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Highly Regioselective Nickel-Catalyzed Cross-Coupling of *N*-Tosylaziridines and Alkylzinc Reagents

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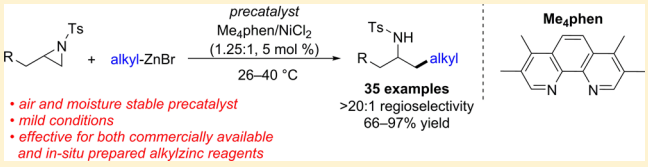
Supporting Information

ABSTRACT: Herein, we report the first ligand-controlled, nickel-catalyzed cross-coupling of aliphatic *N*-tosylaziridines with aliphatic organozinc reagents. The reaction protocol displays complete regioselectivity for reaction at the less hindered C−N bond, and the products are furnished in good to excellent yield for a broad selection of substrates. Moreover, we have developed an air-stable nickel(II) chloride/ligand precatalyst that can be handled and stored outside a glovebox. In addition to increasing the activity of this catalyst system, this also greatly improves the practicality of this reaction, as the use of the very air-sensitive $Ni(cod)_2$ is avoided. Finally, mechanistic investigations, including deuterium-labeling studies, show that the reaction proceeds with overall inversion of configuration at the terminal position of the aziridine by way of aziridine ring opening by Ni (inversion), transmetalation (retention), and reductive elimination (retention).



INTRODUCTION

The transition-metal-catalyzed activation of alkyl halides has attracted enormous attention over the past decade, wherein palladium, nickel, and copper in particular have proven to be exceptionally effective catalysts for many diverse transformations,[1] including $C(sp^3)-C(sp^3)$ bond-forming reactions.[2] Nevertheless, the vast majority of cross-coupling reactions utilize carbon−halogen or carbon−OSO_2R electrophiles; those involving oxidative addition into a C−N bond of the electrophile have received much less attention.[3]

The aziridine functionality represents a versatile building block in contemporary synthetic chemistry. Like other three-membered heterocycles such as epoxides, aziridines possess significant ring strain that renders them susceptible to nucleophilic ring opening. In many cases, these reactions proceed with high regioselectivity, and various carbon- and heteroatom-based nucleophiles have been investigated over the past several years. In particular, the addition of organocuprates has proven to be an efficient strategy for C−C bond-forming reactions with aziridines.[4]

The oxidative addition of transition metals into aziridines to form azametallacycle intermediates can also be effected under mild conditions.[5] For instance, arylaziridines have been shown to undergo facile ring-expanding carbonylation reactions to form β-lactams under rhodium catalysis.[6] This transformation proceeded with high selectivity for insertion into the benzylic C−N bond. Notably, simple alkylaziridines proved unreactive under these conditions.[7]

In 2002, Hillhouse demonstrated that aliphatic *N*-sulfonylaziridines could undergo oxidative insertion of nickel to form stable, isolable azanickelacyclobutane complexes (Scheme 1a).[8,9] Interestingly, the oxidative insertion occurred with complete regioselectivity for insertion into the less substituted aziridine C−N bond. Studies of a deuterium-labeled aziridine provided clear evidence for an S_N2-type mechanism.

A few years later, the Wolfe group reported the stoichiometric insertion of palladium into the terminal position of aliphatic aziridines containing a tethered olefin.[10] Based on the relationship between tether length and reactivity, it was postulated that the alkene was functioning as a directing group, the presence of which was critical for successful insertion. Only after changing the electronic nature of the aziridine, by employing the more strongly activating *N*-nosyl substituent, did it in one instance prove possible to promote the oxidative insertion without the use of the alkene directing group.

Although these pioneering contributions showed great promise for the development of catalytic activation of aziridines in direct cross-coupling reactions, the first actual coupling reaction remained elusive for another decade. In 2012, the first direct cross-coupling reaction was reported by the group of Doyle. In this report, it was shown that styrene-derived *N*-tosylaziridines can undergo facile C−C bond formation with alkylzinc reagents promoted by nickel catalysis (Scheme 1b).[11] The reaction proceeded with complete regioselectivity for the weaker benzylic C−N bond.[12] Notably, it was found necessary to use the electron-deficient alkene ligand, dimethyl fumarate, to induce reductive elimination and prevent β-hydride abstraction.[13] Shortly thereafter, the Doyle group demonstrated that the reaction sequence could be extended to include aliphatic aziridines (Scheme 1c).[14] Interestingly, this type of substrate had proved unreactive under the previously developed conditions. The activation was elegantly achieved by changing the *N*-sulfonyl group from tosyl to cinsyl (Cn), which contains an electron-deficient alkene in the 2-position of the arylsulfonyl group. By using this protecting group, the cross-coupling products were obtained in moderate to good yields as a mixture of inseparable

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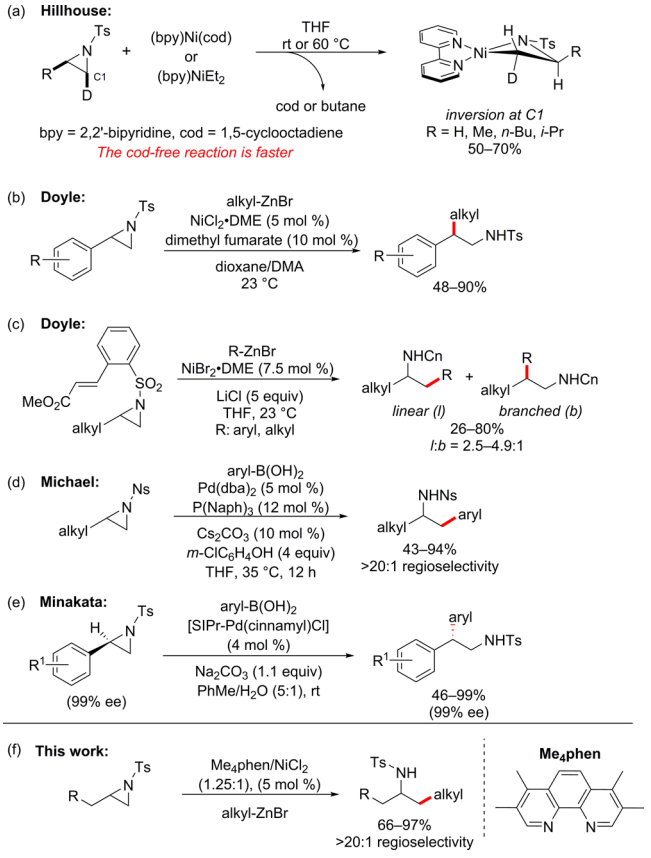
Scheme 1. Previously Reported Activation Studies and Cross-Couplings Reactions of Aziridines



regioisomers, with C−C bond formation on the least substituted side being favored, though in only moderate regioselectivity (<5:1). The majority of the scope focused on arylzinc reagents; however, a few aliphatic examples were also given. The newly designed Cn-sulfonyl group is likely to serve a dual purpose in this transformation by acting as a directing group for the oxidative insertion into the aziridine and by inducing reductive elimination in analogy to the dimethyl fumarate employed in the protocol for styrenylaziridines. Interestingly, in contrast to the stoichiometric studies by Hillhouse[8] and Wolfe,[10a] when a deuterium-labeled aziridine was subjected to the reaction conditions, a mixture of diastereoisomers, arising from epimerization at the terminal position, was obtained. This is indicative of a single-electron transfer (SET) mechanism or an S_N2-type activation followed by Ni−C bond homolysis.

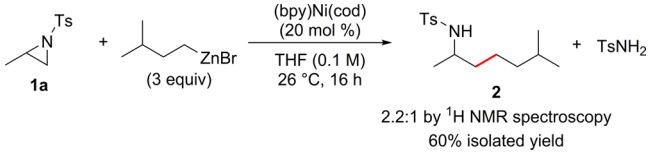
Soon after, the group of Michael reported a highly efficient, palladium-catalyzed cross-coupling of aliphatic *N*-nosylaziridines with arylboronic acids (Scheme 1d).[15] The transformation proceeds with complete regioselectivity for the terminal position, and the products are obtained in good yields. The application of a phenol additive was found to be critical in order to promote transmetalation and to prevent a detrimental *β*-hydride elimination pathway. Through a deuterium-labeling study, the reaction was shown to proceed with complete inversion, which is consistent with the observations previously made on the stoichiometric systems. More recently, Minakata and co-workers demonstrated a stereo- and regiospecific palladium-catalyzed coupling of arylaziridines and arylboronic acids.[16] Through the use of a Pd/NHC catalyst system, the C−N bond activation occurs at the more substituted position with excellent stereospecificity and stereochemical inversion. Interestingly, the enantiopurity is maintained through the reaction, enabling the synthesis of tertiary stereogenic centers (Scheme 1e).

While all of the above-mentioned protocols provide access to a wide variety of sulfonamide products arising from different combinations of aziridines and coupling partners (aryl/alkyl, alkyl/aryl, alkyl/alkyl, aryl/aryl), no C−C bond-forming reaction, with complete regioselectivity, of unactivated aliphatic aziridines and aliphatic coupling partners has been reported to date. Therefore, we decided to study the nickel-catalyzed cross-coupling of aliphatic *N*-tosylaziridines with aliphatic organozinc reagents (Scheme 1f).[17] The reaction protocol developed through these studies displays complete regioselectivity for the terminal position, and the products are furnished in good to excellent yield for a broad selection of substrates. Moreover, we have developed an air-stable nickel(II) chloride/ligand pre-catalyst that can be handled and stored outside a glovebox. This greatly improves the practicality of this reaction, as the use of the very air-sensitive $Ni(cod)_2$ can be avoided. Finally, mechanistic studies, including deuterium-labeling studies to determine the stereochemical course of the reaction, were performed.

RESULTS AND DISCUSSION

We initiated our studies by examining the reaction of methyl-substituted aziridine **1a** using the bipyridine Ni(0) complex employed in the stoichiometric studies by Hillhouse.[8,18] In terms of the aliphatic coupling partner, organozinc reagents were chosen as they generally display high stability and improved functional group compatibility.[19] Furthermore, a number of organozinc reagents are commercially available as THF solutions, and we therefore began our studies using these reagents. Employing 20 mol % of the complex provided the cross-coupled product **2** as a single regioisomer in 60% isolated yield (Scheme 2). Analysis of

Scheme 2. Initial Conditions



the crude reaction mixture after workup showed that the product was formed in a 2.2:1 ratio to $TsNH_2$. This byproduct presumably arises from *β*-hydride abstraction and later hydrolysis of the resulting imine.[20] Reducing the catalyst loading to 10 mol % resulted in similar product distribution and yield; however, the reaction time required for full consumption of the aziridine was significantly increased (44 h).

Consequently, to improve the yield and efficiency of the reaction, a series of bidentate pyridine-derived ligands were screened in combination with $Ni(cod)_2$ (Table 1). Changing the 2,2′-bipyridine (bpy) ligand to the more electron-rich 4,7-$(MeO)_2$(bpy) provided an increase in product ratio (3:1). Notably, the reaction was less clean and a trace of halide-opened aziridine was observed.[21] Employing 1,10-phenanthroline (phen) as the ligand did not improve the product distribution; however, the reaction did turn out to be much faster and cleaner. Further screening of phenanthroline derivatives identified 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4phen) as the best ligand, improving the ratio to 4.5:1 and an isolated

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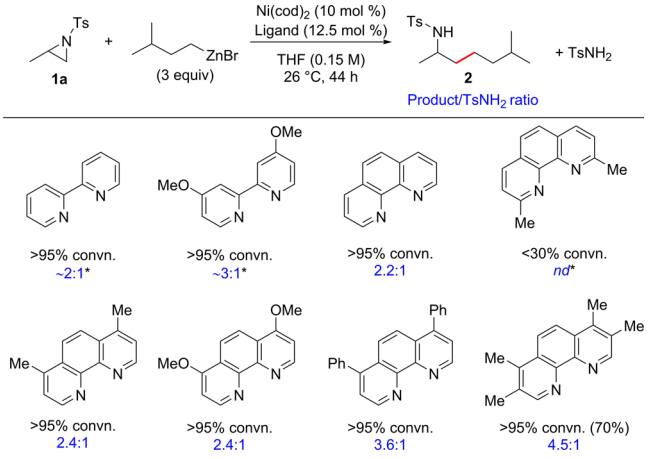
Table 1. Screening of Ligands[a]



[a]Asterisk (*) denotes the formation of halide-opened aziridine byproducts.

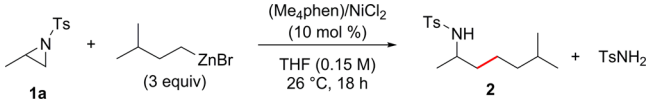
yield of 70%. Notably, low reactivity was observed for the *ortho*-substituted 2,9-dimethyl-1,10-phenanthroline ligand.

In order to improve the practicality of the procedure and avoid the use of $Ni(cod)_2$, we decided to develop a precatalyst system that can tolerate air and atmospheric moisture.[22,23] Furthermore, studies by Hillhouse on the synthesis of azanickelacyclobutanes had demonstrated that a cod-free Ni(0) system underwent insertion into the aziridine at a faster rate than when cod was present. This improved reactivity has also been demonstrated in a number of other instances. Consequently, we desired to identify a cod-free nickel precatalyst system for this transformation. Attempts to use $NiCl_2$·DME as the nickel source led to only low conversion, even after prolonged reaction times, and therefore, a different nickel source was required.

It is well-established that the combination of bpy- or phen-derived ligands with nickel(II) salts in aqueous or ethanolic solutions can yield nickel ligand adducts.[24] However, the identity of the counterion, temperature of synthesis, and solvent system can cause significant differences in the composition of the complex formed. For instance, the combination of phenanthroline and $NiCl_2·6H_2O$ in ethanol initially yields a kinetic complex of the structure $(phen)_3NiCl_2·xH_2O$, even when the ligand and nickel sources are mixed in a 1:1 ratio.[24a,b] Upon extended reaction time at ambient temperature or upon heating, a complex of the nominal composition $(phen)NiCl_2·xH_2O$ is subsequently formed. We found that precatalyst mixtures prepared at ambient and at elevated temperatures gave vastly different outcomes for the catalytic coupling reaction. As established by extensive elemental analyses, the root cause for the difference in outcome was attributed to either an excess of ligand, causing a beneficial outcome, or an excess of nickel, which was significantly detrimental to the reaction. To neutralize these differences, a different approach for the precatalyst synthesis was devised. Rather than isolating the precatalyst as a solid by filtration from the ethanol solution in which it is synthesized, the solvent was removed by rotary evaporation, yielding a solid with a precisely known ratio of ligand to nickel. A series of precatalysts with varying ratios of ligand (Me_4phen) to nickel were synthesized and evaluated in the coupling reaction (Table 2).[25]

In general, all of the precatalysts behaved well, furnishing the sulfonamide product **2** with high selectivity. The ratio of product to $TsNH_2$ generally improved with increasing amounts of ligand. However, the best result in terms of isolated yield

Table 2. Optimization of Ligand-to-Nickel Ratio



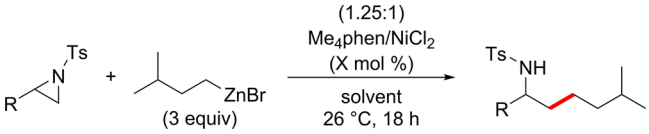
	Me_4phen/Ni	convn	ratio[a]	yield[b] (%)
1	1:1	>95	3.9:1 (80%)	77
2	1.25:1	>95	4.6:1 (82%)	79
3	1.50:1	>95	5.3:1 (84%)	80
4	1.75:1	>95	6.0:1 (86%)	nd
5	2.0:1	>95	6.0:1 (86%)	nd

[a]Yield in parentheses refers to the maximum theoretical yield based on the product distribution. [b]All yields were determined after purification by column chromatography on silica.

versus amount of ligand employed was provided by the precatalyst containing 1.25 equiv of ligand to nickel, furnishing the product in 79% yield.

With this precatalyst and these conditions in hand, we started to evaluate different aziridines. However, the reaction of aziridines with longer and more complex substituents turned out to work less well, providing incomplete conversions and various ratios of $TsNH_2$. For instance, a chlorobutyl-substituted aziridine was tested, and the product was obtained in a yield of 67% along with significant amounts of $TsNH_2$. Consequently, we decided to study the effect of solvent additives (Table 3).

Table 3. Optimization of Reaction Parameters[a]



	R	mol %	solvent	concn (M)	yield (%)
1	$Cl(CH_2)_4$	10	THF	0.15	67
2	$Cl(CH_2)_4$	10	THF/DCM (3:1)	0.125	84[b]
3	$Cl(CH_2)_4$	10	THF/DCE (3:1)	0.125	66
4	$Cl(CH_2)_4$	10	THF/DCE (3:2)	0.1	77
5	$Cl(CH_2)_4$	5	THF/DCE (3:2)	0.1	88
6	Me	5	THF/DCE (3:2)	0.1	85

[a]All yields were determined after purification by column chromatography on silica. [b]An inseparable byproduct derived from the organozinc reagent, 3-methyl-1-butanol, was formed.

Adding CH_2Cl_2 to the reaction had a beneficial effect on the outcome, providing the product in 84% yield. Unfortunately, however, an inseparable byproduct (3-methyl-1-butanol) derived from the organozinc reagent was also formed. The formation of this byproduct was prevented by employing 1,2-dichloroethane (DCE) as an additive, resulting in a yield of 77%.[26] The last improvement was achieved by lowering the catalyst loading to 5 mol %, providing the product in 88% yield. Gratifyingly, these new conditions were also applicable to the initially tested methylaziridine, affording **2** in 85% yield. The optimized conditions were first evaluated by varying the aziridine component.[27]

As demonstrated in Table 4, the reaction worked well for a wide variety of aziridines. Linear and branched aliphatic substituents all provided the products **3**–**6** in good to excellent yields (66–96%). The α-branched cyclohexyl substrate required a slightly elevated temperature to go to completion. Substituents containing additional functional groups were also well-tolerated,

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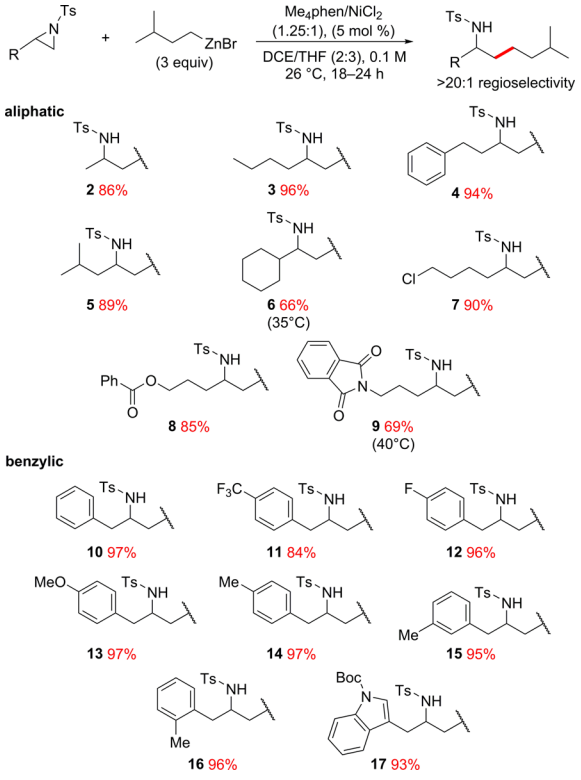
Table 4. Evaluation of Aziridines[a]

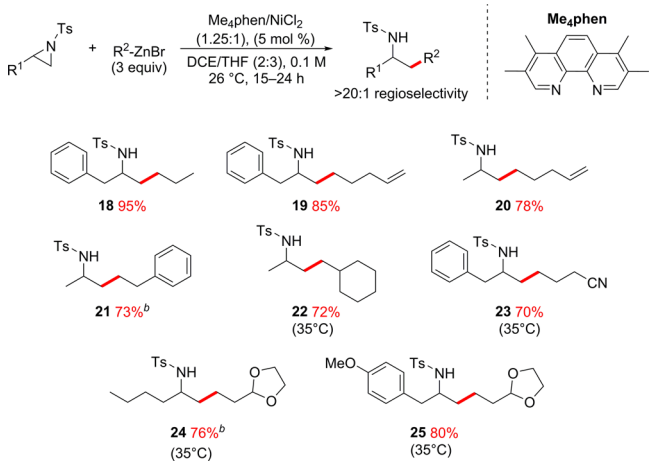


[a]Reactions were performed on 0.50 mmol scale, and yields were determined after purification by column chromatography on silica gel (see Supporting Information for details).

including an alkyl chloride (**7**), ester (**8**), and a phthalimide-protected amine (**9**). Investigation of benzylic substituents was of high priority, as the resulting products complement the motif obtained by the previously published methods that use arylzinc reagents or arylboronic acids as coupling partners.[14,15] Fortuitously, the benzyl-substituted aziridines turned out to work especially well, furnishing the products in excellent yields (84–97%). In general, the outcome seemed to be unaffected by both the electronic properties and the substitution pattern of the aromatic ring. Both electron-withdrawing (**11** and **12**) and electron-donating (**13**–**16**) substituents were tolerated, and the substitution pattern did not affect the outcome. A heterocyclic indole-based substrate also worked well, affording the product **17** in 93% yield. This particular substrate was also evaluated without the *N*-Boc-protecting group; however, this did not lead to the formation of any of the desired coupling product.

Next, a number of organozinc reagents were evaluated.[28] The reaction worked well for both alkene- and arene-containing organozinc reagents, furnishing the products **19**–**21** in good yields (73–85%) (Table 5). Interestingly, the use of 2-phenethylzinc bromide led to significant formation of styrene when the Me_4phen ligand system was employed. By replacing Me_4phen with phenanthroline, the formation of styrene was significantly suppressed and led to a considerably cleaner reaction outcome. The more sterically hindered cyclohexylmethylzinc reagent also underwent cross-coupling to furnish the product **22** in 72% yield. As with the cyclohexylaziridine, a slightly higher temperature was required. Importantly, the reaction proved tolerant of a nitrile-containing organozinc reagent, furnishing the product **23** in 70% yield. The nitrile group is a very versatile

Table 5. Evaluation of Commercially Available Organozinc Reagents in THF[a]

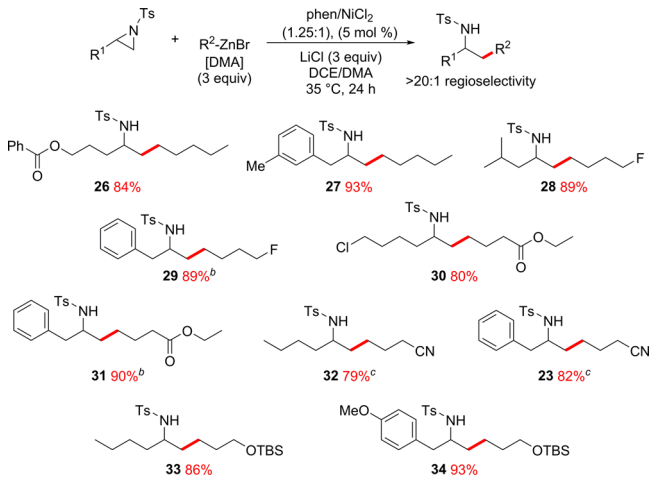


[a]Reactions were performed on 0.50 mmol scale, and yields were determined after purification by column chromatography on silica gel (see Supporting Information for details). [b]1,10-Phenanthroline was employed as ligand.

functional group that can serve as entry to ketones and amines. Notably, the reaction did not proceed when cyanoethylzinc bromide was used. Instead, polymerization of the reaction mixture was observed, presumably due to the formation of acrylonitrile. Finally, an acetal-containing organozinc reagent was evaluated. The products were obtained with high yields (76 and 80%) for both an aliphatic and benzylic aziridine (**24** and **25**).

As a final improvement of the developed cross-coupling reaction, we decided to expand the reaction protocol to include the use of more easily accessible organozinc reagents made in DMA,[29] without the use of highly activated (Rieke-type) zinc (Table 6).[30] Initial attempts to use these reagents showed an

Table 6. Evaluation of Organozinc Reagents Synthesized in DMA[a]



[a]Reactions were performed on 0.50 mmol scale, and yields were determined after purification by column chromatography on silica gel (see Supporting Information for details). [b]3,4,7,8-Tetramethyl-1,10-phenanthroline was employed as ligand. [c]DME used in place of DCE.

almost complete lack of reactivity, suggesting that DMA could be an unsuitable solvent for this transformation. However, when the reaction of a commercially purchased organozinc

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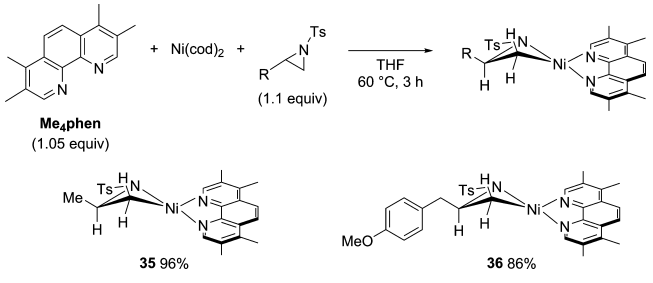
reagent in THF was spiked with DMA, the outcome was not significantly altered. It is well-known that lithium halides can combine with organozinc reagents to form lithium organozincate adducts of the structure $RZnX_2Li$.[31] These zincates generally display improved nucleophilicity over standard organozinc reagents of the type RZnX. This fact led us to suspect that the commercially available alkylzinc halide reagents, made from Rieke zinc, may contain trace amounts of lithium halide salts. Indeed, after a short evaluation of reaction parameters, we found that the addition of LiCl was critical to the reactivity of the organozinc reagents in DMA. In the absence of LiCl, the transmetalation did not occur at an adequate rate to allow the coupling reaction to proceed.

As before, a number of alkylzinc reagents worked well in combination with a variety of aziridines. Both a linear aliphatic and a fluoride-containing reagent furnished the products (**26**–**29**) in good to excellent yields (84–93%). An ester functionality was also tolerated, and the products were formed in high yields (80–90%) for both an aliphatic and a benzylic aziridine (**30** and **31**). The cyanopropyl reagent turned out to work better in DMA than in THF, providing the products (**23** and **32**) in high yields (79–82%). Lastly, a TBS-protected alcohol was evaluated, furnishing the products (**33** and **34**) in high yields (86–93%). It should be noted that the reactivity in DMA is generally diminished compared to the THF system. Consequently, the precatalyst derived from 1,10-phenanthroline was employed for the majority of the reactions.

After having demonstrated that the protocol worked well with a broad selection of substrates, we decided to study the reaction in more detail in order to get a better understanding of the mechanism. Doyle and co-workers have recently described that the azametallacycle formed from styrenylaziridines and (bpy)Ni(cod) did not work well in the coupling reaction.[11] Only with the addition of external dimethyl fumarate ligand were they able to obtain the coupling product, which was formed in a low yield (18%). Consequently, we were interested in elucidating whether the azanickelacyclobutane described by Hillhouse is involved in the present reaction and, if so, whether the oxidative insertion of nickel occurs with inversion. Moreover, we wanted to determine the overall stereochemical course of the terminal carbon (C1) in the cross-coupling reaction sequence through deuterium-labeling studies. We commenced our studies by synthesizing the expected azanickelacyclobutane complexes. Following a similar protocol to that described by Hillhouse,[8] two complexes **35** and **36** were synthesized in excellent yields (86–96%), starting from the Me_4phen ligand and $Ni(cod)_2$ (Scheme 3). The complexes were poorly soluble in

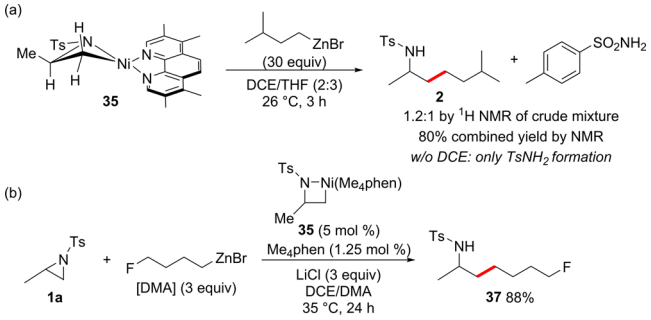
Scheme 3. Synthesis of Azanickelacyclobutane Complexes



THF, allowing their isolation by precipitation from the reaction mixture. In both cases, only the regioisomer derived from oxidative insertion of nickel into the terminal C–N bond was formed. During the synthesis of these complexes, we observed a significant difference in the rate of oxidative insertion depending on the aziridine substituent. For instance, both the PMB- and methylaziridines reacted much faster than the corresponding hexyl-substituted aziridine (not shown). Whereas the insertion occurred at ambient temperature for the two former, elevated temperatures (60 °C) were found to be necessary for the latter case.

With these complexes in hand, we decided to study their ability to undergo transmetalation with the organozinc reagent (Scheme 4a). At first, we subjected the methyl-substituted

Scheme 4. Studies of Azanickelacyclobutane Complexes



complex **35** to the reaction conditions, mimicking the first catalytic turnover (based on 10 mol % catalyst) using 30 equiv of the organozinc reagent. Interestingly, no coupling product was observed under these conditions. All of the metallacycle had been consumed with concomitant formation of *p*-toluenesulfonamide. The reaction was heterogeneous, and we therefore hypothesized that the insolubility of the complex could be the cause of this result. Interestingly, when DCE was added to the mixture, the solution became much less heterogeneous, and in this case, the cross-coupling product **2** was formed in a 1.2:1 ratio to $TsNH_2$ (80% combined NMR yield). This experiment demonstrates that the azametallacycle is indeed a competent reaction intermediate.[32] Moreover, the results suggest that the improved reaction outcome when using DCE as a cosolvent is due to an increased solubility of the catalytic intermediates. The azametallacycle **35** also worked well as a precatalyst (5 mol %) in the coupling reaction between **1a** and fluorobutylzinc bromide, furnishing the product **37** in 88% yield (Scheme 4b). It should be noted that the reaction did not work as well if the additional 1.25 mol % of Me_4phen ligand was not added—the reaction was slower and did not go to full conversion. This is in accordance with the results of the optimization that an excess of ligand relative to nickel is beneficial in this reaction.

After having obtained results that support the intermediacy of the azametallacycle in the reaction mechanism, we decided to examine the stereochemical course of reaction. In order to do so, a deuterium-labeled version of the PMB-substituted aziridine **38** was synthesized and subjected to the coupling conditions (Scheme 5a). The acetal-containing organozinc reagent was chosen for this study since the resulting coupling product easily could be transformed in one step to a cyclic enamine structure **40**.[33] This structure would allow for the determination of stereochemical configuration by NMR analysis. The cross-coupling product **39** was formed in 75% yield, and upon treatment with aqueous HCl in acetone, cyclization to the enamine **40** proceeded in 84% yield. Analysis by NMR spectroscopy showed that the product was formed with essentially complete (>98%)

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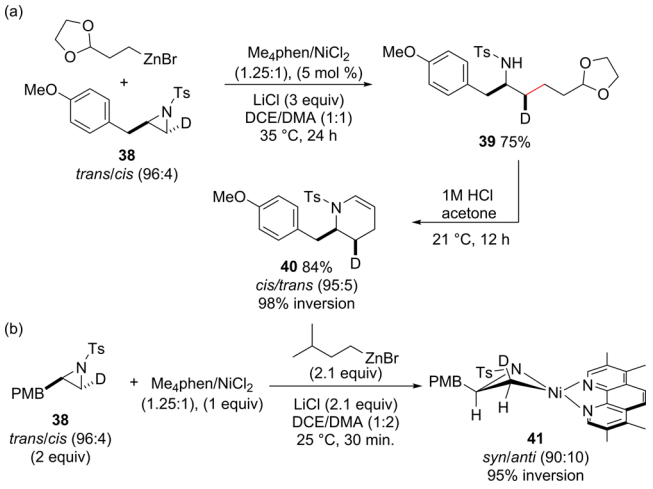
Scheme 5. Cross-Coupling of Deuterium-Labeled Aziridine and Synthesis of the Azametallacycle



inversion at the deuterium-labeled carbon atom.[34] This result is in accordance with the stoichiometric studies by Hillhouse and in contrast to the studies by Doyle, where epimerization is observed at C1 in the coupling reaction.[14]

To further ascertain in which step of the mechanism the inversion occurs, the corresponding azametallacycle of the deuterium-labeled aziridine **38** was investigated (Scheme 5b). Under conditions similar to the cross-coupling reaction, the azanickelacyclobutane **41** was successfully formed with 95% inversion at C1, thereby confirming that the stereochemical inversion occurs in the oxidative insertion step.

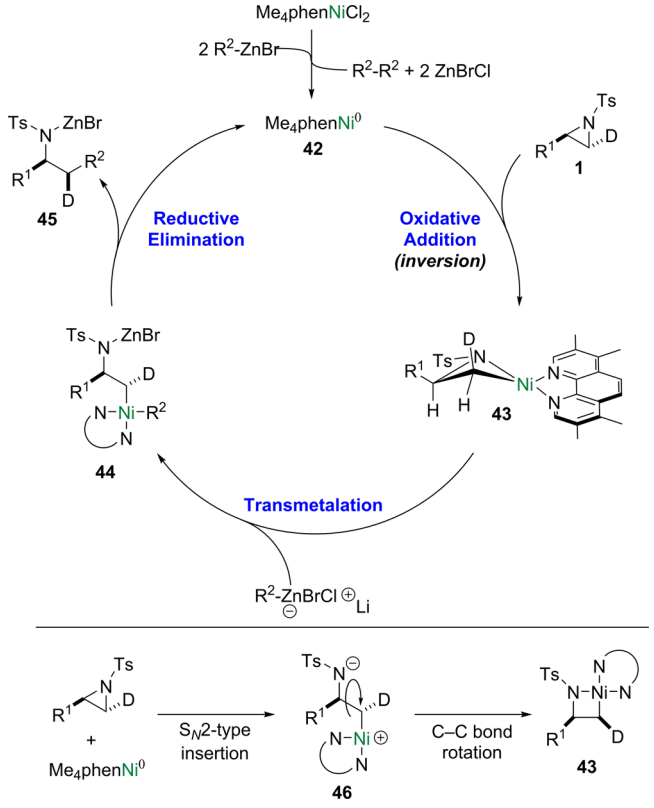
On the basis of these mechanistic studies, we propose a catalytic cycle for the regioselective cross-coupling reaction as outlined in Scheme 6.

The nickel(II) precatalyst is activated by two successive transmetalations of the organozinc reagent followed by reductive elimination.[35] This releases the active nickel(0) catalyst **42**, which undergoes oxidative insertion into the least hindered C−N bond of the aziridine **1**. This step proceeds via an S_N2-type mechanism (inversion) involving attack of nickel at C1 followed by C−C bond rotation (**46**) and ring closure to form azanickelacyclobutane **43**.[36] Subsequent transmetalation[32] (by way of retention) with the organozinc reagent forms intermediate **44**, which undergoes reductive elimination (with retention) to release the product **45** (ZnBr adduct) and a nickel(0) species which re-enters the catalytic cycle.

On the basis of our findings, we hypothesize that the active transmetallating agent is a lithium organozincate, which is known to be more nucleophilic and generally undergoes faster transmetalation than unmodified organozinc reagents. For the reactions performed with DMA as a cosolvent, addition of LiCl was found to be necessary for product formation. As previously discussed, the outcome of the reaction is improved when an excess of ligand-to-nickel is used. Since the oxidative addition proceeds smoothly in the absence of excess ligand, we hypothesize that the additional ligand may be involved in the reductive elimination step.

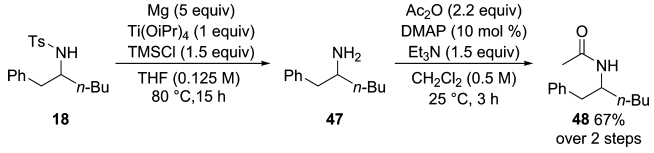
The sulfonamide moiety can be found in a great number of biologically active molecules, including the APIs of numerous drugs, such as sildenafil (erectile dysfunction), sultiame (epilepsy), and brinzolamide (glaucoma).[37] It is also considered a carboxylic acid isostere and has been shown to increase metabolic stability when introduced into certain peptide-like

Scheme 6. Proposed Mechanistic Cycle



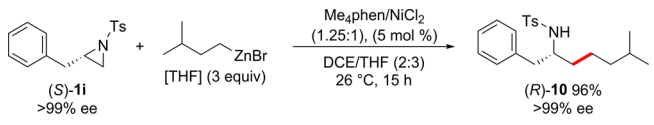
molecules.[38] However, this stability is also the reason why this moiety is sometimes avoided, as it can be challenging to cleave. For that reason, we decided to demonstrate that the tosyl-protecting group can be reductively cleaved to the free amine if desired. Following an adapted literature procedure, the sulfonamide **18** was successfully cleaved using magnesium as a reductant in the presence of titanium tetraisopropoxide.[39] The resulting amine was isolated (after acetylation to form **48**) in 67% yield over two steps (Scheme 7).

Scheme 7. Deprotection of the Sulfonamide



As a final extension, we decided to examine if enantioenriched aziridines could undergo cross-coupling reaction without loss or erosion of enantiopurity. On the basis of the hypothesized mechanism, we anticipated that no erosion should take place, and indeed, when enantiopure benzylaziridine (*S*)-**1i** was subjected to the coupling conditions, the sulfonamide product (*R*)-**10** was formed in excellent yield (96%) and with preserved stereochemistry (>99% ee) (Scheme 8).

Scheme 8. Synthesis of Enantiopure Sulfonamide Product



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CONCLUSIONS

In summary, we have developed the first ligand-controlled, nickel-catalyzed cross-coupling of unactivated aliphatic *N*-tosylaziridines with aliphatic organozinc reagents. The reaction protocol displays complete regioselectivity for reaction at the less hindered C−N bond, and the products are furnished in good to excellent yield for a broad selection of substrates. Moreover, the use of the very air-sensitive $Ni(cod)_2$ was avoided by the development of an air-stable nickel(II) chloride/ligand precatalyst that can be handled and stored outside a glovebox. Besides improving the practicality of the protocol, the exclusion of 1,5-cyclooctadiene from the system also improved the reactivity of the catalyst. Finally, mechanistic investigations, including deuterium-labeling studies, show that the reaction proceeds with overall inversion of configuration at the terminal position of the aziridine by way of aziridine ring opening (S_N2-type) by Ni (inversion), transmetalation (retention), and reductive elimination (retention). These results are in contrast to the previously reported nickel-catalyzed reactions, in which scrambling of the stereoconfiguration at the terminal carbon atom is observed.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data (^1H, ^{13}C, ^{19}F as applicable) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299.

(2) (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (b) Hu, X. *Chem. Sci.* **2011**, *2*, 1867.

(3) For representative examples of nickel-mediated C−N bond activation, see: (a) Wenkert, E.; Han, A.-L.; Jenny, C.-H. *J. Chem. Soc., Chem. Commun.* **1988**, 975. (b) Trost, B. M.; Spagnol, M. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2083. (c) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046. (d) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280. (e) Tobisu, M.; Nakamura, K.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 5587.

(4) (a) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006. (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (c) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (d) Lu, P. *Tetrahedron* **2010**, *66*, 2549. (e) Stanković, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643.

(5) For a recently published review on this topic, see: Huang, C. Y.; Doyle, A. G. *Chem. Rev.* DOI: 10.1021/cr500036t.

(6) (a) Alper, H.; Uros, F.; Smith, D. J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6737. (b) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc.* **1989**, *111*, 931. (c) Lu, S.-M.; Alper, H. *J. Org. Chem.* **2004**, *69*, 3558.

(7) For a stoichiometric $Ni(CO)_4$/LiI-mediated aziridine carbonylation, see: (a) Chamchaang, W.; Pinhas, A. R. *J. Org. Chem.* **1990**, *55*, 2943. For cobalt-catalyzed carbonylation reactions of aziridines, see: (b) Piotti, M. E.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 111. (c) Davoli, P.; Moretti, I.; Prati, F.; Alper, H. *J. Org. Chem.* **1999**, *64*, 518. (d) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2781.

(8) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890.

(9) For a review on azametallacyclobutanes, see: Dauth, A.; Love, J. A. *Dalton Trans.* **2012**, *41*, 7782.

(10) (a) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 15415. For a related study on the Pd-catalyzed isomerization of *N*-tosylaziridines to *N*-tosylimines, see: (b) Wolfe, J. P.; Ney, J. E. *Org. Lett.* **2003**, *5*, 4607.

(11) Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541.

(12) For a Rh(III)-catalyzed C−C coupling between arenes and arylaziridines by C−H activation, see: Li, X. W.; Yu, S. J.; Wang, F.; Wan, B. S.; Yu, X. Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 2577.

(13) For a review on the effect of olefins on transition-metal-catalyzed cross-coupling reactions, see: Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840.

(14) Nielsen, D. K.; Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 13605.

(15) Duda, M. L.; Michael, F. E. *J. Am. Chem. Soc.* **2013**, *135*, 18347.

(16) Takeda, Y.; Ikeda, Y.; Kuroda, A.; Tanaka, S.; Minakata, S. *J. Am. Chem. Soc.* **2014**, *136*, 8544.

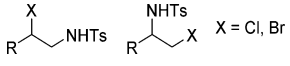
(17) For a review on alkyl-organometallic reagents in cross-coupling reactions, see: Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

(18) For the synthesis of (bpy)Ni(cod) complex, see: Schwalbe, M.; Walther, D.; Schreer, H.; Langer, J.; Görls, H. *J. Organomet. Chem.* **2006**, *691*, 4868.

(19) (a) *Organozinc Reagents, A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(20) Other mechanisms such as retro-[2 + 2] to form a nickel-nitrene and an alkene, radical cleavage, or direct deptronotion by the organozinc reagent cannot be excluded.

(21) Both the Cl- and Br-opened aziridine byproducts were observed. It is anticipated that the source of the chloride could be chloride salts (LiCl) in the organozinc reagents, from the precatalyst, or from DCE when present.



(22) For an overview of the development of nickel(II) precatalysts, see: Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.

(23) For representative examples of the syntheses and applications of Ni(II) precatalysts, see: (a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054. (b) Ge, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12837. (c) Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 1585. (d) Park, N. H.; Teverovskiy, G.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 220. (e) Standley, E. A.; Smith, S. J.; Müller, P.; Jamison, T. F. *Organometallics* **2014**, *33*, 2012.

(24) (a) Pfeiffer, P.; Tappermann, F. *Z. Anorg. Allg. Chem.* **1933**, *215*, 273. (b) Jaeger, F. M.; Dijk, J. A. *Z. Anorg. Allg. Chem.* **1936**, *227*, 273. (c) Fontaine, F. G. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2001**, *57*, m270. (d) Ikotun, O. F.; Ouellette, W.; Lloret, F.; Julve, M.; Doyle, R. P. *Eur. J. Inorg. Chem.* **2007**, 2083. (e) Awad, D. J.; Conrad, F.;

Koch, A.; Schilde, U.; Pöppl, A.; Strauch, P. *Inorg. Chim. Acta* **2010**, *363*, 1488.
(25) See Supporting Information for details on the precatalyst syntheses.
(26) It should be noted that the DCE is able to act as an oxidant by reaction with the nickel(0) catalyst. However, the rate with which this reaction proceeds is lower than the rate of the aziridine activation. When full conversion of the aziridine is obtained, the reaction will eventually discolor due to this reaction. For a reference on this type of reaction, see: (a) Takahashi, S.; Suzuki, Y.; Hagihara, N. *Chem. Lett.* **1974**, *3*, 1363. For a related reaction with DCM, see: (b) Csok, Z.; Vechorkin, O.; Harkins, S. B.; Scopelliti, R.; Hu, X. L. *J. Am. Chem. Soc.* **2008**, *130*, 8156.
(27) It should be noted that these reaction conditions were not applicable to 2-aryl-*N*-tosylaziridines.
(28) Arylzinc reagents did not provide satisfactory results under these conditions, providing the coupling products in low yields.
(29) For the synthesis of alkylzinc reagents in DMA, see Supporting Information and Huo, S. *Org. Lett.* **2003**, *5*, 423.
(30) (a) Rieke, R. D. *Science* **1989**, *246*, 1260. (b) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.
(31) For representative examples, see: (a) Fleckenstein, J. E.; Koszinowski, K. *Organometallics* **2011**, *30*, 5018. (b) Achonduh, G. T.; Hadie, N.; Valente, C.; Avola, S.; O'Brien, C. J.; Organ, M. G. *Chem. Commun.* **2010**, *46*, 4109. (c) Hunter, H. N.; Hadei, N.; Blagojevic, V.; Patschinski, P.; Achonduh, G. T.; Avola, S.; Bohme, D. K.; Organ, M. G. *Chem.—Eur. J.* **2011**, *17*, 7845.
(32) Although the stoichiometric experiments in Scheme 4a indicate that transmetalation with azanickelacyclobutane **43** does proceed, the outcome (product ratios) of those experiments is significantly different from the results obtained in the coupling reaction. Since the relative rates of azametallacycle formation (ring closure) from **46** and transmetalation is unknown, the possibility of transmetalation occurring from the open structure **46** in the catalytic reaction cannot be excluded.
(33) For a study on the synthesis of this type of structures, see: Pattenden, L. C.; Adams, H.; Smith, S. A.; Harrity, J. P. A. *Tetrahedron* **2008**, *64*, 2951.
(34) For a related example, in which the oxidative insertion of nickel into the C−O of an epoxide happens with inversion of configuration, see: Beaver, M. G.; Jamison, T. F. *Org. Lett.* **2011**, *13*, 4140.
(35) For a study on the preparation and reactions of a similar complex (bpy)Ni(Et)$_2$, see: Saito, T.; Uchida, Y.; Misono, A.; Yamamoto, A.; Morifuji, K.; Ikeda, S. *J. Am. Chem. Soc.* **1966**, *88*, 5198.
(36) This mechanism is consistent with the observation of 1,2-disubstituted aziridines being unsuccessful in the coupling reaction.
(37) Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327 and references cited therein.
(38) De Bont, D. B. A.; Sliedregt-Bol, K. M.; Hofmeyer, L. J. F.; Liskamp, R. M. J. *Bioorg. Med. Chem.* **1999**, *7*, 1043.
(39) Shohji, N.; Kawaji, T.; Okamoto, S. *Org. Lett.* **2011**, *13*, 2626.