and the attached acrylate.[39] With an excellent synthetic route to **18** directly from (+)-pulegone available,[40] following preparation, we opted to derivitize at this point.

Formation of arenechromium tricarbonyl complexes is often facilitated by pendant hydroxy functionality, and direct complexation of 8-phenylmenthol proceeded in excellent yield to give the tricarbonylchromium adduct (Scheme 5). Attempted photolytic ligand exchange of this compound under standard conditions, however, was ineffective and accompanied by significant decomposition. Intermediate protection of the alcohol as its trimethylsilyl ether **19** circumvented the problem, allowing for essentially complete ligand exchange **20**. In situ deprotection of the ether, followed by chromatographic purification, thus gave the chromium dicarbonyl complexes **21a**–**d** in excellent yield (Scheme 5). Formation of the

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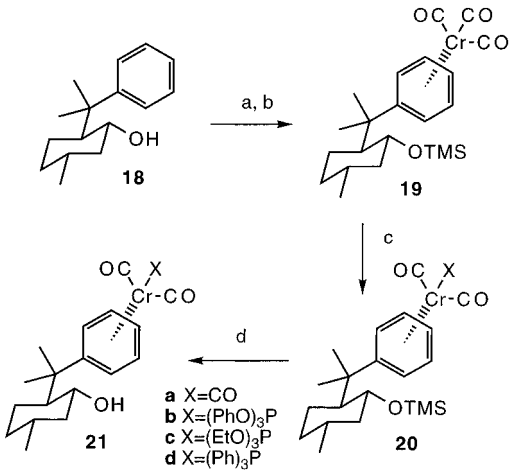
Scheme 5[a]



[a] Reagents: (a) $Cr(CO)_6$, Δ, Bu_2O/THF; (b) TMSOTf; (c) *hν*, X, PhH; (d) K_2CO_3.

Scheme 6

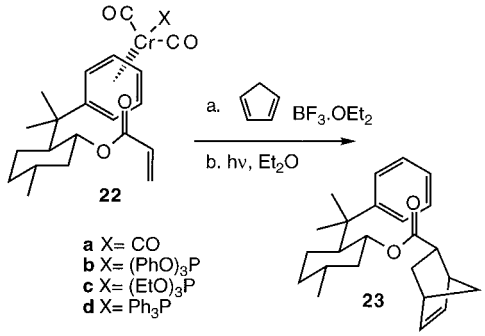


Table 3. Diasteroselective Cycloadditions of Acrylates 22 with Cyclopentadiene[a]

acrylate	*T* (°C)	endo/exo **23**	% de (endo)
22a	−10	90:10	90.2
22c	−10	92:8	92.3
22b	−10	92:8	92.7
uncomplexed	−10	92:8	93.9
22d	−10	93:7	99.1
22a	−30	91:9	91.3

[a] All cycloadditions were conducted in CH_2Cl_2, giving product yields >90% (isolated). Cycloadducts from **22a**−**d** were decomplexed in Et_2O and then analyzed by gradient chiral HPLC (Chiracel OD Column, 0.1−1.25% IPA in hexanes eluent, 1 mL/min flow rate) using a synthetic (9:1 endo/exo, racemic endo) sample of **23** prepared by alternate methods as both an internal and external control.

α,β unsaturated esters was then a trivial operation, giving the chromium complexed acrylates **22** in good (>80%) yield in every case (Scheme 6). For comparison, the uncomplexed acrylate derived from **18** was also prepared. Acrylates **22** were treated with $BF_3{\cdot}Et_2O$ (1.0 equiv) and excess cyclopentadiene in CH_2Cl_2 at −10 °C and allowed to react for 4 h (Scheme 6). The resulting adducts were then decomplexed (Et_2O/*hν*, 8 h, 96−98%) and cycloadducts **23** analyzed by HPLC.

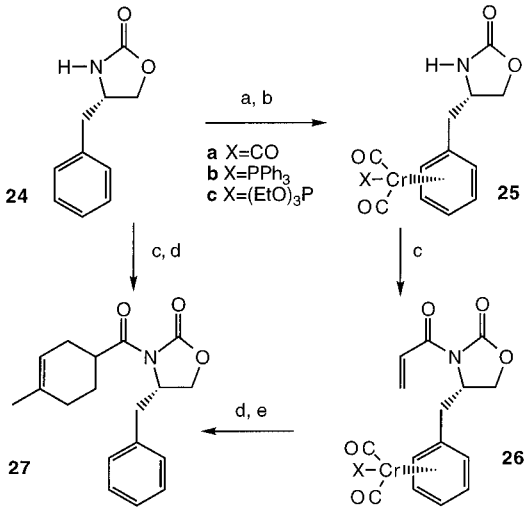
The results clearly show a trend in adduct de that correlates with the electron-donor capacity of the η^6-complexed arenes (Table 3).

Complex **22a**, despite its inherent bulk relative to the "uncomplexed" acrylate, proved inferior both in terms of product exo/endo ratio and diastereocontrol, suggesting subtle electronic effects (Table 3). Complexes **22b**−**d** provide supporting evidence; complexes **22b** and **22c**, which are approximately isoelectronic with the uncomplexed acrylate, indeed afford similar levels of stereocontrol, though they are clearly not isosteric. Additionally, the more electron-rich triphenylphosphine complex **22d** occupies a smaller steric volume than **22b** yet provides enhanced control, effectively negating any argument based solely on steric bulk. In agreement with these findings, Whitesell had previously reported a *decrease* in stereoselectivity when the phenyl ring of an 8-phenylmenthol derivative is replaced with a more bulky cyclohexyl ring.[41] The results herein suggest that a bona fide electronic effect is responsible for the increase in diastereoselectivity in this series and that it can indeed be *modulated by tuning the π-donor ability of the arene*. Selectivity of cycloaddition was not improved significantly at lower reaction temperature, both in terms of product de and exo/endo ratios, and substoichiometric amounts of Lewis acid only served to retard the rate of cycloaddition, having little impact on selectivity (data not shown). The viability of a stacked geometry in this series was supported by X-ray crystallography of **22a** in the absence of Lewis acid.[13] The unit cell contained two conformers consisting of the s-trans and s-cis acrylates, respectively. In the s-trans conformation, the vinyl group sits parallel and approximately 3.6 Å above the arene plane. Though attractive interaction would not be predicted for **22a**, it does indicate the viability of such a geometry. Moreover, the extended π−π distance in this case (3.6 Å) is supportive of a repulsive interaction. A relative rate comparison was conducted for the cycloadditions of acrylates **22**, whereby the cycloadditions were terminated at appropriate intervals (<20% conversion). Surprisingly, complex **22d** was appreciably faster (3-fold) than the other complexes, whose rates were all essentially similar to the "uncomplexed" acrylate. Since the phosphine complex is also the most selective, *it may imply that some form of unique dipole−dipole interaction is established in this system rather than bona fide π-stacking, which could lead to stabilization and concomitant lowering of rate of reaction*. A similar observation was made by Evans in his study of substituted oxazolidinones, wherein a phenyl-substituted derivative gave anomalously high levels of asymmetric induction, yet proceeded at a faster rate.[31] We therefore turned our attention to this system in the hope of revealing more on the nature of these interactions.

(ii) Benzyloxazolidinone Derivatives. The popular oxazolidinone-based chiral auxiliaries introduced by Evans, including **24**, have become common tools in asymmetric synthesis due to their ease of preparation and excellent stereodirective capacity.[31,42] It has been postulated that in the case of acrylate derivatives of **24** attractive (electronic) interactions between the benzyl group of the auxiliary and the vinyl portion of the acrylates may account for the anomalously high levels of asymmetric induction observed in cycloaddition reactions of these derivatives viz. **17**.[42] Attempts to delineate steric contributions from electronic effects of the benzyl group, by employing appropriately substituted analogues of the benzyl oxazolidinone, failed to demonstrate a clear correlation between aryl donor/acceptor ability and observed

(41) Whitesell, J. K.; Lawrence, R. M.; Chen, H.-H. *J. Org. Chem.* **1986**, *51*, 4779.
(42) Evans, D. A.; Chapman, K. T.; Hung, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184.

Scheme 7[a]



[a] Reagents: (a) $Cr(CO)_6$, Δ, Bu_2O/THF; (b) *hν*, X, PhH; (c) $ClCOCH{=}CH_2$, CH_3MgBr; (d) isoprene, Et_2AlCl; (e) *hν*, Et_2O.

levels of diastereocontrol.[31,42] We therefore felt this auxiliary ideal for inclusion in a study where arene π electron density could be directly modulated by a metal carbonyl appendage.

In addition to the reported route,[31] precursor **24** could also be prepared via an expeditious microwave-assisted method involving thermolysis of (2*S*)-2-amino-3-phenylpropan-1-ol and urea, in dimethylacetamide (vide infra). Using this method, high yields of product could be obtained within 3 min on a multigram scale, complimenting previous reports from this laboratory.[43−45] Oxazolidinone **24** was then subjected to complexation conditions to give chromium tricarbonyl derivative **25a** and then converted directly to acrylate **26a** using the Evans procedure (Scheme 7). Photolysis of **25a** in the presence of the appropriate phosphine or phosphite gave **25b** (X = Ph_3P) or **25c** (*X* = $(EtO)_3P$), which, when followed by acrylate formation, yielded **26b** and **26c**. Using the "uncomplexed" acrylate derivative as a control, a series of diethylaluminum chloride promoted cycloadditions of **26a**−**c** with isoprene were then performed.

We were alarmed to find that modification of the auxiliary with *any* arene−chromium appendage decreased diasteroselectivity in the Lewis acid-catalyzed cycloaddition of these acrylates relative to uncomplexed control. Within the series of complexes, however, an apparently similar trend to that observed with the 8-phenylmenthol complexes is revealed, whereby the electron-rich monophosphine complex **26b** gives higher levels of induction than the monophosphite **26c**, which in turn is superior to the electron-deficient tricarbonyl **26a** (Table 4). Mixtures of various cosolvents including toluene invariably resulted in lowering of selectivity, suggesting a polar transition-state complex, if present, does not benefit from additional solvation. It remained to be explained how a trend based on electronic arene-donor ability of the complexes could exist, yet overall the complexes were inferior relative to an "electroneutral" uncomplexed system. Comparison of the relative rates of cycloaddition among the complexes revealed, as was

Table 4. Diastereoselective Cycloadditions of Acrylates 26 with Isoprene

acrylate	*T*/°C	% de **27**
26b	−100	87
26b	−80	74
26b	−30	55
26a	−100	80
26a	−30	60
26c	−100	84
uncomplexed	−100	90
uncomplexed	−30	84

[a] All cycloadditions were conducted in CH_2Cl_2, with product yields >90% (isolated). Products **27** analyzed by capillary VPC (30 m DB1 column, 175−235 °C, 1 °C/min ramp rate).

the case in the 8-phenylmenthol series, that the *phosphine derivative promotes the cycloaddition measurably (1.9 times) faster*, whereas the other derivatives react similarly to the uncomplexed system. As had been observed in the Evans study, stereocontrol was highly dependent on the ratio of Lewis acid/auxiliary. Both complex **26a**,**b** and the uncomplexed acrylate performed poorly when substoichiometric levels of diethylaluminum chloride were employed, whereas above 1.4 equiv, no detectable improvements were evident (Figure 2). As proposed by Evans,[31] this presumably reflects the coordination mode for the Lewis acid, whereby at substoichiometric levels the Lewis acid principally coordinates in a monodentate mode to the acrylate carbonyl group and, when present in excess, in a bidentate mode chelating both carbonyl groups of the auxiliary-substrate system. The monodendate coordination mode would afford greater conformational flexibility for the acrylate vinyl moiety, in turn resulting in a less selective mode of cycloaddition.

Stereoselectivity of cycloaddition as a function of *rate of addition* of Lewis acid to the acrylate/diene solution was also examined. The results suggest that, in each case, a relatively rapid infusion of the Lewis acid is optimal, with diastereoselectivity falling off appreciably with a dropwise addition extended over a 10 min period (Figure 3). This was most pronounced with complex **26a** and, in concert to the data presented in Figure 2, supports the notion that when substoichiometric levels of Lewis acid are present (slow addition rate) the less selective monodentate coordination mode predominates, *which can be partially compensated by π-donor or dipole−dipole interactions with the aryl group of the auxiliary*. In the case of the electron-deficient **26a**, this is, of course, unlikely,[46] rendering the system more vulnerable to the consequences of the increased entropic freedom of the acrylate group.

Since complexes **26** were not amenable to X-ray crystallographic analysis, comparative molecular modeling was performed, employing a conformational search about the carbon−carbon bond connecting the benzylic group to the oxazolidinone ring (24-fold), followed by full geometry minimization of each conformer.[47] It was found that a low-energy conformer of the uncomplexed acrylate

(43) Jones, G. B.; Huber, R. S. *J. Org. Chem.* **1992**, *57*, 5778.
(44) Jones, G. B.; Huber, R. S.; Chau, S. *Tetrahedron* **1993**, *49*, 369.
(45) Jones, G. B.; Chapman, B. J. *J. Org. Chem.* **1993**, *58*, 5558.

(46) A complex in which an arenechromium tricarbonyl group serves to *stabilize* an electron-deficient arene has been reported; see: Kaneta, N.; Mitamura, F.; Uemura, M.; Murata, Y.; Komatsu, K. *Tetrahedron Lett.* **1996**, *37*, 5385.
(47) Modeling performed using an SGI Power Indigo 2. Conformational searching was first performed about the indicated C−C bond (Figure 4) using the MM force field (Sybyl). Low-energy candidates were then submitted to semiempirical (PM3) geometry optimization using Spartan (ver. 4.0.3).

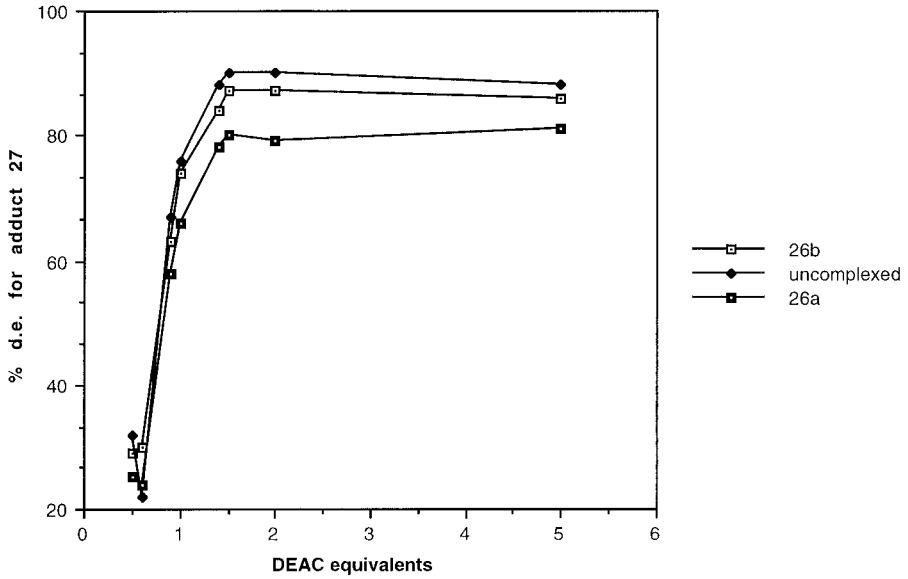


Figure 2. Acrylates **26** and isoprene in CH_2Cl_2 cooled to −100 °C and precooled diethylaluminum chloride (0.5−5.0 equiv) added dropwise down the sides of the vessel over 1−2 min. After 30 min at −100 °C, the reaction was quenched (HCl), extracted with EtOAc, subjected to decomplexation, and analyzed by VPC.

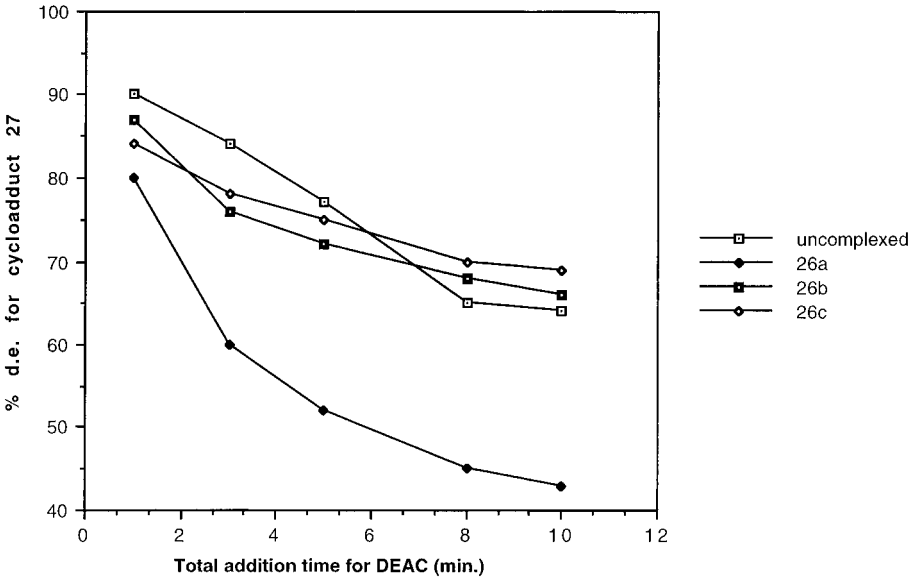


Figure 3. Acrylates **26** and isoprene in CH_2Cl_2 cooled to −100 °C and precooled diethyl aluminum chloride (1.4 equiv) added dropwise down the sides of the vessel over fixed periods (1−10 min). After 30 min at −100 °C, the reaction was quenched (HCl), extracted with EtOAc, subjected to decomplexation, and analyzed by VPC.

exists with the alkene and arene planes approximately parallel (Figure 4a), while in **26a**−**c**, steric buttressing forces a net tilting of the face of the arene by approximately 15° in every case (Figure 4b). Thus, while the vinyl−aryl planes in the uncomplexed system can adopt a parallel orientation and potentially benefit from some from of attractive interaction, the steric demands of the chromium carbonyl appendage in **26a**−**c** are such that these effects are attenuated.

The expected electronic repulsion from the (electron-deficient) arene may then contribute to the lower stereoselectivity observed for complex **26a**. The triethyl phosphite complex **26c**, which should be essentially electroneutral, is superior, and the triphenylphosphine complex **26b** better still, partially overcoming the obvious increase in steric bulk relative to **26a** and **26c**. We therefore conclude that stereocontrol is influenced by the electron-donor donor ability of the arene, but in this specific system overall diastereocontrol is lowered due to the steric buttressing effects of the metal carbonyl appendages themselves.

Conclusion

In summary, the electronic modulation of arenes using mixed ligand η^6 arenechromium carbonyl complexes has been investigated using three independent systems. In the case of aniline mustard agents, the arenechromium carbonyl complex is able to modulate the inductive capacity of the aniline nitrogen atom and, thus, regulate concomitant aziridinium ion formation, as evidenced by nucleophilic addition assays. Further exploitation of such chromium carbonyl arenes as biomolecular probes and inductively triggered devices would thus appear war-

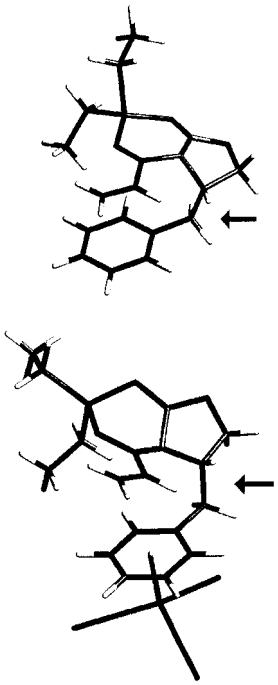


Figure 4. Low-energy conformers for diethylaluminum complexes of uncomplexed acrylate (a) and acrylate **26a** (b) obtained via rotation around the indicated bond using molecular mechanics followed by semiempirical geometry optimization.[47]

ranted.[29] In the case of π basicity modulation, the arenemetal carbonyl complexes examined suggest that important substrate−substrate $\pi-\pi$ interactions do indeed exist in both 8-phenylmenthol and benzyl oxazolidinone acrylates and that such interactions can be modulated by ligand substitution within the metal carbonyl tripod. The exact nature of these interactions remains to be defined and could have origins either in charge transfer or van der Waals-type processes. However, it is apparent from this and other studies[31] that such interactions have limited ability to *stabilize* the counterparts, rendering the electron-deficient component instead more chemically reactive to cycloaddition reactions.[46] The exploitation of this technology in catalytic systems, where variation of such subtle attractive/repulsive forces is likely to have a more profound impact, will be a natural extension of these studies and is expected to have relevance to the field of enantioselective catalysis.[48]

On the basis of the results obtained herein, the incorporation of mixed ligand arenechromium carbonyl complexes in the design of molecular devices represents an encouraging new area. The ease of preparation and chemical stability of the complexes suggest that a variety of applications can be expected, including probes of reaction mechanisms, triggering devices for uni- and bimolecular processes, and as customized Lewis and π bases.

Experimental Methods

General experimental methods and chiral HPLC analysis have been described previously.[11,49] VPC was conducted on a Perkin-Elmer Sigma 3B system using a DB-1 column. Spectrophotometry was performed on a Shimadzu UV-3100 spectrophotometer.

***N,N*-Bis[2-[(1-*tert*-butyl-1,1-dimethylsilyl)oxy]ethyl]-*N*-phenylamine (5).** *N*-Phenyldiethanolamine (1.0 g, 5.52 mmol) was dissolved in CH_2Cl_2 (11 mL) and cooled to −80 °C for the addition of 2,6-lutidine (4.51 mL, 4.15 g, 38.64 mmol) and *tert*-butyldimethylsilyl triflate (2.28 mL, 2.63 g, 12.15 mmol), and the solution was then allowed to warm to room temperature over 1 h. The mixture was poured into ice cold NaOH (50 mL) and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic extracts were washed with 10% HCl (2 × 20 mL), H_2O (2 × 20 mL), and brine (1 × 20 mL) and dried with K_2CO_3. The solution was filtered through a plug of silica and the solvent removed in vacuo to give **5** (2.23 g, 99%) as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 2H), 6.67 (m, 3H), 3.76 (t, J = 6.48 Hz, 4H), 3.51 (t, J = 6.48 Hz, 4H), 0.90 (s, 18H), 0.29 (s, 12H); ^{13}C (75 MHz, $CDCl_3$) δ 144.1, 129.6, 118.7, 113.9, 65.4, 60.3, 20.6, −6.3; IR (neat) 2955, 2918, 2877, 2850, 1614, 1509, 1482, 1271, 1102, 838, 785 cm^{-1}; MS (EI) *m/e* 409 (M^+), 264. Anal. Calcd for $C_{22}H_{43}NO_2Si_2$: C, 64.49; H, 10.58; N, 3.42. Found: C, 64.31; H, 10.39; N, 3.20.

N,N-Bis[3-[(1-*tert*-butyl)-1,1-dimethylsilyl)oxy]propyl]-*N*-phenylamine was similarly prepared (1.93 g, 93%) as a colorless oil from diol **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, J = 7.2 Hz, 2H), 6.73 (d, J = 7.2 Hz, 2H), 6.62 (t, J = 7.2 Hz, 1H), 3.67 (t, J = 7.3 Hz, 4H), 3.39 (t, J = 7.3 Hz, 4H), 1.78 (m, 4H), 0.86 (s, 18H), 0.21 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 129.9, 118.5, 113.4, 61.1, 52.5, 32.6, 20.9, 15.1, −6.7; IR (neat) 2956, 2921, 2882, 2851, 1603, 1507, 1324, 1103, 844 cm^{-1}; MS (EI) *m/e* 437 (M^+), 208. Anal. Calcd for $C_{24}H_{47}NOSi_2$: C, 68.34; H, 11.23; N, 3.32. Found: C, 68.63; H, 11.46; N, 3.09.

***N,N*-Bis[2-[(1-*tert*-butyl-1,1-dimethylsilyl)oxy]ethyl]-*N*-phenylamine−η^6-Tricarbonylchromium Complex (6a).** Silyl ether **5** (3.00 g, 7.33 mmol) and chromium hexacarbonyl (4.80 g, 21.99 mmol) were dissolved in a mixture of THF (8.4 mL) and butyl ether (84.0 mL). The solution was degassed (triple cycle freeze−thaw) and then refluxed for 12 h, cooled to 0 °C, and filtered through a plug of silica gel to remove excess chromium residues. The solvent was then removed carefully in vacuo to give the title compound (3.95 g, 99%) as a yellow solid: mp 75−78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (t, J = 6.6 Hz, 2H), 4.90 (d, J = 6.6 Hz, 2H), 4.76 (t, J = 6.6 Hz, 1H), 3.78 (t, J = 6.0 Hz, 4H), 3.36 (t, J = 6.0 Hz, 4H), 0.88 (s, 18H), 0.05 (s, 12H); ^{13}C NMR (75 MHZ, $CDCl_3$) δ 232.0, 136.0, 98.1, 82.3, 77.4, 59.8, 52.9, 25.8, 18.2, −5.4; IR (neat) 2951, 2933, 2842, 1984, 1851, 1549, 1488, 1282, 1099, 839, 778 cm^{-1}; MS (EI) *m/e* 545 (M^+), 461 (70), 433 (85), 264. Anal. Calcd for $C_{25}H_{43}CrNO_5Si_2$: C, 55.02; H, 7.94; N, 2.57. Found: C, 54.78; H, 8.10; N, 2.79.

N,N-Bis[3-[(1-*tert*-butyl-1,1-dimethylsilyl]oxy]propyl]-*N*-phenylamine−η^6 tricarbonylchromium complex (**10**) was similarly prepared (0.62 g, 94%) as a yellow solid from *N,N*-bis-[3-[(1-*tert*-butyl-1,1-dimethylsilyl)oxy]propyl]-*N*-phenylamine: mp 112 °C dec; ^{1}H NMR (300 MHz, C_6D_6) δ 5.03 (t, J = 7.01 Hz, 2H), 4.57 (t, J = 7.01 Hz, 2H), 4.12 (t, J = 7.02 Hz, 1H), 3.35 (t, J = 5.2 Hz, 4H), 3.01 (t, J = 7.1 Hz, 4H), 1.55 (m, 4H), 0.89 (s, 18H), 0.24 (s, 12H); ^{13}C (75 MHz, C_6D_6) δ 234.8, 96.4, 93.4, 81.4, 73.2, 59.6, 46.6, 29.3, 25.6, −5.8; IR (neat) 2969, 2870, 1962, 1841, 1551, 1362, 1268, 1097, 848, 792 cm^{-1}; MS (EI) *m/e* 573 (M^+), 491, 489 (60), 329. Anal. Calcd for $C_{27}H_{47}CrNO_5Si_2$: C, 56.51; H, 8.26; N, 2.44. Found: C, 56.37; H, 8.02; N, 2.19.

2-[(2-Hydroxyethyl)anilino]-1-ethanol−η^6-Tricarbonylchromium Complex (7a). Complex **6a** (0.10 g, 0.18 mmol) was dissolved in CH_2Cl_2 (17.6 mL) and the solution cooled to 0 °C for the dropwise addition of DIBAL (1.0 mL, 0.78 g, 5.62 mmol) and the resulting mixture stirred at room temperature for 2 h. Ice-cold water was then added dropwise until bubbling ceased, and the mixture was poured onto HCl (1%, 20 mL),

(48) Jones, G. B.; Guzel, M.; Chapman, B. J. *Tetrahedron: Asymmetry* **1998**, *9*, 901.

(49) Jones, G. B.; Wright, J. M.; Rush, T. M.; Plourde, G. W.; Kelton, T. F.; Mathews, J. E.; Huber, R. S.; Davidson, J. P. *J. Org. Chem.* **1997**, *62*, 9379.

extracted with CH_2Cl_2 (5 × 25 mL), and then dried with K_2CO_3. The solvent was removed in vacuo and the residual oil purified by SGC (60:40 EtOAc/hexane) to give the title compound (0.057 g, 98%) as a yellow solid: mp 115−117 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 4.81 (t, J = 7.01 Hz, 2H), 4.17 (t, J = 7.01 Hz, 1H), 3.92 (d, J = 7.01 Hz, 2H), 3.16 (t, J = 4.1 Hz, 4H), 2.72 (t, J = 4.1 Hz, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 235.6, 99.0, 96.2, 83.1, 75.8, 57.5, 52.5; IR (neat) 3404, 2962, 2928, 1947, 1886, 1865, 1840, 1549, 1396, 1080, 854 cm^{-1}; MS (EI) *m/e* 317 (M^+), 233, 157, 150 (100). Anal. Calcd for $C_{13}H_{15}CrNO_5$: C, 49.22; H, 4.77; N, 4.41. Found: C, 49.39; H, 5.03; N, 4.20.

2-[(2-Hydroxyethyl)anilino]-1-ethanol−η^6-dicarbonylmono(triphenylphosphine)chromium complex (**7b**) was similarly prepared (0.072 g, 94%) as a yellow oil from complex **6b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 15H), 5.19 (m, 2H), 4.81 (s, 2H), 4.49 (m, 1H), 4.18 (d, J = 6.1 Hz, 2H), 3.69, (t, J = 4.7 Hz, 4H), 3.35 (t, J = 4.7 Hz, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 242.2, 242.1, 98.7, 95.9, 83.4, 76.8, 56.6, 53.4; MS (EI) *m/e* 551 (M^+), 262. Anal. Calcd for $C_{30}H_{30}CrNO_4P$: C, 65.33; H, 5.48; N, 2.54. Found: C, 65.56; H, 5.74; N, 2.60.

3-[(3-Hydroxypropyl)anilino]-1-propanol−η^6-tricarbonylchromium complex was similarly prepared (1.32 g, 91%) as a yellow solid from complex **10**: mp 142 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.13 (d, J = 7.1 Hz, 2H), 4.99 (t, J = 6.0 Hz, 1H), 4.63 (t, J = 7.1 Hz, 2H), 3.44 (d, J = 5.0 Hz, 4H), 3.22 (t, J = 7.1 Hz, 4H), 1.70 (m, 4H); ^{13}C (75 MHz, C_6D_6) δ 234.1, 96.4, 93.9, 81.3, 73.3, 59.4, 46.7, 29.3; IR (neat) 3431, 2974, 2872, 1966, 1840, 1555, 1364, 1272, 1091, 845, 794 cm^{-1}; MS (EI) *m/e* 345 (M^+), 261. Anal. Calcd for $C_{15}H_{19}CrNO_5$: C, 52.17; H, 5.55; N, 4.06. Found: C, 52.36; H, 5.68; N, 4.30.

2-[2-[(Methylsulfonyl)oxy]ethylanilino]ethyl Methanesulfonate−η^6-Tricarbonylchromium complex (8a). Complex **7a** (0.10 g, 0.32 mmol) was dissolved with Et_3N (0.22 mL, 1.58 mmol) in CH_2Cl_2 (5 mL) and the solution cooled to 0 °C for the dropwise addition of methanesulfonyl chloride (0.06 mL, 0.788 mmol). The mixture was stirred at room temperature for 30 min, diluted with CH_2Cl_2 (5 mL), poured onto ice-cold water (10 mL), and then washed with water (5 × 10 mL) and dried with Na_2SO_4. The solvent was removed in vacuo and the residual oil eluted (60:40 EtOAc/hexane) through a column of silica gel deactivated with 10% Et_3N to afford **8a** (0.136 g, 91%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (t, J = 6.5 Hz, 2H), 4.89 (d, J = 6.5 Hz, 3H), 4.38 (t, J = 5.6 Hz, 4H), 3.64 (t, J = 5.6 Hz, 4H), 3.24 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 236.8, 99.4, 99.3, 97.1, 97.0, 84.4, 63.6, 63.7, 58.4, 58.3, 32.6.

2-[2-[(Methylsulfonyl)oxy]ethylanilino]ethyl methanesulfonate−η^6-dicarbonylmono(triphenylphosphine)chromium complex (**8b**) was similarly prepared (86%) as a yellow oil from **7b**: ^{1}H NMR (300 MHz,C_6D_6) δ 7.52 (m, 15H), 4.39 (t, J = 6.1 Hz, 2H), 4.17 (m, 3H), 3.26 (t, J = 4.8 Hz, 4H), 2.87 (t, J = 4.8 Hz, 4H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 242.1, 242.0, 98.2, 97.5, 92.3, 92.1, 85.4, 64.7, 64.6, 57.4, 57.3, 33.1.

3-(3-[(Methylsulfonyl)oxy]propylanilino)propyl methanesulfonate−η^6-tricarbonylchromium complex **11** was similarly prepared (93%) as a yellow oil from 3-[(3-hydroxypropyl)anilino]-1-propanol−η^6-tricarbonylchromium complex: ^{1}H NMR (300 MHz,$CDCl_3$) δ 5.65 (t, J = 6.4 Hz, 2H), 4.89 (d, J = 6.4 Hz, 3H), 4.38 (t, J = 5.6 Hz, 4H), 3.64 (t, J = 5.6 Hz, 4H), 3.24 (s, 6H), 2.23 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 233.9, 97.1, 94.2, 82.4, 73.9, 58.8, 46.2, 41.3, 28.5; MS (EI) 501 (M^+), 492, 428. Anal. Calcd for $C_{17}H_{23}CrNO_9S_2$: C, 40.72; H, 4.62; N, 2.79. Found: C, 41.03; H, 4.79; N, 2.58.

3-(3-[(Methylsulfonyl)oxy]propylanilino]propyl methanesulfonate **12** was similarly prepared (90%) as a yellow oil from diol **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 2H), 6.72 (m, 3H), 4.28 (t, J = 5.9 Hz, 4H), 3.47 (t, J = 5.7 Hz, 4H), 3.01 (s, 6H), 2.05 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 129.9, 117.8, 113.5, 59.8, 52.4, 33.8, 29.1; IR (neat) 2811, 2794, 1598, 1385, 1141, 762, 691 cm^{-1}; MS (EI) *m/e* 365 (M^+), 333. Anal. Calcd for $C_{14}H_{23}NO_6S_2$: C, 46.01; H, 6.34; N, 3.83. Found: C, 46.28; H, 6.51; N, 3.64.

***N,N*-Bis[2-[(1-*tert*-butyl-1,1-dimethylsilyl)oxy]ethyl]-*N*-phenylamine−η^6-Dicarbonylmono(triphenylphosphine)chromium Complex (6b).** Complex **6a** (0.250 g, 0.46 mmol) and PPh_3 (0.24 g, 0.92 mmol) were stirred in dry benzene (35 mL) for 3 min, and then the resulting solution was degassed (triple freeze−thaw cycles) and maintained under an atmosphere of argon. The solution was irradiated in a quartz tube using a Hg lamp for 30 min and cooled in an ice bath and the resulting precipitate filtered through a short plug of silica gel. The solvent was removed in vacuo and the residual oil purified by SGC (20:80 EtOAc/hexane) to afford the title compound (0.29 g, 83%) as an orange oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 15H), 4.49 (m, 2H), 4.39 (t, J = 6.0 Hz, 1H), 4.05 (d, J = 6.0 Hz, 2H), 3.65 (t, J = 4.9 Hz, 4H), 3.23 (t, J = 4.9 Hz, 4H), 0.88 (s, 18H), 0.01 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 242.1, 242.0, 137.9, 97.1, 81.9, 76.4, 74.9, 59.1, 53.5, 52.1, 26.7, 17.6, −5.1. Anal. Calcd for $C_{42}H_{58}CrNO_4PSi_2$: C, 64.67; H, 7.49; N, 1.80. Found: C, 64.94; H, 7.72; N, 1.73.

3-[(3-Hydroxypropyl)anilino]-1-propanol (9). A mixture of aniline (34.0 g, 42.95 mmol), 3-chloropropanol (24.4 g, 257.7 mmol), and $CaCO_3$ (8.8 g, 85.9 mmol) was refluxed in water (140 mL) with vigorous stirring for 24 h. On cooling, NaOH (2 N) was added to pH 10, and the mixture was extracted with CH_2Cl_2 (3 × 75 mL) and dried with $NaSO_4$. The solvents were removed in vacuo, and the resulting brown oil was purified by SGC (80:20 EtOAc/hexane) to afford **9** (7.64 g, 84%) as white crystals: mp 116−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.74 (m, 3H), 3.78 (t, J = 6.9 Hz, 4H), 3.42 (t, J = 6.9 Hz, 4H), 1.82 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 145.2, 129.2, 117.8, 113.6, 61.9, 53.4, 33.1; IR (neat) 3461, 2861, 2792 cm^{-1}; MS (EI) *m/e* 209 (M^+), 164. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.58; H, 8.90; N, 6.42.

4-(4′-Nitrobenzyl)pyridine Assay. The procedures of Spears,[25] Bardos,[50] and Boger[51] were employed, with the following protocol: Stock solutions (0.2 μM/mL) of the appropriate mustard agent were prepared in ethanol. Aliquots (1.0 mL) were treated with ethanol (1 mL), 4-(4′-nitrobenzyl)pyridine solution (1 mL of 5% w/v in ethanol), and potassium hydrogen phthalate buffer (0.05 M, 1.0 mL). Control samples were identical except for the substitution of ethanol (1.0 mL) for mustard agent. Each assay (and control) vial was placed in a constant temperature water bath (80 °C) for the indicated time period and then removed and immediately cooled to 0 °C. Ethanol (1.0 mL) was then added, followed by KOH (0.6 mL, 0.1 N, in 80% v/v ethanol), and the mixtures were vortexed for 1 min and then analyzed spectrophotometrically (600 nM), using external controls to correct for relative absorbance.

5-Methyl-2-(1-methyl-1-phenylethyl)-1-cyclohexanol−η^6-tricarbonylchromium Complex. Alcohol **18** (3.1 g, 13.4 mmol) and $Cr(CO)_6$ (5.9 g, 26.8 mmol) were suspended in Bu_2O (50 mL) and THF (5 mL) and then heated to 140 °C for 40 h. Upon cooling, the mixture was filtered through a small plug of silica gel and the solvent removed in vacuo. SGC (7:3 hexanes/EtOAc) yielded the title compound as yellow crystals (4.5 g, 91%): mp 126−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (dd, J = 18.5 Hz, J = 6.7 Hz, 2H), 5.45 (t, J = 6.1 Hz, 1H), 5.17 (m, 2H), 3.33 (m, 1H), 0.75−1.85 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 233.7, 123.0, 95.3, 95.0, 94.6, 89.4, 89.3, 72.9, 55.6, 46.5, 39.7, 34.6, 31.5, 27.7, 26.8, 26.1, 21.8; IR (neat, cm^{-1}) 3578, 1956, 1846; $[\alpha]_D$ = +173 (c = 0.033, MeOH). Anal. Calcd for $C_{19}H_{24}CrO_4$: C, 61.95; H, 6.57. Found: C, 61.90; H, 6.60.

Trimethyl[5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl]oxysilane−η^6-Tricarbonylchromium Complex (19). 5-Methyl-2-(1-methyl-1-phenylethyl)-1-cyclohexanol−η^6-tricarbonylchromium complex (2.5 g, 6.8 mmol) and imidazole (1.2 g, 18.2 mmol) were dissolved in DMF (5 mL), and the solution was cooled to 0 °C. Chlorotrimethylsilane (0.93 mL, 7.3 mmol) was added dropwise with stirring, and the reaction was warmed to 25 °C and stirred for 10 h. The solution was then

(50) Bardos, T. J.; Datta-Gupta, N.; Hebborn, P.; Triggle, D. J. *J. Med. Chem.* **1965**, *8*, 167.
(51) Friedman, O. M.; Boger, E. *Anal. Chem.* **1961**, *33*, 906.

poured into cold HCl solution (1%, 25 mL) and extracted with EtOAc (3 × 25 mL). The organic extracts were quickly washed with saturated $NaHCO_3$ (2 × 25 mL) and brine (25 mL), and the solvent was removed in vacuo. SGC (95:5 hexanes/EtOAc) yielded **19** as an orange oil (2.9 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.4−5.6 (m, 3H), 5.15 (m, 2H), 3.43 (m, 1H), 0.75−1.85 (m, 18H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 233.7, 123.6, 95.2, 94.6, 94.5, 89.8, 88.9, 74.2, 54.8, 46.2, 39.8, 34.6, 31.4, 29.1, 27.2, 24.8, 22.0, 1.2; IR (neat, cm^{-1}) 1950, 1870; $[\alpha]_D = +63.6$ ($c = 0.06$, EtOAc).

5-Methyl-2-(1-methyl-1-phenylethyl)-1-cyclohexanol−η^6-Dicarbonylmono(triphenylphosphino)chromium Complex (21d). Complex **19** (0.37 g, 0.84 mmol) and Ph_3P (1.31 g, 5.0 mmol) were dissolved in dry benzene (4 mL). The mixture was degassed (triple freeze−thaw cycles) and then irradiated with ultraviolet light for 4 h under an argon atmosphere. The solvent was removed in vacuo, the residue was suspended in MeOH (5 mL), K_2CO_3 (0.7 g, 5.1 mmol) was added, and the mixture was stirred at 25 °C for 3 h. The K_2CO_3 was then filtered off and the solvent removed in vacuo. SGC (8:2 hexanes/EtOAc) yielded the title compound as an orange oil (0.44 g, 87%): ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.34−7.52 (m, 15H), 5.34 (d, $J = 6.5$ Hz, 1H), 5.14 (d, $J = 6.5$ Hz, 1H), 4.4−4.6 (m, 3H), 3.3 (m, 1H), 0.75−1.85 (m, 18H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 242.4, 242.2, 141.0, 140.6, 133.8, 133.6, 129.6, 128.6, 115.7, 94.8, 92.0, 91.0, 89.5, 89.1, 72.9, 60.0, 56.0, 47.3, 40.7, 35.6, 32.4, 32.2, 28.7, 27.7, 25.7, 22.3; IR (neat, cm^{-1}) 3422, 1878, 1831; $[\alpha]_D = +16.1$ ($c = 0.06$, EtOAc). Anal. Calcd for $C_{36}H_{39}CrO_3P$: C, 71.75; H, 6.52. Found: C, 71.61; H, 6.44.

5-Methyl-2-(1-methyl-1-phenylethyl)-1-cyclohexanol−η^6-Dicarbonylmono(triphenylphosphito)chromium Complex (21b). 21b was similarly prepared from **19** in 91% yield as a yellow oil: ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.1−7.4 (m, 15H), 5.20 (br, 1H), 5.09 (br, 1H), 3.8−4.2 (br m, 3H), 3.15 (br m, 1H), 0.75−1.85 (m, 18H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 238.0, 237.5, 153.3, 130.2, 129.8, 124.8, 122.5, 119.3, 93.6, 92.8, 92.2, 88.8, 88.4, 72.7, 55.5, 47.1, 40.5, 35.4, 32.1, 28.2, 27.5, 26.4, 22.2; IR (neat, cm^{-1}) 3336, 1909, 1839; $[\alpha]_D = +269$ ($c = 0.048$, MeOH). Anal. Calcd for $C_{36}H_{39}CrO_6P$: C, 66.45; H, 6.04. Found: C, 66.61; H, 6.28.

5-Methyl-2-(1-methyl-1-phenylethyl)-1-cyclohexanol−η^6-Dicarbonylmono(triethylphosphito)chromium Complex (21c). 21c was similarly prepared from **19** in 93% yield as a yellow oil: ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 240.0, 239.6, 117.8, 93.3, 92.0, 91.1, 88.4, 87.7, 73.0, 60.0, 55.9, 47.3, 40.6, 35.6, 32.3, 27.8, 25.8, 22.3, 16.6; IR (Neat, cm^{-1}) 3503, 1901, 1823; $[\alpha]_D = +143$ ($c = 0.057$, MeOH). Anal. Calcd for $C_{24}H_{34}CrO_6P$: C, 57.48; H, 6.83. Found: C, 57.75; H, 6.59.

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acrylate. To a solution of 5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol (**18**) (0.2 g, 0.86 mmol) and Et_3N (0.6 mL, 4.3 mmol) in CH_2Cl_2 (3 mL) at −10 °C was added neat acryloyl chloride (0.175 mL 2.15 mmol) dropwise down the sides of the flask over a 5 min period. The deep red solution was warmed to 25 °C and filtered directly, followed by solvent evaporation in vacuo to yield the essentially pure product. SGC (9:1 hexanes/EtOAc) gave the title compound (0.22 g, 91%) as a colorless oil spectroscopically identical with known material:[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.20 (m, 5H), 5.98 (m, 1H), 5.56 (m, 2H), 4.95 (m, 1H), 0.84−1.95 (m, 18H); IR (solution in THF, cm^{-1}) 1721 cm^{-1}; $[\alpha]_D = -16.5°$ ($c = 1$, CH_2Cl_2).

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acrylate−η^6-Tricarbonylchromium Complex (22a). 22a was similarly prepared from **21a** in 80% yield as a pale yellow solid: mp 242−244 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (d, $J = 17.4$ Hz, 1H), 5.79 (m, 2H), 5.47 (m, 3H), 5.07 (m, 2H), 4.73 (m, 1H), 0.84−1.87 (m, 18H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 235.1, 165.3, 131.1, 130.1, 125.4, 97.0, 96.9, 96.5, 91.6, 91.4, 75.0, 52.8, 42.3, 39.9, 35.0, 31.7, 27.9, 27.8, 21.9; IR (solution in THF, cm^{-1}) 1960, 1885, 1724; $[\alpha]_D = +209$ ($c = 0.09$, MeOH). Anal. Calcd for $C_{22}H_{26}CrO_5$: C, 62.55; H, 6.20. Found: C, 62.31; H, 6.47.

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acrylate−η^6-Dicarbonylmono(triphenylphosphito)-chromium Complex (22b). 22b was similarly prepared from **21b** in 82% yield as a yellow solid: mp 88−90 °C; ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 237.8, 237.4, 165.3, 153.3, 130.8, 130.6, 130.2, 128.8, 126.5, 126.1, 125.2, 122.5, 121.5, 120.8, 92.8, 92.3, 89.0, 88.5, 75.0, 74.9, 52.7, 51.1, 42.3, 42.1, 34.9, 32.0, 30.3, 28.7, 27.5, 26.5, 21.8; IR (neat, cm^{-1}) 1900, 1851, 1718, 1715; $[\alpha]_D = -2.9$ ($c = 0.05$, MeOH). Anal. Calcd for $C_{39}H_{41}CrO_7P$: C, 66.47; H, 5.86. Found: C, 66.81; H, 5.98.

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acrylate−η^6-Dicarbonylmono(triphenylphosphino)-chromium Complex (22d). 22d was similarly prepared from **21d** in 88% yield as a yellow oil: ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 242.1, 241.8, 165.3, 152.1, 140.7, 140.3, 133.7, 133.5, 130.7, 130.2, 129.6, 128.6, 128.5, 115.8, 95.2, 91.4, 90.8, 89.1, 88.8, 75.0, 53.0, 42.3, 40.0, 35.1, 32.2, 31.9, 27.6, 26.8, 26.2, 22.0; IR (solution in THF, cm^{-1}) 1891, 1837, 1722; $[\alpha]_D = +141$ ($c = 0.075$, MeOH). Anal. Calcd for $C_{39}H_{41}CrO_4P$: C, 71.33; H, 6.29. Found: C, 71.51; H, 6.38.

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl Acrylate−η^6-Dicarbonylmono(triethylphosphito)chromium Complex (22c). 21c was similarly prepared from **21c** in 85% yield as a yellow oil: ^{1}H NMR (300 MHz, C_6D_6) δ 6.25 (br d, $J = 17$ Hz, 1H), 5.81 (m, 1H), 5.27 (d, $J = 10.1$ Hz, 1H) 4.4−5.0 (m, 6H), 3.44 (m, 6H), 0.5−2.0 (m, 25H); ^{13}C NMR (75 MHz, C_6D_6) δ 238.7, 238.4, 164.8, 117.5, 92.4, 90.8, 90.4, 86.5, 86.3, 74.5, 52.6, 51.0, 41.9, 39.4, 34.6, 31.0, 27.3, 27.1, 26.2, 21.8, 16.6; IR (neat, cm^{-1}) 1901, 1823, 1720; $[\alpha]_D = +291$ ($c = 0.076$, MeOH). Anal. Calcd for $C_{27}H_{41}CrO_7P$: C, 57.85; H, 7.37. Found: C, 58.21; H, 6.99.

5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl-bicyclo[2.2.1]hept-5-ene-2-carboxylate (23). General Procedure. 5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl acrylate (0.029 g, 0.1 mmol) was dissolved in CH_2Cl_2 (5 mL), the solution was then cooled to 0 °C, and freshly distilled cyclopentadiene (1 mL) was added. The mixture was stirred at 0 °C for 20 min, then freshly distilled $BF_3{\cdot}Et_2O$ (0.012 mL, 0.1 mmol) added dropwise down the sides of the flask over a 10 min period. The reaction was stirred at 0 °C for an additional 3.5 h, the solution was poured into saturated $NaHCO_3$ (25 mL) and extracted with EtOAc (3 × 25 mL), the organic extracts were washed with water (25 mL) and brine (25 mL), and the solvent was evaporated to yield **23** as an essentially pure oil (0.032 g, 97%) spectroscopically identical with known material:[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1−7.4 (m, 5H), 5.96−6.12 (m, 2H), 4.77 (m, 1H), 0.5−3.0 (br m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 151.4, 137.1, 132.9, 127.8, 125.7, 125.4, 125.0, 74.3, 50.2, 49.3, 45.1, 43.7, 42.3, 41.8, 39.8, 34.5, 31.2, 29.6, 26.8, 26.6, 26.5, 21.8; HPLC Diacel OD column; 98:2 hexane/isopropyl alcohol eluent; flow rate 1.0 mL/min; endo 1 = 4.44 min, endo 2 = 5.00 min. In the case of the arenechromium carbonyl-complexed acrylates, the crude product was then dissolved in Et_2O (20 mL) and allowed to decomplex (sunlight) completely over a 3 h period. The resulting greenish precipitate was then filtered through a small plug of silica gel and the filtrate condensed in vacuo to yield the cycloadduct **23** as a colorless oil.

(4*S*)-4-Benzyl-1,3-oxazolan-2-one (24). (2*S*)-2-Amino-3-phenylpropan-1-ol (0.95 g, 6.29 mmol) and urea (0.42 g, 6.92 mmol) were dissolved in dimethylacetamide (5 mL) in a 10 mL Erlenmeyer flask. The mixture was then placed in the center of an unmodofied domestic microwave oven (Kenmore, 650 W) and irradiated on full power for 1 min, allowed to cool for 1 min, and then irradiated again for 1 min. The resulting oil was diluted with EtOAc (100 mL), washed with HCl (1%, 50 mL), H_2O (50 mL), and brine (50 mL), and the solvent removed in vacuo to yield **24** (1.0 g, 90%) spectroscopically identical to known material.[31]

(4*S*)-4-Benzyl-1,3-oxazolan-2-one−η^6-Tricarbonylchromium Complex (25a). In a round-bottom flask fitted with a reflux condenser was placed oxazolidione **24** (3.0 g, 16.95 mmol), naphthalene (0.44 g,3.4 mmol), and $Cr(CO)_6$ (7.5 g, 34 mmol). The flask was then charged with Bu_2O (60 mL) and THF (6 mL) and placed in a 140 °C oilbath for 40 h. Upon cooling, the mixture was filtered through a small plug of silica gel and the solvent removed in vacuo. SGC (7:3 EtOAc/

hexanes) yielded **25a** as a yellow green solid (3.24 g, 61%): mp 122−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.5−5.8 (m, 5H), 4.47 (br, 1H), 4.17 (br, 2H), 3.0 (br, 1H), 2.66 (br, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 234.4, 159.4, 109.6, 95.9, 95.4, 93.2, 69.3, 54.0, 40.9; IR (neat, cm^{-1}) 1966, 1898; $[\alpha]_D$ = +77.5 (c = 0.25, MeOH). Anal. Calcd for $C_{13}H_{11}CrNO_5$: C, 49.85; H, 3.54; N, 4.47. Found: C, 50.06; H, 3.47; N, 4.27.

(4*S*)-4-benzyl-1,3-oxazolan-2-one−η^6-Dicarbonylmono(triphenylphosphino)chromium Complex (25b). In a quartz test tube were placed oxazolidinone complex **25a** (0.37 g, 1.18 mmol), Ph_3P (1.55 g, 5.9 mmol), and benzene (4 mL). The mixture was then degassed, placed under argon atmosphere, and irradiated with ultraviolet light for 4 h. The solvent was removed in vacuo and the residue purified by SGC (8:2 EtOAc/hexanes) to yield **25b** (0.46 g, 71%) as an orange solid: mp 49−51 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 6.9−7.5 (br m, 15H), 4.0−5.0 (br m 9H), 2.87 (br, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 241.6, 241.3, 159.3, 140.8, 140.4, 134.5, 134.2, 133.7, 133.6, 130.1, 129.8, 129.6, 129.3, 128.7, 128.6, 127.4, 102.5, 92.8, 92.7, 90.8, 90.4, 89.7, 69.4, 54.2, 41.4; IR (neat, cm^{-1}) 1878, 1839; $[\alpha]_D$ = +31.4 (c = 0.11, $(CH_3)_2CO$). Anal. Calcd for $C_{30}H_{26}CrNO_4P$: C, 65.81; H, 4.79; N, 2.56. Found: C, 66.14; H, 4.84; N, 2.26.

(4*S*)-4-benzyl-1,3-oxazolan-2-one−η^6-Dicarbonylmono(triethylphosphito)chromium Complex (25c). 25c was similarly prepared from **25a** in 84% yield as a yellow solid: mp 66−69 °C; ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.26 (m, 1H), 4.9−5.2 (m, 5H), 4.44 (t, J = 7.3 Hz 1H), 4.15 (m, 2H), 3.87 (m, 6H), 2.60 (m, 2H), 1.18 (t, J = 6.9 Hz, 9H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 239.2, 238.6, 103.3, 91.5, 91.4, 90.9, 90.5, 89.5, 69.2, 60.0, 54.1, 41.2, 16.5; IR (neat, cm^{-1}) 3578, 1956, 1846; $[\alpha]_D$ = +126.7 (c = 0.071, MeOH). Anal. Calcd for $C_{18}H_{26}CrNO_7P$: C, 47.90; H, 5.81; N, 3.10. Found: C, 48.19; H, 5.69; N, 2.71.

(4*S*)-3-acryloyl-4-benzyl-1,3-oxazolan-2-one. To a solution of (4*S*)-4-benzyl-1,3-oxazolan-2-one (**24**) (0.12 g, 0.68 mmol) in THF (5 mL) at 0 °C was added MeMgBr (3M Et_2O, 0.23 mL, 0.69 mmol) dropwise. The solution was stirred at 0 °C for 20 min, acryloyl chloride (0.06 mL, 0.72 mmol) added dropwise, and the solution allowed to warm to 25 °C. The mixture was poured into HCl (1%, 10 mL) and extracted with EtOAc (3 × 25 mL). The organic extracts were washed with water (25 mL) and brine (25 mL), the solvent removed in vacuo, and the residue purified by SGC (7:3 hexanes/EtOAc) to yield the title compound (0.11 g, 74%) as a white solid, mp 74−75 °C, spectroscopically identical with known material:[31] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 17.5, 10.3 Hz, 1H), 7.28 (m, 5H), 6.55 (dd, J = 17.5, 2.1 Hz, 1H), 5.90 (dd, J = 10.1, 2.1 Hz, 1H), 4.79 (m, 1H), 4.15 (m, 2H), 3.42 (dd, J = 13.3, 3.7 Hz, 1H), 2.85 (dd, J = 13.3, 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 165.3, 154.2, 136.7, 131.0, 130.4, 129.5, 128.8, 127.8, 67.1, 55.8, 37.9; IR (neat, cm^{-1}) 1787, 1695; $[\alpha]_D$ = +71.1 (c = 0.043, $CHCl_3$).

(4*S*)-3-Acryloyl-4-benzyl-1,3-oxazolan-2-one−η^6-Tricarbonylchromium Complex (26a). 26a was prepared from **25a** in 71% yield as a yellow oil: ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.40−7.49 (dd, J = 17.0, 10.5 Hz, 1H), 6.45 (dd, J = 17, 2 Hz, 1H), 5.90 (dd, J = 10.5, 2 Hz, 1H), 5.46−5.68 (m, 5H), 4.80−4.87 (m, 1H), 4.45−4.59 (m, 2H), 2.81−2.95 (m, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 234.3, 165.3, 154.1, 131.0, 129.1, 108.7, 95.8, 95.7, 95.6, 93.5, 67.5, 55.8, 38.0; IR (neat, cm^{-1}) 1956, 1901, 1784, 1690; $[\alpha]_D$ = +106.9 (c = 0.063, $CHCl_3$). Anal. Calcd for $C_{16}H_{13}CrNO_6$: C, 52.32; H, 3.57; N, 3.81. Found: C, 52.51; H, 3.47; N, 3.90.

(4*S*)-3-Acryloyl-4-benzyl-1,3-oxazolan-2-one−η^6-Dicarbonylmono(triphenylphosphino)chromium Complex (26b). 26b was prepared from **25b** in 81% yield as a yellow soild: mp 54−55 °C; ^{1}H NMR (300 MHz $(CD_3)_2CO$) δ 7.36−7.49 (m, 16H), 6.48 (dd, J = 17, 1.9 Hz, 1H), 5.89 (dd, J = 10.5, 1.9 Hz, 1H), 4.40−4.80 (m, 8H), 2.72−2.90 (m, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 241.6, 241.3, 165.2, 154.1, 140.7, 140.3, 133.8, 133.6, 131.2, 129.9, 128.8, 128.7, 101.6, 92.5, 92.4, 90.9, 90.5, 89.9, 67.4, 55.9, 38.0; IR (neat, cm^{-1}) 3040, 1909, 1839, 1776, 1699; $[\alpha]_D$ = +112.9 (c = 0.09, C_6H_6). Anal. Calcd for $C_{33}H_{28}CrNO_5P$: C, 65.89; H, 4.69; N, 2.33. Found: C, 65.77; H, 4.81; N, 2.52.

(4*S*)-3-Acryloyl-4-benzyl-1,3-oxazolan-2-one−η^6-Dicarbonylmono(triethylphosphito)chromium Complex (26c). 26c was prepared from **25c** in 84% yield as a yellow oil: ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.46 (dd, J = 17.1, 10.5 Hz, 1H), 6.46 (dd, J = 17.1, 1.9 Hz, 1H), 5.89 (dd, J = 10.5, 1.9 Hz, 1H), 4.7−5.1 (m, 6H), 4.5 (m, 2H), 3.87 (m, 6H), 2.7−2.9 (m, 2H), 1.18 (t, J = 7.2 Hz, 9H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 239.1, 238.7, 165.2, 154.2, 131.2, 128.7, 102.1, 91.3, 91.2, 90.9, 90.8, 89.8, 67.4, 60.1, 55.9, 37.9, 16.5; IR (neat, cm^{-1}) 1893, 1839; $[\alpha]_D$ = +271 (c = 0.053, MeOH). Anal. Calcd for $C_{21}H_{28}CrNO_8P$: C, 49.90; H, 5.58; N, 2.77. Found: C, 50.13; H, 5.75; N, 2.55.

(4*S*)-4-Benzyl-3-[(4-methyl-3-cyclohexenyl)carbonyl]-1,3-oxazolan-2-one (27). (4*S*)-3-Acryloyl-4-benzyl-1,3-oxazolan-2-one (0.1 g, 0.43 mmol) was dissolved in CH_2Cl_2 (1.0 mL) in a 10 mL graduated cylinder, modified with a 14/20 joint, and fitted with a rubber septum. The solution was cooled to −100 °C with stirring. Isoprene (1.0 mL, 10 mmol) was then added down the sides of the vessel. Finally, diethylaluminum chloride (1.8 M in toluene, 0.34 mL, 0.61 mmol) was added dropwise down the sides of the vessel over 1−2 min. After 30 min at −100 °C, the reaction was poured into HCl (1%, 10 mL) and extracted with EtOAc (4 × 50 mL). The organic extracts were then washed with $NaHCO_3$ (25 mL), water (25 mL), and brine (25 mL), and the solvent was evaporated to give the cycloadduct **27** (0.11 g, 93%) spectroscopically identical with known material:[31] ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 7.15−7.30 (m, 5H), 5.40 (br, 1H), 4.72 (m, 1H), 4.21 (m, 2H), 3.30 (m, 1H), 2.75 (br m, 1H), 1.5−2.42 (m, 6H), 1.60 (br s, 3H); VPC (30 m DB-1, 175−235 °C 1 °C/min ramp rate) t_R major 54.0 min, minor 54.4 min.

General Cycloaddition Procedure for Acrylates 26a−c. Following the workup procedure, the yellow-orange residue was then taken into Et_2O and allowed to stand until decomplexation was complete by TLC (approximately 2−3 h). Filtration followed by solvent evaporation gave the cycloadduct **27** spectroscopically identical with known material.

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