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Preparation of acetals from aldehydes and alcohols under basic conditions

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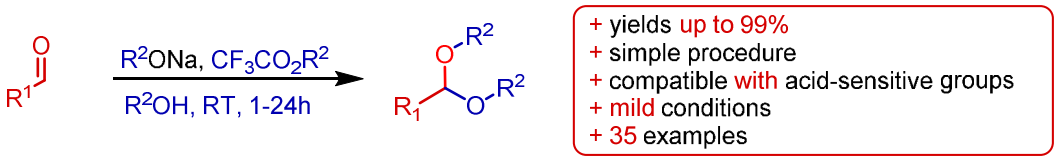

ABSTRACT: A new, simple protocol for synthesis of acetals under basic conditions from non-enolizable aldehydes and alcohols is reported. Such reactivity is facilitated by a sodium alkoxide along with a corresponding trifluoroacetate ester, utilizing formation of sodium trifluoroacetate as a driving force for acetal formation. The usefulness of this protocol is demonstrated by its orthogonality with various acid-sensitive protecting groups and by good compatibility with functional groups, delivering synthetically useful acetals complementarily to the synthesis under acidic conditions from aldehydes and alcohols.

The carbonyl group is, arguably, one of the most important functional groups in contemporary organic synthesis.[1-5] The diverse reactivity of the carbonyl group allows for its facile transformation into a variety of other functional groups, including imines, alcohols, olefins, *etc.* Carbonyl compounds are also commonly encountered as key-building blocks in the synthesis of complex pharmaceutical drugs and biologically active molecules.[6, 7] However, this highly reactive functional group requires protection/deprotection during multistep organic transformations.[8, 9] One of the most common protecting group used for protection of carbonyl compounds is the acetal functionality. Its formation is usually straightforward and entails the reaction of the carbonyl compound with an alcohol in the presence of either a Brønsted or a Lewis acid. However, as in acid catalyzed acetalizations acetals are at equilibrium with aldehydes, they require water scavenger, e.g. trimethyl orthoformate. For example, Thurkauf and colleagues have described a procedure in which diaryl ketones are

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protected using trimethyl orthoformate, methanol and a catalytic amount of triflic acid in nitromethane.[10] Also, Gemal and Luche have published a letter where they describe acetalization of aldehydes in the presence of various lanthanide chlorides.[11] One of the interesting recent reports is the work by Yi and coworkers,[12] in which acetal formation is facilitated by green light and a catalytic amount of Eosin Y. For a thorough review of the protection of carbonyl compounds, we refer to *Greene's Protective Groups in Organic Chemistry.*[13] Despite these considerable advantages, acetalization under acidic conditions can become challenging when acid-sensitive functional groups are present in the molecule. To address these limitations, several complementary methods for acetalization under non-acidic conditions have been developed. These notably include the method for acetalization described by Basu and coworkers, using a catalytic amount of iodine in methanol.[14] Similarly, Karimi and Golshani have prepared cyclic 1,3-dioxanes using 1,3-bistrimethylsiloxypropane (BTSP) in dichloromethane, also in the presence of catalytic amounts of iodine.[15] Additionally, Kumamoto and coworkers have reported that dimethyl acetals are formed at high pressure (0.8 GPa) in methanol in the presence of trialkyl orthoformates.[16] Barbasiewicz and Mąkosza described acetalization of the carbonyl group in the presence of halohydrins.[17] Their method utilizes the formation of the chlorohydrin anion, which is trapped by a carbonyl compound, forming an appropriate hemiacetal, which then forms a cyclic acetal by elimination of the chloride. As the favored reaction for chlorohydrin anions is the formation of oxirane, the process is conducted at -60 ºC. Nevertheless, most of the above-mentioned methods only enable access to the specific group of acetals.

In this communication, we present a general method for synthesis of acetals under mild, basic conditions from non-enolizable aldehydes and alcohols. Recently, we have been investigating an anion receptor containing triptycene.[18] One of the steps in its synthesis required the reaction of trialdehyde **1** with methyl azidoacetate in the presence of sodium methoxide (Scheme 1). However, the outcome of this reaction was different from that expected. Analysis of the ^{1}H, ^{13}C NMR and MS spectra showed that triacetal product **2** was formed instead of the expected Knoevenagel reaction product **3**.[19] On the grounds of this serendipitous observation we hypothesized that methyl azidoacetate might have methylated the hemiacetal formed from aldehyde **1** and sodium methoxide, due to the electron withdrawing nature of azide group, enabling access to acetal formation.

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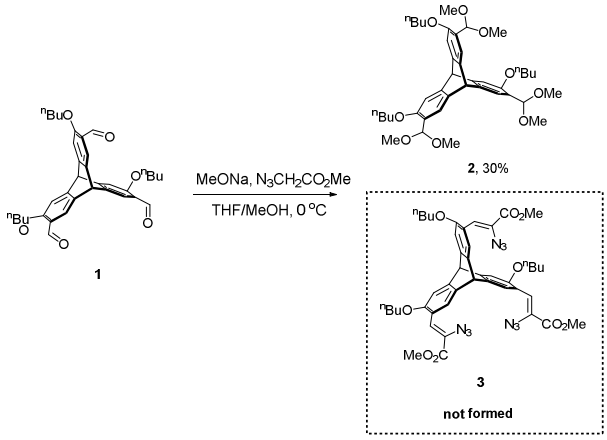
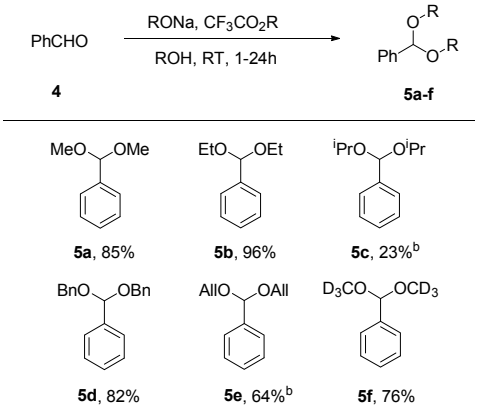


Scheme 1. The serendipitous observation of aldehyde **1** acetalization under basic conditions.

To test this hypothesis, we decided to use methyl trifluoroacetate as a methylating agent. To our delight, when benzaldehyde (**4**) was treated with sodium methoxide and then methyl trifluoroacetate in methanol at room temperature we observed complete conversion of the aldehyde to (dimethoxymethyl)benzene (**5a**) in a good yield of 85%.

We commenced our studies on acetalization of aldehydes under basic conditions by testing the applicability of this protocol to several alcohols (Table 1). We screened methanol, ethanol, isopropanol as a source of alkoxide. Similarly, to (dimethoxymethyl)benzene (**5a**), (diethoxymethyl)benzene (**5b**) was synthesized with an excellent yield of 96%. Diisopropyl acetal **5c**, on the other hand, were synthesized in a lower yield of 23%, probably due to increased steric hindrance of the alcohol.

Table 1. Reaction yields for various alcohol partners [a]



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[a] Reaction conditions: benzaldehyde (10 mmol), alcohol (15 mL), sodium alkoxide (20 mmol), alcohol trifluoroacetate (20 mmol). All yields refer to isolated products. [b] Product purified by column chromatography.

Additionally, we also obtained dibenzyl and diallyl acetals **5d** and **5e** with good yields of 64% and 82%, respectively. Moreover, we synthesized a deuterated acetal **5f** with a good yield of 76%.

After examining the compatibility of our method with various alcohols, we examined a broad spectrum of aromatic carbonyl partners possessing a wide range of functionalities (Table 2a). In most cases, the aldehydes (**6a-u**) were cleanly converted into their dimethyl acetals (**7a-u**) with yields in the 80-90% range, and the presence of either electron-donating groups or mildly electron withdrawing-groups had little effect on the overall yield of the reaction. However, strong electron-withdrawing groups like $-CF_3$, $-NO_2$ or $-B(OR)_2$, by contrast, have a detrimental effect on the purity of the products and the overall yield (**7g, 7l, 7h**), with the notable exception of the nitrile acetal **7m**, which was obtained with an excellent yield of 99%. Moreover, when the $-NO_2$ substituent was present at the *ortho* position towards the carbonyl group, an appropriate acetal could not be isolated, probably due to the strong hydrogen bonding between the $-NO_2$ and -CHO groups, resulting in the increased stability of the carbonyl group against a nucleophilic attack.

In our scope of substrates, we included several aldehydes containing groups which could potentially react under the acetalization reaction conditions, such as ethynyl aldehyde **6i**, and azo aldehyde **6j**. Those substances, however, have proved resistant to the basic reaction conditions and furnished their appropriate acetals **7i** and **7j** in yields of 88% and 99%, respectively. Additionally, the phosphine aldehyde **6k** undergoes acetalization with a yield of 78%, with the only impurities being those resulting from oxidation due to the air exposure during work-up. Although we have successfully isolated the acetal of salicylaldehyde (**7c**) with a yield of 81%, we have not been able to isolate the acetal of 3-formylbenzoic acid in pure form. Also, the naphthalene and anthracene-based acetals (**7n**, **7o**) were obtained in high yields of 96% and 97%, respectively.

Table 2a. Reaction yields for various carbonyl partners [a]

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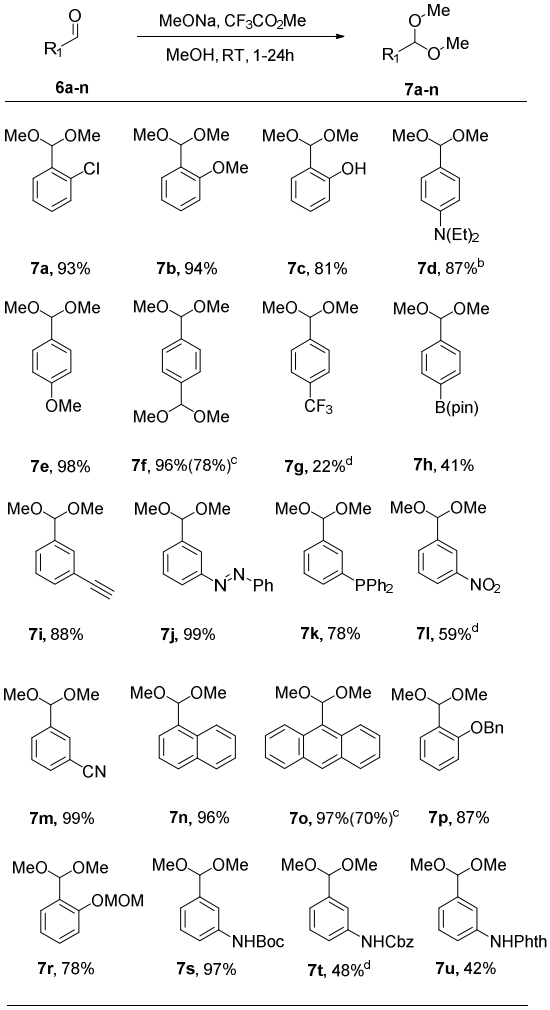

[a] Reaction conditions: aldehyde (10 mmol), methanol (15 mL), sodium methoxide (20 mmol), methyl trifluoroacetate (20 mmol). All yields refer to isolated products [b] 72 h reaction time [c] Yield after recrystallization [d] Product purified by column chromatography.

Next, we turned our attention towards aldehydes containing acid-sensitive protective groups. *N*-protected acetal **7s**, as well as *O*-protected acetals **7p** and **7r,** were isolated with yields of 97%, 87%, and 78%, respectively. However, acetal **7t** containing *NH*-Cbz protective group was obtained in a moderate yield of 48%, as a result of the protective group's susceptibility to the nucleophilic attack of the methoxide. Also, the phthalimide-containing acetal **7u** was obtained with a slightly lower yield of 42%.

Knowing that our method proved compatible with various substituted benzaldehydes, naphthaldehyde and anthraldehyde (Table 2a), we turned our attention to heteroaromatic aldehydes (Table 2b). Thiophene acetal **9a** and pyrrole acetal **9b** were obtained with high

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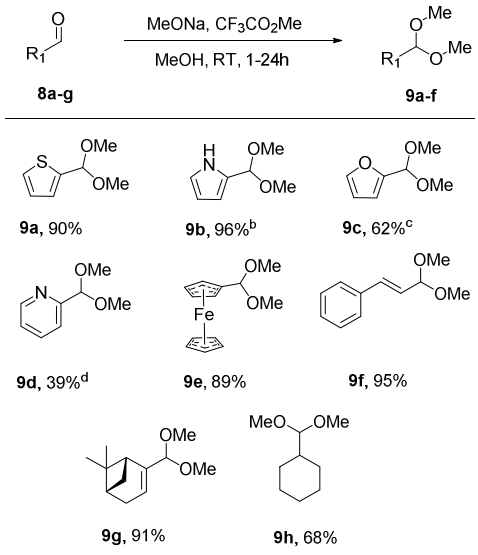
yields of 90% and 96%, respectively. The furaldehyde acetal **9c** was obtained with a diminished yield of 62%, because of furaldehyde's sensitivity towards basic conditions. The pyridine-based acetal **9d** was obtained with a moderate yield of 39%, probably due to the carbonyl group being situated at a very electron-deficient 2-position. Moreover, we have synthesized in considerable yield of 89 % the ferrocene acetal **9e**. This fact suggests that our acetalization method could be successfully applied to other, more complex organometallic compounds. Next, we turned our attention to other carbonyl-containing compounds, such as ketones and non-aromatic aldehydes. Reaction with benzophenone did not result in conversion of starting material to the desired product and the attempted acetalization of acetophenone yielded only the aldol reaction products. Aliphatic aldehydes, such as butyraldehyde yield mostly aldol reaction products, and in effect we were not able to isolate its corresponding acetal in pure. Similarly, α,β-unsaturated aldehydes, such as crotonaldehyde and 3-methylcrotonaldehyde give an intractable mixture of products resulting from both aldol and Michael reactions.

Table 2b. Reaction yields for various carbonyl partners [a]



[a] Reaction conditions: aldehyde (10 mmol), methanol (15 mL), sodium (20 mmol), methyl trifluoroacetate (20 mmol). All yields refer to isolated products [b] Product unstable at room temperature [c] Product purified by vacuum distillation [d] Product purified by column chromatography

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However, cinnamaldehyde cleanly converts into an appropriate dimethyl acetal **9f**, as the double bond is stabilized by the presence of the aromatic ring. Similarly, the myrtenal acetal (**9g**) can be obtained in a yield of 91%, due to the strained nature of the substituted cyclohexyl ring, resulting in an unfavorable geometry for the conjugated addition of methoxide ion. Furthermore, the non-aromatic and weakly enolizable cyclohexylformaldehyde gave the dimethyl acetal **9h** in a good yield of 68%. Next, we have explored the possibility of forming cyclic acetals by employing ω-bromo-substituted aliphatic aldehydes, however the reaction of 4-bromobutyraldehyde and 5-bromovaleraldehyde did not yield neither the expected 2-methoxytetrahydrofuran, nor 2-methoxytetrahydropyran, respectively.

Having established the scope and limitations of our protocol, we decided to gain further insight into the reaction mechanism. We envisioned two plausible reaction pathways for our acetalization reaction (Scheme 2). The first step is identical for both pathways, and involves the nucleophilic addition of methoxide to the carbonyl group, reversibly creating a alkoxide anion **10**. In path A, the alkoxide anion **10** is acylated, forming a trifluoroacetate ester **11**, which in turn is attacked by a methoxide anion, resulting in formation of the desired acetal and a trifluoroacetate anion. In path B the alkoxide is directly methylated by the trifluoroacetate ester, also yielding the final acetal product and a trifluoroacetate anion. The formation of sodium trifluoroacetate drives the formation of the product which makes our method not an equilibrium one, as in case of acid catalyzed acetalizations. Both these mechanisms seem to explain the fact that electron-poor aldehydes are less efficiently converted to their acetals, as their intermediate hemiacetal is a weaker nucleophile compared with electron-rich hemiacetals. An interesting and seemingly contradictory observation is that a very electron-rich aldehyde **6d** requires very long reaction times for a total conversion. This can be explained by the diminished aldehyde electrophilicity, resulting in a lower equilibrium concentration of the hemiacetal.

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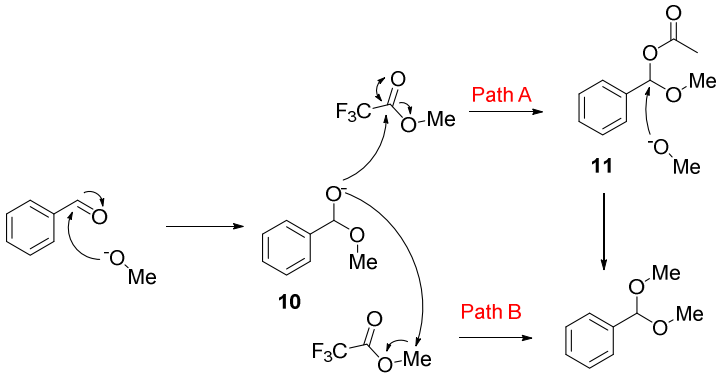

Scheme 2. Possible reaction mechanisms for acetalization of benzaldehyde **4**.

Seeking further evidence in support of the proposed mechanism, we decided to study the kinetic isotope effect for conversion of benzaldehyde (**4a**) to dimethoxy acetal (**5a**) under ^{1}H NMR control. As our reaction conditions involve methanol and a trifluoroacetic acid methyl ester under basic conditions, we were forced to conduct the reaction using methanol-d_4 or and methyl-d_3 trifluoroacetate for its deuterated variant. We studied the reaction kinetics by intermittingly quenching a portion of the reaction mixture by adding it to a known volume of water, extracting the resulting mixture with chloroform-*d* and, after separation, recording the chloroform solution's ^{1}H NMR spectrum. The data fitted to a second order reaction kinetics (Figure 1) revealed a moderate value of kinetic isotope effect (KIE = 2.148), which proves that the intermediate hemiacetal **10** does attack the methyl group of the ester. When we studied the reaction kinetics in methanol-d_3, however, we have found a smaller value of kinetic isotope effect (KIE=1.813), which suggests that the alcohol -OH group plays an important role in stabilizing some of the reaction's transition states.

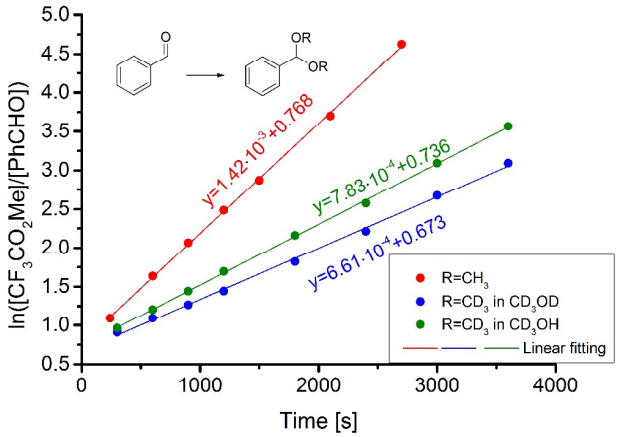

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Figure 1. Benzaldehyde (**4**) conversion at 25 °C fitted to second order kinetic.

In summary, we have developed an efficient yet simple method for acetalization of aldehydes under basic conditions using readily available starting materials. The method's general applicability and good functional group compatibility has been demonstrated in 35 structurally diverse examples (yields up to 99%). Furthermore, we have also determined structural factors necessary for successful acetalization, namely the absence of easily enolizable protons in α position to the carbonyl group or strongly electron-withdrawing functional groups in the aromatic ring. We believe that this methodology will expand the existing methods of acetalization and may find broad application in organic synthesis.

EXPERIMENTAL SECTION

General information All solvents were of reagent grade quality. All reagents were obtained commercially and used without further purification, unless otherwise specified. All reactions were performed under argon atmosphere. Column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh), TLC was carried out on Merck Kieselgel F254 plates. Melting points were determined using a Stanford Research Systems EZ-Melt apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 MHz. Mass spectral analyses were performed with on magnetic sector mass spectrometer *AutoSpec Premier* (*Waters, USA)*, equipped with an electron impact (EI) ion source and the EBE double focusing geometry mass analyzer and on Synapt G2-S HDMS (*Waters Inc*) mass spectrometer equipped with an electrospray ion source and q-TOF type mass analyzer. The instruments were controlled and recorded data were processed using *MassLynx V4.1* software package (*Waters Inc*).

2,7,15-tributoxy-3,6,14-tris(dimethoxymethyl)-9,10-dihydro-9,10-[1,2]benzenoanthracene **2**

A solution of trialdehyde **1** (56 mg, 0.1 mmol) in 1 mL of THF and 1 mL of methanol was cooled to 0 °C. Then, methyl azidoacetate was added (173 mg, 1.5 mmol, 15 eq) along with a solution of sodium methoxide (81 mg, 1.5 mmol, 15 eq) in 1 mL of methanol. The solution was stirred for 24 hours in 0 °C and for the next 24 hours at room temperature. The reaction

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mixture was quenched with a saturated solution of NH_4Cl (5 mL) and extracted with AcOEt (2 x 10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated. The crude product was purified using column chromatography (SiO_2/hexanes:AcOEt, 4:1, v:v) yielding triacetal **2** (20 mg, 0.03 mmol, 30%) as an off-white solid, mp 170-175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (s, 3H), 7.14 (s, 3H), 5.54 (s, 2H), 5.39 (s, 3H), 3.94 (t, J = 6.3 Hz, 6H), 3.20 (s, 18H), 1.72 – 1.61 (m, 6H), 1.48 – 1.35 (m, 6H), 0.91 (t, J = 7.4 Hz, 9H).^{13}C NMR (101 MHz, DMSO-d_6) δ 153.3, 146.4, 138.0, 122.4, 121.3, 109.0, 99.2, 67.9, 53.7, 53.1, 50.2, 30.9, 18.7, 13.6.

HRMS (ESI) calcd for $[C_{41}H_{59}O_9+Na]^+$ 715.3822, found 715.3810. IR (KBr) ν_{max}: 2956, 2933, 2872, 2827.

A General Procedure for the synthesis of acetals: A solution of alkoxide was prepared by dissolving Na (0.46 g, 20 mmol, 2 eq) in anhydrous alcohol (15 mL). To this mixture aldehyde (10 mmol) was added, followed immediately by an appropriate trifluoroacetate ester (20 mmol, 2 eq). The reaction mixture was stirred overnight at room temperature. After confirming the complete conversion of the aldehyde with TLC, alcohol was removed under reduced pressure and to the solid remainings H_2O (50 mL) was added. The aqueous phase was extracted with DCM (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated, yielding an appropriate acetal. The product was not further purified, unless otherwise stated.

*Benzaldehyde dimethyl acetal (**5a**)* Colorless oil (1.29 g, 8.5 mmol, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 – 7.26 (m, 5H), 5.37 (s, 1H), 3.24 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 138.2, 128.3, 128.0, 126.5, 102.7, 52.5. Anal. Calcd. for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.09; H, 8.08.

*Benzaldehyde diethyl acetal (**5b**)* Colorless oil (1.74 g, 9.6 mmol, 96%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 – 7.05 (m, 5H), 5.47 (s, 1H), 3.75 – 3.37 (m, 4H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 139.2, 128.1, 128.0, 126.3, 100.9, 60.7, 15.1 Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.22; H, 9.10.

*Benzaldehyde diisopropyl acetal (**5c**)* Purified using column chromatography (SiO_2/hexanes:AcOEt, 9:1, v:v). Colorless oil (0.10 g, 2.9 mmol, 29%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 – 7.26 (m, 5H), 5.54 (s, 1H), 3.83 (sept, *J* = 6.1 Hz, 2H), 1.12 (d, *J* = 6.2 Hz,

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6H), 1.09 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 140.7, 128.0, 127.9, 126.4, 98.6, 67.4, 22.9, 22.3.

*Benzaldehyde dibenzyl acetal (**5d**)* Colorless oil (2.5 g, 8.2 mmol, 82%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.53 – 7.48 (m, 2H), 7.45 – 7.23 (m, 13H), 5.77 (s, 1H), 4.59 (s, 4H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 138.4, 138.0, 128.5, 128.24, 128.22, 127.5, 127.4, 126.5, 100.7, 67.1. Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 83.04; H, 6.59.

*Benzaldehyde diallyl acetal (**5e**)* Purified using column chromatography (SiO_2/hexanes:AcOEt, 9:1, v:v). Colorless oil (1.33 g, 6.5 mmol, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 – 7.32 (m, 5H), 5.99 – 5.86 (m, 2H), 5.59 (s, 1H), 5.28 (dq, *J* = 17.2, 1.8 Hz, 2H), 5.14 (dq, *J* = 10.4, 1.4 Hz, 2H), 4.03 (dt, *J* = 5.2, 1.3 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) 138.6, 134.8, 128.4, 128.1, 126.4, 116.3, 100.4, 66.1 Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.50; H, 7.89.

Benzaldehyde dimethyl acetal-d_6 (***5f**)* Colorless oil (1.14 g, 7.2mmol, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 – 7.30 (m, 5H), 5.37 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 138.2, 128.2, 128.0, 126.4, 102.5, 51.5 (sep, J = 21.7 Hz). HRMS(ESI/Q-TOF) m/z $[M]^+$ Calcd for $C_9H_6D_6O_2$ 158.1214; Found 158.1216.

*2-Chlorobenzaldehyde dimethyl acetal (**7a**)* Colorless oil (1.73 g, 9.3 mmol, 93%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 – 7.52 (m, 1H), 7.49 – 7.43 (m, J = 5.5, 3.1 Hz, 1H), 7.42 – 7.34 (m, 2H), 5.55 (s, 1H), 3.29 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 135.2, 132.1, 130.2, 129.4, 128.0, 126.9, 100.5, 53.5. Anal. Calcd for $C_9H_{11}ClO_2$: C, 57.92; H, 5.94; Cl, 18.99. Found: C, 57.69; H, 6.02; Cl, 18.91.

*2-Methoxybenzaldehyde dimethyl acetal (**7b**)* Colorless oil (1.71 g, 9.4 mmol, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (dd, J = 7.5, 1.8 Hz, 1H), 7.32 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H), 7.01 (dd, J = 8.3, 0.8 Hz, 1H), 6.95 (td, J = 7.4, 0.7 Hz, 1H), 5.54 (s, 1H), 3.79 (s, 3H), 3.24 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.7, 129.5, 126.8, 125.9, 119.8, 111.1, 98.6, 55.4, 53.2. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.94; H, 7.68.

*2-Hydroxybenzaldehyde dimethyl acetal (**7c**)* Purified by dissolving in DCM and filtering through a layer of silica gel. Yellow, deliquescent solid (1.37 g, 8.1 mmol, 81%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 1H), 7.29 (dd, J = 7.6, 1.5 Hz, 1H), 7.23 – 7.00 (m, 1H), 6.93 – 6.63 (m, 2H), 5.53 (s, 1H), 3.25 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.9, 129.2,

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127.0, 124.1, 118.4, 115.4, 99.2, 53.2. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H 7.19. Found: C, 64.54; H, 7.17.

*N,N-diethyl-4-aminobenzaldehyde dimethyl acetal (**7d**)* Yellow oil (1.95 g, 8.7 mmol, 87%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.9 Hz, 2H), 5.22 (s, 1H), 3.32 (q, J = 7.0 Hz, 4H), 3.19 (s, 6H), 1.08 (t, J = 7.0 Hz, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 147.3, 127.5, 124.4, 110.7, 103.1, 52.1, 43.6, 12.4. HRMS(ESI/Q-TOF) m/z $[M+H]^+$ Calcd for $C_{13}H_{22}NO_2$ 224.1651; Found 224.1646. Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.03; H, 9.48; N, 6.22. IR (CH_2Cl_2, thin film) ν_{max}: 2971, 2933, 2896, 2826,

*4-Methoxybenzaldehyde dimethyl acetal (**7e**) C*olorless oil (1.79 g, 9.8 mmol, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 – 7.25 (m, 2H), 6.95 – 6.89 (m, 2H), 5.31 (s, 1H), 3.75 (s, 3H), 3.21 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.2, 130.3, 127.7, 113.4, 102.5, 55.0, 52.3.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.74; H, 7.68.

*Terepthalaldehyde bis-dimethyl acetal (**7f**)* Recrystallization from methanol. Colorless needles (1.76 g, 7.8 mmol, 78%), mp 53-54 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (s, 4H), 5.39 (s, 2H), 3.24 (s, 12H).^{13}C NMR (101 MHz, DMSO-d_6) δ 138.3, 126.3, 102.4, 52.5. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.72; H, 8.11.

*4-(Trifluoromethyl)benzaldehyde dimethyl acetal (**7g**)* Purified by column chromatography (hexanes:AcOEt, 9:1, v:v). Colorless oil. (0.47 g, 2.2 mmol, 22%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 5.48 (s, 1H), 3.27 (s, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 142.7 (d, J = 1.1 Hz), 128.9 (q, J = 31.8 Hz), 127.4, 125.0 (q, J = 3.9 Hz), 124.1 (q, J = 272.1 Hz), 101.7, 52.7. Anal. Calcd for $C_{10}H_{11}F_3O_2$: C, 54.55; H, 5.04; F, 25.88. Found: C, 54.32; H, 5.09; F, 25.83.

*4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzaldehyde dimethyl acetal (**7h**)* Off-white solid (1.15 g, 4.1 mmol, 41%), mp 63-65 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 5.40 (s, 1H), 3.23 (s, 6H), 1.29 (s, 12H).^{13}C NMR (101 MHz, DMSO-d_6) δ 141.2, 134.2, 125.9, 102.3, 83.6, 52.4, 24.6. HRMS(ESI/Q-TOF) m/z $[M+Na]^+$ Calcd for $C_{15}H_{24}BO_4Na$ 301.1587; Found 359.1581.

*3-Ethynylbenzaldehyde dimethyl acetal (**7i**)* Yellow oil (1.55 g, 8.8 mmol, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) 7.53 – 7.47 (m, 2H), 7.43 (td, J = 7.5, 1.3 Hz, 1H), 7.37 (td, J = 7.5, 1.4 Hz, 1H), 5.59 (s, 1H), 4.40 (s, 1H), 3.29 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 139.9, 132.5, 128.62,

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128.55, 126.1, 120.6, 101.71, 85.1, 80.8, 53.7. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.76; H, 6.80.

*3-Diazophenylbenzaldehyde dimethyl acetal (**7j**)* Red oil (2.55 g, 9.9 mmol, 99%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.86 (m, 4H), 7.66 – 7.54 (m, 5H), 5.52 (s, 1H), 3.30 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 151.9, 151.8, 139.8, 131.6, 129.5, 129.44, 129.36, 123.3, 122.5, 119.7, 102.1, 52.7. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.10; H, 6.31; N, 10.96. IR (CH_2Cl_2, thin film) ν_{max}: 3062, 2991, 2935, 2829.

*3-(Diphenylphosphine)benzaldehyde dimethyl acetal (**7k**)* Purified by dissolving in DCM and filtering through a layer of silica gel. Yellow solid (2.62 g, 7.8mmol, 78%), mp 82-85 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 – 7.56 (m, 1H), 7.45 – 7.27 (m, 8H), 7.24 – 7.14 (m, 4H), 6.95 – 6.88 (m, 1H), 5.89 (d, J = 5.3 Hz, 1H), 3.06 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 142.6 (d, J = 22.6 Hz), 136.5 (d, J = 10.3 Hz), 135.1 (d, J = 18.7 Hz), 133.6, 133.3 (d, J = 19.8 Hz), 128.8, 128.7, 128.57, 128.55, 128.48, 126.18 (d, J = 5.9 Hz), 101.32 (d, J = 22.4 Hz), 53.02 HRMS(ESI/Q-TOF) m/z $[M+Na]^+$ Calcd for $C_{21}H_{21}O_2PNa$ 359.1177; Found 359.1164. IR (CH_2Cl_2, thin film) ν_{max}: 3054, 2987, 2930, 2826.

*3-Cyanobenzaldehyde dimethyl acetal (**7l**)* Yellow oil (1.76 g, 9.9 mmol, 99%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J = 8.5 Hz, 1H), 7.78 (s, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 5.45 (s, 1H), 3.27 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 139.8, 132.2, 131.4, 130.1, 129.5, 118.6, 111.3, 101.5, 52.8. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.43; H, 6.26; N, 7.87.

*3-Nitrobenzaldehyde dimethyl acetal (**7m**)* Purified by column chromatography (hexanes: AcOEt, 4:1, v:v). Yellow oil (1.17 g, 5.9 mmol, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 – 8.20 (m, 1H), 8.20 – 8.17 (m, 1H), 7.86 – 7.80 (m, 1H), 7.70 (t, J = 7.9 Hz, 1H), 5.55 (s, 1H), 3.30 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.7, 140.4, 133.2, 129.9, 123.3, 121.1, 101.3, 52.9. Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found C, 54.72; H, 5.54; N, 6.96.

*1-Naphthaldehyde dimethyl acetal (**7n**)* Colorless oil (1.93 g, 9.6 mmol, 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 – 8.17 (m, 1H), 8.03 – 7.82 (m, 2H), 7.65 (d, J = 6.7 Hz, 1H), 7.61 – 7.44 (m, 3H), 5.91 (s, 1H), 3.31 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 133.4, 133.2, 130.2, 128.9, 128.3, 126.0, 125.7, 124.8, 124.6, 124.3, 102.3, 53.2. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.98; H, 6.90.

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*9-Anthracenecarboxyaldehyde dimethyl acetal (**7o**)* Recrystallization from methanol. Colorless needles (1.76 g, 7.0 mmol, 70%), mp 136-139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 – 8.69 (m, 2H), 8.62 (s, 1H), 8.14 – 8.02 (m, 2H), 7.59 – 7.43 (m, 4H), 6.63 (s, 1H), 3.46 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 130.9, 129.5, 129.2, 128.7, 128.5, 125.7, 125.2, 125.0, 103.3, 55.5. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.77; H, 6.33.

*2-Benzyloxybenzaldehyde dimethyl acetal (**7p**)* Colorless oil (2.24 g, 8.7 mmol, 87%).^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 – 7.44 (m, 2H), 7.43 – 7.37 (m, 3H), 7.35 – 7.26 (m, 2H), 7.10 (d, J = 7.6 Hz, 1H), 7.00 – 6.92 (m, 1H), 5.61 (s, 1H), 5.15 (s, 2H), 3.25 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.7, 137.2, 129.6, 128.4, 127.7, 127.2, 126.9, 126.4, 120.1, 112.6, 98.8, 69.3, 53.3. HRMS(ESI/Q-TOF) m/z $[M+Na]^+$ Calcd for $C_{16}H_{18}O_3Na$ 281.1154; Found 281.1153. Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.36; H, 7.12. IR (CH_2Cl_2, thin film) ν_{max}: 3064, 3034, 2987, 2933, 2906, 2827.

*2-(Methoxymethoxy)-benzaldehyde dimethyl acetal (**7r**)* Yellow oil (1.66 g, 7.8 mmol, 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (dd, J = 7.6, 1.7 Hz, 1H), 7.29 (ddd, J = 8.5, 7.4, 1.8 Hz, 1H), 7.12 – 7.07 (m, 1H), 7.00 (td, J = 7.4, 0.6 Hz, 1H), 5.58 (s, 1H), 5.22 (s, 2H), 3.39 (s, 3H), 3.26 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.1, 129.5, 127.0, 127.0, 121.0, 114.4, 98.7, 93.9, 55.6 53.3. HRMS(ESI/Q-TOF) m/z $[M+Na]^+$ Calcd for $C_{11}H_{16}O_4Na$ 235.0946; Found 235.0944 Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.34; H, 7.60. Found: C, 62.34; H, 7.63. IR (CH_2Cl_2, thin film) ν_{max}: 2988, 2934, 2905, 2828.

*NH-Boc-3-aminobenzaldehyde dimethyl acetal (**7s**)* Yellow solid (2.60 g, 9.7 mmol, 97%) mp 70-73°C ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 7.58 (s, 1H), 7.41 – 7.31 (m, 1H), 7.23 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 5.30 (s, 1H), 3.23 (s, 6H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.7, 139.4, 138.7, 128.2, 120.2, 118.1, 116.3, 102.7, 79.0, 52.4, 28.1.
HRMS(ESI/Q-TOF) m/z $[M+Na]^+$ Calcd for $C_{14}H_{21}NO_4Na$ 290.1368; Found 290.1365 Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found C, 63.12; H, 8.00; N, 5.11. IR (CH_2Cl_2, thin film) ν_{max}: 3324, 2978, 2934, 2830, 1730, 1705.

*NH-Cbz-3-aminobenzaldehyde dimethyl acetal (**7t**)* Purified by column chromatography (SiO_2/DCM). Colorless oil (1.43g, 4.8 mmol, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 1H), 7.57 (s, 1H), 7.46 – 7.18 (m, 7H), 7.01 (d, J = 7.6 Hz, 1H), 5.32 (s, 1H), 5.15 (s, 2H), 3.22 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.4, 139.0, 138.9, 136.7, 128.52, 128.47 (2C), 128.08, 128.05, 126.4, 120.7, 102.5, 65.7, 52.5. HRMS(ESI/Q-TOF) m/z $[M+Na]^+$ Calcd for

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$C_{17}H_{19}NO_4Na$ 324.1212; Found 324.1208. IR (KBr) ν_{max}: 3313, 3064, 3033, 2939, 2830, 1735, 1710.

*N-Phth-3-aminobenzaldehyde dimethyl acetal (**7u**)* Light yellow solid (1.24 g, 4.2mmol, 42%) mp 70-74 ℃ ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 – 7.93 (m, 2H), 7.93 – 7.87 (m, 2H), 7.55 (t, J = 7.7 Hz, 1H), 7.49 (s, 1H), 7.48 – 7.40 (m, 2H), 5.46 (s, 1H), 3.29 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.9, 139.1, 134.6, 131.8, 131.5, 128.6, 127.2, 126.1, 125.4, 123.3, 102.1, 52.6. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 62.90; H, 5.09; N, 4.71. Found: C, 68.63; H, 4.98; N, 4.66. IR (CH_2Cl_2, thin film) ν_{max}: 3063, 2991, 2938, 2905, 2831, 1726.

*Thiophene-2-carboxyaldehyde dimethyl acetal (**9a**)* Yellow oil (1.42 g, 9.0 mmol, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.11 – 7.05 (m, 1H), 7.05 – 7.01 (m, *J* = 5.0, 3.5 Hz, 1H), 5.63 (s, 1H), 3.27 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 141.5, 126.7, 126.1, 125.5, 99.6, 52.4. Anal. Calcd for $C_7H_{10}O_2S$: C, 53.14; H, 6.37; S, 20.26. Found C, 53.24; H, 6.17; S, 20.04.

*Pyrrole-2-carboxyaldehyde dimethyl acetal (**9b**)*[20] Yellow oil (1.35g, 9.6 mmol, 96%). Product unstable at room temperature and sensitive to moisture. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 6.72 – 6.60 (m, 1H), 6.02 – 5.98 (m, 1H), 5.98 – 5.93 (m, 1H), 5.38 (s, 1H), 3.21 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 128.3, 117.7, 107.0, 106.3, 98.7, 52.1. HRMS(ESI/Q-TOF) m/z $[M+Na]^+$ Calcd for $C_7H_{11}NO_2Na$ 164.0687; Found 164.0685.

*2-Furaldehyde dimethyl acetal (**9c**)*[21] Purified by vacuum distillation. Colorless oil (0.88 g, 6.2 mmol, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (dd, J = 1.7, 0.9 Hz, 1H), 6.47 – 6.44 (m, J = 3.2, 1.8 Hz, 1H), 6.44 – 6.41 (m, J = 3.3, 0.8 Hz, 1H), 5.43 (s, 1H), 3.24 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.8, 142.8, 110.1, 108.3, 97.4, 52.5. Anal. Calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.09. Found C, 58.98; H, 6.88.

*Pyridine-2-carboxyaldehyde dimethyl acetal (**9d**)* Purified by column chromatography (SiO_2/DCM: MeOH, 98:2, v:v) Yellow oil (0.60 g, 3.9 mmol, 39%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.83 (td, J = 7.7, 1.8 Hz, 1H), 7.48 (dt, J = 7.9, 0.9 Hz, 1H), 7.37 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 5.27 (s, 1H), 3.30 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.0, 148.7, 136.7, 123.7, 120.7, 104.0, 53.4. HRMS(ESI/Q-TOF) m/z $[M+Na]^+$ Calcd for $C_8H_{11}NO_2Na$ 176.0687, found 176.0686

*Ferrocene 2-carboxyaldehyde dimethyl acetal (**9e**)* Dark brown solid (2.32 g, 8.9 mmol, 89%) mp 115-118 ℃ (decomposition) ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.38 (s, 1H), 4.26 (t, J = 1.8

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Hz, 2H), 4.16 (d, J = 3.6 Hz, 5H), 4.15 – 4.14 (m, 2H), 3.20 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 101.6, 85.0, 68.6, 67.5, 66.8, 51.9.

*E-Cinnamaldehyde dimethyl acetal (**9f**)* Yellow oil (1.74 g, 9.8 mmol, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 – 7.45 (m, 2H), 7.38 – 7.31 (m, 2H), 7.30 – 7.25 (m, 1H), 6.70 (d, J = 16.2 Hz, 1H), 6.23 (dd, J = 16.2, 5.1 Hz, 1H), 4.94 (dd, J = 5.2, 1.1 Hz, 1H), 3.28 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 135.8, 132.6, 128.6, 128.0, 126.6, 126.1, 102.5, 52.3. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found C, 74.16; H, 7.91.

*(1R)-(−)-Myrtenal dimethyl acetal (**9g**)* Yellow oil (1.79 g, 9.1 mmol, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.59 (d, J = 1.1 Hz, 1H), 4.49 (d, J = 0.5 Hz, 1H), 3.19 (s, 3H), 3.17 (s, 3H), 2.40 – 2.16 (m, 4H), 2.12 – 2.01 (m, 1H), 1.26 (s, 3H), 1.07 (t, J = 11.2 Hz, 1H), 0.79 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 144.8, 120.9, 104.4, 53.2, 52.7, 40.9, 40.3, 37.2, 31.1, 30.7, 25.9, 21.1. Anal. Calcd for $C_{12}H_{20}O_2$: C: 73.43; H: 10.27. Found C: 73.33; H: 10.46.

*Cyclohexanecarboxyaldehyde dimethyl acetal (**9h**)* Yellow oil (1.07 g, 6.8 mmol, 68%) ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.97 (d, *J* = 6.9 Hz, 1H), 3.23 (s, 6H), 1.72 – 1.62 (m, 4H), 1.63 – 1.55 (m, 1H), 1.55 – 1.39 (m, 1H), 1.25 – 1.01 (m, 3H), 1.01 – 0.84 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) 107.7, 53.2, 39.6, 27.4, 25.9, 25.2.

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Notes

The authors declare no competing financial interests.

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20. This compound is sensitive to moisture and unstable at room temperature
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