Supporting Information

Direct and Quantitative Monitoring of Catalytic Organic Reactions under Heterogeneous Conditions Using Direct Analysis in Real Time Mass Spectrometry

Koichiro Masuda and Shū Kobayashi*

Table of Contents

1. General

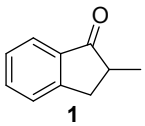
^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX400, JNM-ECA500, and JNM-ECX600 spectrometers in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) and trace $CHCl_3$ in $CDCl_3$ served as internal standard (δ = 0, 7.26) for ^{1}H NMR, and $CDCl_3$ served as internal standard (δ = 77.0) for ^{13}C NMR. Preparative thin-layer chromatography (pTLC) was carried out using a plate with Wakogel B-5F. IR spectra were measured on a JASCO FT/IR-610 spectrometer. All the mass spectrometry measurements were recorded using a JEOL JMS T100TD spectrometer equipped with DART® SVP ion source. All organic solvents were purchased from Wako Pure Chemical Industries as dry solvents. Deionized water from a MILLIPORE MilliQ machine (Gradient A10) was used as solvent without further treatment.

2. Preparation of the materials

A) Direct-type aldol reactions and Mukaiyama aldol reactions

Ketone **1**, silyl enol ether **4**, 2,2'-bipyridine ligand **5** and ScDS were prepared following reported methods.[1–5] Formaldehyde (Kokusan chemical) and NaDS (Fujifilm Wako pure chemical) were used as received.

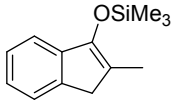
2-methylindan-1-one (**1**)[1]



1

^{1}H-NMR (600 MHz): δ = 1.30 (3H, d, *J* = 7.5 Hz), 2.67 – 2.73 (2H, m), 3.36 – 3.40 (1H, m), 7.35 (1H, dd, *J* = 6.9, 8.2 Hz), 7.44 (1H, d, *J* = 8.2 Hz), 7.57 (1H, dd, *J* = 7.6, 6.9 Hz), 7.74 (1H, *J* = 7.6 Hz); ^{13}C-NMR (125 MHz): δ = 16.1, 34.7, 41.8, 123.7, 126.4, 127.1, 134.5, 136.1, 153.3, 209.2.

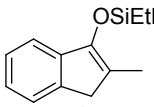
2-methyl-3-(trimethylsilyloxy)indene (**4a**) [6]



4a

^{1}H-NMR (500 MHz): δ = 0.27 (9H, s), 1.97 (3H, s), 3.18 (2H, s), 7.12 (1H, dd, *J* = 7.4, 5.7 Hz), 7.18 (1H, d, *J* = 7.4 Hz), 7.24 (1H, dd, *J* = 5.7, 7.4 Hz), 7.31 (1H, d, *J* = 7.4 Hz); ^{13}C-NMR (125 MHz): δ = 0.7, 12.4, 38.4, 117.2, 120.1, 123.3, 124.0, 125.9, 140.8, 142.7, 147.5.

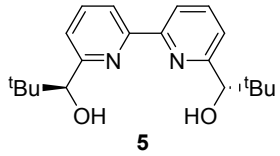
2-methyl-3-(ethyldimethylsilyloxy)indene (**4b**)



4b

^{1}H-NMR (500 MHz): δ = 0.23 (6H, s), 0.75 (2H, q, *J* = 7.9 Hz), 1.03 (3H, t, *J* = 7.9 Hz), 1.98 (3H, s), 3.18 (2H, s), 7.11 (1H, m), 7.20 (1H, m) 7.24 (1H, m), 7.30 (1H, d, *J* = 7.3 Hz); ^{13}C-NMR (125 MHz): δ =-1.4, 6.8, 9.1, 12.4, 38.5, 117.3, 120.0, 123.4, 124.1, 126.1, 140.9, 142.9, 147.7.

(*S,S*)-6,6'-Bis(1-hydroxy-2,2-dimethylpropyl)-2,2'-bipyridine (5)[3–5]

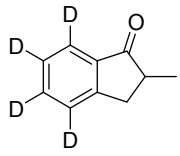


5

^{1}H-NMR (400 MHz): δ = 0.97 (18H, s), 4.41 (2H, br s), 7.23 (4H, d, *J* = 7.3 Hz), 7.79 (2H, t, *J* = 7.8 Hz), 8.31 (2H, d, *J* = 7.8 Hz); ^{13}C-NMR (100 MHz): δ = 25.9, 36.3, 80.2, 119.6, 123.1, 136.6, 153.8, 159.3. HPLC (chiralcel OD, hexanes/^{i}PrOH = 19/1, 1.0 mL/min; t_R = 49.2 min (*S,S*), ND for (*R,R*) isomer)

Tetradeuterated compound **1-*d*$_4$** was synthesized by following Olah's method with slight modification.[1] Triflic anhydride (40 mL, 244 mmol) and water-d_2 (99.8% purity, 4.4 mL, 244 mmol) was mixed in a 100 mL round bottom flask and the mixture was heated at 90 °C for 2 hours under argon atmosphere. After the mixture became single phase, the mixture was cooled to room temperature and then benzene-d_6 (99.5% purity, 5.31 mL, 60 mmol) and methacrylic acid (2.53 mL, 30 mmol; treated with water-d_2 three times before the use) were subsequently added. After stirring the mixture at 75 °C for overnight, the mixture was cooled to room temperature and poured into ice/water. The mixture was extracted with DCM (50 mL for 3 times) and combined organic phase was washed with saturated aq. $NaHCO_3$ until aqueous phase became basic. The organic phase was further washed with brine (30 mL, once) and dried over anhydrous Na_2SO_4. After removal of solvent under vacuum, the mixture was poured into 1N aq. KOH/MeOH mixture (1/9, 10 mL) to stir for 10 min at room temperature. The mixture was acidified with saturated aq. NH_4Cl solution and extracted with DCM then dried over anhydrous Na_2SO_4. This base treatment was conducted 3 times for full D-H exchange of carbonyl α-position. After the removal of solvent, the desired compound **1-*d*$_4$** was obtained (3.86 g, 25.8 mmol, 86% based on methacrylic acid). Obtained compound was used in next step after vacuum distillation (0.53 mmHg, 93 – 97 °C). Compound **2** and **2-*d*$_4$** was obtained following modified procedure of direct-type aldol reactions (*vide infra*).

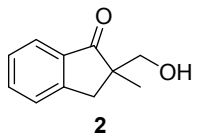
2-methylindan-1-one-4,5,6,7-d_4 (1-d_4)



1-d$_4$

^{1}H-NMR (500 MHz): δ = 1.31 (3H, d, *J* = 7.4 Hz), 2.66-2.74 (2H, m), 3.39 (1H, m), 7.35 (trace, s), 7.44 (trace, s), 7.57 (trace, s), 7.74 (trace, s), ^{13}C-NMR (500 MHz): δ = 16.1, 34.7, 123.4 (t, *J* = 25 Hz), 126.0 (t, *J* = 24.4 Hz), 126.7 (t, *J* = 24.4 Hz), 134.0 (t, *J* = 23.8 Hz), 136.1, 153.2, 209.3.

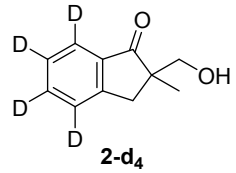
2-(hydroxymethyl)-2-methylindan-1-one (**2**)[2,7]



2

An enantiomeric excess was determined by chiral HPLC analysis (OB-H, hexanes/^{i}PrOH = 100/1, 1.0 mL/min. t_{major} = 41.0 min, t_{minor} = 50.1 min). ^{1}H-NMR (500 MHz): δ = 1.24 (3H, s), 2.48 (1H, br s), 2.89 (1H, d, *J* = 17.6 Hz), 3.26 (1H, d, *J* = 17.0 Hz), 3.62 (1H, dd, *J* = 10.8, 4.0 Hz), 3.83 (1H, dd, *J* = 10.2, 6.8 Hz), 7.34 – 7.38 (1H, m), 7.46 (1H, d, *J* = 7.4 Hz), 7.60 (1H, t, *J* = 7.4 Hz), 7.73 (1H, t, *J* = 7.1 Hz); ^{13}C-NMR (500 MHz): δ = 20.6, 37.8, 50.9, 67.6, 123.7, 126.2, 126.8, 134.6, 153.2, 211.2.

2-hydroxymethyl-2-methylindan-1-one-4,5,6,7-d_4 (2-d_4)



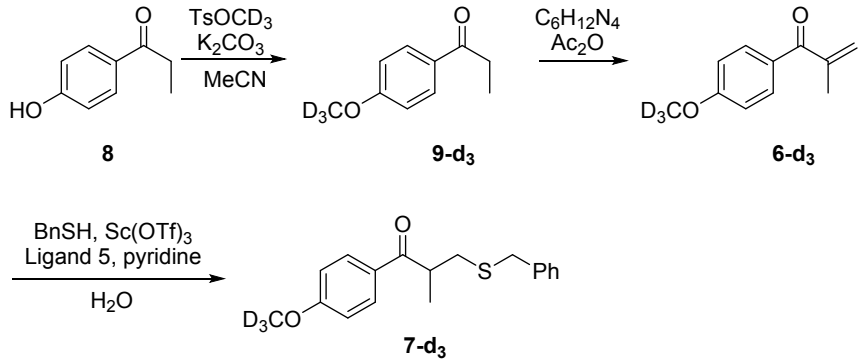
2-d$_4$

^{1}H-NMR (500 MHz): δ = 1.21 (3H, s), 2.78 (1H, br s), 2.88 (1H, d, *J* = 17.6 Hz), 3.27 (1H, d, *J* = 17.0 Hz), 3.60 (1H, d, *J* = 10.7 Hz), 3.81 – 3.85 (1H, m), 7.34 (trace, s) 7.45 (trace, s) 7.59 (trace, s) 7.70 (trace, s); ^{13}C-NMR (125 MHz): δ = 20.6, 37.7, 50.9, 67.6, 123.7 (t, *J* = 26.2 Hz), 126.2 (t, *J* = 23.8 Hz), 134.6 (t, *J* = 23.8 Hz), 135.6, 153.2, 211.2.

B) 1,4-addition/enantioselective protonation reactions

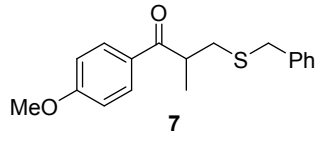
Ketone **6** and Sc(OTf)$_3$ were prepared following reported methods.[8,9] BnSH (TCI) and pyridine (TCI) were used as received. Internal standard **7-d$_3$** was prepared as follows (**Scheme S1**).

Scheme S1. Synthesis of **7-d$_3$**



4-Hydroxypropiophenone **8** (3.73g, 24.8 mmol) was treated with TsOCD$_3$ (3.92g, 20.7 mmol, prepared from methanol-d$_4$) and anhydrous K_2CO_3 (8.58g, 62.1 mmol) in 80 mL of acetonitrile at room temperature for overnight. To a mixture 100 mL of water was added and the phase was separated. Aqueous phase was extracted with ethyl acetate (50 mL x 3) and combined organic phase was washed with brine. After dryness over anhydrous Na_2SO_4 the solvent was removed *in vacuo*. Further purification over silica gel column chromatography (hexanes/ethyl acetate = 9/1 → 5/1) afforded the desired product **9-d$_3$** (3.03 g, 19.7 mmol, 95% based on TsOCD$_3$) which was further converted into **6-d$_3$** and **7-d$_3$** following reported procedures.[8,9]

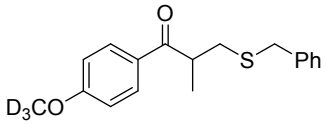
3-benzylthio-2-methyl-1-(4-methoxyphenyl)propan-1-one (**7**)[8]



7

^{1}H-NMR (400 MHz): δ = 1.20 (3H, d, *J* = 6.9 Hz), 2.51 (1H, dd, *J* = 6.8, 12.8 Hz), 2.92 (1H, dd, *J* = 6.9, 12.8 Hz), 3.49 (1H, dd, *J* = 6.9, 14.2 Hz), 3.70 (2H, s), 3.86 (3H, s), 6.91 (2H, d, *J* = 9.2 Hz), 7.22 – 7.30 (5H, m), 7.83 (2H, d, *J* = 9.2 Hz); ^{13}C-NMR (100 MHz) δ = 17.8, 34.9, 37.2, 40.6, 55.4, 113.7, 126.9, 128.5, 128.8, 129.1, 130.6, 138.5, 163.5, 201.2.

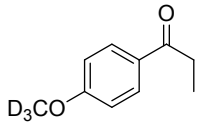
3-benzylthio-2-methyl-1-(4-methoxy-d_3-phenyl)propan-1-one (7-d_3)



7-d_3

^{1}H-NMR (400 MHz): δ = 1.20 (3H, d, *J* = 6.9 Hz), 2.51 (1H, dd, *J* = 6.8, 12.8 Hz), 2.91 (1H, dd, *J* = 6.9, 12.8 Hz), 3.49 (1H, dd, *J* = 6.9, 14.2 Hz), 3.70 (2H, s), 3.86 (trace), 6.90 (2H, d, *J* = 9.2 Hz), 7.22 – 7.30 (5H, m), 7.84 (2H, d, *J* = 9.2 Hz); ^{13}C-NMR (100 MHz) δ = 17.7, 34.9, 37.2, 40.6, 54.6 (t, *J* = 21.6 Hz), 113.7, 126.9, 128.4, 128.8, 129.1, 130.5, 138.4, 163.5, 201.2.

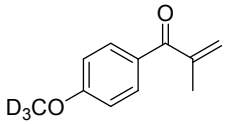
4-methoxypropiophenone-d_3 (9-d_3)[10]



9-d_3

^{1}H-NMR (500 MHz): δ = 1.21 (3H, t, *J* = 7.4 Hz), 2.95 (2H, q, *J* = 7.4 Hz), 6.92 (2H, d, *J* = 9.1 Hz), 7.93 (2H, d, *J* = 9.1 Hz); ^{13}C-NMR (125 MHz) δ = 8.40, 31.4, 113.6, 130.0, 130.2, 163.3, 199.4.

1-(4-methoxyphenyl)-2-methylprop-2-en-1-one (6-d_3)



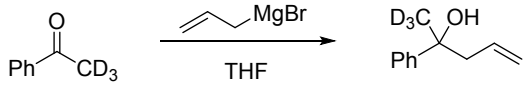
6-d_3

^{1}H-NMR (500 MHz): δ = 2.06 (3H, s), 3.85 (trace), 5.53 (1H, s), 5.79 (1H, s), 6.91 (2H, d, *J* = 6.9 Hz), 7.78 (2H, d, *J* = 6.9 Hz); ^{13}C-NMR (100 MHz) δ = 19.0, 54.6 (tt, *J* = 21.5, 21.5), 113.4, 124.6, 129.9, 131.8, 143.9, 163.0, 197.1.

C) Indium(0) catalyzed allylation reactions in water

Acetophenone **10-d_3**, Allylboronate **11** were prepared following reported methods.[11,12] Indium powder (Aldrich) was used as purchased. Internal standard **12-d_3** was synthesized as follows.

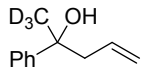
Scheme S2. Preparation of **12-d_3**



10-d_3 **12-d_3**

To a solution of acetophenone-d_3 (**10-d_3**; prepared by literature method,[11] 1.23 g, 10 mmol) in anhydrous THF, a commercial allylmagnesium bromide solution (Aldrich; 1M, 12 mL) was added dropwise at 0 °C. The mixture was stirred 3 hours at room temperature and then was quenched with 1N aq. HCl solution. The mixture was extracted with ethyl acetate and combined organic layer was washed with brine. After dryness over Na_2SO_4 the material was purified over silica gel column chromatography to afford the target compound **12-d_3** (730 mg, 4.42 mmol, 44%).

Phenylpent-4-en-2-ol (12-d_3)



12-d_3

^{1}H-NMR (400 MHz): δ = 1.55 (trace), 2.08 (1H br s), 2.51 (1H, dd, *J* = 8.4, 13.2 Hz), 2.70 (1H, dd, *J* = 6.5, 13.2 Hz), 5.11-5.16 (2H, m), 5.57-5.70 (1H, m), 7.20-7.45 (5H, m); ^{13}C-NMR (100 MHz): δ = 30.0 (multiplet), 48.4, 73.6, 119.4, 124.7, 126.6, 128.1, 133.6, 147.6.

3. DART-MS monitoring experiments

D) Data treatment

The machine was calibrated with PEG-200 before starting experiments. From the total ion chromatogram (TIC) regions from 177.0000 to 177.5000 (for **2-d_0**), from 181.0000 to 181.5000 (for **2-d_4**) were extracted as selected ion chromatograms (SICs). After baseline correction (Sonneveld-Visser method[13]) for SIC, peak integration was taken. Initial reaction rates were determined by limiting the reaction profile up to 40% yield or 1 hour with linear least square regression.

E) Requirements for the reactions and analysis

For the high quantitativity of the reaction monitoring by mass spectrometry, there are several limitations exist on reactions and monitoring methods as follows;

1. (Reaction) No reverse reaction / no decomposition of product

If a chemical reaction has a reverse pathway or a decomposition pathway of a product, an internal standard is decomposed as it is the same chemical as the reaction product. In the monitoring study of a target reaction, the pathway must not exist, or at least must be slow at ignorable level.

2. (Reaction) Fast matter exchange between phases

A reaction proceeds in limited area of a reaction mixture such as interface. A matter exchange between phases is faster than a reaction to keep the ratio of isotopes uniform.

3. (Analysis) No progress of a target reaction on an ionization process

Any further progress of a target reaction after sampling must be avoided to maintain an isotope ratio of a product. An ionization process on mass spectrometry applies large energy to ionize a molecule, and this large energy sometimes induces unexpected chemical reactions. An ionization method must be chosen carefully to keep an isotopic ratio during ionization on mass spectrometry.

4. (Analysis) Fast process without sample preparation

For a real-time monitoring, a lot of data points are required within small time lag. Therefore, each single analysis must be conducted as quickly as possible. Time-taking sample pretreatment must be avoided; in other word, direct analysis is highly desirable of a crude sample from a heterogeneous reaction mixture without any sample pretreatment. An ionization method must be robust enough to analyze a heterogeneous mixture of solid, liquid and gas samples.

F) Representative procedures of direct-type and Mukaiyama aldol reactions.

Direct-type aldol reaction

Before conducting monitoring experiments, some validations were conducted to confirm whether a reaction system satisfies the requirement above; initially a mixture of ketone **1** and formaldehyde in methanol was subjected to DART-MS to detect no signal of the product **2**, indicating no reaction ocurred on a DART ionization process (E-3). Secondary, product **2** was mixed with catalysts in water and the mixture was subjected to DART-MS analysis to detect no signal of ketone **1**, indicating no decomposition of product **2** both under reaction conditions (E-1) and on ionization process (E-3).

To a reaction vessel $Sc(DS)_3$ (33.6 mg, 0.0400 mmol), NaDS (173 mg, 0.600 mmol), 2,2'-bipyridine ligand **5** (15.7 mg, 0.0480 mmol) and water (0.63 mL) were added and stirred vigorously at 30 °C for an hour. Ketone **1** (58.5 mg, 0.400 mmol), **2-d_4** (0.040 mmol, solution in MeOH), and formaldehyde (35% aqueous solution, 167 µL) were added successively. Aliquot sample was taken repeatedly by an autosampler with 1.8 mm glass rod and was subjected to DART-MS. M/z regions corresponding to **2**, **2-d_4** and **1** were recorded for initial stage of the reaction. In addition, to ensure that there is no decomposition of the internal standard, m/z region of **1-d_4**, corresponding to deuterated starting materials, was also recorded to detect nothing. After 42 hours the reaction was quenched by adding DCM, aq. $NaHCO_3$ solution and brine. The mixture was extracted with DCM and dried over anhydrous

Na_2SO_4. After removal of solvent under vacuum condition, a crude mixture was purified over pTLC (hexanes/ethyl acetate = 2/1) to afford the desired product **2** (69.2 mg, 0.392 mmol, 98%, 49% ee).

Mukaiyama aldol reaction

Initial validation of the reaction was conducted in a similar manner to the direct-type aldol reaction.

To a reaction vessel $Sc(DS)_3$ (33.6 mg, 0.0400 mmol), NaDS (173 mg, 0.600 mmol), 2,2'-bipyridine ligand **5** (15.7 mg, 0.0480 mmol), and water (1.83 mL) were added and stirred vigorously at 20 °C for an hour. Silyl enol ether **4** (87.3 mg, 0.400 mmol), **2-d_4** (0.040 mmol, solution in MeOH), and formaldehyde (35% aqueous solution, 167 μL) were added successively. Aliquot sample was taken by an autosampler with 1.8 mm glass rod and was subjected to DART-MS. After an hour the reaction was quenched by adding DCM, aq. $NaHCO_3$ solution and brine. The mixture was extracted with DCM and dried over anhydrous Na_2SO_4. After removal of solvent under vacuum condition, a crude mixture was purified over pTLC (hexanes/ethyl acetate = 2/1) to afford the desired product **2** (54.1 mg, 0.307 mmol, 77%, 87% ee).

Representative mass spectra and selected ion chromatograms (SIC) of the monitoring study of Mukaiyama aldol reactions are shown below (Figures **S1** – **S5**).

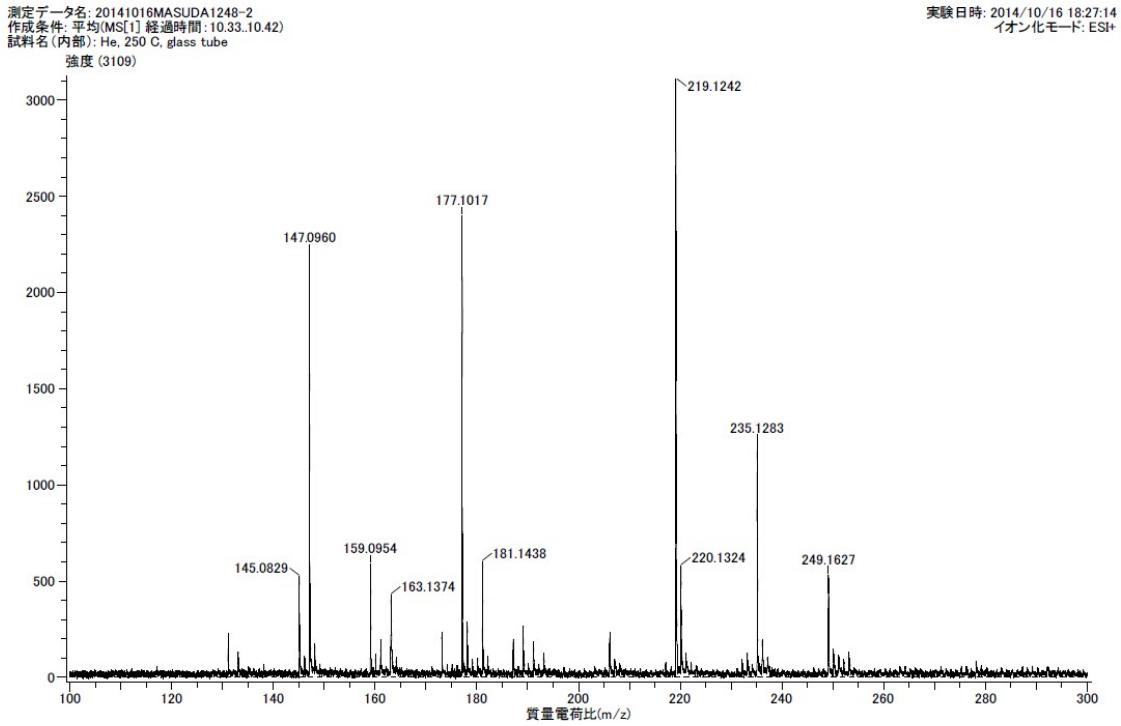


Figure S1. Representative mass spectrum of the Mukaiyama aldol reaction (**Scheme 1**).

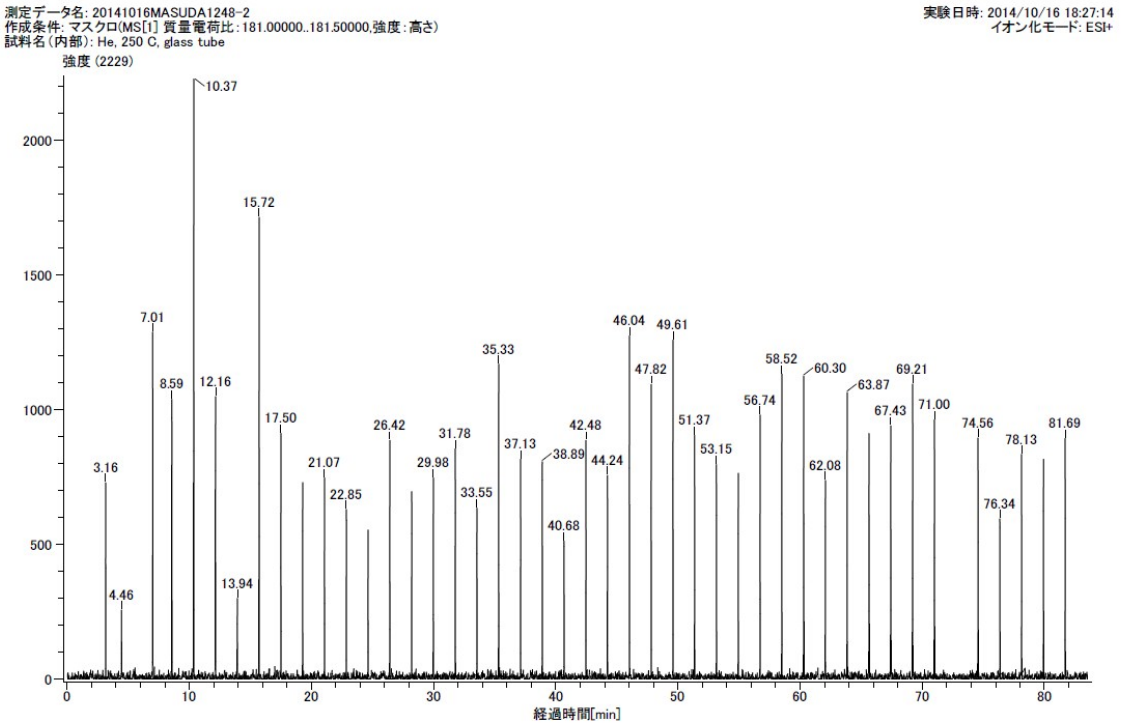


Figure S2. SIC of **2-d$_4$** (Internal standard).

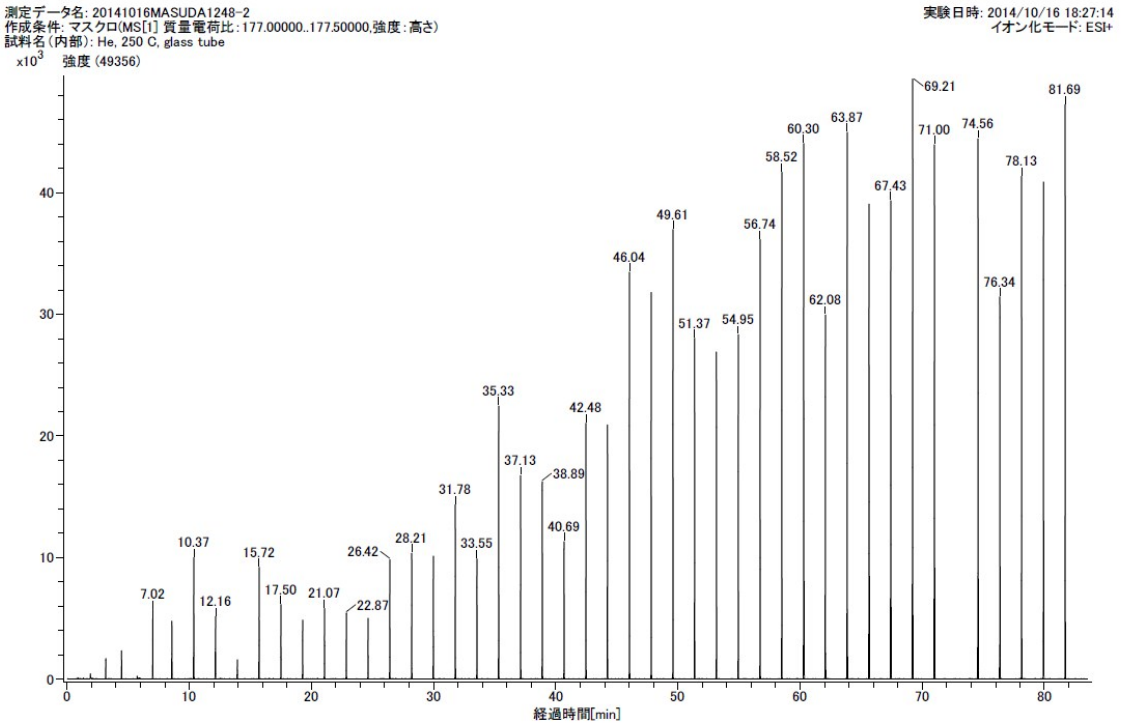


Figure S3. SIC of **2** (non-deuterated; reaction product).

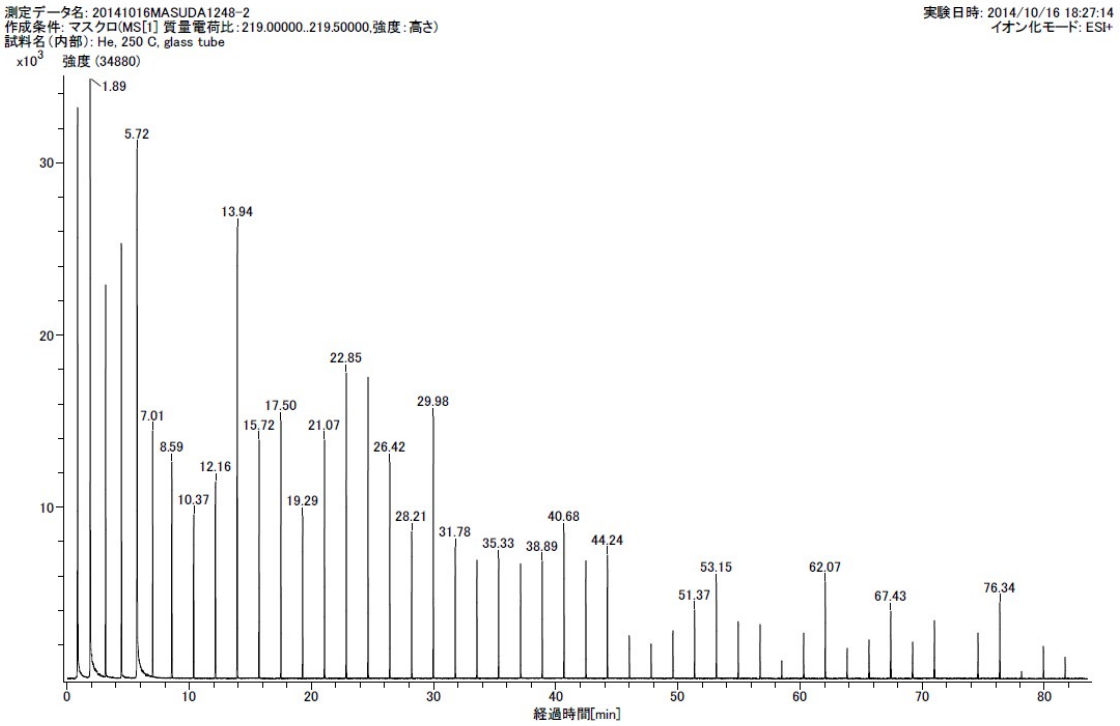


Figure S4. SIC of **4a**.

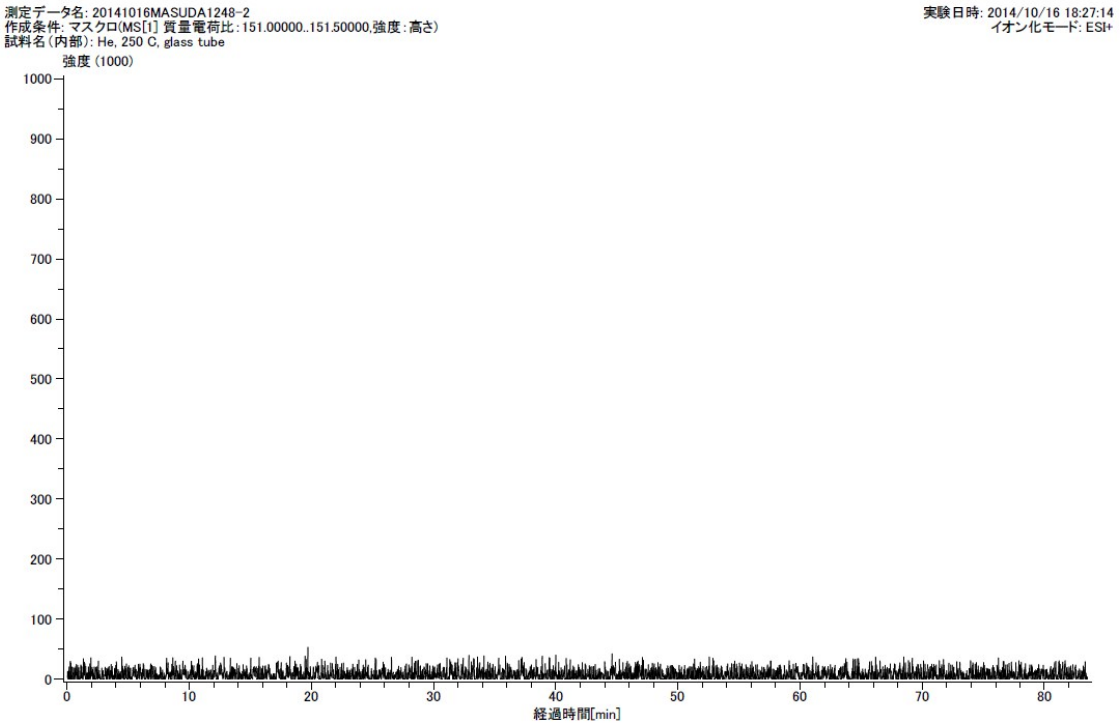
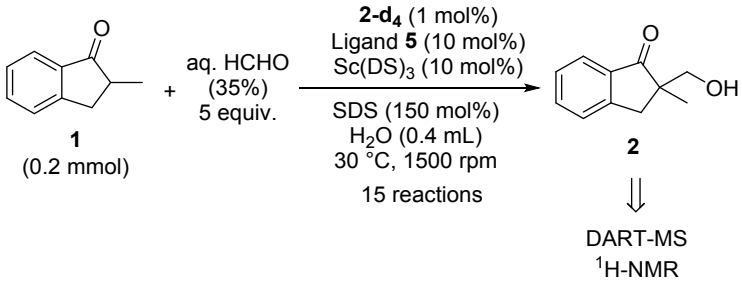


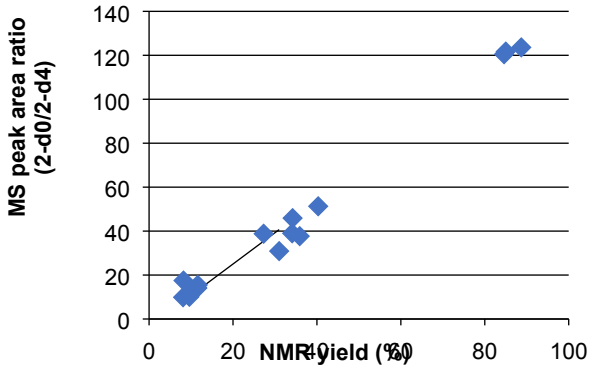
Figure S5. SIC of **1-d$_4$** (corresponding to decomposed internal standard **2-d$_4$**, no detection of peak indicates **2-d$_4$** is stable both under reaction conditions and on DART ionization)

G) Comparison of DART-MS and NMR

To verify the method, comparative experiments of our MS method were conducted with NMR spectrometry. 15 batch reactions were conducted *in the presence of* internal standard **2-d$_4$** following the representative procedure (**Scheme S3**). The reactions were conducted in several different reaction times to compare NMR yield and MS yield in a wide range. Crude NMR yields were determined by using 1,1,2,2-tetrachloroethane as an internal standard and MS yields were determined from the isotope ratio of product **2** in the crude mixture. To avoid the heterogeneity effect in NMR experiment, the yield of the product **2** was determined by quenching all the amount of a batch sample for crude ^{1}H-NMR analysis.

Scheme S3. Comparative experiments between MS and NMR (1)

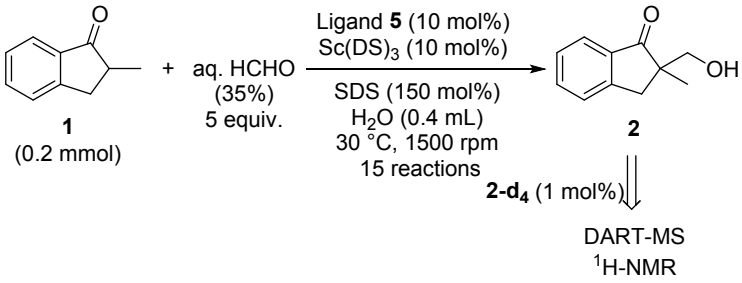


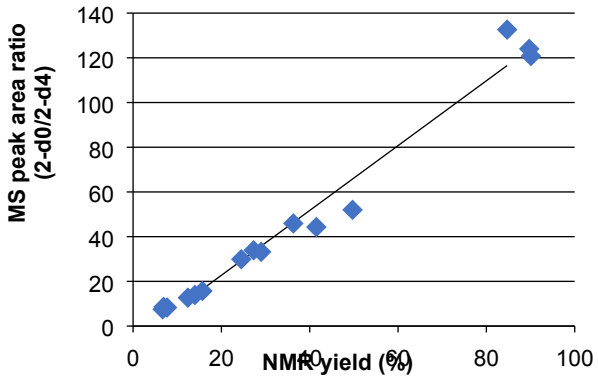


The results showed good correlation beteween MS peak ratio and NMR yield (R^2 = 0.98). In some reactions the product **2** was isolated by pTLC, and isolated yields were in good agreement with NMR yields. In any analysis, no peak of **1-d$_4$** (m/z = 151) was detected during crude DART-MS analysis of any experiment, which implies there is no retro aldol process to decompose **2-d$_4$**.

Then the other set of reactions were conducted *in the absence* of internal standard **2-d$_4$** and quenched following the standard reaction procedure. After quenching internal standard **2-d$_4$** was added and then DART-MS and ^{1}H-NMR analyses were conducted as previous set of experiments.

Scheme S4. Comparative experiments between MS and NMR (2): Late-stage addition of internal standard





As a result, linear relationships between NMR and MS were observed with similar slope to previous experiment. The slopes 1.42 and 1.45 were in good agreement; it is concluded that there was no decomposition of internal standard during the reactions.

No decomposition of **2-d_4** during reaction means that the compound can be used as internal standard, and disagreement of yields calculated by MS and NMR were to be reasoned for some other issues including natural isotope distributions (especially carbon) and contamination of proton during the synthesis of internal standard **2-d_4**. Probably this disagreement is caused by multiplex reasons, but the quantification would be practically possible with calibration between MS and NMR yield.

H) Calibration

A calibration experiment was conducted by mixing compounds **2** and **2-d_4** in several different ratios. Aqueous solutions of compound **2-d_4** (5.055 g/L, 72.0 µL, 2.02 µmol as content) and 0.500, 1.00, 2.00, 5.00 and 10.00 mL of compound **2** solution in water (1.384 g/L) were mixed and analyzed by DART-MS. Each solution was analyzed 6 times and the average was taken for the calibration curve (**Figure S6**). Ideally 1:1 relationship was expected, though the calibration experiment gave 1.4 times larger MS peak ratio (**2**/**2-d_4**) than its molar ratio. This is probably due to the proton contamination in the internal standard **2-d_4**. Commercially available benzene-d_6 and water-d_2 contain d_0 molecules as internal standards (99.5% and 99.8% purities for each), and proton exchange reaction could occur during Friedel-Crafts type acylation/cyclization reaction in trifluoromethanesulfonic acid-d_1 (TfOD, derived from Tf_2O and water-d_2) as a solvent. NMR chart of **2-d_4** clearly shows a contamination of **2-d_3** (or much less deuterated **2**) to decrease actual content of **2-d_4** (**Figure S7**).

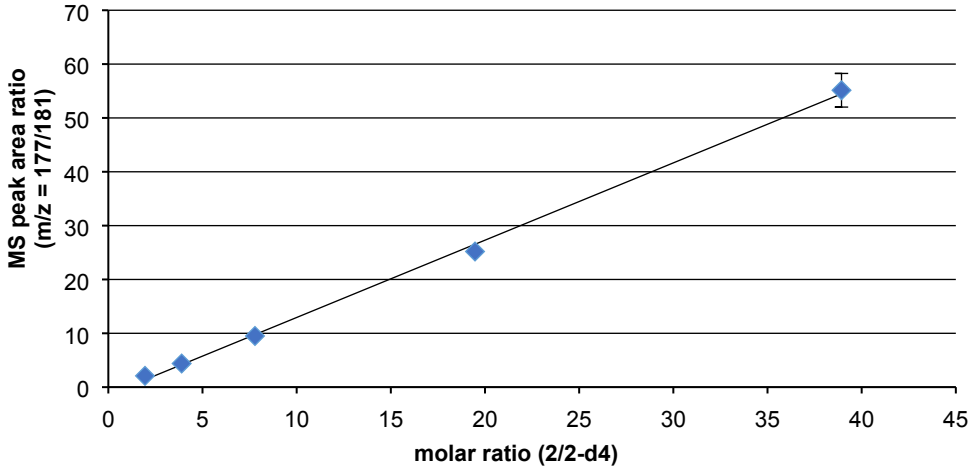


Figure S6. A calibration curve of the yield derived from isotope ratio

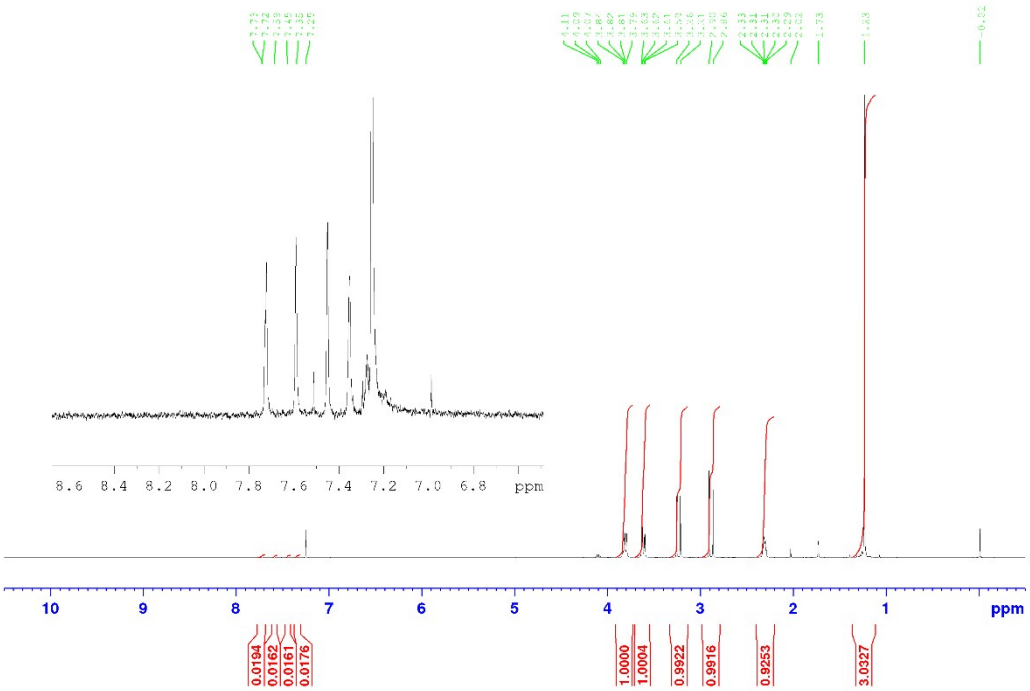
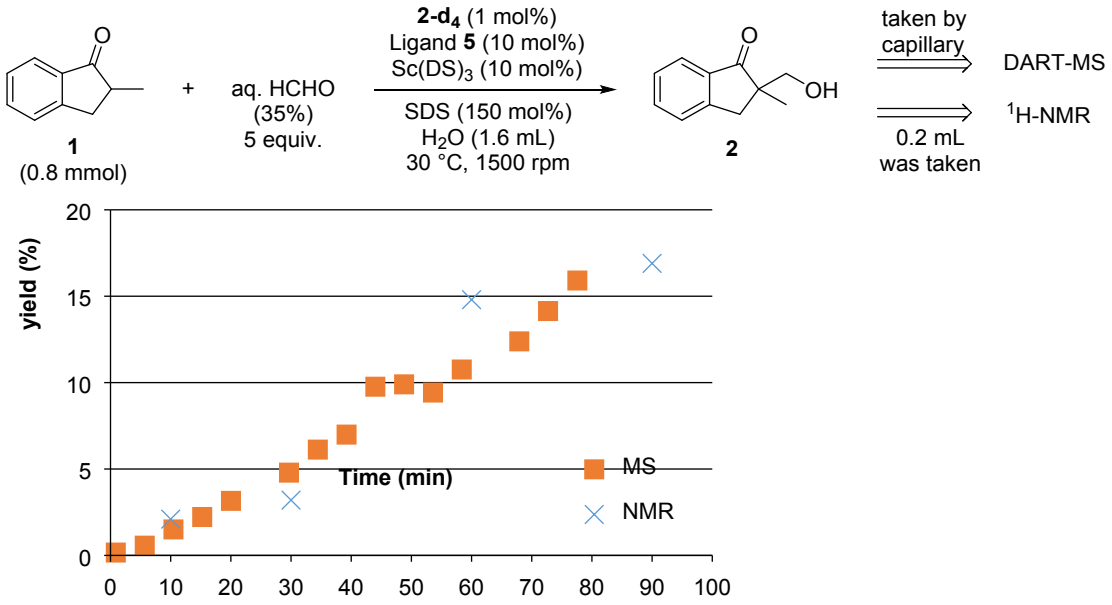


Figure S7. NMR chart of **2-*d_4***

I) Simultaneous monitoring of the reaction by MS and NMR

Direct-type aldol reaction was monitored by DART-MS and by aliquot NMR analysis simultaneously. The reaction was conducted in a large scale (0.8 mmol, total 1.6 mL reaction mixture), then the analytical sample was taken by an auto-sampler with capillary for DART-MS analysis, and 0.20 mL of aliquot was taken by syringe for NMR analysis. MS yield was determined by the isotope ratio of compound **2**, NMR yield was determined by the ratio of starting material **1** and product **2**.

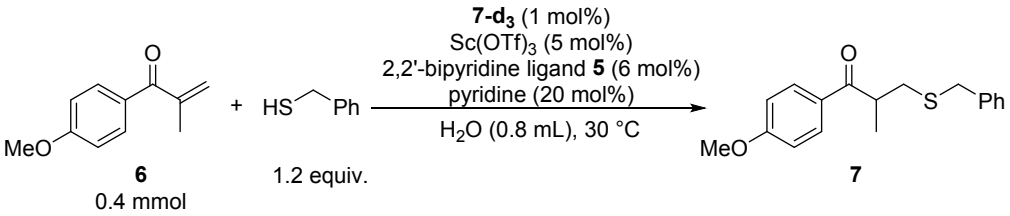
Scheme S5. Direct comparison of MS reaction profile and NMR profile

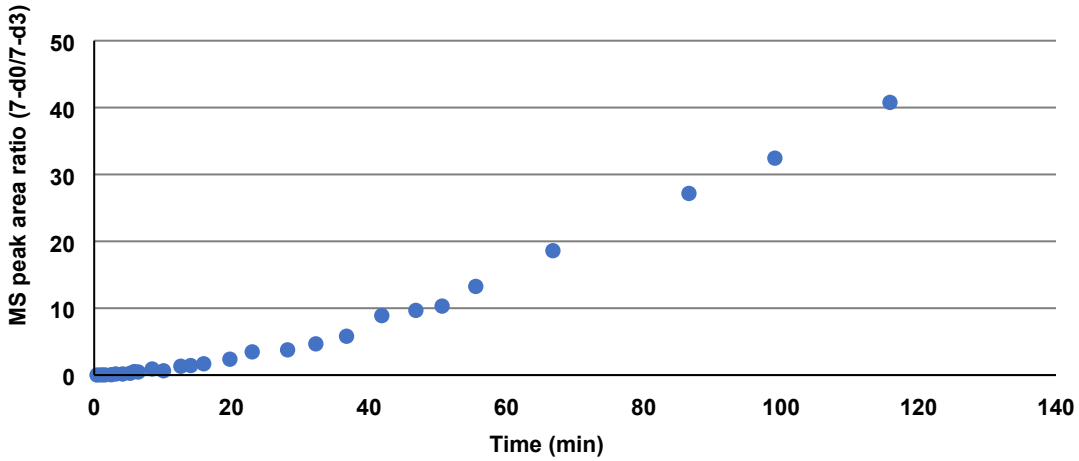


As a result, reaction profile by MS showed much better linearity than by NMR. The result of NMR had some difficulties for quantitativity as an aliquot sample taken from the heterogeneous mixture do not reflect original molar ratio. Excellent linearity of our MS method with isotope labelled internal standard clearly demonstrated the advantage over conventional NMR method.

J) Further examples of reaction monitoring of heterogeneous reactions

Scheme S6. Real-time monitoring study of 1,4-addition/enantioselective protonation reactions in water[8]





In the title reaction mixture, substrates (**6**, BnSH), internal standard **7-d$_3$** and pyridine formed water-immiscible organic particles while the Sc complex solubilized in aqueous media. This water-organic biphasic reaction was successfully monitored under conditions slightly modified from original report.[8] The result is shown in **Scheme 6** (without calibration). Representative mass spectrum of the monitoring experiment is shown in **Figure S8**.

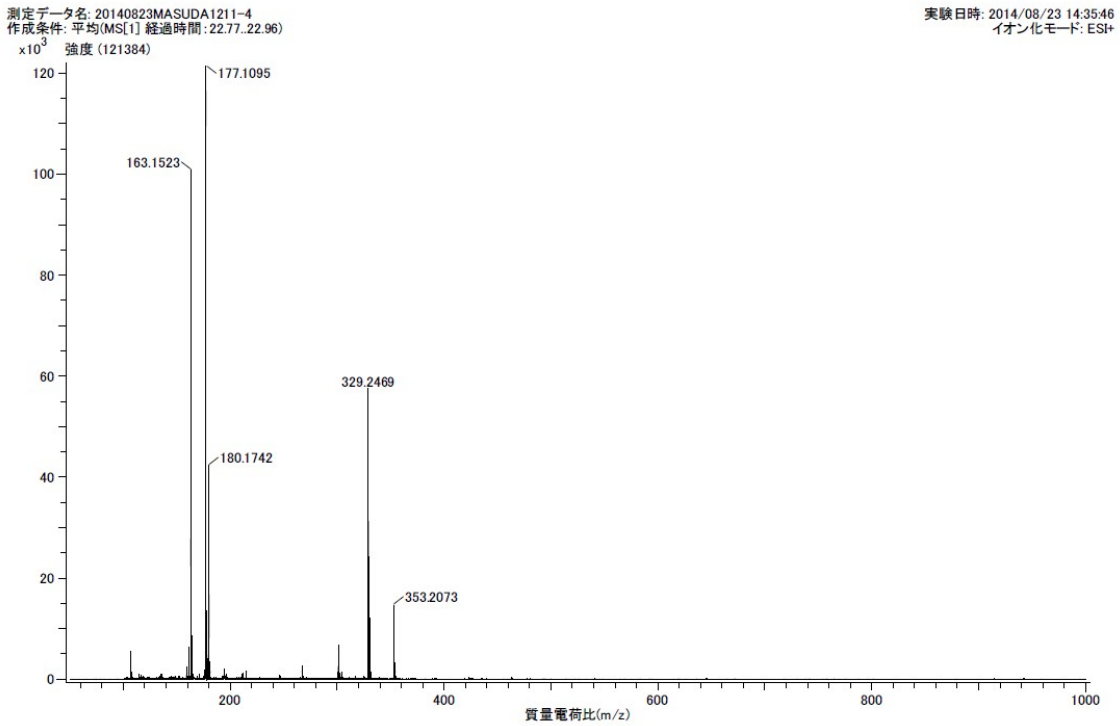
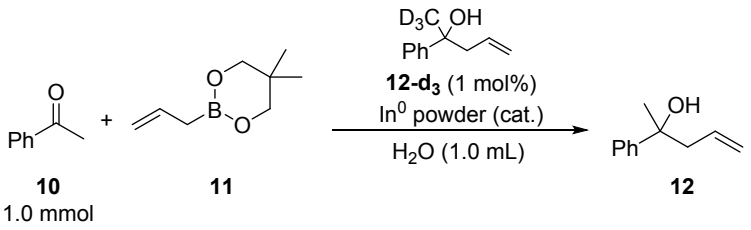
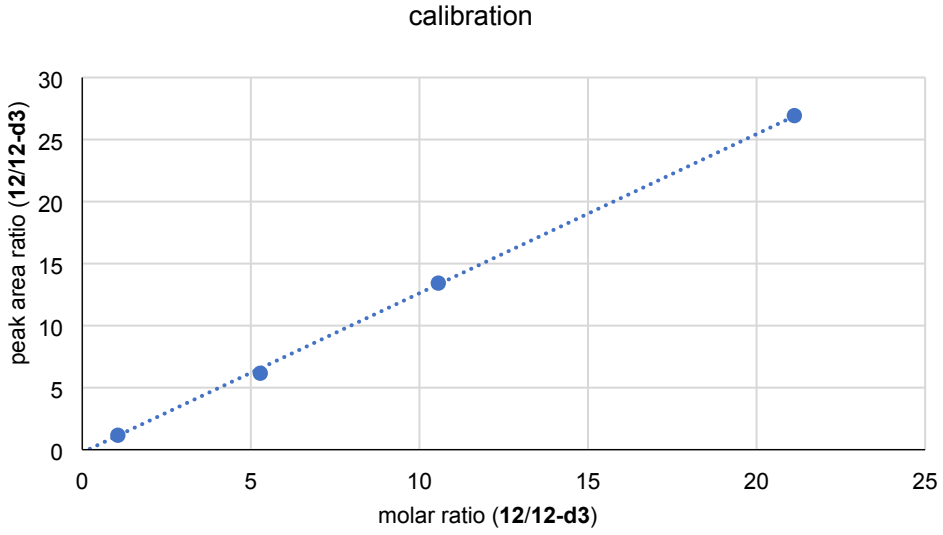


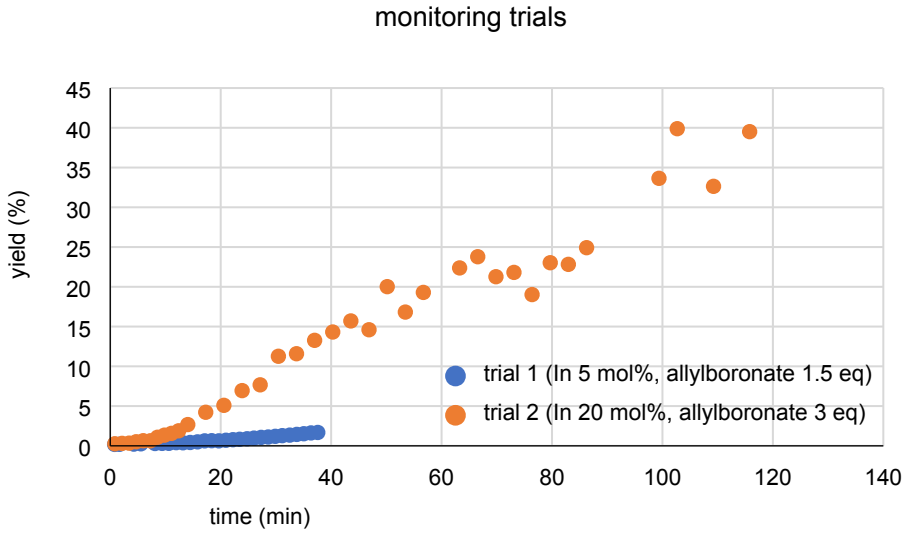
Figure S8. Representative mass spectrum of 1,4-addition reactions (**Scheme S6**).

Scheme S7. Real-time monitoring study of indium(0) catalyzed allylation reactions in water[14]



10 1.0 mmol **11** **12**





In the title reaction, substrates (**10** and **11**) exists as organic liquid and indium exists as a solid in water and the mixture exhibits totally 3 phases (2 liquids, 1 solid). Calibration was conducted of **12** and synthesized internal standard **12-d$_3$**. The monitoring was conducted in the presence of internal standard **12-d$_3$** successfully with slightly modified conditions from original report.[14] In the presence of 5 mol% indium, the reaction was too sluggish to monitor and resulted ~1.5% around 40 min. Under the modified conditions (In 20 mol%, allyl boronate 3 equivalents) the reaction was monitored successfully up to 30% yield within 120 min. Representative mass spectrum is shown in **Figure S10**. Further detailed study of this reaction is currently ongoing in our group.

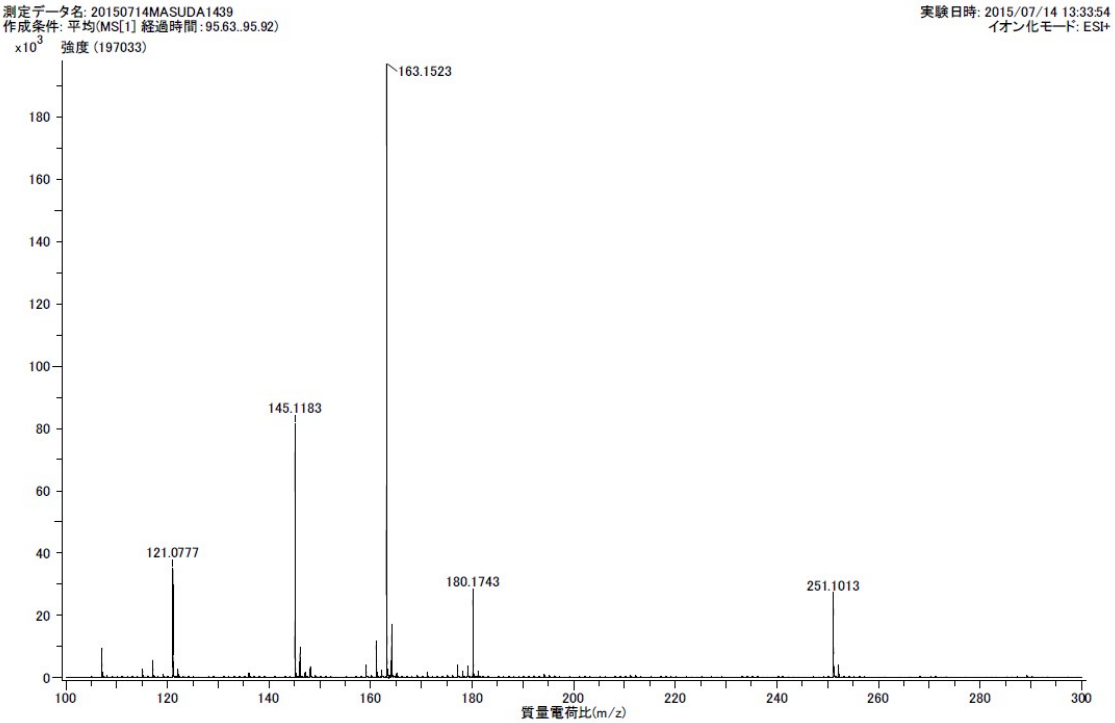


Figure S9. Representative mass spectrum of allylation reactions (**Scheme S7**).

4. Miscellaneous

K) Light scattering in the reaction mixture

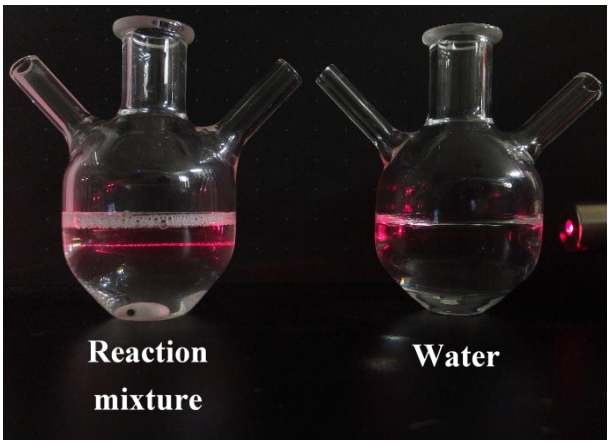


Figure S10. Light scattering in the reaction mixture

L) Wide deviations of non-isotopic internal standard in heterogeneous mixture

For the demonstration, an additional experiment is conducted; Et_3N (200 µL) and $^{i}Pr_2NEt$ (200 µL) were vigorously mixed in pure water (4.0 mL) to form heterogeneosus mixture, and was analyzed by DART-MS with autosampler system (DART: He, 250 °C) for 12 times. The result of the detection is listed in the table S1; Et3N appeared in very small peak intensity probably due to the ion suppression by $^{i}Pr_2NEt$. Within 12 times of repetitive analysis of this mixture, peak intensity of $^{i}Pr_2NEt$ varies from 3000 to 75000 (25 times difference), and the peak ratio of $^{i}Pr_2NEt$ to Et_3N shows random value from 65 to 928, resulting relative standard deviation in 90.3%.

Table S1. Detection trial of amines in water under heterogeneous conditions

Trial	Peak area ($^{i}Pr_2NEt$)	Peak area (Et_3N)	Peak area ratio
1	5986.26	37.58	159.29
2	8901.63	126.65	70.29
3	2996.54	21.77	137.65
4	18253.23	19.67	927.97
5	35213.65	199.54	176.47
6	35919.24	121.84	294.81
7	48428.77	336.39	143.97
8	58261.76	233.82	249.17
9	42110.66	137.3	306.71
10	40677.29	396.97	102.47
11	37406.11	573.35	65.24
12	75515.64	123.78	610.08

5. References

1 G. K. S. Prakash, F. Paknia, H. Vaghoo, G. Rasul, T. Mathew and G. A. Olah, *J. Org. Chem.*, 2010, **75**, 2219–2226.
2 M. Kokubo, C. Ogawa and S. Kobayashi, *Angew. Chemie Int. Ed.*, 2008, **47**, 6909–6911.
3 C. Bolm, M. Ewald, M. Felder and G. Schlingloff, *Chem. Ber.*, 1992, **125**, 1169–1190.
4 C. Bolm, M. Zehnder and D. Bur, *Angew. Chemie Int. Ed. English*, 1990, **29**, 205–207.
5 S. Ishikawa, T. Hamada, K. Manabe and S. Kobayashi, *Synthesis (Stuttg).*, 2005, **2005**, 2176–2182.
6 T. Poisson, V. Dalla, F. Marsais, G. Dupas, S. Oudeyer and V. Levacher, *Angew. Chemie Int. Ed.*, 2007, **46**, 7090–7093.
7 S. Kobayashi, M. Kokubo, K. Kawasumi and T. Nagano, *Chem. - An Asian J.*, 2010, **5**, 490–492.
8 T. Kitanosono, M. Sakai, M. Ueno and S. Kobayashi, *Org. Biomol. Chem.*, 2012, **10**, 7134.
9 A. Bhattacharya, B. Segmuller and A. Ybarra, *Synth. Commun.*, 1996, **26**, 1775–1784.
10 J. Ruan, O. Saidi, J. A. Iggo and J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 10510–10511.
11 I. H. Hillier, S. Smith, S. C. Mason, S. N. Whittleton, C. I. F. Watt and J. Willis, *J. Chem. Soc. Perkin Trans. 2*, 1988, 1345.
12 M. Myslinska, G. L. Heise and D. J. Walsh, *Tetrahedron Lett.*, 2012, **53**, 2937–2941.
13 E. J. Sonneveld and J. W. Visser, *J. Appl. Crystallogr.*, 1975, **8**, 1–7.
14 U. Schneider, M. Ueno and S. Kobayashi, *J. Am. Chem. Soc.*, 2008, **130**, 13824–13825.