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PREVIEW

CATALYTIC IRON- AND COBALT-MEDIATED ENEDIENE
CARBOCYCLIZATIONS

By

Steven J. Mehrman

A DISSERTATION

Presented to the Faculty of

The Graduate College at the University of Nebraska

In Partial Fulfillment of Requirements

For the Degree of Doctor of Philosophy

Major: Chemistry

Under the Supervision of Professor James M. Takacs

Lincoln, Nebraska

August, 1999

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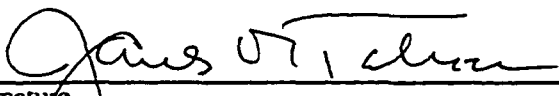
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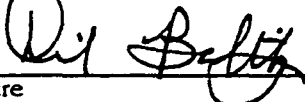
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GRADUATE COLLEGE
UNIVERSITY OF NEBRASKA

CATALYTIC IRON- AND COBALT-MEDIATED ENEDIENE CARBOCYCLIZATIONS

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University of Nebraska, 1999

Adviser: James M. Takacs

The field of organic synthesis continues to evolve toward the construction of highly functionalized, structurally complex targets. Discovering new methods to form carbon-carbon bonds is of the utmost interest. The use of transition metals to perform this task has been evolving very rapidly over the past several years. Transition metal-mediated syntheses often enable novel bond constructions, for which there exists no classical counterpart. It is also worthy to note that the use of catalysis to perform a reaction is a strategy relevant to environmentally friendly synthesis, i.e. green chemistry. Classical approaches employ stoichiometric reagents, the byproducts of which must be removed and disposed of after the reaction. The future of organic synthesis will inevitably lie in the development and application of catalytic methods to perform efficient bond constructions.

The focus of this research has been the efficient construction of highly functionalized ring systems. Construction of tetrasubstituted five membered rings, the

core fragments contained in PGI₂ analogue CicaprostTM, iridoid glucoside (-)-gibboside, isoprostane 15-F_{2t}-IsoP have been accomplished using a catalytic iron-mediated cyclization. CicaprostTM and (-)-gibboside have a common core fragment, which was synthesized in an 80% yield (single isomer) using an iron-mediated cyclization. The tetrasubstituted cyclopentane core contained in 15-F_{2t}-IsoP was constructed in 50% yield and good selectivity (9:1), using an iron-mediated cyclization. A novel cobalt-mediated reductive cyclization catalyst has been used in the construction of trans five- and six-membered rings (50-86% yield) and good to excellent selectivity (7 to 50:1, trans:cis). This catalyst has also been used in cascade cyclizations, where multiple rings can be constructed from an acyclic precursor.

The use of an iron-mediated cyclization in the construction of the core tetrasubstituted cyclopentanes contained in CicaprostTM, (-)-gibboside, 15-F_{2t}-IsoP has been efficient. The cobalt-mediated reductive cyclization catalyst has demonstrated its utility in the formation of five- and six-membered rings, and cascade cyclizations. Catalytic iron- and cobalt-mediated cyclizations appear to be applicable in the efficient construction of a variety of ring containing targets.

Dedications

To my family,
whose love guides me.

PREVIEW

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PREVIEW

CHAPTER I

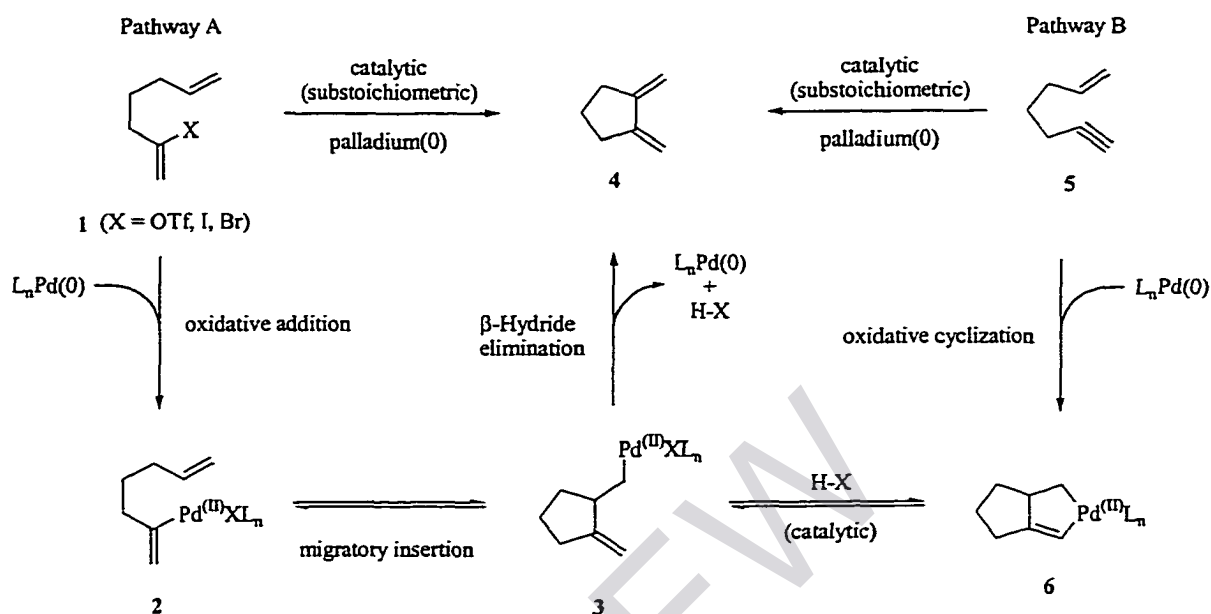
INTRODUCTION

The field of organic synthesis continues to evolve toward the construction of highly functionalized, structurally complex targets.¹⁻¹⁰ Discovering new methods to form carbon-carbon bonds is of the utmost interest. The use of transition metals to perform this task has been evolving very rapidly over the past several years. Transition metal-mediated syntheses often enable novel bond constructions, for which there exists no classical counterpart. Many catalysts offer unique chemo-, regio- and stereo-selectivity that can lead to more efficient synthetic strategies. It is also worthy to note that the use of catalysis to perform a reaction is a strategy relevant to environmentally friendly synthesis, i.e. green chemistry. Classical approaches employ stoichiometric reagents, the byproducts of which must be removed and disposed of after the reaction. The future of organic synthesis will inevitably lie in the development and application of catalytic methods to perform efficient bond constructions.

Literature Review

Takacs has recently noted⁹ two general pathways for carbon-carbon bond formation using transition metal catalysts. These pathways are illustrated in scheme 1 with examples of an intramolecular Heck reaction (pathway A) and an enyne carbocyclization (pathway B). Pathway A involves the initial formation of a carbon-

metal σ -bonded (in some cases η^3 -allyl bonded) intermediate **2**, via the hydro- or carbometallation of an alkene, or an alkyne, or more commonly, via the oxidative addition of a reduced metal center to an appropriate C-X bond. The crucial carbon-carbon bond forming event occurs via migratory insertion of a π -bonded ligand (i.e., a coordinated alkene, alkyne, diene) into the carbon-metal σ -bond, to give an intermediate **3** possessing a new carbon-metal σ -bond useful for further chemistry. Typically, **3** may undergo: a) further intra- or intermolecular insertions with additional unsaturated functional groups; b) reaction with electrophiles or c) β -hydride elimination (illustrated in pathway A). A variety of novel metal-mediated carbocyclizations have been realized via this ligand insertion strategy. The intramolecular Heck reaction A, giving rise to product **4** is a good example (scheme 1). Other examples include insertions of alkenes, dienes, and alkynes into metal-carbon σ -bonded (or η^3 -allyl bonded) intermediates generated via the oxidative addition of a low valent metal complex into a vinyl, aryl or allylic C-X bond (wherein X = halogen, triflate, phosphate, etc.).

Scheme 1. General pathways for metal-mediated carbon-carbon bond formation.

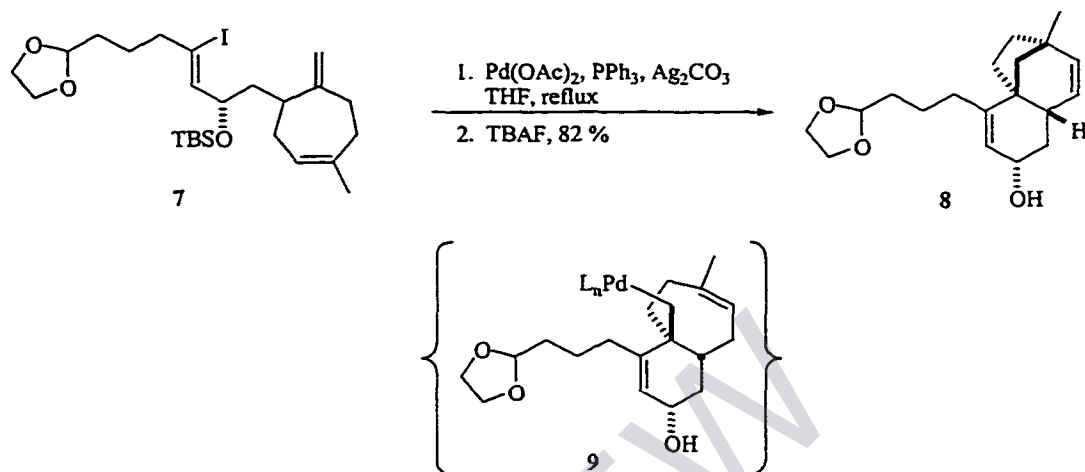
The second general strategy involves the initial complexation (templating or chelating) of yne-ene **5**, for example, about the metal center. The ring forming (carbon-carbon bond forming) event occurs via the oxidative coupling of these π -bonded ligands (oxidative cyclization, in the case of the intramolecular coupling) and the isomerization of the metal chelate to the metallacycle **6**. Intermediate **6** has a variety of pathways available. These include: a) metal-mediated atom transfer, usually hydrogen atom transfer effecting some net cycloisomerization reaction; b) reductive elimination to form a second carbon-carbon bond, effecting a net cycloaddition; c) migratory insertion into another (intra- or intermolecular) unsaturated group or d) as illustrated, Trapping by an H-X reagent resulting in the formation of **3**, which can undergo β -hydride elimination to form product **4**. In such reactions, the structures and reactivities of the relevant organometal intermediates play a dominant role in controlling the regiochemical and

stereochemical course of the carbon-carbon bond construction. Wherein, at the moment relatively poorly defined metal-centered-effects exert the dominate directing effect on the reaction selectivity (i.e., chemoselectivity, regioselectivity, diastereoselectivity, and stereoinduction) is controlled by as yet little understood metal-centered effects.

The following examples highlight metal-mediated cyclizations as key steps in the construction of core fragments for the total synthesis of highly functionalized natural products.

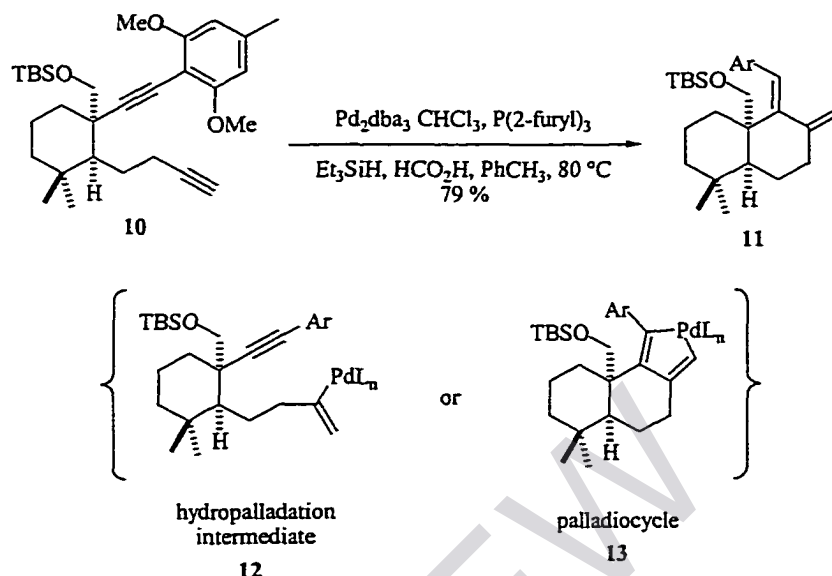
Overman and coworkers have taken advantage of multiple insertion processes to access the scopadulan diterpenes.¹¹ Vinyl iodide **7** was subjected to a palladium(II)acetate catalyst to perform a tandem Heck reaction. In this conversion, migratory insertion of the neighboring exocyclic alkene provided a tricyclic intermediate having no β -hydrogens **9**, which subsequently underwent a transannular 5-exo Heck reaction with the trisubstituted cycloheptene double bond to provide **8** after deprotection (82%). This intermediate was then taken on to (+/-)-scopadulcic acid A.

Scheme 2. Tandem (iterative) Heck insertion reactions in the synthesis of (+/-)-scopadulcic acid A.



In the synthesis of (+/-)-siccanin, Trost has used a palladium mediated reductive cyclization. The reductive diyne cyclization (**10** to **11**) was mediated by palladium using Et_3SiH as the reduction source. This product is the result of hydropalladation of the terminal alkyne (intermediate **12**), insertion of the internal alkyne, hydride transfer to palladium, and reductive elimination, according to Trost. An alternative pathway for product formation involves the formation of a palladiocycle **13**.¹²

Scheme 3. Palladium-mediated reductive cyclization, synthesis of (+/-)-siccanin.



In another example highlighting the utility of palladium catalysis, the vinyl bromide **14** participates in a bimolecular Heck reaction with alkyne **15** and the resulting alkenylpalladium intermediate undergoes an intramolecular Heck reaction with the pendant terminal alkene to provide **15**. Under the reaction conditions, some of the desired product undergoes a [1,7]-hydrogen shift to give **16**. Thermal recycling of **16** provided **15** in a 76% yield. Product **15** was then taken on to (+)-alphacalcidiol and (+)-calcitriol.^{13,14}