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Quick Installation of a 1,4-Difunctionality via Regioselective Nickel-Catalyzed Reductive Coupling of Ynoates and Aldehydes

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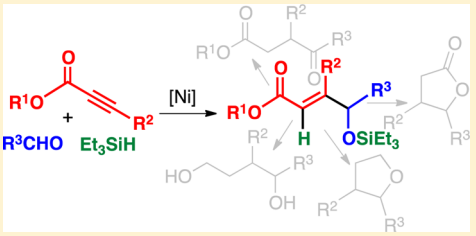
Supporting Information

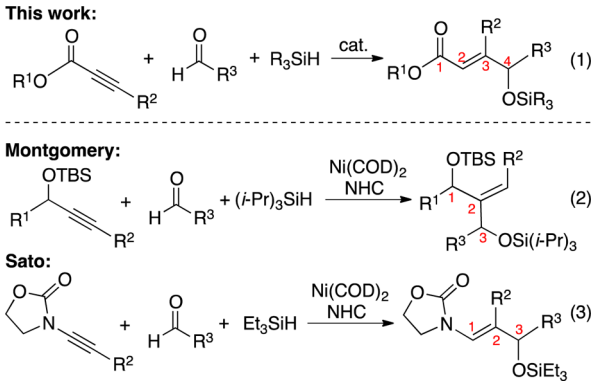
ABSTRACT: The development of efficient methods for the synthesis of molecules with 1,4-difunctionalities has been a dire need of the synthetic community. In this work, intermolecular reductive coupling of ynoates and aldehydes (in the presence of a silane) has been accomplished for the first time using catalytic amounts of $Ni(COD)_2$, an N-heterocyclic carbene ligand, and PPh_3. High regioselectivity has been demonstrated for the multicomponent coupling reactions, and more than a dozen invaluable silyl-protected γ-hydroxy-α,β-enoates have been synthesized. This methodology provides a quick entry to many other 1,4-difunctional compounds and oxygen-containing five-membered rings. The intermediacy of metallacycles in the catalytic process has been established by deuterium-labeling experiments.



INTRODUCTION

One of the challenges that chemists often encounter in target-directed synthesis is how to construct a 1,4-difunctionality in an efficient manner. Disconnecting this structural moiety using a retrosynthetic analysis typically results in "unnatural" synthons such as acyl anions and homoenolates. Accordingly, most strategies for making molecules with a 1,4-difunctionality involve reactivity umpolung of heteroatom-containing carbon chains through tedious protection−deprotection sequences.[1] More recent efforts, aimed at improving the efficiency of the synthesis, have focused on polarity reversal induced by N-heterocyclic carbenes (NHCs)[2] or transition metals,[3] homocoupling[4] or heterocoupling[5] of enolates by metal-based oxidants, and carbonylation of carbonyl derivatives via C−H bond activation.[6] Despite this progress, concise and efficient methods for the installation of a 1,4-difunctionality are still in high demand, particularly if the resulting products can be conveniently transformed into a wide variety of compounds.

One conceptually different approach is to use a low-valent metal species to catalyze regioselective coupling of ynoates and aldehydes in the presence of a reducing agent such as a silane (eq 1). Among various metal complexes for the reductive coupling of alkynes and aldehydes,[7,8] catalytic systems involving $Ni(COD)_2$/L (COD = 1,5-cyclooctadiene, L = a phosphine or an NHC), developed by Montgomery,[9] Jamison,[10] and others,[11] have stood out due to their excellent reactivity and regioselectivity. Of the alkynes applied in these studies, however, very few of them contain functionalities that are adjacent to the C≡C bonds. In these rare cases, 1,3-difunctional products have been obtained as the major regioisomers (eqs 2 and 3).[9g,11c] We hypothesized that the electron-withdrawing nature of the ester group in ynoates might promote C−C bond forming reactions at the β-carbon,[12] leading to the desired silyl-protected γ-hydroxy-α,β-enoates (eq 1). This specific type of 1,4-difunctional compound has been long sought as a versatile precursor to many biologically active molecules.[13]



RESULTS AND DISCUSSION

We initiated our studies (Table 1) following Sato's protocols that had been previously optimized for catalytic reductive coupling of ynamides and aldehydes.[11c] To prevent the trimerization of ynoate, the solution of **1** in THF had to be added last and carried out very slowly (syringe-pump addition over 8 h) to the reaction mixture. When IMes (see Chart 1) was employed as the ligand, two coupling products (**3a**:**3a**′ = 95:5) were detected by GC; however, the combined yield was merely 14% (entry 1). Replacing IMes with other commonly used NHCs did not give satisfactory yields (entries 2−4), but SIPr was identified as our best ligand. Interestingly, when SIPr was generated from its NHC precursor with a BF_4^- counterion instead of the chloride salt, the yield was improved to 61% (entry 5). Although the reason behind the counterion effect

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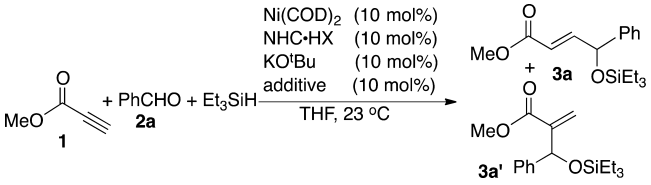
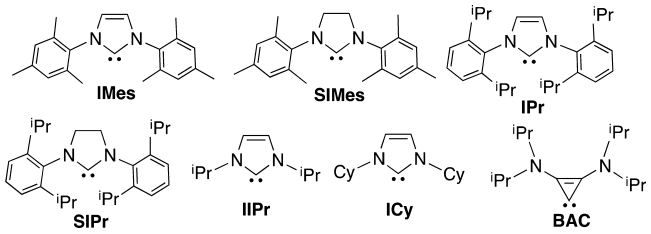
Table 1. Optimization of the Reaction Conditions



entry	NHC·HX	additive	yield (%)[c]
1	IMes·HCl		14
2	SIMes·HCl		15[d]
3	IPr·HCl		27
4	SIPr·HCl		38
5	SIPr·HBF_4		61
6	SIPr·HBF_4	NaCl	37
7[a]	SIPr·HBF_4		trace[d]
8	SIPr·HBF_4	PPh_3	100
9[b]	SIPr·HBF_4	PPh_3	41
10	IIPr·HBF_4	PPh_3	0
11	ICy·HBF_4	PPh_3	0
12	BAC·HBF_4	PPh_3	0

[a]The reaction was conducted at 50 °C. [b]20 mol % PPh_3 was added. [c]Combined GC yield for **3a** and **3a**′. [d]A significant amount of $PhCH_2OSiEt_3$ was detected.

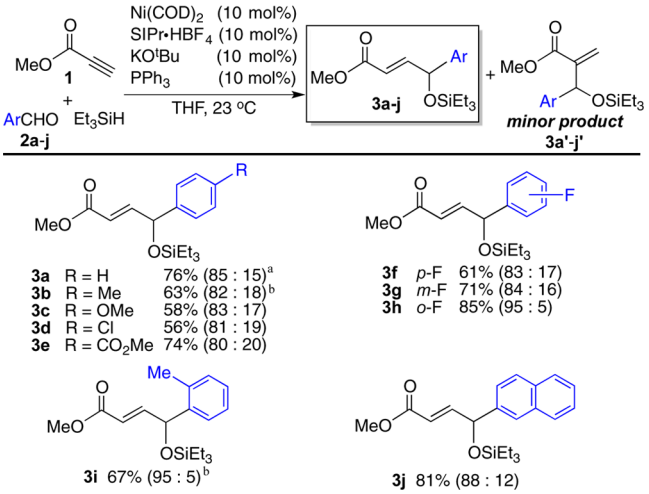
Chart 1. NHCs Employed in This Study



remains unclear to us at the moment, we did observe diminished yield with externally added Cl^- (entry 6). In all of the experiments mentioned above, unreacted PhCHO was seen, which made us suspect that the active catalyst might already be decomposed. Gratifyingly, an attempt to extend the lifetime of the catalyst[14] by adding 10 mol % of PPh_3 (with respect to **1**) showed a quantitative conversion with a 85:15 ratio of **3a** and **3a**′ (entry 8). Adding more PPh_3, however, had a detrimental effect on the yield (entry 9), perhaps by saturating the nickel center to inhibit the reaction. A control experiment with 10 mol % of PPh_3 and no NHC ligand showed no reaction, suggesting that the NHC ligand is a necessity. A few other NHCs were also tested (entries 10−12), but none of them promoted the coupling reaction. The choice of solvent proved to be critical; reaction in CH_2Cl_2, 1,4-dioxane, or DMF under otherwise the same conditions (as those described in entry 8) did not produce any of the coupling products.

To explore the generality of the reaction, reductive coupling of **1** with various aldehydes under the optimized conditions was performed. As shown in Table 2, the methodology is amenable to aldehydes bearing functional groups such as OMe, Cl, and CO_2Me (**2c−e**). In all cases, the 1,4-difunctional compounds were produced as the major isomers and isolated in good yields. The regioselectivity does not appear to be greatly influenced by the electronic property of the substituent at the para position of benzaldehyde. In view of recent intense interest in the synthesis of fluorine-containing molecules, we also examined substrates

Table 2. Reactions of 1 with Various Aldehydes

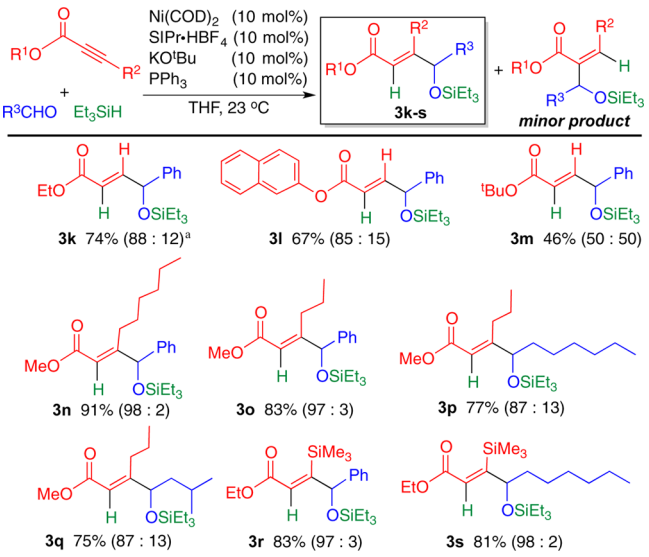


[a]Yield of purified product; the regioselectivity (in parentheses) was determined by ^1H NMR. [b]The solution of **1** in THF was added over 16 h rather than 8 h.

that are fluorinated at different positions of the aromatic ring. Of particular interest is that coupling of *o*-fluorobenzaldehyde gave the 1,4-difunctional product **3h** with a 95:5 regioselectivity. This high selectivity is not unique to fluorine, as the reaction of *o*-tolualdehyde similarly yielded **3i** as the predominant product. Other aromatic aldehydes such as 2-naphthaldehyde are also viable substrates for the synthesis of 1,4-difunctional products. However, reactions with aliphatic aldehydes, including heptaldehyde and isovaleraldehyde, afforded not only 1,3-difunctional compounds as the major isomers (a 2:1 ratio favoring the 1,3-product) but also some trimerization byproducts from **1**.

The scope of the reaction was further investigated by varying the structures of the ynoates (Table 3). In addition to the methyl ester **1**, ethyl or 2-naphthyl propiolate can be utilized to synthesize the corresponding 1,4-regioisomer with a similar

Table 3. Scope of Ynoates and Aldehydes



[a]Yield of purified product; the regioselectivity (in parentheses) was determined by ^1H NMR.

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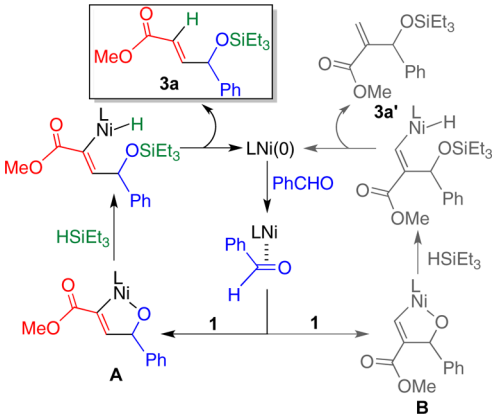
selectivity. In contrast, the coupling of *tert*-butyl propiolate is not selective at all, producing equal amounts of two isomeric products. Ynoates bearing an internal C≡C bond are also feasible coupling partners. As a matter of fact, their reactions are generally more regioselective, and in some cases as high as a 98:2 ratio favoring the 1,4-product (e.g., **3n**) was observed. More importantly, with these internal alkynes, aliphatic aldehydes can now be successfully incorporated in the synthesis of 1,4-difunctional compounds. Trimethylsilyl (TMS)-substituted ynoates can also be coupled with both aromatic and aliphatic aldehydes to yield the 1,4-difunctional compounds (**3r,s**) with excellent regioselectivity. It should be mentioned that syringe-pump addition of these bulky ynoates is no longer needed, because under the reaction conditions their trimerization or oligmerization is noncompetitive. Having the TMS groups in these molecules can be advantageous; further modification at the β position should be possible through Hiyama coupling reactions.[15]

The aforementioned regioselectivity could be rationalized by the mechanistic hypothesis outlined in Scheme 1 (using **1** and PhCHO as representative substrates). A similar mechanism has been proposed in related systems for the coupling of alkynes and aldehydes, where it has been supported by computational studies,[16] kinetics,[17] and even a crystal structure.[18] The electron-withdrawing ester group in our reactions should provide a sufficient electronic bias so that, driven by the formation of a stronger Ni−C bond,[19] C−C bond formation takes place at the β-carbon of **1**. The metallacyclic intermediate **A** would be destabilized when the methyl ester is replaced by a *tert*-butyl ester, possibly due to the increased steric clash between the ester moiety and the ancillary ligand on nickel. This analysis is in agreement with the nonregioselectivity observed for **3m** (Table 3). For internal alkynes, the formation of **A** is expected to be more favorable on the basis of both electronic and steric arguments, resulting in enhanced selectivity for the 1,4-difunctional products. In the case of benzaldehyde bearing an ortho substituent (**2h,i**), the intermediate **B** should be even less favorable, owing to the interaction between the ester group and the aryl ring.

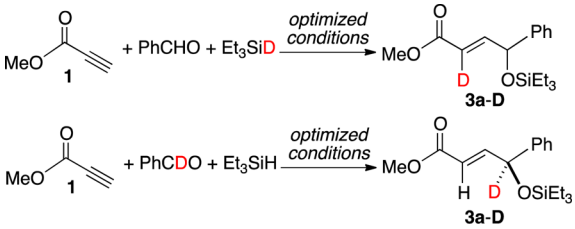
Consistent with the proposed mechanism, selectively labeling the silane hydrogen with deuterium gave rise to **3a-D** with deuterium exclusively at the α-position (Scheme 2). A similar experiment using PhCDO yielded **3a-D** with deuterium at the carbon center originating from the aldehyde. An alternative mechanism involving the activation of silane first, followed by sequential insertions of ynoate and aldehyde, would be inconsistent with our deuterium-labeling studies. Transition-metal-catalyzed hydrosilylation of ynoates that involves analogous silane activation and alkyne insertion typically leads to the addition of silane hydrogen to the β-carbon.[20]

As mentioned earlier, silyl-protected γ-hydroxy-α,β-enoates are important building blocks for a diverse array of compounds. To demonstrate their synthetic utility, compound **3h** was subjected to saturation of the C=C bond followed by lactonization to furnish **5** (Scheme 3). Given the fact that γ-butyrolactones are present in about 10% of all natural products,[21] we anticipate that the method described here may open a new synthetic path to these molecules. Another important class of compounds is substituted tetrahydrofurans,[22] and as illustrated in Scheme 3, they are readily accessible from silyl-protected γ-hydroxy-α,β-enoates following deprotection of the silyl group, reduction of the carbonyls, and cyclodehydration of the resulting diols.

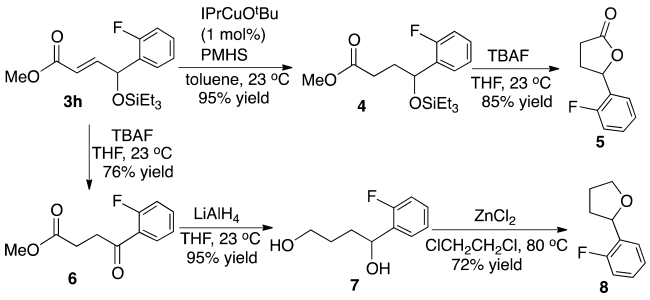
Scheme 1. Proposed Reaction Mechanism



Scheme 2. Deuterium-Labeling Studies



Scheme 3. Synthetic Application of Silyl-Protected γ-Hydroxy-α,β-enoates



CONCLUSION

In summary, we have developed a nickel-based catalytic system for multicomponent coupling of ynoates, aldehydes, and silanes. Labeling studies are in accordance with the formation of metallacycles as the key intermediates. The reactions are applicable to a broad range of substrates and enable regioselective synthesis of a wide variety of silyl-protected γ-hydroxy-α,β-enoates. Further manipulations of these 1,4-difunctional compounds allow for convenient access to oxygen-containing five-membered rings, which are important cores of natural products.

EXPERIMENTAL SECTION

General Experimental Methods. All the reactions were carried out in flame-dried glassware under an argon atmosphere using standard glovebox and Schlenk techniques. Dry and oxygen-free solvents (THF and CH_2Cl_2) were collected from an Innovative Technology solvent purification system and used throughout the experiments. DMF was dried over molecular sieves (4 Å) and then

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degassed by three freeze−pump−thaw cycles. Anhydrous 1,4-dioxane was obtained from Sigma-Aldrich in a Sure/Seal bottle. Aldehydes were purchased from commercial sources and freshly distilled prior to use. BAC·HBF_4 was prepared as described in the literature.[23]

General Procedure for Nickel-Catalyzed Reductive Coupling of an Ynoate and an Aldehyde. In a flame-dried Schlenk flask was added $Ni(COD)_2$ (13.8 mg, 0.050 mmol), SIPr·HBF_4 (23.9 mg, 0.050 mmol), PPh_3 (13.1 mg, 0.050 mmol), and KO^{t}Bu (5.6 mg, 0.050 mmol). THF (4.0 mL) was then added to this flask at 0 °C, and the resulting mixture was stirred at the same temperature for 15 min, followed by the successive addition of Et_3SiH (88 μL, 0.55 mmol) and an aldehyde (0.55 mmol). After the mixture was stirred at 0 °C for 5 min, a solution of an ynoate (0.50 mmol) in 4.0 mL of THF was added at room temperature (23 °C) over a period of 8 h (or 16 h for the synthesis of **3b**,**i**) using a syringe pump. Upon completion of the addition, the reaction mixture was stirred at room temperature for another 1 h before being concentrated under vacuum. The ratio of the two isomers was determined from the ^{1}H NMR spectrum of the crude products. The desired 1,4-difunctional compound was separated from the isomeric mixture using column chromatography (with diethyl ether/hexanes as eluent). For the synthesis of **3r**,**s**, the ynoate solution was added over a period of 1 h and the resulting solution was stirred at room temperature for 36 h prior to workup. Characterization data of the isolated products are given below.

Compound **3a** (colorless oil, 116 mg, 76% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.33−7.24 (m, 5H), 6.99 (dd, J = 15.4, 4.5 Hz, 1H), 6.14 (dd, J = 15.4, 1.7 Hz, 1H), 5.31 (dd, J = 4.5, 1.7 Hz, 1H), 3.71 (s, 3H), 0.90 (t, J = 7.9 Hz, 9H), 0.60−0.54 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.3, 150.8, 141.9, 128.7, 128.0, 126.4, 118.7, 74.1, 51.7, 6.9, 5.0; IR (neat, cm^{-1}) 2953, 2911, 2876, 1722 (ν_{CO}), 1657, 1493, 1454, 1435, 1414, 1295, 1276, 1240, 1191, 1163, 1118, 1084, 1064, 1003, 973, 838, 817, 726, 697; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{26}O_3SiNa$ 329.1549, found 329.1539.

Compound **3a′** (colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.37−7.20 (m, 5H), 6.26−6.25 (m, 1H), 6.10−6.09 (m, 1H), 5.61 (br s, 1H), 3.67 (s, 3H), 0.86 (t, J = 7.9 Hz, 9H), 0.57−0.51 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 166.6, 144.1, 142.9, 128.3, 127.6, 127.3, 124.1, 72.6, 51.8, 6.9, 5.0; IR (neat, cm^{-1}) 2953, 2911, 2876, 1720 (ν_{CO}), 1630, 1493, 1454, 1438, 1413, 1358, 1292, 1256, 1192, 1147, 1084, 1003, 953, 912, 875, 835, 815, 726, 697, 603, 540; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{26}O_3SiNa$ 329.154 34, found 329.154 35.

Compound **3b** (colorless oil, 101 mg, 63% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.20 and 7.13 (AB pattern, J = 8.0 Hz, 4H), 6.98 (dd, J = 15.2, 4.4 Hz, 1H), 6.12 (dd, J = 15.2, 1.6 Hz, 1H), 5.28 (dd, J = 4.4, 1.6 Hz, 1H), 3.71 (s, 3H), 2.33 (s, 3H), 0.90 (t, J = 7.6 Hz, 9H), 0.60−0.53 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.4, 151.0, 138.9, 137.6, 129.4, 126.4, 118.4, 73.9, 51.7, 21.3, 6.9, 4.9; IR (neat, cm^{-1}) 2953, 2912, 2876, 1724 (ν_{CO}), 1657, 1512, 1458, 1435, 1413, 1276, 1239, 1192, 1162, 1118, 1104, 1072, 1004, 974, 843, 815, 720; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{18}H_{28}O_3SiNa$ 343.169 99, found 343.170 07.

Compound **3c** (pale yellow oil, 97 mg, 58% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.22 (d, J = 8.8 Hz, 2H), 6.97 (dd, J = 15.4, 4.5 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 6.11 (dd, J = 15.4, 1.8 Hz, 1H), 5.26 (dd, J = 4.5, 1.8 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 0.89 (t, J = 7.9 Hz, 9H), 0.59−0.52 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.3, 159.3, 151.0, 134.0, 127.7, 118.3, 114.0, 73.6, 55.4, 51.7, 6.9, 4.9; IR (neat, cm^{-1}) 2953, 2911, 2876, 1722 (ν_{CO}), 1657, 1610, 1510, 1244, 1193, 974, 818, 724; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{18}H_{28}O_4SiNa$ 359.164 91, found 359.164 87.

Compound **3d** (pale yellow oil, 95 mg, 56% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.30 and 7.25 (AB pattern, J = 8.4 Hz, 4H), 6.93 (dd, J = 15.4, 4.6 Hz, 1H), 6.11 (dd, J = 15.4, 1.6 Hz, 1H), 5.28 (d, J = 4.6 Hz, 1H), 3.72 (s, 3H), 0.90 (t, J = 7.9 Hz, 9H), 0.60−0.54 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.1, 150.1, 140.5, 133.7, 128.9, 127.8, 119.0, 73.4, 51.8, 6.9, 4.9; IR (neat, cm^{-1}) 2953, 2911, 2876, 1722 (ν_{CO}), 1658, 1488, 1458, 1435, 1409, 1297, 1275, 1240, 1191, 1163, 1120, 1088, 1014, 973, 819, 725; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{25}O_3SiClNa$ 363.115 37, found 363.115 41.

Compound **3e** (colorless oil, 135 mg, 74% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.01 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 6.96 (dd, J = 15.4, 4.5 Hz, 1H), 6.15 (dd, J = 15.4, 1.8 Hz, 1H), 5.36 (dd, J = 4.5, 1.8 Hz, 1H), 3.91 (s, 3H), 3.72 (s, 3H), 0.90 (t, J = 7.9 Hz, 9H), 0.63−0.53 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.0, 166.9, 149.7, 146.9, 130.0, 129.7, 126.3, 119.3, 73.6, 52.2, 51.8, 6.8, 4.9; IR (neat, cm^{-1}) 2953, 2912, 2876, 1721 (ν_{CO}), 1658, 1610, 1458, 1435, 1413, 1242, 1191, 1164, 1108, 1018, 971, 888, 857, 825, 807, 769, 725, 566; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{19}H_{28}O_5SiNa$ 387.1604, found 387.1595.

Compound **3f** (colorless oil, 99 mg, 61% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.28−7.25 (m, 2H), 7.02−6.97 (m, 2H), 6.93 (dd, J = 15.4, 4.6 Hz, 1H), 6.10 (dd, J = 15.4, 1.7 Hz, 1H), 5.27 (d, J = 4.6, 1.7 Hz, 1H), 3.72 (s, 3H), 0.90 (t, J = 7.9 Hz, 9H), 0.58−0.52 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.2, 162.5 (d, J = 246.4 Hz), 150.5, 137.8 (d, J = 2.7 Hz), 128.1 (d, J = 7.1 Hz), 118.9, 115.6 (d, J = 21.4 Hz), 73.4, 51.8, 6.9, 4.9; IR (neat, cm^{-1}) 2954, 2912, 2877, 1722 (ν_{CO}), 1658, 1604, 1507, 1458, 1435, 1414, 1297, 1277, 1222, 1191, 1164, 1156, 1116, 1092, 1072, 1004, 974, 886, 872, 834, 821, 721; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{25}O_3FSiNa$ 347.144 92, found 347.144 98.

Compound **3g** (colorless oil, 115 mg, 71% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.31−7.26 (m, 1H), 7.13−7.01 (m, 2H), 7.01−6.92 (m, 2H), 6.13 (dd, J = 15.4, 1.7 Hz, 1H), 5.30 (dd, J = 4.5, 1.7 Hz, 1H), 3.72 (s, 3H), 0.91 (t, J = 7.9 Hz, 9H), 0.63−0.53 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.1, 163.1 (d, J = 247.1 Hz), 149.9, 144.6 (d, J = 6.7 Hz), 130.2 (d, J = 8.3 Hz), 121.8 (d, J = 2.7 Hz), 119.1, 114.8 (d, J = 22.1 Hz), 113.2 (d, J = 22.1 Hz), 73.4, 51.8, 6.8, 4.9; IR (neat, cm^{-1}) 2954, 2912, 2877, 1722 (ν_{CO}), 1679, 1659, 1614, 1591, 1483, 1448, 1436, 1414, 1348, 1268, 1192, 1166, 1136, 1116, 1004, 977, 945, 911, 870, 825, 789, 770, 727, 690; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{25}O_3FSiNa$ 347.1455, found 347.1458.

Compound **3h** (colorless oil, 138 mg, 85% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.48−7.43 (m, 1H), 7.27−7.23 (m, 1H), 7.16−7.10 (m, 1H), 7.03−6.97 (m, 2H), 6.16 (dd, J = 15.4, 1.7 Hz, 1H), 5.69 (d, J = 4.6, 1.7 Hz, 1H), 3.72 (s, 3H), 0.90 (t, J = 7.6 Hz, 9H), 0.63−0.55 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.2, 159.2 (d, J = 246.4 Hz), 149.2, 129.4 (d, J = 9.1 Hz), 129.0 (d, J = 14.1 Hz), 128.0 (d, J = 4.0 Hz), 124.6 (d, J = 4.0 Hz), 119.0, 115.3 (d, J = 22.2 Hz), 67.0, 51.7, 6.8, 4.8; IR (neat, cm^{-1}) 2954, 2912, 2877, 1725 (ν_{CO}), 1659, 1573, 1458, 1456, 1435, 1296, 1271, 1242, 1223, 1164, 1130, 1087, 1004, 974, 819, 796, 725; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{25}O_3FSiNa$ 347.144 92, found 347.144 92.

Compound **3i** (colorless oil, 107 mg, 67% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.41−7.38 (m, 1H), 7.20−7.08 (m, 3H), 6.96 (dd, J = 15.6, 4.4 Hz, 1H), 6.10 (dd, J = 15.6, 1.6 Hz, 1H), 5.49 (dd, J = 4.4, 1.6 Hz, 1H), 3.70 (s, 3H), 2.33 (s, 3H), 0.89 (t, J = 8.0 Hz, 9H), 0.60−0.52 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.4, 149.8, 139.8, 134.4, 130.7, 127.8, 127.0, 126.5, 118.7, 71.4, 51.7, 19.4, 6.9, 4.9; IR (neat, cm^{-1}) 2952, 2911, 2876, 1723 (ν_{CO}), 1656, 1459, 1435, 1413, 1276, 1239, 1164, 1114, 1091, 1068, 1004, 970, 820, 722; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{18}H_{28}O_3SiNa$ 343.169 99, found 343.170 02.

Compound **3j** (colorless oil, 144 mg, 81% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.82−7.76 (m, 4H), 7.48−7.42 (m, 3H), 7.06 (dd, J = 15.4, 4.5 Hz, 1H), 6.19 (dd, J = 15.4, 1.6 Hz, 1H), 5.48 (dd, J = 4.5, 1.6 Hz, 1H), 3.71 (s, 3H), 0.91 (t, J = 7.9 Hz, 9H), 0.63−0.56 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.3, 150.6, 139.3, 133.5, 133.3, 128.6, 128.2, 127.9, 126.4, 126.2, 125.1, 124.5, 118.9, 74.2, 51.8, 7.0, 5.0; IR (neat, cm^{-1}) 3056, 2952, 2910, 2875, 1721 (ν_{CO}), 1656, 1601, 1508, 1457, 1434, 1413, 1366, 1338, 1298, 1270, 1238, 1191, 1162, 1124, 1108, 1073, 1004, 975, 954, 896, 856, 816, 727; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{21}H_{28}O_3SiNa$ 379.169 99, found 379.170 05.

Compound **3k** (colorless oil, 118 mg, 74% yield): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.33−7.24 (m, 5H), 6.97 (dd, J = 15.4, 4.5 Hz, 1H), 6.11 (dd, J = 15.4, 1.6 Hz, 1H), 5.31 (dd, J = 4.5, 1.6 Hz, 1H), 4.20−4.14 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.9 Hz, 9H), 0.60−0.54 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ) 167.4, 159.4,

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151.0, 134.1, 127.8, 118.4, 114.1, 73.6, 55.5, 51.7, 6.9, 5.0; IR (neat, cm^{-1}) 2955, 2911, 2876, 1718 (ν_{CO}), 1656, 1454, 1413, 1367, 1276, 1238, 1161, 1114, 1064, 1038, 1002, 975, 846, 819, 742, 726, 697; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{18}H_{28}O_3SiNa$ 343.169 99, found 343.170 03.

Compound **3l** (colorless oil, 140 mg, 67% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 7.85−7.78 (m, 3H), 7.58−7.56 (m, 1H), 7.50−7.21 (m, 9H), 6.39 (dd, J = 15.3, 1.8 Hz, 1H), 5.41 (dd, J = 4.3, 1.8 Hz, 1H), 0.94 (t, J = 8.0 Hz, 9H), 0.65−0.58 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 165.4, 152.8, 148.5, 141.6, 133.9, 131.6, 129.5, 128.8, 128.1, 127.9, 127.8, 126.6, 126.5, 125.8, 121.3, 118.7, 118.2, 74.1, 6.9, 4.9; IR (neat, cm^{-1}) 3060, 3029, 2954, 2910, 2874, 1733 (ν_{CO}), 1653, 1630, 1600, 1493, 1463, 1356, 1269, 1237, 1208, 1154, 1122, 1078, 969, 808, 736, 697; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{26}H_{30}O_3SiNa$ 441.185 64, found 441.185 69.

Compound **3m** (colorless oil, 80 mg, 46% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 7.33−7.24 (m, 5H), 6.86 (dd, J = 15.2, 4.8 Hz, 1H), 5.99 (dd, J = 15.4, 1.6 Hz, 1H), 5.28 (dd, J = 4.8, 1.6 Hz, 1H), 1.46 (s, 9H), 0.90 (t, J = 8.0 Hz, 9H), 0.60−0.53 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 166.0, 149.0, 142.0, 128.4, 127.6, 126.3, 120.8, 80.3, 73.9, 28.1, 6.7, 4.8; IR (neat, cm^{-1}) 2955, 2912, 2876, 1712 (ν_{CO}), 1654, 1493, 1454, 1413, 1392, 1367, 1297, 1281, 1246, 1148, 1120, 1064, 1001, 976, 847, 818, 740, 726, 697; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{20}H_{32}O_3SiNa$ 371.201 29, found 371.201 35.

Compound **3n** (colorless oil, 177 mg, 91% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 7.32−7.23 (m, 5H), 6.26 (s, 1H), 5.10 (s, 1H), 3.70 (s, 3H), 2.67−2.61 (m, 1H), 2.06−2.01 (m, 1H), 1.29−1.18 (m, 8H), 0.89−0.83 (m, 12H), 0.57−0.51 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 167.4, 164.9, 142.0, 128.3, 127.9, 127.2, 113.7, 77.8, 51.1, 31.6, 29.9, 29.6, 29.5, 22.7, 14.2, 6.8, 4.9; IR (neat, cm^{-1}) 2953, 2875, 1720 (ν_{CO}), 1649, 1493, 1454, 1433, 1413, 1377, 1312, 1209, 1145, 1102, 1062, 1004, 974, 938, 915, 884, 849, 825, 725, 698; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{23}H_{38}O_3SiNa$ 413.2488, found 413.2492.

Compound **3o** (colorless oil, 144 mg, 83% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 7.32−7.24 (m, 5H), 6.28 (s, 1H), 5.10 (s, 1H), 3.70 (s, 3H), 2.67−2.60 (m, 1H), 2.04−2.01 (m, 1H), 1.33−1.28 (m, 2H), 0.90−0.85 (m, 12H), 0.58−0.50 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 167.4, 164.7, 141.9, 128.3, 127.9, 127.2, 113.8, 77.7, 51.0, 31.5, 22.9, 14.7, 6.8, 4.9; IR (neat, cm^{-1}) 2956, 2912, 2875, 1720 (ν_{CO}), 1649, 1454, 1433, 1377, 1313, 1278, 1240, 1196, 1145, 1099, 1057, 1004, 883, 845, 726, 698; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{20}H_{32}O_3SiNa$ 371.201 29, found 371.201 34.

Compound **3p** (colorless oil, 137 mg, 77% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 5.92 (s, 1H), 4.10 (t, J = 5.4 Hz, 1H), 3.69 (s, 3H), 2.84−2.76 (m, 1H), 2.17−2.08 (m, 1H) 1.54−1.26 (m, 12H), 1.00−0.86 (m, 15H), 0.61−0.55 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 167.4, 166.2, 140.3, 114.2, 75.6, 51.0, 36.7, 31.9, 29.5, 25.2, 23.1, 22.8, 14.9, 14.2, 7.0, 5.0; IR (neat, cm^{-1}) 2954, 2933, 2875, 1721 (ν_{CO}), 1649, 1458, 1433, 1414, 1379, 1329, 1242, 1152, 1126, 1094, 1005, 978, 889, 820, 724; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{20}H_{40}O_3SiNa$ 379.2644, found 379.2646.

Compound **3q** (colorless oil, 123 mg, 75% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 5.91 (s, 1H), 4.15−4.12 (m, 1H), 3.69 (s, 3H), 2.83−2.76 (m, 1H), 2.15−2.08 (m, 1H), 1.76−1.66 (m, 1H), 1.57−1.29 (m, 4H), 1.01−0.89 (m, 18H), 0.61−0.55 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 167.3, 166.8, 114.2, 74.5, 51.0, 46.6, 31.8, 24.5, 23.7, 23.3, 22.3, 15.0, 7.0, 5.0; IR (neat, cm^{-1}) 2955, 2875, 1720 (ν_{CO}), 1650, 1463, 1434, 1414, 1384, 1367, 1329, 1305, 1240, 1155, 1131, 1085, 1002, 961, 900, 724; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{18}H_{36}O_3SiNa$ 351.2332, found 351.2326.

Compound **3r** (colorless oil, 163 mg, 83% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 7.31−7.23 (m, 5H), 6.85 (d, J = 1.3 Hz, 1H), 5.40 (d, J = 1.3 Hz, 1H), 4.24−4.18 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 7.9 Hz, 6H), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 167.6, 164.9, 141.8, 129.6, 128.4, 128.0, 127.8, 78.5, 60.5, 14.5, 7.0, 5.1, 0.1; IR (neat, cm^{-1}) 2954, 2910, 2876, 1718 (ν_{CO}), 1598, 1454, 1413, 1368, 1307, 1244, 1185, 1085, 1039, 1004, 841, 726, 698; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{21}H_{36}O_3Si_2Na$ 415.209 52, found 415.209 51.

Compound **3s** (colorless oil, 162 mg, 81% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 6.61 (s, 1H), 4.39−4.37 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 1.32−1.25 (m, 13H), 0.95 (t, J = 7.9 Hz, 9H), 0.92−0.86 (m, 3H), 0.57 (q, J = 7.9 Hz, 6H), 0.21 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 167.8, 167.6, 128.1, 75.1, 60.2, 38.7, 32.0, 29.4, 26.0, 22.8, 14.4, 14.2, 7.0, 5.0, −0.2; IR (neat, cm^{-1}) 2955, 2933, 2876, 1719 (ν_{CO}), 1603, 1460, 1413, 1378, 1312, 1247, 1139, 1089, 1048, 1005, 843, 740, 681; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{21}H_{44}O_3Si_2Na$ 423.2727, found 423.2723.

Procedure for the Conjugate Reduction of 3h. Following a similar procedure established for the conjugate reduction of α,β-unsaturated carbonyl compounds,[24] [1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene]copper(I) chloride (9.8 mg, 0.020 mmol, 1 mol %) and NaO^{t}Bu (2.0 mg, 0.020 mmol, 1 mol %) were mixed in an oven-dried flask under an argon atmosphere. About 1.0 mL of toluene was added, and the mixture was stirred at room temperature for 10 min, followed by the addition of poly(methylhydrosiloxane) (PMHS; 0.015 mL, 0.20 mmol, 1.0 equiv). After the yellow solution was stirred at room temperature for 5 min, more toluene (2.0 mL) and PMHS (0.045 mL, 0.60 mmol, 3.0 equiv) were added. A solution of **3h** (65 mg, 0.20 mmol, 1.0 equiv) and ^{t}BuOH (0.06 mL, 0.80 mmol, 4.0 equiv) in 1 mL of toluene was then added via a cannula. The reaction mixture was stirred at room temperature until all the starting material was fully converted. The reaction mixture was quenched with water and treated with ethyl acetate. The organic layer was separated, while the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified by column chromatography, and compound **4** was isolated as a yellow oil (62 mg, 95% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 7.51−7.47 (m, 1H), 7.23−7.18 (m, 1H), 7.14−7.09 (m, 1H), 7.00−6.95 (m, 1H), 5.12 (t, J = 5.8 Hz, 1H), 3.63 (s, 3H), 2.44−2.29 (m, 2H), 2.06−2.00 (m, 2H), 0.88 (t, J = 7.9 Hz, 9H), 0.57−0.50 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 174.0, 159.2 (d, J = 245.4 Hz), 131.7 (d, J = 14.1 Hz), 128.7 (d, J = 7.1 Hz), 127.9 (d, J = 4.0 Hz), 124.2 (d, J = 5.1 Hz), 115.0 (d, J = 22.2 Hz), 66.8, 51.6, 34.3, 29.8, 6.8, 4.8; IR (neat, cm^{-1}) 2954, 2912, 2877, 1740 (ν_{CO}), 1616, 1587, 1487, 1456, 1437, 1415, 1366, 1270, 1224, 1159, 1107, 1087, 1067, 1003, 889, 841, 799, 756, 725, 568, 528; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{17}H_{27}O_3FSiNa$ 349.1611, found 349.1611.

Procedure for the Deprotection of the Silyl Group. A similar procedure has been described in the literature.[9e] To a solution of **4** (or **3h** for the synthesis of **6**) in 3 mL of THF was added a 1 M solution of tetrabutylammonium fluoride in THF (2 equiv). The reaction mixture was stirred at room temperature until all the starting material was fully converted. The reaction mixture was then diluted with 1.2 mL of diethyl ether and washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified on silica by column chromatography.

Compound **5** (colorless oil, 18.5 mg, 85% yield, for a 0.12 mmol scale reaction): ^1H NMR (400 MHz, $CDCl_3$, δ) 7.43−7.39 (m, 1H), 7.37−7.31 (m, 1H), 7.20−7.16 (m, 1H), 7.12−7.06 (m, 1H), 5.75 (t, J = 7.2 Hz, 1H), 2.79−2.65 (m, 3H), 2.25−2.15 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 176.8, 159.7 (d, J = 248.5 Hz), 130.1 (d, J = 8.1 Hz), 127.1 (d, J = 12.1 Hz), 126.6 (d, J = 4.0 Hz), 124.6 (d, J = 4.0 Hz), 115.8 (d, J = 21.2 Hz), 76.4 (d, J = 3.0 Hz), 29.9, 28.6; IR (neat, cm^{-1}) 2950 (br), 1770 (ν_{CO}), 1618, 1589, 1490, 1457, 1420, 1375, 1328, 1297, 1236, 1212, 1189, 1171, 1138, 1101, 1038, 1021, 989, 941, 891, 833, 811, 798, 755, 666, 601, 635, 602, 525; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{10}H_9O_2FNa$ 203.0484, found 203.0480.

Compound **6** (colorless oil, 19 mg, 76% yield, for a 0.12 mmol scale reaction): ^1H NMR (400 MHz, $CDCl_3$, δ) 7.92−7.88 (m, 1H), 7.56−7.50 (m, 1H), 7.27−7.21 (m, 1H), 7.17−7.12 (m, 1H), 3.71 (s, 3H), 3.35−3.31 (m, 2H), 2.76 (t, J = 6.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 196.4 (d, J = 5.1 Hz), 173.4, 162.3 (d, J = 255.5 Hz), 134.9 (d, J = 9.1 Hz), 130.8 (d, J = 2.0 Hz), 125.2 (d, J = 13.1 Hz), 124.6 (d, J = 3.0 Hz), 116.8 (d, J = 24.2 Hz), 51.9, 38.4 (d, J = 8.1 Hz), 28.2; IR (neat, cm^{-1}) 2953, 1737 (ν_{CO}), 1688 (ν_{CO}), 1610, 1582, 1481, 1452, 1438, 1411, 1358, 1323, 1274, 1214, 1169, 1153, 1105,

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1069, 1026, 991, 950, 829, 765, 538; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{11}H_{11}O_3FNa$ 233.0590, found 233.0588.

Procedure for the Reduction of 6. At 0 °C under an inert atmosphere, a solution of **6** (200 mg, 0.95 mmol) in 2 mL of THF was added dropwise to a suspension of $LiAlH_4$ (144 mg, 3.80 mmol, 4 equiv) in 3 mL of THF. The reaction mixture was stirred at room temperature until all the starting material was fully converted. The excess $LiAlH_4$ was carefully quenched at 0 °C with 5 mL of EtOAc followed by 5 mL of water, at which point a white precipitate formed. The mixture was then acidified with 15% HCl (ca. 4 mL) until it became a clear solution, and the product was extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography to give compound **7** as a colorless oil (167 mg, 95% yield). ^1H NMR (400 MHz, $CDCl_3$, δ) 7.42−7.38 (m, 1H), 7.19−7.14 (m, 1H), 7.08−7.04 (m, 1H), 6.96−6.92 (m, 1H), 4.94 (t, J = 6.0 Hz, 1H), 4.29 (br s, 2H), 3.57−3.46 (m, 2H), 1.78−1.73 (m, 2H), 1.65−1.50 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 159.6 (d, J = 246.4 Hz), 131.7 (d, J = 13.1 Hz), 128.7 (d, J = 8.1 Hz), 127.4 (d, J = 4.0 Hz), 124.3 (d, J = 3.0 Hz), 115.2 (d, J = 22.2 Hz), 67.7, 62.3, 35.0, 28.8; IR (neat, cm^{-1}) 3311 (br, ν_{OH}), 2941, 2361, 2338, 1717, 1616, 1586, 1487, 1454, 1269, 1221, 1178, 1042, 824, 754, 619; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{10}H_{13}O_2FNa$ 207.0797, found 207.0792.

Procedure for the Synthesis of 8. A similar procedure has been described in the literature.[25] Compound **7** (48 mg, 0.26 mmol) and $ZnCl_2$ (53 mg, 0.39 mmol, 1.5 equiv) were mixed with 5 mL of 1,2-dichloroethane in an oven-dried flask. The reaction mixture was stirred at 80 °C until all the starting material was fully converted. The solution was diluted with 3 mL of CH_2Cl_2 and then washed with water and brine. The organic layer was separated and dried over anhydrous $MgSO_4$. The crude product was purified by column chromatography to give compound **8** as a colorless oil (31 mg, 72% yield): ^1H NMR (400 MHz, $CDCl_3$, δ) 7.47−7.43 (m, 1H), 7.24−7.19 (m, 1H), 7.14−7.10 (m, 1H), 7.03−6.98 (m, 1H), 5.14 (t, J = 7.1 Hz, 1H), 4.13−4.08 (m, 1H), 3.97−3.91 (m, 1H), 2.44−2.36 (m, 1H), 2.04−1.97 (m, 2H), 1.83−1.74 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ) 160.0 (d, J = 246.4 Hz), 131.0 (d, J = 13.1 Hz), 128.6 (d, J = 8.1 Hz), 127.0 (d, J = 4.0 Hz), 124.2 (d, J = 3.0 Hz), 115.3 (d, J = 21.2 Hz), 75.3 (d, J = 2.0 Hz), 68.8, 33.7, 26.2; IR (neat, cm^{-1}) 2977, 2870, 1617, 1588, 1485, 1455, 1364, 1273, 1229, 1185, 1151, 1103, 1059, 939, 923, 821, 753, 516, 493, 461; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{10}H_{11}OFNa$ 189.068 61, found 189.068 57.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text and figures giving details of deuterium-labeling experiments and spectroscopic data for all of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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