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

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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$^{\bullet-}$)Ni^{I} species activates the C–C bond via a concerted asynchronous ring-opening transition state. The resulting alkylnickel(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 D_1.

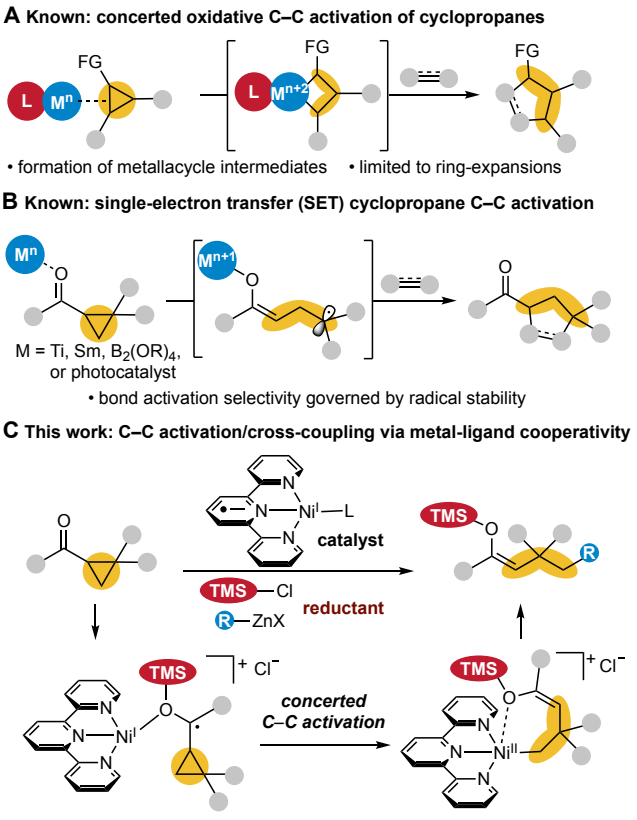
Introduction

Like well-known fragmentations and rearrangements,[1] the selective difunctionalization of C(sp^3)–C(sp^3) 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,[2,3] 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).[4,5–8] 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)[14–25] involve carbon-centered radical intermediates and often provide complementary selectivity to polar mechanisms.[24,26] Like polar reactions, transformations relying on photocatalytic[14–16] or metal-catalyzed[19–22,25] 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).[27,28] Because Me_3Si^+ (TMS^+) activation of the carbonyl is required for this step, the resulting C–C activation / cross-

Scheme 1. Mechanisms of Cyclopropyl Ketone C–C Activation.

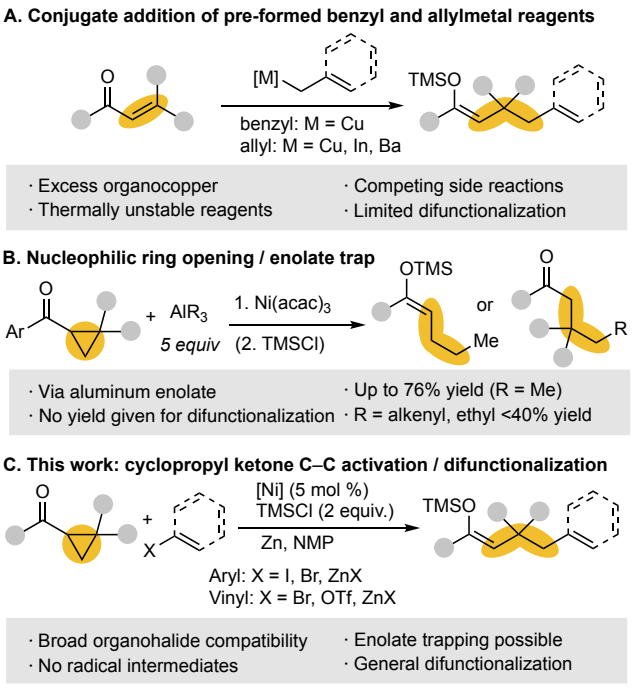


coupling reactions result in regio- and stereo-specific functionalization of both carbons (via cross-coupling and silyl enol ether formation) instead of monofunctionalization. By taking advantage of advances in cyclopropyl ketone synthesis, these new reactions allow for access to intermediates that are 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[29–35] 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).[36–38] Translation of this reactivity to catalytic manifolds, while promising, is currently limited in scope to simple benzylic nucleophiles and cyclic enones.[39] Similarly, conjugate allylation of enones with organometallic reagents (Cu,[40–42] In,[43,44] Ba[45]) is substrate controlled, affording mixtures of 1,2- and 1,4-addition products. Selectivity is further complicated using 1,3-disubstituted allyl reagents due to competing α- and γ-addition.[40,41] Notable advances in selective conjugate allylations using allyl boronic ester nucleophiles have been reported by Morken[46,47] and Jarvo,[48] but these reactions require dialkylidene ketones and α,β-unsaturated *N*-acyl pyrroles, respectively. Hosomi-Sakurai-type allylations afford 1,4-addition products with high selectivity, but typically require stoichiometric strong Lewis acids (e.g., $TiCl_4$), organotin reagents, or are only applicable to cyclic substrates.[49–52] Photoredox Giese reactions[53] allow access to conjugate benzylation products, but do not allow for difunctionalization.[54]. 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.[55,56]

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



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 stereocontrol[66] and the resulting silyl enol ethers would allow for a variety of subsequent C–C, C–O, and C–N bond forming transformations.[67–73] However, while the ring-opening *monofunctionlization* of cyclopropyl ketones has strong precedent[13,74] 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 reactions[9–13] and only couple with alkyl radicals to form monofunctionalized products.[75,76] Other mechanistic approaches, such as photoredox and metalloradical ring-opening,[19–22] 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).[13] This work reported that aluminum enolates formed from nickel-catalyzed nucleophilic opening of phenyl cyclopropyl ketone with $AlMe_3$ could be subsequently trapped by TMS-Cl or an aldehyde (to form an aldol product). Perhaps due to the poor nucleophilicity of alkylnickel species, ethyl and vinyl transfer afforded <40% yield and no follow-up studies have been reported.

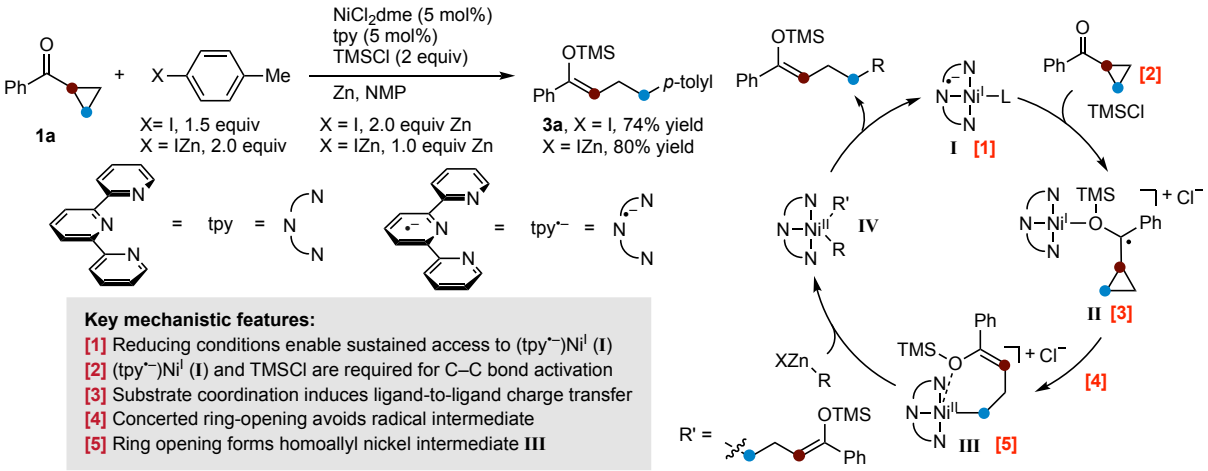
In contrast to monodenate, electron-rich ligands, or "ligandless" nickel complexes, the use of redox-active bi- and tridentate *N*-donor ligands in nickel catalysis[77–81] has been less studied for C–C bond activation. It has been demonstrated, however, that redox-active ligands can enable new reactivity at metal centers,[82–85] and change the mechanism of oxidative addition for alkyl halides.[86] Indeed, nickel terpyridine complexes have been reported to accomplish challenging C–N oxidative additions.[87] 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 (TMSCl) with phenyl cyclopropyl ketone (**1a**) to form acyclic silyl enol ether cross-coupled product (**3a**) (Scheme 3). While catalysts derived from a variety of polypyridine ligands provided measurable product, terpyridine (tpy) was the most effective, affording **3a** in 80% yield and >95:5 *Z*:*E* stereoselectivity (Figure S1). Reactions performed in the presence of a substoichiometric 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$^{\bullet-}$)Ni^{I} intermediate by other [Ni^{II}] 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$^{\bullet-}$)Ni^{I} intermediate is required ([**2**] in Scheme 3), and strongly

Scheme 3. Unified mechanistic proposal for cyclopropyl ketone C–C activation/cross-coupling.[a]



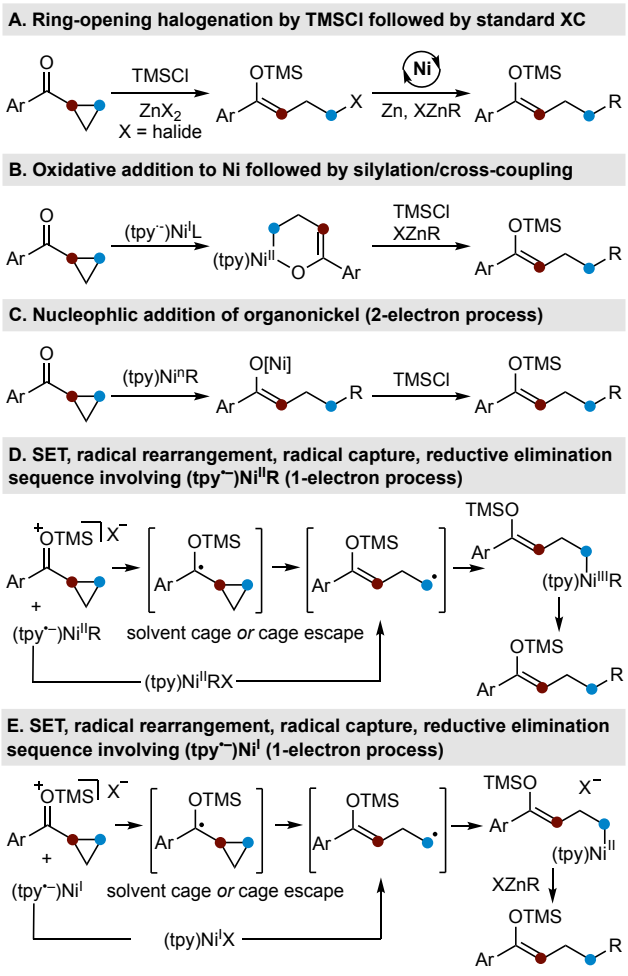
support the proposed C–C activation step ([**3**] and [**4**] in Scheme 3). Initial two-electron reduction of the $(tpy)Ni^{II}Cl_2$ pre-catalyst by Zn metal affords a neutral nickel intermediate with the proposed electronic structure $(tpy^{\bullet-})Ni^{I}L$ (**I-NMP**, L = *N*-methylpyrrolidone (NMP)).[86] 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 $(tpy^{\bullet-})$ to afford partial ketyl-radical character (~50% spin-density) at the carbonyl carbon C_α. **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 Ni^{II} 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 4A-E).

(A) Uncatalyzed silylative ring-opening halogenation of the cyclopropyl ketone by $TMSX/ZnX_2$ to form a γ-halogenated silyl enol ether[88–92] followed by nickel catalyzed Negishi coupling.[77,79–81,93] Potent silyl Lewis acids, such as TMSI, 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 alkyl iodides, 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 nickeladihydropyran intermediate,[9–12] which then reacts with TMSCl and organozinc halide to form product. Nickeladihydropyran intermediates are known with different ligands (monodentate phosphines and NHC ligands), but they have not been demonstrated for silylative functionalization. Two recent reports[75,76] suggest that these intermediates can be protonated and coupled with alkyl halides.

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



(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 $(alkyl)_2Cu(CN)Li_2{\bullet}BF_3$[74] and Fujisawa[13] demonstrated this mechanism for a Ni-catalyzed addition of $AlMe_3$ to cyclopropyl ketones. A combination of TMSCl and ZnX_2 could serve

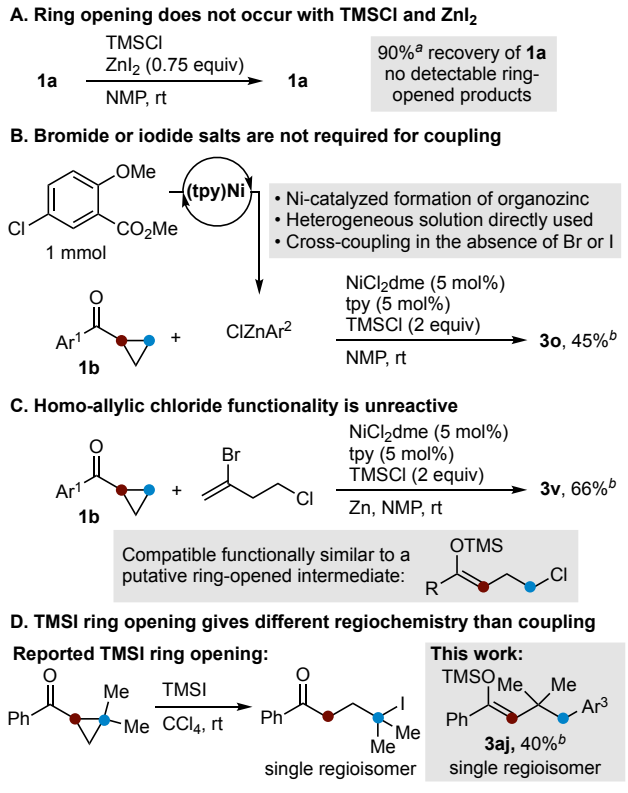
as a Lewis acid,[95–98] which was required in the literature precedents to activate the cyclopropyl ketones toward ring opening rather than 1,2-addition.

(D) Single-electron transfer from $(tpy^{\bullet-})Ni^{II}R$ to a silyloxonium intermediate resulting in an α-silyloxy radical that can rearrange to a primary radical before it is captured by $(tpy)Ni^{II}R$ with subsequent C–C bond formation from $(tpy)Ni^{III}(R)(CH_2CH_2CH{=}C(OTMS)R)$.[77]

(E) Similar to (D), $(tpy^{\bullet-})Ni^{I}Cl$ could transfer an electron to a silyloxonium intermediate resulting in an α-silyloxy radical that can rearrange to a primary radical before capture by $(tpy)Ni^{I}Cl$ to form $(tpy)Ni^{II}(Cl)(CH_2CH_2CH{=}C(OTMS)R)$. 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_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_2 is not a source of nucleophilic iodide, nor does it participate in halide metathesis with TMSCl to liberate TMSI and ZnClI.[99] Similar results were observed employing more Lewis acidic $ZnCl_2$ – even in the presence of low-valent $(tpy)Ni^{I}X$ (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 5D).[88–92]

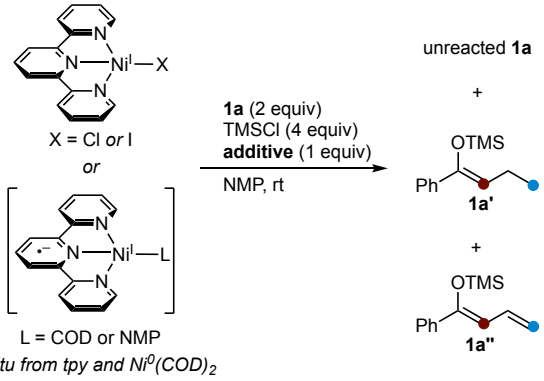
Scheme 5. Experiments that Rule Out Ring Opening Halogenation Mechanism.



[a]GC yield. [b]Isolated yield followed chromatographic purification. Ar^1 = 4-anisyl; Ar^2 = 3-carboxylmethyl-4-methoxyphenyl; Ar^3 = 4-tolyl.

Exclusion of mechanisms involving nickeladihydropyran intermediates (Scheme 4B). While oxidative addition of cyclopropyl ketones to nickel complexes is fast with phosphine and NHC ligands, we observed no reaction of $(tpy^{\bullet-})Ni^{I}$ (**I**) or $(tpy)Ni^{I}X$ (X = I, Cl) with cyclopropyl ketones (Table 1, entries 2–5). A combination of $(tpy^{\bullet-})Ni^{I}$ (**I**), $ZnCl_2$, and TMSCl is required to consume **1a**, forming detectable ring-opened products **1a'** and **1a''** (Table 1, entry 1 and entry 6). The difference in reactivity between terpyridine-ligated and monophosphine- or NHC-ligated nickel(0) complexes is a result of differences in steric environment around the nickel center and changes to the electronic configuration of the nickel complex. Nickel(0) complexes of NHC or phosphine ligands are S=0 with a nickel *d*-orbital as the HOMO.[100–102] In contrast, terpyridine complexes of nickel(0) are better described as terpyridine radical anions bound to nickel(I) (Figure 1 and Figure S18). The electronic ground state has an S=1 spin state with the tpy π* SOMO being significantly higher in energy than the $d_{x^2-y^2}$ SOMO (*vide infra*). This configuration attenuates reactivity in polar processes because the electron-density is delocalized away from the nickel center. A related study using an analogous (tpy)Ni complex arrived at the same calculated electronic structure and showed experimentally that this species reacts via SET from the ligand-based radical anion and not as a Ni-based nucleophile – even with reactive primary alkyl iodides.[86]

Table 1. Experiments that Rule Out Nickeladihydropyran Intermediates.[a]

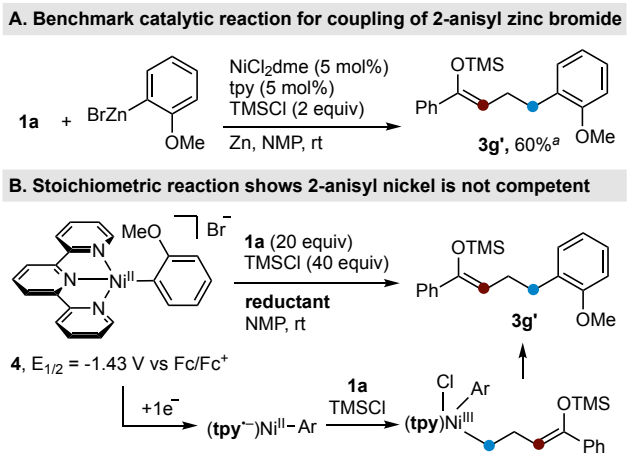


entry	[Ni]	additive	1a (%)	1a' (%)	1a'' (%)
1	$(tpy^{\bullet-})Ni^{I}(COD)$	$ZnCl_2$	1	10	33
2	$(tpy^{\bullet-})Ni^{I}(COD)$	-	48	3	4
3[b]	$(tpy^{\bullet-})Ni^{I}(COD)$	$ZnCl_2$	85	0	0
4	$(tpy)Ni^{I}I$	$ZnCl_2$	88	0	0
5	$(tpy)Ni^{I}Cl$	$ZnCl_2$	90	0	0
6[c]	$(tpy)Ni^{I}Cl$	Zn	42	12	12

[a]GC Yields. Unless otherwise stated, yields are based on the amount of [Ni] and account for 1 equiv excess of **1a**. [b]TMSCl omitted. [c]Yields calculated based on the amount of **1a** instead of [Ni], 1:1 (tpy)Ni^{I}Cl:Zn.

Exclusion of nucleophilic addition (Scheme 4C) and SET ring opening (Scheme 4D) by organonickel complexes. The reaction of pre-formed (tpy)NiI^{II}(2-anisyl)Br (**4**) with cyclopropyl ketone **1a** with or without a variety of reducing agents did not produce more than 8% cross-coupled product **3g'** (Scheme 6B, entries 1–6). Catalytic reactions of 2-anisyl zinc reagents, however, furnished product **3g'** in 60% yield (Scheme 6A). We also noted that the stereochemistry of the products in this paper are ≥95% *Z* while the single published nucleophilic ring opening with $AlMe_3$ afforded a product with *E* configuration.[13] These studies also rule out radical reactions involving (tpy$^{\bullet-}$)Ni^{II}(2-anisyl) (Scheme 4D).[103]

Scheme 6. Experiments that Rule Out Nucleophilic or SET Ring Opening by Organonickel Complexes.



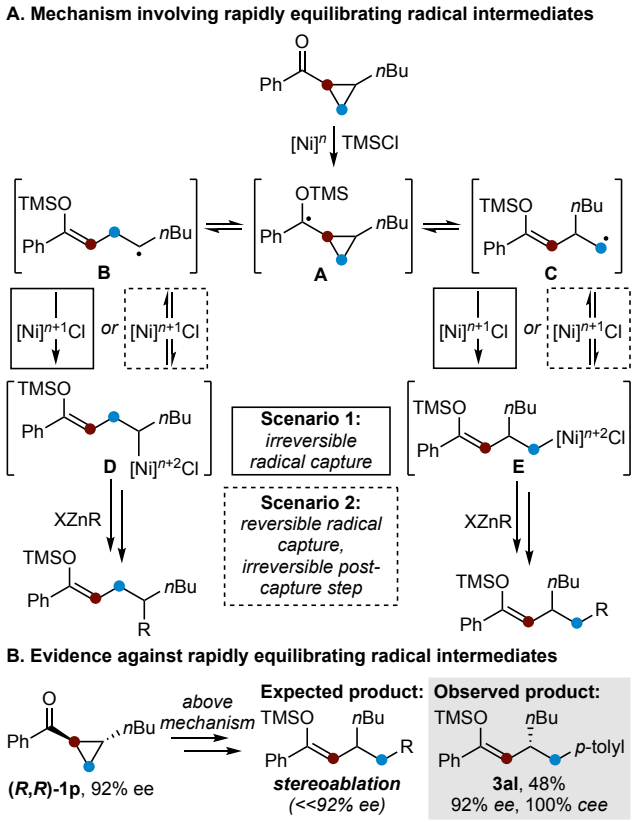
Entry	Reductant	3g' (%)[b]
1	Zn ($E_{1/2}$ ~ -1.5 V vs Fc/Fc$^+$)[104]	6
2	Mn ($E_{1/2}$ ~ -2.0 V vs Fc/Fc$^+$)[104]	0
3	TDAE ($E_{1/2}$ = -1.11 V vs Fc/Fc$^+$)[105]	0
4	Cp*$_2$Co ($E_{1/2}$ = -1.91 V vs Fc/Fc$^+$)[106]	0
5	Cp*$_2$Co, $ZnCl_2$	8
6	no reductant	0

[a]Isolated yield following chromatographic purification. [b]GC yield.

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-α-phenylnitrone (PBN).[19,107] The catalytic reaction of **1a** with 4-iodotoluene 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-disubsituted cyclopropanes, where cross-coupling occurs at the least-substituted carbon (e.g. **3ai**, **3aj**, and **3ak** in Scheme 9, *vide infra*), could be explained by a caged radical process operating under Curtin-Hammett[108] 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, reversible ring opening and fast, reversible radical capture. If transmetallation or reductive elimination from **E** is faster than from **D**, then the less substituted product could also be favored.[109] 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 reversible ring opening (Scheme 7B). *We observe complete retention of configuration (**3al,** 100% cee), ruling out these pathways.*

Scheme 7. Evidence Against Mechanisms Involving Rapidly Equilibrating Radical Intermediates.[a]



[a]Isolated yield following chromatographic purification.

Evidence for the proposed mechanism. While the results of our mechanistic studies are inconsistent with the hypotheses in Scheme 4, they are consistent with our proposed mechanism (Scheme 3). Our experimental studies are consistent with C–C activation by (tpy$^{\bullet-}$)Ni^{I} (**I**) (Table 1, entries 1, 2, and 6) and allow us to rule out the intermediacy of (tpy)Ni^{I}X (X = Cl, I) as the species responsible for C–C bond scission because negligible consumption of **1a** is observed in stoichiometric studies (Table 1, entries 4 and 5, Figure S6).

Furthermore, we observed that cyclopropane C–C activation can be induced by (tpy)Ni^{I}Cl in the presence of Zn, indicating that Zn can generate **I-NMP** under conditions analogous to the catalytic reaction (Table 1, entry 6). Regardless of how the complexes were generated (pre-formed or in situ via reductants), only **I-NMP** reacted to form products derived from ring-opening silylation (**1a'** and **1a''**) (Table 1, entries 1, 2, and 6).

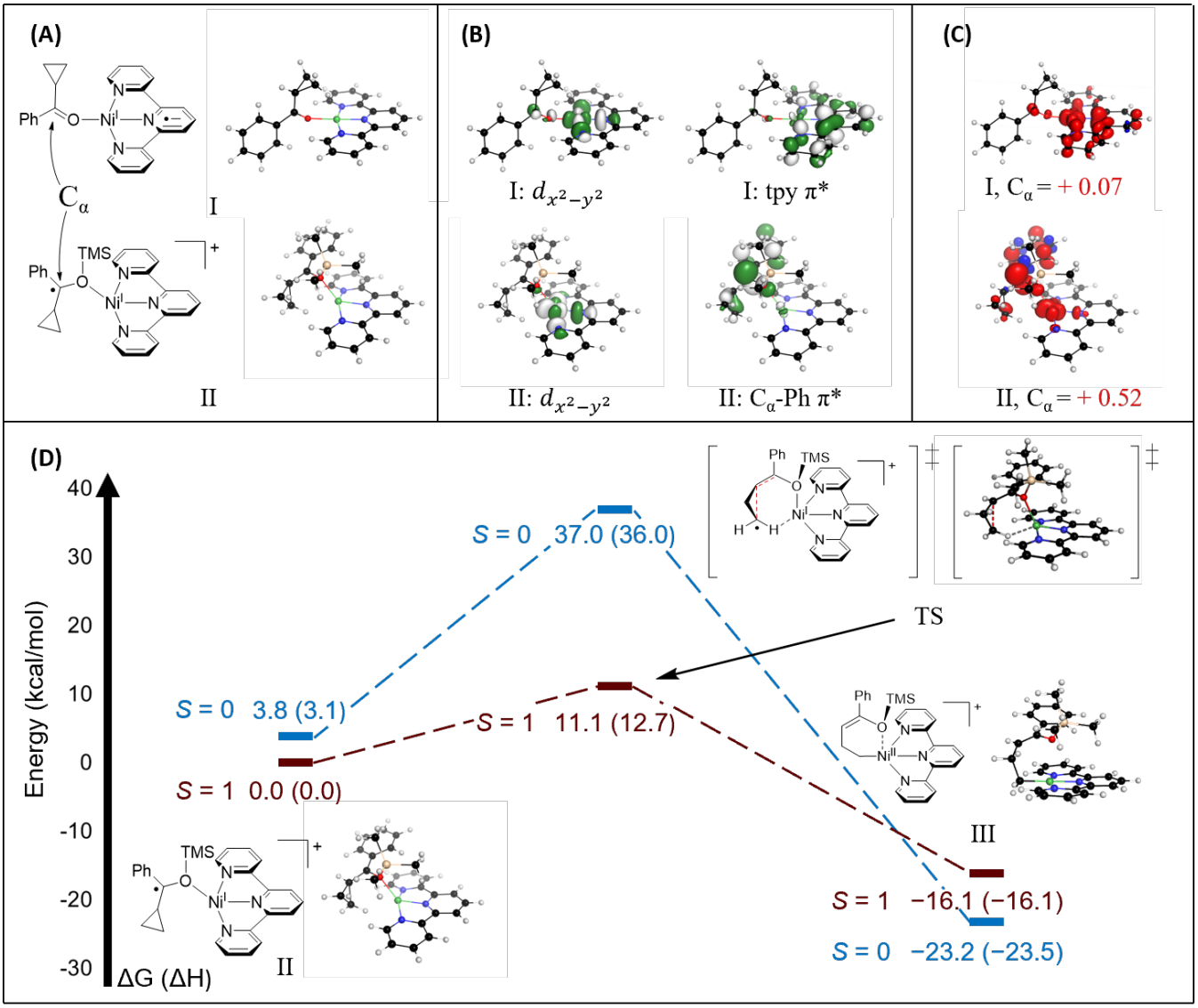


Figure 1. DFT analysis of the Ni-mediated cyclopropane C–C activation step. (A) Chemdraw representations (left) and optimized structures (right) for cyclopropylketone (CPK) bound complex (**I-CPK**) and *O*-TMS silylcarboxonium ion (**II**). (B) Singly-occupied molecular orbitals (SOMOs) of **I-CPK** and **II** show occupation of the Ni $d_{x^2-y^2}$ orbital and a π^*-symmetry orbital localized to either terpyridine as in **I-CPK** or bound substrate as in **II**. (C) Spin-density plots show significant spin population on the carbonyl carbon (C_α) for **II**, but not **I-CPK**. (D) Reaction coordinate diagram for conversion of **II** to C–C activated product **III** on both the singlet and triplet energy surfaces.

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, ZnX_2, 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).[110] Binding of the silyl carboxonium ion to **I** confers significant spin density (i.e., partial radical character) from the $tpy^{\bullet-}$ ligand to the p_z orbital of the carbonyl carbon (Figure 1A–C). While free cyclopropylmethyl radicals undergo rapid radical ring-opening processes ($k_{rearrangement} \sim 10^7\ s^{-1}$),[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

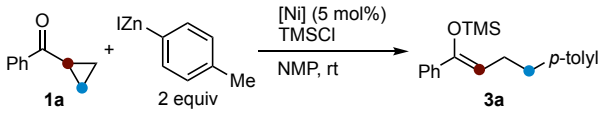
substrate to facilitate ring opening. In this case, the redox-active ligand and triplet ground-state allows access to a lower-energy, asynchronous pathway.

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 intersystem 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).[19] 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[11,12] or *N*-heterocyclic carbene ligands,[10,12] **III** has a weakly-bound oxygen ligand and can dissociate to form a square-planar, cationic nickel complex with open coordination sites for transmetallation.[112] Following transmetalation with organozinc reagents,[113] reductive elimination from the five-coordinate (tpy)$Ni^{II}R_2$ should be fast.[114]

Role of Zn reductant in the redox-neutral cross-coupling reaction. Considering the ubiquity of (tpy)Ni complexes in cross-coupling, and reports on the high reactivity of $Ni^0(cod)_2$ with tpy in oxidative addition,[87] 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 fast, unfavorable speciation. We confirmed that ($tpy^{\bullet-}$)Ni^{II}(*p*-tolyl) is the major observable nickel species obtained from the reduction of (tpy)$Ni^{II}Cl_2$ by (*p*-tolyl)ZnI (Figure S9–S11). DFT studies indicate that comproportionation to form (tpy)$Ni^{I}X$ from **I-NMP** and (tpy)$Ni^{II}X_2$ (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 ($tpy^{\bullet-}$)Ni^{II}(2-anisyl) is fast and highly favorable (Figure S12, Figure S23). Together, these results explain why maintaining a productive ($tpy^{\bullet-}$)Ni^{I} 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 unsustainable oxidation states in enzymatic catalysis, for example the recovery of off-cycle cobalt(II) to cobalt(I) in methionine synthase by methionine synthase reductase.[115]

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. Fc/Fc^+)[116,117] or electrochemical (-1.36 V vs. Fc/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,[118] to the best of our knowledge this is the first example of this strategy applied to a redox neutral C–C cross-couplings.

Table 2. Impact of an external reducing potential on the redox neutral cross-coupling of 1a with IZn(*p*-tolyl).[a]



Entry	[Ni]	Additional Conditions	3g' (%)
1	(tpy)$Ni^{II}Cl_2$	none	24
2[b]	(tpy)$Ni^{II}Cl_2$	none	33
3	(tpy)$Ni^{I}I$	none	12
4	($tpy^{\bullet-}$)Ni^{I}(COD)	none	21
5	(tpy)$Ni^{II}Cl_2$	$ZnCl_2$ (10 mol%)	26
6	(tpy)$Ni^{II}Cl_2$	Zn (10 mol%)	79
7	(tpy)$Ni^{II}Cl_2$	Zn (10 mol%)	75
8	(tpy)$Ni^{I}I$	Zn (10 mol%)	66
9	($tpy^{\bullet-}$)Ni^{I}(COD)	Zn (10 mol%)	61
10[c]	(tpy)$Ni^{II}Cl_2$	Divided cell, -1.36 V	74
11[c]	(tpy)$Ni^{II}Cl_2$	Divided cell, 0 V	28
12[c]	(tpy)$Ni^{I}I$	Divided cell, -1.36 V	52

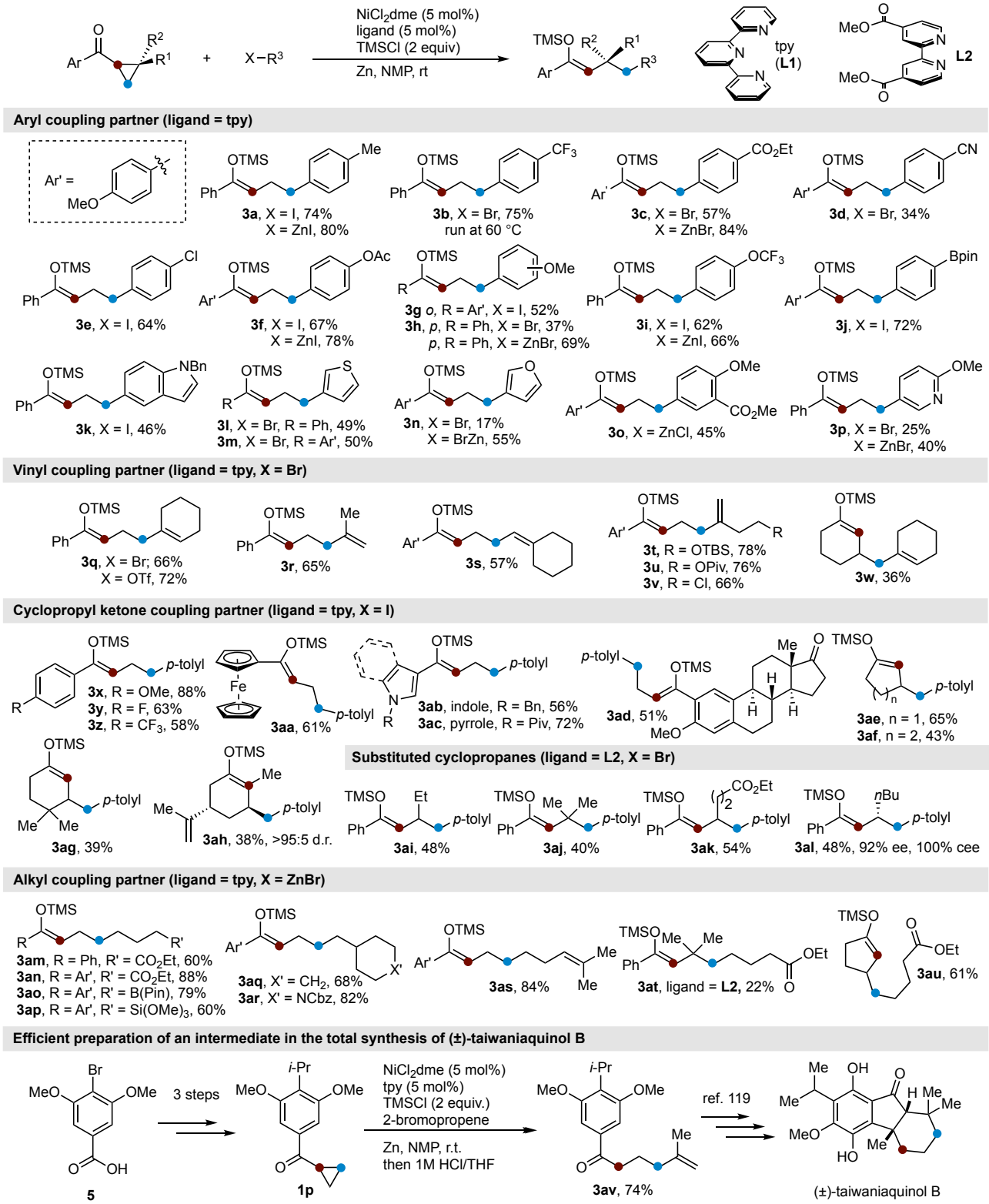
[a]Yields are corrected GC yields vs. dodecane internal standard. [b]Catalyst stirred over 2 equiv activated Zn in NMP, then filtered prior to use. [c]Potential vs. Fc/Fc^+, sacrificial Zn anode.

Scope, applications to natural product synthesis, and silyl enol ether derivatization. In developing synthetic applications of this ring-opening reaction, 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[119] process, operationally like a cross-electrophile coupling,[78] 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)$Ni^{II}Cl_2$ 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 β-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-disubsituted cyclopropyl ketone afforded the cross-coupled product **3al** 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.



[a]Isolated yields after purification. For all acyclic TMS-enol ethers stereochemistry was assigned using NOE correlations.

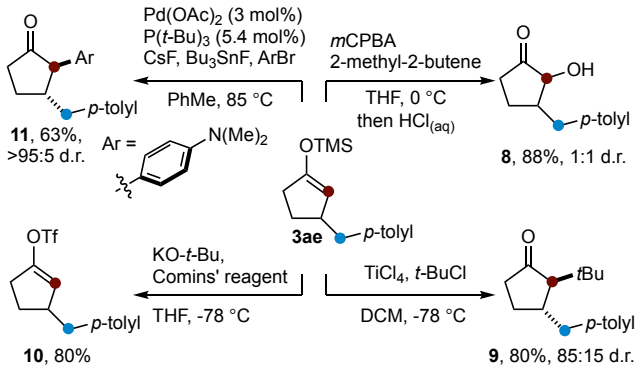
Asymmetric conjugate benzylation has only been accomplished using photoredox catalysis employing coordinating auxiliaries, chiral-at-metal photocatalysts, Hantzch ester or BF_3K radical precursors, and the resulting enolate cannot be trapped, thus precluding difunctionalization.[120–122]

Besides arylzinc reagents, alkenylzincs could be readily substituted as coupling partners (**3q–w**), thus accessing chemical space usually reserved for conjugate allylation. 1,4-Addition of allylic organometallics to acylic enones is notoriously unselective, often yielding substantial amounts of 1,2-addition adducts.[41–45] 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 γ-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 arylzincs and 2° alkyl zinc reagents, coupled in low yield under these conditions. Comparison with related ring-opening alkylations that proceed via nickeladihydropyran (Scheme 4C), reported after our initial disclosure of these results,[27,75,76] 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.[75,76] We anticipate that future studies will shed further light on how these differences arise and how existing limitations might be overcome.

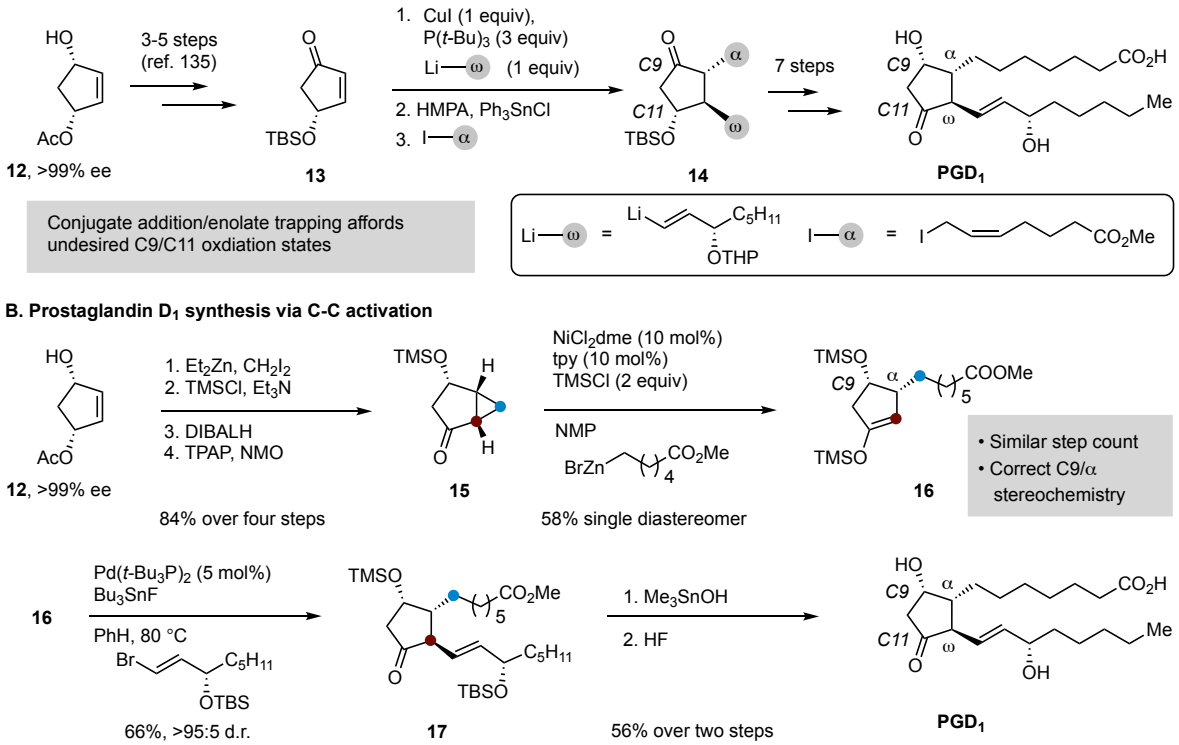
Even without utilization of the silyl enol ether, this method can be helpful in complex molecule synthesis. For example, in Fishlock's (±)-taiwaniaquinol B synthesis we were able to decrease the step count to intermediate **3av** by three steps (out of 7).[29] Our four-step route utilized a different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

Scheme 9. Derivitizations of the TMS-enol-ether functionality.[a]



[a]Isolated yields following chromatographic purification.

Scheme 10. Total synthesis of Prostaglandin D_1 and comparison of C-C activation approach with conjugate addition approach.[a]



[a]See Supporting Information for full experimental details. Yields are isolated yields after purification.

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**),[123] conversion to the corresponding enol triflate **10** (itself another versatile intermediate),[124] and Pd-catalyzed α-arylation (**11**)[67] (Scheme 9). In each example, the products were

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 groups[67,126–132] 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 D_1 (PGD_1) (Scheme 10). Conjugate addition approaches to PGD_1 start with enone **13**,[136,137] an intermediate commonly prepared from **12** in 3-5 steps (Scheme 10A).[138] Because this results in the wrong oxidation state at C9 and C11, seven further steps are required to convert **14** to PGD_1. 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*-stereochemical configuration to the adjacent C9 TMS-protected hydroxyl with concomitant formation of a TMS-enol-ether. The ω-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 PGD_1 in eight total steps and 18% overall yield. This is 3-5 steps shorter than previously established conjugate addition approaches to PGD_1.[139]

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 previously[9–12] and addresses limitations in conjugate additions reactions using benzylic[36–38] 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.

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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.

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