Supplementary Material

Multistep synthesis of a valsartan precursor in continuous flow

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Content

1.1 $^{1}H/^{13}C$-NMR spectra of 5, 11, 12 and 13

NMR-measurements were recorded using a Bruker Avance III 300 MHz spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz). The chemical shift (δ [ppm]) was reported relatively to the corresponding solvent $CDCl_3$ (7.26, s). For designation of multiplicities of observed coupling patterns, following abbreviations were used: s (singlet), d (doublet), dd (duplicated doublet), t (triplet), q (quartet), qi (quintet), m (multiplet), brs (broad signal).

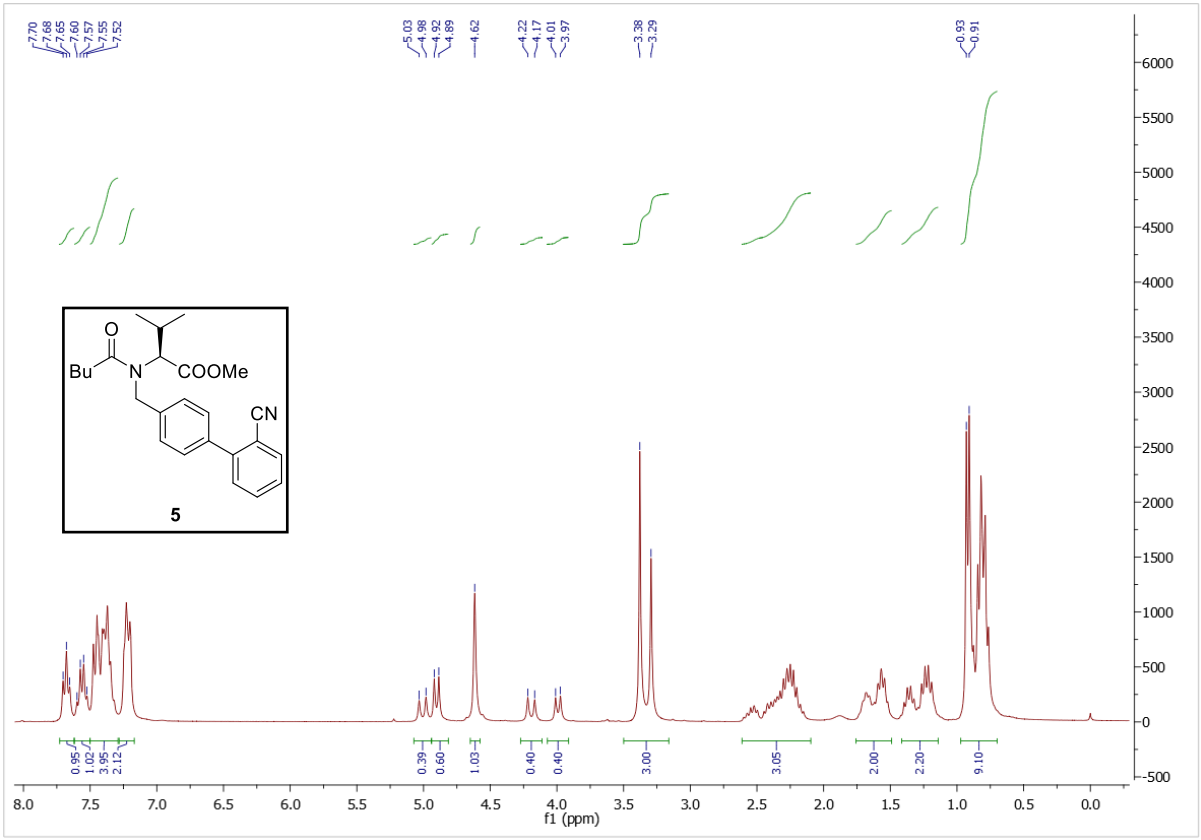


Figure 1: ^{1}H-NMR of **5** in $CDCl_3$.

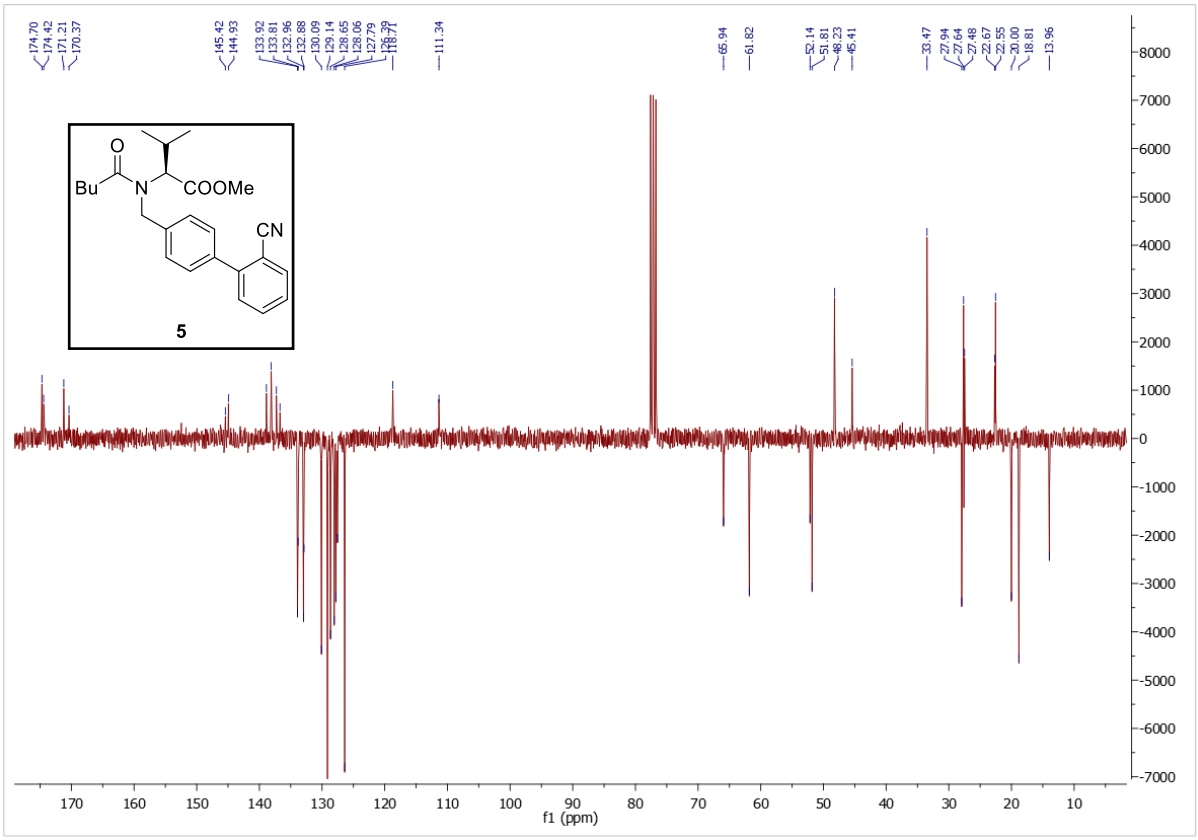


Figure 2: ^{13}C-NMR of **5** in $CDCl_3$.

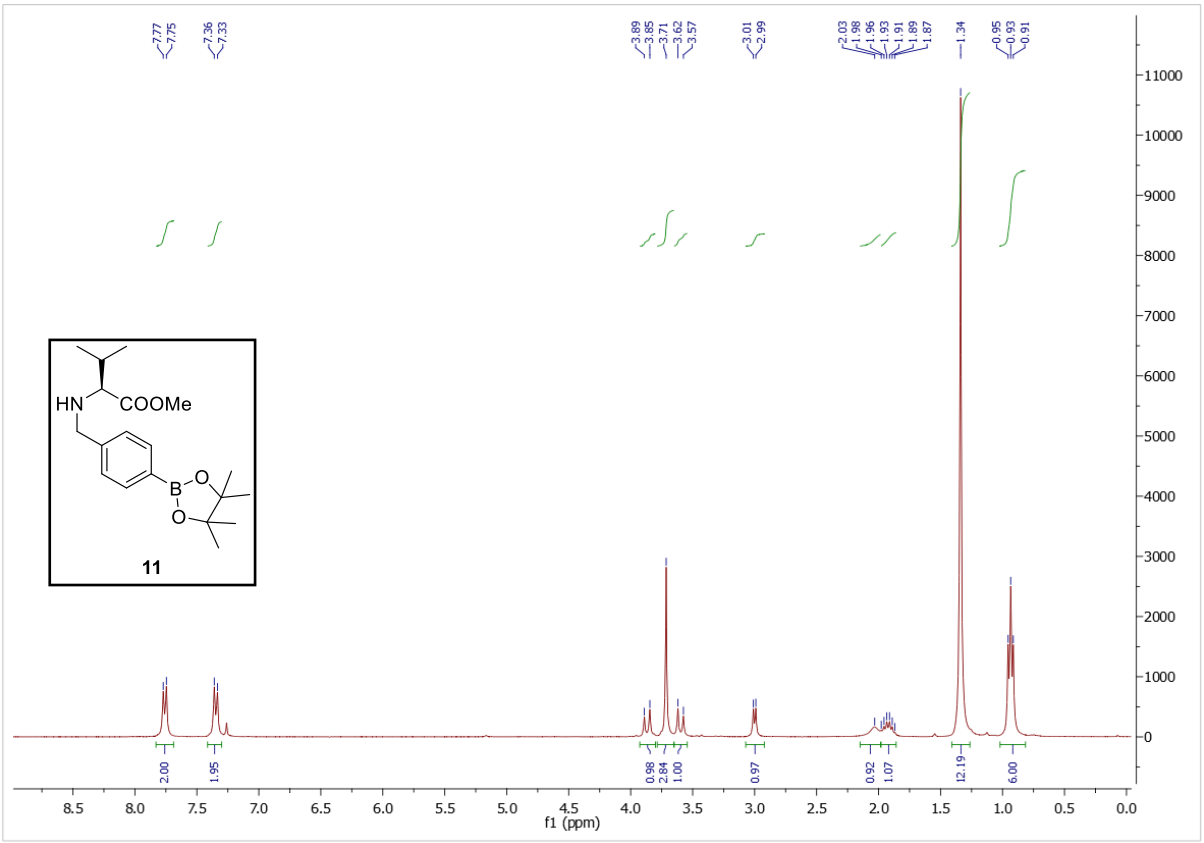


Figure 3: ^{1}H-NMR of **11** in $CDCl_3$.

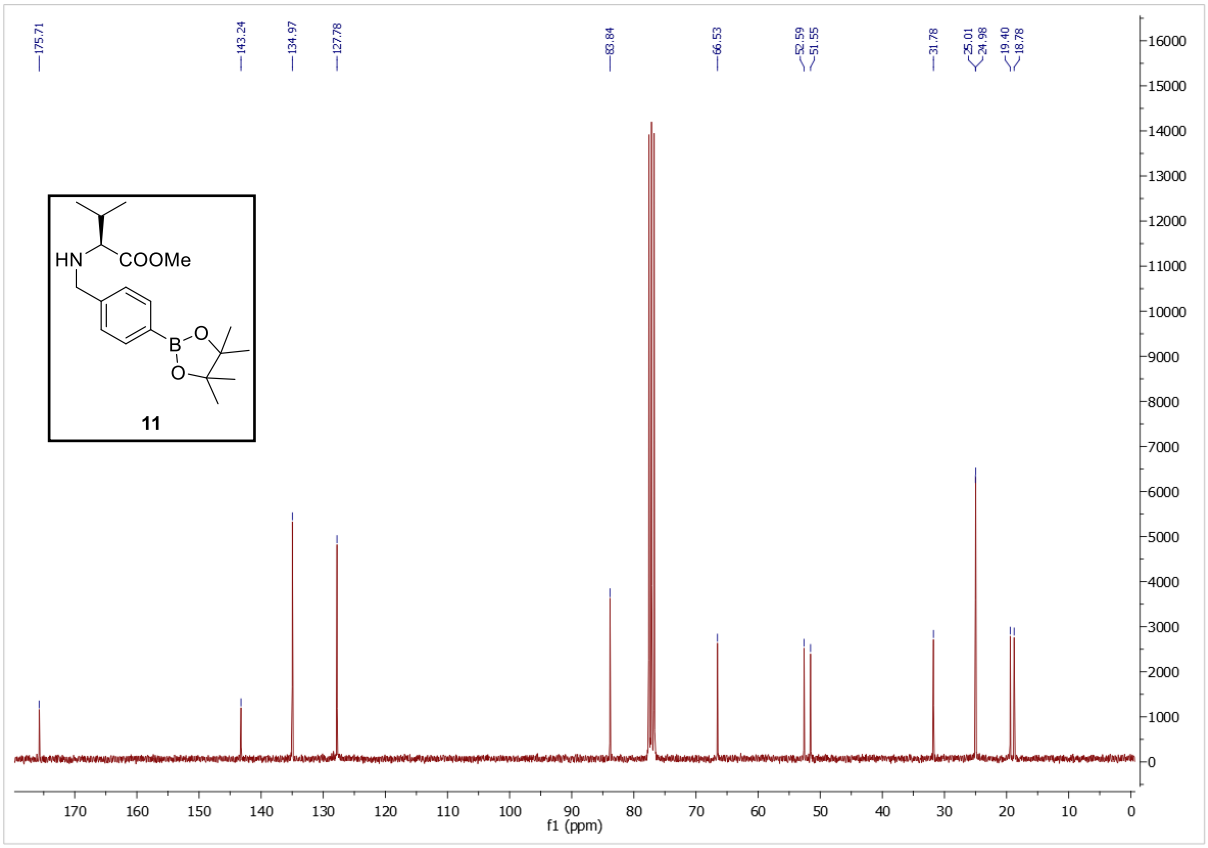


Figure 4: ^{13}C-NMR of **11** in $CDCl_3$.

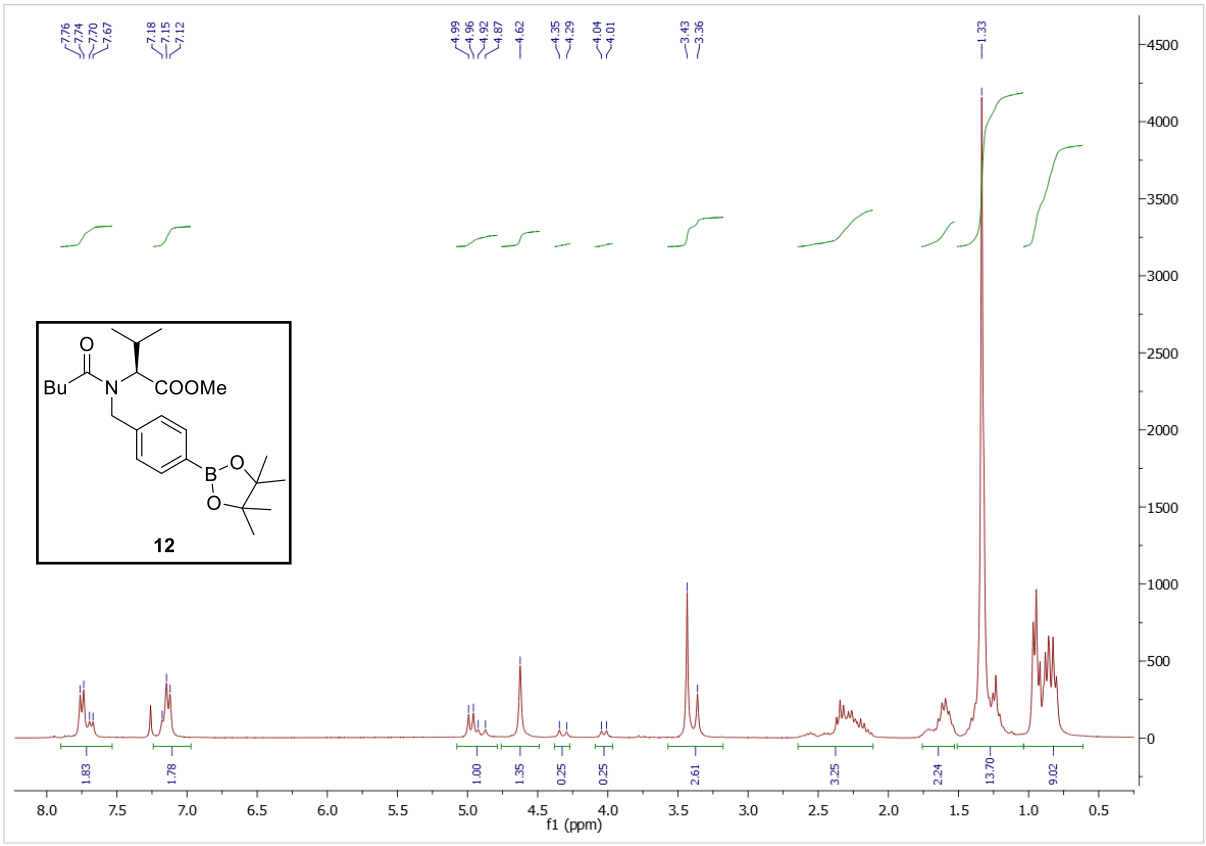


Figure 5: ^{1}H-NMR of **12** in $CDCl_3$.

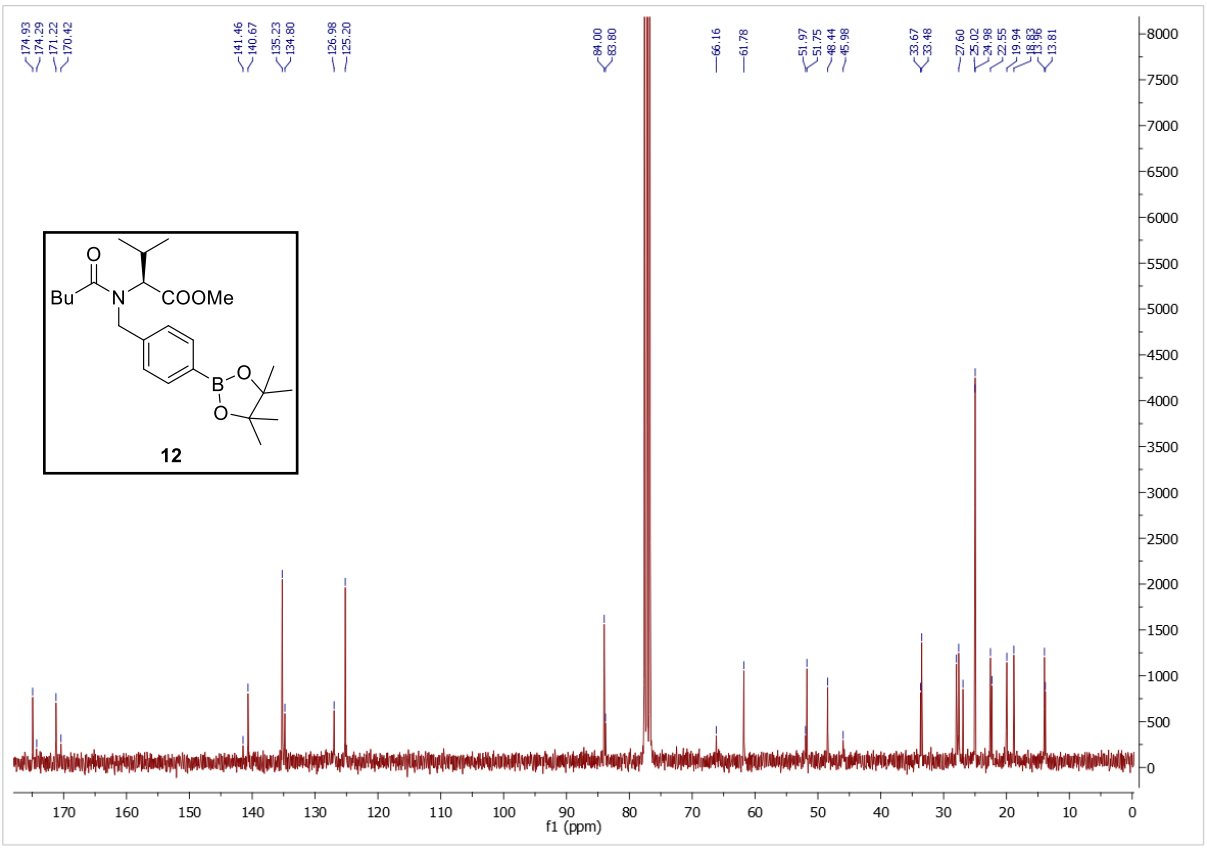


Figure 6: ^{13}C-NMR of **12** in $CDCl_3$.

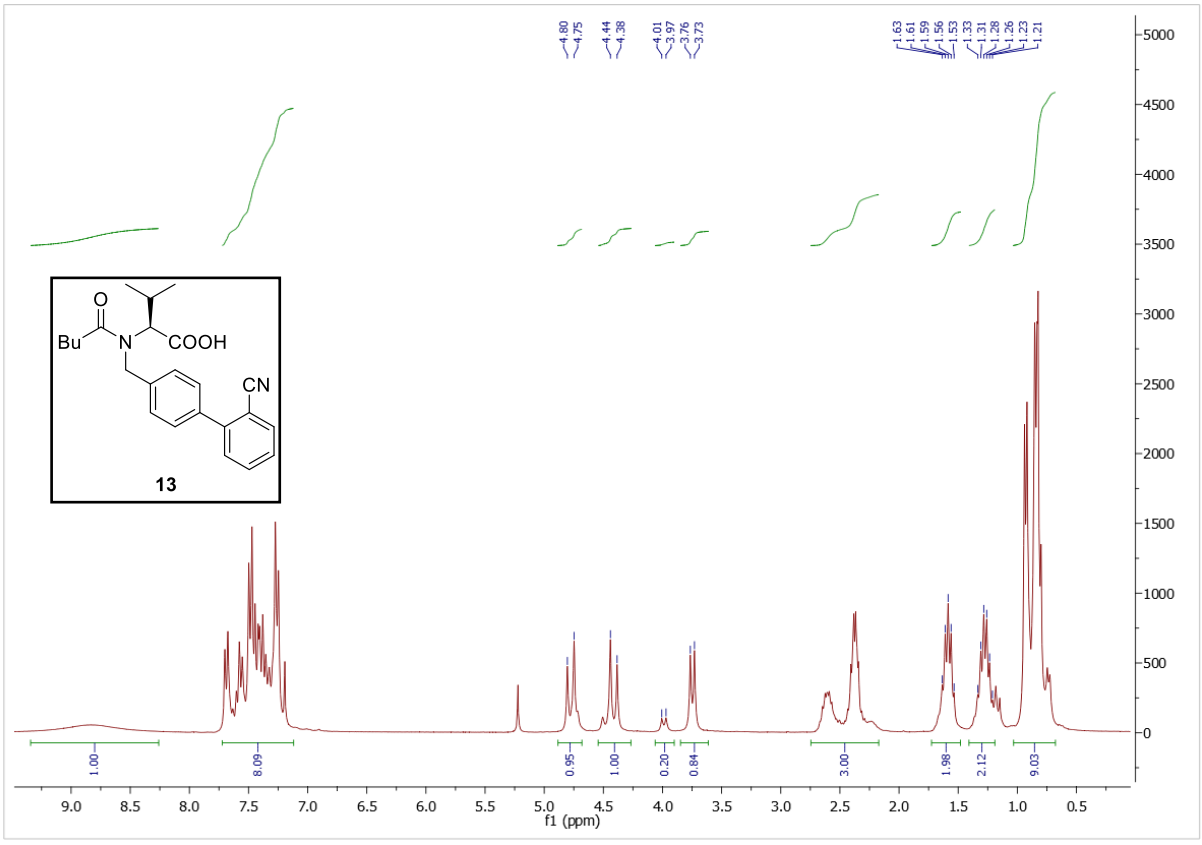


Figure 7: ^{1}H-NMR of **13** in $CDCl_3$.

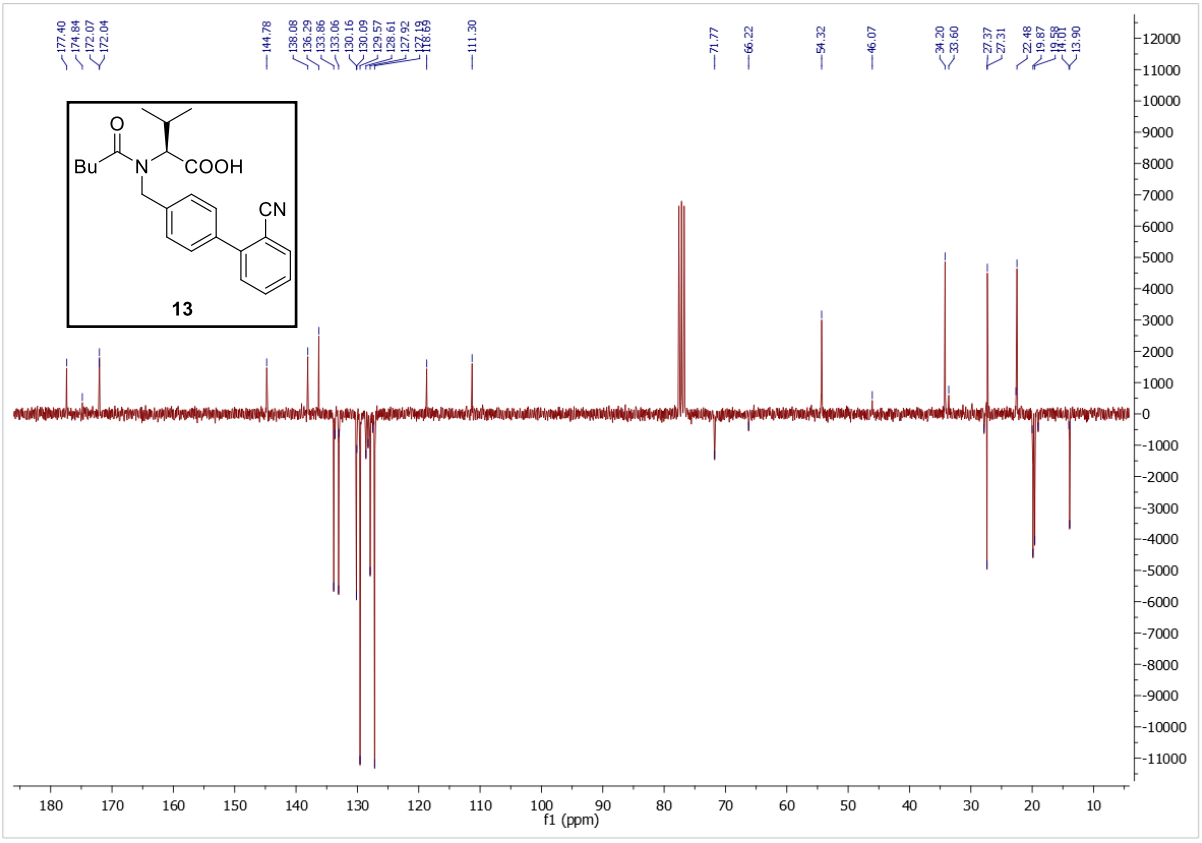


Figure 8: ^{13}C-NMR of **13** in $CDCl_3$.

1.2 High performance liquid chromatography (HPLC)

For monitoring of the reaction progress, reaction samples were analyzed using an Agilent 1100 series HPLC system equipped with an online degasser, quaternary pump, autosampler, thermostated column compartment and UV-visible diode array detector. As mobile phases, MeOH (solvent A) and aq. phosphoric acid (H_2O:H_3PO_4=300:1 v/v; solvent B) were used. Compounds were separated using a ThermoFischer Scientific Accucore™ C18 reversed phase column (50 x 4.6 mm; 2.6 µm) at 25 °C with a flow rate of 1 mL/min and detected by UV-absorption over the run time of 15 min. Used elution methods are summarized in Table 1.

Table 1: HPLC methods (% A = % MeOH, % B = % H_2O:H_3PO_4=300:1 v/v) for monitoring of the reaction progress.

Method	Time [min]	% A (v/v)	% B (v/v)	Sample diluent	Flow [mL/min]
A	0	50	50	MeOH:H_2O=50:50	1
	10	80	20		
	12	50	50		
B	0	55	45	MeOH:H_2O=55:45	1
	10	80	20		
	12	55	45		
C	0	60	40	MeOH:H_2O=60:40	1
	10	80	20		
	12	60	40		

Retention times (t_R) of the respective compounds are apparent from Table 2.

Table 2: Retention times of compounds separated by HPLC.

Compound	Method	λ [nm]	t_R [min]
5	B	230	7.0
	C		5.3
7b	C	230	1.0
7c	B	230	1.4
11	A	230	0.5 (free acid)
12	A	230	4.4 (free acid)
	B		3.5 (free acid)
	C		2.3 (free acid)
13	B	230	5.4
anisole	A	270	2.1
	B		1.7
	C		1.3

1.3 Determination of enantiomeric purity

1.3.1 Determination of enantiomeric purity of 12 and 13 by chiral HPLC

For determination of enantiomeric excess of compounds **12** and **13**, an Agilent 1100 Series HPLC system equipped with a temperature controlled oven and a UV detector was employed. As mobile phase, n-hexane (solvent A) and 2-propanol (solvent B) containing trifluoroacetic acid (TFA) as modifier if necessary was used. Compounds were separated using a Daicel Chiralpak® AD-H column (250 x 4.6 mm) with a flow rate of 0.8-1 mL/min kept at 30 °C over a time period of 20-25 min and detected by UV-absorption (λ= 230 nm). Used elution methods are summarized in Table 3. The chromatographic elution order of the stereoisomers was determined by comparison with synthesized reference

compounds **(*S*)-12** and **(*R*)-12** as well as **(*S*)-13** and **(*R*)-13**, respectively. Due to lacking literature values of optical rotation of **(*S*)-12** and **(*S*)-13**, no polarimetric measurements were performed.

Table 3: HPLC methods (% A = % n-hexane, % B = % 2-propanol) for determination of enantiomeric purity of **12** (Method A) and **13** (Method B).

Method	% A (v/v)	% B (v/v)	Run time [min]	Flow rate [mL/min]	Modifier
A	90	10	20	0.8	-
B	85	15	25	1.0	0.1v% TFA

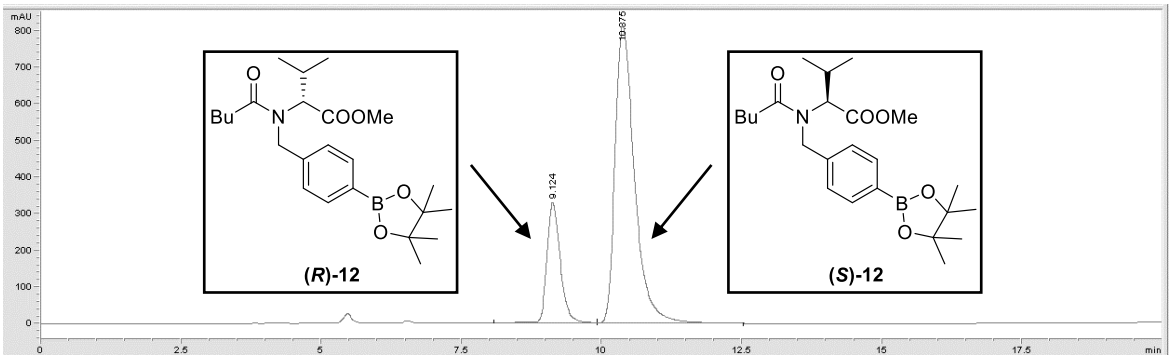


Figure 9: Chiral separation of **(*R*)-** and **(*S*)-12** by HPLC (λ= 230 nm, Method A).

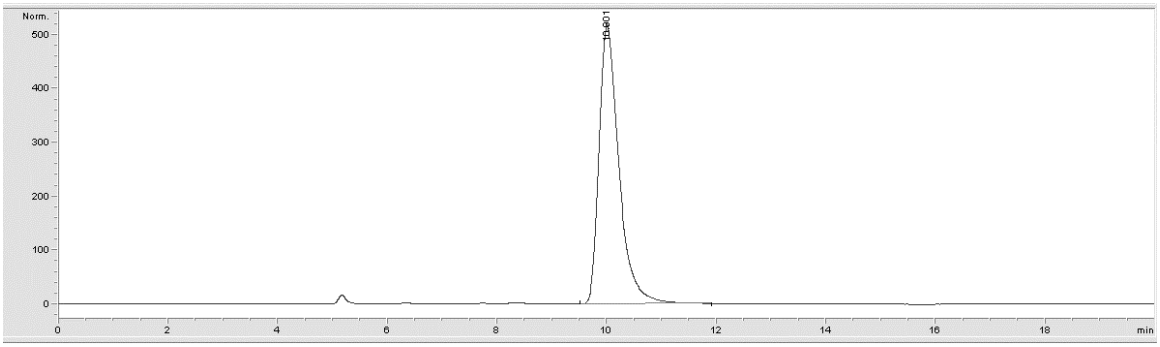


Figure 10: Determination of enantiomeric excess of compound **12** (λ= 230 nm, Method A).

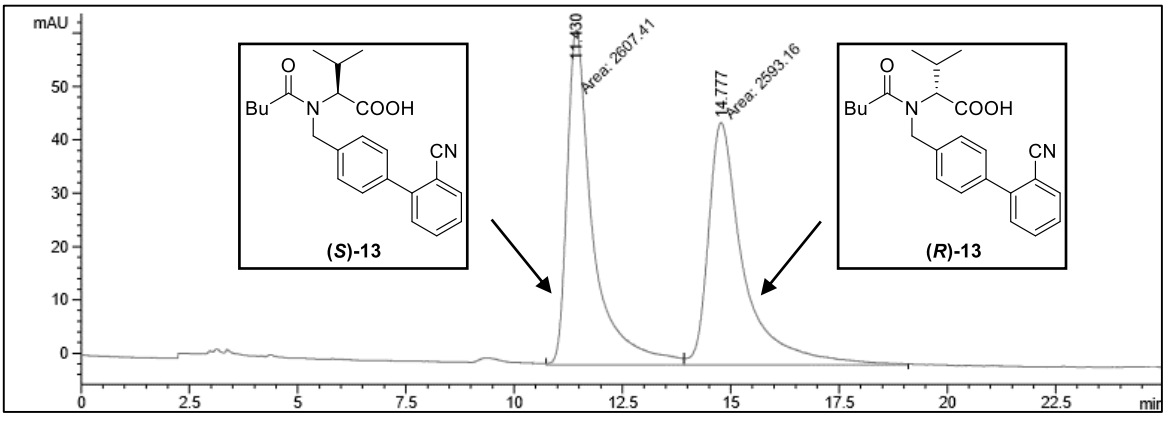


Figure 11: Chiral separation of **(*R*)-** and **(*S*)-13** by HPLC (λ= 230 nm, Method B).

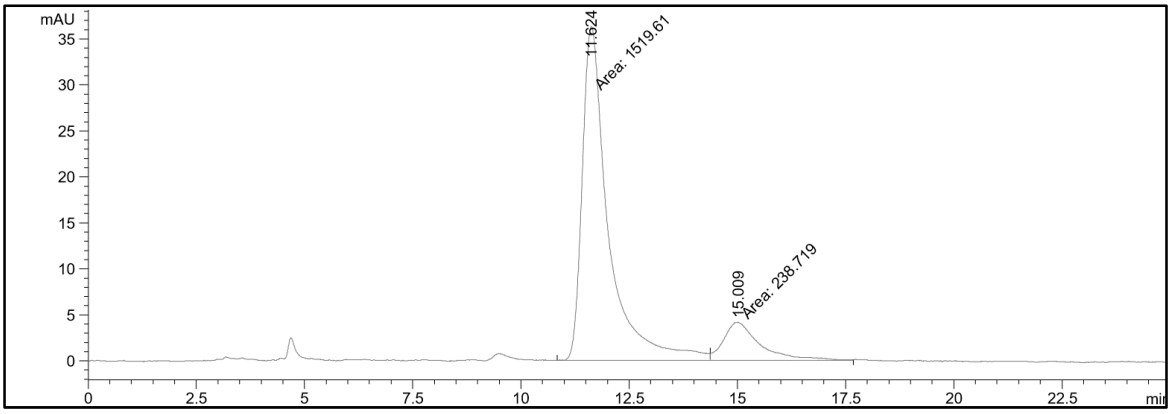


Figure 12: Determination of enantiomeric excess of compound **13** synthesized in the multistep flow process (λ= 230 nm, Method B).

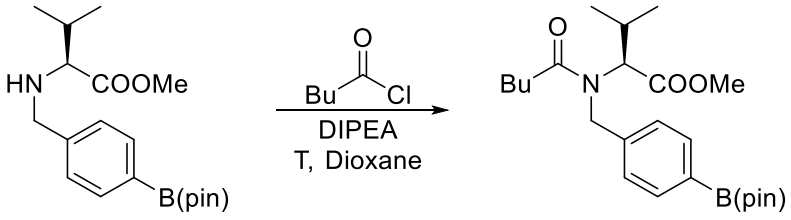
1.3.2 Determination of enantiomeric purity of 5 by optical rotation

According to the measured optical rotation of compound **5** of $[\alpha]_D^{20}$= -44.0 (*c*= 3.5, $CHCl_3$) [Lit.: $[\alpha]_D^{20}$= -38.0 (*c*= 3.5, $CHCl_3$)] [1], no significant racemization seems to take place during the Suzuki coupling step. For measurement of optical rotation of compound **5**, a thermostatically controlled Polarimeter MCP 500 equipped with a 1 dm cuvette was utilized. Used wavelength of the sodium halogen lamp was 589 nm and the temperature during measurement was kept constant at 25 °C. The pure sample was diluted in $CHCl_3$ and for calculation of optical rotation following formula was employed:

$$[\alpha]_{\mathrm{D}}^{\mathrm{temperature}} = \frac{[\alpha]}{[\mathrm{c}] * [\mathrm{l}]} \text{ in } \frac{\mathrm{mL}}{\mathrm{dm} * \mathrm{g}}$$

1.4 Optimization of reaction conditions in batch

1.4.1 Step 1 - Batch



11 **12**

Scheme 1: Batch reaction for optimization of the *N*-acylation step.

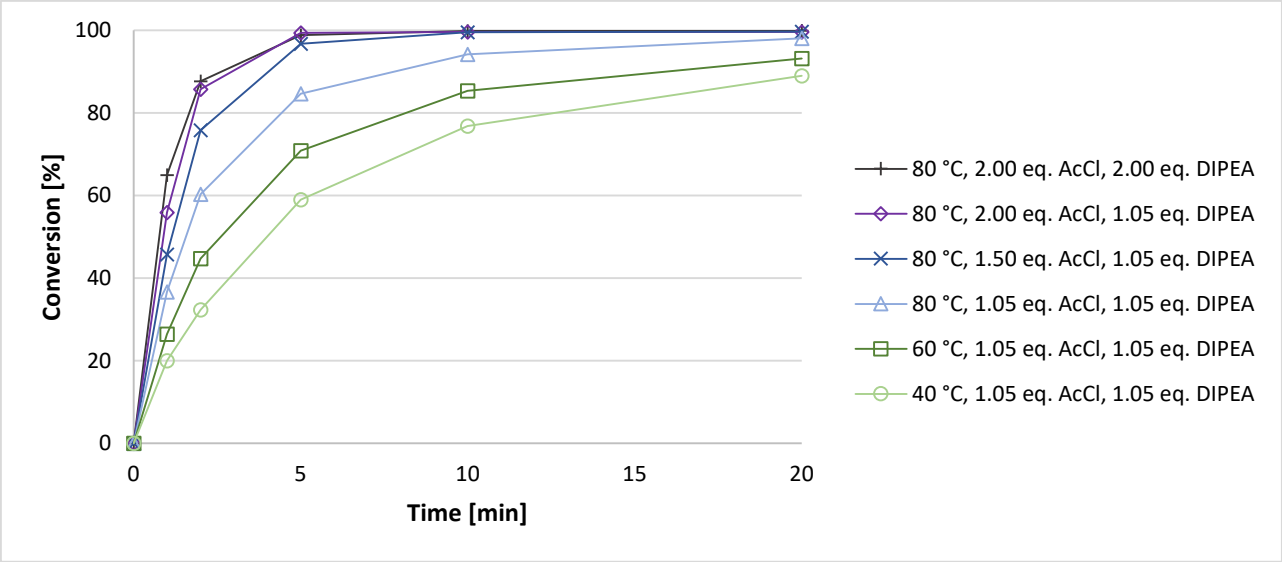
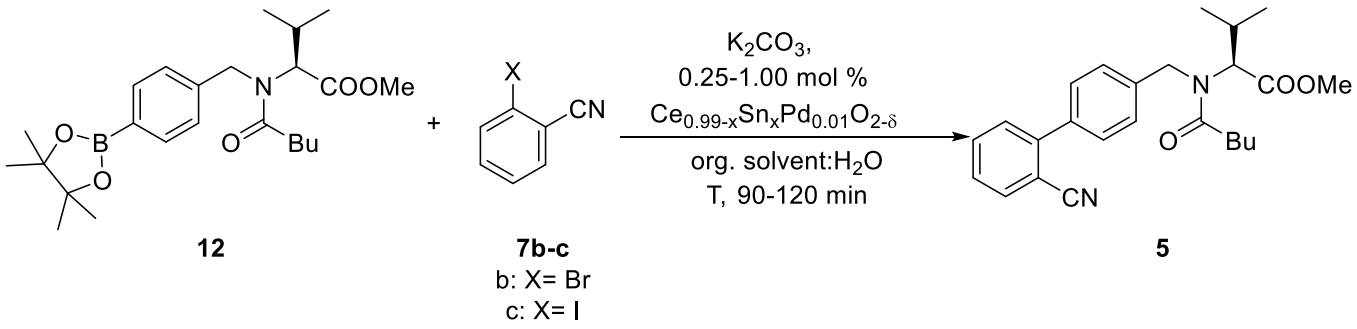


Figure 13: Effect of temperature and molar equivalents of valeryl chloride (AcCl) as well as DIPEA on the conversion of **11** in batch.

1.4.2 Step 2 - Batch



12 **7b-c** b: X= Br c: X= I **5**

Scheme 2: Batch reaction for optimization of the Suzuki-Miyaura cross-coupling step.

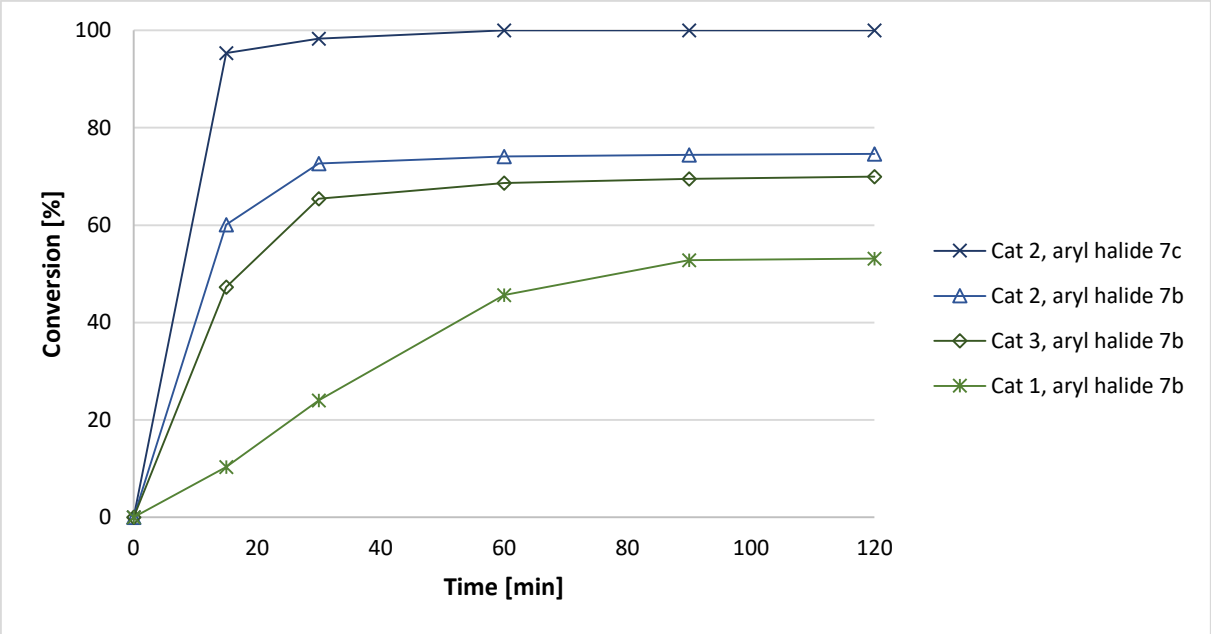


Figure 14: Effect of catalyst and aryl halide coupling partner on the conversion of aryl halide **7b-c** in Suzuki-Miyaura cross-coupling with **12** in EtOH:H_2O=7:3.

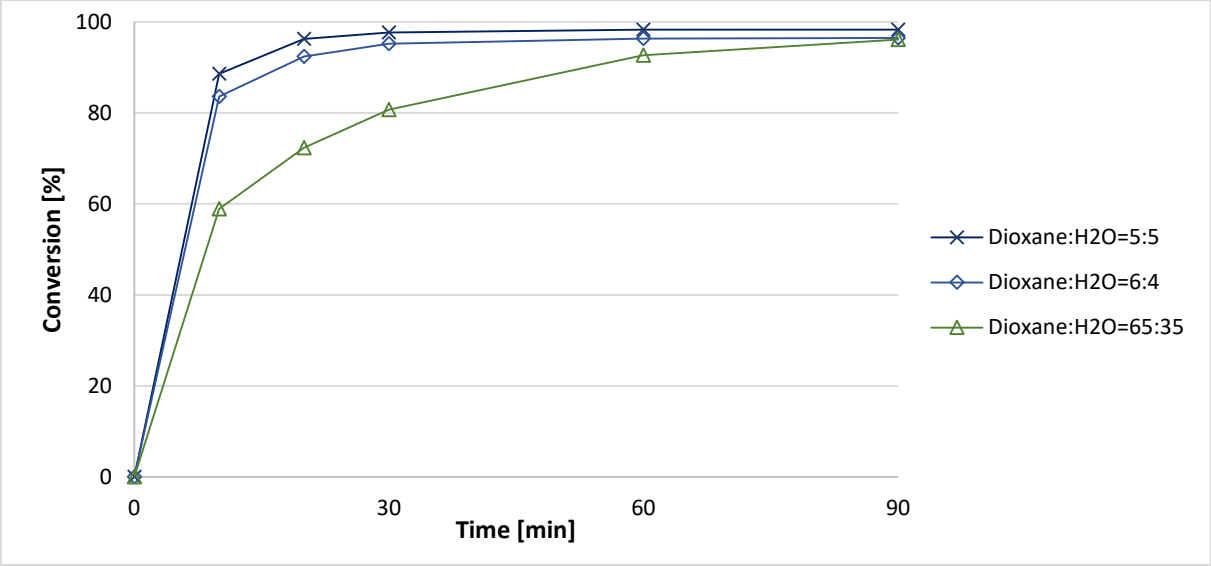


Figure 15: Effect of different solvent compositions of dioxane:H_2O on the conversion of **7c** in Suzuki-Miyaura cross-coupling with **12**.

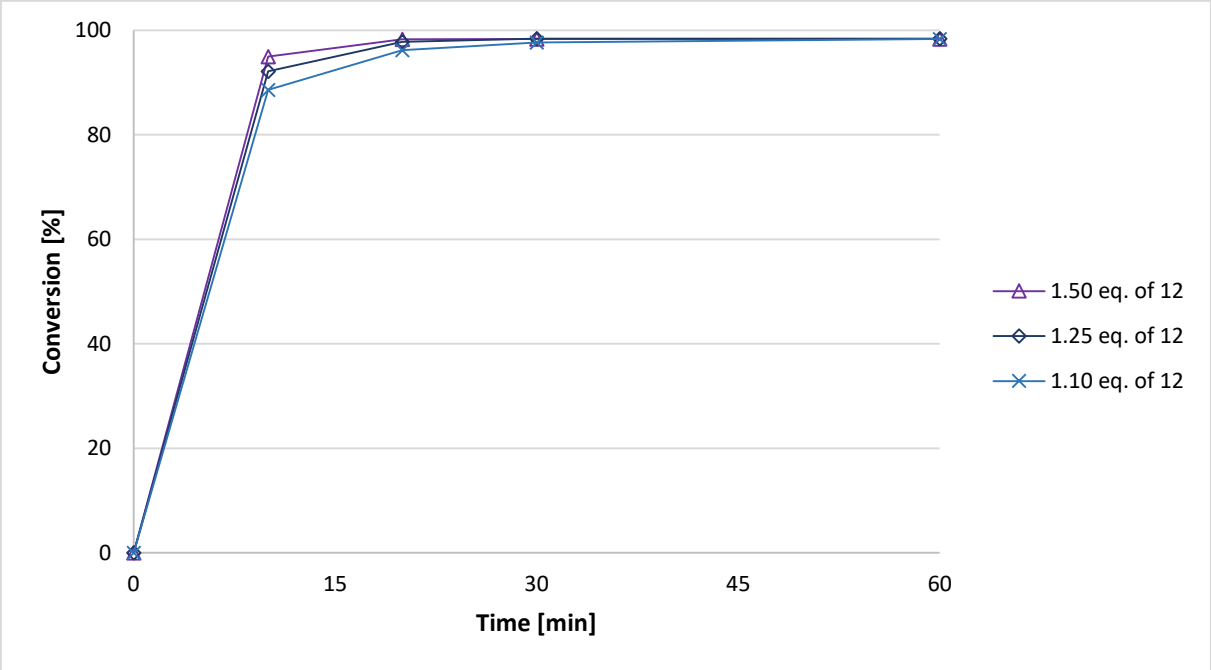


Figure 16: Effect of different molar equivalents of **12** on the conversion of **7c** in Suzuki-Miyaura cross-coupling with **12** in dioxane:H_2O=1:1.

1.4.3 Step 3 - Batch

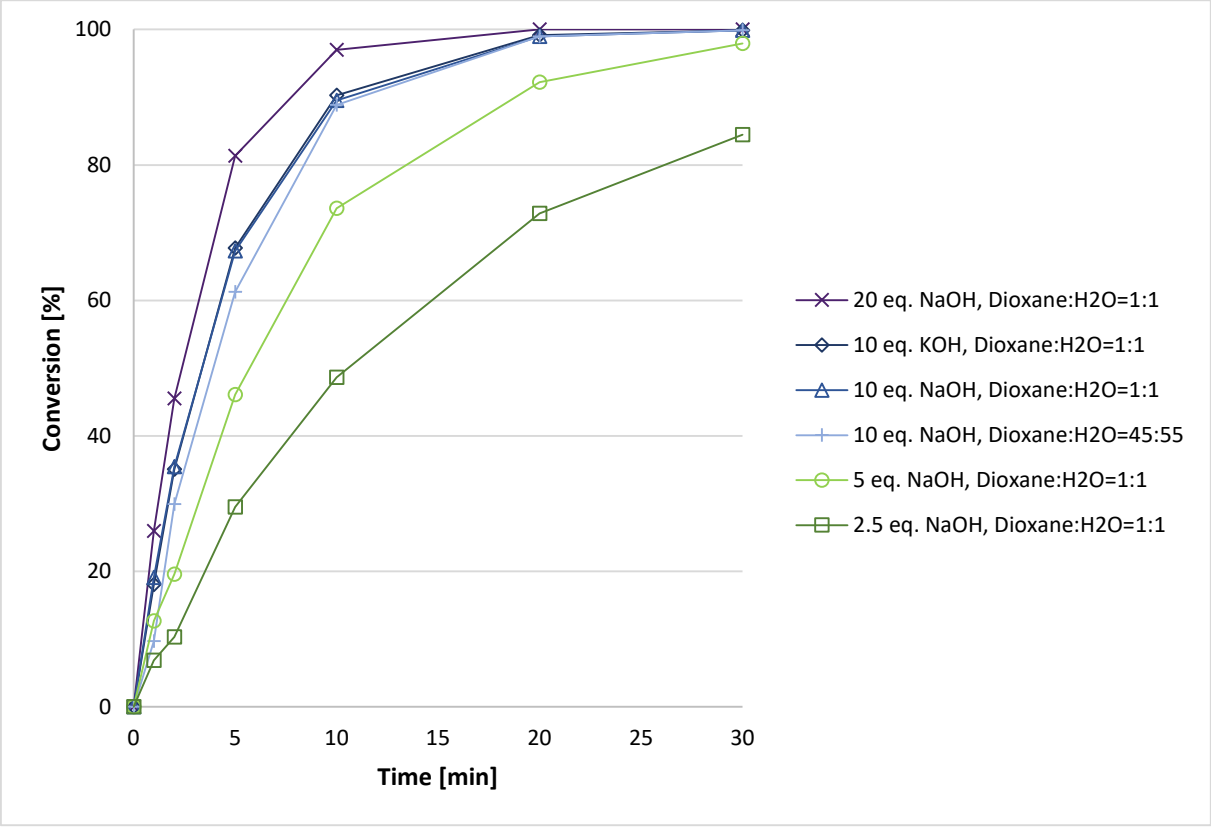


Figure 17: Effect of hydroxide source, molar equivalents of base and solvent composition on the conversion of **5** in methyl ester hydrolysis.

1.4.4 Sequential steps 1 + 2 in one-pot in batch

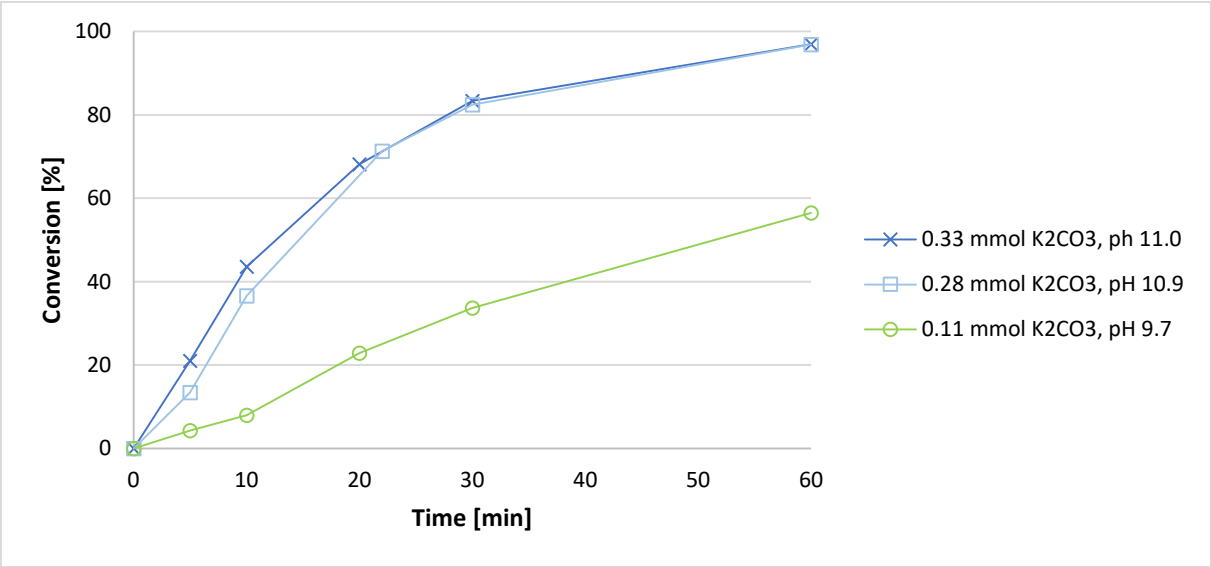


Figure 18: Effect of the pH on the conversion of **7c** in Suzuki coupling with **12** performed after *N*-acylation in one-pot.

1.5 Individual continuous setups

1.5.1 Step 1 – Continuous Flow

For the continuous performance of the *N*-acylation step, a stainless steel coil (L x O.D. x I.D. 3.0 m x 1/16 in. x 0.030 in.) in combination with a split-and-recombine static mixer [2] was utilized. A solution containing boronic acid ester **11** (110 mM), DIPEA (220 mM, 2 mol eq.) as well as anisole as internal standard (264 mM) and another solution containing valeryl chloride (220 mM, 2 mol eq.) were prepared in dioxane. Then the two reagent solutions were filled into separate syringes and introduced into the reactor setup at 80 °C with the same flow rate (0.05-0.10 mL/min for each syringe, corresponding to 0.10-0.20 mL/min total flow rate) using a dual-syringe infusion pump (LA-120, Landgraf). At the outlet, the product stream was collected and after certain time points, an aliquot (20 µL) was quenched with MeOH:H_3PO_4=50:50 (400 µL) and analyzed by HPLC (Method A).

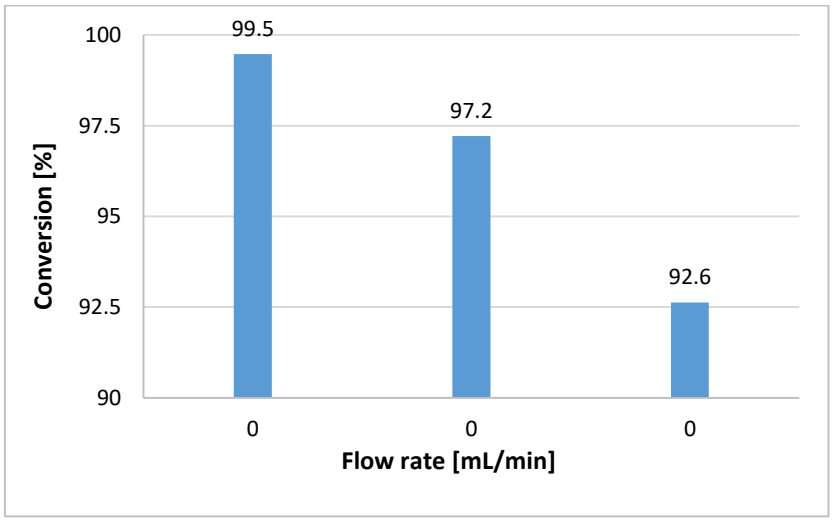


Figure 19: Effect of different flow rates on the conversion of **11** during the *N*-acylation step.

1.5.2 Step 2 – Continuous Flow

Continuous Suzuki coupling of boronic acid ester **12** with 2-iodobenzonitrile **7c** was performed utilizing the Plug & Play reactor [3]. A preparative HPLC column (L x I.D. 120 x 8 mm) was filled with the Pd-catalyst $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ (4.7 g) and introduced into the reactor at 80 °C. Then the reactor setup was flushed with solvent for equilibration of the system and removal of air bubbles. A solution containing 2-iodobenzonitrile **7c** (25 mM), boronic acid ester **12** (27.5 mM, 1.1 mol eq.), potassium carbonate (37.5 mM, 1.5 mol eq.) and anisole (67 mM) as internal standard was prepared in dioxane:H_2O=1:1, degassed in an ultrasonic bath for 30 minutes and filtered through a 0.2 µm membrane filter. The reagent solution was transferred into a stainless steel syringe and pumped through the reactor setup with a flow rate of 0.2 mL/min utilizing a high-pressure syringe pump (VIT-FIT HP, Lambda Instruments). At the outlet, the product stream was collected and after certain time points, an aliquot (40 µL) was quenched with MeOH:H_3PO_4=55:45 (400 µL) and analyzed by HPLC (Method B). For determination of leaching of Pd, Ce and Sn, the reaction solution was acidified (10% HNO_3/HCl, 1+1, v/v) and then analyzed by ICP-MS after microwave assisted acidic digestion.

1.5.3 Step 3 – Continuous Flow

For the continuous performance of the methyl ester hydrolysis, a stainless steel coil (L x O.D. x I.D. 3.0 m x 1/16 in. x 0.030 in.) in combination with a split-and-recombine static mixer was utilized. A solution containing biphenyl **5** (50 mM) as well as anisole (60 mM) as internal standard and another solution containing NaOH (500 mM, 10 mol eq.) were prepared in dioxane:H_2O=1:1. Then the two reagent solutions were filled into separate syringes and introduced into the reactor setup at 80 °C with the same rate (0.05-0.10 mL/min for each syringe, corresponding to 0.10-0.20 mL/min total flow rate) using a dual-syringe infusion pump (LA-120, Landgraf). At the outlet, the product stream was collected and after certain time points, an aliquot (40 µL) was quenched with MeOH:H_3PO_4=55:45 (400 µL) and analyzed by HPLC (Method B).

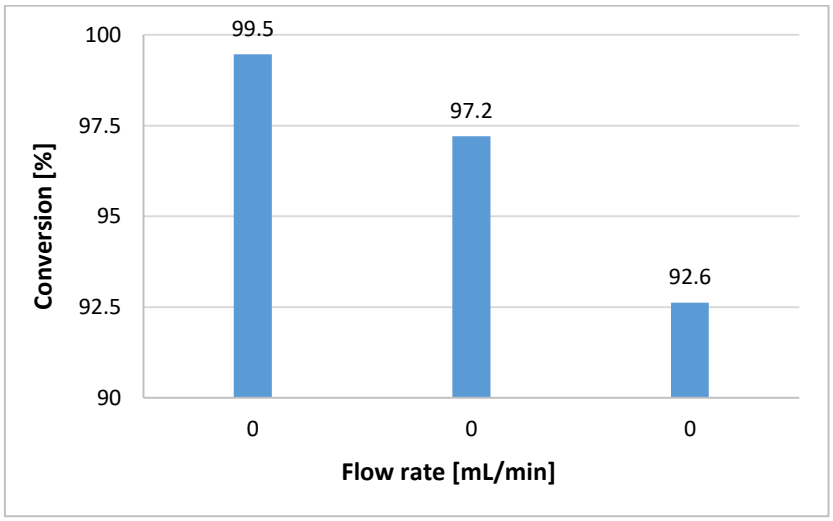


Figure 20: Effect of different flow rates on the conversion of **5** during the methyl ester hydrolysis step.

1.6 Multistep continuous setup

The course of yield over time obtained in the multistep continuous process for formation of **13** is apparent from Figure 1.

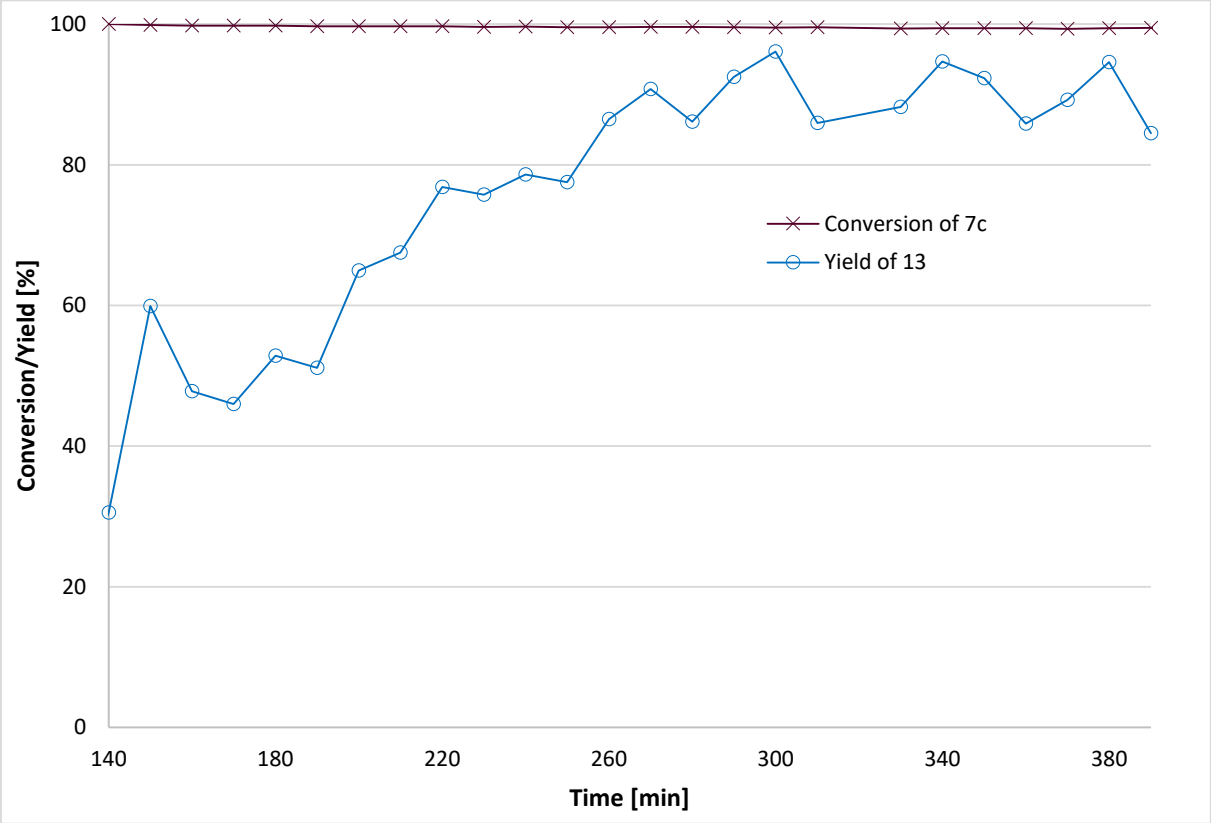
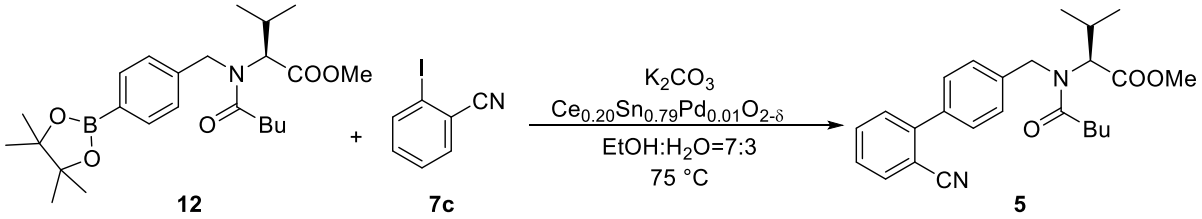


Figure 21: Conversion of **7c** and yield of **13** obtained using the multistep continuous setup for the synthesis of valsartan precursor **13**.

1.7 Chemical syntheses of 5, 11, 12, 13 and $Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$

1.7.1 Synthesis of 5



For synthesis of compound **5**, (*S*)-*N*-(1-oxopentyl)-*N*-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl]methyl]-L-valine methyl ester **12** (0.28 g, 0.66 mmol), 2-iodobenzonitrile **7c** (0.17 g, 0.73 mmol, 1.1 mol eq.) and potassium carbonate (0.14 g, 0.99 mmol, 1.5 mol eq.) were dissolved in EtOH:H_2O=7:3 (20 mL). Then, the catalyst $Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ (50 mg, 0.5 mol%) was added and the reaction mixture was stirred at 75 °C for 1 h. After cooling to room temperature, the solvent was evaporated and diluted with ethyl acetate (25 mL). The Pd-catalyst was removed by filtration and the organic phase was washed with deionized water (2x15 mL) and brine (1x10 mL) successively. Combined organic phases were dried over sodium sulfate and solvent was removed by rotary evaporation. The crude product was purified by column chromatography on silica gel (toluene:ethyl acetate=9:1, R_f= 0.31) to obtain **5**

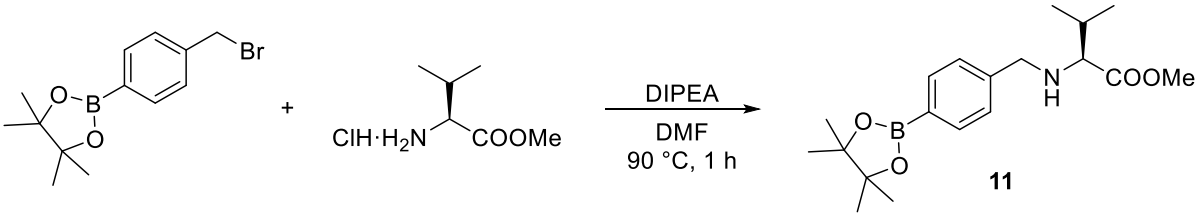
as slightly yellow oil with 70% yield (0.19 mg, 0.46 mmol). ^{1}H- and ^{13}C-NMR data (mix of rotamers) are in accordance with literature [4,5].

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm]= 7.68 (t, *J*= 7.4 Hz, 1H), 7.56 (q, *J*= 7.4 Hz, 1H), 7.50-7.29 (m, 4H), 7.28-7.17 (m, 2H), 5.01 and 4.91 (2d, J_{d1}=15.5 Hz, J_{d2}=10.3 Hz, 1H), 4.62 (s, 1 H), 4.20 (d, *J*= 15.5 Hz, 0.4 H), 3.99 (d, *J*= 10.8 Hz, 0.4 H), 3.38 and 3.29 (2s, 3H), 2.62-2.10 (m, 3H), 1.76-1.49 (m, 2H), 1.41-1.14 (m, 2H), 0.92 and 0.97-0.70 (d+m, *J*= 6.4 Hz, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C [ppm]= 174.7, 174.4, 171.2, 170.4, 145.4, 144.9, 138.9, 138.1, 137.3, 136.7, 133.9, 133.8, 133.0, 132.9, 130.1, 129.1, 128.7, 128.1, 127.8, 127.5, 126.4, 118.7, 111.3, 65.9, 61.8, 52.1, 51.8, 48.2, 45.4, 33.5, 27.9, 27.6, 27.5, 22.7, 22.6, 20.0, 18.8, 14.0.

HPLC/MS-ES (*m/z*) found 407, calcd for $[M+H]^+$ 407.52

1.7.2 Synthesis of 11



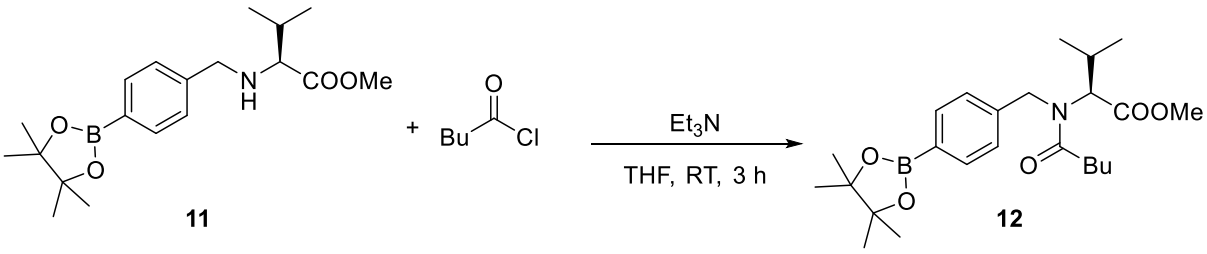
Cfeompound **11** was synthesized based on a reported literature procedure [6]. 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.00 g, 6.73 mmol) and L-valine methyl ester hydrochloride (1.35 g, 8.08 mmol, 1.2 mol eq.) were suspended in *N*,*N*-dimethylformamide (1.6 mL) and *N*,*N*-diisopropylethylamine (2.59 mL, 14.9 mmol, 2.21 mol eq.) was added. The reaction mixture was heated to 90 °C for 1 h. After cooling to room temperature, toluene (20 mL) was added and the organic phase was washed with deionized water (4x10 mL) and dried over sodium sulfate. The solvent was evaporated and obtained crude product was purified by column chromatography on silica gel (n-hexane:ethyl acetate:toluene=50:12:50; R_f= 0.36). The target compound **11** was obtained as colorless oil with 64% yield (1.50 g, 4.32 mmol). ^{1}H- and ^{13}C-NMR data are in accordance with literature [5].

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm]= 7.76 (d, *J*= 7.7 Hz, 2H), 7.35 (d, *J*= 7.7 Hz, 2H), 3.87 (d, *J*= 13.4 Hz, 1H), 3.71 (s, 3H), 3.60 (d, *J*= 13.4 Hz, 1H), 3.00 (d, *J*= 6.0 Hz, 1H), 2.03 (brs, 1H), 1.92 (sex, *J*= 6.6 Hz, 1H), 1.34 (s, 12H), 0.93 (t, *J*= 6.2 Hz, 6H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C [ppm]= 175.7, 143.2, 135.0, 127.8, 83.8, 66.5, 52.6, 51.6, 31.8, 25.0, 19.4, 18.8.

HPLC/MS-ES (*m/z*) found 348, calcd for $[M+H]^+$ 348.27

1.7.3 Synthesis of 12



The synthesis of **12** was performed according to published literature procedure [5]. (*S*)-*N*-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]-L-valine methyl ester **11** (1.00 g, 2.88 mmol) was

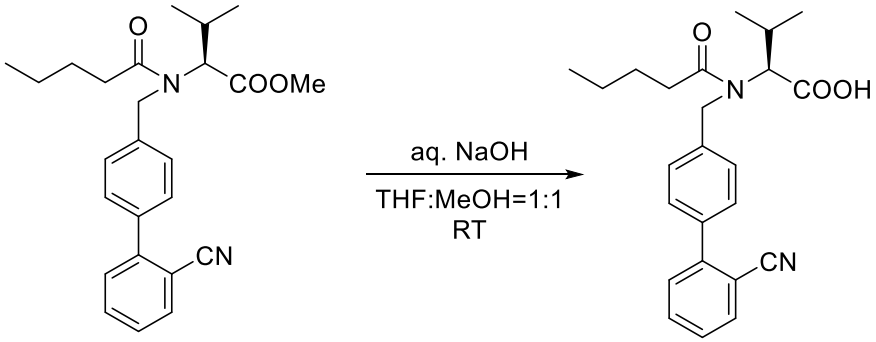
dissolved in dry tetrahydrofurane (25 mL) and triethylamine (0.41 mL, 2.94 mmol, 1.02 mol eq.) was added dropwise. After cooling to 0 °C, valeryl chloride (0.68 mL, 5.76 mmol, 2.0 mol eq.) was added dropwise and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed by rotary evaporation and the residue was diluted with ethyl acetate (50 mL). The organic phase was washed with deionized water (3x20 mL) and brine (1x20 mL) successively, dried over sodium sulfate and the solvent was evaporated. The crude product was purified by column chromatography on silica gel (eluent petrol ether:ethyl acetate=9:1 to 8:2, $R_{f\,9:1}$= 0.35). Product **12** was obtained with 64% yield (0.80 g, 1.84 mmol) as slightly yellow oil. ^{1}H- and ^{13}C-NMR data (mix of rotamers) are in accordance with literature [5].

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm]= 7.75 and 7.69 (2d, *J*= 7.7 Hz, 2H), 7.22-7.05 (m, 2H), 4.98 and 4.90 (2d, J_{d1}=10.4 Hz, J_{d2}=15.4 Hz, 1H), 4.62 (s, 1.5 H), 4.32 (d, *J*= 15.8 Hz, 0.25 H), 4.03 (d, *J*= 10.6 Hz, 0.25 H), 3.43 and 3.36 (2s, 3H), 2.65-2.10 (m, 3H), 1.80-1.52 (m, 2H), 1.51-1.15 (m+s, 14H), 1.03-0.70 (m, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C [ppm]= 174.9, 174.3, 171.2, 170.4, 141.5, 140.7, 135.2, 134.8, 127.0, 125.2, 84.0, 83.8, 66.2, 61.8, 52.0, 51.8, 48.4, 46.0, 33.7, 33.5, 28.0, 27.6, 26.9, 25.0, 22.6, 22.3, 19.9, 18.8, 14.0, 13.8.

HPLC/MS-ES (*m/z*) found 432, calcd for $[M+H]^+$ 432.38

1.7.4 Synthesis of 13



5 **13**

The synthesis of **13** was performed according to a chemical ester hydrolysis procedure stated in literature [7]. (*S*)-*N*-[(2'-cyano[1,1'-biphenyl]-4-yl)methyl]-*N*-(1-oxopentyl)-L-valine methyl ester **5** (25 mg, 0.06 mmol) was dissolved in tetrahydrofuran (0.5 mL) and methanol (0.5 mL) and aqueous sodium hydroxide solution (1 M, 0.62 mL, 10 mol eq.) was added. The reaction mixture was stirred at room temperature for 23 h. Then, organic solvents were removed by rotary evaporation and the reaction mixture was acidified using an aqueous hydrogen chloride solution (6 M) until a pH of ~3 was reached. The aqueous phase was extracted with ethyl acetate (3 x 3 mL), dried over sodium sulfate and solvent was removed. Purification of the crude product by column chromatography on silica gel (petrol ether:ethyl acetate:acetic acid=69.5:70:0.5, R_f= 0.33) gave the product **13** as yellowish solid with 67% yield (16 mg, 0.04 mmol).^{1}H- and ^{13}C-NMR data (mix of rotamers) are in accordance with literature [8].

^{1}H-NMR (300 MHz, $CDCl_3$): δ_H [ppm]= 9.35-8.25 (brs, 1H), 7.72-7.15 (m, 8H), 4.78 (d, *J*=17.0 Hz, 1H), 4.41 (d, *J*=17.0 Hz, 1H), 3.99 (d, *J*= 10.8 Hz, 0.2H), 3.75 (d, *J*= 10.5 Hz, 0.8H), 2.70-2.17 (m, 3H), 1.72-1.50 (m, 2H), 1.41-1.19 (m, 2H), 0.68-1.03 (m, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ_C [ppm]= 177.4, 174.8, 172.0, 144.8, 138.1, 136.3, 133.9, 133.7, 133.1, 133.0, 130.2, 130.1, 129.6, 128.6, 128.3, 127.9, 127.5, 127.2, 118.7, 111.3, 71.8, 66.2, 54.3, 46.1, 34.2, 33.6, 27.9, 27.4, 27.3, 22.7, 22.5, 20.0, 19.9, 19.6, 19.0, 14.0, 13.9.

HPLC/MS-ES (*m/z*) found 393, calcd for $[M+H]^+$ 393.50

1.7.5 Synthesis of $Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$

Catalysts of formula $Ce_{0.99-x}Sn_xPd_{0.01}O_{2-\delta}$ (x= 0.20, 0.79, 0.99) were synthesized using a modification of the solution combustion method reported by Baidya et al [9]. For the synthesis of 3 g catalyst, the respective amounts of ammonium cerium(IV) nitrate, tin(II) oxalate, palladium(II) chloride and glycine (Table 4) were pestled in a mortar to achieve a fine powder. Then, HPLC-grade water (2 mL) was added and the mixture was subjected to ultrasonic radiation for 30 min. After combustion in the oven (350 °C, 1 h), the particle size of the catalyst was again reduced by a mortar and resulting yellow powder was dried in the oven (350 °C) over night. The catalyst was obtained quantitatively and used as such for Suzuki-Miyaura cross-coupling reactions.

Table 4: Amounts of catalyst precursors and fuel used for the synthesis of 3 g Pd-catalyst.

x	Molecular formula	$(NH_4)_2Ce(NO_3)_6$	SnC_2O_4	$PdCl_2$	glycine
0.2	$Ce_{0.79}Sn_{0.20}Pd_{0.01}O_{2-\delta}$	7.758 g	0.741 g	0.032 g	3.445 g
0.79	$Ce_{0.20}Sn_{0.79}Pd_{0.01}O_{2-\delta}$	2.124 g	3.164 g	0.034 g	3.345 g
0.99	$Sn_{0.99}Pd_{0.01}O_{2-\delta}$	-	4.077 g	0.035 g	3.307 g

1.8 References

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