Supporting Information

# Orthoester Exchange: a Tripodal Tool for Dynamic Covalent and Systems Chemistry

René-Chris Brachvogel and Max von Delius*

Department of Chemistry and Pharmacy, University of Erlangen-Nürnberg,

Henkestr. 42, 91054 Erlangen, Germany.

* Fax: +49 9131 85 26864; Tel: +49 9131 85 22946; E-mail: max.vondelius@fau.de

## Contents

## General experimental section

### Reagents and instruments

All commercially purchased reagents were used without further purification. Molecular sieves were dried for 3 days at 200 °C under reduced pressure (8.0 x $10^{-3}$ mbar) before use. $CDCl_3$, DMSO-$d_6$, MeCN-$d_3$ and benzene-$d_6$ were stored over 4Å molecular sieves. Methanol and ethanol were stored over 3Å molecular sieves. NMR spectra were recorded on a Bruker Avance 400 ($^1$H: 400 MHz) spectrometer at 298 K. NMR spectra were referenced to the residual solvent peak ($^1$H: $CDCl_3$, 7.24 ppm). Chemical shifts (δ) are denoted in ppm. GC-FID analysis was performed on a Thermo Quest CE Instrument Trace GC 2000 Series (column: Optima-5 0.25µm; temperature gradient: 50 °C (5min) → 200 °C (over 15 min) → 200°C (5 min)). HPLC-MS analysis was performed on a Shimadzu LCMS 2020 instrument (column: Kinetex C18, 2.6 µm, 100 x 4.6 mm; mobile phase: $H_2O$/MeOH 80% → 100 % MeOH; flow rate: 0.3 mL/min).

### Preparation of stock solutions

To achieve a high level of stoichiometric accuracy, all substrates and reagents were added from stock solutions. In a typical example, orthoester (750 µmol, 1.0 equiv.) and alcohol (2.25 mmol, 3.0 equiv.) were combined and $CDCl_3$ was added to obtain a total volume of 2.0 mL. From this stock solution 100 µL were added to the reaction vessel. To obtain the acid stock solution, trifluoroacetic acid (375 µmol, 28.7 µL) was topped up with $CDCl_3$ to obtain a total volume of 1 mL). Of this solution, 100 µL were topped up with $CDCl_3$ to obtain a total volume of 1 mL. Of this stock solution, 10 µL were added to the reaction vessel.

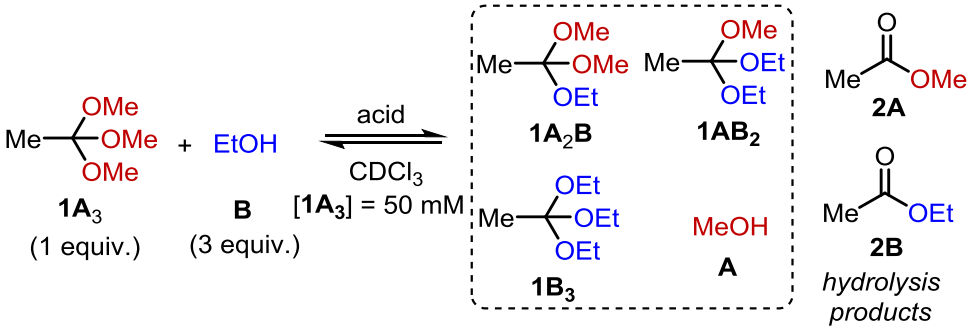
### Exclusion of atmospheric moisture

All solvents were dried over molecular sieves for at least 24 hours. Most reactions were performed in oven-dried, screw-capped NMR tubes, while some reactions were performed in oven-dried, screw-capped scintillation vials. All reactions were carried out under a “non-rigorous” nitrogen atmosphere (no degassing of the reaction solution). Performing the reactions under air also led to acceptable results, but due to the hygroscopic nature of the acid catalysts, the use of sealed/screw-capped reaction vessels was found to be beneficial.

**Note**: these measures are only necessary during the exchange process (when acid catalyst is present). After the acid is quenched, orthoesters can be surprisingly stable, see corresponding paragraph in the manuscript.

**Investigation of acid catalysts**

Reaction scheme:




General procedure: trimethylorthoacetate (**1A**$_3$, 37.5 µmol, 1.0 equiv.), ethanol (112.5 µmol, 3.0 equiv.) and acid catalyst (0.1 to 5 mol%) were added to the reaction vessel from stock solutions, and $CDCl_3$ was added to obtain a total volume of 750 µL. The reaction solution was left standing at room temperature and the reaction progress was monitored regularly by $^1$H NMR spectroscopy.

$^1$H NMR spectra (400 MHz, $CDCl_3$, 298 K):

Table 1, entry 1: **1% PhCOOH**, 24h:

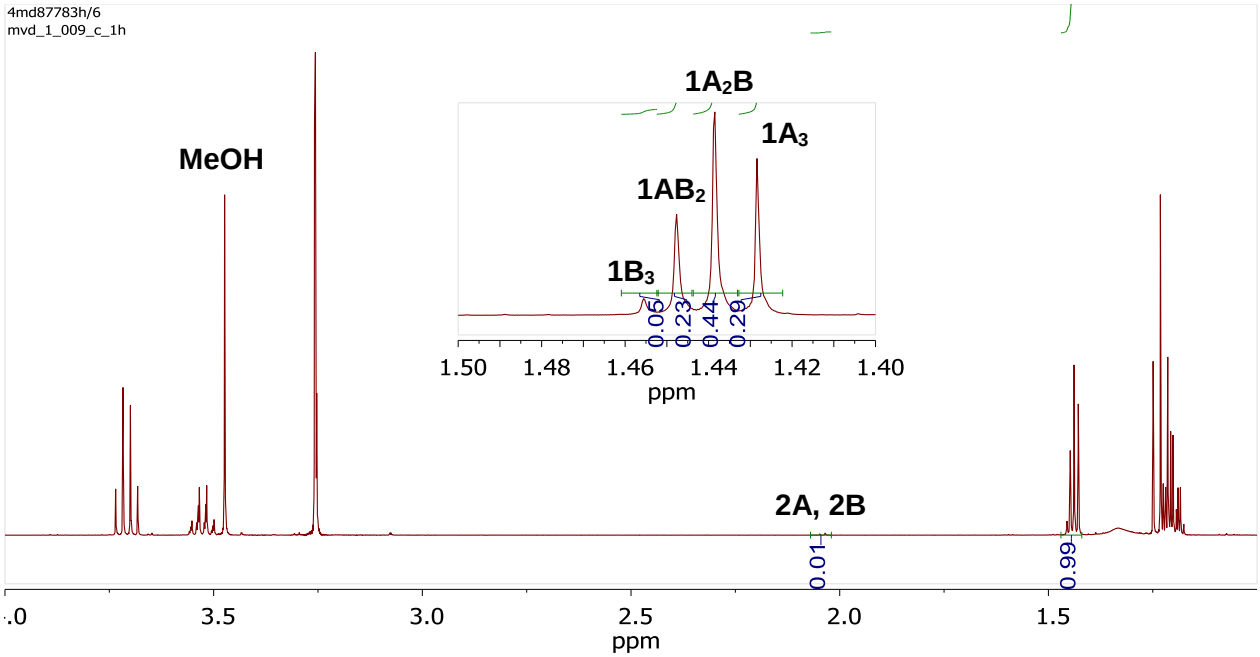


Table 1, entry 2: **1% TFA**, 1h:

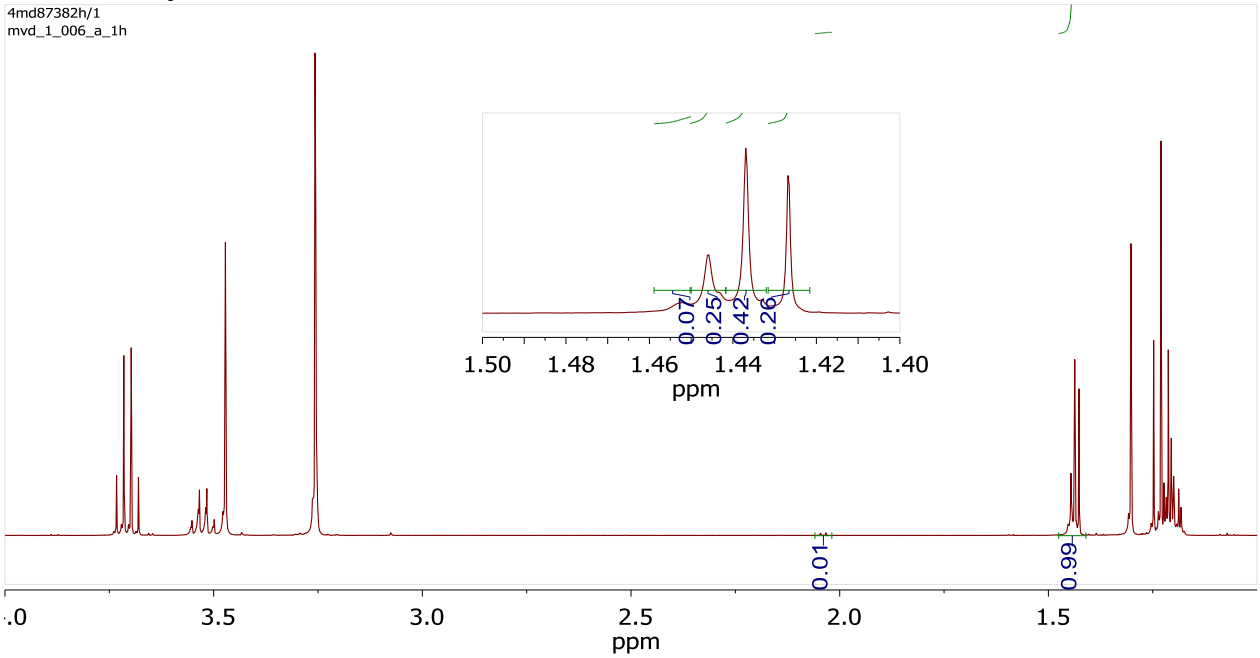



Table 1, entry 3: **0.1% TFA**, 1h:

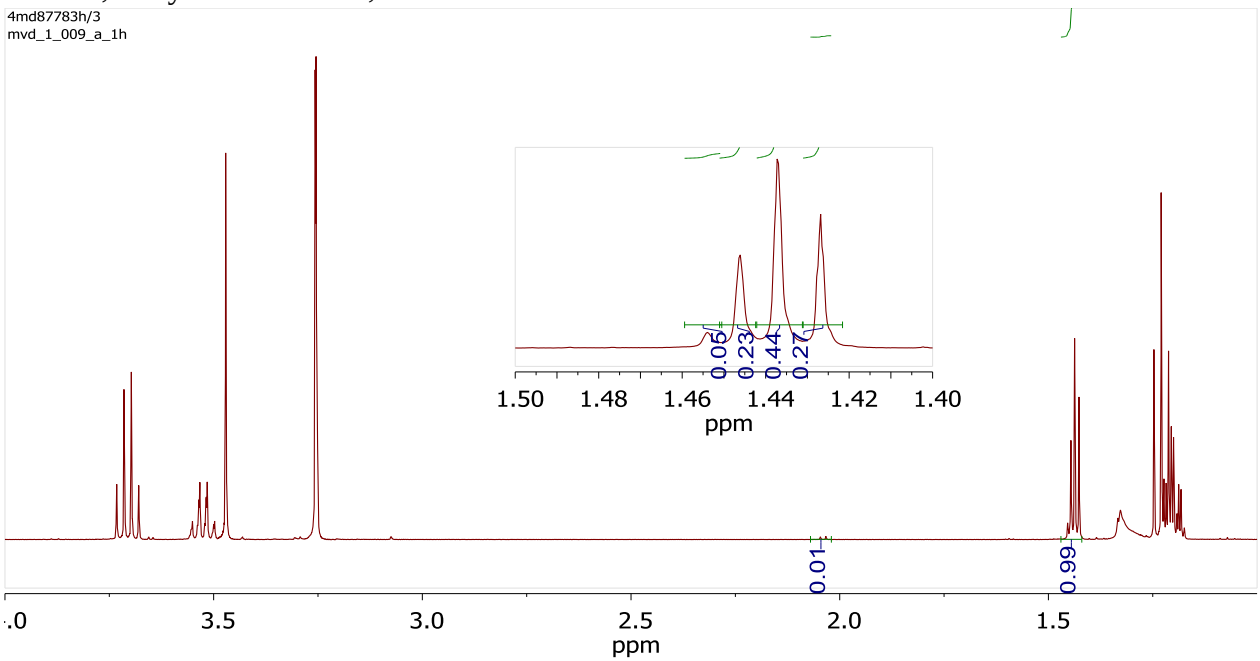


Table 1, entry 4: **1% MsOH**, 1h:

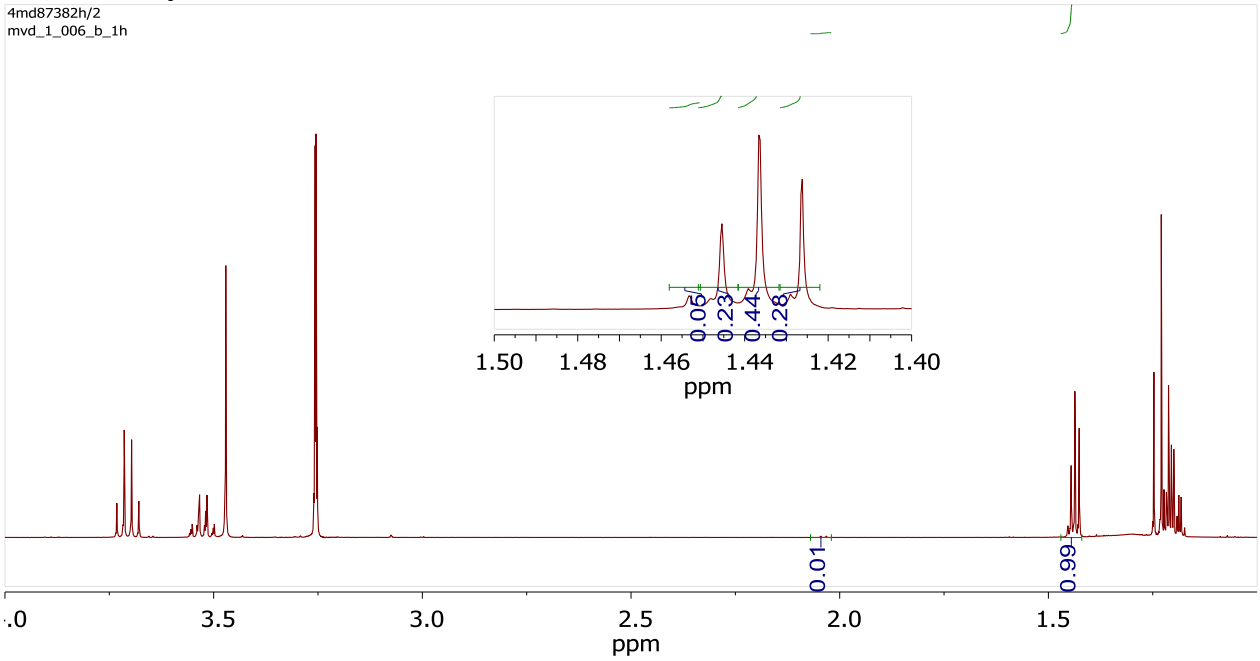



Table 1, entry 5: **1% TfOH**, 1h:

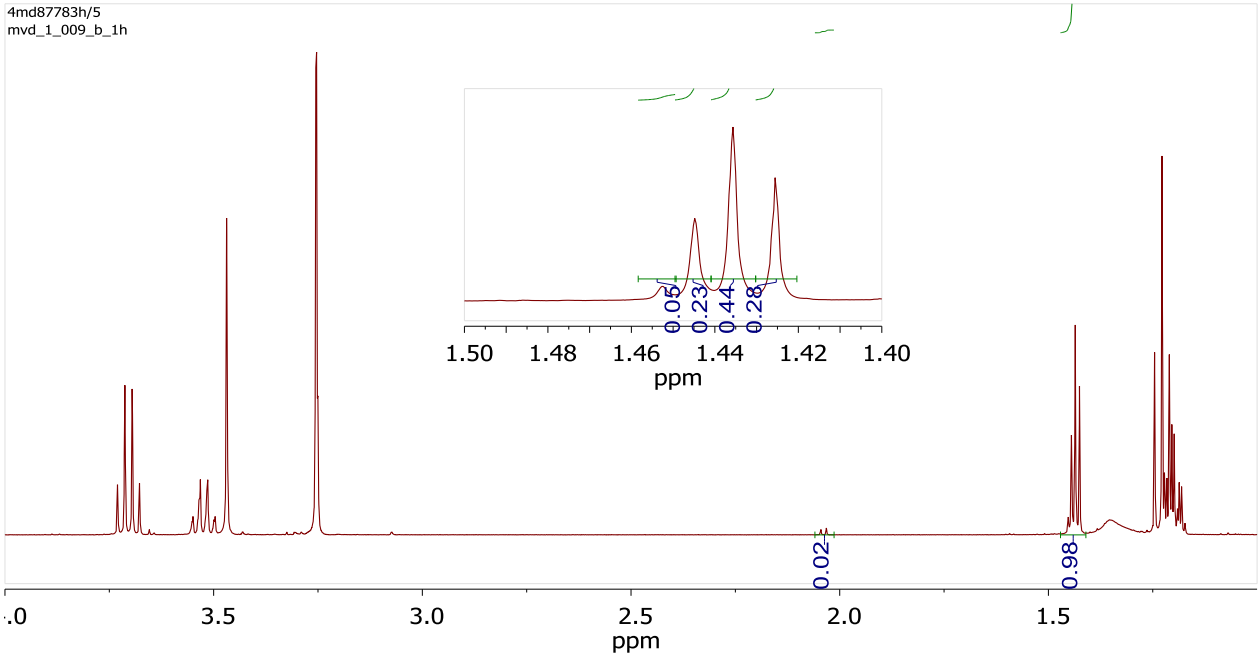
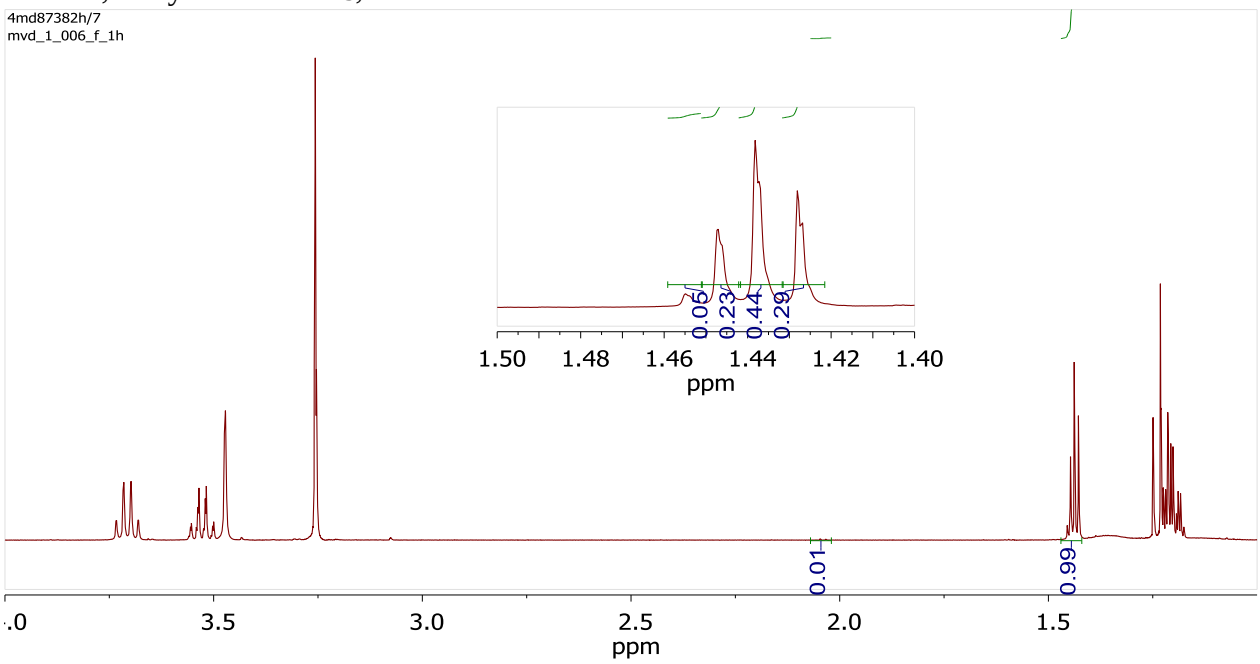
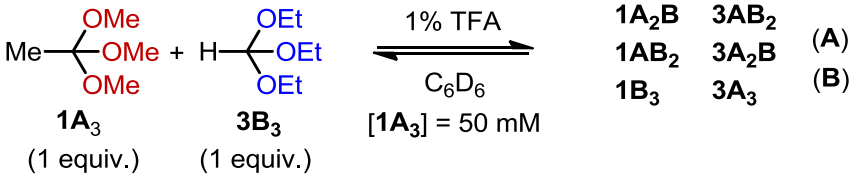


Table 1, entry 6: **1% $AlCl_3$**, 1h:



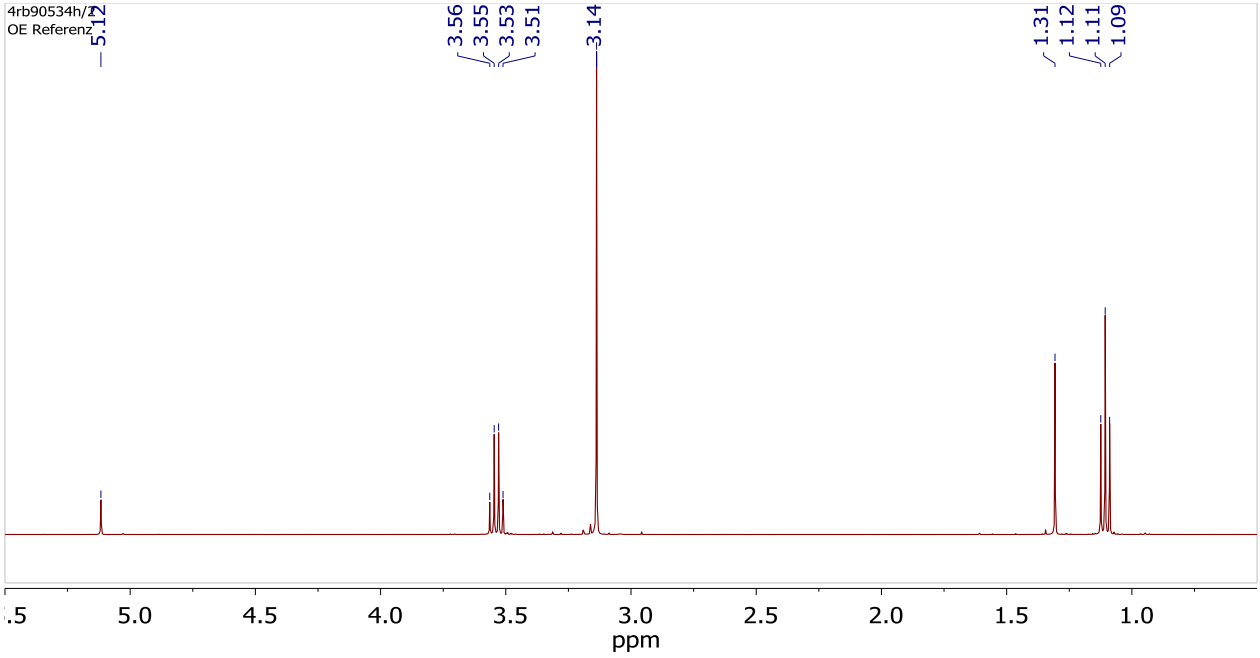
## Reversibility of equilibration

Reaction scheme:

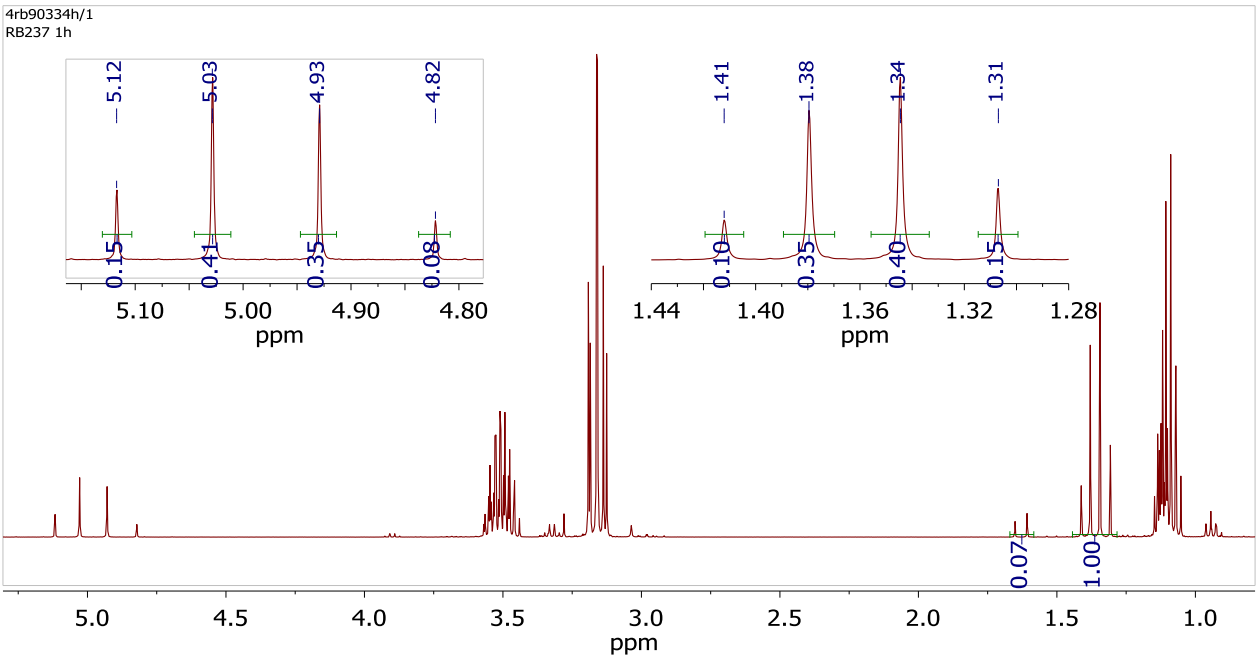



Reaction conditions: trimethyl orthoacetate (37.5 µmol, 1.0 equiv.), triethyl orthoformate (37.5 µmol, 1.0 equiv.) and TFA catalyst (1 mol%) were added to the reaction vessel from stock solutions and $C_6D_6$ was added to obtain a total volume of 750 µL. The reaction solution was left standing at room temperature and the reaction progress was monitored regularly by $^1$H NMR spectroscopy.

$^1$H NMR spectrum (400 MHz, 298 K) of pristine **1A$_3$** and **3B$_3$** in benzene-$d_6$:

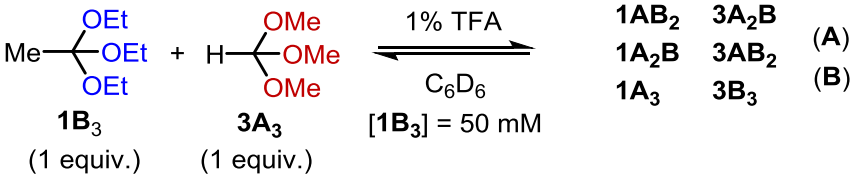


$^1$H NMR spectrum (400 MHz, 298 K), exchange between **1A$_3$** and **3B$_3$** after 1h in benzene-d$_6$:



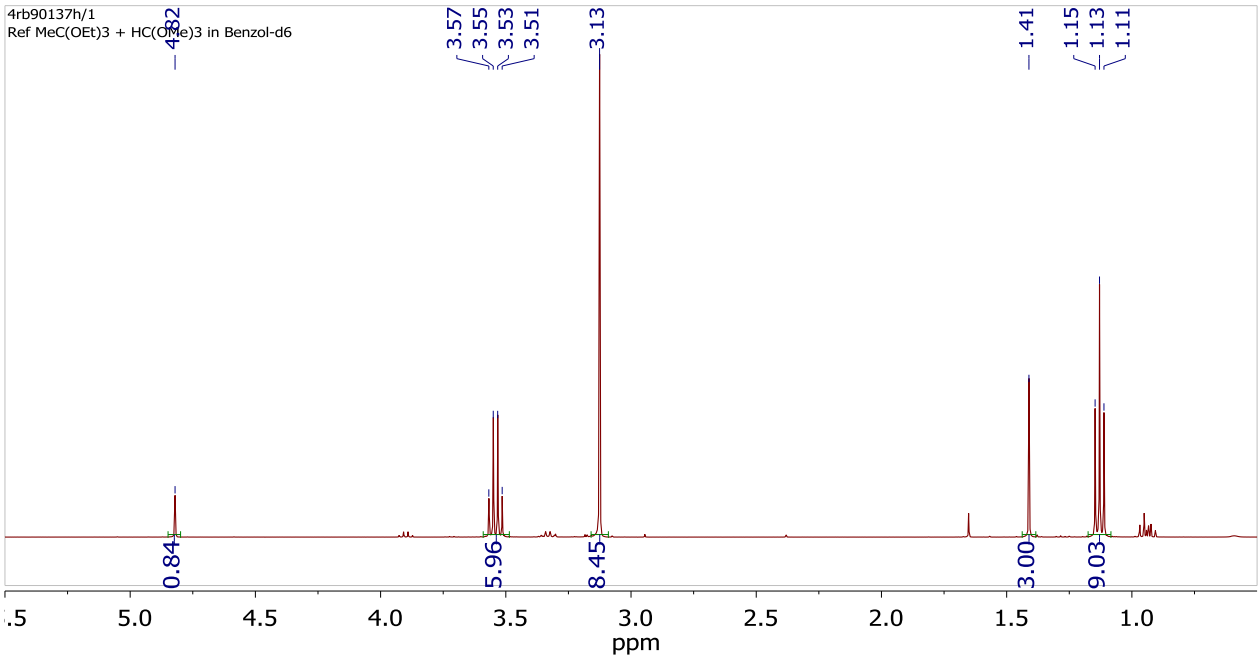

The same exchange experiment was carried out in the opposite direction (i.e. starting from **1B$_3$** and **3A$_3$**) to show that near-identical product distributions are obtained:

Reaction scheme:

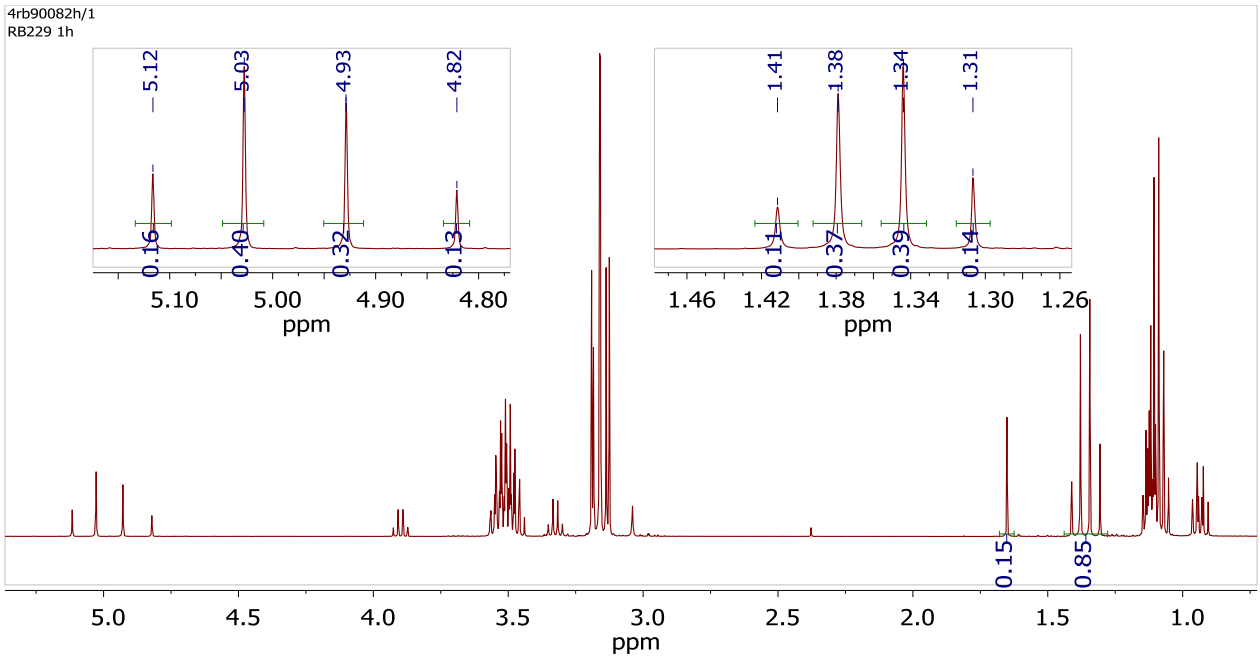



Reaction conditions: triethylorthoacetate (37.5 µmol, 1.0 equiv.), trimethylorthoformate (37.5 µmol, 1.0 equiv.) and TFA catalyst (1 mol%) were added to the reaction vessel from stock solutions and $C_6D_6$ was added to obtain a total volume of 750 µL. The reaction solution was left standing at room temperature and the reaction progress was monitored regularly by $^1$H NMR spectroscopy.

$^{1}$H NMR spectrum (400 MHz, 298 K) of <u>pristine</u> **1B$_3$** and **3A$_3$** in benzene-d$_6$:



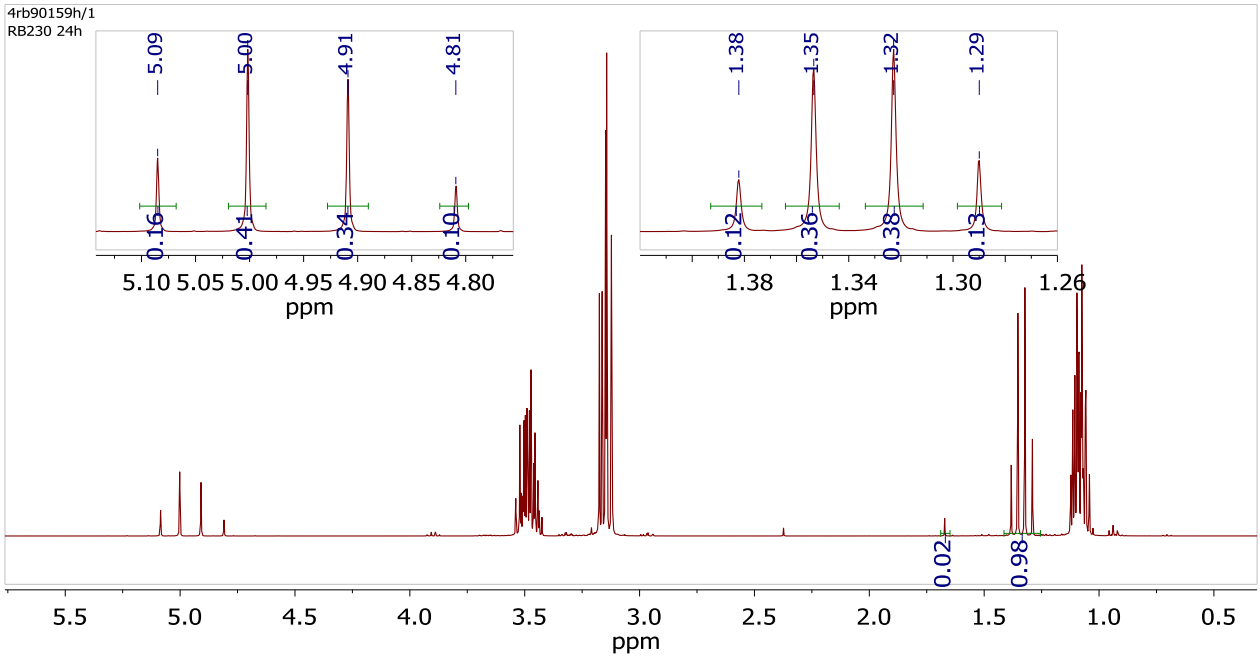

$^{1}$H NMR spectrum (400 MHz, 298 K), exchange between **1B$_3$** and **3A$_3$** after 1h in benzene-d$_6$:



Notes on this type of experiment (exchange between two orthoesters):

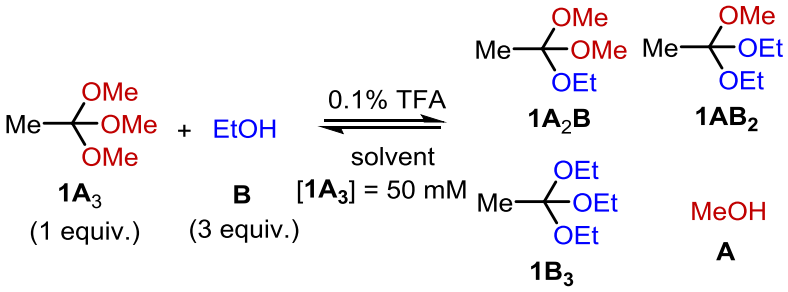
- Our experiments indicate that the concentration of free alcohols (here: **A** and **B**) is the kinetic "bottleneck" of this type of exchange reaction.
- We found that a small amount of residual moisture, which generates alcohols **A** and **B** via hydrolysis, dramatically increases the rate of equilibration. In the absence of any moisture, the reaction generally is too slow to reach equilibrium within a week (with 1% TFA catalyst and at 50 mM concentration).
- High concentration and addition of larger amounts of acid catalyst (e.g. 10%) serve to increase the rate of reaction even in very dry solvent.
- Benzene was found to be a particularly good solvent for this type of reaction. The reaction could also be carried out in dry benzene or in chloroform, but larger quantities of acid catalyst or higher concentrations were generally required for full equilibration. For one example at higher concentration, see below.

$^1$H NMR spectrum (400 MHz, 298 K), exchange between **1A$_3$** and **3B$_3$** after 24h in benzene-d$_6$ (concentration 0.5 M):



## Investigation of solvents

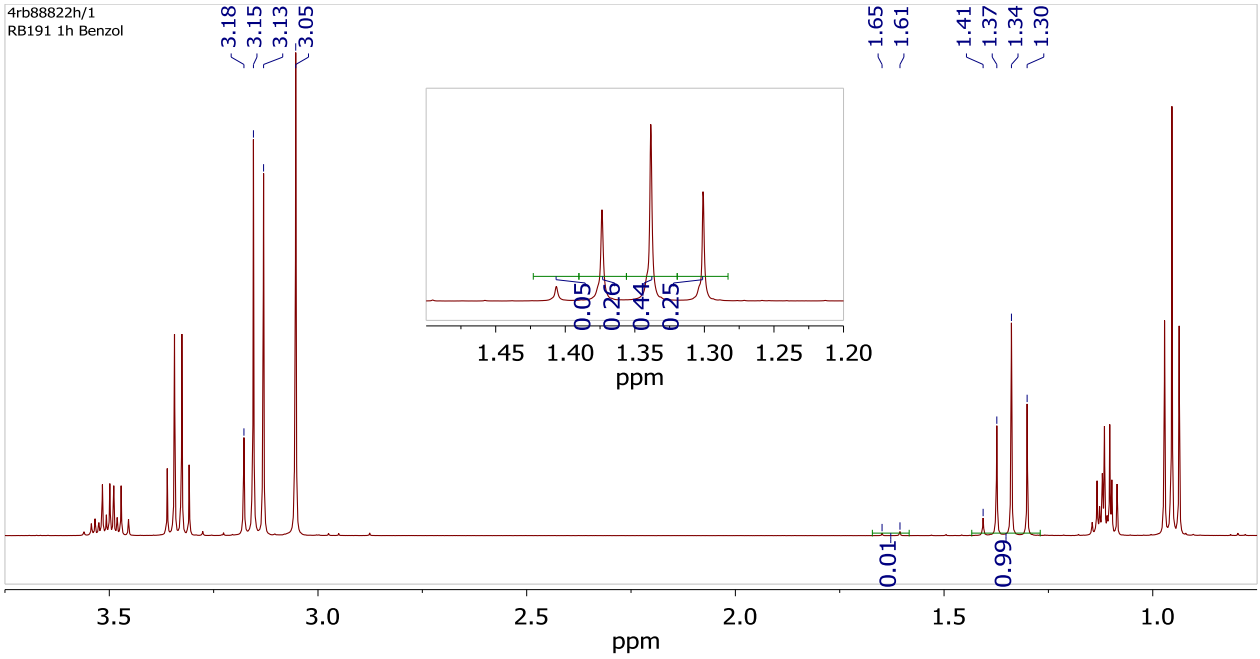
Reaction scheme:



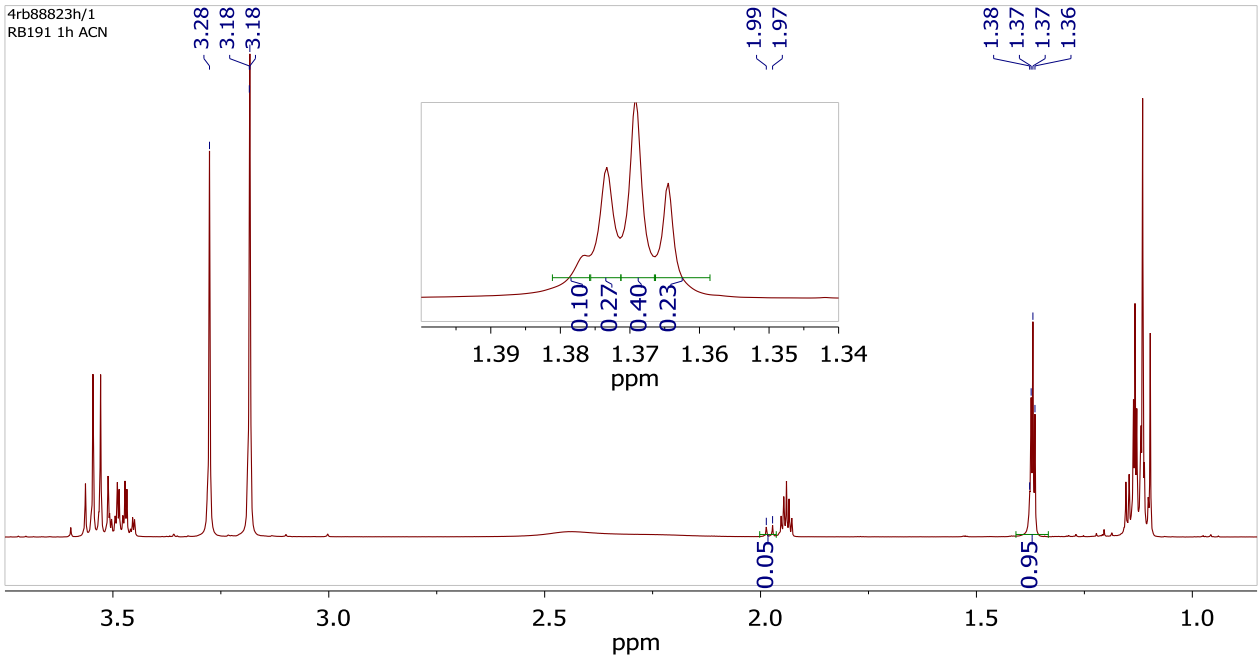

General procedure: trimethylorthoacetate (37.5 µmol, 1.0 equiv.), ethanol (112.5 µmol, 3.0 equiv.) and TFA catalyst (0.1 mol%) were added to the reaction vessel from stock solutions and deuterated solvent was added to obtain a total volume of 750 µL. The reaction solution was left standing at room temperature and the reaction progress was monitored regularly by $^{1}$H NMR spectroscopy.

$^{1}$H NMR spectra (400 MHz, 298 K):

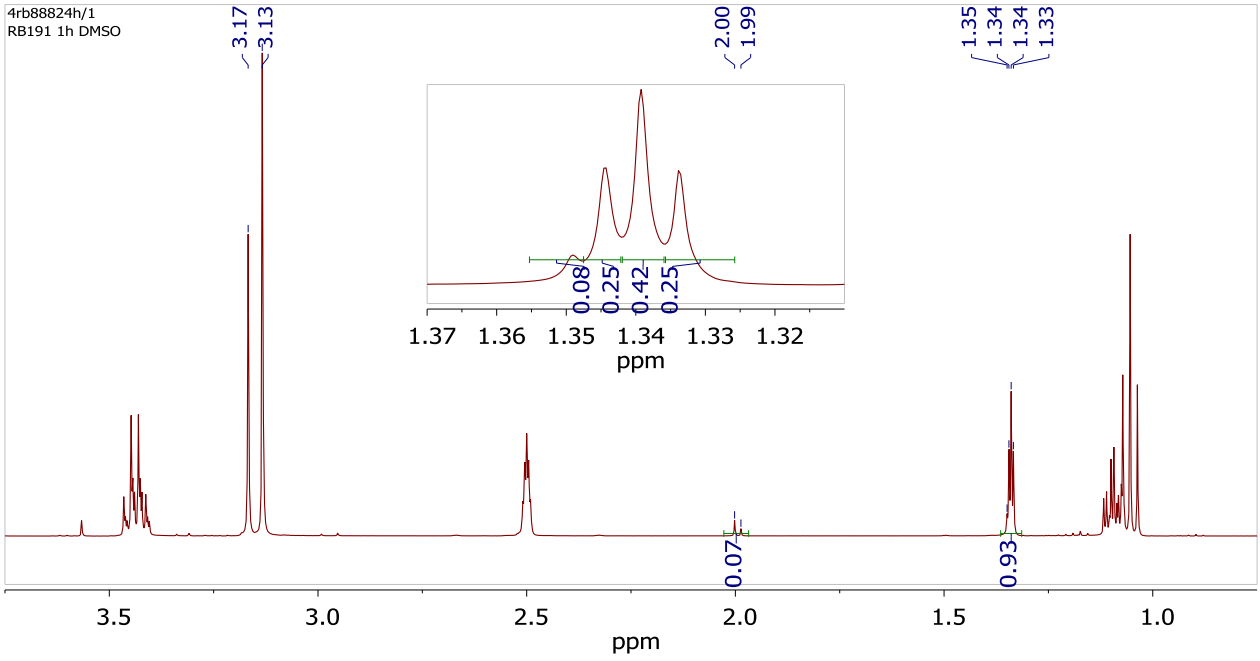
**Solvent benzene-d$_6$**: 0.1% TFA, 1h:



**Solvent $CD_3CN$**: 0.1% TFA, 1h:



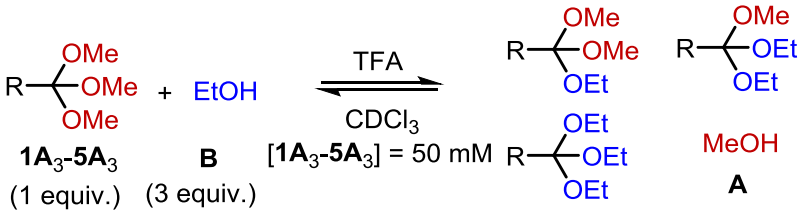

**Solvent DMSO-$d_6$**: 0.1% TFA, 1h:




Note: The integration error in the two spectra above is exceptionally large, but the precise ratio of products is irrelevant to our conclusion in the main text, namely that orthoester exchange proceeds cleanly in a variety of aprotic solvents

## Investigation of different orthoesters

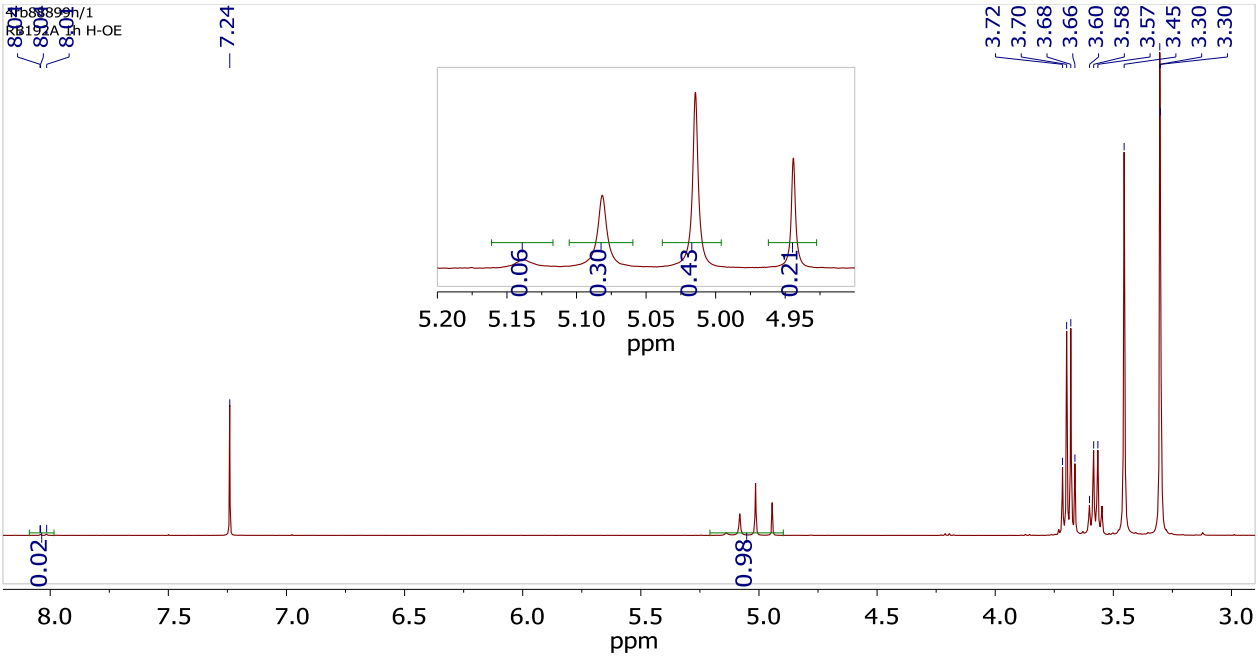
Reaction scheme:



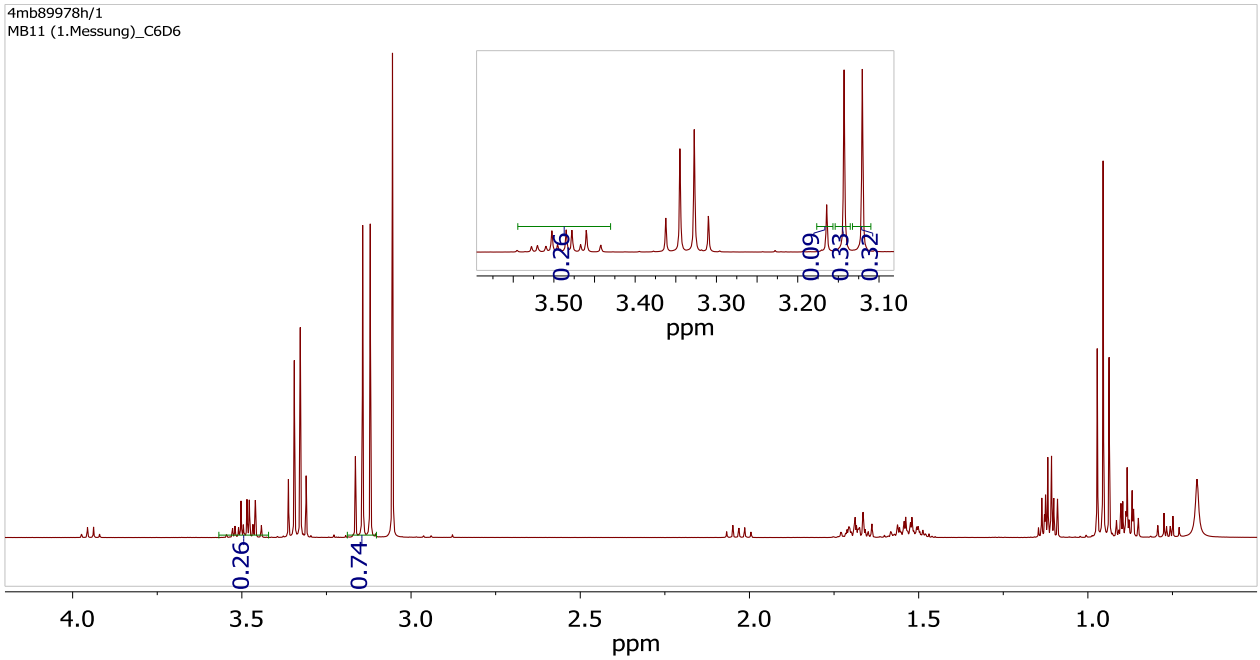

General procedure: Orthoester (37.5 µmol, 1.0 equiv.), ethanol (112.5 µmol, 3.0 equiv.) and TFA catalyst (0.1 to 1 mol%) were added to the reaction vessel from stock solutions and $CDCl_3$ was added to obtain a total volume of 750 µL. The reaction solution was left standing at room temperature and the reaction progress was monitored regularly by $^1$H NMR spectroscopy.

$^1$H NMR spectra (400 MHz, 298 K):

**Trimethylorthoformate (3A$_3$):** 1% TFA, 1h

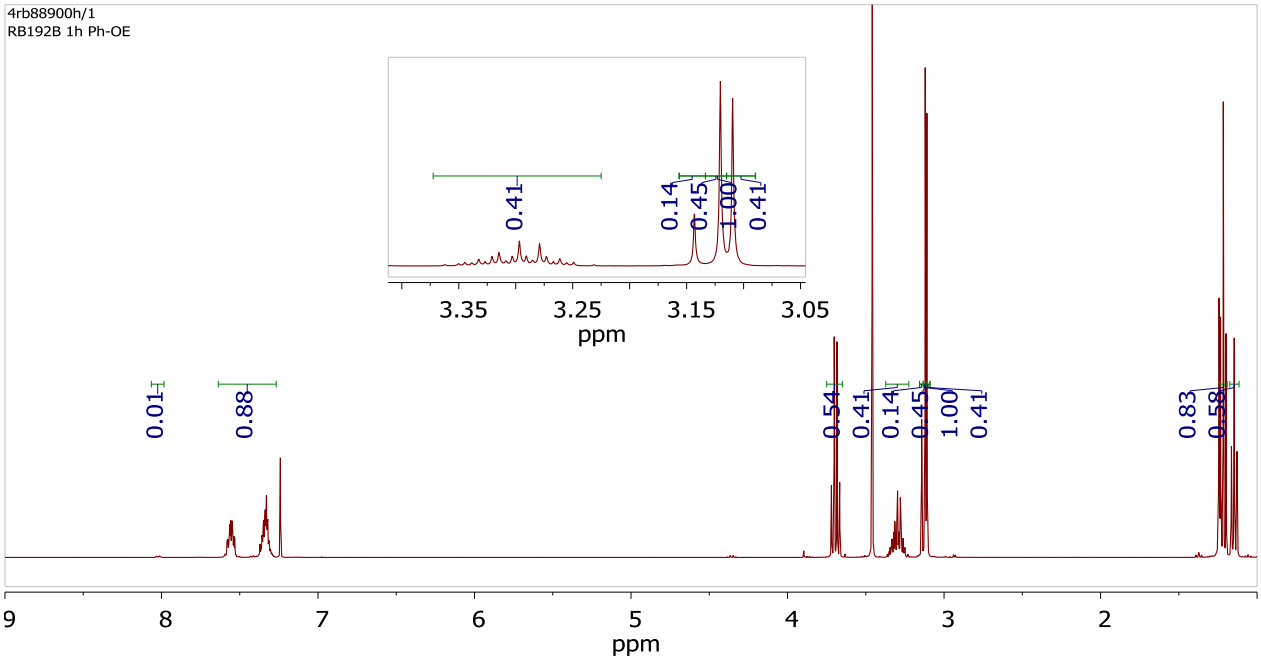


**Trimethylorthobutanoate ($4A_3$):** 0.1% TFA, 1h, **solvent: $C_6D_6$** (peak separation allows accurate integration of OMe signals)




A product ratio of 28:44:24:4 (**$4A_3$**:**$4A_2B$**:**$4AB_2$**:**$4B_3$**) was calculated from the integrals shown in the zoom area (OEt and OMe groups). Spectra after 1h and 24h identical within error margin.

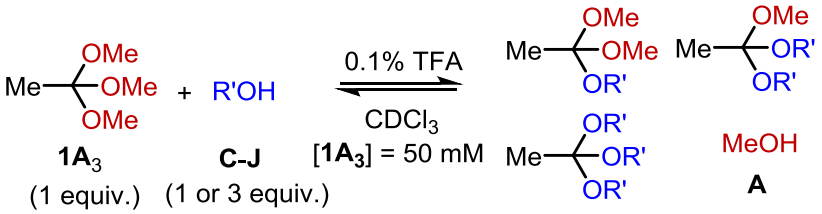
**Trimethylorthobenzoate ($5A_3$):** 1% TFA, 1h




A product ratio of 25:42:26:6 (**$5A_3$**:**$5A_2B$**:**$5AB_2$**:**$5B_3$**) was calculated from the integrals shown in the zoom area (OEt and OMe groups). Spectra after 1h and 24h identical within error margin.

## Investigation of different alcohols

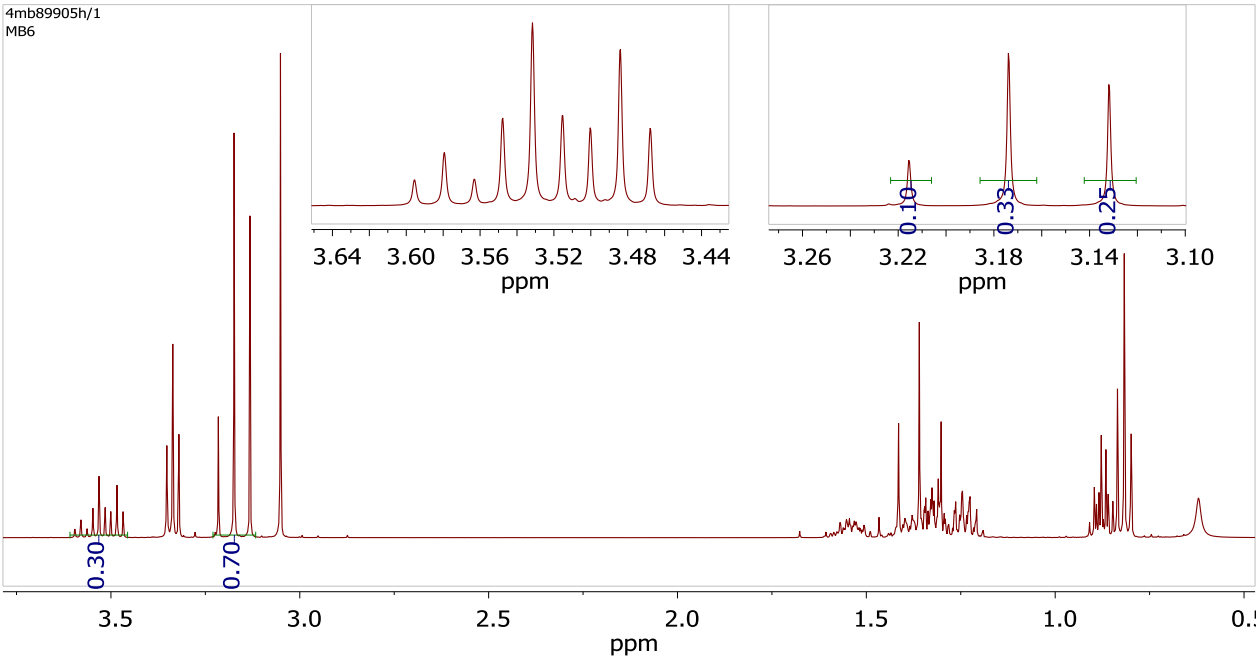
General reaction scheme:




General procedure: trimethylorthoacetate (37.5 µmol, 1.0 equiv.), alcohol (112.5 µmol, 3.0 equiv. for alcohols **C**-**G**; 37.5 µmol, 1.0 equiv. for polyols **H**-**J**) and TFA catalyst (0.1 mol%) were added to the reaction vessel from stock solutions and $CDCl_3$ was added to obtain a total volume of 750 µL. The reaction solution was left standing at room temperature and the reaction progress was monitored regularly by $^1$H NMR spectroscopy.

$^1$H NMR spectra (400 MHz, 298 K):

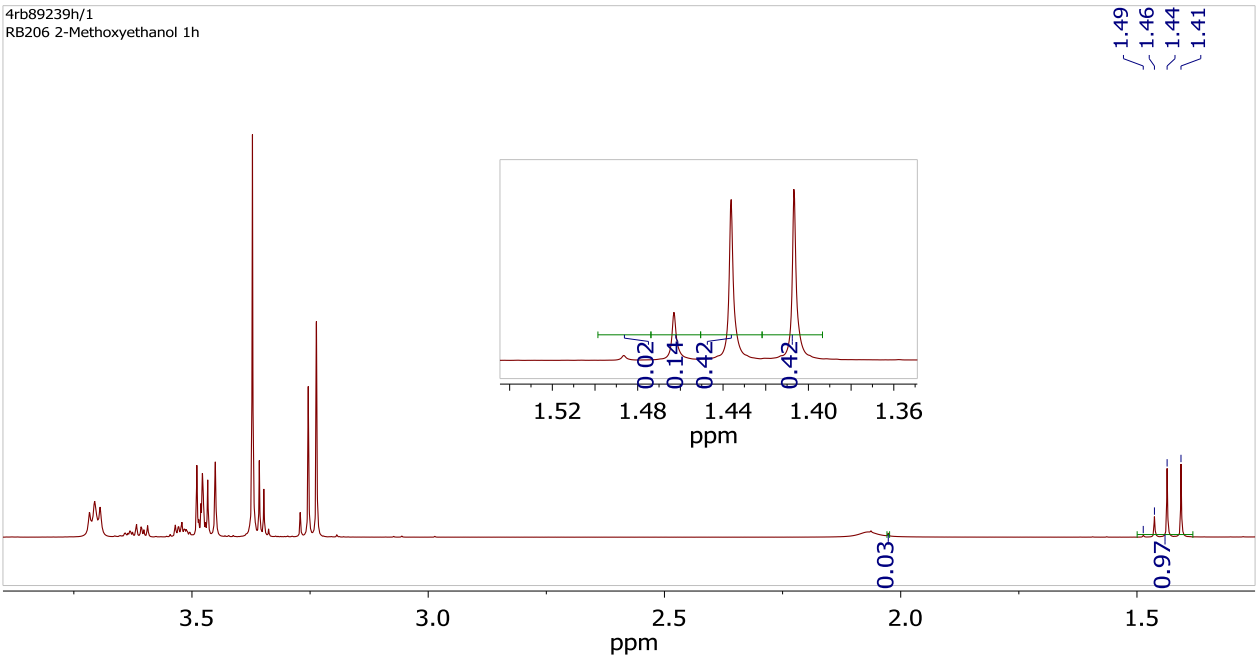
***n*-Butanol (C):** 0.1% TFA, 1h, **solvent: $C_6D_6$** (peak separation allows accurate integration of OMe Signals)




A product ratio of 22:44:27:8 (**5A$_3$**:**5A$_2$C**:**5AC$_2$**:**5C$_3$**) can be calculated from the integrals shown in the zoom area (OEt and OMe groups)

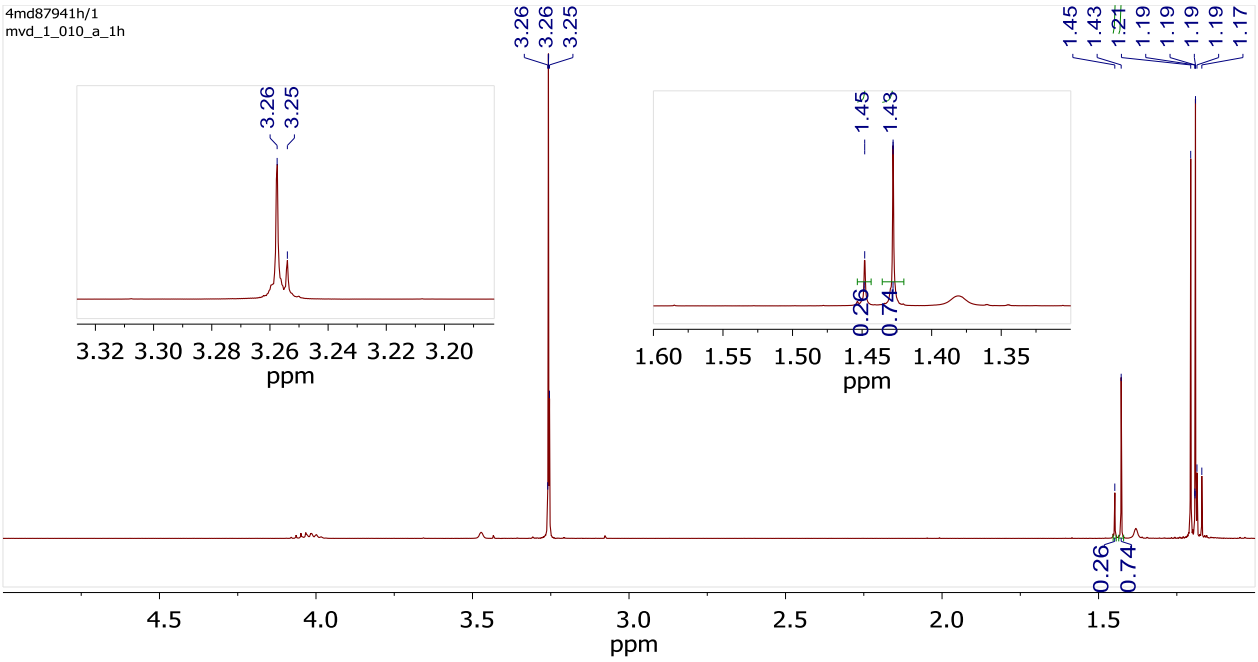
Spectra after 1h and 24h identical within error margin.

**2-Methoxyethanol (D):** 0.1% TFA, 1h



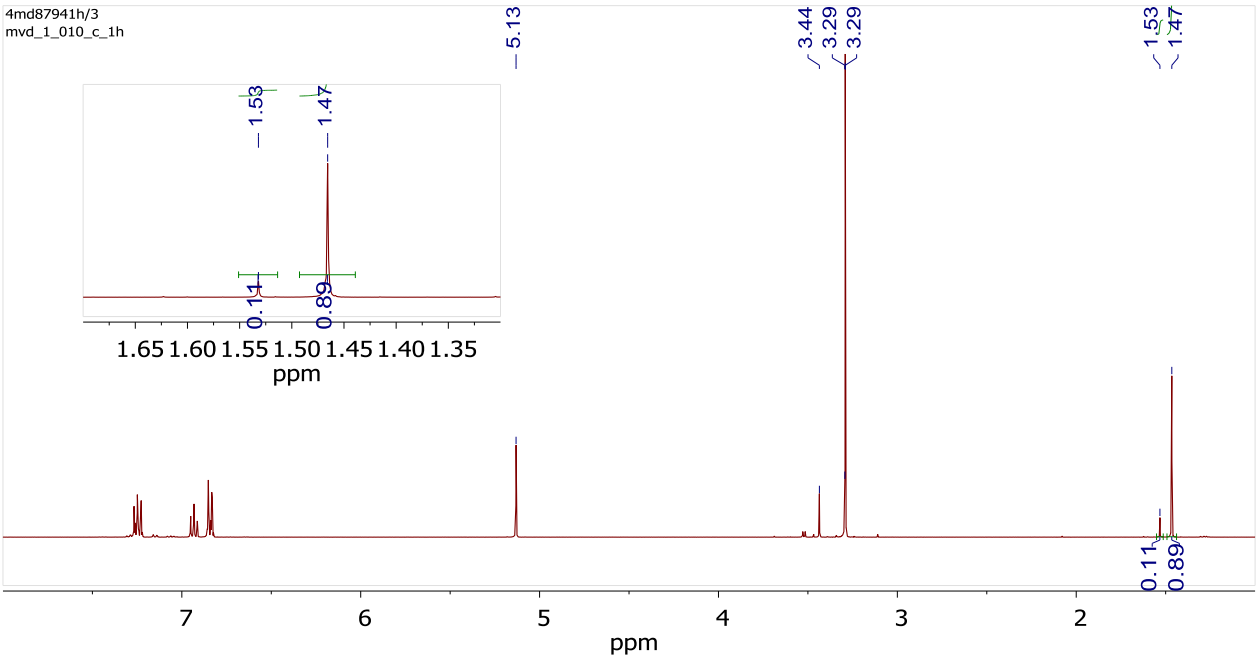

Spectra after 1h and 24h identical within error margin.

**2-Propanol (E):** 0.1% TFA, 1h



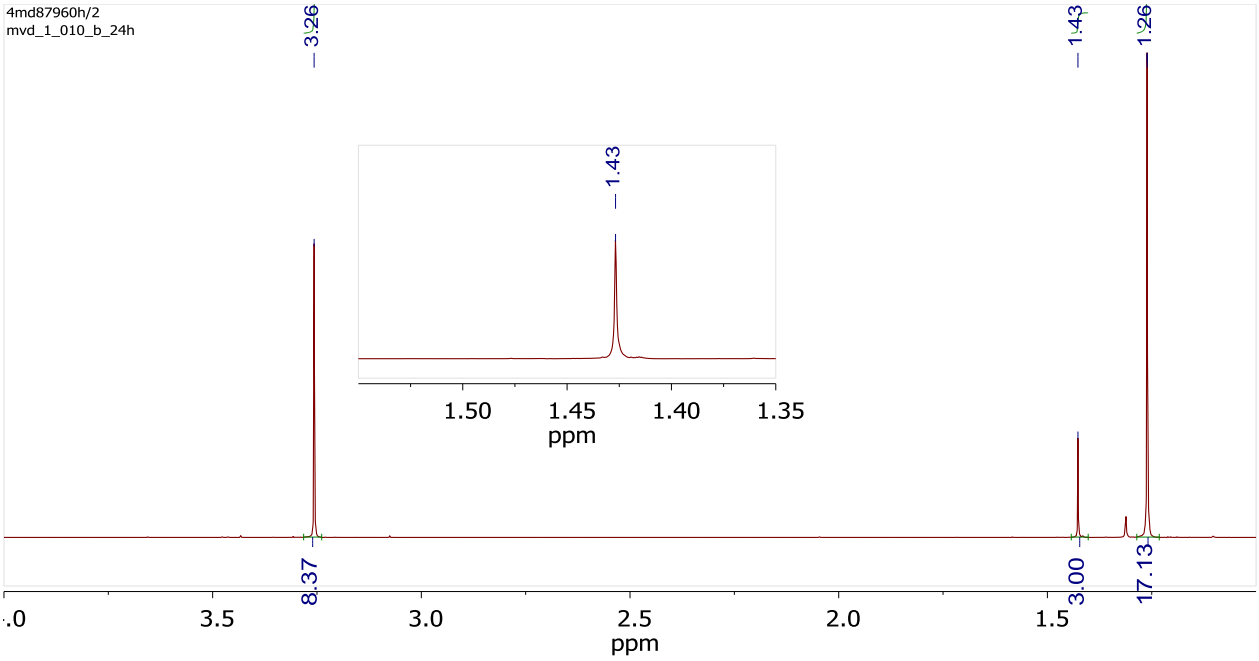

Spectra after 1h and 24h identical within error margin.

**Phenol (F):** 0.1% TFA, 1h



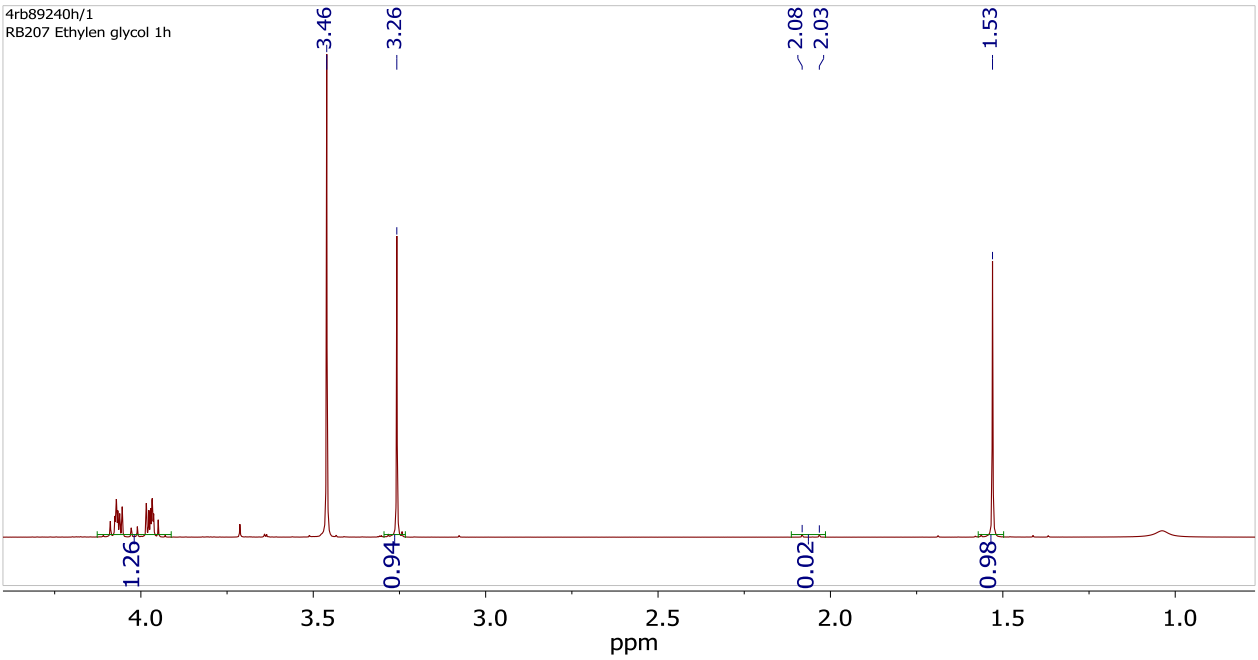

Spectra after 1h and 24h identical within error margin.

***tert*-Butanol (G):** 0.1% TFA, 24h



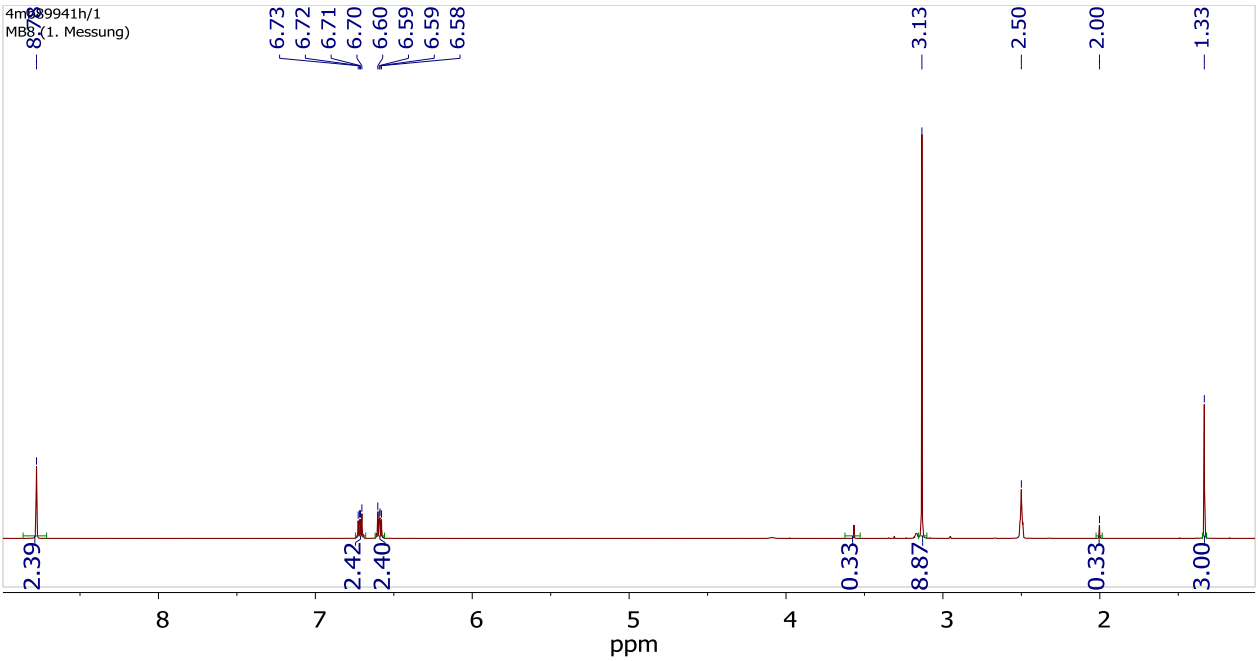

Spectra after 1h and 24h identical within error margin. Not even traces of exchange products could be observed.

**Ethylene glycol (H):** 0.1% TFA, 1h



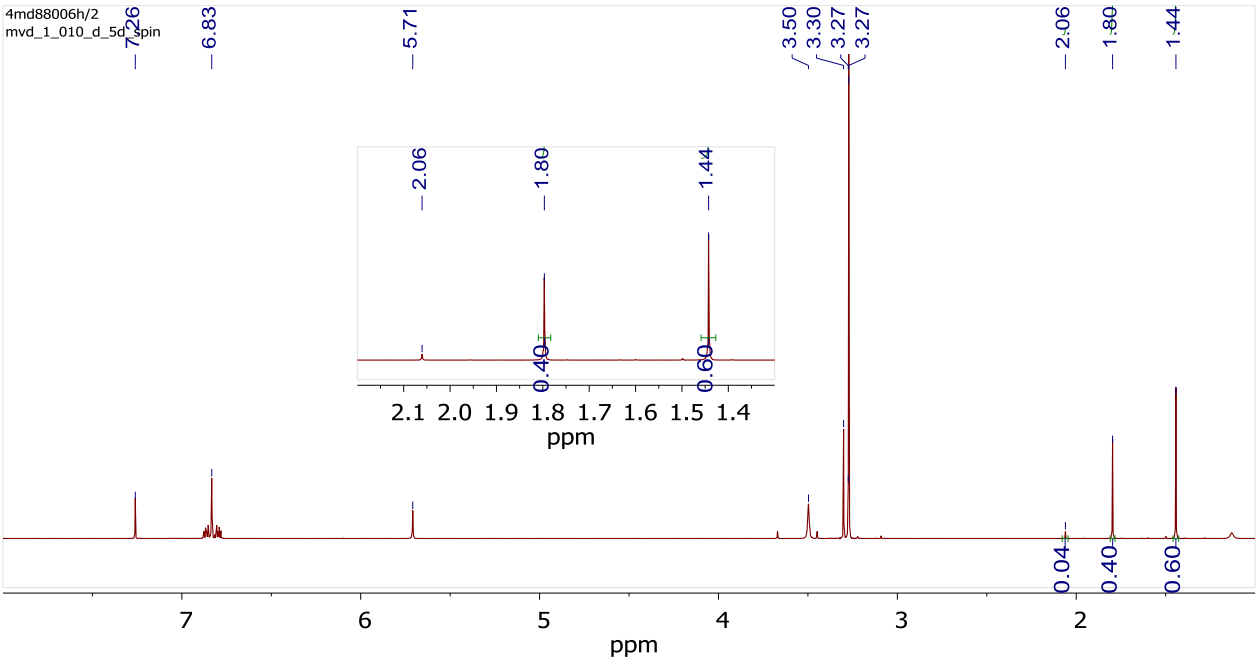

Spectra after 1h and 24h identical within error margin.

**Catechol (I):** 0.1% TFA, 1 h (**DMSO-$d_6$**)




Spectra after 1h and 24h identical within error margin.

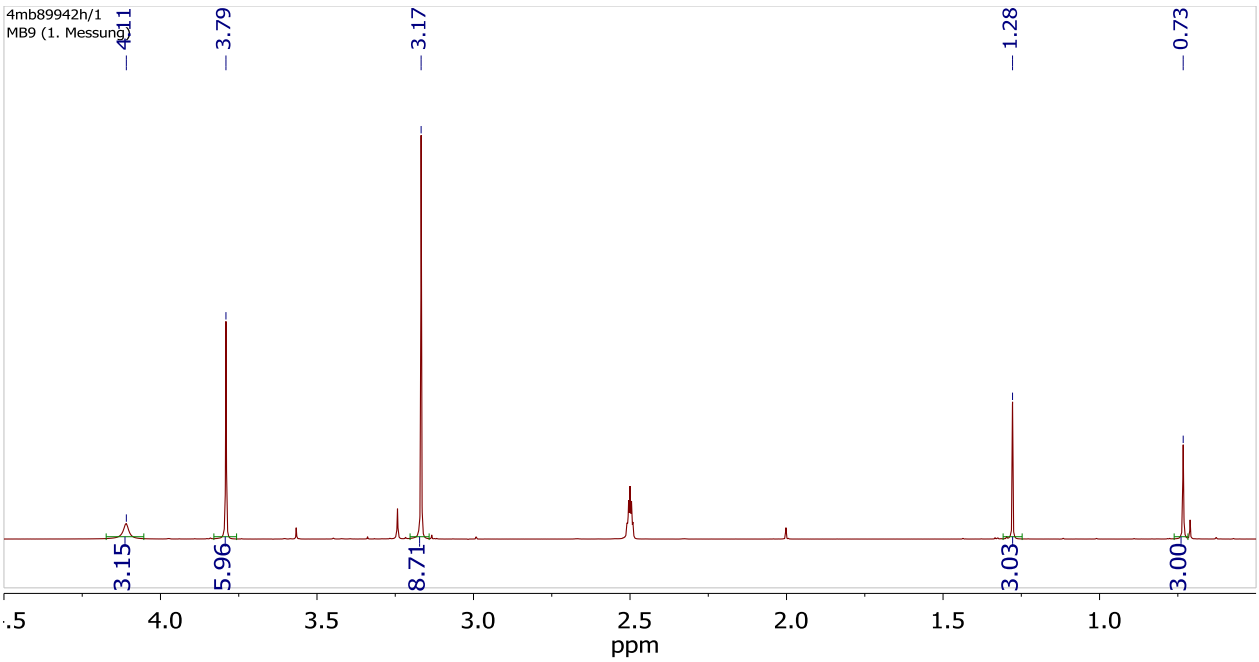
**Catechol (I):** 0.1% TFA, 5d (**$CDCl_3$**)




Due to low solubility of catechol in $CDCl_3$, the exchange reaction proceeds very slowly. As a result, the reaction carried out in DMSO (see above) is more indicative of the equilibrium distribution.

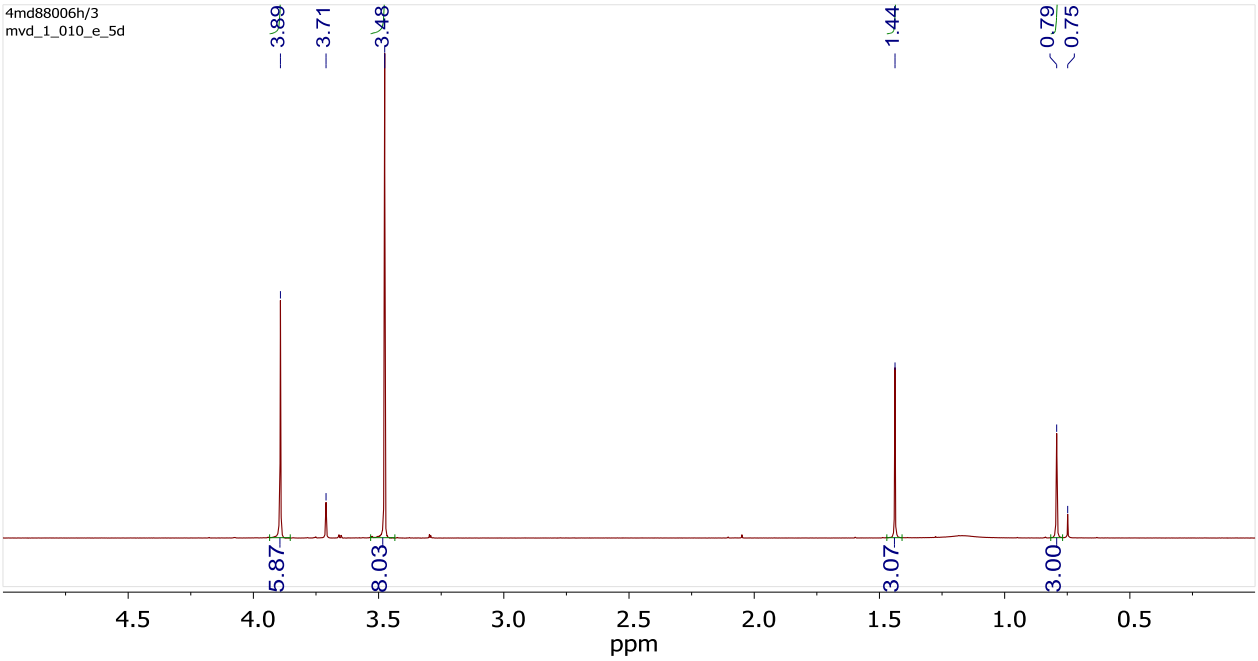
Signals observed for **1AH** (δ = 6.83ppm, 3.30 ppm, 1.79 ppm) are in excellent agreement with literature data on this compound.[S1] The peak observed at 2.06 ppm corresponds to MeOAc.

**1,1,1-Tris(hydroxymethyl)-ethane (J):** 0.1% TFA, 1 h (**DMSO-$d_6$**)



After 1h in DMSO-$d_6$ with 0.1% TFA. Spectra after 1h and 24h identical within error margin.

**1,1,1-Tris(hydroxymethyl)-ethane (J):** 0.1% TFA, 5d (**$CDCl_3$**)

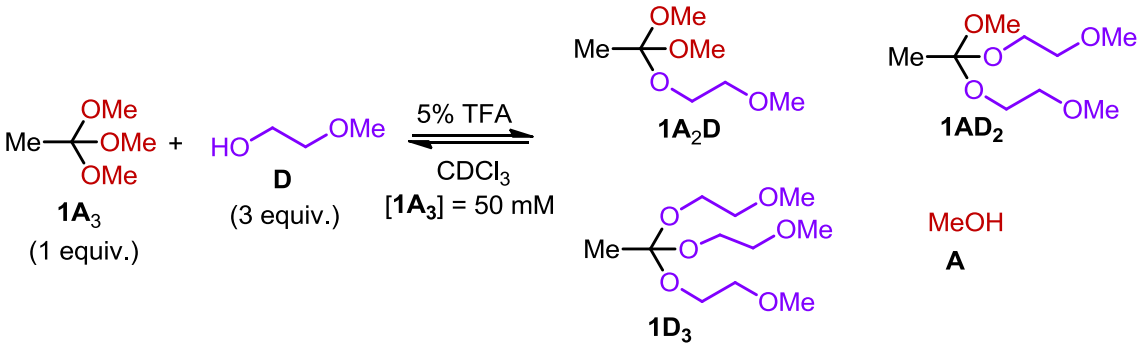



The long reaction time is likely a result of the low solubility of 1,1,1-tris(hydroxymethyl)-ethane in $CDCl_3$. See above for the same reaction DMSO.

Signals observed for exchange product **1J** (δ = 3.89 ppm, 1.44 ppm, 0.79 ppm) are in good agreement with literature data on this compound.[S2] The peak observed at 3.48 ppm corresponds to methanol (~2.7 equiv.). The signals at 3.71 ppm and 0.75 ppm correspond to starting material **J**, which must have been present in slight excess and is more soluble once exchange is complete thanks to the presence of methanol.

## Treatment with bicarbonate solution

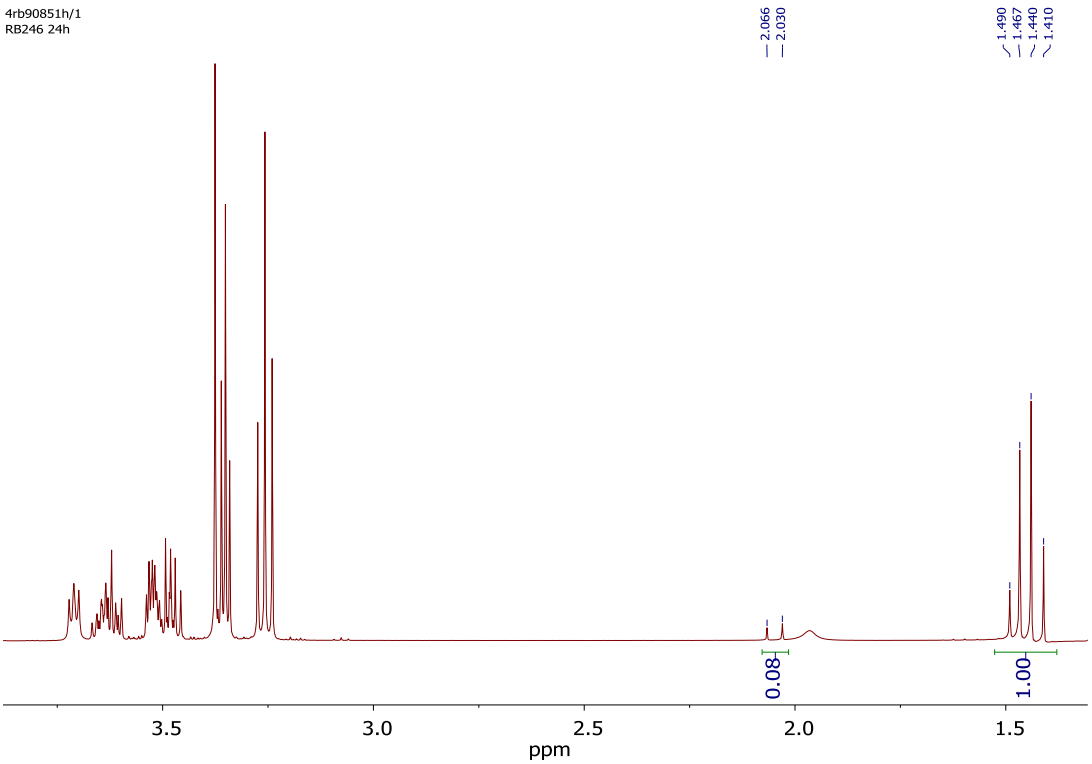
Reaction scheme:



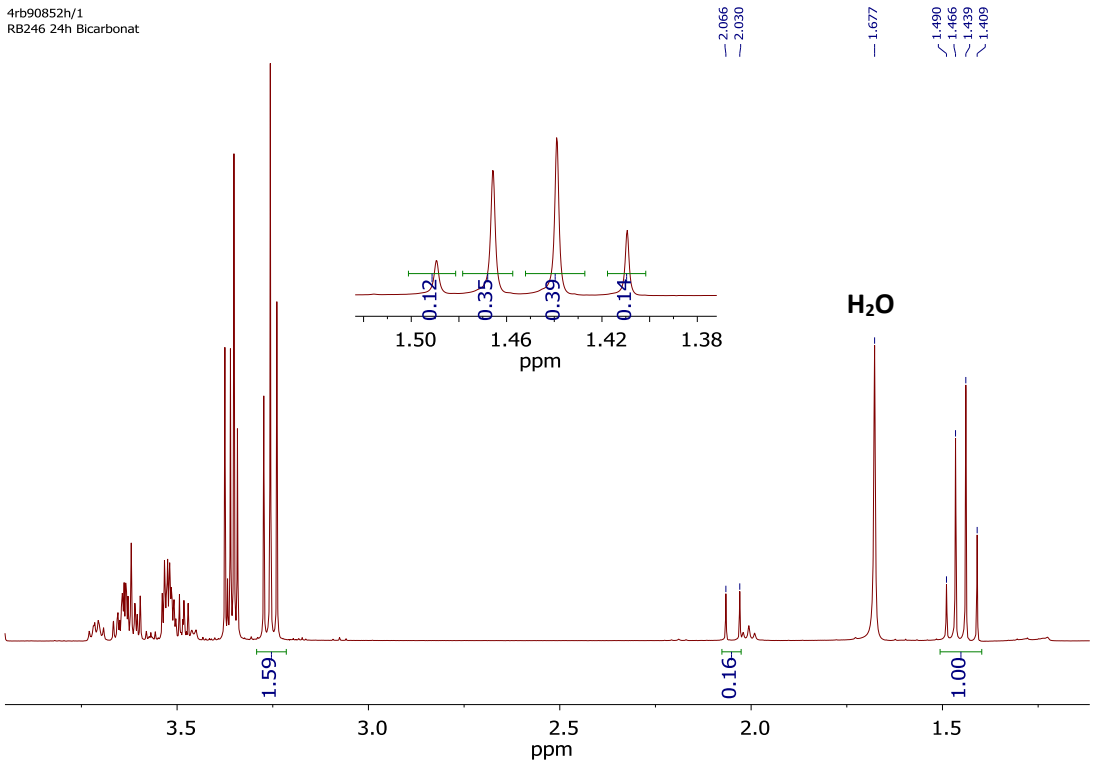

Procedure: 2-methoxyethanol (0.9 mmol, 3.0 equiv.) and $CDCl_3$ (5.89 mL) were added to an oven-dried scintillation vial. 4Å molecular sieves (0.65 g) were added and the mixture was left standing overnight. Trimethyl orthoacetate (0.3 mmol, 1.0 equiv.) and TFA catalyst (5 mol%) were added. The reaction mixture was left standing at room temperature for 24h. The reaction progress was monitored by $^1$H NMR spectroscopy.

1 mL of the solution was treated with 1 mL saturated sodium bicarbonate solution. The mixture was shaken for 5 seconds, the organic layer was separated and dried with $Na_2SO_4$.

$^1$H NMR spectrum before treatment (400 MHz, 298 K, $CDCl_3$) after 24h:



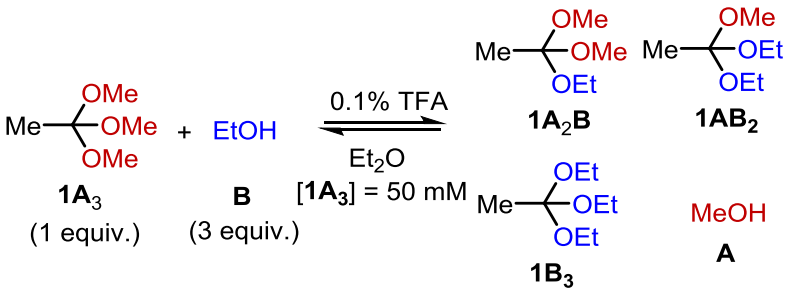
$^{1}$H NMR spectrum after treatment (400 MHz, 298 K, $CDCl_3$):



## Analysis by GC-FID and HPLC-MS

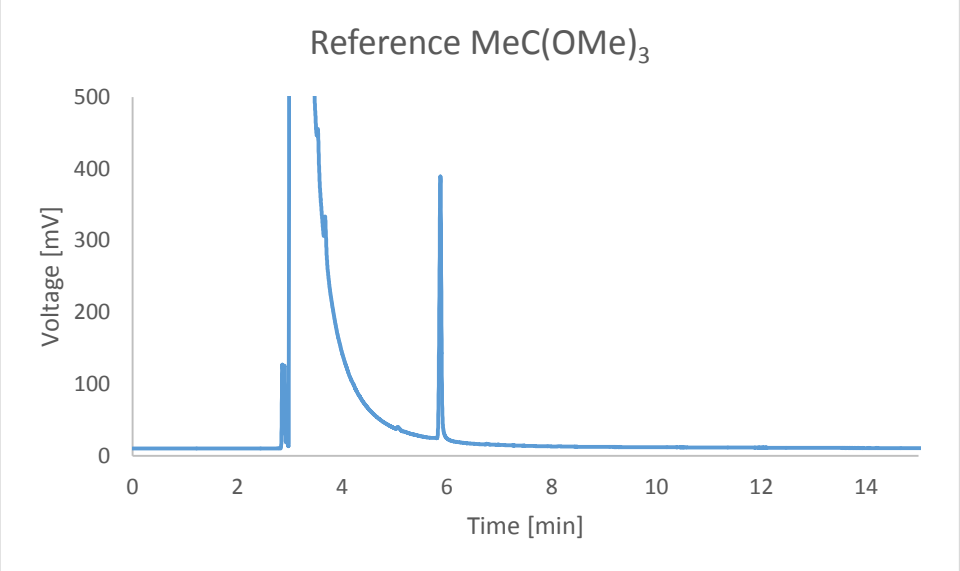
### a) GC-FID

Reaction scheme:

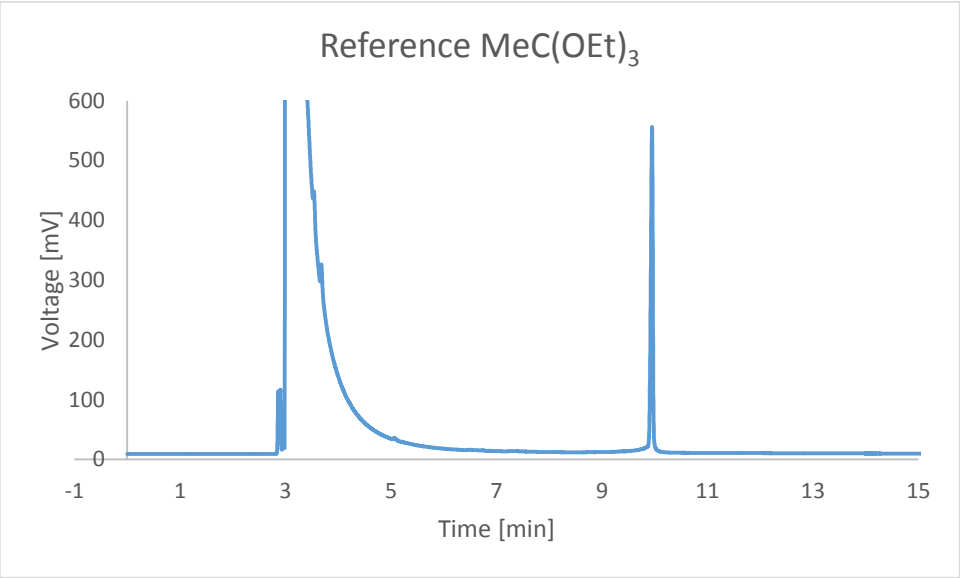



Procedure: trimethyl orthoacetate (37.5 µmol, 1.0 equiv.), ethanol (112.5 µmol, 3.0 equiv.) and TFA catalyst (0.1 mol%) were added to a scintillation vial from stock solutions and anhydrous diethyl ether was added to obtain a total volume of 750 µL. The reaction solution was left standing at room temperature and the reaction progress was monitored after 1h by gas chromatography.

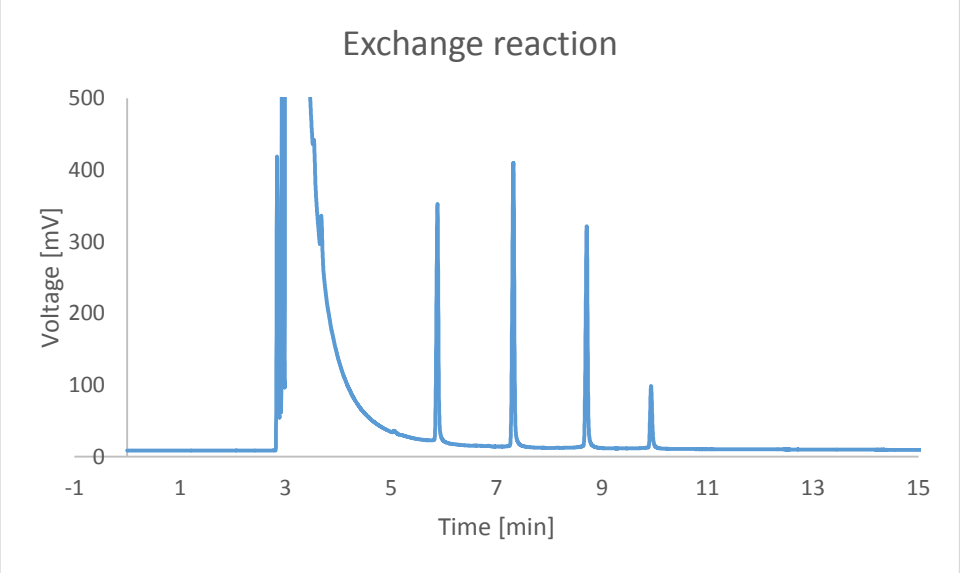
GC chromatogram:




Retention time pristine **1A**$_3$: 5.88 min



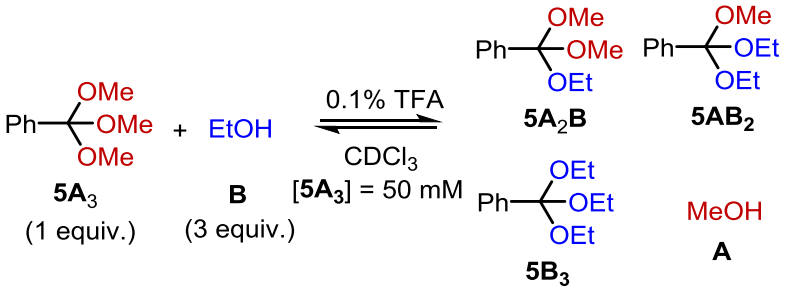

Retention time pristine **1B**$_3$: 9.95 min




Retention times and peak integrals in area percent: 5.88 min (**1A**$_3$, 29%), 7.32 min (**1A**$_2$**B**, 36%), 8.71 min (**1AB**$_2$, 27%), 9.93 min (**1B**$_3$, 8%).

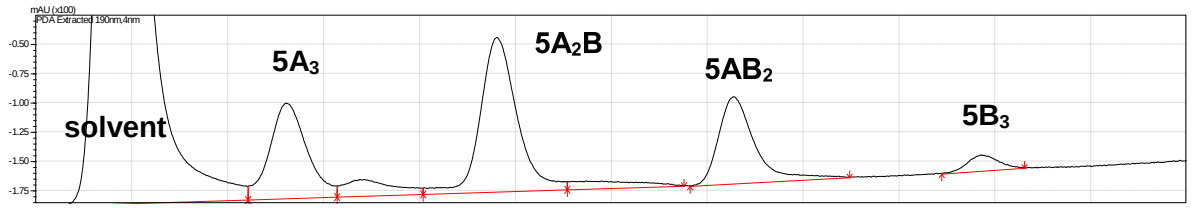
## b) HPLC-MS

Reaction scheme:

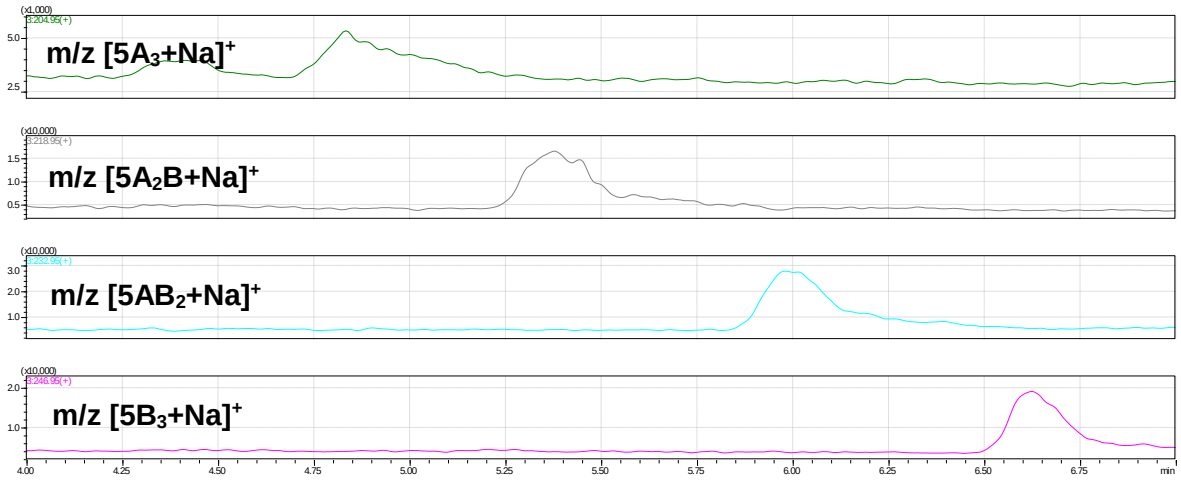



Procedure: trimethyl orthobenzoate (37.5 µmol, 1.0 equiv.), ethanol (112.5 µmol, 3.0 equiv.) and TFA catalyst (0.1 mol%) were added to a scintillation vial from stock solutions and anhydrous acetonitrile was added to obtain a total volume of 750 µL. The reaction solution was left standing at room temperature and the reaction progress was monitored after 1h by HPLC-MS.

HPLC chromatogram (190 nm):




SIM (Selected Ion Monitoring) traces confirm the correct assignment of the peaks:

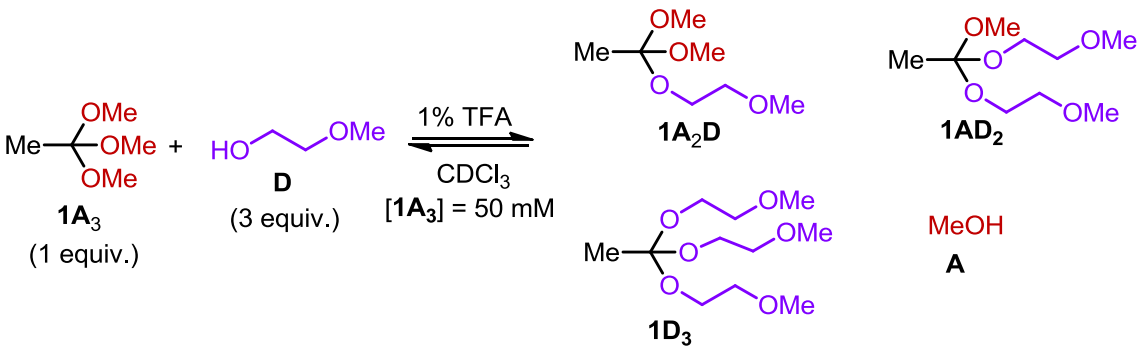



The horizontal scale is 4.0 to 7.0 minutes in each of the above traces. The time delay between diode array detector (DAD) and mass spectrometric detector (MSD) is approximately 0.2 minutes.

## Manipulation of equilibrium distribution

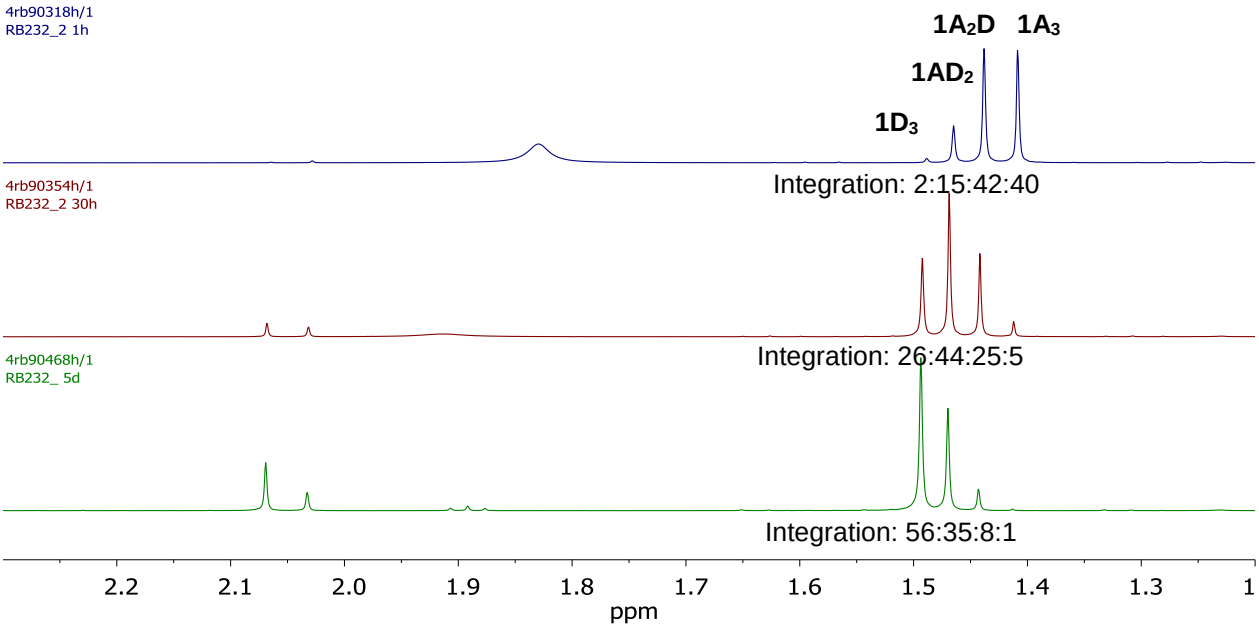
### a) Removal of MeOH using molecular sieves (4Å)

Reaction scheme:



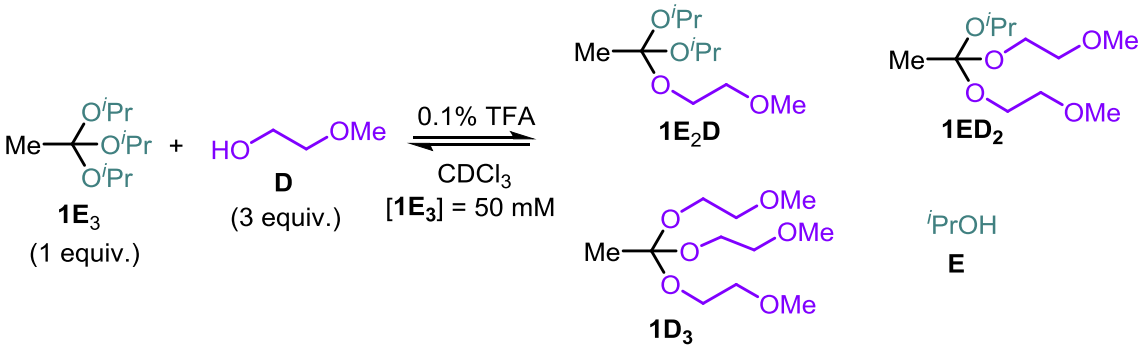

Procedure: 2-methoxyethanol (0.9 mmol, 3.0 equiv.) and $CDCl_3$ (5.89 mL) were added to an oven-dried scintillation vial. 4Å molecular sieves (0.65 g) were added and the mixture was left standing overnight. Trimethyl orthoacetate (0.3 mmol, 1.0 equiv.) and TFA catalyst (1 mol%) were added. The reaction mixture was left standing at room temperature and the reaction progress was monitored regularly by $^1$H NMR spectroscopy.

Partial $^1$H NMR spectra (400 MHz, 298 K,$CDCl_3$) after 1 h, 30 h and 5 d:



**b) Starting from 'high-energy' compound $1E_3$**

Reaction scheme:

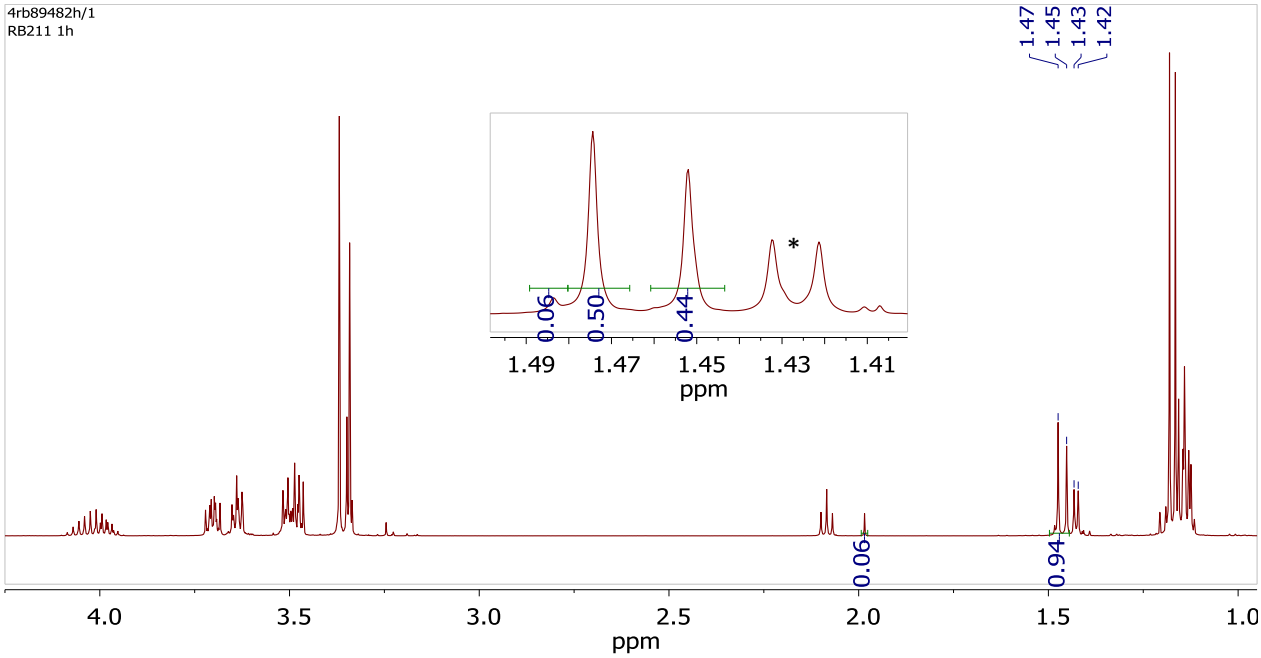



Procedure: triisopropyl orthoacetate (37.5 µmol, 1.0 equiv.), 2-methoxyethanol (112.5 µmol, 3.0 equiv.) and TFA catalyst (0.1 mol%) were added to a scintillation vial from stock solutions and $CDCl_3$ was added to obtain a total volume of 750 µL. The reaction mixture was left standing at room temperature and the reaction progress was monitored regularly by $^1$H NMR spectroscopy.

Product ratio: nd:44:**50**:6 (**1E$_3$**/**1E$_2$D**/**1ED$_2$**/**1D$_3$**)

nd: not detected

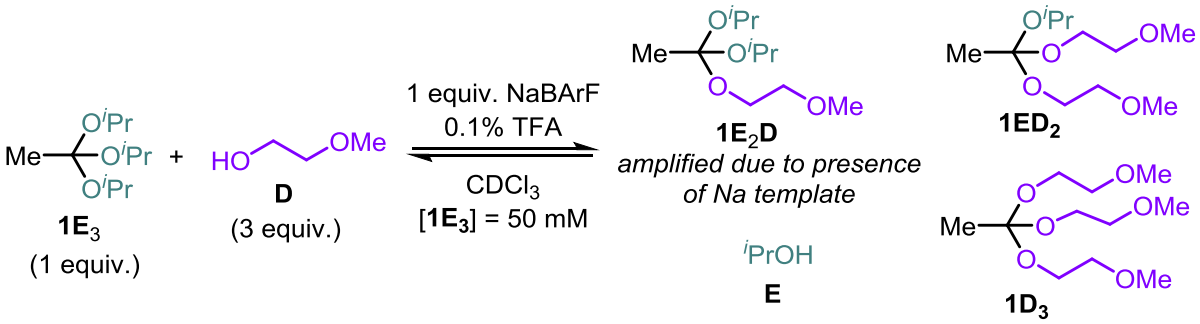
$^1$H NMR spectrum (400 MHz, 298 K,$CDCl_3$) after 1h:




Starting material triisopropyl orthoacetate (**1E$_3$**) was prepared according to a literature procedure.[S3] *: doublet corresponds to acidic proton of $^i$PrOH (**E**) (confirmed via COSY NMR)

## c) Metal template effect

Reaction scheme:

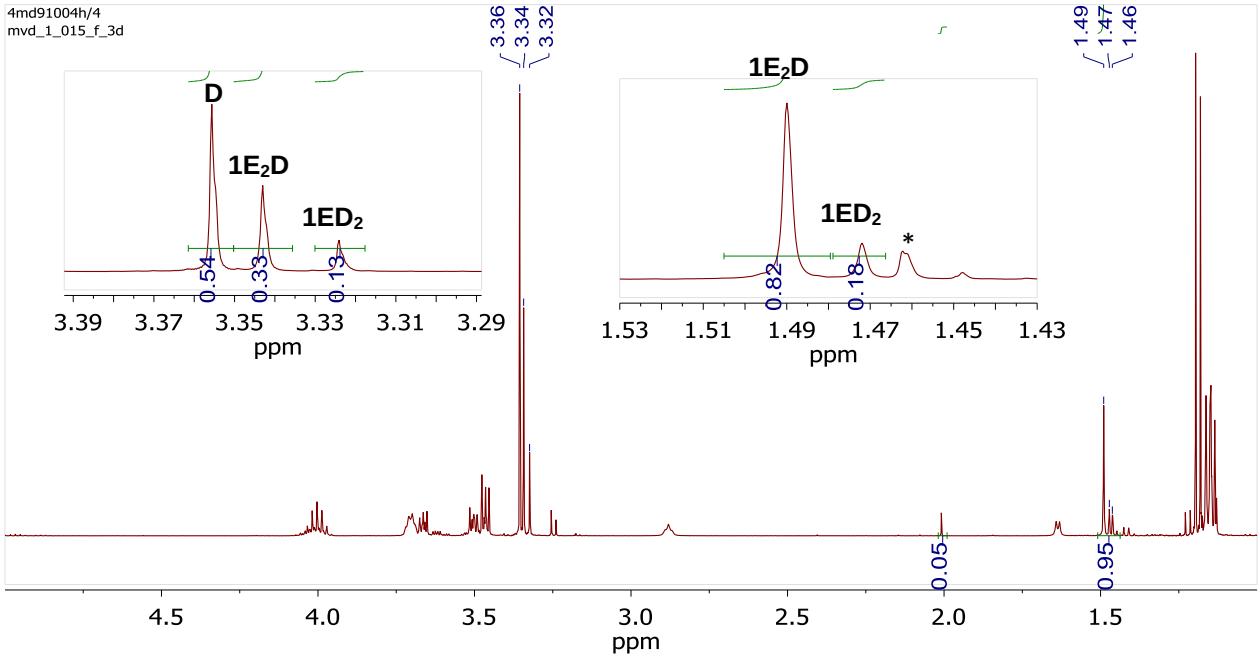



Procedure: triisopropyl orthoacetate (37.5 µmol, 1.0 equiv.), 2-methoxyethanol (112.5 µmol, 3.0 equiv.), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF, 37.5 µmol, 1.0 equiv.) and TFA catalyst (0.1 mol%) were added to a scintillation vial from stock solutions and $CDCl_3$ was added to obtain a total volume of 750 µL. The reaction mixture was left standing at room temperature and the reaction progress was monitored regularly by $^1$H NMR spectroscopy.

Product ratio without template: nd:44:**50**:6 (**1E$_3$**/**1E$_2$D**/**1ED$_2$**/**1D$_3$**)

Product ratio with Na template: nd:**82**:18:nd (**1E$_3$**/**1E$_2$D**/**1ED$_2$**/**1D$_3$**) (nd: not detected)

$^1$H NMR spectrum (400 MHz, 298 K,$CDCl_3$) after 3d:




*: Peak corresponds to compound MeC(O$^i$Pr)$_2$(OMe), a trace impurity present in **1E$_3$**.

## References


[S1] H. G. Thomas and A. Schmitz, *Synthesis* 1985, 31.

[S2] K. Rakus, S. P. Verevkin, W.-H. Peng, H.-D. Beckhaus and C. Ruechardt, *Liebigs Annalen* 1995, 2059.

[S3] K. M. Sureshan, S. Devaraj and M. S. Shashidhar, *Tetrahedron* 2009, **65**, 2703.