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FOUR-COMPONENT COUPLING STRATEGY FOR 2,3,4-TRISUBSTITUTED 3,4-DIHYDROQUINOLINE

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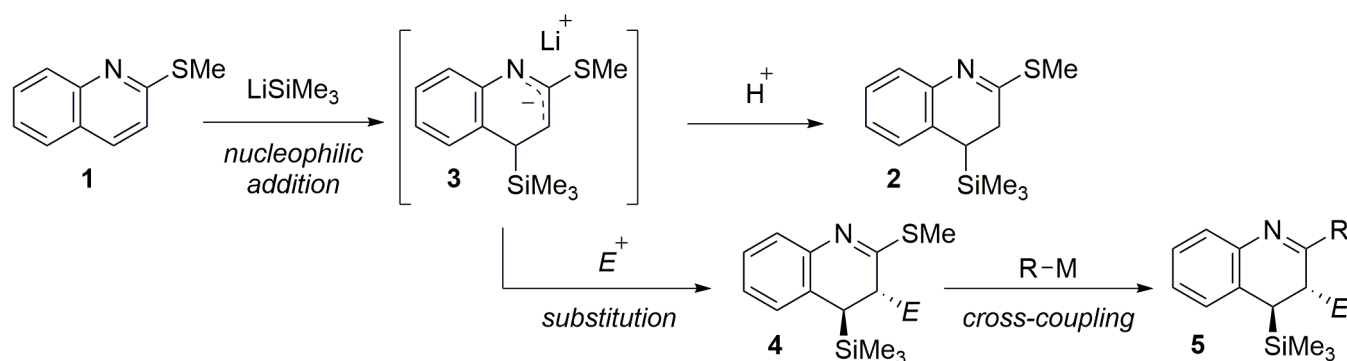
Dedicated to Prof. Dr. Tohru Fukuyama on the occasion of his 70th birthday

Abstract – Trimethylsilyllithium attacked selectively at the 4-position of 2-(methylsulfanyl)quinoline. The lithium enamide intermediate generated *in situ* reacted with a series of electrophiles to introduce a substituent at the 3-position of the dihydroquinoline skeleton. Combined with the conversion of the 2-methylsulfanyl group to an aryl group via palladium-catalyzed Negishi-type coupling reaction, the net four-component coupling transformation in two steps provided a 2,3,4-trisubstituted 3,4-dihydroquinoline skeleton.

INTRODUCTION

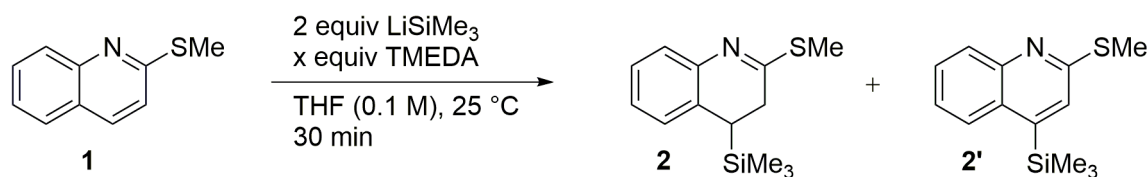
Recognized as promising halogen surrogates in transition metal-catalyzed coupling reactions, sulfur functionalities are attracting vibrant researches in the field of catalytic transformations.¹ During our continuing research campaign toward maximizing the utility of sulfur functionalities in organic synthesis,² we encountered interesting reactivity of 2-(methylsulfanyl)quinoline with silyllithium species³ (Scheme 1). In our present study, trimethylsilyllithium generated *in situ*⁴ from hexamethyldisilane and methyllithium in HMPA was found to attack selectively at the 4-position of 2-(methylsulfanyl)quinoline (**1**) to afford a 4-silylated 3,4-dihydroquinoline skeleton **2** probably through the formation of lithium enamide intermediate **3**. This interesting regioselectivity has been known for the addition of trimethylsilylsodium to pyridine substrates, where the formation of 4-silylated dihydropyridines, via the protonation of an intermediate like **3**, or oxidatively rearomatized 4-silylated pyridines was observed.⁵ It was thus surprising that the reaction of quinolines with explicitly generated silyl alkali metal species had not been examined.⁶ Here we envisioned to take advantage of the regioselectivity of this addition of the silicon nucleophile and the nucleophilicity of lithium enamide intermediate **3** that has potential

opportunity for incorporating a substituent through reactions with electrophiles. In our working hypothesis, the three-component coupling adduct **4** could be functionalized further on the (methylsulfonyl)imidate through transition metal-catalyzed coupling reactions with arylmetal species that would eventually afford 2,3,4-trisubstituted 3,4-dihydroquinolines.



Scheme 1. Our Finding and Working Hypothesis for Four-Component Coupling

Table 1. Screening of Conditions for Addition of Silyllithium



Entry	x (equiv)	NMR yield of 2 (%) ^a	NMR yield of 2' (%) ^a
1	0	61	3
2	1	54	3
3	2	80 (66 ^b)	0
4	5	76	3

^a Determined by ¹H NMR using 1,1,2,2-tetrabromoethane as an internal standard.

^b Isolated yield.

RESULTS AND DISCUSSION

Optimization of reaction conditions began with setting the initial conditions as follows: 1 equiv of 2-(methylsulfonyl)quinoline (**1**), 2 equiv of trimethylsilyllithium generated *in situ*, in THF (0.1 M) at 25 °C for 30 min (Table 1). After protonation of intermediate **3**, 2-methylsulfonyl-4-trimethylsilyl-3,4-dihydroquinoline (**2**) was obtained in 61% NMR yield along with a small amount of 2-methylsulfonyl-4-trimethylsilylquinoline (**2'**), generated probably via autoxidation of **2**, in 3% NMR yield (entry 1). TMEDA was expected as an additive for this reaction to increase the nucleophilicity of silyllithium species by chelation on Li cation. While an addition of 1 equiv of TMEDA

slightly decreased the NMR yield of **2** (entry 2), **2** was selectively obtained in 80% NMR yield (66% isolated yield) with the aid of 2 equiv of TMEDA (entry 3). An excess (5 equiv) of TMEDA did not give better results (entry 4). We thus decided to employ the conditions of entry 3 for further experiments.

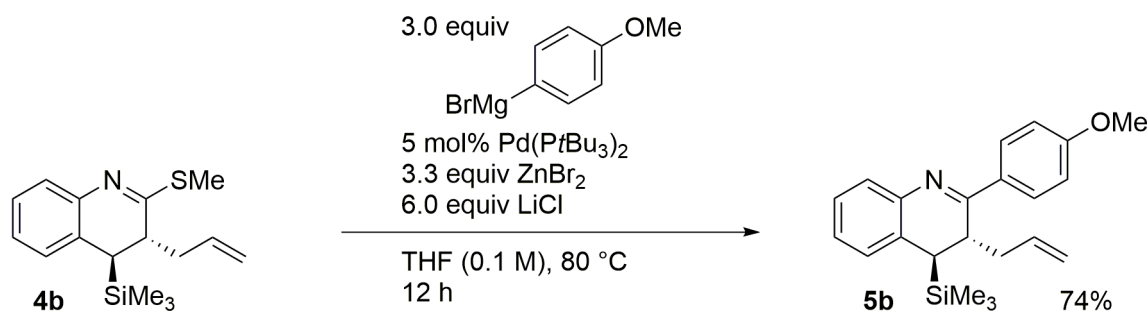
Table 2. Reaction with Electrophiles



Entry	<i>Electrophile</i>	<i>Product</i>	Isolated yield (%)
1	MeI	4a	57
2		4b	81
3		4c	47
4		4d	49
5		4e	41

Next, we examined the reactivity of lithium enamide intermediate **3** with electrophiles (Table 2). When **3**, generated under the optimized reaction conditions, was treated with 3 equiv of iodomethane followed by stirring for 1 h at 60 °C, C-3-methylated *trans*-isomer **4a** was obtained in 57% isolated yield. This example represents a rare case of introducing two distinct substituents on 3- and 4-positions of quinoline substrate to afford a substituted 3,4-dihydroquinoline skeleton.⁷ Trapping with other electrophiles exhibited moderate to good isolated yields of the corresponding *trans* products bearing allyl (**4b**, 81%), propargyl (**4c**, 47%), benzyl (**4d**, 49%), or methoxycarbonylmethyl (**4e**, 41%) substituent (entries 2-5).⁸

The stereochemistry of the products was explained by NMR spectra that showed the J value for C-3 and C-4 protons to be mostly unnoticeable (< 1 Hz), indicating the dihedral angle to be nearly 90° . Because this dihedral angle is possible only when the both two protons on the six-membered skeleton are situated at the equatorial positions, the two substituents on C-3 and C-4 are considered to be heading the opposite axial directions. This eventually confirmed the *trans* configuration of the substituents.



Scheme 2. Transformation of Methylsulfanyl Group

To maximize the versatility of the current methodology for synthesizing a range of dihydroquinolines, the C–S functionality was subjected to catalytic coupling transformations with organometallic reagents. Our screening of the conditions for the cross-coupling reaction at the C–S bond⁹ of **4b** finally found the way to realize this transformation (Scheme 2). With arylzinc species generated *in situ* and 5 mol% of bis(*tri-tert*-butylphosphine)palladium(0), the corresponding coupling product **5b** was obtained in 74% isolated yield. Thus, a method of the synthesis of 2,3,4-trisubstituted 3,4-dihydroquinolines has been established.

In conclusion, we found that the addition of trimethylsilyllithium to 2-(methylsulfanyl)quinoline takes place selectively at the 4-position. The following reactions of ensuing lithium enamide intermediate **3** with electrophiles showed regio- and stereoselectivity for the introduction of 3-substitution, providing *trans*-3,4-dihydroquinolines that would otherwise resort to lengthy synthetic steps from quinoline substrate. The methylsulfanyl group in **4** was subjected to catalytic C–S bond transformation to afford 2,3,4-trisubstituted 3,4-dihydroquinoline **5**.¹⁰ The whole strategy would be easily applied to the short-step synthesis of multiply functionalized dihydroquinolines.

EXPERIMENTAL

¹H NMR (600 MHz) and ¹³C NMR (151 MHz) spectra were taken on a JEOL ECA-600 spectrometer or a JEOL ECZ-600R spectrometer. Chemical shifts (δ) are reported in parts per million in CDCl₃ relative to residual chloroform at 7.26 ppm for ¹H and relative to CDCl₃ at 77.00 ppm for ¹³C. Mass spectra were determined on a Bruker micrOTOF II-KR spectrometer. TLC analyses were performed on commercial

aluminium sheets or glass sheets bearing a 0.25-mm layer of Merck silica gel 60F₂₅₄. Purification was done by column chromatography using silica gel (Wakosil C-300) and preparative TLC using silica gel (Merck 60PF₂₅₄). Preparative recycling gel permeation chromatography (GPC) was performed with a JAI LC-9260 II NEXT system with CHCl₃ as an eluent.

All reactions were performed under nitrogen atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. 2-Chloroquinoline, dehydrated DMF, Pd(P*t*Bu₃)₂, lithium chloride, iodomethane, allyl bromide and propargyl bromide were purchased from Wako Pure Chemical Industries, Ltd. Benzyl bromide, methyl bromoacetate and zinc(II) bromide were purchased from Nacalai tesque, Inc. Methyllithium in diethyl ether (Br free) and dehydrated THF were purchased from Kanto Chemical Co., Inc. and stored under nitrogen atmosphere. Sodium methanethiolate was purchased from Sigma-Aldrich Co. Llc. Hexamethyldisilane was purchased from Tokyo Chemical Industry Co., Ltd. TMEDA was purchased from Wako Pure Chemical Industries, Ltd and used after distillation from *n*BuLi. HMPA was purchased from Tokyo Chemical Industry Co., Ltd and used after distillation from CaH₂. Solutions of trimethylsilyllithium were prepared according to the literature procedure.⁴

Preparation of 2-(methylsulfanyl)quinoline (1)

Starting material **1** was prepared according to the method described by Dahaen with a slight modification.¹¹ A Schlenk tube was charged with 2-chloroquinoline (3.3 g, 20 mmol) and DMF (40 mL). Sodium methanethiolate (90 wt%, 10.3 g, 22 mmol) was added and the resulting mixture was stirred for 12 h at 120 °C. The resulting biphasic solution was extracted with Et₂O (40 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography with an eluent (hexane/AcOEt = 20/1) to give **1** (2.8 g, 16 mmol, 80%) as a white solid.

Procedure for the reaction of 2-(methylsulfanyl)quinoline with trimethylsilyllithium

An oven-dried Schlenk tube was charged with 2-(methylsulfanyl)quinoline (88 mg, 0.50 mmol), TMEDA (0.15 mL, 1.0 mmol) and THF (0.8 mL). Trimethylsilyllithium (0.24 M in HMPA/THF/Et₂O, 4.2 mL, 1.0 mmol) was slowly added over 1 min, and the resulting mixture was stirred for 30 min at 25 °C. The reaction was quenched by adding water to the reaction mixture, and the resulting biphasic solution was extracted with Et₂O (30 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated under a reduced pressure. The resulting residue was purified by GPC with CHCl₃ as an eluent to give **2** (68 mg, 0.33 mmol, 66%) as a colorless oil.

Typical procedure for the reaction with electrophiles

The reaction using allyl bromide as an electrophile is shown as a representative procedure. An oven-dried Schlenk tube was charged with 2-(methylsulfanyl)quinoline (88 mg, 0.50 mmol), TMEDA (0.15 mL, 1.0

mmol) and THF (0.8 mL). Trimethylsilyllithium (0.24 M in HMPA/THF/Et₂O, 4.2 mL, 1.0 mmol) was slowly added, and the resulting mixture was stirred for 30 min at 25 °C. The reaction was cooled to 0 °C and allyl bromide (181 mg, 1.5 mmol) was added. The resulting mixture was allowed to warm to 60 °C and stirred for 1 h. The reaction was quenched by adding water to the reaction mixture, and the resulting biphasic solution was extracted with Et₂O (30 mL × 3). The combined organic layer was dried over Na₂SO₄ and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography twice with eluents (hexane/AcOEt = 20/1, then hexane/DCM = 1/1) to give **4b** (118 mg, 0.41 mmol, 81%) as a pale yellow oil.

2-Methylsulfanyl-4-trimethylsilyl-3,4-dihydroquinoline (2): Obtained as a colorless oil (82 mg, 0.33 mmol, 66%) from **1** (88 mg, 0.50 mmol), purified by GPC with CHCl₃ as an eluent. ¹H NMR (CDCl₃): δ 7.24 (d, *J* = 8.2 Hz, 1H), 7.14 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H), 7.03 (ddd, *J* = 8.2, 7.6, 1.4 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 2.78 (dd, *J* = 15.8 Hz, 1H), 2.50 (dd, *J* = 15.8, 1.4 Hz, 1H), 2.50 (s, 3H), 2.28 (d, *J* = 8.2 Hz, 1H), -0.04 (s, 9H); ¹³C NMR (CDCl₃): δ 167.8, 143.8, 129.9, 126.9, 125.9, 125.3, 125.2, 31.2, 27.1, 12.4, -3.0; HRMS calcd for C₁₃H₂₀NSSi [(M+H)⁺]: 250.1080, found 250.1088.

3-Methyl-2-methylsulfanyl-4-trimethylsilyl-3,4-dihydroquinoline (4a): Obtained as a colorless oil (75 mg, 0.28 mmol, 57%) from **1** (88 mg, 0.50 mmol), purified by silica gel column chromatography with an eluent (hexane/AcOEt = 20/1) and then preparative TLC with an eluent (hexane/AcOEt = 5/1). ¹H NMR (CDCl₃): δ 7.22 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.13 (ddd, *J* = 7.8, 7.5, 1.4 Hz, 1H), 7.04 (ddd, *J* = 7.5, 7.5, 1.4 Hz, 1H), 6.92 (dd, *J* = 7.5, 1.4 Hz, 1H), 2.57 (qd, *J* = 7.1, 1.0 Hz, 1H), 2.47 (s, 3H), 2.04 (s, 1H), 1.07 (d, *J* = 7.1 Hz, 3H), -0.07 (s, 9H); ¹³C NMR (CDCl₃): δ 172.4, 142.8, 128.1, 127.9, 125.7, 125.3, 125.1, 36.0, 35.4, 19.3, 12.3, -3.2; HRMS calcd for C₁₄H₂₂NSSi [(M+H)⁺]: 264.1237, found 264.1247.

3-Allyl-2-methylsulfanyl-4-trimethylsilyl-3,4-dihydroquinoline (4b): Obtained as a pale yellow oil (118 mg, 0.41 mmol, 81%) from **1** (88 mg, 0.50 mmol), purified by silica gel column chromatography twice with eluents (hexane/AcOEt = 20/1, then hexane/DCM = 1/1). ¹H NMR (CDCl₃): δ 7.24 (d, *J* = 7.8 Hz, 1H), 7.14 (ddd, *J* = 7.8, 7.8, 1.4 Hz, 1H), 7.04 (ddd, *J* = 7.5, 7.5, 1.4 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.68 (dddd, 17.0, 10.2, 8.5, 5.4 Hz, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 4.92 (dd, *J* = 17.0, 1.4 Hz, 1H), 2.48 (s, 3H), 2.42 (ddd, *J* = 9.8, 4.8, 0.3 Hz, 1H), 2.27 (s, 1H), 2.25 (ddd, *J* = 13.6, 5.4, 4.8 Hz, 1H), 2.02 (ddd, *J* = 13.6, 9.8, 8.5 Hz, 1H), -0.06 (s, 9H); ¹³C NMR (CDCl₃): δ 171.0, 143.1, 135.1, 127.9, 127.8, 125.7, 125.4, 125.0, 117.6, 40.8, 35.8, 31.1, 12.4, -3.2; HRMS calcd for C₁₆H₂₄NSSi [(M+H)⁺]: 290.1393, found 290.1383.

2-Methylsulfanyl-3-(prop-2-yn-1-yl)-4-trimethylsilyl-3,4-dihydroquinoline (4c): Obtained as a white solid (68 mg, 0.24 mmol, 47%) from **1** (88 mg, 0.50 mmol), purified by GPC with CHCl₃ as an eluent. ¹H NMR (CDCl₃): δ 7.22 (d, *J* = 7.5 Hz, 1H), 7.14 (ddd, *J* = 7.5, 7.1, 1.7 Hz, 1H), 7.06 (ddd, *J* = 7.5, 7.5, 1.4 Hz, 1H), 6.96 (d, *J* = 7.1 Hz, 1H), 2.60 (dd, *J* = 10.9, 4.1 Hz, 1H), 2.56 (s, 1H), 2.47 (s, 3H), 2.36 (ddd, *J* = 16.7, 4.1, 2.7 Hz, 1H), 2.16 (ddd, *J* = 16.6, 10.9, 2.7 Hz, 1H), 2.02 (dd, *J* = 2.7, 2.7 Hz, 1H), -0.05 (s, 9H); ¹³C NMR (CDCl₃): δ 169.3, 142.6, 128.1, 127.2, 125.9, 125.7, 125.2, 81.5, 70.5, 40.6, 31.3, 21.6, 12.5, -3.3; HRMS calcd for C₁₆H₂₂NSSi [(M+H)⁺]: 288.1237, found 288.1248.

3-Benzyl-2-methylsulfanyl-4-trimethylsilyl-3,4-dihydroquinoline (4d): Obtained as a white solid (166 mg, 0.25 mmol, 49%) from **1e** (88 mg, 0.50 mmol), purified by preparative TLC with CHCl₃ as an eluent. ¹H NMR (CDCl₃): δ 7.27–7.30 (m, 3H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.18 (ddd, *J* = 8.3, 7.5, 1.4 Hz, 1H), 7.08 (ddd, *J* = 7.6, 7.5, 1.4 Hz, 1H), 7.04 (d, *J* = 7.1 Hz, 2H), 6.87 (d, *J* = 7.5 Hz, 1H), 2.83 (dd, *J* = 13.3, 4.8 Hz, 1H), 2.61 (ddd, *J* = 10.9, 4.3, 1.0 Hz, 1H), 2.50 (s, 3H), 2.46 (dd, *J* = 13.3, 10.9 Hz, 1H), 2.03 (s, 1H), -0.16 (s, 9H); ¹³C NMR (CDCl₃): δ 171.1, 143.2, 138.6, 129.2, 128.4, 128.0, 127.9, 126.3, 125.8, 125.6, 125.1, 43.1, 37.1, 30.5, 12.5, -3.3; HRMS calcd for C₂₀H₂₆NSSi [(M+H)⁺]: 340.1550, found 340.1544.

Methyl 2-(2-methylsulfanyl-4-trimethylsilyl-3,4-dihydroquinolin-3-yl)acetate (4e): Obtained as a pale yellow solid (66 mg, 0.21 mmol, 41%) from **1** (88 mg, 0.50 mmol), purified by silica gel column chromatography with an eluent (hexane/AcOEt = 20/1). ¹H NMR (CDCl₃): δ 7.22 (d, *J* = 7.5 Hz, 1H), 7.14 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.05 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 3.66 (s, 3H), 2.96 (dd, *J* = 7.1, 7.1 Hz, 1H), 2.47 (s, 3H), 2.41 (d, *J* = 7.1 Hz, 2H), 2.23 (s, 1H), -0.04 (s, 9H); ¹³C NMR (CDCl₃): δ 171.9, 169.2, 142.7, 128.0, 127.4, 125.9, 125.7, 125.2, 51.6, 37.4, 35.8, 32.7, 12.4, -3.3; HRMS calcd for C₁₆H₂₄NO₂SSi [(M+H)⁺]: 322.1292, found 322.1298.

3-Allyl-2-(4-methoxyphenyl)-4-trimethylsilyl-3,4-dihydroquinoline (5b): Obtained as a pale yellow solid (77 mg, 0.22 mmol, 74%) from **7b** (87 mg, 0.30 mmol), purified by silica gel column chromatography with an eluent (hexane/AcOEt = 100/1). ¹H NMR (CDCl₃): δ 8.04 (d, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.19 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H), 7.11 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 5.67–5.73 (dddd, *J* = 16.5, 10.3, 9.6, 4.8 Hz, 1H), 5.05 (d, *J* = 10.3 Hz, 1H), 4.94 (d, *J* = 16.5 Hz, 1H), 3.87 (s, 3H), 3.21 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.46 (s, 1H), 2.19 (ddd, *J* = 13.7, 4.8, 4.8 Hz, 1H), 2.08 (ddd, *J* = 13.7, 9.6, 9.6 Hz, 1H), -0.11 (s, 9H); ¹³C NMR (CDCl₃): δ 166.7, 161.5, 143.5, 135.3, 130.6, 128.7, 128.4, 127.7, 126.7, 126.3, 125.7, 117.5, 113.9, 55.3, 34.9, 34.0, 30.8, -2.9; HRMS calcd for C₂₁H₂₈NOSi [(M+H)⁺]: 350.1935, found 350.1935.

ACKNOWLEDGEMENTS

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 8. A similar reaction of 2-(methylsulfanyl)pyridine or 2-methylsulfanyl-5-phenylpyridine cleanly gave the corresponding 4-trimethylsilyl-3,4-dihydropyridine with the same regioselectivity as the case of quinolines. Unfortunately, it was difficult to isolate 3,4-dihydropyridines due to their highly labile nature to autoxidation under aerobic conditions.
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 10. In an attempt to convert the silicon functionality, **5b** was reacted with 4-chlorobenzaldehyde in the presence of TBAF in THF. The reaction actually provided the coupling adducts, albeit as an inseparable mixture of all four diastereomers.
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