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Cobalt-Catalyzed Intermolecular Hydroacylation of Aldehydes: Station of Hydride Transfer Enables Turnover

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Supporting Information

Contents

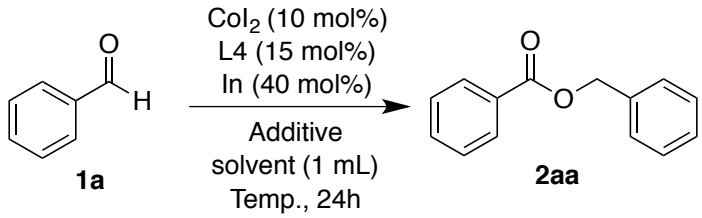
1. General Information.

All reactions were prepared and sealed using a glass flask in a glove box filled with argon. Then the reactions were carried out on a multi-zone reaction platform which was purchased from Tokyo Rikakikai Co., LTD (CCX-1102). Solvents were dried and distilled under argon prior to use. Commercial reagents were purchased from Sigma Aldrich or Alfa Aesar and used as received except for the benzaldehyde which was distilled under argon prior to use. dcpp (1,3-Bis(dicyclohexylphosphine)propane) was used as a prepared solution in toluene (0.1 mg/μL). NMR spectra were recorded on a bruker ASCEND spectrometer (^{1}H, 600 MHz; ^{13}C{^{1}H}, 151 MHz) and (^{1}H, 700 MHz; ^{13}C{^{1}H}, 176 MHz). ^{1}H NMR and ^{13}C NMR, chemical shift δ is given relative to TMS and referenced to the solvent signal. Column chromatography was performed using silica gel. Analytical TLC was done using pre-coated silica gel 60 F_{254} plates. GC analysis was performed using Aglient GC-7890B equipped with a capillary column (DB-FFAP, 30 m×0.32 mm) using a flame ionization detector. GC-MS was performed using GCMS-QP2020 with Rtx-5MS (30 m×0.25 mm) column. UV-vis spectra were recorded with Shimadzu UV-2550.

2 Cobalt-Catalyzed Intermolecular Hydroacylation of Aldehydes

Procedure: To a dry flask containing a toluene (1 mL) solution of cobaltous salt (0.04 mmol, 10 mol%), In (18.4 mg, 0.16 mmol, 40 mol%), phosphine ligand (0.06 mmol, 15 mol%) and additive (1.2 mmol, 3.0 equiv.), benzaldehyde (42.8 mg, 0.4 mmol, 1.0 equiv.) were added in a glove box. The mixture was then stirred and heated up to the designated temperature. After reaction for 24 h, the mixture was cooled to room temperature and extracted with EtOAc (3×10 mL), which was filtered by diatomite subsequently. The filtrate was detected by GC with biphenyl as internal standard.

Table S1. Cobalt-Catalyzed Intermolecular Hydroacylation of Aldehyde[a]



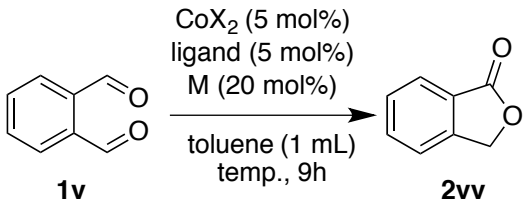
Entry	Additive (equiv.)	Solvent	Temp (^{o}C)	Conv. (%)	Yield[b] (%)
1	*i*Pr$_2$NEt (2.0)	toluene	80	23	21
2	*i*Pr$_2$NEt (3.0)	toluene	80	79	65
3	*i*Pr$_2$NEt (4.0)	toluene	80	55	39
4	*i*Pr$_2$NEt (0.2)	toluene	120	32	9
5	*i*Pr$_2$NEt (1.5)	toluene	120	69	38
6	*i*Pr$_2$NEt (3.0)	toluene	120	99	86
7	*i*Pr$_2$NEt (6.0)	toluene	120	93	60
8	*i*Pr$_2$NEt (9.0)	toluene	120	40	13
9	DBU (3.0)	toluene	80	34	--
10	Pyridine (3.0)	toluene	80	23	9
11	Hantzsch ester (3.0)	toluene	80	38	15
12	Hantzsch ester (3.0)	DMF	80	26	--
13	Hantzsch ester (3.0)	*p*-xylene	80	38	21

[a] General conditions: **1a** (0.4 mmol), CoI_2 (10 mol%), In (40 mol%), L4 (15 mol%), additive (3 eq.), solvent (1 mL), 24 h, [b] Yields determined by GC with biphenyl as internal standard.

3 Cobalt-Catalyzed Intramolecular Hydroacylation of Aldehydes

Procedure: To a dry flask containing a toluene (1 mL) solution of cobaltous salt (0.02 mmol, 5 mol%), element metal (0.08 mmol, 20 mol%), phosphine ligand (0.02 mmol, 5 mol%) and additive (0.02 mmol, 5 mol%), phthalaldehyde (53.7 mg, 0.4 mmol, 1.0 equiv.) were added in a glove box. The mixture was then stirred and heated up to the designated temperature. After reaction for 9 h, the mixture was cooled to room temperature and extracted with EtOAc (3×10 mL), which was filtered by diatomite subsequently. The filtrate was detected by GC with biphenyl as internal standard.

Table S2. Cobalt-Catalyzed Intramolecular Hydroacylation of Aldehyde[a]



1v **2vv**

Entry	Cat.	Metal	Ligand	Temp (^{o}C)	Yield[c](%)
1	CoI_2	Mn	--	150	34
2	CoI_2	In	--	150	90
3	CoI_2	In	L3	80	87
4	CoI_2	In	L3	120	96
5	CoI_2	In	--	120	83

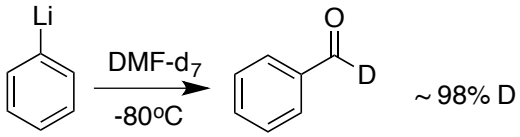
[a] General conditions: **1v** (0.4 mmol), CoX_2 (5 mol%), metal (20 mol%), ligand (5 mol%), toluene (1 mL), 9 h; [c] Yields Determined by GC with biphenyl as internal standard.

4 Mechanistic Insights into the Cobalt-Catalyzed Intermolecular Hydroacylation

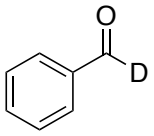
4.1 Deuterium-Labeling Experiments

4.1.1 Synthesis of 1a-*d*

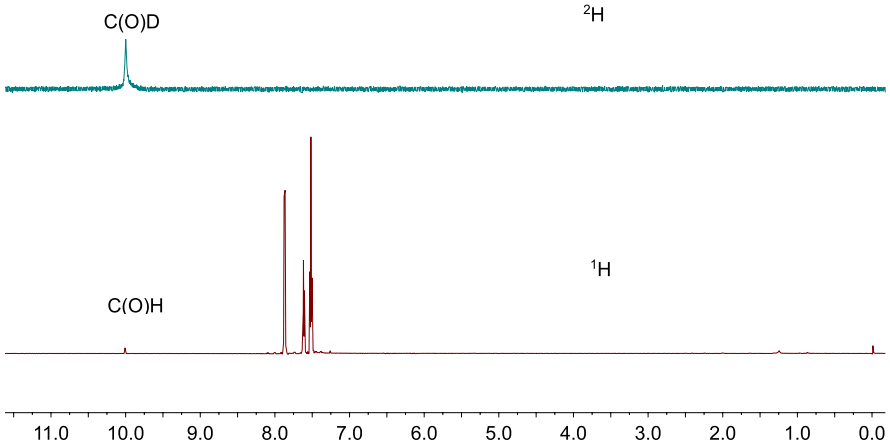
Scheme S1.



N,N-Dimethylformamide-d_7 (1.03 g, 12.9 mmol, 1.1 equiv.) was placed in a three-neck flask in 50 mL of THF at −80 °C. Next, 1.8 M phenyllithium solution (6.5 mL, 11.7 mmol, 1.0 equiv.) was slowly added to the solution at −80 °C under argon. After being stirred for 3 h, the mixture solution was warmed up to room temperature overnight. All solvents were removed by a rotary vacuum at a low temperature about 15 ^{o}C, affording a pale yellow oil. This resulting yellow oil was purified by column chromatography (silica gel, DCM: hexane = 1: 6) to offer a crude product, which was further purified by distillation (100 kPa, 116 ^{o}C, yield: 63%).



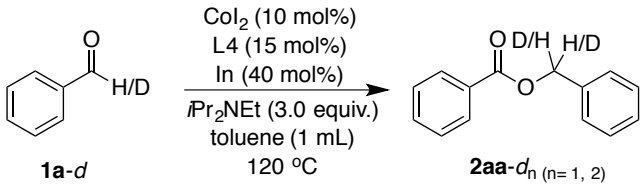
1a-*d*: **^{1}H NMR** (600 MHz, $CDCl_3$, 298K): δ = 10.01 (s, 0.02/1H, CHO), 7.87 (m, 2H, *o*-Ph), 7.62 (m, 1H, *p*-Ph), 7.52 (m, 2H, *m*-Ph). **^{2}H NMR** (46 MHz, $CHCl_3$, 298K): δ = 10.00 (s, C(O)D).



^{1}H (600M, $CDCl_3$, 298K) and ^{2}H NMR (46M, $CHCl_3$, 298K) of **1a**-*d*.

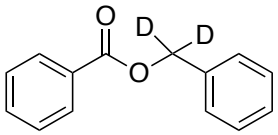
4.1.2 Synthesis of 2aa-d_2

Scheme S2.

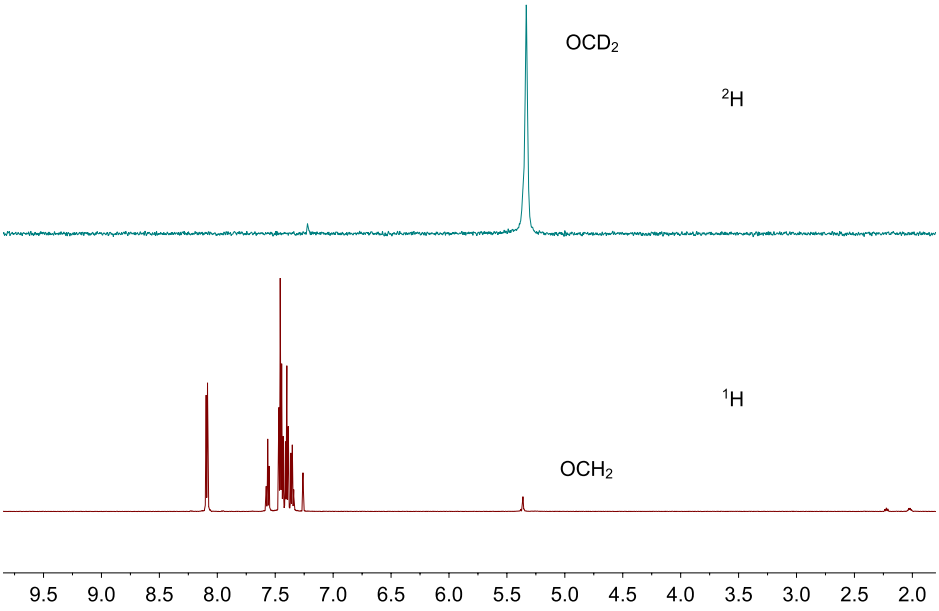


To a dry flask containing a toluene (1mL) of CoI_2 (12.6 mg, 0.04 mmol, 10 mol%), In (18.4 mg, 0.16 mmol, 40 mol%), L_4 (0.1 mg/μL × 261 μL, 0.06 mmol, 15 mol%) and *i*Pr_2NEt (155.1 mg, 1.2 mmol, 3.0 equiv.), benzaldehyde-α-d_1 (42.9 mg 0.40 mmol, 1.0 equiv.) or benzaldehyde **1a** (42.8 mg, 0.4 mmol, 1.0 equiv.) was added in a glove box. The mixture was then stirred and heated to 120°C for 15h. At the end of the reaction, the mixture was cooled to room temperature and extracted with EtOAc (3×10 mL), which was filtered by diatomite subsequently and detected by GC determining the yield. Then the filtrate was dried by Na_2SO_4 overnight and concentrated, then purified by column chromatography (Developing solvent on chromatography purification: petroleum ether/ethyl acetate 30:1; Yield 22.7 mg,

53%).



2aa-*d*$_2$: **^{1}H NMR** (600 MHz, $CDCl_3$, 298 K): δ = 8.09 (m, 2H, *o*-Ph), 7.56 (m, 1H, *p*-Ph), 7.46 (m, 2H, *o*-Ph), 7.45 (m, 2H, *m*-Ph), 7.40 (m, 2H, *m*-Ph), 7.36 (m, 1H, *p*-Ph), 5.36 (s, 0.18/2H, CH_2). ^{2}H **NMR** (92 MHz, $CHCl_3$, 298K): δ = 5.36 (s, CD_2).



^{1}H (600 MHz, $CDCl_3$, 298 K) and ^{2}H NMR (92M, $CHCl_3$, 298 K) of **2aa**-*d*$_2$.

4.1.3 Cross-over Deuterium Experiment

To a dry flask containing a toluene (1mL) of CoI_2 (12.6 mg, 0.04 mmol, 10 mol%), In (18.4 mg, 0.16 mmol, 40 mol%), L_4 (0.1 mg/μL × 261 μL, 0.06 mmol, 15 mol%) and *i*Pr_2NEt (155.1 mg, 1.2 mmol, 3.0 equiv.), benzaldehyde-α-d_1 (42.9 mg 0.40 mmol, 1.0 equiv.) and 4-Me-PhCHO **1b** (48.1 mg, 0.4 mmol, 1.0 equiv.) was added in a glove box. The mixture was then stirred and heated to 120^{o}C for 15h. At the end of the reaction, the mixture was cooled to room temperature and extracted with EtOAc (3×10 mL), which was filtered by diatomite subsequently and detected by GC-MS.

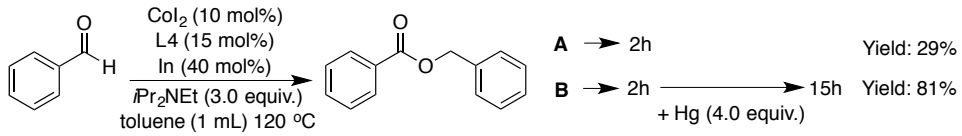
4.2 Experiments for Screening the Induction Period.

Procedure: The reactions were performed in parallel sealed flask for designated

hours on multi-zone reaction platform. To a dry flask containing a toluene (1mL) of CoI_2 (12.6 mg, 0.04 mmol, 10 mol%), In (18.4 mg, 0.16 mmol, 40 mol%), L_4 (0.1 mg/μL × 261 μL, 0.06 mmol, 15 mol%) and *i*Pr_2NEt (155.1 mg, 1.2 mmol, 3.0 equiv.), benzaldehyde **1a** (42.8 mg, 0.4 mmol, 1.0 equiv.) was added in a glove box. A series of parallel reactions was prepared in the same manner and moved out of the glove box. These parallel reactions were heated to designated temperature for designated hours on multi-zone reaction platform. Aliquotes (100 μL) removed of every reaction were immediately frozen at –20 °C to stop further reactions. All samples were extracted with EtOAc (3×10 mL) and filtrated by diatomite. The conversion of substrate **1a** was monitored by GC.

4.3 Amalgamation Reaction

Scheme S3.



Procedure: Two parallel reactions were performed in sealed flask on multi-zone reaction platform. To the dry flask containing a toluene (1mL) of CoI_2 (12.6 mg, 0.04 mmol, 10 mol%), In (18.4 mg, 0.16 mmol, 40 mol%), L_4 (0.1 mg/μL × 261 μL, 0.06 mmol, 15 mol%) and *i*Pr_2NEt (155.1 mg, 1.2 mmol, 3.0 equiv.), benzaldehyde **1a** (42.8 mg, 0.4 mmol, 1.0 equiv.) was added in a glove box. The sealed flasks moved out of the glove box were heated to 120 °C for 2 h. One of them was stopped and the other one was again put into the glove box to add mercury (4.0 mmol, 802.4 mg). Then the latter was sealed and moved out to continue reacting for 13 h at 120 °C. It turned out that the yield of former was 29%, while the latter was 81% (detected by GC with biphenyl as the internal standard) indicating that the catalyst was homogeneous.

4.4 UV-visible analysis

Procedure: To a dry flask containing a toluene (739 μL) solution of CoI_2 (12.6 mg,

0.04 mmol, 10 mol%), In (18.4 mg, 0.16 mmol, 40 mol%), L_4 (0.1 mg/μL × 261 μL, 0.06 mmol, 15 mol%,), [*i*Pr_2NEt (155.1 mg, 1.2 mmol, 3.0 equiv.)], benzaldehyde (0.4 mmol, 1.0 equiv.) was added in the glove box. The reactions were all performed in parallel sealed flask for designated hours at 80°C. Aliquots (30μL) removed were immediately frozen at −20 °C to stop further reactions and was added 2970 μL toluene for UV analysis.

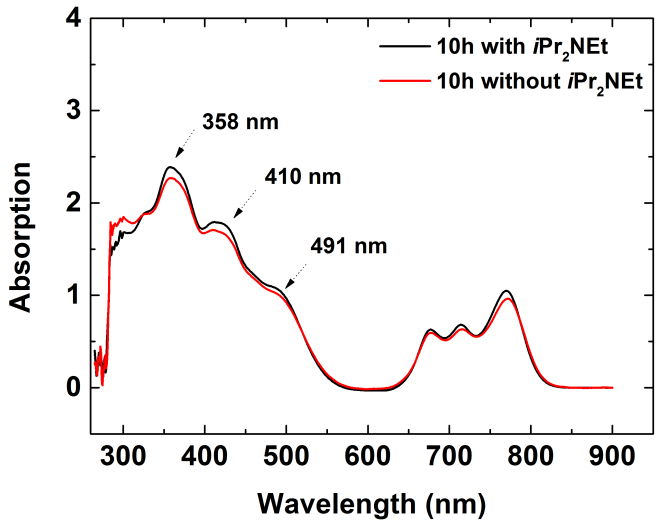


Figure S1. UV-visible Spectra Acquired from Monitoring the Reduction of CoI_2 for 10 h in the absence of **1a**. Conditions: (A) CoI_2 (0.4 mM), CoI_2 : In : L_4 : *i*Pr_2NEt = 1:4:1.5: 30; (B) CoI_2 (0.4 mM), CoI_2 : In : L_4 = 1:4:1.5.

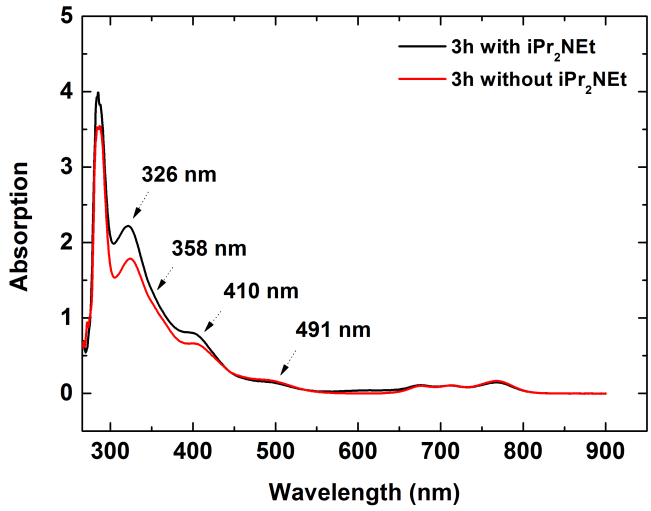


Figure S2. UV-visible Spectra Acquired from Monitoring the Reduction of CoI_2 for 3 h in the presence and absence of *i*Pr_2NEt. Conditions: (A) CoI_2 (0.4 mM), CoI_2 : In : L_4 : **1a** : *i*Pr_2NEt = 1:4:1.5:10:30; (B) CoI_2 (0.4 mM), CoI_2 : In : L_4 : **1a** = 1:4:1.5:10.

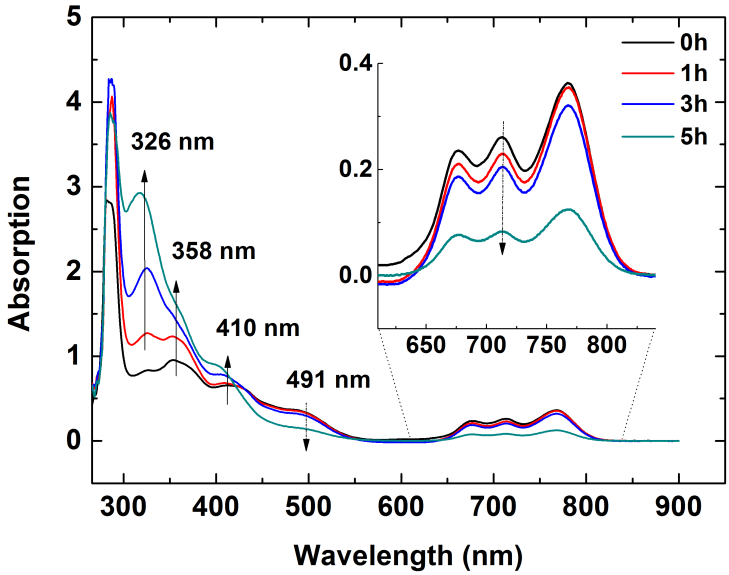


Figure S3. UV-visible Spectra Acquired from Monitoring the Reduction of CoI_2 in the Presence of iPr$_2$NEt. Conditions: CoI_2 (0.4 mM), CoI_2 : In : L_4 : **1a**: iPr$_2$NEt = 1:4:1.5:10: 30.

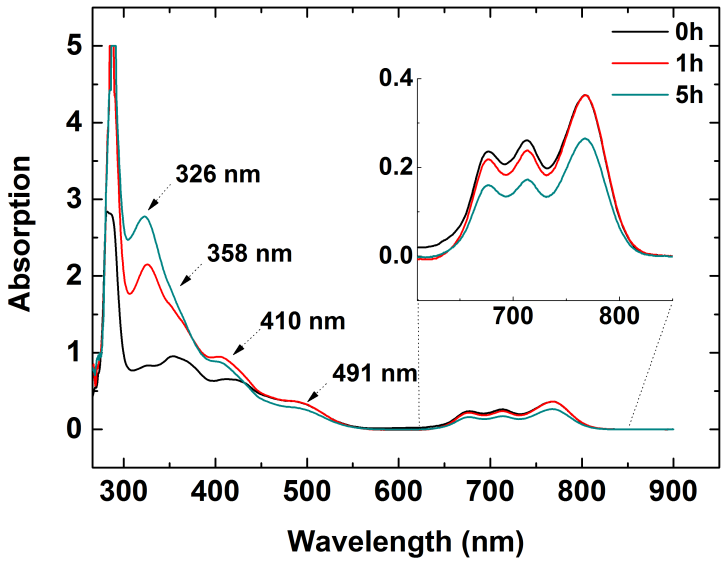


Figure S4. UV-visible Spectra Acquired from Monitoring the Reduction of CoI_2 in the Absence of iPr$_2$NEt. Conditions: CoI_2 (0.4 mM), CoI_2 : In : L_4 : **1a** = 1:4:1.5:10.

4.5 Reaction Order Determination

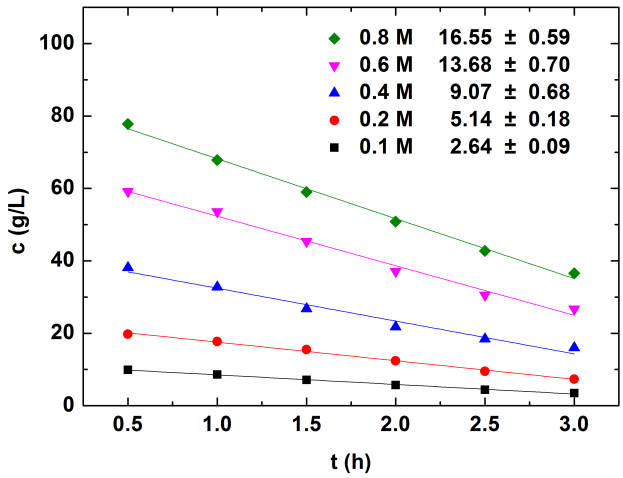


Figure S5. Experiments measuring the concentration of **1a** with respect to time for a series of reactions at varied concentrations of **1a**.

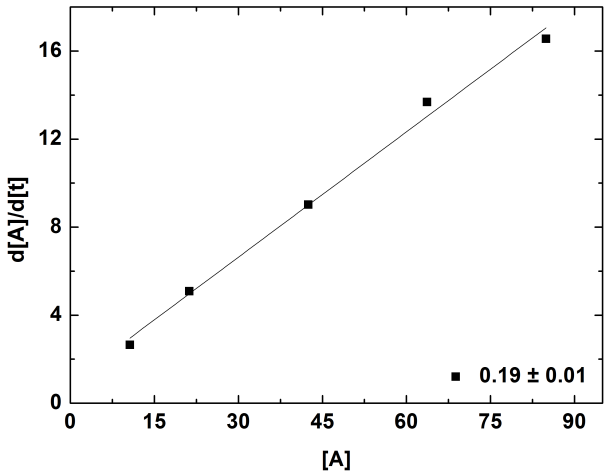
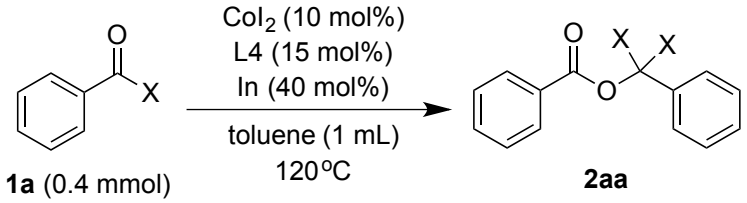


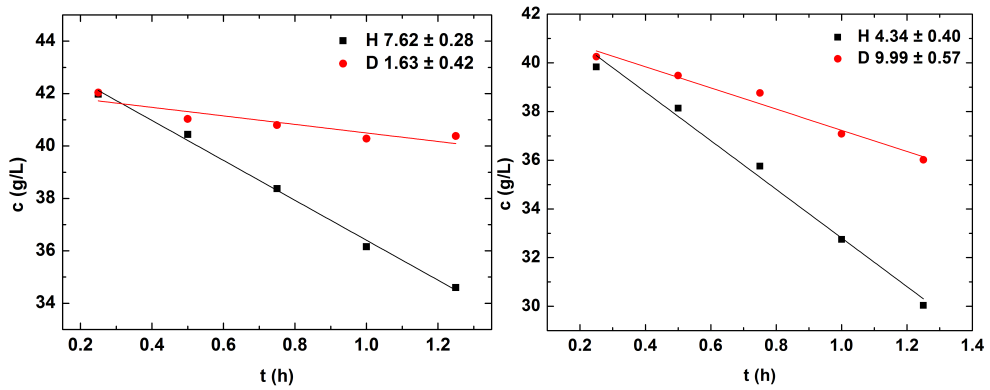
Figure S6. Reaction rates with respect to concentration of **1a**.

4.6 Kinetic Studies.

Procedure: The reactions were performed in parallel sealed flasks for designated time on multi-zone reaction platform. To a dry flask containing a toluene (1 mL) solution of CoI_2 (12.6 mg, 0.04 mmol, 10 mol%), In (18.4 mg, 0.16 mmol, 40 mol%), L_4 (0.1 mg/μL × 261 μL, 0.06 mmol, 15 mol%), [*i*Pr_2NEt (155.1 mg, 1.2 mmol, 3.0 equiv.)], the benzyl aldehyde (0.1~0.8 mmol) was added in the glove box. Five parallel reactions were prepared in the same manner and moved out of the glove box. These parallel reactions were heated to 120 ^{o}C for designated hours on multi-zone reaction platform. Aliquots (100 μL) removed of every reaction were immediately frozen at −20 ^{o}C to stop further reactions. All samples were extracted with EtOAc

(3×10 mL) and filtrated by diatomite. The disappearance of **1a** and appearance of **1ja** were monitored by GC.





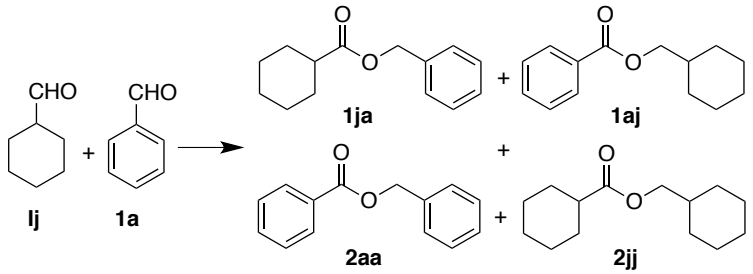
Experiment	X	*i*Pr$_2$NEt	k_x(-/+) / (g•L^{-1}•h^{-1})	KIE(M)
1	H	-	k_H(-) = 7.62 ± 0.28	-
2	D	-	k_D(-) = 1.63 ± 0.42	4.7 ± 0.1
3	H	+	k_H(+) = 4.34 ± 0.40	-
4	D	+	k_D(+) = 9.99 ± 0.57	2.3 ± 0.2

Figure S7. Initial reaction rates with respect to concentration of **1a** or **1a-*d*** in the absence (left) or presence (right) of *i*Pr$_2$NEt.

4.7 Hammett Studies.

4.7.1 Screening of Reaction Conditions of Cross-Esterification for Kinetic Study

Table S3. Conditions Optimization for Hammett Study[a]



Entry	Substrate**1** (equiv.)	Substrate **2** (equiv.)	Yield (%)[b]		
			1ja	**1aj**	**2aa**
1	**1j** (1.0)	**1a** (1.0)	24	14	34
2	**1j** (3.0)	**1a** (1.0)	37	18	15
3	**1j** (5.0)	**1a** (1.0)	45	20	10
4	**1j** (7.0)	**1a** (1.0)	45	20	7

[a] General conditions: **1a** (0.4 mmol), CoI_2 (10 mol%), In (40 mol%), L_4 (15 mol%), iPr$_2$NEt (3.0 equiv.), toluene (1 mL), 120 ^oC, 3 h, yields determined by GC-MS area normalization.

4.7.2 Procedure for Hammett Study

The reactions were performed in parallel sealed flask for designated hours on multi-zone reaction platform. To a dry flask containing a toluene (1 mL) solution of CoI_2 (12.6 mg, 0.04 mmol, 10 mol%), In (18.4 mg, 0.16 mmol, 40 mol%), L_4 (0.1 mg/μL × 261 μL, 0.06 mmol, 15 mol%,) with and without iPr$_2$NEt (155.1 mg, 1.2 mmol, 3.0 equiv.), the respective *para*-substituted benzyl aldehyde (0.4 mmol, 1.0 equiv) and cyclohexanal **1j** (224.3 mg, 2.0 mmol, 5.0 equiv.) were added in the glove box. Five parallel reactions were prepared in the same manner and moved out of the glove box. These parallel reactions were heated to designated temperature for designated hours on multi-zone reaction platform. Aliquots (100 μL) removed of every reaction were immediately frozen at −20 ^oC to stop further reactions. All samples were extracted with EtOAc (3×10 mL) and filtrated by diatomite. The yield of **1j[a,e,f,g]** was monitored by GC. As a result, the reaction rate of each was obtained, then the Hammett slope and electronic effects on induction period were also obtained.

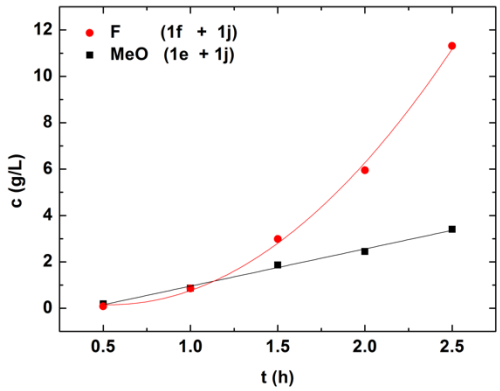


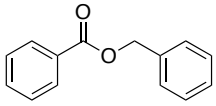
Figure S8. Product formation as a function of time for reactions of **1e**/**1f** and **1g**. Conditions: **1j** (2.0 mmol, 5.0 equiv.), **1**[**e**, **f**] (0.4 mmol, 1.0 equiv.), CoI_2 (10 mol%), In (40 mol%), L4 (15 mol%), toluene (1 mL); iPr$_2$NEt (3.0 equiv.); 120 ^{o}C; yield determined by GC-MS area normalization.

5 Preparation of Esters

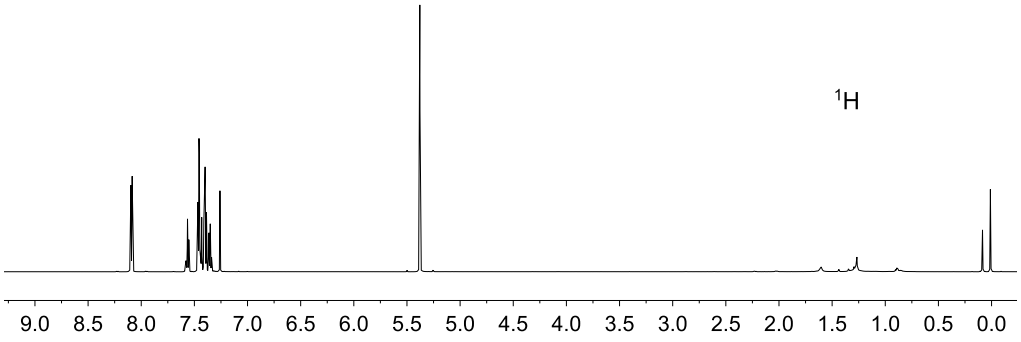
General Procedure

To a dry flask containing a toluene (1 mL) solution of CoI_2 (12.6 mg, 0.04 mmol, 10 mol%), In (18.4 mg, 0.16 mmol, 40 mol%), L4 (0.1 mg/μL × 261 μL, 0.06 mmol, 15 mol%) and iPr$_2$NEt (155.1 mg, 1.20 mmol, 3.0 equiv.), aldehyde (0.4 mmol, 1.0 equiv.) were added in a glove box (a dark brown solution formed immediately upon the addition of toluene to a heterogeneous mixture of CoI_2 and dcpp solution). The mixture was then stirred and heated up to 120^{o}C. After reaction for 15 h, the mixture was cooled to room temperature and extracted with EtOAc (3×10 mL), which was filtered by diatomite subsequently. The filtrate was dried over Na_2SO_4, followed by concentration on rotation machine. The resulted residue was finally purified through column chromatography.

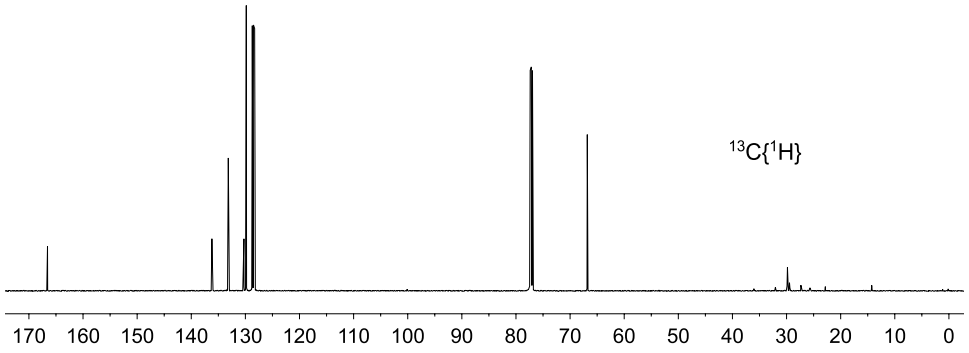
Synthesis of 2aa. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 30:1; Yield 36.5 mg, 86%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 8.09 (m, 2H, *o*-Ph), 7.56 (m, 1H, *p*-Ph), 7.46 (m, 2H, *o*-Ph), 7.44 (m, 2H, *m*-Ph), 7.40 (m, 2H, *m*-Ph), 7.36 (m, 1H, *p*-Ph), 5.38 (s, 2H, CH_2). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K): δ = 166.6 (C=O), 136.2 (*i*-Ph), 133.2 (*p*-Ph), 130.3 (*i*-Ph), 129.8 (*o*-/*m*-Ph), 128.7 (*o*-/*m*-Ph), 128.5 (*o*-/*m*-Ph), 128.4 (*p*-Ph), 128.3 (*o*-/*m*-Ph), 66.8 (CH_2).

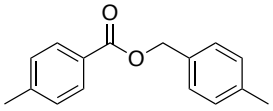


^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2aa**

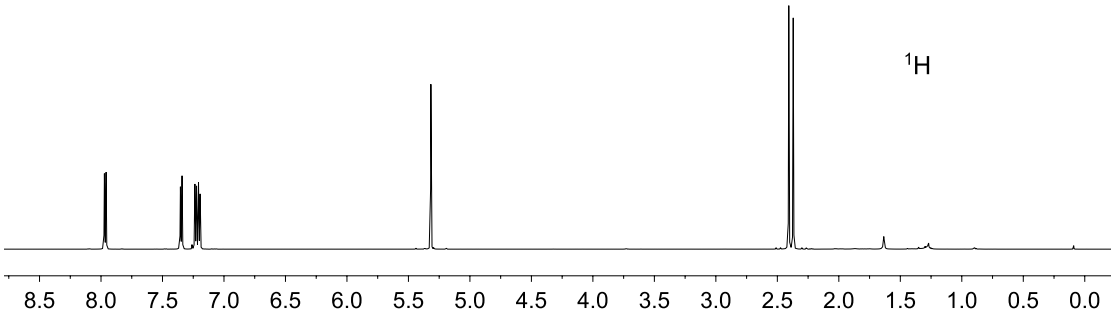


^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K) of **2aa**

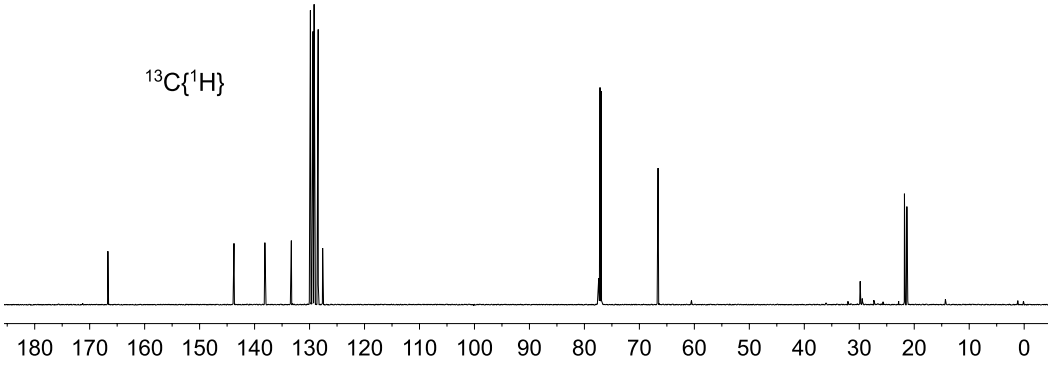
Synthesis of 2bb. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 20:1; Yield 38.4 mg, 80%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.97 (d, $^3J_{HH}$ = 8.2 Hz, 2H, *o*-$Ph^{C=O}$), 7.35 (d, $^3J_{HH}$ = 7.9 Hz, 2H, *o*-Ph^{CH2}), 7.23 (d, $^3J_{HH}$ = 8.2 Hz, 2H, *m*-$Ph^{C=O}$), 7.20 (d, $^3J_{HH}$ = 7.9 Hz, 2H, *m*-Ph^{CH2}), 5.32 (s, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.37(s, 3H, CH_3). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K): δ = 166.7 (C=O), 143.7 (*i*-Ph), 138.1(*i*-Ph), 133.3 (*i*-Ph), 129.8 (*o*-/*m*-Ph), 129.4 (*o*-/*m*-Ph), 129.2 (*o*-/*m*-Ph), 128.4 (*o*-/*m*-Ph), 127.6 (*i*-Ph), 66.6 (CH_2), 21.8 (CH_3), 21.3 (CH_3).

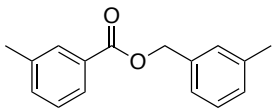


^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2bb**

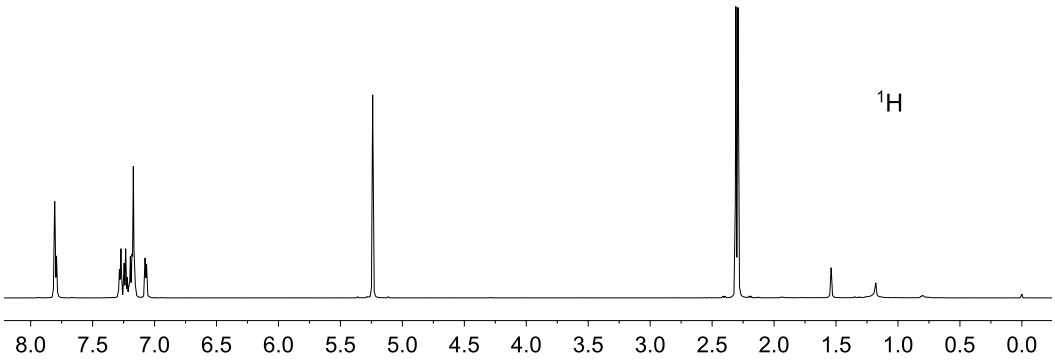


^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K) of **2bb**

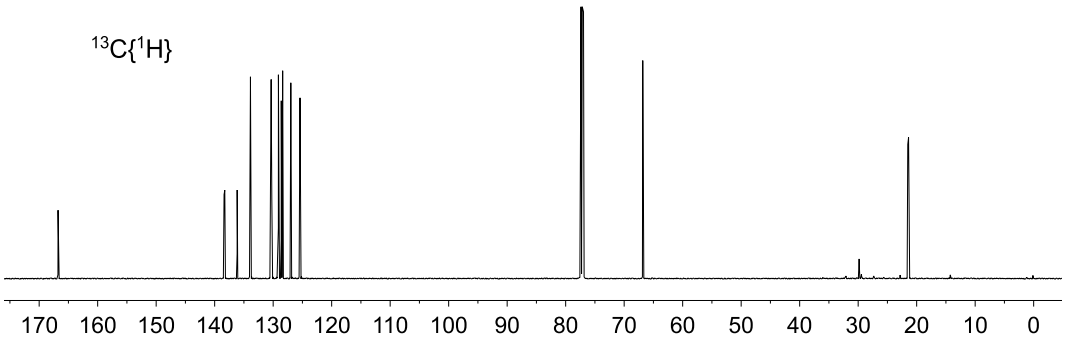
Synthesis of 2cc. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 20:1; Yield 39.9 mg, 83%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.81 (s, 1H, Ph), δ = 7.79 (s, 1H, Ph), 7.28 (m, 1H, Ph), 7.23 (m, 1H, Ph), 7.19 (m, 1H, Ph), 7.17 (m, 2H, Ph), 7.07 (m, 1H, Ph), 5.24 (s, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.31(s, 3H, CH_3). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K): δ = 166.8 (C=O), 138.4 (*i*-Ph), 138.3 (*i*-Ph), 136.2 (*i*-Ph), 133.9 (*o*-/*m*-Ph), 130.3 (*o*-/*m*-Ph), 130.2 (*i*-Ph), 129.1(0) (*o*-/*m*-Ph), 129.0(8) (*o*-/*m*-Ph), 128.6 (*o*-/*m*-Ph), 128.4 (*o*-/*m*-Ph), 127.0 (*o*-/*m*-Ph), 125.4 (*o*-/*m*-Ph), 66.8 (CH_2), 21.5 (CH_3), 21.4 (CH_3).

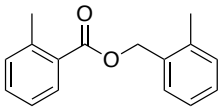


^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2cc**

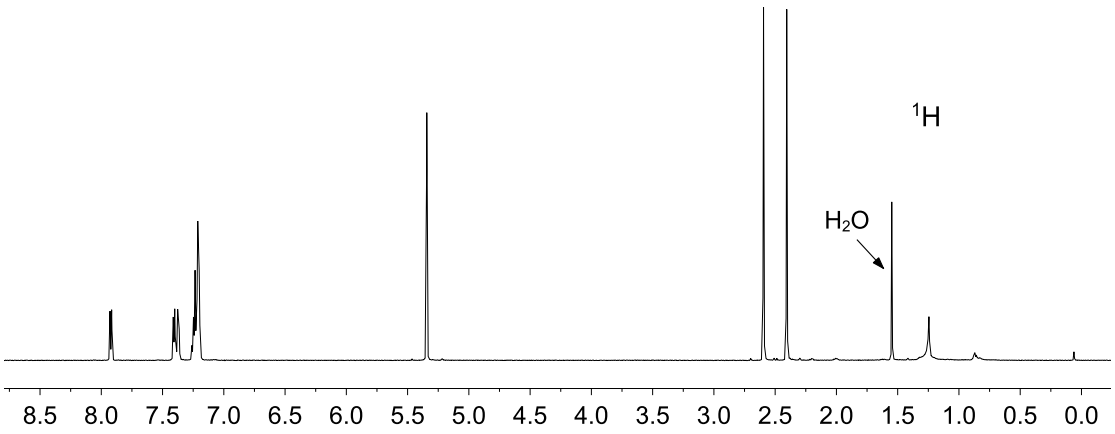


^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K) of **2cc**

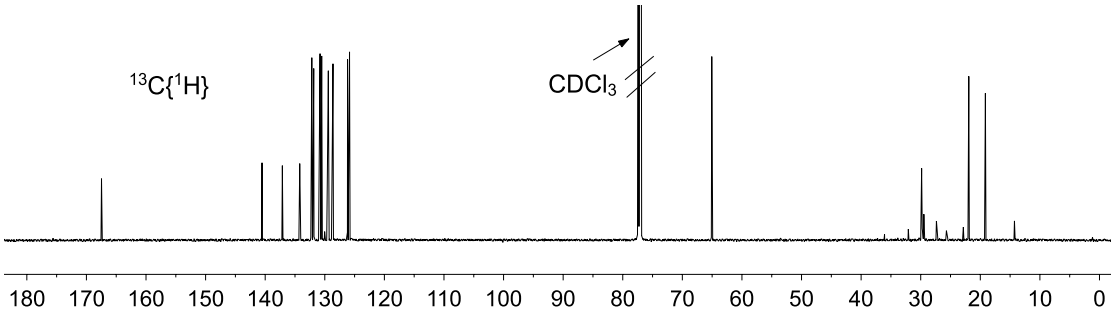
Synthesis of 2dd. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 20:1; Yield 31.2 mg, 65%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.92 (m, 1H, *o*-Ph), 7.35 (m, 1H, *o*-Ph), 7.32 (m, 1H, *m*-Ph), 7.22 (m, 5H, Ph), 5.34 (s, 2H, CH_2), 2.60 (s, 3H, CH_3), 2.41 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K): δ = 167.5 (C=O), 140.5 (*i*-Ph), 137.1 (*i*-Ph), 134.2 (*i*-Ph), 132.2 (*o*-/*m*-Ph), 131.9 (*o*-/*m*-Ph), 130.8 (*o*-/*m*-Ph), 130.5 (*o*-/*m*-Ph), 129.6 (*i*-Ph), 129.4 (*o*-/*m*-Ph), 128.6 (*o*-/*m*-Ph), 126.2 (*o*-/*m*-Ph), 125.8 (*o*-/*m*-Ph), 65.1 (CH_2), 21.9 (CH_3), 19.1 (CH_3).

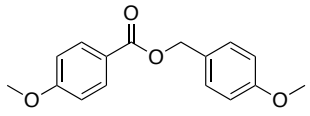


^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2dd**

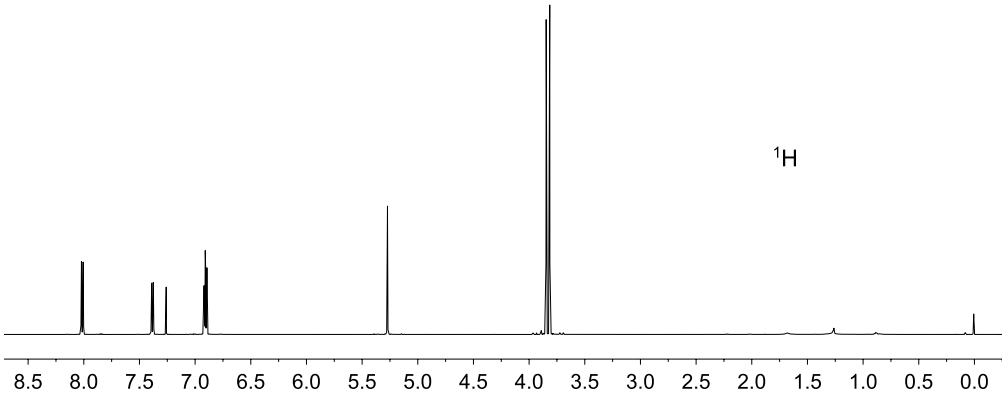


^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K) of **2dd**

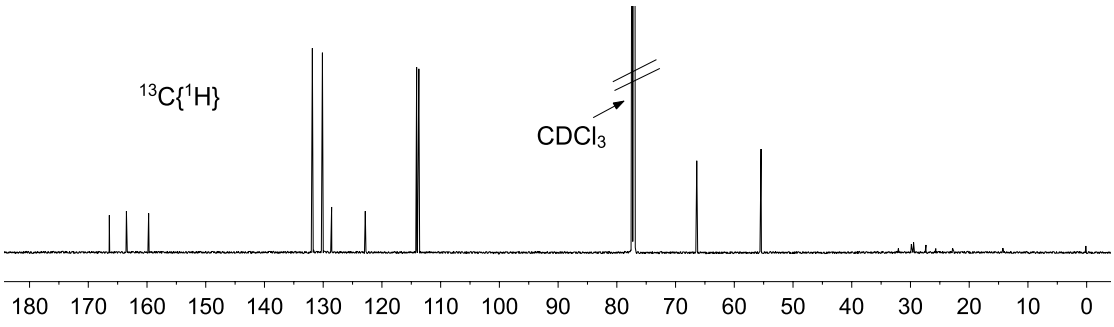
Synthesis of 2ee. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 20:1; Yield 36.4 mg, 67%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 8.02 (m, 2H, *o*-Ph$^{C=O}$), 7.38 (m, 2H, *o*-Ph^{CH2}), 6.91 (m, 2H, *m*-Ph^{CH2}), 6.91 (m, 2H, *m*-Ph$^{C=O}$), 5.27 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K): δ = 166.4 (C=O), 163.5 (*i*-Ph), 159.7 (*i*-Ph), 131.8 (*o*-/*m*-Ph), 130.1(*o*-/*m*-Ph), 128.6 (*i*-Ph), 122.8 (*i*-Ph), 114.1 (*o*-/*m*-Ph), 113.7 (*o*-/*m*-Ph), 66.4 (CH_2), 55.6 (OCH_3), 55.4 (OCH_3).

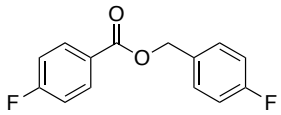


^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2ee**

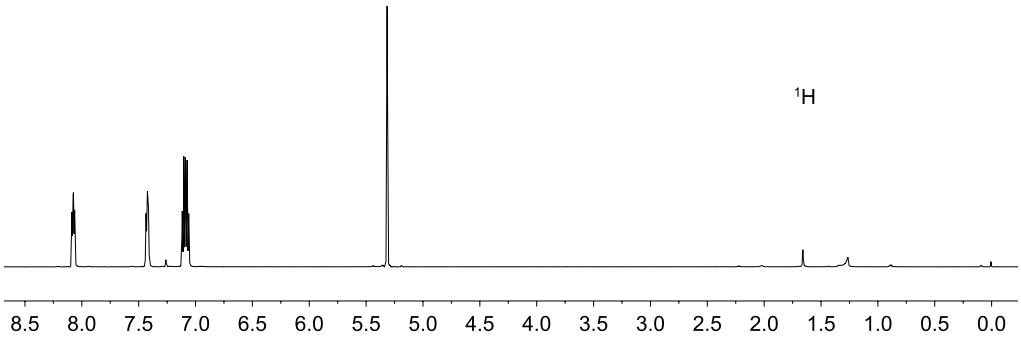


^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K) of **2ee**

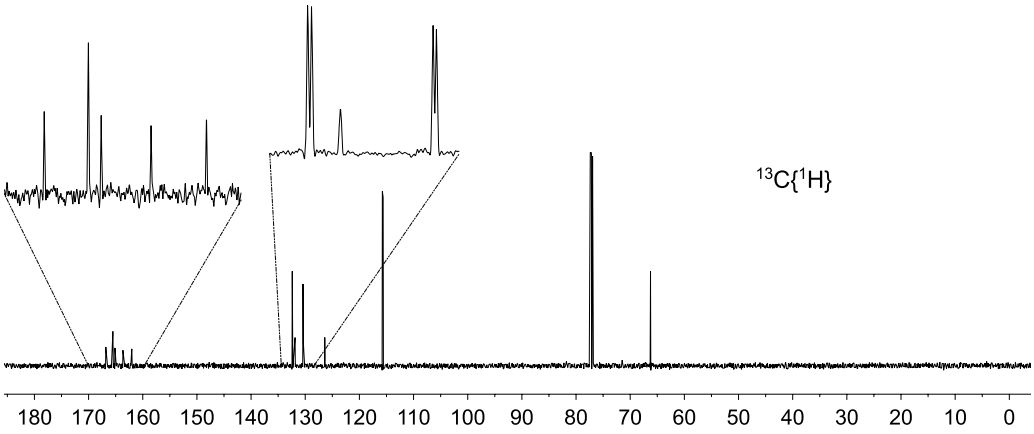
Synthesis of 2ff. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 40:1; Yield 37.2 mg, 75%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 8.07 (m, 2H, Ph), 7.43 (m, 2H, Ph), 7.10 (m, 2H, Ph), 7.07 (m, 2H, Ph), 5.32 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K): δ = 166.0 (m, *i*-Ph^F), 165.5 (C=O), 162.8 (m, *i*-Ph^F), 132.4 (m, *m*-Ph), 131.9 (*i*-Ph), 130.4 (m, *m*-Ph), 126.4 (*i*-Ph), 126.4 (*i*-Ph), 115.8 (*o*-Ph), 115.6 (*o*-Ph), 66.2 (CH_2).



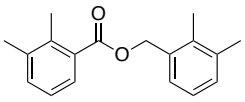
^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2ff**



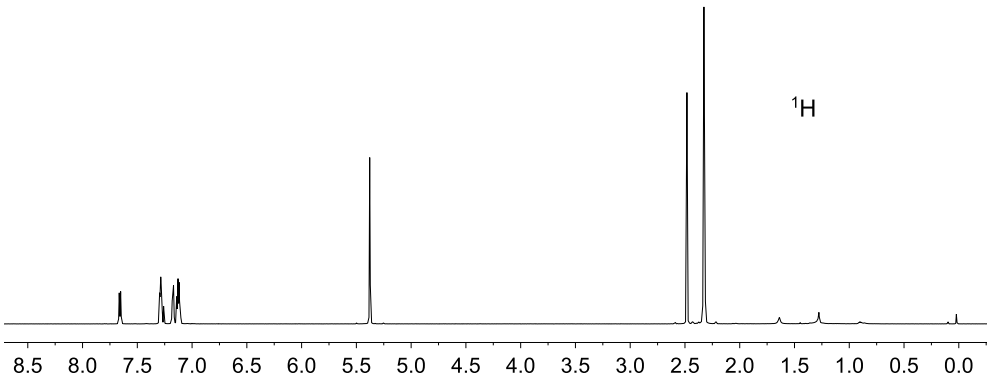
$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K) of **2ff**

Synthesis of 2gg. Yield (29%) determined by ^1H NMR with CH_2Br_2 as internal standard.

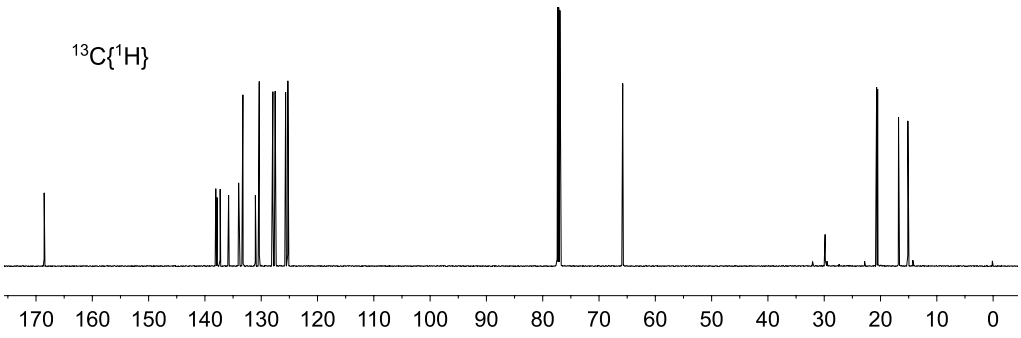
Synthesis of 2hh. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 40:1; Yield 27.9 mg, 52%.



^1H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.66 (d, $^3J_{HH}$ = 7.7 Hz, 1H, *o*-Ph), 7.29 (d, $^3J_{HH}$ = 6.2 Hz, 1H, *o*-Ph), 7.28 (d, $^3J_{HH}$ = 6.2 Hz, 1H, *o*-Ph), 7.18 (d, $^3J_{HH}$ = 7.6 Hz, 1H, *o*-Ph), 7.13 (m, 1H, *m*-Ph), 7.12 (m, 1H, *m*-Ph), 5.38 (s, 2H, CH_2), 2.48 (s, 3H, CH_3), 2.33(1) (s, 3H, CH_3), 2.32(7) (s, 3H, CH_3), 2.32 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K): δ = 168.6 (C=O), 138.1 (*i*-Ph), 137.8 (*i*-Ph), 137.3 (*i*-Ph), 135.8 (*i*-Ph), 134.0 (*i*-Ph), 133.3 (*o*-/*m*-Ph), 131.0 (*i*-Ph), 130.3 (*o*-/*m*-Ph), 127.9 (*o*-/*m*-Ph), 127.5 (*o*-/*m*-Ph), 125.7 (*o*-/*m*-Ph), 125.3 (*o*-/*m*-Ph), 65.8 (CH_2), 20.7 (CH_3), 20.5 (CH_3), 16.8 (CH_3), 15.1 (CH_3).

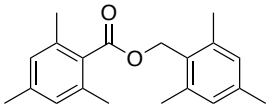


^1H NMR (600 MHz, $CDCl_3$, 298K) of **2hh**

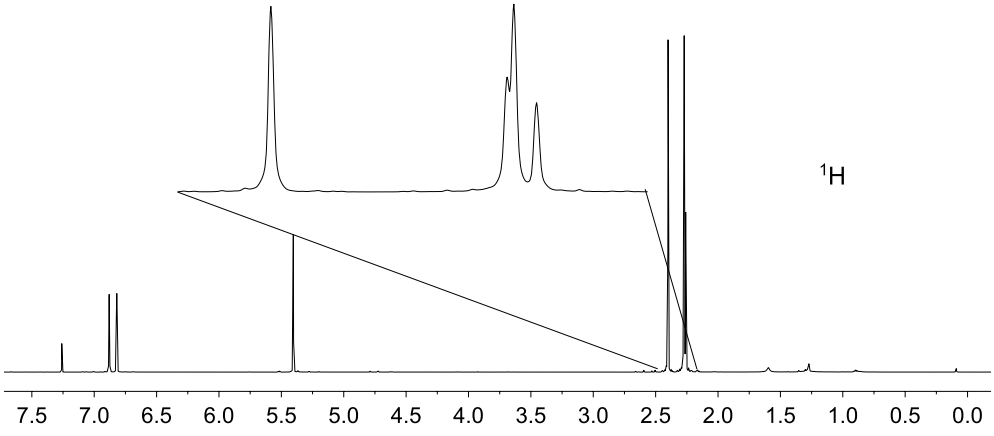


$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K) of **2hh**

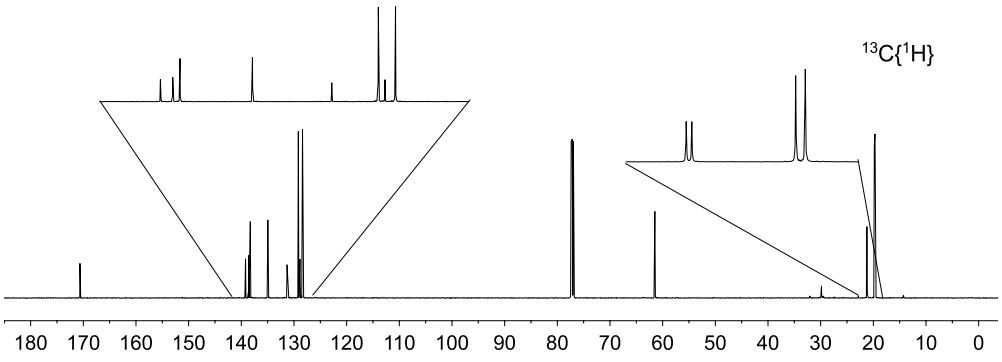
Synthesis of 2ii. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 20:1; Yield 27.9 mg, 47%.



^1H NMR (600 MHz, $CDCl_3$, 298K): δ = 6.88 (s, 2H, *m*-Mes), 6.82 (s, 2H, *m*-Mes), 5.40 (s, 2H, CH_2), 2.40 (s, 6H, $2\times CH_3^{o\text{-Mes}}$), 2.27(5) (s, 3H, $CH_3^{p\text{-Mes}}$), 2.27(1) (s, 6H, $2\times CH_3^{o\text{-Mes}}$), 2.26 (s, 3H, $CH_3^{p\text{-Mes}}$). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K): δ = 170.6 (C=O), 139.2 (*i*-Mes/*p*-Mes), 138.6 (*i*-Mes/*p*-Mes), 138.3(*o*-Mes), 135.0 (*o*-Mes), 131.3 (*i*-Mes/*p*-Mes), 129.2 (*m*-Mes), 128.9 (*i*-Mes/*p*-Mes), 128.4 (*m*-Mes), 61.5 (CH_2), 21.2 ($CH_3^{p\text{-Mes}}$), 21.1 ($CH_3^{p\text{-Mes}}$), 19.8 ($CH_3^{o\text{-Mes}}$), 19.7 ($CH_3^{o\text{-Mes}}$).

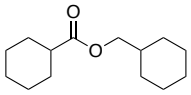


^1H NMR (600 MHz, $CDCl_3$, 298K) of **2ii**

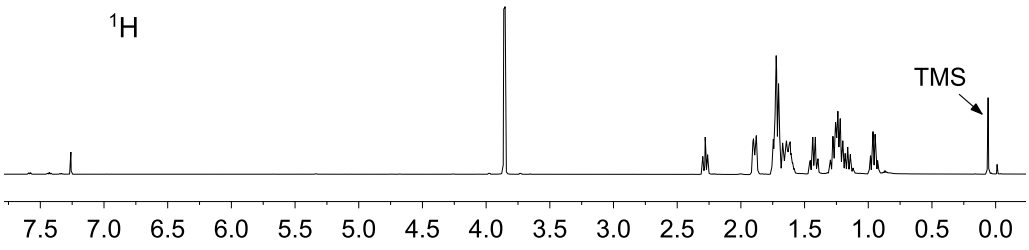


$^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$, 298K) of **2ii**

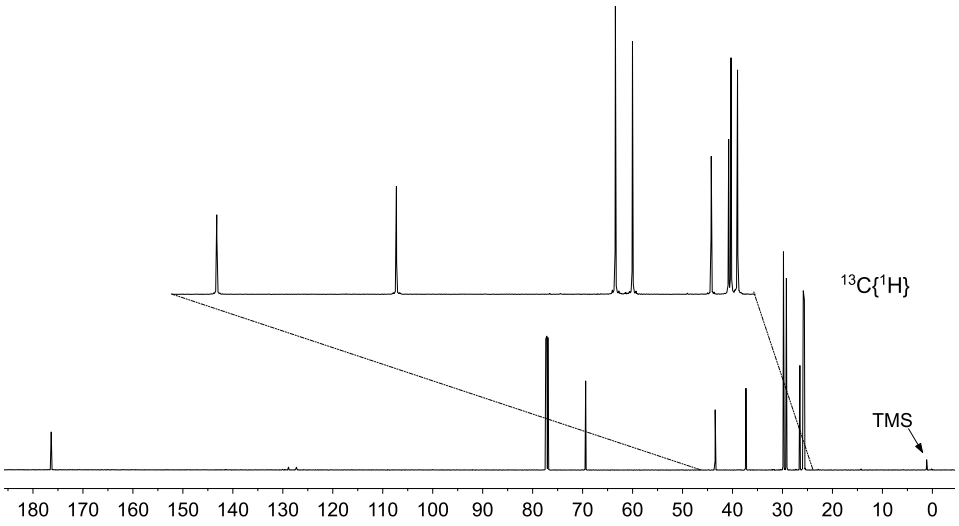
Synthesis of 2jj. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 20:1; Yield 38.1 mg, 85%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 3.86 (d, $^{3}J_{HH}$ = 6.6 Hz, 2H, CH_2), 2.28 (tt, $^{3}J_{HH}$ = 11.4 Hz, $^{3}J_{HH}$ = 3.7 Hz, 1H, $CH^{C=O}$), 1.89 (m, 2H, CH_2), 1.72 (m, 5H, CH_2), 1.64 (m, 3H, CH_2), 1.43 (m, 2H, CH_2), 1.24 (m, 6H, CH_2), 1.16 (m, 1H, CH_2), 0.95 (m, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$, 298K): δ = 176.3 (C=O), 69.4 (OCH_2), 43.5 ($CH^{C=O}$), 37.3 (CH), 29.8 (CH_2), 29.2 (CH_2), 26.5 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.6 (CH_2).

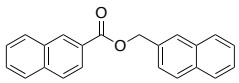


^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2jj**

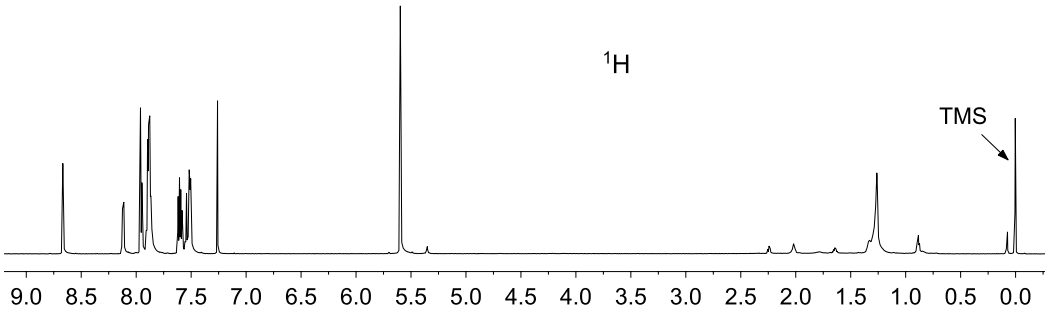


$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K) of **2jj**

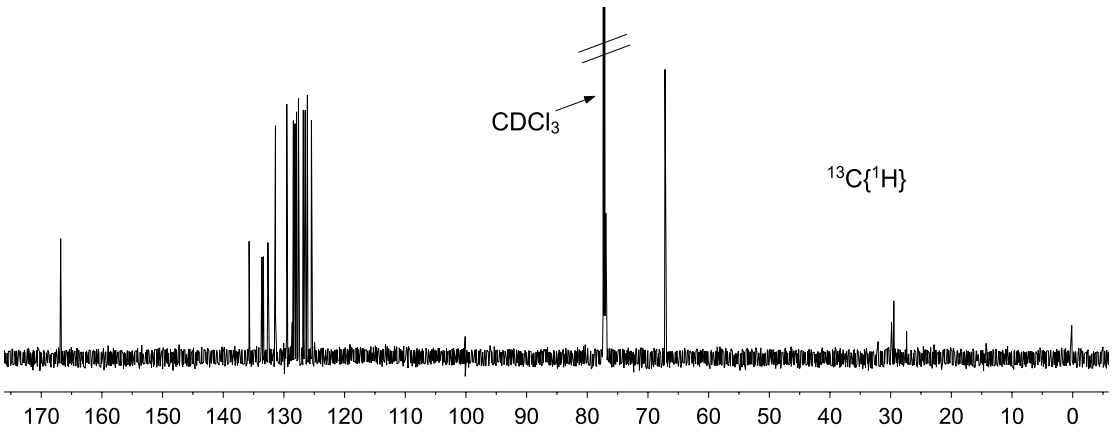
Synthesis of 2kk. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 20:1; Yield 47.5 mg, 76%.



^1H NMR (700 MHz, $CDCl_3$, 298K): δ = 8.67 (s, 1H, Nap), 8.12 (m, 1H, Nap), 7.96 (s, 1H, Nap), 7.95 (m, 1H, Nap), 7.91 (m, 2H, Nap), 7.89 (m, 2H, Nap), 7.87 (m, 1H, Nap), 7.61 (m, 1H, Nap), 7.59 (m, 1H, Nap), 7.54 (m, 1H, Nap), 7.51 (m, 2H, Nap), 5.60 (s, 2H, CH_2). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$, 298K): δ = 166.8 (C=O), 135.7 (*i*-Nap), 133.6 (*i*-Nap), 133.4 (*i*-Nap), 133.3 (*i*-Nap), 132.6 (*i*-Nap), 131.4 ($=CH^{Nap}$), 129.5 ($=CH^{Nap}$), 128.6 ($=CH^{Nap}$), 128.4 ($=CH^{Nap}$), 128.3 ($=CH^{Nap}$), 128.2 ($=CH^{Nap}$), 127.9(1) ($=CH^{Nap}$), 127.8(9) ($=CH^{Nap}$), 127.6 ($=CH^{Nap}$), 127.5 (*i*-Nap), 126.8 ($=CH^{Nap}$), 126.4(9) ($=CH^{Nap}$), 126.4(6) ($=CH^{Nap}$), 126.1 ($=CH^{Nap}$), 125.5 ($=CH^{Nap}$), 67.2 (CH_2).

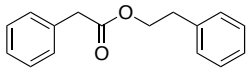


^1H NMR (700 MHz, $CDCl_3$, 298K) of **2kk**

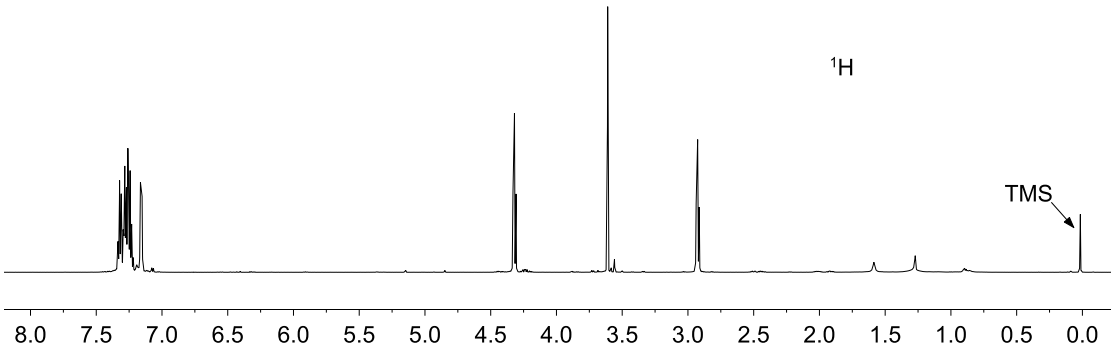


$^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$, 298K) of **2kk**

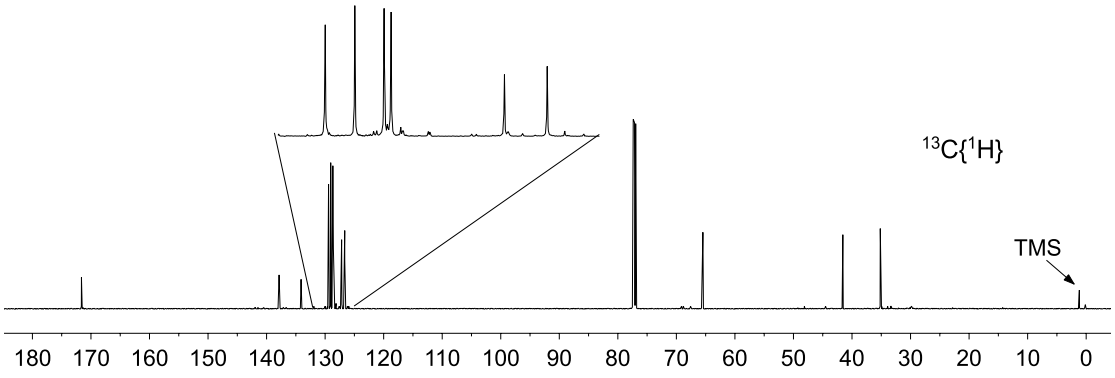
Synthesis of 2ll. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 20:1; Yield 23.1 mg, 48%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ 7.32 (m, 2H, *m*-Ph), 7.29 (m, 1H, *p*-Ph), 7.28 (m, 2H, *m*-Ph), 7.25 (m, 2H, *o*-Ph), 7.23 (m, 1H, *p*-Ph), 7.16 (m, 2H, *o*-Ph), 4.32 (t, $^{3}J_{HH}$ = 7.0 Hz, 2H, OCH_2), 3.61 (s, 2H, $CH_2^{C=O}$), 3.01 (t, $^{3}J_{HH}$ = 7.0 Hz, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$, 298K): δ = 171.6 (C=O), 137.9 (*i*-Ph), 134.1 (*i*-Ph), 129.4 (*o*-/*m*-Ph), 129.0 (*o*-/*m*-Ph), 128.7 (*o*-/*m*-Ph), 128.6 (*o*-/*m*-Ph), 127.2 (*p*-Ph), 126.6 (*p*-Ph), 65.5 (OCH_2), 41.6 ($CH_2^{C=O}$), 35.2 (CH_2).

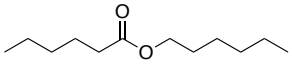


^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2ll**

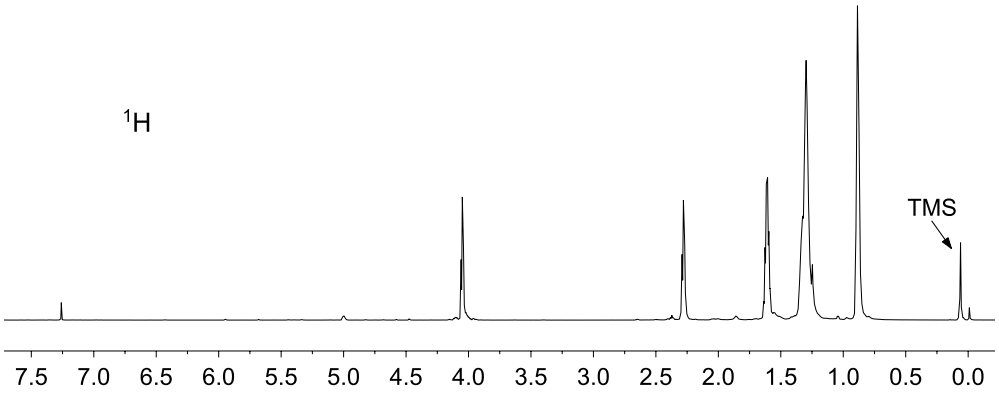


$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K) of **2ll**

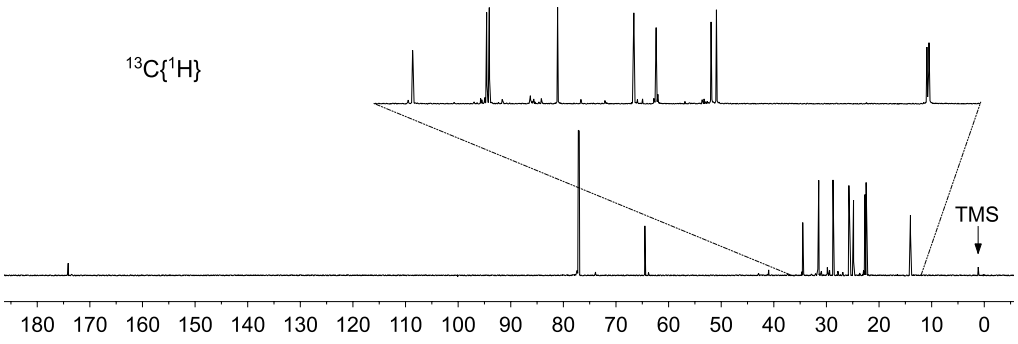
Synthesis of 2mm. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 10:1; Yield 26.8 mg, 67%.



^1H NMR (700 MHz, $CDCl_3$, 298K): δ = 4.05 (m, 2H, OCH_2), 2.28 (m, 2H, CH_2), 1.61 (m, 4H, CH_2), 1.30 (m, 10H, CH_2), 0.89 (m, 6H, CH_3). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$, 298K): δ = 174.1 (C=O), 64.5 (OCH_2), 34.5, 31.6, 31.5, 28.8, 25.7, 24.8, 22.7, 22.5 (CH_2), 14.1 (CH_3), 14.0 (CH_3).



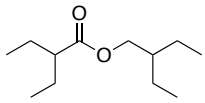
^1H NMR (700 MHz, $CDCl_3$, 298K) of **2mm**



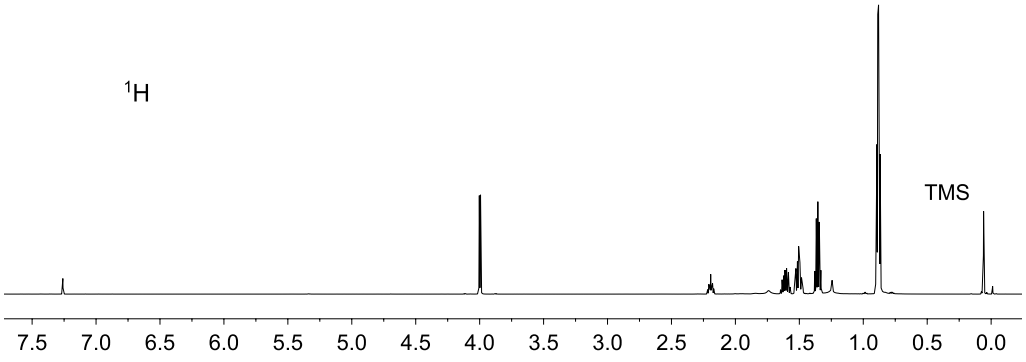
$^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$, 298K) of **2mm**

Synthesis of 2nn. Developing solvent on chromatography purification: petroleum

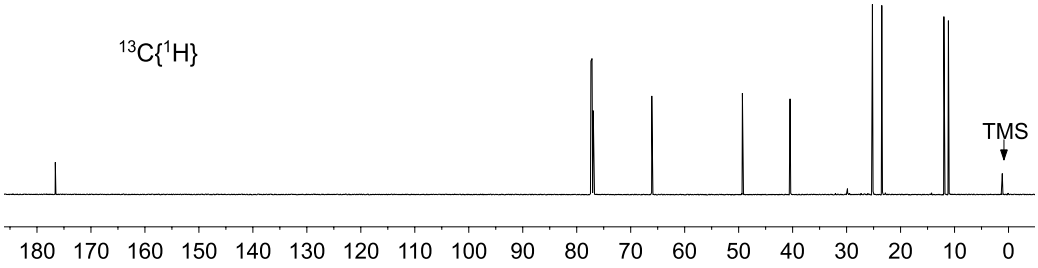
ether/ethyl acetate 20:1; Yield 33.7 mg, 84%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 4.00 (d, $^3J_{HH}$ = 5.8 Hz, 2H, OCH_2), 2.19 (m, 1H, $CH^{C=O}$), 1.60 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.48 (m, 1H, CH), 1.36 (m, 4H, CH_2), 0.88 (m, 12H, CH_3). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K): δ = 176.6 (C=O), 66.1 (OCH_2), 49.3 ($CH^{C=O}$), 40.5 (CH), 25.2 (CH_2), 23.5 (CH_2), 12.0 (CH_3), 11.1 (CH_3).

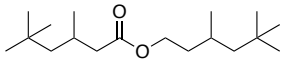


^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2mm**

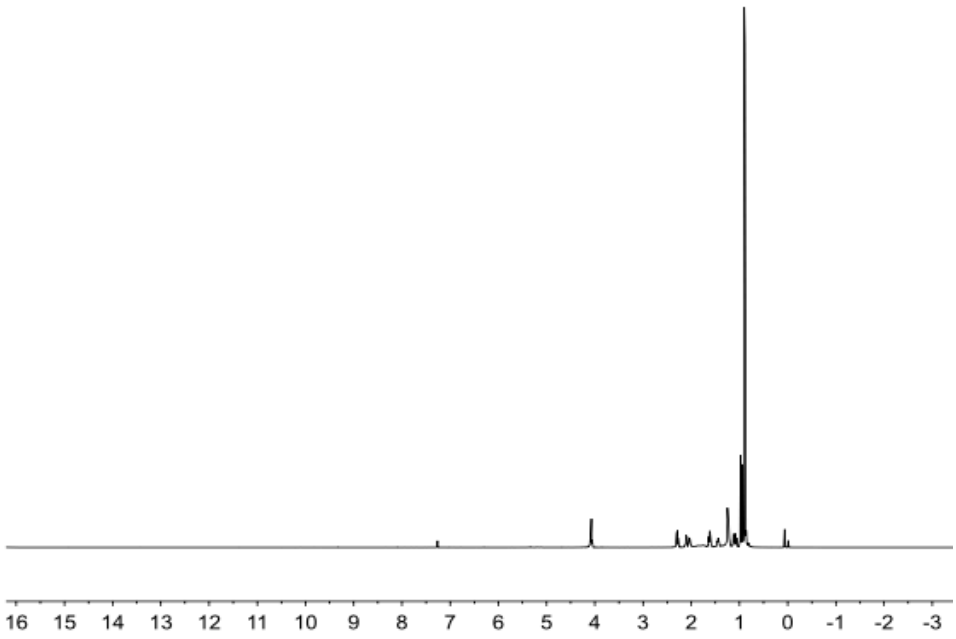


$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K) of **2nn**

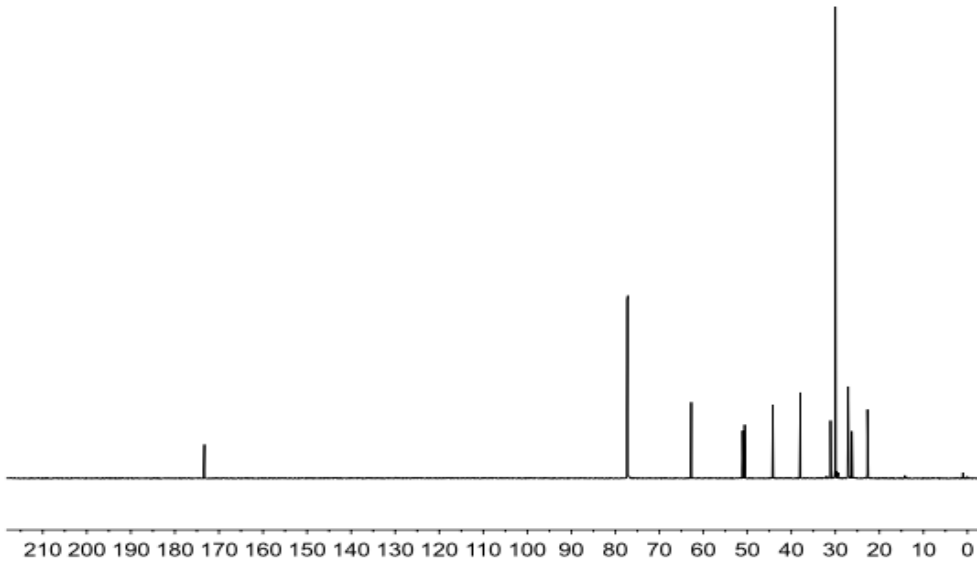
Synthesis of 2oo. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 10:1; Yield 72%, obtained as a diasteremer mixture.



^{1}H NMR (700 MHz, $CDCl_3$, 298K): δ 4.07 (m, 2H, OCH_2), 2.29 (m, 1H, $CH_2^{C=O}$), 2.11 (m, 1H, CH_2), 2.03 (m, 1H, CH), 1.61 (m, 2H, CH_2), 1.44 (m, 1H), 1.23 (m, 2H, CH_2), 1.11 (m, 1H, CH_2), 1.08 (m, 1H, $CH_2^{C=O}$), 0.97 (d, $^3J_{HH}$ = 6.7 Hz, 3H, CH_3), 0.94 (d, $^3J_{HH}$ = 6.5 Hz, 3H, CH_3), 0.90 (s, 9H, CH_3), 0.89 (s, 9H, CH_3). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$, 298K): δ = 173.3 (C=O), 62.7 (OCH_2), 51.1, 51.1, 50.6, 50.6, 44.2, 37.9, 31.2, 31.1, 30.0, 27.1, 26.3, 26.2, 22.7, 22.62, 22.57.



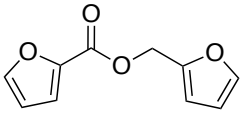
^{1}H NMR (700 MHz, $CDCl_3$, 298K) of **2oo**



^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$, 298K) of **2nn**

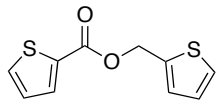
Synthesis of 2pp. Yield (63%) determined by GC-MS area normalization.

Synthesis of 2qq. Yield (78%) determined by GC-MS area normalization.

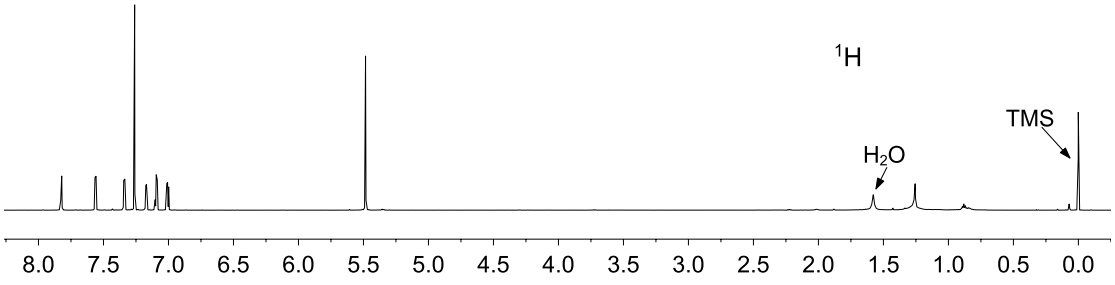


^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.57 (m, 1H, =CH^{Fu}), 7.44 (m, 1H, =CH^{Fu}), 7.20 (m, 1H, =CH^{Fu}), 6.49 (m, 2H, =CH^{Fu}), 6.38 (m, 1H, =CH^{Fu}), 5.29 (s, 2H, CH_2). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298K): δ = 158.4 (C=O), 149.2 (*i*-Fu), 146.7 (=CH^{Fu}), 144.5 (*i*-Fu), 143.6 (=CH^{Fu}), 118.6 (=CH^{Fu}), 112.0 (=CH^{Fu}), 111.3 (=CH^{Fu}), 110.8 (=CH^{Fu}), 58.4 (CH_2).

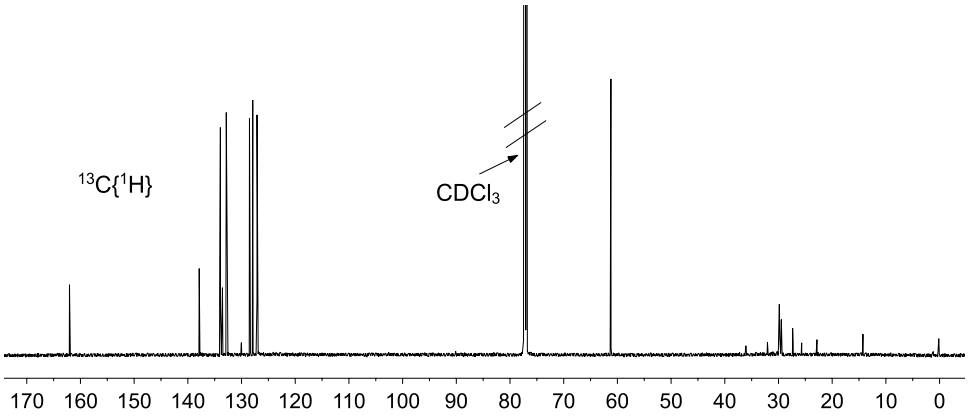
Synthesis of 2rr. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 30:1; Yield 36.8 mg, 82%.



^{1}H NMR (600 MHz, $CDCl_3$, 298K): δ = 7.82 (m, 1H, =CH^{Thio}), 7.56 (m, 1H, =CH^{Thio}), 7.34 (m, 1H, =CH^{Thio}), 7.17 (m, 1H, =CH^{Thio}), 7.09 (m, 1H, =CH^{Thio}), 7.01 (m, 1H, =CH^{Thio}), 5.48 (s, 2H, CH_2). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K): δ = 162.0 (C=O), 137.9 (*i*-Thio), 133.9 (=CH^{Thio}), 133.6 (*i*-Thio), 132.8 (=CH^{Thio}), 128.5 (=CH^{Thio}), 127.9 (=CH^{Thio}), 127.1 (=CH^{Thio}), 127.0 (=CH^{Thio}), 61.2 (CH_2).

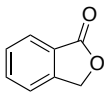


^{1}H NMR (600 MHz, $CDCl_3$, 298K) of **2rr**



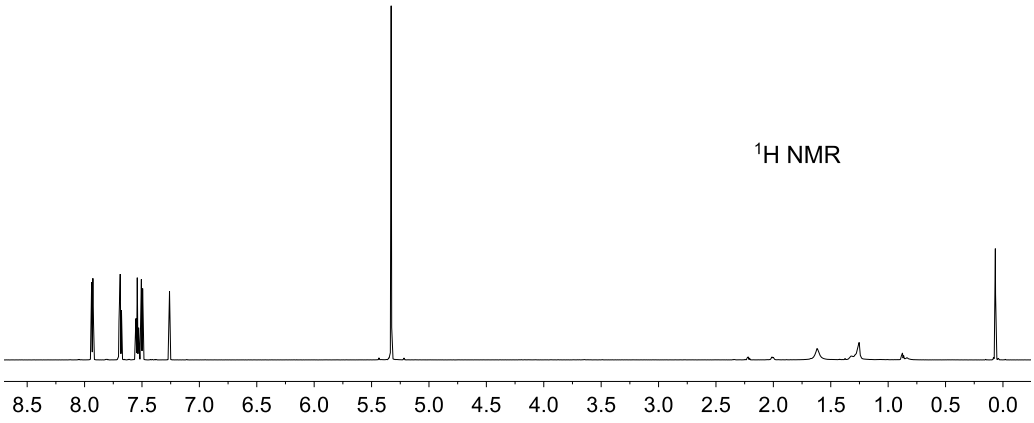
$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$, 298K) of **2rr**

Synthesis of 2vv. Developing solvent on chromatography purification: petroleum ether/ethyl acetate 20:1; Yield 59.8 mg, 93%.

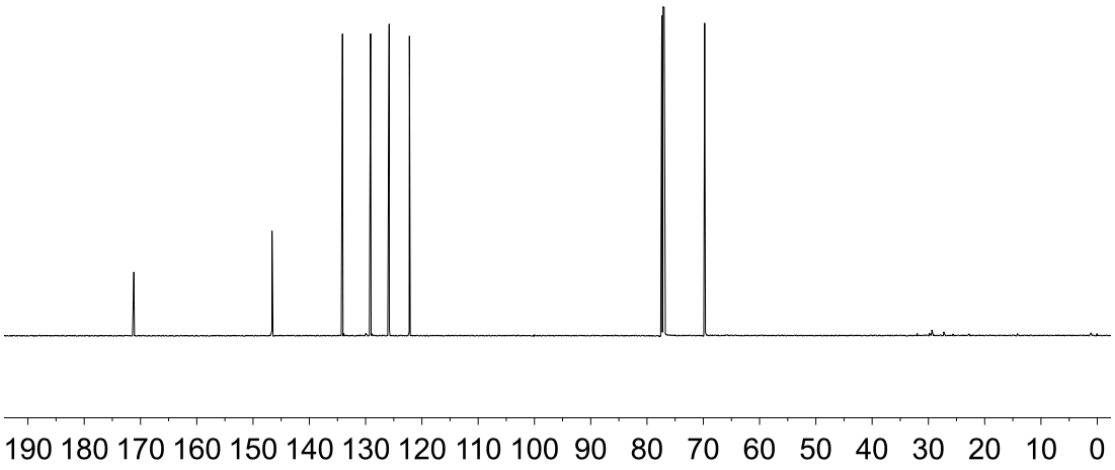


^{1}H NMR (700 MHz, $CDCl_3$, 298K): δ = 7.93 (d, $^3J_{HH}$ = 7.5 Hz, 1H, *o*-$Ph^{C=O}$), 7.69 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, *m*-Ph), 7.54 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.8 Hz, 1H, *m*′-Ph), 7.50 (d, $^3J_{HH}$ = 7.8 Hz, 1H, *o*′-Ph^{CH2}), 5.33 (s, 2H, CH_2). $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$, 298K): δ = 171.2 (C=O), 146.6 (*i*-Ph), 134.1

(*o*-Ph), 129.1 (*m*-Ph), 125.8 (*m*′-Ph), 122.2 (*o*′-Ph), 69.8 (CH_2).



^{1}H NMR (700 MHz, $CDCl_3$, 298K) of **2vv**



$^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$, 298K) of **2vv**