JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

pubs.acs.org/JACS

Directed Nickel-Catalyzed Negishi Cross Coupling of Alkyl Aziridines

Daniel K. Nielsen, Chung-Yang (Dennis) Huang, and Abigail G. Doyle*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

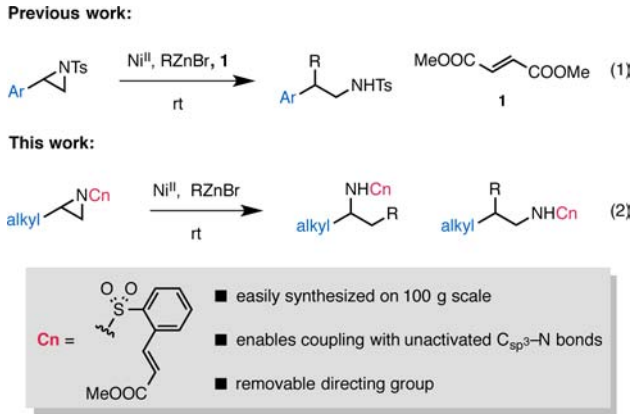
Supporting Information

ABSTRACT: Herein we report a nickel-catalyzed C−C bond-forming reaction between simple alkyl aziridines and organozinc reagents. This method represents the first catalytic cross-coupling reaction employing a nonallylic and nonbenzylic C_{sp^3}−N bond as an electrophile. Key to its success is the use of a new *N*-protecting group (cinsyl or Cn) bearing an electron-deficient olefin that directs oxidative addition and facilitates reductive elimination. Studies pertinent to elucidation of the mechanism of cross coupling are also presented.

INTRODUCTION

The past five years have witnessed the rapid development of innovative cross-coupling methods that enable functionalization of the C−O and C−N bonds of organic substrates. These reactions benefit from the wide availability, low toxicity, and orthogonal reactivity of ethers and amines compared with traditional organic halide electrophiles. Whereas significant progress has been made toward the coupling of aryl, alkenyl,[1] and activated allylic[2] and benzylic[3] C−O/N bond-containing electrophiles, the coupling of substrates bearing unactivated C_{sp^3}−O/N bonds remains essentially unknown.[4] To exploit the full potential of C−O/N activation in cross coupling, it is critical that catalysts and strategies be developed that engage the broad range of less activated amine and ether substrates.

We recently disclosed the first example of catalytic cross coupling of *N*-sulfonyl aziridines with organozinc reagents (eq 1).[5] Good yields and high regio- and diastereoselectivities were



obtained in the synthesis of a variety of β-substituted amines. Unfortunately, however, this reaction was limited to *styrenyl* aziridine substrates, which undergo relatively facile oxidative addition due to (i) attenuation of the C−N bond strength at the benzylic site and/or (ii) precoordination of the nickel catalyst with the arene.[6] Also, the organometallic intermediates resulting from oxidative addition to a styrenyl aziridine likely benefit from greater stability to β-hydride elimination based on π-benzyl stabilization. Indeed, although Hillhouse[7] and Wolfe[8] have shown that transition metals can undergo stoichiometric oxidative addition to aliphatic *N*-tosyl aziridines, no catalytic coupling reactions exploiting this reactivity have been reported. Instead, the reaction of Pd(0) with this class of aziridines affords imines by a β-hydride elimination-initiated isomerization.[9]

Herein we report our efforts to expand the substrate scope of our previously reported method to include simple *alkyl* aziridines. To do so, we considered whether it would be possible to use the protecting group on the nitrogen to coordinate a transition metal catalyst and accelerate the rate of a desired cross-coupling event. In this article, we present the successful design of such a protecting group and its application to cross-coupling reactions of unactivated aziridines (eq 2). To the best of our knowledge, this method represents the first catalytic cross coupling using an electrophile bearing a nonbenzylic or allylic C_{sp^3}−N bond.

The design of the new aziridine protecting group was influenced by two observations made during our work with styrenyl aziridines.[5a] First, and consistent with stoichiometric studies using nickel[7] and palladium,[8] we noted that styrenyl aziridines bearing electron-withdrawing protecting groups were uniquely capable of undergoing productive oxidative addition with a nickel catalyst. Furthermore, we observed that electron-deficient olefin ligands, such as dimethyl fumarate **1**, promoted efficient cross coupling by accelerating reductive elimination, whereas more traditional phosphine or amine-based ligands were unreactive (or led to exclusive β-hydride elimination).[10] Thus, we predicted that a protecting group that combined both of these features would be highly effective: it would activate the alkyl C−N bond toward oxidative addition, stabilize intermediates prone to β-hydride elimination by coordination, and assist in C−C bond-forming reductive elimination. An

Received: July 25, 2013
Published: August 20, 2013

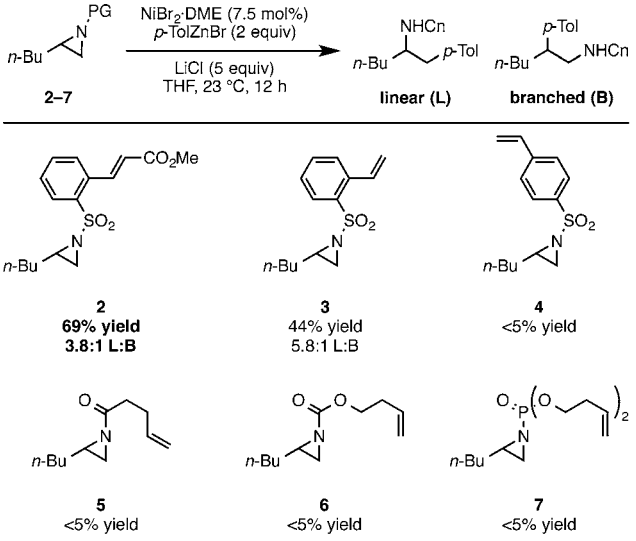
 © 2013 American Chemical Society dx.doi.org/10.1021/ja4076716 | J. Am. Chem. Soc. 2013, 135, 13605−13609

additional attractive feature of this strategy, which distinguishes it from other examples of olefin-directed transition metal-catalyzed reactions,[8,11] would be that the protecting group could be cleaved post cross coupling, thus serving as a removable directing group.[12]

RESULTS AND DISCUSSION

Optimization Studies. Our studies commenced with an examination of a variety of alkene-bearing amide, carbamate, phosphoramide, and sulfonamide-protected aziridines (Table 1).[13] Among these, aziridines bearing aryl sulfonyl groups

Table 1. Evaluation of Alkene-Containing Protecting Groups[a]

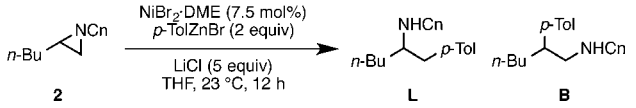


[a]Yields and regioselectivity determined by ^{1}H NMR using triphenylene as a quantitative internal standard.

proved uniquely effective (**2** and **3**), with **2** undergoing cross coupling under the influence of 7.5 mol % $NiBr_2$·DME, 2 equiv of *p*-TolZnBr, and 5 equiv of LiCl to afford a mixture of two regioisomeric products in 69% yield.[14] All other classes of aziridine protecting group provided recovered starting material or starting material decomposition by β-hydride elimination (**5**–**7**). In accord with our previous observations and our hypothesis that an alkene is required to direct C–C bond formation, an aziridine protected with a simple tosyl group was also unreactive. Further studies indicated that modulation of the electronic properties of the alkene moderately influences yield (**2** vs **3**), whereas the spatial arrangement of alkene is critical for reactivity (**2** vs **4**). On the basis of these studies, the aryl sulfonyl protecting group bearing a cinnamate backbone (**2**) was selected for further studies. This protecting group, which we have abbreviated as cinsyl (Cn), can be easily synthesized on 100 g scale in two steps from inexpensive sodium 2-formylbenzenesulfonate.[15]

During our optimization studies with **2** we observed that inclusion of a superstoichiometric amount of LiCl afforded a substantial increase in the yield of cross-coupled product (entries 2 and 3, Table 2). By contrast, other metal halide additives showed a marginal or negative influence on reactivity (entry 4 and Supporting Information). We considered that this effect could be attributed to the reaction of LiCl with aziridine **2**, generating a β-chloroamine intermediate that serves as the active electrophile in the Negishi arylation.[16] However, control

Table 2. Evaluation of Reaction Conditions



entry	conditions	conv (%)	yield (%)[a]	L:B
1	standard conditions	100	69	3.8:1
2	no LiCl	100	44	1.9:1
3	3.0 equiv of LiCl	85	54	3.5:1
4	$MgCl_2$ instead of LiCl	99	42	5.0:1
5	no $NiBr_2$·DME	7	<2	N/A
6	$Ni(cod)_2$ instead of $NiBr_2$·DME	100	56	3.8:1
7	DMA instead of THF	100	<2	N/A
8	15% dimethyl fumarate **1**	100	30	3.0:1

[a]Yields and regioselectivity determined by ^{1}H NMR using triphenylene as a quantitative internal standard.

experiments suggest that this intermediate is not responsible for the observed increase in product formation (see Supporting Information for details). Other possibilities include that the lithium salt serves to break up polymeric zinc aggregates,[17] assists in oxidative addition,[18] or promotes transmetalation via the generation of higher order zincates.[19] All of these effects have been previously invoked in the context of lithium halide-promoted Negishi coupling reactions and may be responsible for the observed increase in reactivity.

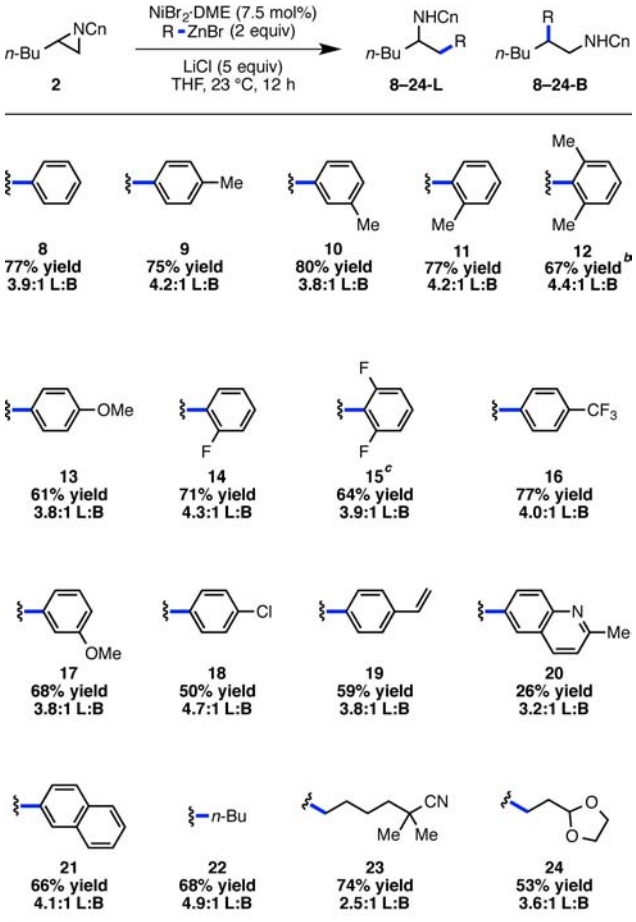
Evaluation of other reaction parameters revealed that a Ni catalyst is necessary for productive C–C bond formation (entries 5 and 6). Use of DMA as solvent, which was found to be important for the cross coupling of styrenyl aziridines, was in fact detrimental in this protocol (entry 7). Furthermore, inclusion of dimethyl fumarate **1**, a necessary ligand additive for styrenyl aziridine cross coupling, resulted in depressed reaction efficiency, presumably by outcompeting the cinsyl protecting group for Ni coordination (entry 8).

It is worth noting that under the standard reaction conditions, cross coupling with **2** delivers a mixture of two regioisomers in 3.8:1 linear:branched ratio. Formation of the linear isomer as the major product is likely due to more facile oxidative addition of Ni to the less hindered C–N bond of the substrate. Notably, the regioselectivity is higher with the inclusion of halide additives (entries 2–4). This improvement would be expected if one of the roles of the halide additive, as discussed above, is to facilitate oxidative addition by the generation of an anionic and bulkier Ni catalyst. Additionally, it appears that the identity of the protecting group has a small but significant influence on the product ratio (Table 1). This influence on regioselectivity may arise from initial association of the Ni catalyst to the protecting group prior to oxidative addition. The data suggest the potential for future optimization by modulation of the protecting group.

Scope Elucidation. The scope of the reaction was first explored by varying the identity of the nucleophile partner. As shown in Table 3, aziridine **2** was found to couple with an array of arylzinc reagents, including *ortho*-, *meta*-, and *para*-substituted nucleophiles (**9**–**11**). Sterically hindered nucleophiles are also viable in this new reaction, including 2,6-dimethylphenyl zinc bromide (**12**). The method is compatible with both electron-rich (**13**) and electron-poor (**14**–**16**) coupling partners, as well as arylzinc reagents bearing a variety of synthetically valuable functional groups (**17**–**19**). Notably, the use of a heteroaromatic nucleophile also led to cross

dx.doi.org/10.1021/ja4076716 | J. Am. Chem. Soc. 2013, 135, 13605–13609

Table 3. Evaluation of Nucleophile Scope[a]

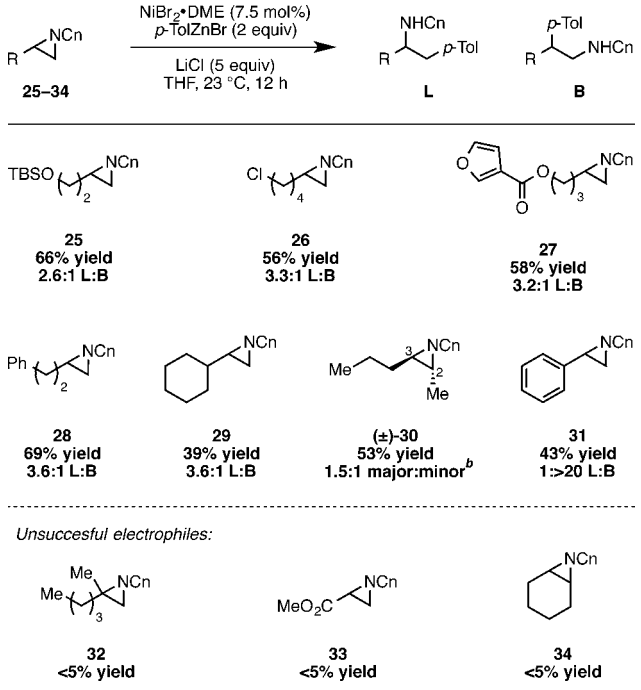


[a]Isolated yields are the average of two runs, 0.08 mmol scale. [b]Reaction was run at 50 °C. [c]Reaction was run at 60 °C.

coupling, albeit in moderate yield (**20**). Attempts to further expand the scope of the nucleophiles to aryl nitrile and ester-substituted zinc reagents were unfruitful, which may result from competitive binding of the unhindered Lewis basic groups to Ni. On the other hand, we were pleased to find that alkyl zinc reagents are suitable nucleophiles (**22**), even though the method was optimized for couplings with arylzinc reagents. For example, alkyl zinc reagents with a tertiary nitrile (**23**) and acetal (**24**) substitution underwent coupling in 74 and 53% yield under otherwise identical reaction conditions.

The scope of the electrophile was examined next (Table 4). Silyl ethers (**25**), alkyl chlorides (**26**), and furanyl esters (**27**) were well tolerated. Notably, the regioselectivity for the coupling reactions remained relatively invariant for these distinct terminal aziridines (and the range of nucleophiles examined in Table 3), in line with our proposal that the regioselectivity arises from a steric influence on oxidative addition. However, a similar regioisomeric ratio was obtained in the arylation of an aziridine bearing α-branching (**29**). This outcome is not entirely consistent with a steric argument and requires further study. Given this result, we were interested in how a 1,2-disubstituted aziridine and a styrenyl aziridine would perform under the coupling conditions. Exposure of 1,2-disubstituted **30** to the Ni-catalyzed conditions furnished the desired arylated product in a 1.5:1 L:B ratio favoring C–C bond formation at the expected less-hindered C2-position. For cinsyl protected styrenyl aziridine **31**, comparable yield to that

Table 4. Evaluation of Electrophile Scope[a]



[a]Isolated yields are the average of two runs, 0.08 mmol scale. [b]Addition at the C2-position of the aziridine afforded the major product.

obtained via our earlier work with the *N*-Ts analogue of **31** was observed. This reaction is selective for the branched product, suggesting that weakening of the benzylic C–N bond overrides steric control. Finally, our investigation has identified certain limitations in the electrophile scope. A 1,1-disubstituted (**32**) and an acrylate-derived (**33**) aziridine did not undergo productive coupling due to the formation of stable β-hydride elimination byproducts. In addition, although *trans*-**30** was reactive, a *cis*-substituted, cyclohexene-derived aziridine (**34**) underwent decomposition by conjugate addition, which can be rationalized on the basis of the known difference in ring-opening reactivity between *cis*- and *trans*-aziridines.[20]

To further demonstrate the practicality of this protocol, a gram-scale reaction set up on the benchtop using aziridine **2** afforded β-substituted amine **9** in 68% yield. Additionally, a preliminary study indicated that the cinsyl group can be removed under standard conditions for Ts deprotection; subsequent protection with an Fmoc-group provided an unoptimized 46% yield for the two-step sequence (see Supporting Information for details).

Mechanistic Studies. Our proposed catalytic cycle is shown in Figure 1. Initial reduction of Ni^{II} to Ni^{0} in the presence of LiCl may generate an anionic Ni^{0}–Cl complex primed for oxidative addition. Transient association of this metal complex with the cinsyl group likely occurs next (**A**), approximating the metal center to the aziridine, which would facilitate oxidative addition into the C–N bond (**B**).[21] Subsequent transmetalation with the organozinc reagent cleaves the metallacyclic Ni–N bond (**C**), thereby allowing effective coordination of the Ni to the electron-deficient π-system (**D**). Assisted by this olefin ligand, reductive elimination furnishes the cross-coupled product.

To better understand the mechanism of oxidative addition, we evaluated two other substrates, one an enantiopure aziridine

dx.doi.org/10.1021/ja4076716 | J. Am. Chem. Soc. 2013, 135, 13605–13609

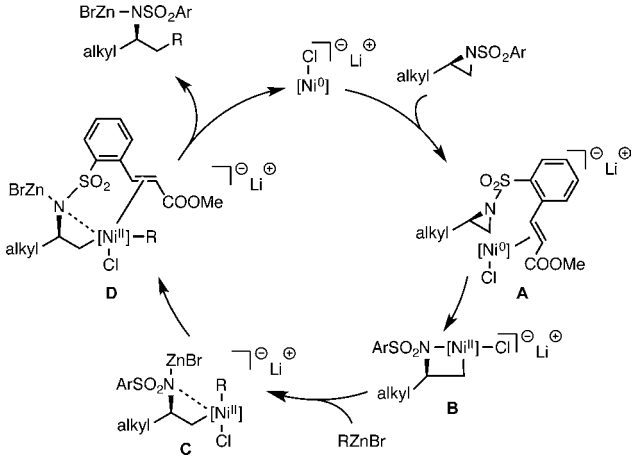
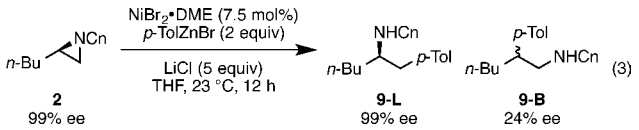


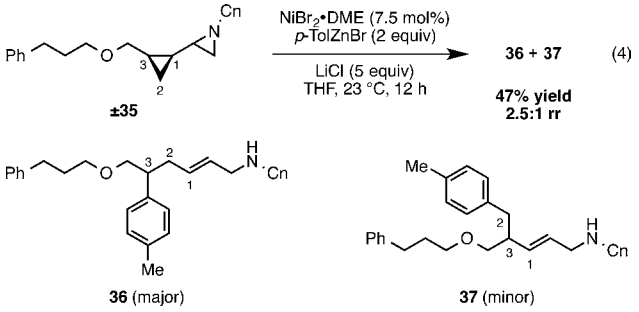
Figure 1. Proposed catalytic cycle.

(**2**) and the other a cyclopropyl-substituted aziridine (**35**). Starting from **2**, we observed the generation of linear and branched β-substituted amines **9-L** and **9-B** in a 3.8:1 ratio. Branched product **9-B** showed substantially eroded ee (24%), whereas the linear product **9-L** was obtained in 99% ee (eq 3).



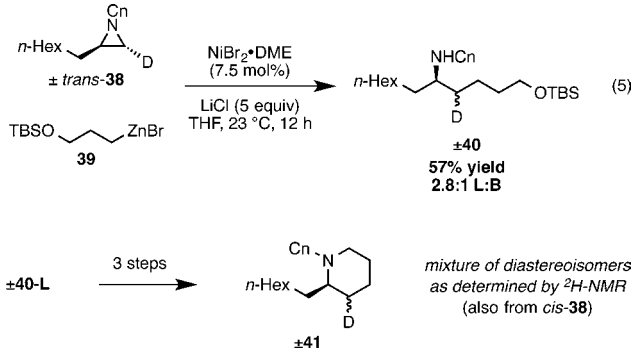
One explanation for this result is that oxidative addition occurs by a single-electron transfer (SET) pathway. Alternatively, oxidative addition could proceed by S_N2 addition of Ni to **2** followed by racemization of an ensuing reaction intermediate due to the configurational instability of the Ni−C bond.[22] The latter mechanism is most consistent with observation of predominantly linear product since a SET pathway would be expected to favor formation of the more substituted organic radical. Mechanistic studies of stoichiometric reactions with Ni and Pd by Hillhouse[7] and Wolfe[8] also support an S_N2 oxidative addition over a SET pathway.[23,24] Additionally, the fact that we observe no erosion in ee in the linear product **9-L** implies that racemization must occur during or after an irreversible step in the catalytic cycle.

The outcome of cross coupling with aziridine **35** containing an adjacent cyclopropyl group was also in line with an S_N2/homolysis mechanism. Specifically, two ring-opened products, **36** and **37**, were isolated in a 2.5:1 ratio when **35** was subjected to the standard reaction conditions (eq 4). Both of these



products arise from oxidative addition at the more substituted carbon of the aziridine, presumably due to the fact that a cyclopropyl group, like the aromatic ring in substrate **31**, facilitates oxidative addition at the adjacent electrophilic site by π-donation. Subsequent cyclopropane ring-opening, followed by C−C bond formation, would deliver **36** and **37**. This outcome implies the intermediacy of a radical intermediate:[25] the major product (**36**) would derive from a secondary radical at C3, whereas the minor product (**37**) would originate from a less-stable primary radical at C2.

We also prepared deuterium-labeled *cis*- and *trans*-**38** to determine whether oxidative addition of Ni to the terminal position occurs by a mechanism similar to that for internal coupling. Performing a cross-coupling reaction with *trans*-**38** (utilizing alkyl zinc reagent **39** as nucleophile) gave **40** in 57% yield and 2.8:1 L:B ratio. In order to determine the stereochemical composition of **40**, both isomers of **40** were converted into piperidine **41** and its regioisomer (not shown) by a three-step procedure. ^{2}H NMR analysis of **41** and comparison with authentic material prepared by an alternative synthetic protocol (see Supporting Information for details) revealed that **40L** was formed as a mixture of diastereoisomers and suggests that oxidative addition to the terminal position proceeds by the same S_N2/homolysis mechanism as that for internal addition. As further confirmation, we found that the same diastereomeric mixture of products (**41**) was obtained when the reaction was initiated with *cis*-**38**.



CONCLUSIONS

In conclusion, we have developed a novel aziridine protecting group, which is able to sequentially activate an aziridine toward oxidative addition, direct the nickel catalyst to the C−N bond, and promote reductive elimination. This system represents the first use of a nonbenzylic or allylic $C_{sp}3$−N bond as an electrophile in metal-catalyzed cross coupling and affords phenylethylamine derivatives.[26] We have shown that C−C bond formation occurs in a stereoconvergent manner most consistent with an S_N2/homolysis mechanism for oxidative addition. Efforts to utilize alkene-containing directing groups to enable cross coupling with other traditionally unreactive electrophiles, as well as further mechanistic studies, are currently underway.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, optimization tables, mechanism studies. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

agdoyle@princeton.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by Princeton University, Bristol-Myers Squibb, and Eli Lilly. A.G.D. is an Alfred P. Sloan Foundation Fellow, Eli Lilly Grantee, Amgen Young Investigator, and Roche Early Excellence in Chemistry Awardee. The authors also thank Lotus Separations for chiral separation of **2** and Istvan Pelczer for help with NMR experiments.

■ REFERENCES

(1) For a review on the functionalization of C_{sp^2}–O bonds, see: (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2010**, *111*, 1346–1416. For a recent example of the functionalization of C_{sp^2}–N bonds, see: (b) Koreeda, T.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 7238–7239.

(2) For a leading reference on allylic C–N bond activation, see: (a) Li, M.-B.; Wang, Y.; Tian, S.-K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2968–2971. For a leading reference on allylic C–O bond activation, see: (b) Yatsumonji, Y.; Ishida, Y.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2007**, *9*, 4603–4606.

(3) For leading references on the use of benzylic C–O/N bond-containing substrates as electrophiles, see: (a) Yu, D.-G.; Wang, X.; Zhu, R.-Y.; Luo, S.; Zhang, X.-B.; Wang, B.-Q.; Wang, L.; Shi, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 14638–14641. (b) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307–3310. (c) Li, M.-B.; Tang, X.-L.; Tian, S.-K. *Adv. Synth. Catal.* **2011**, *353*, 1980–1984. (d) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280–285.

(4) For examples of reductive coupling of nonactivated epoxides with aldehydes and alkynes, see: (a) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076–8077. (b) Molinaro, C.; Jamison, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 129–132. (c) Beaver, M. G.; Jamison, T. F. *Org. Lett.* **2011**, *13*, 4140–4143.

(5) (a) Huang, C.-Y. D.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541–9544. For Suzuki couplings of epoxides, see: (b) Nielsen, D. K.; Doyle, A. G. *Angew. Chem., Int., Ed.* **2011**, *50*, 6056–6059.

(6) (a) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319–6332. (b) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544–3553. (c) Ariafard, A.; Lin, Z. *Organometallics* **2006**, *25*, 4030–4033. (d) Li, Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815–8823.

(7) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890–2891.

(8) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 15415–15422.

(9) Wolfe, J. P.; Ney, J. E. *Org. Lett.* **2003**, *5*, 4607–4610.

(10) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840–871.

(11) For the use of electron-withdrawing styrenes as ligands in catalytic cross coupling of alkyl electrophiles, see: (a) Giovannini, R.; Stüdemann, T.; Gaelle, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387–2390. (b) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186–11187. (c) Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544–3553. (d) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79–85.

(12) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450–2494.

(13) See the Supporting Information for the evaluation of other alkene-containing protecting groups.

(14) Side products arising from conjugate addition of the aryl zinc reagent to the starting material/product, as well as uncharacterized polymeric material, account for the mass balance of most reactions.

(15) Ahn, K. H.; Baek, H.-H.; Lee, S. J.; Cho, C.-W. *J. Org. Chem.* **2000**, *65*, 7690–7696.

(16) For Negishi couplings of alkyl chlorides, see: (a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. (b) Hadei, N.; Achonduh, G. T.; Valente, C.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 3896–3899. For a Suzuki coupling of *β*-chloroamines, see: (c) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157.

(17) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336. (b) Ochiai, H.; Jang, M.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 2681–2683.

(18) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47.

(19) (a) Achonduh, G. T.; Hadei, N.; Valente, C.; Avola, S.; O'Brien, C. J.; Organ, M. G. *Chem. Commun.* **2010**, *46*, 4109–4111. (b) 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*, 7845–7851. (c) Fleckenstein, J. E.; Koszinowski, K. *Organometallics* **2011**, *30*, 5018–5026. (d) McCann, L. C.; Hunter, H. N.; Clyburne, J. A. C.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7024–7027.

(20) For examples, see compound **27** in ref 5a and: (a) Stamm, H.; Sommer, A.; Woderer, A.; Wiesert, W.; Mall, T.; Assithianakis, P. *J. Org. Chem.* **1985**, *50*, 4946–4955. (b) Mall, T.; Stamm, H. *J. Org. Chem.* **1987**, *52*, 4812–4814. (c) Park, G.; Kim, S.-C.; Kang, H.-Y. *Bull. Korean Chem. Soc.* **2005**, *26*, 1339–1343.

(21) For a review on 2-azametallacyclobutanes, see: Dauth, A.; Love, J. A. *Dalton Trans.* **2012**, *41*, 7782–7791.

(22) Bellos, K.; Stamm, H.; Speth, D. *J. Org. Chem.* **1991**, *56*, 6846–6849.

(23) Alkyne-directed oxidative addition to the terminal position of epoxides also goes through an S_N2 pathway. See: Beaver, M. G.; Jamison, T. F. *Org. Lett.* **2011**, *13*, 4140–4143.

(24) It is noteworthy that the authors of refs 7 and 8 do not observe racemization using a similar class of substrates to the ones reported in this manuscript. One explanation to address this discrepancy is that the distinct ligands (bipyridines) and reaction conditions used in their studies impart greater configurational stability to the resulting azametallacyclic intermediates. Alternatively, in our system, racemization by reversible Ni–C bond homolysis may occur at an intermediate other than **B** in Figure 1.

(25) A nonradical mechanism analogous to the elementary step in intramolecular [5 + 2] cycloaddition of vinylcyclopropanes could also provide the ring-opening products, but a **36**:**37** ratio favoring **37** would be expected: Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179.

(26) Medicinally relevant phenylethylamine derivatives: Berry, M. D. *J. Neurochem.* **2004**, *90*, 257–271.