



Reductive Cyclopropanations Catalyzed by Dinuclear Nickel Complexes

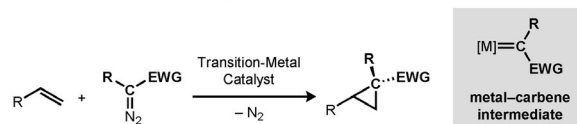
You-Yun Zhou and Christopher Uyeda*

Abstract: Dinuclear Ni complexes supported by naphthyridine-diimine (NDI) ligands catalyze the reductive cyclopropanation of alkenes with CH_2Cl_2 as the methylene source. The use of mild terminal reductants (Zn or Et_2Zn) confers significant functional-group tolerance, and the catalyst accommodates structurally and electronically diverse alkenes. Mononickel catalysts bearing related N chelates afford comparatively low cyclopropane yields ($\leq 20\%$). These results constitute an entry into catalytic carbene transformations from oxidized methylene precursors.

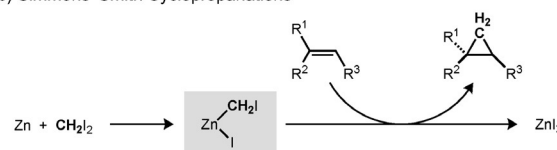
Transition-metal-mediated carbene transfer processes have emerged as the preeminent catalytic approach for selective cyclopropane synthesis.^[1] The most established subclass of these reactions revolves around the controlled decomposition of diazoalkanes, which undergo facile N_2 extrusion to generate transient $\text{M}=\text{CR}_2$ species (Figure 1a). Since the seminal studies on using homogeneous Cu complexes,^[2] this manifold has provided a rich arena for catalyst discovery, and much of the d block has now been surveyed in pursuit of efficient cyclopropanation catalysts.^[1] Despite the collective synthetic utility of these reactions, a persistent limitation is the scope of carbene precursors. Diazoalkane reagents are inherently unstable in the absence of electron-withdrawing substituents. Consequently, diazoacetates, and their derivatives, are the most common class of substrates in reported methods. Given the abundance of natural products, pharmaceutical compounds, and fine chemicals containing cyclopropanes with one or more unsubstituted carbon atoms, a general catalytic approach for the transfer of the parent CH_2 group would be of significant value.^[3]

In principle, the use of diazomethane in carbene transfer reactions^[4] could be circumvented by accessing reactive methylene equivalents reductively from dihalomethanes. Indeed, the Simmons–Smith cyclopropanation, which was first reported in 1958, operates in this way and continues to represent the most viable method for CH_2 transfer (Figure 1b).^[5] The active intermediate is formulated as an $(\text{ICH}_2)\text{ZnI}$ species, which is generated in situ from the reduction of CH_2I_2 with Zn. In contrast to their redox-neutral counterparts, reductive cyclopropanations have been remarkably resistant to catalysis. Previous efforts have focused on the use of Lewis acids^[6] or organic additives^[7] to intercept the

(a) Catalytic Redox-Neutral Cyclopropanations



(b) Simmons–Smith Cyclopropanations



(c) Catalytic Reductive Cyclopropanations

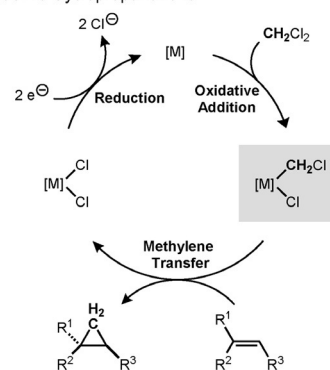


Figure 1. Noncatalytic and transition-metal-catalyzed alkene cyclopropanation reactions.

intermediate $(\text{XCH}_2)\text{Zn}$ species and accelerate the methylene transfer step. This approach has been successfully applied to allylic alcohols, culminating in enantioselective variants; however, few methods have extended this mode of activation more generally to substrates without directing groups.^[8]

We envisioned an alternative catalytic strategy for reductive carbene transformations centered on the use of transition metals to facilitate carbon–halogen bond activation (Figure 1c). In our proposed scheme, a low-valent metal complex engages the dihalomethane reagent in an oxidative addition, forming a $(\text{XCH}_2)\text{MX}$ species. Methylene transfer to an organic substrate yields an oxidized MX_2 complex, which then undergoes two-electron reduction to close the catalytic cycle. Whereas carbon(sp^3)–halogen bond activations are well-precedented in Ni-catalyzed cross-coupling^[9] and reductive cross-coupling reactions,^[10] little is known about the ability of $(\text{XCH}_2)\text{M}$ intermediates to undergo efficient methylene transfer. Herein, we report an entry into transition-metal-catalyzed reductive carbene transfer processes in the context of a cyclopropanation mediated by the dinuclear Ni complexes **1–3** (Figure 2).^[11] The procedure allows CH_2Cl_2 ,^[12]

[*] Dr. Y.-Y. Zhou, Prof. C. Uyeda
Department of Chemistry, Purdue University
560 Oval Dr., West Lafayette, IN 47907 (USA)
E-mail: cuyeda@purdue.edu

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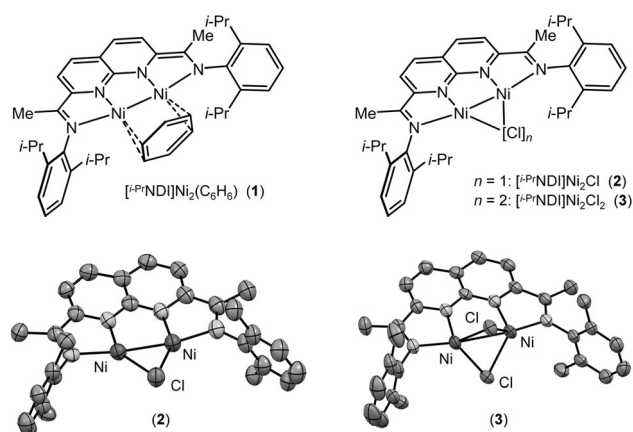


Figure 2. Dinuclear Ni catalysts for reductive cyclopropanations.

a previously inert substrate in the Simmons–Smith reaction, to function as a methylene source when used in combination with Zn or Et₂Zn as terminal reductants. Structurally and electronically diverse classes of alkenes are cyclopropanated in high yield under these conditions.

In the initial stages of reaction development, key steps of the proposed catalytic cyclopropanation were validated by examining the ability of the low-valent [i-PrNDI]Ni₂(C₆H₆) complex **1** to stoichiometrically activate CH₂Cl₂ and promote methylene transfer (Figure 3a). Complex **1** is rapidly oxidized by CH₂Cl₂, generating the dichloride complex **3** in 10 min at

room temperature. In the presence of 4-methoxystyrene (20 equiv), the CH₂ equivalent is trapped in 54 % efficiency as the cyclopropanated product. The intermediate species responsible for methylene transfer is fleeting under these conditions. When complex **1** is premixed with CH₂Cl₂ for 20 min prior to the addition of the alkene, only traces of the cyclopropane are obtained. The one-electron-oxidized monochloride complex **2** is also competent at effecting the reductive cyclopropanation and provides a slightly diminished yield of 33 %. With (*E*)- or (*Z*)-β-methyl-(4-methoxy)-styrene, the cyclopropanation is stereospecific, affording the *trans*- or *cis*-configured products, respectively (Figure 3b). This stereochemical outcome excludes mechanisms that involve stepwise ring formation through long-lived radical intermediates.

The remaining criterion for catalytic turnover was the identification of a suitable reductant to regenerate either **1** or **2** from dichloride complex **3** (Figure 3c). Cyclic voltammetry experiments indicated a chemically reversible one-electron reduction for **3** at −1.15 V vs. Cp₂Fe/Cp₂Fe⁺. The large peak-to-peak separation (530 mV at a scan rate of 100 mV s^{−1}) is consistent with halide dissociation upon reduction. Based on this electrochemical behavior, we hypothesized that a variety of mild chemical reductants, particularly those that efficiently sequester chloride, might be capable of converting **3** into **2**. Accordingly, treatment of **3** with excess Zn powder cleanly effects the one-electron reduction to monochloride complex **2**. Et₂Zn (1.0 equiv) also reduces **3** to **2** with concomitant evolution of ethane and ethylene. With ≥ 2.0 equiv of Et₂Zn, the monochloride complex **2** is further reduced to **1**.

Collectively, these preliminary studies revealed a viable strategy for achieving catalytic cyclopropanations. At 5 mol % loading, complex **1** catalyzes the cyclopropanation of 4-methoxystyrene in CH₂Cl₂ using Zn as a terminal reductant (Table 1, entry 1). No background conversion was observed without the catalyst under otherwise identical conditions (entry 2). Several noteworthy observations were made during our optimization studies. First, the inclusion of *N,N*-dimethylacetamide (DMA) in the solvent mixture is critical to obtaining high product yields as it presumably serves to activate the heterogeneous Zn surface. Second, mononickel catalysts bearing structurally related N chelates (complexes **4–8**) uniformly afforded low yields, despite significant consumption of the alkene starting material (entries 4–8).^[13] For these catalysts, the appearance of broad resonances in the ¹H NMR spectrum is consistent with polymerization being a dominant side reaction. Third, the halide complexes **2** and **3** were equally efficient catalysts compared to **1**, indicating facile entry into the cyclopropanation manifold from a variety of oxidation states (entries 9 and 10).

Under the optimized catalytic conditions, the scope of styrene derivatives was examined (Table 2). Common electron-withdrawing and electron-donating substituents are tolerated. It is significant that 2-chlorostyrene is cyclopropanated in high yield, demonstrating that CH₂Cl₂ activation outcompetes reduction or reductive coupling of the aryl chloride. Furthermore, a boronate ester and a trialkoxysilane, functional groups commonly used in cross-coupling reactions, are compatible with the cyclopropanation conditions.

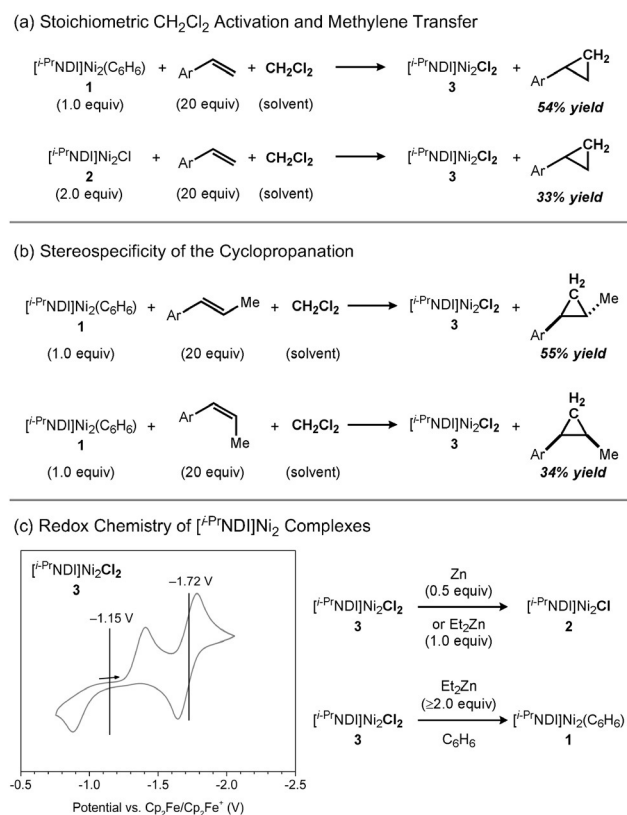


Figure 3. Stoichiometric reactivity of [NDI]Ni₂ complexes relevant to catalytic cyclopropanation. Ar = 4-MeOC₆H₄.

Table 1: Catalyst comparison.^[a]

Ar = 2,6-diisopropylphenyl

Entry	Catalyst	Conversion [%]	Yield [%]
1	[<i>i</i> -Pr ² NDI]Ni ₂ (C ₆ H ₆) (1)	> 99	69
2	—	0	0
3	Ni(COD) ₂	35	2
4	[<i>i</i> -Pr ² PD]NiCl ₂ (4)	> 99	19
5	[<i>i</i> -Pr ² PD]NiCl (5)	> 99	20
6	[<i>i</i> -Pr ² IP]Ni(COD) (6)	52	19
7	[BPY]Ni(COD) (7)	82	8
8	[<i>i</i> -Pr ² DAD]Ni(COD) (8)	38	2
9	[<i>i</i> -Pr ² NDI]Ni ₂ Cl (2)	> 99	76
10	[<i>i</i> -Pr ² NDI]Ni ₂ Cl ₂ (3)	> 99	64

[a] Reactions were run on a 0.5 mmol scale in CH₂Cl₂ (0.4 mL) and DMA (50 μ L). Conversions of the starting material and yields of the cyclopropane product were determined by ¹H NMR integration against an internal standard.

Table 2: Scope of styrene derivatives in the catalytic cyclopropanation.^[a]

Ar	Yield [%]	Ar	Yield [%]
	74 ^[b]		60
	74		66
	80		70
	84		69
	73		83
	70		65

[a] Reactions were conducted on a 0.5 mmol scale in CH₂Cl₂ (0.4 mL) and DMA (50 μ L). Yields of isolated products after purification are given. [b] Yield determined by ¹H NMR integration against an internal standard.

The catalytic cyclopropanation using **1** can be extended to other classes of alkenes (Table 3). Internal alkenes react stereospecifically, affording access to both *cis*- and *trans*-

Table 3: Scope of alkenes in the catalytic cyclopropanation.^[a]

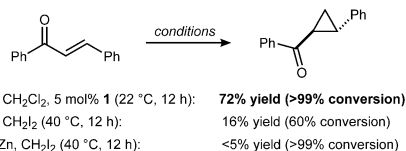
Entry	Product	Reductant	Yield	Entry	Product	Reductant	Yield
Acyclic Alkenes				Carbocyclic and Heterocyclic Alkenes			
1		Et ₂ Zn	81%	12 ^[b]		Et ₂ Zn	93%
2		Et ₂ Zn	83%	13 ^[b]		Et ₂ Zn	99%
3		Et ₂ Zn	81%	14 ^[b]		Zn	77%
4		Et ₂ Zn	72%	15 ^[b]		Zn	93%
5		Et ₂ Zn	76%	16		Zn	55%
6		Et ₂ Zn	89%	α,β-Unsaturated Carbonyl Compounds			
7		Zn	64%	17		Zn	82%
8		Zn	83%	18		Zn	72%
9		Zn	88%	19		Zn	80%
10		Zn	62%	Synthesis of Deuterated Cyclopropanes^[c]			
11		Et ₂ Zn	83%	20		Zn	66%
				21		Et ₂ Zn	77%

[a] Reactions were conducted on a 0.5 mmol scale. Full procedures are reported in the Supporting Information. Yields of isolated products after purification are given. [b] Yields determined by ¹H NMR integration against an internal standard. [c] CD₂Cl₂ instead of CH₂Cl₂.

disubstituted cyclopropanes from their corresponding alkene stereoisomers (entries 1–6). For these substrates, the use of Et₂Zn instead of Zn has a beneficial impact on rate and yield. A diene (entry 7) is selectively cyclopropanated at the less hindered terminal double bond. 1,1-Disubstituted alkenes (entries 8–11), carbocyclic (entries 12–14) and heterocyclic (entries 15 and 16) alkenes, and α,β -unsaturated carbonyl compounds (entries 17–19) also react efficiently under the catalytic conditions. α -Cyclopropylstyrene reacts to form the dicyclopropane product without rearrangement, providing further support for a non-radical pathway (entry 11). Aliphatic terminal alkenes are a current limitation, undergoing competing hydrogenation with Et₂Zn as the reductant. Finally, cyclopropanes with deuterium substitution are generated using CD₂Cl₂ (entries 20 and 21).

The Ni-catalyzed cyclopropanation and the uncatalyzed Simmons–Smith reaction exhibit distinct selectivity profiles. Simmons–Smith-type (XCH₂)Zn reagents are generally electrophilic,^[5] reacting sluggishly with electron-deficient alkenes.^[14] For example, the cyclopropanation of chalcone with CH₂I₂ and Et₂Zn produces low yields of the cyclopropane (16%), and the reaction is accompanied by extensive decomposition of the starting material (Figure 4a). By con-

(a) Electron-Deficient Alkenes: Chalcone



(b) Steric and Directing-Group Effects: Limonene Derivatives

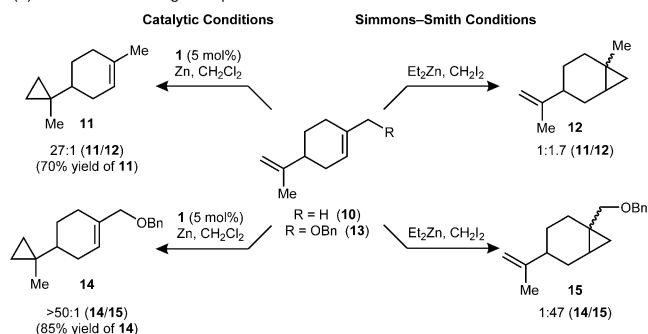


Figure 4. A comparison of the Ni₂-catalyzed cyclopropanation and the uncatalyzed Simmons–Smith reaction. The products of ring cyclopropanation were formed as mixtures of diastereomers.

trast, ambiphilic behavior is observed under the Ni₂-catalyzed conditions, constituting an unusual case of a catalytic cyclopropanation where both electron-rich and electron-deficient substrates react with equivalent efficiency. The catalytic cyclopropanation of chalcone reaches full conversion after 12 h at ambient temperature, yielding the *trans* cyclopropane in 72% yield.

The selectivity properties of the catalytic procedure can be exploited with substrates containing multiple alkenes. In the case of limonene (**10**), the catalytic cyclopropanation using **1** is sensitive to steric effects, preferentially engaging the less hindered exocyclic alkene over the endocyclic trisubstituted alkene (Figure 4b). Under Furukawa-type Simmons–Smith conditions, there is relatively little steric bias, resulting in low site selectivity.^[15] For benzyloxy-substituted limonene **13**, there is a reversal in selectivity between the Ni₂-catalyzed conditions and the uncatalyzed Simmons–Smith reaction. The former is highly selective for cyclopropanation of the exocyclic alkene, whereas the latter exhibits a strong directing-group effect and favors the bicyclic product **15**. Aside from demonstrating synthetic complementarity between the catalytic and noncatalytic conditions, these results provide an important mechanistic indication that the Ni catalyst does not promote the formation of kinetically competent (XCH₂)Zn cyclopropanation agents.

In summary, we have shown that the dinuclear Ni catalysts **1–3** directly engage CH₂Cl₂ in cyclopropanation reactions in the presence of mild reductants, such as Zn or Et₂Zn, to achieve turnover. These complexes enable the catalytic transfer of unsubstituted methylene, providing a useful complement to cyclopropanation methods that employ diazoalkane reagents bearing stabilizing electron-withdrawing substituents. In principle, this mode of reductive dihalomethane activation might be extended to other catalytic carbene transformations. The application of the [NDI]Ni₂ platform to these reactions is currently studied in our laboratory.

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Keywords: alkenes · carbene transfer · cyclopropanation · nickel catalysis · reductive cycloaddition

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