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# Diverse Reactivity Manifolds of Alkynyl Enone- and Alkynyl Enal-Derived Nickelacycles: Discovery of Nickel-Promoted [3+2] and [2+1] Cycloadditions

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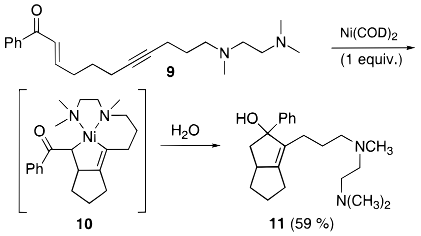
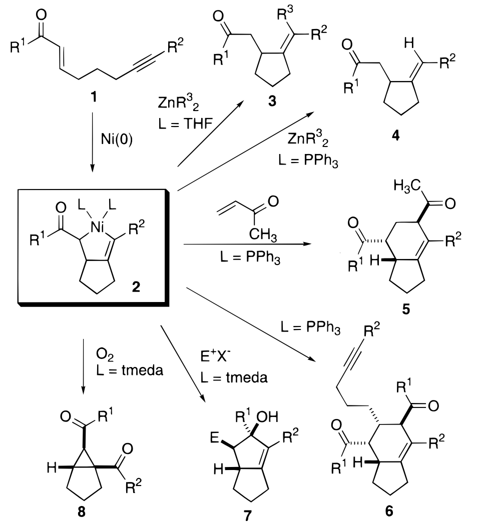
The nickel-catalyzed cyclization of alkynyl enones has been extensively investigated in our laboratories over the past few years.[1] The reactions developed in this program include the alkylative cyclization of alkynyl enones in the presence of organozincs and Ni(COD)$_2$ to produce **3**,[2,3] the reductive cyclization of alkynyl enones in the presence of organozincs and Ni(COD)$_2$/PPh$_3$ to produce **4**,[2] and the [2+2+2] cycloaddition of alkynyl enones and simple enones in the presence of Ni(COD)$_2$/PPh$_3$ to produce **5** (Scheme 1).[4] We speculated that nickel metallacycles **2**[5] were common intermediates in each of these pathways, although efforts to isolate or spectroscopically characterize the proposed metallacycles were unsuccessful. The rapid dimerization of alkynyl enones via the [2+2+2] cycloaddition pathway to produce **6** is a major reason that the metallacycles have proven to be elusive (Scheme 1).[4]

We envisioned that oxidative cyclization of an alkynyl enone or alkynyl enal to metallacycle **2** could potentially provide a novel entry to synthetically valuable nickel enolates if the facile dimerization to **6** could be suppressed. To suppress the undesired dimerization manifold, alkynyl enone **9**, which possesses a covalently tethered bidentate ligand, was prepared (eq 1). Upon treatment of **9** with a stoichiometric quantity of Ni(COD)$_2$, a homogeneous red solution resulted for which we tentatively propose structure **10**. The $\eta^1$-*C*-enolate shown and the corresponding $\eta^1$-*O*-enolate and $\eta^3$-enolate structures are all reasonable formulations for **10**. Although isolation of metallacycle **10** was not achieved, bicyclooctenol **11** was obtained upon quenching the reaction with aqueous Na$_2$CO$_3$. The process constitutes a previously unknown formal [3+2] cycloaddition between an enone and alkyne.[6]



(1)

**Scheme 1**



To explore this novel reaction in a synthetically useful context, we examined the reactivity of simple alkynyl enones and alkynyl enals that lacked the tethered diamine functionality. Whereas monodentate (PPh$_3$) and bidentate (Ph$_2$PCH$_2$CH$_2$PPh$_2$) phosphine ligands led predominantly to substrate dimerization to afford **6**, treatment of alkynyl enones and alkynyl enals with 1 equiv of the complex generated from Ni(COD)$_2$ and tmeda afforded the desired [3+2] cycloadducts (Table 1). Cyclization of enals **1a** and **1b** that possess aliphatic or aromatic substituents on the alkyne cleanly afforded bicyclooctenols **7a** and **7b** in 82% and 72% isolated yields, respectively (entries 1 and 2). Six-membered-ring product **7c** was produced in 40% isolated yield, and 18% of monocyclic product **4c** was also obtained. Electron-deficient alkyne **1d** was much less efficient in the desired [3+2] cyclization, and compound **7d** was obtained in 15% isolated yield. Terminal alkyne **1e** was also a poor substrate, and only product **4e** was obtained in 27% isolated yield. Enones **1f** and **1g** also participated in the [3+2] cycloadditions in similar fashion. However, upon workup with dilute acid, rearranged tertiary alcohols **12f** and **12g** were obtained in 53% and 52% isolated yields.

We speculate that the mechanism of this novel [3+2] cycloaddition involves initial generation of nickelacycle **2** which could exist as the *O*- or *C*-enolate tautomer **2a** or **2b** or in the corresponding $\eta^3$ form (Scheme 2). Double protonation of **2a** or **2b** would afford monocyclic product **14** (E = H), which was observed as a minor byproduct in two cases. However, the primary pathway for the formal [3+2] cycloaddition likely involves selective monoprotonation of **2** followed by carbonyl insertion into the nickel−carbon bond of **13**. The resulting nickel alkoxide **15** undergoes hydrolysis upon workup to produce the observed bicyclooctenol **7** (E = H).

The above experiments suggest that other enolate alkylation/carbonyl insertion sequences could be accessed from metallacycle **2**. Accordingly, the complex derived from Ni(COD)$_2$, tmeda, and enal **1a** was treated with methyl iodide prior to aqueous workup (eq 2). After the mixture was stirred at 0 °C for 1 h, compound **17** was produced as a single diastereomer in 68% yield, presumably via *C*-alkylation of nickel enolate **2a** or **2b** with methyl iodide followed by carbonyl insertion as described above (Scheme 2). The enolate of metallacycle **2**, derived from enal

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(2) (a) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099−2100. (b) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911−4920. (c) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139.

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10.1021/ja0012624 CCC: $19.00

**Scheme 2.** Mechanism of [3+2] and [2+1] Cycloadditions

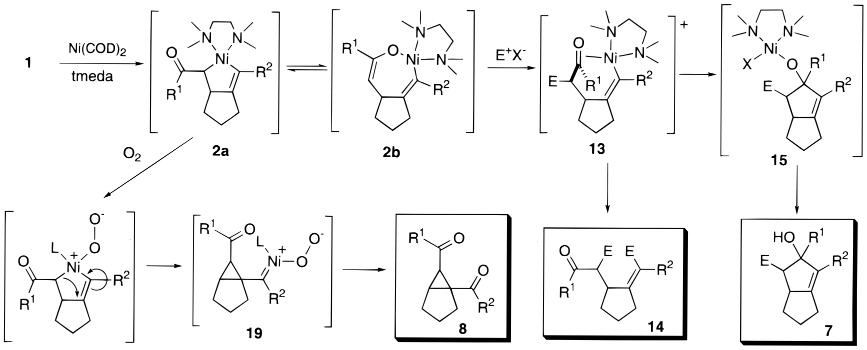
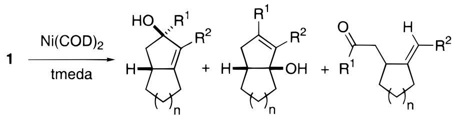


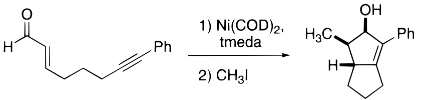
**Table 1**



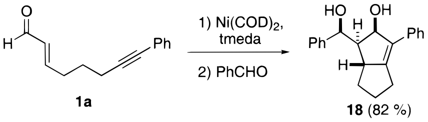
**7** **12** **4**

| entry | substrate | *n* | $R^1$ | $R^2$ | yield |
|---|---|---|---|---|---|
| 1 | **1a** | 1 | H | Ph | **7a** (82) |
| 2 | **1b** | 1 | H | $CH_3$ | **7b** (72%) |
| 3 | **1c** | 2 | H | Ph | **7c** (40%), **7c** (18%) |
| 4 | **1d** | 1 | H | $COCH_3$ | **7d** (15%) |
| 5 | **1e** | 1 | Ph | H | **4e** (27) |
| 6 | **1f** | 1 | Ph | Ph | **12f** (53%) |
| 7 | **1g** | 1 | Ph | $CH_3$ | **12g** (52%) |

**1a**, was also efficiently trapped via an aldol reaction with benzaldehyde, followed by carbonyl insertion to afford aldol product **18** as a single diastereomer in 82% yield (eq 3).[7] It is worth noting that treatment of metallacycle **2** with dimethylzinc resulted in the clean production of ketone **3** which is the same product as that obtained in the Ni(COD)$_2$-catalyzed coupling of enone **1** and dimethylzinc (Scheme 1). This observation provides further evidence for the structure of metallacycle **2** in [3+2] cycloadditions since the [3.3.0]bicyclooctene ring system of the product is clearly not irreversibly formed upon treatment of enone **1** with Ni(COD)$_2$ and tmeda.



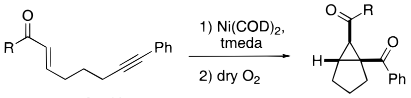
**1a** **17** (68 %) (2)



**1a** **18** (82 %) (3)

Nickel enolates have been proposed as intermediates in numerous catalytic sequences, but the only comprehensive study of their structure and reactivity was reported by Bergman and Heathcock.[8] In that study, the nickel enolates underwent complex Tishchenko-type condensations[9] with aldehydes, and simple aldol adducts were not cleanly obtained. Thus, it appears that nickel enolates within a metallacycle framework such as **2a** and **2b** may be uniquely selective in further synthetic transformations.

Whereas the processes described above apparently involve reactivity of the nickel enolate portion of metallacycle **2**, a surprising result was found in oxidations of **2**. Treatment of the stoichiometrically generated nickel complex **2**, derived from **1a** or **1f**, with dry $O_2$ resulted in the formation of [3.1.0]bicyclohexane **8** (eq 4).[10] In contrast to the protonation, alkylation, and aldol reactions which were selective for the enolate portion of metallacycle **2**, the oxidation of **2** was selective for the alkyne-derived fragment instead.[11] This complete regiochemical reversal in the electrophilic cleavage of unsymmetrical metallacycles is, to our knowledge, unprecedented.[10] Although the mechanism of this novel oxidative rearrangement is unknown, we suspect that an oxidatively promoted rearrangement of metallacycle **2** to carbene intermediate **19**[12] may be involved (Scheme 2).



**1a**, R = H
**1f**, R = Ph

**8a**, 48 %
**8f**, 35 % (4)

In summary, formal [3+2] and [2+1] intramolecular cycloadditions between an unsaturated carbonyl and an alkyne have been developed. Both processes appear to be derived from the selective electrophilic cleavage of a common nickel metallacycle. Significantly, the nickel enolate portion of metallacycle **2** undergoes selective protonation, alkylation, and aldol addition, whereas the vinyl nickel portion of metallacycle **2** undergoes selective oxidation with $O_2$. Efforts to explore the scope and mechanism of the new processes and to develop catalytic variants are currently in progress.

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**Supporting Information Available:** Full experimental details, copies of $^1H$ NMR spectra of all compounds, and copies of X-ray crystallographic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Parallels to this reaction are found in the work of Sato involving titanium-promoted cyclizations of electron-deficient enynes. In contrast to our studies which require oxidation to promote cyclopropane formation, titanium metallacycles derived from ynoates undergo thermal rearrangement to titanium carbenes without oxygen atom introduction. See ref 6. A rearrangement of a rhenium metallacyclopentane to a cyclopropane has also been reported: Yang, G. K.; Bergman, R. G. *Organometallics* **1985**, *4*, 129.

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