

Nickel-catalyzed cyclizations of alkynyl enones and alkynyl enals*

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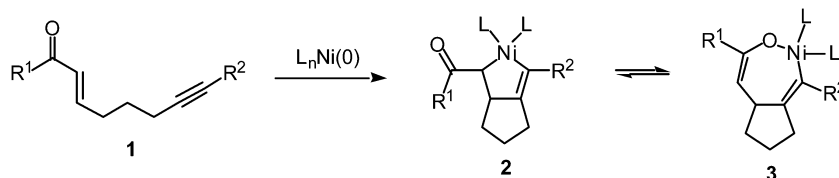
Abstract: Substrates that possess an α,β -unsaturated carbonyl tethered to an alkyne have been utilized in a variety of nickel-catalyzed processes. Depending on ligand structure, reagent structure, reaction conditions, and workup conditions, several different monocyclic and bicyclic ring systems may be accessed from a common substrate. Evidence for a nickel metallacycle as a common intermediate is provided.

INTRODUCTION

Metal-catalyzed cyclizations of polyunsaturated substrates have established a prominent role in complex molecule synthesis [1]. Many different transition metals are known to catalyze complex polycyclization processes involving a broad range of substrates and a variety of distinct mechanisms. Our laboratory has recently demonstrated that the oxidative cyclization of a nickel(0) catalyst with two different π -components provides an ideal template for the development of cascade cyclizations [2]. Cyclization precursors that possess an alkyne and an activated alkene as the two π -components have served as an effective substrate class in an extraordinarily diverse range of nickel-catalyzed processes. The discussion below describes the development of various cyclization processes that utilize alkynyl enones and alkynyl enals, as well as evidence for a common mechanistic motif that involves nickel metallacycles.

RESULTS AND DISCUSSION

The oxidative cyclization of an alkynyl enone or alkynyl enal **1** with a nickel(0) catalyst provides a metallacycle that is extremely well suited for the development of complex polycyclizations (Scheme 1). During the oxidative cyclization, a carbon–carbon bond, a nickel–carbon bond, and a nickel–oxygen bond are formed. Significantly, the nickel–carbon and the nickel–oxygen bonds display substantially different reactivities, thus providing the opportunity for these two bonds to be differentially substituted. The nickel enolate produced from the enone-derived fragment may potentially exist as the carbon-bound or oxygen-bound tautomers **2** or **3** (*vide infra*) [3].

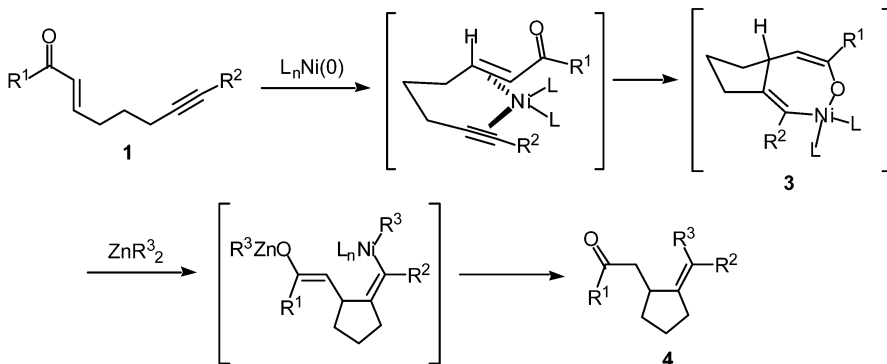


Scheme 1

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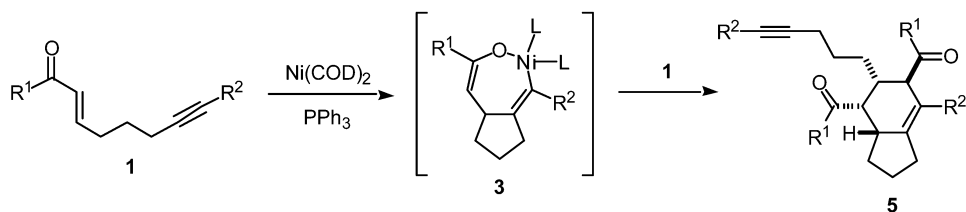
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Many distinct processes for the conversion of the alkynyl enone-derived metallacycles into useful organic products may be envisioned. One such process that we have extensively examined is the transmetalation reaction with organozincs [4,5]. Accordingly, treatment of an alkynyl enone with an organozinc in the presence of catalytic quantities of $\text{Ni}(\text{COD})_2$ leads to the very clean production of cycloadducts **4** that possess a stereodefined exocyclic alkene moiety (Scheme 2). This observation is consistent with a mechanism that involves metallacycle formation via oxidative cyclization, followed by a transmetalation/reductive elimination sequence.



Scheme 2

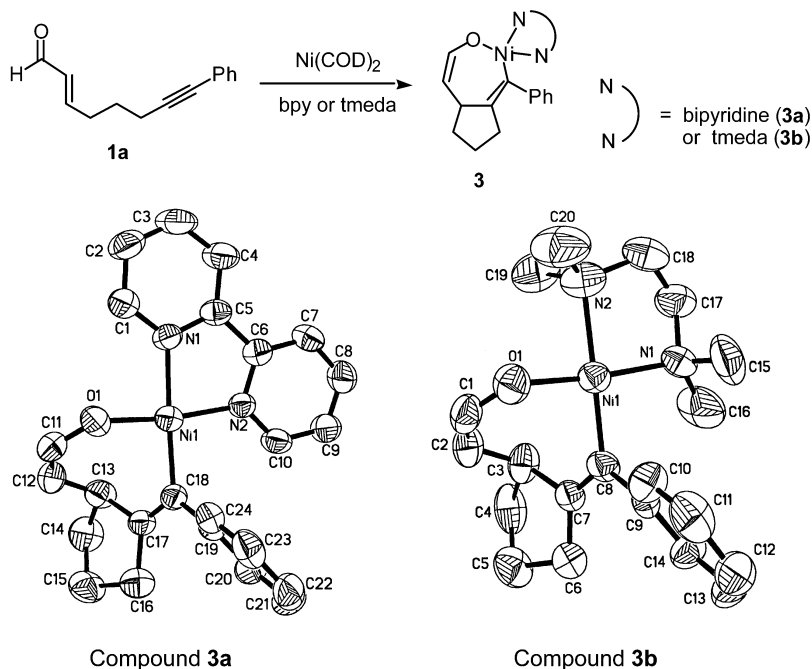
Whereas metallacycles are commonly invoked as intermediates in many metal-catalyzed cyclizations of enynes, there is surprisingly little precedent for this transformation. For instance, despite the many nickel- and palladium-catalyzed transformations of enynes that are known, a single report from Pörschke describes the only example of a metallacyclopentene known for these two metals prior to our work [6]. Therefore, we became quite interested in preparing and characterizing the nickel metallacycle derived from an alkynyl enone or alkynyl enal in order to provide precedent for the mechanism proposed above, as well as to guide our development of new synthetically useful reactions. However, all efforts to isolate an alkynyl enone-derived metallacycle utilizing $\text{Ni}(\text{COD})_2$ alone or functionalized with monodentate phosphines were unsuccessful, because these catalyst systems rapidly and efficiently dimerized the alkynyl enone starting materials (Scheme 3). This observation led to the development of a novel [2+2+2] cycloaddition procedure that is interesting in its own right, but we recognized that the initial objective of isolating the metallacycle of interest would not be a simple proposition [7].



Scheme 3

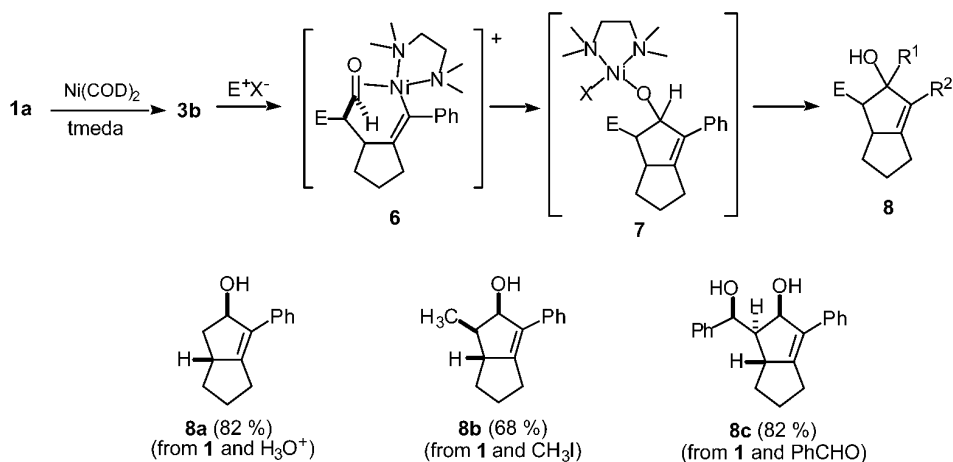
Reasoning that the alkynyl enone dimerization likely involves the intermediacy of the desired metallacycle **3**, we considered alternative ligand systems that should stabilize the metallacycle and suppress formation of the alkynyl enone dimer. Conversion of metallacycle **3** into dimer **5** likely requires ligand dissociation and coordination of the alkenyl unit of the alkynyl enone **1** to the metal center. Therefore, choosing a bidentate ligand system with a high binding constant should suppress uptake of the second equivalent of starting material, and perhaps allow isolation of the metallacycle. Bipyridine

(bpy) and tetramethylethylene diamine (tmeda) were thus obvious ligand systems to examine next. We were pleased to observe that this ligand modification did, indeed, allow isolation of the desired metallacycles (Scheme 4). Both the bpy- and tmeda-substituted nickel metallacycles **3a** and **3b** were isolated and fully characterized. The metallacycles were characterized as the oxygen-bound η^1 tautomer both in the solid state and in solution [8].



Scheme 4

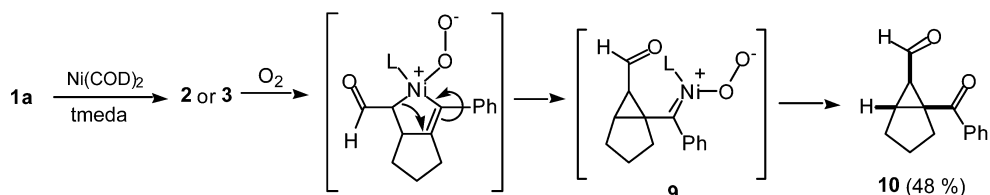
With a procedure in hand that allows the clean generation of metallacycles from the oxidative cyclization of alkynyl enals with Ni(0), we examined the reactivity of the stoichiometrically generated metallacycles [9]. Treatment of an alkynyl enal with one equivalent each of Ni(COD)₂ and tmeda afforded the metallacycle *in situ*, and the nickel enolate functionality could be cleanly alkylated with electrophiles such as H₃O⁺, MeI, and PhCHO (Scheme 5). In each case, a [3.3.0]-bicyclooctenol prod-



Scheme 5

uct was obtained. The reaction mechanism likely involves formation of metallacycle **3b** followed by protonation or alkylation of the enolate at carbon to afford intermediate **6**. At this stage, insertion of the alkenyl nickel functionality into the coordinated carbonyl leads to nickel alkoxide **7**, which undergoes protonation on workup to provide the observed products **8**.

Whereas the above pathway appears to be general for a variety of electrophiles, the behavior of alkynyl enal-derived metallacycles toward oxidation with molecular oxygen is quite different. When the metallacycle derived from **1a** is treated with dry oxygen, an oxidatively driven rearrangement occurs to produce [3.1.0]-bicyclohexane **10** (Scheme 6). The closest precedent for this remarkable transformation comes from the thermal rearrangement chemistry of titanium metallacycles reported by Sato [10,11]. We speculate that the mechanism of this oxidative rearrangement may involve oxidation of the metal center, followed by σ -bond migration to afford nickel carbene intermediate **9**. Oxidative cleavage of the metal carbene fragment affords the ketone unit of product **10**.



Scheme 6

CONCLUSIONS

This work demonstrates the utility of nickel metallacycles in the development of cascade cyclization processes. When treated with a Ni(0) catalyst, alkynyl enones and alkynyl enals are transformed into reactive nickel metallacycles. The metallacycles may be functionalized via catalytic or stoichiometric processes into a variety of products by mechanisms including transmetalation (with organozincs), migratory insertion (of alkenes), alkylation (by alkyl halides or aldehydes), protonation (with H_3O^+), or oxidation (with molecular oxygen). The ring systems obtained include alkylidene cyclopentanes, [3.4.0]-bicyclononenes, [3.3.0]-bicyclooctenols, and [3.1.0]-bicyclohexanes. These processes have been utilized as key steps in complex molecule total syntheses [12].

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