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Catalytic Cyclooligomerization of Enones with Three Methylene Equivalents

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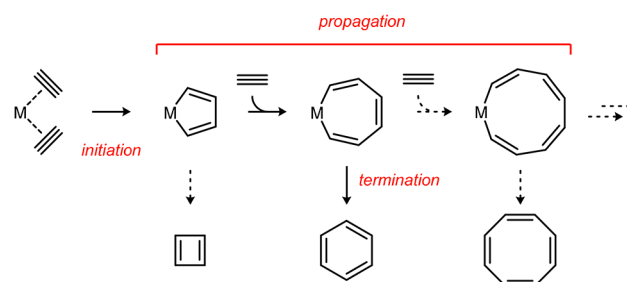Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907, United States

S *Supporting Information*

ABSTRACT: Cyclic structures are highly represented in organic molecules, motivating a wealth of catalytic methods targeting their synthesis. Among the various ring-forming processes, cyclooligomerization reactions possess several attractive features but require addressing a unique challenge associated with controlling ring-size selectivity. Here we describe the catalytic reductive cocyclooligomerization of an enone and three carbene equivalents to generate a cyclopentane, a process that constitutes a formal $[2 + 1 + 1 + 1]$-cycloaddition. The reaction is promoted by a (quinox)Ni catalyst and uses CH_2Cl_2/Zn as the C_1 component. Mechanistic studies are consistent with a metallacycle-based pathway, featuring sequential migratory insertions of multiple carbene equivalents to yield cycloalkanes larger than cyclopropanes.
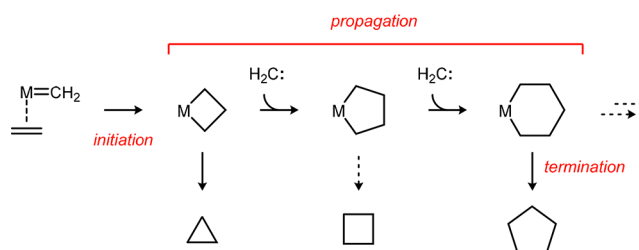
Cyclooligomerization reactions are a mechanistically interesting subclass of cycloadditions that currently have limited utility in organic synthesis.[1] The potential value of these reactions derives from their ability to directly assemble cyclic molecules from the repeated coupling of a simple building block. However, this same feature introduces a significant challenge associated with controlling ring-size selectivity. The most prominent class of cyclooligomerization reactions involves the use of alkynes as substrates.[2] Cyclotrimers are favored under most transition-metal-catalyzed conditions because of the high thermodynamic stability of benzenes relative to cyclobutadienes, cyclooctatetraenes, and higher-order annulenes. Cyclooligomerization reactions using other π-components, such as 1,3-dienes[1a,3] and allenes,[4] have also been studied but generally exhibit poor selectivity and narrow substrate scopes.

Catalytic alkyne cyclotrimerizations are commonly initiated by an oxidative coupling reaction at a low-valent metal center to form a metallacyclopentadiene (Figure 1a).[5] This intermediate then undergoes ring expansion through additional alkyne insertion events until the cyclic product is eliminated from the catalyst. In principle, a related mechanism may be accessible using a C_1 component as the monomer unit (Figure 1b). For example, a $[2 + 2]$-cycloaddition between a M=CR$_2$ species and an alkene would likewise generate a metallacycle, in this case a saturated metallacyclobutane. The reaction would then propagate by iterative insertions of carbene equivalents and terminate by C−C reductive elimination. Because the cycloalkane would be constructed one carbon at a time, any ring size is potentially accessible by this pathway. Here, we describe a
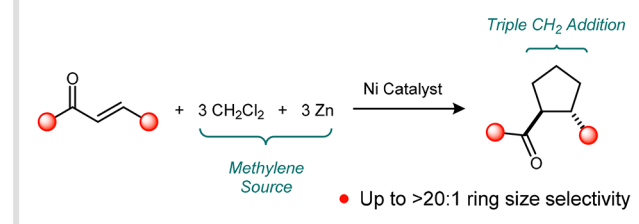

Figure 1. Cyclooligomerization strategies for the synthesis of cyclic molecules. (a) Transition-metal-catalyzed cyclotrimerization reactions of alkynes proceeding through metallacyclic intermediates. (b) A proposed cyclooligomerization reaction using a carbene as the propagating monomer. (c) A catalytic reductive $[2 + 1 + 1 + 1]$-cycloaddition of enones with CH_2Cl_2/Zn to generate cyclopentanes.

catalytic reductive cocyclooligomerization of an enone and three methylene equivalents to generate a cyclopentane (Figure 1c). The reaction constitutes a formal $[2 + 1 + 1 + 1]$-cycloaddition and uses CH_2Cl_2 as the C_1 partner in combination with Zn metal as a stoichiometric reductant.

Table 1. Effect of Catalyst Structure on Ring-Size Selectivity[a,b]

entry	metal source	ligand	conversion of **1**	yield C3 (**2**)	yield C5 (**3**)
1	Ni(acac)$_2$	**L1**	38%	36%	2%
2	Ni(acac)$_2$	**L2**	40%	26%	6%
3	Ni(acac)$_2$	**L3**	38%	27%	6%
4	Ni(acac)$_2$	**L4**	85%	16%	9%
5	Ni(acac)$_2$	**L5**	93%	26%	17%
6	Ni(acac)$_2$	**L6**	92%	32%	30%
7	Ni(acac)$_2$	**L7**	92%	18%	29%
8	Ni(acac)$_2$	**L8**	85%	25%	60%
9	Ni(acac)$_2$	**L9**	89%	21%	62%
10	Ni(acac)$_2$	**L10**	95%	12%	70%
11	Ni(dme)Br$_2$	**L10**	85%	21%	42%
12	Co(acac)$_2$	**L10**	0%	0%	0%
13	Fe(acac)$_2$	**L10**	46%	0%	0%
14	Ni(acac)$_2$	none	10%	0%	0%

[a]Conversions of **1**, yields of **2** (C3), and yields of **3** (C5) were determined from crude reaction mixtures by GC analysis against mesitylene as an internal standard. Reaction conditions: **1** (0.7 mmol, 1.0 equiv), Zn (6.0 equiv), metal source (0.15 equiv), ligand (0.15 equiv), 1.25:1 CH$_2$Cl$_2$/DMA (0.3 mL). [b]Selectivities for cyclopropane vs cyclopentane formation are expressed as excess values, defined as $[(C5 - C3)/(C5 + C3)] \times 100\%$.

We discovered the reductive cyclooligomerization unexpectedly while studying transition-metal-catalyzed variants of the Simmons–Smith reaction. The key intermediates of the classical Simmons–Smith reaction are Zn carbenoids (XZnCH$_2$Y species), which are electrophilic in character and known to react preferentially with electron-rich alkenes.[6] Kanai et al. observed that electron-deficient alkenes, such as enones, are also amenable to cyclopropanation under CH$_2$X$_2$/Zn conditions by the addition of NiX$_2$ salts in catalytic loadings.[7] The active carbenoid species could not be unambiguously identified but was hypothesized to be a nucleophilic Ni=CH$_2$ complex that undergoes cyclopropanation by a stepwise [2 + 2]-cycloaddition/C–C reductive elimination pathway. Studies by Grubbs, Miyashita,[8] and Hillhouse[9] probing the stoichiometric reactivity of Ni=CR$_2$ species and their associated nickel-acyclobutanes lend credence to this proposal.

Our initial interest was in examining ligand effects in the nickel-catalyzed Simmons–Smith reaction. Accordingly, catalysts generated from Ni(acac)$_2$ and nitrogen-based bidentate ligands (**L1**–**L10**) were tested in the cyclopropanation of model enone **1** (Table 1). The relatively inert CH$_2$Cl$_2$ reagent was selected as the methylene source because of the absence of any background cyclopropanation using Zn as a stoichiometric reductant. Across the range of ligand types examined, the yield of cyclopropane **2** was found to vary significantly but never exceed 36%. GC-MS analyses of the crude reaction mixtures indicated the formation of a single major byproduct with a mass corresponding to the enone (**1**) bearing three additional CH$_2$ equivalents. Subsequent isolation and spectroscopic characterization of this species revealed its structure to be a *trans*-disubstituted cyclopentane, derived from a formal reductive [2 + 1 + 1 + 1]-cycloaddition process. To the extent that other cyclooligomers, such as cyclobutanes or cyclohexanes, are formed, they fall below the limits of GC-MS detection; masses corresponding to these other cyclooligomers are found in trace quantities using other enones. The ratio of cyclopropane to cyclopentane is strongly dependent on the identity of the supporting ligand. For example, *t*-Bu-Biox **L1** forms cyclo-

(a)

(±)-**C5**   (±)-**C3**

(±)-(*t*-Bu-Quinox)Ni(acac)$_2$ **4**

3	R = H	71% Yield (5.8:1 C5/C3)
5	R = F	68% Yield (5.9:1 C5/C3)
6	R = CF$_3$	71% Yield (9.1:1 C5/C3)
7	R = CN	62% Yield (>20:1 C5/C3)
8	R = SMe	51% Yield (5.4:1 C5/C3)
9	R = OMe	41% Yield (3.8:1 C5/C3)
10	R = Cl	72% Yield (6.7:1 C5/C3)

11 54% Yield (5.6:1 C5/C3)

12 72% Yield (>20:1 C5/C3)

13 77% Yield (7.7:1 C5/C3)

14 57% Yield (5.7:1 C5/C3)

15 63% Yield (6.3:1 C5/C3)

16 50 % Yield (3.8:1 C5/C3)

17 62% Yield (7.1:1 C5/C3)

18 42% Yield (2.9:1 C5/C3)

19 78% Yield (>20:1 C5/C3)

20 69% Yield (4.3:1 C5/C3)

21 50% Yield (6.1:1 C5/C3)

22 37% Yield (1.4:1 C5/C3)

23 45% Yield (2.2:1 C5/C3)

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(b)

24 80% Yield (rr = 14:1)
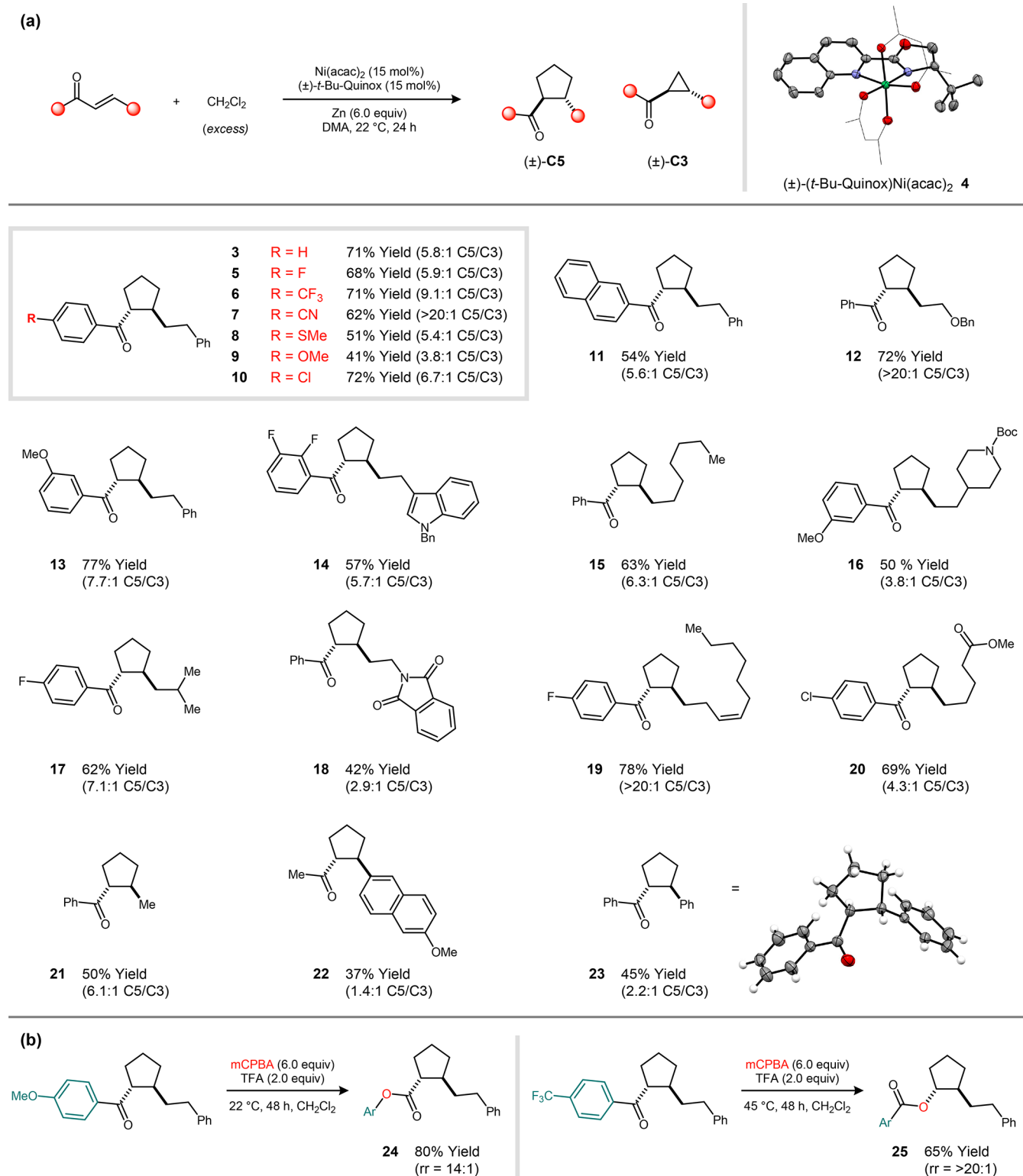
25 65% Yield (rr = >20:1)

Figure 2. Substrate scope studies. (a) Yields are of the isolated cyclopentane following purification. C5/C3 ratios were determined from the crude reaction mixtures by ^{1}H NMR integration. Reaction conditions: enone (1.0 equiv, 0.21 mmol); Zn (6.0 equiv); Ni(acac)$_2$ (0.15 equiv); (±)-**L10** (0.15 equiv); CH$_2$Cl$_2$ (0.5 mL); DMA (0.4 mL); 22 °C, 16 h. (b) Baeyer−Villiger oxidations of aryl cyclopentyl ketone products.

propane nearly exclusively (**2:3** = 18:1), whereas *t*-Bu-quinox **L10** is selective for cyclopentane formation (**2:3** = 1:5.8).

Summarized in Figure 2a is the substrate scope of the nickel-catalyzed reductive cyclooligomerization reaction under conditions that were optimized for cyclopentane formation. Yields are of the isolated cyclopentane following separation from the

cyclopropane byproduct. Common functional groups are tolerated, including nitriles, ethers, protected alcohols, protected amines, electron-rich heterocycles, and esters. Thioethers are susceptible to ylide formation in the Simmons−Smith reaction but are left untouched under the catalytic cyclooligomerization conditions (**8**).[10] Likewise, aryl chlorides, which participate in
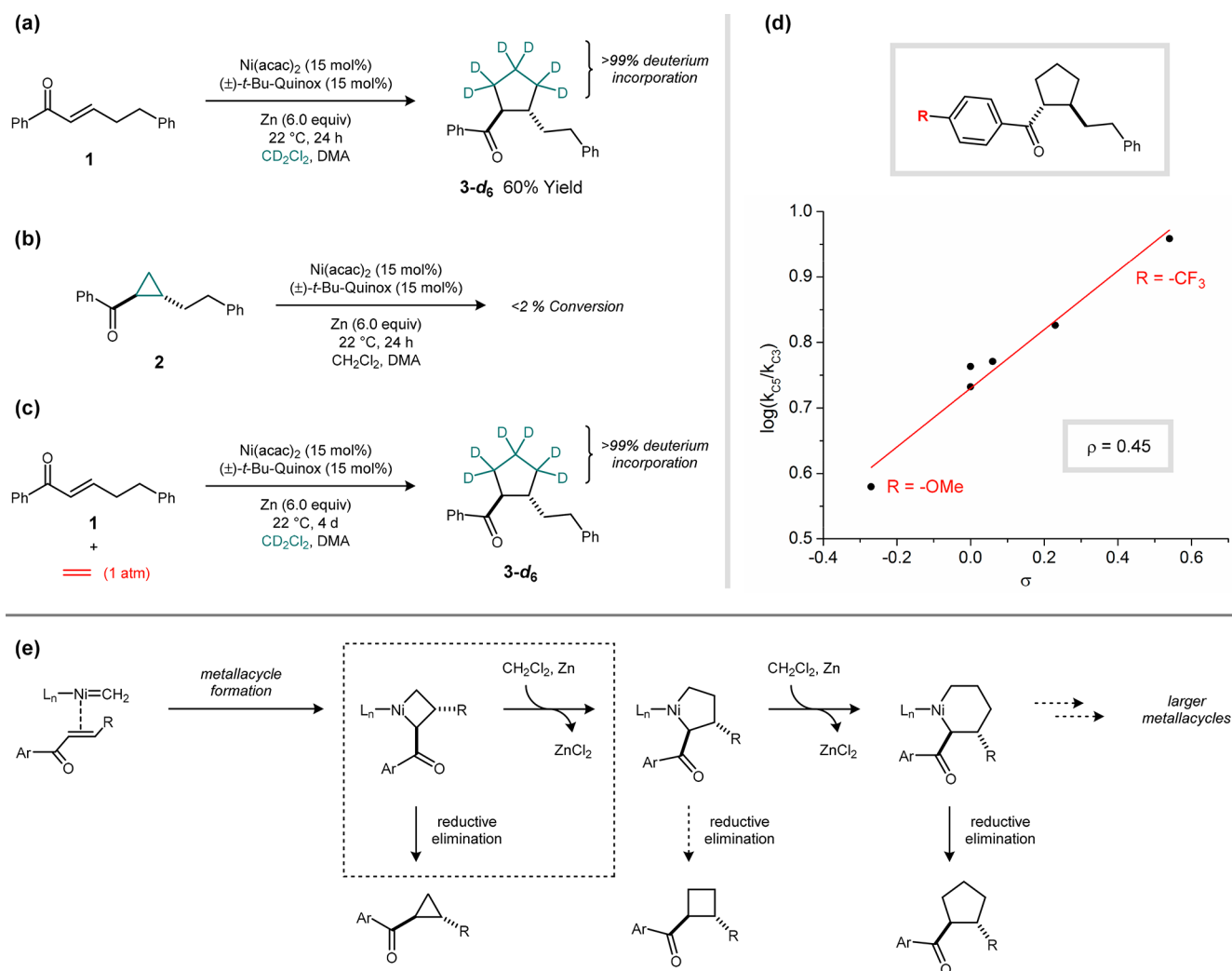
Figure 3. Mechanistic studies. (a) Experiment identifying the origin of the −(CH₂)₃− fragment in product **3**. (b) Excluding a mechanism involving cyclopropane ring-opening. (c) Excluding a mechanism involving a coupling of enone **1** and ethylene. (d) Hammett plot of the C5/C3 selectivity vs the substituent σ parameters. (e) A proposed cyclooligomerization mechanism involving metallacycle ring expansion. The branch point for cyclopentane vs cyclopropane formation is highlighted.

nickel-catalyzed reductive cross-coupling reactions,[11] are not competitively activated. A substrate possessing two alkenes, one conjugated with a ketone and the other substituted only with alkyl groups, reacts exclusively at the electron-deficient alkene (**19**). The highest selectivities for cyclopentane formation were observed using substrates containing an aryl ketone and an alkyl substituent at the β-position of the alkene. For example, methyl ketone **22** and chalcone **23**, which do not fulfill these criteria, were viable substrates for the reaction but afforded only modest selectivities for cyclopentanation (≤2.2:1). The product of this latter reaction (**23**) proved to be a crystalline solid, whose structure was assigned by X-ray diffraction analysis.

The aryl ketones present in the cyclopentanation products may be converted to other useful functional groups by the Baeyer−Villiger oxidation (Figure 2b).[12] For example, **9** bearing an electron-rich 4-methoxyphenyl group is oxidized to ester **24** with high regioselectivity (rr = 14:1). The alternative regioisomeric ester is also accessible by employing the electron-deficient 4-trifluoromethyl group (**25**), which possesses a low migratory aptitude (rr = >20:1). Upon ester hydrolysis, the former product would provide a cyclopentane carboxylic acid and the latter a cyclopentanol.

Given the unusual nature of this transformation, our first mechanistic experiment sought to confirm the origin of the −(CH₂)₃− fragment in product **3** (Figure 3a). When the catalytic cyclopentanation of **1** was conducted using CD₂Cl₂ in the place of CH₂Cl₂, the expected CD₂-incorporation was observed to form **3-d₆** (60% isolated yield). Second, a tandem cyclopropanation−ring-opening mechanism was ruled out by subjecting the separately synthesized cyclopropane **2** to the standard catalytic condition (Figure 3b). In this experiment, the cyclopropane was recovered in >98% yield, and no conversion to cyclopentane **3** was observed. Third, we examined a potential mechanism involving the oxidative coupling of enone **1** with ethylene, which could be generated from the reductive coupling of two CH₂Cl₂ equivalents (Figure 3c). Miyashita previously observed the formation of ethylene from the dimerization of a proposed transient Ni=CH₂ species.[8b] Furthermore, ethylene is known to undergo nickel-mediated oxidative coupling reactions with electron-deficient π-systems.[13] The catalytic cyclopentanation of enone **1** was carried out using labeled CD₂Cl₂ under an atmosphere of nondeuterated ethylene gas. The presence of ethylene was found to inhibit the rate of cyclopentanation, but product **3-d₆** was nonetheless obtained in fully deuterium-

labeled form. This result suggests that either ethylene is not an intermediate in the reaction or that it is generated but remains tightly bound to Ni and thus cannot exchange with free ethylene.

Finally, during our substrate scope studies, we noted a pronounced dependence of the selectivity for cyclopropane versus cyclopentane formation on the electronic properties of the aryl ketone (Figure 3d). For a series of 4-substituted aryl enones (**3**, **5−10**), there is a linear relation between the selectivity values (C5/C3) and the substituent σ parameters (ρ = 0.45).[14] Electron-withdrawing substituents result in the highest selectivities for cyclopentane formation. One possible interpretation of this trend is in the context of the metallacycle-based mechanism proposed by Kanai. In this pathway, the selectivity for cyclopropanation versus cyclooligomerization would be governed by the relative rates of reductive elimination (termination) and carbene insertion (propagation). Carbon−carbon reductive elimination reactions are known to be accelerated by the presence of an electron-donating group conjugated to one of the carbons undergoing bond formation; electron-donating groups generally destabilize M−C bonds to a greater extent than the product C−C bond.[15] On the other hand, the carbene insertion step would likely be insensitive to the electronic properties of the aryl group. Previous kinetics studies have shown that CO migratory insertion reactions occur preferentially at more electron-rich M−C bonds.[16] The analogous process in the reductive cyclooligomerization would therefore favor carbene insertion into the Ni−alkyl over the Ni−enolate bond such that the aryl group would exert only an indirect effect on the rate of this step.

In summary, zinc carbenoid additions to alkenes have been extensively studied since the seminal work of Emschwiller,[17] Simmons, and Smith.[18] However, in no cases have these reactions been observed to access pathways that lead to multiple CH$_2$ addition, presumably because of the concerted nature of the carbene-transfer mechanism. In this context, transition-metal-bound carbenes are attractive as alternative CH$_2$ transfer agents because of their potential to react through stepwise organometallic pathways. By intercepting transient metallacyclic intermediates prior to C−C reductive elimination, it is possible to develop new transformations that form ring systems other than cyclopropanes. This strategy is demonstrated here in the context of a nickel-catalyzed [2 + 1 + 1 + 1]-cycloaddition of enones using three methylene equivalents derived from CH$_2$Cl$_2$ and six reducing equivalents supplied by Zn metal. Together, these results point to opportunities for the development of other multicomponent cycloaddition reactions using reductively generated CH$_2$ as a C$_1$ partner.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b08296.

> Experimental procedures and characterization data (PDF)
> C$_{18}$H$_{18}$O X-ray crystallography data (CIF)
> C$_{59}$H$_{72}$N$_4$Ni$_2$O$_{10}$ X-ray crystallography data (CIF)

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