Ligand-Metal Cooperation Enables Net Ring-Opening C–C Activation / Difunctionalization of Cyclopropyl Ketones

Michael M. Gilbert, Michael J. Trenerry, Victoria R. Longley, Anthony J. Castro, John F. Berry, Daniel J. Weix

ABSTRACT: Reactions that cleave C–C bonds and enable functionalization at both carbon sites are powerful strategic tools in synthetic chemistry. Stereodefined cyclopropyl ketones have become readily available and would be an ideal source of 3-carbon fragments, but general approaches to net C–C activation / difunctionalization are unknown. Herein we demonstrate the cross-coupling of cyclopropyl ketones with organozinc reagents and chlorotrimethylsilane to form 1,3-difunctionalized, ring-opened products. A combination of experimental and theoretical studies rule out more established mechanisms and shed light on how cooperation between the redox-active terpyridine (tpy) ligand and the nickel atom enables the C–C bond activation step. The reduced (tpy•-)NiII species activates the C–C bond via a concerted asynchronous ring-opening transition state. The resulting alkynickel(II) intermediate can then be engaged by aryl-, alkenyl-, and alkylzinc reagents to furnish cross-coupled products. This allows quick access to products that are difficult to make by conjugate addition methods, such as β-allylated and β-benzylated enol ethers. The utility of this approach is demonstrated in the synthesis of a key (±)-taiwaniaquinol B intermediate and the total synthesis of prostaglandin D3.

Introduction

Like well-known fragmentations and rearrangements,1 the selective difunctionalization of C(sp3)–C(sp3) bonds by transition metals has the potential to be a powerful strategic tool in organic synthesis, by converting an accessible carbon skeleton into a more challenging one. The underlying challenge of this approach, even for activated substrates like cyclopropyl ketones,23 is selective cleavage of the target C–C bond in the presence of more reactive functional groups in a way that allows for difunctionalization rather than monofunctionalization.

To date, successful approaches have generally utilized one of two strategies, based upon polar or radical chemistry. Polar oxidative addition of poorly-reactive C–C bonds is enabled by electron-rich, low-coordinate metal centers with strong σ-donor ligands (Scheme 1A).5,6,8 While this approach has enabled nickel-catalyzed “cut-and-sew” reactions of cyclopropyl ketones with alkenes and alkynes,9–12 difunctionalization to ring-opened products has been elusive.13 Single electron transfer (SET) approaches (Scheme 1B)14–21 involve carbon-centered radical intermediates and often provide complementary selectivity to polar mechanisms.14,26 Like polar reactions, transformations relying on photocatalytic14–16 or metal-catalyzed19,22,25 SET are also commonly limited to ring expansions with π components or monofunctionalization.18,24

We show here a new, cooperative mechanism for cyclopropane C–C activation that includes aspects of both strategies: charge transfer from the terpyridine ligand to the substrate followed by concerted asynchronous ring-opening and Ni–C bond formation (Scheme 1C).25,26 Because Me3Si (TMS') activation of the carbonyl is required for this step, the resulting C–C activation / cross-
coupling reactions result in regio- and stereo-specific functionalization of both carbons (via cross-coupling and silyl enol ether formation) instead of monofunctionalization. By taking advantage of advances in cyclopropyl ketone synthesis, these new reactions allow for access to intermediates that are difficult to access using conventional conjugate addition reactions.

Background

The ring-opening C–C activation/cross-coupling of cyclopropyl ketones results in valuable γ-substituted silyl enol ethers that can be challenging to access by other approaches (Scheme 2). The most-developed approach to these products is conjugate addition under conditions to trap the enolate as the silyl enol ether, but this can be challenging for certain substitution patterns and functional groups. For example, reliable conjugate benzylation necessitates the use of excess pre-formed, thermally unstable organocopper reagents (Scheme 2A).56–58 Translation of this reactivity to catalytic manifolds, while promising, is currently limited in scope to simple benzylic nucleophiles and cyclic enones.59 Similarly, conjugate alkylation of enones with organometallic reagents (Cu,60–62 In,54,55 Ba46) is substrate controlled, affording mixtures of 1,2- and 1,4-addition products. Selectivity is further complicated using 1,3-disubstituted alkyl reagents due to competing α- and γ-addition.30,61 Notable advances in selective conjugate alkylations using alkyl boronic ester nucleophiles have been reported by Morken63,64 and Jarvo,65 but these reactions require dialkylidene ketones and α,β-unsaturated N-acyl pyrroles, respectively. Hosomi-Sakurai-type alkylations afford 1,4-addition products with high selectivity, but typically require stoichiometric strong Lewis acids (e.g., TiCl4), organotin reagents, or are only applicable to cyclic substrates.66,67 Photoredox Giese reactions68 allow access to conjugate benzylation products, but do not allow for difunctionalization.69 Finally, directed C–H activation methods have been developed to overcome the limitations of using benzylic or allylic nucleophiles in conjugate addition, but again do not offer difunctionalization opportunities.55,69

Scheme 2. Synthesis of γ-alkenyl and aryl silyl enol ethers.

A. Conjugate addition of pre-formed benzyl and allylmetal reagents

B. Nucleophilic ring opening / enolate trap

C. This work: cyclopropyl ketone C–C activation / difunctionalization

The use of cyclopropyl ketones leverages decades of advances that have made substituted, stereodefined cyclopropyl ketones readily accessible from a variety of starting materials.57–65 General approaches to open and difunctionalize these stereodefined rings could address challenges in acyclic stereocontrol76 and the resulting silyl enol ethers would allow for a variety of subsequent C–C, C–O, and C–N bond forming transformations.77–79 However, while the ring-opening monofunctionalization of cyclopropyl ketones has strong precedent54,72 and exciting recent developments, general net difunctionalization approaches are limited (Scheme 2B and 2C).

The lack of net C–C activation / difunctionalization reactions can be attributed, in part, to limitations inherent to the mechanisms of the previously reported chemistry. While nickel complexes with electron-rich, monodentate ligands promote oxidative addition of cyclopropyl ketones to form metalacyclic intermediates that are useful in ring-expansion reactions with unsaturated π-systems, these metalacyclic intermediates appear to be unreactive for Negishi cross-coupling reactions70–73 and only couple with alkyl radicals to form monofunctionalized products.74–76 Other mechanistic approaches, such as photoredox and metalloradical ring-opening,72,75 have not yet been demonstrated to afford net difunctionalized products.

Fujisawa reported the first example of net ring-opening difunctionalization of cyclopropyl ketones, using Ni(acac)3 as the catalyst without any added ancillary ligand (Figure 2B).75 This work reported that aluminum enolates formed from nickel-catalyzed nucleophilic opening of phenyl cyclopropyl ketone with AlMe3 could be subsequently trapped by TMS-Cl or an aldehyde (to form an aldol product). Perhaps due to the poor nucleophilicity of alkyl nickel species, ethyl and vinyl transfer afforded <40% yield and no follow-up studies have been reported.

In contrast to monodenate, electron-rich ligands, or “ligandless” nickel complexes, the use of redox-active bi- and tridentate N-donor ligands in nickel catalysis77–81 has been less studied for C–C bond activation. It has been demonstrated, however, that redox-active ligands can enable new reactivity at metal centers,73,74,75,82–84 and change the mechanism of oxidative addition for alkyl halides.66 Indeed, nickel terpyridine complexes have been reported to accomplish challenging C–N oxidative additions.66 We show here how changing the ligand on nickel to terpyridine can enable a new mechanism that overcomes the limitations of previous approaches (Scheme 2C).

Results and Discussion

Mechanistic Proposal. Preliminary studies found that (tpy)Ni complexes are effective at catalyzing the cross-coupling of (p-tolyl)ZnI and chlorotrimethylsilane (TMSCI) with phenyl cyclopropyl ketone (1a) to form acyclic silyl enol ether cross-coupled product (3a) (Scheme 3). While catalysts derived from a variety of polyphenylidene ligands provided measurable product, terpyridine (tpy) was the most effective, affording 3a in 80% yield and >95:S:Z:E stereoselectivity (Figure S1). Reactions performed in the presence of a stoichiometric amount of Zn, even for redox-neutral reactions with organozinc reagents, gave superior outcomes (Figure S8). We attribute these findings to the fast oxidation and deactivation of the key (tpy−)Ni2 intermediate by other [Ni2+] species in solution, requiring occasional re-activation by Zn reductant (vide infra).

A collection of experimental and theoretical studies allow us to propose a mechanism for this new reaction (Scheme 3), explain the need for Zn metal reductant (1) in Scheme 3, show that a (tpy−)Ni2 intermediate is required (2) in Scheme 3, and strongly
support the proposed C–C activation step ([3] and [4] in Scheme 3). Initial two-electron reduction of the (tpy)NiCl₃ pre-catalyst by Zn metal affords a neutral nickel intermediate with the proposed electronic structure (tpy⁻⁻)NiL (1-NMP, L = N-methylpyrrolidone (NMP)).⁶⁶ Putative intermediate II is proposed to form by coordination of the electron-accepting silyl carboxonium cation to the nickel center of I, which induces a transfer of electron density from (tpy⁻⁻) to afford partial ketyl-radical character (~50% spin-density) at the carbonyl carbon C. II then undergoes concerted, but asynchronous, C–C bond activation and Ni–C bond formation via an energetically accessible triplet transition state (see calculations in Figure 1). The resulting homoallyl nickel(II) intermediate III can react with an organozinc intermediate to form IV. Fast reductive elimination from five-coordinate Ni⁵ complex IV completes the cycle.

**Alternative mechanisms.** Before arriving at the proposed mechanism in Scheme 3, five other possible mechanisms were systematically evaluated based on known reactivity of cyclopropyl ketones and nickel (Scheme 4-A-E).

(A) Uncatalyzed silylative ring-opening halogenation of the cyclopropyl ketone by TMSX/ZnX₂ to form a γ-halogenated silyl enol ether³⁴–⁵¹ followed by nickel catalyzed Negishi coupling.⁷⁷,⁷⁹,⁸⁳–⁸⁵ Potent silyl Lewis acids, such as TMSCl, can generate the requisite halogenated silyl enol ethers at ambient temperatures. Moreover, various chlorosilanes are capable of participating in ring-opening chlorination of cyclopropyl ketones in the presence of a suitable Lewis acid.⁹² While subsequent Ni-catalyzed Negishi coupling at ambient temperatures is well-precedented with alkylidoles, alkyl bromides and chlorides would not be expected to couple at this temperature.⁷⁷,⁹³,⁹⁴

(B) Oxidative addition of the cyclopropyl ketone to a low-valent nickel species to form a nickel(II)-silylcarboxylate intermediate,⁴¹–⁵² which then reacts with TMSCl and organozinc halide to form product. Nickel(II)-silylcarboxylate intermediates are known with different ligands (monodentate phosphines and NHC ligands), but they have not been demonstrated for silylative functionalization. Two recent reports⁷⁷,⁸⁶ suggest that these intermediates can be protonated and coupled with alkyl halides.

![Scheme 3. Unified mechanistic proposal for cyclopropyl ketone C–C activation/cross-coupling.*](image)

**Key mechanistic features:**

- [1] Reducing conditions enable sustained access to (tpy⁻⁻)NiL (I)
- [2] (tpy⁻⁻)NiL (I) and TMSCl are required for C–C bond activation
- [3] Substrate coordination induces ligand-to-ligand charge transfer
- [5] Ring opening forms homoallyl nickel intermediate III

![Scheme 4. Alternative mechanisms for Ni-Catalyzed C-C activation/cross-coupling.](image)

**Scheme 4. Alternative mechanisms for Ni-Catalyzed C–C activation/cross-coupling.**

A. Ring-opening halogenation by TMSCl followed by standard XC

B. Oxidative addition to Ni followed by silylation/cross-coupling

C. Nucleophilic addition of organonickel (2-electron process)

D. SET, radical rearrangement, radical capture, reductive elimination sequence involving (tpy⁻⁻)NiR (1-electron process)

E. SET, radical rearrangement, radical capture, reductive elimination sequence involving (tpy⁻⁻)NiL (1-electron process)

(C) Nucleophilic addition of an organonickel intermediate to the cyclopropyl ketone followed by subsequent silylation of the resultant nickel enolate. Nucleophilic ring-opening without silylation has been demonstrated by Falck for (alkyl)₂Cu(CN)Li₂BF₄ and Fujisawa.¹⁵ demonstrated this mechanism for a Ni-catalyzed addition of AlMe₃ to cyclopropyl ketones. A combination of TMSCl and ZnX₂ could serve...
as a Lewis acid,\textsuperscript{95-98} which was required in the literature precedents to activate the cyclopropyl ketones toward ring opening rather than 1,2-addition.

(D) Single-electron transfer from (tpy\textsuperscript{−})Ni\textsuperscript{II}R to a silyloxonium intermediate resulting in an α-silyloxy radical that can rearrange to a primary radical before it is captured by (tpy)Ni\textsuperscript{II}R with subsequent C–C bond formation from (tpy)Ni\textsuperscript{III}\textsubscript{2}(R)(CH\textsubscript{2}CH\textsubscript{2}CH=C(OTMS))R.\textsuperscript{77}

(E) Similar to (D), (tpy\textsuperscript{−})NiCl could transfer an electron to a silyloxonium intermediate resulting in an α-silyloxy radical that can rearrange to a primary radical before capture by (tpy)Ni\textsuperscript{II}Cl to form (tpy)Ni\textsuperscript{II}Cl(\textsubscript{}CH\textsubscript{2}CH\textsubscript{2}CH=C(OTMS))R. Subsequent transmetalation with the organozinc reagent followed by reductive elimination would afford the product.

**Exclusion of mechanisms involving uncatalyzed ring-opening halogenation by TMSCl (Scheme 4A).** Several results led us to rule out ring-opening halogenation. First, we were unable to detect ring-opened halogenation products under a variety of conditions related to our optimized conditions. Omission of Zn from the optimized reaction resulted in 99% recovery 1a demonstrating that TMSCl alone does not participate in C–C activation (Figure S2). Subjecting 1a to TMSCl and ZnI\textsubscript{2} (0.75 equiv, the maximum amount generated in the optimized catalytic reaction employing 1a and 4-iodotoluene) resulted in a 90% recovery of 1a and no detectable new organic products (Scheme 5A). This demonstrated that ZnI\textsubscript{2} is not a source of nucleophilic iodide, nor does it participate in halide metathesis with TMSCl to liberate TMSI and ZnCl\textsubscript{2}.\textsuperscript{99}

**Scheme 5. Experiments that Rule Out Ring Opening Halogenation Mechanism.**

A. Ring opening does not occur with TMSCl and ZnI\textsubscript{2}

\[
\text{1a}\xrightarrow{\text{TMSCl (0.75 equiv)} NMP, rt} \text{1a}
\]

90%\textsuperscript{a} recovery of 1a

B. Bromide or iodide salts are not required for coupling

\[
\text{OMe} + \text{Cl} + \text{NiCl}_2 \xrightarrow{\text{tpy (5 mol%) NiCl}_2 \text{dme (5 mol%) (COD)NiCl}_2 \text{NMP, rt}} \text{3o}, 45\%
\]

C. Homo-allylic chloride functionality is unreactive

\[
\text{Cl} + \text{Br} + \text{NiCl}_2 \xrightarrow{\text{tpy (5 mol%) NiCl}_2 \text{dme (5 mol%) (COD)NiCl}_2 \text{NMP, rt}} \text{3v}, 66\%
\]

D. TMSI ring opening gives different regiochemistry than coupling

**Reported TMSI ring opening:**

\[
\text{Ph} + \text{Me} \xrightarrow{\text{TMSI, CCl}_4 \text{NMP, rt}} \text{Ph} + \text{Me}
\]

**This work:**

\[
\text{Ph} + \text{Me} \xrightarrow{\text{TMSI, CCl}_4 \text{NMP, rt}} \text{Ph} + \text{Me}
\]

\textsuperscript{a}GC yield. \textsuperscript{b}Isolated yield followed chromatographic purification.

\textsuperscript{c}Previously observed. \textsuperscript{d}Entry 3 produced a 3:1 mixture of regioisomers.

**Table 1. Experiments that Rule Out Nickeladihydropyran Intermediates.**

<table>
<thead>
<tr>
<th>entry</th>
<th>[Ni]</th>
<th>additive</th>
<th>1a (%)</th>
<th>1a\textprime (%)</th>
<th>1a\textdoubleprime (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(tpy\textsuperscript{−})Ni\textsuperscript{II}(COD)</td>
<td>ZnCl\textsubscript{2}</td>
<td>10</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(tpy\textsuperscript{−})Ni\textsuperscript{II}(COD)</td>
<td>-</td>
<td>48</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(tpy\textsuperscript{−})Ni\textsuperscript{II}(COD)</td>
<td>ZnCl\textsubscript{2}</td>
<td>85</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(tpy)Ni\textsuperscript{I}</td>
<td>ZnCl\textsubscript{2}</td>
<td>88</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(tpy)NiCl</td>
<td>ZnCl\textsubscript{2}</td>
<td>90</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(tpy)NiCl</td>
<td>Zn</td>
<td>42</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Results were observed employing more Lewis acidic ZnCl\textsubscript{2} – even in the presence of low-valent (tpy)Ni\textsuperscript{I}X (X = I, Cl) (Table 1, entries 4 and 5). We also note that efficient cross-coupling is possible in the absence of bromide or iodide (Scheme 5B), yet cross-coupling of alkyl chlorides does not occur (Scheme 5C). Finally, the regiochemistry of our cross-coupling reaction with phenyl 2,2-dimethylcyclopropyl ketone is opposite what is reported for ring-opening silylation and halogenation (Scheme SD).\textsuperscript{84-92}
Exclusion of SET ring opening (Scheme 4E) by halonickel complexes. Evidence of free radical intermediates, as proposed in Scheme 4E, was sought using the radical spin trap N-tert-butyl-a-phenylnitrone (PBN). The catalytic reaction of 1a with 4-iododotoluene formed cross-coupled product 3a, even in the presence of PBN (0.5 equiv), and aliquots removed from the reaction were EPR silent. This finding suggests that the intermediacy of a freely-diffusing C-centered radical is unlikely, but does not exclude the possibility of a caged radical.

Indeed, the selectivity observed for 1,2-disubstituted cyclopropanes, where cross-coupling occurs at the least-substituted carbon (e.g. 3ai, 3a), and 3ak in Scheme 9, vide infra), could be explained by a caged radical process operating under Curtin-Hammett conditions (Scheme 7A). If a reduction of the silyl-activated ketone by a low-valent nickel catalyst forms a ketyl-like intermediate A, two possible scenarios could lead to the observed selectivity. First, reversible ring-opening of A would afford a mixture of the more stable 2” radical (B) and the less stable 1” radical (C), favoring B. If radical capture of C to form E is faster than capture of B to form D, then the less substituted product could be favored. The second alternative involves fast, irreversible ring opening and fast, irreversible radical capture. If transmetallation or reductive elimination from E is faster than from D, then the less substituted product could also be favored. If fast equilibration between A, B, and C was occurring, then an enantio-enriched cyclopropyl ketone would have to result in racemic products due to stereoablation upon irreversible ring opening (Scheme 7B). We observe complete retention of configuration (3ai, 100% ee), ruling out these pathways.

Scheme 7. Evidence Against Mechanisms Involving Rapidly Equilibrating Radical Intermediates.

A. Mechanism involving rapidly equilibrating radical intermediates

B. Evidence against rapidly equilibrating radical intermediates

*Isolated yield following chromatographic purification. GC yield.

GC Yields. Unless otherwise stated, yields are based on the amount of [Ni] and account for 1 equiv excess of 1a. TMSCl omitted. Yields calculated based on the amount of 1a instead of [Ni], 1:1 (tpy)NiCl:Zn.
DFT studies shed light on how the unusual electronic structure of I enables cyclopropane C–C scission under these reaction conditions. Initial activation of the cyclopropyl ring appears dependent on the interaction of the cyclopropyl ketone substrate with both TMSCl and (tpy)Ni components, as DFT results do not predict substrate-based radical character in the electronic ground state of I-CPK (L = 1a), where the cyclopropyl ketone substrate binds to I but TMSCl is absent (Figure 1A–C). This interpretation is consistent with experimental data: there is negligible substrate consumption by I-NMP in the absence of TMSCl, but rapid substrate consumption when TMSCl is present (Table 1, entries 1 and 3).

The reason for this change in reactivity with TMSCl is that a transient silyl carboxonium ion, formed by interaction of TMSCl, ZnX₂, and the ketone, is a better electron acceptor that reacts with I to generate an intermediate (II), which is primed for C–C activation (Figure 1D). Binding of the silyl carboxonium ion to I confers significant spin density (i.e., partial radical character) from the tpy•–ligand to the p, orbital of the carbonyl carbon (Figure 1A–C). While free cyclopropylmethyl radicals undergo rapid radical ring-opening processes (k_rarr = 10⁷ s⁻¹),¹¹¹ the bound substrate of II performs sequential oxidative ring opening and Ni–C bond formation to yield the metallacycle species III (Figure 1D). Intrinsic reaction coordinate (IRC) and nudged elastic band (NEB) calculations following the S = 1 transition state TS predict C–C bond cleavage and Ni–C bond formation to proceed in concerted asynchronous fashion (Figure S19). Upon ring-opening, unpaired electron density grows more concentrated on the terminal carbon of the cleaved C–C bond (Figure S20). The radical character of this “avoided intermediate” is stabilized by an agostic interaction with the nickel center preceding the heavily favored Ni–C bond formation to yield III. Curiously, conversion of II to III along the S = 0 spin surface is predicted to instead proceed via a concerted synchronous pathway (akin to that proposed for other nickel systems) with significantly higher activation energy, likely due to an absence of radical character in the bound

https://doi.org/10.26434/chemrxiv-2021-hjdbr-v3 ORCID: https://orcid.org/0000-0002-9552-3378 Content not peer-reviewed by ChemRxiv. License: CC BY-NC-ND 4.0
substrate to facilitate ring opening. In this case, the redox-active ligand and triplet ground-state allows access to a lower-energy, asynchronous pathway.

The resulting intermediate III, a square-planar nickel(II) complex with a weak apical silyl-ether interaction, favors a $S = 0$ spin state, indicating that the overall transformation from II to III ($\Delta G = -23.2$ kcal/mol) involves inter system crossing following the more energetically preferred $S = 1$ transition state TS. Experimentally, analysis of an aliquot of the catalytic reaction of 1a and 4-iodotoluene in the presence of a spin trap was EPR silent, consistent with a diamagnetic III resting state and disfavoring any mechanisms involving longer-lived radicals (see Supporting Information section V for experimental details). This coordination/rearrangement sequence also helps explain the observed Z-enol-ether geometry in the product (Figure S22). Finally, unlike C,O-metallacycles formed with monophosphine or N-heterocyclic carbene ligands, III has a weakly-bound oxygen ligand and can dissociate to form a square-planar, cationic nickel complex with open coordination sites for transmetallation. Following transmetallation with organozinc reagents, reductive elimination from the five-coordinate (tpy)NiCl$_2$ should be fast.

**Role of Zn reductant in the redox-neutral cross-coupling reaction.** Considering the ubiquity of (tpy)Ni in cross-coupling, and reports on the high reactivity of Ni(acac)$_2$: with tpy in oxidative addition, we were at first surprised that C(sp$^3$)–C(sp$^3$) activation reactivity has not previously been reported. We propose this is because sustained access to I-NMP in the absence of a reductant under Negishi cross-coupling conditions is not possible due to, unfavorable speciation. We confirmed that (tpy$^-$)Ni(tpy-tolyl) is the major observable nickel species obtained from the reduction of (tpy)NiCl$_2$ by (tpy-tolyl)ZnI (Figure S9–S11). DFT studies indicate that this coordination/rearrangement sequence can decompoision to form (tpy)NiX from I-NMP and (tpy)NiX(H (X = halide) is essentially irreversible (X = Cl, $\Delta G = -20.6$ kcal/mol) (Figure S24). Furthermore, experiments and calculations demonstrate that speciation between I-NMP and 4 to form (tpy$^-$)Ni(tpy-2-ansilyl) is fast and highly favorable (Figure S12, Figure S23). Together, these results explain why maintaining a productive (tpy$^-$)Ni form of the catalyst in the absence of a reductant is challenging, even when using a Ni(0) precatalyst (as in Table 2, entries 1–5). We note that in nature, external reductant systems are used to maintain unsustained oxidation states in enzymatic catalysis, for example the recovery of off-cycle cobalt(II) to cobalt(III) in methionine synthase by methionine synthase reductase.

Consistent with these findings, low conversion of cyclopropyl ketone 1a to product 3a was observed without an external reductant (2–6 turnovers), regardless of the oxidation state of the starting catalyst (as in Table 2, entries 1–5). This suggests that, as above, the active nickel catalyst I-NMP is competitively deactivated and requires a “reductase-like” external reducing force to re-establish the reduced tpy species (Table 2, entries 6–10, 12). We found that either chemical (Zn, $E_{1/2} = -1.38$ V vs. Fe/Fc) or electrochemical (-1.36 V vs. Fe/Fc) reductants enabled sustained access to I-NMP and reactions with reductants provided improved yields of 3a and increased turnover numbers (52–79% yield, 10–16 turnovers). While the use of a catalytic reductant has been shown to enhance yields of Ni-catalyzed C=O and C=N bond forming reactions to the best of our knowledge this is the first example of this strategy applied to a redox neutral C=C cross-couplings.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Ni] Additional Conditions</th>
<th>3g (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(tpy)Ni$^{II}$Cl$_2$</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>(tpy)Ni$^{II}$Cl$_2$</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>(tpy)Ni$I$</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>(tpy$^-$)Ni(I)(COD)</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>(tpy)Ni$I^+Cl^-$</td>
<td>ZnCl$_2$ (10 mol%)</td>
</tr>
<tr>
<td>6</td>
<td>(tpy)Ni$I^+Cl^-$</td>
<td>Zn (10 mol%)</td>
</tr>
<tr>
<td>7</td>
<td>(tpy)Ni$I^+Cl^-$</td>
<td>Zn (10 mol%)</td>
</tr>
<tr>
<td>8</td>
<td>(tpy)Ni$I^+$</td>
<td>Zn (10 mol%)</td>
</tr>
<tr>
<td>9</td>
<td>(tpy$^-$)Ni(I)(COD)</td>
<td>Zn (10 mol%)</td>
</tr>
<tr>
<td>10</td>
<td>(tpy)Ni$I^+Cl^-$</td>
<td>Divided cell, -1.36 V</td>
</tr>
<tr>
<td>11</td>
<td>(tpy)Ni$I^+Cl^-$</td>
<td>Divided cell, 0 V</td>
</tr>
<tr>
<td>12</td>
<td>(tpy)Ni$I^+$</td>
<td>Divided cell, -1.36 V</td>
</tr>
</tbody>
</table>

*Yields are corrected GC yields vs. dodecane internal standard. *Catalyst stirred over 2 equiv activated Zn in NMP, then filtered prior to use. *Potential vs. Fe/Fc, *sacrificial Zn anode.

**Scope, applications to natural product synthesis, and silyl enol ether derivatization.** In developing synthetic applications of this ring-opening process, we found two sets of conditions that allowed the use of a variety of coupling partners while employing a single nickel catalyst (Scheme 8). The first is an auto-tandem process, operationally like a cross-electrophile coupling, where aryl halides are converted in situ into arylzinc reagents by the same nickel catalyst that performs the C–C activation/cross-coupling (Figure S13–S16). The second is a decoupled version, wherein an aryl or vinyl halide is converted to the corresponding organozinc halide in one flask by (tpy)NiCl$_2$ and a zinc reductant, followed by immediate use of this reagent in the C–C activation/cross-coupling in a second flask. Both sets of conditions provided the desired products as the TMS silyl enol ethers with ≥95:5 Z/E stereoselectivity.

The resulting reaction is robust, coupling a variety of aryl and alkyl cyclopropyl ketones with a diverse set of aryl, alkenyl, and alkylzinc reagents (Scheme 8). Efficient coupling of (hetero)arylzinc reagents occurred regardless of arene electronics (3b, 3c, 3g, 3h), Lewis basic heteroatoms (3k, 3p), or reactive functionalities that can be used in subsequent cross-coupling reactions (3e, 3j). More complex cyclopropyl ketones, including those with additional substitution and bicyclic structures, were also competent substrates, demonstrating that the reaction is not limited to aryl cyclopropyl ketones and can be further expanded to alkyl analogs (3ae–3ah). The mass balance of lower-yielding reactions consisted of varying amounts of uncoupled (reduced) ring-opened silyl enol ether and silyl dieneol ether (as in Table 1). These side products are presumed to occur from the protodemetalation or α-hydride elimination of intermediate III. While more hindered cyclopropyl ketones coupled in lower yield (3ai–3al), improved reactivity was obtained by adjusting our ligand to be less sterically demanding but still easily reduced. Bidentate
4,4′-bis(carboxymethyl)-2,2′-bipyridine (L2) with added N,N-dimethylaminopyridine was effective for products 3ai–3al, suggesting that cooperative ligand-nickel mechanisms might be general for a variety of catalysts. Employing an enantioenriched 1,2-disubstituted cyclopropyl ketone afforded the cross-coupled product 3a with complete retention of stereochemistry (92% ee starting material, 92% ee product, 100% cee) and >95:5 Z/E selectivity. We note that the Cu-catalyzed asymmetric benzylation of enones has yet to be demonstrated, which is likely due to the instability of benzylic organocopper complexes (vide supra).

Scheme 8. Scope of the Net 1,3-Difunctionalization Reaction and the Formal Synthesis of (+)-Taiwaniaquinol B.

Aryl coupling partner (ligand = tpy)

Vinyl coupling partner (ligand = tpy, X = Br)

Cyclopropyl ketone coupling partner (ligand = tpy, X = I)

Alkyl coupling partner (ligand = tpy, X = ZnBr)

Efficient preparation of an intermediate in the total synthesis of (+)-Taiwaniaquinol B

*Isolated yields after purification. For all acyclic TMS-enol ethers stereochemistry was assigned using NOE correlations.
Asymmetric conjugate benzylation has only been accomplished using photoredox catalysis employing coordinating auxiliaries, chiral-at-metal photocatalysts, Hantzsch ester or BF₃•K radical precursors, and the resulting enolate cannot be trapped, thus precluding difunctionalization.⁴¹⁻⁴⁴

Besides arylic reagents, alkenylzincs could be readily substituted as coupling partners (3g–w), thus accessing chemical space usually reserved for conjugate alkylation. 1,4-Addition of alkyl organometallics to acyclic enones is notoriously unselctive, often yielding substantial amounts of 1,2-addition adducts.⁴¹⁻⁴⁴ Unpredictable selectivity is particularly exacerbated in reactions promoted by TMSCl where isolation of products as the silyl enol ether is possible.⁴¹⁻⁴⁴ This work demonstrates a complementary approach to α-alkenylation with complete regiofidelity dictated by the metal catalyst.

Alkyl zinc reagents also worked as coupling partners with minimal adjustment to the reaction conditions and demonstrated functional-group compatibility consistent with other Negishi-type cross-coupling reactions. Notably, esters (3am), ethers (3an), protected amines (3ar), alkyl trimethoxysilane (3ap), and alkyl boronic acid pinacol esters (3ao) were all compatible. Sterically hindered zinc reagents, such as ortho-substituted arylics and 2⁺ arylic reagents, coupled in low yield under these conditions. Comparison with related ring-opening alkylations that proceed via nickeladhydropropyan (Scheme 4C), reported after our initial disclosure of these reagents, are informative on how mechanistic differences can lead to differences in reactivity and scope. Those reactions are able to couple alkyl bromides instead of alkylzinc reagents, but are limited to monofunctionalization (γ-functionalization) of aryl cyclopropyl ketones.⁶⁶⁻⁶⁷ We anticipate that future studies will shed further light on how these differences arise and how existing limitations might be overcome.

Even without utilization of the silyl enol ether, this method can be helpful in complex molecule synthesis. For example, in Fishlock’s (±)-taiwianquinol B synthesis we were able to decrease the step count to intermediate 3av by three steps (out of 7).²⁹ Our four-step route utilized a different starting material (5) of similar complexity and the same oxidation state as in the Fishlock synthesis.

**Scheme 9. Derivatizations of the TMS-enol-ether functionality.**

The TMS enol ether group can serve as a “blank slate” for generation of a myriad of other functionalities. We demonstrate here a small selection: oxidation to form acyloin 8, installation of an α-tert-butyl group (9), conversion to the corresponding enol triflate 10 (itself another versatile intermediate),²⁹ and Pd-catalyzed arylation (11)⁶⁷ (Scheme 9). In each example, the products were

**Scheme 10. Total synthesis of Prostaglandin D₃ and comparison of C-C activation approach with conjugate addition approach.**

**A. Prostaglandin D₃ synthesis via conjugate addition**

1. CuI (1 equiv), P(t-Bu)₃ (3 equiv)
2. HMPA, PhN₂Cl
3. Li⁺

**B. Prostaglandin D₃ synthesis via C-C activation**

1. Et₂Zn, CH₂Cl₂
2. TMSCl, Et₃N
3. DIBALH
4. TPAP, NMO
5. NiCl₂dme (10 mol%), tpy (10 mol%), TMSCI (2 equiv)
6. Me₂SnOH
7. HF

“See Supporting Information for full experimental details. Yields are isolated yields after purification.
synthesized as a single regioisomer, which would not be possible using enolate nucleophiles generated through deprotonation of the corresponding ketone.125

Finally, we developed a more general protocol for the isolation of TMS silyl enol ethers, which can be prone to hydrolysis in workup and during chromatography. This is needed because many silyl enol ether derivatization reactions require TMS groups87,126-132 or demonstrate diminished reactivity when using bulkier, more easily isolated congeners.133,134 We found that careful control of pH in the workup coupled with non-aqueous reverse phase chromatography allowed for relatively easy isolation in yields identical to the GC yield (80% GC yield, 80% isolated yield of 3a).135 The proliferation of automated chromatography instruments and reusable stationary phases has dramatically lowered the barrier to employing reverse-phase purification technologies on preparative scale.

The net difunctionalization approach offers a useful complement to conjugate addition chemistry, as demonstrated in the total synthesis of prostaglandin D1 (PGD1) (Scheme 10). Conjugate addition approaches to PGD1 start with enone 13,156,157 an intermediate commonly prepared from 12 in 3-5 steps (Scheme 10A).156 Because this results in the wrong oxidation state at C9 and C11, seven further steps are required to convert 14 to PGD1. Our C–C activation approach starts from key cyclopropyl ketone intermediate 15, available in four steps from common starting material 12 (Scheme 10B). Leveraging our C–C activation/cross-coupling approach, the α-side chain is installed to give 16 with the desired syn-stereocchemical configuration to the adjacent C9 TMS-protected hydroxyl with concomitant formation of a TMS-enol-ether. The α-side chain is conveniently installed by Pd-catalyzed cross-coupling of TMS-enol ether 17 in 66% yield and >95:5 d.r. Finally, hydrolysis of the methyl ester protecting group and global silyl-group deprotection affords PGD1 in eight total steps and 18% overall yield. This is 3-5 steps shorter than previously established conjugate addition approaches to PGD1.159

Conclusions

These studies illustrate the potential of C–C activation of cyclopropyl ketones in synthesis when coupled to net difunctionalization of the resulting ring-opened products. This work complements difunctionalization by ring expansion that had been reported previously1-12 and addresses limitations in conjugate additions reactions using benzylic15-38 or allylic nucleophiles.40-45 Studies on how this new reaction can be leveraged in complex molecule synthesis are ongoing in our lab and will be reported in due course. Additionally, this work reports a new type of C–C activation mechanism that includes aspects of both concerted oxidative addition and alkyl radical intermediates. This reactivity appears to be enabled by metal-ligand cooperativity and is a new application of redox-active ligands that could be of wide use in catalysis. Moreover, these results outline a strategy to regulate catalyst oxidation states by incorporating an external reducing force, thereby minimizing unproductive speciation in redox neutral C–C cross-couplings.118 Further studies on how reducing conditions and redox-active ligands alter fundamental organometallic steps could enable many new transformations.

AUTHOR INFORMATION

Corresponding Author
*dweix@wisc.edu

Author Contributions

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

ASSOCIATED CONTENT

Supporting Information

Additional tables of data, full experimental details, calculation details and coordinates, characterization data and copies of NMR spectra.

ACKNOWLEDGMENT

We thank Dr. Heike Hofstetter (UW-Madison CIC) for assistance with EPR experiments, Colleen Chernowsky and Prof. Zach Wickens (UW-Madison) for assistance with the divided cell experiments, and Prof. Shannon Stahl for helpful discussions. We thank Joe Barendt and Chiral Technologies for the kind donation of achiral SFC columns used in this work. Analytical data were obtained from the CENTC Elemental Analysis Facility at the University of Rochester, funded by NSF CHE-0650456. MJT and JFB thank the U.S. Department of Energy, Chemical Sciences, Geosciences, and Biosciences Division, Office of Basic Energy Sciences, Office of Science (DE-SC0021021). This work was supported by the NIH (R01GM097243 to DJW). Instrumentation in the PBCIC was supported by NIH S10OD020022, NSF CHE-1048642; NIH S10OD012245, and a generous gift from P. J. and M. M. Bender.

REFERENCES


Due to the importance of prostaglandins, versatile, advanced intermediates, such as the Corey lactone, are commercially available. This comparison does not take into account the considerable and excellent work done in this and related areas of prostaglandin synthesis. See the following references and citations within: (a) Coulthard, G.; Erb, W.; Aggarwal, V. K. Stereocatalytically Organocatalytic Synthesis of Prostaglandin PGF2α in Seven Steps. Nature 2012, 489, 278–281. (b) Peng, H.; Chen, F.-E. Recent Advances in Asymmetric Total Synthesis of Prostaglandins. Org. Biomol. Chem. 2017, 15, 6281–6301.

TOC Graphic