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# Synthesis of Cyclopentenols and Cyclopentenones via Nickel-Catalyzed Reductive Cycloaddition

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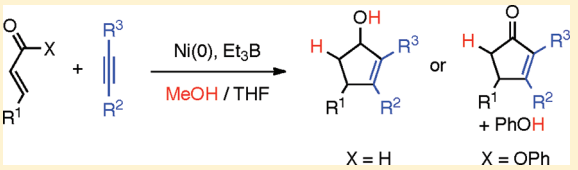
Supporting Information

**ABSTRACT:** Strategies for the reductive cycloaddition of enals or enoates with alkynes have been developed. The enal−alkyne cycloaddition directly affords cyclopentenols, whereas the enoate−alkyne cycloaddition affords the analogous cyclopentenones. The mechanism of these processes likely involves formation and protonation of a metallacyclic intermediate. The general strategy provides a straightforward entry to five-membered ring products from simple, stable $\pi$-systems.

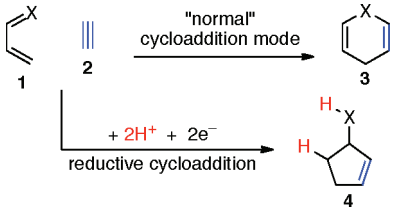



## INTRODUCTION

The assembly of five-membered rings by cycloaddition has been the subject of considerable study in many different contexts. It has traditionally been accomplished by the use of two-component cycloadditions involving 1,3-dipolar species,[1] vinyl carbenoid species,[2] or multifunctional cyclopropanes.[3] Additionally, a number of multicomponent cycloadditions typified by the Pauson−Khand reaction provide attractive and versatile cycloaddition entries to five-membered ring products.[4] Alternatively, compared with more specialized or reactive reagents, the routine use of only simple, stable $\pi$-systems such as alkenes, alkynes, dienes, or unsaturated carbonyls in a two-component cycloaddition would present advantages, including ease of access to the requisite reagents and the ability to advance the cycloaddition precursors through more complex linear synthetic sequences. In a generic example involving substrates **1** and **2**, cycloaddition where the terminal atoms participate in bond formation would afford a six-membered ring product **3** by hetero-Diels−Alder cycloaddition (Scheme 1).[5] The direct formation of a five-membered ring cycloadduct from these precursors would require formation of a biradical species or a more complex fused ring bicyclic product. This complexity in accessing five-membered ring products by cycloaddition of simple unsaturated systems has rendered the use of 1,3-dipolar species, functionalized cyclopropanes, and vinylcarbenoids exceptionally useful in five-membered ring synthesis.

The inability to form a stable nonradical five-membered ring product by cycloaddition of precursors such as **1** and **2** can be avoided if the atomic connectivity is rearranged during the cycloaddition. For example, the cycloaddition of allyl silanes as a three-atom component directly affords five-membered ring products by a process that involves a 1,2-silicon shift during the ring-forming process.[6] Similarly, a number of organocatalytic processes have been reported to form five-membered ring products by cascade sequences that involve a 1,2-hydrogen shift.[7] Many other classes of five-membered ring cycloadditions share the feature of a 1,2-shift accompanying the cycloaddition, and this strategy provides a conceptual solution to the limitations

**Scheme 1. Redox Description of Cycloaddition Modes**




cited above in the assembly of five-membered ring products from simple $\pi$-components.

An alternate and distinct strategy for allowing the assembly of five-membered rings by two-component processes involves a change in substrate oxidation state during the cycloaddition. For example, using the substrates **1** and **2** highlighted above, a net two-electron reduction during cycloaddition would allow a stable five-membered product **4** to be formed without requiring any change of the original atomic connectivity established in the starting reagents (Scheme 1). We report herein the development of a general strategy for effecting reductive cycloadditions of this type utilizing a nickel-catalyzed operation. Building upon our initial communication of [3 + 2]-reductive cycloadditions of enals and alkynes to afford cyclopentenols,[8] we now describe a more detailed analysis of the strategy and document a related sequence involving [3 + 2]-reductive cycloaddition of enoates and alkynes as a new entry to cyclopentenones. Including important recent advances from Cheng that documented the cobalt-catalyzed [3 + 2] reductive cycloaddition of enones and allenes,[9] from Sato that documented intramolecular titanium-mediated [3 + 2] reductive cycloadditions of enoates and alkynes,[10] from Krische that illustrated a three-component reductive cycloaddition,[11] as well as other classes of processes that generate reactive vinyl dianion synthetic equivalents,[12]

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**Scheme 2. Envisioned Pathway for Catalytic Reductive Cycloadditions of Enals and Alkynes**

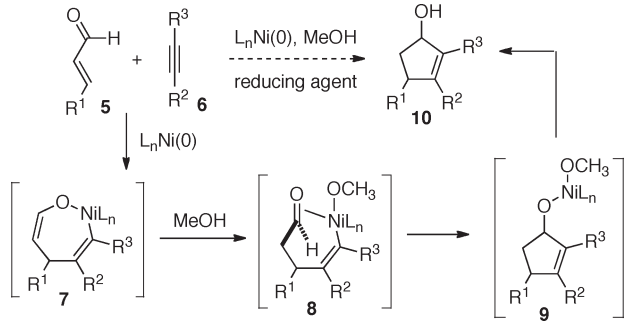
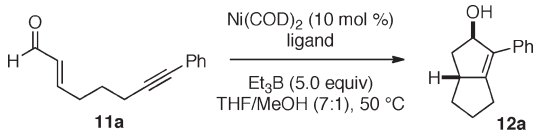



**Table 1. Ligand Selection in Intramolecular Reductive Cycloadditions of Enals and Alkynes**




| entry | ligand (mol %) | yield (%) |
|---|---|---|
| 1 | tmeda[a] (10) | 77 |
| 2 | dppe[b] (10) | 47 |
| 3 | DPEphos[c] (10) | 87 |
| 4 | dppf[d] (10) | 82 |
| 5 | $PPh_3$ (20) | 24 |
| 6 | $PBu_3$ (20) | 50 |

[a] tmeda, tetramethyl(ethylene)diamine. [b] dppe, 1,2-bis(diphenylphosphino)ethane. [c] DPEphos, bis(2-diphenylphosphinophenyl)ether. [d] dppf, 1,1′-bis-(diphenylphosphino)ferrocene.

this work begins to establish the generality of reductive cycloaddition entries for five-membered ring synthesis.[13]

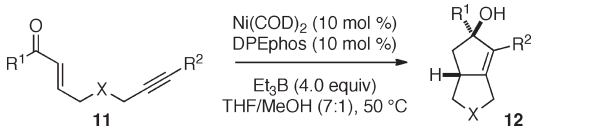
## RESULTS

**Enal−Alkyne Reductive Cycloadditions.** In the course of studying nickel-catalyzed cyclizations of alkynyl enals, our lab previously documented the preparation of a nickel metallacycle derived from the oxidative cyclization of Ni(0) with the enal and alkyne units.[14] A broad range of processes involving protonation and alkylation of the nickel enolate motif were described in a series of publications,[14] but the development of an efficient catalytic process with substoichiometric loadings of nickel proved elusive. In analogy to demonstrations in stoichiometric processes, the mechanism of the desired catalytic reductive cycloaddition involving the conversion of enal **5** and alkyne **6** into cyclopentenol **10** was envisioned to involve formation of metallacycle **7**, protonation to afford intermediate **8**, and then vinyl nickel addition to the carbonyl to afford nickel alkoxide **9** (Scheme 2). A requirement for achieving a substoichiometric catalytic version of this transformation is the in situ reduction of the nickel(II) alkoxide **9** to release the desired cyclopentenol product **10** and regenerate the active Ni(0) catalyst.

A key hurdle was the need to have a Ni(0) active catalyst, a Brønsted acid or electrophile, and an effective reducing agent all present in the reaction medium. While many potential solutions proved ineffective, the combination of a $Ni(COD)_2$-derived (COD = 1,5-cyclooctadiene) complex, an organoborane reducing agent, and a cosolvent system involving an alcohol component ultimately provided an effective solution.[15] To explore the potential for a catalytic reductive cycloaddition, simple alkynyl enal **11a** was first examined in the production of bicyclooctenol **12a**. As illustrated (Table 1), a number of monodentate and bidentate ligands were effective in promoting the organoborane-mediated procedure when a THF/methanol cosolvent system was employed.

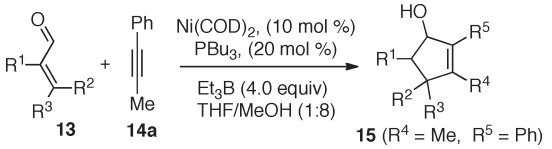
On the basis of the high chemical yields achieved with a nickel DPEphos (bis(2-diphenylphosphinophenyl)ether) catalyst (Table 1, entry 3), a few examples were explored under these conditions. As illustrated (Table 2), bicyclooctenol products **12** were efficiently obtained with substrates that possessed aryl and alkyl-substituted alkynes (entries 1 and 2). Additionally, an oxygen heterocycle could be accessed in moderate yield (entry 3). While these experiments duplicated the types of compounds that had previously been accessed

**Table 2. Scope of Intramolecular Reductive Cycloadditions of Enals and Alkynes**




| entry | $R^1$ | $R^2$ | X | yield (%) |
|---|---|---|---|---|
| 1 | H | Ph | $CH_2$ | 87 |
| 2 | H | Me | $CH_2$ | 78 |
| 3 | H | Ph | O | 44 |

**Table 3. Enal Variation in Intermolecular Reductive Cycloadditions of Enals and Alkynes**



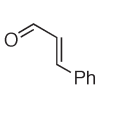
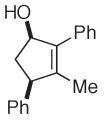
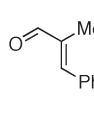
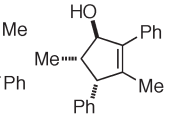
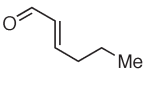
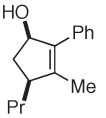
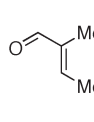
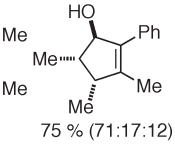
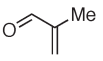
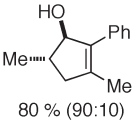
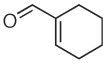
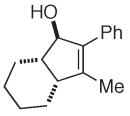
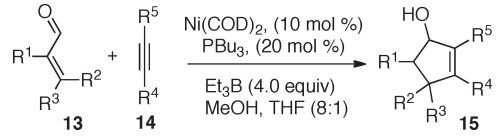
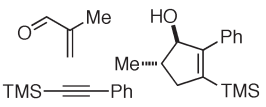
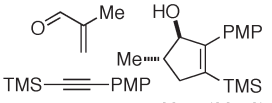
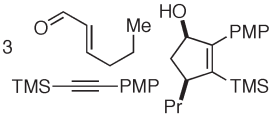
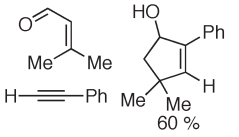
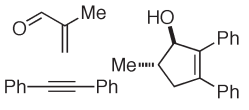
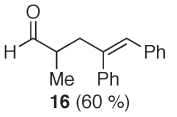
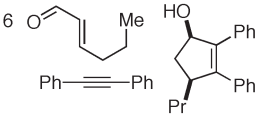
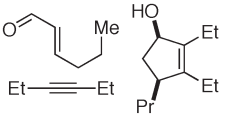

| entry | 13 | 15 (yield, dr) | entry | 13 | 15 (yield, dr) |
|---|---|---|---|---|---|
| 1 |  |  56 % (81:19) | 4 |  |  57 % (81:11:8) |
| 2 |  |  85 % (87:13) | 5 |  |  75 % (71:17:12) |
| 3 |  |  80 % (90:10) | 6 |  |  68 % (87:13) |

**Table 4. Alkyne Variation in Intermolecular Reductive Cycloadditions of Enals and Alkynes**



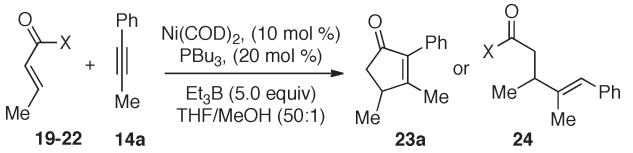

| entry | 13 & 14 | 15 (yield, dr) |
|---|---|---|
| 1 |  | 60 % (82:18) |
| 2 |  | 69 % (90:10) |
| 3 |  | 78 % (92:8) |
| 4 |  | 60 % |
| 5 |  | 30 % (84:16) |
| |  | **16** (60 %) |
| 6 |  | 74 % (82:18) |
| 7 |  | 64 % (63:37) |

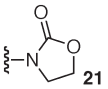
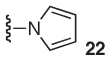
in stoichiometric procedures,[14] we quickly turned our attention to intermolecular variants. As seen with the stoichiometric procedures, catalytic intermolecular processes were completely ineffective with the Ni(0)-DPEphos catalyst.

Upon reexamining the ligands from Table 1 in intermolecular processes, we found that monodentate phosphines, while less effective than DPEphos in intramolecular processes, were significantly more effective than bidentate ligands in intermolecular processes. Using an optimized procedure with $Ni(COD)_2$, $PBu_3$, $Et_3B$, and THF:MeOH (1:8), a broad range of intermolecular reductive cycloadditions involving the conversion of enals **13** and phenyl propyne into cyclopentenols **15** were accessible (Table 3). Enals with a single substituent at the α- or β-position were effective participants, as examples with aromatic or aliphatic substituents at the β-position or a methyl substituent at the α-position proceeded in good to excellent yield (Table 3, entries 1−3). Additionally, acyclic and cyclic enals with a trisubstituted alkene underwent effective cycloaddition (Table 3, entries 4−6), with the latter case providing access to bicyclic products.

Significant variation of the alkyne is also possible, as demonstrated with the use of silyl alkynes (Table 4, entries 1−3), terminal alkynes (Table 4, entry 4), and internal alkynes with two aromatic (Table 4, entries 5 and 6) or two aliphatic (Table 4, entry 7) substituents. Embedded within these examples are further illustrations of the involvement of α-substituted and β-substituted enals. A single example with a β,β-disubstituted enal is provided (Table 4, entry 4); however, this substrate class is only effective with terminal alkynes due to the substantial steric demand of coupling a β,

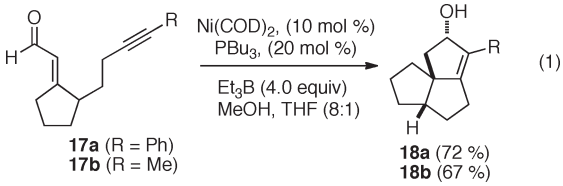
**Table 5. Comparison of Enoate Derivatives in Reductive Cycloadditions of Enoates and Alkynes**




| entry | X | product (% yield) |
|---|---|---|
| 1 | $OCH_3$ **19** | --- |
| 2 | OPh **20** | **23** (75) |
| 3 |  **21** | **23** (64) |
| 4 |  **22** | **23** (5) + **24** (90) |

β-disubstituted enal with an internal alkyne. In some instances, acyclic reductive coupling processes were observed as minor components of the reaction mixture. This was particularly prevalent with internal alkynes undergoing addition to enals with an α-substituent, as illustrated (Table 4, entry 5), where 60% yield of the acyclic reductive coupling product **16** was observed. This acyclic pathway also dominates when couplings of enones and alkynes are attempted, and a full description of the acyclic addition pathway in this context has been reported elsewhere.[16,17]

Given the superiority of DPE-Phos-promoted intramolecular versions, the $PBu_3$ procedure was not extensively studied in tethered systems. However, two examples involving the formation of a triquinane framework **18** from substrate **17** were established using the optimized $PBu_3$-promoted procedure (eq 1).




(1)

**Enoate−Alkyne Reductive Cycloadditions.** While the cyclopentenol products described above are useful building blocks for many applications, the corresponding cyclopentenones are also broadly useful in a variety of synthetic transformations. Rather than preparing the starting enals **13** for reductive cycloaddition, and then reoxidizing the cyclopentenol product **15** into a desired cyclopentenone, we realized that the direct conversion of a more stable and readily accessible enoate derivative into a cyclopentenone product would be considerably more efficient. With an eye toward developing this transformation, we examined a number of enoate derivatives **19**−**22** in Ni(0)-$PBu_3$-promoted reductive cycloadditions with phenyl propyne (Table 5). While simple methyl enoates **19** were unreactive in the reductive cycloaddition procedure (entry 1), the use of more reactive phenyl enoates **20**, unsaturated acyl oxazolidinones **21**, and unsaturated *N*-acylpyrroles **22**[18] participated in effective coupling procedures to afford the desired cyclopentenone **23a** or acyclic reductive coupling products **24**


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**Table 6. Ligand Selection in Reductive Cycloadditions of Enoates and Alkynes**


| entry | ligand (mol %) | % yield |
|---|---|---|
| 1 | $PBu_3$ (20 mol %) | 44 |
| 2 | $PPh_3$ (20 mol %) | 35 |
| 3 | $PCy_3$ (20 mol %) | 81 |
| 4 | IMes (10 mol %) | 87 |
| 5 | IPr (10 mol %) | 46 |

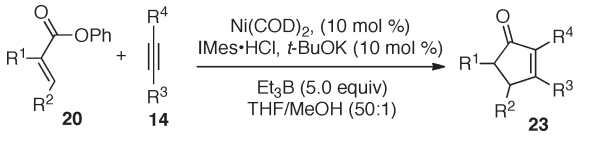
(entries 2−4). While *N*-acylpyrroles participated in very efficient reductive couplings with alkynes to afford acyclic product **24** (entry 4), the unsaturated acyl oxazolidinone and phenyl enoate participated in efficient reductive cycloaddition to produce the desired cyclopentone **23a** while expelling the acyl substituent (entries 2 and 3). On the basis of the slightly higher chemical yield and simpler access to phenyl enoates **20** compared with acyl oxazolidinones **21**, phenyl enoates were selected for further study.

Employing 10 mol % $Ni(COD)_2$ and $Et_3B$ in THF:MeOH (50:1), a number of ligands were examined in reductive cycloadditions of phenyl enoate **20a** and alkyne **14b** to produce cyclopentenone **23b** (Table 6). As depicted, $PCy_3$ and the N-heterocyclic carbene IMes emerged as the optimum ligands for promoting the transformation. Further study with other substrate classes illustrated the best generality with IMes, and this N-heterocyclic carbene was therefore the major focus of our further studies.

A series of examples of the Ni(0)-IMes-promoted reductive cycloaddition to produce cyclopentenones **23** were illustrated under optimized conditions (Table 7). The process is efficient with simple unsubstituted enoates using either internal or terminal alkynes (entries 2−4). While regioselectivities with the terminal alkyne were good using IMes, improved regioselectivity was seen with the bulkier ligand IPr (entry 4), as anticipated from our recent studies of ligand size-controlled regioselection in another reaction class.[19] Although yields were comparable between IMes and IPr for this particular substrate combination, other examples were generally lower yielding with IPr. Additional examples (entries 5−8) illustrate that a variety of α- and *β*-substituted enoates undergo this cycloaddition. While cycloadditions of α-substituted enoates are effective with terminal alkynes (entry 8), the major pathway of this enoate with an internal alkyne leads to production of the acyclic reductive coupling product (entry 6). The mechanistic implication of this finding is discussed below. Additionally, a number of functional groups, including free hydroxyls, secondary amines, and simple esters, are tolerated under the reductive cycloaddition conditions (entries 9−12).

**Catalytic Alkylative [3 + 2] Cycloadditions.** All of the above methods rely on a methanol-mediated protonation, likely of a nickel or boron enolate species. The derivatization of these intermediate enolate species through aldol functionalization or alkylation would represent an important advance for the catalytic methods reported herein, although considerable additional challenges in both reactivity and chemoselectivity are presented by advances of this type. Earlier reports of intramolecular stoichiometric processes described a range of alkylation reactions for the isolated metallacyclic species,[10,14] but

**Table 7. Scope of Reductive Cycloadditions of Enoates and Alkynes**

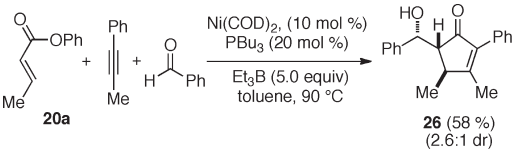



| entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | % yield (regiosel) |
|---|---|---|---|---|---|
| 1 | H | Me | Hex | Hex | 87 (--) |
| 2 | H | H | Me | Ph | 69 (93:7) |
| 3 | H | H | Oct | H | 67 (90:10) |
| 4 | H | H | Oct | H | 66 (99:1)[a] |
| 5 | H | Me | Me | Ph | 77 (86:14) |
| 6 | Me | H | Me | Ph | 19 (64:36)[b] |
| 7 | H | Ph | Me | Ph | 97 (95:5) |
| 8 | Me | H | Oct | H | 63 (97:3)[c] |
| 9 | H | Pr | $(CH_2)_2OH$ | Me | 68 (87:13)[c] |
| 10 | H | Ph | $(CH_2)_3OH$ | Ph | 89[d] |
| 11 | H | Ph | $(CH_2)_3NHBn$ | Ph | 78[d] |
| 12 | H | Pr | $(CH_2)_2CO_2Me$ | Ph | 78 (92:8) |

[a] Ligand = IPr. [b] The major product is the acyclic reductive coupling product **25** (63% yield, see Scheme 4 for discussion). [c] $PCy_3$ (20 mol %) was used as ligand in this example. [d] Yield is of the single regioisomer shown. The minor regioisomer is unstable, and its yield was not quantified.

no reports of related catalytic or intermolecular [3 + 2] alkylative cycloadditions have appeared.

Although processes of this type have not yet been generalized or optimized, a preliminary example to document the feasibility of catalytic alkylative [3 + 2] cycloadditions is now illustrated (eq 2).



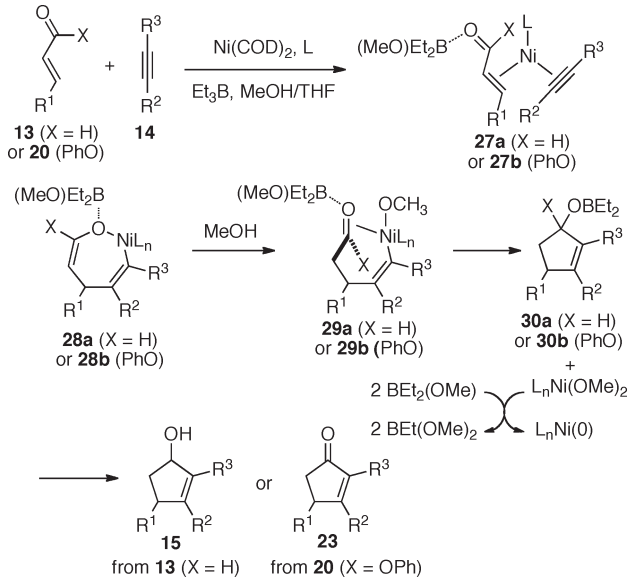
(2)

Upon treating a mixture of phenyl enoate **20a**, phenyl propyne, and benzaldehyde with triethylborane and a catalyst derived from $Ni(COD)_2/PBu_3$ in toluene, a 58% yield of two diastereomers of product **26**, epimeric at the secondary hydroxyl, was obtained. Aprotic solvents become necessary in the aldol variant of this procedure, to avoid the rapid enolate protonation that leads to reductive cycloaddition products such as those illustrated in Table 7. Further study of the scope and generality of alkylative cycloadditions of this type is in progress.

## DISCUSSION

As described above, earlier developments in stoichiometric reductive cycloadditions of enals and alkynes presented a rational mechanistic framework for the [3 + 2] reductive cycloaddition of enals and alkynes.[14] On the basis of this analogy, a likely mechanistic pathway for the organoborane-mediated catalytic reductive cycloaddition of enals **13** and alkynes **14** to cyclopentenols **15** involves oxidative cycloaddition of complex **27a** to metallacycle **28a** (Scheme 3). Triethylborane is known to undergo partial methanolysis to $Et_2B(OMe)$,[20] which is therefore depicted in reactions conducted in cosolvent systems involving methanol.

**Scheme 3. Mechanism of Catalytic Reductive Cycloadditions**



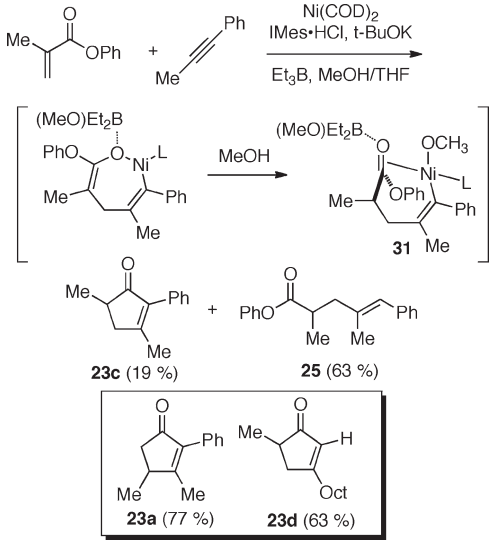

Complexation of the borane in intermediate **27a** likely accelerates the rate of the oxidative cyclization. In the presence of methanol, fast monoprotonation of the enolate unit of **28a** would afford vinyl nickel species **29a**, and direct addition of the vinyl nickel unit to the borane-complexed aldehyde of **29a** would afford boron alkoxide **30a** with release of a Ni(II) species. The borane then serves as the reducing agent to regenerate the active Ni(0) catalyst.

The precise nature of the interaction of the organoborane in species **27a** is unclear. While a simple Lewis acidic interaction of the borane with the aldehyde carbonyl is depicted for simplicity, computational studies suggested a more complex interaction in similar organozinc-mediated oxidative cyclizations when no phosphine or N-heterocyclic carbene ligands were employed.[21] The role of organoborane Lewis acidity was recently studied in other classes of oxidative cyclization processes.[22] Furthermore, several possibilities exist for the structure of the initially formed alkoxide product. Mechanisms can be envisioned that generate either boron alkoxide **30a** as shown or alternatively a nickel alkoxide during addition of the vinyl nickel unit to the aldehyde in structure **29a**. However, it is important to note that, in the absence of triethylborane, no five-membered ring cyclization is observed when enals are employed. Instead, an internal redox reaction predominates in the absence of borane, leading to acyclic products where the aldehyde is converted to a methyl ester during the coupling event.[23] This result suggests that borane complexation to the aldehyde in intermediate **29a** is a necessary step in promoting ring closure to cyclopentenol products.

On the basis of the above analysis for enal−alkyne cycloadditions, we propose that cycloadditions involving the conversion of enoates **20** and alkynes **14** into cyclopentenones **23** proceed via a similar pathway (Scheme 3). Formation of metallacycle **28b** followed by ester enolate protonation and then vinyl nickel addition to the borane-complexed ester **29b** would afford borane hemiacetal **30b**. Collapse of this tetrahedral species with phenoxide loss would then lead to the cyclopentenone product **23**, and the borane would again serve to regenerate the active Ni(0) catalyst.

Given the general lability of ester enolates, it is possible that the enolate motif of metallacycle **28b** undergoes extrusion of phenoxide. However, the fact that the phenyl ester is maintained in the product in select hindered examples suggests that this is not the case. As seen in one example (from Table 7, entry 6), acyclic product **25** is generated by the major reaction pathway, and the desired cyclopentenone **23c** is seen only as a minor product (Scheme 4). We attribute this outcome to the increased steric hindrance in intermediate **31**, which likely impedes the addition of the vinyl unit to the complexed ester. Observation of this product illustrates that the ester enolate generated in this example does not eliminate phenoxide under catalytically relevant conditions in the presence of the methanol solvent component. Notably, by removal of either the enoate α-substituent (product **23a** Table 7, entry 5) or the acetylenic substituent (product **23d** Table 7, entry 8), five-membered ring closure efficiently occurs, and acyclic products are not observed (Scheme 4). Furthermore, while this study largely focuses on the reaction of phenyl enoates, it is worth noting that unsaturated acyl oxazolidinones, which also undergo efficient reductive cycloadditions (Table 5), have been demonstrated to undergo many metallacycle-based transformations without extrusion of the oxazolidinone unit.[24]

**Scheme 4. Role of Substrate Sterics in Cyclization vs Coupling**




The preliminary alkylative cycloaddition example involving aldol addition (product **26**, eq 2) may involve a pathway similar to that depicted in Scheme 3 for reductive cycloadditions of enoates. In this instance with an aprotic solvent, $Et_3B$ is likely the active reducing agent rather than $(MeO)BEt_2$. Rather than protonation of metallacycle **28b** by methanol as seen in reductive cycloadditions, the enolate motif of **28b** likely undergoes aldol addition instead but otherwise follows the illustrated sequence analogous to that shown for product **23**. Given the slower rate of aldol addition compared with proton transfer, alternate pathways such as that involving phenoxide extrusion from intermediate **28b** may be likely in cases involving aldol addition. Future studies of the scope and mechanism of alkylative versions of the [3 + 2] cycloadditions will be reported in due course.

## CONCLUSIONS

In summary, a series of [3 + 2] cycloaddition reactions that proceed by formal reductive cycloaddition has been illustrated. The processes involve addition of an enal or enoate to an alkyne. By altering the starting material oxidation state, the procedure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provides either cyclopentenol or cyclopentenone products. Intermolecular procedures provide monocyclic products, whereas the corresponding intramolecular versions provide bicyclic or tricyclic compounds. A mechanistic pathway involving the formation of metallacyclic enolates followed by rapid protonation and carbonyl addition is most consistent with the results obtained. In contrast to well-established cycloaddition procedures for assembly of five-membered rings, the use of simple $\pi$-components as starting reagents is made possible by the net two-electron reduction that occurs during cyclizations. We envision that many classes of odd-numbered ring cycloadditions may become possible by strategies of this type.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Detailed experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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