



Substrate and reagent control of diastereoselectivity in transition metal mediated processes :  
development of a catalytic photopromoted Pauson-Khand reaction  
by Brian L Pagenkopf

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in  
Chemistry  
Montana State University  
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Abstract:

Several of the factors that influence substrate based control of diastereoselection in Cp<sub>2</sub>Zr(II) mediated enyne cyclizations have been illuminated by examination of an extensive series of substituted enynes. An eminently practical, catalytic, photopromoted Pauson-Khand reaction that proceeds under mild reaction conditions (50-55 °C) under 1 atm of CO was developed. The photopromoted Pauson-Khand reaction is compatible with substrates bearing of a wide variety of functional groups and substitution patterns. In some instances, substrate modification resulted in improved yields and increased diastereoselection. Studies directed toward the synthesis of carbacyclin resulted in a short enantiocontrolled synthesis of the epi-carbacyclin core. The key steps of this synthesis were an Evans syn-aldol condensation and ring closure by the catalytic photopromoted Pauson-Khand reaction.

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APPROVAL

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Brian L. Pagenkopf

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

12/3/96  
Date

Tom Ely  
Chairperson, Graduate Committee

Approved for the Major Department

12/3/96  
Date

David M. Dwyer  
Head, Major Department

Approved for the College of Graduate Studies

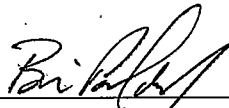
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*For the Believers*

Satisfaction lies in the effort not in the attainment. Full effort is full victory.

Mahatma Gandhi

Character is higher than intellect. A great soul will be strong to live, as well as to think.

Ralph Waldo Emerson

One science only will one genius fit: So vast is art, so narrow human wit.

Alexander Pope

There is no great genius without a tincture of madness.

Seneca

Don't be afraid to challenge the pros, even in their own backyard. Just as important, never neglect details, even to the point of being a pest.

Colin Powell

There is great ability in knowing how to conceal one's ability.

Francis, Duc de La Rochefoucauld

As for *work*, we haven't any of any consequence.

Henry David Thoreau

Not by years but by disposition is wisdom acquired.

Plautus

Four to six weeks in the lab can save you an hour in the library.

G. C. Quaderer, Dow Chemical

In matters of style, swim with the current; in matters of principle, stand like a rock.

Thomas Jefferson

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### Abstract

Several of the factors that influence substrate based control of diastereoselection in  $\text{Cp}_2\text{Zr(II)}$  mediated enyne cyclizations have been illuminated by examination of an extensive series of substituted enynes. An eminently practical, catalytic, photopromoted Pauson-Khand reaction that proceeds under mild reaction conditions (50 - 55 °C) under 1 atm of CO was developed. The photopromoted Pauson-Khand reaction is compatible with substrates bearing of a wide variety of functional groups and substitution patterns. In some instances, substrate modification resulted in improved yields and increased diastereoselection. Studies directed toward the synthesis of carbacyclin resulted in a short enantiocontrolled synthesis of the epi-carbacyclin core. The key steps of this synthesis were an Evans syn-aldol condensation and ring closure by the catalytic photopromoted Pauson-Khand reaction.

## 1. Introduction

In recent years, the development of new transition metal mediated processes has become one of the most active and exciting areas of research in synthetic chemistry. The power of metal mediated processes often lies in their ability to confer a high degree of molecular complexity to inexpensive and structurally simple starting materials with relatively little cost or effort. The direct formation of bicyclic metallocyclopentenes from simple enynes by group IV metallocene reagents illustrates the synthetic potential of this class of reactions. Because the intermediate metallocyclopentenes can be further functionalized by a variety of electrophiles, an array of cyclic products is available from the same acyclic precursor.

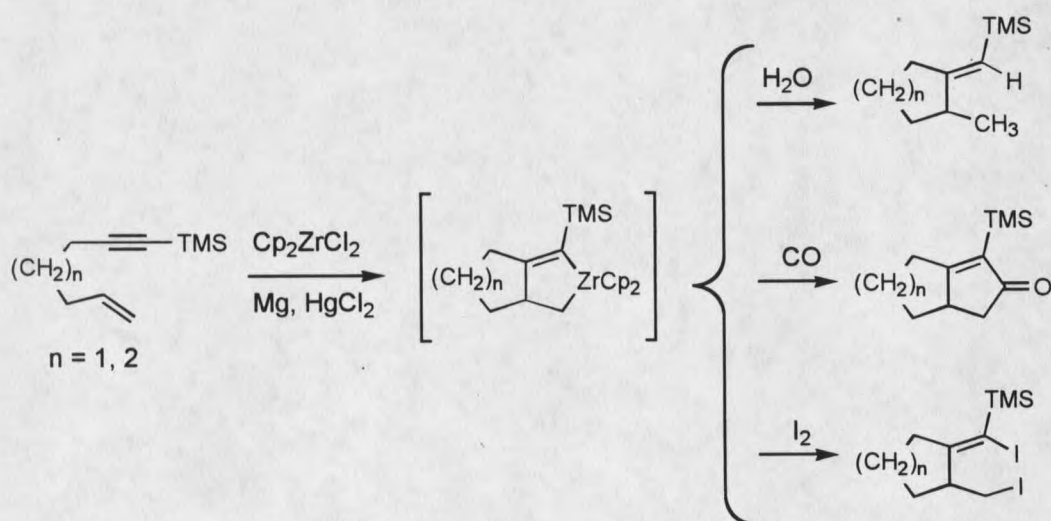
In order to further understand factors that contribute to substrate control of diastereoselectivity in  $\text{Cp}_2\text{Zr(II)}$  mediated enyne cyclizations, a diverse series of substituted enynes has been synthesized and subsequently studied in cyclization reactions. The results of these experiments led to the evolution of several synthetic strategies directed toward the synthesis of carbacyclin. The key ring forming step of these synthetic endeavors focused on the use of a  $\text{Cp}_2\text{Zr(II)}$  mediated enyne cyclization and tandem carbonylation sequence. The search for an improved

cyclization protocol to effect this transformation has led to the development of a novel, catalytic photopromoted Pauson-Khand reaction.

## 2. Background

### 2.1 Early Zirconium(II) Chemistry

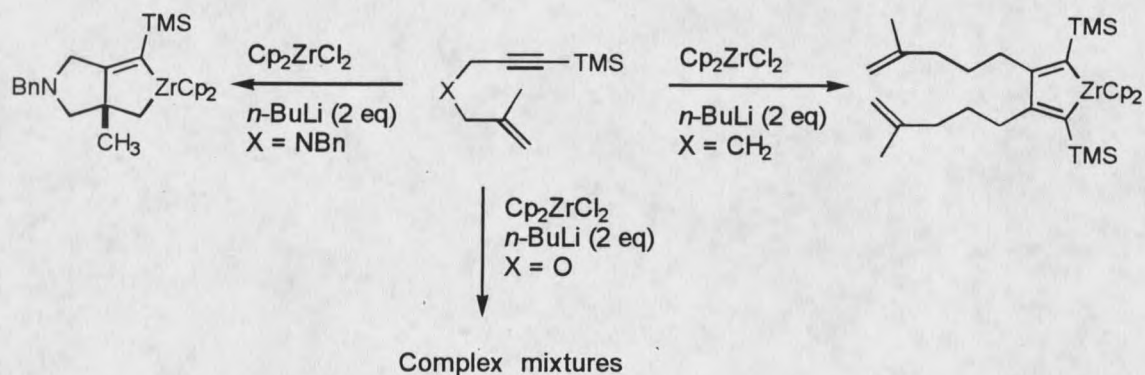
In 1985, Negishi reported that a zirconocene equivalent, i.e. "Cp<sub>2</sub>Zr", generated by the treatment of Cp<sub>2</sub>ZrCl<sub>2</sub> with Mg and HgCl<sub>2</sub> was effective for converting various non-terminal enynes to zirconocyclopentenes (**Scheme 1**).<sup>1</sup> The chemistry of these metallocycles proved to be diverse and powerful, in that functionalized carbocycles could be obtained from simple acyclic precursors. The intermediate zirconocycles could be protonated to yield the methyldiene substituted cyclopentanes, treated with CO (1 atm), to provide the corresponding  $\alpha$ -silyl



**Scheme 1**

cyclopentenones, or treated with  $I_2$ , to give the 1-vinyl-4-alkyl diiodo derivatives, all in moderate yields. Negishi later reported that treatment of  $Cp_2ZrCl_2$  with two equivalents of  $n-BuLi$  at low temperatures offered an easy and economical method for the *in situ* preparation of a zirconocene equivalent.<sup>2</sup> This disclosure resulted in the rapid acceptance of "zirconocene" as a useful synthetic reagent. The flourish of research since Negishi's initial disclosure has resulted in many contributions leading to the rich and interesting chemistry of zirconium(II) species.<sup>2b,3</sup>

Some heteroatom linkages were found not only to be tolerant of the reaction conditions, but increased the reactivity of 1- or 2-substituted alkenynes (**Scheme 2**).<sup>4</sup> Substituted alkenes with a carbogenic tether failed to react in the usual manner, but instead dimerized to give zirconocyclopentadienes in good yield. The heteroatom contraction offered by a benzylamine linkage resulted in the expected zirconocyclopentene product even with substituted alkenes. Oxygen tethers resulted in complex product mixtures,<sup>5</sup> although with dienes (*vide infra*, section 2.3 (Chapter 2, subsection 3)) this reactivity has been attenuated to become a route to allylic- and propargyliczirconocene derivatives.<sup>6</sup>

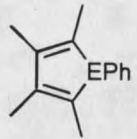
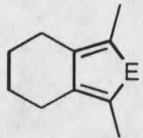
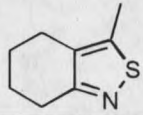


Scheme 2

Fagan and Nugent later showed that zirconocyclopentadienes effectively transmetallated with main group electrophiles to afford main group heterocycles (Table 1).<sup>7</sup> Substrates 1 and 2 were easily prepared from 2-butyne or 2,8-decadiyne. Entry 3 was prepared by the addition of 1-cyano-5-heptyne to a solution of  $\text{Cp}_2\text{Zr}(n\text{-Bu})_2$  reduced *in situ* in the presence of bis(trimethylsilyl)acetylene. These preparations represented a superior route to these main group heterocycles.



**Table 1. Main Group Heterocycles by Metallacycle Transfer from Zirconium.**

Electrophile	Product	Element, (Yield)
1. PhECl <sub>2</sub>		E = P, (85%) As, (76%) Sb, (78%) Bi, (70%)
2. E <sub>2</sub> Cl <sub>2</sub>		E = S, (55%) Se, (50%)
3. S <sub>2</sub> Cl <sub>2</sub>		(65%) <sup>a</sup>

<sup>a</sup> Based on recovered starting material.

Although both the sp<sup>2</sup> and sp<sup>3</sup> carbons bound to zirconium effectively transmetallate to main group electrophiles, they have sufficiently different nucleophilicity to allow selective mono functionalization. The sp<sup>3</sup> carbon reacts readily with one equivalent of electrophile, whereas initial reaction at the sp<sup>2</sup> carbon is virtually unknown. Deuteration of a zirconocyclopentene with deuterio-methanol (1 eq) followed by aqueous work-up afforded the cyclopentane in excellent yield with deuterium incorporation solely on the methyl group. Treatment of the zirconocycle with methanol (1 eq) followed by an acidic deuterium oxide quench provided the cyclopentane with deuterium incorporation solely at the vinylic position.<sup>8</sup> Other electrophiles, such as iodine also followed the same reactivity pattern (**Scheme 3**).<sup>9</sup>

































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































































