Ni/Photoredox-Catalyzed $C(sp^3)–C(sp^3)$ Coupling between Aziridines and Acetals as Alcohol-Derived Alkyl Radical Precursors

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ABSTRACT: Aziridines are readily available $C(sp^3)$ precursors that afford valuable β-functionalized amines upon ring-opening. In this article, we report a Ni/photoredox methodology for $C(sp^3)–C(sp^3)$ cross-coupling between aziridines and methyl/1º/2º aliphatic alcohols activated as benzaldehyde dialkyl acetals. Orthogonal activation modes of each alkyl coupling partner facilitate cross-selectivity in the $C(sp^3)–C(sp^3)$ bond-forming reaction: the benzaldehyde dialkyl acetal is activated via hydrogen atom abstraction and β-scission via bromine radical (generated *in situ* from single-electron oxidation of bromide), whereas the aziridine is activated at the Ni center via reduction. We demonstrate that an Ni(II) azametallacycle, conventionally proposed in aziridine cross-coupling, is not an intermediate in the productive cross-coupling. Rather, stoichiometric organometallic and linear free energy relationship (LFER) studies indicate that aziridine activation proceeds via Ni(I) oxidative addition, a previously unexplored elementary step.

INTRODUCTION

Selective cross-coupling of two different carbon electrophiles, commonly known as cross-electrophile coupling, has emerged as an enabling strategy for C–C bond formation.[1] These processes often operate on readily available and stable organic (pseudo)halides under mild conditions. Extensive progress has been made in developing $C(sp^3)–C(sp^2)$ cross-electrophile coupling reactions, with Ni catalysis offering a particularly general platform.[2] Mechanistic studies on select Ni-catalyzed reactions have revealed that distinct, hybridization-dependent activation mechanisms give rise to the cross-selectivity with $C(sp^2)$ and $C(sp^3)$ electrophiles.[3,4] In contrast, methods for selective coupling of two $C(sp^3)$ electrophiles remain underdeveloped, owing to the more subtle differences in reactivity between the two reaction partners (Figure 1A).[5] Nevertheless, there has been important recent progress made in this area using Ni[6] or Cu catalysis[7] with chemical reductants and electrochemical methods.[8] These approaches typically rely on substrate stoichiometry, differences in (pseudo)halide identities or differences in substitution at the carbon center to achieve selectivity. Alternatively, redox-neutral metallaphotoredox catalysis[9] can provide a platform for the development of chemoselective $C(sp^3)–C(sp^3)$ cross coupling in part by relying on orthogonal redox-dependent activation mechanisms of the two alkyl coupling partners. This approach offers the opportunity to use nontraditional reaction partners beyond alkyl (pseudo)halides while retaining many of the positive attributes of cross-electrophile coupling. For example, researchers have recently found success coupling two $C(sp^3)$ fragments arising from carboxylic acids, activated alcohols, alkyl halides, and C–H bonds.[10] These examples highlight how the identification of strategies that engage distinct classes of $C(sp^3)$ coupling partners in $C(sp^3)–C(sp^3)$ bond formation can be of broad value from a synthetic and mechanistic perspective.

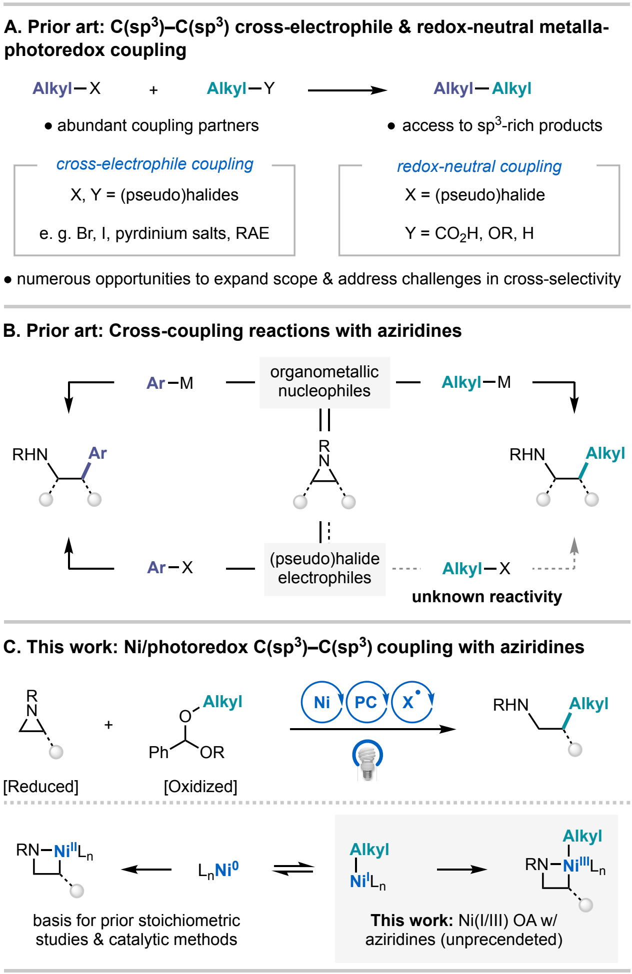


Figure 1. Cross-electrophile coupling with $C(sp^3)$ electrophiles.

Aziridines have been employed successfully as $C(sp^3)$ electrophiles in a number of cross-coupling reactions. Work from our lab,[11] Michael,[12] Jamison,[13] Takeda/Minakata,[14] May[15] and Xiao[16] has demonstrated that coupling reactions with aziridines can afford access to substituted ethylamines, important nitrogen-containing motifs in medicinal chemistry (Figure1B).[17] Organometallic nucleophiles such as organozinc halides or organoboron reagents, have been employed as coupling partners to form both C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) bonds (Figure 1B, top). Recently, our lab demonstrated that aziridines can also participate in cross-electrophile coupling reactions with aryl iodides, using either a stoichiometric inorganic reductant[18] or a photo-assisted reductive coupling (PARC) strategy.[19] Like other C(sp^3)–C(sp^2) cross-electrophile coupling reactions, these methods take advantage of the difference in hybridization of each coupling partner to impart selectivity (Figure 1A, bottom).[20] Unfortunately, direct extension of the methods for cross-selective C(sp^3)–C(sp^3) coupling with unactivated alkyl halides was not possible as both precursors undergo indiscriminate reduction at the Ni center. To address this challenge, we questioned whether we could design a selective redox-neutral C(sp^3)−C(sp^3) cross coupling with aziridines by using an alternative C(sp^3) partner where the activation mode is decoupled from that of aziridines.

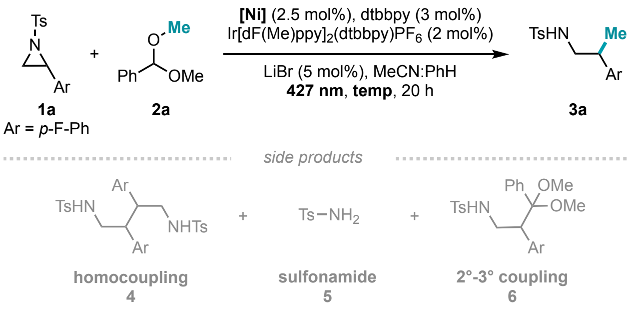
Herein, we report progress toward this goal in the development of a redox-neutral Ni/photoredox-catalyzed alkylation of aziridines to generate 2°–Me, 2°–1°, 2°–2° alkyl bonds (Figure 1C). The method facilitates the synthesis of a range of β-substituted sulfonamides that were previously inaccessible by traditional cross-coupling methods with aziridines. Benzaldehyde dialkyl acetals serve as the second C(sp^3) coupling partner in the method, functioning to activate unactivated alcohols toward homolytic C(sp^3)–O cleavage in an oxidative process[21] that is orthogonal to aziridine activation via reduction. Differentiation of the activation modes affords an opportunity to independently tune the rate of reaction of the two partners to achieve cross-selectivity using easy to manipulate variables like light intensity. Mechanistic studies suggest that these conditions favor a Ni(0)−(I)−(III) cycle wherein aziridine activation does not occur via Ni(0) oxidative addition, but rather via Ni(I), an elementary step that has no prior stoichiometric or catalytic precedent.[22,23]

RESULTS AND DISCUSSION

Reaction Optimization

We began reaction optimization using 2-(4-fluorophenyl)-1-(*p*-tolylsulfonyl)aziridine (**1a**) and benzaldehyde dimethyl acetal (**2a**) as a methyl radical precursor. On the basis of prior studies, including our own recent work,[21] we explored the use of halide salts as precursors to halogen radicals for HAT. We were pleased to find that using 2.5 mol% Ni(cod)$_2$, 5 mol% NH_4Br ($E_{1/2}$ [Br^-/$Br\cdot$] = +0.80 V vs SCE in DCE), and 2 mol% Ir[dF(Me)ppy]$_2$(dtbbpy)PF$_6$(Ir^{II}/Ir^{III*} = +0.97V vs SCE in MeCN)[2g,24] with a 427 nm Kessil lamp at 25 °C, the desired cross-coupled product **3a** was formed in 22% yield (Table 1, entry 1). Because hydrolysis of the acetal **2a** was also observed under these conditions, we next evaluated non-protic bromide salts, including LiBr, which led to the formation of **3a** in 32% yield (Table 1, entry 2). In both these reactions, numerous undesired side products also accompanied product formation, including the dimerized aziridine (**4**), sulfonamide **5**,[25] and the direct product of cross-coupling with the 3° carbon of the acetal (**6**). Since **4** and **5** both presumably arise from unproductive consumption of an azanickellacycle intermediate, we hypothesized that increasing the rate of methyl radical formation from **2a** might lead to better selectivity for the cross-coupled product **3a**.[26] Consistent with this hypothesis, we found that simply adding another lamp and increasing the lamp intensity, variables that should both differentially impact the HAT cycle, afforded **3a** in 70% yield (Table 1, entry 3-4). Increasing the acetal equivalents from 1.8 to 2.4 also afforded a modest improvement in the yield of **3a** (Table 1, entry 5).

Table 1. Optimization of aziridine alkylation with benzaldehyde dialkyl acetals.



Entry	Acetal equiv	[Ni]	Light intensity /no. of lamps	Temp (°C)	Yield (%) 3 (rsm)	4	5	6
1	1.8	Ni(COD)$_2$	25%/1	25[a,b]	22 (59)	3	12	7
2	1.8	Ni(COD)$_2$	25%/1	25[b]	32 (50)	2	10	7
3	1.8	Ni(COD)$_2$	25%/2	28[b]	68	4	10	6
4	1.8	Ni(COD)$_2$	50%/2	31[b]	70	4	5	6
5	2.4	Ni(COD)$_2$	50%/2	31[b]	79	4	7	5
6	2.4	Ni(COD)$_2$	50%/1	26[b]	34	3	22	5
7	2.4	Ni(COD)$_2$	50%/1	38[c]	72	5	7	5
8	2.4	NiBr$_2$•glyme	50%/1	38[c]	82	6	5	4
9	1.1	NiBr$_2$•glyme	50%/1	38[c]	58	10	8	7
10	1.8	NiBr$_2$•glyme	50%/1	38[c]	68	8	10	7
11	2.4	NiBr$_2$•glyme	50%/1	38[c]	47	11	12	3

Reactions performed on 0.1 mmol scale, with 1-fluoronaphthalene as the external standard (^{19}F NMR yield for **3**,**4**,**6**, ^{1}H NMR yield for **5**). Entries 1-2 were performed at 0.04M, and entries 3-10 were performed at 0.057M. For reactions with 25% intensity, vials were placed 1.5 cm away from Kessil lamp and for 50% intensity, vials were placed 3cm away. Entries without (rsm) showed full conversion of the aziridine. [a] NH_4Br was used instead of LiBr [b] Three fans were used to cool the reaction. [c] No fans were used to cool the reaction. Reaction with either no light, no photocatalyst, no nickel, or no nickel/ligand all gave 0% yield of the desired product.

Although the conditions in entry 5 afforded a high yield of the desired product, we sought to test the robustness of the reaction under a more simplified light set-up. Interestingly, while only one lamp with fan-cooling afforded 34% yield of **3a**, simply removing the fans to increase the reaction temperature gave a significant increase in the yield of **3a** to 72% (Table 1, Entry 6,7), potentially because higher temperatures facilitate *β*-scission and increases the concentration of Me radical in solution. Finally, evaluation of Ni precatalyst identity showed that NiBr$_2$·glyme gave a 10% increase in yield over Ni(cod)$_2$ (Table 1, Entry 8).

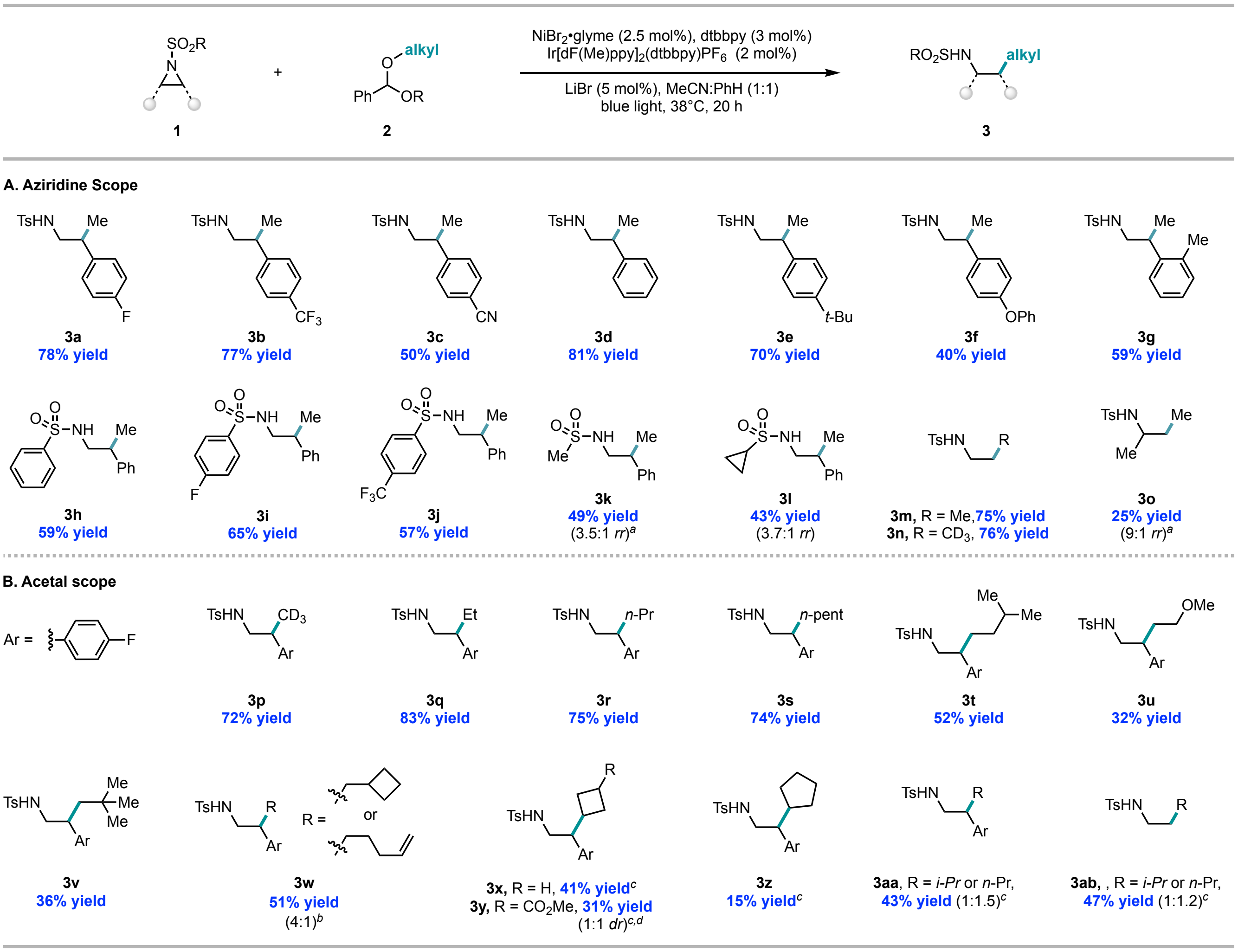
With these optimized reaction conditions, we were pleased to find that **3a** can be obtained in useful yield even with reduced equivalents of the acetal (Table 1, Entries 9 & 10). Moreover, although NiBr$_2$·glyme can serve as the sole source of bromide for HAT, control reactions omitting LiBr led to diminished reactivity, consistent with previous observations that the counter cation of the additive may facilitate stabilization of the anionic sulfonamide and product release (Table, Entry 11).[20c]

Substrate scope

Methylation of C(sp^3) carbons is a powerful strategy in medicinal chemistry that can lead to an increase in potency, higher selectivity among bioreceptors, alteration in solubility, and enhanced protection against enzyme metabolism.[27] Accordingly, amines and sulfonamides bearing *β*-methyl groups are a highly sought structural motif in pharmaceuticals.[28] Nevertheless, methylation of aziridines has only been accomplished with highly nucleophilic organometallic reagents, such as Grignard reagents, organocuprates, and AlMe$_3$, and often results in poor regioselectivity.[29] Moreover, there have been no reports of successful Ni- or Pd-catalyzed cross-coupling of aziridines with methyl nucleophiles.[11-14] Therefore, with the optimized reaction conditions in hand, we investigated the scope of the reaction with various aziridines using benzaldehyde dimethyl acetal as a methylating reagent.

We were excited to find that a broad range of styrenyl aziridines were compatible with this Ni/photoredox methylation reaction (Table 2). Substrates bearing electron-deficient groups such as *p*-CF$_3$ (**3b**) or *p*-CN (**3c**) gave the *β*-methylated sulfonamide products in 77% and 50% yield, respectively. An unsubstituted styrenyl aziridine (**3d**) as well as those baring electron-donating groups such as *p*-*t*-Bu (**3e**) or *p*-OPh (**3f**) also afforded the methylated products in good yield. The reaction showed minimal sensitivity to steric hindrance on the arene, with **3g** formed in 59% yield.

Table 2. Reaction substrate scope with aziridines and benzaldehyde dialkyl acetals.



Reactions performed on 0.2 mmol scale. 0.48 mmol of the acetal coupling partner was used. [a] 48 h instead of 20 h [b] Ratio of ring-closed to ring-opened isomers. [c] 5,5'-difluoro-2,2'-bipyridine was used instead dtbbpy. 'rr' denotes regiomeric ratio of branched/linear ring opened aziridines. [d] 1:1 *dr* at the benzylic stereogenic censer of the *trans* cyclobutane.

As sulfonamides have been frequently employed in medicinal chemistry, we also investigated aziridines with sulfonyl substituents other than a tosyl group. Both aryl (**3h-3j**) and alkyl sulfonamides,[30] such as methanesulfonamide (**3k**)[30c] and cyclopropanesulfonamide (**3l**)[30d,e] were tolerated in the reaction, albeit the alkyl sulfonamides were formed as mixtures of regioisomers with methylation favoring the benzylic position. Finally, an unsubstituted aziridine was also converted to the deuteromethyl- and methylated products **3m** and **3n** in 75% and 76% yield, respectively. A current limitation of the methodology is that aliphatic aziridines give poor conversion to the product, even with prolonged reaction times (**3o**).

We next explored the scope of the acetal partner using 2-(4-fluorophenyl)-1-(*p*-tolylsulfonyl)aziridine (**1a**). We found that deuteromethyl (**3p**) as well as other unactivated linear alkyl groups such as Et (**3q**), *n*-propyl (**3r**), *n*-pentyl (**3s**), and isoamyl (**3t**) all afforded the desired products in 52–83% yield. Alkyl groups bearing heteroatom substitution (**3u**) were also competent substrates, albeit lower yielding. Moreover, *β*−substituted alkyl coupling partners such as neopentyl (**3v**) were effective in the reaction. As another example, a methylene cyclobutyl group could be transferred in 51% yield (**3w**), wherein both the direct cross-coupling (**3w1**) and the radical ring-opened terminal alkene (**3w2**) were observed in a 4:1 ratio.

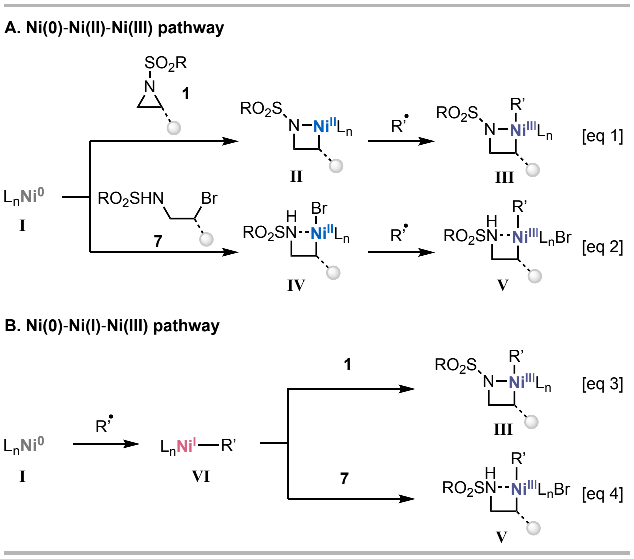
We were also excited to observe reactivity between 2º alkyl coupling partners and aziridines, given that cross-coupling of 2º alkyl groups with aziridines is not feasible under reported Negishi conditions.[11,13] Moreover, 2º−2º C−C bond formation presents a particular challenge in cross-electrophile strategies, with only a few examples reported to date.[6d,e] When testing the reactivity between 2º alkyl coupling partners and aziridines, we found that application of 5,5'-difluoro-2,2'-bipyridine rather than dtbbpy as ligand enabled higher conversion to the desired product (See supporting information). Both cyclic and acyclic secondary alkyl groups underwent coupling. The reaction was most efficient with cyclobutane derivatives (**3x** and **3y**). A decrease in yield was observed as the ring size was expanded to cyclopentylation (**3z**). Interestingly, use of isopropyl acetal as the 2º coupling partner afforded cross-coupled product with a 1:1.5 ratio of branched and linear propyl groups (**3aa**). Isomerization was also observed when using an unsubstituted aziridine as coupling partner (**3ab**), indicating that isomerization is not restricted to only congested 2º−2º C–C bond formation (*vide infra*).

Possible mechanistic pathways

Oxidative addition of aziridines to Ni(0) has been established in stoichiometric studies,[22] with the resulting Ni(II) azametallacycle proposed as a common catalytic intermediate in cross-coupling reactions with aziridines.[11-13,15,16,23] Therefore, at the outset of our reaction design, we initially hypothesized that the oxidative addition of Ni(0) **I** to generate Ni(II) azametallacycles **II** would be operative; subsequent capture of the alkyl radical to generate Ni(III) **III** followed by reductive elimination would furnish the desired product (Scheme 1, eq1). Alternatively, Ni(II) complex **IV** could instead arise via oxidative addition of Ni(0) to benzylbromide **7** generated *in situ*, given the catalytic presence of bromide in solution (Scheme 1, eq 2).[19,23b]

Nevertheless, the generation of linear/branched isomers using acyclic secondary alkyl reaction partners appeared inconsistent with these pathways (Table 2, **3aa**, **3ab**). In particular, *β*-hydride elimination and reinsertion should be much more favorable at a low-valent Ni(I) **VI** center as opposed to the Ni (III) intermediate **III** in eqs 1 and 2 since isomerization necessitates a vacant coordination site and an intermediate with a relatively long lifetime.[31] Interestingly, the intermediacy of a Ni(I) alkyl **VI** would imply that aziridine activation takes place by Ni(I)−Ni(III) oxidative addition, an elementary step that does not have precedent in stoichiometric studies for aziridines (Scheme 1, eq3). Or an analogous Ni(I)−Ni(III) pathway could also be proposed with benzyl bromide **7** (Scheme 1, eq 4).

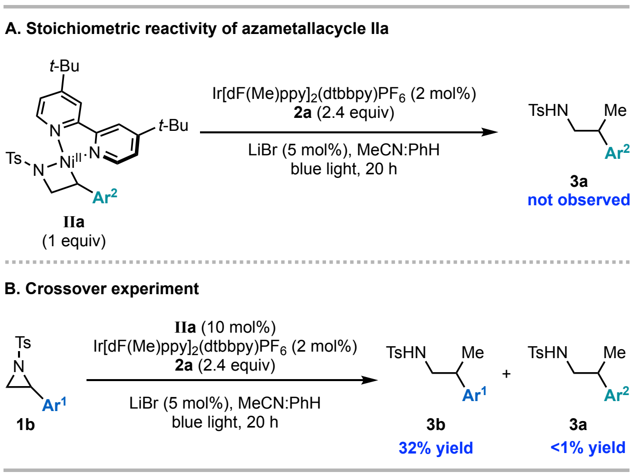
Scheme 1. Possible mechanistic pathways for accessing Ni(III) to enable product formation.



Mechanistic Investigations

To interrogate the mechanism of aziridine activation, we first sought to synthesize the Ni(II) **II** oxidative adduct and test its intermediacy in the coupling reaction (Scheme 1, eq1). Complex **IIa** was independently synthesized by reacting $Ni(cod)_2$ with **1a** in the presence of dtbbpy (Scheme 2A). The stoichiometric reaction of **IIa** under the standard reaction conditions did not result in the formation of product. Instead, **IIa** underwent conversion (30%) to a mixture of aziridine dimer **4a**, sulfonamide **5** and reduced aziridine (see supporting information). To determine if **IIa** accesses a catalytically-relevant intermediate and if the attached aziridine in the Ni complex can be directly converted to the desired methylated product, a crossover experiment was designed using *p*-CF_3 styrenyl aziridine **1b** as a substrate in the presence of 10 mol % azametallacycle **IIa** as the sole nickel catalyst source (Scheme 2B). However, less than 1% of the product originating from **IIa** (**3a**) was obtained, whereas the product from **1b** was formed in 32% yield. These results provide evidence against the pathway shown in Scheme 1, eq 1. Furthermore, when a time-course experiment was performed, **IIa** was never spectroscopically observed (see supporting information for details).

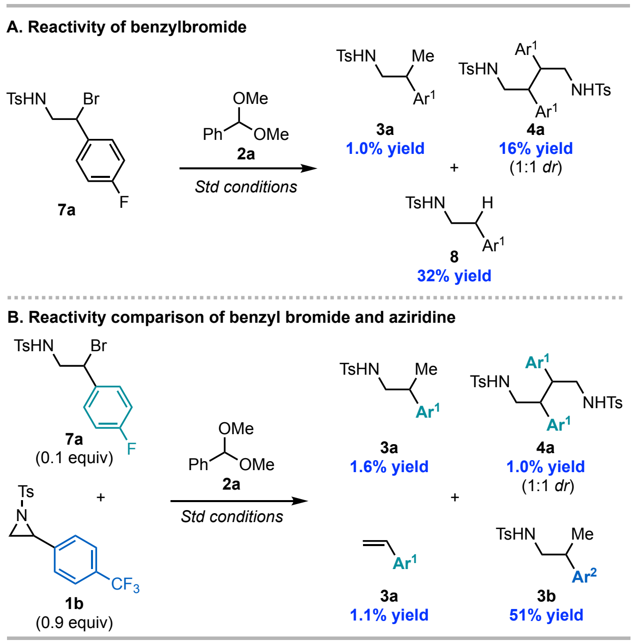
Scheme 2. Crossover experiment and stoichiometric studies with azametallacycle IIa.



1-fluoronaphthalene was used as the external standard for ^{19}F NMR yield.

Next, we investigated the intermediacy of benzylbromide **7**, pertinent to Scheme 1, eq2 or eq4, which could be generated by the 7.5% of bromide (2.5% from NiBr$_2$·glyme and 5% from LiBr) in the reaction mixture. When benzyl bromide **7a** was subjected to the reaction, only 1% of the product was generated. Instead, the majority of bromide **7a** was converted to dimer **4a** and reduced aziridine **8** (Scheme 3A).

Scheme 3. Reactivity of benzylbromide 7a.



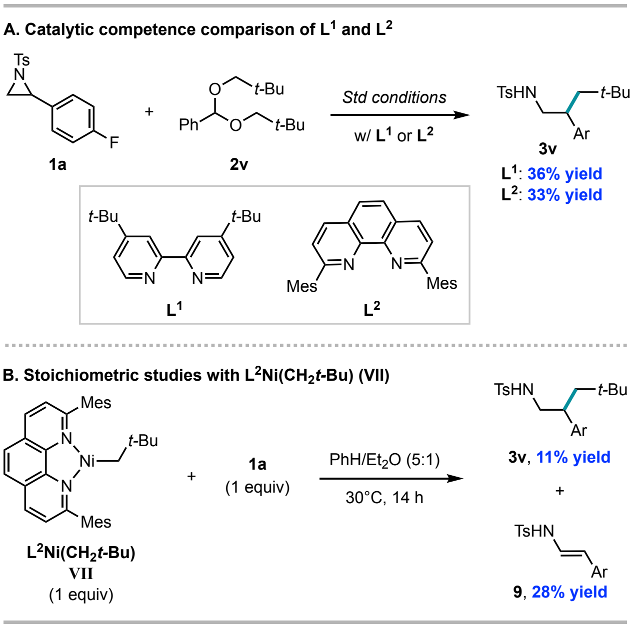
(A) Reaction performed 0.1 mmol scale using stoichiometric amount of benzylbromide **7a** vs. (B) catalytic amount of benzylbromide **7a** (0.01 mmol) and aziridine (0.09 mmol). Ar^1 = *p*-F-benzene Ar^2= *p*-CF$_3$-benzene. Yields are based on 0.1 mmol 1-fluoronaphthalene as the external standard by ^{19}F NMR.

When **7a** was used in catalytic quantities in the presence of aziridine **1b**, as a way to simulate the catalytic formation of **7a** under the standard condition, 1.6% of the product originating from **7a** was observed, whereas the product derived from **1b** was formed in 51% yield (Scheme 3B). Based on these observations, we propose that any *in situ* generated **7** most likely leads to off-cycle byproducts, presumably via oxidative addition of the benzyl bromide or halogen abstraction to generate the benzylic radical, followed by free-radical recombination, a common off-cycle pathway in aryl benzylation with benzylic halides.[32]

Ni(0)−Ni(I)−N(III) mechanistic pathway

Taken together, these data are most consistent with a Ni(0)−Ni(I)−Ni(III) pathway wherein Ni(I) undergoes oxidative addition to the aziridine (Scheme 1, eq 3). Since this step has not been previously observed, we sought direct experimental evidence for the stoichiometric oxidative addition of Ni(I) to aziridine **1a**. Unfortunately, an isolable dtbbpyNi(I)(alkyl) complex has not previously been prepared. However, in their investigation of the reactivity of CO$_2$ at Ni(I), the Martin group reported the synthesis of a (mesityl-phenanthroline)Ni(I)(CH$_2$*t*-Bu) **VII** (Scheme 4).[33] Therefore, we sought to test this Ni(I) alkyl complex for oxidative addition reactivity with **1a**. Prior to exploring stoichiometric studies with **VII**, we established that mesityl-substituted phenanthroline (L^2) gives similar yield as dtbbpy (L^1) in the catalytic reaction. Indeed, mesityl-substituted phenanthroline afforded 33% yield of **3v**, in close agreement with the 36% yield of **3v** seen with dtbbpy (Scheme 4A).

Scheme 4. Stoichiometric studies with Ni(I) complex.



(A) Control experiments with L^1 (4,4'-di-tert-butylbipyridine) and L^2 (2,9-dimesityl-1,10-phenanthroline) (B) Reactivity of L$_2$Ni(CH$_2$t-Bu) complex **VII** with aziridine **1a**.

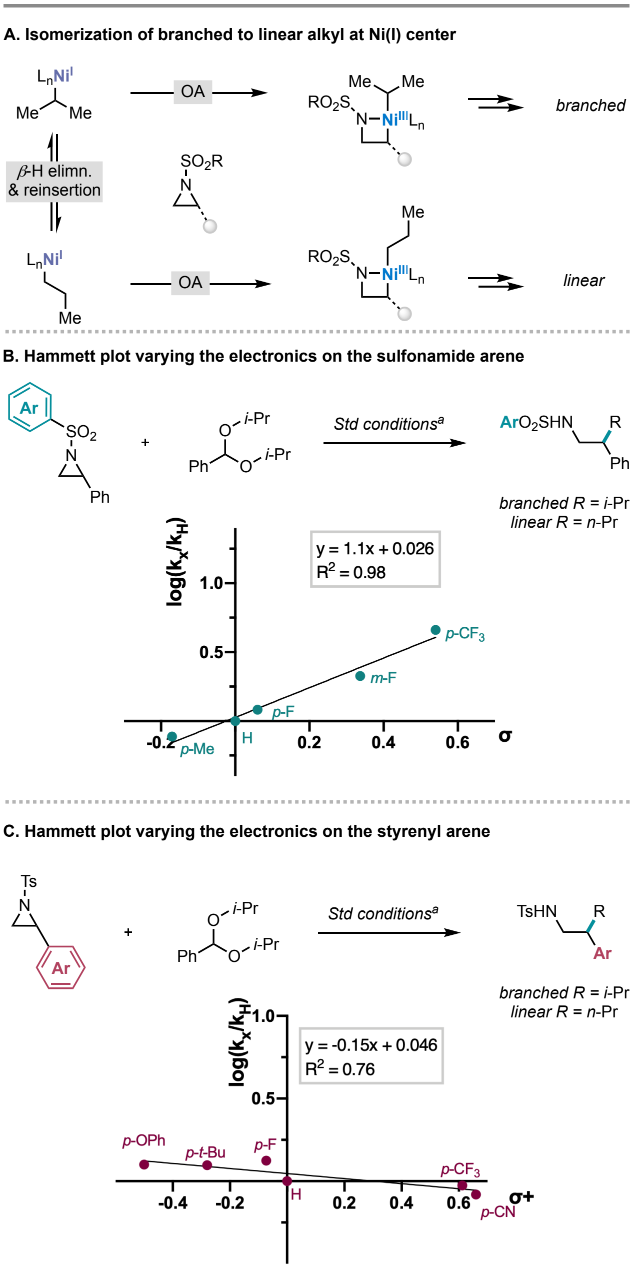
Having confirmed the catalytic competence of L^2, we turned our attention to the stoichiometric reaction (Scheme 4B). **VII** was generated *in situ*, by adding a solution of neopentylMgBr to L^{2}Ni(I)Br,[32] with the resulting complex then subjected to aziridine **1a**. This led to a full consumption of the aziridine, affording 11% of the cross-coupled product **3v** and 28% of enamide **9**, which could result from oxidative addition at the Ni(I) center, followed by elimination.[34] It is possible that enamide **9** serves as a source for sulfonamide formation **5**, which is observed under the catalytic conditions with L^1 and L^2. Taken together, these data support the catalytic relevance of a Ni(I) species for aziridine activation.

Having established the catalytic relevance of Ni(I), we sought to understand the mechanism of aziridine activation via Ni(I) by evaluating the impact of aziridine substitution on the catalytic reaction outcome (Hammett analysis). Rather than using the relative rate of product formation as a readout, we chose to use the branched/linear ratio of product arising from alkylation with *i*-Pr acetal **2aa**. Isomerization of the Ni(I)(*i*-Pr) can occur prior to oxidative addition, and aziridines that undergo faster oxidative addition to Ni(I) should therefore afford higher branched/linear ratios of the product according to our proposed mechanism (Scheme 5A).

Two sites of the aziridine were independently evaluated: the benzene sulfonamide (Scheme 5B) and the benzylic arene (Scheme 5C). When the electronics on the arene ring of the sulfonamide were varied, we observed a high linear correlation between the $\log(k_X/k_H)$ (k = branched/linear) with a positive ρ value ($R^2 = 0.98$, $\rho = 1.1$) (Scheme 5B). The positive, but relatively low magnitude, slope indicates that electron-withdrawing groups on the sulfonamide facilitate faster oxidative addition, consistent with either a single-electron transfer or concerted oxidative addition. When the electronics of the benzylic aryl group were modified and plotted against Hammett–Brown constants σ^+,[35] or with Jiang's spin-delocalization substituent constants $\sigma_{JJ}^{\bullet}$ (indicative of a radical stabilization effect),[36] a negative correlation was observed with $\log(k_x/k_H)$ (for σ^+, $R^2 = 0.76$, $\rho = -0.15$; for $\sigma_{JJ}^{\bullet}$ $R^2 = 0.87$, $\rho = -0.15$) (Scheme 5B). The negative slopes for both σ^+ and $\sigma_{JJ}^{\bullet}$ indicate that a more electron-donating group on the benzylic fragment facilitates oxidative addition. The correlation with $\sigma_{JJ}^{\bullet}$ also suggests a buildup of radical character on the benzylic carbon. These trends are consistent with analyses of benzyl halide oxidative addition to Co(I),[37] where it is proposed that after halogen abstraction by Co(I) to generate a benzylic radical, a radical addition back onto the Co(II) metal center generates Co(III); it is the latter step which would be accelerated by electron-donating (nucleophilic) benzyl groups.

Overall, the opposite slope of ρ for the arene on the sulfonamide versus the arene on the benzylic site is most consistent with a single electron transfer oxidative addition, where Ni(I) reduces the aziridine to generate a Ni(II)-sulfonamide complex and a benzylic radical, which is followed by recombination of benzylic radical to afford Ni(III).[11a] The observed LFERs are inconsistent with a concerted oxidative addition, which would be expected to have a positive ρ value for both experiments. Although S_N2-type oxidative addition has been proposed for Ni(0) and negative ρ values have been observed for Lewis-acid-catalyzed nucleophilic ring opening of styrenyl aziridines,[38] the higher R^2 for a radical descriptor $\sigma_{JJ}^{\bullet}$ over σ^+ and the low magnitude of the ρ value are inconsistent with this mechanism.[38] It is also worth noting that these results contradict the possibility of isomerization occurring at Ni(III) (Scheme 1, eq1), where more electron-deficient arenes on the benzylic site would also be expected to lead to faster reductive elimination and reduced isomerization (i.e.. both ρ values > 0).[39] Furthermore, the higher magnitude of the ρ value of sulfonamide arene than that of the styrenyl arene further corroborates the lack of participation of benzyl bromide **7a** as a productive intermediate in the catalytic cycle (Scheme 1, eq 2 or 4).

Scheme 5. Hammett plot analysis.



(A) Isomerization of branched to linear alkyl species at Ni center. (B) Hammett plot of branched vs linear product against varying substituents on aryls on sulfonamide and (C) styrenyl arene. Reaction was performed on 0.2 mmol scale using under standard condition. [a] Standard condition for 2° alkyl cross-coupling, where 5,5'-difluoro-2,2'-bipyridine was used instead dtbbpy.

Proposed Catalytic Cycle

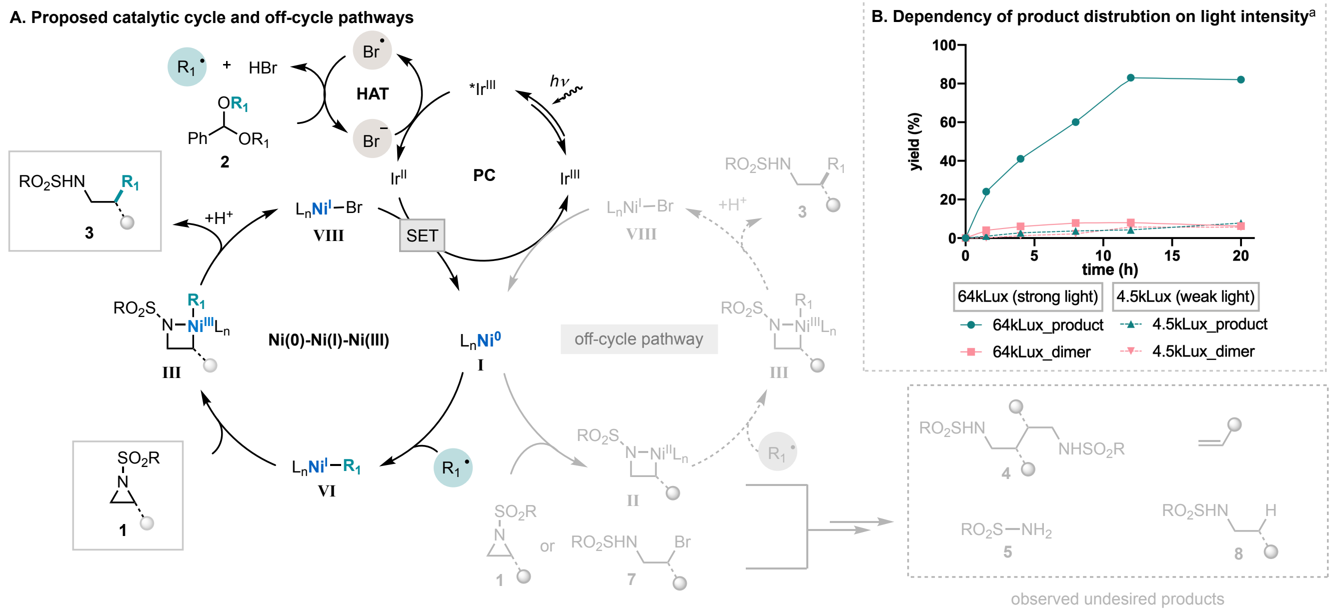
On the basis of our mechanistic investigations, we propose the following catalytic cycle (Scheme 6A, black). Upon irradiation with blue light, the excited Ir photocatalyst oxidizes bromide anion. The resulting bromine radical can abstract the 3° benzylic C−H of the benzaldehyde dialkyl acetal, followed by β−scission to generate the alkyl radical and ester byproduct.[21b] Concurrently, the $NiBr_2$·glyme precatalyst can be reduced to Ni(0) **I** by Ir(II) to enter the Ni catalytic cycle, which can capture the alkyl radical generated from the β−scission event.

Based on our stoichiometric, catalytic and spectroscopic observations, we propose that Ni(I) **I** undergoes oxidative addition to the aziridine by a single electron transfer mechanism. Reductive elimination from the resulting Ni(III) **III** complex then affords the cross-coupled product with regeneration of Ni(I) **VIII**. Finally, **VIII** would be reduced by the Ir(II) species to turnover the catalytic reaction.[40]

We also identified off-cycle pathways that lead to undesired byproducts (Scheme 6B, gray). For instance, if aliphatic radical generation by HAT/β-scission or trapping by Ni(0) **I** is slow, Ni(0) **I** oxidative addition to the aziridine would afford Ni(II) azametallacycle **II** and resulting degradation products. Moreover, any generation of benzylbromide **7** could lead to undesired dimer **4** and reduced aziridine **8**. Sulfonamide **5** and styrene formation may arise from inefficient cross-coupling, on the grounds of observing enamide **9** formation using Ni(I) oxidative addition in the stoichiometric studies.

This proposed competition of light-mediated cross-reactivity with off-cycle speciation pathways is further supported by comparing the relative product and dimer formation with varying light intensity (Scheme 6C, see SI for details). For example, when performing a time-course study comparing the ratio of product **3a** to dimer **4a** at high versus low light intensity (64 kLux, Table 1, condition 7 vs 4.5 kLux, condition 6), the lower light intensity conditions result in the formation of nearly 1:1 ratio of the desired product to the dimer. Suppression of off-cycle speciation is therefore partially dependent on having sufficient light penetration to favor the productive catalytic pathway.

Scheme 6. Proposed mechanistic pathway and off-cycle pathways.



[a] Strong light emission: 50% light intensity where the vials were placed 3 cm away from the Kessil lamp, maintained at 38 °C. Weak light emission: 25% light intensity where the vials were placed 20 cm away from the Kessil lamp while heating in an oil bath at 38 °C.

CONCLUSION

In conclusion, we have developed a C(sp^3)–C(sp^3) cross-coupling methodology between aziridines and benzaldehyde dialkyl acetals as latent alkyl radical sources. The transformation employs a diverse set of styrenyl aziridines with varying substitution on the sulfonamide. Moreover, methyl, 1° and 2° unactivated aliphatic coupling partners can be installed efficiently. The orthogonal activation of each coupling component and ligation at distinct Ni oxidation states imparts cross-selectivity between two C(sp^3) precursors. Specifically, mechanistic studies support a pathway for activation of aziridines via Ni(I)–Ni(III) oxidative addition, distinct from the commonly proposed oxidative addition of aziridines to Ni(0). These mechanistic studies shed light on the nature of the activation modes for unconventional C(sp^3) precursors, which we anticipate can lead to the expansion of C(sp^3)–C(sp^3) cross-coupling methodologies in future studies.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org/

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Notes

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