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Nickel-Catalyzed Negishi Alkylations of Styrenyl Aziridines

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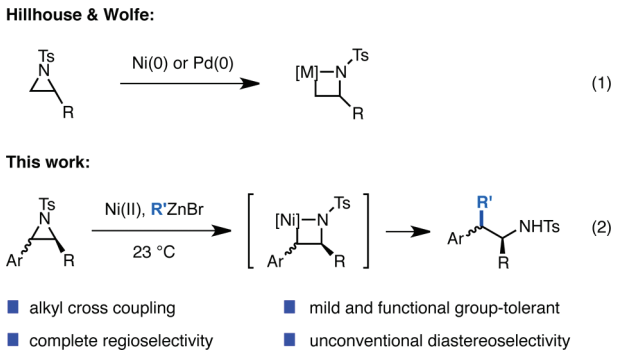
Supporting Information

ABSTRACT: A nickel-catalyzed cross-coupling reaction between *N*-sulfonyl aziridines and organozinc reagents is reported. The catalytic system comprises an inexpensive and air-stable Ni(II) source and dimethyl fumarate as ligand. Regioselective synthesis of β-substituted amines is possible under mild and functional-group-tolerant conditions. The stereoselectivity of the reaction is consistent with a stereoconvergent mechanism wherein the sulfonamide directs C−C bond formation.

Transition-metal-catalyzed cross-coupling reactions have evolved to be one of the most powerful methods for constructing carbon−carbon bonds. Whereas the field of alkyl halide cross-coupling has undergone many significant advances over the past 10 years,[1] comparatively little progress has been made toward the coupling of non-halogen-containing alkyl electrophiles such as ethers and amines.[2] Given that ethers and amines are readily available and have orthogonal reactivity to alkyl halides, practical methods that allow cross-coupling would be extremely attractive for complex molecule synthesis. During the past year, we have described the development of nickel-catalyzed methods that effect C_{sp^3}−C bond formation with classic ether-containing electrophiles, including styrenyl epoxides[3] and allylic *N,O*-acetals.[4] As part of this program, we became interested in developing cross-coupling reactions with aziridines due to their significant value in the preparation of β-substituted amines.[5]



Established methods for alkylation and arylation of aziridines require the use of strong nucleophiles and often afford poor regioselectivity.[6] A transition-metal-catalyzed coupling reaction offers a potentially mild, general, and regioselective solution to these problems. Furthermore, such a process could deliver complementary diastereoselectivity to aziridine ring-opening reactions that classically proceed by inversion of configuration. Here we describe a novel catalyst system that effects room-temperature C−C bond formation between styrenyl aziridines and a broad range of organozinc reagents (eq 2). This operationally simple method affords β-substituted amines with complete regioselectivity and unconventional diastereoselectivity.

The chief barriers to progress in the development of cross-coupling reactions with alkyl electrophiles have been associated with oxidative addition and β-hydride elimination. In the case of aziridines, Hillhouse[7] and Wolfe[8] have demonstrated that oxidative addition with Ni and Pd is relatively facile, affording isolable azametallacyclobutane intermediates from insertion into the less hindered C−N bond of aliphatic *N*-sulfonyl aziridines (eq 1). Nevertheless, coupling reactions that proceed by metal insertion into the C−N bond of an aziridine are not known. Instead, the reaction of Pd(0) with aziridines has been shown to afford imines by a β-hydride-elimination-initiated isomerization.[9] Alternatively, since CO insertion can outcompete β-hydride elimination, aziridines have been converted to β-lactams by various transition-metal catalysts.[10]

To overcome this challenge, we chose a Negishi coupling as our starting point. We hypothesized that organozinc reagents might be effective organometallic partners for cross-coupling with aziridines, as their azaphilicity would facilitate transmetalation. The numerous advantages pertaining to organozinc reagents, including their high functional-group tolerance and preparation under mild conditions, were also key factors in our selection of this reaction manifold.[11] Initial attempts to cross-couple unactivated alkyl aziridines under a range of conditions (Ni source, ligand, solvent) gave no desired product. Instead, we identified a catalyst system that facilitated alkylation of styrenyl aziridines (Table 1).[12] Under the optimal conditions, coupling of *n*-butylzinc bromide with 2-phenyl-*N*-tosylaziridine **2a** in the presence of 5 mol% of a Ni catalyst afforded the cross-coupled product **3** in 71% yield (entry 1).[13] In the absence of a metal catalyst, no product formation was observed (entry 2). In the presence of Ni, C−C bond formation takes place with complete regioselectivity for the internal position, presumably due to the lability of the benzylic C_{sp^3}−N bond and the stability of the resulting complex. These standard conditions are straightforward to execute:[14] the relatively air-stable $NiCl_2$·glyme precatalyst provides an inexpensive and convenient source of Ni, allowing the reaction to be set up on the benchtop rather than in a glovebox.

A screen of privileged ligands, such as phosphines and amines, revealed that none were effective (Table 1, entry 5). Instead, the electron-deficient olefin, dimethyl fumarate **1**, was found to be optimal (compare entries 1 and 6−8).[15] In its

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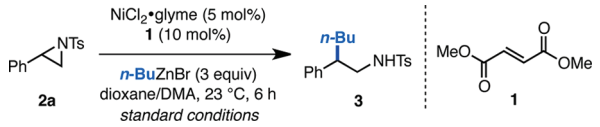
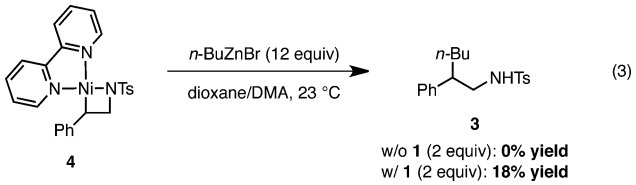
Table 1. Evaluation of Reaction Conditions



entry	conditions	yield[a] (%)	conv[a,b] (%)
1	standard conditions	71	>99
2	no $NiCl_2$·glyme	<2	7
3	$Ni(cod)_2$ instead of $NiCl_2$·glyme	46	>99
4	no dimethyl fumarate (**1**)	4	26
5	10% PPh_3, PCy_3, BINAP, or bpy instead of **1**	<2	12–25
6	10% 4-fluorostyrene instead of **1**	5	47
7	10% maleic anhydride instead of **1**	8	62
8	10% dimethyl maleate instead of **1**	69	>99
9	with 10% bipyridine and 10% **1**	<2	10

[a]Determined by HPLC, 0.05 mmol scale. [b]*N*-Tosyl-2-phenylethylamine (reduced product) was the major byproduct.

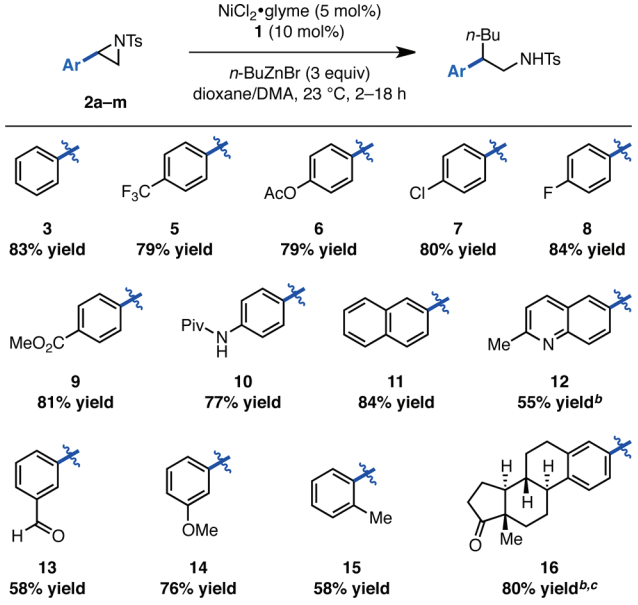
absence, only trace product was detected (entry 4). Electron-deficient olefins have been shown to accelerate reductive elimination by association to a metal center,[16] and Knochel has utilized electron-withdrawing styrenes as ligands in catalytic cross-coupling reactions of alkyl electrophiles.[17] We propose that dimethyl fumarate plays a similar role, accelerating reductive elimination from a dialkylorganonickel intermediate. To evaluate this proposal, we performed a stoichiometric study between azametallacyclobutane **4**, prepared according to the procedure of Hillhouse,[7] and *n*-BuZnBr. Only in the presence of **1** did C–C bond formation take place to afford **3** (eq 3). The result provides preliminary support for the role of **1** in facilitating C–C bond formation. Nevertheless, the reaction efficiency of this stoichiometric process was quite low due to the presence of bipyridine as a ligand, which was required for isolation of **4** but is itself a poor ligand in the catalytic reaction (Table 1, entries 5 and 9).



(3)

The scope of this methodology was first examined by varying the aziridine component. Electron-deficient and electron-rich *para*- and *meta*-substituted styrenyl aziridines reacted with high efficiency (Table 2, **3**–**10**, **13**, **14**). As a probe for the relative reactivity of the electrophile, a substrate bearing a *p*-chloro substituent was subjected to the standard reaction conditions. This substrate underwent coupling in 80% yield, with the aryl chloride remaining intact (**7**).[18] The orthogonal reactivity of the aziridine and chloro groups provides a useful opportunity for elaboration of the amine products by cross-coupling. Various functional groups that are incompatible with the strong nucleophiles required for traditional aziridine ring-opening protocols were also tolerated, including a protic amine (**10**), benzaldehyde (**13**), and ketone (**16**), as was *ortho*-substitution (**15**). Finally, promising reactivity was observed with heteroaryl-containing substrates (**12**) despite the presence of a strongly Lewis basic site that could poison the catalyst system. To demonstrate the practicality of the protocol, a gram-scale reaction was performed with *p*-fluoroaziridine **2e** to afford **8** in 77% yield.

Table 2. Scope of Styrenyl Aziridines[a]



[a]Yields are the average of two runs, 0.50 mmol scale. [b]One run, 0.15 mmol scale. [c]5.3:1 dr (unassigned), see SI for details.

The scope of the zinc reagents was explored next. We found that a wide variety of functional groups were tolerated, including alkyl chlorides (**18**), silyl ethers (**19**), acetals (**20**), boronate esters (**21**), and nitriles (**22**) (Table 3). However, unhindered Lewis basic functional groups in addition to secondary alkyl groups proved problematic.[19] Notably, the use of an aryl nucleophile results in modest reactivity (**24**) and provides an attractive complement to Friedel–Crafts arylations of styrenyl aziridines with electron-rich arenes.[20]

The reaction is not limited to terminal aziridines. 1,2-Disubstituted aziridines are also suitable substrates, although higher catalyst loading is required. For instance, the indene-derived aziridine **25** underwent coupling to afford **26** in 52% yield (eq 4). Especially interesting is that the reaction delivered **26** exclusively as the *cis* diastereomer, a stereochemical outcome inaccessible to conventional nucleophilic aziridine ring-opening reactions.[21] Since the enantiomeric excess of **25** was completely conserved in the formation of product, it appears that C–C bond formation outcompetes β-hydride elimination/hydride

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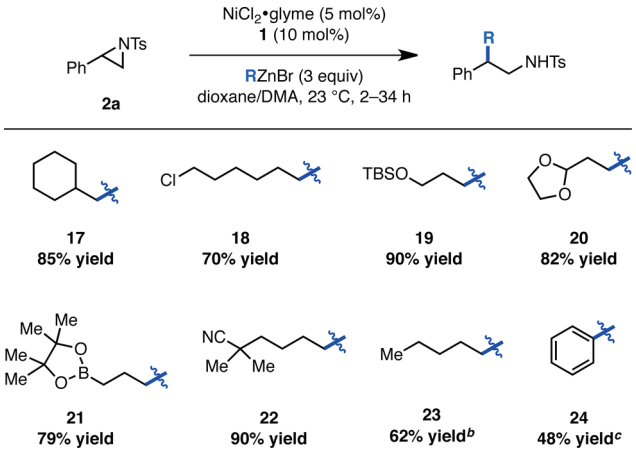
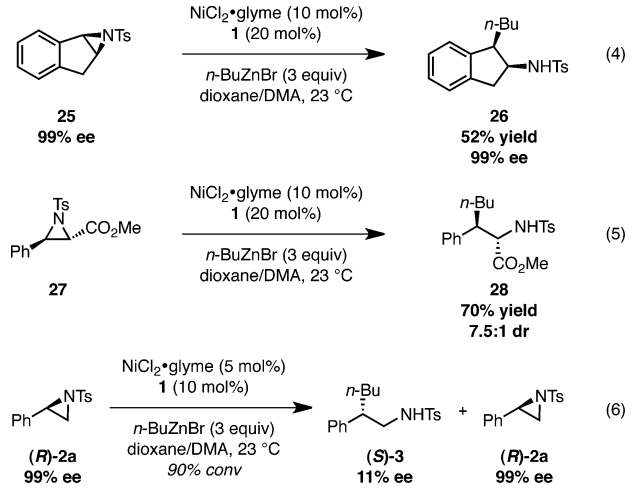
Table 3. Scope of Organozinc Reagents[a]



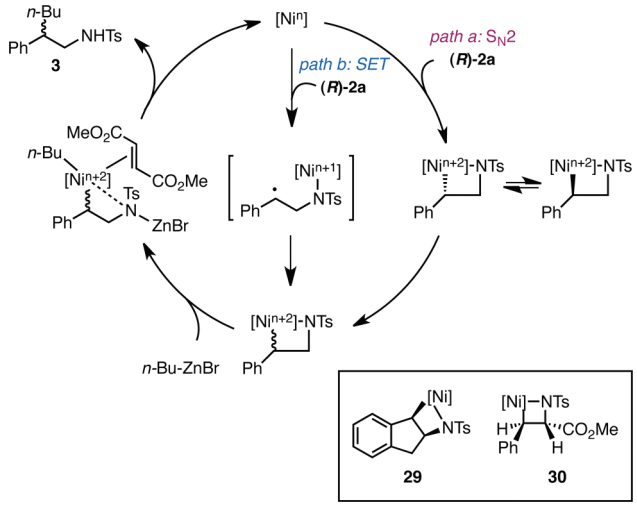
[a]Yields are the average of two runs, 0.50 mmol scale. [b]*n*-PentylZnI. [c]PhZnBr inTHF.

insertion processes. Additionally, cross-coupling with the aziridine derived from *trans*-methyl cinnamate **27** gave the α-amino acid derivative **28** in 70% yield (eq 5). In line with the results for indene-derived aziridine **25**, C−C bond formation with **27** proceeded primarily with retention of configuration, delivering **28** in 7.5:1 dr.[22]



To gain a better mechanistic understanding of the stereochemical course of these reactions, we subjected enantiopure styrenyl aziridine (*R*)-**2a** to the standard reaction conditions (eq 6). The cross-coupled product **3** was generated in 11% ee, with the major enantiomer corresponding to inversion of configuration. In addition, the ee of recovered aziridine **2a** remained unchanged throughout the course of the reaction. An S_N2-type oxidative addition accompanied by reversible homolysis of the benzylic Ni−C bond,[23] or an irreversible single-electron transfer (SET) oxidative addition, could account for these data (Scheme 1, path a or b). Hillhouse[7] and Wolfe[8] have demonstrated that an S_N2 mechanism is operative for oxidative addition of Ni and Pd to aliphatic *N*-Ts aziridines. A few features of our catalytic system, however, are not entirely consistent with this mechanism and prior observations. Namely, aliphatic aziridines are unreactive and styrenyl aziridines undergo alkylation with regioselectivity opposite to that expected in an S_N2 process.[24,25] This substrate dependence and regioselectivity are more consistent with a SET oxidative addition, which has been proposed for Ni-catalyzed cross-

Scheme 1. Proposed Catalytic Cycle



coupling reactions with alkyl halides.[26] Nevertheless, it is less clear how a SET mechanism would afford predominantly inversion in the alkylation of (*R*)-**2a**.

Both mechanisms are consistent with the results obtained with aziridines **25** and **27**. It is expected that sulfonamide coordination to Ni directs radical recombination and subsequent C−C bond formation.[27] In the case of indene-derived aziridine **25**, the *n*-butyl group is delivered on the same face of the indenyl ring as the sulfonamide via metallacycle **29**. In the case of the *trans*-methyl cinnamate-derived aziridine **27**, the major diastereomer is obtained from the more stable *trans*-azametallacycle **30**. Sulfonamide coordination may also be important in preventing β-H elimination by limiting the conformational flexibility of intermediate alkylnickel species.[28] Although a Ni(I)/Ni(III) cycle cannot be precluded, a Ni(0)/Ni(II) cycle is proposed since the Ni(II)-azametallacycle **4** was a competent substrate for C−C bond formation. Finally, dimethyl fumarate **1** is expected to accelerate reductive elimination by association to the metal center.

In conclusion, we have developed a Ni-catalyzed ring-opening reaction of styrenyl aziridines with organozinc reagents. The alkyl cross-coupling reaction is accomplished by a novel catalytic system consisting of a Ni(II) source and dimethyl fumarate as ligand. In contrast to traditional nucleophilic aziridine ring-opening chemistry, the mild conditions of this protocol tolerate a wide variety of functional groups. We propose that a sulfonamide-directed C−C bond-forming mechanism is responsible for the high diastereoselectivity. Our future efforts will be directed at elucidating the mechanism of this process and its synthetic scope.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, details of optimization studies, and spectroscopic data 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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(13) Other *N*-protecting groups showed inferior reactivity: *N*-Boc, 25% yield; *N*-Ns, 10% yield.

(14) Experimental procedure: In the air, a threaded tube was charged with $NiCl_2$·glyme (0.05 equiv), dimethyl fumarate (0.10 equiv), and aziridine (1.0 equiv), and the tube was sealed and evacuated/refilled with argon three times. DMA, dioxane, and then the zinc reagent (3.0 equiv as a 1.6 M solution in DMA) were added. The mixture was stirred at room temperature under argon. See SI for more details.

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