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Palladium-Catalyzed Cross-Coupling of Aziridinylmetal Species, Generated by Sulfinyl−Magnesium Exchange, with Aryl Bromides: Reaction Optimization, Scope, and Kinetic Investigations

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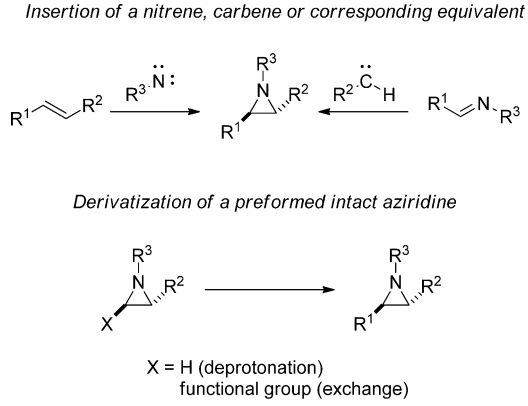
Supporting Information

ABSTRACT: A series of novel, highly substituted *N*-PMP aziridines have been accessed in high yields by palladium-catalyzed cross-coupling of intact aziridines. The cross-coupling employed aryl bromides and tertiary organometallic aziridines, generated from sulfinylaziridines by sulfinyl−magnesium exchange and transmetalation to the aziridinylzinc with zinc chloride. A wide range of electron-rich and electron-poor aryl bromides were utilized to afford the functionalized aziridine products as single diastereoisomers with retention of configuration at the reacting center. Assessment of the reaction kinetics showed zero-order in both the aziridine species and the aryl bromide. This indicated that the rate-determining step was reductive elimination from the palladium(II) species bearing both the aziridine and aryl groups to form the hindered C−C bond. The intermediate aziridinylzinc species underwent a progressive, background degradation that led to a plateau in yield and afforded reduced yields in substrates with *ortho*-substituted aryl groups, which are less reactive due to the additional steric demands.

INTRODUCTION

Aziridines are widely used and valuable intermediates in synthetic chemistry.[1] They have found particular use in nucleophilic ring-opening reactions, because of strain in the 3-membered ring, to afford β-functionalized amines.[2] In addition, aziridines can undergo a range of cycloaddition and rearrangement reactions, allowing their application in the synthesis of a variety of heterocycles.[3,4] As a consequence of their utility, a range of methods for the synthesis of aziridines has been developed, often involving the addition of carbene or nitrene equivalents to imines or alkenes respectively (Scheme 1).[5]

Scheme 1. Strategies for the Synthesis of Aziridine Derivatives



In order to access a range of functionalized aziridine products, a conceptually appealing strategy is to transform an already constructed aziridine scaffold. To date, such functionalization has been achieved through the generation of aziridinyl anions followed by reaction with, typically highly reactive, electrophiles.[6] The required aziridinyl metal species have been generated by two approaches: direct deprotonation[7] and exchange of a suitable functional group.[8] Deprotonation of aziridines with organolithium and lithium amide bases can proceed with high regio- and stereoselectivity, which is determined by the structure of the aziridine.[6c,7] In a complementary, alternative approach, metal-functional group exchange has been shown to afford aziridinyl anions at the preassigned position.[6,8,9] Utilizing such aziridinylmetal intermediates, Satoh disclosed a copper(I)-mediated alkylation reaction with reactive alkyl halides.[9] Vedejs recently reported the seminal example of catalytic cross-coupling of an aziridinyl metal species with aryl and vinyl halides (Scheme 2a).[10] In this methodology, aziridinyltin compounds were treated with butyllithium at low temperature to promote exchange. With careful temperature control, the resulting aziridinyllithium was then converted to the organozinc before the addition of a Pd catalyst and aryl halide to effect the cross-coupling. Similarly, an example of the cross-coupling of an in situ generated metalated epoxide is known.[11]

Metal−sulfinyl exchange is a methodology that is gaining increased use in the generation of complex organometallic species for strategic C−C bond-forming reactions. The required

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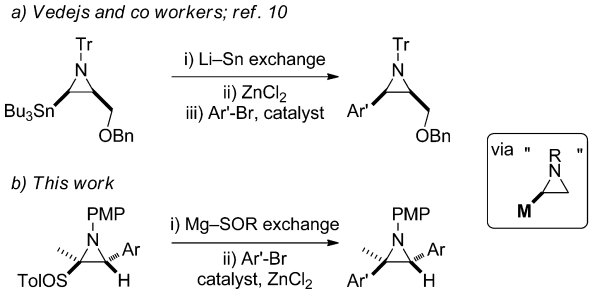
Scheme 2. Cross-Coupling of Aziridinylmetal Species



sulfoxide compounds are attractive precursors since they are typically stable and can function as the source of chiral information.[12−14] Treating sulfoxides with organometallic reagents (RLi or RMgX) leads to substitution at sulfur, expelling a new, more stable, organometallic species.[15] Sulfoxide exchange has been used to generate three-membered ring organometallics, in the form of aziridines,[16,8b,9] epoxides,[17] and cyclopropanes,[18] for reaction with reactive electrophiles. Exchange from aryl sulfoxides has previously been used in combination with palladium-catalyzed cross-coupling reactions with aryl halides,[12a] but this approach has not been applied to the catalytic cross-coupling of small rings or sp^3 centers to date.

We are interested in methods for the derivatization of intact heterocyclic rings. To achieve this, we were keen to investigate the cross-coupling of aziridines to access novel, highly substituted aziridines and, in particular, to determine whether cross-coupling at a *tertiary*-aziridinyl organometallic species could be achieved.[19] Recent years have seen major advances in the transition-metal-catalyzed cross-coupling of secondary,[20] and to a lesser extent tertiary,[21] alkylmagnesium and -zinc reagents. For this purpose, the development of ligands for palladium and nickel catalysis has enabled reactions to occur at low temperatures appropriate for the potentially unstable organometallic species involved. With this in mind, we were inspired by a remarkable observation from Satoh and co-workers that an *N*-PMP aziridinylmagnesium species, generated by sulfoxide exchange, was "stable at room temperature for several hours without decomposition and structural isomerization".[16a] We envisaged that this could provide an opportunity to efficiently access novel, highly substituted aziridines with cross-coupling to sp^2 centers.

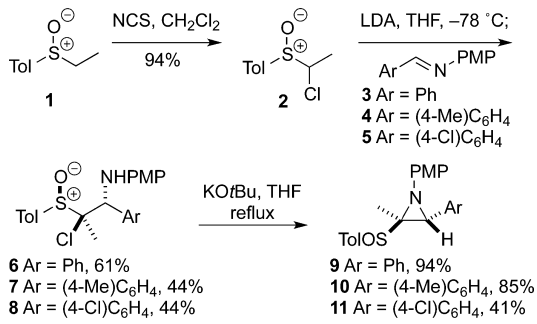
The stability of aziridinyl metals is not well established under cross-coupling conditions. In Vedejs' seminal work, a CH_2OBn group was installed on the same face of the aziridine as the metal, which may be viewed as a stablilizing, coordinating group for the intermediate aziridinylmetal species (M = Zn, Pd). We envisaged that in the absence of a coordinating group the potential instability of the aziridinyl species would dictate that a rapid cross-coupling reaction would be crucial for success. Consequently, we were keen to gain further insight into the cross-coupling by examining the reaction kinetics. Furthermore, we intended to investigate a less toxic alternative to the Bu_3Sn group used in the Vedejs reaction.

Here, we report studies into the palladium-catalyzed cross-coupling of aziridinyl metal species formed by sulfinyl exchange and transmetalation with zinc chloride, affording novel highly substituted aziridine structures in high yields (Scheme 2b). We report the optimization of each stage of the reaction and the scope of the cross-coupling of the in situ generated tertiary organometallics with a wide range of aryl bromides. We also report our studies into the kinetics of this catalytic cross-coupling and assessment of the stability of the azirdinyl metal species.

RESULTS AND DISCUSSION

Synthesis of Sulfinylaziridines and Reaction Optimization. The sulfinylaziridine substrates were prepared by the route previously reported by Satoh (Scheme 3).[16,8b] First, ethyl

Scheme 3. Preparation of Sulfinylaziridines 9−11



tolyl sulfoxide **1** was chlorinated at the α-position by treatment with NCS.[22−24] Deprotonation of chlorosulfoxide **2** with LDA was followed by addition to *N*-PMP imines **3**−**5** bearing aromatic substituents. In each case, the addition proceeded with >95:5 diastereoselectivity[25] to efficiently install three contiguous stereocenters in β-chloroamines **6**−**8**. Subsequent base-mediated cyclization on treatment with KO-*t*-Bu proceeded efficiently to give sulfinylaziridines **9**−**11**.[16,8b]

With sulfinyl aziridines **9**−**11** in hand, we initially examined conditions for sulfinyl−metal exchange by modifying those used by Satoh. In the generation of aziridinylmagnesium species for reaction with electrophiles, Satoh used 3.5 equiv of EtMgBr with addition of the substrate to the Grignard reagent and a reaction time of 2 h.[8b] Since the Grignard reagent could interfere with the desired cross-coupling reaction or cause other side reactions, we reduced this quantity. It was found that the use of 1.5 equiv of EtMgBr was sufficient to consume all of the sulfinylaziridine, generating ethyl tolyl sulfoxide as a side product and the desired aziridinylmagnesium. Although the sulfinyl exchange occurred at a temperature above −20 °C, the reaction mixture was warmed from a lower temperature for improved temperature control and to allow the excess Grignard reagent to scavenge any trace water present prior to exchange. Under these conditions, quenching the intermediate after 30 min at room temperature afforded a 65% yield of aziridine **12** (Scheme 4). Quenching the intermediate with MeOD-d_4 afforded [**D**]-**12** with complete deuterium incorporation. These conditions for SOR−Mg exchange from sulfinylaziridine **9** were employed for our initial investigation into the cross-coupling reaction.

A large number of metal and ligand systems were screened to effect the cross-coupling with PhBr in THF and form aziridine **13**. Reactions were performed at room temperature due to concerns for the stability of the aziridinylmetal at higher temperatures. Applying conditions recently developed for comparable alkyl cross-coupling reactions,[20b,c,21a] we initially examined nickel catalysts. However, all attempts were unsuccessful, both with and without transmetalation of the nucleophile with $ZnCl_2$. Next, we examined a range of palladium metal sources and despite widely screening ligands

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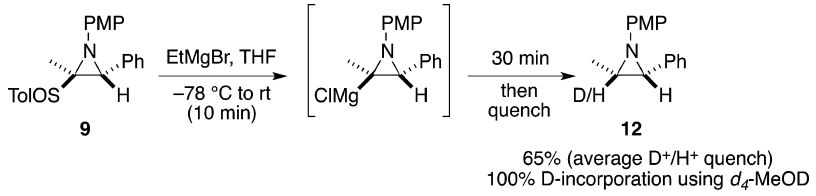
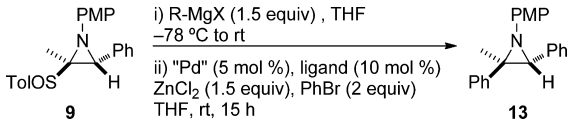
Scheme 4. Sulfinyl−Magnesium Exchange from Aziridine 9 To Generate the Required Aziridinylmagnesium and Proton Quench To Form Aziridine 12



were unable to effect the desired cross-coupling directly from the aziridinylmagnesium intermediate. In these cases, protonated aziridine **12** was commonly recovered from the reaction mixture after aqueous workup. Therefore, we examined the reaction with added zinc salts to facilitate transmetalation through the intermediacy of an aziridinylzinc. Formation of this aziridinylzinc was carried out in situ to simplify the reaction setup: a solution of the catalyst mixture and zinc chloride was added to the solution of the aziridinylmagnesium.[26] In the presence of $ZnCl_2$, and using 2 equiv of bromobenzene, a wide variety of ligands were tested with $Pd(OAc)_2$ and $Pd_2(dba)_3$, though the vast majority were unsuccessful in promoting the coupling reaction, including Ph_3P, $(o\text{-Tol})_3P$, Cy_3P, $(furyl)_3P$, Mor-DalPhos, dppf, diop, and PEPPSI-IPr. Only the use of palladium catalysts with bulky, electron-rich ligands was effective, indicating a narrow tolerance of the reaction for ligand structure (Table 1, entries 1−6). The combination of

Table 1. Successful Palladium/Ligand Combinations and Selected Optimization in Cross-Coupling Reactions To Afford Aziridine 13



entry	RMgX	Pd source	ligand	yield[a] (%)
1	EtMgBr	$Pd_2(dba)_3$	$(t\text{-Bu})_3P$	45
2	EtMgBr	$Pd(OAc)_2$	BrettPhos	13
3	EtMgBr	$Pd(OAc)_2$	DavePhos	8
4	EtMgBr	$Pd(OAc)_2$	RuPhos	17
5	EtMgBr	$Pd(OAc)_2$	SPhos	20
6	EtMgBr	$Pd(OAc)_2$	4′-MeO-SPhos	24
7[b]	EtMgBr	$Pd_2(dba)_3$	$(t\text{-Bu})_3P$	24
8	*i*-PrMgCl	$Pd_2(dba)_3$	$(t\text{-Bu})_3P$	61
9	*i*-PrMgCl·LiCl	$Pd_2(dba)_3$	$(t\text{-Bu})_3P$	38
10	*t*-BuMgCl	$Pd_2(dba)_3$	$(t\text{-Bu})_3P$	0[c]

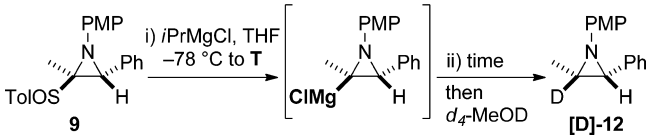
[a]Yield determined by ^1H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene). [b]One equivalent of TolS(O)Et added following exchange. [c]60% remaining sulfinylaziridine **9** observed.

$Pd_2(dba)_3$ and tri-*tert*-butylphosphine at room temperature gave the highest yield of aziridine **13** (45%, entry 1). Running the reaction at 0 °C did not give conversion, while performing the reaction at 40 °C afforded yields similar to those obtained with the room temperature procedure. The application of zinc chloride afforded marginally superior yields compared to zinc bromide, and a palladium/ligand ratio of 1:2 was found to be optimal. Several Buchwald ligands in combination with $Pd(OAc)_2$ also afforded the desired compound (entries 2−6) in low yields, though these were unsuccessful in combination with $Pd_2(dba)_3$.

The specific Grignard reagent used for sulfinyl−magnesium exchange was then examined. We were aware that the presence of the sulfoxide side product (TolSOEt **1** when using EtMgBr) generated in stoichiometric amounts may have an effect on the catalytic cross-coupling process. The addition of 1 equiv of sulfoxide **1** to the reaction mixture immediately after sulfoxide exchange afforded a reduced yield of aziridine **13** in the overall cross-coupling process (Table 1, entry 7). Switching to *i*-PrMgCl afforded an improved yield (entry 8), and further studies continued with this reagent. The use of the *i*-PrMgCl·LiCl complex was detrimental to the result (entry 9), and the use of *t*-BuMgCl did not result in effective exchange (entry 10).

Having changed the Grignard reagent employed, we examined more closely the sulfinyl−magnesium exchange protocol to determine optimum conditions and time frame for the exchange prior to addition of the cross-coupling reagents. To carry out this investigation, the aziridinyl Grignard intermediate was formed using *i*-PrMgCl (1.5 equiv) before quenching with MeOD-d_4. Under the conditions used above for sulfinyl−magnesium exchange (Table 1), the deuteroaziridine [**D**]-**12** was formed in only 66% yield (100% D incorporation, Table 2, entry 1). The reaction concentration, time before quench, temperature of exchange, and order of addition were examined, and each variable led to an improvement in the aziridine yield (entries 2−5). Combination of these improvements afforded [**D**]-**12** in quantitative yield (entry 6). In each case, 100% D-incorporation was observed by ^1H NMR.

Table 2. Sulfinyl−Magnesium Exchange Reaction of Sulfinyl Aziridine 9 Quantified by Quenching with MeOD-d_4 To Form [D]-12



entry	conc (M)	temp T[a] (°C)	time (min)	yield[b] (%)
1[c]	0.30	rt	30	66
2[c]	0.15	rt	30	73
3[c]	0.15	rt	0	77
4[c]	0.15	0	30	79
5[d]	0.15	rt	30	88
6[d,e]	0.15	0	0	98

[a]In all cases, the reaction was warmed to the temperature over 10 min in a water bath and then held at that temperature for the specified time before the addition of MeOD-d_4. [b]Yield determined by ^1H NMR spectroscopy with reference to an internal standard (1,3,5-trimethoxybenzene); 100% D-incorporation was observed in all cases. [c]Aziridine **9** added to *i*-PrMgCl (1.5 equiv) at −78 °C. [d]*i*-PrMgCl (1.5 equiv) added to aziridine **9** at −78 °C. [e]This exchange procedure was used for subsequent investigations.

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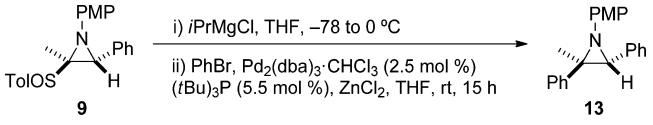
Pleasingly, applying the improved procedure for the generation of the aziridinylmetal increased the cross-coupling yield to 77% under otherwise similar conditions (Table 3, entry 1). Following the recent report by Ananikov, on the purity of commercial $Pd_2(dba)_3$,[27] we prepared the catalyst precursor $Pd_2(dba)_3{\cdot}CHCl_3$ by recrystallization from $CHCl_3$. The use of this catalyst afforded a slight improvement in yield (entry 2). This palladium source also allowed a reduction in the ligand loading from 10 mol % to 5.5 mol %, presumably due to more uniform Pd species, which gave a further increase in yield (entry 3). Under these conditions an 80% yield of aziridine **13** was obtained following chromatography on basic alumina (entry 3 and Table 4, entry 1); a reduced yield was obtained when **13** was purified on silica gel due to decomposition of the products. The application of both chloro- and iodobenzene was unsuccessful with these conditions.

Table 3. Final Optimization of Catalyst System



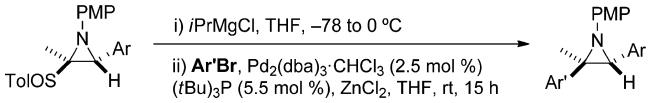
entry	Pd source (2.5 mol %)	ligand loading (%)	yield[a] (%)
1	$Pd_2(dba)_3$	10	77
2	$Pd_2(dba)_3{\cdot}CHCl_3$	10	82
3	$Pd_2(dba)_3{\cdot}CHCl_3$	5	87 (80)

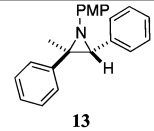
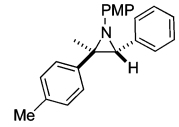
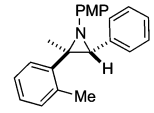
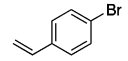
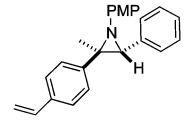
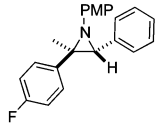
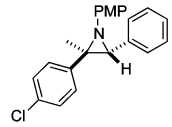
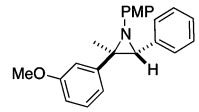
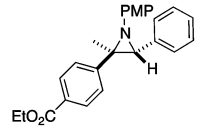
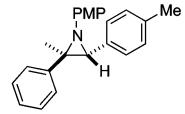
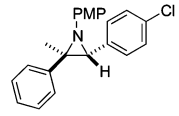
[a]Determined by ^{1}H NMR spectroscopy with respect to an internal standard (1,3,5-trimethoxybenzene) except where given in parentheses.

Reaction Scope. Using our optimized set of reaction conditions, we examined the scope of the reaction by varying the aryl bromide component. The reaction was found to be successful for a variety of aryl bromides, forming novel aziridine derivatives in high yields (Table 4). A high yield was achieved with *p*-tolyl bromide, but a significantly lower yield was obtained for *o*-tolyl bromide (entries 2 and 3) due to the additional steric demands. Vinyl and fluoro substituents were well tolerated (entries 4 and 5), and the selectivity for aryl bromides over chlorides permitted the use of 1-bromo-4-chlorobenzene, which afforded the chloride-containing aziridine product exclusively (entry 6). The 3-methoxy-substituted aziridine **19** was formed in high yield (entry 7). However, all attempts to form the 4-methoxy derivative were unsuccessful leading to decomposition, presumably due to opening of the aziridine ring to form the highly stabilized tertiary benzylic carbocation under the reaction conditions. Ester functionality was tolerated in the presence of the Grignard reagents, and the corresponding cross-coupled aziridine was formed in high yield (entry 8). In this example, and also the styryl example, a minor side product due to dimerization of the aryl bromide was observed. Finally, the cross-couplings of aziridines **10** and **11**, bearing different substitution on the aziridine aromatic group, with PhBr were successful giving aziridines **21** and **22** in good yield (entries 9 and 10).

In all cases, the isolated products were single diastereoisomers with retention at the cross-coupled center as defined in the sulfinylaziridine.[28] The stereochemistry of aziridine **17** was examined by a selective NOE experiment (Figure 1 and Supporting Information). On irradiation of the aziridinyl proton (NCH, δ = 4.05), a strong enhancement was observed for the signal of the fluorophenyl group (5.48%, δ = 7.24–

Table 4. Scope of Aziridine Cross-Coupling Procedure



entry[a]	sulfinyl-aziridine	ArBr	product	yield (%)[b]
1	**9**	PhBr	 **13**	80
2	**9**	(4-Me)C_6H_4Br	 **14**	70
3	**9**	(2-Me)C_6H_4Br	 **15**	28[c,d]
4	**9**		 **16**	82[e,d]
5	**9**	(4-F)C_6H_4Br	 **17**	70
6	**9**	(4-Cl)C_6H_4Br	 **18**	65
7	**9**	(3-MeO)C_6H_4Br	 **19**	81
8	**9**	(4-EtO_2C)C_6H_4Br	 **20**	72[e,d]
9	**10**	PhBr	 **21**	63
10	**11**	PhBr	 **22**	65

[a]Reaction conditions: sulfinylaziridine **9**/**10**/**11** (0.265 mmol), *i*-PrMgCl (0.397 mmol), −78 to 0 °C; ArBr (0.530 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), (*t*-Bu)$_3$P (5.5 mol %), $ZnCl_2$ (0.397 mmol), 15 h, rt. [b]Isolated yields. [c]Contained aziridine **12** as an inseparable impurity (6% yield). [d]Yield calculated based on desired product only. [e]Contained Ar–Ar dimer as an inseparable impurity (<1:9).

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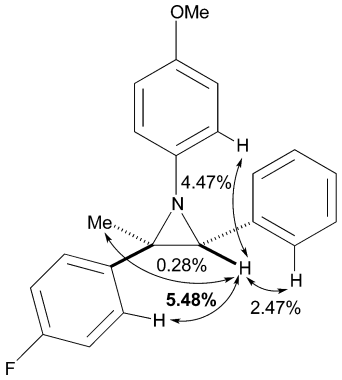

Figure 1. Selective NOE NMR experiment in aziridine **17**.

7.19), with only a weak enhancement to the signal of the methyl group (0.28%, δ = 1.49). These data are consistent with a *cis*-relationship between the aziridinyl proton (NCH) and the fluorophenyl group as in the stereochemistry assigned. Indeed, the fluorophenyl signal displays the largest enhancement. By analogy, the other products (**13**−**16**, **18**−**22**) are assumed to have the same stereochemistry. This is consistent with the stereochemical outcomes of the quenching experiments to form **12** from the aziridinylmagnesium intermediates (characteristic *cis*-coupling constants, ^3J NCH-NCH = 6.5 Hz). This is also consistent with the stereochemical outcome observed by Vedejs[10] and in other transmetalation and cross-coupling reactions of 3-membered rings.[18,16,29]

Stability of Aziridinylzinc Species and Cross-Coupling Reaction Kinetics. As reported by Satoh,[16a] the aziridinylmagnesium appears to be largely stable even at relatively high temperatures. In the quenching experiments above, using MeOD, 100% D incorporation is observed with both the EtMgX and *i*-PrMgX exchange protocols. This demonstrates that there is no proton transfer from the α-protons of the sulfoxide byproduct, resulting in quenching of the organomagnesium intermediate, as this would result in the formation of **12** bearing a proton on the aziridine. This is important to enable use of a smaller excess of Grignard reagent compared with the conditions reported by Satoh; in that protocol, the excess Grignard could deprotonate the TolS(O)CHR_2 formed preventing proton transfer to the substrate.[30] This indicates that the aziridinyl Grignard formed is not sufficiently basic to abstract a proton from the α-position of the sulfoxide side product under the conditions employed.

It was notable during optimization that for reactions performed in the presence of $ZnCl_2$ where the desired aziridine was not formed, aziridine-containing side products were not observed. For comparable attempted reactions in the absence of zinc salts, on quenching the reaction aziridine **12** was formed in good yield. However, following the addition of $ZnCl_2$, attempts to quench the aziridinylzinc intermediate with proton sources including H_2O, MeOH, or AcOH did not form **12** in more than a few percent yield. Unfortunately, we were unable to identify any side products from the decomposition of the aziridinylmetal intermediates.

Having established effective reaction conditions, we examined the kinetics of the palladium-catalyzed cross-coupling to provide some insight into the rate and mechanism of the reaction with its complex organometallic partner. Negishi-type cross-coupling reactions typically display rapid transmetalation and rate-determining oxidative addition or reductive elimination, but the exact mechanisms of these elementary steps and the resulting rate laws are highly sensitive to variations in the conditions and additive effects.[31]

Determination of reaction kinetics was achieved through a sampling assay. To achieve this, the reaction was carried out in the presence of an internal standard (1,3,5-trimethoxybenzene), which had been verified to have no effect on the yield. Aliquots of the reaction mixture were quenched by addition to MeOH and inorganic salts were removed by filtration through a plug of silica to give a sample for ^{1}H NMR analysis. Yields at a given sampling time were then determined by comparison of the NMR integrals of the product **13** and the internal standard. An increased ligand loading (10 mol %) was employed compared to the standard reaction conditions because with a lower loading catalyst degradation occurred, which led to inconsistent results; this was presumably due to loss of inertion during the sampling process and resulting loss of the highly oxygen-sensitive phosphine ligand. In addition, aliquots required careful handling and rapid processing to avoid product degradation in the crude mixture prior to analysis.

Monitoring the appearance of cross-coupled product **13** by ^{1}H NMR showed the reaction using aziridine **9** and PhBr was complete in approximately 4 h. Strikingly, the reaction progress was linear for the duration of the reaction until a plateau was reached at maximum yield of 78% under these sampling conditions (Figure 2, closed black circles).

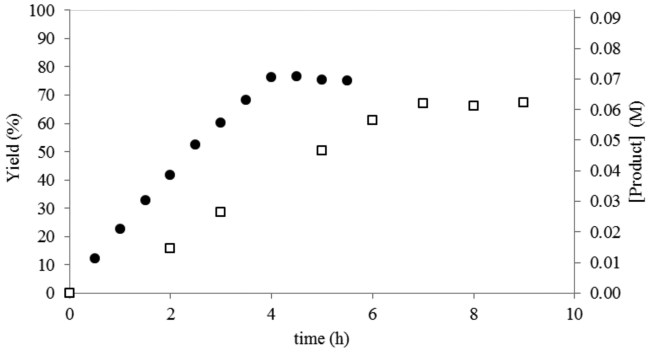

Figure 2. Reaction profiles for the formation of product **12** by Pd-catalyzed cross-coupling of in situ generated aziridinyl Grignard reagent with PhBr. Reaction conditions: (closed black circles) **9** (0.265 mmol), *i*-PrMgCl (0.397 mmol), PhBr (0.530 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), P(*t*-Bu)$_3$ (10 mol %), $ZnCl_2$ (0.397 mmol), 1,3,5-trimethoxybenzene (as I.S.), k_{obs} = 0.0178 M h^{-1}; (open black squares) **9** (0.265 mmol), *i*PrMgCl (0.397 mmol), PhBr (0.530 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (1.25 mol %), P(*t*-Bu)$_3$ (5 mol %), $ZnCl_2$ (0.397 mmol), 1,3,5-trimethoxybenzene (as I.S.), k_{obs} = 0.0097 M h^{-1}.

In order to ensure that the use of 2 equiv of bromobenzene in the standard procedure did not induce pseudo-zero-order conditions, the reaction monitoring was repeated with 1 equiv, and an identical straight line plot was observed. The rate of the reaction performed with half the catalyst loading (1.25 mol %) was around half that of the normal reaction, again with a plateau at a lower final yield (62%). These results demonstrate that the reaction proceeds with zero-order kinetics for both the aryl halide and organometallic and that the rate equation is only dependent on the catalyst loading: rate = $k_{obs}[cat]_{tot}$. This implies that reductive elimination to form the C−C bond is rate determining, given that it involves neither of the reactants. These results parallel those found by Lei and co-workers for an

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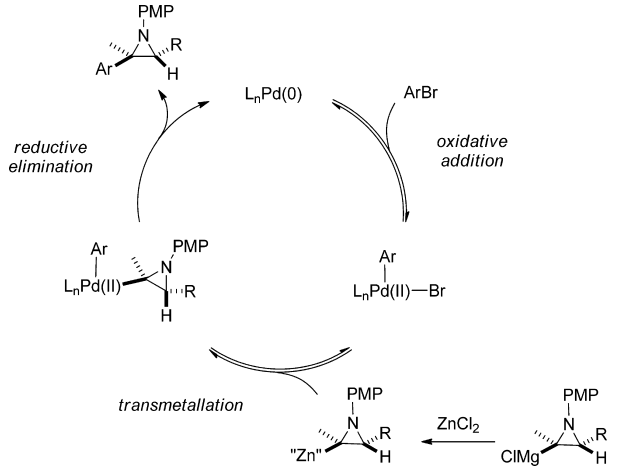
sp^2–sp^2 oxidative Negishi coupling.[32] Our proposed catalytic cycle is shown in Scheme 5.

Scheme 5. Proposed Catalytic Cycle

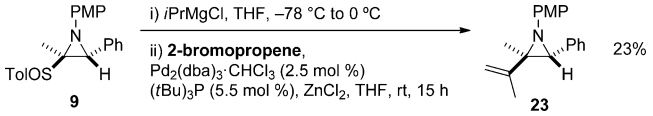


The sudden halt to reaction progress cannot be explained by catalyst deactivation since this would lead to decreased reaction rate over time and hence curvature in the yield vs time relationship. In spite of this, the yield plateaus at a final amount, and this can be explained by the existence of a competing degradation process by which the aziridinylmetal species is depleted. As noted above, attempts to quench the aziridinylzinc with proton sources were unsuccessful, preventing the design of a quenching experiment to monitor the stability of this species. So, in order to test the hypothesis, we decided to use the cross-coupling reaction itself to determine the stability of the intermediate aziridinyl zinc. To do this, the reaction mixture was aged in the absence of the PhBr for 1 h by formation of the aziridinyl magnesium, followed by addition of the catalyst mixture in the usual manner (Scheme 6). Subsequent addition of PhBr afforded a similar reaction profile, but which halted at 65% yield. Aging the reaction for 2 and 3 h gave yields of 48% and 42%, respectively.

It follows that factors that reduce the rate of the reaction will inevitably lead to a lower maximum yield due to the background degradation of the substrate. For example, *o*-tolyl bromide gave a much reduced yield (Table 2, entry 3), presumably due to a decrease in the rate of cross-coupling with the additional steric demands. The yield could be improved by increasing the catalyst loading so the coupling rate is increased over the degradation rate. For the coupling of *o*-tolyl bromide, raising the catalyst loading to 10 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ (4-fold increase) afforded aziridine **15** in 64% yield by ^1H NMR.

Aziridine Alkenylation: Initial Investigation. Without further optimization of the reaction conditions, the cross-coupling of 2-bromopropene was also successful, providing vinylaziridine **23** in low yield (Scheme 7). Other bromoalkenes tested (vinyl bromide, bromostyrenes, bromoacrylates) proved

Scheme 7. Aziridine Cross-Coupling with a Bromoalkene



unreactive under these conditions, highlighting the need for further development of conditions for this substrate class.

In an attempt to boost the yield of **23**, the catalyst loading was increased to 10 mol %. However, under these conditions, a different major product was unexpectedly formed (Scheme 8). This dihydrobenzoazepine product is a constitutional isomer of the expected aziridine product (**23**) and is likely to have formed directly from **23** by a formal aza-Claisen rearrangement. Since this transformation was not observed at lower catalyst loading, we postulate that it occurs through a π-allyl-Pd intermediate. A similar [3,3]-sigmatropic rearrangement has been reported from an amino-cyclopropane derivative.[33] Compounds **23** and **24** have structures that have not previously been accessed, and while the best yields for each are low, further development of the reaction conditions is underway.

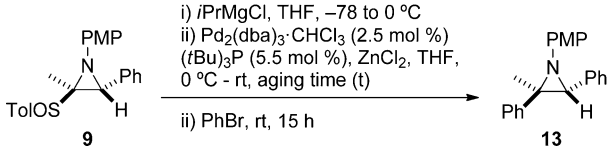
CONCLUSION

We have established an effective sulfinyl–magnesium exchange/cross-coupling protocol to afford highly substituted aziridines in high yield. The reaction tolerates aryl bromides with a wide range of electronic properties and functionality. Kinetics studies revealed that the cross-coupling proceeds with zero-order kinetics implying that reductive elimination is the rate-determining step. The results also suggest that a progressive degradation of the aziridinyl zinc intermediate limits the reaction yield. Formation of a vinylaziridine was also found to be possible without further optimization of the procedure, and a rearrangement reaction generating a dihydrobenzoazepine structure was also discovered.

EXPERIMENTAL SECTION

General Considerations. All nonaqueous reactions were run under an inert atmosphere (argon) with oven or flame-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (THF, diethyl ether, CH_2Cl_2). Flash column chromatography was performed using 230–400 mesh silica or 50–200 μm Brockmann I basic alumina with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel plates or precoated, aluminum-backed alumina gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or aqueous potassium permanganate stain. Infrared spectra (ν_{max}, FTIR ATR) were recorded in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded on 400 MHz spectrometers. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ = 7.27 ppm). Data were reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet and br = broad),

Scheme 6. Organometallic Substrate Aging Experiments



t (h)	yield (%)
0	80
1	65
2	48
3	42

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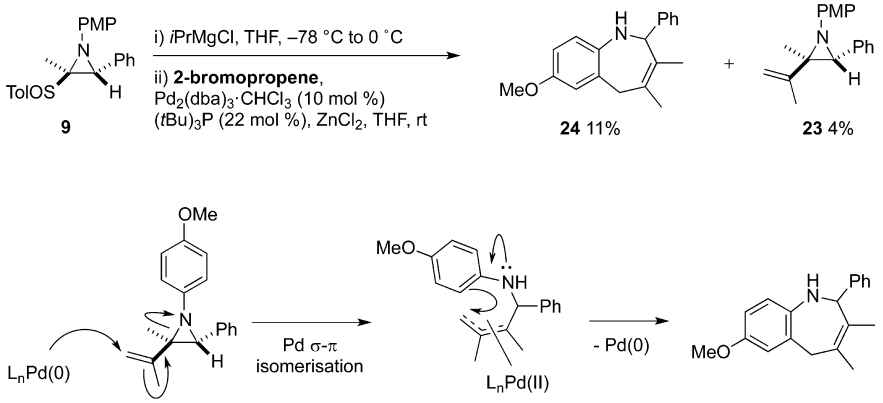
Scheme 8. Formation of a Dihydrobenzoazepine Byproduct in the Aziridine Cross-Coupling Reaction of Bromopropene and Postulated Mechanism



coupling constant in Hz, integration]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.0 ppm). *J* values are reported in hertz. Melting points are uncorrected. **Reagents:** Commercial reagents were used as supplied or purified by standard techniques where necessary. Palladium(II) acetate: 99.98% purity. $Pd_2(dba)_3{\cdot}CHCl_3$ was prepared and recrystallized according to the method of Ananikov and co-workers.[23] Zinc chloride: powder, anhydrous, ≥99.995 purity. Chlorosulfoxide **2** was prepared according to the method of Blakemore and co-workers.[13b] Imines **3**–**5** were prepared according to the procedure of Danheiser and co-workers.[34] *β*-Chloroamines (**6**–**8**) were prepared by a modified version of the method of Satoh and co-workers.[35]

Synthesis of Sulfinyl Aziridines 9–11. *Ethyl 4-Methylphenyl Sulfoxide (1).* Bromoethane (60 mL, 805 mmol) was added portionwise to a stirred suspension of 4-methylbenzenethiol (100 g, 805 mmol) and K_2CO_3 (122 g) in acetone (1 L). The reaction mixture was stirred at rt for 20 h and then filtered through Celite and the filtrate concentrated under reduced pressure. The resulting colorless oil was taken up in diethyl ether (200 mL) and washed with a solution of aqueous NaOH (5% w/v, 3 × 100 mL) and then saturated aqueous NaCl solution (100 mL). The organic layer was dried (Na_2SO_4) and filtered and the solvent removed under reduced pressure to afford ethyl 4-methylphenyl sulfide as a pale yellow oil (121 g, 99%): R_f = 0.38 (1% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.0, 2H), 7.11 (d, *J* = 8.0, 2H), 2.91 (q, *J* = 7.3, 2H), 2.33 (s, 3H), 1.30 (t, *J* = 7.3, 3H). The observed data (^1H NMR) was consistent with that previously reported in the literature.[36] 3-Chloroperbenzoic acid (11.79 g, 68.3 mmol) was added portionwise to a solution of ethyl 4-methylphenyl sulfide (8.00 g, 52.5 mmol) in CH_2Cl_2 (250 mL) at −30 °C, maintaining a temperature <−10 °C. The reaction mixture was stirred for 10 min at −10 °C before being quenched with aqueous $Na_2S_2O_3$ (10% w/v, 250 mL). The layers were separated, and the aqueous partition was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with aqueous NaOH (1 M, 200 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield a colorless oil. Purification by flash column chromatography (80% EtOAc/hexane) afforded sulfoxide **1** as a colorless oil (8.11 g, 92%): R_f = 0.19 (50% EtOAc/hexane); IR ν_{max} 2982, 2936, 2876, 1713, 1654, 1601, 1495, 1456, 1403, 1379, 1086, 1045, 1017, 970, 811, 776; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.2, 2H), 7.33 (d, *J* = 8.2, 2H), 2.88 (dq, *J* = 13.3, 7.4, 1H), 2.77 (dq, *J* = 13.3, 7.4, 1H), 1.19 (t, *J* = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 139.9, 129.8, 124.1, 50.3, 21.3, 6.0. The observed data was consistent with that previously reported in the literature.[37]

1-Chloroethyl-4-methylphenyl Sulfoxide (2). *N*-Chlorosuccinimide (12.4 g, 92.8 mmol) was added portionwise to a solution of ethyl 4-methylphenyl sulfoxide **1** (15.6 g, 92.8 mmol) in CH_2Cl_2 (500 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h before being quenched with aqueous NaI (10% w/v, 200 mL). The layers were separated, and the organic partition was washed with aqueous $Na_2S_2O_3$ (10% w/v, 200 mL). The aqueous layer was then extracted with $CHCl_3$ (2 × 200 mL), the combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. Purification by flash column chromatography (30% Et_2O/hexane) afforded sulfoxide **2** as a colorless oil (17.6 g, 94%) as a mixture of diastereomers (9:1 *syn*:*anti*): R_f = 0.19 (40% EtOAc/hexane); IR ν_{max} 3052, 3024, 2925, 1602, 1496, 1449, 1400, 1218, 1083, 1055, 1016, 813, 742; ^1H NMR (400 MHz, $CDCl_3$) major (*syn*) δ 7.57 (d, *J* = 8.2, 2H), 7.35 (d, *J* = 8.2, 2H), 4.69 (q, *J* = 6.7, 1H) 2.44 (s, 3H), 1.61 (d, *J* = 6.7, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major (*syn*) δ 142.6, 135.3, 129.5, 125.8, 70.8, 21.5, 17.1. The observed data was consistent with that previously reported in the literature.[8b,13b]

(E)-N-Benzylidene-4-methoxyaniline (3). Benzaldehyde (10.2 mL, 100 mmol) was slowly added to a stirred suspension of *p*-anisidine (12.3 g, 100 mmol) and $MgSO_4$ (12.0 g) in CH_2Cl_2 (500 mL), and the reaction was stirred at rt for 48 h. The mixture was then filtered and washed with CH_2Cl_2 (2 × 50 mL). The filtrate was concentrated under reduced pressure to afford the crude imine as a beige solid. Purification by recrystallization (ethanol/water 1:1) afforded imine **3** as golden flakes (13.8 g, 65%): R_f = 0.35 (15% EtOAc/hexane); mp (ethanol/water 1:1) = 68–70 °C (lit.[38] mp = 66–68 °C); IR ν_{max} 2962, 2913, 2837, 1626, 1253, 834; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.94–7.87 (m, 2H), 7.51–7.44 (m, 3H), 7.25 (d, *J* = 8.7, 2H), 6.95 (d, *J* = 8.7, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 158.2, 144.8, 136.4, 131.0, 128.7, 128.5, 122.2, 114.3, 55.5. The observed data was consistent with that previously reported in the literature.[39]

(E)-N-4-Methylbenzylidene-4-methoxyaniline (4). 4-Tolualdehyde (3.14 mL, 23 mmol) was added to a stirred suspension of *p*-anisidine (2.82 g, 23 mmol) and $MgSO_4$ (3.56 g) in CH_2Cl_2 (50 mL), and the reaction was stirred at rt for 24 h. The mixture was then filtered and washed with CH_2Cl_2 (2 × 50 mL). The filtrate was concentrated under reduced pressure to afford the crude imine as a yellow solid. Purification by recrystallization (ethanol) afforded imine **4** as yellow crystals (3.74 g, 72%): R_f = 0.44 (25% ethyl acetate/hexanes); mp = 82–84 °C (lit.[39] mp = 88–90 °C); IR ν_{max} 3002, 2968, 2915, 2889, 2840, 1624, 1501, 1237, 1031, 836; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.80 (d, *J* = 8.1, 2H), 7.31–7.26 (m, 2H), 7.24 (d, *J* = 8.9, 2H), 6.94 (d, *J* = 8.7, 2H), 3.84 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 158.0, 144.4, 141.2, 133.7, 129.3, 128.4, 122.0, 114.2, 55.2, 21.4. The observed data was consistent with that previously reported in the literature.[39]

(E)-N-4-Chlorobenzylidene-4-methoxyaniline (5). 4-Chlorobenzaldehyde (3.25 g, 23.0 mmol) was slowly added in portions to a stirred suspension of *p*-anisidine (2.82 g, 23.0 mmol) and $MgSO_4$ (2.75 g) in CH_2Cl_2 (50 mL), and the reaction was stirred at rt for 24 h. The mixture was then filtered and washed with CH_2Cl_2 (2 × 50 mL). The filtrate was concentrated under reduced pressure to afford the crude imine as a brown solid. Purification by recrystallization (ethanol) afforded imine **5** as silver crystals (3.84 g, 68%): R_f = 0.44 (25% ethyl

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acetate/hexanes). mp =123−125 °C (lit.[40] mp = 127−129 °C); IR ν_{max} 3013, 2964, 2882, 2840, 1620, 1246, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.84 (d, J = 8.4, 2H), 7.44 (d, J = 8.4, 2H), 7.25 (d, J = 8.9, 2H), 6.95 (d, J = 8.9, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 156.6, 144.4, 136.9, 134.9, 129.6, 129.2, 122.2, 114.4, 55.5. The observed data was consistent with that previously reported in the literature.[40]

(1R,2R*,S_R*)-2-Chloro-1-(4-methoxyphenylamino)-1-phenyl-2-(p-tolylsulfinyl)propane (**6**).* *n*-BuLi (1.60 M solution in hexane, 7.73 mL, 12.36 mmol) was added to a solution of diisopropylamine (1.88 mL, 13.4 mmol) in THF (20 mL) at −78 °C. After 30 min at −78 °C, a solution of α-chlorosulfoxide **2** (2.09 g, 10.30 mmol) in THF (10 mL) was added dropwise to the reaction mixture. After a further 10 min at −78 °C, a solution of imine **3** (2.61 g, 12.36 mmol) in THF (10 mL) was added dropwise to the reaction mixture. The resulting solution was stirred at −78 °C for 1 h and then quenched by the addition of saturated aqueous NH_4Cl solution (100 mL). The aqueous mixture was extracted with $CHCl_3$ (3 × 75 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (100 mL), dried (Na_2SO_4), and filtered and the solvent removed under reduced pressure. Purification by trituration (10:1 ethyl acetate/hexane) afforded β-chloroamine **6** as a white solid (2.62 g, 61%): R_f = 0.34 (25% EtOAc/hexane); mp = 165−166 °C (lit.[8b] mp = 165−168 °C); IR ν_{max} 3304br, 1517, 1458, 1241, 1182, 1091, 1038, 910, 812, 729, 704. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 2H), 7.45−7.39 (m, 2H), 7.33−7.28 (m, 3H), 7.23−7.18 (m, 2H), 6.66−6.61 (m, 2H), 6.42−6.37 (m, 2H), 5.76 (d, J = 2.0, 1H), 4.36 (d, J = 2.0, 1H), 3.69 (s, 3H), 2.40 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 143.0, 140.6, 137.4, 134.2, 129.3, 129.2, 128.2, 128.1, 127.4, 115.2, 114.5, 83.3, 67.8, 55.6, 21.7, 21.5. The observed data (^{1}H NMR, IR) was consistent with that previously reported in the literature.[8b]

(1R,2R*,S_R*)-2-Methyl-1-(4-methoxyphenylamino)-1-(4-methyl)phenyl-2-(p-tolylsulfinyl)propane (**7**).* *n*-BuLi (1.45 M solution in hexane, 8.17 mL, 11.8 mmol) was added to a solution of diisopropylamine (1.80 mL, 12.8 mmol) in THF (20 mL) at −78 °C. After 30 min at −78 °C, a solution of α-chlorosulfoxide **2** (2.00 g, 9.87 mmol) in THF (10 mL) was added dropwise to the reaction mixture. After a further 10 min of stirring at −78 °C, a solution of imine **4** (2.67 g, 11.84 mmol) in THF (10 mL) was added dropwise to the reaction mixture. The resulting solution was stirred at −78 °C for 1 h and then quenched by the addition of saturated aqueous NH_4Cl solution (100 mL). The aqueous mixture was extracted with $CHCl_3$ (3 × 75.0 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution (100 mL), dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. Purification by trituration (10:1 ethyl acetate/hexane) afforded β-chloroamine **7** as a white solid (1.84 g, 44%): R_f 0.26 (25% ethyl acetate/hexanes); mp =135−142 °C; IR ν_{max} 3304, 1595, 1372, 1251, 1241, 1177, 1113, 1031, 1012, 824, 809; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.9, 2H), 7.30 (d, J = 7.7, 2H), 7.20 (d, J = 7.9, 2H), 7.11 (d, J = 7.8, 2H), 6.64 (d, J = 8.7, 2H), 6.41 (d, J = 9.0, 2H), 5.77 (br s, 1H), 4.34 (s, 1H), 3.68 (s, 3H), 2.38 (s, 3H), 2.32 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 142.9, 140.6, 138.0, 134.3, 134.2, 129.2(1), 129.1(6), 128.9, 127.5, 115.3, 114.5, 83.5, 66.7, 55.6, 21.8, 21.5, 21.2; HRMS (ESI/TOF) m/z calcd for $C_{23}H_{24}Cl_2NO_2S^+$ $[M + H]^+$ 448.0899, found 448.0905.

(1R,2R*,S_R*)-2-Chloro-1-(4-methoxyphenylamino)-1-(4-chloro)-phenyl-2-(p-tolylsulfinyl)propane (**8**).* *n*-BuLi (2.2 M solution in hexane, 1.68 mL, 3.70 mmol) was added to a solution of diisopropylamine (0.57 mL, 4.07 mmol) in THF (20 mL) at −78 °C. After 30 min at −78 °C, a solution of α-chlorosulfoxide 2 (750 mg, 3.70 mmol) in THF (6 mL) was added dropwise to the reaction mixture. After a further 10 min of stirring at −78 °C, a solution of imine **5** (910 mg, 3.70 mmol) in THF (6 mL) was added dropwise to the reaction mixture. The resulting solution was stirred at −78 °C for 2 h and then quenched by the addition of saturated aqueous NH_4Cl solution (75 mL). The aqueous mixture was extracted with $CHCl_3$ (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% diethyl ether/hexanes) afforded β-chloroamine **8** (723 mg, 44%) as a golden solid: R_f = 0.23 (25% ethyl acetate/hexanes); mp = 150−151 °C; IR ν_{max} 3337, 2834, 1598, 1511, 1494, 1441, 1413, 1382, 1237, 1183, 1087, 1039, 1015, 851, 813, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2, 2H), 7.36 (d, J = 8.6, 2H), 7.28 (d, J = 8.6, 2H, 2 × ClAr-H), 7.19 (d, J = 8.2, 2H), 6.64 (d, J = 9.0, 2H), 6.38 (d, J = 9.0, 2H), 5.82 (br s, 1H), 4.28 (br s, 1H), 3.69 (s, 3H), 2.38 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 143.1, 140.2, 136.0, 134.1, 133.9, 130.6, 129.3, 128.4, 127.4, 115.3, 114.6, 82.5, 66.2, 55.6, 21.6, 21.5; HRMS (ESI/TOF) m/z calcd for $C_{23}H_{24}Cl_2NO_2S^+$ $[M + H]^+$ 448.0899, found 448.0905.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(p-tolylsulfinyl)-aziridine (**9**).* A solution of KO-*t*-Bu (1 M in THF, 27.5 mL, 27.5 mmol) was added to a solution of β-chloroamine **6** (4.55 g, 11.0 mmol) in THF (100 mL). The reaction mixture was heated under reflux for 15 min and then quenched with saturated aqueous NH_4Cl (50 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a yellow oil. Purification by flash chromatography (20% EtOAc/hexane) afforded aziridine **9** as light yellow crystals (3.91 g, 94%): R_f = 0.24 (30% EtOAc/hexane); mp = 92−94 °C (lit.[8b] mp = 88−91 °C); IR ν_{max} 3046, 2996, 2931, 2839, 1602, 1503, 1448, 1402, 1297, 1235, 1183, 1084, 1035, 842, 813, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.8, 2H), 7.42−7.29 (m, 7H), 7.01 (d, J = 8.7, 2H), 6.88 (d, J = 8.7, 2H), 4.54 (s, 1H), 3.80 (s, 3H), 2.42 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 142.5, 140.6, 138.1, 135.1, 129.9, 128.3, 127.6, 127.5, 126.4, 120.2, 114.4, 64.2, 55.4, 41.3, 21.5, 13.8. The observed data was consistent with that previously reported in the literature.[8b]

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-(4-methylphenyl)-2-(p-tolylsulfinyl)aziridine (**10**).* A solution of KO-*t*-Bu (1 M in THF, 9.64 mL, 9.64 mmol) was added to a solution of β-chloroamine **7** (1.65 g, 3.86 mmol) in THF (50 mL). The reaction was then heated under reflux, monitoring the reaction progress by thin-layer chromatography. After 1 h at reflux, the reaction mixture was cooled and quenched by the addition of saturated aqueous NH_4Cl solution (50 mL). The aqueous mixture was extracted with $CHCl_3$ (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% ethyl acetate/hexane) afforded sulfinyl aziridine **10** as a pale orange solid (1.29 g, 85%): mp = 59−61 °C; IR ν_{max} 3035, 2923, 2834, 1598, 1504, 1234, 1038, 910, 814, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2, 2H), 7.32 (d, J = 8.0, 2H), 7.27 (m, 2H), 7.16 (d, J = 8.0, 2H), 6.99 (d, J = 8.9, 2H), 6.87 (d, J = 8.9, 2H), 4.51 (s, 1H), 3.80 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 142.4, 140.6, 138.2, 137.2, 131.9, 129.8, 129.0, 127.5, 126.4, 120.2, 114.4, 64.1, 55.4, 41.4, 21.4, 21.1, 13.6; HRMS (ESI/TOF) m/z calcd for $C_{24}H_{26}NO_2S^+$ $[M + H]^+$ 392.1679, found 392.1680.

*2-Methyl-1-(4-methoxyphenyl)-3-(4-chloro)phenyl-2-(p-tolylsulfinyl)aziridine (**11**).* A solution of KO-*t*-Bu (1 M in THF, 3.69 mL, 3.69 mmol) was added to a solution of adduct **8** (662 mg, 1.48 mmol) in THF (25 mL). The reaction mixture was heated under reflux for 45 min and then quenched with saturated aqueous NH_4Cl solution (50 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to give an orange oil. Purification by flash column chromatography (25% EtOAc/hexane) afforded sulfinylaziridine **11** as red/orange crystals (250 mg, 41%): R_f = 0.14 (25% EtOAc/hexane); mp = 61−63 °C; IR ν_{max} 3040, 2997, 2929, 2835, 1505, 1491, 1236, 1086, 1039, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2, 2H), 7.34−7.31 (m, 6H), 6.98 (d, J = 8.9, 2H), 6.87 (d, J = 8.9, 2H), 4.49 (s, 1H), 3.79 (s, 3H), 2.42 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 142.7, 140.8, 138.3, 135.2, 130.0, 128.4, 127.7, 127.6, 126.6, 120.3, 114.6, 64.4, 55.6, 41.4, 21.6, 14.0; HRMS (ESI/TOF) m/z calcd for $C_{23}H_{23}ClNO_2S^+$ $[M + H]^+$ 412.1133, found: 412.1134.

*cis-2-Methyl-1-(4-methoxyphenyl)-3-phenylaziridine (**12**).* A solution of ethylmagnesium bromide (0.40 mL, 0.98 M, 0.39 mmol) in THF (0.65 mL) was stirred at −78 °C for 15 min. A solution of

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sulfinylaziridine **9** (100 mg, 0.27 mmol) in THF (0.5 mL) was added dropwise to the reaction mixture and stirred for 10 min. The reaction mixture was placed in a water bath at rt for 10 min, removed, and stirred at rt for 30 min. The reaction mixture was quenched with anhydrous methanol (0.5 mL) followed by satd aq NH_4Cl solution (4 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by flash column chromatography (5% EtOAc/hexane) afforded aziridine **12** as a colorless oil (44 mg, 70%): R_f = 0.26 (5% EtOAc/hexane); IR ν_{max} 3058, 2993, 2960, 2838, 1604, 1506, 1459, 1414, 1242, 1182, 1036, 903, 834, 757, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.2, 2H), 7.37 (t, J = 7.2, 2H), 7.29 (t, J = 7.2, 1H), 6.99 (d, J = 8.9, 2H), 6.81 (d, J = 8.9, 2H), 3.78 (s, 3H), 3.24 (d, J = 6.5, 1H), 2.48 (dq, J = 6.5, 5.6, 1H), 1.14 (d, J = 5.6, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 148.4, 137.0, 128.0, 127.7, 126.9, 120.8, 114.3, 55.5, 46.7, 42.0, 13.5; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{18}NO^+$ $[M + H]^+$ 240.1383, found 240.1388. Prepared according to the procedure of Satoh and co-workers.[8b]

*2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-deuteroaziridine ([**D**]-**12**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 7.2, 2H), 7.38 (t, J = 7.2, 2H), 7.30 (t, J = 7.2, 1H), 7.00 (d, J = 8.9, 2H), 6.82 (d, J = 8.9, 2H), 3.79 (s, 3H), 3.24 (s, 1H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 148.4, 137.0, 128.0, 127.7, 126.9, 120.8, 114.3, 55.6, 46.6, 41.7 (t, J_{CD} = 25.9), 13.3; HRMS (ESI/TOF) m/z calcd for $C_{16}H_{17}DNO^+$ $[M + H]^+$ 241.1441, found 241.1451.

Synthesis of Aziridines 12−23 by Palladium-Catalyzed Cross-Coupling. *General Procedure.* A 1.90 M solution of *i*-PrMgCl (209 μL, 0.397 mmol) in THF was added dropwise to a stirred solution of the sulfinylaziridine (0.265 mmol) in THF (1.56 mL) at −78 °C. The mixture was stirred at −78 °C for 15 min before being warmed to 0 °C over 10 min in an ice bath. After this time, a solution of $Pd_2(dba)_3$·$CHCl_3$ (6.85 mg, 0.0662 mmol), $(t\text{-Bu})_3P$ (2.95 mg, 0.0265 mmol), and anhydrous $ZnCl_2$ (54.2 mg, 0.397 mmol) in THF (1.0 mL) was added, followed by the appropriate aryl bromide (0.530 mmol). After 15 h, the reaction mixture was quenched by addition of MeOH (0.5 mL), passed through a plug of basic alumina, and concentrated under reduced pressure. The residual crude product was then purified by flash column chromatography (basic alumina, 1% EtOAc/hexane).

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-phenylaziridine (**13**):* colorless oil (66.8 mg, 80%); R_f = 0.16 (alumina, 1% EtOAc/hexane); IR ν_{max} 3060, 3030, 2997, 2958, 2929, 2905, 2833, 1604, 1506, 1447, 1236; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, J = 7.3), 7.44 (t, J = 7.3, 2H), 7.37 (t, J = 7.3, 1H), 7.32−7.17 (m, 5H), 6.76 (d, J = 8.9, 2H), 6.67 (d, J = 8.9, 2H), 4.14 (s, 1H), 3.72 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 142.6, 138.0, 137.5, 128.4, 128.2, 127.9, 127.7, 127.18, 127.17, 121.5, 113.8, 55.3, 51.1, 50.8, 20.5; HRMS (ESI/TOF) m/z calcd for $C_{22}H_{22}NO^+$ $[M + H]^+$ 316.1696, found 316.1694.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(4-methylphenyl)-aziridine (**14**):* colorless oil (61.5 mg, 70%); R_f = 0.17 (alumina, 1% EtOAc/hexane); IR ν_{max} 3060, 3030, 2993, 2958, 2928, 2834, 1738, 1506, 1451, 1236, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.5, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5, 1H), 7.16 (d, J = 8.2, 2H), 7.05 (d, J = 8.2, 2H), 6.79 (d, J = 9.0, 2H), 6.67 (d, J = 9.0, 2H), 4.09 (s, 1H), 3.71 (s, 3H), 2.29 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 142.8, 137.6, 136.8, 135.0, 128.6, 128.25, 128.20, 127.7, 127.1, 121.5, 113.9, 55.3, 50.9, 50.8, 20.9, 20.7; HRMS (ESI/TOF) m/z calcd for $C_{23}H_{24}NO^+$ $[M + H]^+$ 330.1852, found 330.1858.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(2-methylphenyl)-aziridine (**15**):* colorless oil (29.5 mg, 28%); contains **12** as a coeluting impurity (yield based on **15** only); R_f = 0.25 (alumina, 1% EtOAc/hexane); IR ν_{max} 3062, 3031, 2993, 2956, 2927, 2835, 1506, 1454, 1241, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.4, 2H), 7.42 (t, J = 7.4, 2H), 7.32 (t, J = 7.4, 1H), 7.14−6.98 (m, 4H), 6.94 (d, J = 8.9, 2H), 6.71 (d, J = 8.9, 2H), 3.89 (s, 1H), 3.73 (s, 3H), 2.43 (s, 3H), 1.44 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 141.3, 139.2, 137.2, 136.8, 130.6, 130.3, 128.2, 128.1, 127.1, 127.0, 125.3, 124.0, 113.6, 55.3, 54.4, 49.1, 21.6, 20.8; HRMS (ESI/TOF) m/z calcd for $C_{23}H_{24}NO^+$ $[M + H]^+$ 330.1852, found 330.1859.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(4-vinylphenyl)-aziridine (**16**):* colorless oil (79.9 mg, 82%); contains Ar−Ar dimer as an impurity (yield based on **16** only); R_f = 0.15 (alumina, 1% EtOAc/hexane); IR ν_{max} 3089, 3062, 3036, 2998, 2958, 2932, 1506, 1239, 1039; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.0, 2H), 7.41 (t, J = 7.0, 2H), 7.33 (t, J = 7.0, 1H), 7.27 (d, J = 8.0, 2H), 7.19 (d, J = 8.0, 2H), 6.72 (d, J = 8.9, 2H), 6.68−6.60 (m, 3H), 5.70 (d, J = 17.6, 1H), 5.22 (d, J = 10.9, 1H), 4.08 (s, 1H), 3.70 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 142.6, 137.6, 137.4, 136.3, 136.2, 128.5, 128.2, 127.7, 127.2, 125.7, 121.4, 114.0, 113.9, 55.4, 51.1, 50.8, 20.4; HRMS (ESI/TOF) m/z calcd for $C_{24}H_{24}NO^+$ $[M + H]^+$ 342.1852, found 342.1855.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(4-fluorophenyl)-aziridine (**17**):* colorless oil (61.8 mg, 70%); R_f = 0.14 (alumina, 1% EtOAc/hexane); IR ν_{max} 3063, 3032, 2998, 2961, 2932, 2836, 1605, 1506, 1453 1233; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.5, 2H), 7.41 (t, J = 7.5, 2H), 7.35 (t, J = 7.5, 1H), 7.24−7.19 (m, 2H), 6.91 (t, J = 8.7, 2H), 6.72 (d, J = 8.9, 2H), 6.65 (d, J = 8.9, 2H), 4.05 (s, 1H), 3.71 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (J_{CF} = 247), 154.8, 142.4, 137.3, 133.9 (J_{CF} = 2.9), 130.0 (J_{CF} = 8.1), 128.3, 127.7, 127.3, 121.6, 114.8 (J_{CF} = 21.3), 113.9, 55.4, 50.7, 50.6, 20.7; ^{19}F NMR (377 MHz, $CDCl_3$) −115.0; HRMS (ESI/TOF) m/z calcd for $C_{22}H_{21}FNO^+$ $[M + H]^+$ 334.1602, found 334.1601.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(4-chlorophenyl)-aziridine (**18**):* colorless oil (60.4 mg, 65%); R_f = 0.12 (alumina, 1% EtOAc/hexane); IR ν_{max} 3063, 3034, 2997, 2963, 2932, 2834, 1505, 1452, 1238, 1106; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.50 (m, 2H), 7.45−7.39 (m, 2H), 7.38−7.31 (m, 1H), 7.20 (d, J = 8.6, 2H), 7.17 (d, J = 8.6, 2H), 6.72 (d, J = 8.9, 2H), 6.67 (d, J = 8.9, 2H), 4.05 (s, 1H), 3.72 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 142.2, 137.1, 136.7, 133.1, 129.7, 128.3, 128.0, 127.7, 127.3, 121.5, 114.0, 55.3, 50.9, 50.5, 20.4; HRMS (ESI/TOF) m/z calcd for $C_{22}H_{21}ClNO^+$ $[M + H]^+$ 350.1306, found 350.1312.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(3-methoxyphenyl)aziridine (**19**):* pale yellow oil (74.6 mg, 81%); R_f = 0.38 (alumina, 5% EtOAc/hexane); IR ν_{max} 3060, 3032, 3000, 2961, 2934, 2835, 1601, 1505, 1452, 1230, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6, 2H), 7.53 (t, J = 7.6, 2H), 7.35 (t, J = 7.6, 1H), 7.16 (t, J = 8.0, 1H), 6.88 (d, J = 8.0, 1H), 6.80−6.72 (m, 4H), 6.68 (d, J = 8.9, 2H), 4.08 (s, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 154.7, 142.6, 139.7, 137.4, 128.8, 128.2, 127.7, 127.2, 121.4, 120.9, 114.6, 113.9, 112.3, 55.4, 55.1, 51.0 (C and CH), 20.5; HRMS (ESI/TOF) m/z calcd for $C_{23}H_{24}NO_2^+$ $[M + H]^+$ 346.1802, found 346.1808.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(4-ethoxycarbonylphenyl)aziridine (**20**):* colorless oil (80.8 mg, 72%); contains Ar−Ar dimer as an impurity (yield based on **20** only): R_f = 0.31 (alumina, 5% EtOAc/hexane); IR ν_{max} 3064, 2035, 2984, 2933, 2907, 2835, 1715, 1611, 1507, 1276, 1240, 1108; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.5, 2H), 7.53 (d, J = 7.5, 2H), 7.42 (t, J = 7.5, 2H), 7.34 (t, J = 7.5, 1H), 7.29 (d, J = 8.5, 2H), 6.71 (d, J = 8.9, 2H), 6.64 (d, J = 8.9, 2H), 4.35 (q, J = 7.1, 2H), 4.12 (s, 1H), 3.70 (s, 3H), 1.52 (s, 3H), 1.38 (t, J = 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 154.8, 143.2, 142.1, 137.1, 129.2, 129.0, 128.3, 128.2, 127.7, 127.4, 121.4, 114.0, 60.9, 55.3, 51.2, 50.7, 20.2, 14.3; HRMS (ESI/TOF) m/z calcd for $C_{25}H_{26}NO_3^+$ $[M + H]^+$ 388.1907, found 388.1911.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-(4-methylphenyl)-2-phenyl-aziridine (**21**):* colorless oil (54.9 mg, 63%); R_f = 0.16 (alumina, 1% EtOAc/hexane); IR ν_{max} 3060, 3030, 2993, 2928, 2834, 1738, 1506, 1451, 1236, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.5, 2H), 7.42 (t, J = 7.5, 2H), 7.34 (t, J = 7.5, 1H), 7.05 (d, J = 8.2, 2H), 7.16 (d, J = 8.2, 2H), 6.75 (d, J = 9.0, 2H), 6.66 (d, J = 9.0, 2H), 4.09 (s, 1H), 3.71 (s, 3H), 2.29 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 142.8, 137.6, 136.8, 135.0, 128.6, 128.3, 128.2, 127.7, 127.1, 121.5, 113.9, 55.3, 50.9, 50.8, 20.9, 20.7; HRMS (ESI/TOF) m/z calcd for $C_{23}H_{24}NO^+$ $[M + H]^+$ 330.1852, found 330.1858.

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*(E)-2-Methyl-1-(4-methoxyphenyl)-3-(4-chlorophenyl)-2-phenylaziridine (**22**):* colorless oil (60.3 mg, 65%); R_f = 0.17 (alumina, 1% EtOAc/hexane); IR ν_{max} 3060, 3036, 2994, 2959, 2932, 2833, 1505, 1442, 1237, 1038, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5, 2H), 7.38 (d, J = 8.5, 2H), 7.26−7.16 (m, 5H), 6.71 (d, J = 8.9, 2H), 6.64 (d, J = 8.9, 2H), 4.06 (s, 1H), 3.70 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 142.3, 137.7, 136.1, 133.0, 129.1, 128.4, 128.3, 127.9, 127.3, 121.5, 113.9, 55.3, 51.3, 50.0, 20.5; HRMS (ESI/TOF) m/z calcd for $C_{22}H_{21}ClNO^+$ $[M + H]^+$ 350.1306, found 350.1312.

*(E)-2-Methyl-1-(4-methoxyphenyl)-3-phenyl-2-(1-methyl)-vinylaziridine (**23**):* colorless oil (16.8 mg, 23%); R_f = 0.33 (alumina, 1% EtOAc/hexane); IR ν_{max} 3064, 3035, 2992, 2958, 2929, 2861, 2835, 1728, 1507, 1241; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.3, 2H), 7.37 (t, J = 7.3, 2H), 7.30 (t, J = 7.3, 1H), 6.90 (d, J = 8.9, 2H), 6.78 (d, J = 8.9, 2H), 5.19 (s, 1H), 5.08 (s, 1H), 3.84 (s, 1H), 3.77 (s, 3H), 1.47 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 143.4, 142.8, 137.7, 128.1, 127.7, 127.0, 120.8, 116.6, 114.0, 55.5, 52.1, 49.2, 21.8, 19.1; HRMS (ESI/TOF) m/z calcd for $C_{19}H_{22}NO^+$ $[M + H]^+$ 280.1696, found 280.1705.

*7-Methoxy-3,4-dimethyl-2-phenyl-2,5-dihydro-1H-benzo[b]-azepine (**24**).* A solution of *i*-PrMgCl (1.83 M, 220 μL, 0.397 mmol) in THF was added dropwise to a stirred solution of the sulfinylaziridine **9** (100 mg, 0.265 mmol) in THF (1.55 mL) at −78 °C. The mixture was stirred at −78 °C for 15 min before being warmed to 0 °C over 10 min in an ice bath. After this time, a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (27.4 mg, 0.0265 mmol), $(t\text{-Bu})_3P$ (11.8 mg, 0.0583 mmol), and anhydrous $ZnCl_2$ (54.2 mg, 0.397 mmol) in THF (1.0 mL) was added, followed by the appropriate aryl bromide (0.530 mmol). After 22 h, the reaction mixture was quenched by addition of MeOH (0.5 mL), passed through a plug of basic alumina, and concentrated under reduced pressure. The residual crude product was then purified by flash column chromatography (silica, 10% EtOAc/hexane) to yield the title compound as a white solid (8.8 mg, 11%): mp = 88−90 °C; R_f = 0.28 (alumina, 10% EtOAc/hexane); IR ν_{max} 3341, 3060, 3027, 2996, 2933, 2857, 2834, 1607, 1506, 1465, 1272, 1235; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.23 (m, 5H), 6.70 (d, J = 2.9, 1H), 6.56 (dd, J = 8.4, 2.9, 1H), 6.49 (d, J = 8.4, 1H), 4.61 (s, 1H), 3.82 (d, J = 15.0, 1H), 3.76 (s, 3H), 3.30 (br s, 1H), 3.25 (d, J = 15.0, 1H), 1.88 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 143.8, 139.3, 137.5, 128.2, 128.13, 128.09, 127.2, 126.9, 121.7, 113.9, 111.3, 67.8, 55.5, 39.5, 22.6, 19.4; HRMS (ESI/TOF) m/z calcd for $C_{19}H_{22}NO^+$ $[M + H]^+$ 280.1696, found 280.1710.

Sampling Procedure for Kinetic Experiments. A solution of *i*-PrMgCl (0.397 mmol) in THF was added dropwise to a stirred solution of sulfinylaziridine **9** in THF (sufficient to make reaction concentration 0.15 M after addition of Grignard) at −78 °C. The mixture was stirred −78 °C for 15 min before being warmed to 0 °C over 10 min in an ice bath. After this time, a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0662 mmol), $(t\text{-Bu})_3P$ (0.0265 mmol), anhydrous $ZnCl_2$ (54.2 mg, 0.397 mmol), and a known amount of 1,3,5-trimethoxybenzene (as an internal standard) in THF (1.0 mL) were added, followed by bromobenzene (55.8 μL, 0.530 mmol) at t = 0. The reaction was monitored by periodic sampling: An aliquot (ca. 50 μL) was quenched by addition to MeOH (100 μL), filtered through a plug of silica, concentrated under reduced pressure, redissolved in $CDCl_3$, and analyzed by ^{1}H NMR spectroscopy to determine the NMR yield of **13**. Note, the samples required careful handling and rapid processing to avoid product degradation in the crude mixture.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for 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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