Heteroannulations mediated by titanium imido complexes : methods development and applications to the total syntheses of (½)-monomorine I and (+)-preussin
by Paul Leo McGrane

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

Abstract:
Highly reactive titanium imido complexes have been generated by the reaction of primary amines with monocyclopentadienyl titanium (IV) complexes. These transient imido complexes have been trapped via intramolecular [2 + 2] cycloadditions with tethered alkynyl moieties. This transformation has been used to prepare a variety of representative heterocycles via catalytic (CpTiCl3 mediated] and stoichiometric [CpTi(CH3)2Cl mediated] annulations of alkynylamines.

Additionally, the azatitanetines generated in stoichiometric [2+2] imido-alkyne cycloadditions have been shown to engage nucleophiles in subsequent bond-forming reactions.

The utility of these new methods in natural products synthesis was shown by their use in concise total syntheses of (±)-monomorine I and (+)-preussin.

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APPROVAL

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Paul Leo McGrane

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.

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Date 1-10-93

Dedicated to the memory of my father and namesake, Leo Charles McGrane. May your Irish eyes always smile upon us.

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ABSTRACT

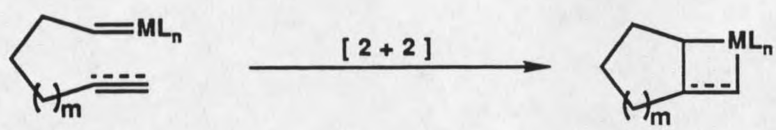
Highly reactive titanium imido complexes have been generated by the reaction of primary amines with monocyclopentadienyl titanium (IV) complexes. These transient imido complexes have been trapped *via* intramolecular [2 + 2] cycloadditions with tethered alkynyl moieties. This transformation has been used to prepare a variety of representative heterocycles *via* catalytic [$CpTiCl_3$ mediated] and stoichiometric [$CpTi(CH_3)_2Cl$ mediated] annulations of alkynylamines.

Additionally, the azatitanetines generated in stoichiometric [2 + 2] imido-alkyne cycloadditions have been shown to engage nucleophiles in subsequent bond-forming reactions.

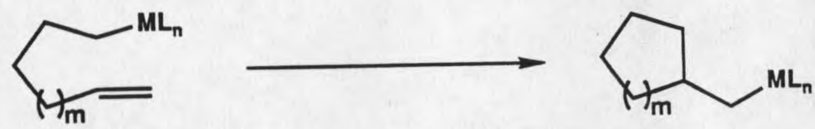
The utility of these new methods in natural products synthesis was shown by their use in concise total syntheses of (±)-monomorine I and (+)-preussin.

INTRODUCTION

The development of transition metal mediated carboannulation methods has greatly enhanced the chemist's ability to elaborate the cyclic skeletons of many biologically active carbogens. Two powerful examples of these methods are intramolecular carbene cycloaddition[1,2] and ligand cyclization reactions[3] (Eq. 1 and Eq. 2).

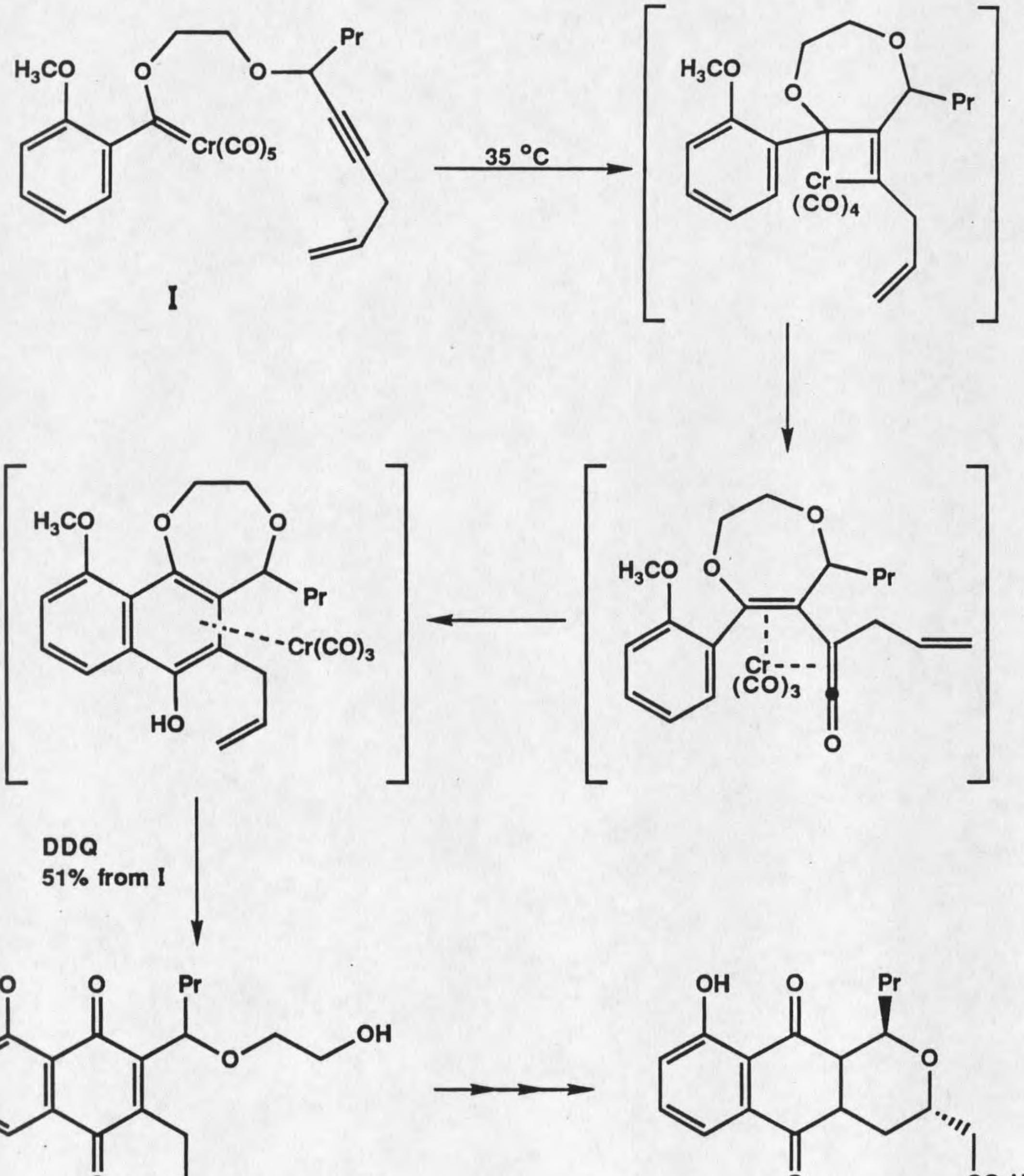


Eq. 1



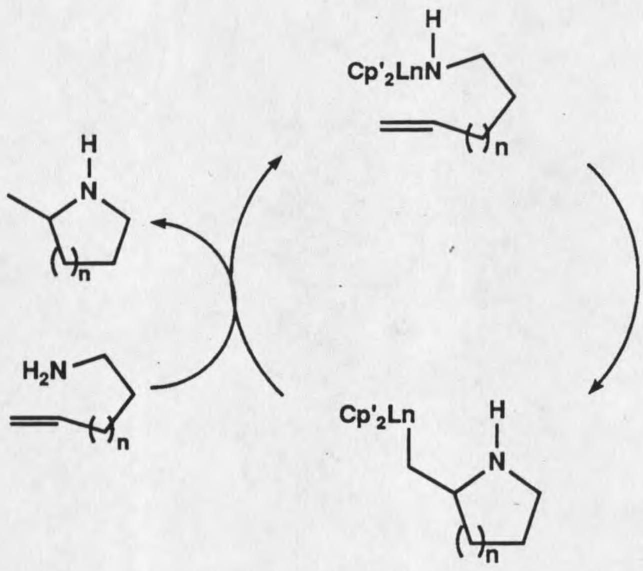
Eq. 2

While the reactions in Eq. 1 and Eq. 2 both effect ring annulation, the [2 + 2] cycloaddition of Eq. 1 has the added advantage of generating a metallocyclobutane or metallocyclobutene which may serve as an intermediate for further elaboration. The utility of intramolecular carbene-alkyne cycloadditions in natural product synthesis was exemplified by Semmelhack's synthesis of deoxyfrenolicin[4] (Scheme 1).



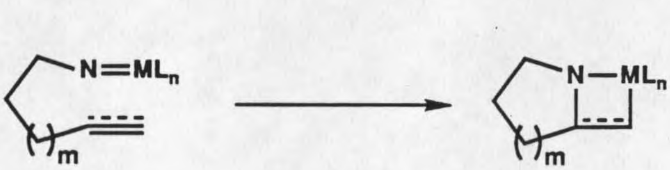
Scheme 1

The analogous transformations of amido and imido complexes that would lead to heterocyclic products have received little or no attention. Recently, Marks described the catalytic hydroamination of terminal alkenes proceeding *via* amidolanthanide complexes[5,6] (Scheme 2).



Scheme 2

Prior to the work reported in this thesis, there were no examples of the imido analog of the intramolecular carbene cycloaddition reaction. As with the carbene-olefin cycloaddition, imido complex-olefin cycloadditions could potentially provide exploitable metallocyclic intermediates (Eq. 3).



Eq. 3