

# Nickel-Catalyzed Cyclizations, Couplings, and Cycloadditions Involving Three Reactive Components

JOHN MONTGOMERY\*

Department of Chemistry, Wayne State University,  
Detroit, Michigan 48202-3489

Received December 14, 1999

## ABSTRACT

Transition-metal-catalyzed processes that allow the efficient coupling of three reactive components in a chemoselective and stereoselective fashion are particularly useful in the synthesis of complex organic molecules from simple, readily available substrates. This account outlines work primarily from the author's laboratory on the development of nickel-catalyzed multicomponent coupling processes. An overview of new synthetic methods, a discussion of potential mechanisms, and a description of applications in complex-molecule synthesis are provided.

## Introduction

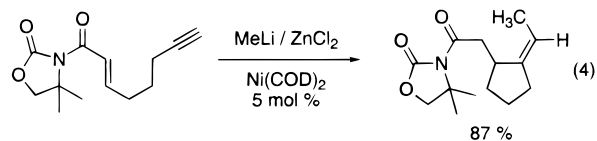
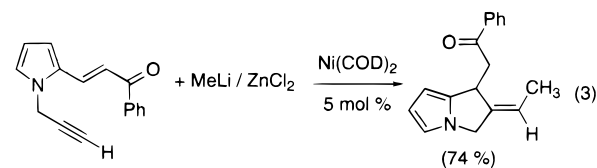
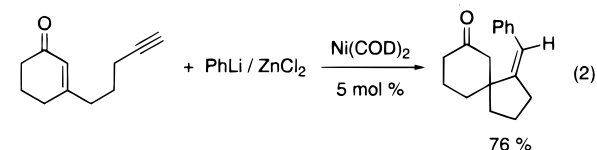
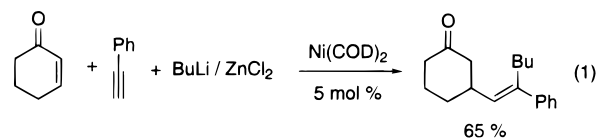
Transition-metal catalysis provides the opportunity to generate complex molecular frameworks from simple, readily available substrates in an efficient and selective manner.<sup>1–5</sup> Whereas many important metal-catalyzed processes have been developed that involve couplings or cyclizations of two reactive functionalities, those processes that involve three or more reactive functional groups have particular promise in the generation of molecular complexity.<sup>6</sup> Chemoselectivity becomes an important consideration in the design of any multicomponent coupling process, and transition metal catalyzed variants are often quite difficult to optimize due to complications such as competing oligomerization or polymerization of one of the components. Entropic considerations do facilitate partially or fully intramolecular processes, whereas the corresponding fully intermolecular processes are usually particularly demanding.

A major goal of the research in my laboratories has been to develop new nickel-catalyzed processes that allow three reactive functionalities to participate in complex catalytic sequences in either an inter- or intramolecular sense. Much of the chemistry involves the coupling of two unsaturated components with an organozinc reagent. In

most instances, there is direct precedent for the nickel-catalyzed coupling of an organozinc with both of the unsaturated components. Thus, chemoselectivity becomes a particularly critical issue in the design of multicomponent couplings of this general class. Four basic types of coupling reactions will be discussed: (1) the coupling of an enone, alkyne, and organozinc; (2) the coupling of two enones and an alkyne; (3) the coupling of an aldehyde, alkyne, and either an organozinc or silane; and (4) the coupling of two enones with an organozinc. The development of inter- and intramolecular variants of each of these processes and their application in the synthesis of complex molecules will be described.

## Coupling of an Enone, Alkyne, and Organozinc

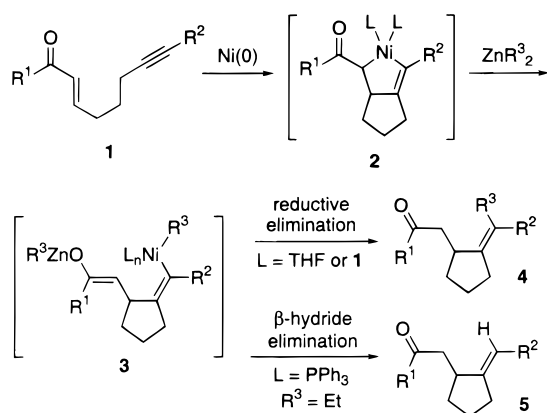
The addition of organozincs to enones in the presence of nickel catalysts is one of the most important methods for effecting conjugate additions to sterically hindered enones.<sup>7</sup> Given the facility of this process, the development of nickel-catalyzed multicomponent coupling processes involving an enone and an organozinc poses an interesting challenge in chemoselectivity since simple conjugate additions must be avoided. Studies from our group<sup>8–12</sup> and from Ikeda and Sato<sup>13</sup> have demonstrated that three-component couplings of enones, alkynes, and organozincs efficiently proceed to generate products in which the organozinc formally adds to the alkyne, not to the enone (eqs 1–4). The method produces  $\gamma,\delta$ -unsaturated ketones



John Montgomery was born in 1965 in Concord, N. C. He received his A.B. degree from the University of North Carolina at Chapel Hill in 1987, and he carried out undergraduate research under the direction of Professors Joe Templeton and Maurice Brookhart. He received his Ph.D. at Colorado State University in 1991 under the direction of Professor Lou Hegedus. He was an American Cancer Society Postdoctoral Fellow at the University of California at Irvine from 1991 to 1993 with Professor Larry Overman. In 1993, he began his independent career at Wayne State University where he is now Associate Professor of Chemistry. His work at Wayne State has focused on applications of organonickel chemistry in reaction discovery, synthetic methodology development, and total synthesis and on the development of new methods for the synthesis of amino acids utilizing nitroacetates as glycine templates.

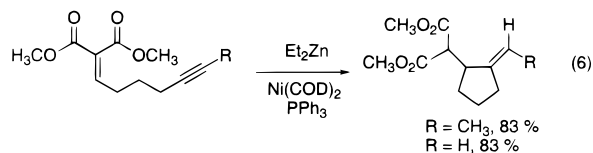
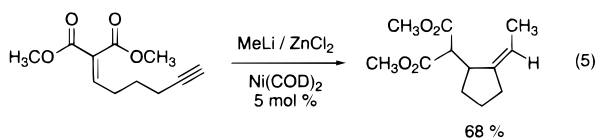
with the alkene being generated in a completely stereoselective fashion. The reaction may be carried out in a fully intermolecular fashion<sup>9,13</sup> or the enone and alkyne may be covalently linked by a tether chain (eqs 1–3).<sup>8,10–12</sup> Whereas enoates are poor substrates in this class of

Scheme 1



reactions, unsaturated acyl oxazolidinones perform very satisfactorily (eq 4).<sup>14</sup>

An interesting ligand effect was observed in intramolecular variants.<sup>8,11</sup> As demonstrated above (eq 1), organozincs that possess  $\beta$  hydrogens are cleanly introduced during the three-component coupling processes when Ni(COD)<sub>2</sub> is utilized as the catalyst. However, if the Ni(COD)<sub>2</sub> is pretreated with four equivalents of triphenylphosphine prior to substrate introduction, a hydrogen atom is cleanly introduced at the exocyclic double-bond position if the organozinc possesses a  $\beta$  hydrogen. If no  $\beta$  hydrogen is present in the organozinc (i.e., ZnMe<sub>2</sub>), then the addition of triphenylphosphine does not alter the reaction outcome. The combination of these two observations provides a powerful method for exocyclic double-bond introduction since it allows either the *E* or *Z* isomer of the exocyclic double bond to be efficiently generated (eqs 5 and 6). Either commercial organozincs or organozincs

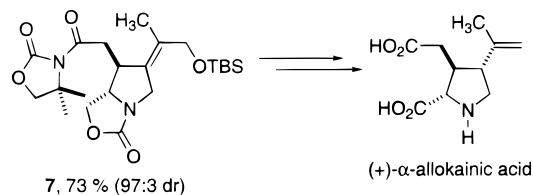
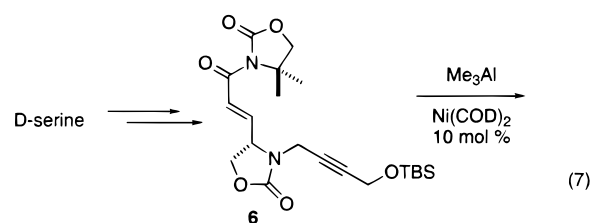


prepared in situ from a 1.5:1 mixture of organolithium or organomagnesium and zinc chloride may be utilized in the alkylative cyclizations (eq 5). Reductive cyclizations, however, proceed most efficiently with commercial diethylzinc (eq 6). The use of BuLi/ZnCl<sub>2</sub> or EtMgBr/ZnCl<sub>2</sub> with Ni(COD)<sub>2</sub>/PPh<sub>3</sub> as catalyst leads to mixtures of the reductive and alkylative cyclization products.

We propose that the mechanism of the couplings involves formation of metallacycle **2** from the oxidative cyclization of a nickel (0)  $\pi$ -complex of **1** (Scheme 1).<sup>11</sup> Transmetalation of the organozinc would lead to alkenyl intermediate **3** which likely is a common intermediate in the generation of products **4** and **5**. Although the role of triphenylphosphine in promoting the  $\beta$ -hydride elimina-

tion pathway is not clear, we suspect that the effect is derived from the  $\sigma$ -donating ability of the phosphine. Direct reductive elimination of **3** is accompanied by a two-electron reduction of the metal and should therefore be disfavored by the coordination of good  $\sigma$ -donors such as PPh<sub>3</sub>. On the contrary,  $\pi$ -acidic ligands accelerate reductive eliminations by withdrawing electron density from the metal center.<sup>15–19</sup> In the absence of triphenylphosphine, the unreacted enone substrate may coordinate to nickel in intermediate **3** and lead to an acceleration of the rate of reductive elimination relative to competing  $\beta$ -hydride elimination.

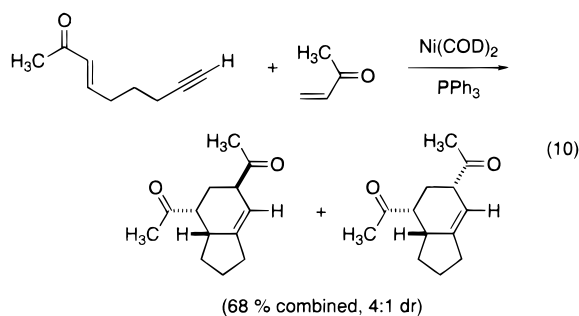
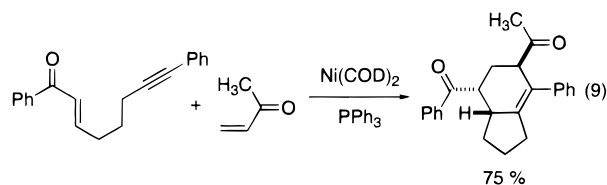
The total syntheses of the neuroexcitatory amino acid natural products (+)- $\alpha$ -allokainic acid<sup>20</sup> and (–)- $\alpha$ -kainic acid<sup>21</sup> were carried out utilizing the nickel-catalyzed cyclization methodology as key steps (eqs 7 and 8).



Substrate **6**, conveniently prepared from D-serine, was efficiently cyclized in the presence of trimethylaluminum and catalytic Ni(COD)<sub>2</sub>. Adduct **7** was then converted into a key intermediate for the synthesis of (+)- $\alpha$ -allokainic acid. In a variation of the procedure, allene-containing substrate **8** was cyclized in the presence of MeLi/ZnCl<sub>2</sub>, Ti(O-*ipr*)<sub>4</sub>, and catalytic Ni(COD)<sub>2</sub> to afford the cycloadduct **9**. This pyrrolidine derivative was efficiently converted to the diastereomeric natural product (–)- $\alpha$ -kainic acid. The complementary nature of the alkyne and allene cyclizations thus provided an efficient stereodivergent approach to these two epimeric natural products.

## Coupling of Two Enones and an Alkyne

As described above, three-component couplings involving an enone, an alkyne, and an organozinc are likely initiated by the formation of a metallacycle derived from oxidative cyclization of nickel(0) with the enone and alkyne. We envisioned that such a metallacycle could be generated in the absence of the organozinc and then utilized in other classes of transformations.<sup>12</sup> Consistent with this objective, we observed that an efficient [2+2+2] cycloaddition proceeds when an alkynyl enone is treated with a simple enone such as methyl vinyl ketone in the presence of catalytic quantities of Ni(COD)<sub>2</sub>/PPh<sub>3</sub> (eqs 9 and 10).<sup>22</sup>

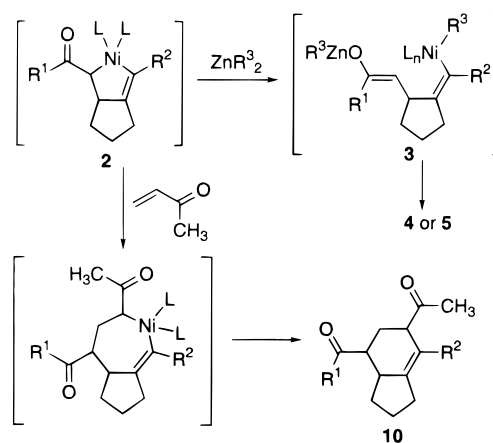


Aromatic and aliphatic enones tethered to either internal or terminal alkynes cleanly participate in the [2+2+2] cycloaddition to produce functionalized bicyclononenes. The scope is reasonably broad with respect to the alkynyl enone component, although simple enones, more functionalized than methyl vinyl ketone, are generally not cleanly introduced due to the rapid rate of competing alkynyl enone dimerization. The reaction generally proceeds with high stereoselectivity, but with no stereospecificity. The unusual stereochemical issues were discussed in detail in our original report of this work.<sup>22</sup>

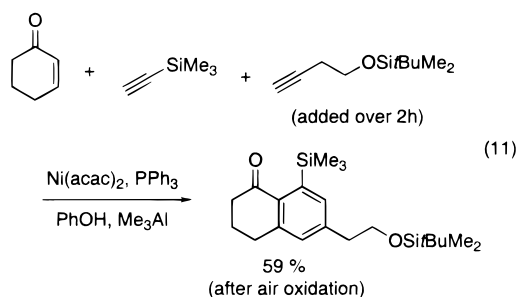
These experiments are all fully consistent with the proposed intermediacy of a nickel metallacycle **2** derived from the oxidative cyclization of nickel(0) with an enone and alkyne (Scheme 2). If the metallacycle **2** is formed in the presence of an organozinc, then transmetalation occurs to generate either alkylative or reductive cyclization products **4** or **5** depending on the ligand environment. Alternatively, if metallacycle **2** is generated in the presence of a simple enone, then insertion of the alkene occurs to ultimately produce bicyclononene product **10**. This series of experiments suggests that alkynyl enone-derived nickelacycles may participate in a rich variety of coupling and cycloaddition processes, and new directions utilizing these intermediates are being explored.

An important series of experiments from Ikeda demonstrated that the chemoselectivity of fully intermolecular cycloadditions involving enones and alkynes is altered to

Scheme 2



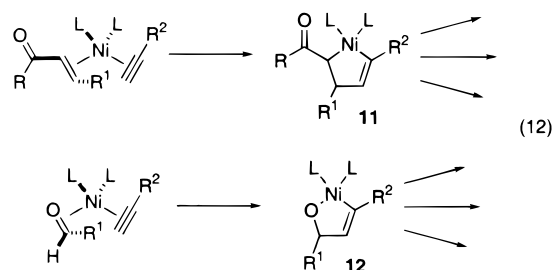
favor coupling of one enone and two alkynes.<sup>23,24</sup> Significantly, a selective 1:1:1 cyclotrimerization of an enone and two different alkynes becomes possible in certain instances (eq 11).<sup>25</sup> The chemoselectivity of this procedure



is impressive given the many isomers that conceivably could be produced.

## Coupling of an Aldehyde, Alkyne, and Organozinc or Silane

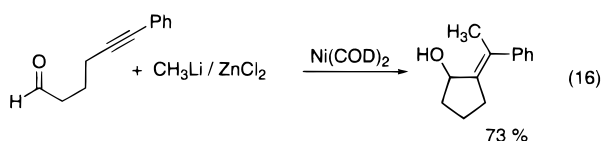
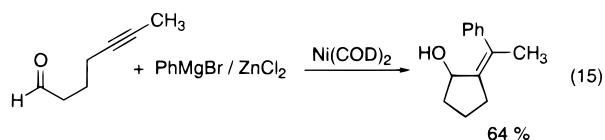
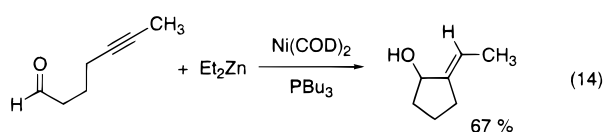
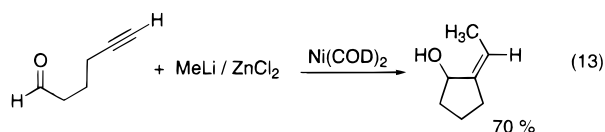
Given the broad utility of metallacycles **11** derived from enones and alkynes demonstrated above, we became interested in developing catalytic procedures based on the analogous oxametallacycles **12** derived from aldehydes and alkynes (eq 12). Important catalytic processes have



been developed based on the reactivity of early-metal oxametallacycles derived from aldehydes and alkenes or alkynes,<sup>26–28</sup> but the corresponding late-metal-catalyzed processes have received little attention.<sup>29</sup> Potential advantages of late-metal catalysis compared with early-metal catalysis include (1) simpler preparation and handling of the catalysts, (2) better compatibility with Lewis basic

functionality, (3) weaker metal–oxygen bonds leading to more efficient catalytic turnovers of metal alkoxide intermediates, and (4) access to reductive elimination chemistry generally not accessible to early-metal dialkyl species.

Our studies involving the participation of aldehydes in nickel-catalyzed processes were initiated with the coupling of ynals and organozincs.<sup>30</sup> The desired cyclizations proceeded efficiently in direct analogy to the corresponding alkynyl enone/organozinc couplings. Treatment of an ynal with an organozinc and catalytic Ni(COD)<sub>2</sub> cleanly provided cyclic allylic alcohols with stereodefined exocyclic tri- or tetrasubstituted alkenes (eqs 13–16). As with



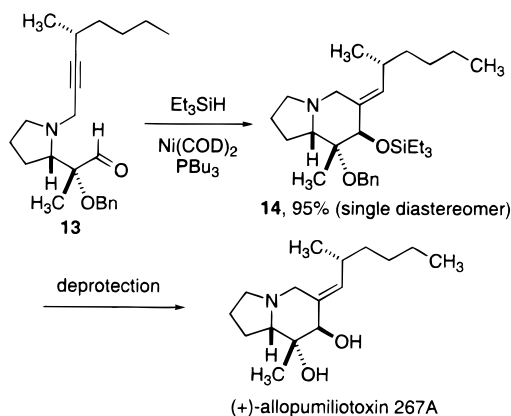
the enone cyclizations, pretreatment of Ni(COD)<sub>2</sub> with a basic phosphine (in this instance PBU<sub>3</sub> was most efficient) allowed reductive cyclizations to proceed cleanly, whereas alkylation cyclizations resulted in the absence of phosphine ligands. This combination of results allows either isomer of tri- and tetrasubstituted alkenes to be introduced in a completely stereoselective fashion.

Intermolecular couplings involving aldehydes, alkynes, and organozincs also proceed with a high degree of chemoselectivity.<sup>30</sup> However, unlike the intramolecular variants, direct addition of more reactive organozincs to the aldehyde becomes problematic. As a result, the scope appears to be limited to the addition of sp<sup>3</sup>-hybridized organozincs since sp<sup>2</sup>-hybridized organozincs undergo direct addition to the aldehyde faster than the three-component couplings occur (eq 17).

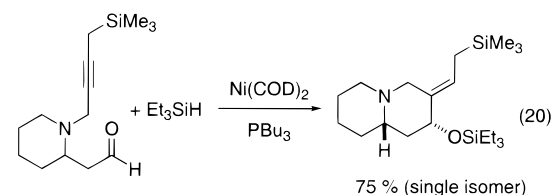
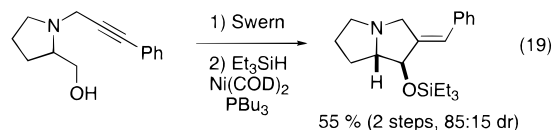
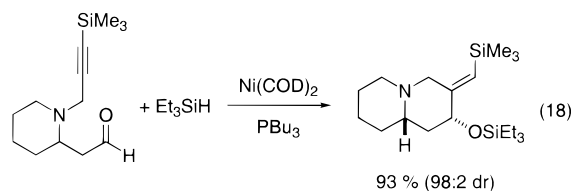


Studies of more complex reductive cyclizations involving diethylzinc and Ni(COD)<sub>2</sub>/PBU<sub>3</sub> catalysis were unsuccessful due to competing addition of diethylzinc to the aldehyde. However, a significantly more efficient protocol

Scheme 3



was found involving triethylsilane as the reducing agent in place of diethylzinc. This protocol for ynals cyclization is the most general procedure among all of the nickel-catalyzed processes that we have studied (eqs 18–20);<sup>31,32</sup>

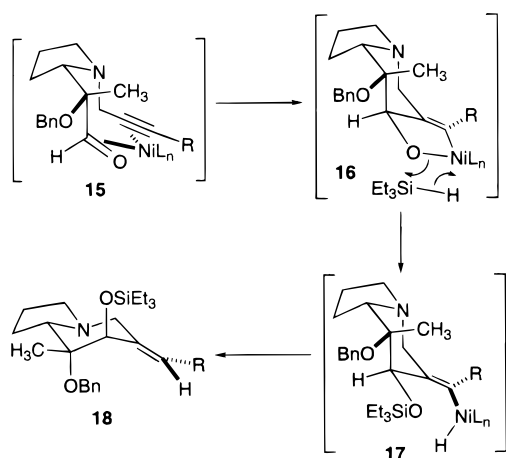


however, intermolecular couplings are not efficient with triethylsilane.

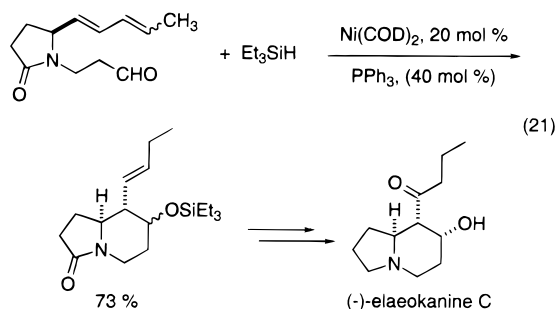
Discovery of the triethylsilane-promoted ynals cyclization was an exciting breakthrough since we felt that this new procedure would allow us to address increasingly challenging problems. To test its efficiency in a complex setting, we designed an approach for the synthesis of (+)-allopumiliotoxin 267A that relies on a late-stage ynals reductive cyclization (Scheme 3).<sup>31</sup> Compound **13**, which was efficiently prepared from L-proline, underwent efficient cyclization at 0 °C in THF in the presence of triethylsilane (5 equiv) and Ni(COD)<sub>2</sub>/PBU<sub>3</sub> (2:1, 20 mol % Ni) to afford indolizidine alkaloid **14** as a single diastereomer in 95% isolated yield. The completely selective formation of the trans diol is consistent with a mechanism involving a metallacycle produced via the Ni(0) π-complex **15** in a cis-hydrindane conformation (Scheme 4). Oxidative cyclization to **16** followed by σ-bond metathesis would afford product **18** upon reductive elimination of **17**.



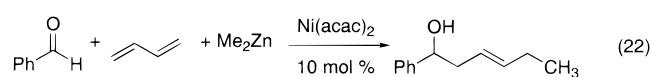
Scheme 4



A related class of transformations involving the nickel-catalyzed cyclization of diene aldehydes has been developed over the past few years by Mori.<sup>33,34</sup> Those studies demonstrated that diene aldehydes undergo efficient cyclizations in the presence of triethylsilane and Ni(acac)<sub>2</sub> that was pretreated with diisobutylaluminum hydride. The reaction is a reductive coupling and may produce either  $\gamma,\delta$ -unsaturated or  $\delta,\epsilon$ -unsaturated silyl ethers as products. The net transformation is very similar to the ynal cyclizations described above, and metallacycles may be involved although two possible mechanisms have been proposed. An efficient formal synthesis of (-)-elaeokanine C was completed utilizing a diene aldehyde cyclization as a key step (eq 21).<sup>35,36</sup> An attractive three-component coupling



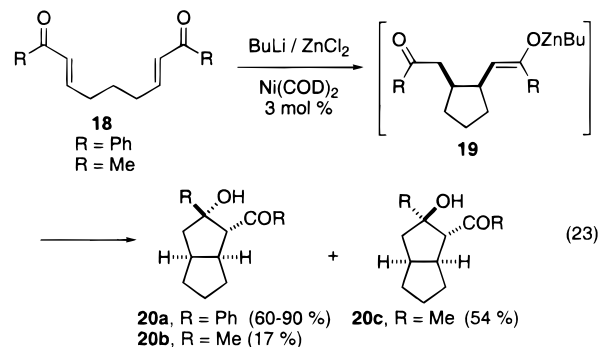
of dienes, aldehydes, and organozincs was recently reported by Tamaru and Kimura<sup>37</sup> and by Mori,<sup>38</sup> and these results further support the involvement of nickel oxametallacycles in the couplings of aldehydes and dienes (eq 22).



### Coupling of Two Enones and an Organozinc

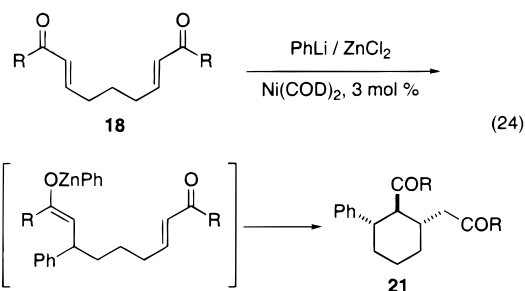
In contrast to the above classes of reactions involving alkynes, distinctly different behavior was demonstrated by bis-enones in nickel-catalyzed cyclizations.<sup>11,39</sup> In the presence of organozincs and Ni(COD)<sub>2</sub>, this particular

substrate class undergoes reductive cyclizations in the presence of organozincs only if the organozinc is sp<sup>3</sup> hybridized. Furthermore, the organozinc substituent is never incorporated in reductive cyclizations, irrespective of ligand structure. These issues are demonstrated by the reactions of bis-enone **18** with either BuLi/ZnCl<sub>2</sub> or PhLi/ZnCl<sub>2</sub>. In the presence of BuLi/ZnCl<sub>2</sub> and Ni(COD)<sub>2</sub>, bis-enone **18** undergoes efficient reductive cyclization to enolate **19**, which ultimately provides bicyclooctanol **20** after aldol addition (eq 23). The substrate is reduced by



two electrons, and the organozinc apparently is oxidized, but the organozinc substituent is not incorporated. Little is known about the mechanism of this class of bis-enone reductive cyclizations, although it is possible that a metallacycle-based pathway is involved. Six-membered rings may be produced by the homologous substrate, albeit in decreased yield.<sup>9</sup>

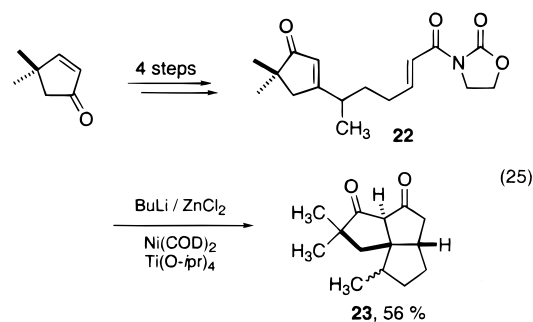
Most classes of reactions described in this account tolerate a variety of organozinc components. However, under conditions identical to those described for reductive cyclizations of bis-enones, only substituting PhLi/ZnCl<sub>2</sub> for BuLi/ZnCl<sub>2</sub>, a completely different cyclization manifold results. In this instance, conjugate addition of diphenylzinc to bis-enone **18** occurs, followed by an intramolecular Michael addition to afford the all-equatorial trisubstituted cyclohexane **21** (eq 24). Given that nickel-catalyzed con-



jugate additions have long been recognized as effective methods for functionalizing enones,<sup>7</sup> it is perhaps surprising that organozinc addition to the enone is observed with so few of the substrate classes described in this review.

The reductive cyclization/aldol addition sequence was expanded to include cyclizations involving unsaturated acyl oxazolidinones.<sup>14</sup> This variation allows reductive cyclization to be followed by a Dieckmann condensation rather than an aldol addition. 1,3-Dicarbonyl compounds are therefore directly obtained, and this advance was

utilized in the synthesis of the triquinane framework common to a number of natural products of the pentalene class (eq 25). Treatment of substrate **22** with BuLi/



ZnCl<sub>2</sub> in the presence of 5 mol % Ni(COD)<sub>2</sub> directly afforded compound **23**, which was an intermediate in the Crimmins approach to pentalenic acid<sup>40</sup> and related structures. Although the diastereoselectivity of the cyclization with respect to the C-ring methyl substituent was less than satisfactory, the opportunity to generate a functionalized triquinane in only five steps from dimethylcyclopentenone provides one of the most direct and efficient approaches to the angular triquinane skeleton.

## Conclusions

Transition metal catalyzed processes that involve the coupling of three or more different components are typically complicated by challenging issues in chemoselectivity. However, a number of nickel-catalyzed processes have been developed that assemble complex molecular architectures from three simple components in a highly chemoselective and stereoselective fashion. A number of synthetic challenges that are of central importance in organic synthesis are effectively addressed by the newly developed nickel-catalyzed processes. These challenges include the stereoselective generation of tri- and tetra-substituted alkenes, the rapid generation of polycyclic ring systems with multiple contiguous stereocenters, and the coupling of various functional groups in fundamentally new ways. Additional new manifolds of novel and useful reactivities will undoubtedly continue to emerge from further studies of processes involving nickel catalysis.

*I greatly appreciate the hard work and dedication of the students and postdoctorals in my laboratories at Wayne State who carried out the work described in this account. I also appreciate many helpful discussions with my colleagues at Wayne State and with my former mentors Lou Hegedus and Larry Overman. Generous financial support for this work was kindly provided by a National Science Foundation Career Award, the National Institutes of Health, the Petroleum Research Fund, a Camille Dreyfus Teacher Scholar Award, the Elsa U. Pardee Foundation, 3M Pharmaceuticals, Parke-Davis Pharmaceutical Research, and Wayne State University.*

## References

- Trost, B. M.; Shi, Y. Palladium-Catalyzed Cyclizations of Polyenes. A Palladium Zipper. *J. Am. Chem. Soc.* **1993**, *115*, 9421–9438.
- Fox, M. E.; Li, C.; Marino, J. P.; Overman, L. E. Enantiodivergent Total Syntheses of (+)- and (–)-Scopadulcic Acid A. *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.
- Negishi, E.; Copéret, C.; Ma, S.; Liou, S. Y.; Liu, F. Cyclic Carbopalladation. A Versatile Synthetic Methodology for the Construction of Cyclic Organic Compounds. *Chem. Rev.* **1996**, *96*, 365–393.
- Bao, J.; Wulff, W. D.; Dragsich, V.; Wenglowky, S.; Ball, R. G. Three-Component Intramolecular Two-Alkyne Annulations of Fischer Carbene Complexes: New Strategies for Steroid Synthesis. *J. Am. Chem. Soc.* **1994**, *116*, 7616–7630.
- Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. Tandem Use of Cobalt-Mediated Reactions to Synthesize (+)-Epoxydictymene, a Diterpene Containing a Trans-Fused 5–5 Ring System. *J. Am. Chem. Soc.* **1997**, *119*, 4353–4363.
- For an overview of nonmetal-catalyzed examples, see: Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. *Acc. Chem. Res.* **1996**, *29*, 123–131.
- Petrier, C.; de Souza Barbosa, J. C.; Dupuy, C.; Luche, J.-L. Ultrasound in Organic Synthesis. 7. Preparation of Organozinc Reagents and their Nickel-Catalyzed Reactions with  $\alpha,\beta$ -Unsaturated Carbonyl Compounds. *J. Org. Chem.* **1985**, *50*, 5761–5765.
- Montgomery, J.; Savchenko, A. V. Nickel-Catalyzed Cyclizations of Alkynyl Enones with Concomitant Stereoselective Tri- or Tetrasubstituted Alkene Introduction. *J. Am. Chem. Soc.* **1996**, *118*, 2099–2100.
- Montgomery, J.; Seo, J.; Chui, H. M. P. Competition Between Insertion and Conjugate Addition in Nickel-Catalyzed Couplings of Enones with Unsaturated Functional Groups. *Tetrahedron Lett.* **1996**, *37*, 6839–6842.
- Montgomery, J.; Chevliakov, M. V.; Briemann, H. L. Nickel-Catalyzed Heterocycle Construction with Stereoselective Exocyclic Alkene Introduction. *Tetrahedron* **1997**, *53*, 16449–16462.
- Montgomery, J.; Oblinger, E.; Savchenko, A. V. Nickel-Catalyzed Organozinc-Promoted Carbocyclizations of Electron-Deficient Alkenes with Tethered Unsaturation. *J. Am. Chem. Soc.* **1997**, *119*, 4911–4920.
- Montgomery, J.; Seo, J. Synthetic Studies and Mechanistic Observations in Nickel-Catalyzed Polycyclizations. *Tetrahedron* **1998**, *54*, 1131–1144.
- Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. Nickel-Catalyzed Tandem Coupling of Chlorotrimethylsilane, Alpha, Beta-Enones, Alkynes, and Dimethylzinc. *Organometallics* **1995**, *14*, 5015–5016.
- Seo, J.; Fain, H.; Blanc, J. B.; Montgomery, J. Nickel-Catalyzed Cyclizations of Enolate Equivalents; Application to the Synthesis of Angular Triquinanes. *J. Org. Chem.* **1999**, *64*, 6060–6065.
- Yamamoto, T.; Abia, M. Reductive Elimination of Et-Et From NiEt<sub>2</sub>(bpy) Promoted By Electron-Accepting Aromatic Compounds. *J. Organomet. Chem.* **1997**, *535*, 209–211.
- Yamamoto, T.; Yamamoto, A.; Ikeda, S. Study of Organo-(dipyridyl)nickel Complexes. II. Stabilities of Olefin-Nickel Bonds in Olefin-Coordinated Dipyridylnickel and Dialkyl(dipyridyl)nickel Complexes. *J. Am. Chem. Soc.* **1971**, *93*, 3360–3364.
- Yamamoto, T.; Yamamoto, A.; Ikeda, S. Study of Organo-(dipyridyl)nickel Complexes. I. Stability and Activation of the Alkyl-Nickel Bonds of Dialkyl(dipyridyl)nickel by Coordination with Various Substituted Olefins. *J. Am. Chem. Soc.* **1971**, *93*, 3350–3359.
- Sustmann, R.; Lau, J.; Zipp, M. Alkylation of Aryl Bromides with Tetra Alkyl Tin Compounds in the Presence of (2,2'-Bipyridine)Fumaronitrile Palladium(0). *Tetrahedron Lett.* **1986**, *27*, 5207–5210.
- Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. New Efficient Nickel-Catalyzed Cross-Coupling Reaction Between Two Csp<sup>3</sup> Centers. *J. Org. Chem.* **1999**, *64*, 3544–3553.
- Chevliakov, M. V.; Montgomery, J. Nickel and Palladium Catalysis in the Stereoselective Synthesis of Functionalized Pyrrolidines: Enantioselective Formal Synthesis of (+)- $\alpha$ -Allokainic Acid. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3144–3146.
- Chevliakov, M. V.; Montgomery, J. A Stereodivergent Approach to (–)- $\alpha$ -Kainic Acid and (+)- $\alpha$ -Allokainic Acid Utilizing the Complementarity of Alkyne and Allene Cyclizations. *J. Am. Chem. Soc.* **1999**, *121*, 11139–11143.
- Seo, J.; Chui, H. M. P.; Heeg, M. J.; Montgomery, J. Novel Chemoselectivity and Stereochemical Aspects of Nickel-Catalyzed [2+2+2] Cycloadditions. *J. Am. Chem. Soc.* **1999**, *121*, 476–477.
- Ikeda, S.; Mori, N.; Sato, Y. Regioselective Cyclic Cotrimerization of Alpha,Beta-Enones and Alkynes by a Nickel–Aluminum Catalyst System. *J. Am. Chem. Soc.* **1997**, *119*, 4779–4780.
- Ikeda, S.; Watanabe, H.; Sato, Y. Nickel- and Zinc-Promoted [2+2+2] Cycloaddition of Dienes and Alpha,Beta-Enones. *J. Org. Chem.* **1998**, *63*, 7026–7029.

- (25) Mori, N.; Ikeda, S.; Sato, Y. Selective Cyclotrimerization of Enones and Alkynes by a Nickel and Aluminum Catalytic System. *J. Am. Chem. Soc.* **1999**, *121*, 2722–2727.
- (26) Kablaoui, N. M.; Buchwald, S. L. Reductive Cyclization of Enones by a Titanium Catalyst. *J. Am. Chem. Soc.* **1995**, *117*, 6785–6786.
- (27) Kablaoui, N. M.; Buchwald, S. L. Development of a Method for the Reductive Cyclization of Enones by a Titanium Catalyst. *J. Am. Chem. Soc.* **1996**, *118*, 3182–3191.
- (28) Crowe, W. E.; Rachita, M. J. Titanium-Catalyzed Reductive Cyclization of  $\delta,\epsilon$ -Unsaturated Ketones and Aldehydes. *J. Am. Chem. Soc.* **1995**, *117*, 6787–6788.
- (29) For alternative routes to nickel oxametallacycles, see the following: Koo, K.; Hillhouse, G. L. Formation of a Substituted Tetrahydrofuran by Formal [2+2+1] Coupling of an Oxygen Atom with Two Olefins at a Nickel Center. *Organometallics* **1998**, *17*, 2924–2925.
- (30) Oblinger, E.; Montgomery, J. A New Stereoselective Method for the Preparation of Allylic Alcohols. *J. Am. Chem. Soc.* **1997**, *119*, 9065–9066.
- (31) Tang, X. Q.; Montgomery, J. Nickel Catalysis in the Stereoselective Preparation of Quinolizidine, Pyrrolizidine, and Indolizidine Alkaloids: Total Synthesis of (+)-Allopumillotoxin 267A. *J. Am. Chem. Soc.* **1999**, *121*, 6098–6099.
- (32) Qi, X.; Montgomery, J. New Three-Component Synthesis of 1,3-Dienes Employing Nickel Catalysis. *J. Org. Chem.* **1999**, *64*, 9310–9313.
- (33) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. Novel Stereoselective Cyclization Via  $\pi$ -Allylnickel Complex Generated From 1,3-Diene and Hydride Nickel-Complex. *J. Am. Chem. Soc.* **1994**, *116*, 9771–9772.
- (34) Sato, Y.; Takimoto, M.; Mori, M. Remarkable Regio-Controlled Effect of 1,3-Diene as a Ligand on Nickel-Promoted Cyclization. *Tetrahedron Lett.* **1996**, *37*, 887–890.
- (35) Sato, Y.; Saito, N.; Mori, M. Efficient Synthesis of Pyrrolizidine and Indolizidine Derivatives Using Nickel-Catalyzed Cyclization of 1,3-Diene and Aldehyde: Formal Total Synthesis of (–)-Elaeokanine C. *Tetrahedron Lett.* **1997**, *38*, 3931–3934.
- (36) Sato, Y.; Saito, N.; Mori, M. Stereoselective Synthesis of Nitrogen-Containing Heterocycles Via Nickel-Catalyzed Cyclization of 1,3-Diene and Aldehyde: Formal Total Synthesis of (–)-Elaeokanine C. *Tetrahedron* **1998**, *54*, 1153–1168.
- (37) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. Nickel(0)-Catalyzed Three-Component Connection Reaction of Dimethylzinc, 1,3-Dienes, and Carbonyl Compounds. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3386–3388.
- (38) Sato, Y.; Takanashi, T.; Mori, M. Study on Transmetalation of a Nickelacycle with Organometallic Reagents. *Organometallics* **1999**, *18*, 4891–4893.
- (39) Savchenko, A. V.; Montgomery, J. Organozinc/Nickel(0)-Promoted Cyclizations of Bis-Enones. *J. Org. Chem.* **1996**, *61*, 1562–1563.
- (40) Crimmins, M. T.; DeLoach, J. A. Intramolecular Photocycloadditions-Cyclobutane Fragmentation: Total Synthesis of ( $\pm$ )-Pentalenene, ( $\pm$ )-Pentalenic Acid, and ( $\pm$ )-Deoxypentalenic Acid. *J. Am. Chem. Soc.* **1986**, *108*, 800–806.

AR990095D