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# Carboxylation with $CO_2$ via Brook Rearrangement: Preparation of α-Hydroxy Acid Derivatives

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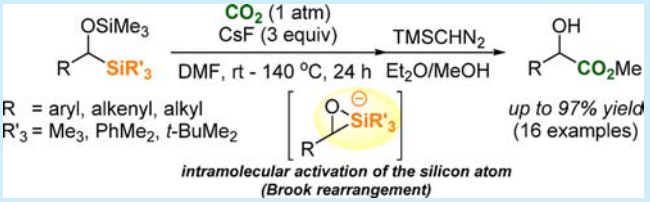
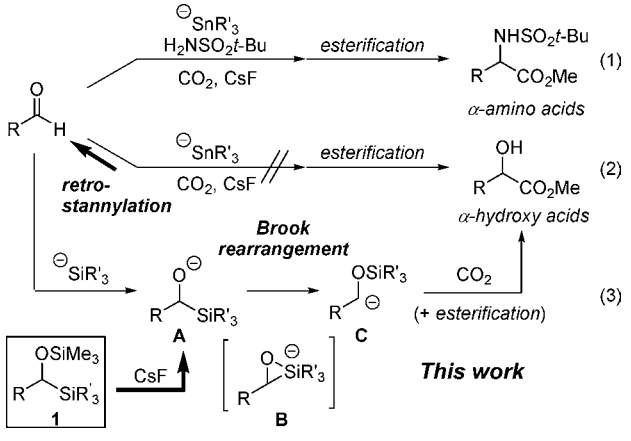
Supporting Information

**ABSTRACT:** In the presence of CsF, a wide range of α-substituted α-siloxy silanes were carboxylated under a $CO_2$ atmosphere (1 atm) via Brook rearrangement. A variety of α-substituents including aryl, alkenyl, and alkyl groups were tolerated to afford α-hydroxy acids in moderate-to-high yields. One-pot synthesis from aldehydes using $PhMe_2SiLi$ and $CO_2$ was also possible, providing α-hydroxy acids without the isolation of an α-hydroxy silane.




Carbon dioxide ($CO_2$) is an abundant, inexpensive, and relatively nontoxic C1 feedstock that has become widely used in current advanced organic chemistry for the synthesis of various organic compounds such as carboxylic acid derivatives, (poly)carbonates, and carbamates.[1] Although transition-metal-catalyzed $CO_2$ incorporation is a mainstream in this area, much attention has still been focused toward the exploration of efficient carboxylations by simple reagent combination. To meet this purpose, we have already reported a novel one-step α-amino acid synthesis from $CO_2$, aldehydes, and sulfonamides in the presence of CsF and a bismetal reagent such as a silylstannane or a distannane (Scheme 1, eq 1).[2] In this reaction sequence, both an *N*-sulfonylimine and an α-amino stannane were characterized as intermediates, and CsF played two important roles: (1) in promoting bismetal activation to generate a stannyl anion[2,3] and (2) in promoting the carboxylation of the α-amino stannane intermediate.[4]

**Scheme 1. α-Hydroxy Acid Synthesis via Brook Rearrangement**




Our next conceivable target is the synthesis of α-hydroxy acids, which are also very useful building blocks in organic synthesis.[5] However, when the reaction was conducted without a sulfonamide (an amine component), carboxylated products were not obtained at all, mainly because retro-stannylation should be operative owing to the high stability of the released stannyl anion (eq 2).[2,4] Therefore, we considered employing a silyl anion equivalent instead of a stannyl anion since the corresponding α-silyl alkoxide **A** might undergo Brook rearrangement[6] driven by the high oxophilicity of the silicon atom before the undesired retro-silylation, leading to productive carboxylation with $CO_2$ through intermediates **B** and/or **C** (eq 3).

On the basis of this synthetic strategy, we selected α-siloxy silane **1** as a precursor for the *in situ* generation of α-silyl alkoxide **A**. If an appropriate fluoride source is present, alkoxide **A** should be generated quickly and quantitatively by simultaneous removal of the $Me_3Si$ group. To the best of our knowledge, there are no reports on fluoride-mediated carboxylation[7−9] of α-siloxy silanes via Brook rearrangement.[10] Thus, this unique strategy provides a new entry to $CO_2$ incorporation chemistry as well as α-hydroxy acid synthesis.

First, α-siloxy silane **1aa** was prepared from benzaldehyde[11] and subjected to fluoride-mediated carboxylation with $CO_2$ (1 atm) in DMF (Table 1, entries 1−5). Screening of various fluoride sources such as CsF, TMAF, TBAT, KF, and LiF revealed that CsF exhibited the best performance for carboxylation (entry 1). To facilitate the isolation process, the obtained carboxylic acid was derivatized into its methyl esters by esterification with $TMSCHN_2$,[12] giving **2a** in 92% yield. Next, potential solvents were screened and it was revealed that DMA and DMI were also compatible for this carboxylation (entries 6 and 7), but the use of DMSO decreased the yield to

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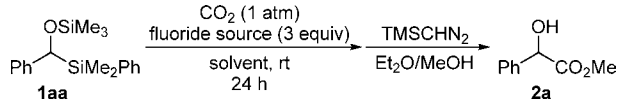
**Table 1. Condition Screening**




| entry | solvent | fluoride source | yield (%)[a] |
|---|---|---|---|
| 1 | DMF | CsF | 90 (92) |
| 2 | DMF | TMAF | 52 |
| 3 | DMF | TBAT | 69 |
| 4 | DMF | KF | 10 |
| 5 | DMF | LiF | – |
| 6 | DMA | CsF | 93 (91) |
| 7 | DMI | CsF | 94 (90) |
| 8 | DMSO | CsF | 74 |
| 9 | $CH_3CN$ | CsF | 9 |
| 10 | $CH_2Cl_2$ | CsF | – |
| 11[b] | THF | CsF | – |
| 12[b] | THF | TMAF | – |

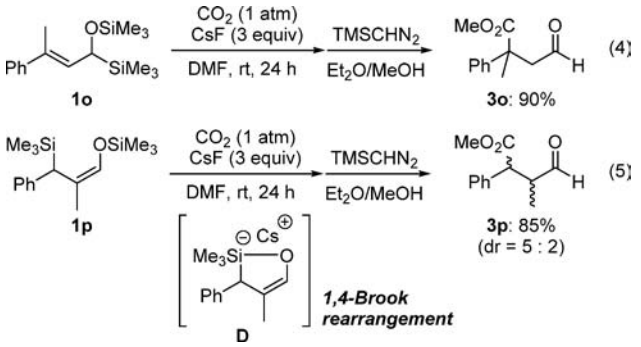
[a]Yields were determined by $^1$H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses. [b]Reaction time: 15 h. DMI = 1,3-dimethyl-2-imidazolidinone. TMAF = tetramethylammonium fluoride. TBAT = tetrabutylammonium triphenyldifluorosilicate.

74% (entry 8).[13] Other solvents including $CH_3CN$, $CH_2Cl_2$, and THF suppressed the desired carboxylation, but PhCH(OH)$SiMe_2$Ph, which was formed via removal of the $SiMe_3$ group from **1aa** by acidic quenching, mainly remained (entries 9–12). Reported conditions for the Brook rearrangement–alkylation sequential process from α-siloxy silanes by Scheidt (TMAF, THF at rt[10]) did not afford carboxylated products (entry 12).

Having established optimal conditions, various α-siloxy silanes **1** were examined with 3 equiv of CsF in DMF under 1 atm of $CO_2$ atmosphere ($CO_2$ balloon).[14] All substrates listed in Figure 1 were successfully carboxylated; however, the suitable temperature for each reaction depended on the electronic character of the α-substituent of the substrate: substrates possessing electron-rich aryl, alkenyl, and alkyl groups required higher reaction temperatures (60–140 °C) because the generation of carbanion **C** might be retarded in response to their electron-donating character. α-Siloxy silanes **1aa**, **1ab**, and **1ac** possessing different α-silyl groups ($Me_3Si$, $PhMe_2Si$, *t*-$BuMe_2Si$) all gave the desired α-hydroxy acids in good yields. However, a sterically bulky substituent such as a *t*-$BuMe_2Si$ group at the α-position needed a higher temperature (**1ac**). Concerning the accessibility to substrates from aldehydes, the $PhMe_2Si$ group was selected as an optimal α-substitution.[15] Reactions of α-siloxy silanes possessing substituted arenes (**1b–1f**) all gave high yields regardless of the location of the substituent on the aromatic ring. 2-Naphthyl (**1g**) and heteroaromatic substrates (**1h** and **1i**) possessing 2-furyl and 2-thienyl groups were also active. In addition, α-siloxy silanes bearing α-alkenyl groups were moderately reactive (**1j–1l**). Furthermore, carboxylations of α-alkyl substrates (**1m** and **1n**) produced the corresponding α-hydroxy acids in about 60% yields at 140 °C. α-Alkyl substrates were totally inactive in our previous α-amino acid synthesis,[2−4] highlighting an advantage of the intramolecular activation of the α-silicon atom via Brook rearrangement (vide infra).

Next, α-siloxy silane **1o** possessing an olefin conjugated with the phenyl group was tested for carboxylation (Scheme 2, eq

**Scheme 2. Carboxylation with $CO_2$ at the γ-Position**



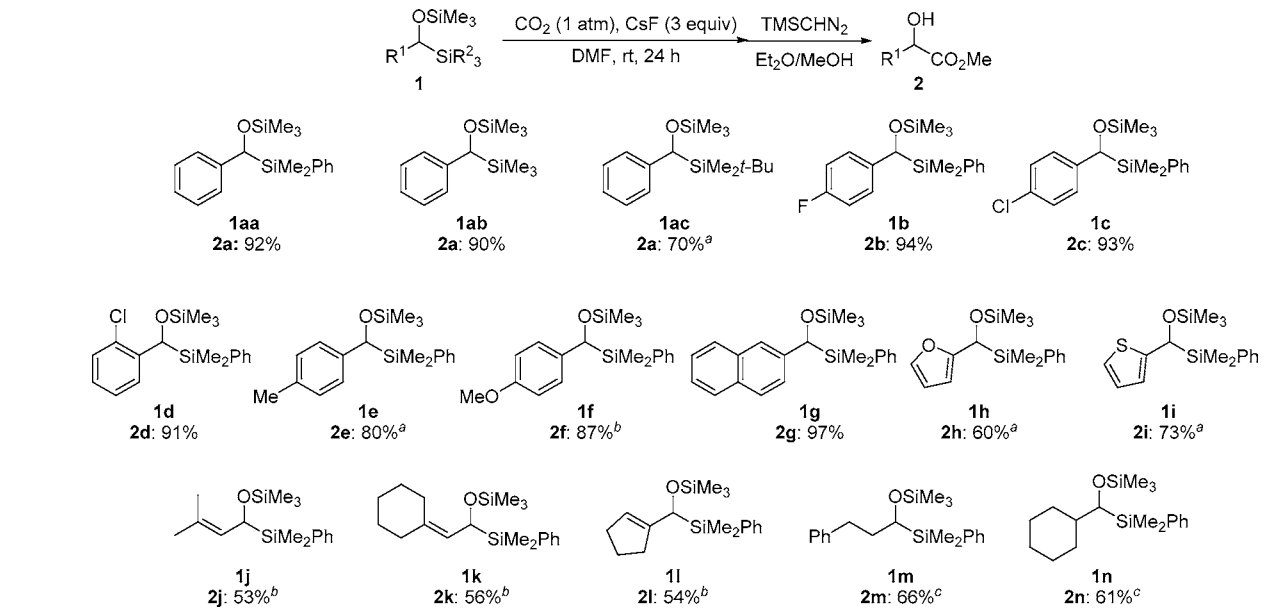




**Figure 1.** Carboxylation of various α-siloxy silanes **1**. Reagents and conditions: substrate **1** (0.1 mmol), CsF (3 equiv), DMF (2 mL), rt, 24 h, then $TMSCHN_2$. Isolated yields are shown. [a] Reaction was performed at 60 °C. [b] Reaction was performed at 80 °C. [c] Reaction was performed at 140 °C.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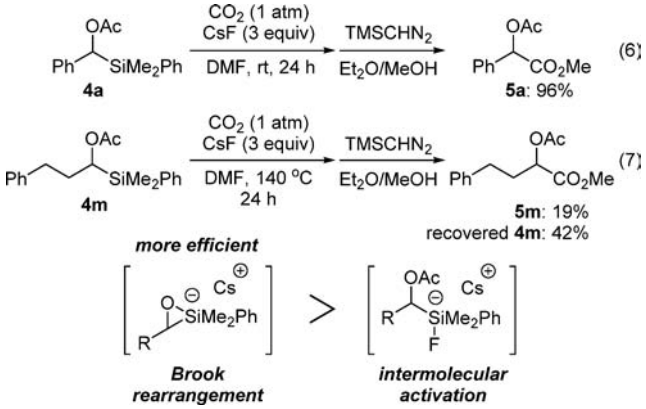
4). As a result, the generated carbanion completely migrated to the benzylic position and then carboxylated with $CO_2$ to afford **3o** in 90% yield. Moreover, when γ-silyl silyl enol ether **1p** was used for the substrate, γ-carboxylated product **3p** was obtained exclusively in 85% yield with a 5:2 diastereomeric ratio, suggesting that this γ-carboxylation might proceed through the 1,4-Brook rearrangement pathway (eq 5).[16]

According to a related study on Brook rearrangement−alkylation reactions by Scheidt,[10] this carboxylation would also proceed via a Brook rearrangement pathway because the silyloxy moiety ($Me_3SiO$−) is more prone to be activated by fluoride than are α-$Me_3Si$, $Me_2PhSi$, and *t*-$BuMe_2Si$ moieties. However, when α-acetoxy benzylsilane **4a** was used as a substrate for carboxylation, the corresponding hydroxy acid derivative **5a** was obtained in 96% yield, indicating that carboxylation could also proceed via direct activation of benzylic silanes by a fluoride (Scheme 3, eq 6).[8] In contrast,

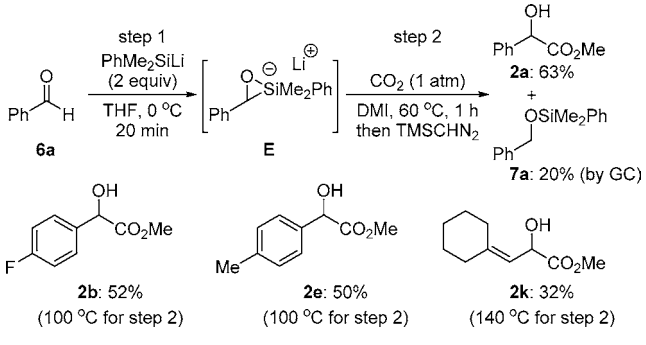
**Scheme 3. Advantages of Intramolecular Activation**




the carboxylation of α-acetoxy α-alkyl silane **4m** was significantly suppressed and **5m** was obtained in only 19% yield with unreacted **4m** remaining (42%) (eq 7), while the reaction of **1m** smoothly proceeded to afford **2m** in 66% yield (Figure 1). These experimental data suggest that activation of the silicon atom via Brook rearrangement works very well for less reactive substrates since intramolecular silane activation by an alkoxide would be more efficient than the intermolecular one by a fluoride.

Finally, we attempted a one-pot synthesis of α-hydroxy acid from benzaldehyde (**6a**) using $PhMe_2SiLi$ (Scheme 4). After the completion of the silylation of **6a** in THF, the reaction solvent was replaced with DMI (1,3-dimethyl-2-imidazolidinone), the best solvent among those screened for further carboxylation with $CO_2$. As a result, **2a** was obtained in 63% yield together with silyl-protected benzylalcohol **7a** in 20% yield.[17] Reactions of electron-donating and -withdrawing aldehydes also worked well to afford the corresponding α-hydroxy acids **2b** and **2e** in moderate yields. In addition, carboxylation of α-alkenyl aldehyde gave **2k** in 32% yield at higher temperature.[18] Compared to the CsF-mediated Brook rearrangement−carboxylation of α-siloxy silanes (Figure 1), the $SiMe_3$-protection of a hydroxy group and the use of CsF could be eliminated. Although the product yield was moderate, this one-pot synthesis demonstrates the power of the Brook rearrangement−carboxylation sequential protocol just by using aldehydes, $PhMe_2SiLi$, and $CO_2$ as starting materials.

**Scheme 4. One-Pot α-Hydroxy Acid Synthesis from Aldehydes**




In conclusion, we have developed the carboxylation of α-siloxy silanes with $CO_2$ via Brook rearrangement using CsF as a mild and efficient promoter. A wide range of α-aryl, alkenyl, and alkyl substrates were carboxylated to afford the corresponding α-hydroxy acid derivatives in moderate-to-high yields. In addition, the one-pot synthesis of α-hydroxy acids was achieved using aldehydes, $PhMe_2SiLi$, and $CO_2$.

## ■ ASSOCIATED CONTENT

### Supporting Information

Details of experimental procedures and physical properties of 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.

## ■ ACKNOWLEDGMENTS

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