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Catalytic reductive [4 + 1]-cycloadditions of vinylidenes and dienes

You-Yun Zhou and Christopher Uyeda*

Cycloaddition reactions provide direct and convergent routes to cycloalkanes, making them valuable targets for the development of synthetic methods. Whereas six-membered rings are readily accessible from Diels-Alder reactions, cycloadditions that generate five-membered rings are comparatively limited in scope. Here, we report that dinickel complexes catalyze [4 + 1]-cycloaddition reactions of 1,3-dienes. The C_1 partner is a vinylidene equivalent generated from the reductive activation of a 1,1-dichloroalkene in the presence of stoichiometric zinc. Intermolecular and intramolecular variants of the reaction are described, and high levels of asymmetric induction are achieved in the intramolecular cycloadditions using a C_2-symmetric chiral ligand that stabilizes a metal-metal bond.

Natural products display a variety of carbocyclic structures that are readily assembled within the active sites of cyclase enzymes but are challenging to prepare de novo in the laboratory (*1*). It is also common for synthetic molecules to incorporate ring systems to impose geometric constraints or to arrange functional components at well-defined positions in three-dimensional space. For these reasons, methods that provide convenient access to common cycloalkanes are of substantial value to synthetic chemists. Whereas six-membered rings may be prepared using the Diels-Alder reaction, no cycloaddition of equivalent generality is available for the synthesis of five-membered rings. Current leading approaches include transition metal–catalyzed [2 + 2 + 1]-cycloadditions, such as the Pauson-Khand reaction (*2*), and [3 + 2]-cycloadditions using trimethylenemethane equivalents (*3*).

It is attractive to consider an alternative route to five-membered rings (*4*, *5*) that would rely on a [4 + 1]-cycloaddition between a 1,3-diene and a suitable C_1 partner (Fig. 1A). A major impediment to realizing such a reaction by a concerted mechanism is the competing [2 + 1]-cycloaddition, which is often favored and generates vinylcyclopropanes as products (Fig. 1B). Quantum mechanical models for the reaction between singlet methylene and 1,3-butadiene attribute this selectivity to excessive closed-shell repulsion between the carbene lone pair and the filled Ψ_1 orbital of the diene in the symmetry-allowed transition state geometry (*6*–*8*). Consequently, direct [4 + 1]-cycloadditions are exceedingly rare beyond specialized classes of substrates (*9*–*11*). A viable alternative is to carry out a sequential [2 + 1]-cycloaddition followed by a vinylcyclopropane 1,3-rearrangement; however, preparatively useful variants of this process require an activating substituent, an additional strain element, or a catalyst to accelerate the rearrangement step (*12*–*17*)—the rearrangement of the parent vinylcyclopropane molecule occurs at >300°C and has an activation energy of ~50 kcal/mol (*18*, *19*). In light of these challenges, transition metal–catalyzed [4 + 1]-cycloadditions have also been explored, culminating in the discovery of methods that allow for the addition of CO to various cumulene-containing dienes (*20*–*23*).

We recently reported a dinickel catalyst that promotes the [2 + 1]-cycloaddition of vinylidenes and alkenes to form methylenecyclopropane products (*24*). 1,1-Dichloroalkenes, which are conveniently prepared from the corresponding aldehyde or ketone in a single step, serve as vinylidene precursors (*25*), and Zn is used as a stoichiometric reductant. Experiments using stereochemically labeled alkenes were suggestive of a stepwise mechanism for cyclopropane formation. The intermediacy of a metallacycle generated from the addition of a Ni_2(C=CHR) species to the alkene could account for this observation. Subsequent C–C reductive elimination would then close the three-membered ring. We reasoned that such a process might be adapted to 1,3-dienes as a means of circumventing the electronic constraints of the pericyclic [4 + 1]-cycloaddition pathway. In this scenario, the partitioning between vinylcyclopropane and cyclopentene products would be dictated by the relative facility of the two possible C–C reductive eliminations. Here, we report that dinickel catalysts induce highly selective [4 + 1]-cycloadditions of vinylidenes and simple 1,3-dienes, providing a direct synthetic entry into polysubstituted cyclopentenes.

The Ni_2 catalyst ***3*** was previously shown to promote the reductive methylenecyclopropanation reaction and thus served as a starting point for our investigations of a model [4 + 1]-cycloaddition (Fig. 1C). In an initial survey of reaction parameters, the use of a polar solvent such as *N*-methyl-2-pyrrolidone was found to promote high conversions of the 1,1-dichloroalkene. The catalyst generated from Ni(dme)Br_2 (10 mol %) (dme, 1,2-dimethoxyethane) and **L3** (5 mol %) afforded cyclopentene product **2** in up to 52% yield. The steric profile of the catalyst proved to be a critical determinant of reaction efficiency. When the isopropyl (*i*-Pr) substituents of the flanking *N*-aryl groups were replaced with methyl (Me) or ethyl (Et) (**L1** or **L2**, respectively), the yield of **2** decreased to 22% or less. Conversely, the more-hindered cyclopentyl-substituted ligand (**L4**) provided a near-quantitative yield of **2**. There was no competing [2 + 1]-cycloaddition to generate a vinylcyclopropane, nor did the catalyst isomerize the skipped diene of product **2** into conjugation. The importance of the dinuclear catalyst structure was examined by comparing the efficiency of catalysts generated using related mononucleating ligands (**L5** to **L9**). In no case did we observe substantial yields of cyclopentene **2** using a mononickel catalyst.

The substrate scope of the reductive [4 + 1]-cycloaddition reaction is summarized in Fig. 2. A variety of common functional groups are tolerated, including thioethers, trifluoromethyl groups, nitriles, esters, ethers, protected amines, epoxides, acetals, and boronate esters. Products containing exocyclic vinyl ethers (**20**) are accessible, albeit in moderate yield owing to competing reductive decomposition of the alkoxy-substituted 1,1-dichloroalkene. Aryl bromides (**7**), which are often employed in Ni-catalyzed cross-coupling reactions, are left untouched in the cycloaddition because of the comparatively rapid oxidative addition of the 1,1-dichloroalkene by the catalyst. Butadiene is a viable substrate (**22** to **24**), and the relatively unhindered alkene in the product is not susceptible to a secondary methylenecyclopropanation. 1,1-Dichloroethylene provides a source of the parent vinylidene fragment (**25** and **26**), yielding cyclopentene products with no substituents on the exocyclic methylene. Products containing tetrasubstituted alkenes are generated using ketone-derived 1,1-dichloroalkenes (**27** and **28**). Representative 1-substituted (**32**), 2-substituted (**33**), 1,2-disubstituted (**34**), and 1,3-disusbstituted (**35**) dienes were found to react efficiently with a model 1,1-dichloroalkene. In the case of 1,3-disubstituted dienes (**35** to **40**) the cycloadditions proceeded with high *E* selectivity (9:1 to >20:1 ratio of stereoisomers).

To explore the synthetic utility of this method, the 4-methylene-1-cyclopentene products were converted into other classes of cyclopentane derivatives commonly featured in organic and organometallic compounds (Fig. 3A). The direct products of the [4 + 1]-cycloaddition possess the same degree of unsaturation as a cyclopentadiene motif. Accordingly, deprotonation of **41** with *n*-BuLi afforded a cyclopentadienyl anion equivalent that was quenched with $FeBr_2$ (0.6 equiv) to yield a hexasubstituted ferrocene (**42**). Additionally, the two trisubstituted alkenes in **41** could be readily differentiated in a reaction

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with BH_3•SMe_2, which adds to the ring alkene but leaves the exocyclic alkene intact. Next, the 2-siloxy substituted diene **44** was subjected to the standard catalytic cycloaddition conditions to afford a silyl enol ether product. Subsequent silyl deprotection and alkene isomerization yielded cyclopentenone **45**. Finally, the disubstituted diene **46**, containing a free alcohol, proved to be a viable substrate for the cycloaddition. A directed hydrogenation of both double bonds in the resulting cycloadduct afforded saturated trisubstituted cyclopentane **47**.

Intramolecular [4 + 1]-cycloadditions were carried out using substrates in which the two reacting partners were connected by a two- or three-atom tether (Fig. 3C). For example, substrate **56** reacts under standard catalytic conditions to provide 5,6-bicyclic amine **57**, which is a substructure found in several terpene alkaloid natural products (*26*). Heteroarenes may be incorporated into the tether without loss of reaction efficiency (**50** and **52**). The intramolecular cycloaddition is also amenable to the formation of 5,5-bicyclic systems (**55**).

We next turned our attention to demonstrating a catalytic asymmetric variant of the [4 + 1]-cycloaddition reaction. The imine substituents of the naphthyridine-diimine (NDI) ligand presented the most straightforward opportunity for the incorporation of chirality, and a series of chiral catalysts were prepared by condensing commercially available α-secondary amines with 2,7-diacetyl-1,8-naphthyridine. The ligand derived from (*S*)-1-cyclohexylethylamine [(***S,S***)-**L10**] afforded enantiomeric excesses of up to 90% for the intramolecular [4 + 1]-cycloaddition reaction (Fig. 3B). Additionally, substrate **54**, which was prepared in enantiomerically enriched form from a carbohydrate precursor, reacted with high diastereoselectivity (18:1 diastereomeric ratio) using (***S,S***)-**L10**.

To examine the chiral environment presented by the (***S,S***)-**L10** ligand, its corresponding [NDI]Ni_2Br_2 complex [(***S,S***)-**58**] was prepared by a comproportionation route using $Ni(COD)_2$ (1.0 equiv) and $Ni(dme)Br_2$ (1.0 equiv). The pre-synthesized dinickel complex (***S,S***)-**58** exhibits the same enantioselectivity as the catalyst generated in situ using $Ni(dme)Br_2$ and (***S,S***)-**L10** for the cycloaddition of **48**. In the solid state, catalyst (***S,S***)-**58** adopts a C_2-symmetric geometry (Fig. 3B). The stereogenic *N*-(1-cyclohexylethyl) substituents are in a 1,3-allylic strain-minimized orientation, which places the C–H bond in an eclipsing geometry relative to the C=N bond of the imine. This conformation projects the larger cyclohexyl groups and smaller methyl groups in opposing quadrants of the substrate-binding pocket, suggesting a steric rationale for the high degree of asymmetric induction imparted by this catalyst design.

Our initial mechanistic studies were aimed at distinguishing between a direct [4 + 1]-cycloaddition pathway and a tandem [2 + 1]-cycloaddition followed by a vinylcyclopropane 1,3-rearrangement (Fig. 4A). To address this question, we synthesized vinylcyclopropanes **60** and **61** (mixture of stereoisomers), which would correspond to the putative intermediates of this stepwise process. Under standard catalytic conditions, the [4 + 1]-cycloaddition between 1,1-dichloroalkene **1** and diene **59** proceeded efficiently to form **41** in 76% yield. Neither vinylcyclopropane regioisomer was observed to form at partial conversions. When separately prepared **60** or **61** was subjected to the same reaction conditions, there was no detectable rearrangement after 24 hours of reaction time at room temperature.

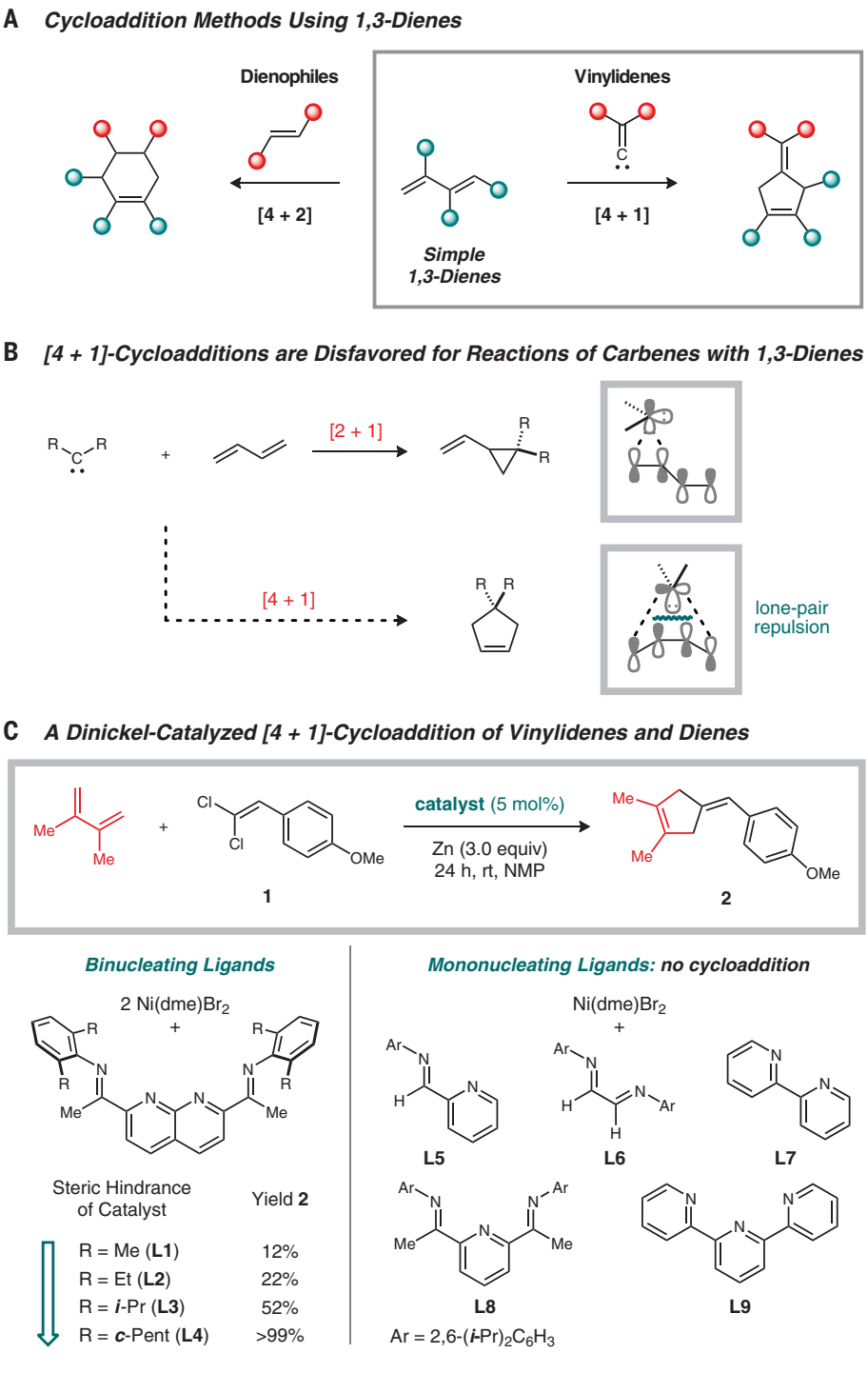

Fig. 1. Reaction development. (**A**) Complementary cycloaddition routes to five- and six-membered rings from 1,3-dienes. (**B**) Pericyclic [4 + 1]-cycloadditions suffer from large electronic barriers due to repulsion between the carbene lone pair and the Ψ_1 orbital of the 1,3-diene. (**C**) Dinickel-catalyzed reductive [4 + 1]-cycloaddition of 1,1-dichloroalkenes and 1,3-dienes. NMP, *N*-methyl-2-pyrrolidone; rt, room temperature; *c*-Pent, cyclopentyl.

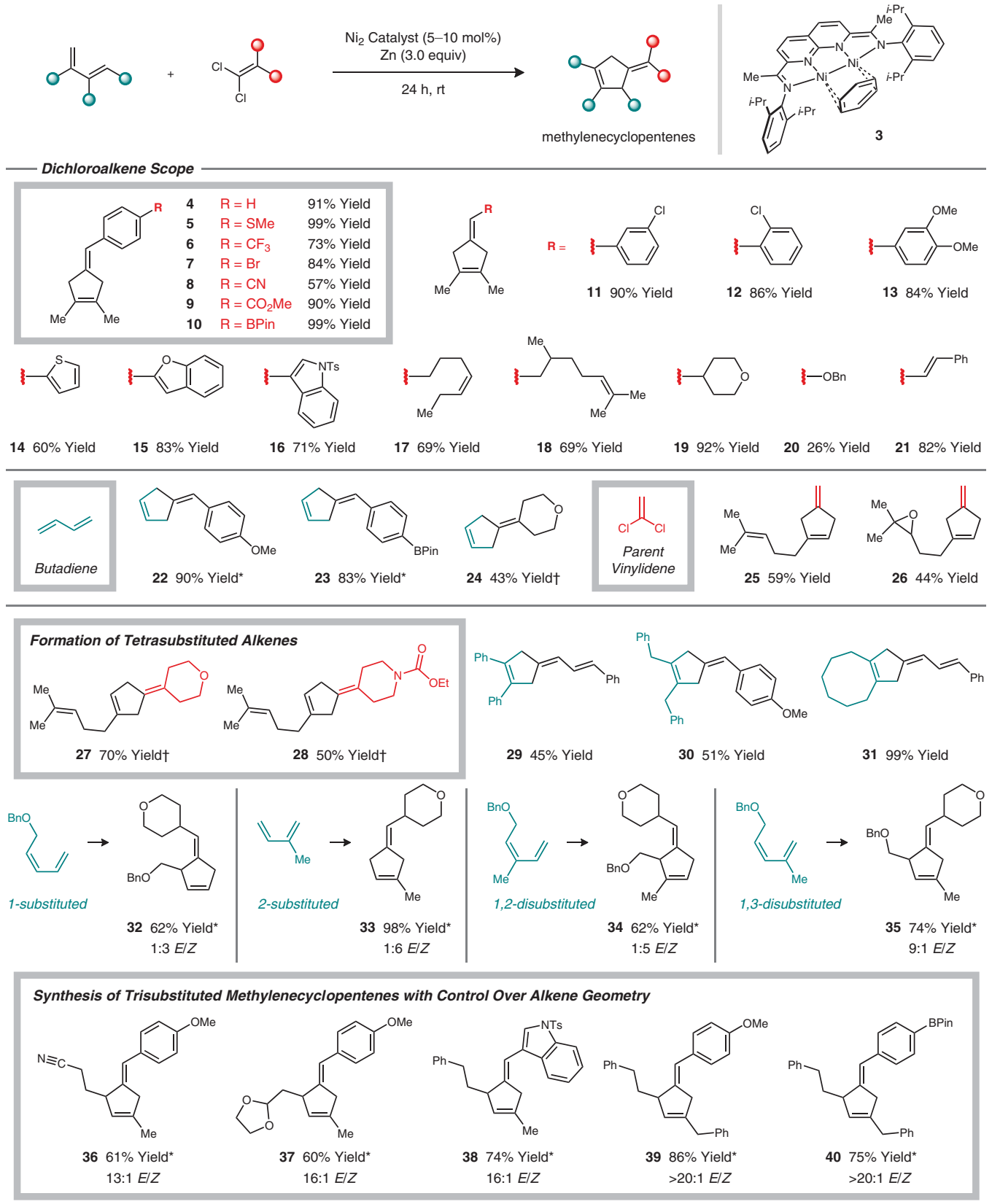

Fig. 2. Reaction scope. Reactions were conducted on a 0.2 mmol scale, and isolated yields were determined after purification. Standard reaction conditions: 1,1-dichloroalkene (1.0 equiv), 1,3-diene (2.0 to 3.0 equiv), Zn (3.0 equiv), Ni(dme)Br_2 (10 to 20 mol %), **L4** (5 to 10 mol %). See supplementary materials for experimental details. *Using catalyst **3**. †Using Ni(dme)Br_2/**L10**. Ph, phenyl; Pin, pinacolato.

We next sought to determine whether Zn was playing a necessary role in the formation of the [4 + 1]-cycloadducts or simply serving as a terminal reductant. A single-turnover experiment was carried out using the isolable [NDI]Ni_2Cl complex (**62**), which is the most reduced form of the catalyst that is accessible at Zn potentials (Fig. 4B). When [NDI]Ni_2Cl complex **62** (3.0 equiv) was added to a solution containing 1,1-dichloroalkene **1** (1.0 equiv) and excess 2,3-dimethylbutadiene, it was rapidly oxidized to the green paramagnetic [NDI]Ni_2Cl_2 complex **63**, and the cycloaddition product **2** was obtained in 49% yield. Decreasing the amount of [NDI]Ni_2Cl (**62**) to 2.0 equiv leads to a precipitous decrease

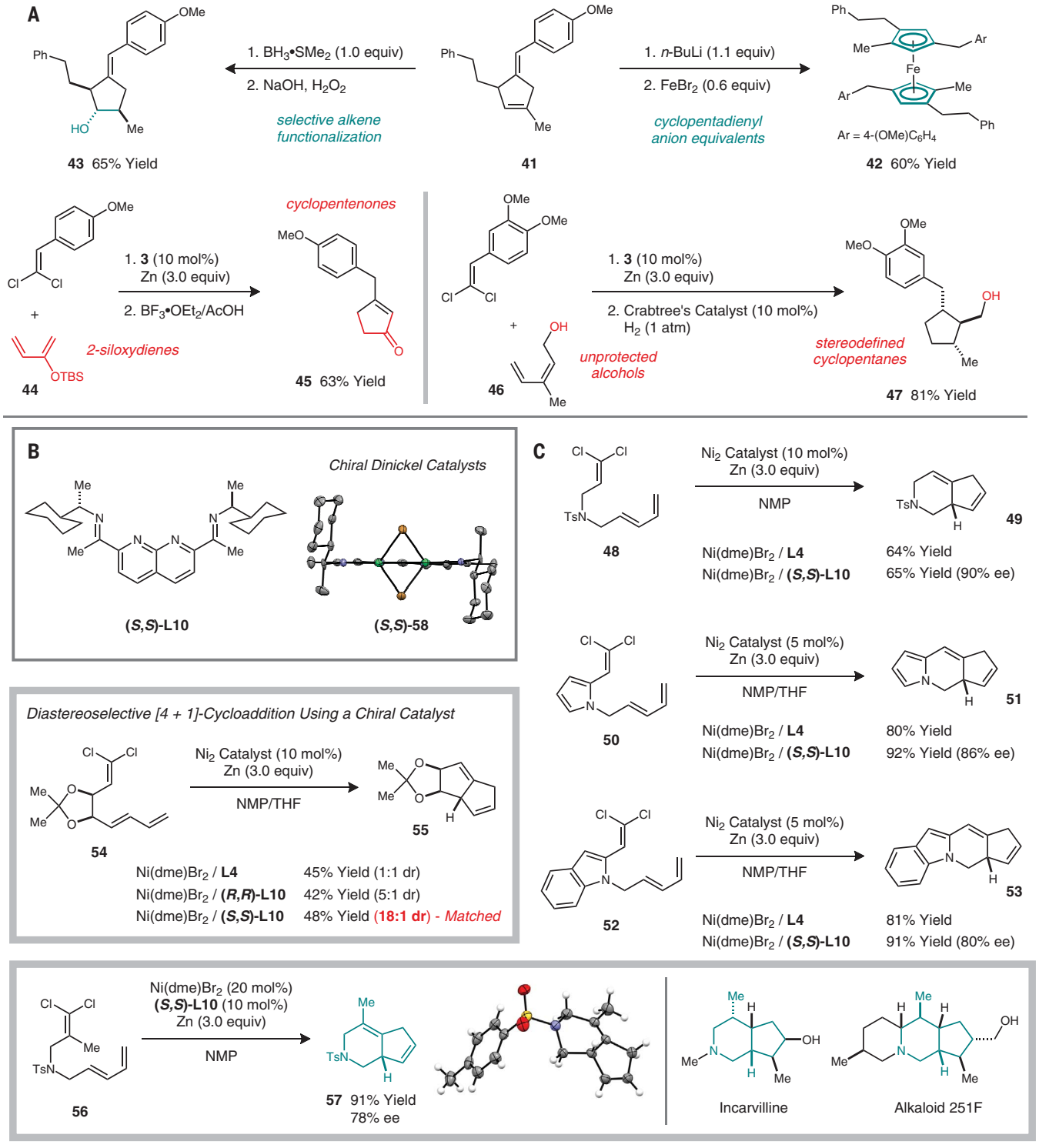

Fig. 3. Synthetic applications of the catalytic [4 + 1]-cycloaddition reaction. (**A**) [4 + 1]-Cycloaddition approaches to the synthesis of cyclopentenones, stereodefined cyclopentanes, and cyclopentadienyl metal complexes. (**B**) Chiral dinickel catalyst using a C_2-symmetric ligand. (**C**) Intramolecular and asymmetric [4 + 1]-cycloaddition reactions (reaction times: 12 to 24 hours; reaction temperatures: rt to 50°C). Bu, butyl; Ac, acetyl; TBS, *tert*-butyldimethylsilyl; ee, enantiomeric excess.

in the yield of **2** (down to 7%). This reaction stoichiometry suggests that the high-yielding pathway for the [4 + 1]-cycloaddition is accessible only when two additional equivalents of the [NDI]Ni_2Cl complex are present to serve as Cl abstractors.

A proposed catalytic mechanism based on these observations is shown in Fig. 4C. Initial oxidative addition of the 1,1-dichloroalkene by the [NDI]Ni_2Cl complex would generate a high-valent species that can undergo one-electron reduction by Zn to generate the chloroalkenyl complex **64**. A second reduction event, followed by C–Cl oxidative addition, then forms a reactive Ni_2(vinylidene)(Cl) species (**65**). The pathway for cycloaddition from this intermediate was

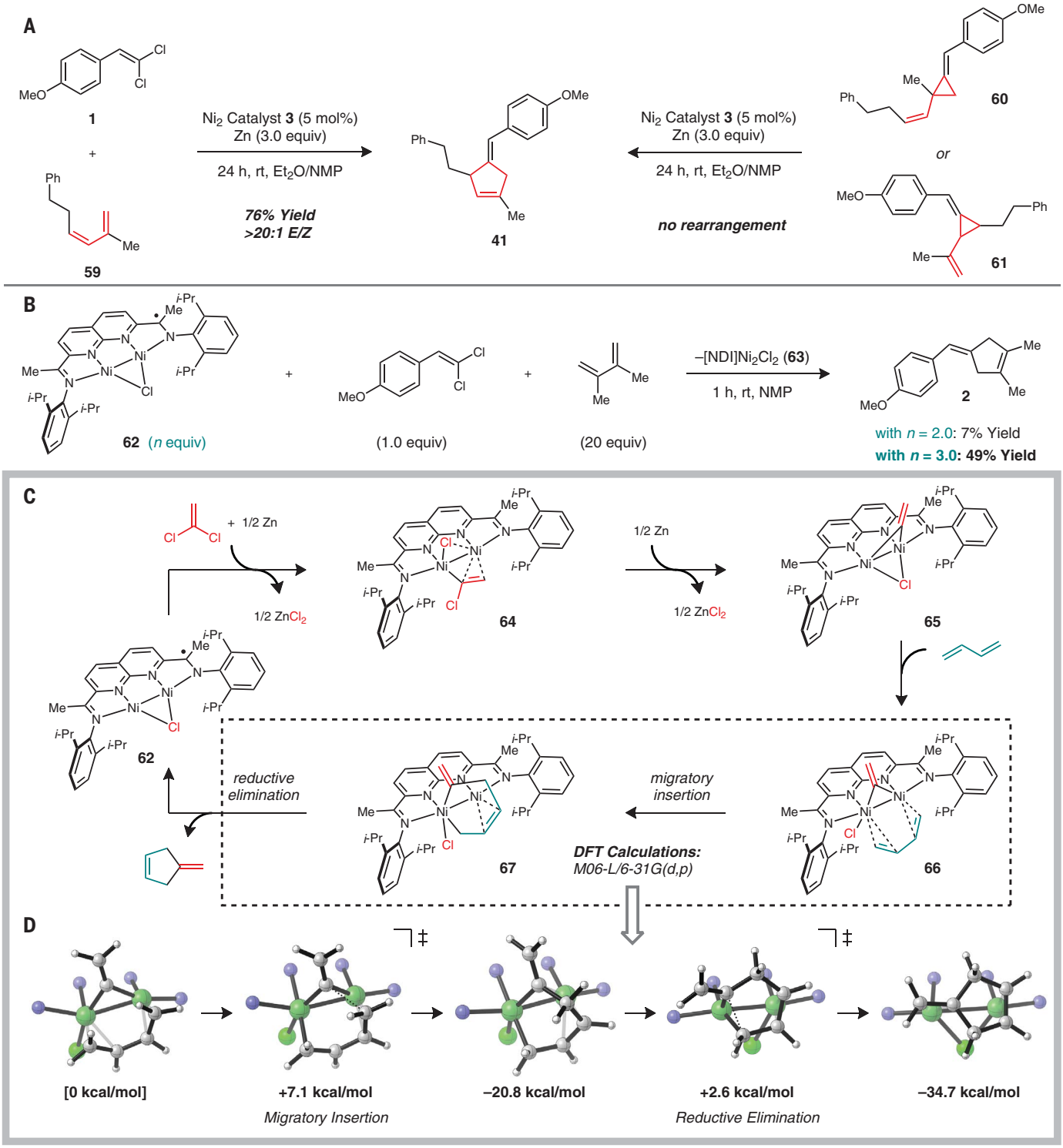

Fig. 4. Mechanistic investigations. (**A**) Distinguishing between direct [4 + 1]-cycloaddition and tandem [2 + 1]-cycloaddition/1,3-rearrangement mechanisms. (**B**) Stoichiometric [4 + 1]-cycloaddition using an isolable low-valent [NDI]Ni_2Cl complex. (**C**) Proposed catalytic mechanism. (**D**) DFT models for the stepwise migratory insertion–reductive elimination pathway. Energies are relative to that of **66**, and all structures are fully optimized at the M06-L/6-31G(d,p) level of DFT ($S = {}^1/_2$ spin state). ‡Transition state.

evaluated using computational methods (Fig. 4D). According to density functional theory (DFT) models, the diene first coordinates symmetrically across the Ni–Ni bond in an η^4 fashion (**66**). This geometry permits the two Ni centers to stabilize the incipient allyl fragment as the diene undergoes migratory insertion (activation barrier = 7.1 kcal/mol). The resulting metallacycle **67** is structurally related to a Ni_2 azametallacycle that we previously characterized from a vinylaziridine ring-opening reaction (*27*). The final C–C reductive elimination is calculated to have a barrier of 23.4 kcal/mol and generates the product complex, which is thermodynamically favored over intermediate **67** by 13.9 kcal/mol. A salient feature of the Ni_2 active site is the ability of the two metals to cooperatively stabilize the π systems in the reacting vinylidene and diene fragments as they undergo C–C bond formation. Collectively, these studies demonstrate that dinickel catalysts can take advantage of these interactions to provide an efficient pathway for cycloadditions that are challenging to achieve under thermal conditions.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S13
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Catalytic reductive [4 + 1]-cycloadditions of vinylidenes and dienes

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Five-membered rings for two nickels

The Diels-Alder reaction is widely used to make six-membered rings by adding four-carbon dienes to two-carbon alkenes. It would seem straightforward to likewise access five-membered rings from dienes and one-carbon sources, or carbenes, but that does not tend to work. Instead, the carbene adds to just half of the diene to form a cyclopropane. Zhou and Uyeda now show that a catalyst with two nickel centers can steer this reaction toward the cyclopentyl products (see the Perspective by Johnson and Weix). A chiral version of the catalyst rendered the reaction enantioselective in intramolecular cases.

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