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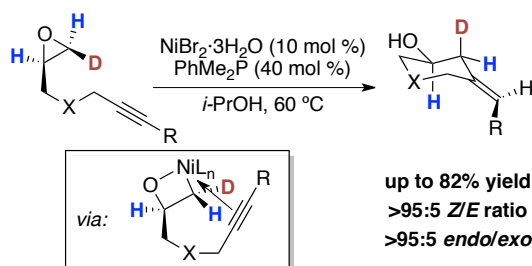
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ABSTRACT

A Ni-catalyzed reductive coupling of alkynes and epoxides using Ni(II) salts and simple alcohol reducing agents is described. Whereas previously reported conditions relied on Ni(cod)$_2$ and Et$_3$B, this system has several advantages including the use of air-stable and inexpensive Ni(II) precatalysts (e.g., NiBr$_2$·3H$_2$O) as the source of Ni(0) and simple alcohols (e.g., 2-propanol) as the reducing agent. Deuterium-labeling experiments are consistent with oxidative addition of an epoxide C–O bond that occurs with inversion of configuration.

The development of methods for transition metal-catalyzed C–C bond formation using air-stable and inexpensive reagents continues to offer a challenge to synthetic chemists. Recent improvements in the scope and utility of Ni-catalyzed C–C bond forming reactions present a significant advance towards this goal.[1,2] The advent of methods employing Ni(II) precatalysts, for example, has obviated the need to handle air-sensitive Ni(0) sources.[3] In many cases, however, Ni-catalyzed coupling protocols are limited by the inclusion of air- and moisture-sensitive reducing agents. Herein, we describe a practical method for the Ni-catalyzed reductive coupling of alkynes and epoxides using air-stable and inexpensive Ni(II) salts as the precatalysts and 2-propanol (*i*-PrOH) as

[1] For reviews, see: a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908. b) Montgomery, J.; Sormunen, G. J. *Top. Curr. Chem.* **2007**, *279*, 1–23. c) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. *Chem. Commun.* **2007**, 4441–4449. d) Kimura, M.; Tamaru, Y. *Top. Curr. Chem.* **2007**, *279*, 173–207. e) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346–1416.
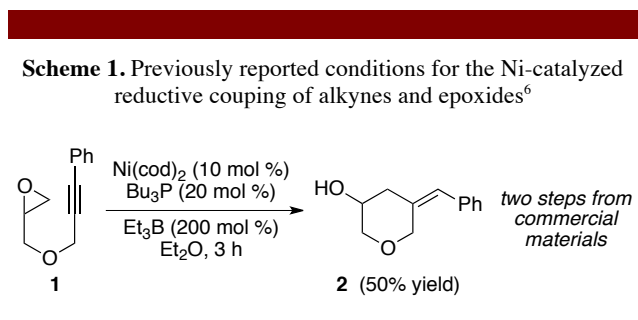
[2] For selected examples of recent advances in Ni-catalyzed C–C bond forming reactions, see: a) Malik, H. A.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2010**, *132*, 6304–6305. b) Matsubara, R.; Jamison, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 6880–6881. c) Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 7576–7577. d) Zhou, C.-Y.; Zhu, S.-F.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132*, 10955–10957. e) Li, W.; Chen, N.; Montgomery, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8712–8716. f) Ho, C.-Y.; He, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9182–9186. g) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.;

Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389–391. h) Hoshimoto, Y.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2011**, *133*, 4668–4671.

[3] For selected examples of C–C bond forming methods employing Ni(II) precatalysts, see: a) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594–12595. b) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422–14423. c) Williams, C. M.; Johnson, J. B.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14936–14937. d) Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920–921. e) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029. f) Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11908–11909.

the reducing agent.[4,5] Mechanistic analysis of the reductive coupling process via deuterium-labeling studies provides evidence that oxidative addition of the epoxide C–O bond occurs with inversion of configuration.

Our laboratory has previously demonstrated that alkynes and epoxides undergo reductive coupling in the presence of Ni(cod)$_2$, Bu$_3$P, and Et$_3$B.[6,7,8] For example, Ni-catalyzed reductive coupling of epoxide **1** provided homoallylic alcohol **2** in 50% yield (Scheme 1). The combination of Ni(cod)$_2$ and Bu$_3$P, both of which are exceedingly prone to air oxidation, was found to provide optimal results. In addition, the inclusion of Et$_3$B, a highly pyrophoric reducing agent, was critical for the desired transformation to proceed. We hypothesize that Et$_3$B may serve as a Lewis acid to facilitate oxidative addition of the epoxide, in addition to its standard role as a reducing agent.

Scheme 1. Previously reported conditions for the Ni-catalyzed reductive couping of alkynes and epoxides[6]

the epoxide C–O bond could be facilitated by hydrogen-bonding interactions between the epoxide oxygen and the alcohol solvent.[9b,10] Second, the appropriate alcohol could serve as a reducing agent to provide the desired homoallylic alcohol product (**2**) and regenerate the active Ni(0) catalyst (*vide infra*, Scheme 2).[4,5,11] In this manner, simple alcohols (e.g., *i*-PrOH) could serve as mild, air-stable, and inexpensive alternatives to Et$_3$B.

Table 1. Influence of Reaction Parameters on the Ni-Catalyzed Reductive Coupling of an Alkyne and Epoxide

entry	variation from standard conditions	yield (%)[a]	Z/E[b]
1	none[c]	82	90:10
2	Ni(cod)$_2$ instead of NiBr$_2$·3H$_2$O[d]	82	95:5
3	NiBr$_2$·diglyme instead of NiBr$_2$·3H$_2$O	76	88:12
4	NiCl$_2$·6H$_2$O instead of NiBr$_2$·3H$_2$O	74	89:11
5	5 mol % NiBr$_2$·3H$_2$O and 20 mol % PhMe$_2$P instead of standard catalyst/phosphine loading	75	95:5
7	THF instead of *i*-PrOH	<5[e]	---
8	no NiBr$_2$·3H$_2$O	<5[e]	---
9	30 mol % PhMe$_2$P instead of 40 mol %	90:10	76
10	20 mol % PhMe$_2$P instead of 40 mol %	91:9	52
11	no PhMe$_2$P	<5[e]	---

[a] Isolated yield of the mixture of olefin isomers. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Complete conversion of starting material observed within 3 h. [d] Phosphine loading was 20 mol % instead of 40 mol %. [e] Determined by ^{1}H NMR spectroscopy relative to mesitylene as an internal standard.

In light of our recent studies involving regioselective epoxide-opening cascades promoted by hydroxylic solvents,[9] we envisioned that alcohol solvents might promote the Ni-catalyzed reductive coupling of alkynes and epoxides. In this setting, the role of the alcohol solvent would be two-fold. First, oxidative addition of

Our investigations revealed that *i*-PrOH was an effective reducing agent for the Ni-catalyzed reductive coupling of alkynes and epoxides. For example, employing *i*-PrOH as the solvent in the presence of PhMe$_2$P and either NiBr$_2$·3H$_2$O (Table 1, entry 1) or Ni(cod)$_2$ (entry 2) provided high yields of the desired homoallylic alcohol **2a**.[12,13,14] The use of air-stable Ni(II)

[4] Alcohols bearing β-hydrogen atoms have proven to be competent reducing agents in Ni-catalyzed reductive coupling reactions: a) Herath, A.; Li, W.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 469–471. b) Li, W.; Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2009**, *131*, 17024–17029. c) Phillips, J. H.; Montgomery, J. *Org. Lett.* **2010**, *12*, 4556–4559.

[5] For additional examples of *i*-PrOH-mediated reductive C–C bond-forming reactions see: a) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134–15135. b) Bower, J. F.; Patman, R. L.; Krische, M. J. *Org. Lett.* **2008**, *10*, 1033–1035. c) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338–6339. d) Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066–2067.

[6] Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076–8077.

[7] For examples of the utility of Ni-catalyzed alkyne–epoxide reductive coupling in the context of natural product synthesis, see: a) O'Brien, K. C.; Colby, E. A.; Jamison, T. F. *Tetrahedron* **2005**, *61*, 6243–6248. b) Woodin, K. S.; Jamison, T. F. *J. Org. Chem.* **2007**, *72*, 7451–7454. c) Sparling, B. A.; Simpson, G. L.; Jamison, T. F. *Tetrahedron* **2009**, *65*, 3270–3280. d) Trenkle, J. D.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5366–5368.

[8] Reductive opening of epoxides has also been observed under titanocene catalysis: a) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101–103. b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.

[9] See, for example: a) Vilotijevic, I.; Jamison, T. F. *Science*, **2007**, *317*, 1189–1192. b) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383–6385. c) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175–3192.

[10] a) Hine, J.; Linden, S.-M.; Kanagasabapathy, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 1082–1083. b) Hine, J.; Linden, S.-M.; Kanagasabapathy, V. M. *J. Org. Chem.* **1985**, *50*, 5096–5099. c) Yamada, T.; Morisseau C.; Maxwell, J. E.; Argiriadi, M. A.; Christianson, D. W.; Hammock, B. D. *J. Biol. Chem.* **2000**, *275*, 23082–23088. d) Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2000**, *65*, 2464–2471. e) Fleming, E. M.; Quigley, C.; Rozas, I.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 948–956. e) Wurst, J. M.; Liu, G.; Tan, D. S. *J. Am. Chem. Soc.* **2011**, *133*, 7916–7925.

[11] For selected reviews describing transition-metal catalyzed transfer hydrogenation, see: a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051–1069. b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102. c) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34–46.

[12] Details of substrate synthesis are provided as Supporting Information.

[13] Subjecting enantioenriched epoxide **1a** (88% ee) to the standard conditions for Ni-catalyzed reductive coupling provided homoallylic alcohol **2a** (88% ee) with complete preservation of optical purity. See Supporting Information for details.

[14] Preliminary investigation of the reaction conditions indicated that *i*-PrOH was the optimal alcohol reducing agent. See Supporting

precatalysts and reducing agents (i.e., NiBr$_2$·3H$_2$O and *i*-PrOH, as opposed to previous conditions employing Ni(cod)$_2$ and Et$_3$B)[6] allowed us to set-up and perform the coupling reactions outside of a glovebox. Furthermore, all reactions listed in Table 1 could be performed without drying of the reagents or glassware. Of note, reactions employing inexpensive NiX$_2$·hydrate salts (entries 1 and 4) were of comparable efficiency to reactions performed with anhydrous NiBr$_2$·diglyme (entry 3). Decreasing the catalyst loading to 5 mol % was tolerated and provided the desired homoallylic alcohol **2a** in only slightly lower yields (entry 5). No product formation was observed in the absence of *i*-PrOH, the nickel catalyst, or phosphine ligand (entries 7, 8, 11).

Increased phosphine loadings were found to provide the highest yields of homoallylic alcohol **2a** for reactions in which NiX$_2$ salts were employed as the catalyst. Previously, a 2:1 (R$_3$P:Ni) ratio was determined to be the optimal loading for reductive coupling reactions of epoxides and alkynes using Ni(cod)$_2$ (Table 1, entry 2).[6] When NiBr$_2$·3H$_2$O was employed as the catalyst, however, a phosphine loading of 20 mol % did not result in complete conversion of starting material (entry 10). Increasing the phosphine loading to 30 mol % led to complete consumption of the starting material and increased yields (entry 9). Finally, a phosphine loading of 40 mol % was found to provide the highest yield of homoallylic alcohol **2a** (entry 1). We attribute the requirement for excess phosphine ligand to its involvement in the reduction of the Ni(II) precatalyst to the active Ni(0) species, which has been observed previously for both Ni(II)[15] and Pd(II)[16] precatalysts. Alternatively, excess phosphine may be necessary to suppress the formation of catalytically-inactive Ni(O*i*-Pr)$_2$ species.[17]

In all cases examined, reductive coupling of epoxide **1a** proceeded to provide the desired tetrahydropyran product (**2a**) as a single regioisomer with respect to both the epoxide and the alkyne. Stereospecific cis addition to the alkyne occurred to provide the trisubstituted olefin (*Z*-**2a**);[4] however, isomerization of the olefin geometry was observed to a limited extent under the standard conditions for reductive coupling. The amount of undesired isomerization product (*E*-**2a**) could be minimized by judicious choice of catalyst identity and loading (entries 1,2 and 5).

The mild conditions for Ni-catalyzed reductive coupling were found to effect product formation for substrates containing variation within the epoxide–alkyne tether. Both substituted cyclohexane (Table 2, entries 1 and 2) and piperidine (entry 3) derivatives could be prepared in this manner.[12]

Varying the substituent on the alkyne had a more significant impact on the efficiency of reductive coupling. Alkyl-substitution was tolerated and provided the desired homoallylic alcohol (**2e**) in yields comparable to those observed for phenyl-substituted alkynes (Table 2, entries 1–4). Conversely, subjecting alkynoate **1f** to the standard conditions for reductive coupling did not result in formation of the desired product (entry 5).[18] Terminal alkynes are a particularly difficult class of substrates in Ni(0)-catalyzed coupling reactions, as this moiety often succumbs to deleterious cyclotrimerization.[19] Under these conditions for reductive coupling, however, terminal alkyne **1g** underwent reductive coupling in 55% yield (entry 6).

Table 1. Investigation of Reaction Scope
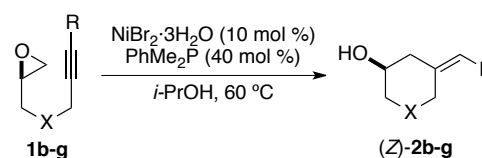
entry	X	R	product	yield (%)[a]	Z/E[b]
1	CH$_2$	Ph	**2b**	70	88:12
2	C(CO$_2$Me)$_2$	Ph	**2c**	76	>95:5
3	NBn	Ph	**2d**	74	88:12
4	O	*n*-C$_5$H$_{11}$	**2e**	75	>95:5
5	O	CO$_2$Me	**2f**	<5[c]	---
6	O	H	**2g**	55[d]	---

[a] Isolated yield of the mixture of olefin isomers. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Determined by ^{1}H NMR spectroscopy relative to mesitylene as an internal standard. [d] Dropwise addition of substrate via syringe pump.

The proposed mechanism for Ni-catalyzed reductive coupling of epoxides and alkynes involves initial oxidative addition of the epoxide C–O bond to form nickella(II)oxetane **5** (Scheme 2).[6] Previous reports have demonstrated that oxidative addition of epoxides with group 10 metals occurs with either inversion (Pd and Pt)[20,21] or scrambling (Ni)[22] of configuration, corresponding to S$_N$2 ring opening or homolytic C–O bond cleavage, respectively. To the best of our

Information for additional details of reaction optimization including alcohol reducing agent, Ni(II) precatalyst and temperature.

[15] Ananikov, V. P.; Gayduk, K. A.; Starikova, Z. A.; Beletskaya, I. P. *Organometallics* **2010**, *29*, 5098–5102.

[16] a) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009–3013. b) Ozawa, F.; Kubo, A. Hayashi, T. *Chem. Lett.* **1992**, 2177–2180. c) Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505–3508.

[17] a) Sacco, A.; Mastrorilli, P. *J. Chem. Soc., Dalton Trans.* **1994**, 2761–2764. b) Hubert-Pfalzgraf, L. G.; Kessler, V. G.; Vaisserman, J. *Polyhedron* **1997**, *16*, 4197–4203.

[18] Phosphine-catalyzed conjugate addition of *i*-PrOH to the alkynoate was observed, which has been reported previously: a) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241–244. b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050.

[19] Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915.

[20] a) Aye, K.-T.; Gelmini, L.; Payne, N. C.; Vittal, J. J.; Puddephatt, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 2464–2465. b) Bäckvall, J.-E.; Bökman, F.; Blomberg, M. R. A. *J. Am. Chem. Soc.* **1992**, *114*, 534–538. c) Kulasegaram, S.; Kulawiec, R. J. *Tetrahedron* **1998**, *54*, 1361–1374.

[21] Oxidative addition of epoxides with [Lewis acid][Co(CO$_4$)] complexes has also been observed to occur with inversion of configuration: Church, T. L.; Getzler, Y. D. Y. L.; Coates, G. W. *J. Am. Chem. Soc.* **2006**, *128*, 10125–10133.

[22] Bäckvall, J.-E.; Karlsson, O.; Ljunggren, S. O. *Tetrahedron Lett.* **1980**, *21*, 4985–4988.

knowledge, there is no experimental evidence describing oxidative addition of an epoxide C–O bond with Ni(0) that occurs with inversion of configuration.[23]

To gain insight into the oxidative-addition process, we prepared monodeuterated epoxide **3** and observed the relative configuration of the deuterated carbon center after subjection to the standard conditions for Ni-catalyzed reductive coupling (Scheme 2). Monodeuterated epoxide **3** was prepared with 83% deuterium incorporation at the terminal epoxide site bearing a cis relationship to the alkyne tether.[12] Subjecting epoxide **3** to the standard conditions for reductive coupling provided homoallylic alcohol **4** with complete inversion of configuration at the deuterated carbon center.[24] This result is consistent with inversion of configuration in the oxidative addition step to afford the nickella(II)oxetane intermediate (**5**), followed by migratory insertion that occurs with retention of configuration.[25] We propose that inversion of configuration in the oxidative addition step occurs via S_N2 attack by the nucleophilic Ni(0) species facilitated by hydrogen-bond activation of the epoxide.[10] Importantly, identical results were obtained when epoxide **3** was subjected to the previously described conditions for reductive coupling (Scheme 1, PhMe$_2$P instead of Bu$_3$P) indicating that the active Ni(0) catalyst is responsible for the inversion process.

Following C–C bond formation, i-PrOH serves as a mild reducing agent to complete the catalytic cycle. Protonolysis of the Ni–O bond of strained bicyclic oxanickellacycle **6** results in formation of the L$_n$Ni(Oi-Pr) species (**7**) necessary for catalytic turnover. Subsequent β-H elimination occurs to liberate acetone, which is inert under the reaction conditions, followed by reductive elimination to afford homoallylic alcohol **4** and regenerate the active Ni(0) catalyst.

In summary, we have developed novel conditions for the Ni-catalyzed reductive coupling of alkynes and epoxides that employ air-stable and inexpensive reagents. These reaction conditions are significantly milder and more convenient than those previously used for similar reductive coupling reactions in which a combination of Ni(cod)$_2$ and Et$_3$B was necessary to effect C–C bond formation. Further investigation of the electrophile/π-nucleophile scope is warranted in an effort to improve the efficiency of previously developed methods and for the invention of novel reductive coupling procedures.

Scheme 2. Deuterium-Labeling Experiment and Proposed Mechanism for Ni-Catalyzed Reductive Coupling
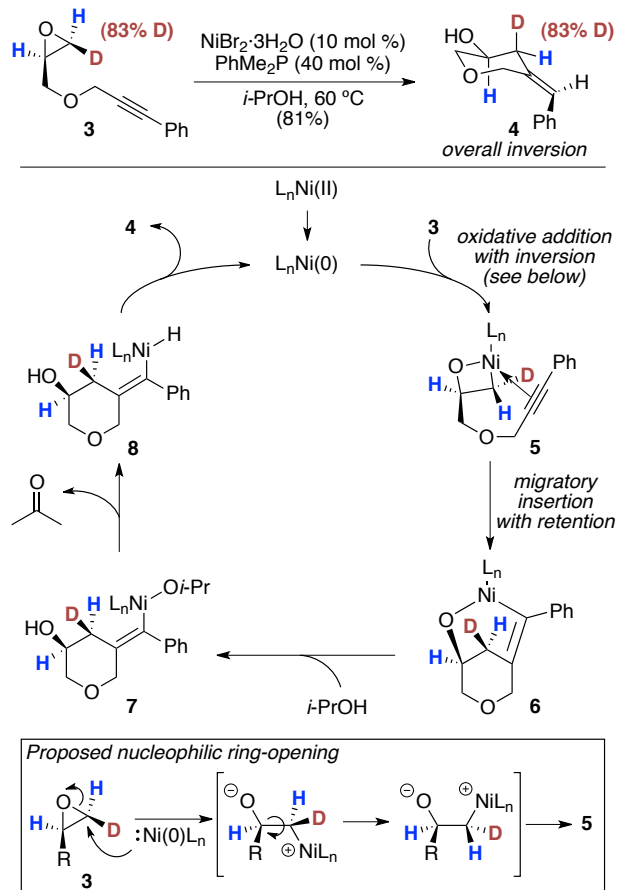
Supporting Information Available. Complete experimental procedures and characterization data of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org

[23] Oxidative addition of tosyl-aziridines with Ni(0) has been observed to occur with inversion of configuration: Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890–2891.

[24] The relative stereochemistry of monodeuterated tetrahydropyran **4** was confirmed by synthesis of the *tert*-butyldiphenyl silyl ether (TBDPS-**4**) and comparison to the protio-congener (TBDPS-**2a**). See Supporting Information for complete experimental details and stereochemical analysis.

[25] The mechanism of migratory insertion is generally accepted to occur with retention of configuration at the metal-bonded carbon. For the seminal study, see: Bock, P. L.; Boschetto, D. J.; Rasmussen, J. R.; Demers, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2814–2825. For further discussion of migratory insertion as it pertains to the stereochemical outcome of transition-metal mediated processes, see: a) Lau, K. S. Y.; Wong, P. K.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 5832–5840. b) Spencer, J.; Pfeffer, M. *Tetrahedron: Asymmetry* **1995**, *6*, 419–426. c) Malinakova, H. C. *Chem.–Eur. J.* **2004**, *10*, 2636–2646. d) Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2004**, *69*, 4701–4715.