Studies into the Stereoselectivity of Diels-Alder Reactions with η 6- Ruthenium Arene Complex Substituents

Kerri McInnis
Carroll College, Helena, MT
This thesis for honors recognition has been approved for the
Department of Chemistry & Physics.

DAVID M. HITT  4/30/18
Director

Print Name

CAROLINE PHARR  4/30/18
Reader

Print Name

DEBRA BEKLANDI  4/30/18
Reader

Print Name
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Kerri M. McInnis

Department of Chemistry and Physics, Carroll College, Helena, MT 59625

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Abstract

In organic chemistry, $\eta^6$-ruthenium arene complexes are able to act as powerful electron-withdrawing groups, thereby facilitating the nucleophilic aromatic substitution and deprotonation of benzylic and aromatic positions.\textsuperscript{1–7} Additionally, having the metal complex bound to a non-symmetrical arene provides a source of chirality, allowing for stereoselective chemistry.\textsuperscript{1,6,8–18} It is well known that Diels-Alder (DA) reactions with an electron-rich diene can be accelerated by electron-withdrawing substituents on the dienophile. Previous studies by the Hitt research group have suggested that $\eta^6$-ruthenium arene complexes can accelerate DA reactions involving adjacent alkenes.\textsuperscript{19} However, the effect of using a chiral ruthenium arene substituent on the dienophile as a stereocontrol element has not been analyzed.

In this vein, the compound [CpRu($\eta^6$-(ethyl 2-chlorocinnamate))]PF$_6$ was synthesized in several steps from 2-chlorobenzaldehyde and used as a model dienophile in the DA reaction with 2,3-dimethyl-1,3-butadiene. Herein, we report the details of the dienophile synthesis and our attempts at a successful DA reaction.

Introduction

It has long been known that $\eta^6$-metal arene complexes act as potent electron-withdrawing groups.\textsuperscript{1–7} For this reason, the complexes are able to facilitate aromatic reactivity often accessible only under harsh conditions, such as the nucleophilic aromatic substitution and deprotonation of benzylic and aromatic positions. Furthermore, arene complexes that contain non-symmetrically-substituted aromatic rings contain an element of planar chirality, thus enabling the possibility for stereoselective chemistry.\textsuperscript{1,6,8–18}
The most well-known metal fragment used in organic synthesis for electron-withdrawing purposes is the \( \eta^6 \)-chromium tricarbonyl \([Cr(CO)_3] \) moiety.\(^7\) A prime example of research that utilizes both the electron-withdrawing effect and planar chirality of the \([CrCO)_3] \) fragment is in acceleration and stereoinduction of DA reactions where the \( \eta^6 \)-arene is a substituent on the dienophile.\(^1,2,5,9-16,18\) For example, the research group led by Ishimaru\(^15\) predicted that attaching a planar chiral (1,2- or 1,3- disubstituted arene)chromium moiety to a benzaldimine derivative would increase enantioselectivity of the piperidone produced through a DA reaction with silyloxybutadiene. Indeed, their results exhibited a complete facially diastereoselective reaction and further demonstrated that the piperidone was a highly enantiomerically enriched trans- diastereomer (with respect to the \( C_2 \) and \( C_6 \) positions of the piperidone ring) (3, Scheme 1).

**Scheme 1**: Mechanistic model proposed by Ishimaru to explain stereoselectivity of benzaldimine DA reaction.\(^15\)

The researchers concluded that the diastereoselectivities of the respective DA products were increased with an increase in the steric bulk of the \( \alpha \)-substituent of the dienophile. For this reason, a bulky tricarbonylchromium substituent was attached to the dienophile, resulting in a planar chiral complex, thereby increasing stereocontrol. As can be seen in the favored transition state (1), the diene attacks the dienophile on the face *anti-* to the metal fragment. Furthermore, the \( \eta^6 \)-aryl moiety prefers the *exo-* position of
the boat structure (also presumably due to steric), which disfavors formation of the cis-diastereomer. The model used by the Ishimaru group incorporates a Lewis acid, TMSOTf, which serves to chelate the substituents, thus restricting conformational mobility. The involvement of the Lewis acid is critical for the stereoselectivity observed in their product (Scheme 1) and therefore restricts the usefulness of the model.

Alternatives to chromium moieties have not been explored thoroughly as activating groups in DA reactions. One metal fragment of particular interest is the cationic η⁵-cyclopentadienylruthenium(II) group (CpRu⁺), which forms air-stable η⁶-arene complexes existing as an ion pair with a non-coordinating anion such as PF₆⁻. These compounds have proven to be very valuable in organic synthesis, yet have only been tested twice as dienophiles in DA reactions, both of which occurred in isolated examples without comparison to the non-complexed dienophile. First, Lindel et al. observed the formation of DA products in a one-pot synthesis of η⁶-ruthenium arene complexes from ruthenium(III) chloride. The DA reaction presumably occurred between the unreacted ligand, pentamethylcyclopentadiene (Cp*H), and the η⁶-ruthenium arene complex of ethyl trans-cinnamate. However, the group reported the byproducts as “undesirable” and didn’t explore the reactivity further. Second, the Glatzhofer research group showed that DA adduct 6 could be formed as the sole diastereomer when the metal complex of anthracene derivative (4) was reacted with 2,3-dimethyl-1,3-butadiene (5) via a mechanism where the diene attacks exclusively from the face anti- to the metal fragment (Scheme 2).
Scheme 2: Previous work by Glatzhofer et. al using [CpRu(η⁶-arene)]PF₆ dienophile (4).

Given that η⁶-ruthenium arene substituents are exceedingly electron-withdrawing, it follows that these moieties ought to accelerate normal electron-demand DA reactions when bound to the dienophile component.⁴,⁵ Although both Lindel²⁰ and Glatzhofer³ performed the Diels-Alder reaction with η⁶-ruthenium arene complexes, neither group made a direct rate comparison of complexed versus free arene dienophile. To this end, previous research by the Hitt research group involved qualitative observation of the DA reaction involving free ethyl trans-cinnamate vs. [CpRu(η⁶-(ethyl trans-cinnamate))]PF₆ (7) with 2,3-dimethyl-1,3-butadiene (5) (Scheme 3).¹⁹ Indeed, the reaction involving metal-arene dienophile (7) went to completion in 48 hours, whereas the free arene dienophile showed no evidence of product after 8 days, thus showing the metal complex’s drastic ability to accelerate the DA reaction.

Scheme 3: Previous work by Hitt research group indicating accelerating abilities of [CpRu(η⁶-arene)]PF₆ dienophile (7).
The goal of this study is to explore the stereocontrol effects imparted by a planar chiral \( \eta^6 \)-ruthenium aryl substituent on the DA reaction. Although the ability of the metal complex to provide stereoinduction was shown by the Glatzhofer research group,\(^3\) their system is predictable and synthetically restrictive, since the dienophile, a CpRu(\( \eta^6 \)-bound anthracene) (4), has a locked conformation due to the cyclic system. In this study, we plan to investigate the stereoselectivity of a conformati∞ionally unrestricted dienophile (9, Scheme 4). Unlike the arene complex used previously (4, Scheme 2), we plan to study an ortho substituted arene complex that contains an element of planar chirality. The absolute stereochemistry of these complexes can be assigned in an analogous fashion to chirality centers by determining the rotational direction from the highest priority to the subsequent highest priority substituent, as viewed from the face of the arene anti- to the metal fragment. Depending on whether the rotation is clockwise or counter-clockwise, the planar chirality would be assigned as \( R_p \) or \( S_p \), respectively.\(^{19}\) Furthermore, most complexed dienophiles previously analyzed in Diels-Alder reactions with the tris(carbonyl)chromium aryl moiety are nitrogen-based, whereas the dienophile used in this study (9, Scheme 4) is carbon-based. All these characteristics of our system increase the breadth to which the results could be synthetically applicable.
Scheme 4: Proposed conformational equilibrium dictating major and minor stereoisomer (10) products resulting from DA reaction of Ru-dienophile complex (9) with diene (5).

Although the diene would likely approach the dienophile from the face opposite the metal substituent, the dienophile (9) is freely rotating in our system, enabling both faces to undergo the DA reaction, which would negate any stereoselectivity if unrestricted. However, we propose that the conformer 9-maj would be favored due to minimized steric interactions between the ortho substituent and the reactive alkene. If this proves true, a preference for diastereomer 10-maj over 10-min might be observed (Scheme 4). A similar model has been used to explain the stereocontrol of 1,3-dipolar cycloadditions using ortho-substituted (η⁶-styrene)Cr(CO)₃ complexes. In that vein, the purpose of this study was to more thoroughly examine this conformational effect and any resulting stereoselectivity. Herein are reported our findings regarding the synthesis of the dienophile substrate and preliminary investigations into the stereoselectivity of a Diels-Alder reaction using planar chiral η⁶-ruthenium arene complex substituents.
Results and Discussion

Scheme 5: Retrosynthesis of model dienophile substrate (9).

To initiate our study, Ru-arene complex 9 was chosen as a model substrate that contains a cinnamate ester arene and a Cp ligand. These arene complexes typically form easily when the precursor benzenoid (14) is reacted with [CpRu(NCMe)3]PF6 (13). The free arene dienophile was envisioned to originate from a Wittig reaction between a commercially available aldehyde (11) and a stabilized ylide (12). We chose a chloro substituent to establish the planar chirality due to its ability to undergo facile substitution when treated with moderate to strong nucleophiles, thus providing the possibility for further synthetic manipulation after the DA cycloaddition.

The first step in synthesizing the model dienophile substrate (9) was the Wittig olefination of 2-chlorobenzaldehyde (11, Equation 1) to ethyl 2-chlorocinnamate (14). This reaction proceeded smoothly under refluxing conditions in benzene, followed by purification by recrystallization and chromatography. An IR spectrum of the resulting product exhibited the appearance of a new alkene stretch at 1634 cm⁻¹, along with a change of the carbonyl stretch to 1711 cm⁻¹ (Appendix 2). Analysis by ¹H NMR revealed
that it consisted of a mixture of cis- and trans- isomers, given that there were two sets of signals for each unique hydrogen (Appendix 1). The cis- and trans- stereoisomers were assigned based on the vinyl hydrogen coupling constant, which for the trans- doublet is $J_{HH} = 16.04$ Hz, and for the cis- doublet is $J_{HH} = 10.24$ Hz. Relative integrations suggest that it is an 85:15 ratio of trans- to cis- isomers. Originally, the cis- and trans-diastereomers of the crude product were fully separated by column chromatography, as confirmed by $^1$H NMR spectroscopy. However, it was observed that the compound undergoes isomerization during metal complexation (vide infra) and it was therefore found most efficient to proceed directly to the next synthetic operation without further purification.

![Diagram](image)

The second step was the attachment of the precursor benzenoid (14, Equation 2) to [CpRu(NCMe)$_3$]PF$_6$ (13). The reaction mixture was stirred in acetone at room temperature, then washed with ethyl ether and purified by column chromatography. Successful coupling of the substituent (13) to ethyl 2-chlorocinnamate (14) was confirmed by an upfield shift of the aromatic hydrogens by approximately 1 ppm, to resonances of $\delta$ 6.1 - $\delta$ 6.5 in $^1$H NMR analysis (Appendix 3). Additionally, a new singlet peak at $\delta$ 5.5 corresponding to the Cp substituent appeared in a 53:47 ratio with the aryl hydrogens. Akin to the analysis of ethyl 2-chlorocinnamate, a mixture of stereoisomers was suggested by the appearance of two sets of peaks for each unique hydrogen, with the trans- associated peaks slightly more downfield and with a larger
coupling constant for the vinyl hydrogen signals than the *cis*-associated signals. In order to simplify analysis of the crude DA reaction mixture, we found it necessary to separate the mixture of stereoisomers, which was accomplished by column chromatography and confirmed by $^1$H NMR spectroscopy.

**Scheme 6:** Proposed DA reaction of stereopure [CpRu(η⁶-arene)]PF₆ dienophile (9) with diene (5).

Initial attempts to run a DA reaction with the metalated dienophile (9) and diene 5 were not successful (Scheme 6), even after several days under reflux conditions. In subsequent trials, diethylaluminum chloride was used as a catalyst in dichloromethane solvent, but still no DA products were observed. Since the reaction has been successful previously without the catalyst by the Hitt research group, it was speculated that the reagents being used were old or inactive. Nitromethane can contain aldehyde, nitroethane, water, and alcohol impurities, which may be removed by drying with CaCl₂ or distillation, followed by drying with CaSO₄.²³ It is our hypothesis that water is the source of impurity in the nitromethane, given that the Glatzhofer research group specified that dry nitromethane was used in their study.³ Therefore, had time allowed, we would have followed published drying procedures for nitromethane and reattempted the DA reaction (Scheme 6).
Conclusion

In summary, we have proposed and synthesized a model dienophile substrate (5), composed of an $\eta^6$-ruthenium arene complex, to be used in a Diels-Alder reaction. The Hitt research group has demonstrated the use of such metal-complexed dienophiles as accelerators in DA reactions, due to the electron-withdrawing capacity of the substituent. It has also been determined that the substrate is isomerized during the ruthenium-binding step, resulting in a mixture of diastereomers and necessitating product purification in order to analyze the stereocontrol abilities of the metal-complex substituent. Furthermore, the group suggests that the bound ruthenium substituent on the dienophile provides a source of planar chirality, and therefore serves as a stereocontrol element throughout the DA reaction, resulting in a diastereospecific product. Future studies will be focused toward developing a more productive DA reaction protocol using the given dienophile and diene substrates, as well as identification of other potential metal-arene dienophiles.

Experimental

General Information. All reagents used were purchased from chemical suppliers and used as received. Flash column chromatographic purification of synthetic intermediates and substrates was performed using silica gel (60 Å, particle size 43-60 μm, 230-400 mesh) or activated neutral alumina (50-200 micron, Acros Organics).

Instrumentation. NMR spectra were recorded on a Bruker BioSpin Ascend Aeon 400 ($^1$H, 400 MHz; $^{13}$C 100 MHz) spectrometer. $^1$H and $^{13}$C NMR chemical shifts (δ) were reported in parts per million (ppm) relative to tetramethylsilane ($^1$H and $^{13}$C, δ0.00 ppm),
with reference to the residual proton or carbon resonance for CDCl$_3$ ($^1$H, $\delta$ 7.26 ppm; $^{13}$C $\delta$ 77.16 ppm). Infrared (IR) spectra were recorded on a ThermoFisher Nicolet Smart iTR iS10 FTIR.

**Synthesis of Ethyl 2-chlorocinnamate (14).** A mixture of 2-chlorobenzaldehyde (0.8 mL, 7.11 mmol), (carbethoxymethylene)triphenylphosphorane (2.73 g, 7.83 mmol), and benzene (7 mL, 78.9 mmol) was stirred under reflux conditions for 6 h. The resulting yellow liquid was concentrated under reduced pressure and purified by recrystallization (EtOAc/hexanes) to remove triphenylphosphine oxide. After removing the solid by filtration, the resulting crude mixture was purified by flash column chromatography (30:1 silica gel/crude product, 98:2 hexanes/EtOAc) to afford a 1:0.18 (NMR) of cis/trans-ethyl 2-chlorocinnamate (14) as a yellow oil (0.448 g, 30% yield). IR (ZnSe, neat): 3066 (=C=H) cm$^{-1}$, 1711 (C=O) cm$^{-1}$, 1634 (alkene C=C) cm$^{-1}$, 1590 (aryl C=C) cm$^{-1}$, 1175 (C-O) cm$^{-1}$. $^1$H NMR $\delta$ 1.19 (t, $^3$J$_{HH}$ = 7.12 Hz, 3 H, cis-CH$_2$CH$_3$), $\delta$ 1.37 (t, $^3$J$_{HH}$ = 7.12 Hz, 3 H, trans-CH$_2$CH$_3$), $\delta$ 4.15 (q, $^3$J$_{HH}$ = 7.12 Hz, 2 H, cis-CH$_2$CH$_3$), $\delta$ 4.30 (q, $^3$J$_{HH}$ = 7.12 Hz, 2 H, trans-CH$_2$CH$_3$), $\delta$ 6.09 (d, $^3$J$_{HH}$ = 10.24 Hz, 1 H, cis-CHC=O), $\delta$ 6.45 (d, $^3$J$_{HH}$ = 16.04 Hz, 1 H, trans-CHC=O), $\delta$ 7.1-7.55 (m, 5.12 H, C$_6$H$_5$), $\delta$ 7.63 (d, $^3$J$_{HH}$ = 11.0 Hz, 1 H, cis-CHC=O), $\delta$ 8.11 (d, $^3$J$_{HH}$ = 16.0 Hz, 1 H, trans-CHC=O).

**Synthesis of (η$^6$-(1-chloro-2-(2-ethoxycarbonylethenyl)phenyl)-η$^5$-(cyclopentadienyl)tris(acetonitrile) ruthenium(II) hexafluorophosphate (6).** A nitrogen-saturated solution of ethyl 2-chlorocinnamate (48.4 mg, 0.2303 mmol) in acetone (51.2 mL, 0.697 mol) was added to a nitrogen-purged vessel containing tris(acetonitrile)cyclopentadienylruthenium(II)hexafluorophosphate (60 mg, 0.1382 mmol) via cannula transfer at RT. The resulting orange solution was stirred for 3 h at RT
under a positive pressure of nitrogen, then concentrated under reduced pressure. The
residual solid was washed with ethyl ether (3 x 4 mL), and purified by flash column
chromatography (neutral alumina, CH₂Cl₂, then 95:5 CH₂Cl₂/acetone to afford (6) as a
white solid (9 mg, 18.5% yield, >95% trans). ¹H NMR. δ 1.4 (t, ³JHH = 6.8 Hz, 3 H,
CH₂CH₃), δ 4.34 (q, ³JHH = 6.16 Hz, 2 H, CH₂CH₃), δ 5.51 (s, 5 H, Cp), δ 6.4-6.7 (m, 4 H,
C₆H₅), δ 6.68 (d, ³JHH = 16.8 Hz, 1 H, CH₂CH₂CO), δ 7.82 (d, ³JHH = 17.0 Hz, 1 H,
CH₂CH₂CO).

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Appendix 1: $^1$H NMR of ethyl 2-chlorocinnamate (14).

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Appendix 2: IR of ethyl 2-chlorocinnamate (14).

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Appendix 3: $^1$H NMR of ($\eta^6$-(1-chloro-2-(2-ethoxycarbonylethenyl)phenyl)-$\eta^5$-tris(acetonitrile)cyclopentadienylruthenium(II))hexafluorophosphate (9).

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