Synthetic Methods

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Lithiation of a Silyl Ether: Formation of an *ortho*-Fries Hydroxyketone**

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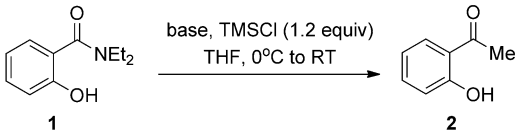
Dedicated to Professor E. J. Corey on the occasion of his 86th birthday

Abstract: *A hydroxy-directed alkylation of an N,N-diethylarylamide using CIPE-assisted α-silyl carbanions (CIPE = complex-induced proximity effect) has been developed using a simple reagent combination of LDA (lithium diisopropylamide) and chlorosilane. A study of the mechanism, and the application of the procedure to an anionic Snieckus–Fries rearrangement for a highly efficient synthesis of the potent phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002, are reported.*

The expanding use of silicon reagents in organic synthesis resulting from their low cost, versatile properties, and application to a wide range of reactions, has greatly increased the prominence of organosilicon chemistry. In 1967, Peterson[1] reported the successful metalation, using *t*BuLi and *N*,*N*,*N*',*N*'-tetramethyl-1,2-ethane (TMEDA), of the very weakly acidic compounds tetramethylsilane and *n*-butyltrimethylsilane. The formation of the corresponding silylmethyllithium compounds provided the first demonstration of the enhanced acidity of the α-hydrogen atoms of unactivated organosilanes. The stabilization of α-silyl carbanions has been attributed to the (p-σ*)π overlap between the antibonding σ* orbital of the C–Si bond and the adjacent carbanionic π orbital (or highly polarized carbon–metal bond).[2] Several unactivated α-silyl carbanions formed by LDA (lithium diisopropylamide) and assisted by a strong direct-metalation group (DMG) have since been sporadically reported[3] and have limited synthetic applications. Among these α-silyl carbanions, Snieckus et al.[3d] reported an interesting α-silyl metalation that converted *ortho*-silylated benzamides into *ortho*-fluorosilylated acetophenones by treatment with LDA. This finding led us to examine whether the hydroxy group of a hydroxyarylamide could similarly direct the alkyl arrangement through the metalation of silyl ether.[4] Herein, we report the general application of hydroxy-directed nucleophilic acyl alkylations of hydroxyarylamides and salicylic acid and a mechanistic study. The transformation involves: 1) a complex-induced proximity effect (CIPE)[5] in the deprotonation step, 2) an intramolecular Peterson-type[6] reaction of the resulting α-silyl carbanion with the amide group, and 3) fission of the final β-oxygenated silyl intermediate. The scope of this procedure is also investigated in the anionic Snieckus–Fries rearrangement[7] using a variety of chlorosilane substrates and its use in the efficient synthesis of the potent phosphatidylinositol 3-kinase (PI3K) inhibitor LY294002[8] is demonstrated.

The first step of the procedure involved the treatment of *N*,*N*-diethyl salicylamide (**1**) with TMSCl (1.2 equiv) in the presence of LDA (2 equiv) in THF at 0 °C. Surprisingly, *o*-hydroxyacetophenone was isolated in 44 % yield, along with 30 % of residual starting material after 30 min at room temperature (Table 1, Entry 1). No silyl ether was observed,

Table 1: Optimization of reaction conditions.



1 **2**

Entry	Base (equiv)	Solvent	*t* [h] at RT	Yield [%][a]
1	LDA (2)	THF	0.5	44
2	LDA (3)	THF	0.5	76
3	**LDA (4)**	**THF**	**0.5**	**85**
4	LDA (4)	Et_2O	2	49
5	$LiNEt_2$ (4)	THF	12	0[b]
6	NaH (4)	THF	12	0[b]
7	LHMDS (4)	THF	12	0[c]
8	KHMDS (4)	THF	12	0[c]
9	*sec*-BuLi (4)	THF	0.5	0[d]
10	LTMP (4)	THF	0.5	67

[a] Yield of isolated product. [b] Starting material was recovered. [c] Minor amount of silyl ether was isolated along with residual starting material. [d] *sec*-Butyl acylated product was isolated. Highlighted line indicates optimum reaction conditions.

and the use of LDA (4 equiv, pK_a 35.7[9]) provided the optimal yield (85 %, Entry 3). Employing lithium 2,2,6,6-tetramethylpiperidide (LTMP, pK_a 37.3[9]) resulted in a lower yield (67 % yield, Entry 10), whereas the use of other lithium amides with weaker basicities, such as lithium diethylamide ($LiNEt_2$, pK_a 31.7[9,10]) and lithium hexamethyldisilazide (LHMDS, pK_a 29.5[9]), did not afford the desired reaction products (Entries 5 and 7). Less-hindered bases, such as *sec*-butyl-

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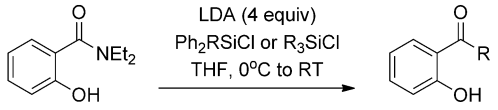
lithium (pK_a 51[11]), reacted nucleophilically with the amide to form, for example, 2-hydroxyphenyl-*sec*-butylketone (Entry 9). Reactions with potassium hexamethyldisilazide (KHMDS, pK_a 29.5[9]) and NaH did not afford the desired product (Entries 8 and 6, respectively). A trace amount (0.5–1%) of dimethyl(bis(trimethylsilyl)methyl)silylether **3** (see Supporting Information) was detected in the reactions in Entries 2, 3 and 10 in Table 1. This observation strongly suggests the occurrence of a CIPE-assisted α-methyl silyl deprotonation in this transformation.

We next examined the possibility of transferring alkyl groups from various chlorosilanes. The results are summarized in Table 2. Interestingly, a phenyl group on the silicon

Table 2: Scope of chlorosilane substrates.



1 **2**, **2a - 2f**

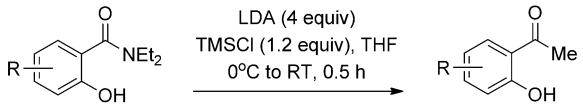
Entry	Silyl chloride	Product (R group)	*t* [h] at RT	Yield [%][a]
1	$Ph_2MeSiCl$	**2** (Me)	0.5	92
2	$tBuMe_2SiCl$	**2** (Me)	0.5	73
3	Et_3SiCl	**2a** (Et)	4	84
4	Pr_3SiCl	**2b** (Pr)	8	80
5	Bu_3SiCl	**2c** (Bu)	8	78
6	$Ph_2BuSiCl$	**2c** (Bu)	8	80
7	$Ph_2PentSiCl$	**2d** (Pent)	8	76
8	Hex_3SiCl	**2e** (Hex)	8	84
9	$Ph_2iBuSiCl$	**2f** (*i*Bu)	15	67
10	Ph_3SiCl	- (Ph)	12	-
11	iPr_3SiCl	- (*i*Pr)	12	-
12	$Ph_2tBuSiCl$	- (*t*Bu or Ph)	12	-

[a] Yield of isolated product.

atom promoted the methyl shift (Entry 1, 92%), whereas the *tert*-butyl group was slightly inhibitory (Entry 2, 73%). Other silyl substituents with two secondary α-protons were readily transferred to the acyl group in moderate to good yields, although steric effects significantly slowed the reaction rate (Entries 3–9). No desired products were observed when triphenylchlorosilane, triisopropyl chlorosilane, and *tert*-butyldiphenyl chlorosilane were used in the reaction (Entries 10–12). Notably, in addition to the ability of a phenyl group to promote the rearrangement of the geminal alkyl group, the straightforward preparation of alkyldiphenylchlorosilanes from commercially available diphenyldichlorosilane and alkyllithium make them particularly useful silyl reagents for this transformation.

The substrate scope of the amide group in the methyl rearrangement reaction was next explored. As shown in Table 3, a wide range of base-stable aryl substrates were compatible with this transformation. Electron-donating (**1a**–**1j**) and electron-withdrawing (**1k**) functional groups and heteroaryl substrates (**1l**) were all tolerated in the reaction, and the corresponding products (**4a**–**4l**) were isolated in good to excellent yields. In contrast, the reaction of **1m** and **1n**, which have methoxy groups *ortho* to the reaction center that

Table 3: Scope of aryl substrates.



1a - 1q **4a - 4p**, **2**

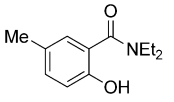
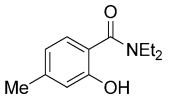
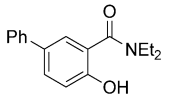
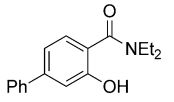
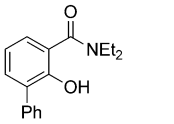
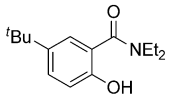
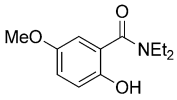
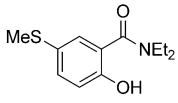
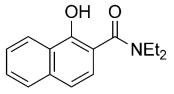
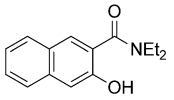
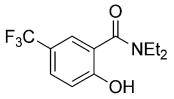
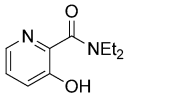
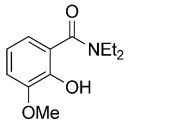
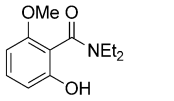
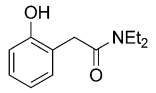
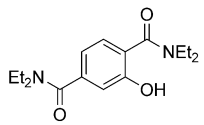
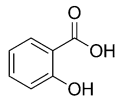
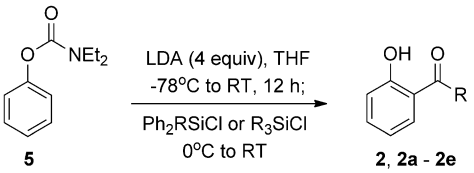
Entry	Reactant	Product		Yield [%][a]
1		**1a**	**4a**	90
2		**1b**	**4b**	70
3		**1c**	**4c**	86
4		**1d**	**4d**	82
5		**1e**	**4e**	96
6		**1f**	**4f**	89
7		**1g**	**4g**	81
8		**1h**	**4h**	66 (80)[b]
9		**1i**	**4i**	97
10		**1j**	**4j**	90
11		**1k**	**4k**	69
12		**1l**	**4l**	72
13		**1m**	**4m**	38
14		**1n**	**4n**	4

Table 3: (Continued)

Entry	Reactant	Product		Yield [%][a]
15		**1o**	-	-[c]
16[d]		**1p**	**4p**	52
17[e]		**1q**	**2**	79

[a] Yield of isolated product. [b] Yield based on recovered starting material. [c] No reaction occurred. [d] $Ph_2MeSiCl$ instead of TMSCl was used. [e] LDA (5 equiv) and TMSCl (3 equiv) were used.

Table 4: Ketone-functionalized products formed from anionic Snieckus–Fries rearrangements with various chlorosilanes.



5 **2**, **2a** - **2e**

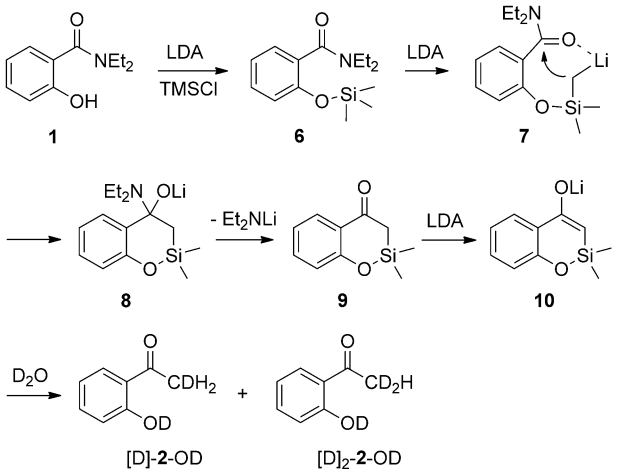
Entry	Chlorosilane	Product (R group)	*t* [h] at RT	Yield [%][a]
1	TMSCl	**2** (Me)	0.5	68
2	$Ph_2MeSiCl$	**2** (Me)	0.5	77
3	Et_3SiCl	**2a** (Et)	8	77
4	Pr_3SiCl	**2b** (Pr)	8	80
5	$Ph_2BuSiCl$	**2c** (Bu)	8	63
6	$Ph_2PentCl$	**2d** (Pent)	8	79
7	Hex_3SiCl	**2e** (Hex)	8	61

[a] Yield of isolated product.

may interfere with lithium coordination, afforded **4m** and **4n** in poor yields. No desired products were observed when *N*,*N*-diethyl-2-(2-hydroxyphenyl)acetamide (Entry 15), a substrate with an additional atom between the DMG and the reaction center, was subjected to the standard reaction procedure. The selective methylation of terephthalamide **1p** demonstrates an important feature of this transformation: the hydroxy group can be used to direct the alkylation of the *o*-amide group (Entry 16). In addition to the amide moiety, a carboxylic acid also underwent this directed alkylation in 79% yield when TMSCl (3 equiv) was applied (Entry 17).

The successful use of LDA and chlorosilanes in the directed alkylation of hydroxyarylamides prompted us to examine the application of the procedure to anionic Snieckus–Fries rearrangements. The anionic Snieckus–Fries rearrangement occurs when *ortho*-lithiated O-aryl carbamates undergo a facile intramolecular [1,3]-acyl migration to afford substituted *o*-carbamoyl phenolates at room temperature. Gratifyingly, when the anionic Snieckus–Fries rearrangement of phenyl diethylcarbamate (**5**), using an excess amount of LDA, was quenched by TMSCl or $Ph_2MeSiCl$ at 0 °C, *o*-hydroxyacetophenone, that would usually arise from an acid-catalyzed Fries rearrangement of a phenyl ester, was obtained in 68% and 77% yields, respectively (Table 4, Entries 1 and 2). The use of different chlorosilane reagents readily provided ethyl, propyl, butyl, pentyl, and hexyl ketones in moderate to good yields (Entries 3–7).

Scheme 1 outlines the most likely mechanism for the formation of **2** from **1**, which is supported by the detection of dimethyl(bis(trimethylsilyl)methyl)silylether (**3**) and mass spectral analysis of the reaction mixture during the first few minutes. The sequence shown in Scheme 1 involves an amide-directed (CIPE-assisted) deprotonation of silyl ether **6** to form **7**, which undergoes an intramolecular Peterson-type reaction to form the cyclized intermediate **8** (HRMS (ES^-): calcd for $C_{14}H_{22}LiNO_2Si$ *m*/*z* 271.1580 [M^-]; found *m*/*z* 271.1588), which loses a diethyl amide anion to form the β-oxygenated silyl intermediate **9** (HRMS (ES^-): calcd for $C_{10}H_{12}O_2Si$ *m*/*z* 192.0607 [M^-]; found *m*/*z* 192.0616). We then quenched the reaction with D_2O, and the formation of

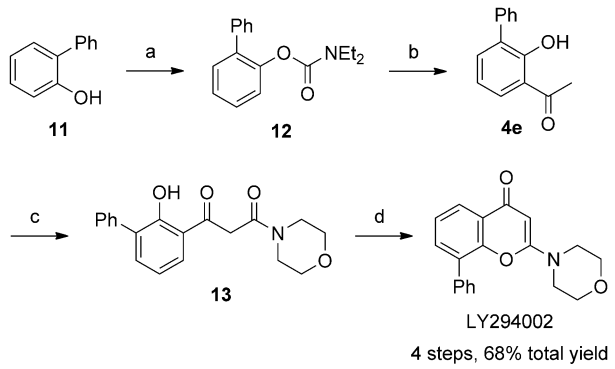


Scheme 1. Proposed reaction mechanism for the *ortho*-directed nucleophilic acyl methylation of a hydroxyarylamide (arrows may be considered to indicate equilibria) and the D_2O quenching experiment.

[D]$_2$-**2**-OD (ES^-: $[M\text{-}H]^-$ *m*/*z* 138.1) supports the presence of **10**.

The extended anionic Snieckus–Fries rearrangement was employed in the highly efficient synthesis of the PI3K inhibitor LY294002. The product was obtained in 4 steps and with a 68% total yield from the inexpensive and commercially available starting material *o*-phenylphenol. As shown in Scheme 2, diethylcarbamate **12**, which was quantitatively prepared from *o*-phenylphenol and diethylcarbamoyl chloride, was subjected to our anionic Snieckus–Fries rearrangement–methylation procedure to afford **4e** in 93% yield. The enolate was coupled with 4-morpholinecarbonyl chloride to yield salicylacetamide **13** in 91% yield. Subsequent cyclodehydration with trifluoromethanesulfonic anhydride[12] afforded LY294002 in 81% yield.

In summary, we have developed a hydroxy-directed acyl alkylation of both hydroxyarylamides and salicylic acid through anionic Si→C alkyl migration, which also gives silyl ether a new role in organic synthesis. This reaction was further



Scheme 2. Synthesis of the PI3K inhibitor LY294002 by application of the extended anionic Snieckus–Fries rearrangement. Reagents and conditions: a) $ClCONEt_2$ (1.5 equiv), K_2CO_3 (1.5 equiv), CH_3CN, reflux, 99%. b) LDA (1.2 equiv), THF, −78 °C→RT; LDA (2.8 equiv), TMSCl (1.2 equiv), 0 °C→RT, 93%. c) LHMDS (3.0 equiv), 4-morpholine-carbonyl chloride (1.1 equiv), THF, −78 °C→RT, 91%. d) trifluoromethanesulfonic anhydride (3.1 equiv), CH_2Cl_2, 81%.

developed for application to an extended anionic Snieckus–Fries rearrangement. The exceptional functional group transformations that can be achieved using the simple reagent combination of LDA and chlorosilane make these reactions highly valuable for the synthesis of natural products and medicinally important compounds, such as the PI3K inhibitor LY294002.

Experimental Section

Hydroxy-directed methylation of *N*,*N*-diethyl salicylamide (**1**): TMSCl (67.4 mg, 0.62 mmol) was added slowly to a stirred solution of **1** (100 mg, 0.52 mmol) and LDA (2 M in THF, 1.0 mL) in dry THF (0.8 mL) under a nitrogen atmosphere at 0 °C. After the addition, the reaction mixture was stirred at 0 °C for 10 min and then the cooling bath was removed. After stirring at room temperature for 20 min, the reaction was quenched with 1N HCl (2 mL) at 0 °C. The resulting mixture was extracted with ethyl acetate. The aqueous layer was saturated with NaCl and extracted twice with ethyl acetate. The combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, reduced in volume, and purified by column chromatography on silica (eluting with 1% ethyl acetate/n-hexane) to give **2** (60 mg, 85%) as a colorless oil.

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