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Stereochemistry of Transmetalation of Alkylboranes in Nickel-Catalyzed Alkyl−Alkyl Cross-Coupling Reactions

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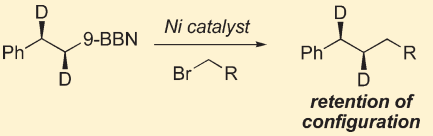
Supporting Information

ABSTRACT: Deuterium-labeled alkylborane reagents **2a** and **2b** were prepared and subjected to cross-coupling reactions in the presence of a nickel catalyst. NMR analysis of the products indicates that transmetalation from boron to nickel proceeds with retention of configuration. These results demonstrate that alkylnickel intermediates are configurationally stable under Suzuki cross-coupling conditions.

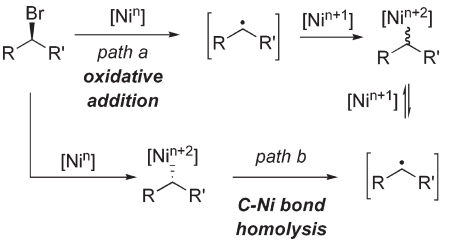


Transition-metal-catalyzed cross-coupling reactions have revolutionized the synthesis of natural products and medicinal agents and provided rapid synthetic access to a diverse range of molecules for biological testing.[1] The development of cross-coupling reactions of alkyl electrophiles and alkyl nucleophiles is important because these reactions generate new C−C bonds between sp^3-hybridized carbons.[2] Such transformations are less well-developed than related reactions of aryl and vinyl reaction partners,[3] in part due to competing side reactions of the alkylmetal intermediates. Many of the inherent challenges to sp^3−sp^3 cross-couplings have been overcome with the use of nickel catalysts.[4,5] In contrast to palladium-catalyzed cross-couplings, in which detailed mechanistic studies have led to major advances in cross-coupling methods,[6,7] the mechanistic details of nickel-catalyzed reactions are less well-understood. Additional mechanistic data concerning the elementary steps of nickel-catalyzed reactions are important for the continued development of these reactions.

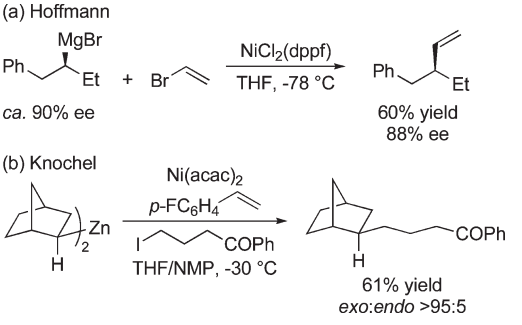
Our interest in the development of a stereospecific nickel-catalyzed cross-coupling reaction required that all steps involving alkylnickel intermediates proceed with stereochemical fidelity.[8] It has been shown that nickel-catalyzed cross-coupling reactions of alkyl halides lead to loss of stereochemical information from the alkyl halide.[9,10] Stille proposed two possible rationales for this observation: oxidative addition via a radical mechanism (path a, Scheme 1) or reversible homolysis of Ni−C bonds to provide radical intermediates (path b, Scheme 1).[11] Recent studies of Negishi cross-coupling reactions by the groups of Vicic,[12] Cárdenas,[5d] and Phillips[13] have provided support for a radical mechanism for oxidative addition. On the other hand, Halpern has shown that benzylnickel(II) complexes undergo rapid and reversible Ni−C bond homolysis at room temperature.[14] Since racemization of alkylnickel complexes would preclude a stereospecific cross-coupling reaction, we set out to examine the stereochemical integrity of nonbenzylic alkylnickel complexes using a chiral organometallic cross-coupling partner.

Nickel-catalyzed cross-coupling reactions of chiral alkylmagnesium and alkylzinc reagents have been studied at low temperatures, where racemization of the alkylmetal reagent is suppressed

Scheme 1. Possible Mechanisms for Racemization of Alkyl Halides in Nickel-Catalyzed Cross-Coupling Reactions



Scheme 2. Stereochemical Studies of Alkylmetal Reagents in Nickel-Catalyzed Cross-Coupling Reactions



(Scheme 2).[15,16] Hoffmann found that cross-coupling of Grignard reagents proceeds with retention of configuration.[17] While, to the best of our knowledge, detailed studies of the stereochemical outcome of transmetalation from alkylzinc reagents and nickel catalysts have not been reported, Knochel has reported diastereoselective cross-coupling of a norbornylzinc reagent that procedes with retention of configuration.[18,19] In

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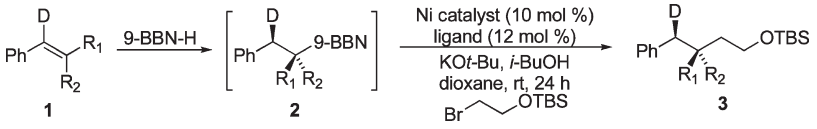
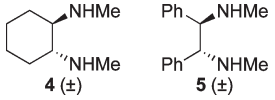
Table 1. Stereospecific Boron−Nickel Transmetalation in Suzuki Cross-Coupling Reactions



entry	styrene	R_1	R_2	catalyst	ligand	product	yield (%)
1	**1a**	D	H	$NiCl_2 \cdot DME$	**4**	**3a**	85
2	**1b**	H	D	$NiCl_2 \cdot DME$	**4**	**3b**	71
3	**1b**	H	D	$Ni(cod)_2$	**5**	**3b**	56



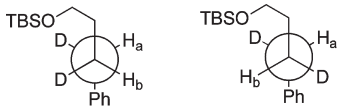


Figure 1. Newman projections of predominant conformers of cross-couping products.

this report, we examine the nickel-catalyzed cross-coupling of alkylboranes, common reagents in sp^3-sp^3 cross-coupling reactions that show robust stereochemical integrity at room temperature.

We designed a stereochemical test using deuterium labeling, inspired by the work of Whitesides,[20] Woerpel,[6a] and Soderquist.[6b] Deuterium-labeled styrenes **1a** and **1b** were prepared and subjected to hydroboration to provide boranes **2a** and **2b**, respectively (Table 1).[21] Application of cross-coupling conditions developed by Fu and co-workers furnished the products **3a** and **3b**, respectively.[5a] Analysis by ^{2}H-decoupled ^{1}H NMR indicated that the products were formed as single diastereomers (>95%) using two different nickel catalysts.[22] The products **3a** and **3b** can be distinguished based on their H_a-H_b coupling constants because the predominant conformers in solution should be *anti*-**3a** and *anti*-**3b** (Figure 1). The H_a-H_b coupling constant in *anti*-**3a** (in which H_a and H_b are gauche) is expected to be significantly smaller than in *anti*-**3b** (in which H_a and H_b are anti).[20] The H_a-H_b coupling constants for **3a** and **3b** were found to be 6.3 and 9.1 Hz, respectively, supporting the relative stereochemistry shown in Table 1.[23] These results are consistent with retention of configuration in the transmetalation step of the cross-coupling reaction.[24]

In conclusion, we have demonstrated that nickel catalysts obtained from diamine ligands **4** and **5** undergo transmetalation with an alkylborane with retention of configuration during cross-coupling reactions. The formation of **3a** and **3b** as single diastereomers is consistent with slow racemization of alkylnickel complexes at room temperature under Suzuki cross-coupling conditions. This result precludes Ni−C bond homolysis under these conditions (path b, Scheme 1) and lends indirect support for a radical mechanism for oxidative addition as the process in which alkyl halides lose stereochemical information during nickel-catalyzed reactions. The stereospecificity of transmetalation to nickel catalysts is important for the further development of asymmetric alkyl−alkyl cross-coupling reactions, particularly reactions that will employ secondary organometallic reagents.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an atmosphere of N_2. All glassware was oven- or flame-dried prior to use. Tetrahydrofuran (THF), diethyl ether (Et_2O), and toluene (PhMe) were degassed with Ar and then passed through two columns of anhydrous neutral A-2 alumina (activated under a flow of argon at 350 °C for 12 h) to remove H_2O. Dioxane was freshly distilled from sodium benzophenone ketyl prior to use. Isobutanol (*i*-BuOH) was distilled from CaH_2 prior to use. Proton chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane (TMS, δ 0.00). Carbon chemical shifts are reported in parts per million (δ) relative to TMS with the solvent resonance as the internal standard ($CDCl_3$, δ 77.23 ppm). Deuterium chemical shifts are reported in parts per million (δ) relative to TMS with the solvent resonance as the internal standard ($CDCl_3$, δ 7.24 ppm). NMR data were collected at 25 °C. Flash chromatography was performed using EMD Geduran silica gel 60A (0.040−0.063 μm).

*cis-1,2-Dideuteriostyene (**1a**)* was prepared by treating phenylacetylene with Cp_2ZrDCl, followed by D_2O, according to a procedure by Bercaw et al.[25] ^{1}H NMR spectroscopy indicated 93% deuterium incorporation, in accord with reported spectral data.[26] The product was stored at −20 °C and used within 12 h of isolation.

*trans-1,2-Dideuteriostyene (**1b**)* was prepared by treating deuteriophenylacetylene with Cp_2ZrDCl, followed by H_2O, according to a procedure by Bercaw et al.[25] *Note:* there is a typo in the reported procedure: the metalated complex must be treated with H_2O, rather than D_2O. ^{1}H NMR spectroscopy indicated 95% deuterium incorporation, in accord with reported spectral data.[26] The product was stored at −20 °C and used within 12 h of isolation.

*syn-3,4-Dideuterio-4-phenylbutoxy(tert-butyl)dimethylsilane (**3a**).* The procedure reported by Saito and Fu was adapted.[5a] In a N_2 atmosphere glovebox, styrene **1a** (240 mg, 2.26 mmol) was added to a suspension of 9-BBN dimer (275 mg, 1.13 mmol dimer) in dioxane (0.6 mL). The flask was sealed with a septum and removed from the glovebox. A N_2 inlet was introduced, and the mixture was stirred at 60 °C for 1 h. The mixture was then cooled to rt and returned to the glovebox. The clear solution was transferred to a vial, and dioxane was added to produce a total volume of 4.5 mL (0.5 M). A portion of the resulting solution of **2a** (4.0 mL, 2.0 mmol, 0.5 M) was added to a mixture of KO*t*-Bu (150 mg, 1.34 mmol) and *i*-BuOH (0.21 mL, 2.3 mmol) in a 6 mL vial. The solution was stirred vigorously for 30 min.[27]

To the resulting white suspension was added a solution of $NiCl_2 \cdot$DME (24 mg, 0.11 mmol) and *rac-trans-N,N′*-dimethyl-1,2-cyclohexanediamine (**4**, 19 mg, 0.13 mmol) in dioxane (1 mL), followed by 2-bromoethoxy-(*tert*-butyl)dimethylsilane[28] (263 mg, 1.10 mmol). The vial was capped, and the mixture was stirred at rt for 24 h, after which it was passed through a pad of silica gel eluting with Et_2O/pentane (1:1, 20 mL) and concentrated in vacuo. The product was purified by flash chromatography (3% Et_2O/pentane) to afford **3a** as a colorless oil (250 mg, 85%): TLC R_f = 0.3 (5% Et_2O/pentane); $^1H\{^2H\}$ NMR (600 MHz, $CDCl_3$) δ 7.27 (t, J = 7.5 Hz, 2H), 7.19−7.15 (m, 3H), 3.62 (t, J = 6.4 Hz, 2H), 2.60 (d, J = 6.3 Hz, 1H), 1.64 (q, J = 7.0 Hz, 1H), 1.55 (q, J = 6.8 Hz, 2H), 0.89 (s, 9H), 0.04 (s, 6H); $^2H\{^1H\}$ NMR (92 MHz, $CHCl_3$) δ 2.62, 1.67; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 128.6, 128.5, 125.8, 63.2, 35.4 (t, $^1J_{CD}$ = 19.5 Hz), 32.5, 27.4 (t, $^1J_{CD}$ = 18.9 Hz), 26.2, 18.6, −5.1; IR (thin film) 3025, 2954, 2858, 2150, 1105 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{26}D_2OSi$ $(M + H)^+$ 267.2113, found 267.2121.

*anti-3,4-Dideuterio-4-phenylbutoxy(tert-butyl)dimethylsilane (**3b**).* In a N_2 atmosphere glovebox, styrene **1b** (160 mg, 1.51 mmol) was added to a suspension of 9-BBN dimer (183 mg, 0.750 mmol dimer) in dioxane (0.4 mL). The flask was sealed with a septum and removed from the glovebox. A N_2 inlet was introduced, and the mixture was stirred at 60 °C for 1 h. The mixture was then cooled to rt and returned to the glovebox. The clear solution was transferred to a vial, and dioxane was added to produce a total volume of 3.0 mL (0.5 M). A portion of the resulting solution of **2b** (0.80 mL, 0.40 mmol, 0.5 M) was added to a mixture of KO*t*-Bu (30 mg, 0.27 mmol) and *i*-BuOH (0.041 mL, 0.44 mmol) in a 6 mL vial. The solution was stirred vigorously for 30 min. To the resulting white suspension was added a solution of $NiCl_2 \cdot$DME (4.8 mg, 0.022 mmol) and *rac-trans-N,N′*-dimethyl-1,2-cyclohexanediamine (**4**, 3.7 mg, 0.026 mmol) in dioxane (0.2 mL), followed by 2-bromoethoxy(*tert*-butyl)dimethylsilane (52 mg, 0.22 mmol). The vial was capped, and the mixture was stirred at rt for 24 h, after which it was passed through a pad of silica gel eluting with Et_2O/pentane (1:1, 20 mL) and concentrated in vacuo. The product was purified by flash chromatography (3% Et_2O/pentane) to afford **3b** as a colorless oil (42 mg, 71%): TLC R_f = 0.3 (5% Et_2O/pentane); $^1H\{^2H\}$ NMR (600 MHz, $CDCl_3$) δ 7.27 (t, J = 7.6 Hz, 2H), 7.19−7.15 (m, 3H), 3.62 (t, J = 6.5 Hz, 2H), 2.60 (d, J = 9.1 Hz, 1H), 1.64 (q, J = 8.1 Hz, 1H), 1.55 (q, J = 6.8 Hz, 2H), 0.89 (s, 9H), 0.04 (s, 6H); $^2H\{^1H\}$ NMR (92 MHz, $CHCl_3$) δ 2.62, 1.67; ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 128.6, 128.5, 125.8, 63.2, 35.4 (t, $^1J_{CD}$ = 18.9 Hz), 32.5, 27.4 (t, $^1J_{CD}$ = 19.5 Hz), 26.2, 18.6, −5.1; IR (thin film) 3026, 2922, 2910, 2150, 1110 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{26}D_2OSi$ $(M + H)^+$ 267.2113, found 267.2117.

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra for all new compounds, Figure S1, and Table S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) ^{1}H spectra without ^{2}H decoupling gave comparable coupling constants (5.6 Hz for **3a** and 9.5 Hz for **3b**). See Supporting Information for details and a comparison of the ^{1}H NMR signals for **3a** and **3b** (Figure S1).

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