Ligand-Metal Cooperation Enables C–C Activation Cross-Coupling Reactivity 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 linear 3-carbon fragments, but C–C activation / difunctionalization reactions of this type 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 mixture of experimental and theoretical studies 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.

Introduction

The selective activation of $C(sp^3)$–$C(sp^3)$ bonds by transition metals has the potential to be a powerful strategic tool in organic synthesis, but presents considerable fundamental challenges. Like well-known fragmentations and rearrangements,[1] catalytic C–C bond cleavage coupled with the formation of new C–C bonds can enable novel retrosynthetic strategies based on converting an accessible carbon skeleton into an elusive scaffold. The underlying challenge of this approach, even for activated substrates like cyclopropyl ketones,[2,3] is selective activation of the target C–C bond in the presence of more reactive functional groups to create intermediates that are suitable for further derivatization.

The focus to date has been to use electron-rich, low-coordinate metal centers with strong σ-donor ligands to overcome the low reactivity of C–C bonds towards oxidative addition.[4] This strategy has enabled the discovery of many new reactions, such as ring expansions of cyclopropyl ketones with π systems (Figure 1A), but broadening the reactivity of the metallacyclic intermediates derived from cyclopropane oxidative addition remains challenging.[5,6] For example, while nickel-catalyzed "cut-and-sew" reactions of cyclopropyl ketones with alkenes and alkynes has transformed how cyclopentanes are synthesized,[7–10] difunctionalization to acyclic products has been elusive.[11]

Single electron transfer (SET) approaches enable a mechanistically distinct avenue for cyclopropyl ketone activation based on radical rearrangements (Figure 1B).[12–22] Bond activation selectivity in these systems is dictated by the stability of the resulting ring-opened, C–centered radical. Accordingly, selectivity in SET-mediated pathways is often different from polar metal-catalyzed processes, which favor the most accessible bond.[22,23] Despite operating by a distinct mechanism, transformations relying on photocatalytic[12–14] or metal-catalyzed[17–20] SET cyclopropyl ketone activation are also commonly limited to ring expansions with π components. Although elaboration of cyclopropyl ketones to form acyclic products using SET has seen recent developments, transformations are limited to cyanation[22] or reduction.[16]

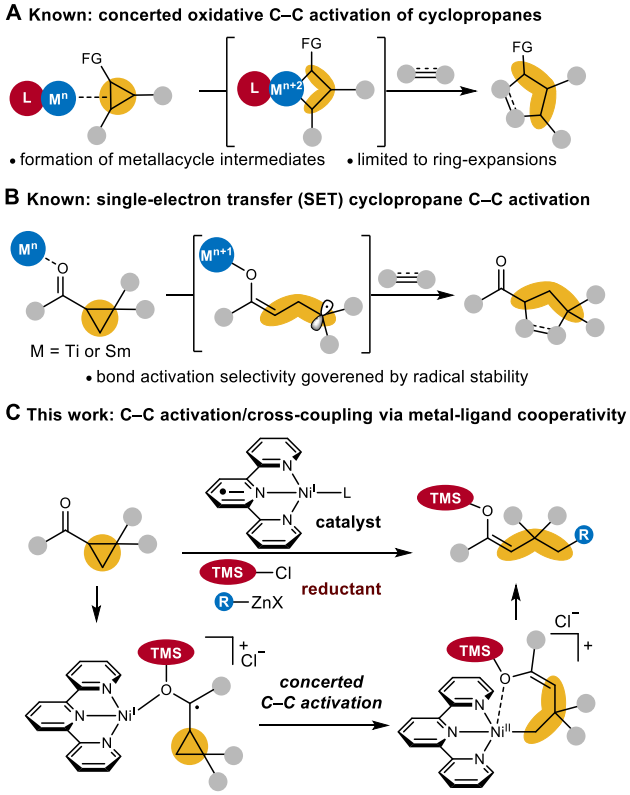


Figure 1. Cyclopropyl ketone C–C activation/cross-coupling.

We show here a new, cooperative mechanism for cyclopropane C–C activation that includes aspects of both previous mechanisms: charge transfer from the terpyridine ligand to the substrate followed by concerted asynchronous ring-opening and Ni–C bond formation (Figure 1C). Early in reaction development we recognized the ligands that promote concerted nickel(0) oxidative addition of cyclopropyl ketones, such as monodentate phosphines and *N*-heterocyclic carbenes, form metallacyclic intermediates that are unreactive for Negishi cross-coupling reactions.[7–11] On the other

hand, while it is known that bi- and tridentate *N*-donor ligands promote cross-coupling reactions with alkyl halides to form $C(sp^2)$–$C(sp^3)$ and $C(sp^3)$–$C(sp^3)$ bonds,[24–28] these ligands have not been reported for C–C bond activation reactions. Building upon studies showing redox-active ligands can enable new reactivity at metal centers,[29–32] our solution to this long-standing challenge relies upon forcing a well-known cross-coupling catalyst, nickel terpyridine ((tpy)Ni), into a reactive, reduced state, that turns on C–C activation activity while retaining cross-coupling activity. This approach relies on metal-ligand cooperativity between a nickel metal center and a multidentate π-acceptor ligand capable of storing significant spin-density. Redox changes at both the ligand and metal center enable concerted C–C oxidative addition in a manner that is distinct from concerted mechanisms involving redox changes only at the metal center,[7–10,23] or SET/radical fragmentation.[12–22] In this new mechanism, upon substrate binding, charge transfer from the terpyridine ligand to the substrate π* orbital "turns on" subsequent C–C activation by weakening the C–C bond. In contrast to metalloradical ring-opening reactions,[17–20] this approach avoids a free-radical intermediate and results in a functionalized alkylnickel intermediate suitable for cross-coupling with organozinc reagents.

This C–C activation/cross-coupling approach could have immediate synthetic impact if applied to the ring-opening of cyclopropyl ketones to versatile, substituted acyclic silyl enol ethers (Figure 2). This approach leverages decades of advances that have made substituted, stereodefined cyclopropyl ketones readily accessible from a variety of accessible starting materials.[33–41] General approaches to open these stereodefined rings into linear fragments could address challenges in acyclic stereocontrol.[42] Finally, the immediate versatility of C–C activation/1,3-difunctionalization is maximized if one site could be further diversified by a collection of reactions, such as with a silyl enol ether, allowing subsequent C–C, C–O, and C–N bond forming transformations.[43–49]

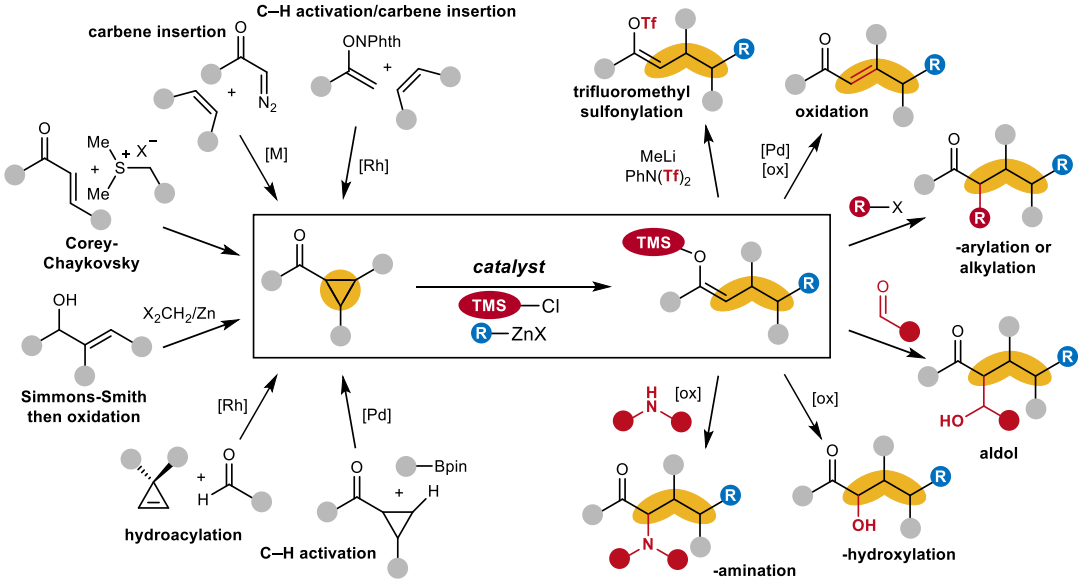
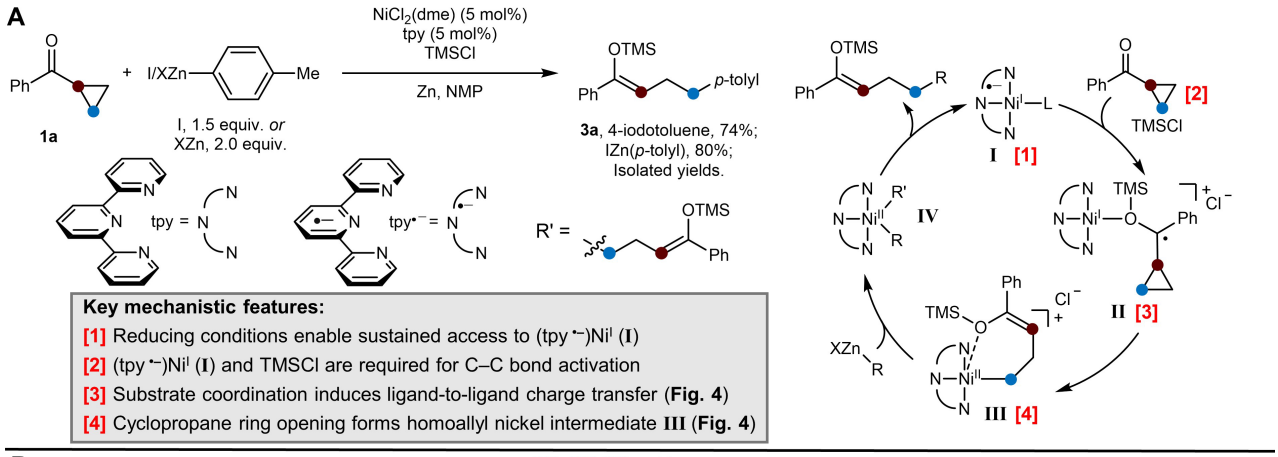


Figure 2. C–C Activation and cross-coupling allows the use of readily accessible cyclopropyl ketones as linear α,γ-difunctionalized butanone equvalents. The silyl enol ether is a versatile handle that can be used for C–C, C–O, and C–N bond formation.

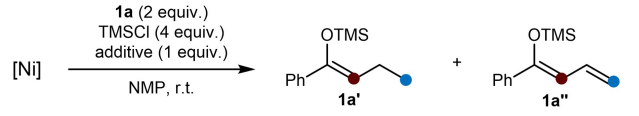
Results and Discussion

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 the acyclic silyl enol ether cross-coupled product (**3a**) (Figure 3A). 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, gave superior outcomes (Figure S11). 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 (*vide infra*).

A collection of experimental and theoretical studies (Figure 3) allow us to propose a mechanism for this new reaction (Figure 3A), explain the need for Zn metal (flake, -325 mesh) reductant ([**1**] in Figure 3), show that a $(tpy^{\bullet-})Ni^{I}$ intermediate is required ([**2**] in Figure 3), and strongly support the proposed C–C activation step ([**3**] and [**4**] in Figure 3). Initial 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)).[50] 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 4). 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.

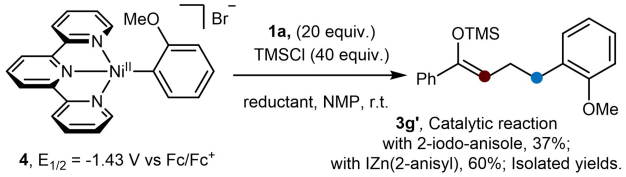


B (tpy•−)Ni^I activates C–C bonds, (tpy)Ni^IX is unreactive [1], [2], [4]



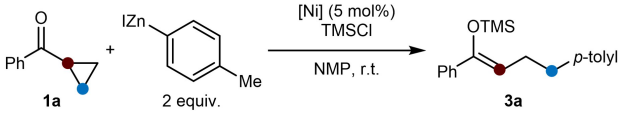
Entry	[Ni]	Additive	Time (h)	1a (%)	1a' (%)	1a'' (%)
1[a]	(tpy•−)Ni^I(COD)	$ZnCl_2$	3	1	10	33
2[a]	(tpy•−)Ni^I(COD)	-	3	48	3	4
3[a,b]	(tpy•−)Ni^I(COD)	$ZnCl_2$	3	85	0	0
4[a]	(tpy)Ni^II	$ZnCl_2$	3	88	0	0
5[a]	(tpy)Ni^ICl	$ZnCl_2$	16	90	0	0
6[c]	(tpy)Ni^ICl	Zn	16	42	12	12

C (tpy•−)Ni^IIAr does not react to form product [2]



Entry	Reductant	3g' (%)
1	Zn	6
2	Mn	0
3	TDAE	0
4	Cp^*_2Co	0
5	Cp^*_2Co, $ZnCl_2$	8

D Reductant is still required in a redox-neutral process [1]



Entry	[Ni]	Additional Conditions	3a (%)
1	(tpy)Ni^IICl2	-	24
2[d]	(tpy)Ni^IICl2	-	33
3	(tpy)Ni^II	-	12
4	(tpy•−)Ni^I(COD)	-	21
5	(tpy)Ni^IICl2	$ZnCl_2$ (10 mol%)	26
6	(tpy)Ni^IICl2	Zn (10 mol%)	79
7[d]	(tpy)Ni^IICl2	Zn (10 mol%)	75
8	(tpy)Ni^II	Zn (10 mol%)	66
9	(tpy•−)Ni^I(COD)	Zn (10 mol%)	61
10[e]	(tpy)Ni^IICl2	divided cell, -1.36 V	74
11[e]	(tpy)Ni^IICl2	divided cell, 0 V	28
12[e]	(tpy)Ni^II	divided cell, -1.36 V	52

Figure 3. Unified mechanistic proposal for cyclopropyl ketone C-C activation/cross-coupling. Unless otherwise stated, yields are calibrated GC yields vs. dodecane internal standard. [a]Yields account for 1 equiv. excess **1a**. [b]TMSCl omitted. [c]Yields calculated based on the amount of **1a** instead of [Ni]. [d]Catalyst stirred over 2 equiv. activated Zn in NMP, then filtered prior to use. [e]Voltage vs. Fc/Fc^+, sacrificial Zn anode.

First, our experimental studies are consistent with C–C activation by (tpy•−)Ni^I (**I**) and allow us to rule out the intermediacy of (tpy)Ni^IX (X = Cl, I) (Figure 3B, entries 1–5, Figure S9). Furthermore, we observed that cyclopropane C–C activation can be induced by (tpy)Ni^ICl in the presence of Zn, indicating that Zn can generate **I-NMP** under conditions analogous to the catalytic reaction (Figure 3B, 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''**). We separately verified that the reaction of (tpy•−)Ni^II(Ar), an intermediate, commonly invoked in nickel(I/III) Negishi cross-coupling reactions with organohalides, does not react with cyclopropyl ketone **1a** to form the cross-coupled product. (Figure 3C, Figure S10).[24,27]

The useful C–C bond activation reactivity of this reduced (tpy)Ni catalyst is a consequence of metal-ligand cooperativity. Consistent with studies by Vicic,[24,51] Chirik,[32] and Weighardt,[52] our DFT studies show that the (tpy)Ni catalyst system exhibits redox changes at both the metal and the ligand. These calculations predict a radical anion terpyridine ligand and formal nickel(I) oxidation state for neutral complexes with L-type ancillary ligands (Figure 4A–C, Figure S19, Figure S26–S28) [50]. In each case, a triplet ground state is favored with unpaired electrons in nickel $d_{x^2-y^2}$ and tpy π^* singly-occupied molecular orbitals (SOMOs). Ferromagnetic coupling of the unpaired

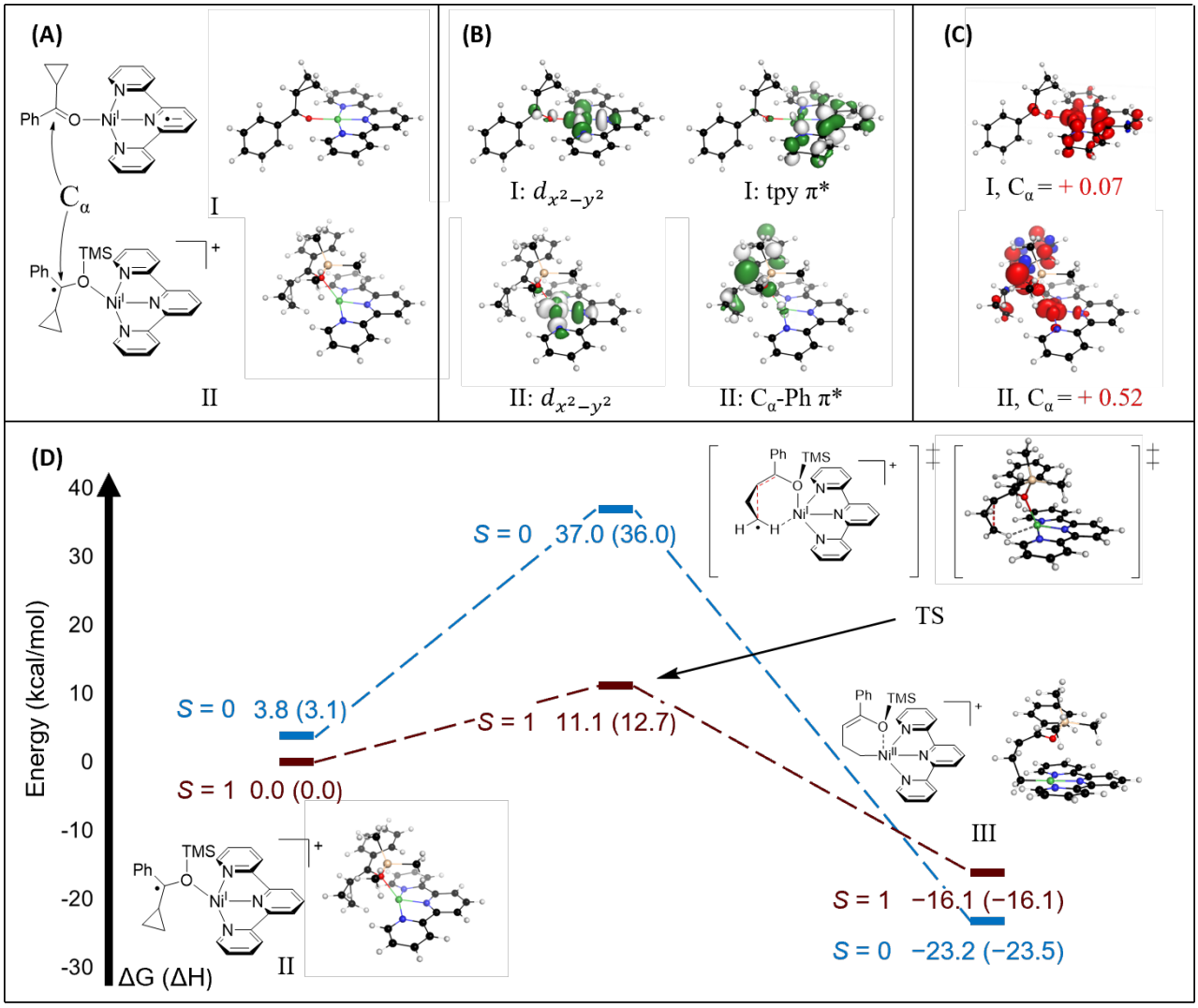


Figure. 4. DFT analysis of the Ni-mediated cyclopropane C–C activation step. (A) Chemdraw representations (left) and optimized structures (right) for cyclopropylketone (CPK) bound complex (**I-CPK**) and *O*-TMS silylcarboxonium ion (**II**). (B) Singly-occupied molecular orbitals (SOMOs) of **I-CPK** 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-density 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.

electrons to give an overall S = 1 spin state is consistent with the Goodenough-Kanamori rules, as the two SOMOs possess orthogonal symmetries.[53]

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,[54] 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 S6–S8). 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, ΔG = −20.6 kcal/mol) (Figure S25). 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 S24). 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 nickel(0) precatalyst (as in Figure 3D, entries 1–5). We note that in the natural world, 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.[55]

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 Figure 3D, 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 (Figure 3D, entries 6–10, 12). We found that either chemical (Zn, $E_{1/2}$ = −1.38 V vs. Fc/Fc^+)[56,57] 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).

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 4A–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 (Figure 3E, entries 1,3).

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 4D).[58] 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 4A–C). While free cyclopropylmethyl radicals undergo rapid radical ring-opening processes ($k_{rearrangement} \sim 10^7\ s^{-1}$),[59] the bound substrate of **II** performs sequential oxidative ring opening and Ni–C bond formation to yield the metallacycle species **III** (Figure 4D). 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 S20). Upon ring-opening, unpaired electron density grows more concentrated on the terminal carbon of the cleaved C-C bond (Figure S21). 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 bound substrate which could 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** (ΔG = −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 supplementary information section V for experimental details).[17] Stronger evidence for the absence of a radical intermediate can be found in the regioselectivity observed for 1,2-substituted cyclopropanes (**3ai**-**3ak** in Figure 5); the regiochemistry is the opposite observed in known metalloradical and free-radical reactions.[12–22] This coordination/rearrangement sequence also helps explain the observed *Z*-enol-ether geometry in the product (Figure S23). Moreover, the only example of a nickel-catalyzed ring-opening difunctionalization of **1a** with a trimethylaluminum nucleophile afforded the (*E*)-TMS-enol-ether in >95:5 selectivity, consistent with the different mechanisms proposed for the C–C activation steps.[11] Finally, unlike *C,O*-metallacycles formed with monophosphine[9,10] or *N*-heterocyclic carbene ligands,[8,10] **III** has a weakly-bound oxygen ligand and can dissociate to form a square-planar, cationic nickel complex with open coordination sites for transmetallation.[60] Following transmetalation with lithium-salt-free organozinc reagents,[61] reductive elimination from the five-coordinate $(tpy)Ni^{II}R_2$ should be fast.[62]

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 (Figure 5). The first is an auto-tandem process, operationally like a cross-electrophile coupling,[25] where aryl halides are converted in situ into arylzinc reagents by the same nickel catalyst that performs the C–C activation/cross-coupling (Figure S14–S17). 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 (Figure 5). Efficient 1,3-difunctionalization 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 bicycles 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**). While more hindered cyclopropyl ketones coupled in lower yield (**3ai**–**3ak**), 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**, **3aj**, and **3ak**, suggesting that ligand-nickel cooperative mechanisms might be general for a variety of catalysts.

Besides arylzinc reagents, alkenyl and alkyl zinc reagents both worked with minimal adjustment to the reaction conditions and demonstrated functional-group compatibility consistent with other Negishi-type cross-coupling reactions. Notably, esters (**3al**), ethers (**3am**), protected amines (**3aq**), alkyl trimethoxysilane (**3ao**), and alkyl boronic acid pinacol esters (**3an**) were all compatible. Sterically hindered zinc reagents, such as *ortho*-substituted arylzincs and 2° alkyl zinc reagents, coupled in low yield under these conditions.

Synthetically, this reaction is notable because there are few examples of $C(sp^3)$–$C(sp^3)$ bond activation/skeletal rearrangements with concomitant $C(sp^3)$–$C(sp^3)$ cross-coupling. When this reaction is paired with a second $C(sp^3)$–$C(sp^3)$ bond-forming reaction at the silyl enol ether (Figure 2), this process will facilitate the insertion of saturated triads between two other components. Even in this initial proof-of-concept iteration, and without exploiting the power of silyl enol ethers, this method can be used to shorten syntheses. For example, in Fishlock's (±)-taiwaniaquinol B synthesis we were able to decrease the step count to intermediate **3au** by three steps (out of 7).[63] Our four-step route utilized a different starting material (**5**) of similar complexity and the same oxidation state as in the Fishlock synthesis.

A key feature of this method is access to reliable difunctionalization (Figure 2) and this requires isolation of reactive silyl enol ethers. To maximize yield and simplify isolation, many reports either hydrolyze the enol ethers and isolate the ketone or substitute

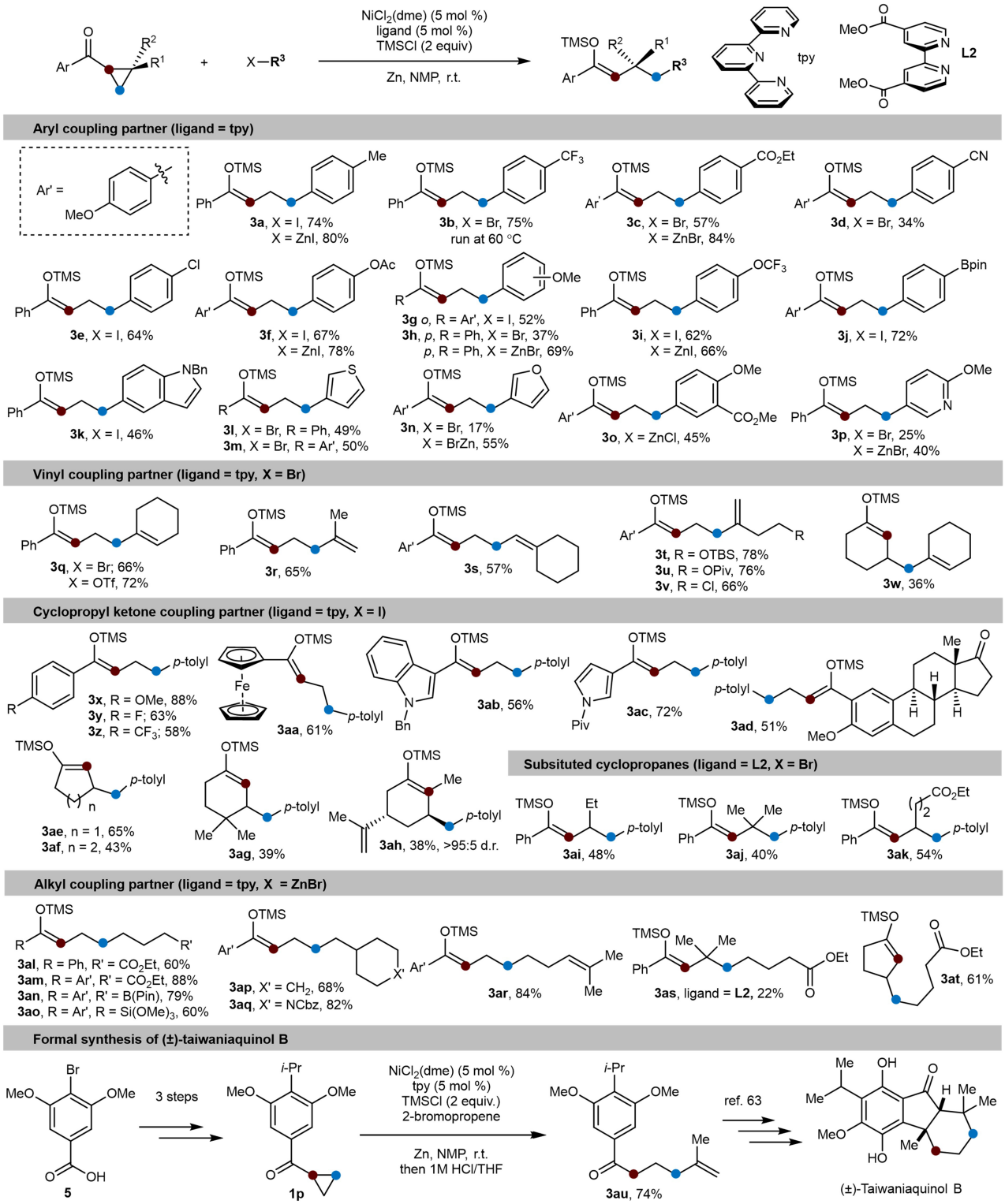


Figure 5. Scope of the 1,3-difunctionalization reaction and the formal synthesis of (±)-taiwaniaquinol B. Isolated yields after purification.

a more stable, but less useful silicon group for isolation. 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**).[64] While once cost-prohibitive, the proliferation of automated chromatography instruments and reusable stationary phases has dramatically lowered the barrier to employing reverse-phase purification technologies on preparative scale.

Conclusions

These studies illustrate the potential of new mechanisms of C–C activation in synthesis by showing how a novel mechanism enables the first general C–C activation of cyclopropyl ketones to enable 1,3-difunctionalization. This metal-ligand cooperativity is a new application of redox-active ligands that could be of wide use in catalysis. We anticipate that these results will enable the rapid devel-

opment of a variety of C–C activation/difunctionalization reactions of cyclopropyl ketones.

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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Author Contributions

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

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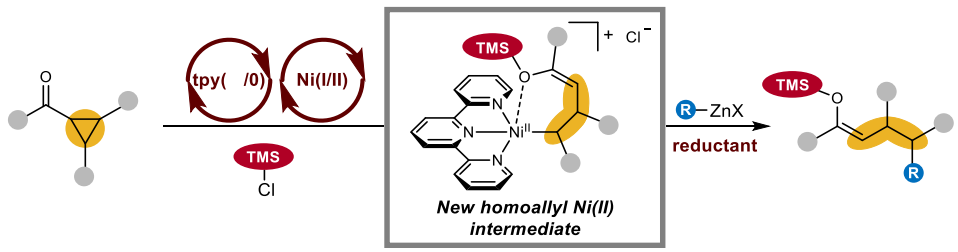
TOC Graphic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