Electronic Supplementary Material (ESI) for Chemical Science.

Formamide Catalyzed Activation of Carboxylic Acids – Versatile and Cost-Efficiency Amidations and Esterifications

Peter H. Huy*, C. Mbouhom

Saarland University, Institute for Organic Chemistry, P. O. Box 151150, 66041 Saarbruecken, Germany

Homepage: Peterhuylab.de

*Email: peter.huy@uni-saarland.de

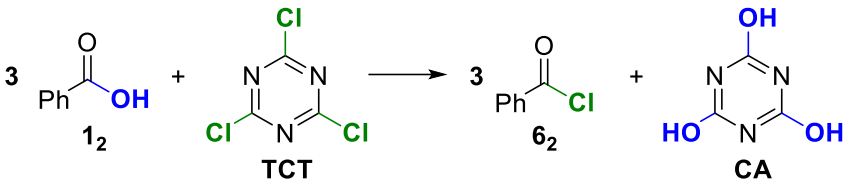
Content

Footnotes (x)
Endnotes [y]

1 Atom and Cost-Efficiency

1.1 Synthesis of Carboxylic Acid Chlorides

For the reason of comparability, atom economies (= AE) of various methods were determined for the dehydroxychlorination of benzoic acid (**1**$_2$) furnishing benzoyl chloride (**6**$_2$) as a low molecular-weight benchmark example (Figure S1). Thereby, the atom economies were calculated accounting coefficients of the respective balanced reaction equations. The ideal atom-efficiency of 88% would be realized engaging HCl, in which H_2O is formed as exclusive by-product. However, we are not aware of any examples, in which HCl was applied as reagent to convert carboxylic acids into the corresponding chlorides. Most likely, the thermodynamic driving force is modest and activation barriers are too high. For the present method the balanced reaction equation is as follows:



The atom economy can be either calculated from the molar masses M of all products or starting materials.

$$AE = \frac{3 \cdot M(\mathbf{2_3})}{3 \cdot M(\mathbf{1_3}) + M(\boldsymbol{TCT})} = \frac{3 \cdot 140.6\,{}^{g}/_{mol}}{3 \cdot 122.1\,{}^{g}/_{mol} + 184.4\,{}^{g}/_{mol}} = 77\%$$

$$AE = \frac{3 \cdot M(\mathbf{2_3})}{3 \cdot M(\mathbf{2_3}) + M(\boldsymbol{CA})} = \frac{3 \cdot 140.6\,{}^{g}/_{mol}}{3 \cdot 140.6\,{}^{g}/_{mol} + 129.1\,{}^{g}/_{mol}} = 77\%$$

From this assessment it is immediately apparent that TCT (33 mol%) enables a superior atom efficiency in comparison to all other conventional chlorination reagents (Figure S1). In terms of atom-economy, dichlorodiphenylmethane and PCl_5 are the poorest reagents. Also a range of very frequently employed acid chlorides such as $OPCl_3$, PCl_3, oxalyl and thionyl chloride allow for moderate atom-efficiencies between 51-58%. Surprisingly, chlorination of benzoic acid by means of *Ghosez´s* and the *Vilsmeier* reagent proceed in acceptable AEs of 55-56%. However, both reagents require one of the aforementioned acid chlorides or phosgene for the preparation (and one equivalent of NEt_3 in the case of *Ghosez´*s agent). If this is taken into account, the overall atom-efficiency is significantly lower. Furthermore, phosgene exhibits the best atom-economy (64%) with the exception of the current method. With 45% the protocol of *Venkataraman* employing 50 mol% of TCT (50 mol%) and NEt_3[23] shows a depleted AE.

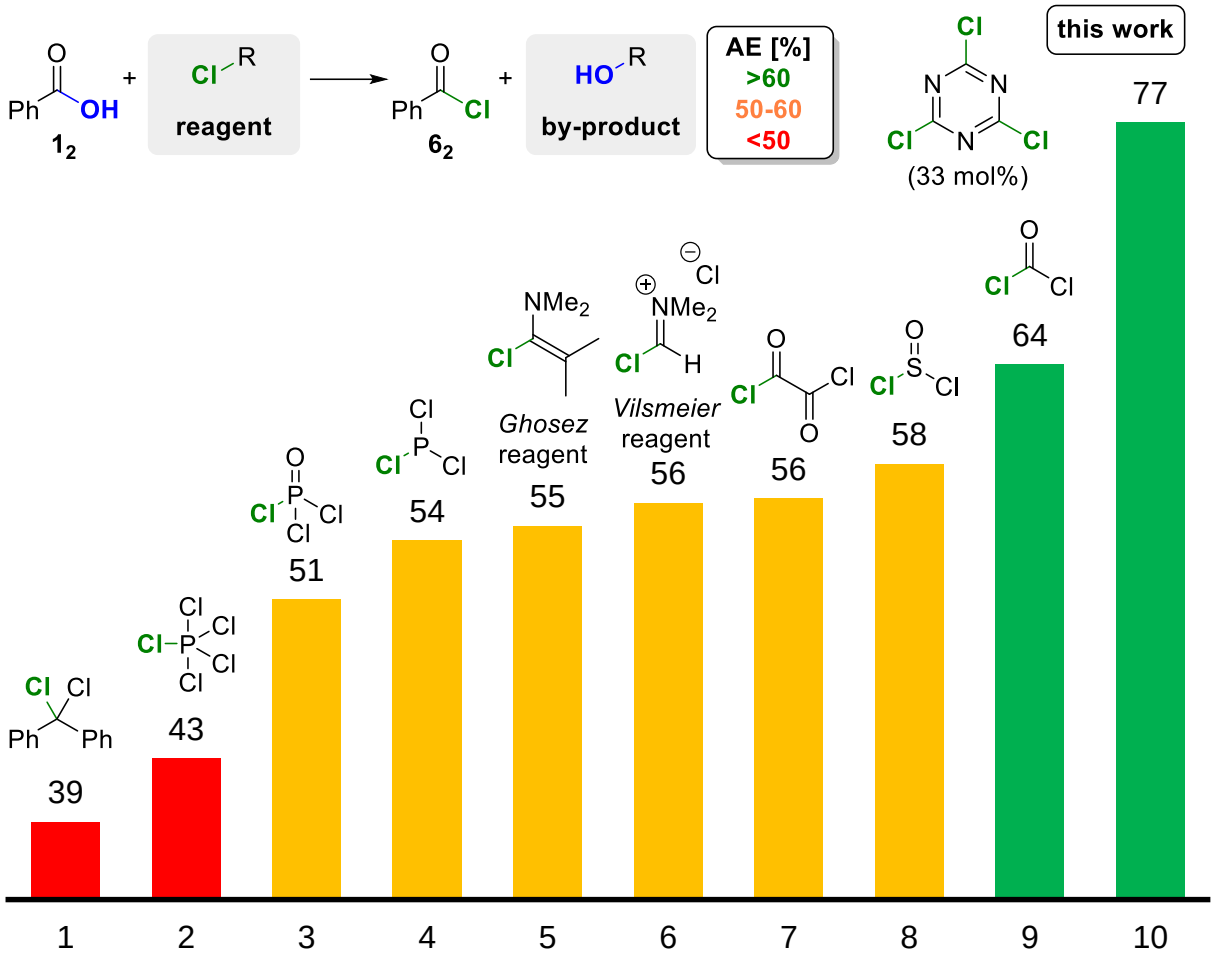


Figure S1. Comparison of the atom economies (AE) of various methods for the conversion of carboxylic acids into the respective acid chlorides.

The relative order of reagents changes dramatically, when the costs per mol of converted starting material are compromised (Figure S2 and Table S1). For this analysis the least expensive prices were collected from Sigma-Aldrich in April 2nd, 2019. Of course, on an industrial scale the costs for chlorination chemicals would drop significantly. Albeit the absolute prices would be lower, we are convinced that the relative sequence is quite well reflected by the costs compiled. Apparently from Figure S2, TCT also facilitates the highest level of cost-efficiency under consideration of the favourable substrate/reagent stoichiometry of 3:1. Already, simple acid chlorides like PCl_3, $SOCl_2$, PCl_5 and $OPCl_3$ are three to four times as expensive. Oxalyl chloride on the other hand is associated to almost 10-fold higher costs. The more complex *Ghosez* and *Vilsmeier* reagent and dichlorodiphenylmethane are by far out of range. Commercial prices are located between 300-1200 €.

Table S1. Costs for reagents and atom economies (AE) for the chlorination of benzoic acid.

entry	reagent	M [g/mol]	Batch	AE [%]	Price [€/mol]	Ref.
1	*Ghosez* reagent	133.6	250 mL/2260 €	55	**1196**	[1]
2	*Vilsmeier* reagent	128.0	25 g/113 €	56	**579**	[2]
3	ClClCPh$_2$	237.1	100 g/141 €	39	**334**	[3]
4	Cl(C=O)COCl	126.9	2.5 kg/682 €	56	**23.1**	[4]
5	ClP(=O)Cl$_2$	153.3	1 kg/80.3 €	51	**12.3**	[4]
6	ClPCl$_4$	208.4	1 kg/55.40 €	43	**11.5**	[4]
7	Cl(S=O)Cl	119.0	1 L/138 €	58	**10.1**	[4]
8	ClPCl$_2$	137.3	1 L/105 €	54	**9.2**	[5]
9	TCT (33 mol%)	184.4/3	1 kg/45 €	77	**2.8**	**This work**
10	Cl(C=O)Cl	98.9	n.d.	64	**n.d.**	[4]

The prices were collected from Sigma-Aldrich at April, 2nd 2019. The lowest price for the biggest batch available was chosen. Atom economies were calculated based on the molecular weights of BzCl (140.6 g/mol), BzOH (122.1 g/mol) and the respective reagent under consideration of the reaction stoichiometry.

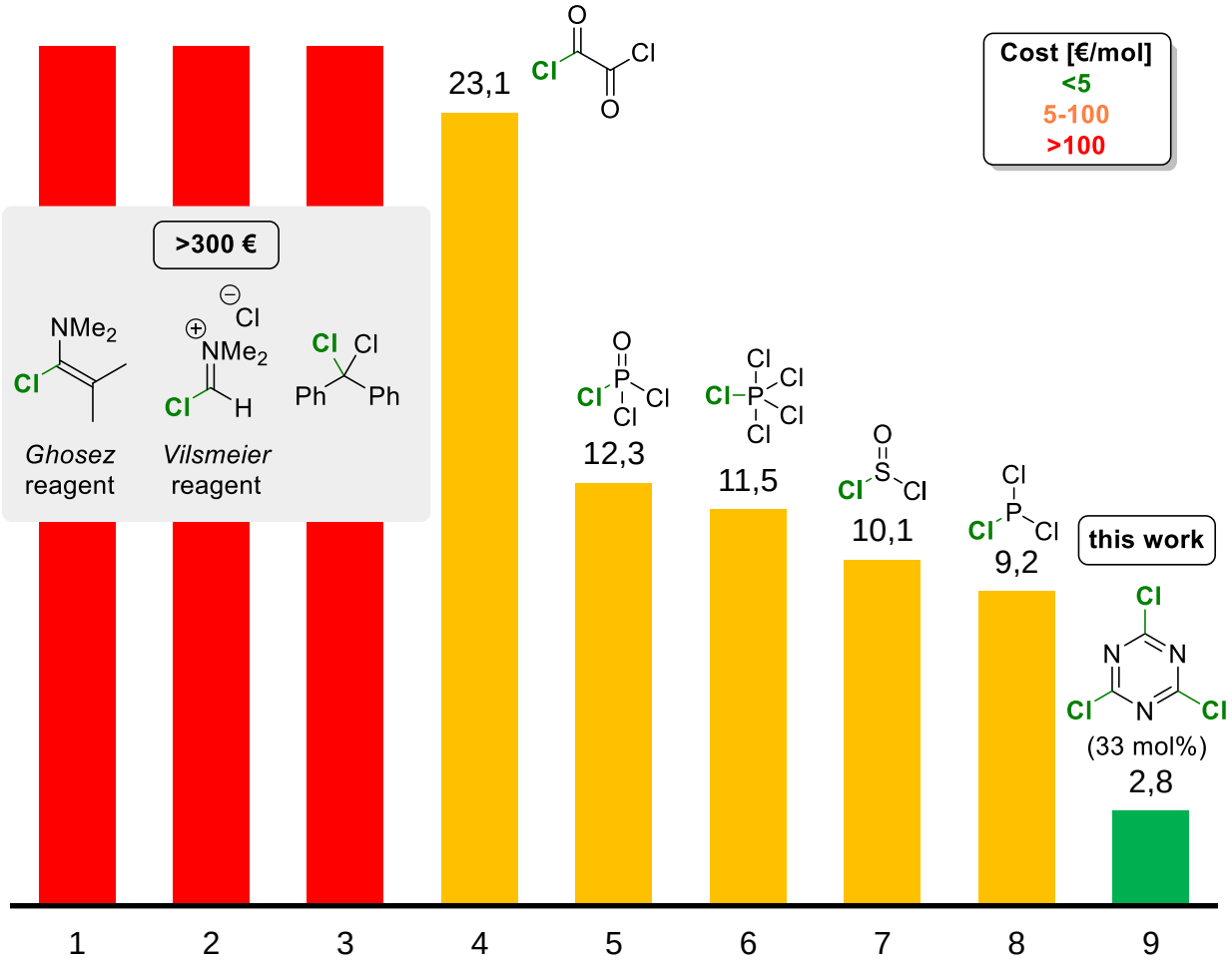
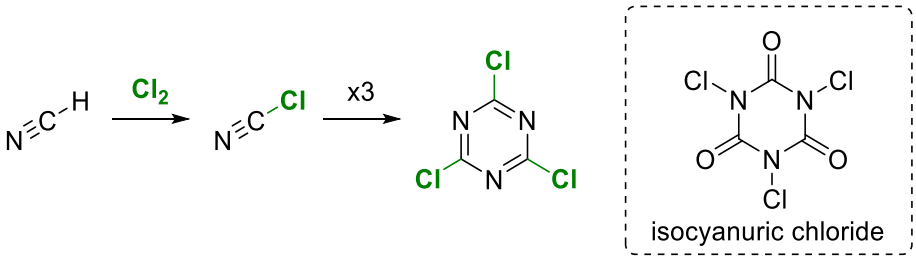


Figure S2. Comparison of prices for reagents for the chlorination of carboxylic acids (see Table S1 for details).

Other methods based on oxalyl chloride as reagent, which either require di-*iso*-cyclopropenone and DIPEA[6] or tropone in stoichiometric quantities,[7] are associated with noticeably higher

levels of costs and depleted atom-economies. Since phosgene is only commercial available at Sigma-Aldrich as rather expensive solution in toluene (278 €/0.5 L for a 20wt% solution), it was not included in the present cost assessment. As carbonyldichloride is produced in industry from CO and Cl_2, levels of costs should be at least comparable to TCT.

In fact, TCT is a bulk chemical, which is produced on an amount >100.000 t/year, and mainly used for the synthesis of disinfectants and herbicides.[8] The low price level of TCT is not only reasoned by the high demand but also by the simple industrial synthesis (Scheme S1). The acid chloride is prepared in industry by chlorination of hydrocyanic acid and subsequent formal [2+2+2] cycloaddition at elevated temperatures.

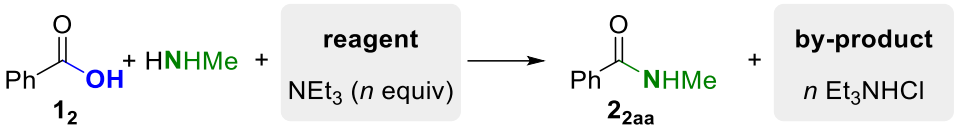


Scheme S1. Technical Synthesis of TCT and structure of isocyanuric chloride.

Cyanuric acid is an important bulk chemical as well, which is prepared on a multi thousand ton scale.[8] While cyanuric acid is mainly utilized as stabilizer for chlorine, for instance in swimming pools, the largest amount is oxidized by chlorine to isocyanuric acid (for structure see Scheme S1). Isocyanuric acid in turn is applied as swimming pool disinfectant and active ingredient of bleaches, cleansers and sanitizers.

1.2 Synthesis of Amides

Since activation of carboxylic acids towards nucleophilic substitution is not only accomplished by transformation into the respective acid chloride, a second study with regard to atom- and cost-efficiency is described in the following. As model reaction for amidations and esterifications in general, the conversion of benzoic acid and methylamine to *N*-methyl benzamide was selected (Scheme S2). Through the low molecular weight of the product, methods can be more clearly differentiated based on atom-efficiency.



Scheme S2. Model reaction to evaluate atom- and cost-efficiency of reagents for amidations.

Thereby, NEt_3 was chosen as generic base. Depending on the reagent applied, the amount of base required varies between 0 and 2 equiv (see Table S2 for details). In the case of the synthesis of amides and esters using oxalyl ($C_2O_2Cl_2$) and thionyl chloride ($SOCl_2$) and phosgene ($COCl_2$), respectively, two equivalents of HCl are released, which affords two equivalents of base. Nevertheless, for the current assessment only one equivalent of NEt_3 was included. Herein, removal of one equivalent of HCl through evaporation of the reaction solvent after transformation of the carboxylic acid **1** into the respective acid chloride **6** was anticipated.

Worthy of note, some protocols require more complex and expensive bases than NEt_3 such as *Hünig´*s base (DIPEA). Albeit in most examples of the current manuscript NMM or K_2CO_3 have been used, NEt_3 is an equally well suitable base. Naturally, the direct condensation of benzoic acid with methylamine to yield amide $\mathbf{2_{2aa}}$, in which water is formed as only by-product, is distinguished by an optimal atom efficiency of 88%. Catalysts feasible to promote direct amide syntheses are boron containing *Lewis*-acids[9] and hafnocendichloride,[10] in which aromatic substrates are often classified as challenging.

In Figure S3 various methods for the stoichiometric activation of carboxylic acids are compared. First of all, the respective amidation of benzoic acid shows significantly depleted atom-economies than the afore-mentioned chlorination (see Figure S1). In both assessments, TCT (33 mol%, this method) allows for the best AEs of 77 and 43%, respectively. The deteriorated result is mainly explained by the additional molecular weight of triethylamine of 101 g/mol. Nevertheless, also in the case of the examined amidation reaction a clear trend is apparent. Applications of carbodiimides such as DCC and EDC effect comparative AEs than TCT, because no additional base is required. Again, TCT turned out to be superior with respect to AE in comparison to phosgene and a range of other chlorination agents (35-38%).

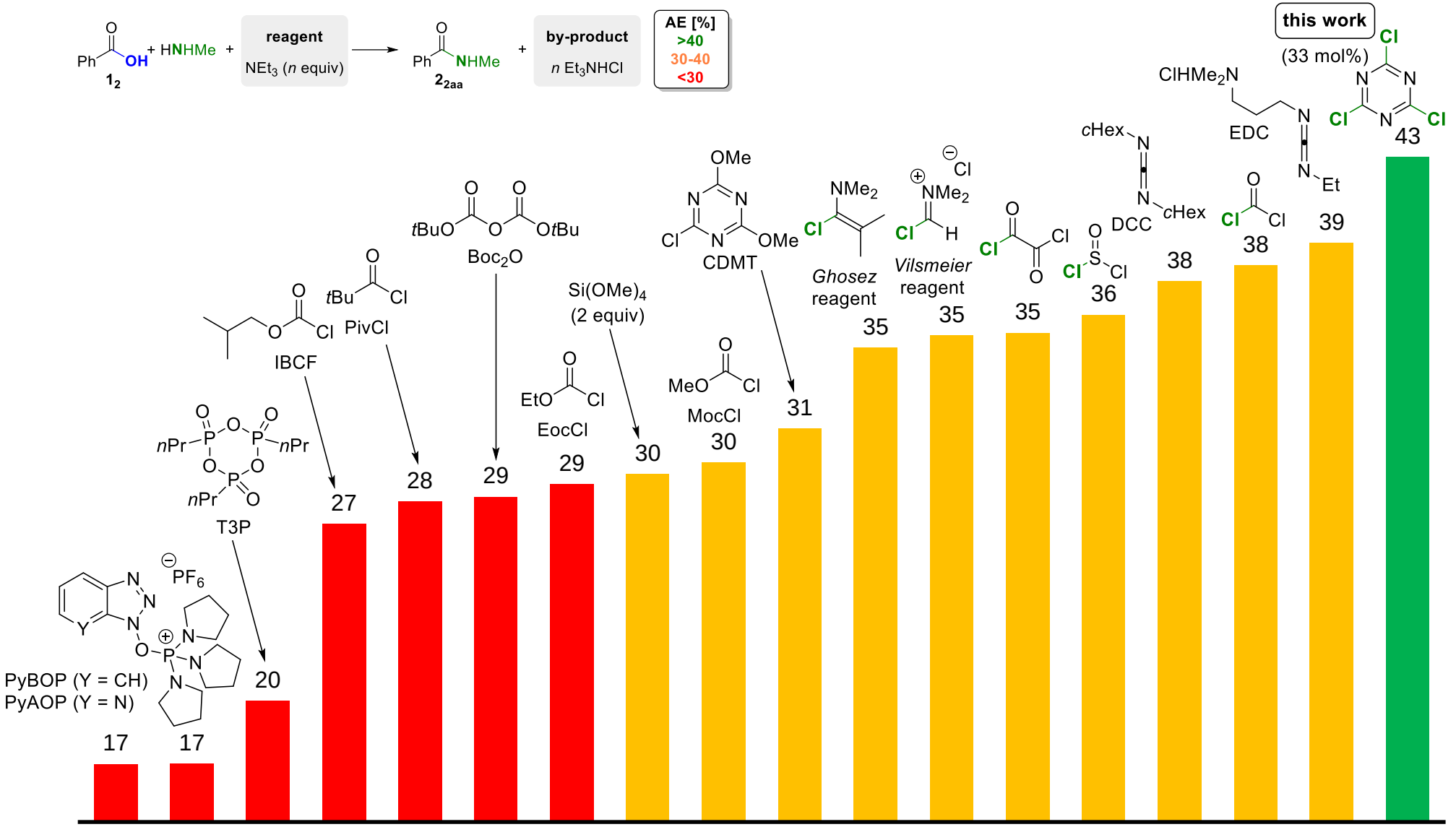


Figure S3. Comparison of the atom economies (AE) of various methods for the conversion of carboxylic acids into amides.

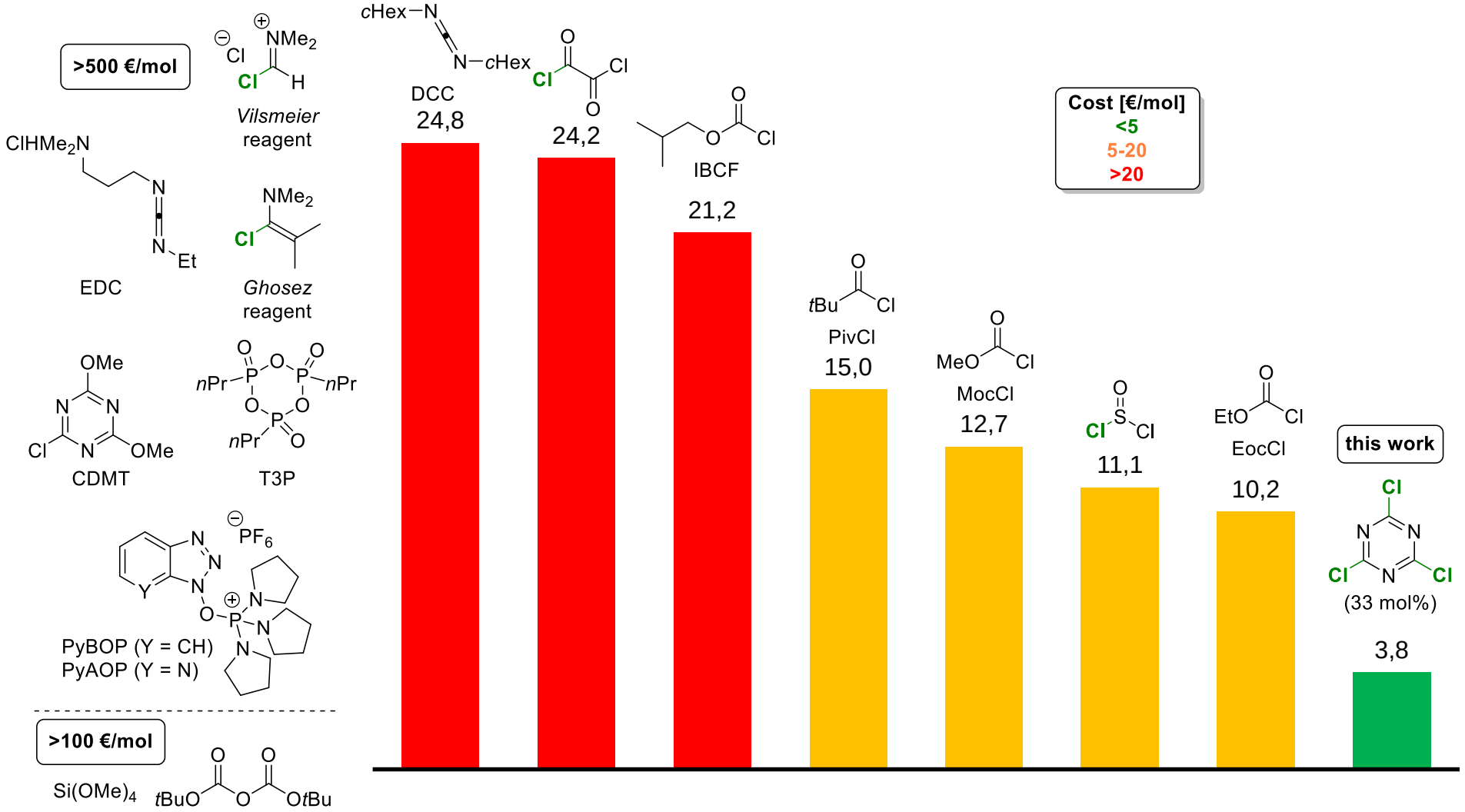


Figure S4. Comparison of prices for reagents for the synthesis of amides from carboxylic acids considering the required amount of NEt_3 (see Table S2 for details).

Condensation reactions of carboxylic acids promoted by simple chloro formats and acid chlorides already exhibit significantly decreased atom-economies (here 27-30%), since two equivalents of base have to be engaged. Finally, coupling reactions by means of more sophisticated reagents like T3P, PyBOP and PyAOP, which are mainly employed for the synthesis of structurally complex peptides, are hampered by rather poor AEs (here 17-20%).

A cost assessment based on the lowest Sigma-Aldrich prices for reagents, which are feasible to promote coupling reactions involving carboxylic acids, and the necessary minimum amount of NEt_3 (1.07 €/mol) unveils TCT as most effective candidate, too (Figure S4, for details see). Taking the beneficial stoichiometry into account (**1**/TCT 3:1), the estimated costs are below 4 € per mol converted acid, which is similar to the value determined for the preparation of benzoyl chloride (Figure S2). In fact, atom-economy not necessarily correlates with cost-efficiency. For instance, in the presented ranking TCT is followed by ethoxycarbonyl chloride (EocCl) with an approximated price of 10 €/mol, which is not one of the most effective agents in regard to AE (29%). With a reasonable but at least three-fold increased price level compared to TCT are $SOCl_2$, MoCl and pivaloyl chloride are associated. Costs for oxalyl chloride, *iso*-butyl chloro formate (IBCF) and DCC, the latter two of which account to the most-widely used coupling reagents, were determined to be >20 €/mol, already. Remarkably, all other agents for the activation of carboxylic acids included in this representative study are inevitably connected with a significantly higher price level above 100 €/mol. As discussed in the previous chapter, phosgene might allow for reduced costs in comparison to TCT.

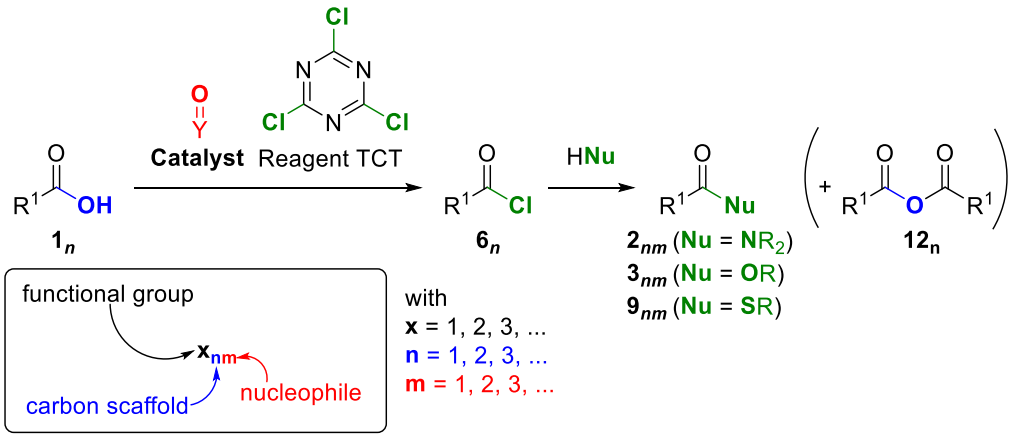
Table S2. Costs for reagents and atom economies (AE) for the synthesis of *N*-methyl benzamide.

entry	reagent	M [g/mol]	Batch	equiv NEt_3	AE [%]	Price [€/mol]	Ref.
1	PyAOP	521.4	5 g/327 €	1	17	**34100**	[11]
2	PyBOP	520.4	100 g/265 €	1	17	**1380**	[12]
3	*Ghosez* reagent	133.6	250 mL/2260 €	1	35	**1197**	[1]
4	CDMT	175.6	5 g/31.6 €	1	31	**1111**	[13]
5	EDC	191.7	5 kg/21390 €	0	39	**820**	[14]
6	*Vilsmeier* reagent	128.0	25 g/113 €	1	35	**580**	[2]
7	T3P	318.2	500 mL/418 €	2	20	**500**	[15]
8	Boc_2O	218.3	500 g/378 €	1	29	**166**	[16]
9	$Si(OMe)_4$ (2 equiv)	152.2	1 L/385 €	0	30	**115**	[17]
10	DCC	206.3	2,5 kg/300 €	0	38	**24.8**	[18]
11	**Cl**(C=O)COCl	126.9	2.5 kg/682 €	1	35	**24.2**	[4]
12	IBCF	136.6	2.5 kg/349 €	2	27	**21.2**	[19]
13	PivCl	120.5	500 mL/52.3 €	2	28	**15.0**	[19]
14	MocCl	94.5	500 g/56.1 €	2	30	**12.7**	[19]
15	**Cl**(S=O)Cl	119.0	1 L/138 €	1	36	**11.1**	[4]
16	EocCl	108.5	1 L/84.1 €	2	29	**10.2**	[19]
17	T**C**T (0.33 mol%)	184.4/3	1 kg/45 €	1	43	**3.8**	**This work**
18	**Cl**(C=O)Cl	98.9	n.d.	1	38	**n.d.**	[4]

The prices were collected from Sigma-Aldrich at April, 2nd 2019. The lowest price for the biggest batch available was chosen. NEt_3 was included with a price of 1.07 €/mol (432 €/40 kg) in the cost estimation. Atom economies were calculated based on the molecular weights of BzNHMe (135.2 g/mol), BzOH (122.1 g/mol), NH_2Me (31.1 g/mol), NEt_3 (101.2 g/mol) and the respective reagent under consideration of the reaction stoichiometry.

2 Numbering System for Compounds

The current method allows for the transformation of carboxylic acids **1** into acid chlorides **6** amides **2**, esters **3** and **9**, respectively, in the presence of *Lewis* base catalysts. For a better transparency a systematic numbering system for compounds was introduced (Scheme S3). The capital compound number **x** describes the key functional group. Substances with the number **1** are starting acid and **6** acid chlorides. Carboxylic acid amides are referred to as **2**, esters as **3** and thioesters as **9**. Carboxylic acid anhydrides, which form as side-products in the conversion of **1** into **6**, are denoted as number **12**.



Scheme S3. Transformations of carboxylic acids $\mathbf{1_n}$ into acid chlorides $\mathbf{6_n}$ and amides and esters of type $\mathbf{2_n}$ and $\mathbf{3_n}$, respectively.

The first subscript character **n** (= 1, 2, 3, …) describes the carbon scaffold in the order of appearance. For instance, n = **1** was assigned to a *meta*-tolyl carbon skeleton, n = **2** to a phenyl moiety. Compound $\mathbf{1_2}$ accords to benzoic acid, whereas $\mathbf{6_2}$ is assigned to benzoyl chloride. The index ***m*** describes the nucleophile H**Nu** introduced. Hence, geranyl benzoate is described as compound $\mathbf{3_{2g}}$, for example.

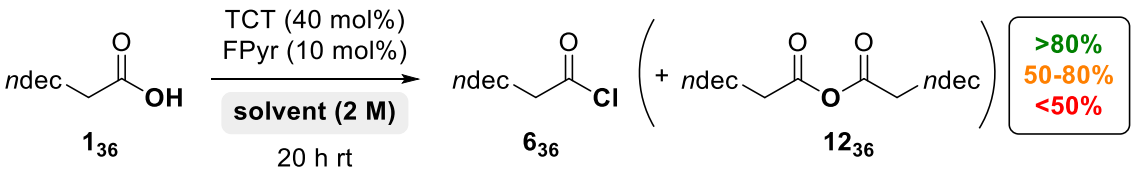
3 Method Development

3.1 Optimization of Catalytic Chlorination

3.1.1 Solvent and Temperature Optimization Using Dodecanoic Acid (Table S3+Table S4)

At the outset, dodecanoic acid (**1**$_{36}$) was selected as model substrate for aliphatic carboxylic acids. A first solvent screening was conducted at room temperature with 10 mol% FPyr and 40 mol% TCT with a reaction duration of 20 h (Table S3). In terms of yield of **6**$_{36}$ dioxane, THF, EtOAc and MeCN emerged as superior reaction medias (entry 1-4).

Table S3. Solvent Optimization at room temperature.



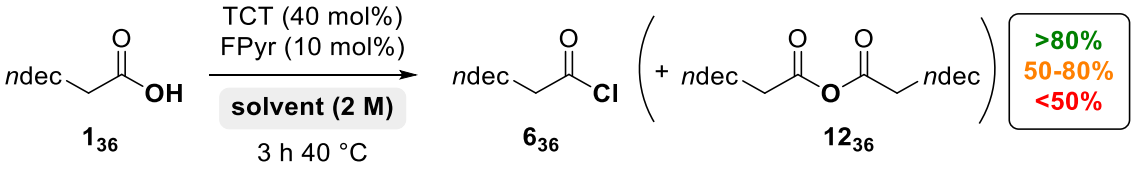
entry	solvent	conv.[1] [%]	yield 6$_{36}$[2] [%]	Lab journal no.
1	dioxane[a]	95/98	**90/98**	PH2325a/PH3681
2	THF[b]	98	**90**	PH2327d
3	EtOAc[b]	95	**88**	PH2325c
4	MeCN[a]	94	**87**	PH2325b
5	acetone[b]	98	**83**	PH2327b
6	2-MeTHF[b]	73	**65**	PH2337
7	MTBE[b]	71	**55**	PH2325d
8	CH_2Cl_2[b]	66	**50**	PH2327a
9	toluene[b]	53	**41**	PH2327c
10	$CHCl_3$[b]	35	**20**	PH2333b
11	cHex[b]	19	**9**	PH2333a
12[c]	THF[c]	≥98	**≥98**	PH2360a
13[d]	Dioxane[a]	≤2	**≤2**	PH2321d

According to general procedure 1 (see chapter 3.1.1 on page 44) dodecanoic acid **6**$_{35}$ (0.50 mmol, 1.0 equiv) was allowed to react with TCT in the presence FPyr (10 mol%) in the stated **solvent** (2 M) for 20 h at room temperature. a. Dry solvent used. b. Reagent grade solvent used. c. With 20 mol% FPyr. d. w/o FPyr with 45 mol% TCT.

[1] The conversion of **1**$_{36}$ was determined from the ^{1}H-NMR spectra of the crude materials through the ratio of the triplets of the CH_2-groups next to the carbonyl function of compounds **1**$_{36}$ at 2.35, **6**$_{36}$ at 2.88 and **12**$_{36}$ at 2.44 ppm.
[2] The yield was determined from the ^{1}H-NMR spectra of the crude product with the aid of 1,3,5-trimethoxybenzene as internal standard (s at 3.77 ppm) under reference to the above mentioned triplets.

While acetone gave rise to **6**$_{36}$ in still 83% yield, usage of 2-MeTHF, MTBE and CH_2Cl_2 resulted in inferior yields of 50-65% (entries 5-8). Toluene, $CHCl_3$ and cHex proved to be inefficient (entries 9-11). When the FPyr loading was increased to 20 mol%, full conversion of **1**$_{36}$ was accomplished after 20 h of reaction time in THF (entry 12), while in the absence of FPyr no product formation was observed at all (entry 13). In order to more clearly identify the optimal solvent and shorten the reaction time, the best solvents were probed for the same transformation at 40 °C for 3 h (Table S4). Both, THF and MeCN turned out as optimal with respect to of yield (entries 1+2). Nevertheless, application of acetone and EtOAc, respectively, as solvents delivered product **6**$_{36}$ also in good yields of 70-80% (entries 3+4). Therefore, these solvents were selected to enhance the sustainability. Surprisingly, usage of dioxane resulted in lower yields at 40 °C (two separate experiments, entry 7), while application of toluene furnished acid chloride **6**$_{36}$ in a rather poor yield. However, none of the solvents allowed full consumption of the starting material **1**$_{36}$ within 3 h. Either an increase of the catalyst loading to 20 mol% or an extended reaction time of 20 h eventually facilitated virtually full conversion of acid **1**$_{36}$ in THF (entries 8-9). Importantly, also at 40 °C no reaction was achieved in the absence of FPyr (entry 10).

Table S4. Solvent Optimization at 40 °C.



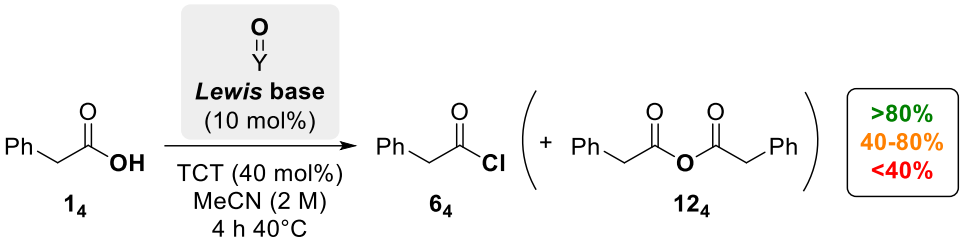
entry	solvent	conv.[(1)] [%]	yield 6$_{35}$[(2)] [%]	Lab journal no.
1	THF[a]	96/93	**93/89**	PH2335a/PH2338c
3	MeCN[b]	95	**89**	PH2335b
4	acetone[a]	97	**80**	PH2338b
5	EtOAc[a]	81	**70**	PH2335c
6	dioxane[b]	66	**53/53**	PH2335d/PH3671
7	toluene[a]	26	**18**	PH2338a
8[c]	THF[a]	97	**96**	PH2360b
9[d]	THF[a]	≥98	**96**	PH2350a
10[d,e]	THF[a]	≤2	**≤2**	PH2350b

According to general procedure 1 (see chapter 3.1.1 on page 44) acid **1**$_{36}$ (0.50 mmol, 1.0 equiv) was allowed to react with TCT in the presence FPyr (10 mol%) in the stated **solvent** (2 M) for 3 h at 40 °C. a. reagent grade solvent used. b. Dry solvent used. c. With 20 mol% FPyr. d reaction time 20 h. e. w/o FPyr.

3.1.2 Catalyst Screening Employing Phenylacetic Acid (Table S5)

Further optimization studies were performed with phenyl acetic acid (**1**$_4$) as model for aliphatic substrates, since the CH_2-group of this acid, the chloride **6**$_4$ and the anhydride **12**$_4$ appear as clean singlets in the ^{1}H-NMR spectrum. To establish a thorough structure activity relationship in regard to the catalyst, a variety of different *Lewis* bases (10 mol%) were probed in the transformation of aliphatic acid **1**$_4$ into acid chloride **6**$_4$ as shown in Table S5.

Table S5. Screening of various *Lewis*-bases in the reaction of **1**$_4$ with TCT.



entry	*Lewis* base	conv.[3] [%]	yield 6$_4$[4] [%]	lab journal no.
1	FPyr	91/95	**86/90**	PH3515/PH3527
2	DMF	73	**47**	PH3517
3[a]	DMF	95	**88**	PH3528
4	MF	58	**19**	PH3516
5	F	≤2	**≤2**	PH3523
6	DMA	6	**≤2**	PH3525
7	TMU	8	**1**	PH3524
8	Ph_3PO	≤2	**≤2**	PH3521
9	TPPA	20	**2**	PH3522
10	DMSO	≤2	**≤2**	PH3540
11	MPMSO	≤2	**≤2**	PH3541
12	tropone	14	**≤2**	PH3520
13	DPC	18	**8**	PH3519
14	DEC	58	**52**	PH3518
15	*p*TsOH	≤2	**≤2**	PH3665
16	/	≤2	**≤2**	PH3529

According to general procedure I (see chapter 3.1.1 on page 44) acid **1**$_2$ (0.50 mmol, 1.0 equiv) was allowed to react with TCT (40 mol% in the presence of the given ***Lewis* base** (10 mol%) in dry MeCN (2 M) for 4 h at 40 °C.
a. With 20 mol% DMF.

[3] The conversion of **1**$_4$ was determined from the ^{1}H-NMR spectra of the crude materials through the ratio of the singlets of the CH_2-group of compounds **1**$_4$ at 3.65**, 6**$_4$ at 4.13 and **12**$_4$ at 4.71 ppm.

[4] The yield was determined from the ^{1}H-NMR spectra of the crude products with the aid of dibenzylether as internal standard (s at 4.56 ppm) in reference to the singlets of the aforemntioned CH_2-group.

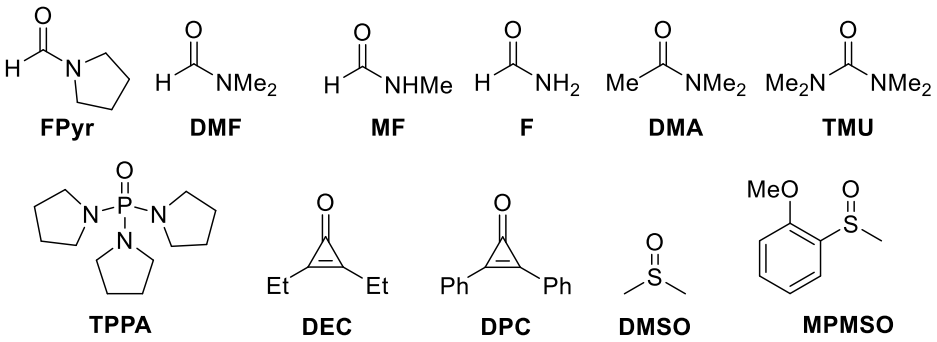


Figure S5. *Lewis* bases used in the screening.

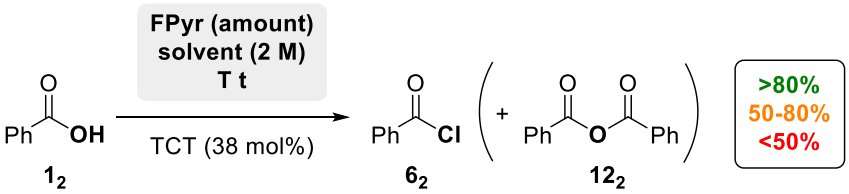
The respective catalyst structures are depicted in Figure S5. While engagement of FPyr afforded acid chloride **6₄** in 86-90% yield in two separate experiments, substitution by DMF effected a strongly diminished yield of 47% (entries 1+2). Nevertheless, utilisation of 20 mol% of DMF allowed to enhance the yield to useful 88% (entry 3). Hence, FPyr can be most likely substituted in general by DMF, if the catalyst quantity is doubled. Utilisation of methylformamide (MF) caused the formation of phenylacetyl chloride in a strongly deteriorated yield of 19% (entry 4), which was unexpected, because this formamide has been identified as a feasible catalyst for our previous alcohol chlorinations.[25] Not surprisingly, formamide (F), dimethylacetamide (DMA), and tetramethylurea (TMU) do not promote the transformation of **1₄** into **6₄**, which is in agreement with our previous observation employing alcohols as substrates.[20,25] Along these line, other stronger *Lewis* bases such as triphenylphosphineoxide, the HMPTA derivative TPPA, DMSO, sulfoxide MPMSO, tropone and diphenylcyclopropenone (DPC), most of which have been used as catalysts for related chlorinations of alcohols with either oxalyl or benzoyl chloride, are virtually inactive (entries 8-13). Solely, diethylcyclopropenone (DEC) facilitated the conversion **1₄** to **6₄**, albeit in a moderate yield of 58% (entry 14). Finally, application of *p*TsOH did not allow the generation of product **6₄** (entry 15), thus Brønsted acid catalysis does not enable the transformation of carboxylic acids with TCT into acid chlorides of type **6**. Worthy of note, in the absence of a suitable catalyst no reaction of acid **6₄** with TCT could be observed (entry 16).

3.1.3 Temperature, Solvent and Catalyst Loading Optimization using Benzoic Acid (Table S6)

Since aromatic carboxylic acids differ in terms of reactivity from aliphatic ones, a separate optimization using the solvents MeCN and EtOAc with benzoic acid **1₂** as model compound was performed (Table S6). Slightly above 90% conversion were reached at reaction temperatures of 25 and 40 °C with durations of 18 and 4 h, respectively, when 20 mol% of FPyr were engaged (entries 1+2). Full consumption of **1₂** is assured at 80 °C, whereby 10 mol% of FPyr are sufficient (entry 3). In the absence of FPyr under elsewise identical

conditions product **6₂** was formed in 7% yield at maximum (entry 4). Benzoyl chloride and benzoic acid anhydride cannot be distinguished clearly in the ^{1}H-NMR spectrum due to signal overlapping. Thus, without utilization of FPyr benzoic anhydride could be the major product. Nevertheless, in the presence of FPyr, BzCl is obtained as major product as demonstrated by a 500 mmol scale synthesis in a yield of 90% after purification by means of distillation (see chapter 5.4.1.1, page 58). Utilizing EtOAc as more environmental-benign solvent conversions >90% are accomplished at 40 °C (entry 5), whereas reaction at 80 °C allowed for full consumption of the starting acid (entry 6). Again, without utilization of FPyr only trace amounts of either benzoyl chloride or benzoic acid anhydride are generated (entry 7).

Table S6. Temperature, solvent and catalyst loading optimization using benzoic acid.



entry	FPyr (mol%)	solvent	T [°C]	t [h]	conv.[5] [%]	yield 6₂[6] [%]	lab journal no.
1	20	MeCN	rt	18	93	**86**	PH3534
2	”	“	**40**	4	92	**84**	PH3533
3	10	“	**80**	“	≥98	**85**	PH3666
4	**0**	“	80	“	7	**7**	PH3668
5	20	**EtOAc**	40	4	92	**86**	PH3670
6	10	“	**80**	“	≥98	**93**	PH2857
7	**0**	“	80	“	8	**8**	PH3669

According to general procedure 1 (see chapter 3.1.1 on page 44) acid **1₂** (0.50 mmol, 1.0 equiv) was allowed to react with TCT in the presence of FPyr (**0-20 mol%**) in the stated stated **solvent** (2 M) for the time **t** at the temperature **T**.

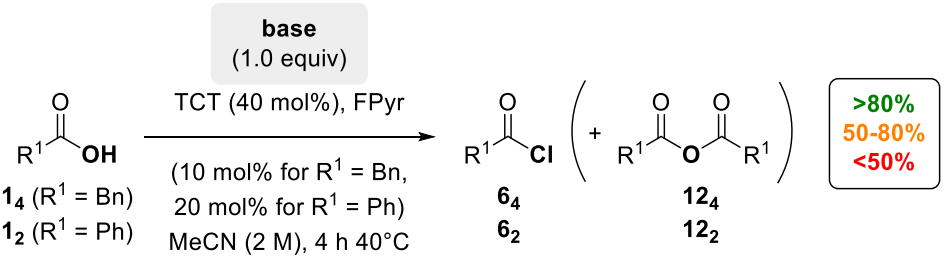
[5] The conversion of **1** was determined from the ^{1}H-NMR spectrum of the crude material through the ratio of the triplets of *para*-CH of **1₂** at 7.62 ppm**, 6₂** and **12₂,** both at 7.69 ppm.

[6] The yield was determined from the ^{1}H-NMR spectra of the crude products by means of mesitylene as internal standard (s at 2.28 ppm) in reference to the above mentioned triplets.

3.1.4 Base Screening Employing Phenylacetic and Benzoic Acid (Table S7)

To test the compatibility of amine bases with the present method, the halogenation of phenyl acetic and benzoic acid **1₄** and **1₂**, respectively, was conducted in the presence of NEt_3, lutidine and 2,6-bis-*tert*-butylpyridine (1.0 equiv, Table S7). For comparison the results of the transformation **1→6** in the absence of additives are given in entries 4 and 8. In the case of aliphatic acid **1₄** NEt_3 and lutidine supress formation of the corresponding acid chloride entirely (entries 1+2). Only with sterically encumbered 2,6-bis-*tert*-butylpyridine, the activated carboxylic acid derivative **6₄** was obtained in a moderate yield of 41% (in comparison to 86-90% yield, see entry 4). This results might be rationalized by a low stability of enolizable product **6₄** in the presence of bases, which is also supported by the low yield in an amidation. When the addition order of the nucleophile pyrrolidine and the base *N*-methylmorpholine was reversed in the synthesis of phenylacetylpyrrolidine, the yield declined from 83 to 22% (see Table S11, entries 4+7). Indeed, in the dehydroxychlorination of benzoic acid, which does no bear any protons in the α-position, bases do impact the reaction outcome much less (entries 5-8). The yield of benzoyl chloride (**6₂**) is only diminished by 7% at most. These results further suggest that *Brønsted* acid catalysis is not involved in the present transformations.

Table S7. Base Screening.



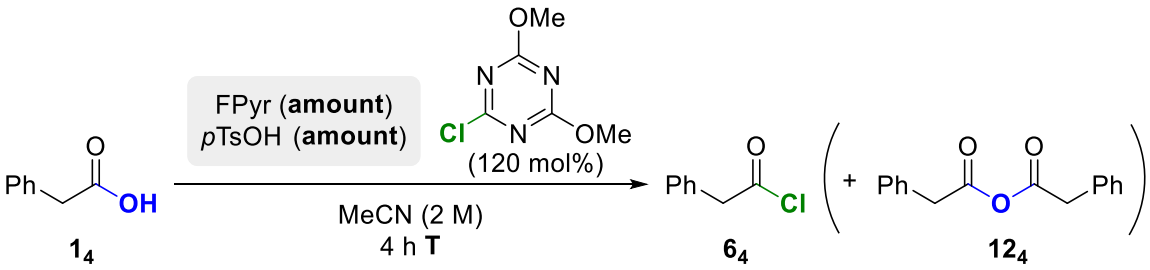
entry	R	base	conv.[3,5] [%]	yield 6[4,6] [%]	lab journal no.
1	Bn	NEt_3 (1.0)	≥98	**≤2**	PH3545
2	"	2,6-lutidine (1.0)	90	**≤2**	PH3544
3	"	2,6-*t*Bu_2Py (1.0)	96	**41**	PH3552
4	"	/	91/95	**86/90**	PH3515/PH3527
5	Ph	NEt_3 (1.0)	≥95	**82**	PH3554
6	"	2,6-lutidine (1.0)	≥95	**77**	PH3555
7	"	2,6-*t*Bu_2Py (1.0)	86	**77**	PH3564
8	"	/	92	**84**	PH3533

According to general procedure 1 (see chapter 3.1.1 on page 44) acid **1₂/1₄** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (40 mol%) in the presence of FPyr (10-20 mol%) and the given **base** (1.0 equiv) in dry MeCN (2 M) for 4 h at 40 °C.

3.1.5 Comparison Experiments with CDMT (Table S8)

Finally, comparison experiments with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) were performed, which is a closely related derivative of the plausible reaction intermediate 2-chloro-4,6-hydroxy-1,3,5-triazine (Table S8). In agreement with our previous protocol for the conversion of alcohols into chloro alkanes promoted by TCT,[20] at a reaction temperature of 40 and 80 °C no formation of the chlorine containing product **6₄** was detectable in the presence of FPyr (entries 1+2). As sole product, the carboxylic acid anhydride **12₄** was obtained in trace amounts at 80 °C. Application of *p*TsOH instead of FPyr delivered some anhydride **12₄**, while no acid chloride **6₄** was generated (entry 3). Surprisingly, even a combination of *p*TsOH and FPyr did not allow for formation of phenyl acetyl chloride (entry 4). The latter two results are in contrast to the observations previously made in similar transformations of alcohols into alkyl chlorides.[20] Noteworthy, cyanuric acid was verified as major coupled product by ^{13}C-NMR of the solid precipitate forming in approximately 80% theoretical yield (see chapter 5.4.1.1 on page 58). This unambiguously testifies that 2-chloro-4,6-hydroxy-1,3,5-triazine must be a productive reaction intermediate.

Table S8. Comparison experiments with CDMT.



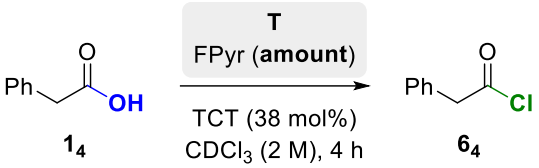
entry	FPyr [mol%]	*p*TsOH [mol%]	T [°C]	conv. 1_2[3] [%]	yield 2_2[4] [%]	lab journal no.
1	10	0	40	≤2	**≤2**	PH3542
2	"	"	**80**	16	**≤2**	PH3543
3	0	**10**	40	19	**≤2**	PH3557
4	**10**	10	"	4	**≤2**	PH3558

According to general procedure 1 (see chapter 3.1.1 on page 44) acid **1₂** (0.50 mmol, 1.0 equiv) was allowed to react with CDMT (120 mol%) in the presence of FPyr (0-10 mol%) and *p*TsOH (0-10 mol%) in dry MeCN (2 M) for 4 h at the respective temperature **T**.

3.1.6 Determination of Reaction Order in FPyr according to Burés (Table S10)

In order to follow the conversion of the phenyl acetic acid (**1₄**) as model substrate into acid chloride **6₄** experiments were carried out in $CDCl_3$ (Table S9). This allowed monitoring of the reaction progress with the aid of ^{1}H-NMR analysis through dilution of a small aliquot of the heterogeneous reaction mixture with further $CDCl_3$ and filtration over $MgSO_4$. Initially, experiments indicated that a reaction temperature **T** of 60 °C was required and no conversion was observed in the absence of FPyr (even not to anhydride **12₄**, see Table S9).

Table S9. Optimization reaction temperature **T** for the transformation **1₄** into **6₄** in $CDCl_3$.



1₄ **6₄**

entry	T [°C]	FPyr [mol%]	conv. **1₄**$^{(3)}$ [%]	yield **6₄**$^{(7)}$ [%]	lab journal no.
1	40	10	80	56	PH2916
2	**60**	"	87	71	PH2938
3	**70**	"	≥98	89	PH2931
4	"	**0**	≤2	≤2	PH2932

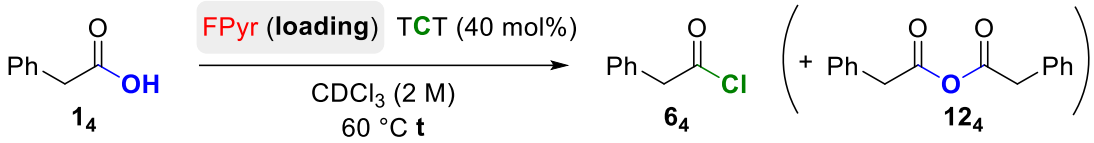
According to general procedure 1 (see chapter 3.1.1 on page 44) acid **1₄** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (38 mol%) in the presence of FPyr (0-10 mol%) in $CDCl_3$ at the reaction temperature **T** for 4 h.

According to the normalized time scale method of Burés[21] three different kinetics were recorded with catalyst FPyr loadings of 20, 10 and 5 mol%, respectively (Table S10). The normalized time scale reaction concentration profiles with respect to the starting material **1₄** show the highest level of congruence when plotted against t•[FPyr]$^{\mathbf{1}}$ and t•[FPyr]$^{\mathbf{1.5}}$ (Figure S6 **C** + **D**). Further adjustment of the time scale t•[FPyr]^n to the power of 1.1, 1.2, 1.3 and 1.4 finally revealed the best agreement of all kinetics in the case of t•[FPyr]$^{\mathbf{1.2}}$ (Figure S7 **B**). According to this power value the reaction order in terms of the catalyst FPyr is determined to be 1.2, which corresponds in an order of approximately 1.

From the kinetic in Figure S8 and the underlying staggered ^{1}H-NMR spectra in Figure S9 it is evident that in the beginning both the carboxylic acid chloride **6₄** and anhydride **12₄** are formed. The latter is consumed at the end of the reaction, which verifies that the generation of acid anhydrides is indeed reversible.

(7) The yield was determined from the ^{1}H-NMR spectra of the crude products with the aid of 1,3,5-trimethoxybenzene as internal standard (s at 3.77 ppm) in reference to the singlet of the CH_2-group of **6₄** at 4.13 ppm.

Table S10. Reaction kinetics via ^{1}H-NMR at different catalyst concentrations.



entry	t [min]	conv. [%]	1_4[(3)]	yield[(8)] [%]			[1_4]	See Figure S6			See Figure S7			
				1_4	6_4	12_4	[mol/L]	t•[FPyr]$^{0.5}$	t•[FPyr]^{1}	t•[FPyr]$^{1.5}$	t•[FPyr]$^{1.1}$	t•[FPyr]$^{1.2}$	t•[FPyr]$^{1.3}$	t•[FPyr]$^{1.4}$
With 20 mol% FPyr ([FPyr] = 0.4 mol/L, PH3841):														
1	30	42		57	31	5	1.14	19.0	12.0	7.6	10.9	10.0	9.1	8.3
2	60	79		27	59	7	0.54	37.9	24.0	15.2	21.9	20.0	18.2	16.6
3	90	92		8	81	4	0.16	56.9	36.0	22.8	32.8	30.0	27.3	25.0
4	120	98		1	93	1	0.02	75.9	48.0	30.4	43.8	40.0	36.5	33.3
5	180	98		0	93	0	0.00	113.8	72.0	45.5	65.7	59.9	54.7	49.9
With 10 mol% FPyr ([FPyr] = 0.2 mol/L, PH3843):														
1	30	18		84	13	3	1.68	13.4	6.0	2.7	5.1	4.3	3.7	3.2
2	60	33		66	25	4	1.32	26.8	12.0	5.4	10.2	8.7	7.4	6.3
3	90	50		52	41	6	1.04	40.2	18.0	8.0	15.3	13.0	11.1	9.5
4	120	60		41	50	6	0.82	53.7	24.0	10.7	20.4	17.4	14.8	12.6
5	180	81		20	68	5	0.40	80.5	36.0	16.1	30.6	26.1	22.2	18.9
6	240	94		6	85	4	0.12	107.3	48.0	21.5	40.9	34.8	29.6	25.2
7	300	98		1	96	1	0.02	134.2	60.0	26.8	51.1	43.5	37.0	31.5

(8) The yields were determined from the ^{1}H-NMR spectra with the aid of dodecane as internal standard (t at 0.88 ppm) in reference to the singlets of the CH_2-group of compounds **1_4** at 3.65**, 6_4** at 4.13 and **12_4** at 4.71 ppm. Dodecane was selected as inert internal standard to avoid reaction with product **6_4**.

Table S10 continued:

entry	t [min]	conv. 1_4[(3)] [%]	yield[(9)] [%]			[1_4]	See Figure S6			See Figure S7			
			1_4	6_4	12_4	[mol/L]	t•[FPyr]$^{0.5}$	t•[FPyr]^{1}	t*[FPyr]$^{1.5}$	t•[FPyr]$^{1.1}$	t•[FPyr]$^{1.2}$	t•[FPyr]$^{1.3}$	t•[FPyr]$^{1.4}$
With 5 mol% FPyr ([FPyr] = 0.1 mol/L, PH3842):													
1	30	7	94	5	2	1.88	9.5	3.0	0.9	2.4	1.9	1.5	1.2
2	60	15	86	12	2	1.72	19.0	6.0	1.9	4.8	3.8	3.0	2.4
3	90	24	79	19	3	1.58	28.5	9.0	2.8	7.1	5.7	4.5	3.6
4	120	31	69	24	4	1.38	37.9	12.0	3.8	9.5	7.6	6.0	4.8
5	180	46	56	38	5	1.12	56.9	18.0	5.7	14.3	11.4	9.0	7.2
6	240	59	43	50	6	0.86	75.9	24.0	7.6	19.1	15.1	12.0	9.6
7	300	70	31	58	6	0.62	94.9	30.0	9.5	23.8	18.9	15.0	11.9
8	360	78	22	68	5	0.44	113.8	36.0	11.4	28.6	22.7	18.0	14.3
9	480	91	9	81	5	0.18	151.8	48.0	15.2	38.1	30.3	24.1	19.1

According to general procedure 1 (see chapter 1.1.1 on page 44) acid **1_4** (1.0 mmol, 1.0 equiv) was allowed to react with TCT (40 mol%) in the presence of FPyr (5-20 mol%) in $CDCl_3$ (0.60 mL, 2 M) at 60 °C for the given time **t**.

(9) The yields were determined from the ^{1}H-NMR spectra with the aid of dodecane as internal standard (t at 0.88 ppm) in reference to the singlets of the CH_2-group of compounds **1_4** at 3.65**, 6_4** at 4.13 and **12_4** at 4.71 ppm. Dodecane was selected as inert internal standard to avoid reaction with product **6_4**.

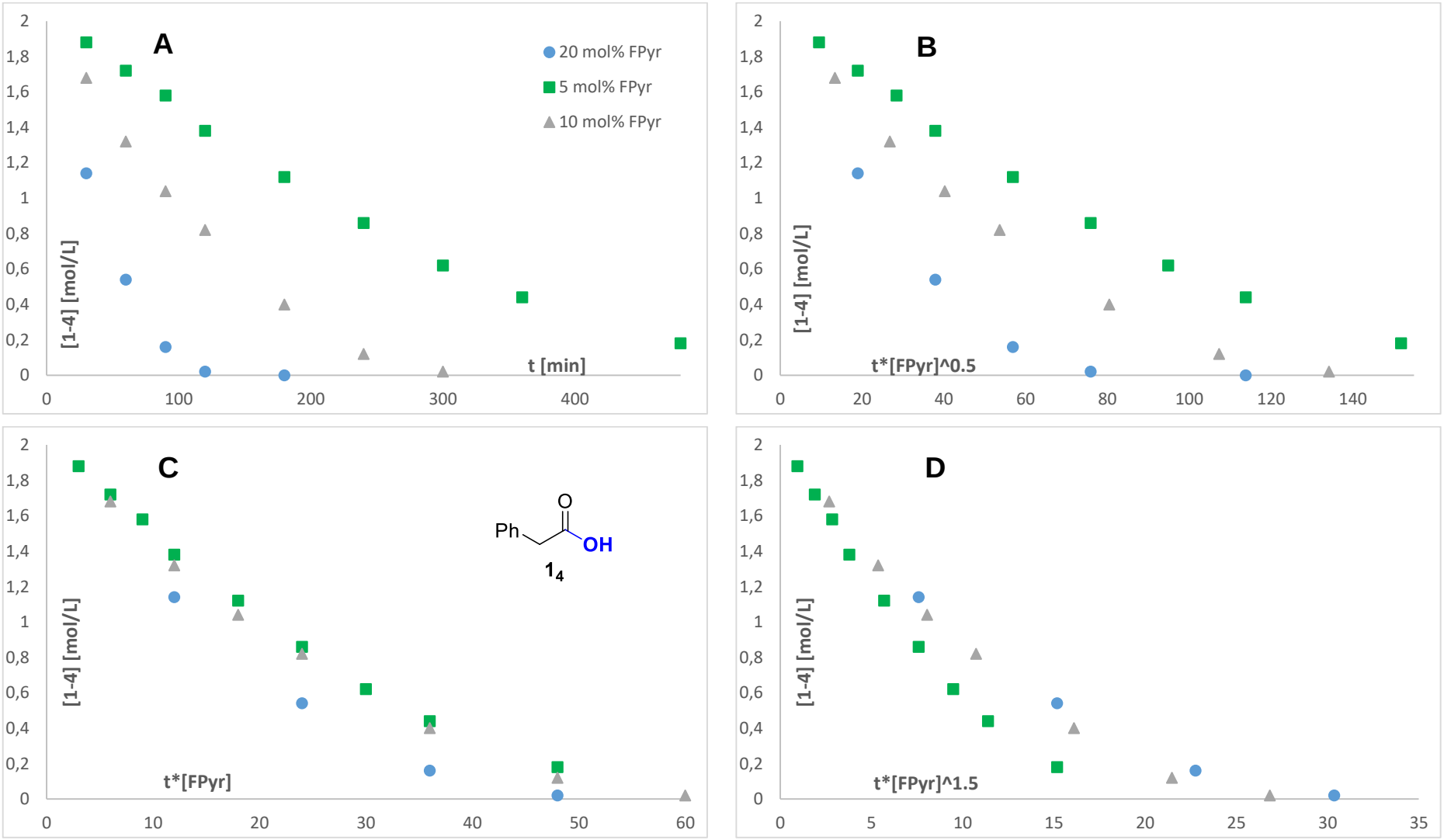


Figure S6. Concentration profiles for the starting material phenyl acetic acid ($\mathbf{1_4}$).

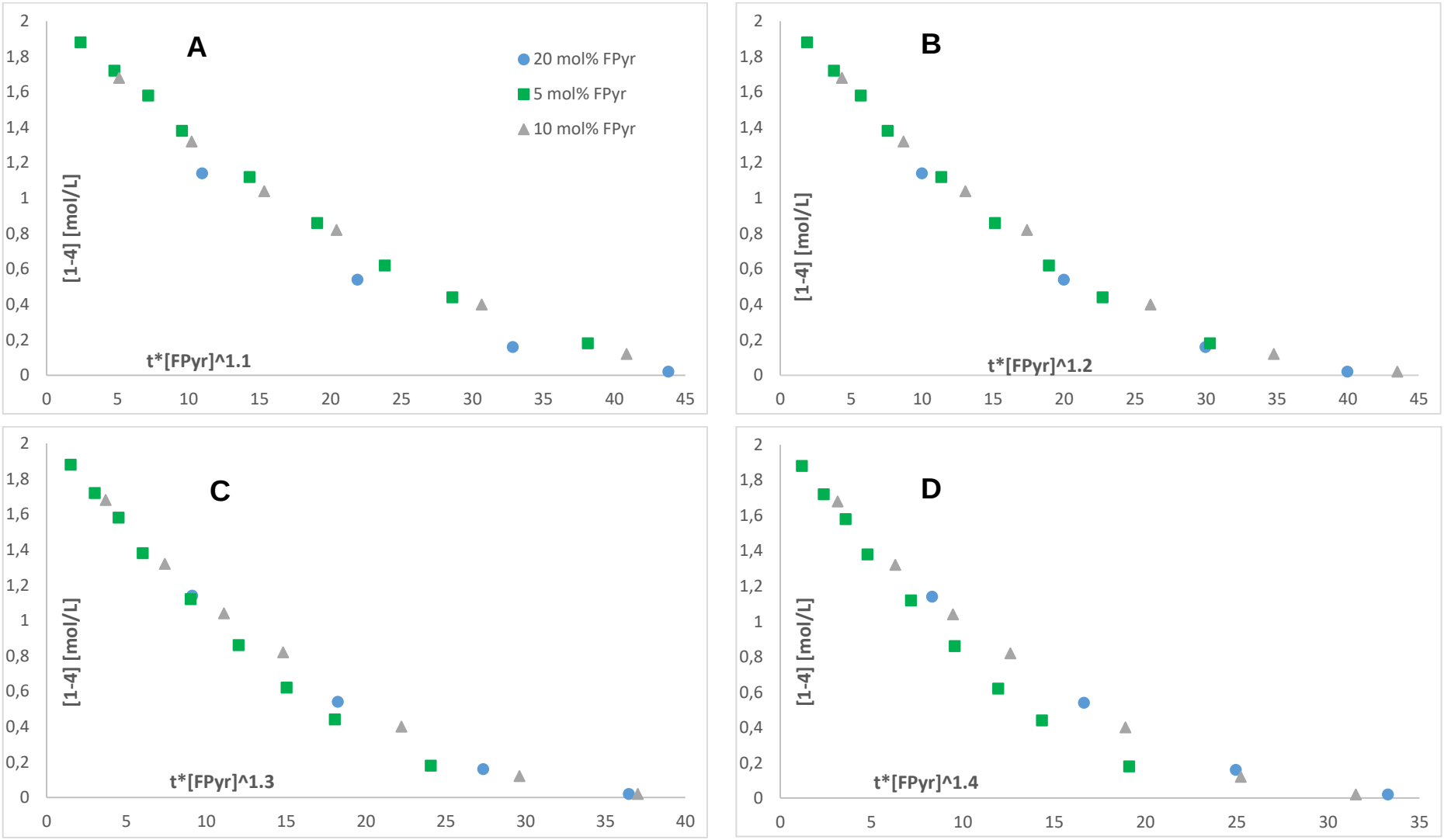


Figure S7. Concentration profiles for the starting material phenyl acetic acid against time and time normalized by catalyst concentration ($\mathbf{1}_4$).

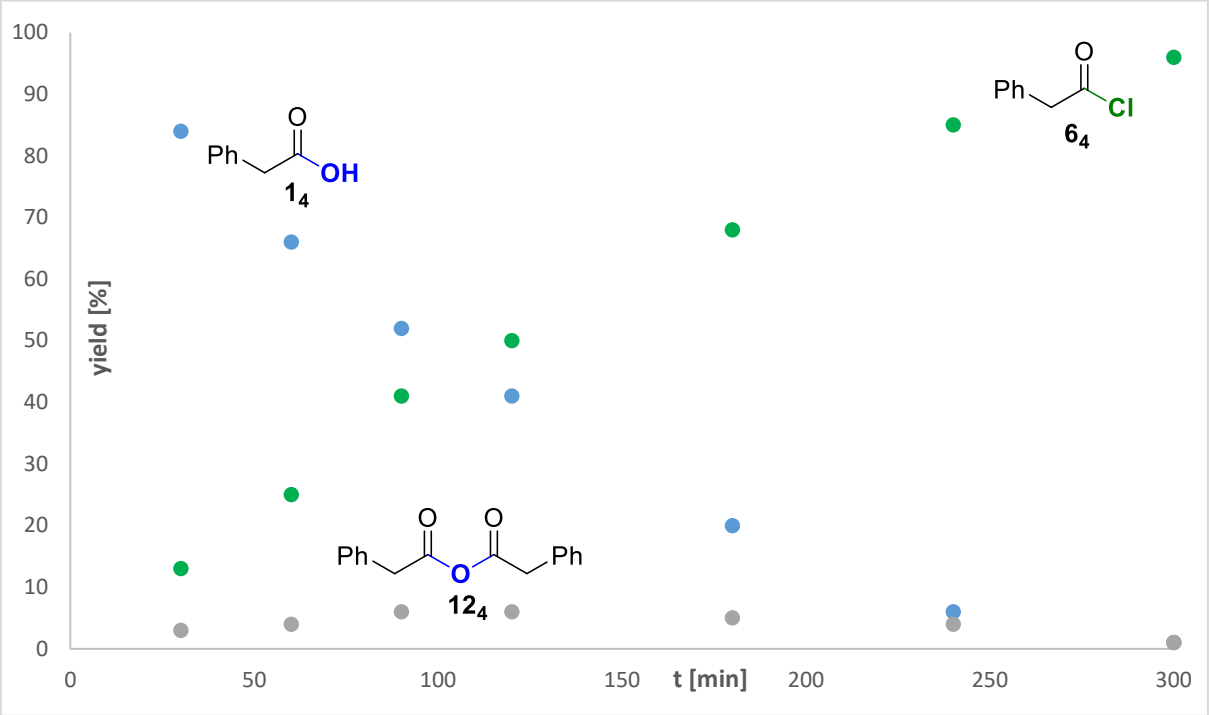


Figure S8. Reaction profiles against time using 10 mol% of FPyr (blue = **1**$_4$, green = **6**$_4$, grey = **12**$_4$).

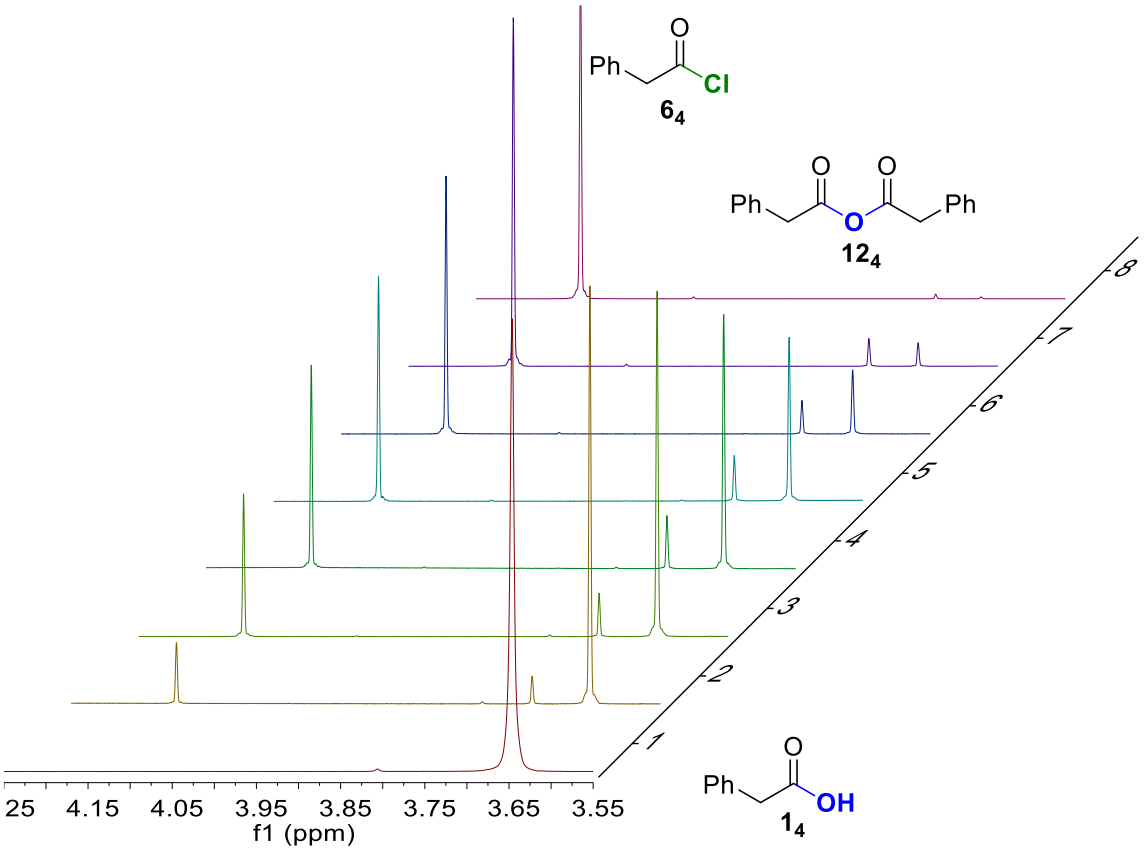


Figure S9. Extract of the ^{1}H-NMR spectra showing the singlets of the CH_2-groups of **1**$_4$, **6**$_4$ and **12**$_4$ for the reaction monitoring using 10 mol% of FPyr.

3.2 Optimization of One-Pot Amidation and Esterification

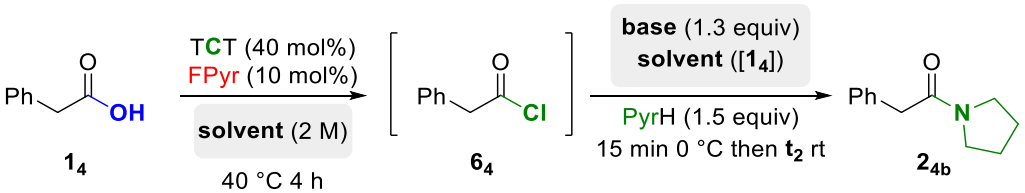
The reaction conditions for the subsequent had to be optimized separately based on the type of nucleophile and starting acid. While phenylacetylpyrrolidine served as model system for the condensation of aliphatic acids **1** with amines, the preparation of *N*-(quinolin-8-yl) 2-methylbenzamide was harnessed to find the best reaction conditions for the synthesis of amides deduced form aromatic acids. With respect to the preparation of esters, 1-naphthyl phenylacetate and 4-*tert*-butylbenzyl benzoate were selected as case studies for the coupling of aliphatic acids with aromatic alcohols and aromatic acids with aliphatic alcohols, respectively. In the synthesis of amides and esters the conversion could not be determined, because acid chlorides of type **6** are largely hydrolysed and carboxylic acids **1** are removed during the necessary aqueous work up.

3.2.1 Optimization Synthesis of Phenylacetylpyrrolidine (2_{4b}, Table S11)

The production of phenylacetylpyrrolidine ($\mathbf{2_{4b}}$) from phenyl acetic acid ($\mathbf{1_4}$) and pyrrolidine was chosen as model transformation for the amidation of aliphatic acids (Table S11). Since MeCN and EtOAc had been identified as the optimal solvents for the chlorination step **1→6** (see Table S4), they were selected to establish conditions for the conversion of $\mathbf{6_4}$ into $\mathbf{2_{4b}}$. In fact, plain K_2CO_3 and *N*-methylmorpholine (NMM) allow both for the formation of amide $\mathbf{2_{4b}}$ in 90% yield (entries 1+2). Replacement of MeCN with more environmental-friendly and less expensive EtOAc caused slightly diminished but still good yields of 82-83% (entries 3+4). The amount of TCT could be reduced from 40 to 35 mol% with virtually no impact on the yield of $\mathbf{2_{4b}}$ (compare entry 5 with 4).

An extension of the reaction time of the second transformation $\mathbf{6_4 \rightarrow 2_{4b}}$ from 13 to 20 h did not improve the reaction outcome (entry 6), while the inversion of the addition order of pyrrolidine and NMM resulted in a significant drop of the yield from 83 to 22% (entry 7). As discussed earlier (see chapter 3.1.4 on page 16), NMM might cause a decomposition of the acid chloride $\mathbf{6_4}$ prior to its reaction with pyrrolidine. Pleasingly, the reaction of the acid chloride $\mathbf{6_4}$ with pyrrolidine can also be performed in a 1 M concentration with respect to the starting acid $\mathbf{1_4}$ (entry 8). Higher concentrations of the starting material $\mathbf{1_4}$ (e.g. 1.5 M) result in solidification of the reaction mixture. In general, the solvent amount, which is necessary to maintain stir-ability in the second conversion **6→2**, is determined by the starting material **1**, the nucleophile, the base and the solvent applied. Nevertheless, most of the transformations in the present manuscript could be conducted in a 1 M concentration.

Table S11. Optimization of the synthesis of phenylacetyl pyrrolidine.



entry	base	solvent ([1_4] in mol/L)	t_2 [h]	yield 2_{4b}[(10)] [%][a]	lab journal no.
1	**K_2CO_3**	MeCN (0.8)	13	**90**	PH2726
2	**NMM**	MeCN (1)	13	**90**	PH2737
3	K_2CO_3	**EtOAc** (0.8)	13	**82/83**	PH2738/PH2780
4	**NMM**	EtOAc (0.8)	13	**83**	PH2739
5[a]	NMM	EtOAc (0.8)	13	**82**	PH2740
6	NMM	EtOAc (0.8)	**20**	**81**	PH2756
7[b]	NMM	EtOAc (0.8)	20	**22**	PH2757
8	K_2CO_3	MeCN (**1**)	13	**90**	PH2779

According to general procedure 3 (see chapter 5.3.3 on page 49) acid **1_4** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (40 mol%) in the presence of FPyr (10 mol%) in the described **solvent** (2 M) for 4 h at 40 °C. Next, the reaction mixture was diluted with further **solvent** (0.8-1 M) cooled to 0 °C and pyrrolidine (1.5 equiv) and the **base** (1.3 equiv) added. a. with 35 mol% TCT instead of 40 mol%. b. Addition order first NMM then PyrH. Concentration [$\mathbf{1_2}$] refers to initial concentration of **1_2** in mol/L. PyrH = pyrrolidine.

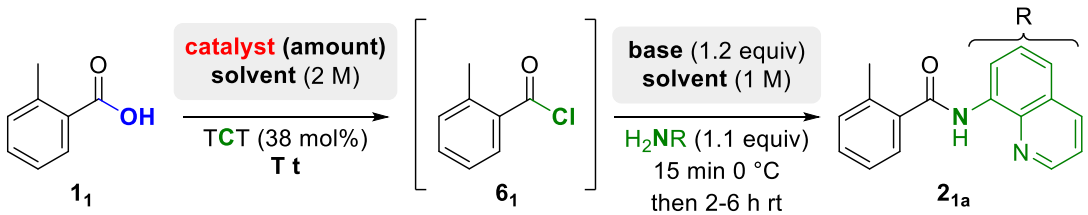
3.2.2 Optimization Synthesis of *N*-(quinolin-8-yl) 2-methylbenzamide (Table S12)

Next, the condensation of 2-methylbenzoic acid (**1_1**) and 8-aminoquinoline was exploited as test reaction for the amidation of aromatic acids (Table S12). In contrast to the other optimization studies yields for **2_{1a}** refer to isolated material. The highest yield of 90% was achieved with MeCN as solvent (entry 1), whereas condensation in EtOAc provided amide **2_{1a}** still in a reasonable yield of 85% (entry 2). The reaction temperature of the initial activation of acid **1_1** could be lowered from 80 to 40 °C without a negative impact on the yield, when 20 mol% of FPyr were employed instead of 10 (entry 3). After reaction of substrate **1_1** at room temperature for 8 h, product **2_{1a}** could be isolated in 78% yield (entry 4), which is a useful information considering related acids with sensitive functional groups. Furthermore, even 5 mol% FPyr assured formation of **2_{1a}** in an unaltered yield of 90% (compare entry 1+5). Importantly, FPyr could be substituted by DMF under doubling of the catalyst quantity (compare entry 3+6). NMM could be replaced by cheaper K_2CO_3 (entry 7) and NEt_3 (entry 8),

(10) Determined from ^{1}H-NMR-spectra of the crude products by means of mesitylene as internal standard (s at 2.28 ppm) in reference to the singlet of CH_2-group of **2_{1a}** at 3.66 ppm.

respectively. A switch to acetone as reaction solvent, however, furnished amide **2$_{1a}$** in a diminished yield of 71% (entry 9).

Table S12. Optimization of catalyst, solvent and bases for the production of *N*-(quinolin-8-yl) 2-methylbenzamide.



entry	cat. (mol%)	solvent	base	T [°C]	t [h]	yield 2$_{1a}$[a] [%]	lab journal no.
1	FPyr (10)	MeCN	NMM	80	2	**90**	PH3145
2	"	**EtOAc**	"	"	3	**85**	PH3125
3	FPyr (**20**)	"	"	**40**	8	**84**	PH3126
4	"	MeCN	"	**rt**	8	**78**	PH3140
5	FPyr (**5**)	"	"	80	10	**90**	PH3285
6	**DMF (40)**	EtOAc	"	**40**	8	**83**	PH3178
7[b]	FPyr (10)	EtOAc	**K_2CO_3**	**80**	3	**88**	PH3251
8	FPyr (10)	MeCN	**NEt_3**	"	2	**91**	PH3245
9[b]	FPyr (10)	**acetone**	"	**80**	1.5	**71**	PH3267
10[(11)]	**no catalyst**	MeCN		**80**	8	**11**	PH3181

According to general procedure 4 (see chapter 5.3.4 on page 50) acid **1$_1$** (1.00 mmol, 1.0 equiv) was allowed to react with TCT (40 mol%) in the presence of the given **catalyst** (0-40 mol%) in the stated **solvent** (2 M) for the time period **t** at the temperature **T** before further **solvent** (1 M), 8-amino quinoline (1.1 equiv) and the respective **base** (1.3 equiv) were added. a. Determined after column chromatographic purification. b. Concentration conversion **6$_{1a}$→2$_{1a}$** 0.5 M.

Although a more diluted reaction medium (0.5 M) was applied, the reactions using K_2CO_3 as base turned solid. Finally, amidation without FPyr gave rise to product **2$_{1a}$** in only 11% yield, which verifies its crucial role as catalyst.

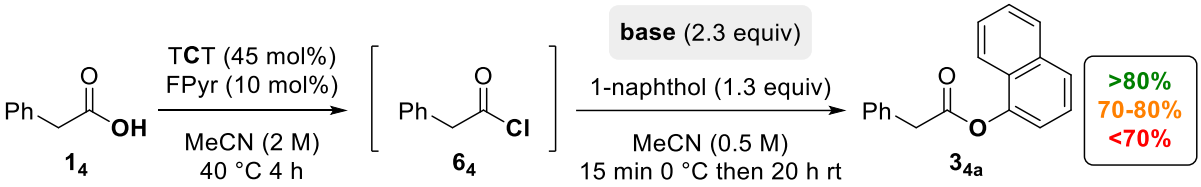
3.2.3 Optimization Synthesis of 1-Naphthyl phenylacetate (3$_{4a}$, Table S13 to Table S16)

Next, the condensation of phenyl acetic acid (**1$_4$**) with 1-naphthol to yield **3$_{4a}$** was chosen as model system for the synthesis of aromatic esters derived from aliphatic carboxylic acids (Table S13). At the outset, several common amine bases were screened on their capability to

[11] Yield determined with the aid of 1,3,5-trimethoxybenzene (s at 3.77 ppm) as internal standard from the ^{1}H-NMR-spectrum of the crude material in reference to the singlet of the CH_3-group of **2$_{1a}$** at 2.61 ppm.

promote the transformation of acid chloride **6₄** into ester **3₄ₐ**. Both, NEt_3 and NMM emerged as optimal bases furnishing product **3₄ₐ** in 87% yield (entries 1+2).

Table S13. Optimization of the base.



entry	Base	yield 3_{4a}[(12)] [%]	lab journal no.
1	NEt_3	**87**	PH2601a
2	NMM	**87**	PH2604a
3	2,6-lutidine	**84**	PH2604c
4	DIPEA	**82**	PH2601b
5	pyridine	**73**	PH2604b
6	DBU	**64**	PH2604d
7	K_2CO_3	**63**	PH2576a
8[a]	K_2CO_3	**61**	PH2613
9[b]	K_2CO_3	**57**	PH2576b
10[c]	no base	**19**	PH2688

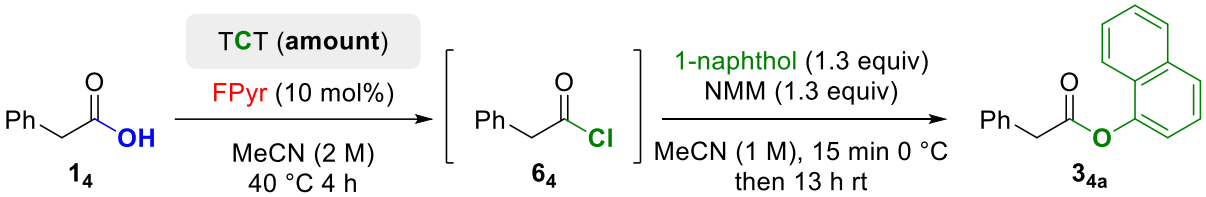
According to general procedure 3 (see chapter 5.3.3 on page 49) acid **1₄** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (45 mol%) in the presence of FPyr (10 mol%) in MeCN (2 M) for 4 h at 40 °C before further MeCN (0.5 M), 1-naphthol (1.3 equiv) and the **base** (2.3 equiv) were added. a. With 0.3 equiv NMM. b. Reaction time **6₄** → **3₄ₐ** 48 h. c. Concentration conversion time **6₄** → **3₄ₐ** 1 M. DIPEA = di-*iso*-propylethylamine, DBU = 1,8-diazabicyclo[5.4.0]unde-7-cene.

Additionally, lutidine and DIPEA granted yields above 80% (entries 3+4), but are more expensive than NEt_3 and NMM. While esterification in the presence of pyridine afforded **3₄ₐ** still in a useful yield of 73% (entry 5), DBU and K_2CO_3 were realized as less feasible bases with yields in the range of 63-64% (entries 6+7). The reaction outcome employing inexpensive K_2CO_3 could not be enhanced, when NMM was added in substoichiometric amounts (30 mol%) or through an elongated reaction duration of 2 d (entries 8+9). K_2CO_3 is most likely not basic enough to generate the more nucleophilic naphtholate anion from 2-naphthol in a significant concentration. Pyridine and DBU might also act as *Lewis* base catalysts, which facilitate formation of acyl pyridinium and amidinium type intermediates. These highly electrophilic species could be prone to side-reactions, which would rationalize the lower yields in

(12) Determined from ^{1}H-NMR-spectra of the crude products by means of 1,3,5-trimethoxybenzene as internal standard (s at 3.77 ppm with respect to s of CH_2-group of **3₄ₐ** at 4.02 ppm).

comparison to NMM and NEt_3. The necessity of a base was verified through an experiment without, in which ester **3$_{4a}$** was obtained in only 19% yield (entry 10). Afterwards, the optimal amount of TCT was explored under usage of NMM (1.3 equiv) in MeCN (Table S14). Importantly, just 35 mol% of cyanuric chloride was sufficient to furnish ester **3$_{4a}$** in an improved yield of 89% (entry 1). An increase to 40 mol% allowed for the synthesis of **3$_{4a}$** in 93% yield (entry 2). Higher TCT amounts resulted in deteriorated yields (entries 3-5), which underpins the necessity of low TCT quantities for an effective condensation reactions of carboxylic acids with nucleophiles in one-pot.

Table S14. Optimization of the TCT amount in MeCN.



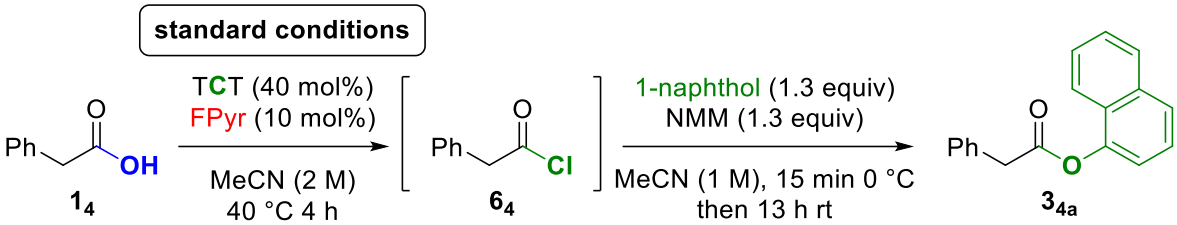
entry	TCT amount [mol%]	yield 3$_{4a}$$^{(12)}$ [%]	lab journal no.
1	35	**89**	PH2664
2	40	**93**	PH2654
3[a]	45	**86**	PH2612b
4	50	**82**	PH2665
5	60	**68**	PH2666

According to general procedure procedure 3 (see chapter 5.3.3 on page 49) acid **1$_4$** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (35-60 mol%) in the presence of FPyr (10 mol%) in MeCN (2 M) for 4 h at 40 °C before further MeCN (1 M), 1-naphthol (1.3 equiv) and NMM (1.3 equiv) were added. a. With 2.3 equiv NMM instead of 1.3.

Based on entry 2 in Table S14 as standard conditions, the synthesis of naphthylester **3$_{4a}$** was further optimized (Table S15, entry 1). Neither an increased nor a shortened reaction duration for the amidation step had a positive effect (entries 2+3). When the NMM amount was raised to 2.3 equiv, a lower yield in **3$_{4a}$** was attained (entry 4). Addition of NMM by means of a syringe pump over 30 min did not result in an enhancement (entry 5). Furthermore, FPyr could be replaced by cheaper DMF (entry 6), while reaction of **1$_4$** with TCT in the absence of a feasible catalyst produced ester **3$_{4a}$** in a strongly reduced yield of 44% (entry 7). Additionally, chlorination **1→6** in a higher dilution of 1 M and at room temperature overnight caused a slight decrease of the yield (entries 8+9). While NEt_3 could be used instead of NMM (entry 10), the base K_2CO_3 was confirmed to be no adequate substitute (entry 11). Remarkably, exchange of MeCN with less toxic EtOAc gave rise to ester **3$_{4a}$** in an unchanged yield (entry 12). In contrast, transformation of acid **1$_3$** into **3$_{4a}$** in THF, which was found to be the optimal solvent for the

conversion **1→6** (see Table S3 and Table S4), proceeded in a declined yield of 83% (entry 13).

Table S15. Further fine tuning of reaction conditions.

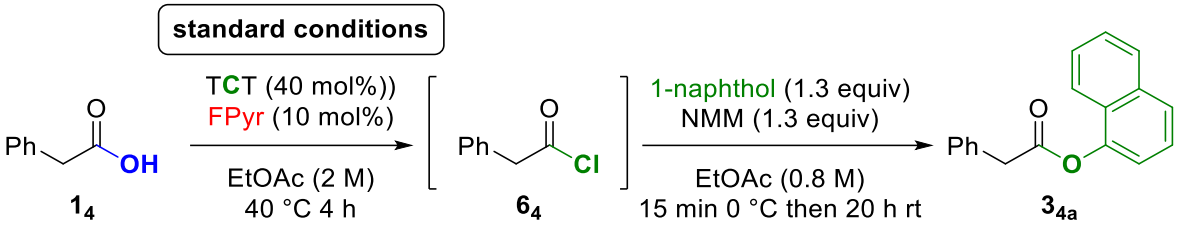


entry	deviation from standard conditions	yield 3_{4a}[12] [%]	lab journal no.
1	/	**93**	PH2654
2	**6_4→3_{4a} 20 h** instead of 13 h	**88**	PH2638
3	**6_4→3_{4a} 4 h** instead of 13 h	**86**	PH2655
4	**2.3 equiv** NMM instead of 1.3	**89**	PH2619a
5	2.3 equiv NMM **syringe pump addition**	**88**	PH2637
6	**DMF** instead of FPyr	**89**	PH2667
7	**no FPyr**	**44**	PH2687
8	**1_4→6_4** [1_4] = 1 M	**88**	PH2676
9	**1_4→6_4** at rt for 20 h	**86**	PH2641
10	2.3 equiv **NEt_3** instead of NMM	**89**	PH2619b
11	**K_2CO_3** instead of NMM	**63**	PH2794
12[c]	**EtOAc** instead of MeCN	**93**	PH2709
13[c]	**THF** instead of MeCN	**83**	PH2635

According to general procedure procedure 3 (see chapter 5.3.3 on page 49) acid **1_4** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (40 mol%) in the presence of FPyr (10 mol%) in MeCN (2 M) for 4 h at 40 °C before further MeCN (1 M), 1-naphthol (1.3 equiv) and NMM (1.3 equiv) were added. a. [**1_4**] in **6_4→3_{4a}** 0.8 M.

Schotten-Baumann type reaction conditions, in which the reaction mixture was diluted after chlorination **1→6** in either MeCN or EtOAc with water, furnished the desired product in only 34-39% yield, when K_2CO_3 was applied as base (not shown, PH2568a+PH2568b). Since EtOAc has been demonstrated to be a reasonable alternative for MeCN, the reaction conditions were further varied (Table S16). Thereby, the reaction conditions in entry 1 were defined as standard conditions. At a reaction duration of 4 h for the initial activation **1_4→6_4** both, a decrease of the FPyr loading and an replacement by DMF caused lower yields (entries 1-6). Nevertheless, the TCT amount could be lowered to 35 mol% without a strong impact on the yield of **3_{4a}** (entries 7-8).

Table S16. TCT amount and catalyst optimization for the synthesis of 1-naphthyl phenylacetate in EtOAc.



entry	deviation from standard conditions	yield 3_{4a}[(12)] [%]	lab journal no.
1	/	**92**	PH2675
2	**5 mol%** FPyr	**81**	PH2703
3	**2.5 mol%** FPyr	**71**	PH2704
4	**DMF** instead of FPyr	**73**	PH2725
5	**5 mol% DMF** instead of FPyr	**68**	PH2705
6	**2.5 mol% DMF** instead of FPyr	**68**	PH2706
7	**35 mol%** TCT instead of 40	**84**	PH2727
8	duration **1_4→6_4** 6 h	**89**	PH2763

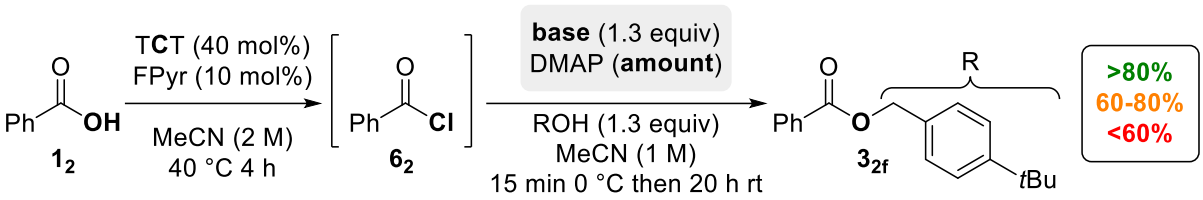
According to general procedure procedure 3 (see chapter 5.3.3 on page 49) acid **1_4** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (35-40 mol%) in the presence of the **catalyst** (2.5-10 mol%) in EtOAc (2 M) for 4 h at 40 °C before additional EtOAc (1 M), 1-naphthol (1.3 equiv) and the NMM (1.3 equiv) were added.

3.2.4 Optimization Synthesis of 4-*tert*-Butylbenzyl benzoate (3_{2f})

As final model transformation we investigated in the synthesis of 4-*tert*-butylbenzyl benzoate (**3_{12f}**), which was commenced to a screening of various bases (Table S17). Esterification utilizing both, DMAP (dimethylaminopyridine) and pyridine furnished product **3_{2f}** in good yields of 83-86% (entries 1+2). Lutidine, NEt_3 and DBU delivered the desired ester in moderate yields of 61-71% (entries 3-5), whereas NMM, DIPEA and in particular K_2CO_3 provided an access to amide **3_{2f}** in very low efficiency (entries 6-8). The predominance of DMAP and pyridine is most probably explained by the formation of highly electrophilic acyl pyridinium intermediates, which accelerate the acylation of 4-*tert*-butylbenzyl alcohol significantly.

However, utilization of DMAP in stoichiometric amounts is not very desirable in terms of cost-efficiency. Therefore, DMAP was employed in catalytic quantities (10 mol%) in the presence of 1.3 equiv of NMM, which afforded ester **3_{2f}** in an improved yield of 77-78% (two independent experiments, entry 9). Use of 30 mol% allowed for the preparation of ester **3_{2f}** in enhanced 82% yield (entry 10). Interestingly, the combination of pyridine and DMAP (10 mol%) showed a similar effectiveness in comparison with NMM/DMAP (entry 11).

Table S17. Testing of bases for the synthesis of 4-*tert*-butylbenzyl benzoate in MeCN.



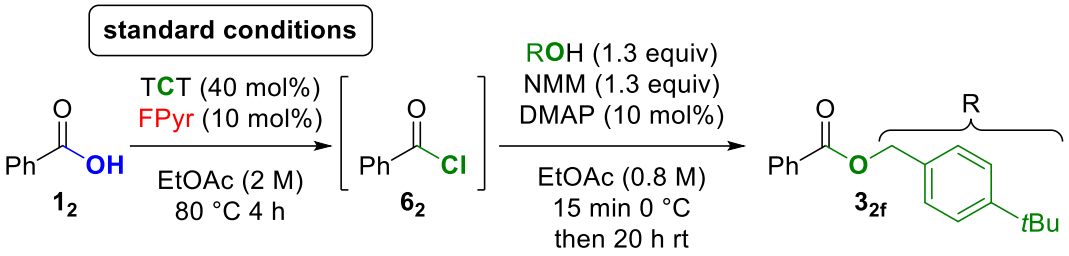
entry	base	DMAP [mol%]	yield 3_{2f}[(13)] [%]	lab journal no.
1[b]	/	120	**86**	PH2673
2	pyridine	0	**83**	PH2669
3	2,6-lutidine	”	**71/68**	PH2650/PH2672
4	NEt_3	”	**61**	PH2649
5	DBU	”	**61**	PH2671
6	NMM	”	**51**	PH2651
7	DIPEA	”	**39**	PH2670
8[a]	K_2CO_3	0	**20**	PH2795
9	NMM	10	**77/78**	PH2678/PH2707
10	NMM	30	**82**	PH2708
11	pyridine	10	**78**	PH2679

According to general procedure procedure 3 (see chapter 5.3.3 on page 49) acid **1_2** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (40 mol%) in the presence of FPyr (10 mol%) in MeCN (2 M) for 4 h at 40 °C before further MeCN (1 M), 4-*tert*-butylbenzyl alcohol (1.3 equiv), the **base** (1.3 equiv) and DMAP (0-120 mol%) were added. a. Concentration **6_2→3_{2f}** 0.5 mol/L to maintain stir-ability.

Since EtOAc is a more desirable solvent in terms of sustainability than MeCN, a second study was pursued (Table S18). Herein, the reaction temperature of the chlorination of **1_2** to yield **6_2** had to be increased from 40 to 80 °C to allow for the synthesis of ester **3_{2f}** in a good yield (entries 1-3). Therefore, the experiment in entry 3 is referred to as standard conditions in the following. Both, a prolonged reaction duration of 48 h and an increased temperature of 40 °C of the esterification step **6_2→3_{2f}** facilitated slightly improved yields of 88-89% (entries 4+5). A decrease of the TCT amount to 35 mol% on the other hand effect a poorer yield of 80% (entry 6), which might be compensated through extended reaction durations for the transformation of **1_2** into **6_2**. In EtOAc more toxic pyridine turned out to be a less feasible base than NMM (entry 7), while stoichiometric quantities of DMAP allowed to the highest yield in ester **3_{2f}** (entry 8).

(13) Determined from ^{1}H-NMR-spectra of the crude products by means of 1,3,5-trimethoxybenzene (s at 3.77 ppm) as internal standard referring to the singlet of the CH_2-group of **3_{2f}** at 5.34 ppm

Table S18. Optimization of 4-*tert*-butylbenzyl benzoate in EtOAc.



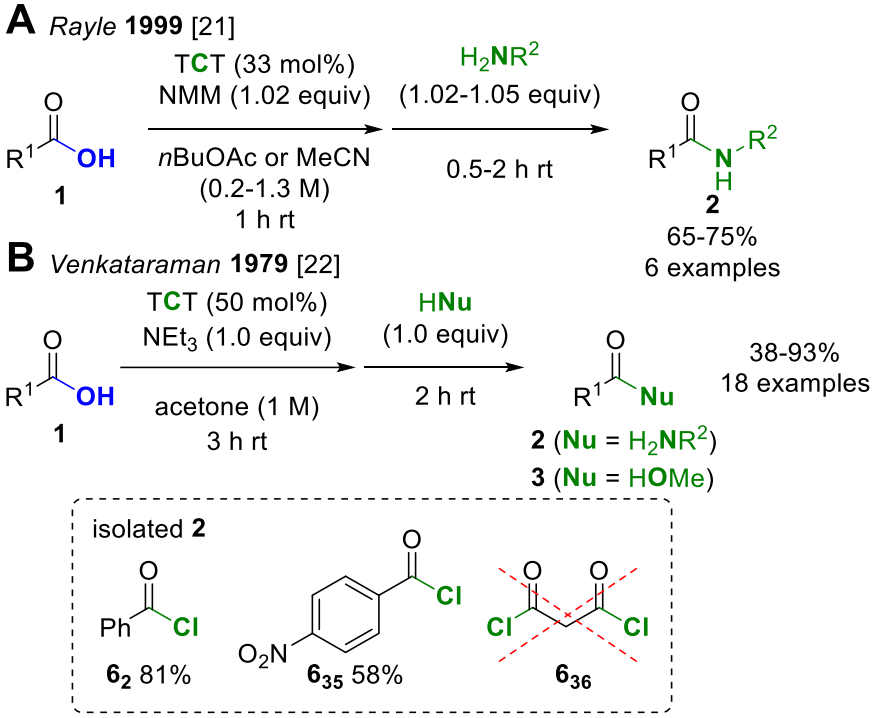
entry	deviation from standard conditions	yield 3_{2f} [13] [%]	lab journal no.
1	temperature **1_2→6_2 40 °C**	**71**	PH2716
2	temperature **1_2→6_2 60 °C**	**82**	PH2717
3	/	**86**	PH2718
4	time **6_2→3_{2f} 48 h**	**88**	PH2728
5	temperature **6_2→3_{2f} 40 °C**	**89**	PH2729
6	**35 mol% TCT** instead of 40	**80**	PH2751
7	**pyridine** instead of NMM/DMAP	**82**	PH2749
8	**1.2 equiv DMAP** instead of NMM/DMAP	**94**	PH2750
9[a]	**K_2CO_3** instead of NMM/DMAP	**32**	PH2770
10	**K_2CO_3** instead of NMM	**43**	PH3672

According to general procedure procedure 3 (see chapter 5.3.3 on page 49) acid **1_2** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (40 mol%) in the presence of FPyr (10 mol%) in EtOAc (2 M) for 4 h at 80 °C before further EtOAc (0.8 M), 4-*tert*-butylbenzyl alcohol (1.3 equiv), the NMM (1.3 equiv) and DMAP (0-120 mol%) were added. a. Concentration **6_2→3_{2f}** 0.5 mol/L to maintain stir-ability.

As unambiguously proven by the experiments in entries 9+10, K_2CO_3 is not a feasible base for the preparation of esters even not in the presence of DMAP (10 mol%). In conclusion, the conditions in entry 3 were selected as optimal for the synthesis of esters from aromatic carboxylic acids and aliphatic alcohols, since stoichiometric use of DMAP is avoided and a reaction duration of 2 d such as in entry 4 is inconvenient.

4 Literature Comparison Experiments

In order to allow a thorough assessment of the current method with previous reported protocols for amidations and chlorinations of carboxylic acids using TCT in substoichiometric amounts two protocols were selected as shown in Scheme S4: (**A**) Activation of acids **1** with 33 mol% TCT and NMM in MeCN before addition of an amine nucleophile according to *Rayle*.[22] (**B**) Chlorination of acids **1** with TCT (50 mol%) and NEt_3 in acetone by *Venkataraman*.[23] The latter protocol was also applied for amidations and esterification through addition of the respective nucleophile after chlorination. Nevertheless, for comparison purposes we focused on transformation of acids **1** into chlorides **6**. Other related literature procedures exclusively lead either to carboxylic acid azides, diazoketones or hydroxamic acids and were therefore not considered.[24]



Scheme S4. Literature protocols for the amidation and esterification of carboxylic acids using substoichiometric amounts of TCT.

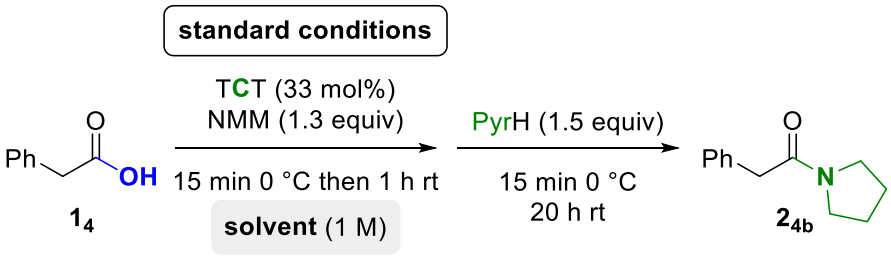
In case of protocol **A** moderate yields were noted by the authors (65-75%) and the formation of acid chlorides of type **6** as intermediates was excluded, which could be confirmed by own experiments (see chapter 4.1.5 on page 37). The authors of method **B** proposed the generation of acid chloride **6** as intermediates, two aromatic acid chlorides were isolated while malonic acid could neither be converted into chloride $\mathbf{6_{36}}$ nor in an amide. The current method allows for the amidation of malonic acid (example $\mathbf{2_{9i}}$).

4.1 Amidation and Esterification using TCT and NMM[22]

4.1.1 Optimization Synthesis of Phenylacetylpyrrolidine (2_{4b})

For the comparison experiments the reaction conditions given in Table S19 were specified as standard conditions. Without any deviation amide **2_{4b}** resulted in 60% yield, when MeCN was employed as solvent (entry 1). Under the original conditions according to Rayle using 1.05 equiv of NMM,[22] which did not include cooling to 0 °C during the addition of NMM and pyrrolidine, a slightly depleted yield of 55% was obtained (entry 2). That the amount of NMM has only a marginal influence on the yield was confirmed by the experiment in entry 3, in which 1.3 equiv of NMM were applied. Since the yield was slightly enhanced under cooling to 0 °C, most of the other experiments were conducted accordingly. As these condensation reactions were performed on a smaller 0.5 mmol scale, a slight excess of NMM (1.3 equiv) was preferred. Stirring overnight (20 h) with the nucleophile pyrrolidine should secure full conversion.

Table S19. Optimization of the synthesis of phenylacetylpyrrolidine according to the protocol in reference [22].



entry	deviation from standard conditions	solvent	yield 2_{4b}[10] [%]	lab journal no.
1	/	MeCN	**60**	PH2790
2	**1.05 equiv** NMM**, no cooling to 0 °C**	MeCN	**55**	PH2965
3	**no cooling to 0 °**C	”	**58**	PH2959
4	**40 mol%** TCT	”	**62**	PH2792
5[a]	**K_2CO_3** instead of NMM	MeCN	**≤2/≤2**	PH2793/2939
6	/	**EtOAc**	**57**	PH2791
7	**/**	**$CHCl_3$**	**64**	PH2940
8	**no cooling to 0 °C**	“	**61**	PH2960
9	**1.05 equiv** NMM	”	**69**	PH2990
10	**This Work** (Table S11, entries 1+2)		**90/90**	PH2726/2737

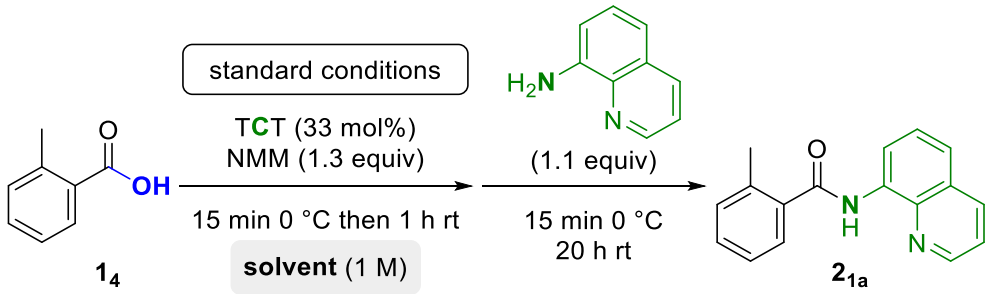
According to general procedure 5 (see chapter 5.3.5 on page 56) acid **1_4** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (33-40 mol%) and the **base** (1.05-1.3 equiv) in the **solvent** (1 M) before pyrrolidine (1.5 equiv) was introduced. a. The reaction mixture had to be diluted with further MeCN (500 μL, 0.5 M) to allow stir-ability. PyrH = pyrrolidine.

Next, an increased TCT amount allowed for a marginal improvement in regard to of yield (entry 4), while NMM cannot be replaced by cheaper K_2CO_3 (entry 5, two separate experiments). Moreover, EtOAc as substitute for *n*-butyl acetate in the literature delivered the desired coupling product in a comparable yield of 57% (entry 6). Since experiments to study the nature of carboxylic acid activation (see chapter 4.1.5 on page 37) were performed in $CDCl_3$, chloroform was tested as reaction medium as well. Surprisingly, improved (albeit moderate) yields of **2_{4b}** were attained (at maximum 69%, entries 7-9). As $CHCl_3$ is of high toxicity the present method was compared with reactions in MeCN and EtOAc. Indeed, the current protocol facilitated the synthesis of amide **2_{4b}** in 90% yield (entry 10).

4.1.2 Optimization Synthesis of *N*-(Quinolin-8-yl) 2-methyl benzamide (2_{1a})

Also in the case of the preparation of amide **2_{1a}** low yields between 17-45% were observed when the literature protocol [22] was applied (Table S20). Surprisingly, the best yield was accomplished in EtOAc as solvent (entry 2), while reaction in MeCN and $CHCl_3$ gave rise to product **2_{1a}** in lower efficiency (entries 1+3). Again, utilization of K_2CO_3 as base instead of NMM effected a deteriorated yield (17%, entry 4), whereas higher amounts of TCT resulted in depleted yields (entry 5, compare entry 3). In fact, the presented protocol delivered aromatic amide **2_{1a}** in 90-91% yield (entry 6).

Table S20. Optimization of the synthesis of *N*-(quinolin-8-yl) 2-methyl-benzamide according to the protocol in reference [22].



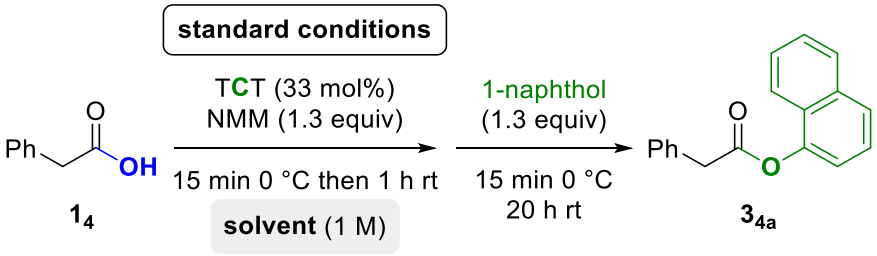
entry	deviation from standard conditions	solvent	yield 4_{4b}[(11)] [%]	lab journal no.
1	/	MeCN	**26**	PH3179
2	/	**EtOAc**	**45**	PH3185
3	/	**$CHCl_3$**	**37**	PH3180
4	**K_2CO_3** instead of NMM	MeCN	**17**	PH3290
5	**38 mol% TCT** instead of 33	$CHCl_3$	**27**	PH3186
6	**This Work** (Table S12, entries 1+9)		**90/91**	PH3145/3245

According to general procedure 5 (see chapter 5.3.5 on page 56) acid **1_4** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (33-38 mol%) and the **base** (1.3 equiv) in the stated **solvent** (1 M) before 1-naphthol (1.3 equiv) was introduced.

4.1.3 Optimization Synthesis of 1-Naphthyl phenylacetate (3_{4a})

Ester $\mathbf{3_{4a}}$ was obtained in 55-58% yield under literature conditions using either MeCN or EtOAc as solvent (Table S21, entries 1+2). Both, higher amounts of NMM and TCT had a negative effect (entries 3-5), whereas the current method delivered ester $\mathbf{3_{4a}}$ in 92-93% yield (entry 6).

Table S21. Optimization of the synthesis of 1-naphthyl phenylacetate according to the protocol in reference [22].



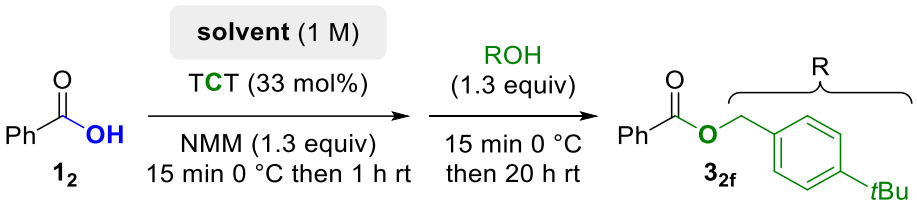
entry	deviation from standard conditions	solvent	yield 3_{4a}[12] [%]	lab journal no.
1	/	MeCN	**58**	PH2775
2	/	**EtOAc**	**55**	PH2692
3[a]	**2.3 equiv** NMM instead of 1.3	MeCN	**52**	PH2643
4[a]	**40 mol%** TCT and **2.3 equiv** NMM	”	**48**	PH2653
5	**40 mol%** TCT instead of 33	”	**51**	PH2776
6	**This Work** (Table S15, entry 12 + Table S16, entry 1)		**93/92**	PH2709/ PH2675

According to general procedure 5 (see chapter 5.3.5 on page 56) acid $\mathbf{1_4}$ (0.50 mmol, 1.0 equiv) was allowed to react with TCT (33-40 mol%) and NMM (1.3-2.3 equiv) in the respective **solvent** (0.5-1 M) before 1-naphthol (1.3 equiv) was introduced. a. Conducted in MeCN (0.5 M) to maintain stir-ability.

4.1.4 Synthesis of 4-*tert*-Butylbenzyl benzoate (3_{2f})

Both, reaction in MeCN and EtOAc gave rise to the benzoate ester 3_{2f} in moderate yields 24-37%, while the present method facilitated yields between 86 and 94% (Table S22).

Table S22. Optimization of the synthesis of 4-*tert*-butylbenzyl benzoate according to the protocol in reference [22].



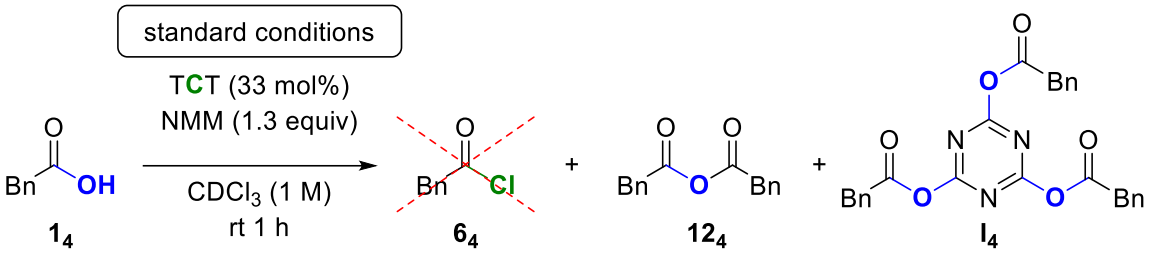
entry	solvent	yield 3_{2f}[13] [%]	lab journal no.
1	MeCN	**24**	PH2771
2	**EtOAc**	**37**	PH2772
3	**This Work** (Table S18, entries 3+8)	**86/94**	PH2718/PH2750

According to general procedure 5 (see chapter 5.3.5 on page 56) acid $\mathbf{1_2}$ (0.50 mmol, 1.0 equiv) was allowed to react with TCT (33mol%) and NMM (1.3 equiv) in the **solvent** (1 M) before 4-*tert*-butylbenzyl alcohol (1.3 equiv) was introduced.

4.1.5 Studies Towards Intermediates

Both, *Rayle*[22] and *Forbes*[24a] reported that no acid chlorides of type **6** are formed as intermediates in TCT/NMM-mediated condensations. Nevertheless, we decided to examine the nature of carboxylic acid activation in these protocols as shown in Table S23. For this purpose, the experiments were performed in $CDCl_3$, because the reaction mixture could be directly subjected to ^{1}H-NMR spectroscopy after filtration to separate solid components. After stirring of model substrate $\mathbf{1_4}$ with NMM and TCT for 1 h at room temperature the reaction mixture contained no trace of phenylacetoyl chloride $\mathbf{6_4}$, while the acid anhydride $\mathbf{12_4}$ was observed in 26% yield (generated from 52% of acid $\mathbf{1_4}$). For the proposed mixed anhydride $\mathbf{I_2}$ no evidence could be gathered.

Table S23. Studies towards intermediates.



entry	deviation from standard conditions	yield[14] [%] 6_4	yield[14] [%] 12_4	lab journal no.
1	/	**≤2**	26	PH2918
2	cooling to 0 °C during NMM addition	**≤2**	29	PH2951
3	**1.05 equiv** NMM	**≤2**	31	PH2964
4	**K_2CO_3** instead of NMM	**≤2**	9	PH2952
5	**This work** (see Table S9 18, page)	**89**	≤2	PH2931

According to general procedure 5 (see chapter 5.3.5 on page 56) acid **1_4** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (33 mol%) and NMM (1.05-1.3 equiv) in $CDCl_3$ (1 M) at rt for 1 h.

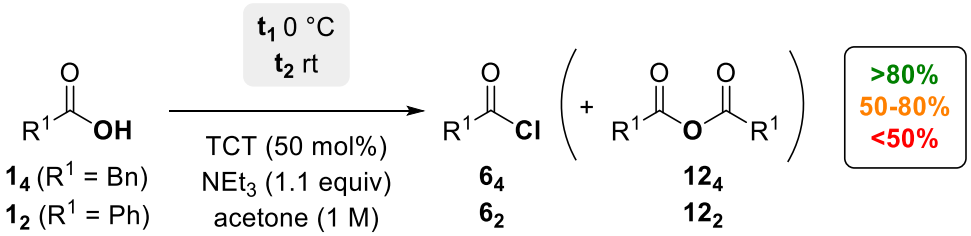
Indeed, mixed anhydrides of cyanuric acid and the starting carboxylic acid might be poorly soluble in the reaction solvent and as the consequence could not be validated by liquid state NMR. In comparison to the ^{1}H-NMR spectra of compounds **1_4**, **6_4** and **12_4** a singlet between 3.6 and 4.7 ppm for the CH_2-groups of **I_4** would be predicted. Also cooling of the reaction mixture to 0 °C during NMM addition and lowering of the NMM amount to 1.05 equiv both delivered the anhydride **12_4** in 29-31% yield as exclusively verifiable product (entries 2+3). Using K_2CO_3 instead of NMM the yield of **12_4** declined to 9% (entry 4), while the current method allowed formation of acid chloride **6_4** in 89% yield (entry 5). Since carboxylic acid anhydrides of type **12** only allow to transfer one acyl residue, the generation of these species as activated intermediates in 26-31% yield could be one explanation of the low yields of carboxylic acid condensations employing TCT/NMM.

(14) The yield was determined with the aid of 1,3,5-trimethoxybenzene (s at 3.77 ppm) as internal NMR-standard in reference to the singlets of the CH_2-group of compounds **6_4** at 4.13 and **12_4** at 4.71 ppm.

4.2 Chlorination using TCT and NEt_3 According to [23]

Ultimately, comparison experiments following the protocol of *Venkataraman* utilizing 50 mol% of TCT and NEt_3 in acetone[23] were pursued as summarized in Table S24. In fact, reaction of phenyl acetic acid **1_4** with TCT in the presence of NEt_3 mainly afforded the corresponding carboxylic acid anhydride **12_4** in 29-43% yield (formed from 58-86% **1_4**), whereas the carboxylic acid chloride **6_4** was only identified in traces (entries 1-3). In contrast, benzoic acid **1_4** could be converted into benzoyl chloride in moderate yields of 63-78% (entries 4-6). However, benzoic acid anhydride (**12_2**) and chloride (**6_4**) cannot be clearly distinguished in the ^{1}H-NMR spectra (see chapter 3.1.3 on page 14).

Table S24. Optimization chlorination with TCT and NEt_3 according to reference [23].



entry	R	t_1 [h]	t_2 [h]	yield[6,14] [%] 6	12	lab journal no.
1	Bn	0.25	7	**7**	43	PH3549
2	”	0	8	**10**	29	PH3501
3	”	”	6	**6**	43	PH3508
4	Ph	0.25	7	**78**	n. d.	PH3548
5	”	0	6	**63**	n. d.	PH3507
6	”	”	7	**70**	n. d.	PH3497
7	Bn	**This Work** (Table S5, entry 1)		**86/90**	≤2/≤2	PH3515/PH3527
8	Ph	**This Work** (Table S6, entry 6)		**93**	n. d.	PH2857

According to general procedure 6 (see chapter 5.3.6 on page 57) acid **1** (0.50 mmol, 1.0 equiv) was allowed to react with TCT (50 mol%) and NEt_3 (1.1 equiv) in acetone (1 M). n. d. = not determined. Due to signal overlap in the ^{1}H-NMR of the crude materials the conversion cannot be determined.

The formation the corresponding carboxlic acid anhydride **12_4** in the case of substrate **1_4** as major product could be rationalized by the low stability of carboxylic acid chlorides bearing protons in α-position (see chapter 3.1.4, page 16). As carboxylic acid anhydrides only allow for the reaction of one acyl residue with a nucleophile, the protocol of *Venkataraman* might be less feasible for enolizable carboxylic acids.

5 Experimental Part

5.1 General Conditions

Unless otherwise stated all ^{1}H-, ^{19}F- and ^{13}C-NMR spectra, the latter of which were recorded broadband proton decoupled, were recorded at room temperature in $CDCl_3$ on Bruker instruments (Avance II 400 or Avance I 500). Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) using the residual solvent resonance (^{13}C-NMR) or TMS (^{1}H-NMR) as the internal standard ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). High resolution mass spectra were recorded either on a MAT 95Q spectrometer (CI) of *Finnigan* or on a *Bruker* SolariX 7 Tesla MALDI/ESI/APPI FTICR imaging spectrometer (ESI). Optical rotations were determined on a *Perkin Elmer* polarimeter 341. Melting points (uncorrected) were determined on a MEL-TEMP II machine of *Laboratory Devices Inc.*

Analytical TLC was carried out using precoated silica gel plates (*Fluka* TLC plates silica gel 60 F_{254} on PET-foils). TLC plates were visualized under UV irradiation (254 nm) or with $KMnO_4$-(3 g $KMnO_4$ and 20 g K_2CO_3 in 300 mL water) and $Ce(SO_4)_2$/PMA (= posphomolybdic acid, 10 g $Ce(SO_4)_2$-4 H_2O, 25 g PMA, 80 mL 95% H_2SO_4, 920 mL water) stain solutions. Flash column chromatographic purifications were performed with technical grade silica gel M 60 from *Macherey-Nagel* (40-63 μm, 60 A).

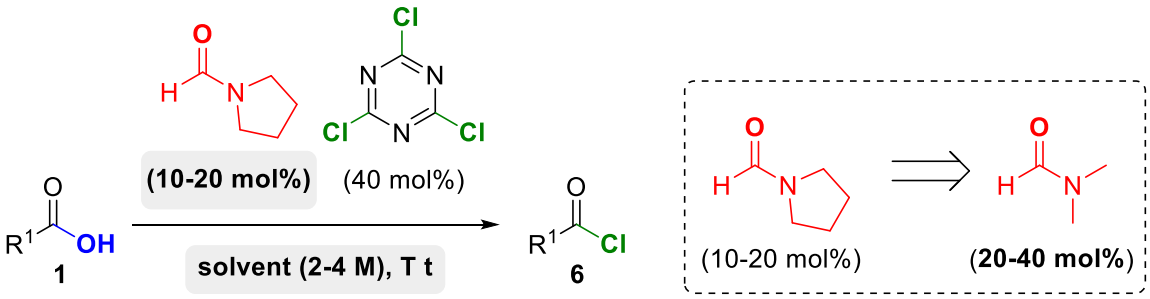
Gas chromatography (GC) was conducted on a GC-2010 from *Shimadzu* with a CP-Chirasil-DX CB column (length 25 m, diameter 0.25 mm, 0.25 μm layer thickness) from *Agilent Technologies* and a *FS Supreme-5 MS* column (length 25 m, diameter 0.25 mm, 0.25 μm layer thickness) from *EMR*, respectively, and nitrogen as carrier gas. Compounds were either detected by an FID (Chirasil-DX CB column) or a GCMS-QP2010 Plus mass detector from *Shimadzu* (Supreme 5 MS column). High pressure liquid chromatography (HPLC) was conducted on a D-7000 machine from *Merck-Hitachi* with a Chiracel OD-H column of *Daicel Industries* (length 250 mm, diameter 4.6 mm). Visualisation was realized by a diode array UV detector (wavelength 190-300 nm)

Chemicals were purchased from *Sigma-Aldrich, Acros*, *TCI chemicals*, *Carbolution* and *Alfa Aesar* and used without further purification. Petrolether (bp. 40-60 °C, technical grade) was distilled prior usage; all other solvents were utilized without further purification. Dry solvents were purchased from *Acros*.

5.2 Reaction Conditions Guide

In Table S25 conditions for the conversion of carboxylic acids **1** into carboxylic acid chlorides **6** are summarized in dependence on the degree of substitution of the α-C-atom of the substrate. In general, secondary (2°), tertiary (3°) and aromatic carboxylic acids require higher reaction temperatures than primary (1), which is caused by a depleted electrophilicity due to steric shielding of the carboxyl carbon atom and the electron donating effect of adjacent aryl portions, respectively. Moreover, utilization of MeCN as solvent allowed for lower reaction temperatures **T** and shorter durations **t** in the initial chlorination step in comparison to EtOAc. Indeed, full conversion of the starting material in EtOAc often affords a final heating period to 80 °C. In most cases high starting material concentrations of 2-4 mol/L were sufficient to maintain stir-ability. Increased solvent amounts effected lower conversions at elsewise comparable conditions.

Table S25. Reaction conditions guide for the conversion of acids **1** into acid chlorides **6**.



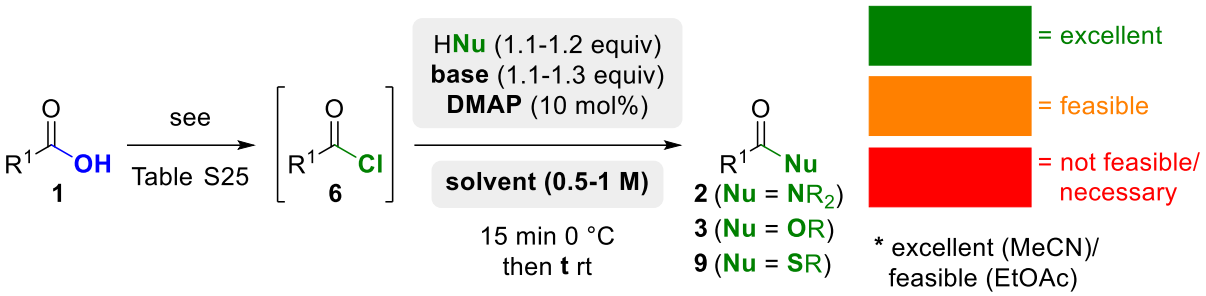
R^1	T [C]	t [h]	FPyr (mol%)	solvent MeCN	solvent EtOAc	examples
2°, 3°	80	4	10			**6_1, 6_2, 6_3, 2_{6f}, 2_{7g}, 2_{9i}, 2_{11k}, 2_{12l}, 2_{12m}, 2_{13n}, 2_{14o}, 2_{15f}, 2_{17q}, 2_{18r}, 2_{14f}, 2_{22v}, 2_{23w}, 2_{24x}, 2_{3y}, 3_{2f}, 9_{29a}, 3_{30c}, 3_{32e}, 3_{2g}, 3_{34h}**
2°, 3°	**40**	8	**20**			**2_{1a}, 2_{6f}, 2_{12l}, 2_{20f}, 2_{21u}, 3_{20i},**
2°, 3°	**rt**	≥12	"			**2_{1a}, 2_{20f}, 2_{21u}, 2_{27z}, 3_{20i}**
1°	40	4	10			**6_4, 2_{5b}, 2_{5f}, 2_{8h} 2_{10j}, 2_{19m}, 3_{27b}, 3_{31d}, 3_{33g}, 3_{35j}**
1°	40	**8**	10			**6_4, 2_{5b}, 2_{16p}, 3_{4a}**
1°	**rt**	≥12	10			**6_4**

= excellent
= feasible
= not feasible/ necessary

Catalyst loading between 10 and 20 mol% are recommended in general. Application of 20 mol% FPyr enables chlorination at room temperature. FPyr can be replaced by DMF, if the catalyst loading is doubled. Furthermore, in Table S26 reaction conditions for the amidation and esterification of the intermediate acid chloride are concluded. The type of nucleophile employed determines the base required. Good nucleophiles such as amines and thiols facilitate the use of plain K_2CO_3, albeit yields are sometimes higher when NMM (*N*-methylmorpholine) is engaged. Generally, NMM can also be replaced by NEt_3. Reaction of primary carboxylic acids with aromatic alcohols only requests for NMM, whereas in the case of aromatic acid chlorides usage of DMAP as catalyst effects significantly enhanced yields. The synthesis of esters deduced from primary and secondary aliphatic alcohols in good yields, however, necessitates DMAP (10-20 mol%) and NMM (or NEt_3). Esters derived from tertiary aliphatic alcohols are only accessible in moderate yields, even when DMAP is employed as Lewis base catalyst. Since bases are introduced in the second reaction step, the reaction mixture has to be diluted with additional solvent in order to maintain stir-ability. Depending on the substrate, nucleophile and base engaged, concentrations had to be varied between 1 and 0.25 mol/L, whereby 0.7-1 M are typically. Overall, reactions in EtOAc need higher solvent volumes than in MeCN. Also condensations applying K_2CO_3 typically require a more diluted

reaction media. Apart from the stir-ability, the yield of the product is less influenced by the type of solvent (e.g. MeCN, EtOAc) than in the foregoing chlorination process.

Table S26. Reaction conditions guide for the transformation of acid chloride **6** into amides and esters of type **2**, **3** and **9**.



		t	base			solvent		
R^1	HNu	[h]	K_2CO_3	NMM	DMAP	MeCN	EtOAc	examples
3°	HNR_2	4					*	2_{1a}, 2_{7g}, 2_{9i}, 2_{12l}, 2_{12m}, 2_{13n}, 2_{14o}, 2_{15f}, 2_{18r}, 2_{14s}, 2_{20t}, 2_{21u}, 2_{22v}, 2_{23v}, 2_{24x}, 2_{3y}, 2_{27z}
3°	HOAr	“						3_{30c}
3°	HOR	≥12						3_{32c}, 3_{2f}, 3_{2g}, 3_{20i}
3°	HSR	4					*	9_{29a}
2°	HNR_2	8					*	2_{6f}, 2_{11k}
2°	HOR	≥12					*	3_{34h}
1°	HNR_2	≤4					*	2_{4b}, 2_{4c}, 2_{4d}, 2_{4e}, 2_{5b}, 2_{5f}, 2_{8h}, 2_{10j}, 2_{16p}, 2_{17q}, 2_{19m}
1°	HOAr	≥12						3_{4a}, 3_{28b}
1°	HOR	≥12						3_{31d}, 3_{33g}, 3_{34j}
2°	HSR	≤4					*	/

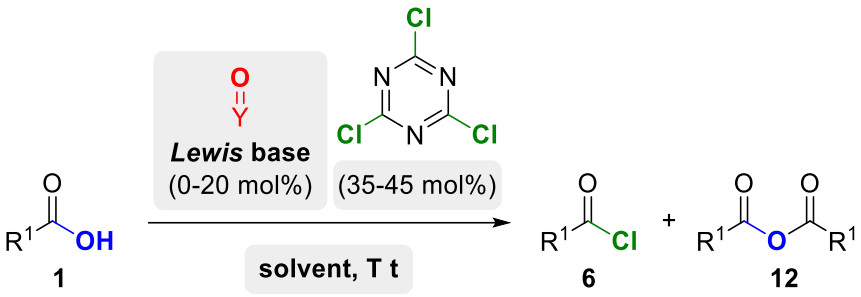
The transformation of carboxylic acids into the respective chlorides is possible under magnetic stirring even on a 500 mmol scale with starting material concentrations of 4 mol/L. On such a reaction scale interruption of stirring may result in coagulation of the precipitating cyanuric acid, which can cause difficulties in terms of stirring. In the conversion of the intermediate acid chloride into amides and esters, respectively, mechanical stirring by means of an overhead stirrer is recommended on a 500 mmol scale, while magnetical stirring is unproblematic in up to a 100 mmol scale at least. Under mechanical stirring low conversions of the intermediate acid chloride have been observed, when K_2CO_3 was harnessed as base.

5.3 General Procedures

Caution, TCT, a fine-powdered, dusty solid with a typical chlorine like smell, is (inter alia) very toxic by inhalation. Therefore, it should be only handled in a well ventilated fume hood. Outside a fume hood we strongly recommend to handle TCT only in closed vessels such as dram vials with a screw cap or one-necked flasks with a stopper.

Commercial *N*-Formylpyrrolidine (FPyr) can be conveniently prepared from formic acid, Ac_2O and pyrrolidine on a 2 mol scale using standard laboratory glassware ≤1 L.[25]

5.3.1 General Procedure 1: *Lewis* base catalyzed Chlorination of Acids (yield determination via internal standard)



A 4 mL glass vial with a stir bar is charged successively with the carboxylic acid **1** (1.0 equiv, 0.5 mmol), the ***Lewis*-base** (e.g. FPyr, 0-20 mol%) and the **solvent** (1-2 M). In the following, **TCT** (35-45 mol%) is added at ambient temperature,(15) the reaction vial is closed with a screw cap and placed in an alumina carousel, which has been preheated to the reaction temperature **T**. Then, the reaction mixture is stirred with a speed of 400 rpm for the time period **t** (≤24 h) at the temperature **T** (rt to 80 °C). In the following, the reaction suspension is allowed to cool down to room temperature and transferred with CH_2Cl_2 (ca. 5 mL) to a 10 mL flask and concentrated *in vacuo*. The crude product is subsequently dried for 5 min at 20 mbar. Next, an exactly weight amount of a suitable internal NMR-standard (either dibenzylether, 1,3,5-trimethoxybenzene or mesitylene, 20-40 mg) is added to the residue, the mixture is diluted with $CDCl_3$ (500 μL) and a 50 μL aliquot of the resulting suspension is filtered through a disposable glass pipette with a plug of wool and a ca. 5 mm layer of $MgSO_4$ with further $CDCl_3$ (500 μL) directly into a NMR-tube.(16)

(15) TCT typically dissolves completely after addition to the reaction solution (e.g. in acetone, EtOAc, MeCN, dioxane). During the course of the reaction cyanuric acid precipitates. If TCT does not dissolve completely in the beginning, the utilized TCT batch might contain cyanuric acid through hydrolysis during storage.

(16) At the outset, the reaction suspension was diluted with Et_2O (4 mL), filtered over a layer of $MgSO_4$ (ca. 5 mm) through a sintered funnel by suction and the reaction vial was rinsed with further Et_2O (2 x 2 mL). Next, the collected filtrates were concentrated *in vacuo* and the remaining crude material was treated with the NMR-standard and diluted with $CDCl_3$. Since the accordingly obtained crude material was often not completely soluble in $CDCl_3$ a

Deviations from General Procedure

Table S6 on page 15: After addition of the solvent the respective **base** (1.0 equiv) was added to the reaction mixture.

Table S8 on page 17: Instead of TCT 120 mol% of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) was used.

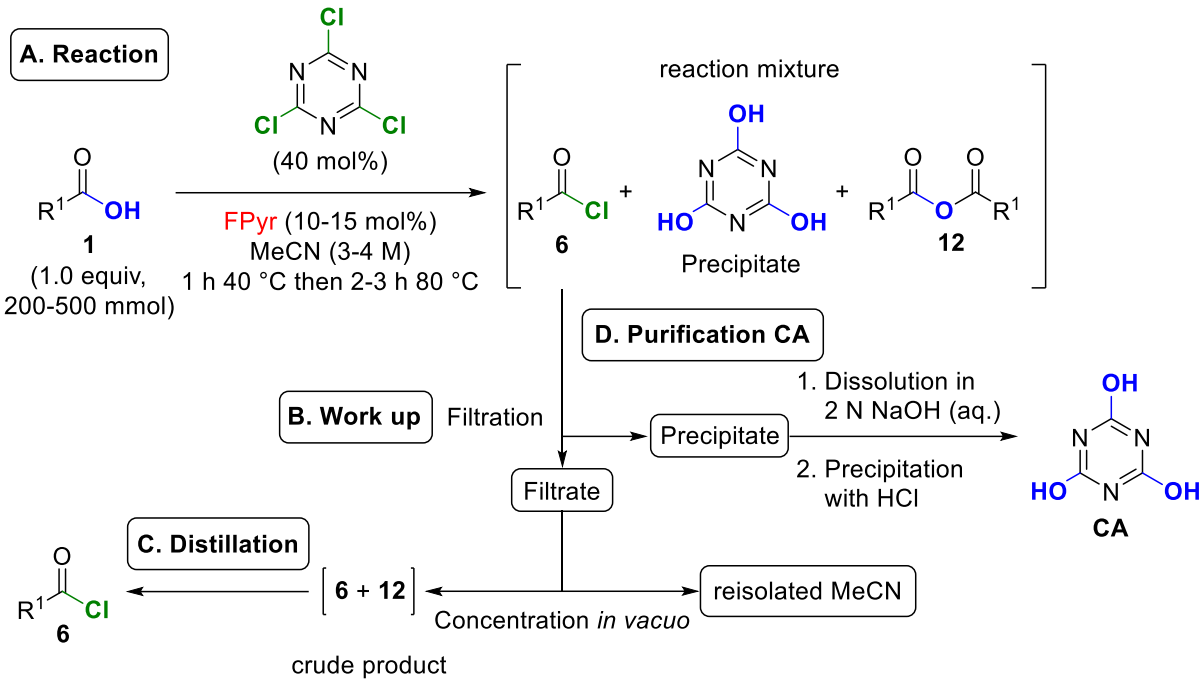
Table S9 on page 18: For work up the reaction suspension was allowed to cool down to room temperature, an exactly weighed amount of 1,3,5-trimethoxybenzene (20-40 mg) was added as internal standard and 50 μL of the mixture were filtered with further $CDCl_3$ (500 μL) through a disposable glass pipette containing a plug of wool and a ca. 5 mm layer of $MgSO_4$ directly into a NMR-tube.

Table S10 on page 19 (PH3841 + PH3842 + PH3843): For the purpose of reaction monitoring a 4 mL glas vial was charged with phenyl acetic acid (**1**$_4$, 136 mg, 1.00 mmol, 1.0 equiv) and dodecane as internal standard (24.6-26.2 mg). Next, the appropriate amount of a 0.4 M stock solution of FPyr in $CDCl_3$ (125-500 μL, 0.1-0.4 mmol, 5-20 mol%), which had been prepared from FPyr (81.5 mg, and 2 mL $CDCl_3$), was added and the resulting solution was diluted with further $CDCl_3$ to a substrate **1**$_4$ concentration of 2 mol/L (0-375 μL $CDCl_3$). Then, TCT (75 mg, 0.40 mmol, 40 mol%) was added to the reaction solution and the reaction vial was immediately places in an alumina carousel preheated to 60 °C.

The reaction progress was followed by dilution of a 30 μL aliquot of the reaction suspension (measured with the aid of an Eppendorf-pipette) with further $CDCl_3$ (500 μL) and filtration of a disposable glass pipette containing a plug of wool and a ca. 5 mm layer of $MgSO_4$ directly into a NMR-tube. In order to allow cooling down for each sample the reaction vial was removed from the reaction carousel heated to 60 °C and after 20 seconds the vial was opened and a small sample was withdrawn. ^{1}H-NMR spectra were recorded on a 500 MHz NMR with 16 scans and a d1 of 2 s.

second filtration as described in the general procedure was mandatory. Therefore, the stated simplified procedure was preferred.

5.3.2 General Procedure 2: Formamide catalyzed Chlorination of Acids (isolated yield)



A. Reaction: A 250/500 mL NS 29 one-necked, round-bottom flask (200/500 mmol scale) with a strong stir bar is charged with the acid **1** (200-500 mmol, 1.0 equiv), FPyr (10-15 mol%) and reagent-grade MeCN (3-4 M). The reaction flask is placed in an oil bath and TCT (40 mol%) is added in one single portion under stirring (400-600 rpm).[17] Next, the reaction mixture is heated in oil bath temperature to 40 °C (in 10 min)[18] and stirred for 1 h at this temperature. After the apparatus has been equipped with a reflux condenser, the mixture is heated to 80 °C

(17) In order to handle TCT safely, a 25-50 mL one necked flask with a NS 14 conical joint with a rubber stopper was tared on a balance and charged with the described amount of TCT in the fume hood. ***Outside of the fume hood, TCT should be only handled in a closed container.*** Next, TCT is added in one portion to the reaction mixture through a NS 29 conical joint of the reaction flask.

(18) While directly after TCT addition the internal temperature typically dropped for a few degrees, the maximum temperature is reached after approximately 30 min of stirring at 40 °C and did never exceed 40 °C.

(in 10-20 min) and stirred until reaction monitoring with ^{1}H-NMR after micro-work up indicated full consumption of **1** (typically after 2-3 h).[19,20,21]

B. Work up:[22] In the following, the oil bath is removed, the reaction suspension is diluted with further MeCN ([**6**] = 2-3 M, V(MeCN)/n(**1**) 0.1-0.25 mol/L), which should reduce loss of **6** during the successive filtration, and allowed to stir at ambient temperature for 1 h and for 5 min at 0 °C to complete precipitation of cyanuric acid. Next, the mixture was filtered over a sintered funnel (porosity level 3) by suction and the filtrate was transferred to 250/500 mL flask depending on the reaction scale (200/500 mmol of **1**). MeCN was added to the reaction flask for the purpose of rinsing, the flask was chilled in the ice bath (ca. 1 min) and the filter cake was triturated with the cold MeCN thoroughly with the aid of a spatula (**2 x portions**, V(MeCN)/n(**1**) 0.1-0.125 mol/L). Finally, the collected filtrates were concentrated in *vacuo*, whereby the pressure was gradually lowered from 160 to 120 mbar, and the residue was dried for 10-20 min at 100 mbar at the rotary evaporator.[23,24]

C. Distillation: Distillation through a micro distillation apparatus with a NS 29 cooling finger without a distillation dispenser at reduced pressure and a stirring speed of 400-1000 rpm[25] under cooling of the collecting flask in an ice bath furnishes the acid chloride **6** as colourless

(19) For micro work up stirring was interrupted and ca. 20 μL of the reaction mixture were transferred to a 10 mL one necked flask with the aid of an Eppendorf pipette. After drying at 100 mbar for 5 min at the rotary evaporator the residue was diluted with $CDCl_3$ (ca. 600 μL) and filtered through a pipette with a plug of wool and a ca. 5 mm layer of $MgSO_4$ directly into a NMR-tube. If the carboxylic acid **1** is poorly soluble in the reaction solvent or in $CDCl_3$, the determination of the consumption could be falsified.

(20) For the isolation of acid chlorides of type **6** a final heating period to 80 °C is required, since remaining FPyr cannot be removed through an aqueous work up (which causes hydrolysis of the product **6**). At 80 °C FPyr decomposes slowly as verified through ^{1}H-NMR after micro work up (see above). Therefore, codistillation with **6** during the subsequent purification is prevented.

(21) Due to the high concentrations of the reactants, no reflux occurred at 80 °C using EtOAc. In the case of MeCN only a weak reflux was observed.

(22) Aqueous work up protocols effect partial hydrolysis of acid chlorides **6** and are therefore not feasible.

(23) In the case of incomplete conversion of **1**, the starting acid **1** usually precipitates from the crude material. Thus, the level of conversion should be determined by micro work up as stated above before evaporation of MeCN.

(24) MeCN can be reisolated in in a purity ≥98% according to ^{1}H-NMR and can be reused as demonstrated through several chlorinations **1→6** on a 0.5 mmol scale.

(25) Typically, the crude products contained a thick, oily precipitate. To avoid sticking to the glass wall of the flask containing the crude material, the stir bar was added shortly before distillation and stirring was started immediately. At the end of the distillation process a thick oil remained in the distillation flask. Therefore, the stirring speed had to be reduced until stirring becomes impossible at the very end.

liquids in purities ≥98% as shown by ^{1}H-NMR. Thereby, the pressure[26] is applied by a high vacuum pump. By means of a needle valve as an artificial leak the pressure is adjusted to accomplish a boiling point ≤60 °C, which allows to minimize thermal decomposition of **6**. To avoid boiling retardation, in the beginning the pressure is gradually lowered from 50 mbar to the desired distillation pressure by means of the needle valve. Boiling retardation is also diminished by using a relatively large flask for the crude material (250-500 mL). In order to maintain a constant distillation process, the oil bath temperature has to be gradually raised, when the head temperature declines.

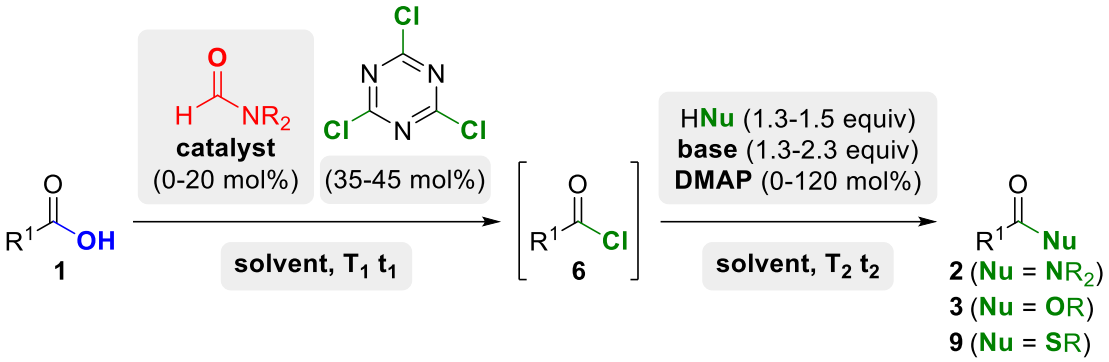
D. Precipitation CA: In order to isolate cyanuric acid, the filter cake from the filtration obtained during the work up procedure (see above) is left to dry in the air overnight and is then transferred to a one-necked 250/500 mL round bottom flask (with respect to 200/500 mmol of **1**). Next, the solid residue in the flask is pestled with a stir bar retriever and dried at the rotary evaporator for approximately 1 h at 5 mbar.[27] In several experiments ^{13}C-NMR of the solid residue (around 80% yield) confirmed cyanuric acid to be the major by-product.[28] Then, the crude cyanuric acid is dissolved under an exothermic reaction in a minimum amount of 2 N NaOH-solution in water (0.8 equiv referred to **1**), the resulting solution is cooled in an ice bath and under vigorous stirring (600 rpm) an excess of 37wt% HCl-solution (aq., 1.0 equiv) is added dropwise with the aid of a dropping funnel within 10-20 min. The solid precipitate is collected by filtration through a sintered funnel (porosity level 3) by suction, whereby the filtrate showed a pH of ca. 2. Subsequently, to the afore-used flask is successively added aqueous 1 N HCl-solution and two portions of acetone (each volume/n(**1**) 0.1 L/mol), each time the flask is cooled in the ice bath for approximately 1 min and the filter cake is triturated thoroughly with the aid of a spatula with the ice-cold HCl-solution/acetone. Finally, the filter cake is dried by suction for 10 min, transferred to a 250 mL flask and dried for 1 h at 5 mbar at the rotary evaporator,[27] which furnishes cyanuric acid as a fine-powdered colourless solid in a purity ≥98% according to ^{1}H- and ^{13}C-NMR.[28]

(26) The pressure was measured between the cooling trap and the vacuum pump and might hence be slightly lower than the pressure in the distillation apparatus.

(27) To avoid dusting, the pressure is gradually lowered from 50 to 5 mbar.

(28) The respective NMR-samples were prepared as follows: 30 mg of the residue were dissolved entirely in DMSO-d^6 (600 μL) under heating with a heat gun. Cooling down to room temperature did not result in precipitation of cyanuric acid.

5.3.3 General Procedure 3: Amidation and Esterification of Acids (yield determination via internal standard)



A 4 mL glass vial with a stir bar is charged successively with the acid **1** (1.0 equiv, 0.30-0.50 mmol), the **solvent** (e.g. dry MeCN, reagent-grade EtOAc, acetone or THF, 1-2 M) and the formamide **catalyst** (either DMF or FPyr, 0-40 mol%).[29] Next, TCT (35-45 mol%) is added in one portion.[15] In the following, the reaction vial is sealed with a screw cap, placed in an alumina carousel, which has been preheated to the reaction temperature $\mathbf{T_1}$ (rt to 80 °C), and stirred at the temperature $\mathbf{T_1}$ with a stirring speed of 400 rpm for the time period $\mathbf{t_1}$ (1-24 h). Subsequently, the reaction suspension is allowed to cool down to ambient temperature for approximately 10 min, diluted with further **solvent** ([**6**] = 0.5-1 mol/L), cooled to 0 °C and the nucleophile H**Nu** (1.3-1.5 equiv), the **base** (0-2.3 equiv, e.g. K_2CO_3, NMM or NEt_3)[30] and DMAP (0-120 mol%) are added under stirring (600 rpm). After 15 min the ice bath is removed and the mixture was allowed to stir in alumina carousel at the temperature $\mathbf{T_2}$ (typically room temperature, in some cases 40 °C) for the time period $\mathbf{t_2}$ (2-48 h).

Eventually, the reaction suspension is diluted with EtOAc (3 mL), taken up with a 20 mL syringe,[31] the reaction vial is rinsed with EtOAc/1 N NaOH solution in water (2 x 1.5/1.5 mL) and the phases are separated with the aid of the 20 mL syringe. The organic phase is washed with brine (1 x 3 mL), dried over $MgSO_4$, concentrated under reduced pressure and dried at 20 mbar for 5 min at the rotary evaporator. To the crude material is added an exactly weighed amount of a feasible internal NMR-standard (20-40 mg dibenzylether, 1,3,5-trimethoxybenzene, mesitylene or dodecane), the mixture is dissolved in $CDCl_3$ (500 µL) and

(29) Liquid starting materials and the formamide catalysts were added via Eppendorf pipette. Due to the high viscosity of for instance some starting materials **1** the amount of substance was additionally controlled by weighing (in the reaction vial).

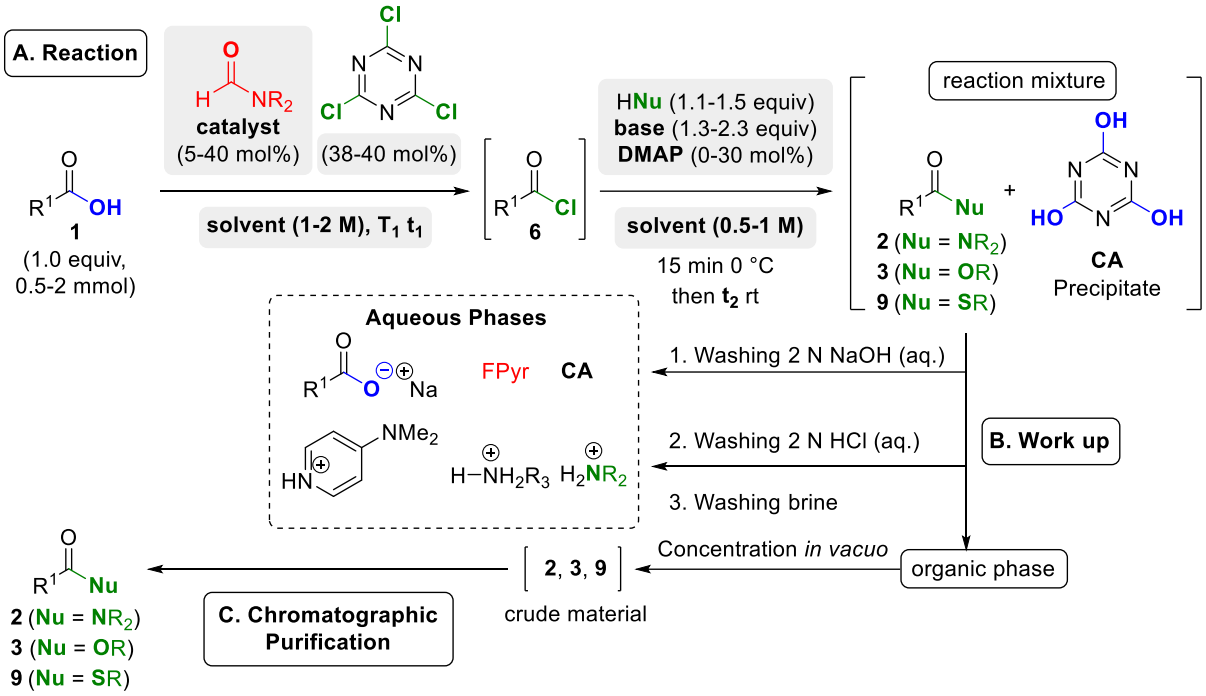
(30) Liquid bases were added drop-wise with the aid of a syringe. Freshly pestled, fine-powdered K_2CO_3 was used.

(31) Although the mixtures are heterogeneous, they can be collected with a syringe with a standard needle. To avoid hydrolysis of esters **3** and **9**, the crude reaction mixture was first diluted with EtOAc and then with aqueous NaOH-solution. In the case of amides **2**, the reaction mixture can be diluted with 2 N NaOH (aq.)/EtOAc (2/1 mL) to dissolve the solid precipitate.

50 µL of this solution are diluted with further $CDCl_3$ (500 µL) and subjected to ^{1}H-NMR spectroscopy. Since both, the starting carboxylic acid **1** and the acid chloride **6** (after hydrolysis) are removed during the aqueous work up, conversions cannot be determined. However, the conversion of the nucleophile can be calculated based on its remaining quantity (if not removed by 2 N HCl washing).

5.3.4 General Procedure 4: Amidation and Esterification of Acids (isolated yield)

5.3.4.1 0.5-2 mmol Scale



A. Reaction: A 4 mL vial with a stir bar is charged with the carboxylic acid **1** (0.5-2.0 mmol, 1.0 equiv), the formamide **catalyst** (FPyr or DMF, 5-40 mol%) and the **solvent** (dry MeCN, reagent-grade EtOAc or acetone, 2 M)[29] and TCT (38-40 mol%) is added in a single portion at ambient temperature. The reaction vial is closed with a screw cap and stirred (400 rpm) in an alumina carousel, which had been preheated to the temperature $\mathbf{T_1}$ (rt to 80 °C) for the time period $\mathbf{t_1}$ (1-24 h). The conversion of **1** to **6** can be monitored through ^{1}H-NMR spectroscopy after micro work as described in general procedure 2 (chapter 5.3.2, page 46).

The reaction vial vessel is removed from the carousel and allowed to cool down to ambient temperature for circa 10 min. Then, the reaction suspension is diluted with further **solvent** (0.5-

1 M)[32,33] in order to secure stir-ability and cooled in an ice bath. Under vigorous stirring (600 rpm) the nucleophile H**Nu** (1.1-1.5 equiv),[34] the **base** (NMM, NEt_3 or K_2CO_3, 1.3-2.3 equiv)[35,36,37] and optionally DMAP (0-30 mol%, added at once) are added successively. After 15 min the reaction cooling bath is removed and the reaction suspension is allowed to stir for the time period $\mathbf{t_2}$ (1-24 h) at room temperature. The reaction progress of **6** to **2**, **3** and **9**, respectively, can be also followed by ^{1}H-NMR after micro work as stated in general procedure 2 (chapter 5.3.2, page 46). Thereby, the ^{1}H-NMR after micro work up after the transformation **1→6** is taken as reference into account.

In cases where (1) the nucleophile is considered as more valuable than the acid **1** or (2) an excess nucleophile is difficult to separate from the desired product, we recommend to use the substrate **1** in excess. For example, 1.3 equiv of acid **1** can be transformed with 49-52 mol% TCT (= 1.47-1.56 equiv) into acid chlorides of type **6**, while 1.0 equiv nucleophile is employed as limiting reactant. In these instances, the yield is determined based on the amount of nucleophile engaged. If the nucleophile carries acid sensitive groups, it is added drop-wise as a solution containing the **base** to the reaction mixture with acid chloride **6** under cooling to 0 °C

B. Work up: The reaction suspension is diluted with EtOAc (2-3 mL) and taken up with a 20 mL syringe.[31] Subsequently, the reaction vial is rinsed with 2 N NaOH[38] solution (aq.)/EtOAc (2

(32) The minimum amount of solvent to maintain stir ability is influenced by the starting material **1**, the nucleophile, the base and the solvent type. While a 1 M concentration referred to **1** is a good guide value, utilization of K_2CO_3 as base instead of NMM or NEt_3 requests for higher solvent quantities. Reactions in EtOAc often afford higher solvent volumes than in MeCN and acetone, respectively.

(33) In the case of volatile acid chlorides derived from (trideutero)acetic acid and crotonic acid, for instance, the reaction vial was cooled in an ice bath **before** further solvent was added.

(34) While alcohols can be added even at ambient temperature in one portion, more reactive liquid amines are added drop-wise with the aid of a syringe.

(35) NMM and NEt_3 are added drop-wise by means of a syringe. Freshly pestled, fine powdered K_2CO_3 was added in one portion.

(36) The addition order of first nucleophile and as second base is extremely crucial, since especially enolizable acid chlorides tend to decompose in the presence of amine bases (see e.g. Table S11, page 22). In the case of hydrochloride salts of amines as nucleophiles 2.1-2.3 equiv of base are required.

(37) Even when just 1.3 equiv of K_2CO_3 were used, only a weak pressure evolution was observed.

(38) The basic work up allows to separate remaining carboxylic acid **1** as carboxylate salt. As observed in the synthesis (2,2-dimethyl-1,3-trioxolan-4-yl)methyl hexadecanoate, some sodium carboxylates are poorly soluble in water. In these cases, utilization of KOH solution is recommended, since the solubility of the analogous potassium carboxylates in water can be higher.

x 2/2 mL) and EtOAc (2 mL) and the phases are separated by means of the syringe.[39,40] Optionally, the organic phase can be washed by 2 N HCl solution (aq., 1 x 4 mL) to remove excess amine nucleophiles, NMM, NEt_3 and DMAP. Finally, washing with brine (1 x 4 mL), drying over $MgSO_4$, concentration under reduced pressure, and drying for 5 min at 20 mbar at the rotary evaporator provides the crude coupling products **2**, **3** and **9**, respectively.

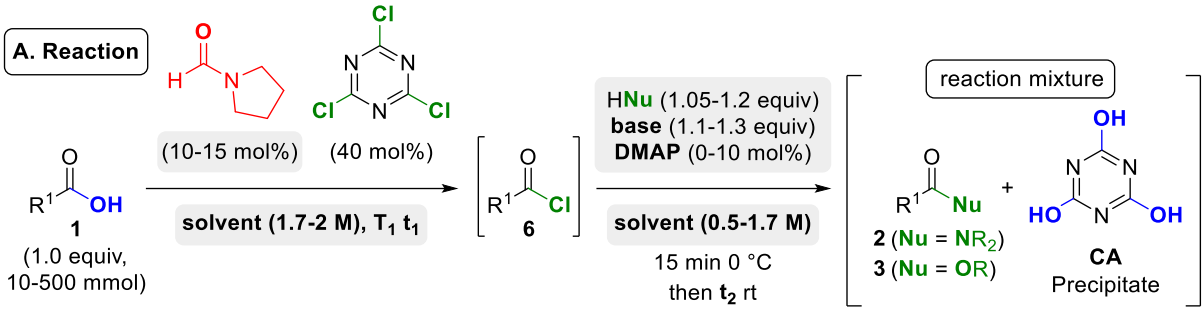
C. Chromatographic Purification: In order to load the crude material onto the silica gel column, it is dissolved in the eluent (ca. 0.5 mL). If the solubility in the eluent is too low, the crude product is dissolved in CH_2Cl_2 (5-10 mL), silica gel is added (ratio mass crude material/SiO_2 1:2-3), the solvent is evaporated *in vacuo* and the residue is dried at the rotary evaporator at 20 mbar for 5 min. The resulting fine powder is subjected to column chromatographic purification on silica gel (ratio mass crude product/SiO_2 1:50-100 depending on the separation difficulty) with EtOAc/*n*Hex mixtures (fraction size 5-10 mL). In the case of a poor solubility of the product in the applied EtOAc/*n*Hex-mixture, EtOAc/CH_2Cl_2-mixture is utilized as eluent instead. Low solubility is indicated by crystallization of the product in the collecting vials and at the outlet glass tube of the column and by a strong diffusion during chromatography, which results in the distribution of the reaction product over many fractions (albeit an R_f-value of 0.30-0.35 in the eluent). Finally, the product containing fractions are collected, concentrated under reduced pressure, dried for 5 min at 5 mbar, dissolved in CH_2Cl_2 (circa 2-20 mL), concentrated again and dried for 10-30 min at 5 mbar at the rotary evaporator remove all remaining solvent traces. Occasionally, the product has to be dried in high vacuum in order to get rid of residual solvents.

5.3.4.2 10-500 mmol Scale

The general procedure refers to experiments on a 100-500 mmol scale. For reactions using less than 100 mmol of starting material the volume of solvents and aqueous phases in the work up are typically increased to allow a more convenient handling. For examples see chapter 5.4.2.17 (page 125), 5.4.2.29 (page 165), 5.4.3.4 (page 191) and 5.4.3.5 (page 196).

(39) The aqueous work up is crucial to remove poorly soluble cyanuric acid (most likely as sodium dialcoholate) and simultaneously extracts hydrophilic FPyr and DMF into the aqueous phase. Aromatic alcohols such as 1-naphthol cannot be sufficiently removed by washing with diluted NaOH solution (even not through several washings).

(40) As already observed in our TCT mediated dehydroxychlorinations of alcohols,[20] aqueous NaOH solution causes hydrolysis of EtOAc. Therefore, on a larger scale in a work up involving EtOAc cyanuric acid does not dissolve completely due to the lower pH of aqueous phase. Hence, the precipitate has to be removed by filtration after dilution with HCl-solution in water (*vide infra*). Aqueous $NaHCO_3$- and K_2CO_3-solutions on the other hand, are not suitable to dissolve cyanuric acid completely.



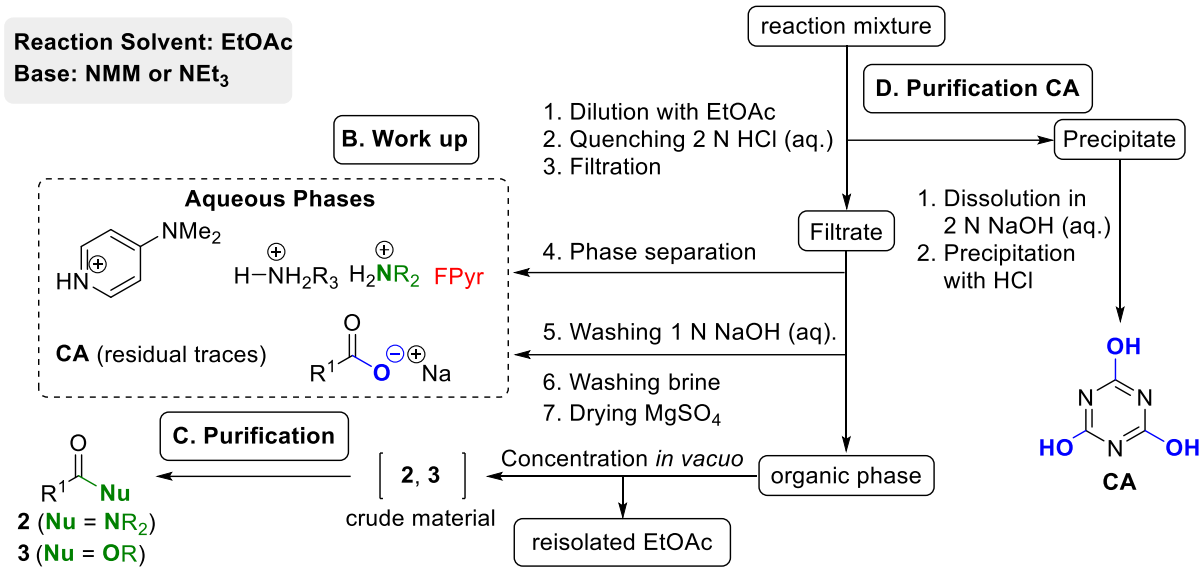
A. Reaction: The deviations from the operating procedure on a smaller scale are as follows. The reaction is conducted in an appropriately sized one necked flask with a strong stir bar. On a 500 mmol scale the use of an overheads stirrer is recommended. The reaction flask is placed in an oil bath and TCT is added at ambient temperature in a single portion, which is typically accompanied by an immediate decline of the internal temperature by a few degrees. Thereupon, the reaction mixture is heated to the desired reaction temperature $\mathbf{T_1}$ and stirred for the reaction time $\mathbf{t_1}$ with a stirring speed of 400 rpm. In the case of a reaction temperature $\mathbf{T_1}$ of 80 °C, typically the reaction mixture is stirred for 1 h at 40 °C before heating to 80 °C.[41] The reaction progress can be monitored by micro-work up and ^{1}H-NMR.[42] Then, the oil bath is removed, the reaction suspension is allowed to stir for approximately 10 min, is diluted with further solvent (EtOAc or MeCN, 0.5-1 M) and cooled in an ice bath. At an elevated stirring speed of 600-800 rpm initially the **nucleophile** followed by the **base** and **DMAP** (optionally) are added. While fine-powdered K_2CO_3 is added in one portion, liquid bases such as NMM and NEt_3 are added drop wise by means of a dropping funnel or syringe pump.[43] The consumption of the acid chloride **6** can be followed by micro-work up and ^{1}H-NMR.[42]

Protocol Applying EtOAc as Reaction Solvent and an Amine Bases

(41) Due to the high concentrations of the reactants, no reflux occurred at 80 °C using EtOAc. In the case of MeCN only a weak reflux was observed.

(42) For micro work up stirring was interrupted and ca. 20 μL of the reaction mixture were transferred to a 10 mL one necked flask with the aid of an Eppendorf pipette. After drying at 100 mbar for 5 min at the rotary evaporator the residue was diluted with $CDCl_3$ (ca. 600 μL) and filtered through a pipette with a plug of wool and a ca. 5 mm layer of $MgSO_4$ directly into a NMR-tube. If the carboxylic acid **1** is poorly soluble in the reaction solvent or in $CDCl_3$, the determination of the consumption could be falsified. Since the transformation of **6** into **2** and **3**, respectively, is performed in a higher dilution, a 40 μL aliquot is separated.

(43) Like in the case of the synthesis of DEET (*N,N*-diethyl 3-methylbenzamide), a mixture of the base and nucleophile and base (e.g. diethylamine and NMM) is added, because a sequential addition effected a poorer stir-ability.



B. Work up:[40,44] When an amine base (NMM or NEt_3) had been used, aqueous 2 N HCl solution (V(HCl)/n(**1**) = 0.4 L/mol) is added in a single portion to the reaction mixture (n(**1**)/V(EtOAc) = 0.5-1.7 M) at ambient temperature and stirring is continued for 5 min to dissolve ammonium salts completely. Next, the mixture is filtered through a sintered funnel (porosity level 3) by suction and the filtrated is poured into an extraction funnel.[45] In the following the reaction flask is rinsed and subsequently the filter cake is thoroughly triturated with a spatula with EtOAc (V(aq. HCl)/n(**1**) = 0.1 L/mol, 2 portions) and the combined filtrates are transferred to the extraction funnel. The filter cake can be further processed as described in part **D** below to facilitate isolation of cyanuric acid. The phases are separated, the organic phase is washed with 1 N NaOH-solution (aq., V(aq. NaOH)/n(**1**) = 0.4 L/mol) and brine (V(brine)/n(**1**) = 0.4 L/mol) dried over $MgSO_4$ under stirring for 5 min, concentrated under reduced pressure and dried at 20 mbar for 10-20 min at the rotary evaporator. The solvent evaporation allows to reisolate EtOAc. Despite a purity of ≥98% according to ^{1}H-NMR, reuse as reaction solvent resulted in strongly depleted yields.

(44) The following work up protocol for a 20 mmol scale experiment reproducibly resulted in the precipitation of cyanuric acid: The reaction suspension (30 mL EtOAc) was transferred to 100 mL extraction funnel and the reaction flask was rinsed with further EtOAc (2 x 15 mL). 2 N NaOH solution (aq., 30 mL) were added to the reaction flask, stirred in an ice bath for a couple of minutes and poured into the extraction funnel. Upon shaking all solid components dissolved. During phase separation, which required 20 min, a solid precipitated formed again. The phases were separated, whereby little precipitate remained in the organic phase. Subsequently, the EtOAc phase was washed successively with 2 N HCl (aq., 1 x 30 mL, duration phase separation 5 min) and brine (1 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Neither the utilization of more EtOAc (+30 mL) nor the addition of brine (10 mL) enhanced the initial phase separation after addition of NaOH solution.

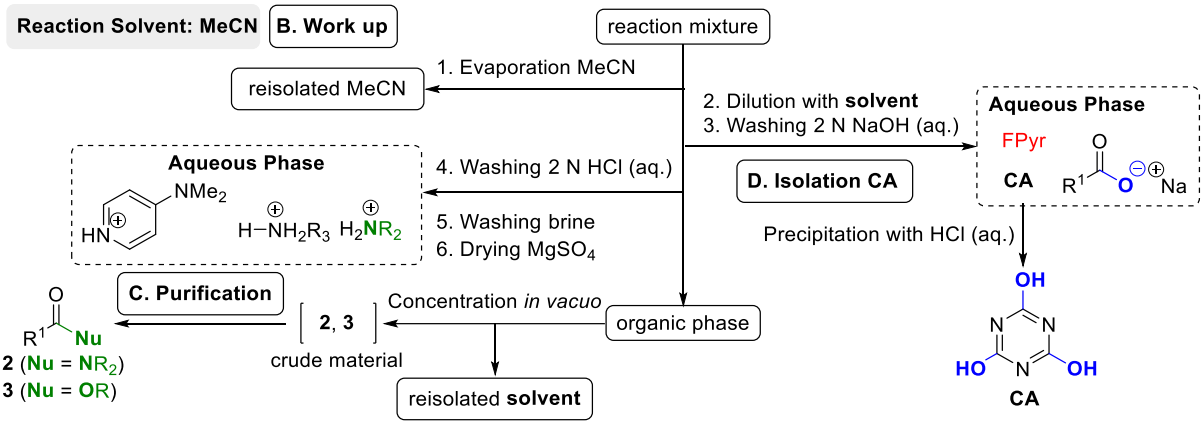
(45) Direct filtration of the reaction mixture and subsequent washing with 2 N HCl solution in water resulted in lower yields of amide and ester products **2** and **3**, respectively. Thus it is important to dissolve ammonium salts of the base utilized to avoid adsorption of product onto the precipitate.

C. Purification: Purification was either conducted by means of chromatography or distillation under reduced pressure. In the case of distillation, a micro distillation apparatus with a NS 29 cooling finger without a distillation dispenser is used. Thereby, the pressure[(46)] is applied by a high vacuum pump. By means of a needle valve as an artificial leak the pressure is adjusted to effect a boiling point ≤100 °C. In order to exchange the collecting flask, heating is interrupted and the apparatus was ventilated. To avoid boiling retardation, at the outset, the pressure is gradually lowered from 50 mbar to the desired pressure by means of the needle valve. Boiling retardation is also diminished by using a relatively large flask for the crude material (250-500 mL) and a high stirring speed of 800 rpm. In order to maintain a constant distillation process, the oil bath temperature has to be gradually raised, when the head temperature declines. For solid products recrystallization is be recommended.

D. Purification of Cyanuric Acid: See step **D** in general procedure 2 in chapter 5.3.2 on page 46.

Protocol Applying MeCN as Reaction Solvent

Under mechanical stirring a low conversion of an acid chloride intermediate of type **6** was observed, when K_2CO_3 was used as base on 500 mmol scale reaction. Thus magnetically stirring might be required to grind solid K_2CO_3 to facilitate full consumption of **6**.



B. Work up: In order to improve phase separation, MeCN is evaporated *in vacuo*, whereby the pressure is gradually lowered from 180→120 mbar. ^{1}H-NMR of the reisolated MeCN verified a purity of ≥98% and reuse as reaction solvent showed no alteration in product yield. Next, the residue is diluted with an appropriate organic **solvent** depending on the solubility of the product (V(solvent)/n(**1**) = 1 mol/L, MTBE, Et_2O or CH_2Cl_2), aqueous 2 N NaOH solution is added (V(aq. NaOH)/n(**1**) = 1 L/mol) and the heterogeneous mixture is poured into a extraction funnel. The reaction flask is rinsed with further **solvent** and 2 N NaOH solution (2 portions V/n(**1**) = 0.1 mol/L each). The total amount of 2 N NaOH solution (V(aq. NaOH)/n(**1**) =

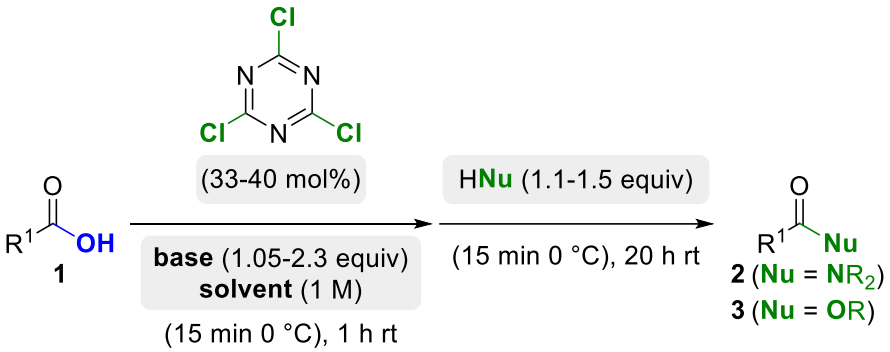
(46) The pressure was measured between the cooling trap and the vacuum pump and might hence be slightly lower than the pressure in the distillation apparatus.

1.2 L/mol → 2.4 equiv NaOH) is typically sufficient to dissolve the solid precipitate entirely. In the instance of incomplete dissolution, further NaOH solution is applied. Next, the phases are separated, whereby phase separation can be improved through addition of water. The organic phase is washed with aqueous 2 N HCl solution (V(aq. HCl)/n(**1**) = 0.7 L/mol), when an amine base has been used, and brine (aq. HCl/n(**1**) = 0.5 L/mol), dried over $MgSO_4$, concentrated and dried at the rotary evaporator at 20 mbar for 10-20 min. For the purpose to isolate cyanuric acid, the basic aqueous phase can be treated further as illustrated in step **D** below.

C. Purification: Purification was either conducted by means of chromatography or distillation under reduced pressure. Distillations were executed as described above. For solid products recrystallization is recommended.

D. Isolation of Cyanuric Acid: The aqueous basic NaOH-phase (2.4 equiv referred to **1**) is transferred to a one necked round bottom flask with a strong stir bar, cooled in an ice bath and acidified to a pH ≤2 through the drop-wise addition of a 37 wt% solution of HCl in water (12.3 N, 4 equiv when K_2CO_3 has been employed as base) by means of a dropping funnel under vigorous stirring (800 rpm). The thereby formed precipitate is collected by filtration through a sintered funnel (porosity level 3) by suction. Subsequently, to the above-used flask is successively added H_2O and two portions of acetone (each volume/n(**1**) 0.2 L/mol), the flask is cooled each time in the ice bath for approximately 1 min and the filter cake is triturated thoroughly with the aid of a spatula with the ice-cold water and acetone, respectively. Finally, the filter cake is dried by suction for 10 min, transferred to a 250 mL flask and dried for 1 h at 5 mbar at the rotary evaporator,[27] which furnishes cyanuric acid as a fine-powdered colourless solid in a purity ≥98% according to ^{1}H- and ^{13}C-NMR.[28]

5.3.5 General Procedure 5: Amidation and Esterification of Acids in Alignment to *Rayle*[22]



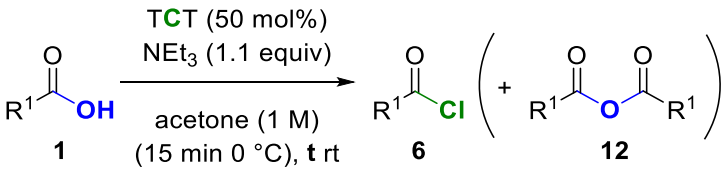
In alignment to the original protocol of *Rayle*[22] a 4 mL vial with a stir bar is charged with the acid **1** (0.50 mmol, 1.0 equiv), the **solvent** (dry MeCN, reagent grade EtOAc or $CHCl_3$, 1 M) and TCT (33-40 mol%). The resulting mixture is cooled in an ice bath, the **base** (NMM or

K_2CO_3, 1.05-2.3 equiv)[30] is added,[47] and the reaction suspension is stirred at a speed of 400 rpm for 15 min at 0 °C and 1 h at room temperature. Then, the mixture is again cooled to 0 °C, the nucleophile H**Nu** (e.g. pyrrolidine, 2-naphthol or 8-amino quinoline, 1.3-1.5 equiv) is introduced (drop-wise in the case of liquid reactants) and the reaction mixture is allowed to stir for 15 min at 0 °C and overnight (20 h) at room ambient temperature. In some experiments the reaction suspension was not cooled in an ice bath during the addition of the base and the nucleophile. The work up was performed as described in general procedure 3 in chapter 5.3.3 on page 49.

Deviations from General Procedure

Table S23 on page 38: The respective experiments were conducted in $CDCl_3$. After stirring for 1 h at ambient temperature, an exactly weighed amount of 1,3,5-trimethoxybenzene was added to the reaction suspension. A 50 µL aliquot was filtered through a disposable glass pipette with wool and a ca. 5 mm layer of $MgSO_4$ into an NMR-tube.

5.3.6 General Procedure 6: Chlorination of Acids According to *Venkataraman*[23]



According to *Venkataraman*[23] a 4 mL glass vial with a stir bar is charged with the acid **1** (0.50 mmol, 1.0 equiv), reagent-grade acetone (500 µL, 1 M) and TCT (47 mg, 0.25 mmol, 50 mol%). Next, NEt_3 (75 µL, 0.55 mmol, 1.1 equiv) is added dropwise and the resulting suspension is stirred for the time period **t** (6-8 h). In some cases, the reaction mixture was cooled in an ice bath prior to NEt_3 addition and 15 min the ice bath is removed. The work up was conducted as described in general procedure 1 (chapter 3.1.1, page 44).

(47) When K_2CO_3 was used as base, the reaction mixture had to be diluted occasionally with further **solvent** (0.5 M) to maintain stir-ability.

5.4 Experimental Procedures and Analytical Data

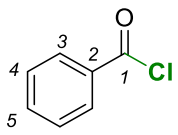
5.4.1 Synthesis of Acid Chlorides 6 (Scheme 2)

5.4.1.1 Synthesis of Benzoyl Chloride (6_2)

entry	conditions	yield 6_2 [%]	yield CA[a] [%]
1	TCT (40 mol%), FPyr (10 mol%), MeCN (4 M), 1 h 40 °C, then 3 h 80 °C	90[a] (**63 g**)	59[a]
2	TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 80 °C	85[b]	n.d.
3	TCT (40 mol%), FPyr (10 mol%), **reused** MeCN (2 M), 4 h 80 °C	85[b]	n.d.
5	TCT (40 mol%), **no FPyr**, MeCN (2 M), 4 h 80 °C	7[b]	n.d.
6	TCT (40 mol%), **no FPyr**, **EtOAc** (2 M), 4 h 80 °C	8[b]	n.d.

a. Yield determined from mass of isolated material after distillation and precipitation, respectively. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of mesitylene as internal standard. CA = cyanuric acid.

Benzoyl chloride was synthesized on a 500 mmol scale in 90% yield utilizing standard laboratory equipment ≤0.5 L (entry 1). Alongside cyanuric acid could be obtained in 59% yield, while MeCN was reisolated in 80% yield. Importantly, the reisolated MeCN could be reused (entries 2 + 3). In the absence of FPyr, BzCl only formed in negligible trace amounts (entries 4 + 5). The optimization of the preparation of benzoyl chloride can be found in chapter 3.1.3 on page 14.



6_2

Entry 1, PH3651: According to general procedure 2 (chapter 5.3.2, page 46) a suspension of benzoic acid (**1_2**, 61.05 g, 500 mmol, 1.0 equiv) and FPyr (5.1 mL, 4.91 g, 50 mmol, 10 mol%) in MeCN (125 mL, 4 M) was treated with TCT (37.63 g, 200 mmol, 40 mol%). After 1 h of stirring at 40 C, reaction control through micro work up verified 77% conversion and 10 mol% remaining FPyr with respect to **6_2** and **1_2**. A maximum internal temperature of 40 °C was achieved after 50 min of duration at 40 °C oil bath temperature The reaction suspension was further stirred for 3 h at 80 °C, whereupon reaction monitoring showed full consumption of **1_2** and FPyr.

After cooling to 0 °C the pale yellow reaction suspension was treated with MeCN (50 mL) and subjected to filtration as stated in the underlying general procedure. In order to rinse the reaction flask and triturate the filter cake with a spatula, further MeCN was used (2 x 50 mL). After removal of the solvent, crude **6_2** was obtained as a yellow, thin liquid containing a sticky, oily precipitated (86.11 g, 122%). Besides, MeCN was reisolated in a yield of 80% (220 mL).

Distillation at 2.2 mbar and a stirring speed of 400 rpm afforded the title compound as a colourless liquid (63.26 g, 450 mmol) in 90% yield with a boiling point of 61-62 °C. Thereby, the oil bath temperature was gradually increased from 80 to 150 °C to enable a constant

distillation process. When the distillation ceased at an oil bath temperature of 150 °C, the micro distillation apparatus was carefully heated with a heat gun.

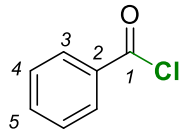
After drying of the filter cake, a colourless solid was obtained in 84% yield referred to the amount of TCT engaged (21.58 g), of which ^{13}C-NMR confirmed cyanuric acid to be the main component (see below). The solid residue was dissolved in 2 N NaOH solution (200 mL, 0.8 equiv with respect to acid **1$_2$**) and crude cyanuric was precipitated though the addition of 37 wt% HCl solution in water (40 mL, 490 mmol, 1.0 equiv). After washing (1 x 50 mL aq. 1 N HCl, 3 x 50 mL acetone) and drying, trihydroxytriazine was isolated as a colourless, fine-powdered solid in a yield of 59% (15.32 g, 119 mmol). The calculation of the E-factor of this experiment is described below.

Entry 2, PH3666: As given in general procedure 1 (chapter 5.3.1, page 44) benzoyl chloride was produced from benzoic acid (61 mg, 0.50 mmol, 1.0 equiv), FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%) and TCT (36 mg, 190 μmol, 38 mol%) in dry **MeCN** (250 μmol, 2 M) under heating to 80 °C for 4 h. ^{1}H-NMR with mesitylene (24.1 mg) revealed full conversion of **1$_2$** and the title compound in 85% yield.

Entry 3, PH3687: BzOH (0.50 mmol, 1.0 equiv) was allowed to react with TCT (38 mol%) in the presence of FPyr (10 mol%) in **MeCN** (2 M), which had been **reisolated** from the preparation of the title compound described in entry 1 (PH3651), as given in general procedure 1 (chapter 5.3.1, page 44). Finally, ^{1}H-NMR verified the title compound in 85% yield by means of mesitylene as internal standard (23.7 mg, conversion of **1** ≥98%)

Entry 4, PH3668: As stated in general procedure 1 (chapter 5.3.1, page 44) the title compound was synthesized from **1$_2$** (0.50 mmol, 1.0 equiv), TCT (38 mol%) and FPyr (10 mol%) in reagent grade **EtOAc** (250 μL, 2 M) under stirring at 80 °C for 4 h. ^{1}H-NMR with mesitylene as internal standard (25.9 mg) uncovered BzCl in 89% at a conversion of ≥98%.

Entry 5, PH3669: In the absence of FPyr, benzoic acid (0.50 mmol, 1.0 equiv) was reacted with TCT (38 mol%) in EtOAc for 4 h at 80 °C as delineated in general procedure 1 (chapter 5.3.1, page 44). Finally, ^{1}H-NMR uncovered the title compound (or benzoic anhydride) in 8% yield beside unconverted starting material in 91% yield (8% conversion), as determined with the aid of mesitylene (26.6 mg) as internal standard.

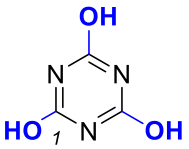


Benzoyl Chloride

M (C_7H_5OCl) = 140.610 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.13-8.11 (m, 2H, 3-H), 7.71-7.66 (m, 1H, 5-H), 7.54-7.50 (m, 2H, 4-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 168.39 (C-1), 135.30 (C-5), 133.22 (C-2), 131.39 (C-3), 128.94 (C-4).

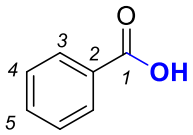
The NMR-data matched data from a commercial sample and from literature.[26]

Cyanuric Acid (CA)



M ($C_3H_3N_3O_3$) = 129.075 g/mol; **^{1}H-NMR** (400 MHz, DMSO-d^6) δ [ppm] = 11.15 (br. s, 3H, HO); **^{13}C-NMR** (100 MHz, DMSO-d^6) δ [ppm] = 150.0 (C-1). The NMR data is in agreement with the literature.[20]

Benzoic Acid (commercial sample)



M ($C_7H_5O_2H$) = 122.123 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 12.60 (br. s, CO_2H), 8.14-8.13 (m, 2H, 3-H), 7.63-7.59 (m, 1H, 5-H), 7.49-7.46 (m, 2H, 4-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 172.57 (C-1), 133.81 (C-5), 130.20 (C-2), 129.30 (C-3 or C-4), 128.46 (C-3 or C-4).

Determination of E-Factor in the Case of Entry 1

Calculation of E-factor considering chemicals used for the reaction solely:

$$E-factor = \frac{m(\mathbf{1}) + m(FPyr) + m(MeCN) + m(TCT) - m(\mathbf{2}) - m(\boldsymbol{CA})}{m(\mathbf{2}) + m(\boldsymbol{CA})}$$

$$= \frac{61.1\ g + 5.1\ g + 98\ g + 37.6\ g - 63.3\ g - 15.3\ g}{63.3\ g + 15.3\ g} = \frac{123{,}2\ g}{78.6\ g} = \mathbf{1.6}$$

Determination of E-Factor accounting all chemicals used with respect to isolated benzoic acid, cyanuric acid and reisolated solvent:

$$E-factor$$

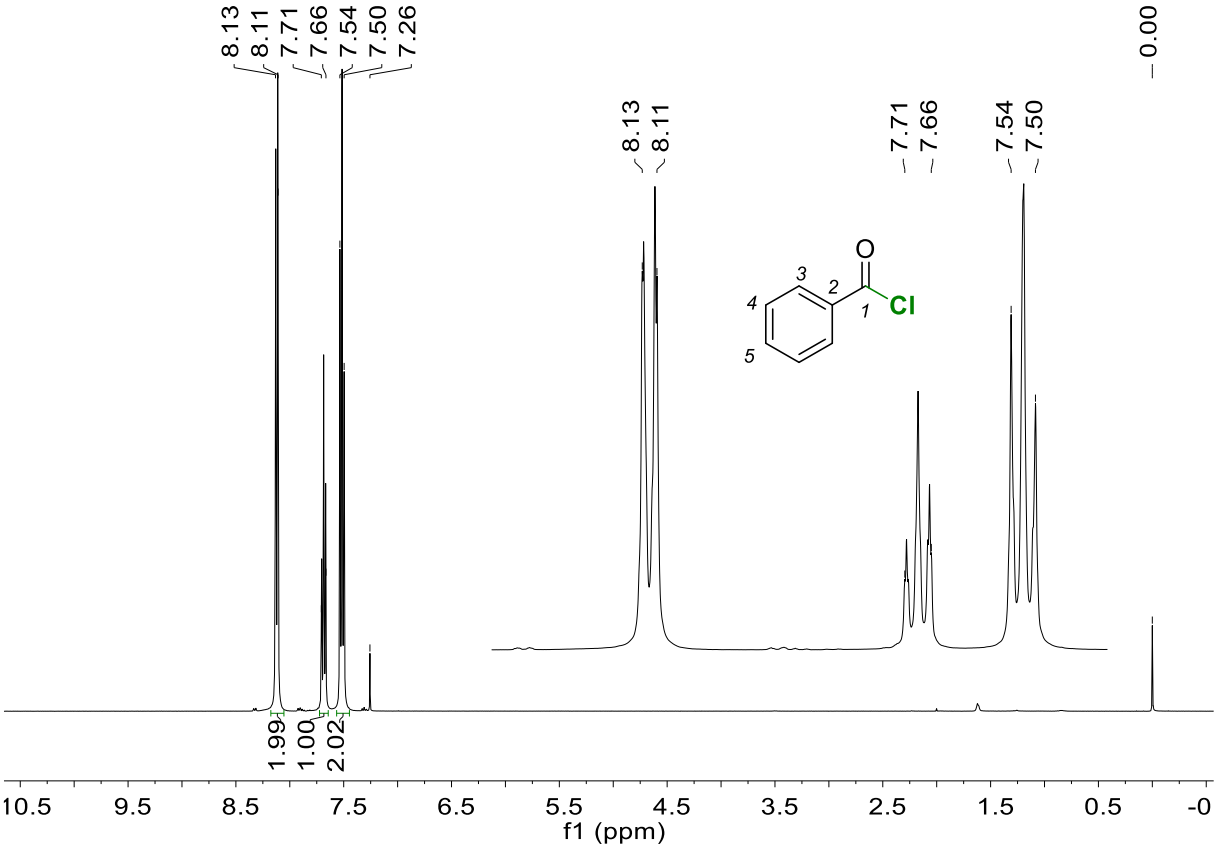
$$= \frac{m(\mathbf{1}) + m(FPyr) + m(MeCN) + m(TCT) - m(\mathbf{2}) - m(\boldsymbol{CA})}{m(\mathbf{2}) + m(\boldsymbol{CA})}$$

$$+ \frac{m(MeCN, work\ up) + m(HCl) + m(NaOH) + m(acetone) - m(MeCN, reisolated)}{m(\mathbf{2}) + m(\boldsymbol{CA})}$$

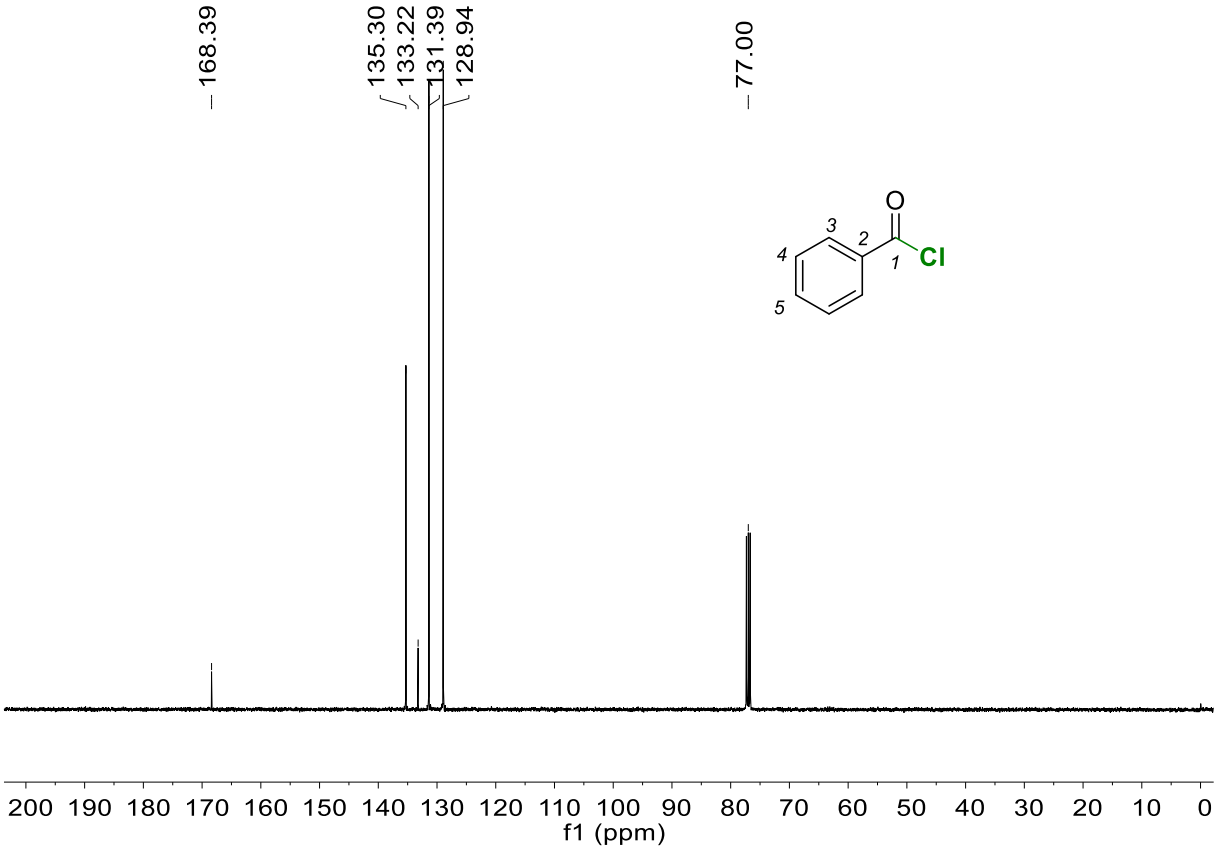
$$= 1.6 + \frac{118\ g + (14.8\ g + 1.8) + 16.0\ g + 119\ g - 173\ g}{63.3\ g + 15.3\ g} = 1.6 + \frac{96.6}{78.6\ g} = 2.8$$

component	M [g/mol]	density [g/mL]	V [mL]	m (g)
1	122.1	/	/	61.05
FPyr	99.1	1.04	4.9	5.1
MeCN (reaction)	41.1	0.786	125	98
TCT	184.41	/	/	37.63 g
MeCN (work up)	41.1	0.786	150	118
MeCN (reisolated)	41.1	0.786	220	173
2 M NaOH (aq.)	40.0	/	200	16.0
HCl (37 wt%, aq.)	36.46	1.2	40	14.8
1 N HCl (aq.)	36.46	/	50	1.8
acetone	58.08	0.791	150	119

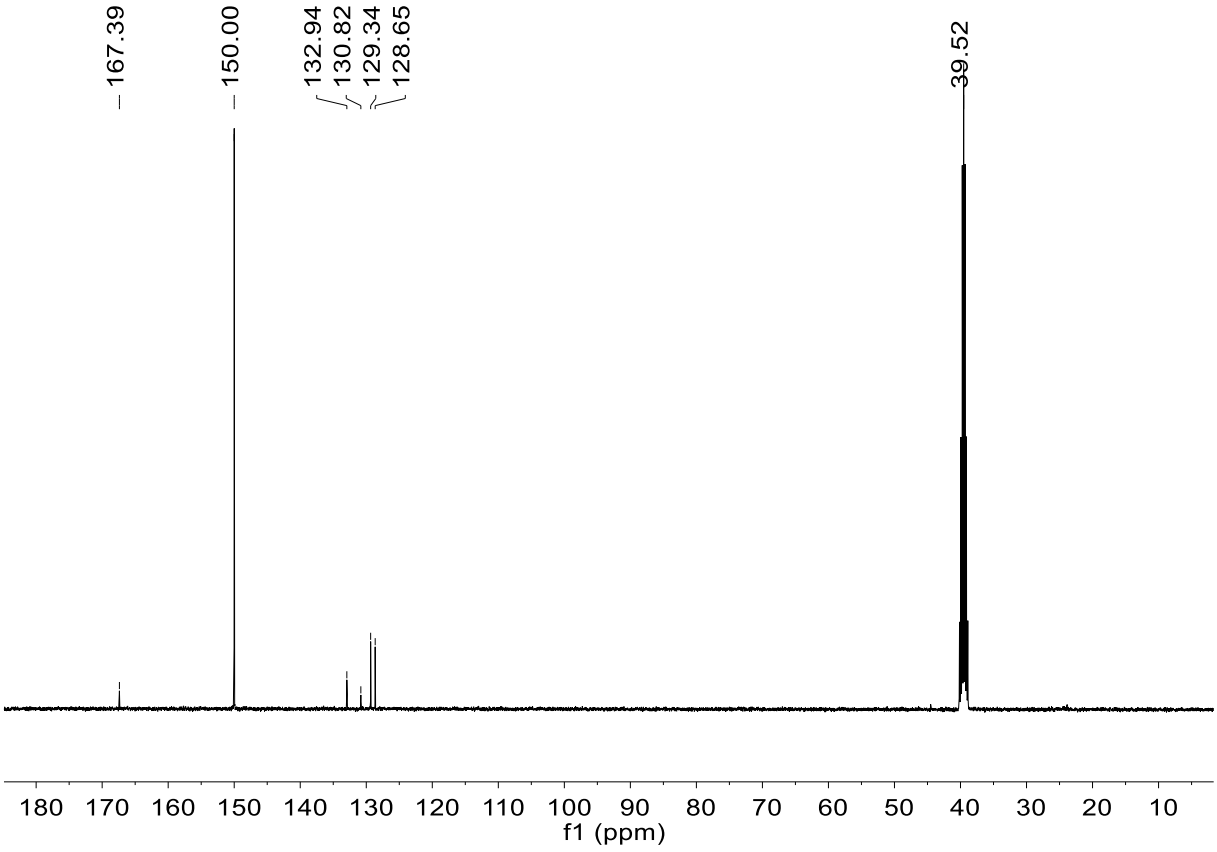
6_2	140.6	/	/	63.26
CA	129.1	/	/	15.32



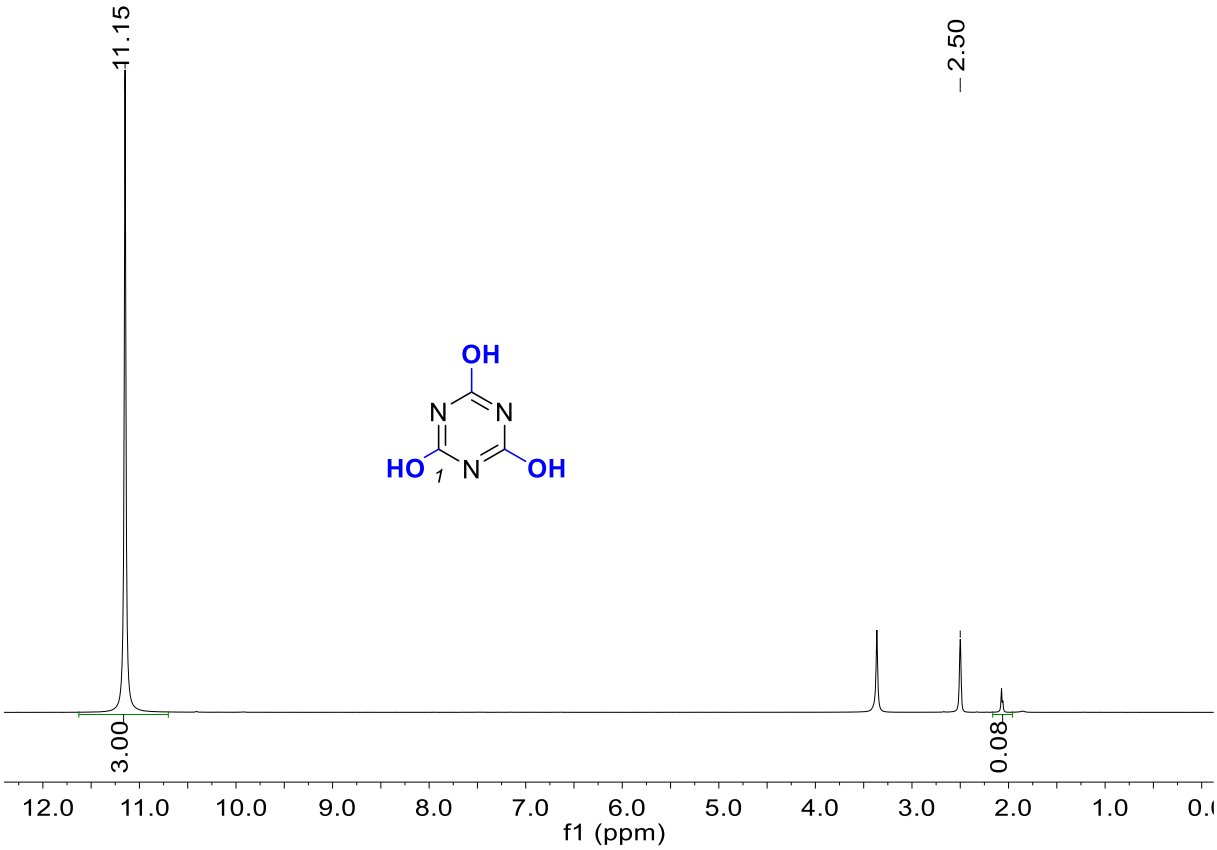
^{1}H-NMR spectrum of benzoyl chloride (400 MHz, $CDCl_3$).



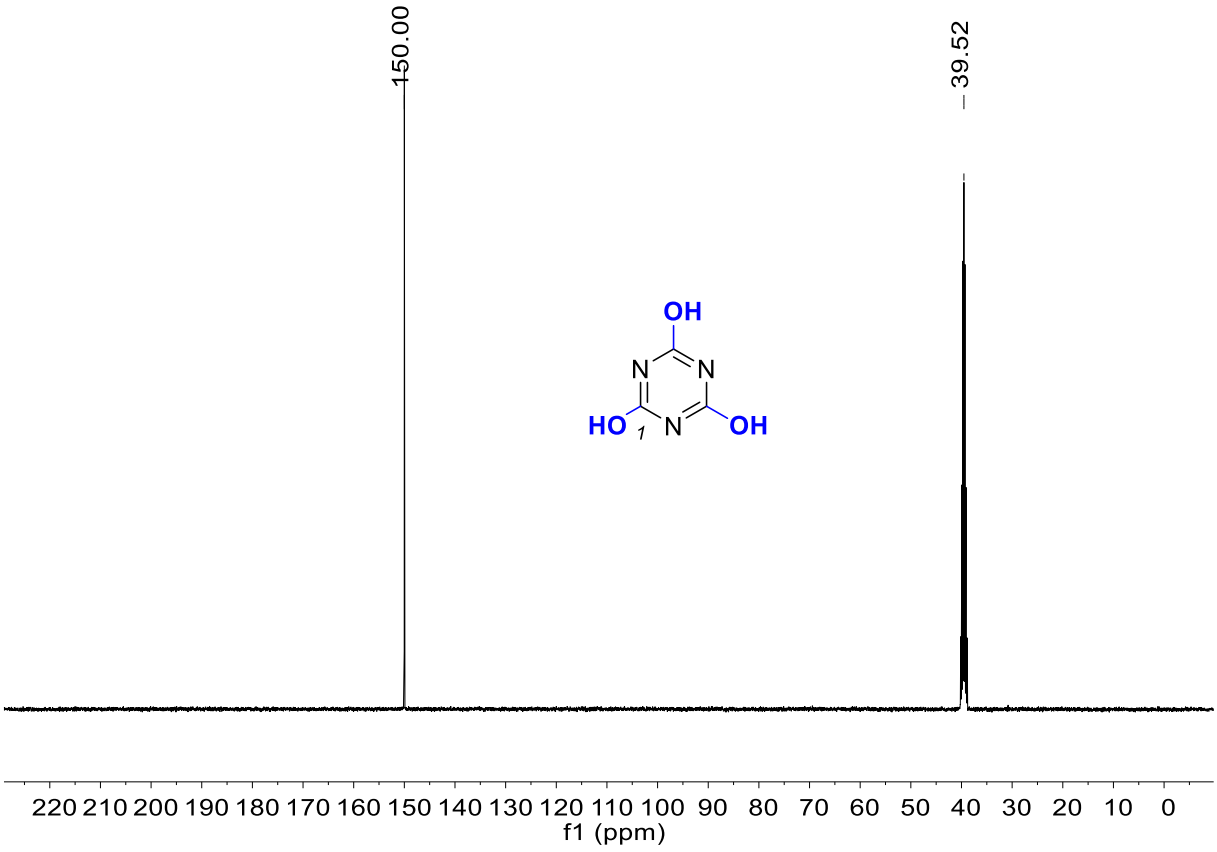
^{13}C-NMR spectrum of benzoyl chloride (100 MHz, $CDCl_3$).



^{13}C-NMR spectrum of the crude cyanuric acid obtained after drying of the filter cake (100 MHz, DMSO-d^6).



^{1}H-NMR spectrum of the precipitated cyanuric acid (400 MHz, DMSO-d^{6}).



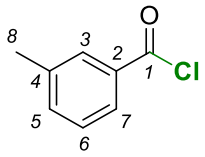
^{13}C-NMR spectrum of the precipitated cyanuric acid (100 MHz, DMSO-d^{6}).

5.4.1.2 Synthesis of 3-Methylbenzoyl chloride (6_3)

entry	conditions	yield 6_3 [%]	CA[a] [%]
1	TCT (40 mol%), FPyr (10 mol%), MeCN (4 M), 1 h 40 °C, then 2.5 h 80 °C	88[a] (**27.1 g**)	48
2	TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 80 °C	98[n]	n.d.
3	TCT (40 mol%), FPyr (10 mol%), **reused** MeCN (2 M), 4 h 80 °C	93[b]	n.d.
4	TCT (38 mol%), **no FPyr**, MeCN (2 M), 4 h 80 °C	<2[b]	n.d.

a. Yield determined from mass of isolated material after distillation and precipitation, respectively. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of dibenzylether as internal standard. CA = cyanuric acid.

The title compound was produced on a 200 mmol scale in 88% yield, whereby cyanuric acid was obtained in 48% yield (entry 1). As demonstrated through entries 2+3, MeCN reisolated from the afore-mentioned experiment in 79% yield, gave rise to the 3-methylbenzoyl chloride in virtually identical yield as in dry MeCN. Finally, the crucial role of FPyr was proven by an experiment without, in which the title compound could not be detected (entry 4).



6_3

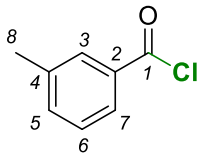
Entry 1, PH3615: In alignment to general procedure 2 (chapter 5.3.2, page 46) 3-methylbenzoic acid (27.32 g, 200 mmol, 1.0 equiv) was allowed to react with TCT (15.05 g, 80.0 mmol, 40 mol%) in the presence of FPyr (1.97 mL, 2.04 g, 20.0 mmol, 10 mol%) in MeCN (50 mL, 4 M) for 1 h at 40 °C and for 2.5 h at 80 °C. Reaction control by means of ^{1}H-NMR after micro work up revealed 69% conversion and 10 mol% FPyr in regard to **1_3** and **6_3** after stirring at 40 °C for 1 h and full consumption of **1_3** after heating to 80 °C, whereby no FPyr could be detected. After cooling down to ambient temperature the reaction mixture was diluted with MeCN (50 mL), filtered and the filter cake was triturated with further MeCN (2 x 20 mL). Evaporation of the solvent afforded the crude title compound as a yellow liquid (37.02 g, 120 %) and MeCN (110 mL, 79%), which could be successfully reused on a smaller scale reaction.

Eventually, distillation at 1.1 mbar furnished the acid chloride with a boiling point of 72-74 °C as a colourless liquid (27.12 g, 175.4 mmol, 88%). After the distillation had ceased, heating of the micro distillation apparatus with a heat gun delivered a second fraction of the title compound as a colourless oil in approximately 90% purity as judged by ^{1}H-NMR (913 mg). During distillation the oil bath temperature was stepwise raised from 90 to 150 °C to secure a constant distillation process. The filter cake from the work up protocol was dried at the rotary evaporator to yield a colourless solid (8.33 g, 81%), which was dissolved in 2 N NaOH solution in water (90 mL, 180 mmol, 0.90 equiv). Finally, precipitation utilizing 37 wt% aqueous HCl (17 mL, 209 mmol, 1.05 equiv) and washing with water (1 x 20 mL) and acetone (2 x 20 mL) delivered cyanuric acid as a colourless solid in 48% yield (4.97 g, 38.4 mmol).

Entry 2, PH3511: As described in general procedure 1 (chapter 5.3.1, page 44) carboxylic acid **1_3** (68 mg, 0.50 mmol, 1.0 equiv) was converted with TCT (36 mg, 190 μmol, 38 mol%) in the presence of FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%) in MeCN (dry, 250 μL, 2 M) under heating to 80 °C for 4 h into 3-methylbenzoyl chloride in 98% yield as determined via ^{1}H-NMR with dibenzylether (27.8 mg) as internal standard (≥98% conversion).

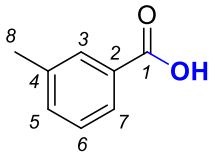
Entry 3, PH3688: According to general procedure 1 (chapter 5.3.1, page 44) the transformation of 3-methylbenzoic acid (0.50 mmol, 1.0 equiv) into the corresponding acid chloride was conducted in **MeCN reisolated from the in entry 1 delineated 200 mmol scale experiment** (2 M) with TCT (38 mg, 200 μmol, 40 mol%) and FPyr (10 mol%). After 4 h of heating to 80 °C, ^{1}H-NMR with dibenzylether as standard (29.9 mg) verified title compound in 93% yield, whereas no starting material was visible (≥98% conversion).

Entry 4, PH3512: Following general procedure 1 (chapter 5.3.1, page 44) aromatic acid **1_3** was treated with TCT (38 mol%) **in the absence of FPyr** in MeCN (dry, 2 M) and stirred for 4 h at 80 °C. ^{1}H-NMR uncovered unconverted starting material in 95% yield as judged by dibenzylether as internal standard (30.7 mg) and showed no trace of the title compound (≤2% conv.).



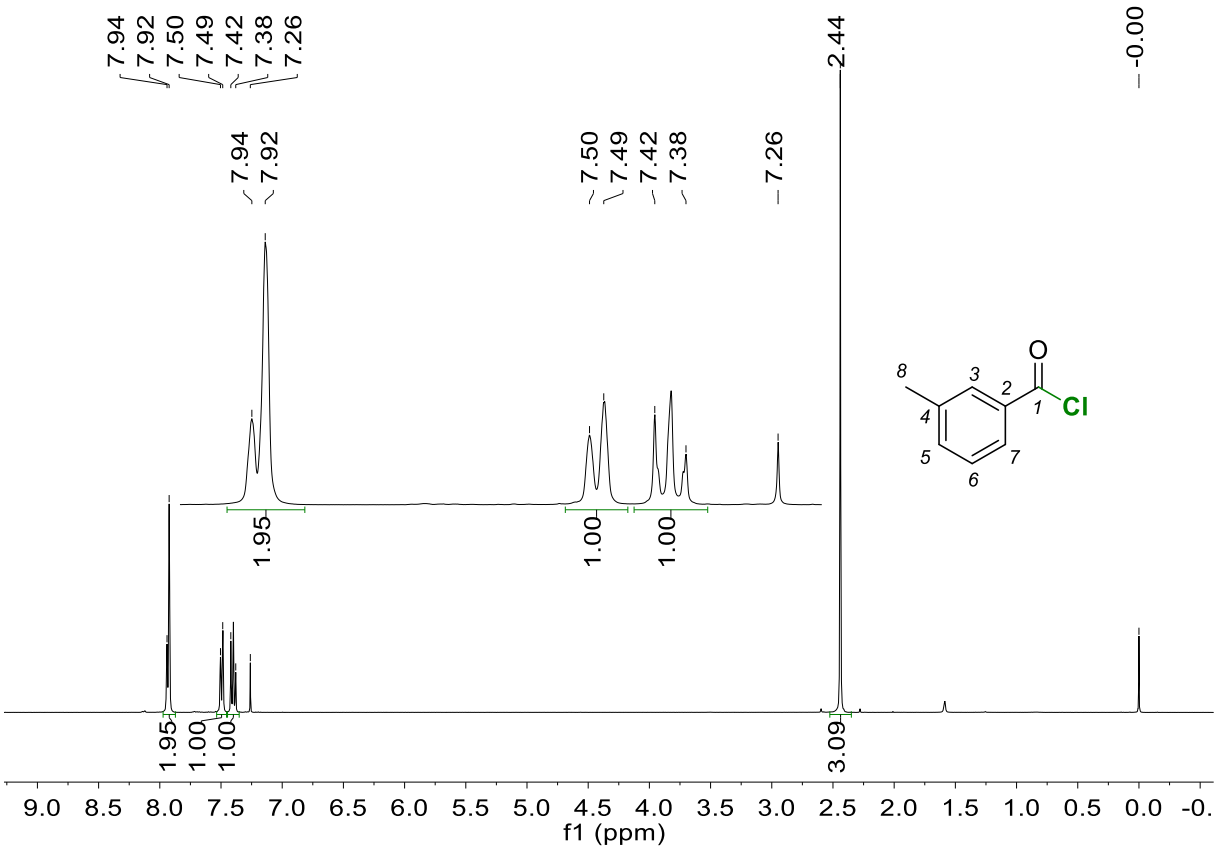
3-Methylbenzoyl chloride

M (C_8H_7OCl) = 154.593 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$,) δ [ppm] = 7.93 (ψ-d, 2H, *J* = 6.9 Hz, 3-H, 7-H), 7.50 (ψ-d, *J* = 7.3 Hz, 1H, 5-H), 7.42-7.38 (m, 1H, 6-H), 2.44 (s, 3H, 8-H); **^{13}C-NMR** (125 MHz, $CDCl_3$,) δ [ppm] = 168.48 (C-1), 138.96 (C-4), 136.12 (C-5), 133.17 (C-2), 131.74 (C-3), 128.79/128.73 (C-6, C-7), 21.17 (C-8).

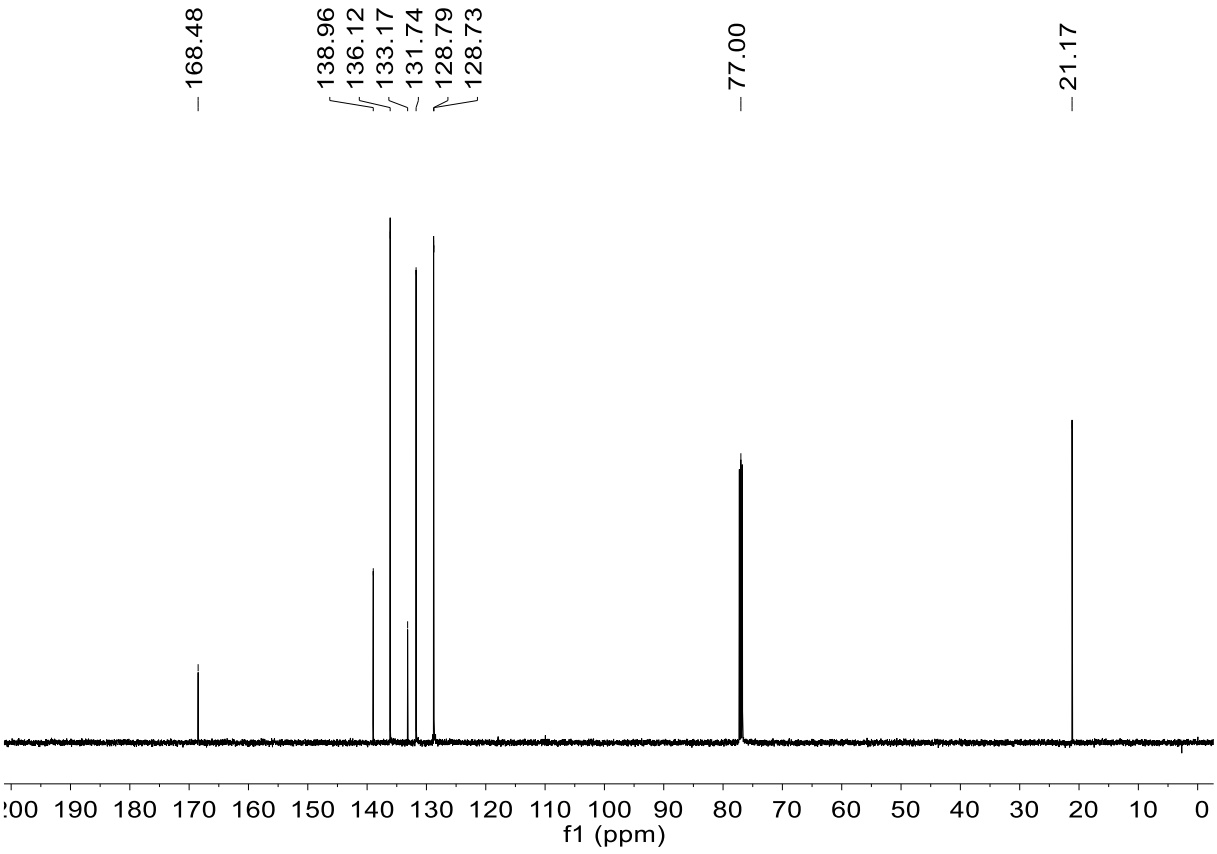


2-Methylbenzoic acid (commercial sample)

M ($C_8H_8O_2$) = 1236.150 g/mol; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 12.30 (br. s, 1H, CO_2H), 7.94-7.91 (m, 2H), 7.43-7.40 (m, 1H), 7.37-7.34 (m, 1H), 2.41 (s, 3H, 8-H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 172.73 (C-1), 138.27, 134.58, 130.68, 129.23, 128.35, 127.36, 21.22 (C-8).



^{1}H-NMR spectrum of 3-methylbenzoyl chloride (400 MHz, $CDCl_3$,).



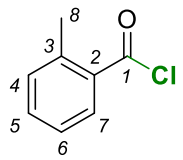
^{13}C-NMR spectrum of 3-methylbenzoyl chloride (125 MHz, $CDCl_3$,).

5.4.1.3 Synthesis of 2-Methylbenzoyl chloride (6_1)

entry	conditions	yield 6_1 [%]	CA[a] [%]
1	TCT (40 mol%), FPyr (10 mol%), MeCN (3 M), 1 h 40 °C, then 3 h 80 °C	90[a] (**27.9 g**)	59
2	TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 80 °C	93[b]	n.d.
3	TCT (40 mol%), FPyr (10 mol%), **reused MeCN** (2 M), 4 h 80 °C	95[b]	n.d.
4	TCT (40 mol%), **no FPyr**, MeCN (2 M), 4 h 80 °C	≤2[b]	n.d.

a. Yield determined from mass of isolated material after distillation and precipitation, respectively. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of dibenzylether as internal standard. CA = cyanuric acid.

2-Methylbenzoyl chloride was synthesized on a 200 mmol scale in 90% yield, whereby cyanuric acid was isolated in 59% yield (entry 1). Entries 2 and 3 verify that MeCN, which had been reisolated from the above-mentioned multigram scale experiment, can be reused since the yields are almost identical. Eventually, without FPyr the title compound was not formed (entry 4).



6_1

Entry 1, PH3610: In accordance with general procedure 2 (chapter 5.3.2, page 46) a suspension of 2-methylbenzoic acid (27.23 g, 200 mmol, 1.0 equiv) and FPyr (1.97 mL, 2.04 g, 20.0 mmol, 10 mol%) in reagent-grade MeCN (70 mL) was treated with TCT (15.05 g, 80.0 mmol, 40 mol%) and stirred for 1 h at 40 and for 3 h at 80 °C. Afterwards the reaction mixture was diluted with MeCN (30 mL), filtered and the filter cake was triturated with further MeCN (2 x 25 mL). Reaction control via ^{1}H-NMR after micro work up proved 60% conversion after 1 h at 40 °C and 10 mol% FPyr were observed with respect to **1_1** and **6_1**. Finally, after 3 h of stirring at 80 °C reaction monitoring confirmed a conversion ≥95%, while no FPyr remained. Concentration and drying at the rotary evaporator furnished the crude title compound as a yellow oil (38.64 g, 125%) and MeCN in 87% yield (130 mL).

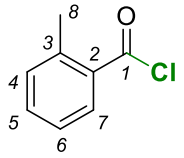
Fractioned distillation at 1.3 mbar delivered the title compound with a boiling point of 71-72 °C as a colourless liquid in a yield of 90% (27.88 g, 180.4 mmol), whereby the temperature of the oil bath was increased from 90 to 150 °C. Heating of the micro distillation apparatus with the aid of a heat gun allowed to isolate further 2-methylbenzoyl chloride (1.335 g) as a colourless liquid in a purity of circa 90% as determined by ^{1}H-NMR. Moreover, drying of the filter cake obtained during work up afforded crude cyanuric acid in 73% yield (7.56 g). Dissolution in 2 N NaOH (aq., 68 mL, 136 mmol, 0.68 equiv), acidification with the aid of a 37 wt% HCl solution in water (13 mL, 160 mmol, 0.8 equiv), filtration and washing of the filter cake (1 x 20 mL water, 2 x 20 mL acetone) enabled the isolation of cyanuric acid as a colourless, fine-powdered solid in 59% yield (6.05 g, 46.9 mmol).

Entry 2, PH3509: According to general procedure 1 (chapter 5.3.1, page 44) 2-methylbenzoic acid (68 mg, 0.50 mmol, 1.0 equiv) was transformed with TCT (36 mg, 190 μmol, 38 mol%)

and FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%) in MeCN (dry, 250 μL, 2 M) through heating to 80 °C for 4 h into the title compound in 93% yield as determined by means of ^{1}H-NMR with dibenzylether (31.0 mg) as internal standard (≥98% conversion).

Entry 3, PH3689: Following general procedure 1 (chapter 5.3.1, page 44) the title compound was produced from *ortho*-toluic acid (0.50 mmol, 1.0 equiv) and TCT (38 mg, 200 μmol, 40 mol%) using FPyr (10 mol) under application of **MeCN**, which had been **reisolated** in the afore-mentioned experiment in entry 1. After 4 h of stirring at 80 °C, ^{1}H-NMR with dibenzylether (19.7 mg) as internal standard proved 2-methylbenzoyl chloride in 95% yield, while the starting material was found to be fully consumed (≥98% conversion).

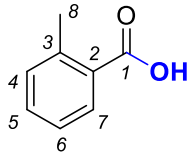
Entry 4 PH3510: As given in general procedure 1 (chapter 5.3.1, page 44) 2-methylbenzoic acid (0.50 mmol, 1.0 equiv) was allowed to react with TCT (38 mol%) in MeCN (dry, 2 M) **in the absence of FPyr** for 4 h at 80 °C. Next, ^{1}H-NMR with dibenzylether (23.3 mg) as internal standard revealed remaining starting material in 100% yield (≤2%), whereas the title compound could not be identified.



2-Methylbenzoyl chloride

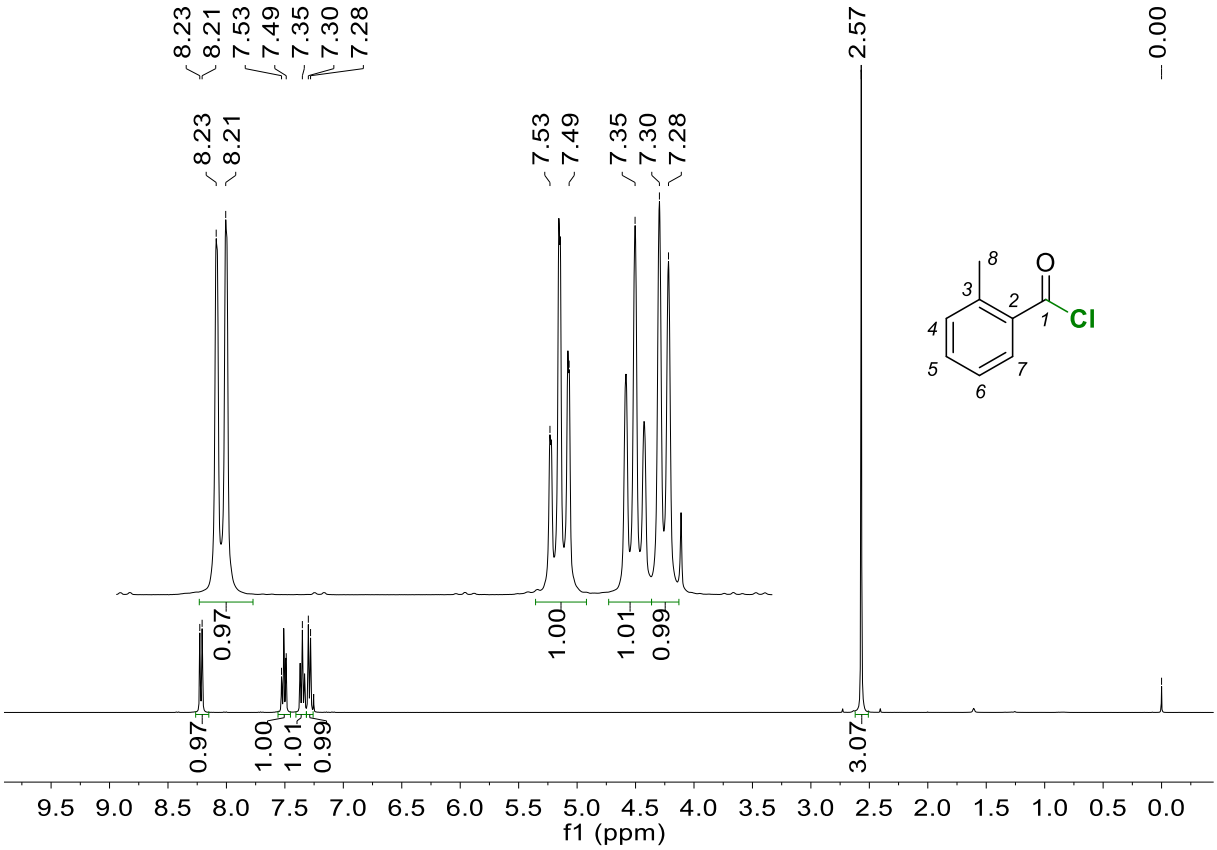
M (C_8H_8OCl) = 140.610 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.23-8.21 (m, 1H, 7-H) 7.51 (ψ-dt, *J* = 7.5/1.1 Hz, 1H, 5-H), 7.35 (ψ-t, *J* = 7.7 Hz, 1H, 6-H), 7.29 (d, *J* = 7.6 Hz, 1H, 4-H), 2.57 (s, 3H, 8-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 167.50 (C-1), 141.38 (C-3), 134.13 (C-5 or C-7), 133.93 (C-5 or C-7), 132.39 (C-2), 131.89 (C-4), 126.34 (C-6), 22.02 (C-8).

The NMR data is in agreement with the literature.[26]

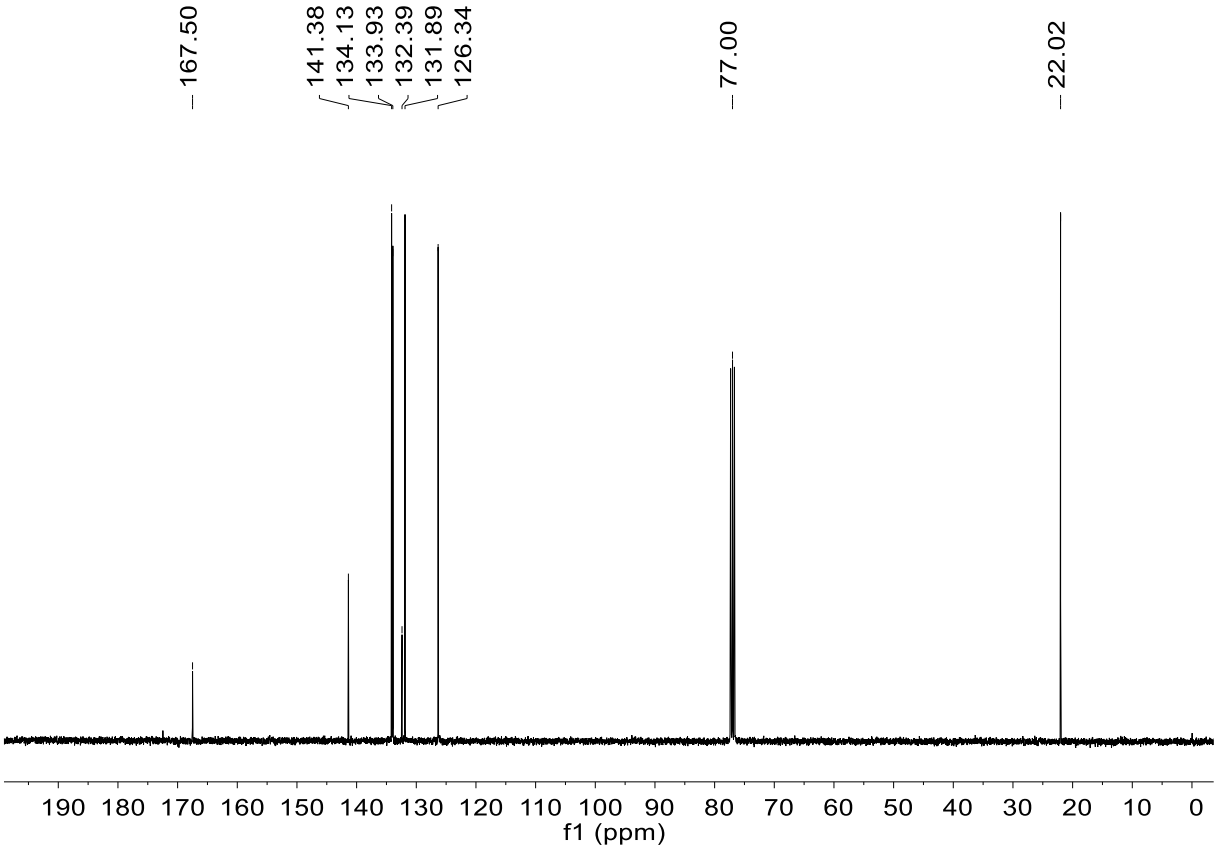


2-Methylbenzoic acid (commercial sample)

M ($C_8H_8O_2$) = 1236.150 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 11.96 (br. s, 1H, CO_2H), 8.09-8.07 (m, 1H) 7.46 (ψ-dt, *J* = 7.5/1.3 Hz, 1H), 7.30-7.27 (m, 1H, 6-H), 7.29 (d, *J* = 7.6 Hz, 1H, 4-H), 2.67 (s, 3H, 8-H).



^{1}H-NMR spectrum of 2-methylbenzoyl chloride (400 MHz, $CDCl_3$).



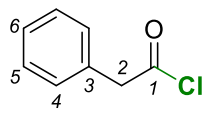
^{13}C-NMR spectrum of 2-methylbenzoyl chloride (125 MHz, $CDCl_3$).

5.4.1.4 Synthesis of Phenylethanoyl chloride (6_4)

entry	conditions	yield 6_4 [%]	CA[a] [%]
1	TCT (40 mol%), FPyr (15 mol%), MeCN (4 M), 1 h 40 °C, then 3 h 80 °C	79[a] (**24.4 g**)	63
2	TCT (40 mol%), FPyr (10 mol%), MeCN (2 M), 7 h 40 °C	90[b]	n.d.
3	TCT (40 mol%), FPyr (10 mol%), **reused** MeCN (2 M), 4 h 40 °C	95[b]	n.d.
4	TCT (40 mol%), **no FPyr**, MeCN (2 M), 4 h 80 °C	≤2[b]	n.d.

a. Yield determined from mass of isolated material after distillation and precipitation, respectively. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of dibenzylether as internal standard

Phenyl acetyl chloride was isolated in 79% yield together with 63% cyanuric acid on a 200 mmol scale (entry 1). MeCN, which had been reisolated from the previous experiment, could be reused without a deteriorative effect on the yield (entries 2+3). Without usage of FPyr acid chloride **1_4** was not formed (entry 4). Phenyl acetic acid was applied as substrate for the optimization of the current method (see chapter 3.1.2 beginning on page 13).



6_4

Entry 1, PH3643: According to general procedure 2 (chapter 5.3.2, page 46) to a solution of phenyl acetic acid (27.24 g, 200 mmol, 1.0 equiv) and FPyr (2.95 mL, 3.07 g, 60.0 mmol, 15 mol%) in MeCN (50 mL, 4 M) was added TCT (15.05 g, 80.0 mmol, 40 mol%) and the resulting suspension was stirred for 1 h at 40 °C and for 1.5 h at 80 °C. Thereafter, ^{1}H-NMR after micro work up confirmed a conversion of 95%. After cooling down to ambient temperature, the yellow reaction suspension was diluted with MeCN (25 mL), filtered and the filter cake was washed with further MeCN (2 x 25 mL). Concentration *in vacuo* allowed to isolate the crude title compound as a dark red oil (41.31 g, 134%) and MeCN (100 mL, 80%). Next, fractioned distillation at 0.07 mbar and a stirring speed of 1200 rpm provided phenylacetoyl chloride with a boiling point of 54-55 °C in a yield of 79% (24.37 g, 157.7 mmol). Thereby, the oil bath temperature was increased gradually from 65 to 150 °C to ensure a constant distillation process. Finally, heating of the micro distillation apparatus with a heat gun delivered a small fraction of the title compound in a purity of approximately 90% according to ^{1}H-NMR (292 mg). Since the phenylethanoyl chloride is of a relatively high viscosity, a high stirring speed is essential to avoid boiling retardation. When a smaller micro distillation apparatus with NS 14 conical joints (instead of NS 29) was used, no constant boiling point was achieved and the product was obtained in a much lower yield.

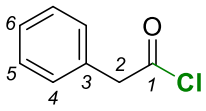
Additionally, drying of the filter cake obtained in the work up delivered a pale yellow solid (8.00 g, 78%), of which ^{13}C-NMR proved cyanuric acid as the main component (see below). After dissolution in aqueous 2 N NaOH (74 mL, 148 mmol, 0.75 equiv), precipitation with 37 wt% HCl solution in water (14 mL, 170 mmol, 0.85 equiv), filtration, washing of the filter cake with aqueous 1 N HCl-solution (1 x 20 mL) and acetone (2 x 20 mL) and drying at the

rotary evaporator cyanuric acid was isolated as a colourless, fine-powdered solid (6.545 g, 50.7 mmol, 63%).

Entry 2, PH3527: As described in general procedure 1 (chapter 5.3.1, page 44) phenyl acetic acid (68 mg, 500 μmol, 1.0 equiv) was reacted with TCT (38 mg, 200 μmol, 40 mol%) in the presence of FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%) in MeCN (250 μmol, 2 M) for 7 h at 40 °C. Eventually, ^{1}H-NMR with dibenzylether as internal standard (35.6 mg) revealed the title compound in 90% yield, while 5% of remaining starting material were detected (95% conversion).

Entry 3, PH3690: As delineated in general procedure 1 (chapter 5.3.1, page 44) the title compound was prepared from phenyl ethanoic acid (500 μmol, 1.0 equiv) and TCT (40 mol%) applying FPyr (10 mol%) and **MeCN (2 M), reisolated** from the in entry 1 described experiment. After 4 h of heating to 40 °C, ^{1}H-NMR showed phenyl ethanoyl chloride in 95% yield beside small traces of residual starting material (≤2%, ≥98% conversion) as determined by means of dibenzylether as internal standard (33.6 mg).

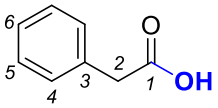
Entry 4, PH3529: In the absence of FPyr phenyl ethanoic acid (500 μmol, 1.0 equiv) was allowed to react with TCT (40 mol%) in MeCN (2 M) for 4 h at 40 °C as stated in general procedure 1 (chapter 5.3.1, page 44). Finally, in the ^{1}H-NMR spectrum of the crude material no phenyl ethanoyl chloride could be detected, while remaining starting material was observed in 87% yield as judged with the aid of dibenzylether as standard (31.8 mg).



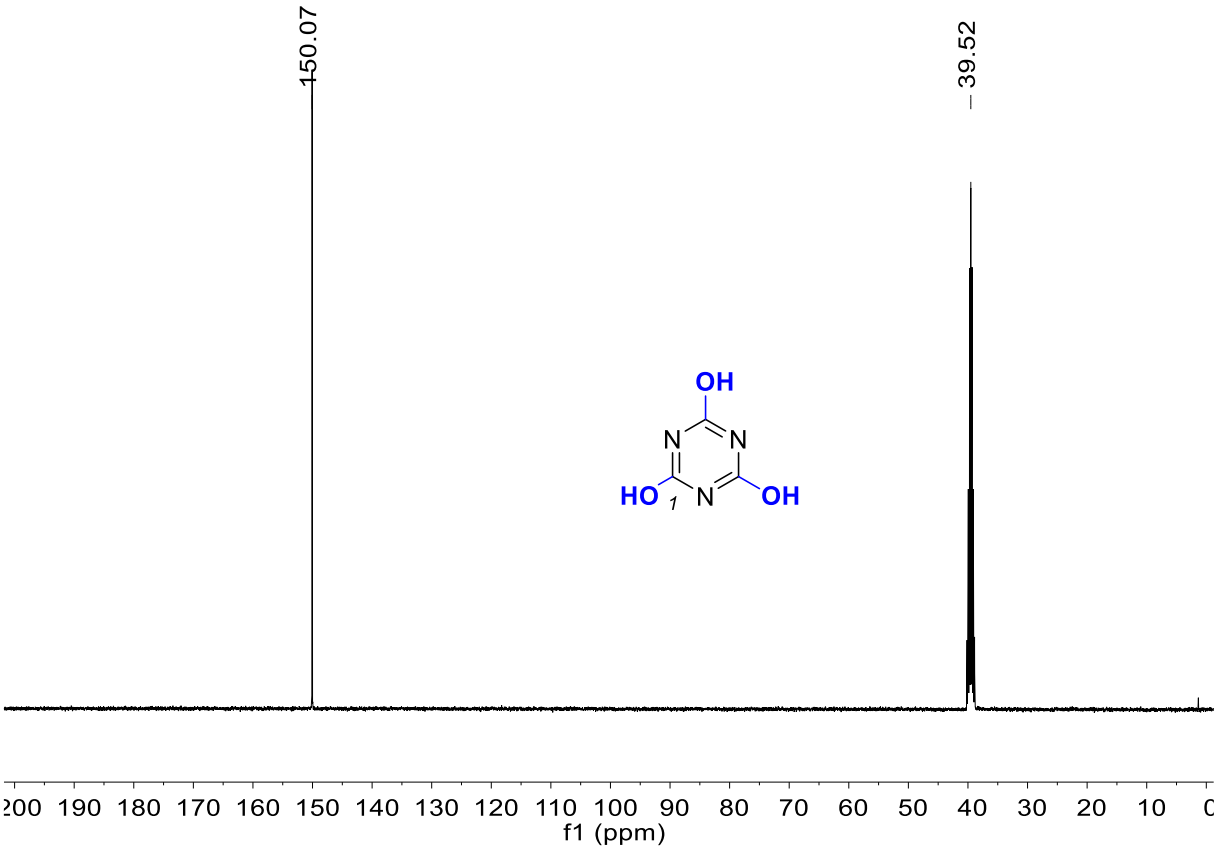
Phenylethanoyl chloride

M (C_8H_7OCl) = 154.593 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.39-7.31 (m, 3H, 5-H, 6-H), 7.27-7.25 (m, 2H, 4-H), 4.13 (s, 2H, 2-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 171.89 (C-1), 131.19 (C-3), 129.48 (C-4), 128.92 (C-5), 128.14 (C-6), 53.00 (C-2).

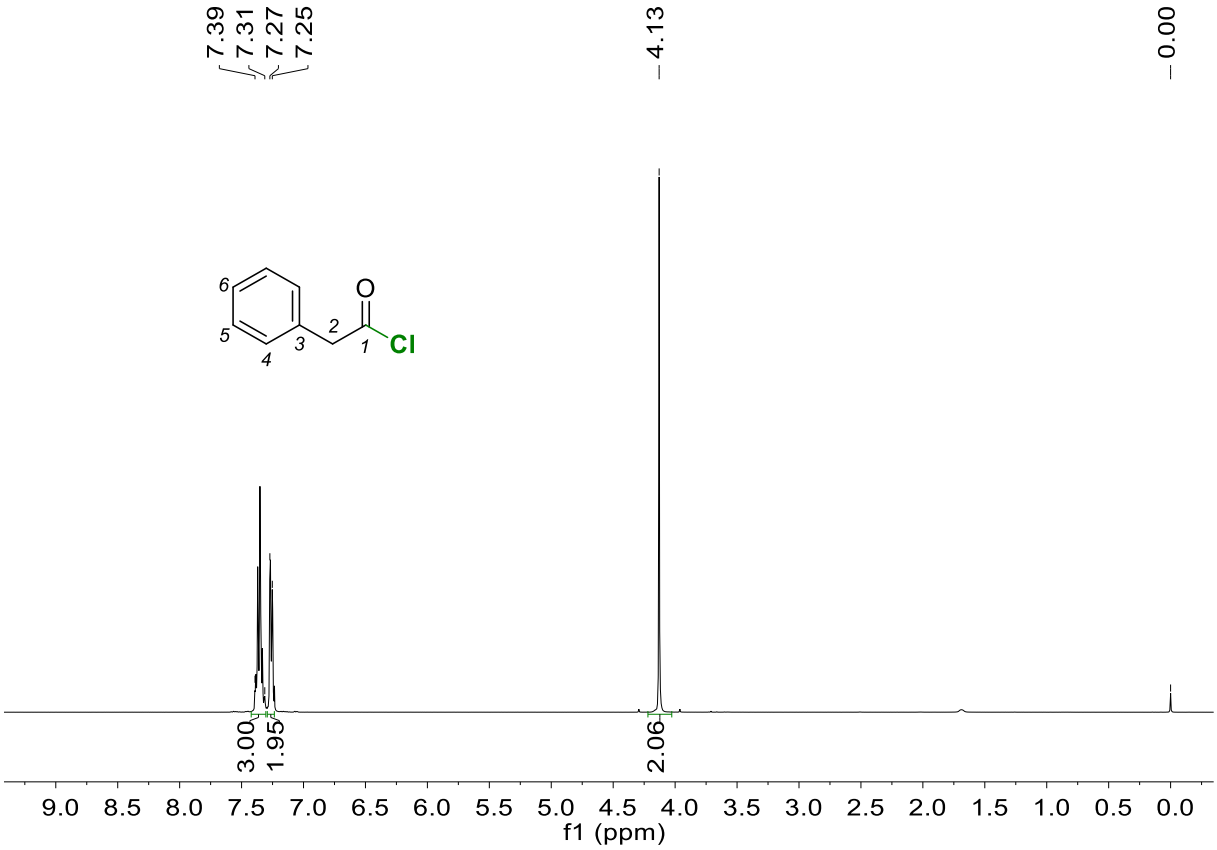
Phenylethanoic acid (commercial sample)



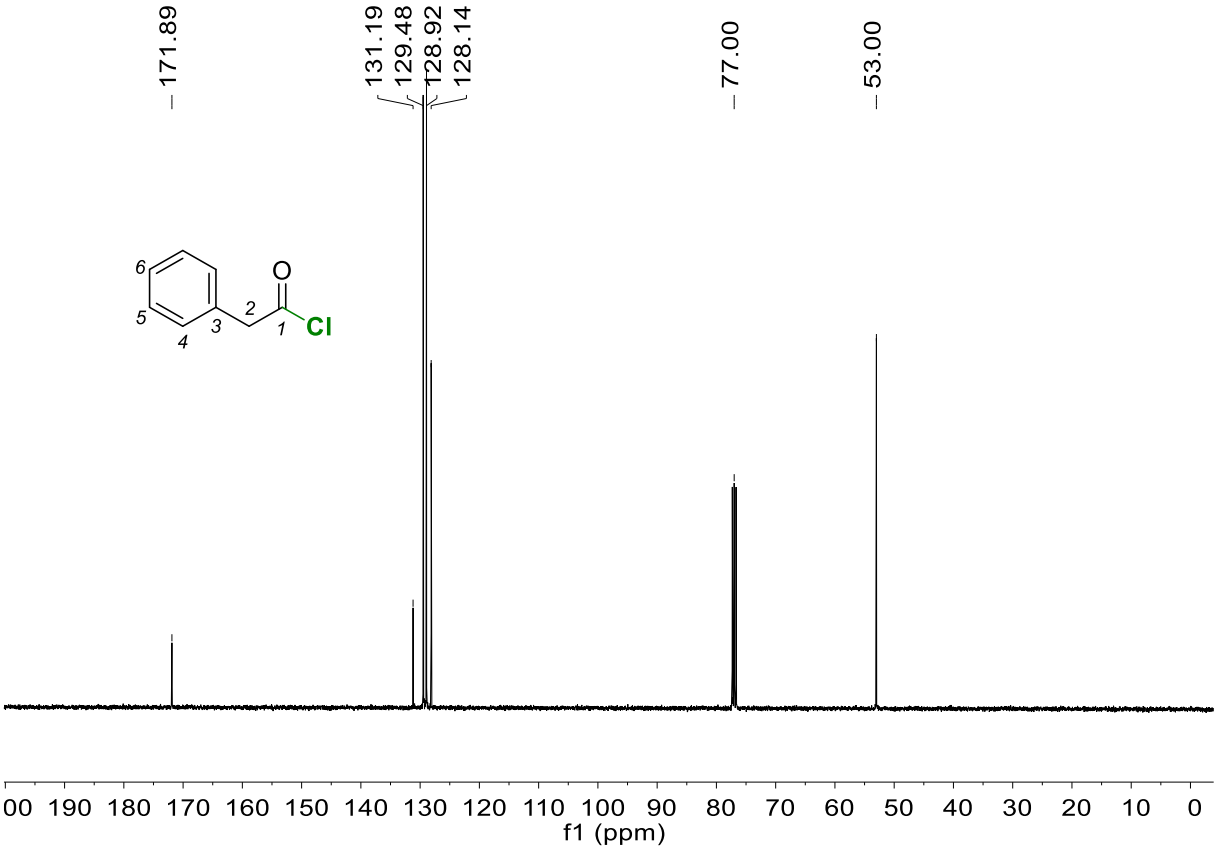
M ($C_8H_8O_2H$) = 136.150 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 9.96 (br. s, 1H, CO_2H) 7.35-7.25 (m, 5H, 4-H, 5-H, 6-H), 3.65 (s, 2H, 2-H).



^{13}C-NMR spectrum of crude cyanuric acid (100 MHz, DMSO-d^{6},).



^{1}H-NMR spectrum of phenylethanoyl chloride (400 MHz, $CDCl_3$,).



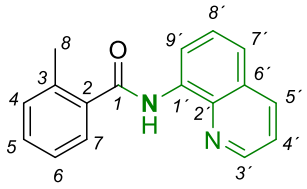
^{13}C-NMR spectrum of phenylethanoyl chloride (125 MHz, $CDCl_3$,).

5.4.2 Synthesis of Amides 2 (Scheme 3+4)

5.4.2.1 Synthesis of *N*-(Quinol-8-yl) 2-methylbenzamide (2_{1a})

entry	conditions	yield 2_{1a}[a] [%]
1	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 2 h 80 °C 2. H**Nu** (1.1 equiv), NMM (1.3 equiv), MeCN (1 M), 15 min 0°C then 5 h rt	90
2	1. TCT (38 mol%), FPyr (10 mol%), **EtOAc** (2 M), 3 h 80 °C 2. H**Nu** (1.1 equiv), NMM (1.3 equiv), **EtOAc** (1 M), 15 min 0°C then 5 h rt	85
3	1. TCT (38 mol%), FPyr (**20 mol%**), EtOAc (2 M), 8 h **40 °C** 2. H**Nu** (1.1 equiv), NMM (1.3 equiv), EtOAc (1 M), 15 min 0°C then 15 h rt	84
4	1. TCT (38 mol%), FPyr (20 mol%), MeCN (2 M), 14 h **rt** 2. H**Nu** (1.1 equiv), NMM (1.3 equiv), MeCN (1 M), 15 min 0°C then 4 h rt	78
5	1. TCT (38 mol%), FPyr (**5 mol%**), MeCN (2 M), 10 h 80 °C 2. H**Nu** (1.1 equiv), NMM (1.3 equiv), MeCN (1 M), 15 min 0°C then 4 h rt	90
6	1. TCT (38 mol%), **DMF** (40 mol%), EtOAc (2 M), 8 h 40 °C 2. H**Nu** (1.1 equiv), NMM (1.3 equiv), EtOAc (1 M), 15 min 0°C then 19 h rt	83
7[b]	1. TCT (38 mol%), FPyr (10 mol%), EtOAc (2 M), 8 h 80 °C 2. H**Nu** (1.1 equiv), **K_2CO_3** (1.3 equiv), EtOAc (0.8 M), 15 min 0°C then 2 h rt	88
8	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 2 h 80 °C 2. H**Nu** (1.1 equiv), **NEt_3** (1.3 equiv), MeCN (0.8 M), 15 min 0°C then 4 h rt	91
9[b]	1. TCT (38 mol%), FPyr (10 mol%), **acetone** (2 M), 2 h 80 °C 2. H**Nu** (1.1 equiv), **NEt_3** (1.3 equiv), **acetone** (0.7 M), 15 min 0°C then 2 h rt	71
10	1. TCT (38 mol%), **no catalyst**, MeCN (2 M), 8 h 80 °C 2. H**Nu** (1.1 equiv), NMM (1.3 equiv), MeCN (1 M), 15 min 0°C then 20 h rt	11[b]

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of 1,3,5-trimethoxybenzene as internal standard. H**Nu** = 8-amino quinolone.



2_{1a}

The results for the amide **2_{1a}** have been discussed in the manuscript and the chapters 3.2.2 and 4.1.2 on page 25 and 35, repectively.

Entry 1, PH3145: According to general procedure 4 (chapter 5.3.4 page 50) 2-methylbenzoic acid (136 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) for 2 h at 80 °C. Next, the reaction suspension was diluted with more MeCN (0.50 mL→1 M), chilled in an ice bath and successively 8-amino quinoline (159 mg, 1.10 mmol, 1.1 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were added. After 5 h of stirring at ambient temperature aqueous work up without HCl-washing provided the crude material as a pale yellow solid (278 mg, 106%). Afterwards, chromatographic purification on silica gel (21.6 g, mass ratio crude product/SiO_2 1:77) with EtOAc/*n*Hex 15:85 afforded the title compound as a colourless solid (235.4 mg, 0.897 mmol, 90%). Due to low solubility of the title

amide in the eluent, the crude material was dissolved in CH_2Cl_2 (ca. 10 mL), silica gel was added (0.64 g, relation of weight crude amide **2_{1a}**/SiO_2 1.2.3) and all volatile components were removed *in vacuo*.

Entry 2, PH3125: Following general protocol 4 (chapter 5.3.4 page 50) 2-methylbenzoic acid (1.00 mmol, 1.0 equiv) was transformed into the respective acid chloride by means of TCT (38 mol%) using FPyr (10 mol%) in **EtOAc** (0.50 mL, 2 M) under heating to 80 °C for 3 h. Next, the reaction mixture was treated with additional EtOAc (0.50 mL→1 M), at 0 °C 8-amino quinoline (1.1 equiv) and NMM (1.3 equiv) were added and the reaction suspension was stirred for 5 h at ambient temperature. Finally, purification of the crude material (290 mg, 111%, pale yellow solid) on silica gel (20.8 g, mass ratio **2_{1a}**/SiO_2 1:72) with EtOAc/*n*Hex 15:85 gave the title compound as a colourless solid in 85% yield (223.5 mg, 0.852 mmol) after adsorption on silica gel (0.61 g).

Entry 3, PH3126: In accordance with general procedure 4 (chapter 5.3.4 page 50) 2-methylbenzoic acid (1.00 mmol, 1.0 equiv) was combined with **FPyr** (19.6 μL, 20.4 mg, 200 μmol, **20 mol%**), EtOAc (2 M) and TCT (38 mol%) and the resulting mixture was stirred at **40 °C** for 8 h. Afterwards, the reaction suspension was diluted with more EtOAc (→1 M), at 0 °C 8-amino quinoline (1.1 equiv) and NMM (1.3 equiv) were introduced and stirring was continued for 15 h. In the end, column chromatographic purification of the crude title compound (299 mg, 113%, pale yellow solid) using silica gel (16.9 g) and EtOAc/*n*Hex 15:85 furnished the amide **2_{1a}** as a colourless solid in 84% yield (221.5 mg, 0.844 mmol, 84%). Thereby, the crude material was adsorbed on silica gel (0.68 g) in order to charge the silica gel column.

Entry 4, PH3140: Based on general procedure 4 (chapter 5.3.4 page 50) TCT (38 mol%) was added to a mixture of 2-methylbenzoic acid (1.00 mmol, 1.0 equiv) and FPyr (20 mol%) in MeCN (2 M) and the mixture was stirred overnight (14 h) at **room temperature**. In the following, further MeCN (→1 M) and at 0 °C 8-amino quinoline (1.1 equiv) and NMM (1.3 equiv) were added and the reaction suspension was continued to stir for 4 h at ambient temperature. At last, column chromatographic purification on silica gel (20.2 g) of the crude product (310 mg, 118%, pale yellow solid) applying EtOAc/*n*Hex 15:85 as eluent afforded the title amide as a colourless solid (203.7 mg, 0.777 mmol, 78%). In order to load the crude material onto the silica gel column, it was adsorbed on silica gel (0.64 g).

Entry 5, PH3285: Relying on general procedure 4 (chapter 5.3.4 page 50) 2-methylbenzoic acid (1.00 mmol, 1.0 equiv) was converted to the corresponding acid chloride by means of TCT (38 mol%) in the presence of **FPyr** (4.9 μL, 5.1 mg, 50 μmol, **5 mol%**) in MeCN (2 M) under heating to 80 °C for 10 h. After dilution with MeCN (→1 M) and cooling in an ice bath 8-amino quinoline (1.1 equiv) and NMM (1.3 equiv) were added and the reaction suspension was stirred for 4 h at ambient temperature. Eventually, purification of the crude product (299 mg, yellow solid, 114%) on silica gel (23.0 g) with EtOAc/*n*Hex 15:85 facilitated the

isolation of the title amide in 90% yield as a colourless solid (235.1 mg, 0.896 mmol). Thereby, the crude amide **2_{1a}** was loaded onto silica gel (0.93 g).

Entry 6, PH3178: Following general procedure 4 (chapter 5.3.4 page 50) a mixture of 2-methylbenzoic acid (1.00 mmol, 1.0 equiv) and **DMF** (30.9 μL, 29.2 mg, 400 μmol, **40 mol%**) in EtOAc (2 M) was treated with TCT (38 mol%) and heated to 40 °C for 8 h. After dilution with more EtOAc (→1 M) and cooling to 0 °C, to the reaction suspension were added sequentially 8-amino quinoline (1.1 equiv) and NMM (1.3 equiv) and stirring was continued for 19 h at room temperature. After aqueous work up and drying over $MgSO_4$, silica gel (0.97 g) was added to the organic phase and all volatiles were removed *in vacuo*. The residual fine powder was loaded onto a silica gel column (21.8 g) and elution with EtOAc/*n*Hex 15:85 delivered the title amide as a colourless solid in 83% yield (218.4 mg, 0.833 mmol).

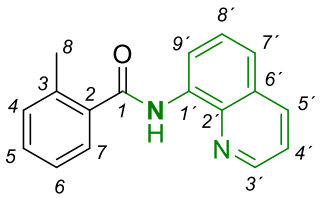
Entry 7, PH3251: In orientation on general procedure 4 (chapter 5.3.4 page 50) 2-toluic acid (1.00 mmol, 1.0 equiv) was reacted with TCT (38 mol%) using FPyr (10 mol%) in EtOAc (2 M) for 3 h at 80 °C. Next, the reaction suspension was diluted with EtOAc (750 μL→0.8 M) and under cooling in an ice bath 8-amino quinoline (1.1 equiv) and **K_2CO_3** (180 mg, 1.3 mmol, 1.3 equiv) were added. After 2 h of stirring at room temperature the reaction mixture turned solid. Past aqueous work up and drying over $MgSO_4$, the organic phase was treated with silica gel (0.94 g) and all volatile components were evaporated under reduced pressure. In the end, column chromatographic purification on silica gel (19.3 g) applying EtOAc/PE 15:85 facilitated the isolation of the title amide as a colourless solid (229.9 mg, 0.876 mmol, 88%).

Entry 8, PH3245: In alignment to general procedure 4 (chapter 5.3.4 page 50) to a mixture of 2-methylbenzoic acid (1.00 mmol, 1.0 equiv) and FPyr (10 mol%) in MeCN (2 M) was added TCT (38 mol%) and the forming reaction suspension was heated to 80 °C for 2 h. Then, further MeCN (0.75 mL→0.8 M) and under chilling in an ice bath 8-amino quinoline (1.1 equiv) and **NEt_3** (180 μL, 1.3 mmol, 1.3 equiv) were added. After stirring for 4 h at room temperature, aqueous work up and drying over $MgSO_4$, silica gel (0.93 g) was added to the organic phase and all volatiles were removed *in vacuo*. Ultimately, purification with the aid of column chromatography on silica gel (24.2 g) employing EtOAc/PE 15:85 as eluent system gave the amide **2_{1a}** as a colourless solid (237.3 mg, 0.905 mmol, 91%).

Entry 9, PH3267: As described in general procedure 4 (chapter 5.3.4 page 50) TCT (38 mol%) was added to a mixture of FPyr (10 mol%) and 2-methylbenzoic acid (1.00 mmol, 1.0 equiv) in **acetone** (0.50 mL, 2 M) and the resulting mixture was stirred for 1.5 h at 80 °C. Subsequently, the reaction suspension was diluted with further acetone (1.0 mL→0.7 M), cooled in an ice bath and 8-amino quinoline (1.1 equiv) and K_2CO_3 (1.3 equiv) were added. After 2 h of stirring at ambient temperature the reaction mixture had turned solid. Past aqueous work up and drying over $MgSO_4$, the organic phase was treated with SiO_2 (0.71 g) and all volatiles were evaporated under reduced pressure. Column chromatographic purification on silica gel

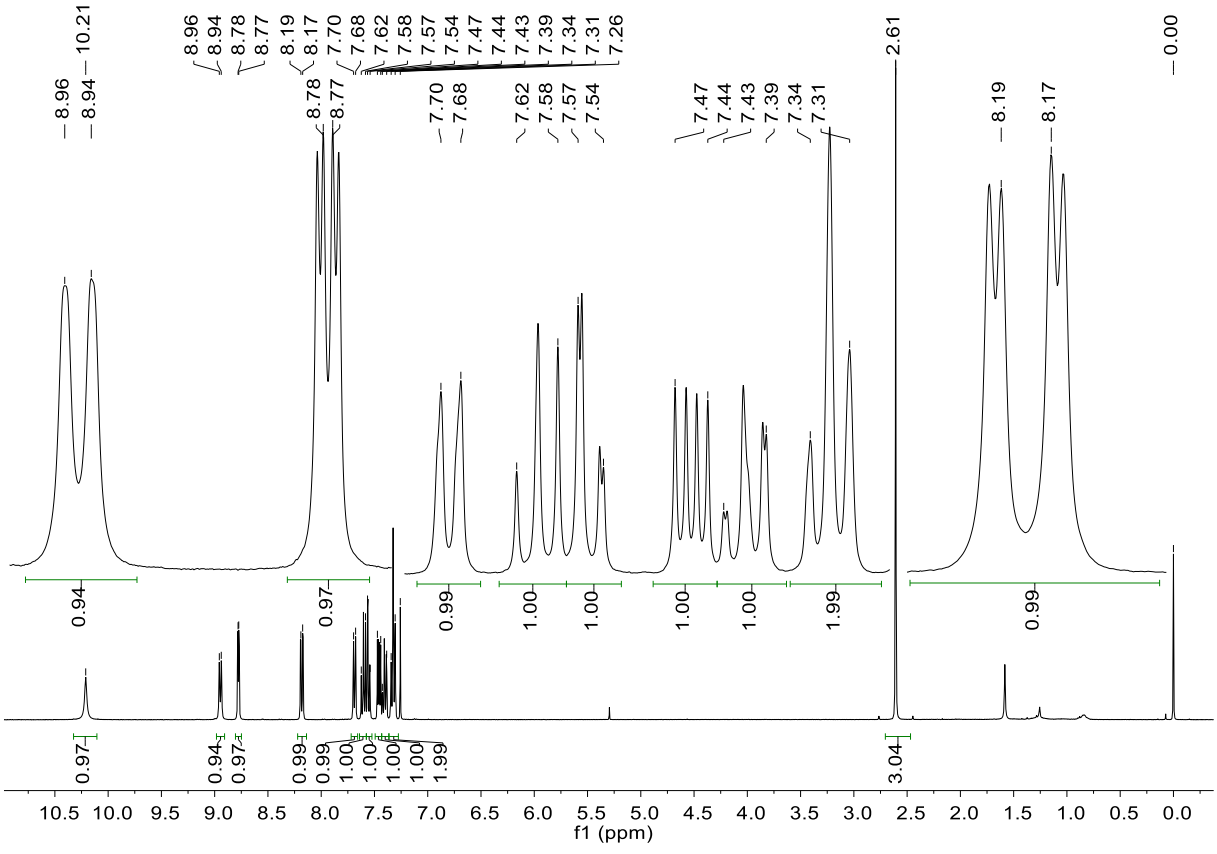
(22.0 g) utilizing EtOAc/*n*Hex 15:85 furnished the amide **2$_{1a}$** as a pale yellow solid (186.3 mg, 0.710 mmol, 71%).

Entry 10, PH3181: Based on general protocol 3 (chapter 5.3.3, page 49) 2-methylbenzoic acid (68 mg, 0.50 mol, 1.0 equiv) were heated with TCT (36 mg, 190 μmol, 38 mol%) in MeCN (0.25 mL, 2 M) for 8 h to 80 °C. Then, more MeCN (0.25 mL→1 M) and at 0 °C 8-amino quinoline (79 mg, 0.55 mmol, 1.1 equiv) and NMM (75 μmol, 0.65 mmol, 1.3 equiv) were added. After 20 h of stirring at room temperature and aqueous work up, ^{1}H-NMR with 1,3,5-trimethoxybenzene (19.5 mg) as internal standard verified the title compound in 11% yield).

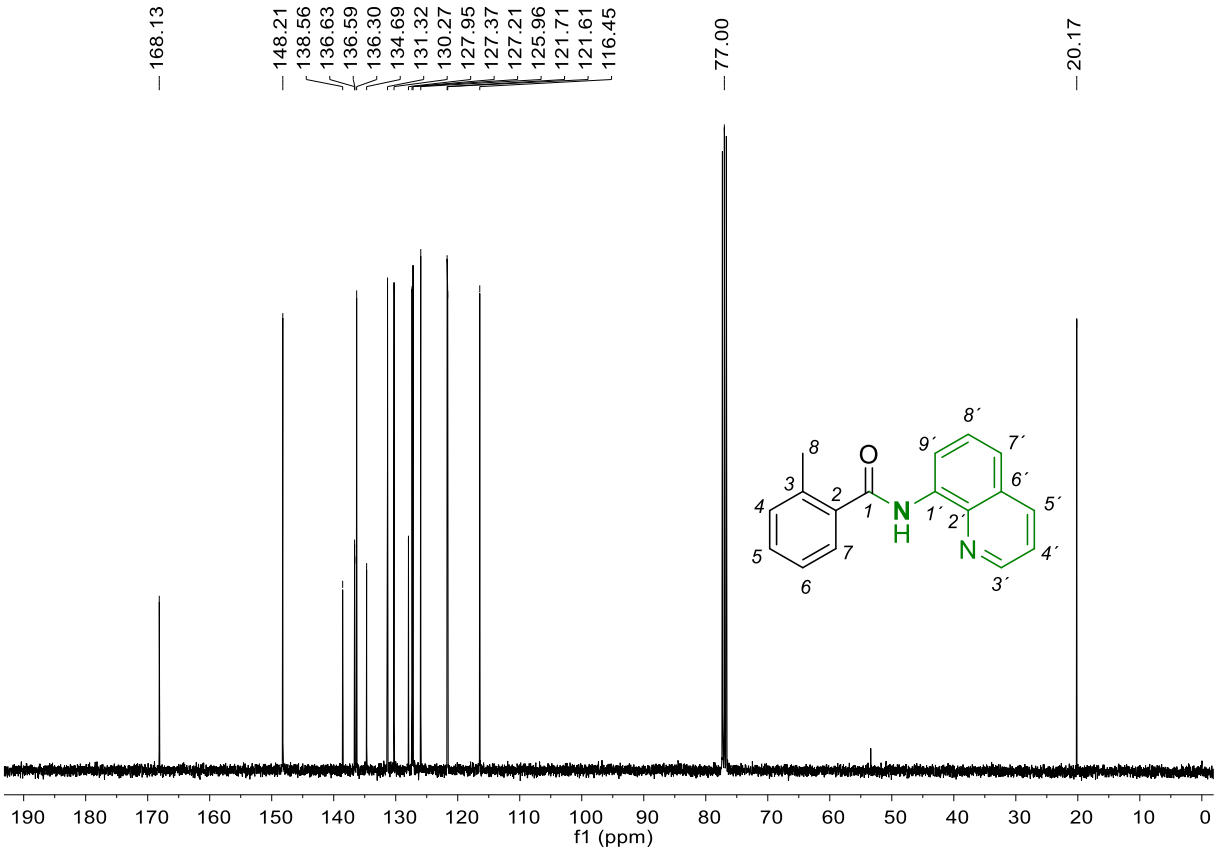


M ($C_{17}H_{14}N_2O$) = 262.312 g/mol; **mp.** 100-102 °C (); **r$_f$** (SiO_2, EtOAc/*n*Hex 15:85) = 0.42; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 10.21 (br. s, 1H, NH), 8.95 (d, ^{3}J = 7.5 Hz, 1H, 9´-H), 8.78 (dd, ^{3}J = 4.2 Hz, ^{4}J = 1.6 Hz, 1H, 3´-H), 8.18 (dd,^{3}J = 8.3 Hz, ^{4}J = 1.6 Hz, 1H, 5´-H), 7.70-7.68 (m, 1H, 7-H), 7.62-7.58 (m, 1H, 8´-H), 7.56 (dd, ^{3}J = 8.3, ^{4}J = 1.5 Hz, 1H, 7´-H), 7.46 (dd, ^{3}J = 8.3, ^{3}J = 4.2 Hz, 1H, 4´-H), 7.43-7.39 (m, 1H, 5-H), 7.34-7.31 (m, 2H, 4-H, 6-H), 2.61 (s, 2H, 8-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 168.13 (C-1), 148.21 (C-3´), 138.56 (C-2´), 136.63 (C-3), 136.59 (C-2), 136.30 (C-5´), 134.69 (C-6´), 131.32 (C-4), 130.27 (C-5), 127.95 (C-1´), 127.37 (C-8´), 127.21 (C-7), 125.96 (C-6), 121.71 (C-7´), 121.61 (C-4´), 116.45 (C-9´), 20.17 (C-8).

The NMR data is in match with the literature.[27]



^{1}H-NMR spectrum of *N*-(quinol-8-yl) 2-methylbenzamide (400 MHz, $CDCl_3$).

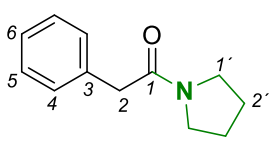


^{13}C-NMR spectrum of *N*-(quinol-8-yl) 2-methylbenzamide (100 MHz, $CDCl_3$).

5.4.2.2 Synthesis of 1-(2-Phenylethanoyl) pyrrolidine (2_{4b})

entry	conditions	yield 2_{4b} [%]
1	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. PyrH (1.5 equiv), K_2CO_3 (2.3 equiv), MeCN (1 M), 15 min 0°C then 17 h rt	90[a]
2	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. **K_2CO_3** (2.3 equiv), PyrH (1.5 equiv), MeCN (0.8 M), 15 min 0°C then 14 h rt	89[a]
3	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. PyrH (1.5 equiv), **NMM** (1.3 equiv), MeCN (1 M), 15 min 0°C then 13 h rt	89[a]
4[22]	1. TCT (33 mol%), NMM (1.3 equiv), MeCN (1 M), 15 min 0°C then 1 h rt 2. PyrH (1.5 equiv), 15 min 0°C then 20 h rt	60[b]

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of mesitylene as internal standard. PyrH = pyrrolidine



2_{4b}

The title compound was produced in excellent yields of 89-90% using K_2CO_3 as base, whereby the addition order of K_2CO_3 and pyrrolidine had no impact on the yield (entries 1+2). NMM proved to be equally suitable as base (entry 3), while the literature protocol [22] gave rise to the amide **2_{4b}** in a deteriorated yield of 60%. Importantly, when amine bases such as NMM are used, the nucleophile must be introduced to the reaction mixture before the base (see chapter 3.2.1, page 24). The details on the optimization of the

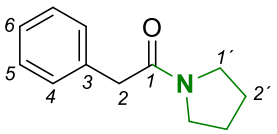
synthesis of the title compound can be found in chapter 3.2.1 on page 24. Optimization studies applying the literature protocol [22] have been described in chapter 4.1.1 on page 34.

Entry 1, PH2936: According to general procedure 4 (chapter 5.3.4 page 50) the title compound was prepared from phenyl acetic acid (136 mg, 1.0 mmol, 1.0 equiv), TCT (72 mg, 380 μmol, 38 mol%), pyrrolidine (130 μL, 1.50 mmol, 1.5 equiv) and K_2CO_3 (320 mg, 2.30 mmol, 2.3 equiv) using FPyr (9.8 μL,10.2 mg, 100 μmol). While chlorination was conducted at $\mathbf{T_1}$ = 40 °C for $\mathbf{t_1}$ = 4 h in MeCN (2 M), amidation was performed at room temperature (= $\mathbf{T_2}$) under stirring for $\mathbf{t_2}$ = 17 h after dilution with MeCN to 1 M. Finally, the crude material (202 mg, yellow oil) was subjected to column chromatography on silica gel (16.4 g, mass crude material/SiO_2 1:81) with EtOAc as eluent, which afforded the title amide as a pale yellow oil in 90% yield (169.9 mg, 0.898 mmol) after drying for 10 min at 10 mbar at the rotary evaporator.

Entry 2, PH2953: This experiment was performed as described in entry 1 with the deviations that **K_2CO_3 was added to the reaction mixture before pyrrolidine** and that the conversion of the intermediate acid chloride to the title amide was accomplished in a 0.75 M concentration (with respect to **1**) within 17 h. Next, column chromatography of the crude material (194 mg, 103%, yellow oil) on silica gel (16.3 g, mass crude product/SiO_2 1:84) with EtOAc delivered the title compound as a pale yellow oil in a virtually identical yield of 89% (168.7 mg, 0.891 mmol).

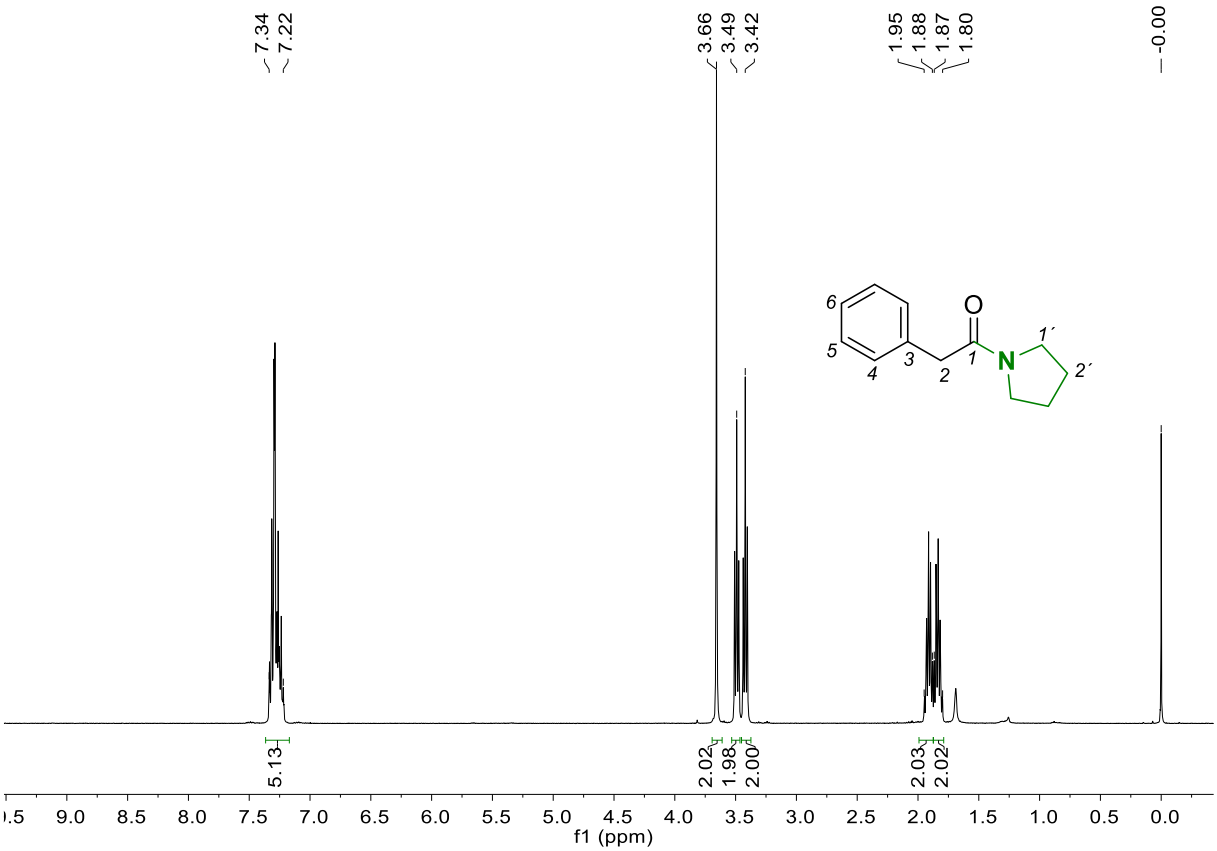
Entry 3, PH2847: As given in general procedure 4 (chapter 5.3.4 page 50) phenyl acetic acid (270 mg, 2.0 mmol, 1.0 equiv) was subjected to chlorination with TCT (143 mg, 0.76 mmol, 38 mol%) in the presence of FPyr (19.7 μL, 20.4 mg, 200 μmol, 10 mol%) in MeCN (1.0 mL, 2 M) under stirring for 4 h at 40 °C. Next, the resulting acid chloride was converted into the title compound using pyrrolidine (250 μL, 3.00 mmol, 1.5 equiv) and NMM (290 μL, 2.60 mmol, 1.3 equiv) in MeCN (addition of 1.0 mL → 1 M). After stirring for 13 h at room temperature and work up, the isolated crude amide $\mathbf{2_{4b}}$ (reddish oil, 389 mg, 103%) was purified by means of column chromatography on silica gel (18.2 g, mass ratio crude product/SiO_2 1:47) employing EtOAc/*n*Hex 95:5 as eluent, which delivered the title compound in 89% yield as a yellow oil (336.5 mg, 1.78 mmol).

Entry 4, PH2790:[22] In agreement with general procedure 5 in chapter 5.3.5 on page 56, phenyl ethanoic acid (68 mg, 0.50 mmol, 1.0 equiv) was initially allowed to react with TCT (31 mg, 0.165 mmol, 33 mol%) and NMM (75 μL, 0.65 mmol, 1.3 equiv) in MeCN (0.50 mL, 1 M) for 15 min at 0 C and 1 h at room temperature. Subsequently, pyrrolidine (65 μL, 0.75 mmol, 1.5 equiv) was added under cooling in ice bath and the reaction suspension was stirred for 20 h at ambient temperature. Finally, ^{1}H-NMR of the crude material with mesitylene (23.9 mg) as internal standard revealed the title compound in 60% yield.

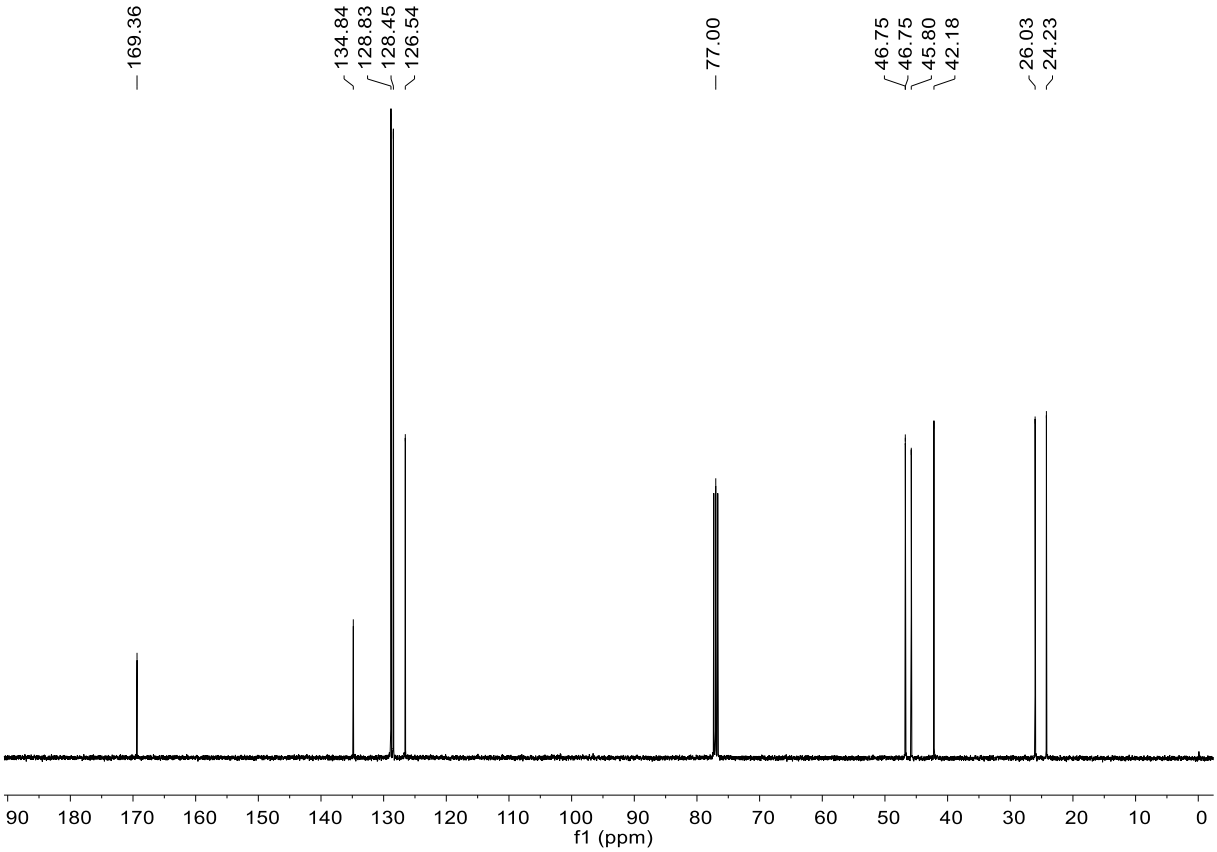


M ($C_{12}H_{15}NO$) = 189.258 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc) = 0.30; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.34-7.22 (m, 5H, 4-H, 5-H. 6-H), 3.66 (s, 2H, 2-H), 3.49 (t, $^3J_{1',2'}$ = 6.7 Hz, 2H, 1´-H_a), 3.42 (t, $^3J_{1',2'}$ = 6.6 Hz, 2H, 1´-H_b),, 1.95-1.88 (m, 2H, 2´-H_b), 1.87-1.80 (m, 2H, 2´-H_a); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 169.36 (C-1), 134.84 (C-3), 128.83 (C-4 or C-5), 128.45 (C-4 or C-5), 126.54 (C-6), 46.75 (C_b-1´), 45.80 (C_a-1´), 42.18 (C-2), 26.03 (C_b-2´), 24.23 (C_a-2´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 230 (1, $[M+allyl]^+$), 218 (20, $[M+Et]^+$), 204 (3, $[M+Me]^+$), 190 (100, $[M+H]^+$), 160 (1), 98 (20, $[(H_2C)_4NCO]^+$), 91 (3, $[Bn]^+$), 72 (2, [pyrrolidine+H]$^+$), 70 (2, [pyrrolidine-H]$^+$), 55 (5).

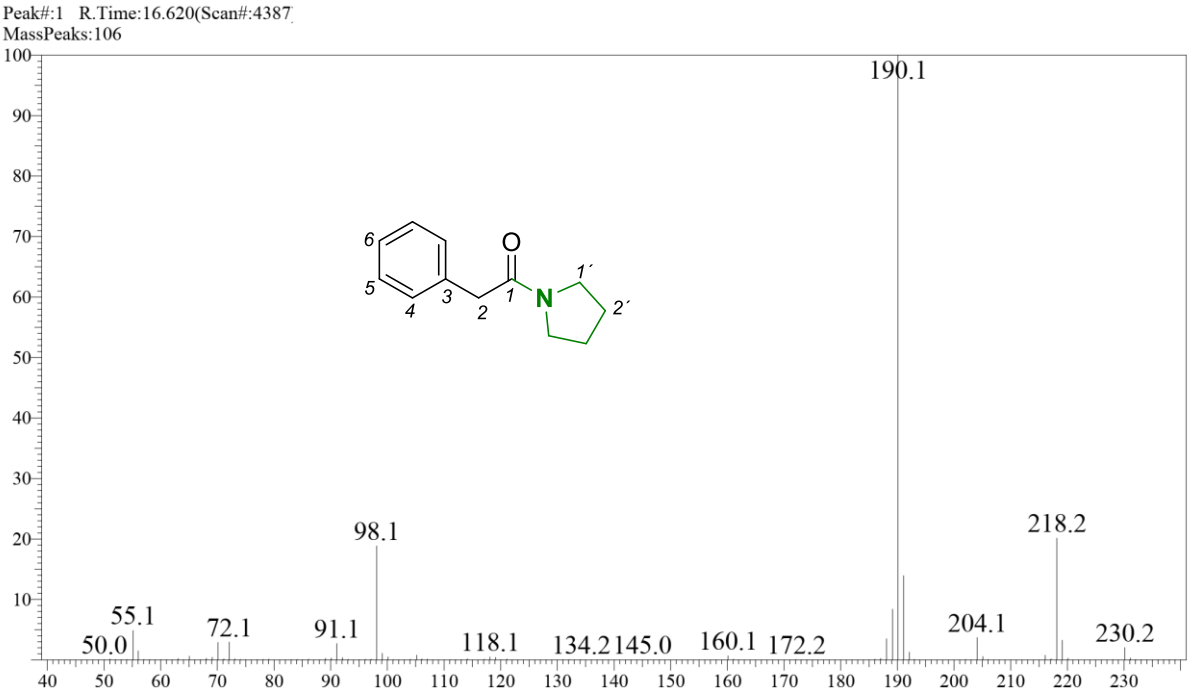
The analytical data is in agreement with the literature.[28]



^{1}H-NMR spectrum of 1-(phenylacetyl) pyrroldine (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of 1-(phenylacetyl) pyrroldine (100 MHz, $CDCl_3$).

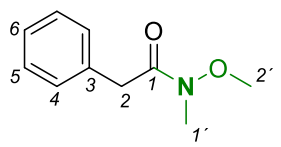


Mass spectrum of 1-(phenylacetyl) pyrroldine (CI, 70 eV).

5.4.2.3 Synthesis of *N*-Methoxy-*N*-methyl 2-phenylethanoic acid amide (2_{4c})

entry	conditions	yield 2_{4c} [%]
1	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. MeO(Me)NH_2Cl (1.3 equiv), K_2CO_3 (3.3 equiv), MeCN (1 M), 15 min 0 °C, 16 h rt	75[a]
2	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 5 h 40 °C 2. MeO(Me)NH_2Cl (1.3 equiv), K_2CO_3 (**2.5 equiv**), MeCN (1 M), 15 min 0 °C, 15 h rt	68[a]
2	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. MeO(Me)NH_2Cl (1.3 equiv), **NMM** (2.3 equiv), MeCN (0.8 M), 15 min 0 °C, 16 h rt	56[b]
3[22]	1. TCT (33 mol%); NMM (2.3 equiv)., MeCN (1 M), 15 min 0 °C, 1 h rt 2. MeO(Me)NH_2Cl (1.3 equiv), 15 min 0 °C, 22 h rt	52[b]

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of mesitylene as internal standard.



2_{4c}

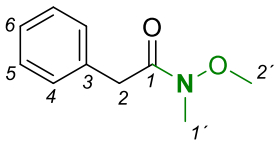
In the case of the Weinreb amide **2_{4c}** K_2CO_3 was realized as optimal base, which allowed the synthesis of the title compound in 75% yield (entries 1+3). Since the nucleophile is engaged as a hydrochloride salt, at least one additional equivalent of base if necessary. Nevertheless, 3.3 equiv of K_2CO_3 instead of 2.5 facilitated an enhanced yield (compare entries 1+2). The literature protocol [22] allowed for the production in a clearly diminished yield of 52%.

Entry 1, PH2926: As stated in general procedure 4 (chapter 5.3.4 page 50) to a solution of phenyl acetic acid (136 mg, 1.00 mmol, 1.0 equiv) and FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) was added TCT (72 mg, 380 μmol, 38 mol%) and the resulting suspension was stirred for 4 h at 40 °C. Next, the reaction mixture was diluted with MeCN (0.50 mL→1 M) and successively MeO(Me)NH_2Cl (127 mg, 1.3 mmol, 1.3 equiv) and K_2CO_3 (456 mg, 3.3 mmol, 3.3 equiv) were introduced. After stirring at room temperature overnight (16 h), the crude material (151 mg, 84%, yellow oil) was purified with the aid of column chromatography on silica gel (16.6 g, ratio mass crude product/SiO_2 1:110) utilizing EtOAc/*n*Hex 40:60. Finally, the title amide was obtained as a pale yellow oil in 75% yield (133.8 mg, 0.747 mmol) after drying at the rotary evaporator at 10 mbar for 10 min.

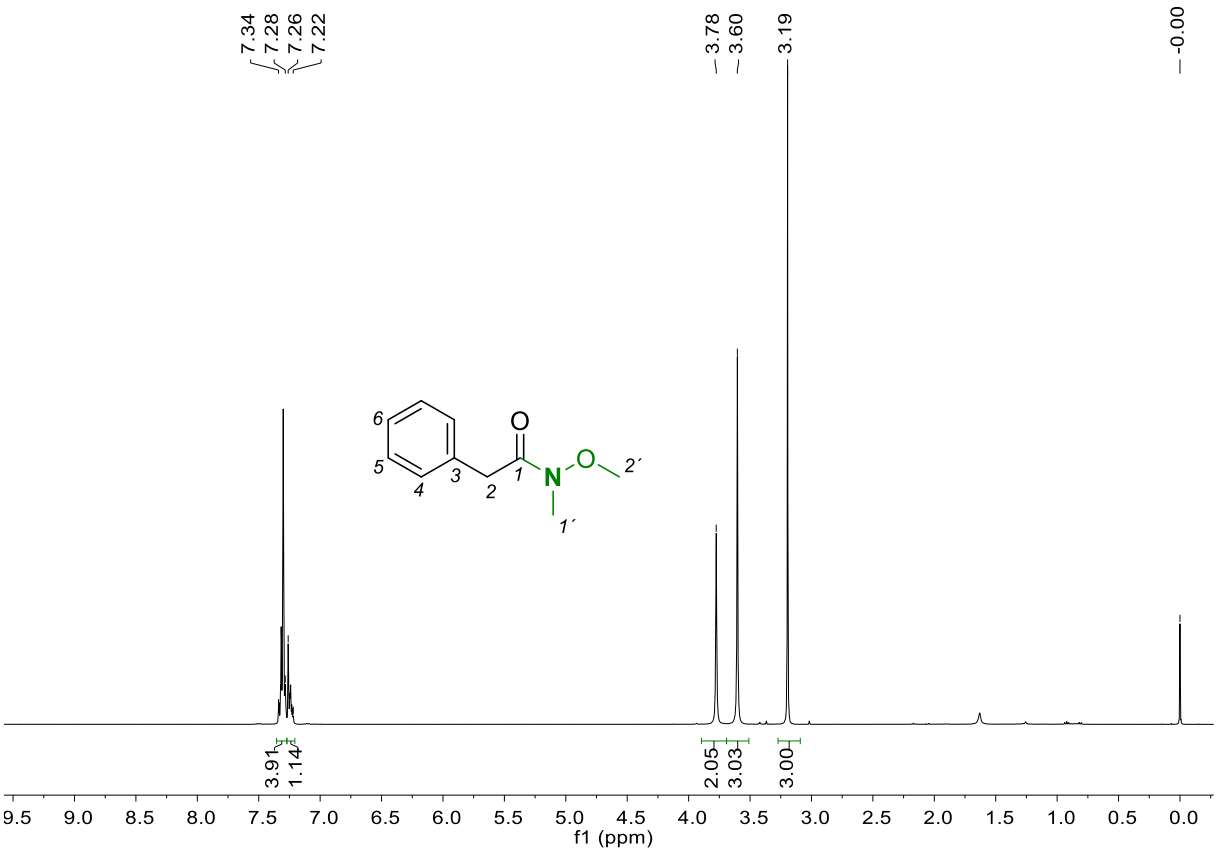
Entry 2, PH2865: As delineated in to general procedure 4 (chapter 5.3.4 page 50), phenyl ethanoic acid (1.00 mmol, 1.0 equiv) was reacted with TCT (38 mol%) in the presence of FPyr (10 mol%) in MeCN (2 M) for 5 h at 40 °C. Afterwards, the acid chloride formed was transformed with MeO(Me)NH_2Cl (1.3 equiv) and K_2CO_3 (346 mg, 2.50 mmol, 2.5 equiv) in MeCN (1 M) through stirring for 15 h at room temperature into the tile amide. Chromatographic purification of the crude material (146 mg, 81%, yellow oil) on silica gel (12.2 g, mass crude product/SiO_2 1:84) furnished the title compound as a pale yellow oil in 68% yield (121.5 mg, 0.678 mmol).

Entry 3, PH2852: To a solution of phenyl acetic acid (68 mg, 0.50 mmol, 1.0 equiv) and FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%) in MeCN (250 μmol, 2 M) was added TCT (38 mg, 200 μmol, 40 mol%) and the emerging suspension as stirred for 4 h at 40 °C as described in general procedure 3 (chapter 5.3.3, page 49). Next, the reaction mixture was diluted with MeCN (250 μmol, 1 M) and treated with MeO(Me)NH_2Cl (63 mg, 0.65 mmol, 1.3 equiv) and NMM (130 μmol, 1.15 mmol, 2.3 equiv) and stirred for 13 h at room temperature. Eventually, the title compound was obtained in 56% yield as determined by means of the ^{1}H-NMR spectrum of the crude material with mesitylene as internal standard (23.7 mg).

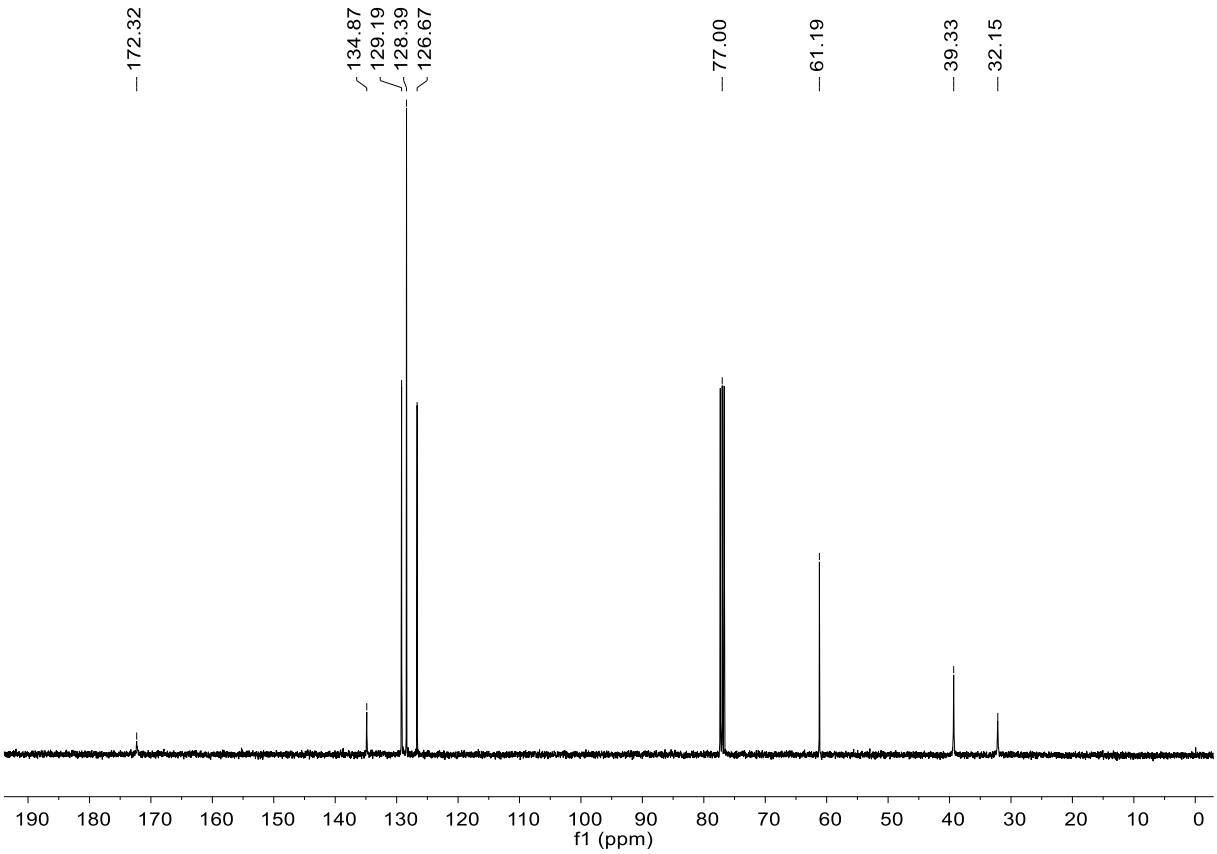
Entry 4, PH2851:[22] Following general protocol 5 in chapter 5.3.5 on page 56 phenyl acetic acid (0.50 mmol, 1.0 equiv) was initially reacted with TCT (31 mg, 0.165 mmol, 33 mol%) and NMM (2.3 equiv) in MeCN (0.50 mL, 1 M). Then, MeO(Me)NH_2Cl (1.3 equiv) was added and the reaction mixture was stirred for 22 h at room temperature. At the end, the title compound was identified in 52% yield according to ^{1}H-NMR of the crude product using mesitylene as internal standard (23.5 mg).



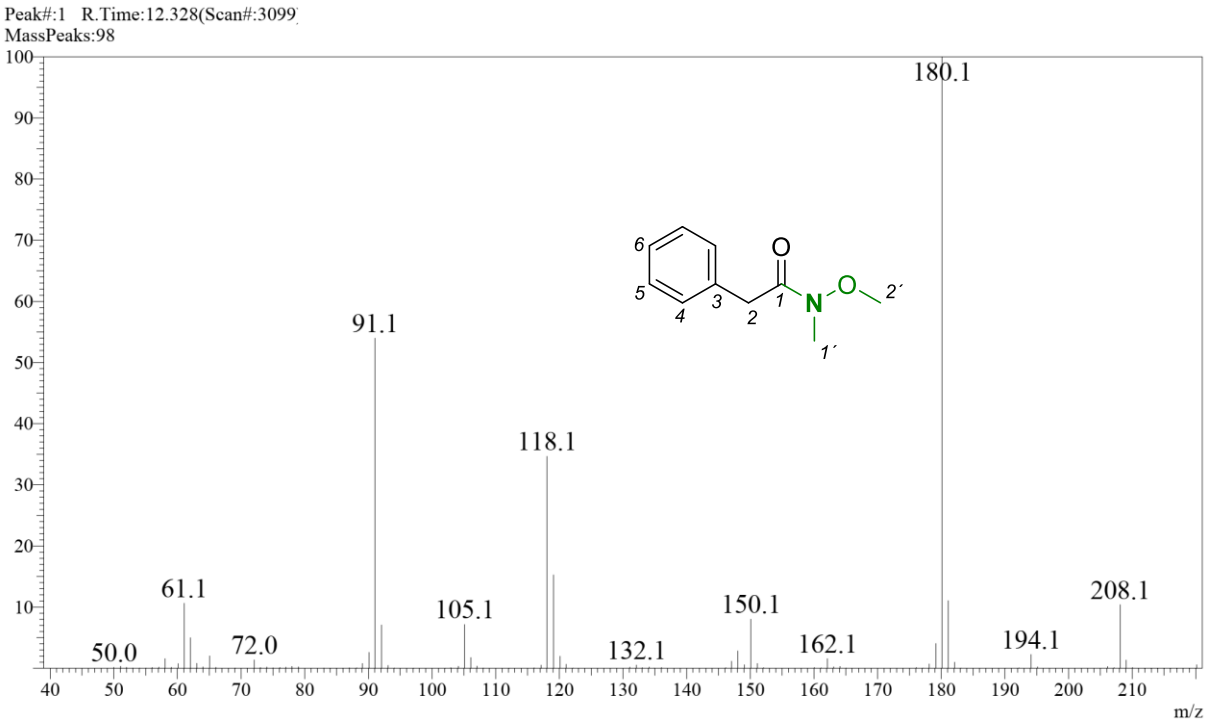
M ($C_{10}H_{13}NO_2$) = 179.219 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 40:60) = 0.31; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.34-7.28 (m, 4H, 4-H, 5-H), 7.26-7.22 (m, 1H, 6-H), 3.78 (s, 2H, 2-H), 3.60 (s, 3H, 2´-H), 3.19 (s, 3H, 1´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 172.32 (C-1), 134.87 (C-3), 129.19 (C-4 or C-5), 128.39 (C-4 or C-5), 126.67 (C-6), 61.19 (C-2´), 39.33 (C-2), 32.15 (C-1´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 208 (11, $[M+Et]^+$), 194 (2, $[M+Me]^+$), 180 (100, $[M+H]^+$), 162 (2), 150 (10), 119 (15, $[BnCO]^+$), 118 (35, $[PhCHCO]^+$), 105 (9, $[PhCO]^+$), 91 (52, $[Bn]^+$), 61 (11, $[HN(Me)OMe]^+$). The NMR data is in agreement with the literature.[29]



^{1}H-NMR spectrum of 1-(phenylacetyl) pyrroldine (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of 1-(phenylacetyl) pyrroldine (100 MHz, $CDCl_3$).

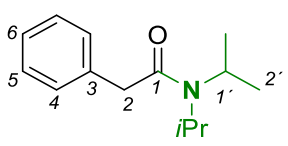


Mass spectrum of 1-(phenylacetyl) pyrroldine (CI, 70 eV).

5.4.2.4 Synthesis of *N,N*-Di-*iso*-propyl 2-phenylethanoic acid amide (2_{4d})

entry	conditions	yield 2_{4d} [%]
1	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4.5 h 40 °C 2. HN*i*Pr$_2$ (1.3 equiv), NMM (1.3 equiv), MeCN (1 M), 15 min 0 °C, 15 h rt	75[a]
2	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4.5 h 40 °C 2. HN*i*Pr$_2$ (1.3 equiv), **K_2CO_3 (2.3 equiv)**, MeCN (1 M), 15 min 0 °C, 16 h rt	71[a]
3	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 5.5 h 40 °C 2. HN*i*Pr$_2$ (1.3 equiv), K_2CO_3 **(1.3 equiv)**, MeCN (1 M), 15 min 0 °C, 16 h rt	68[a]
4	1. TCT (40 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. HN*i*Pr$_2$ (1.3 equiv), **NMM (1.3 equiv)**, MeCN (1 M), 15 min 0 °C, 13 h rt	87[b]
5	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. HN*i*Pr$_2$ (1.3 equiv), **K_2CO_3** (1.3 equiv), MeCN (1 M), 15 min 0 °C, 13 h rt	76[b]
6[22]	1. TCT (33 mol%), NMM (1.3 equiv), MeCN (1 M), 15 min 0 °C, 1 h rt 2. HN*i*Pr$_2$ (1.3 equiv), 15 min 0 °C, 22 h rt	57[b]

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of mesitylene as internal standard.



2_{4d}

In the instance of amide **2_{4d}** application of NMM as base effected a higher yield than K_2CO_3 (entries 1+2). Thereby, the use of 2.3 equiv of K_2CO_3 secured a yield of 71%, whereas 1.3 equiv resulted in a slightly deteriorated outcome (entries 2+3). Since a site-product of a similar polarity had to be separated through chromatography, which caused some lost of the title coumpound, yields determined by internal standard by means of

the crude material are higher (entries 4+5). Finally, the literature procedure [22] gave rise to the title amide in 57% yield only (entry 6).

Entry 1, PH2867: In accordance with general procedure 4 (chapter 5.3.4 page 50) in the beginning phenyl acetic acid (135 mg, 1.00 mmol, 1.0 equiv) was transformed with TCT (72 mg, 0.360 mmol, 38 mol%) in MeCN (0.50 mL, 2 M) into the respective acid chloride using FPyr as catalyst (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) through stirring for 4.5 h at 40 °C. After addition of further MeCN (0.50 mL→1 M), di-*iso*-propylamine (180 μL, 1.3 mmol, 1.3 equiv) and NMM (145 equiv, 1.3 mmol, 1.3 equiv) and stirring for 15 h at room temperature the crude title compound was isolated as a yellow oil (210 mg, 96%). In the end, purification with the aid of column chromatography on silica gel (13.2 g, ratio mass crude material/SiO_2 1:63) employing EtOAc/*n*Hex 20:80 and drying for 10 min at 10 mbar at the rotary evaporator facilitated the isolation of the title amide in 75% yield as a pale yellow oil (163.4 mg, 0.745 mmol).

Entry 2, PH2911: Following general procedure 4 (chapter 5.3.4 page 50) the title compound was produced from phenyl ethanoic acid (1.00 mmol, 1.0 equiv), TCT (38 mol%), di-*iso*-propylamine (1.3 equiv) and **K_2CO_3** (320 mg, 2.30 mmol, 2.3 equiv) using FPyr (10 mol%). Thereby, the chlorination was conducted in MeCN (2 M) at 40 °C under stirring for 4.5 h (= **t_1**) and the subsequent amidation was accomplished under dilution with further MeCN (1 M) under stirring for 16 h (= **t_2**) at room temperature. Thereafter, column chromatographic purification of the crude material (189 mg, 86%, yellow solid) on silica gel (20.4 g, mass crude product/SiO_2 1:108) with EtOAc/*n*Hex 20:80 gave rise to the title amide as a colourless solid (155.2 mg, 0.708 mmol, 71%). In order to load the crude material onto the column, it was dissolved in CH_2Cl_2 (0.5 mL).

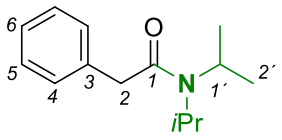
Entry 3, PH2887: The title compound was prepared as described in entry 2 with the difference that 1.3 equiv of K_2CO_3 were used (180 mg, 1.30 mmol, 1.3 equiv) under marginally modified reaction times (**t_1** = 5.5 h, **t_2** = 16 h). Eventually, the crude material (190 mg, 86%, yellow solid) was purified through column chromatography with EtOAc/*n*Hex 20:80 utilizing silica gel (14.9 g, mass crude product/silica 1:78), which facilitated the isolation of the title amide in 68% yield as a colourless solid (150.0 mg, 0.684 mmol, 68%).

Entry 4, PH2848: According to general protocol 3 (chapter 5.3.3, page 49) phenyl acetic acid (68 mg, 0.50 mmol, 1.0 equiv) was transformed into *N,N*-di-*iso*-propyl phenylacetamide employing TCT (38 mg, 0.200 mmol, 40 mol%), FPyr (4.9 μmol, 5.1 mg, 50 μmol, 10 mol%), di-*iso*-propylamine (90 μL; 0.650 mmol, 1.3 equiv) and NMM (75 μL, 0.65 mmol, 1.3 equiv). At the outset, chlorination was performed in MeCN (250 μL, 2 M) at 40 °C for 4 h, while amidation was carried out under stirring for 13 h at ambient temperature. ^{1}H-NMR of the crude material

verified the title compound in a yield of 87% as determined by means of mesitylene (23.2 mg as internal standard.

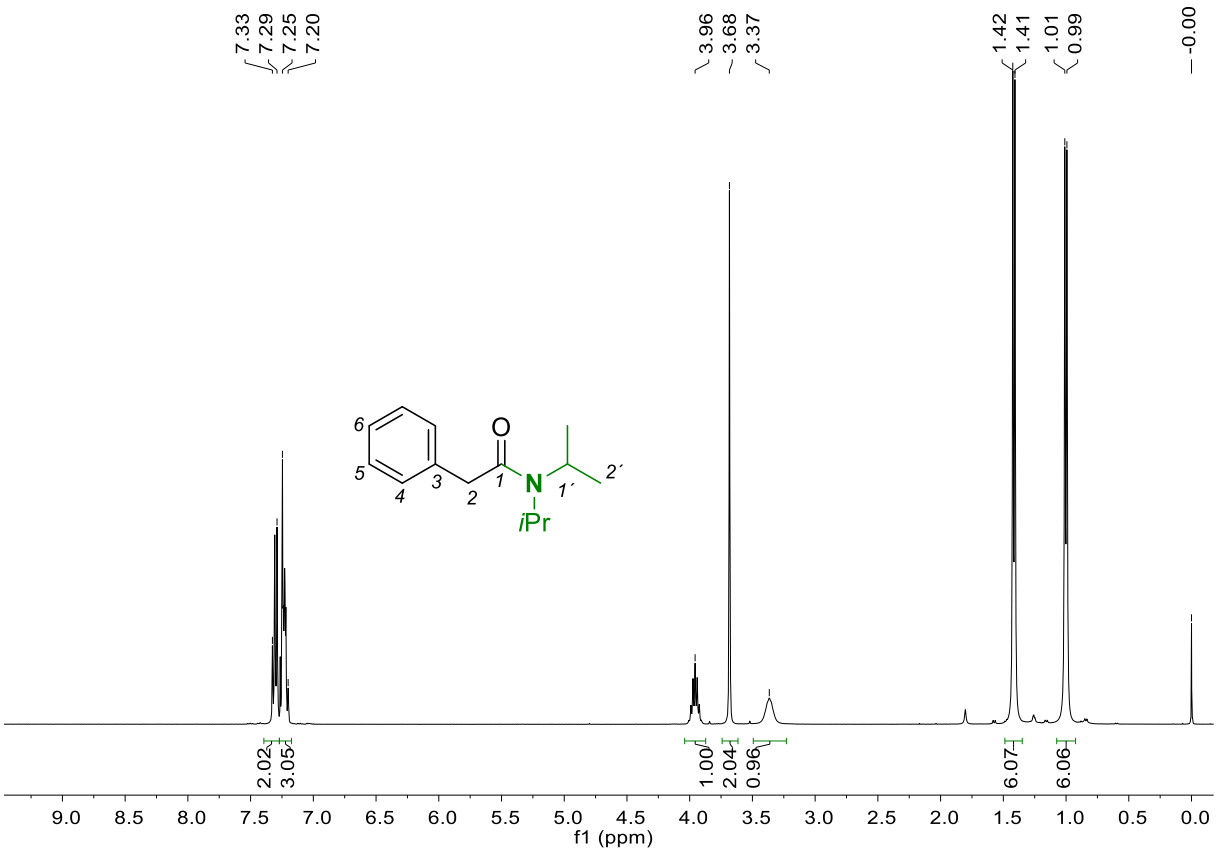
Entry 5, PH2849: This experiment was executed as described in entry 4 with the deviation that **K_2CO_3** (90 mg, 0.65 mmol,1.3 equiv) was used as base instead of NMM. In the end, the title compound was proved in 76% yield according the ^{1}H-NMR spectrum of the crude material with mesitylene (22.3 mg) as internal standard.

Entry 6, PH2850:[22] Following general protocol 5 (chapter 5.3.5 on page 56) NMM (1.3 equiv) was added to a suspension of phenyl acetic acid (0.50 mmol, 1.0 equiv) and TCT (31 mg, 0165 mmol, 33 mol%) in MeCN (0.50 mL, 1 M) at 0 °C. After 1 h of stirring at ambient temperature, di-*iso*-propylamine (1.3 equiv) was introduced and stirring was continued to 22 h at room temperature. Next, ^{1}H-NMR of the crude material indicated the title amide in 57% yield as judged by mesitylene (23.8 mg) as internal standard.

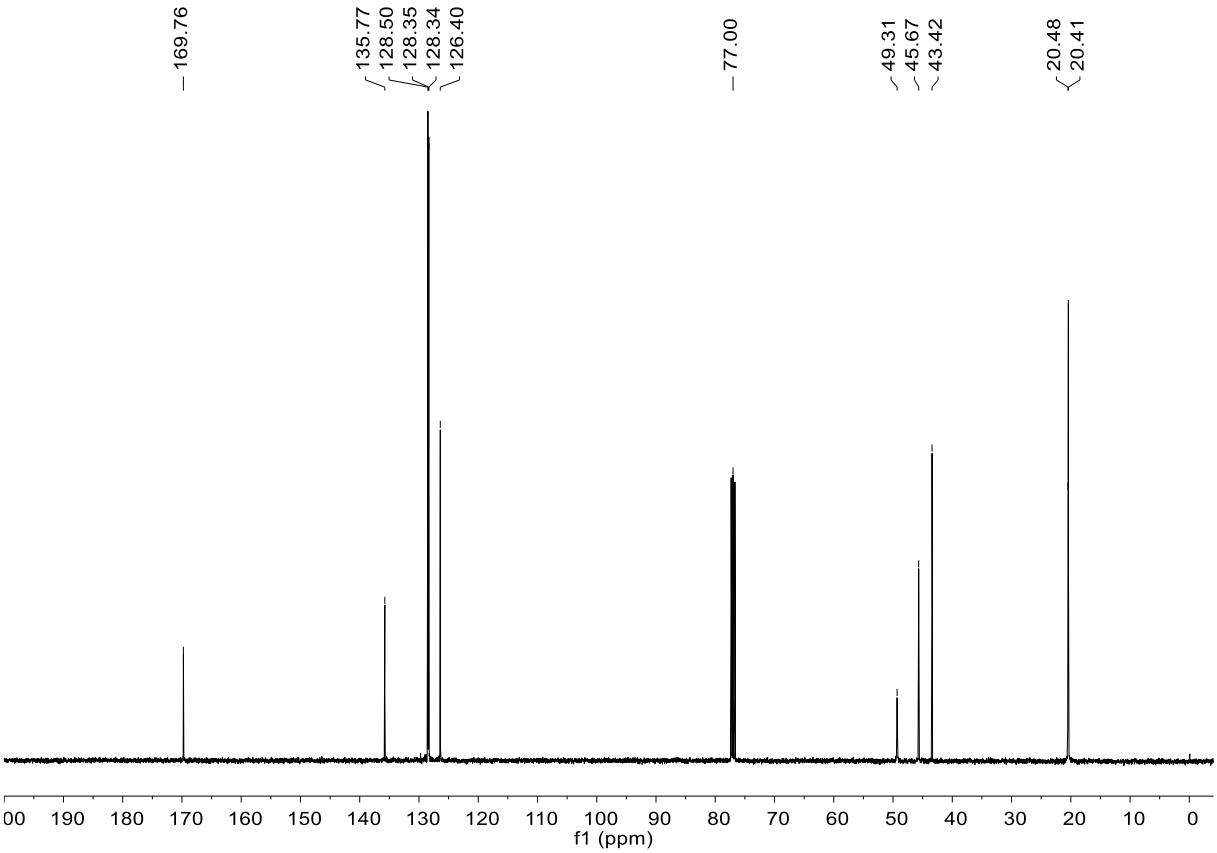


M ($C_{14}H_{21}NO$) = 219.328 g/mol; **mp.** = 49-51 °C; **lit.-mp.** 45-47 °C;[30] **r_f** (SiO_2, EtOAc/*n*Hex 20:80) = 0.33; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.33-7.29 (m, 2H, 5-H), 7.25-7.20 (m, 3H, 4-H, 6-H), 3.96 (sept., $^3J_{1´,2´}$= 6.7 Hz, 1H, 1´-H_a), 3.68 (s, 2H, 2-H), 3.37 (br. s, 1H, 1´-H_b), 1.42 (d, $^3J_{1´,2´}$ = 6.9 Hz, 6H, 2´-H_b), 1.00 (d, $^3J_{1´,2´}$ = 6.7 Hz, 6H, 2´-H_a); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 169.76 (C-1), 135.77 (C-3), 128.50 (C-4 or C-5), 128.35 (C-4 or C-5), 126.40 (C-6), 49.31 (C_a-1´), 45.67 (C_b-1´), 43.42 (C-2), 20.48 (C_a-2´), 20.41 (C_b-2´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 260 (1, [M+allyl]$^+$), 248 (25, [M+Et]$^+$), 234 (2, [M+Me]$^+$), 220 (100, [M+H]$^+$), 206 (2), 192 (4), 176 (6, [M-*i*Pr]$^+$), 150 (3), 128 (31, [*i*Pr$_2$NCO]$^+$), 91 (11, [Bn]$^+$), 86 (31, [*i*PrN(H)CHCH$_3$]$^+$).

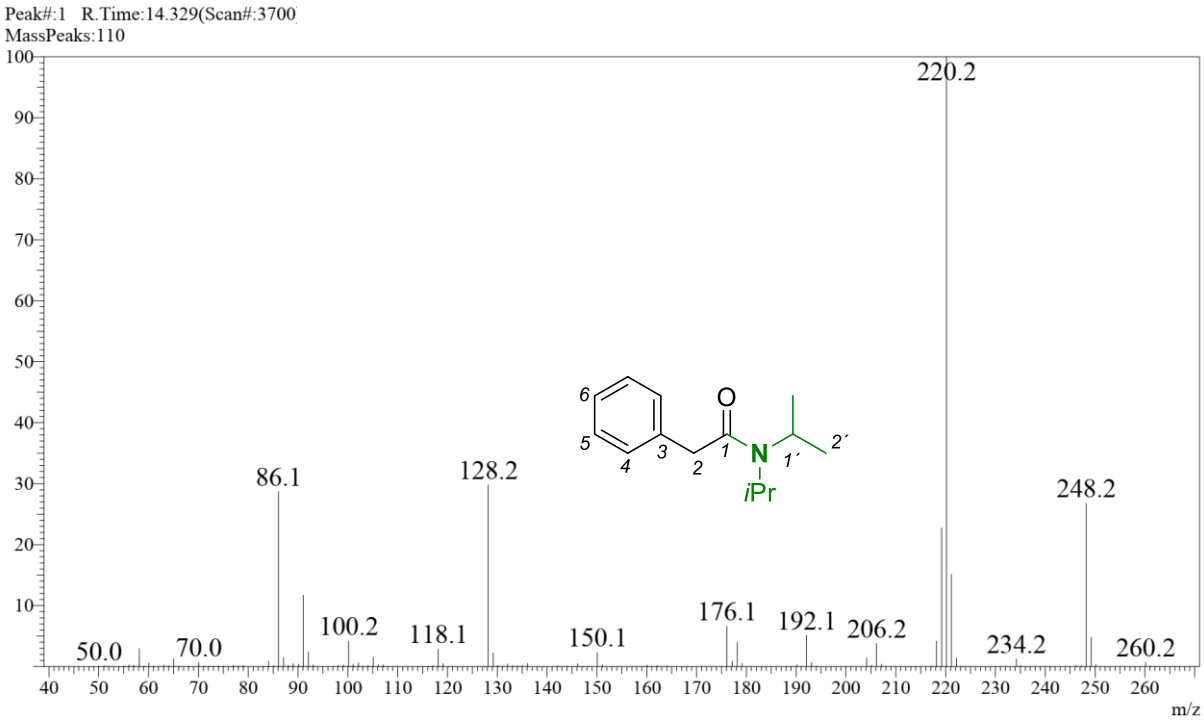
The NMR data is in agreement with the literature.[30]



^{1}H-NMR spectrum of *N,N*-di-*iso*-propyl 2-phenylethanoic acid amide (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *N,N*-di-*iso*-propyl 2-phenylethanoic acid amide (100 MHz, $CDCl_3$).

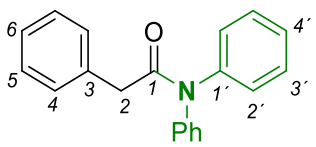


Mass spectrum of *N,N*-di-*iso*-propyl 2-phenylethanoic acid amide (CI, 70 eV).

5.4.2.5 Synthesis of *N,N*-Diphenyl 2-phenylethanoic amide (2_{4e})

entry	conditions	yield 2_{4e} [%]
1	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. $HNPh_2$ (1.2 equiv), K_2CO_3 (1.3 equiv), MeCN (1 M), 15 min 0 °C, 18 h rt	68[a]
2	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. $HNPh_2$ (1.2 equiv), K_2CO_3 (1.3 equiv), MeCN (1 M), 15 min 0 °C, 13 h rt	72[b]
3	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. $HNPh_2$ (1.2 equiv), **NMM** (1.3 equiv), MeCN (1 M), 15 min 0 °C, 13 h rt	34[b]
4[22]	1. TCT (33 mol%), NMM (1.3 equiv), MeCN (1 M), 15 min 0 °C, 1 h rt 2. $HNPh_2$ (1.3 equiv), 15 min 0 °C, 19 h rt	47[b]

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of mesitylene as internal standard.



2_{4e}

Coupling of sterically demanding diphenylamine with phenyl acetic acid provided the title compound in 68/72% yield, when K_2CO_3 was used as base. NMM turned out to be less feasible, since it gave rise to the diphenylamide **2_{4e}** in only 34% yield (entry 3). Interestingly, the literature protocol [22] furnished the title amide in only 47% yield (entry 4).

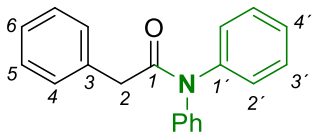
Entry 1, PH2970: In accordance with general procedure 4 (chapter 5.3.4 page 50) phenyl acetic acid (136 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL,

2 M) for 4 h at 40 °C. Next, MeCN (0.50 mL→1 M), diphenylamine (204 mg, 1.20 mmol, 1.2 equiv) and K_2CO_3 (180 mg, 1.30 mmol, 1.3 equiv) were added successively and the reaction mixture was stirred for 18 h at room temperature. Column chromatographic purification of the crude product (301 mg, 105%, yellow oil, ratio **2$_{4e}$**/$HNPh_2$ 59:41 according to ^{1}H-NMR) on silica gel (23.4 g, mass ratio crude material/SiO_2 1:81) harnessing EtOAc/*n*Hex as eluent mixture, concentration with chloroform to remove residual solvent impurities (2 x 2 mL) and drying at 5 mbar at the rotary evaporator for 15 min enabled the isolation of the title amide as a pale yellow oil (194.9 mg, 0.678 mmol, 68%), which turned solid upon storage at ambient temperature.

Entry 2, PH2871: As stated in general protocol 3 (chapter 5.3.3, page 49) phenyl ethanoic acid (68 mg, 0.50 mmol, 1.0 equiv) was converted to the analogous acid chloride with TCT (36 mg, 0.19 mmol, 38 mol%) and FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%) in MeCN (0.25 mL, 2 M) through stirring for 4 h at 40 °C. Afterwards, the reaction suspension was treated with further MeCN (0.25 mL→1 M), $HNPh_2$ (102 mg, 0.60 mmol, 1.2 equiv) and K_2CO_3 (90 mg, 0.65 mmol, 1.3 equiv) and stirred for 13 h at room temperature. Eventually, the ^{1}H-NMR spectrum of the crude material revealed the title compound in 72% yield as judged by means of mesitylene (23.5 mg) as internal standard.

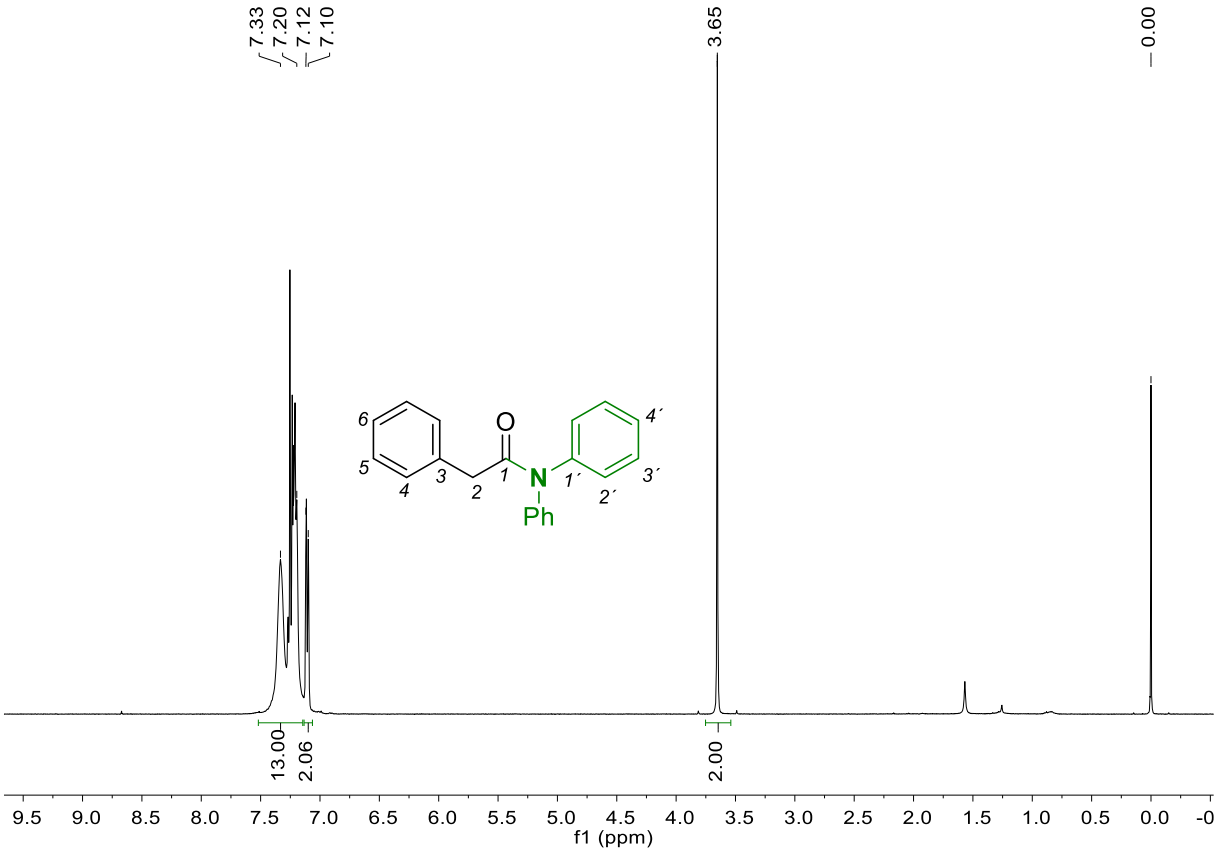
Entry 3, PH2872: This experiment was performed as described in entry 2 with the deviation that **NMM** (75 μL, 0.65 mmol, 1.3 equiv) was used instead of K_2CO_3. This alteration resulted in the formation of the title amide in a deteriorated yield of 34% as determined by the ^{1}H-NMR spectrum of the crude material with the aid of mesitylene (23.2 mg) as internal standard.

Entry 4, PH2908:[22] As described in general protocol 5 (chapter 5.3.5 on page 56) phenyl ethanoic acid (0.50 mmol, 1.0 equiv) was reacted with TCT (31 mg, 0.19 mmol, 38 mol%) and NMM (1.3 equiv) in MeCN and afterwards diphenylamine (1.2 equiv) was added. Post stirring for 19 h at ambient temperature, ^{1}H-NMR of the crude material with mesitylene (23.4 mg) as internal standard revealed the title compound in 47% yield.

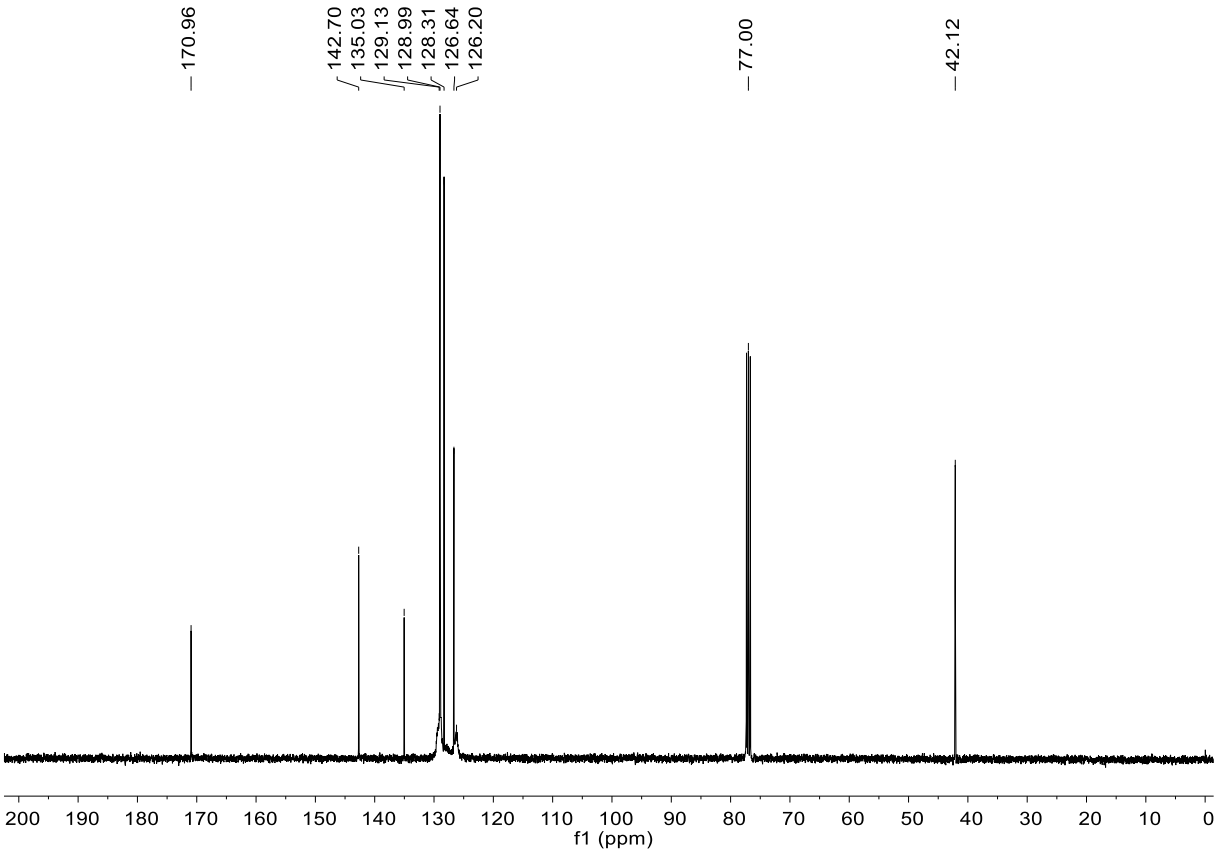


M ($C_{20}H_{17}NO$) = 287.362 g/mol; **mp.** = 71-73 °C, **lit.-mp.** = 70-71 °C;[30] **r_f** (SiO_2, EtOAc/*n*Hex 20:80) = 0.30; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.33-7.20 (m, 13H, 5-H, 6-H, 2´-H, 3´-H, 4´-H), 7.12-7.10 (m, 2H, 4-H), 3.65 (s, 2H, 2-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 170.96 (C-1), 142.70 (C-1´), 135.03 (C-3), 129.13 (br., C-3´, C-4´ or C-5´), 128.99 (C-5), 128.31 (C-4), 126.64 (C-6), 126.20 (br., C-3´, C-4´ or C-5´), 42.12 (C-2); **GC-MS** (CI, 70 eV) m/z [u] (%) = 328 (2, $[M+ally]^+$), 316 (38, $[M+Et]^+$), 302 (3, $[M+Me]^+$), 288 (100, $[M+H]^+$), 193 (4), 169 (31, $[HNPh_2]^+$), 91 (5, $[Bn]^+$).

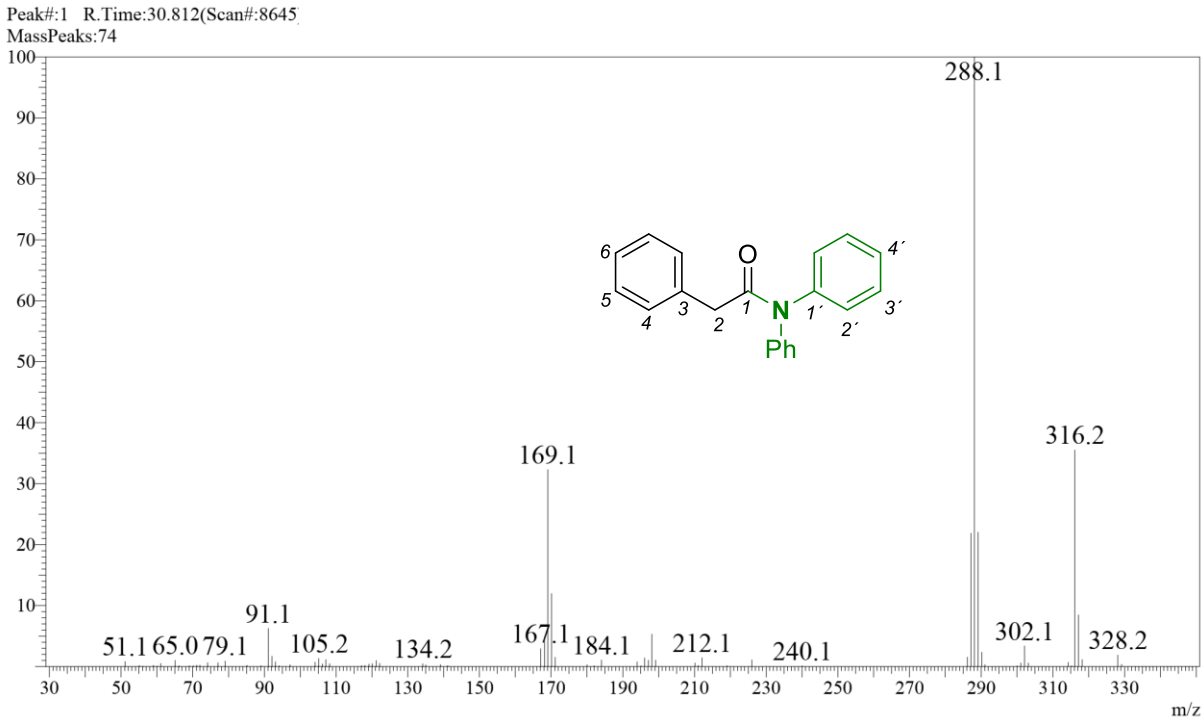
The NMR data is in agreement with literature.[30]



^{1}H-NMR spectrum of *N,N*-diphenyl phenylethanoic amide (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *N,N*-diphenyl phenylethanoic amide (100 MHz, $CDCl_3$).

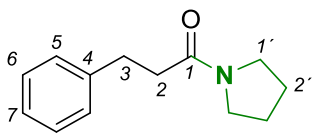


Mass spectrum of *N,N*-diphenyl phenylethanoic amide (CI, 70 eV).

5.4.2.6 Synthesis of 1-(3-Phenylpropanoyl)pyrrolidine (2_{5b})

entry	conditions	yield 2_{5b} [%]
1	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. PyrH (1.5 equiv), K_2CO_3 (2.3 equiv), MeCN (0.8 M), 15 min 0 °C, 13 h rt	91[a]
2	1. TCT (38 mol%), FPyr (10 mol%), **EtOAc** (2 M), 6 h 40 °C 2. PyrH (1.5 equiv), K_2CO_3 (1.3 equiv), **EtOAc** (1 M), 15 min 0 °C, 2 h rt	86[a]
3	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4.5 h 40 °C 2. PyrH (1.5 equiv), K_2CO_3 (2.3 equiv), MeCN (1 M), 15 min 0 °C, 2 h rt	97[a]
4	1. TCT (38 mol%), FPyr (10 mol%), **EtOAc** (2 M), 6 h 40 °C 2. PyrH (1.5 equiv), K_2CO_3 (1.3 equiv), **EtOAc** (1 M), 15 min 0 °C, 2 h rt	97[a]
5	1. TCT (38 mol%), FPyr (10 mol%), **THF** (2 M), 6 h 40 °C 2. PyrH (1.5 equiv), K_2CO_3 (2.3 equiv), **THF** (1 M), 15 min 0 °C, 2 h rt	98
6	1. TCT (38 mol%), FPyr (10 mol%), THF (2 M), 6 h 40 °C 2. PyrH (1.5 equiv), K_2CO_3 (**1.3 equiv**), THF (1 M), 15 min 0 °C, 2 h rt	86

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of mesitylene as internal standard. PyrH = pyrrolidine



2_{5b}

The title compound was produced in excellent yields of 86-91% using either MeCN or EtOAc as solvent (entries 1+2). Since chromatographic purification usually results in the loss of some material, yields determined from the ^{1}H-NMR spectra of the crude material by means of an internal standard are higher (entries 3+4). Finally, also THF was realized as suitable solvent for the synthesis of the title amide (entries 5+6). Thereby, utilization of 2.3 equiv K_2CO_3 instead of 1.3 effected an enhanced yield.

Entry 1, PH2962: In accord with general procedure 4 (chapter 5.3.4 page 50) 3-phenyl propionic acid (150 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mol, 38 mol%) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) at 40 °C for 4 h. Next, to the reaction suspension were added further MeCN (0.75 mL→0.8 M), pyrrolidine (130 μL, 1.5 mmol, 1.5 equiv) and K_2CO_3 (320 mg, 2.3 mmol, 2.3 equiv). After stirring for 13 h at room temperature and work up, the crude title compound (215 mg, 106%, yellow oil) was subjected to purification by means of column chromatography on silica gel (18.7 g, crude **2**$_{5b}$/SiO_2 1:87) with EtOAc. Drying at the rotary evaporator at 5 mbar for 15 min allowed the isolation of the title compound in 91% yield as a pale yellow oil (185.3 mg, 0.911 mmol).

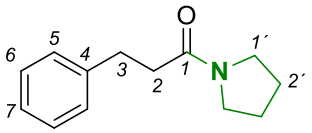
Entry 2, PH2982: In agreement with general protocol 4 (chapter 5.3.4 page 50) 3-phenyl propanoic acid (1.00 mmol, 1.0 equiv) was transformed into the corresponding acid chloride with TCT (38 mol%) and FPyr (10 mol%) in **EtOAc** (0.50 mL, 2 M) through heating to 40 °C for 6 h. In the following, the reaction suspension was diluted with further EtOAc (0.50 mL→1 M) and treated with pyrroldine (1.5 equiv) and K_2CO_3 (180 mg, 1.3 mmol, 1.3 equiv) and stirred for 2 h at room temperature. Finally, column chromatographic purification of the crude product (188 mg, 93%, yellow oil) on silica gel (17.0 g, mass ratio crude material/silica 1:90) with EtOAc delivered the title amide as a colourless oil in 86% yield (174.5 mg, 0.858 mmol).

Entry 3, PH2980: As described in general protocol 3 (chapter 5.3.3, page 49) to a mixture of 3-phenyl propanoic acid (75 mg, 0.50 mmol, 1.0 equiv) and FPyr (4.9 μL, 5.1 mg, 50 μL, 10 mol%) was added TCT (36 mg, 0.19 mmol, 38 mol%) and the resulting suspension was stirred at 40 °C for 4.5 h. Next, further MeCN (0.25 mL→1 M), pyrroldine (65 μL, 0.75 mmol, 1.5 equiv) and K_2CO_3 (160 mg, 1.15 mmol, 2.3 equiv) were introduced and stirring was continued for 2 h at room temperature. Finally, ^{1}H-NMR of the crude material with mesitylene (25.0 mg) as internal standard indicated the title amide in 97% yield.

Entry 4, PH2975: As stated in general protocol 3 (chapter 5.3.3, page 49) 3-phenyl propanoic acid (0.50 mmol, 1.0 equiv) was converted with TCT (38 mol%) in the presence of FPyr (10 mol%) in **EtOAc** (0.25 mL, 2 M) through stirring at 40 °C for 6 h. Thereafter, amidation was accomplished after addition of further EtOAc (0.25 mL→1 M) with pyrrolidine (1.5 equiv) and **K_2CO_3** (90 mg, 0.65 mmol, **1.3 equiv**) under stirring for 2 h at room temperature. In the end, the title compound was unveiled in 97% yield as determined by ^{1}H-NMR with mesitylene (25.0 mg) as internal standard.

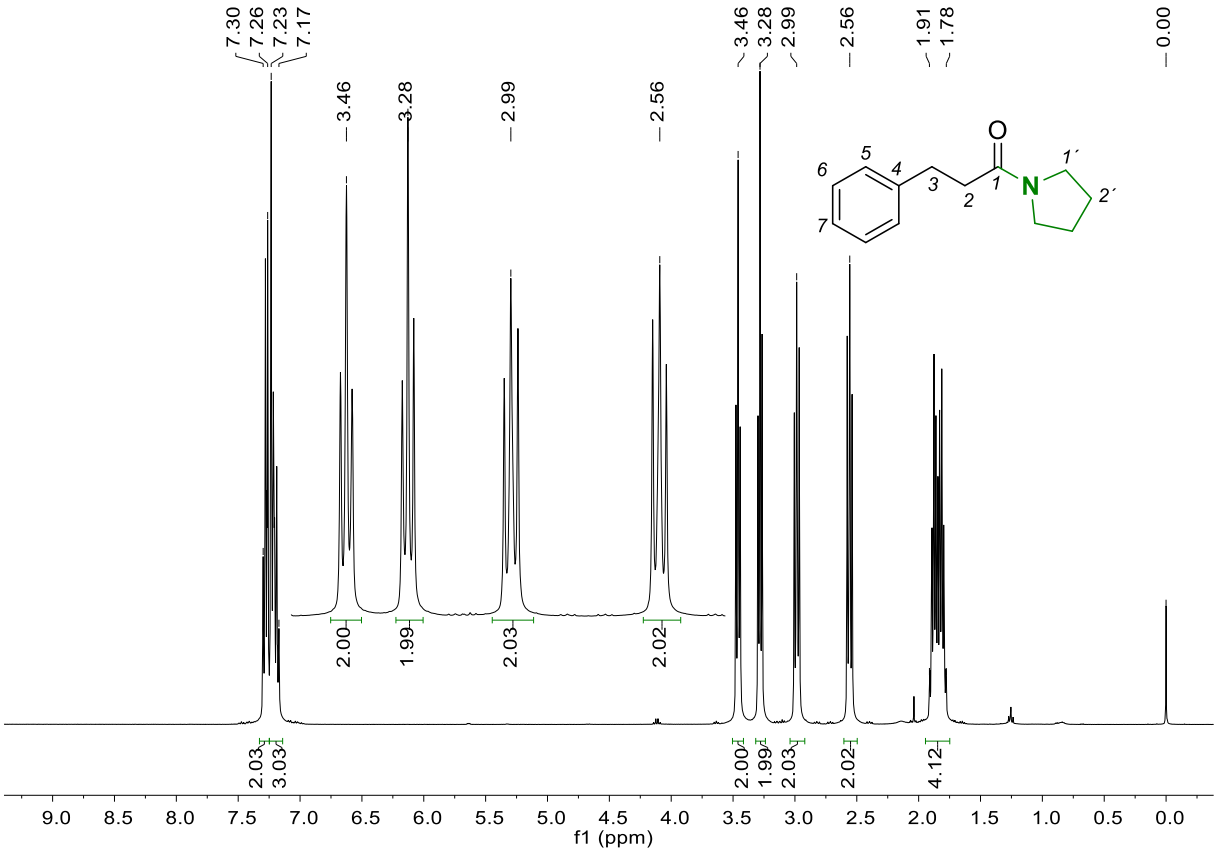
Entry 5, PH2963: The current experiment was performed as given in entry 3 with the difference that **THF** (reagent-grade) was exploited as solvent instead of MeCN and the amidation step **6→2** was stirred overnight (13 h). Eventually, ^{1}H-NMR of the crude product showed the title amide in 98% yield using mesitylene (25.1 mg) as internal standard.

Entry 6, PH2977: This experiment was conducted as given in entry 4 with the alteration that **THF** (reagent-grade) was used as reaction solvent instead of EtOAc. The title compound could by verified in 86% yield, which was determined by ^{1}H-NMR of the crude material with mesitylene (24.8 mg) as internal standard.

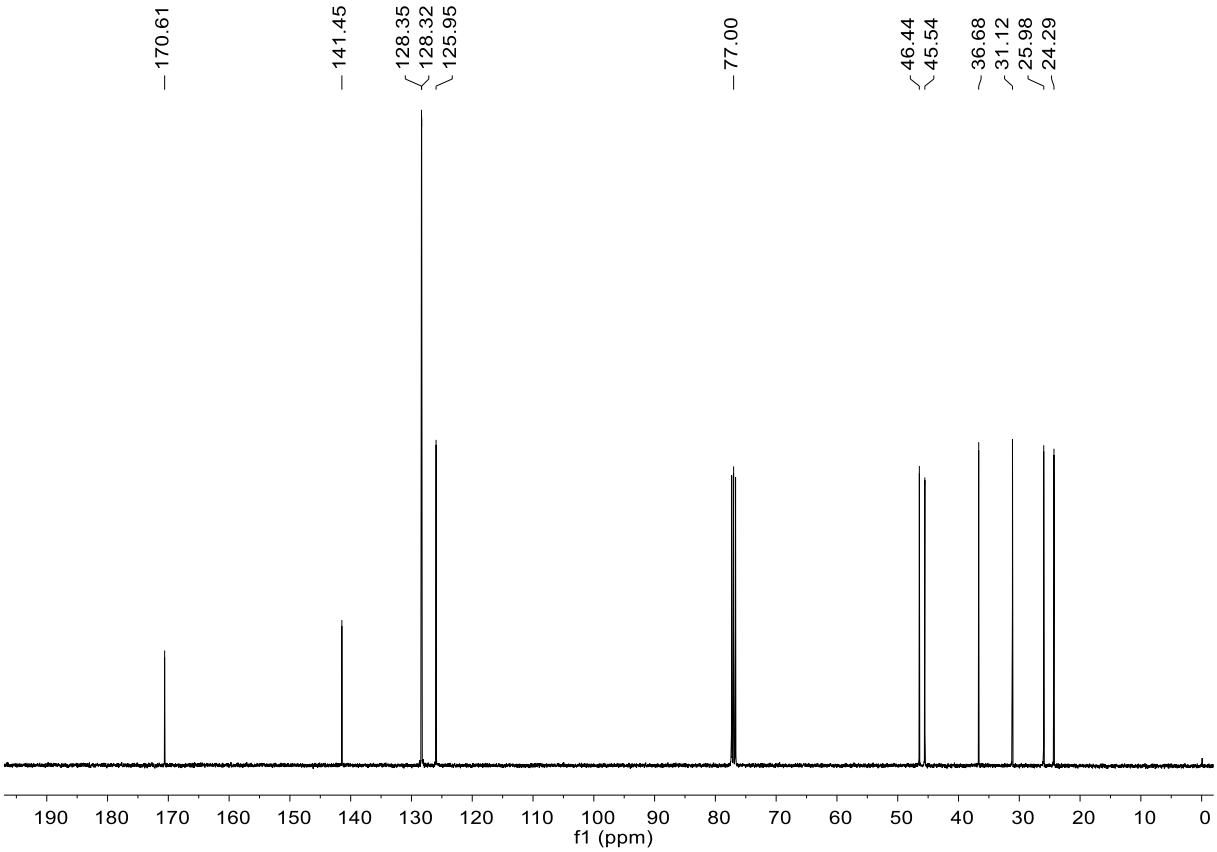


M ($C_{13}H_{17}NO$) = 203.285 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc) = 0.29; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.30-7.26 (m, 2H, 6-H), 7.23-7.17 (m, 3H, 5-H, 7-H), 3.46 (t, $^{3}J_{1´,2´}$ = 6.6 Hz, 2H, 1´-H_a), 3.28 (t, $^{3}J_{1´,2´}$ = 7.0 Hz, 2H, 1´-H_b), 2.99 (t, $^{3}J_{3,2}$ = 8.3 Hz, 2H, 3-H), 2.56 (t, $^{3}J_{2,3}$ = 8.0 Hz, 2H, 2-H), 1.91-1.78 (m, 4H, 2´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 170.61 (C-1), 141.45 (C-4), 128.35 (C-5 or C-6), 128.32 (C-5 or C-6), 125.95 (C-7), 46.44 (C_b-1´), 45.54 (C_a-1´), 36.68 (C-2), 31.12 (C-3), 25.98 (C_b-2´), 24.29 (C_a-2´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 244 (2, $[M+allyl]^+$), 232 (27, $[M+Et]^+$), 218 (3, $[M+Me]^+$), 204 (100, $[M+H]^+$), 112 (4), 98 (3, $[(H_2C)_4NCO]^+$), 91 (2, $[Bn]^+$), 72 (5, $[pyrrolidine+H]^+$), 70 (4, $[pyrrolidine-H]^+$).

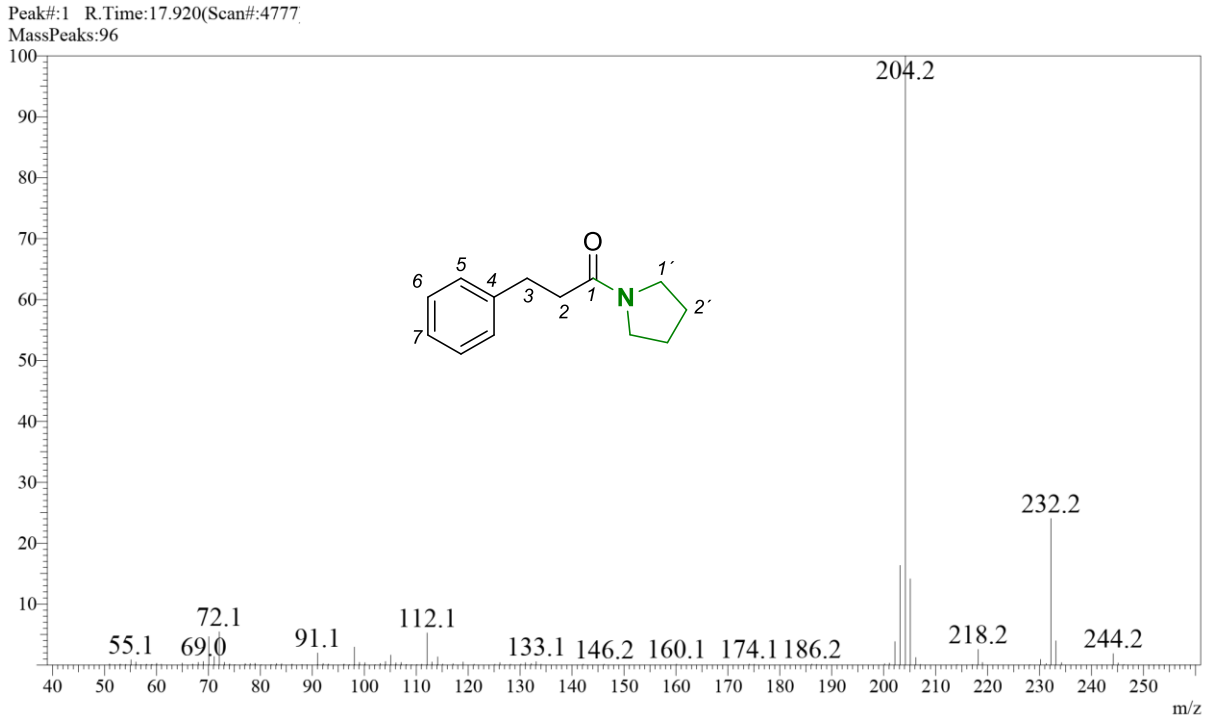
The NMR data is in agreement with the literature.[31]



^{1}H-NMR spectrum of 1-(3-phenylpropanoyl)pyrrolidine (400 MHz, $CDCl_3$).

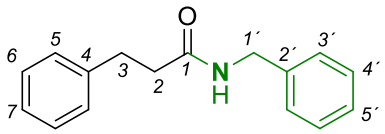


^{13}C-NMR spectrum of 1-(3-phenylpropanoyl)pyrrolidine (100 MHz, $CDCl_3$).



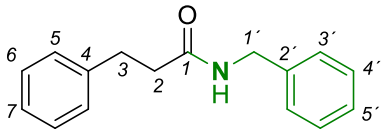
Mass spectrum of 1-(3-phenylpropanoyl)pyrrolidine (CI, 70 eV).

5.4.2.7 Synthesis of *N*-Benzyl 3-phenylpropanoic acid amide (2_{5f})



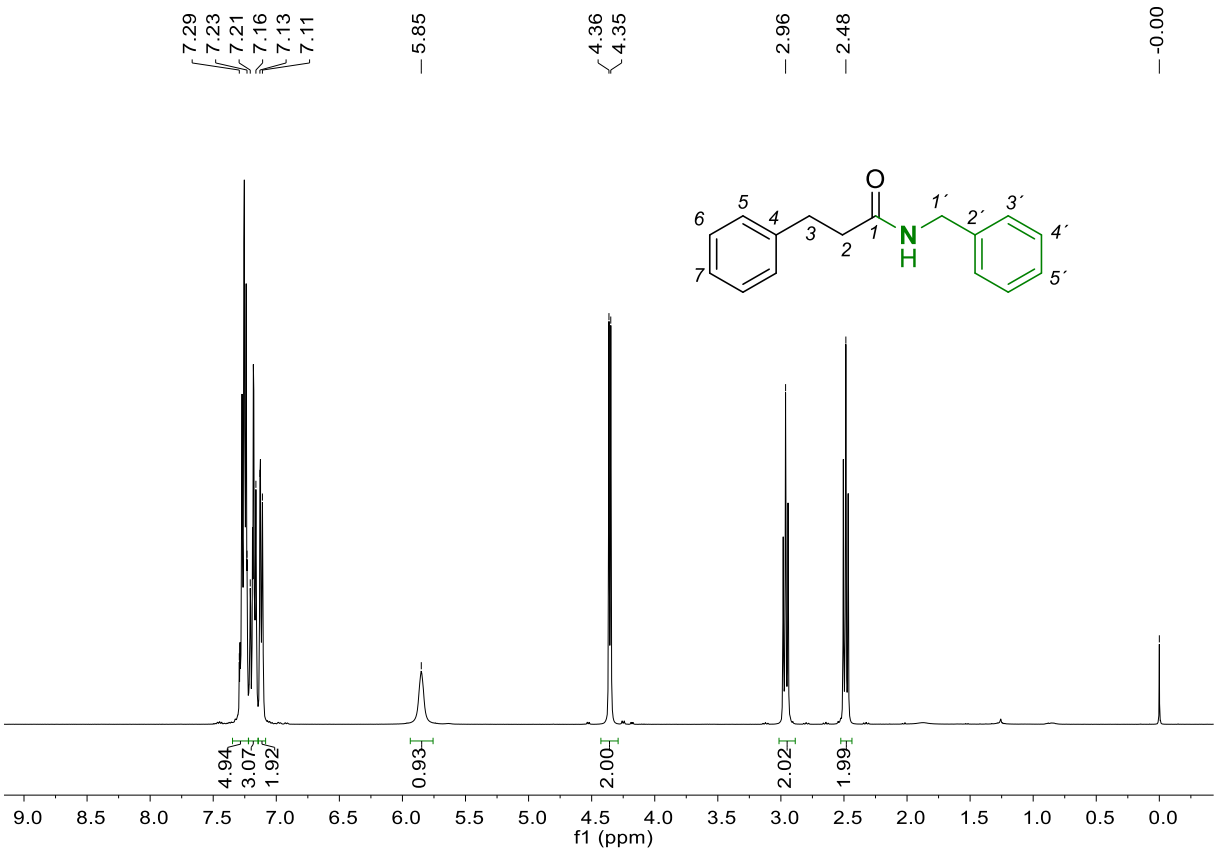
2_{5f}

PH2986: In accordance with general procedure 4 (chapter 5.3.4 page 50) 3-phenyl propionic acid (150 mg, 1.00 mmol, 1.0 equiv) reacted with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in EtOAc (0.50 mL, 1 M) at 40 °C for 6 h. Afterwards the resulting reaction suspension containing 3-phenyl propanoyl chloride was diluted with EtOAc (0.50 mL→1 M) and benzylamine (140 μL, 1.3 mmol, 1.3 equiv) and K_2CO_3 (180 mg, 1.3 mmol, 1.3 equiv) were added at 0 °C and stirring was continued at room temperature overnight (14 h). Finally, the title compound was isolated as a colourless solid (191.1 mg, 0.799 mmol, 80%) after chromatographic purification of the crude material (246 mg, 103%, pale yellow solid) on silica gel (17.3 g, mass crude product/SiO_2 1:71) using EtOAc/*n*Hex 50:50 as eluent mixture, concentration with $CHCl_3$ (2 x 2 mL) to remove solvent impurities and drying at the rotary evaporator for 15 min at 5 mbar.

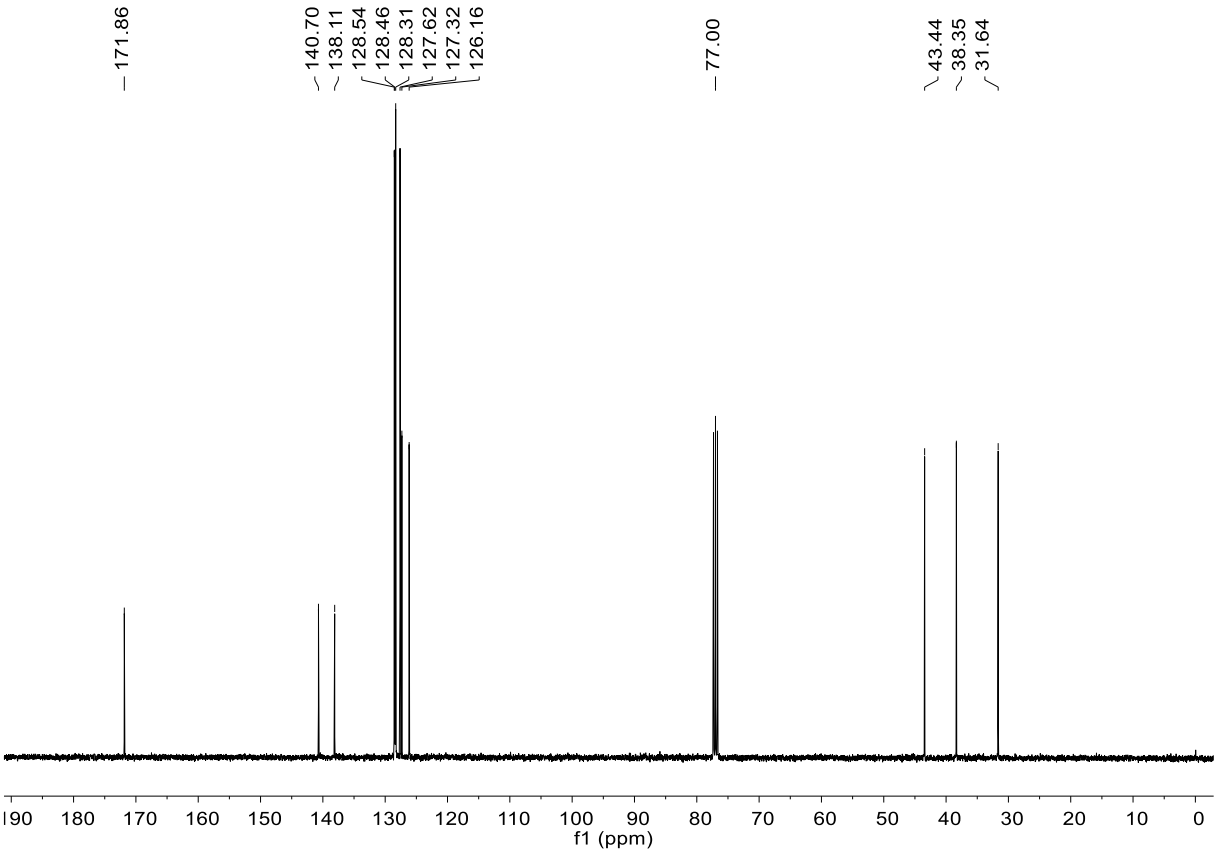


M ($C_{16}H_{17}NO$) = 239.318 g/mol; **mp.** 81-83 °C ; **lit.-mp.** 77-81 °C;[32] **r_f** (SiO_2, EtOAc/*n*Hex 50:50) = 0.37; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.29-7.23 (m, 5H, 6-H, 7-H, 4´-H), 7.21-7.16 (m, 3H, 5-H, 5´-H), 7.13-7.11 (m, 2H, 3´-H), 5.85 (br. s, 1H, NH), 4.36 (d, $^3J_{1´,NH}$ = 5.7 Hz, 2H, 1´-H), 2.96 (t, $^3J_{3,2}$ = 7.8 Hz, 2H, 3-H), 2.48 (t, $^3J_{3,2}$ = 7.5 Hz, 2H, 3-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 171.86 (C-1), 140.70 (C-4), 138.11 (C-2´), 128.54 (C-5, C-6 or C-4´), 128.46 (C-5, C-6 or C-4´), 128.31 (C-5, C-6 or C-4´), 127.62 (C-3´), 127.32 (C-5´), 126.16 (C-7), 43.44 (C-1´), 38.35 (C-2), 31.64 (C-3); **GC-MS** (CI, 70 eV) m/z [u] (%) = 280 (1, $[M+allyl]^+$), 268 (20, $[M+Et]^+$), 254 (2, $[M+Me]^+$), 240 (100, $[M+H]^+$), 150 (3), 149 (6), 133 (4, $[PhCH_2CH_2CO]^+$ or $[PhCH_2NCO]^+$), 119 (4), 106 (5, $[PhCHNH_2]^+$), 105 (5, $[PhCO]^+$), 91 (14, $[Bn]^+$), 65 (2, $[Cp]^+$).

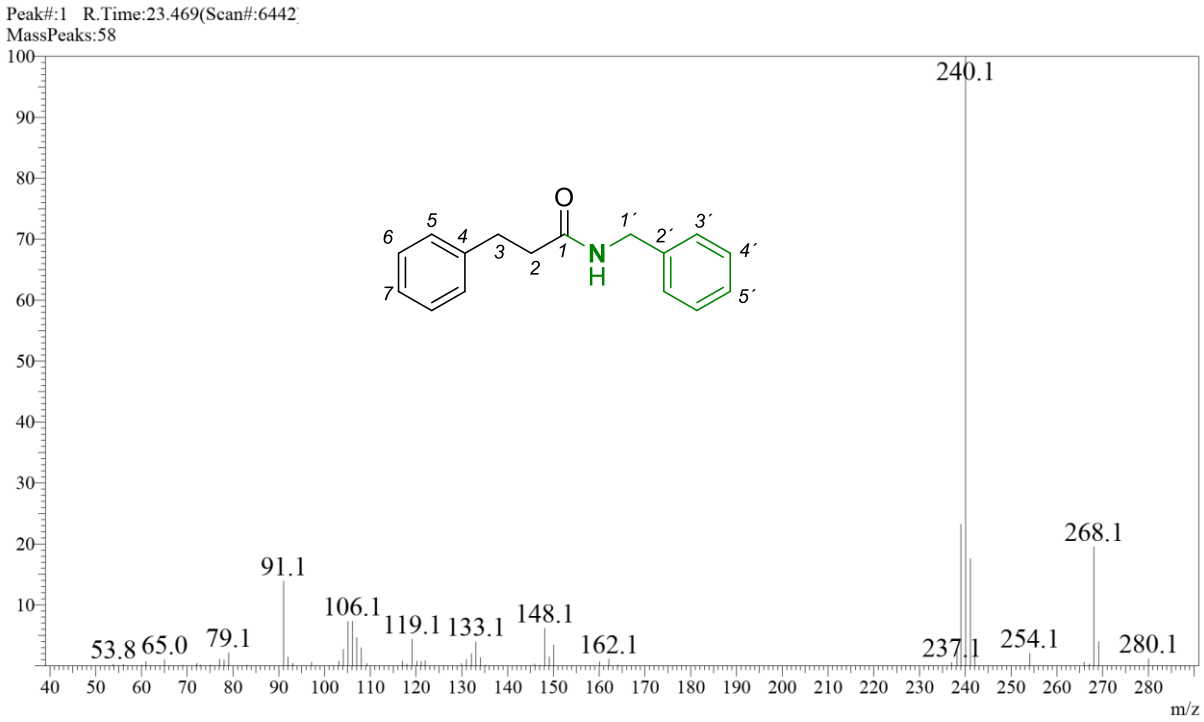
The NMR data is in agreement with the literature.[32]



^{1}H-NMR spectrum of *N*-benzyl 3-phenylpropanoic acid amide (400 MHz, $CDCl_3$).

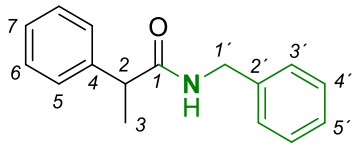


^{13}C-NMR spectrum of *N*-benzyl 3-phenylpropanoic acid amide (100 MHz, $CDCl_3$).



Mass spectrum of *N*-benzyl 3-phenylpropanoic acid amide (CI, 70 eV).

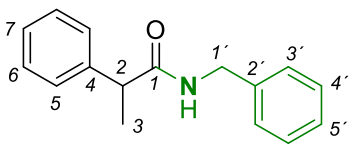
5.4.2.8 Synthesis of *rac*-*N*-Benzyl 2-phenylpropanoic acid amide (2_{6f})



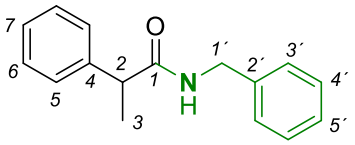
2_{6f}

PH3034: As stated in general procedure 4 (chapter 5.3.4 page 50) 3-phenyl propionic acid (150 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) **at 80 °C for 4 h**. Next, the reaction suspension was diluted with further MeCN (0.50 mL→1 M) and benzylamine (140 μL, 1.2 mmol, 1.2 equiv) and K_2CO_3 (320 mg, 2.3 mmol, 2.3 equiv) were added at 0 °C. After stirring overnight (16 h) at room temperature and work up, the crude title compound (255 mg, 107%, yellow oil) was purified by means of column chromatography on silica gel (20.9 g, mass crude material/SiO_2 1:87) exploiting EtOAc/*n*Hex 30:70 as eluent, which furnished the title amide as a colourless solid (187.7 mg, 0.784 mmol, 78%).

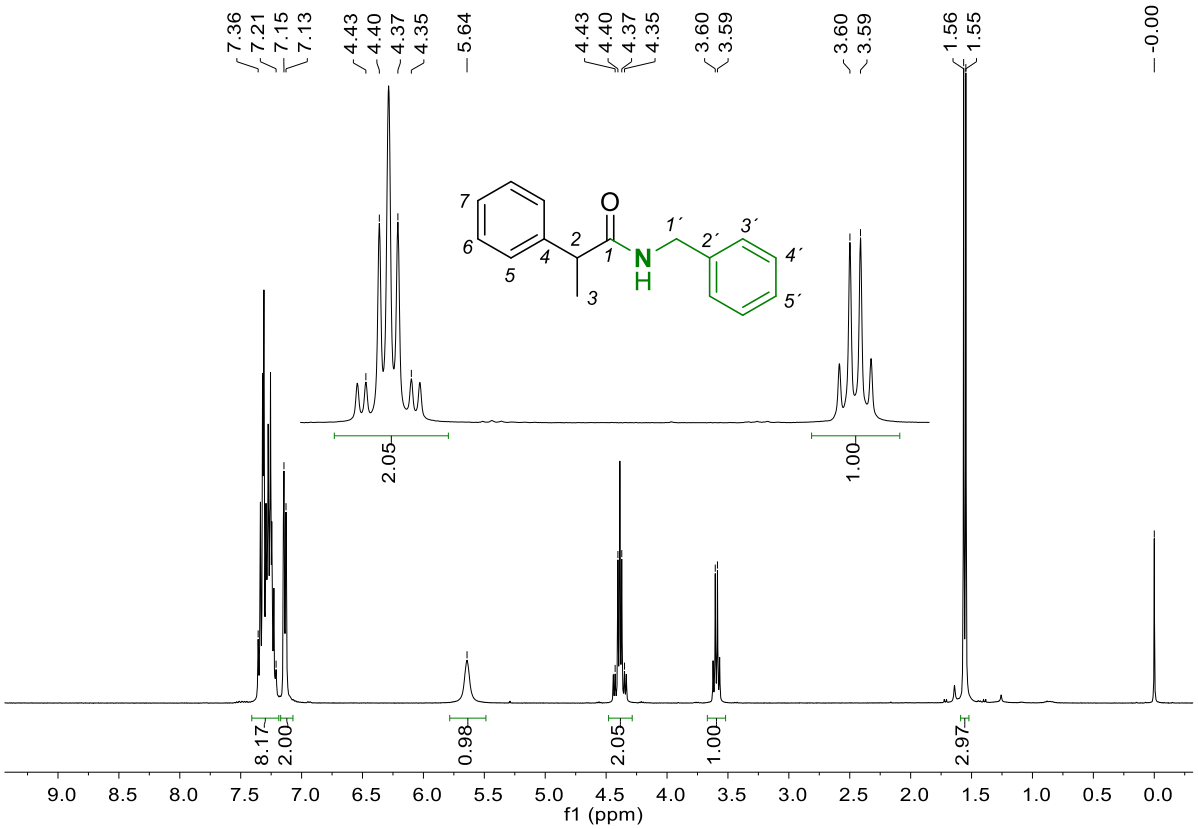
PH2988: The title compound was prepared according to general procedure 4 (chapter 5.3.4 page 50) from 3-phenyl propanoic acid (1.00 mmol, 1.0 equiv) through initial reaction with TCT (38 mol%) in the presence of FPyr (10 mol%) in MeCN (2 M) under heating to **40 °C for 14 h**. Thereafter, the reaction suspension was diluted with further MeCN (→1 M), benzylamine (1.2 equiv) and K_2CO_3 (1.3 equiv) were added under cooling in an ice bath and stirring was continued at room temperature for 6 h. In the end, column chromatographic purification of the crude product (245 mg, 103%, yellow oil) on silica gel (22.2 g, ratio mass crude material/silica 1:91) applying EtOAc/*n*Hex 25:75→30:70 as eluent gave rise to the title compound as a



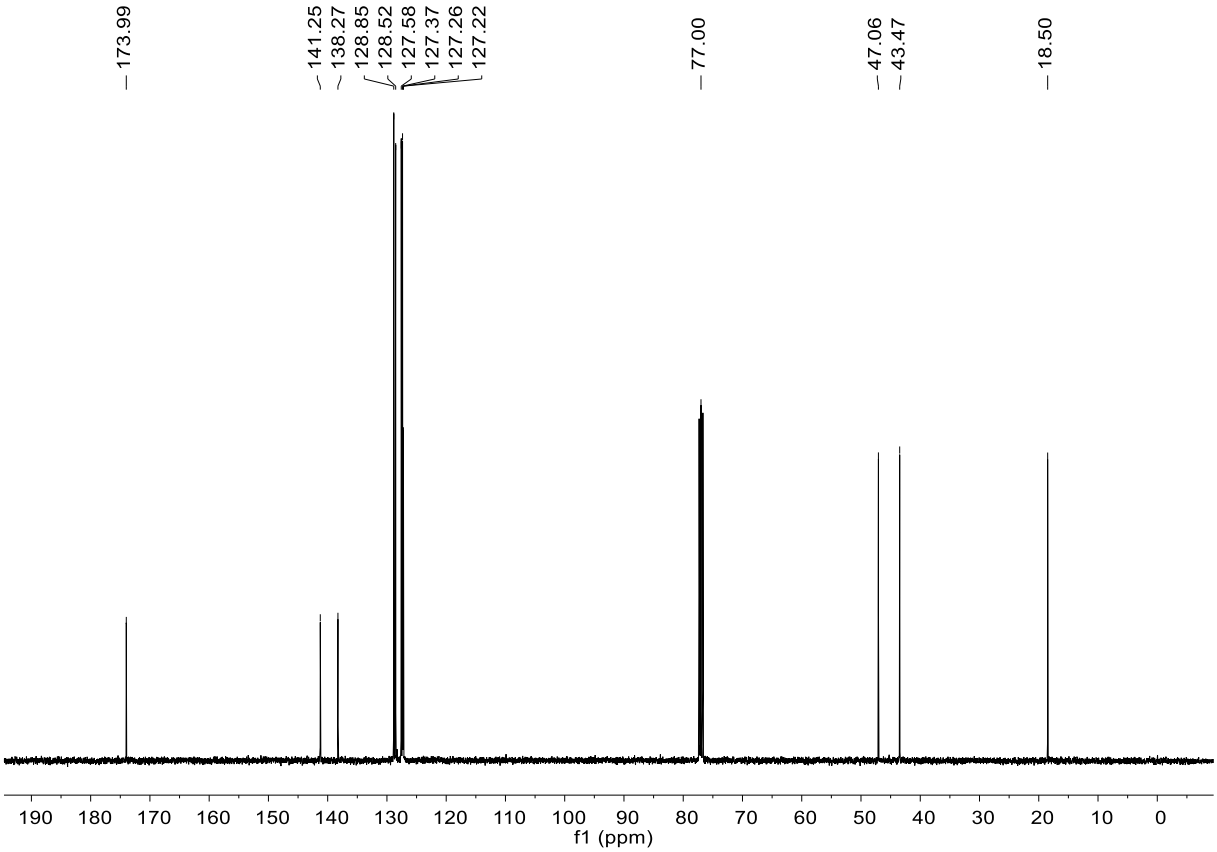
colourless oil (185.2 mg). Since ^{1}H-NMR showed 9 mol% EtOAc with respect to the title amide, compound **2_{6f}** was isolated in a yield of 75% (0.749 mmol).



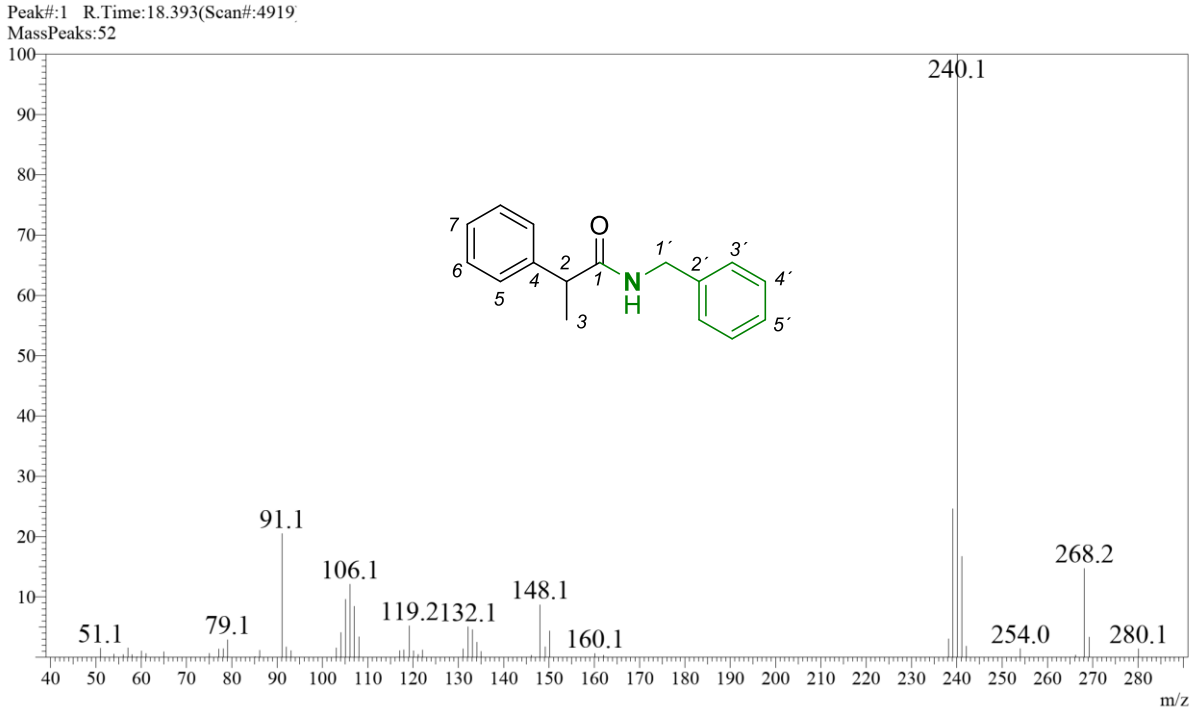
M ($C_{16}H_{17}NO$) = 239.318 g/mol; **mp.** 76-77 °C; lit.-mp. 76-77 °C **r_f** (SiO_2, EtOAc/*n*Hex 30:70) = 0.29; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.36-7.21 (m, 8H, 5-H, 6-H, 7-H, 4´-H, 5´-H), 7.15-7.13 (m, 2H, 3´-H), 5.64 (br. s, 1H, NH), 4.43 (dd, $^{2}J_{a,b}$ = 9.2 Hz, $^{3}J_{1´,NH}$ = 5.8 Hz, 1H, 1´-H_a), 4.40 (dd, $^{2}J_{a,b}$ = 9.2 Hz, $^{3}J_{1´,NH}$ = 5.8 Hz, 1H, 1´-H_b), 4.36 (q, $^{3}J_{3,2}$ = 7.2 Hz, 1H, 2-H), 3.60 (q, $^{3}J_{2,3}$ = 7.2 Hz, 1H, 2-H), 1.56 (d, $^{3}J_{3,2}$ = 7.2 Hz, 3H, 3-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 173.99 (C-1), 141.25 (C-4), 138.27 (C-2´), 128.85 (C-6 or C-4´), 128.52 (C-6 or C-4´), 127.58 (C-5), 127.37 (C-3´), 127.26 (C-7 or C-5´), 127.22 (C-7 or C-5´), 47.06 (C-2), 43.47 (C-1´), 18.50 (C-3); **GC-MS** (CI, 70 eV) m/z [u] (%) = 280 (1, $[M+allyl]^+$), 268 (14, $[M+Et]^+$), 254 (1, $[M+Me]^+$), 240 (100, $[M+H]^+$), 150 (4), 148 (10), 132 (6), 106 (13, $[PhCHNH_2]^+$), 91 (21, $[Bn]^+$).
The NMR data is in agreement with the literature.[33]



^{1}H-NMR spectrum of *rac*-*N*-benzyl 2-phenylpropanoic acid amide (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *rac*-*N*-benzyl 2-phenylpropanoic acid amide (100 MHz, $CDCl_3$).

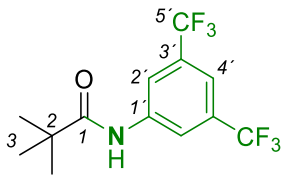


Mass spectrum of *rac*-*N*-benzyl 2-phenylpropanoic acid amide (CI, 70 eV).

5.4.2.9 Synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl) pivalamide (2_{7g})

entry	conditions	yield 2_{7g} [%]
1	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 80 °C 2. H**Nu** (1.2 equiv), NMM (1.3 equiv), MeCN (1 M), 15 min 0 °C, 15 h rt	92[a]
2	1. TCT (38 mol%), FPyr (**20 mol%**), MeCN (2 M), **15 h 40 °C** 2. H**Nu** (1.1 equiv), NMM (1.3 equiv), MeCN (1 M), 15 min 0 °C, 8 h rt	76[a]
3	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 80 °C 2. H**Nu** (1.2 equiv), NMM (1.3 equiv), **DMAP (20 mol%)** MeCN (1 M), 15 min 0 °C, 15 h rt	90[b]

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of mesitylene as internal standard. H**Nu**= 3,5-di(trifluoromethyl)aniline



2_{7g}

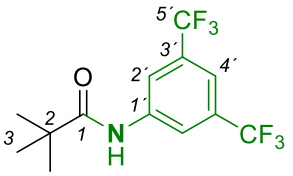
Dehydrative coupling of pivalic acid as model substrate for a α-quaternary aliphatic carboxylic acid and 3,5-di(trifluoromethyl)phenyl amine following the current method facilitated the synthesis of the title compound in 92% yield (entry 1). When the reaction temperature for the initial chlorination was reduced from 80 to 40 °C under elongation of the duration, the title amide could be isolated in 76% yield (entry 2). Furthermore, utilization of DMAP (20 mol%) in the transformation of pivaloyl chloride into amide **2_{7g}** had no impact (entry 3).

Entry 1, PH3148: According to general protocol 4 (chapter 5.3.4 page 50) pivalic acid (102.1 mg, 1.00 mmol, 1.0 equiv) was combined with FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%), MeCN (0.50 mL, 2 M) and TCT (72 mg, 0.38 mmol, 38 mol%) and a the resulting reaction suspension was heated to 80 °C for 3 h. Then, the reaction mixture was cooled to 0 °C, successively further MeCN (0.50 mL→1 M), di(trifluoromethyl)phenyl amine (190 μL, 1.2 mmol, 1.2 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were introduced and stirring was continued at ambient temperature overnight (15 h). At last, the crude material (390 mg, 124%, pale yellow oil) was purified with the aid of column chromatography on silica gel (23.2 g, mass ratio crude product/SiO_2 1:60) with CH_2Cl_2/*n*Hex 30:70→40:60. Drying at the rotary evaporator at 5 mbar for 2 h furnished the title compound as colourless solid as 92% yield (287.0 mg, 0.916 mmol). In order to load the crude mixture onto the column, it was dissolved under careful heating by means of a heat gun in CH_2Cl_2 (ca. 20 mL), silica gel was added (0.84 g, ratio of masses crude material/silica 1:2.2) and concentrated under reduced pressure.

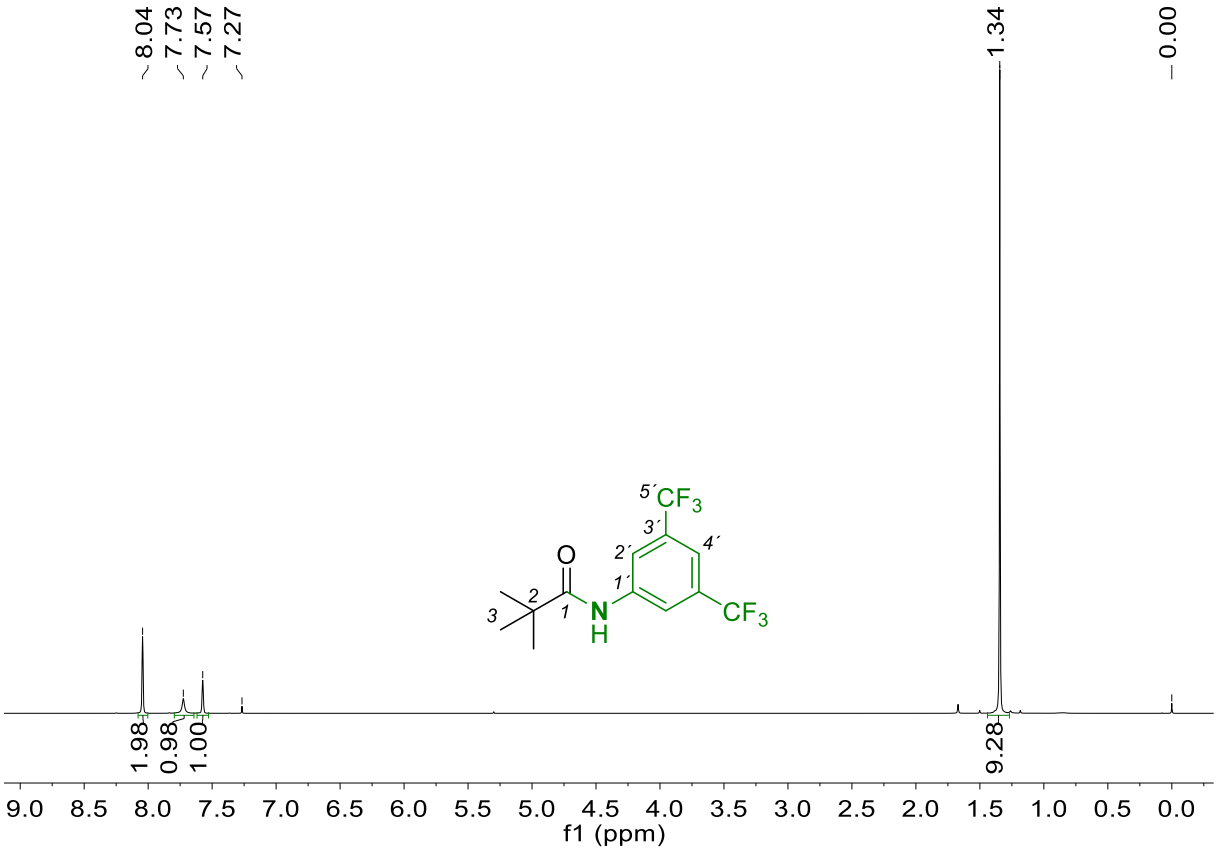
Entry 2, PH3152: Following general protocol 4 (chapter 5.3.4 page 50) pivalic acid (1.00 mmol, 1.0 equiv) was converted into pivaloyl chloride by means of TCT (38 mol%) and FPyr (10 mol%) under stirring at 40 C for 15 h in MeCN (2 M). Next, the resulting reaction suspension was placed in an ice bath and further MeCN (→1 M), 3,5-di(trifluoromethyl)aniline

(170 μL, 1.1 mmol, 1.1 equiv) and NMM (1.3 equiv) were added. Past 8 h of stirring at ambient temperature a slightly modified work up procedure was applied. The reaction mixture was taken up with EtOAc (8 mL) and aqueous 2 N NaOH solution (4 mL), the organic phase was washed with brine (1 x 4 mL), dried over $MgSO_4$, silica gel was added (0.71 g, ratio masses theoretical yield/SiO_2 1:2.4), the solvent was removed *in vacuo* and the residue was dried at the rotary evaporator for 15 min at 5 mbar. Finally, the residual fine powder was applied to column chromatography using silica gel (23.5 g relation masses theoretical yield/SiO_2 1:81) and CH_2Cl_2/*n*Hex 40:60→50:50, which furnished the title compound as colourless solid in 76% yield (238.1 mg, 0.760 mmol) after drying in high vacuum for 30 min.

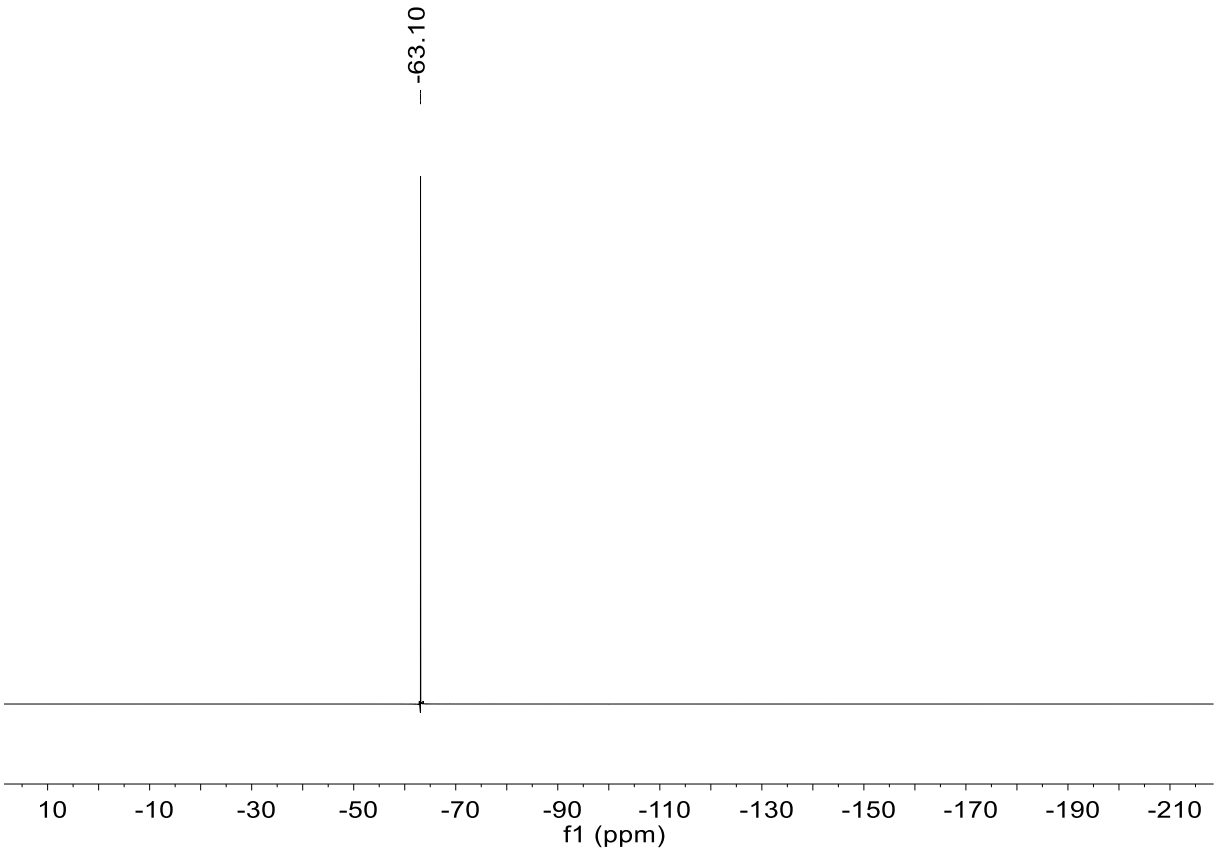
Entry 3, PH3142: As given in general protocol 3 (chapter 5.3.3, page 49) 2,2,-dimethylpropionic acid (51.5 mg, 0.50 mmol, 1.0 equiv) was allowed to react with TCT (36 mg, 0.19 mmol, 38 mol%) and FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%) in MeCN (0.25 mL, 2 M) for 4 h at 80 °C. Subsequently, transformation to the intermediate acid chloride into the title amide was accomplished through cooling of the reaction mixture to 0 °C, addition of MeCN (0.25 mL→1 M), 3,5-di(trifluoromethyl)aniline (90 μL, 0.60 mmol, 1.2 equiv), NMM (75 μL, 0.65 mmol, 1.3 equiv) and DMAP (12.2 mg, 100 μmol, 20 mol%) and stirring for 15 h at ambient temperature. Ultimately, ^{1}H-NMR of the crude material utilizing mesitylene (24.0 mg) as internal standard demonstrated the title compound in 90% yield.



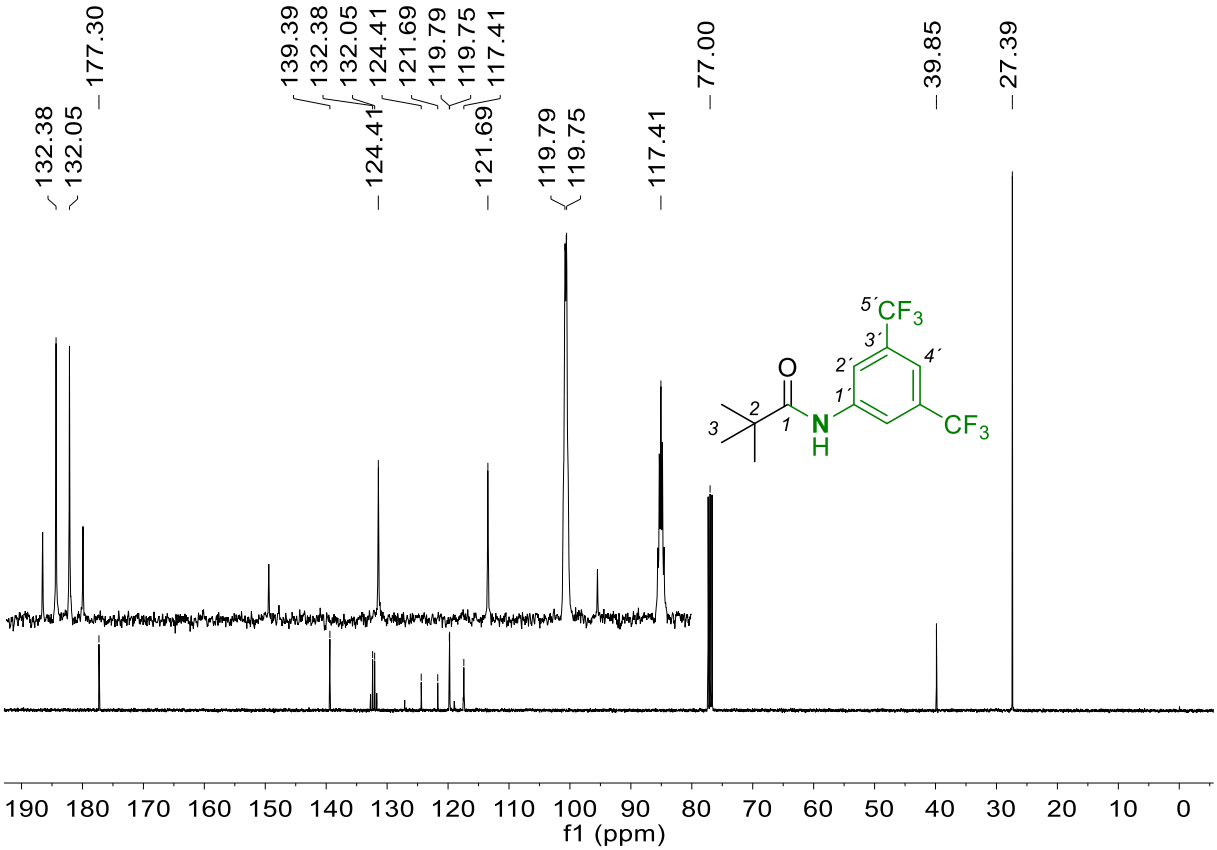
M ($C_{13}H_{13}F_6NO$) = 313.243 g/mol; **M** ($C_{13}H_{13}NOF_6$) = 313.24 g/mol; **mp**. = 130-132 °C; $\mathbf{r_f}$ (SiO_2) = 0.27 (CH_2Cl_2/*n*Hex 30:70), 0.34 (CH_2Cl_2/*n*Hex 50:50); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.04 (s, 2H, 2´-H), 7.73 (s, 1H, NH), 7.57 (s, 1H, 4´-H), 1.34 (s, 9H, 3-H); **^{19}F-NMR** (376 MHz, $CDCl_3$) δ [ppm] = -63.10 (5´-F); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 177.30 (C-1), 139.39 (C-1´), 132.22 (q, $^2J_{3´,F}$ = 34 Hz, C-3´), 123.05 (q, $^1J_{5´,F}$ = 274 Hz, C-5´), 119.77 (q, $^3J_{2´,F}$ = 4 Hz, C-2´), 117.41 (ψ-pen, $^3J_{4´,F}$ = 4 Hz, C-4´), 39.85 (C-2), 27.39 (C-3); **GC-MS** (CI, 70 eV) m/z [u] (%) = 354 (1, $[M+allyl]^+$), 342 (21, $[M+Et]^+$), 328 (2, $[M+Me]^+$), 314 (100, $[M+H]^+$), 294 (47, $[M-F]^+$), 229 (2), 85 (5), 57 (18, $[t\text{Bu}]^+$); **HR-MS** ($[C_{13}H_{14}NOF_6]^+$) calc. 314.0980 u found 314.0989 u.



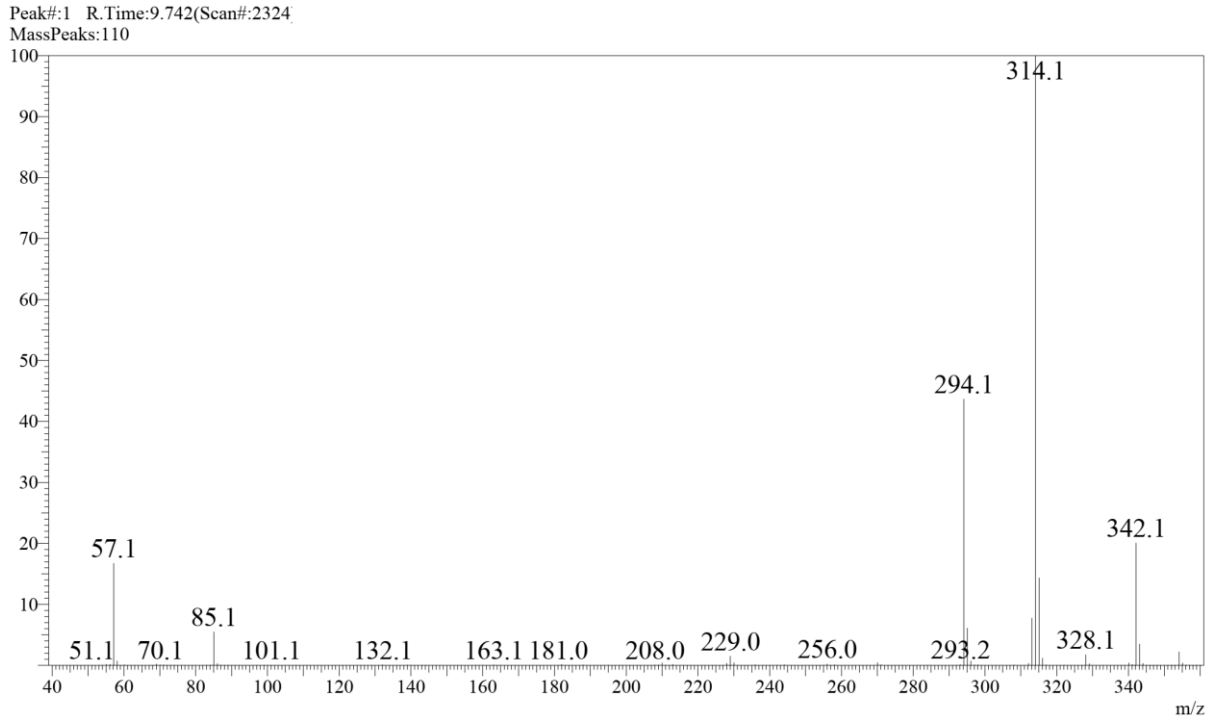
^{1}H-NMR spectrum of *N*-(3,5-bis(trifluoromethyl)phenyl) pivalamide (400 MHz, $CDCl_3$).



^{19}F-NMR spectrum of *N*-(3,5-bis(trifluoromethyl)phenyl) pivalamide (376 MHz, $CDCl_3$).

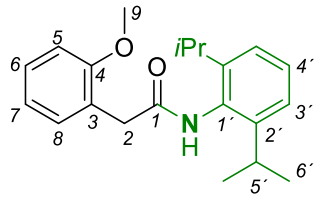


^{13}C-NMR spectrum of *N*-(3,5-bis(trifluoromethyl)phenyl) pivalamide (100 MHz, $CDCl_3$).



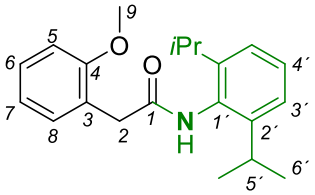
Mass spectrum of *N*-(3,5-bis(trifluoromethyl)phenyl) pivalamide (CI, 70 eV).

5.4.2.10 Synthesis of *N*-(2,6-Di-*iso*-propylphenyl) 2-(2-methoxyphenyl) acetamide (2_{8h})

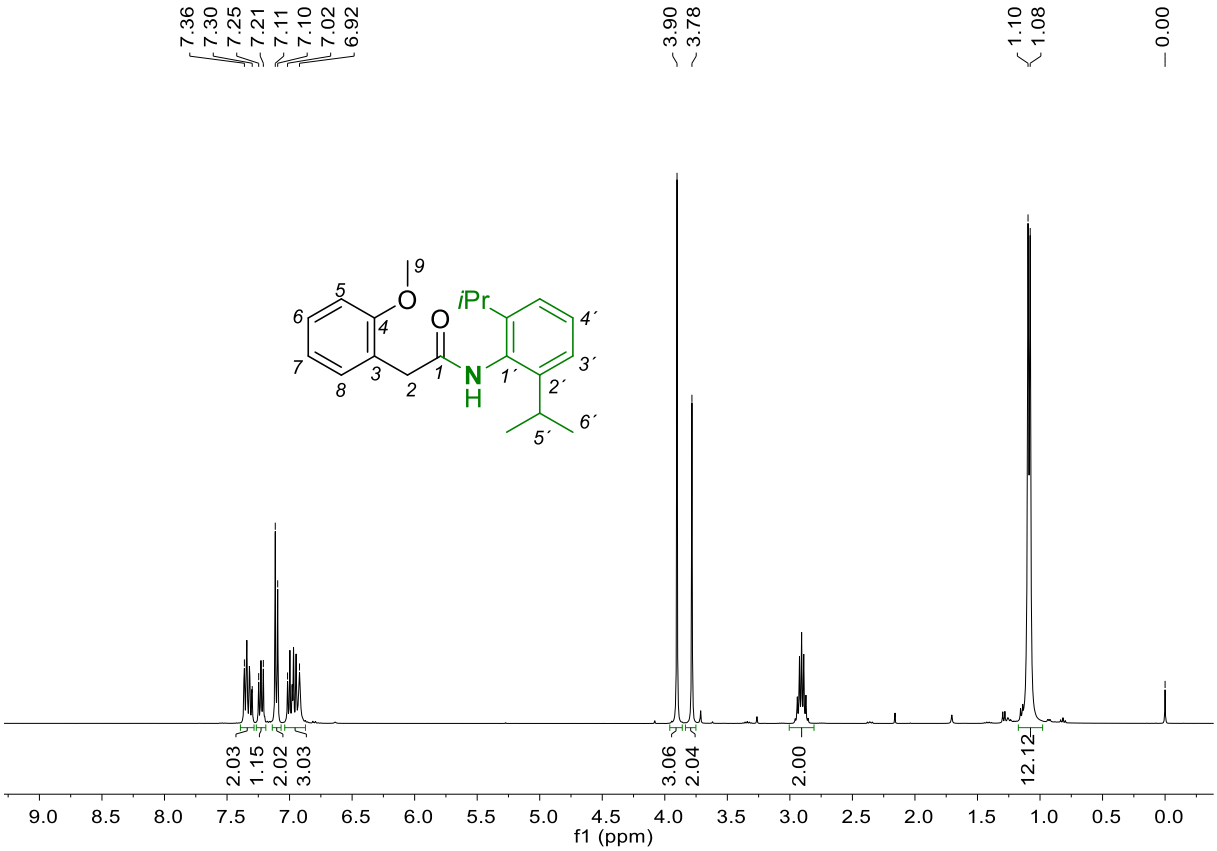


2_{8h}

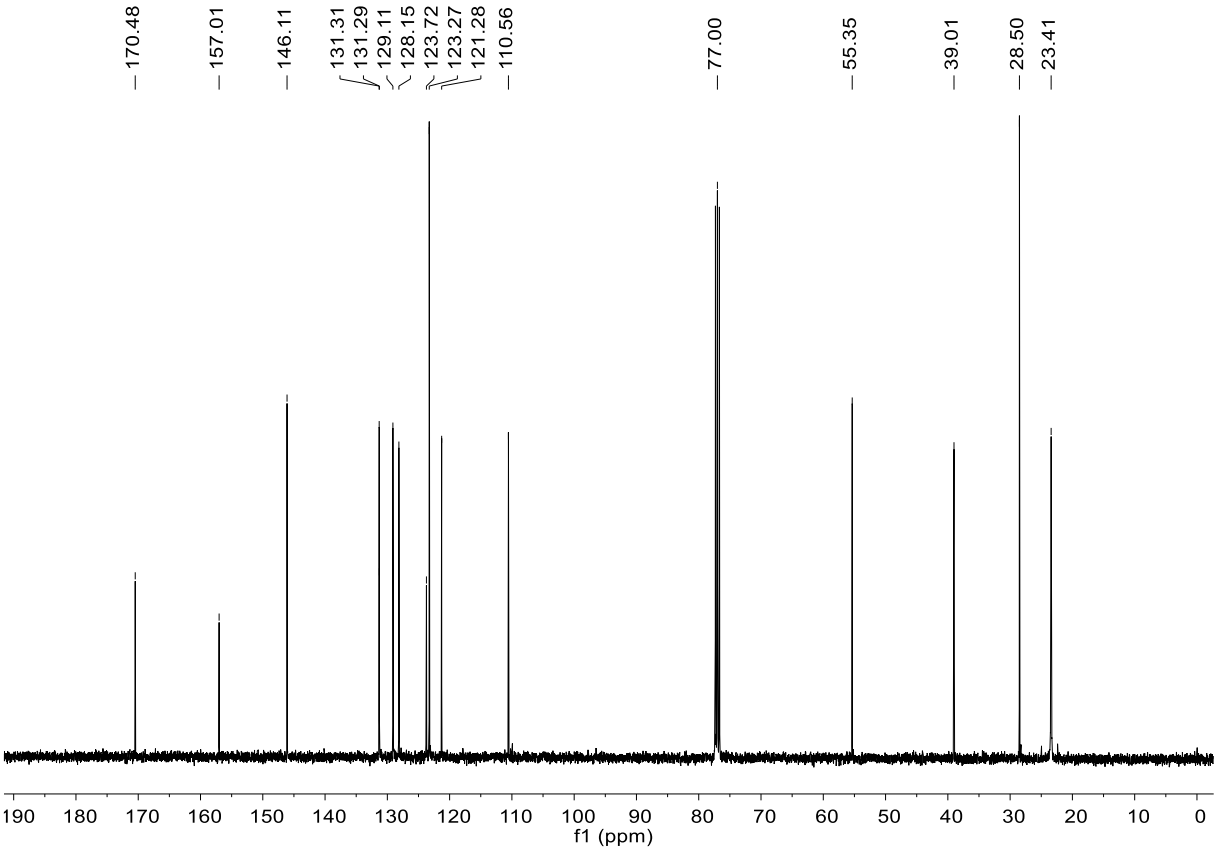
PH3058: In alignment to general protocol 4 (chapter 5.3.4 page 50) (2-methoxyphenyl) ethanoic acid (166 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mmol, 38 mol%) utilizing FPyr (9.8 μL, 10.2 mg, 100 μL, 10 mol%) in MeCN (0.50 mL, 2M) for 4 h at 40 °C. Subsequently, the reaction mixture containing the corresponding acid chloride was diluted with further MeCN (0.50 mL→1 M), cooled to 0 °C and 2,6-di-*iso*-propylaniline (240 μL, 1.0 equiv, 1.00 mmol) and K_2CO_3 (180 mg, 1.3 mmol, 1.3 equiv) were added. Past stirring at room temperature overnight (15 h), the crude amide **2_{8h}** (353 mg, 108%, pale brownish solid) was purified with the aid of column chromatography on silica gel (20.6 g, mass crude product/SiO_2 1:58) with EtOAc/*n*Hex 25:75. In order to load the crude material onto the silica gel column, it was dissolved in CH_2Cl_2 (0.5 mL). Finally, concentration with CH_2Cl_2 and drying at the rotary evaporator at 5 mbar for 90 min enabled isolation of the title compound in 81% yield as a colourless solid (263.2 mg, 0.809 mmol).



M ($C_{20}H_{17}NO$) = 287.362 g/mol; **mp**. 159-161 °C; **r_f** (SiO_2, EtOAc/*n*Hex 25:75) = 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.36-7.30 (m, 2H, 6-H, 8-H), 7.25-7.21 (m, 1H, 4´-H), 7.11 (d, $^3J_{3´,4´}$ = 7.5 Hz, 2H, 3´-H), 7.02-6.92 (m, 3H, 5-H, 7-H, NH), 3.90 (s, 3H, 9-H), 3.78 (s, 2H, 2-H), 2.91 (sept. $^3J_{5´,6´}$ = 6.9 Hz, 2H, 6-H), 1.09 (d, $^3J_{6´,5´}$ = 7.0 Hz, 12H, 6´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 170.48 (C-1), 157.01 (C-4), 146.11 (C-2´), 131.31 (C-8), 131.29 (C-3), 129.11 (C-6), 128.15 (C-4´), 123.72 (C-1´), 123.27 (C-3´), 121.28 (C-5), 110.56 (C-7), 55.35 (C-9), 39.01 (C-2), 28.50 (C-5´), 23.41 (C-6´); **HR-MS** (CI, $[C_{21}H_{28}NO_2]^+$) calc. 324.2115 u found 326.2106 u.

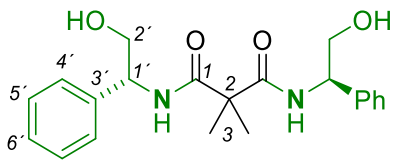


^{1}H-NMR spectrum of *N,N*-diphenyl phenylethanoic amide (400 MHz, $CDCl_3$).



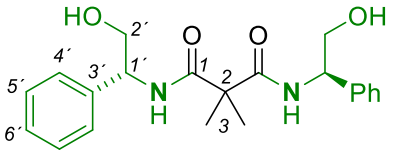
^{13}C-NMR spectrum of *N,N*-diphenyl phenylethanoic amide (100 MHz, $CDCl_3$).

5.4.2.11 Synthesis of *N,N´*-Bis((*R*)-2-hydroxy-2-phenylethyl) 2,2-dimethylmalonamide (2_{9i})



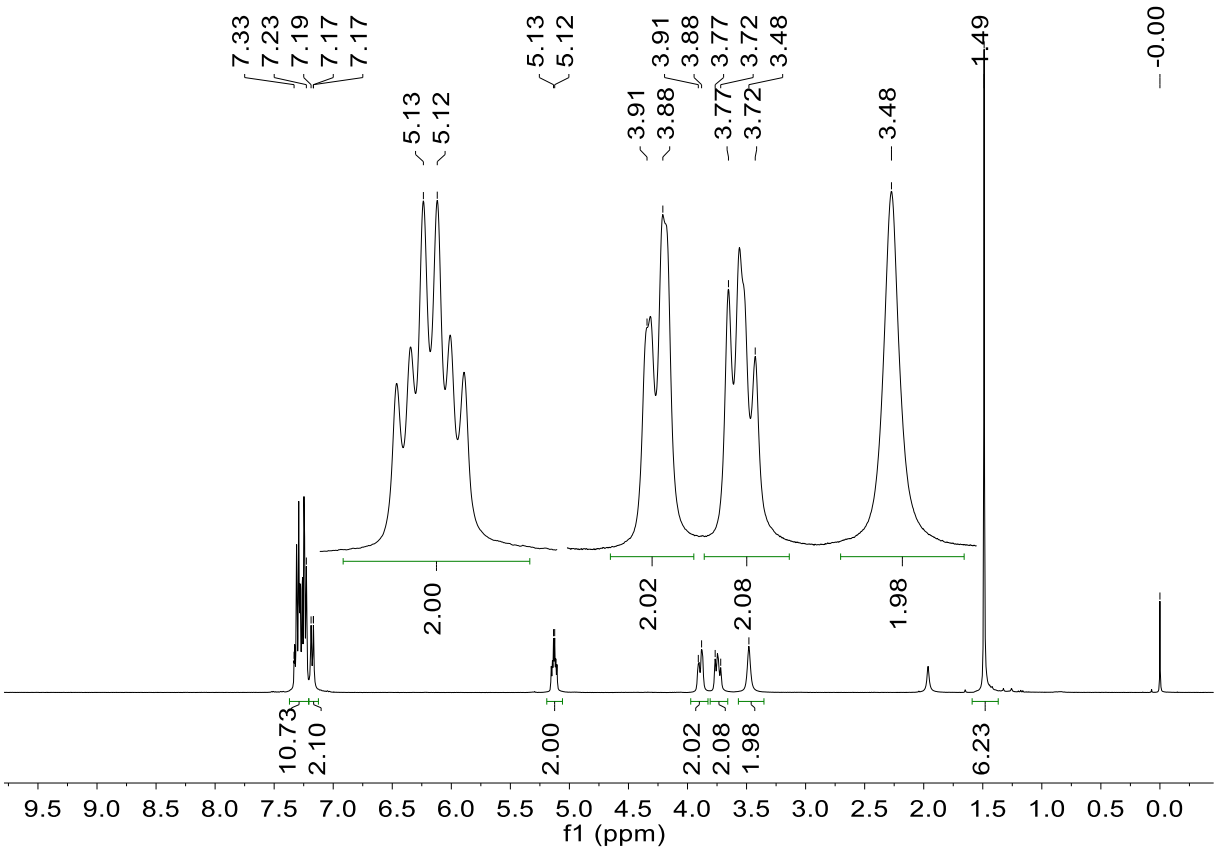
2_{9i}

PH3244: In agreement with general protocol 4 (chapter 5.3.4, page 50) 2,2-dimethylmalonic acid (**1_9**, 118 mg, 1.0 equiv) was allowed to react with TCT (143 mg, 0.76 mmol, 76 mol%) using FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) at 80 °C for 4 h. In the following the reaction suspension was diluted with MeCN (1.0 mL→0.7 M), cooled to 0 °C and (*R*)-phenylglycinol (288 mg, 2.1 mmol, 2.1 equiv) and NMM (260 μL, 2.3 mmol, 2.3 equiv) was added and the reaction mixture was stirred at ambient temperature overnight (17 h). Work up without HCl-washing delivered the crude title amide as a yellow foamy solid (374 mg, 101%), of which ^{1}H-NMR confirmed a ratio of **2_{9i}** with respect to phenylglycinol of 78:22. Eventually, column chromatographic purification on silica gel (25.8 g, mass ratio crude product/SiO_2 1:69) in MeOH/EtOAc 2:98, concentration with CH_2Cl_2 and drying for 4 h in high vacuum enabled the isolate of the malonic acid derived amide **2_{9i}** as a colourless solid (243.8 mg, 0.658 mmol, 66%). In order to load the crude material onto the silica gel column, it was dissolved in CH_2Cl_2 (ca. 20 mL) under gentle heating with a heat gun, silica gel was added (0.87 g, ratio mass crude material in relation to silica 1:2.4), the mixture was concentrated and dried at the rotary evaporator for 10 min at 20 mbar.

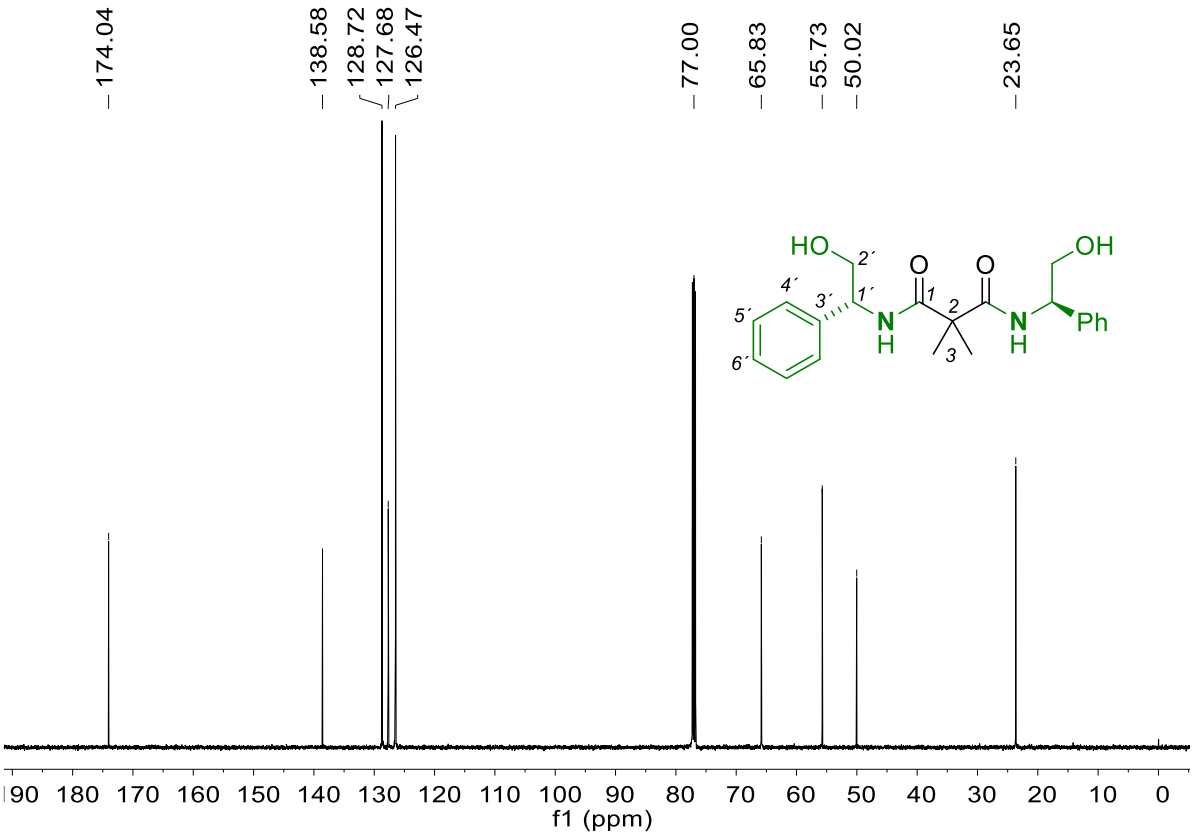


M ($C_{21}H_{26}N_2O_4$) = 370. 45 g/mol, **mp.** = 128-130 °C (lit.-mp. 127-128);[34] **r_f** (SiO_2,) = 0.33 (MeOH/EtOAc 2.98), 0.22 (EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.33-7.23 (m, 10H, 4´-H, 5´-H, 6´-H), 7.18 (d, $^3J_{NH,1´}$ = 7.9 Hz; 2H, NH), 5.13 (ψ-td, ^3J = 7.7, 4.0 Hz, 2H, 1´-H), 3.91-3.88 (m, 2H, 2´-H_a), 3.77-3.72 (m, 2H, 2´-H_b), 3.48 (br. s, 2H, OH), 1.49 (s, 6H, 3-H); **^{13}C-NMR** (125 MHz, $CDCl_3$2) δ [ppm] = 174.04 (C-1), 138.58 (C-3´), 128.72 (C-5´), 127.68 (C-6´), 126.47 (C-4´), 65.83 (C-2´), 55.73 (C-1´), 50.02 (C-2), 23.65 (C-3); **^{1}H-NMR** (500 MHz, DMSO-d_6) δ [ppm] = 7.88 (d, $^3J_{NH.1´}$ = 8.0 Hz, 2H, NH), 7.27-7.25 (m, 8H, 4´-H, 5´-H), 7.24-7.20 (m, 2H, 6´-H), 4.94 (ψ-t, $^3J_{OH,2´}$ = 5.7 Hz, 2H, OH), 4.92-4.88 (m, 2H, 1´-H), 3.64-3.57 (m, 4H, 2´-H), 1.37 (s, 6H, 3-H); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ [ppm] = 172.82 (C-1), 140.96 (C-3´), 128.03 (C-5´), 126.76 (C-4´), 126.68 (C-6´), 64.47 (C-2´), 55.34 (C-1´), 49.48 (C-2), 23.83 (C-3); **$[\alpha]_D^{20}$** (c = 0.915 g/mol, $CHCl_3$) = -94.4.

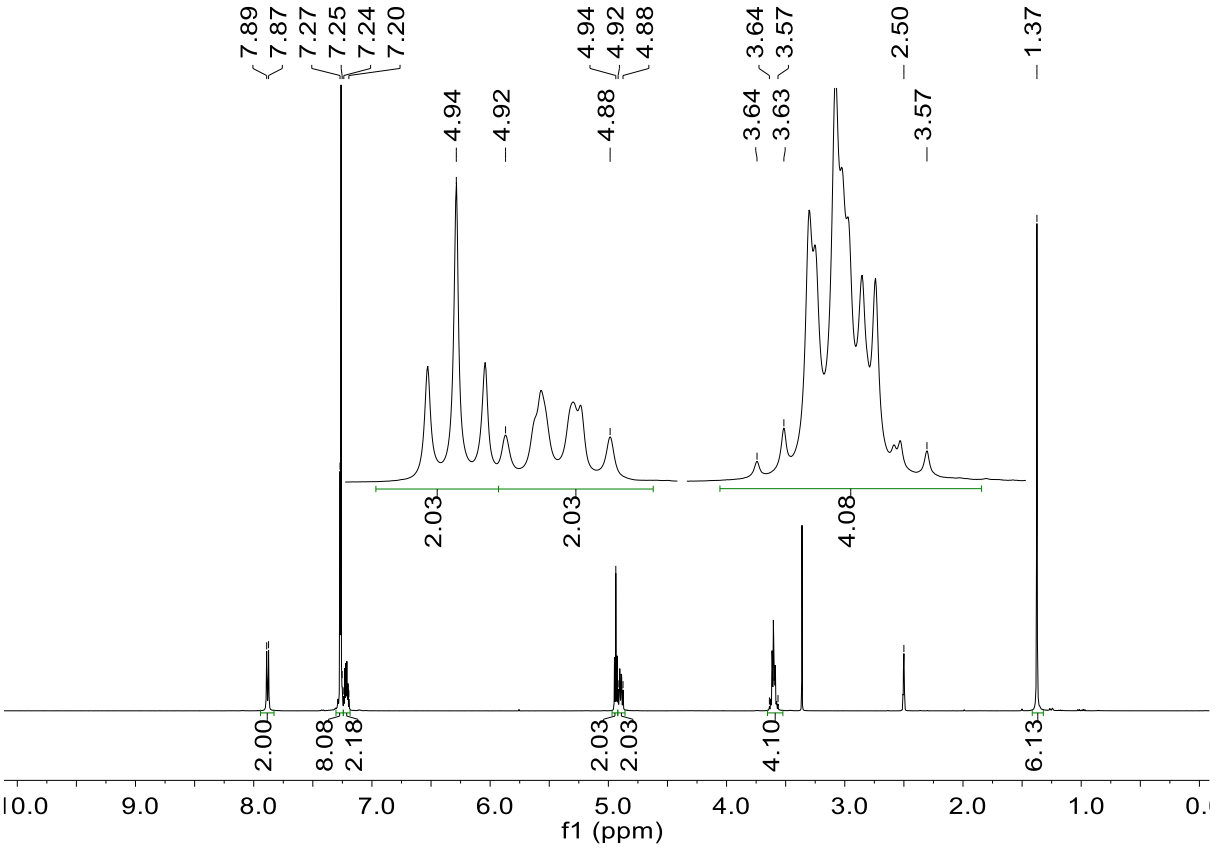
The NMR data in DMSO-d^6 is in agreement with the literature.[46]



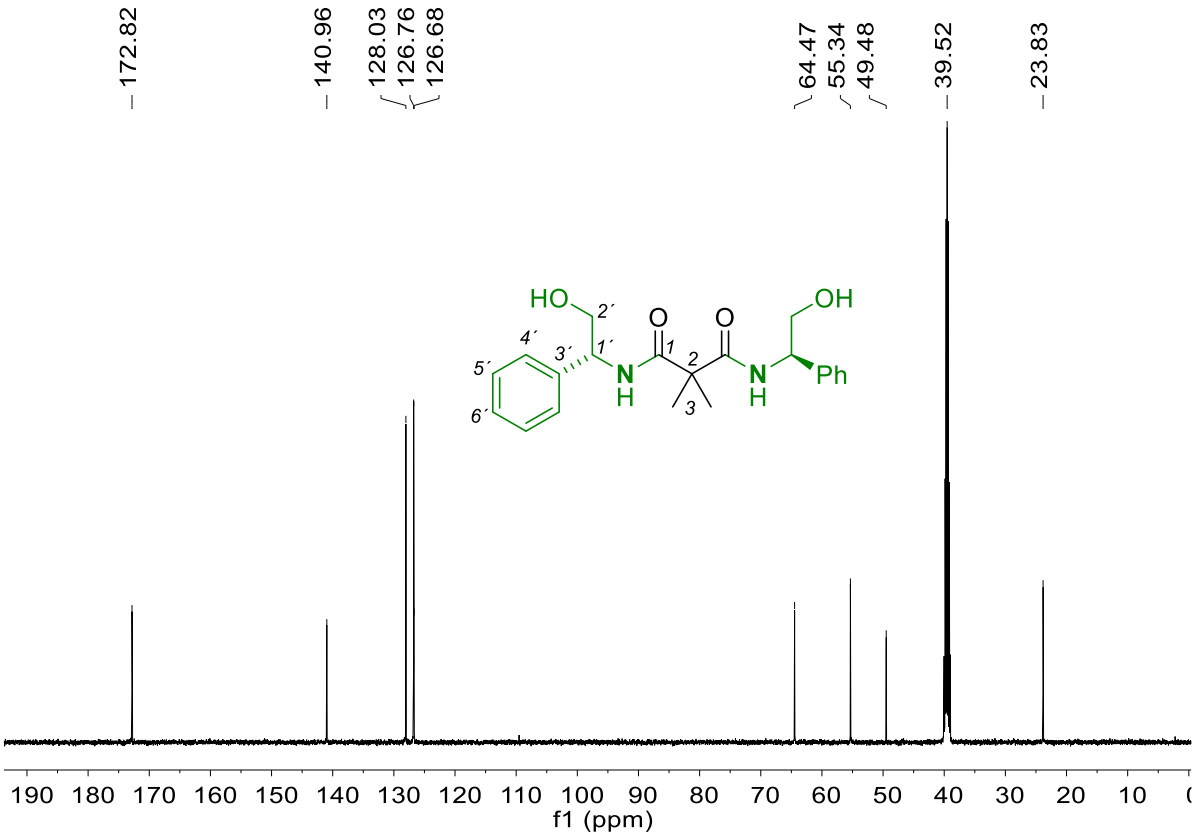
^{1}H-NMR spectrum of *N,N´*-bis((*R*)-2-hydroxy-2-phenylethyl) 2,2-dimethylmalonamide (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *N,N´*-bis((*R*)-2-hydroxy-2-phenylethyl) 2,2-dimethylmalonamide (125 MHz, $CDCl_3$).



^{1}H-NMR spectrum of *N,N´*-bis((*R*)-2-hydroxy-2-phenylethyl) 2,2-dimethylmalonamide (500 MHz, DMSO-d_6).

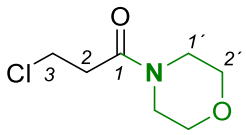


^{13}C-NMR spectrum of *N,N´*-bis((*R*)-2-hydroxy-2-phenylethyl) 2,2-dimethylmalonamide (125 MHz, DMSO-d_6).

5.4.2.12 Synthesis of 4-(3-Chloropropanoyl) morpholine (2_{10j})

entry	conditions	yield 2_{10j} [%]
1	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. morpholine (1.2 equiv), K_2CO_3 (1.3 equiv), MeCN (1 M), 15 min 0 °C, 4 h rt	52[a]
2	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 4 h 40 °C 2. morpholine (1.2 equiv), K_2CO_3 (1.3 equiv), MeCN (1 M), 15 min 0 °C, 5 h rt	65[b]
3	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), **8 h** 40 °C 2. morpholine (1.2 equiv), **NMM** (1.3 equiv), MeCN (1 M), 15 min 0 °C, 3 h rt	76[b]
4	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), 8.5 h 40 °C 2. morpholine (1.2 equiv), NMM (**2.3** equiv), MeCN (1 M), 15 min 0 °C, 2 h rt	74[b]

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of naphthalene as internal standard.



2_{10j}

The engagement of K_2CO_3 enabled the production of the title compound in 65% yield according to internal NMR-standard, whereas the isolated after chromatographic purification is slightly diminished (entries 1+2). An increase of the reaction duration from 4 to 8 h and the usage of NMM as base resulted in an enhanced yield of 76% (entry 3), which could not be further improved raising the amount of NMM from 1.3 to 2.3 equiv (entry 4). Independently from the base employed in all cases approximately 10 mol% of *N*-propenoyl morpholine with regard to the title compound were formed, which is reasoned by HCl elimination from β-chloroamide **2_{10j}**.

Entry 1, PH3065: The preparation of the title amide was initiated by reaction of 3-chloropropanoic acid (109 mg, 1.00 mmol, 1.0 equiv) with TCT (72 mg, 0.19 mmol, 38 mol%) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) for 4 h at 40 °C as delineated in general protocol 4 (chapter 5.3.4 page 50). Thereafter, the reaction suspension was cooled to 0 °C, MeCN (0.50 mL→1 M), morpholine (110 μL, 1.2 mmol, 1.2 equiv) and K_2CO_3 (180 mg, 1.3 mmol, 1.3 equiv) were added successively and stirring was continued for 4 h at room temperature. ^{1}H-NMR of the crude material (137.2 mg, 77%, pale yellow oil) proved the amide **2_{10j}** alongside with 10 mol% of *N*-propenoyl morpholine. In the end, purification by means of column chromatography with EtOAc as eluent on silica gel (21.5 g, mass ratio crude product/silica 1:157) facilitated the isolation the title compound as a pale yellow oil in 52% yield (92.4 mg, 0.520 mmol) after drying at the rotary evaporator at 5 mbar for 15 min.

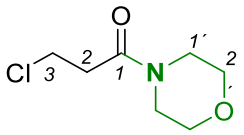
Entry 2, PH3078: As given in general protocol 3 (chapter 5.3.3, page 49) 3-chloropropanoic acid (54.2 mg, 0.50 mmol, 1.0 equiv) was combined successively with FPyr (4.9 μL, 5.1 mg, 50 μL, 10 mol%), MeCN (0.25 mL, 2 M) and TCT (36 mg, 0.19 mmol, 38 mol%) and heated to 40 °C for 4 h (= **t_1**). Then, under cooling to 0 °C further MeCN (0.25 mL→1 M), morpholine

(55 μL, 0.60 mmol, 1.2 equiv) and K_2CO_3 (90 mg, 0.65 mmol, 1.3 equiv) were added and the resulting suspension was stirred for 5 h (= **t_2**) at room temperature. Finally, the title compound was obtained in 65% yield together with *N*-propenoyl morpholine in 6% yield (10 mol% in regard to **2_{10j}**) as determined by ^{1}H-NMR spectrum of the crude material using naphthalene (23.9 mg) as internal standard.

Entry 3, PH3085: The title compound was prepared as stated in entry 3 with the differences that the duration of the chlorination **1→6** increased to **8 h** (= **t_1**) and that **NMM** (75 μL, 1.2 mmol, 1.2 equiv) as base was used instead of K_2CO_3. After stirring for 3 h (= **t_2**) ^{1}H-NMR spectrum of the crude material with naphthalene as internal standard (33.3 mg) revealed the amide **2_{10j}** in 76 and *N*-propenoyl morpholine in 8% yield (10 mol% with respect to **2_{10j}**).

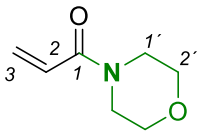
Entry 4, PH3095: This experiment was performed as given in entry 4 with the alteration that **2.3 equiv of NMM** (130 μL, 1.25 mmol) were applied and that the reaction duration of the amidation step was shortened to 2 h (= **t_2**). After all, the title compound was formed in 74% yield and *N*-propenoyl morpholine was observed as side product in 8% yield (10 mol% in relation to **2_{10j}**) as judged by ^{1}H-NMR of the crude product by means of naphthalene (21.1 mg) as internal standard.

4-(3-Chloropropanoyl) morpholine

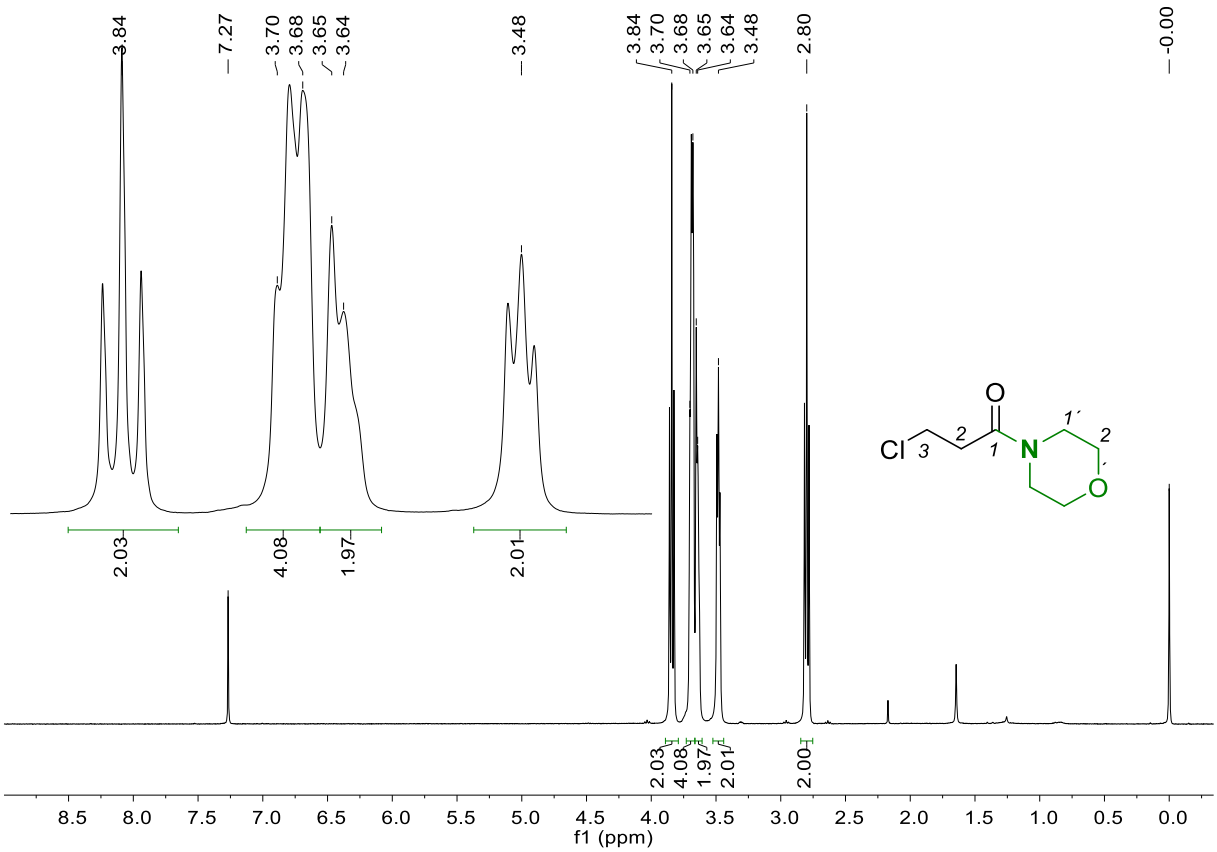


M ($C_7H_{12}ClNO_2$) = 177.628 g/mol; **r_f** (SiO_2, EtOAc) = 0.28; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 3.84 (t, $^3J_{3.2}$ = 6.9 Hz, 2H, 3-H), 3.70-3.68 (m, 4H, 2´-H), 3.65-3.64 (m, 2H, 1´-H_a), 3.48 (t, ^3J = 4.9 Hz, 2H, 1´-H_b), 2.80 (t, $^3J_{2.3}$ = 7.1 Hz, 2H, 2-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 168.19 (C-1), 66.73 (C_a-2´), 66.46 (C_b-2´), 45.79 (C_a-1´), 41.92 (C_b-1´), 39.76 (C-3), 35.75 (C-2); **GC-MS** (CI, 70 eV) m/z [u] (%) = 220 (<1, [M(^{37}Cl)+allyl]$^+$), 218 (2, (M(^{35}Cl)+allyl]$^+$), 208 (3, [M(^{37}Cl)+Et]$^+$), 206 (11, [M(^{35}Cl)+Et]$^+$), 194 (<1, [M(^{37}Cl)+Me]$^+$), 192 (2, [M(^{35}Cl)+Me]$^+$), 180 (33, [M(^{37}Cl)+H]$^+$), 178 (100, [M(^{35}Cl)+H]$^+$), 164 (<1), 162 (2), 142 (95, [M-Cl]$^+$), 116 (6), 114 (9, [O(CH_2CH_2)$_2$NCO]$^+$), 88 (30); **HR-MS** ([$C_7H_{13}NO_2{}^{35}Cl$]$^+$) calc. 178.0635 u found 178.0622 u.

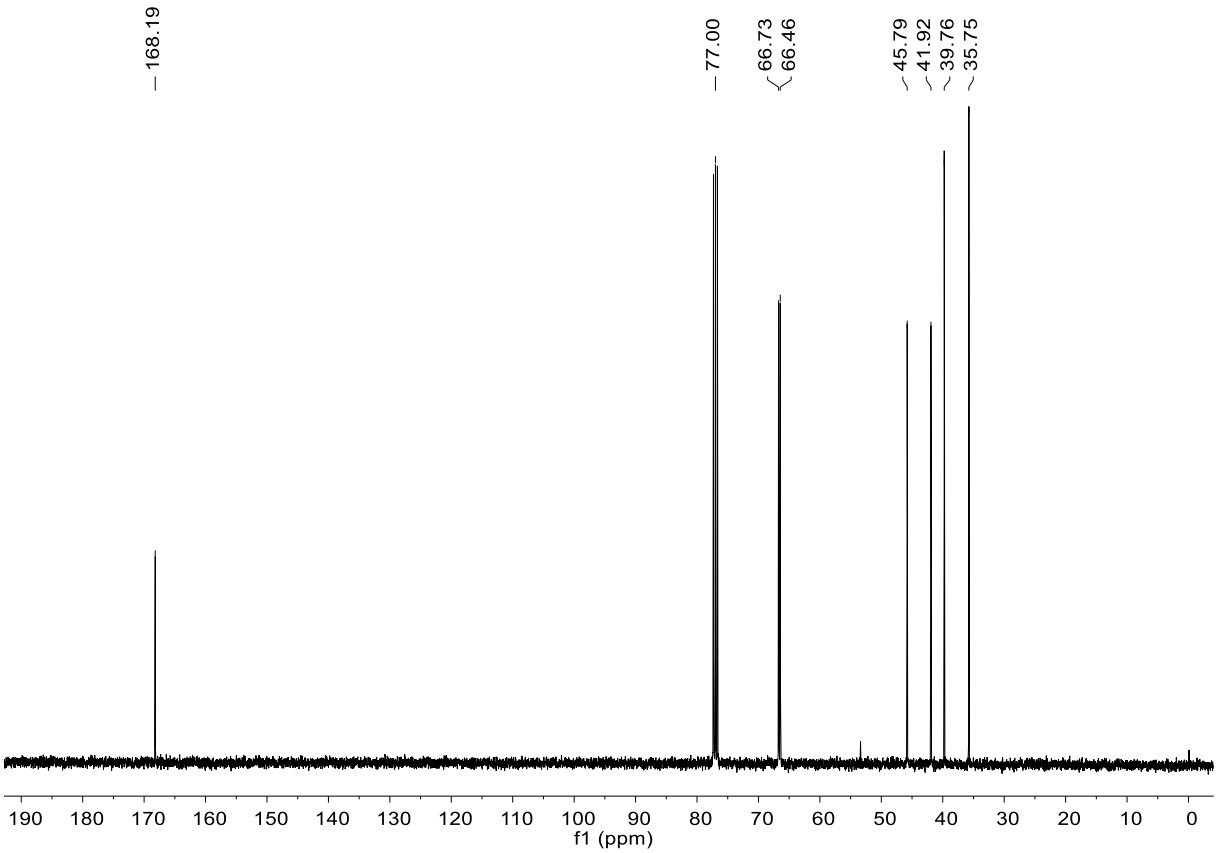
4-Propenoyl morpholine (characterized in mixture with **2_{10j}**, only selected signals noted)



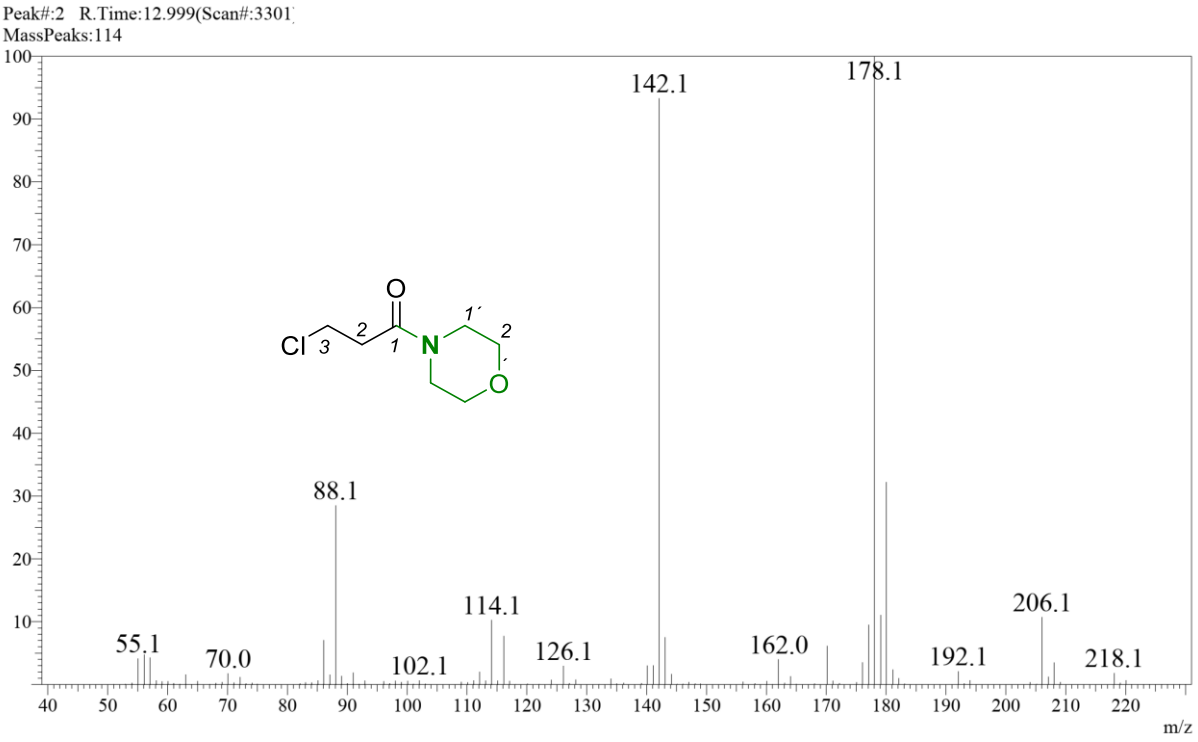
M ($C_7H_{11}NO_2$) = 141.170 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 6.54 (dd, $^3J_{2,3E}$ = 16.9 Hz, $^3J_{2,3Z}$ = 10.5 Hz, 1H, 2-H), 6.32 (dd, $^3J_{3,2}$ = 16.8 Hz, $^2J_{3,3}$ = 1.9 Hz, 1H, 3-H_E(dd, $^3J_{3,2}$ = 10.5 Hz, $^2J_{3,3}$ = 1.8 Hz, 1H, 3-H_Z); **GC-MS** (CI, 70 eV) m/z [u] (%) = 182 (3, [M+allyl]$^+$), 170 (24, [M+Et]$^+$), 142 (100, [M+H]$^+$), 126 (6), 88 (18)



^{1}H-NMR spectrum of 4-(3-chloropropanoyl) morpholine (400 MHz, $CDCl_3$).

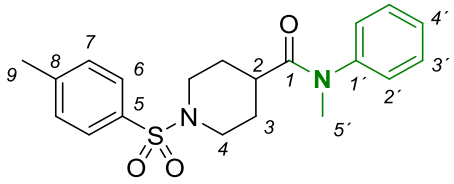


^{13}C-NMR spectrum of 4-(3-chloropropanoyl) morpholine (100 MHz, $CDCl_3$).



Mass spectrum of 4-(3-chloropropanoyl) morpholine (CI, 70 eV).

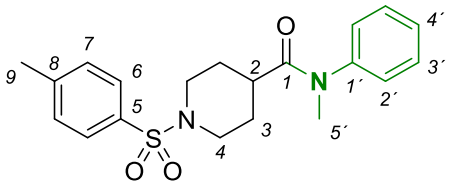
5.4.2.13 Synthesis of *N*-Methyl-N-phenyl-1-tosylpiperidine-4-carboxamide (2_{11k})



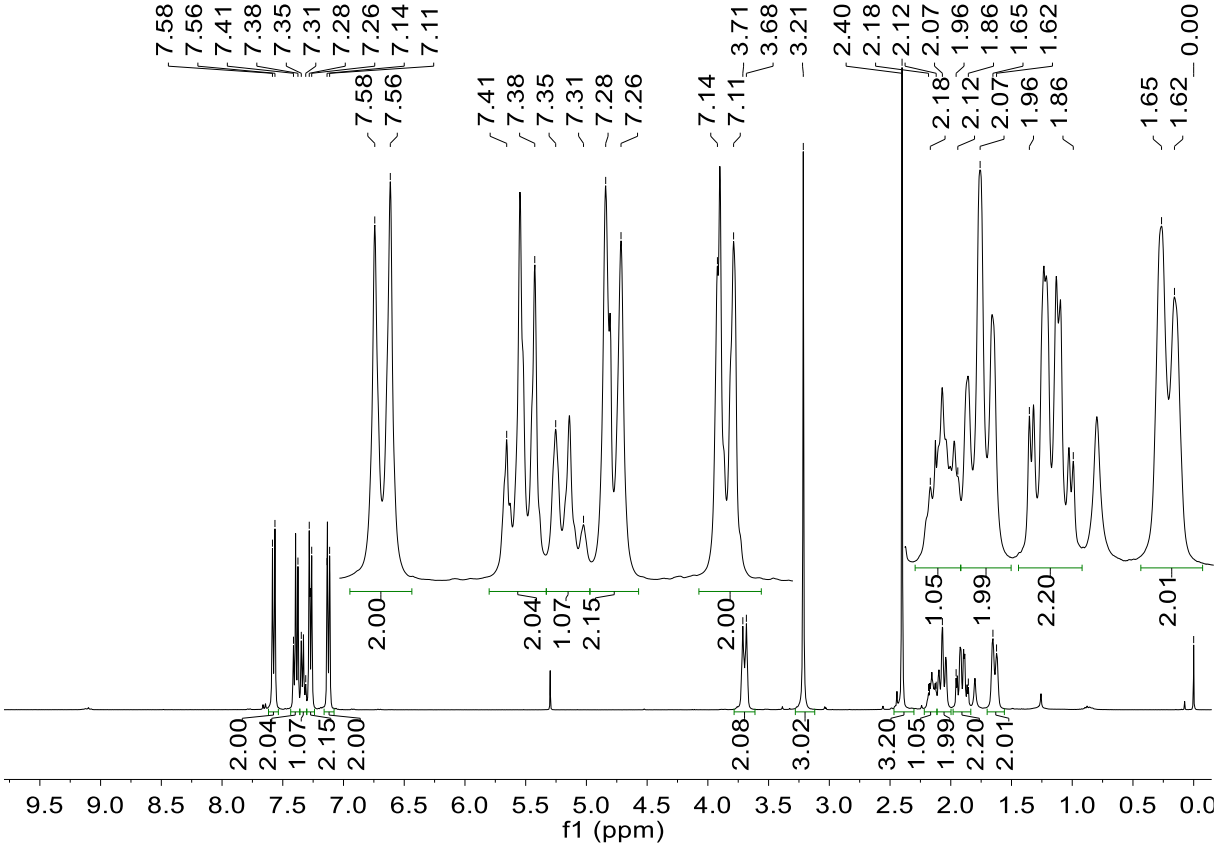
2_{11k}

The synthesis of 1-tosylpiperidine-4-carboxylic acid (**1_{11}**) is described in chapter 5.4.5.1 on page 236.

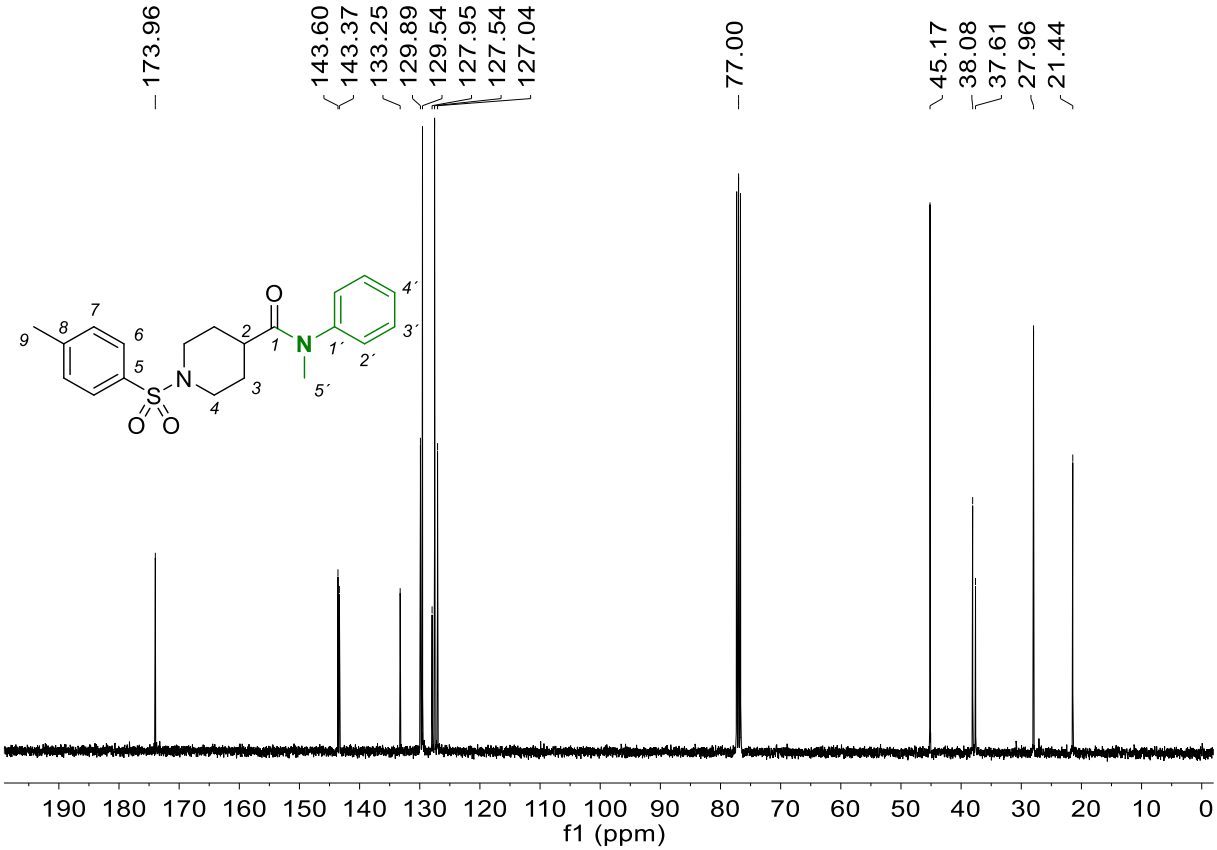
PH3454: In accordance with general procedure 4 (chapter 5.3.4, page 50) a suspension of acid **1_{11}** (142 mg, 0.50 mmol, 1.0 equiv) and FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%) in MeCN (0.50 mL, 1 M) was combined with TCT (36 mg, 190 μmol, 38 mol%) and stirred at 80 °C for 4 h. Next, the colourless reaction suspension was cooled in an ice bath and successively *N*-methyl aniline (65 μL, 0.60 mmol, 1.2 equiv) and NMM (75 μL, 0.65 mmol, 1.3 equiv) were added. After stirring for 4 h at room temperature, aqueous work up provided the crude material as a yellow oil (247 mg, 132%). Lastly, chromatographic purification on silica gel (19.7 g, mass ratio crude material/SiO_2 1:79) with EtOAc/*n*Hex 55:45 afforded the title amide as a colourless, foamy solid in 89% yield (165.7 mg, 0.445 mmol). In order to charge the silica gel column, the crude product was dissolved in CH_2Cl_2 (ca. 10 mL), SiO_2 was added (0.63 g, relation weight crude **2_{11k}** with respect to silica gel 1:2.5) and the solvent was removed under reduced pressure. Interestingly, *N*-methyl aniline (r_f = 0.78 in EtOAc/*n*Hex 55:45, fractions yellow coloured) was eluted prior to the title compound.



M ($C_{20}H_{24}N_2O_3S$) = 372.48 g/mol; **mp.** 138-140 °C; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 55:45) = 0.42; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.57 (d, ^3J = 8.2 Hz, 2H, 6-H), 7.41-7.38 (m, 2H, 3´-H), 7.35-7.31 (m, 1H, 4´-H), 7.28-7.26 (m, 2H, 7-H), 7.14-7.11 (m, 2H, 2´-H), 3.71-3.68 (m, 2H, 4-H_a), 3.21 (s, 3H, 5´-H), 2.40 (s, 3H, 9-H), 2.18-2.12 (m 1H, 2-H), 2.07 (ψ-t, *J* = 11.6 Hz, 2H,4-H_b), 1.96-1.86 (m, 2H, 3-H_a), 1.65-1.62 (m, 2H, 3-H_b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 173.96 (C-1), 143.60 (C-1´), 143.37 (C-8), 133.25 (C-5), 129.89 (C-3´), 129.54 (C-7), 127.95 (C-4´), 127.54 (C-6), 127.04 (C-2´), 45.17 (C-4), 38.08 (C-2), 37.61 (C-5´), 27.96 (C-3), 21.44 (C-9); **HR-MS** ($[C_{20}H_{25}N_2O_3{}^{32}S]^+$) calc. 373.1586 u found 373.1610 u.



^{1}H-NMR spectrum of *N*-Methyl-N-phenyl-1-tosylpiperidine-4-carboxamide (400 MHz, $CDCl_3$).

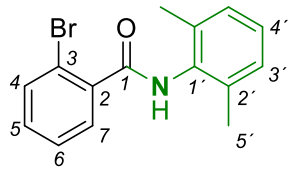


^{13}C-NMR spectrum of *N*-Methyl-N-phenyl-1-tosylpiperidine-4-carboxamide (100 MHz, $CDCl_3$).

5.4.2.14 Synthesis of *N*-(2,6-Dimethylphenyl) 2-bromobenzoyl amide (2_{12l})

entry	conditions	yield [%]	2_{12l}
1	1. TCT (38 mol%), FPyr (10 mol%), EtOAc (2 M), 4.5 h 80 °C 2. 2,6-Me_2PhNH_2 (1.2 equiv), NMM (1.3 equiv), EtOAc (0.8 M), 15 min 0 °C, 14 h rt	89[a]	
2	1. TCT (38 mol%), FPyr (10 mol%), **MeCN** (2 M), 4 h 80 °C 2. 2,6-Me_2PhNH_2 (1.2 equiv), **K_2CO_3** (1.3 equiv), **MeCN** (0.7 M), 15 min 0 °C, 17 h rt	83[a]	
3	1. TCT (38 mol%), FPyr (10 mol%), MeCN (2 M), **8.5 h 40 °C** 2. 2,6-Me_2PhNH_2 (1.2 equiv), K_2CO_3 (1.3 equiv), MeCN (0.7 M), 15 min 0 °C, 15 h rt	82[a]	
4	1. TCT (38 mol%), FPyr (10 mol%), EtOAc (2 M), 4.5 h 80 °C 2. 2,6-Me_2PhNH_2 (1.2 equiv), NMM (1.3 equiv), **DMAP (20 mol%)**, EtOAc (1 M), 15 min 0 °C, 14 h rt	77[b]	

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of 1,3,5-trimtethoxybenzene as internal standard.



2_{12l}

The title compound was produced in 89% isolated yield using NMM as base and EtOAc as solvent (entry 1). When NMM was replaced by K_2CO_3 and EtOAc by MeCN, the title amide was formed in a reduced yield of 83% (entry 3). Under these conditions the temperature for the chlorination step **1→6** could be lowered from 80 to 40 °C without an impact on the yield (entry 3). Finally, the usage of DMAP (10 mol%) in the

second amidation step had no beneficial impact, since the amide **2_{12l}** was obtained in 77% yield (entry 4).

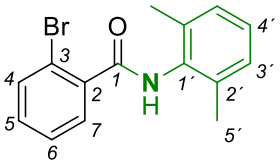
Entry 1, PH3098: In agreement with general protocol 4 (chapter 5.3.4 page 50) to a mixture of 2-bromobenzoic acid (201 mg, 1.00 mmol, 1.0 equiv) and FPyr (9.8 μL, 10.2 mg, 100 μL, 10 mol%) in EtOAc (0.50 mL, 2 M) was added TCT (72 mg, 0.38 mmol, 38 mol%) and the reaction mixture was stirred for 4.5 h at 80 °C. Next, the reaction suspension was diluted with EtOAc (0.75 mL→0.8 M), cooled to 0 °C, treated successively with 2,6-dimethylaniline (150 μL, 1.2 mmol, 1.2 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) and stirred for 14 h at room temperature. After work up including washing with 2 N HCl solution in water, the crude material (285 mg, 94%, colourless solid) was subjected to column chromatographic purification on silica gel (20.5 g, ratio mass crude **2_{12l}**/SiO_2 1:72) with EtOAc/CH_2Cl_2 2:98[(48)] furnished the title amide as a colourless solid in 89% yield (270.5 mg, 0.889 mmol, 89%). In order to load crude **2_{12l}** onto the silica gel column, it was dissolved in CH_2Cl_2 (ca. 10 mL), SiO_2 was added (1.09 g, ratio crude material/SiO_2 1:3.8) and concentrated under reduced pressure.

Entry 2, PH3116: Following general protocol 4 (chapter 5.3.4 page 50) 2-bromobenzoic acid (1.00 mmol, 1.0 equiv) was converted with TCT (38 mol%) in the presence of FPyr (10 mol%) in **MeCN** (0.50 mL, 2 M) under heating for 4 h (= **t_1**) to 80 °C into the respective acid chloride. Subsequently, amidation was accomplished after dilution with further MeCN (1 mL→0.7 M) engaging 2,6-dimethylaniline (1.2 equiv) and **K_2CO_3** (180 mg, 1.3 mmol, 1.3 equiv). Past 17 h (= **t_2**) of stirring at room temperature, the crude product (282 mg, 93%, colourless solid) was purified by means of column chromatography on silica gel (18.9 g, relation of masses crude material/SiO_2 1:67) using EtOAc/CH_2Cl_2 3:97 afforded the title compound as a colourless solid in 83% yield (252.5 mg, 0.830 mmol). In order to load the chromatography column, the crude product was dissolved in CH_2Cl_2 (ca. 10 mL), SiO_2 was added (0.70 g, masses crude **2_{12l}**/silica 1:2.5) and the mixture was concentrated *in vacuo*.

Entry 3, PH3105: The title compound was synthesized as described in entry 3 with the alteration that the chlorination **1→6** was performed under heating to **40 °C for 8.5 h** (= **t_1**) and that during amidation **6→2** the reaction suspension was allowed to stir for 15 h (= **t_2**). Eventually, column chromatographic purification of the crude title compound (270 mg, 88%, colourless solid) utilizing silica gel (18.5 g, mass ratio crude product/SiO_2 1:69) yielded amide **2_{12l}** as a colourless solid (250.6 mg, 0.824 mmol, 82%).

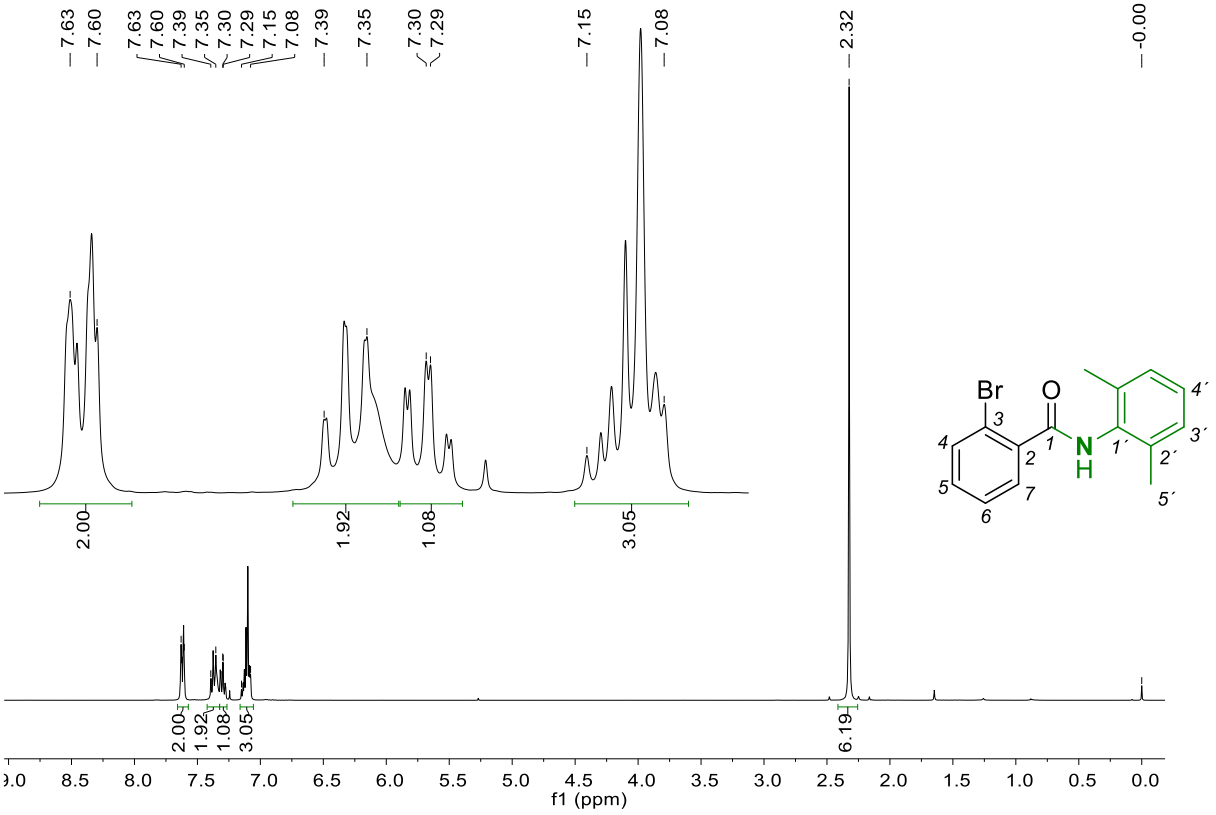
(48) Due to the low solubility of the title compound in *n*Hex, the utilization of EtOAc/CH_2Cl_2 mixtures as eluent was essential for isolation in high yields. A purification through column chromatography with EtOAc/*n*Hex 25:75 resulted in strongly depleted yields.

Entry 4, PH3090: As described in general protocol 3 (chapter 5.3.3, page 49) 2-bromobenzoic acid (101 mg, 0.50 mmol, 1.0 equiv) was combined with FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%), EtOAc (0.25 mL, 1 M) and TCT (36 mg, 0.19 mmol, 38 mol%) and allowed to react at 80 °C for 4 h. Next, further EtOAc (0.25 mL→1 M), 2,6-dimethylaniline (75 μL, 0.60 mmol, 1.2 equiv), NMM (75 μL, 0.65 mmol, 1.3 equiv) and **DMAP** (12.2 mg, 100 μmol, **20 mol%**) were added and the reaction mixture was continued to stir for 15 h at room temperature. Eventually, ^{1}H-NMR with 1,3,5-trimethoxybenzene (29.0 mg) as internal standard revealed the title compound in 77% yield.

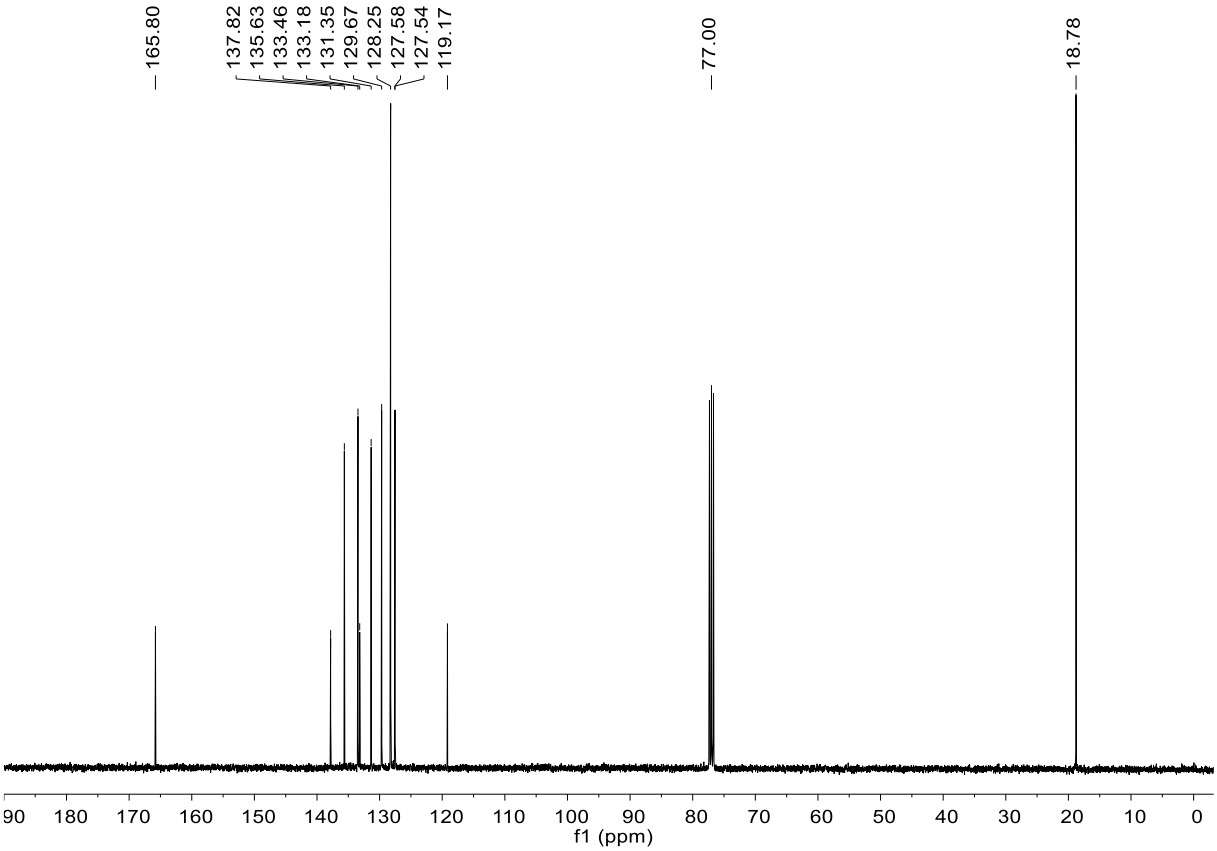


M ($C_{15}H_{14}BrNO$) = 304.187 g/mol; **mp.** 166-168 °C; $\mathbf{r_f}$ (SiO_2) = 0.33 (EtOAc/CH_2Cl_2 2:98), 0.35 (EtOAc/*n*Hex 25:75); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.63-7.60 (m, 2H, 4-H, 7-H), 7.39-7.35 (m, 2H, 6-H, NH), 7.30 (dt, *J* = 7.7, 1.7 Hz, 1H, 5-H), 7.15-7.08 (m, 3H, 3´-H, 4´), 2.32 (s, 6H, 5´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 165.80 (C-1), 137.82 (C-2), 135.63 (C-2´), 133.46 (C-4), 133.18 (C-1´), 131.35 (C-5), 129.67 (C-7), 128.25 (C-3´), 127.58 (C-6 or C-4´), 127.54 (C-6 or C-4´), 119.17 (C-3), 18.78 (C-5´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 346 (2, [M(^{81}Br)+allyl]$^+$), 344 (2, [M(^{79}Br)+allyl]$^+$), 334 (28, [M(^{81}Br)+Et]$^+$), 332 (27, [M(^{79}Br)+Et]$^+$), 306 (96, [M(^{81}Br)+H]$^+$), 304 (100, [M(^{79}Br)+H]$^+$), 254 83), 226 (10), 185 (16, [2-^{81}BrC_6H_4CO]$^+$), 183 (16, [2-^{79}BrC_6H_4CO]$^+$), 148 (6, [2,6-$(H_3C)_2C_6H_3$NHCO]$^+$), 120 (2, [2,6-$(H_3C)_2C_6H_3$NH]$^+$), 91 (3, [Bn]$^+$).

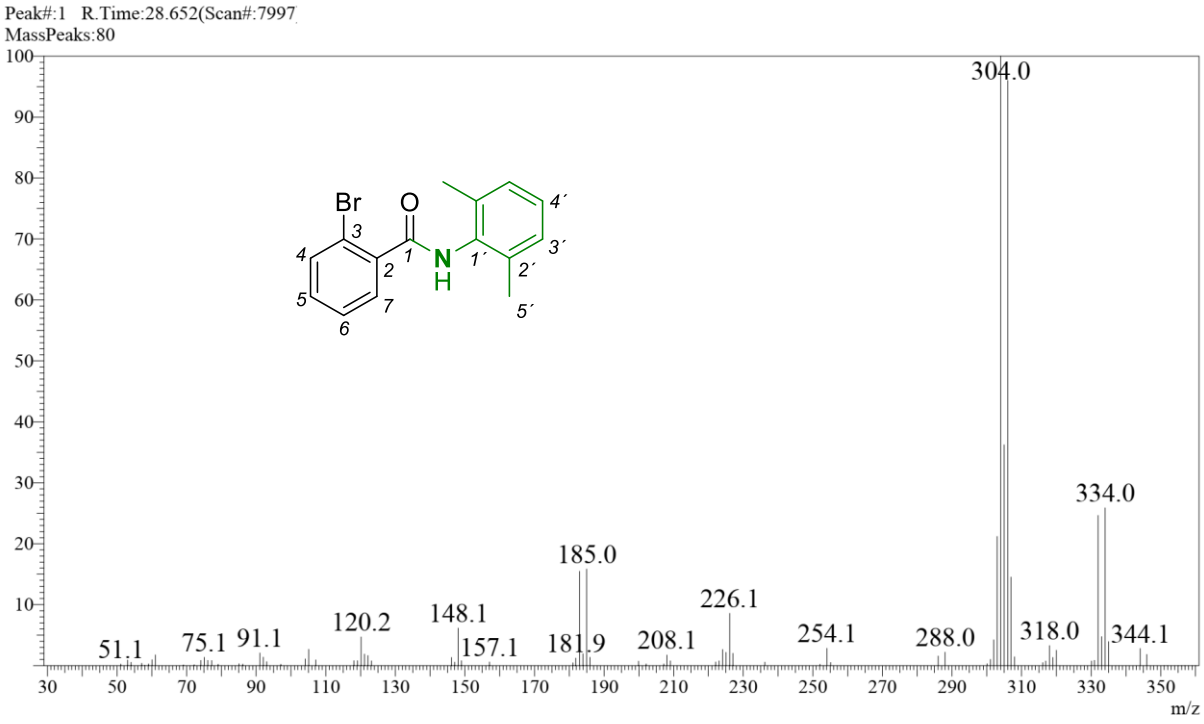
The NMR data is in agreement with the literature.[35]



^{1}H-NMR spectrum of *N*-(2,6-Dimethylphenyl) 2-Bromobenzoyl amide (400 MHz, $CDCl_3$).

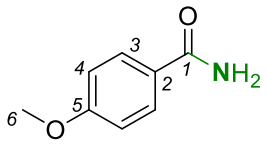


^{13}C-NMR spectrum of *N*-(2,6-Dimethylphenyl) 2-Bromobenzoyl amide (100 MHz, $CDCl_3$).



Mass spectrum of *N*-(2,6-Dimethylphenyl) 2-Bromobenzoyl amide (CI, 70 eV).

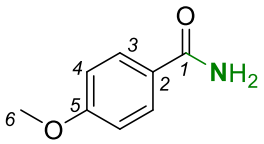
5.4.2.15 Synthesis of 4-Methoxybenzamide (2_{12m})



2_{12m}

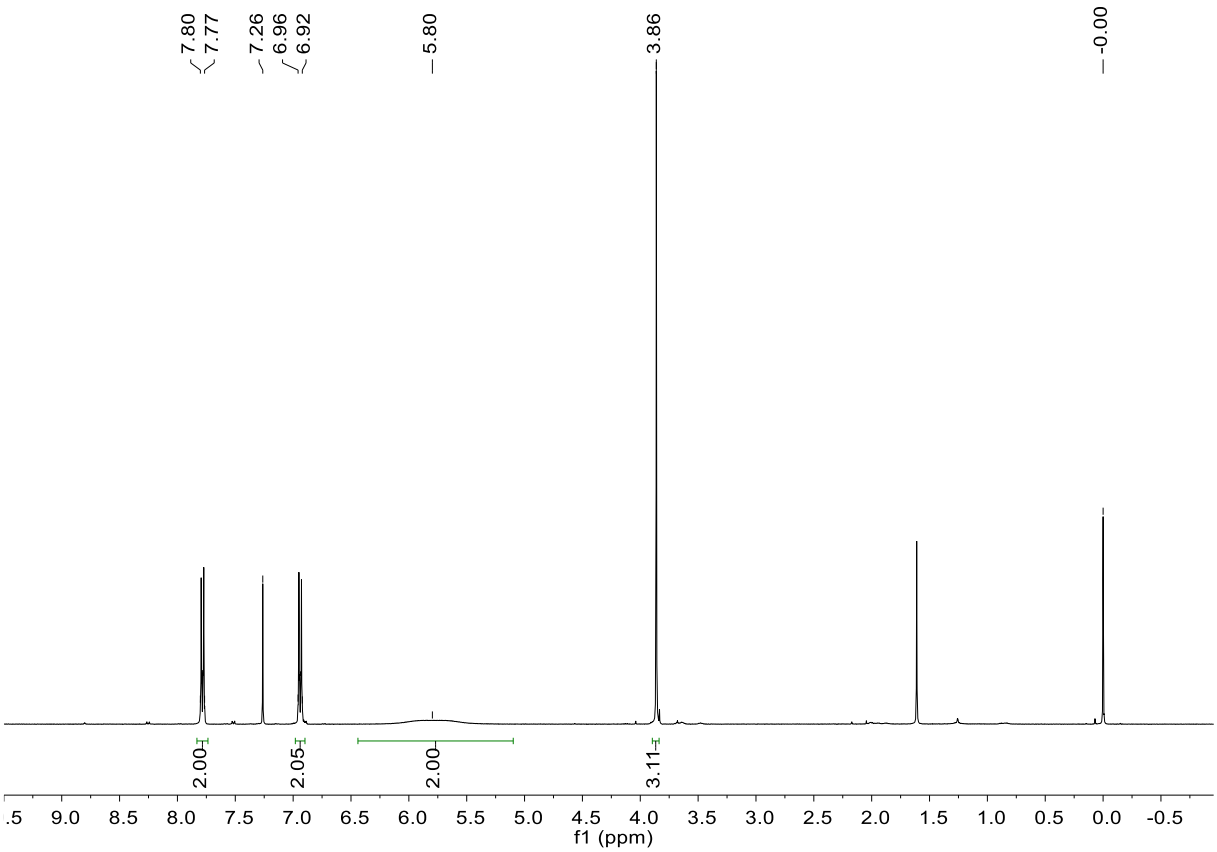
PH3132: According to general protocol 4 (chapter 5.3.4, page 50) 4-methoxybenzoic acid (152 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.380 mmol, 38 mol%) in the presence of FPyr (9.8 μL, 10.2 mmol, 10 mol%) in MeCN (0.50 mL, 2 M) for 2 h at 80 °C. Then, MeCN (0.50 mL→1 M) an at 0 °C 32 wt% ammonia solution in water (90 μL,1.5 mmol, 1.5 equiv) and K_2CO_3 (180 mg, 1.3 mmol, 1.3 equiv) was added and the resulting reaction suspension was stirred for 4 h at room temperature. After aqueous work up, silica gel (0.52 g) was added and the solvent was removed under reduced pressure. The residue was subjected to column chromatographic purification on silica gel (13.0 g) using MeOH/EtOAc 2:98, which afforded the title compound as a colourless solid (130.8 mg, 0.865 mmol, 87%).

PH3128: Following general procedure 4 (chapter 5.3.4, page 50), 4-methoxy benzoic acid (1.00 mmol, 1.0 equiv) was combined with FPyr (10 mol%), **EtOAc** (0.50 mL, 2 M) and TCT (38 mol%) and heated to 80 °C for 3 h. Next, further EtOAc (0.50 mL→1 M) and under chilling to 0 °C 32 wt% aqueous ammonia solution (1.5 equiv) and K_2CO_3 (1.3 equiv) were added. After 3 h of stirring at ambient temperature work up gave the crude material as a colourless solid (136.0 mg, 90%). In the end, purification by means of column chromatography on silica gel (14.5 g) utilizing MeOH/EtOAc 2:98 furnished the title amide as a colourless solid (125.9 mg, 0.833 mmol, 83%). Thereby, the crude product was dissolved in EtOAc (20 mL), silica gel was added (0.53 g) and the mixture was concentrated under reduced pressure to dryness.

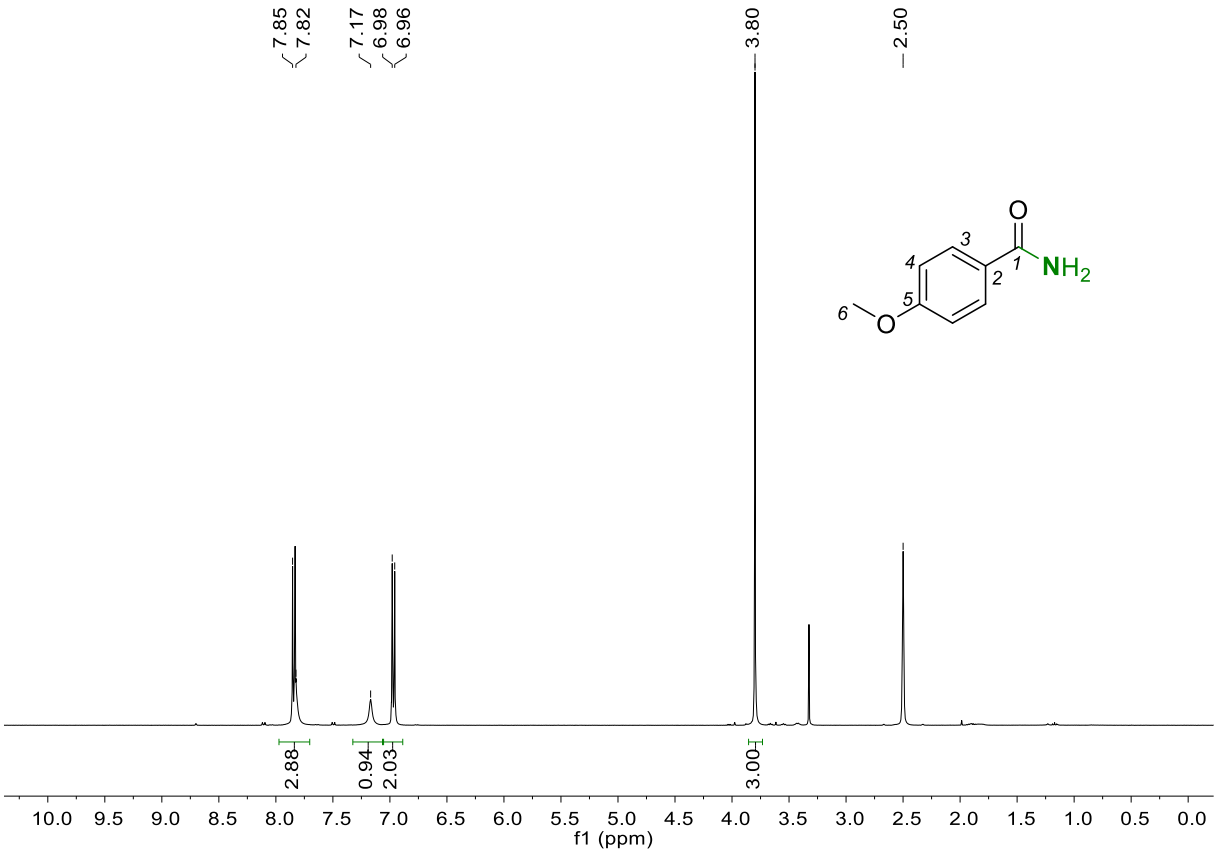


M ($C_8H_9NO_2$) = 151.165 g/mol; **mp**. = 158-160 °C $\mathbf{r_f}$ (SiO_2, EtOAc) = 0.33; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.80-7.77 (m, 2H, -H), 6.96-6.92 (m, 2H), 5.80 (br. s, 2H, NH_2), 3.86 (s, 3H, 6-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 168.84 (C-1), 162.57 (C-5), 129.26 (C-3), 129.13 (C-2), 125.54, 113.78 (C-4), 55.42 (C-6); **^{1}H-NMR** (400 MHz, DMSO-d^6) δ [ppm] = 7.85-7.82 (m, 3H, 3-H, NH), 7.17 (br. s, 1H, NH), 6.98-6.96 (m, 2H, 4-H), 3.80 (s, 3H, 6-H); **^{13}C-NMR** (100 MHz, DMSO-d^6) δ [ppm] = 167.43 (C-1), 161.57 (C-5), 129.35 (C-3), 126.51 (C-2), 113.37 (C-4), 55.30 (C-6); **GC-MS** (CI, 70 eV) m/z [u] (%) = 180 (9, $[M+Et]^+$), 166 (1, $[M+Me]^+$), 152 (100, $[M+H]^+$), 151 (21, $[M]^+$), 134 (81), 109 (14), 90 (4), 60 (8).

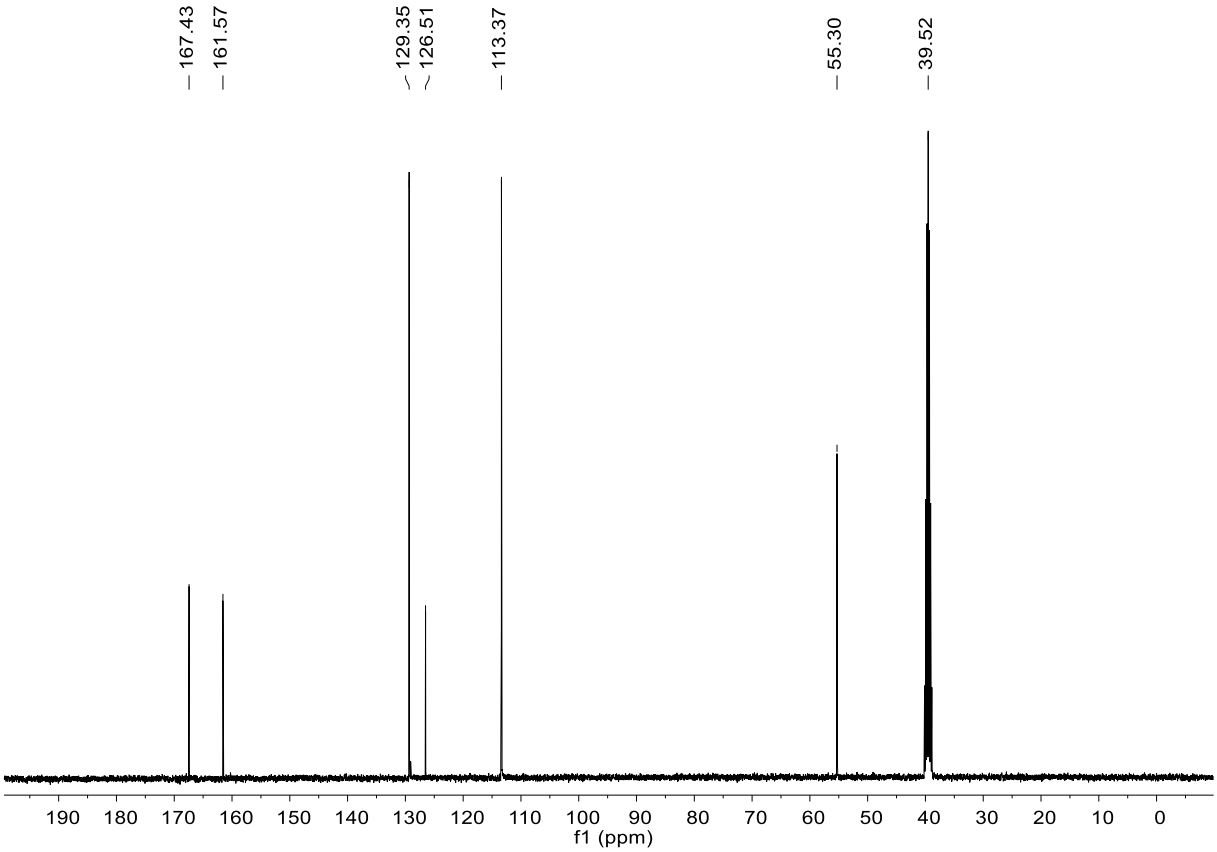
The ^{1}H-NMR is in fair agreement with the literature.[36]



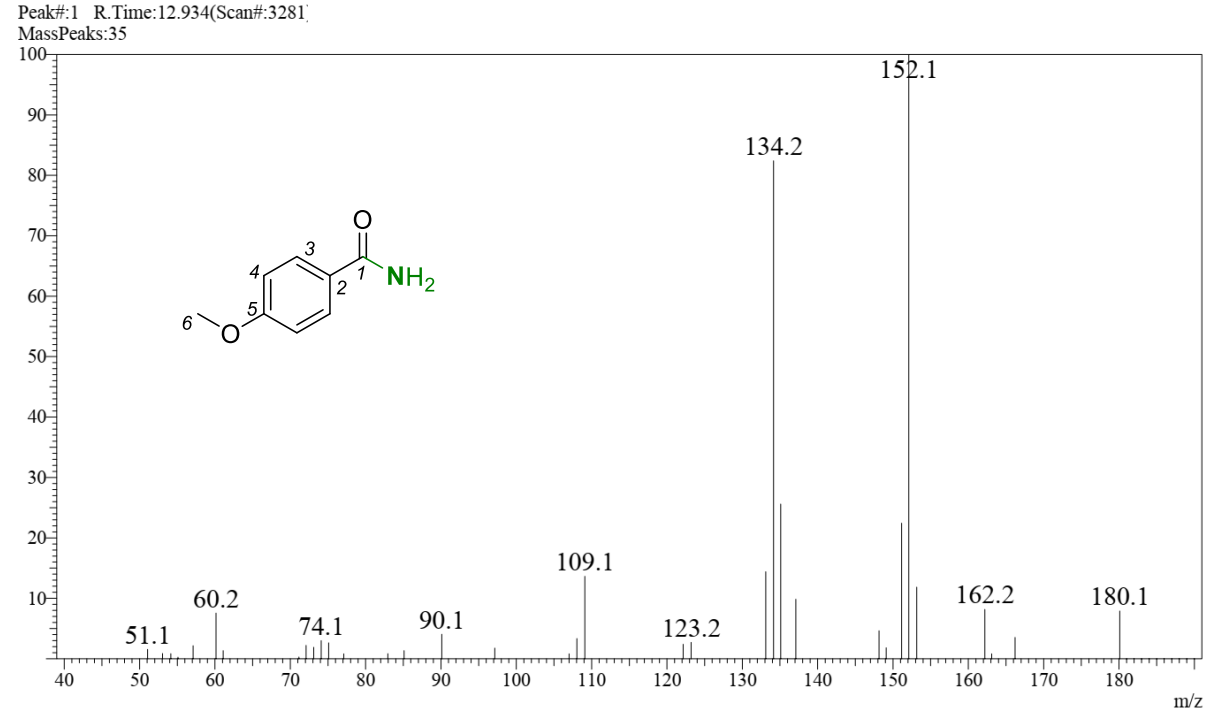
^{1}H-NMR spectrum of 4-methoxybenzamide (400 MHz, $CDCl_3$).



^{1}H-NMR spectrum of 4-methoxybenzamide (400 MHz, DMSO-d^6).



^{13}C-NMR spectrum of 4-methoxybenzamide (100 MHz, $CDCl_3$).

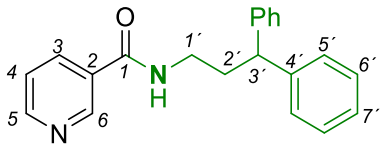


Mass spectrum of 4-methoxybenzamide (CI, 70 eV).

5.4.2.16 Synthesis of 3,3-Diphenylpropyl nicotinic acid amide (2_{13n})

entry	conditions	yield 2_{13n} [%]
1	1. **1_{13}** (1.3 equiv), TCT (49 mol%), FPyr (10 mol%), MeCN (1 M), 8 h 80 °C 2. H**Nu** (1.0 equiv), NMM (1.7 equiv), MeCN (0.7 M), 15 min 0 °C then 13 h rt	83[a]
2	1. TCT (**38 mol%**), FPyr (10 mol%), MeCN (1 M), 10 h 80 °C 2. H**Nu** (**1.1 equiv**), NMM (1.3 equiv), MeCN (0.7 M), 15 min 0 °C then 13 h rt	72[a]
3[22]	1. TCT (33 mol%), NMM (1.3 equiv), MeCN (1 M), 15 min 0° C then **1 h rt** 2. H**Nu** (1.1 equiv), MeCN (0.5 M) 15 min 0° C then 20 h rt	54[b]

a. Yield determined from mass of isolated material after column chromatographic purification. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of dibenzylether as internal standard. H**Nu** = 3,3-diphenylpropylamine, **1_{13}** = 3-pyridinecarboxylic acid



2_{13n}

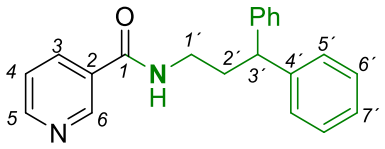
The title compound was isolated in 83% yield, when pyridine-3-carboxylic acid (**1_{13}**) was used in a slight excess (1.3 equiv, entry 1). Nevertheless, coupling of 1.0 equiv acid **1_{13}** with 1.1 equiv of 3,3-diphenylpropylamine afforded amide **2_{13n}** in a reasonable yield of 72% after chromatographic purification (entry 2). In our hands, the literature protocol [22] gave rise to the title compound in a diminished yield of 54% as judged by means of an internal NMR-standard.

Entry 1, PH3276: In accordance of general protocol 4 (chapter 5.3.4, page 50) 3-carboxy pyridine (**1_{13}**, 160 mg, 1.30 mmol, 1.3 equiv) was allowed to react with TCT (92 mg, 0.49 mmol, 49 mol%) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in acetonitrile (1.0 mL) for 8 h at 80 °C. Next, a solution of 3,3-diphenylethyl amine (211 mg, 1.0 mmol, 1.0 equiv) and NMM (190 μL, 175 mg, 1.7 mmol, 1.7 equiv) in MeCN (0.5 mL→0.7 M) was added drop-wise at 0 °C and the reaction suspension was stirred at ambient temperature over-night (13 h). Aqueous work without HCl-washing delivered the crude material as a red oil (403 mg, 127%), of which ^{1}H-NMR verified full consumption of 3,3-diphenylpropylamine. In order to load the crude compound **2_{13n}** onto a silica gel column, it was dissolved in CH_2Cl_2, silica gel was added (1.0 g, mass ratio crude product/SiO_2 1:2.5) and the solvent was removed *in vacuo*. Chromatographic purification on silica gel (26.4 g, mass crude title compound in relation to silica gel 1:66) using EtOAc/*n*Hex 90:10→100:0 finally furnished the amide **2_{13n}** as a pale yellow solid (263.5 mg, 0.833 mmol, 83%) after drying in high vacuum for 30 min.

Entry 2, PH3293: In alignment general procedure 4 (chapter 5.3.4, page 50) 3-carboxypyridine (**1_{13}**, 123 mg, 1.0 mmol, 1.0 equiv) was heated with TCT (72 mg, 0.38 mmol, 38 mol%) and FPyr (10 mol%) in MeCN (1.0 mL, 1 M) for 10 h to 80 °C. Thereupon, the brown reaction suspension was cooled in an ice bath, a solution of 3,3-diphenylpropylamine (232 mg,

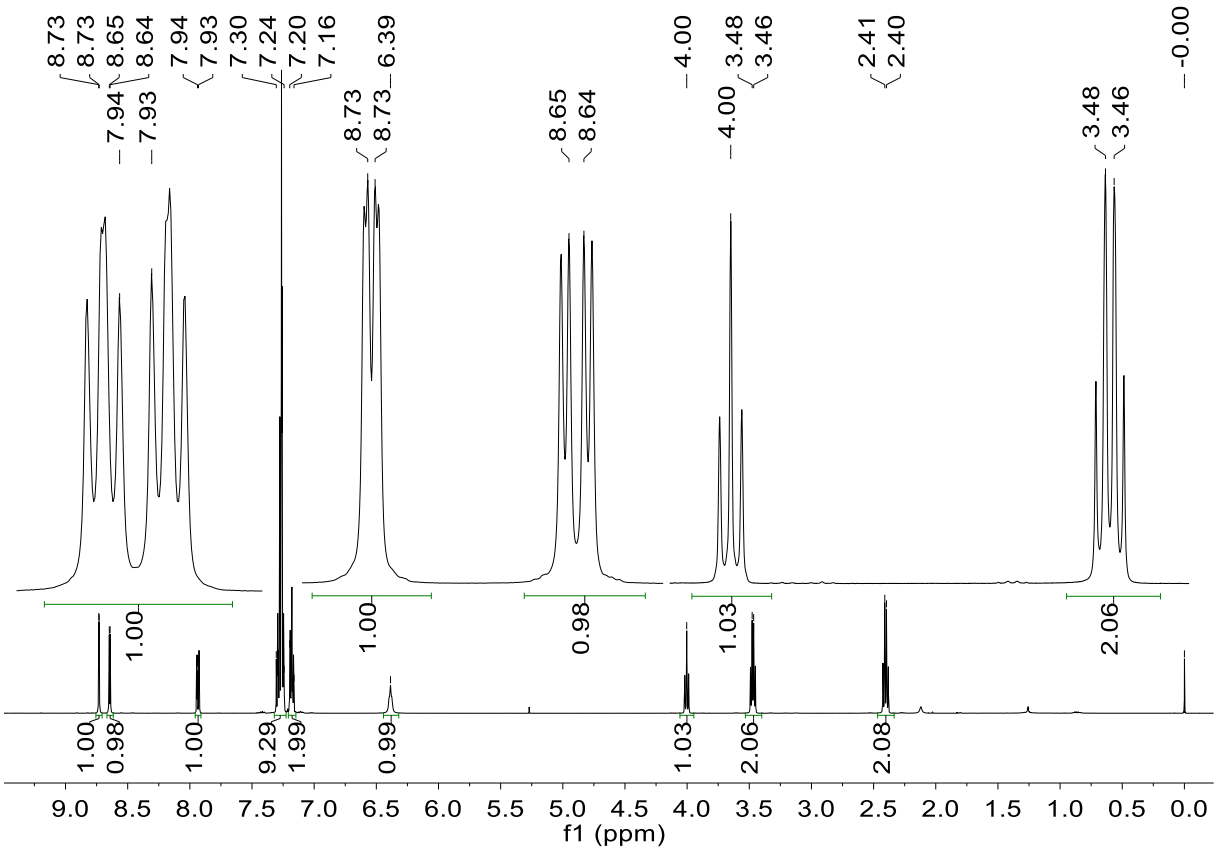
1.1 mmol, 1.1 equiv) and NMM (146 μL; 134 mg, 1.3 mmol, 1.3 equiv) was introduced drop-wise and the reaction mixture was stirred for 13 h at room temperature. Then, aqueous work up without HCl-washing gave rise to the crude title compound as orange solid (307 mg, 97%), whereby ^{1}H-NMR confirmed 6 mol% of residual 3,3-diphenylpropyl amine in respect to amide **2$_{13n}$**. Eventually, purification by means of column chromatography on silica gel (22.6 g, mass relation crude product/SiO_2 1:73) with EtOAc furnished pyridine derivative **2$_{13n}$** as a pale yellow solid in 72% yield (227.7 mg). To charge the silica gel column with the crude material, the crude title compound was adsorbed on silica gel (0.81 g, mass ratio crude **2$_{13n}$**/SiO_2 1:2.6) as described in entry 1).

Entry 3, PH3302: Following general procedure 5 (chapter 5.3.5 on page 56)[22] a mixture of the acid **1$_{13}$** (62 mg, 0.50 mmol, 1.0 equiv) in MeCN (0.50 mL, 1 M) was treated successively with TCT (31 mg, 165 μmol, 33 mol%) at room temperature and NMM (75 μL, 0.65 mmol, 1.3 equiv) at 0 °C and the resulting suspension was allowed to for stir for 15 min at 0 °C and subsequently for 20 h at ambient temperature. Since the reaction mixture turned solid upon stirring at 0 °C, further MeCN (0.50 mL→0.5 M) was added. Next, 3,3-diphenylpropylamine (116 mg, 0.55 mmol, 1.1 equiv) was introduced under cooling in an ice bath and the resulting reaction mixture was stirred for 20 h at room temperature. Finally, after aqueous work up without 1 N HCl-washing, ^{1}H-NMR of the crude material with dibenzylether as internal standard (30.5 mg) showed amide **2$_{13n}$** in 54% yield alongside with 59% of unreacted 3,3-diphenylpropylamine.

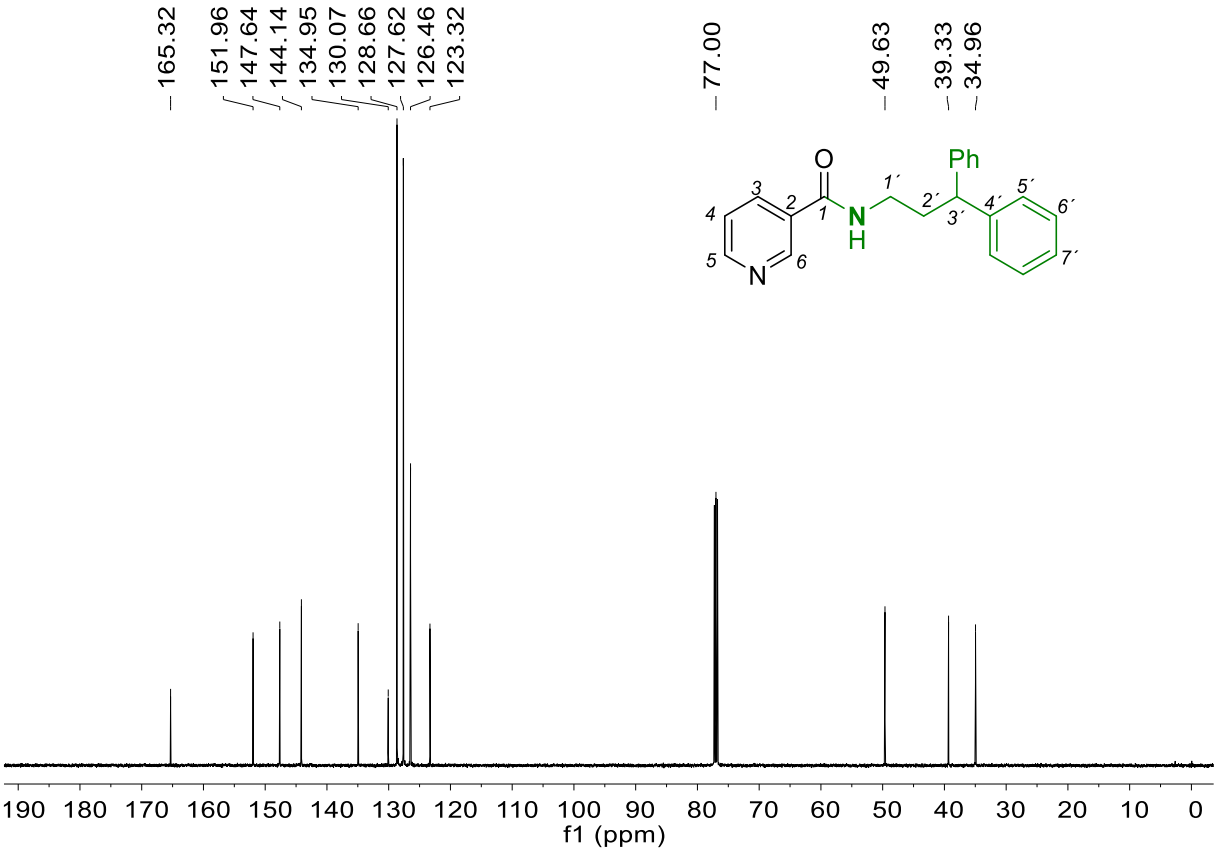


M ($C_{21}H_{20}N_2O$) = 316.40 g/mol; **mp**. = 130-132 °C; **r$_f$** (SiO_2, EtOAc) = 0.34; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.73 (dd, $^{4}J_{6,3}$ = 2.3 Hz, $^{5}J_{6,4}$ = 0.7 Hz, 1H, 6-H), 8.65 (dd, $^{3}J_{5,4}$ = 4.8 Hz, $^{4}J_{5,3}$ = 1.7 Hz, 1H, 5-H), 7.94 (ddd, $^{3}J_{3,4}$ = 7.9 Hz, $^{4}J_{3,6}$ = 2.2, $^{4}J_{3,5}$ = 1.8 Hz, 1H, 3-H), 7.30-7.24 (m, 9H, 4-H, 5´-H, 6´-H), 7.20-7.16 (m, 2H, 7´-H), 6.39 (t, $^{3}J_{NH,1´}$ = 5.1 Hz, 1H, NH), 4.00 (t, $^{3}J_{3´,4´}$ = 7.8 Hz, 1H, 3´-H), 3.48 (td, ^{3}J = 6.6 Hz, 2H, 1´-H), 2.41 (td, ^{3}J = 6.6 Hz, 2H, 2´-H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 165.32 (C-2), 151.96 (C-5), 147.64 (C-6), 144.14 (C-4´), 134.95 (C-3), 130.07 (C-2), 128.66 (C-6´), 127.62 (C-5´), 126.46 (C-7´), 123.32 (C-4), 49.63 (C-3´), 39.33 (C-1´), 34.96 (C-2´).

The ^{1}H-NMR data is in match with reported values.[37]

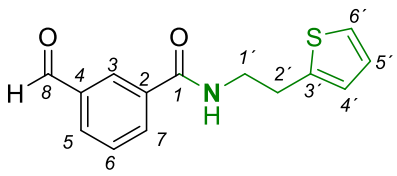


^{1}H-NMR spectrum of 3,3-diphenylpropyl nicotinic acid amide (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of 3,3-diphenylpropyl nicotinic acid amide (125 MHz, $CDCl_3$).

5.4.2.17 Synthesis of *N*-2-(Thiophen-2-yl)ethyl 3-formylbenzamide (2_{14o})

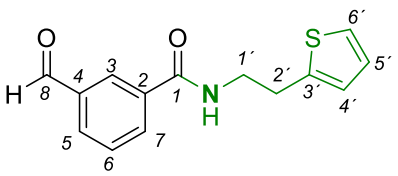


2_{14o}

PH3712: According to general protocol 4 (chapter 5.3.4, page 50) a 50 mL flask was charged with 3-formylbenzoic acid (**1_{14}**, 1.50 g, 10.0 mmol, 1.0 equiv), FPyr (147 μL, 153 mg, 1.5.0 mmol, 15 mol%) and EtOAc (reagent-grade, 5 mL, 2 M) and TCT (753 mg, 4.0 mmol, 40 mol%) was added at ambient temperature. Then, the reaction suspension was heated for 1 h to 40 and 4 h to 80 °C. After cooling down to ambient temperature, the reaction mixture was diluted with EtOAc (10 mL→0.7 M), cooled in an ice bath and successively 2-(2-thiopenyl)ethylamine (1.28 mL, 11.0 mmol, 1.1 equiv) and NMM (1.35 mL, 12.0 mmol, 1.2 equiv) were added by means of syringe pumps within 15 min.

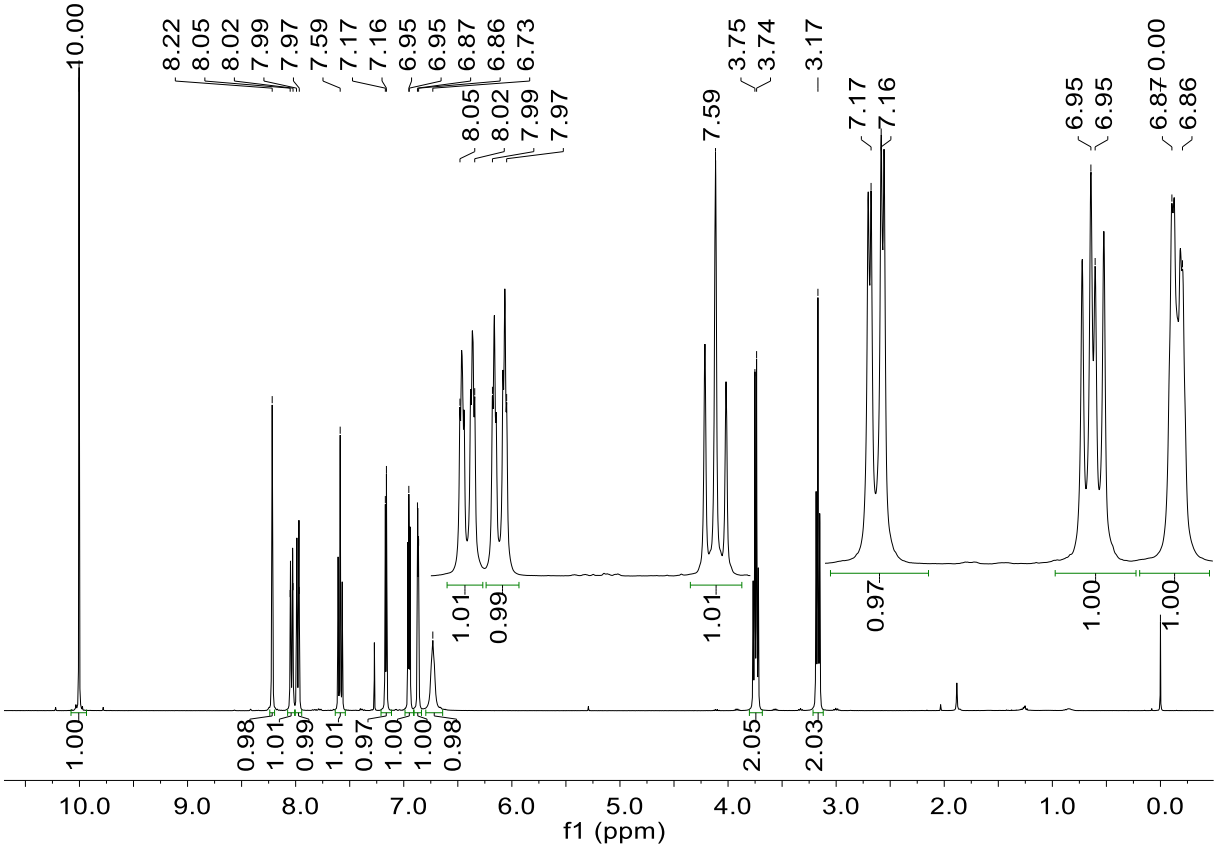
Past 15 min of stirring at 0 °C and 1 h at room temperature, EtOAc (10 mL) and 2 N HCl solution (aq., 10 mL) were added, the mixture was stirred vigorously for 5 min and filtered over a sintered funnel (porosity level 3, diameter 6 cm) by suction. The filtrated was poured into a 100 mL extraction funnel, the reaction flask/filter cake was rinsed/triturated with the aid of a spatula with further EtOAc (2 x 10 mL). From the combined filtrates the organic phase was separated, washed with aq. 1 N NaOH solution (1 x 10 mL) and brine (1 x 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the crude title compound as a brownish oil (2.76 g, 107%). Finally, chromatographic purification on silica gel (47.8 g, mass ratio SiO_2/crude product 17:1) using EtOAc/CH_2Cl_2 15:85, drying for 60 min at the rotary evaporator at 5 mbar and subsequently for 2 h in high vacuum facilitated the isolation of the title compound as a colourless solid in 87% yield (2.248 g, 8.67 mmol). Thereby, the crude material was dissolved in the eluent (3 mL) for the purpose of charging the SiO_2 column.

PH3723: Following the **literature protocol [22]** as described in general procedure 5.3.5 on page 56 3-formylbenzoic acid (75 mg, 0.50 mmol, 1.0 equiv) was allowed to react with TCT (31 mg, 0.165 mmol, 33 mol%) and NMM (75 μL, 0.65 mg, 1.3 equiv) in EtOAc (1.5 mL, 0.3 M) for 15 min at 0 °C and 1 h at room temperature. Next, 2-(2-thiophenyl)ethylamine (70 μL, 0.60 mmol, 1.2 equiv) was added at 0 °C and the reaction suspension was stirred for 20 h at ambient temperature. After aqueous work up including washing with 2 N HCl solution (1x3 mL), ^{1}H-NMR with dibenzylether (31.4 mg) as internal standard revealed the title compound in 45% yield.

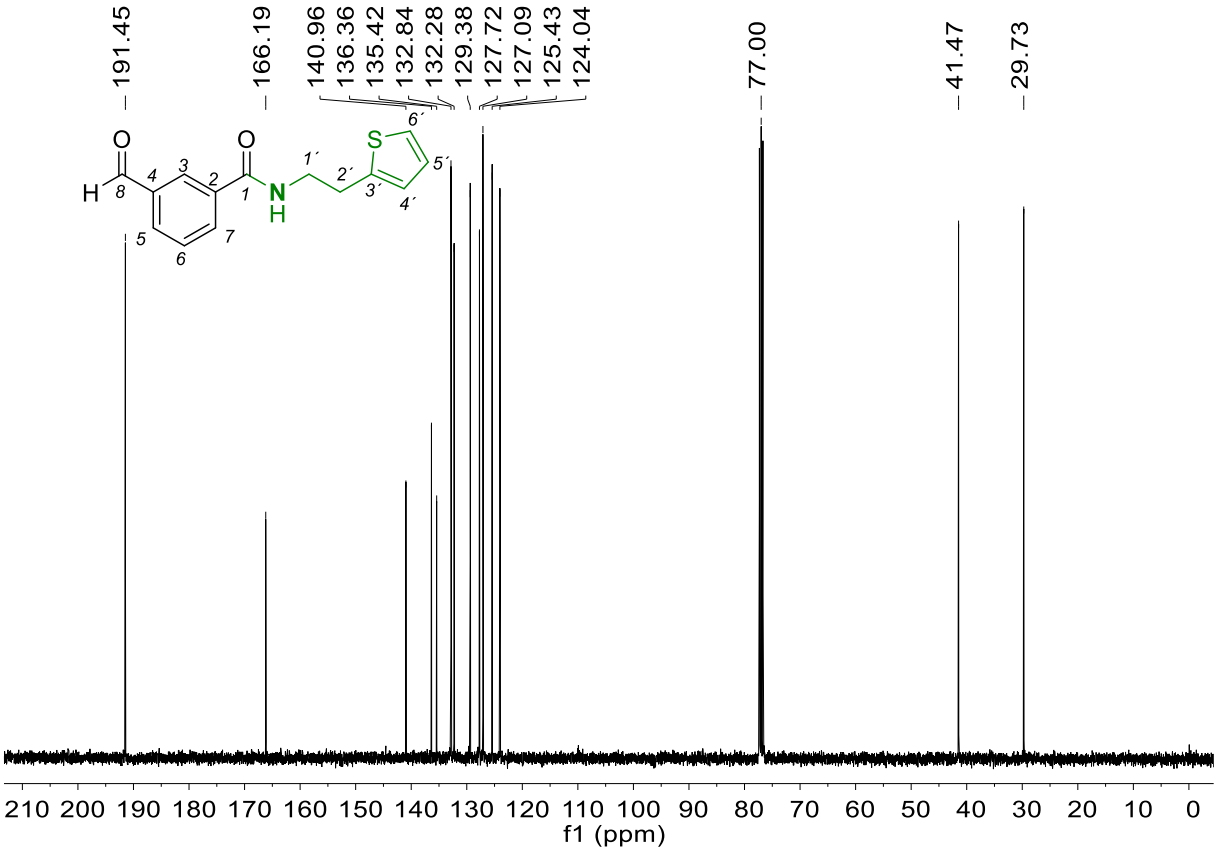


M ($C_{14}H_{13}NO_2S$) = 259.32 g/mol; **mp.** = 84-86 °C ; $\mathbf{r_f}$ (SiO_2, EtOAc/CH_2Cl_2 15:85) = 0.34; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 10.00 (s, 1H, 8-H), 8.22 (ψ-t, ^3J = 1.5 Hz, 1H, 3-H), 8.05-8.02 (m, 1H, 7-H), 7.99-7.97 (m, 1H, 5-H), 7.59 (ψ-t, ^3J = 7.7 Hz, 1H, 6-H), 7.17 (dd, $^3J_{6',5'}$ = 5.1 Hz, $^4J_{6',4'}$ = 1.1 Hz, 1H, 6´-H), 6.95 (dd, $^3J_{5',6'}$ = 5.1, $^3J_{5',4'}$ = 3.4 Hz, 1H, 5´-H), 6.87-6.86 (m, 1H, 4´-H), 6.73 (br. s, 1H,

NH), 3.75 (qd, $^3J_{1',NH}$ = $^3J_{1',2'}$ = 6.4 Hz, 2H, 1´-H), 3.17 (t, $^3J_{2',1'}$ = 6.7 Hz, 2´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 191.45 (C-8), 166.19 (C-1), 140.96 (C-3´), 136.36 (C-4), 135.42 (C-2), 132.84 (C-7), 132.28 (C-5), 129.38 (C-5), 127.72 (C-3), 127.09 (C-5´), 125.43 (C-4´), 124.04 (C-6´), 41.47 (C-1´), 29.73 (C-2´); **HR-MS** (ESI, $[C_{14}H_{14}NO_2S]^+$) calc. 260.0745 u found 260.0746 u.

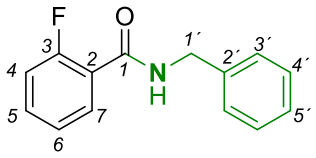


^{1}H-NMR spectrum of *N*-2-(thiophen-2-yl)ethyl 3-formylbenzamide (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *N*-2-(thiophen-2-yl)ethyl 3-formylbenzamide (100 MHz, $CDCl_3$).

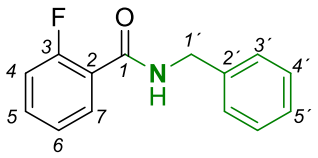
5.4.2.18 Synthesis of Benzyl 2-fluorobenzoic amide (2_{15f})



2_{15f}

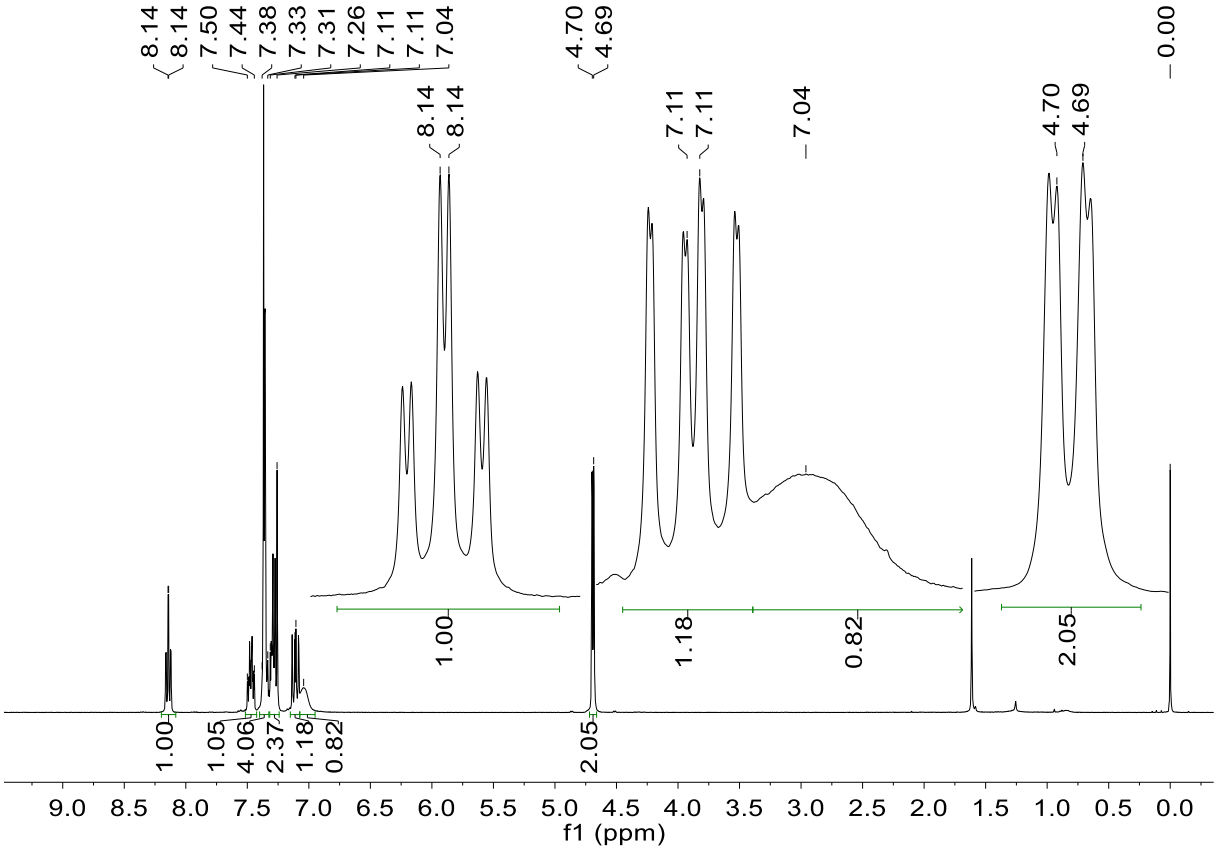
PH3291: As delineated in general protocol 4 (chapter 5.3.4, page 50) 2-fluorobenzoic acid (140 mg, 1.0 mmol, 1.0 equiv) was transformed into 2-fluorobenzoyl chloride with TCT (72 mg, 0.38 mmol, 38 mol%) applying FPyr (9.8 μL, 10.2 mg, 100 μL, 10 mol%) in MeCN (0.50 mL, 2 M) at 80 °C under stirring for 4 h. Afterwards, MeCN (0.50 mL→1 M) was added followed by dibenzylamine (130 μL, 1.2 mmol, 1.3 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) at 0 °C. Past 13 h of stirring at room temperature and aqueous work up, the crude product was isolated as yellow oil (250 mg, 109%). In the end, purification by means of column chromatography using silica gel (20.3 g, relation of weight crude product in respect to SiO_2 1:89) and EtOAc/*n*Hex 25:75 furnished the desired title compound as a pale yellow oil in 86% yield (197.1 mg, 0.860 mmol, 86%).

M ($C_{14}H_{12}FNO$) = 229.25 g/mol; **mp**. = 49-50 °C (lit.-mp. 48.9-49.9 °C);[38] $\mathbf{r_f}$ (SiO_2, EtOAc/PE 25:75) = 0.35; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.14 (ψ-td, J = 7.9, 1.8 Hz, 1H, 7-H), 7.50-7.44 (m, 1H, 5-H), 7.38-7.33 (m, 4H, 3´-H, 4´-H), 7.31-7.26 (m, 2H, 5´-H, 6-H), 7.11 (ddd, $^3J_{4,F}$ = 12.2 Hz, $^3J_{4,5}$ = 8.3 Hz, $^4J_{4,6}$ = 0.9 Hz, 1H, 4-H), 7.04 (br. s, 1H, NH), 4.70 (dd, $^3J_{1´,NH}$ = 5.6 Hz,

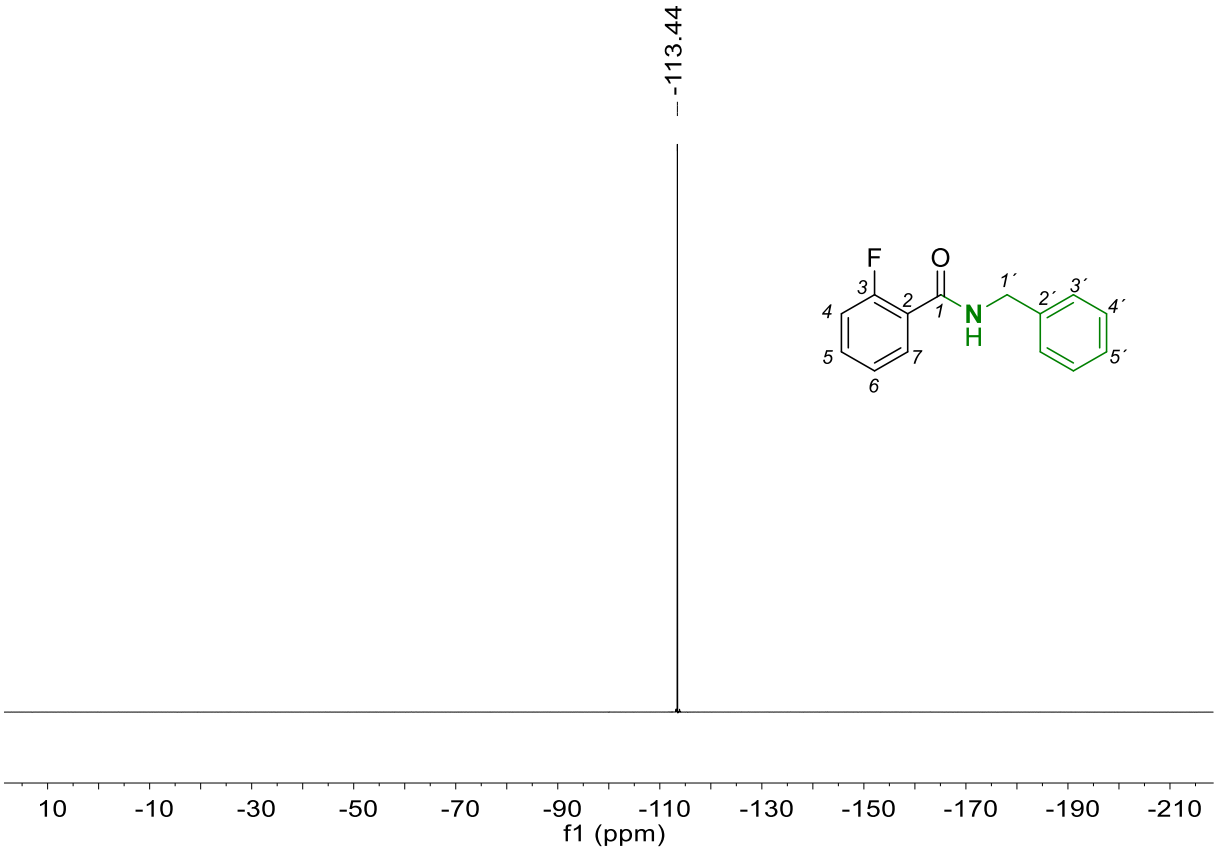


$^{4}J_{1´,3´}$= 1.3 Hz, 2H, 1´-H); **^{19}F-NMR** (375 MHz, $CDCl_3$,) δ [ppm] = -113.4; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 163.19 (d, $^{3}J_{1,F}$ = 3 Hz C-1), 160.57 (d, $^{1}J_{3,F}$ = 247 Hz, C-3), 137.96 (C-2´), 133.27 (d, $^{3}J_{5,F}$ = 9 Hz, C-5), 132.08 (d, $^{3}J_{6,F}$ = 2 Hz, C-7), 128.69 (C-4´), 127.67 (C-3´), 127.49 (C-5´), 124.77 (d, $^{4}J_{6,F}$ = 3 Hz, C-6), 120.91 (d, $^{2}J_{2,F}$ = 12 Hz, C-2), 115.93 (d, $^{2}J_{7,F}$ = 25 Hz, C-4), 44.00 (C-1´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 270 (1, $[M+allyl]^+$), 258 (13, $[M+Et]^+$), 230 (100, $[M+H]^+$), 229 (43, $[M]^+$), 152 (6, $[M-Ph]^+$), 123 (32, $[M-NHBn]^+$), 119 (10), 105 (5, $[PhCHNH]^+$), 91 (20, $[Bn]^+$).

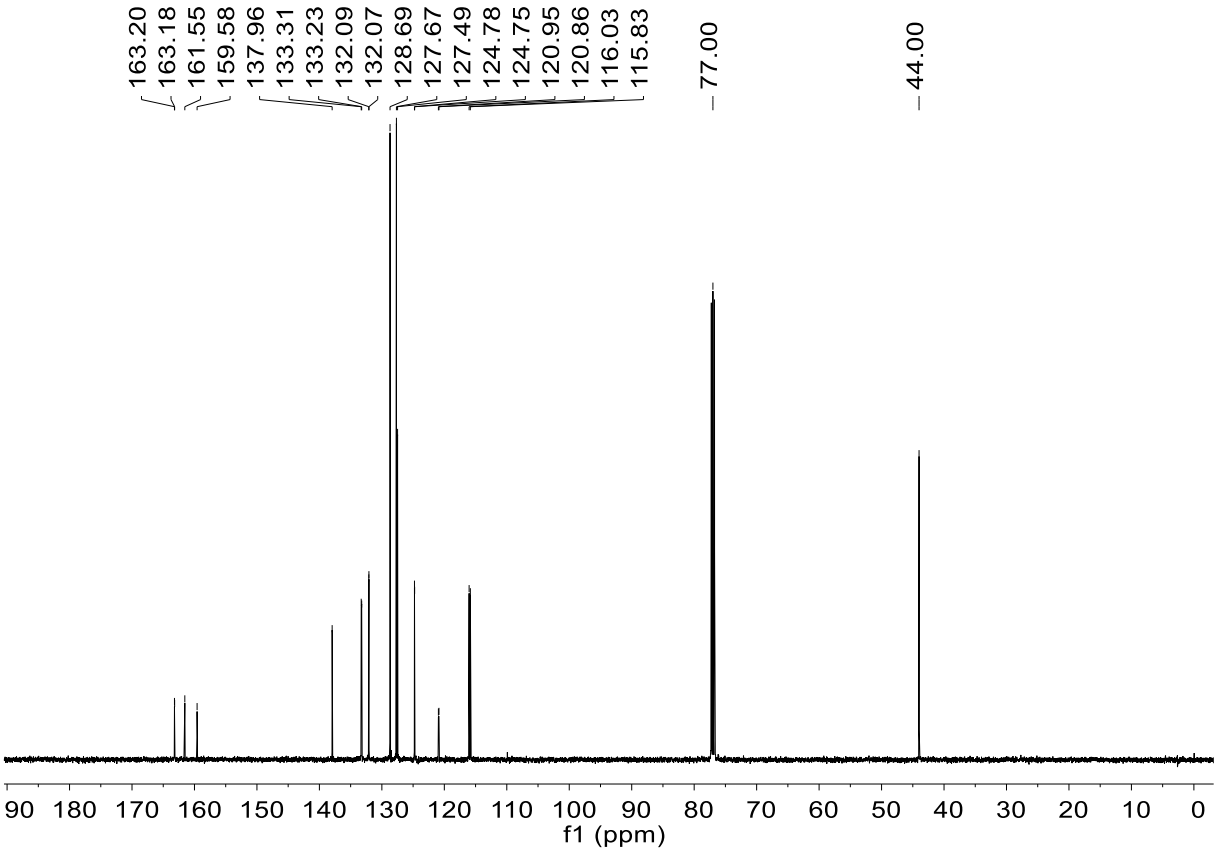
The NMR data is in agreement with the literature.[38]



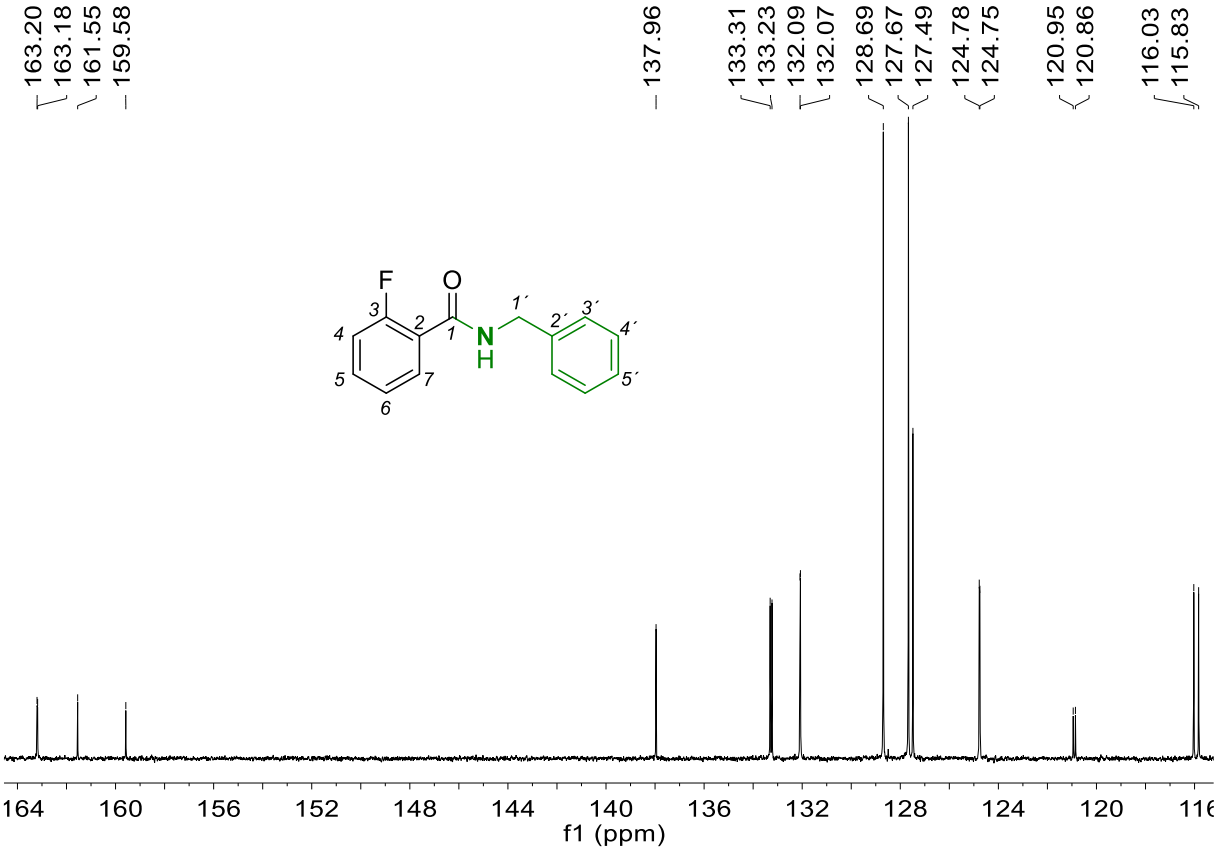
^{1}H-NMR spectrum of benzyl 2-fluorobenzoic amide (400 MHz, $CDCl_3$).



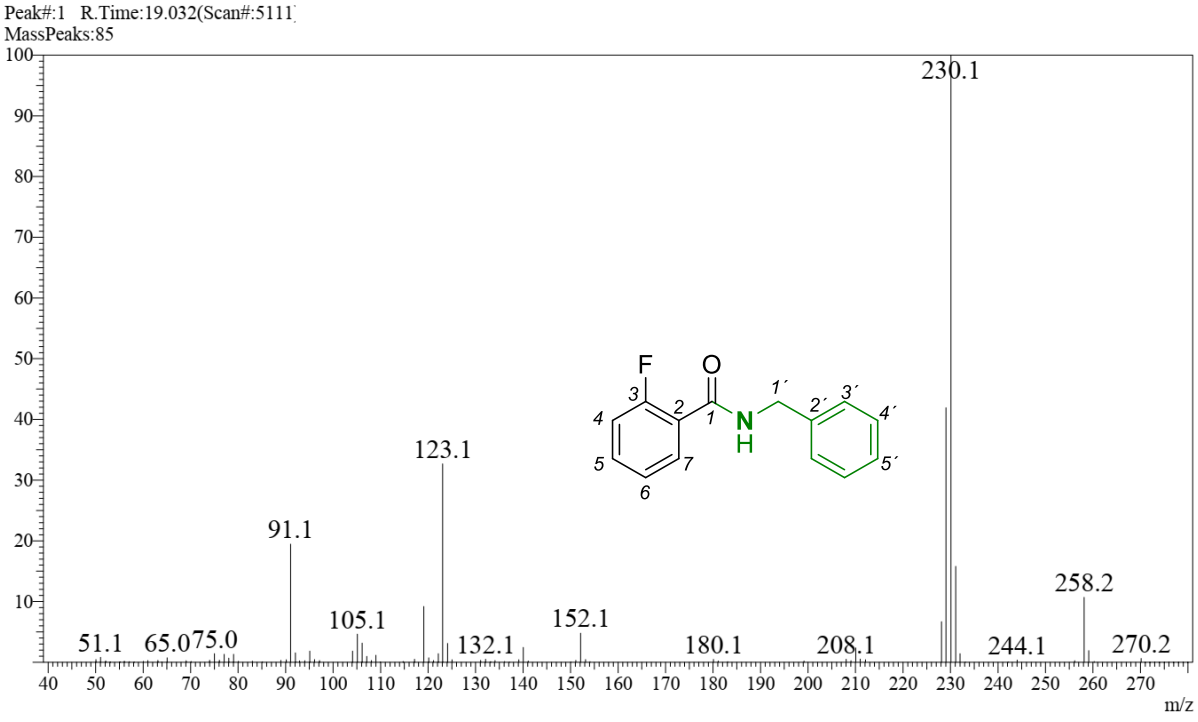
^{19}F-NMR spectrum of benzyl 2-fluorobenzoic amide (375 MHz, $CDCl_3$).



^{13}C-NMR spectrum of benzyl 2-fluorobenzoic amide (100 MHz, $CDCl_3$).

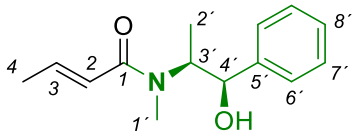


Zoom of ^{13}C-NMR spectrum of benzyl 2-fluorobenzoic amide (100 MHz, $CDCl_3$).



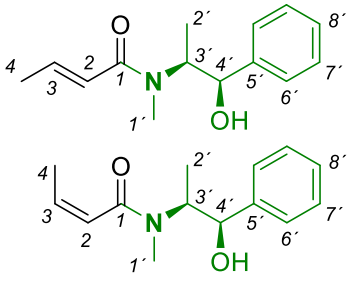
Mass spectrum of benzyl 2-fluorobenzoic amide (CI, 70 eV).

5.4.2.19 Synthesis of *N-E*-Crotonyl ephedrine (2_{16p})



2_{16p}

PH3101: In agreement with general protocol 4 (chapter 5.3.4 page 50) ***E*-crotonic acid** (2-butenoic acid, 112 mg, 1.3 mmol, **1.3 equiv**) was converted to crotonoyl chloride using **TCT** (92 mg, 0.49 mmol, **49 mol%**) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 1 M with respect to ephedrine) under heating to 40 °C for 9 h. Next, a solution of **ephedrine** (165 mg, 1.00 mmol, **1.0 equiv**) in MeCN (0.50 mL, 2 M) was added dropwise under cooling of the resulting reaction suspension to 0 °C followed by **NMM** (190 μL, 1.7 equiv, 1.7 mmol). After stirring overnight (13 h) at room temperature and aqueous work up without washing with 2 N HCl solution (aq.) the ^{1}H-NMR spectrum of the crude material (265 mg, 113% yellow oil) proved a ratio of the title amide with regard to ephedrine of 83:17. Column chromatographic purification on silica gel (23.5 g, mass ratio crude product/SiO_2 1:89) with EtOAc/*n*Hex 70:30 facilitated the isolation of the title amide as a pale yellow oil (190.3 mg, 0.816 mmol, 82%), which crystalized at ambient temperature to give a colourless solid, after concentration with CH_2Cl_2 (2 x 2 mL) and drying in high vacuum for 14 h. Thereby, the crude material was dissolved in the eluent (0.5 mL) under careful heating with a heat gun for the purpose of loading the silica gel column. **PH3033:** Following general protocol 4 (chapter 5.3.4 page 50) ***E*-crotonic acid** (86 mg, 1.00 mmol, **1.0 equiv**) was allowed to react with **TCT** (72 mg, 0.38 mmol, **38 mol%**) utilizing FPyr (10 mol%) in MeCN (0.50 mL, 2 M) under stirring for 8 h at 40 °C. In the following, the reaction suspension was diluted with MeCN (0.50 mL→1 M), cooled to 0 °C and **ephedrine** (198 mg, 1.2 mmol, **1.2 equiv**) and **K_2CO_3** (320 mg, 2.3 mmol, 2.3 equiv) were added. After stirring for 16 h at room temperature and aqueous work up (no HCl-washing), analysis of the crude material (277 mg, yellow oil, 119%) by means of ^{1}H-NMR confirmed a ratio of the title compound in regard to ephedrine of 67:33. Eventually, column chromatographic purification on silica gel (20.5 g, ratio mass crude **2_{16p}**/SiO_2 1:74) with EtOAc/*n*Hex 70:30 afforded the title amide as a colourless solid (171.6 mg, 74%) after concentration with CH_2Cl_2 and drying in high vacuum for 5 h.

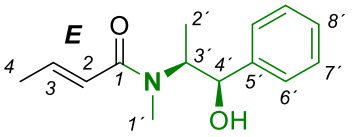


M ($C_{14}H_{19}NO_2$) = 233.311 g/mol; **mp**. 76-78 °C; **r_f** (SiO_2, EtOAc/*n*Hex 70:30) = 0.29; **GC-MS** (CI, 70 eV) m/z [u] (%) = 274 (<1, $[M+allyl]^+$, 262 (19, $[M+Et]^+$), 244 (6, $[M-OH+Et]^+$), 234 (31, $[M+H]^+$), 232 (13, $[M-H]^+$), 216 (100, $[M-OH]^+$), 192 (4, $[M-MeCHCH]^+$), 176 (10), 164 (8, $[ephedrine-H]^+$), 148 (28), 126 (52, $[M-PhCHOH]^+$), 107 (90, $[PhCHOH]^+$), 100 (21), 91 (10, $[Bn]^+$), 79 (17), 69 (35, $[MeCHCHCO]^+$), 58 (46); **$[\alpha]^D_{20}$** (c = 1.430 g/100 mL) = -162.1; **HR-MS** (CI, $[C_{14}H_{20}NO_2]^+$) calc. 234.1489 u found 234.1495 u.

Determination of Ratio of E/Z-Diastereoisomers

The diastereomeric ratio of **2_{16p}** was determined by three distinctive ^{1}H-NMR spectra from measurements (**A**) in $CDCl_3$ at 298 K and in DMSO-d^6 (**B**) at 298 K and (**C**) at 373 K. In the case of **A** and **B** each stereoisomer showed two different rotamers in regard to the C-N amide bond, whereby rotameric ratios (= *rr*) of the *E*-configured title compound were determined to be 80:20 and 57:43, respectively. For the measurement **A** in $CDCl_3$ the configuration was found to be *s-cis* according to the NOESY-NMR spectrum. In general, the main rotamer was denoted as rotamer 1 (= rot 1) and the minor as rotamer 2 (= rot 2). The rotamer ratios *rr* were determined form the integral ratios of the respective multiplet pairs for the same H-atom and the initially stated value refers to the actually described signal. According to the three NMR measurements **A** to **C** diastereomer ratios *E/Z* are 95:5, 97:3 and 97:3, respectively. Thus, the average ***E/Z*-2_{16p}** relation is 97:3. The relative configuration of the double bond could not be verified by NOE NMR-spectroscopy (**A** and **B**). Nevertheless, constants $^{3}J_{2,3}$ between 14.7-15.2 Hz for the coupling of 2-H with 3-H verified a relative *E*-configuration.

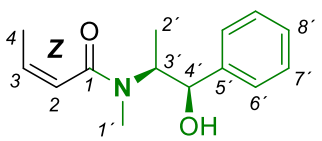
A. NMR data measurement at 298 K in $CDCl_3$:



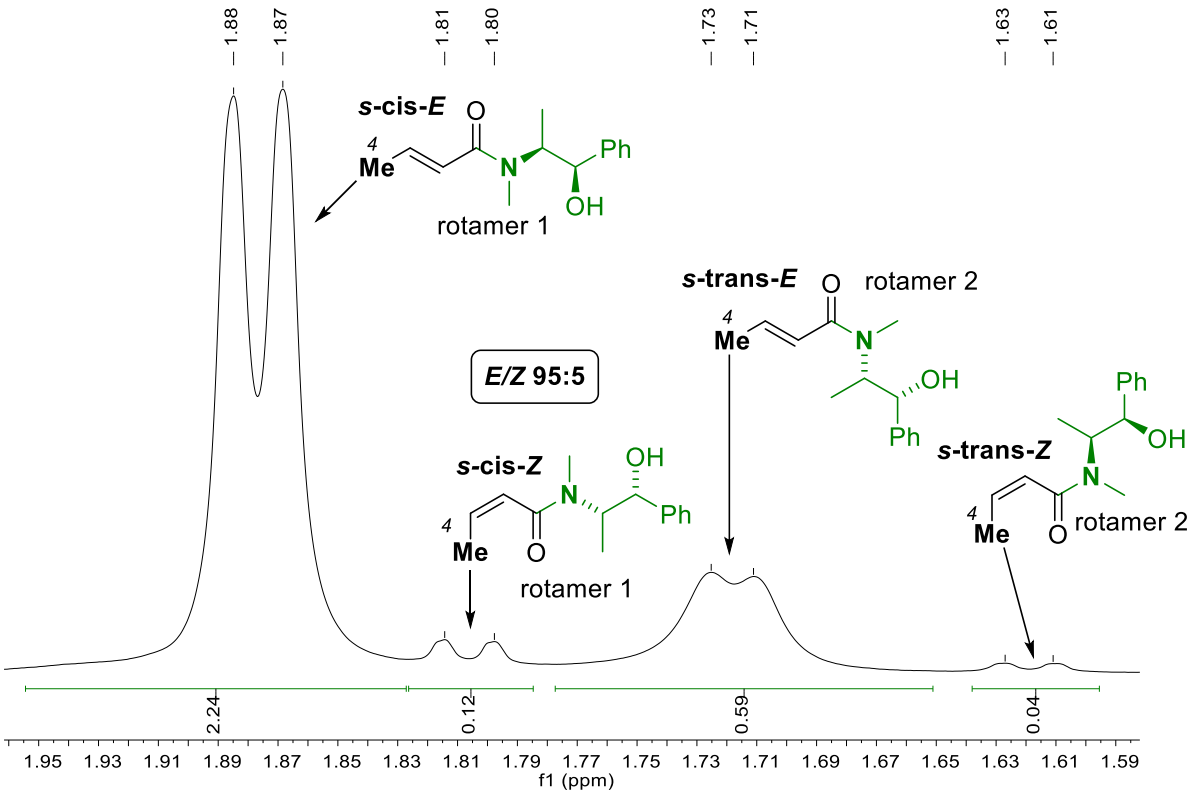
***E*-Crotonyl ephedrine**

^{1}H-NMR (400 MHz, $CDCl_3$, in average 80:20 mixture of rotamers) δ [ppm] = 7.37-7.23 (m, 5H, 6´-H, 7´-H, 8´-H), 6.95-6.86 (dq, $^{3}J_{3,2}$ = 14.8 Hz, $^{3}J_{3,4}$ = 7.0 Hz, 1H, 3-H_{rot1}, *rr* = 81:19), 6.50-6.45 (m, 1H, 3-H_{rot2}, *rr* = 19:81), 6.17 (d, $^{3}J_{2,3}$ = 14.9 Hz, 1H, 2-H_{rot1}, *rr* = 79:21, *E/Z* = 97:3), 5.98-5.94 (m, 1H, 2-H_{rot2}, *rr* = 21:79), 4.86 (s, 1H, 4´-H_{rot1}, *rr* =79:21), 4.72 (s, 1H, OH_{rot1}, *rr* = 81:19), 4.64 (d, $^{3}J_{4´,3´}$= 5.1 Hz, 1H, 4´-H_{rot2}, *rr* = 21:79) 4.50-4.48 (m, 1H, 3´-H_{rot1}, *rr* = 81:19), 4.12-4.09 48 (m, 1H, 3´-H_{rot2}, *rr* = 19:81), 3.15 (br. s, 1H, OH_{rot2}, *rr* = 19:81) 2.82 (s, 3H, 1´-H_{rot2}, *rr* = 19:81), 2.73 (s, 3H, 1´-H_{rot1}, *rr* = 81:19), 1.88 (d, $^{3}J_{4,3}$ = 6.5 Hz, 3H, 4-H_{rot1}, *rr* = 79:21, *E/Z* = 95:5), 1.72 (d, $^{3}J_{4,3}$ = 5.6 Hz, 3H, 4-H_{rot2}, *rr* = 21:79, *E/Z* = 94:6), 1.33 (d, $^{3}J_{2´,3´}$ = 6.3 Hz, 3H, 2´-H_{rot2}, *rr* = 21:79), 1.20 (d, $^{3}J_{2´,3´}$ = 6.3 Hz, 3H, 2´-H_{rot1}, *rr* = 79:21); **^{13}C-NMR** (100 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 168.47 (C_{rot1}-1), 167.46 (C_{rot2}-1), 142.38 (C_{rot1}-3), 141.75 (C_{rot1}-5´), 139.85 (C_{rot2}-3), 128.28 (C_{rot2}-7´), 128.05 (C_{rot1}-7´), 127.92 (C_{rot2}-8´), 127.33 (C_{rot1}-8´), 126.28 (C_{rot1}-6´), 126.07 (C_{rot2}-6´), 122.22 (C_{rot1}-2), 77.20 (C_{rot1}-4´), 76.09 (C_{rot2}-4´), 58.38 (C_{rot1}-3´), 58.01 (C_{rot2}-3´), 33.28 (C_{rot1}-1´), 28.37 (C_{rot2}-1´), 18.21 (C_{rot1}-4), 18.07 (C_{rot2}-4), 14.43 (C_{rot2}-2´), 11.98 (C_{rot1}-2´).

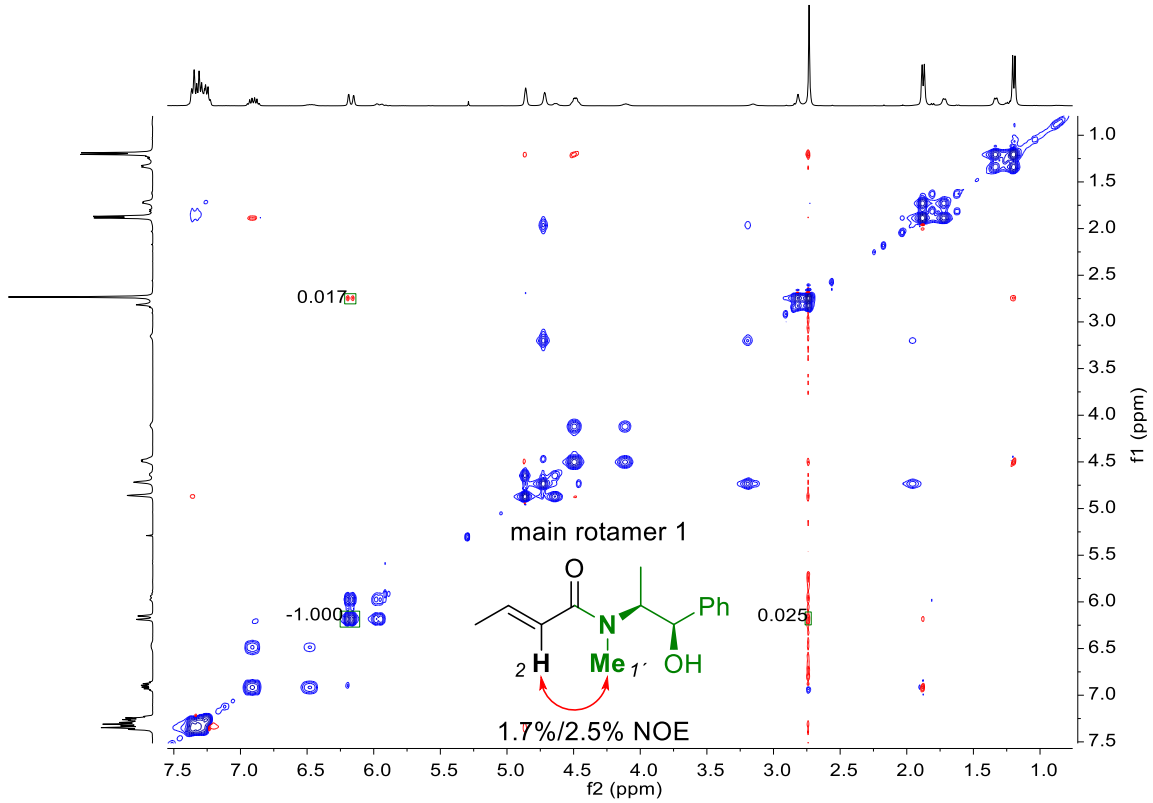
***Z*-Crotonyl ephedrine** (only clearly distinctive signals noted)



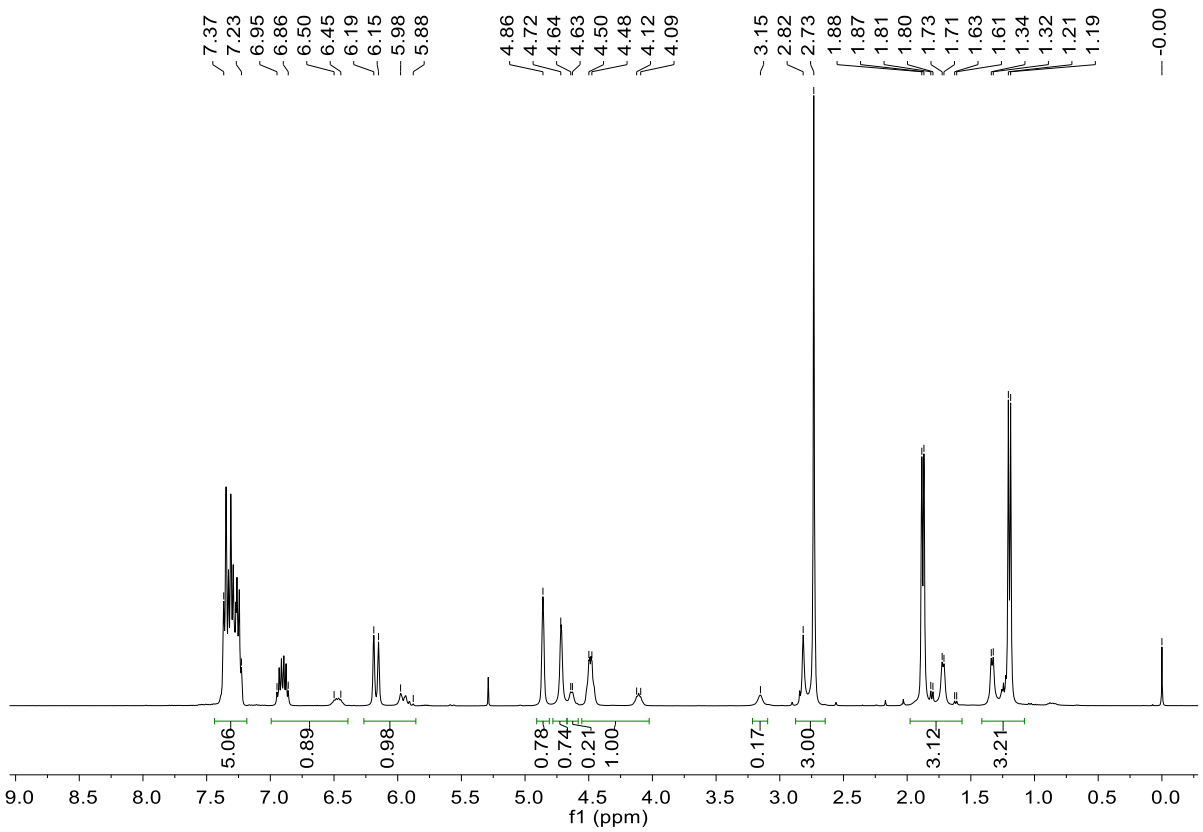
^{1}H-NMR (400 MHz, $CDCl_3$, 75:25 mixture of rotamers) δ [ppm] = 5.91-5.88 (m, 1H, 2-H, *Z/E* = 3:97), 1.81 (d, $^{3}J_{4,3}$ = 6.7 Hz, 4-H_{rot1}, *rr* = 75:25), (d, $^{3}J_{4,3}$ = 6.7 Hz, 4-H_{rot1}, *rr* = 75:25, *Z/E* = 5:95), 1.63 (d, $^{3}J_{4,3}$ = 6.5 Hz, 4-H_{rot2}, *rr* = 25:75, *Z/E* = 6:94); **^{13}C-NMR** (100 MHz, $CDCl_3$, main rotamer 1) δ [ppm] = 136.05 (C-3), 123.33 (C-2), 15.11 (C-4), 12.09 (C-2´).



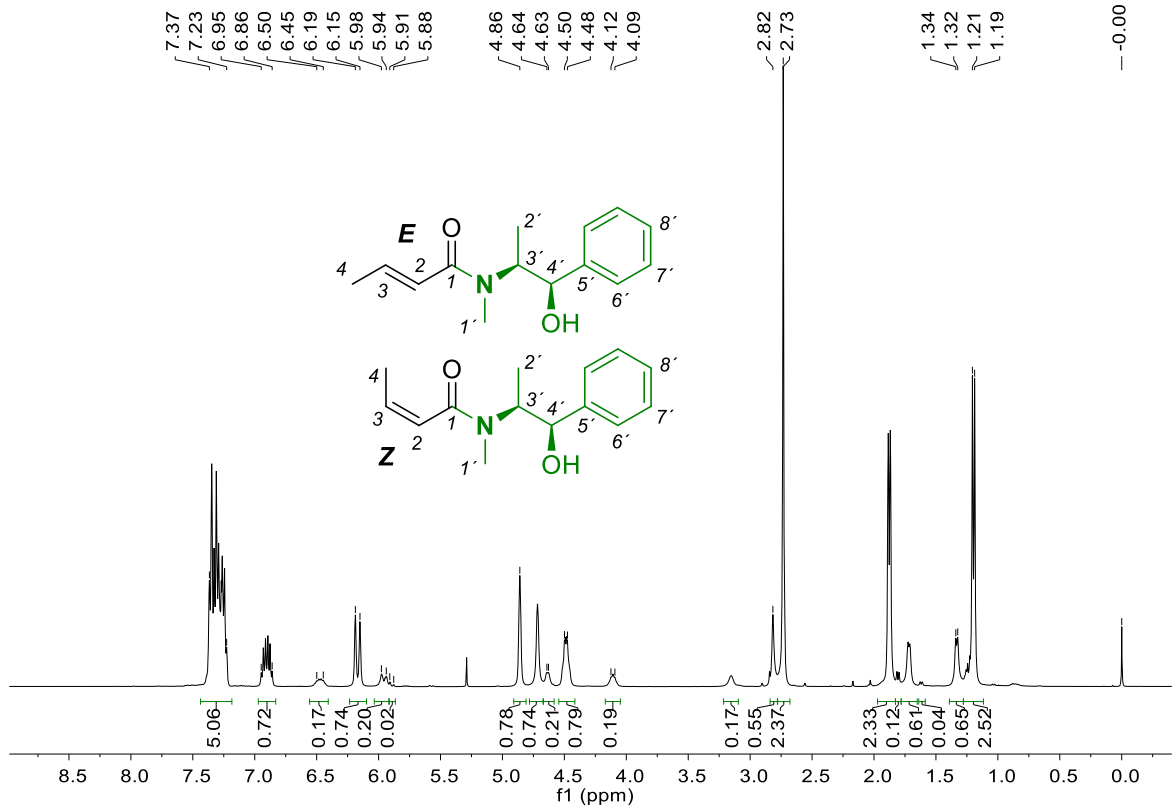
Determination of *E/Z*-ratio by means of the ^{1}H-NMR spectrum (400 MHz, $CDCl_3$).



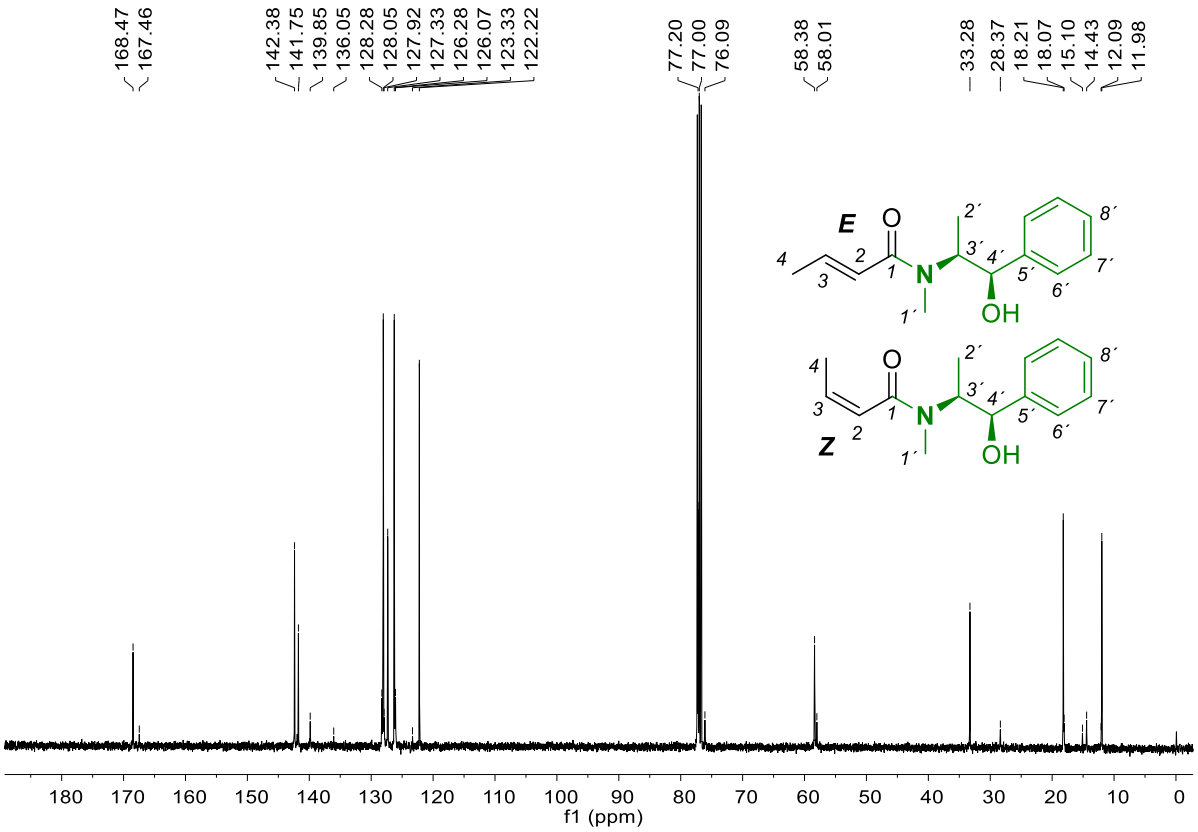
Determination of the configuration of the amide C-N bond of the main rotamer 1 by means of NOESY-NMR (400 MHz, $CDCl_3$).



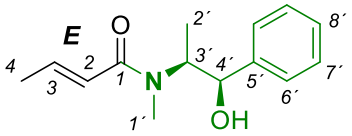
^{1}H-NMR spectrum of *N*-*E*-crotonyl ephedrine with collective integration of rotamers, if possible (400 MHz, $CDCl_3$).



^{1}H-NMR spectrum of *N*-*E*-crotonyl ephedrine with separated integration rotamers and diastereomers (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *N*-*E*-crotonyl ephedrine (100 MHz, $CDCl_3$).

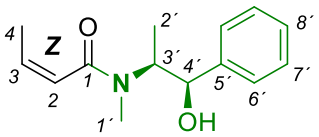


B. NMR data measurement at 298 K in DMSO-d^6:

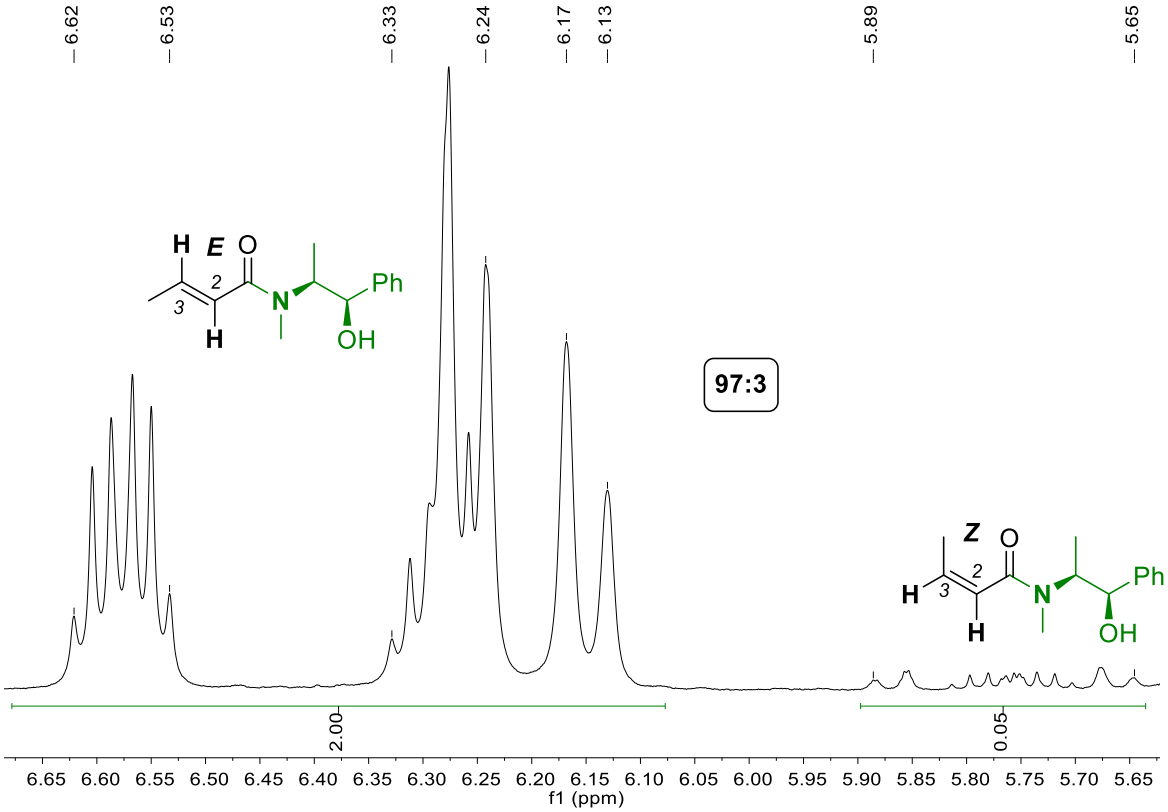
***E*-Crotonyl ephedrine**

^{1}H-NMR (400 MHz, DMSO-d^6, in average 57:43 mixture of rotamers) δ [ppm] = 7.30-7.27 (m, 4H, 6´-H, 7´-H), 7.22-7.19 (m, 1H, 8´-H), 6.57 (dq, $^3J_{3,2}$ = 14.7 Hz, $^3J_{3,4}$ = 7.0 Hz, 1H, 3-H$_{rot1}$, *rr* = 58:42 with respect to 2-H$_{rot2}$), 6.33-6.24 (m, 2H, 2-H$_{rot1}$, 3-H$_{rot2}$), 6.15 (d, $^3J_{2,3}$ = 15.1 Hz, 1H, 2-H$_{rot2}$, *rr* = 42:58 with respect to 3-H$_{rot1}$), 5.58 (d, $^3J_{OH,4´}$ = 4.8 Hz, 1H, OH$_{rot2}$, *rr* = 42:58), 5.42 (d, $^3J_{OH,4´}$ = 4.9 Hz, 1H, OH$_{rot1}$, *rr* = 58:42), 4.65-4.57 (m, 2H, 3´-H$_{rot1}$, 4´-H$_{rot1}$), 4.54-4.51 (m, 1H, 4´-H$_{rot2}$, *rr* = 43:57 in regard to 3´-H$_{rot1}$ + 4´-H$_{rot1}$), 4.08 (ψ-pent, *J* = 7.0 Hz, 1H, 3´-H$_{rot2}$, *rr* = 41:59 in regard to 3´-H$_{rot1}$ + 4´-H$_{rot1}$), 2.87 (s, 3H, 1´-H$_{rot1}$, *rr* = 59:41), 2.69 (s, 3H, 1´-H$_{rot2}$, r = 41:59), 1.78 (d, $^3J_{4,3}$ = 6.1 Hz, 3H, 4-H$_{rot1}$, *rr* = 58:42), 1.71 (d, $^3J_{4,3}$ = 6.2 Hz, 3H, 4-H$_{rot2}$, *rr* = 42:58), 1.26 (d, $^3J_{2´,3´}$ = 6.6 Hz, 3H, 2´-H$_{rot2}$, *rr* = 44:56), 1.08 (d, $^3J_{2´,3´}$ = 6.8 Hz, 3H, 2´-H$_{rot2}$, *rr* = 56:44); **^{13}C-NMR** (100 MHz, DMSO-d^6, mixture of rotamers) δ [ppm] = 165.82 (C$_{rot2}$-1), 165.25 (C$_{rot1}$-1), 143.72 (C$_{rot1}$-5´), 143.28 (C$_{rot2}$-5´), 140.11 (C$_{rot1}$-3), 138.50 (C$_{rot2}$-3), 127.74 (C-7´), 127.17 (C$_{rot2}$-8´), 126.82 (C$_{rot1}$-8´), 126.47 (C$_{rot2}$-6´), 126.16 (C$_{rot1}$-6´), 122.89 (C$_{rot1}$-2), 122.79 (C$_{rot2}$-2), 74.65 (C-4´), 57.36 (C$_{rot2}$-3´), 54.11 (C$_{rot1}$-3´), 30.90 (C$_{rot1}$-1´), 27.88 (C$_{rot2}$-1´), 17.71 (C$_{rot1}$-4), 17.68 (C$_{rot2}$-4), 14.98 (C$_{rot2}$-2´), 12.17 (C$_{rot1}$-2´).

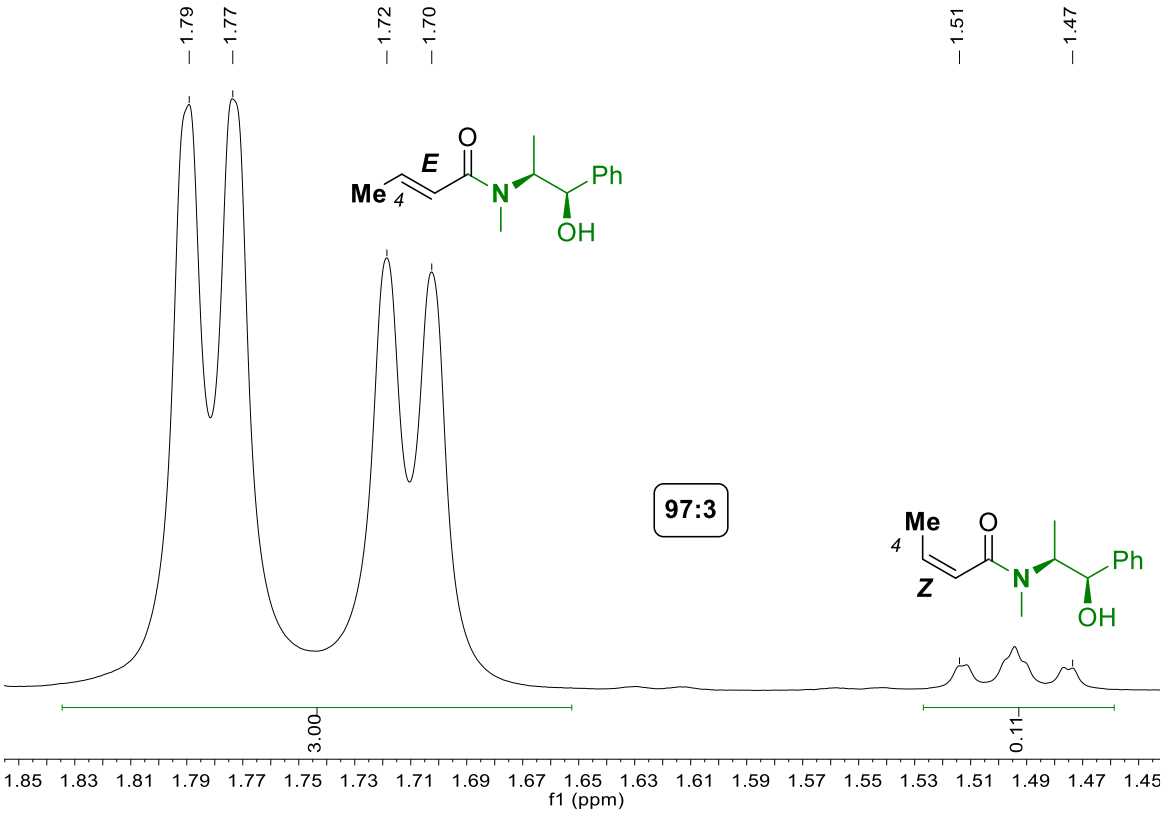
***Z*-Crotonyl ephedrine** (only clearly distinctive signals noted)



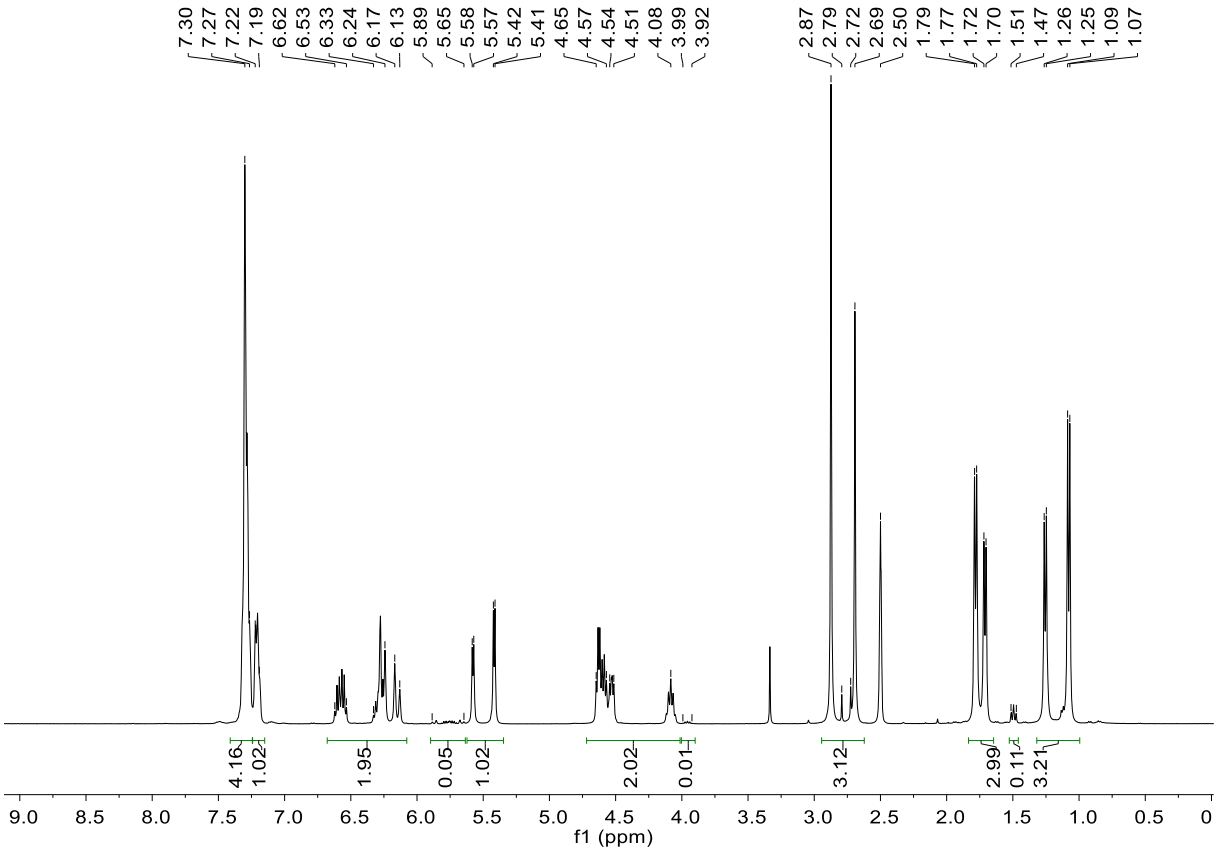
^{1}H-NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] =5.89-5.65 (m, 2H, 2-H, 3-H, *Z/E* = 3:97), 3.99-3.92 (m, 1H, 3´-H_{rot1}), 2.79 (s, 3H, 1´-H_{rot2}), 2.72 (s, 3H, 1´-H_{rot1}), 1.51-1.47 (m, 3H, 4-H, *Z/E* = 3:97).



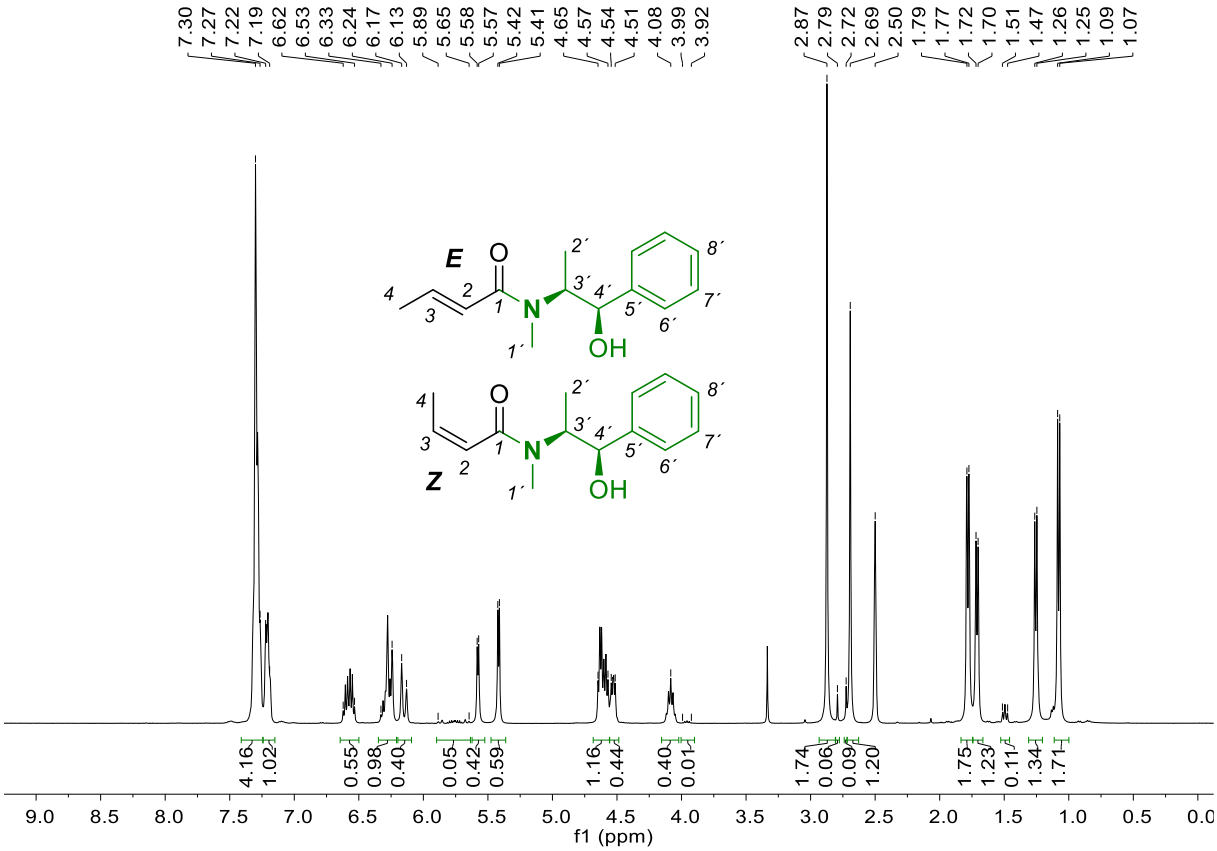
Determination of *E/Z*-ratio by means of the ^{1}H-NMR spectrum according to multiplets for 2-H and 3-H (400 MHz, DMSO-d^6).



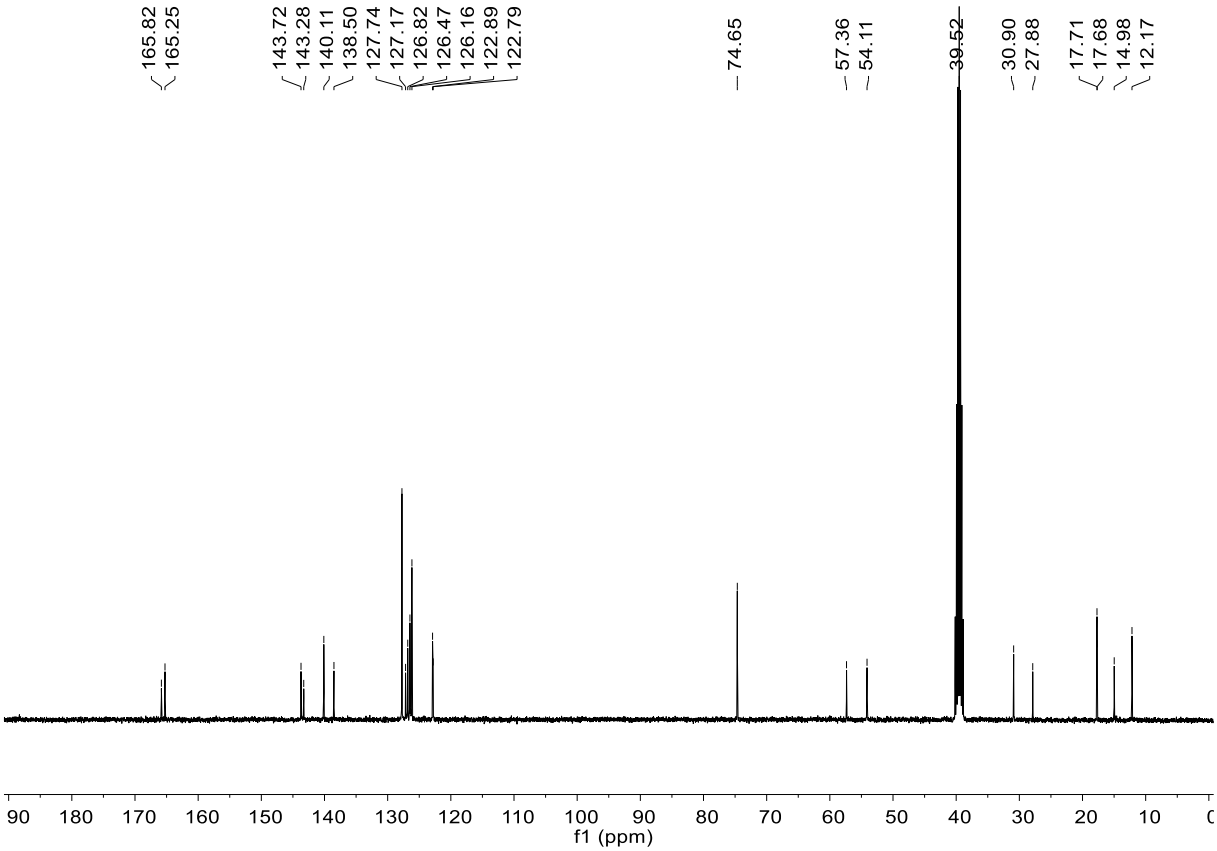
Determination of *E/Z*-ratio by means of the ^{1}H-NMR spectrum according to multiplets for 4-H (400 MHz, DMSO-d^{6}).



^{1}H-NMR spectrum of *N-E*-crotonyl ephedrine with collective integration of rotamers if possible (400 MHz, DMSO-d^{6}).



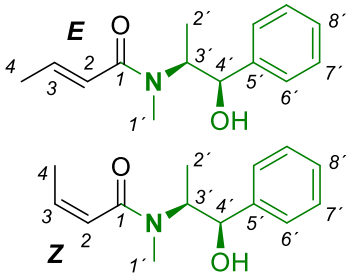
^{1}H-NMR spectrum of *N*-*E*-crotonyl ephedrine with separated integration rotamers and diastereomers (400 MHz, DMSO-d^{6}).



^{13}C-NMR spectrum of *N*-*E*-crotonyl ephedrine (100 MHz, DMSO-d^{6}).

C. NMR data measurement at 373 K in DMSO-d^6:

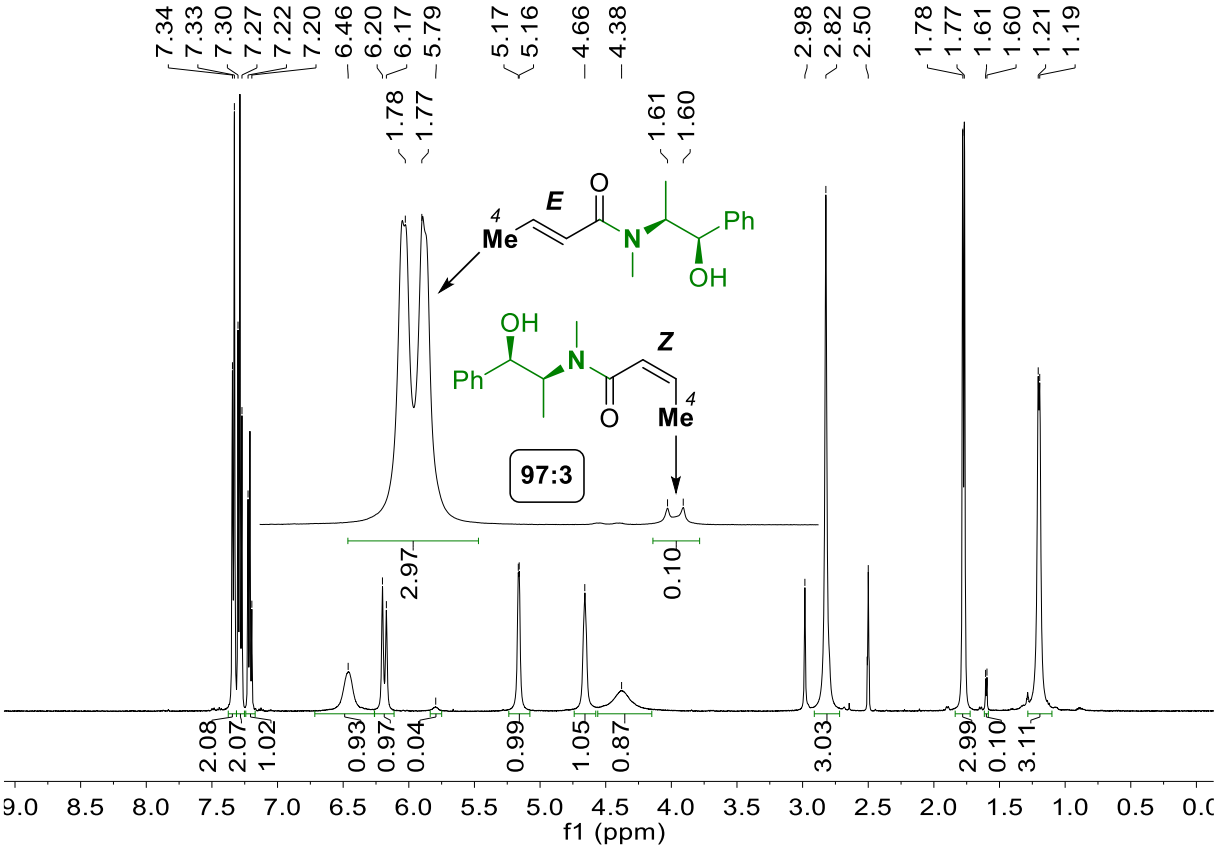
***E*-Crotonyl ephedrine** (C-1´ neither appeared in the ^{13}C- nor in HSQC-NMR spectrum)



^{1}H-NMR (500 MHz, DMSO-d^6) δ [ppm] = 7.34-7.33 (m, 2H, 6´-H), 7.30-7.27 (m, 2H, 7´-H), 7.22-7.20 (m, 1H, 8´-H), 6.46 (br. s., 1H, 3-H), 6.18 (d, $^3J_{2,3}$ = 15.0 Hz, 1H, 2-H), 5.17 (d, $^3J_{OH,4'}$ = Hz, 1H, OH), 4.66 (s, 1H, 4´-H), 4.38 (br. s, 1H, 3´-H, 2.82 (s, 3H, 1´-H), 1.78 (dd, $^3J_{4,3}$ = 6.7 Hz, $^4J_{4,2}$ = 1.0 Hz, 3H, 4-H), 1.20 (d, $^3J_{2',3'}$ = 5.8 Hz, 3H, 2´-H); **^{13}C-NMR** (125 MHz, DMSO-d^6) δ [ppm] = 165.41 (C-1), 143.09 (C-5´), 138.02 (C-3), 127.11 (C-7´), 126.30 (C-8´), 125.76 (C-6´), 122.91 (C-2), 74.44 (C-4´), 16.80 (C-4), 13.37 (C-2´).(49)

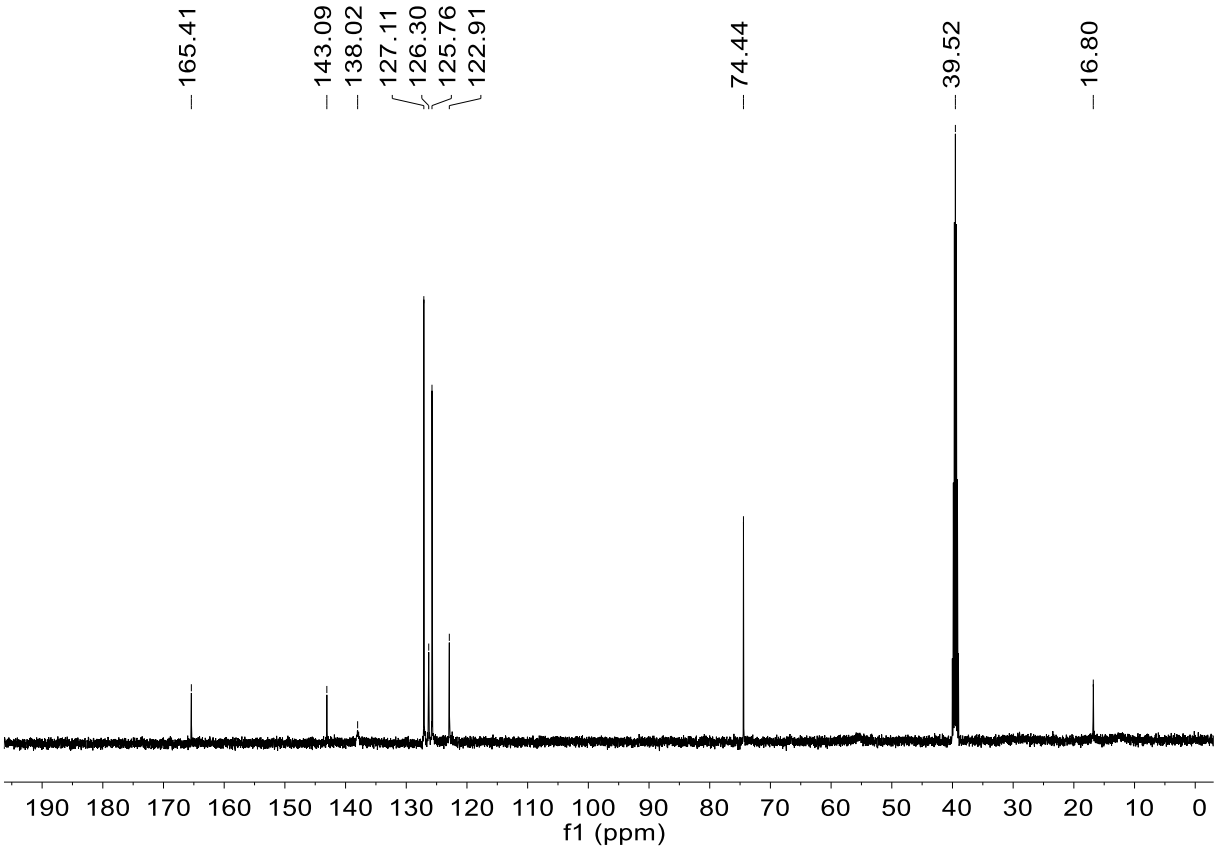
***Z*-Crotonyl ephedrine** (only clearly distinctive signals noted)

^{1}H-NMR (500 MHz, DMSO-d^6) δ [ppm] = 5.79 (br. s, 2-H, 0.04H), 1.61 (d, $^3J_{4,3}$ = 5.2 Hz, 0.10 H, 4-H); **^{13}C-NMR** (125 MHz, DMSO-d^6) δ [ppm] = 14.59 (C-4).(49)

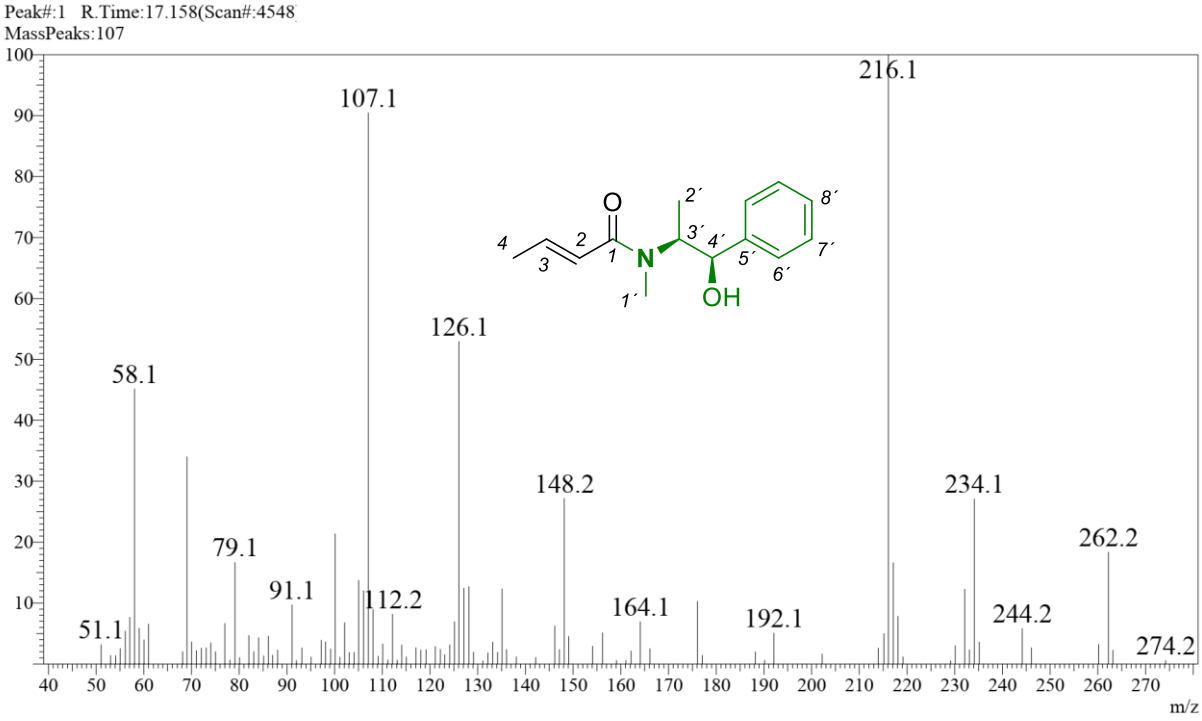


^{1}H-NMR spectrum of *N*-*E*-crotonyl ephedrine at 373 K (500 MHz, DMSO-d^6).

(49) Extracted from HSQC-NMR.

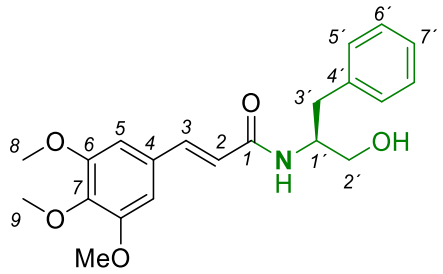


^{13}C-NMR spectrum of *N*-*E*-crotonyl ephedrine at 373 K (125 MHz, DMSO-d^6).



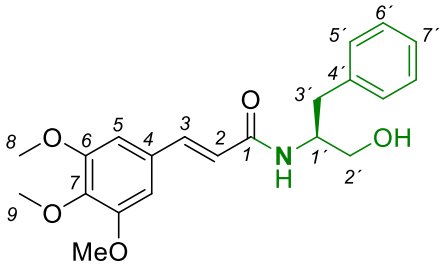
Mass spectrum of *N*-*E*-crotonyl ephedrine (CI, 70 eV).

5.4.2.20 Synthesis of *E*-(*S*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-3-(3,4,5-trimethoxy phenyl)propenoic amide (2_{17q})

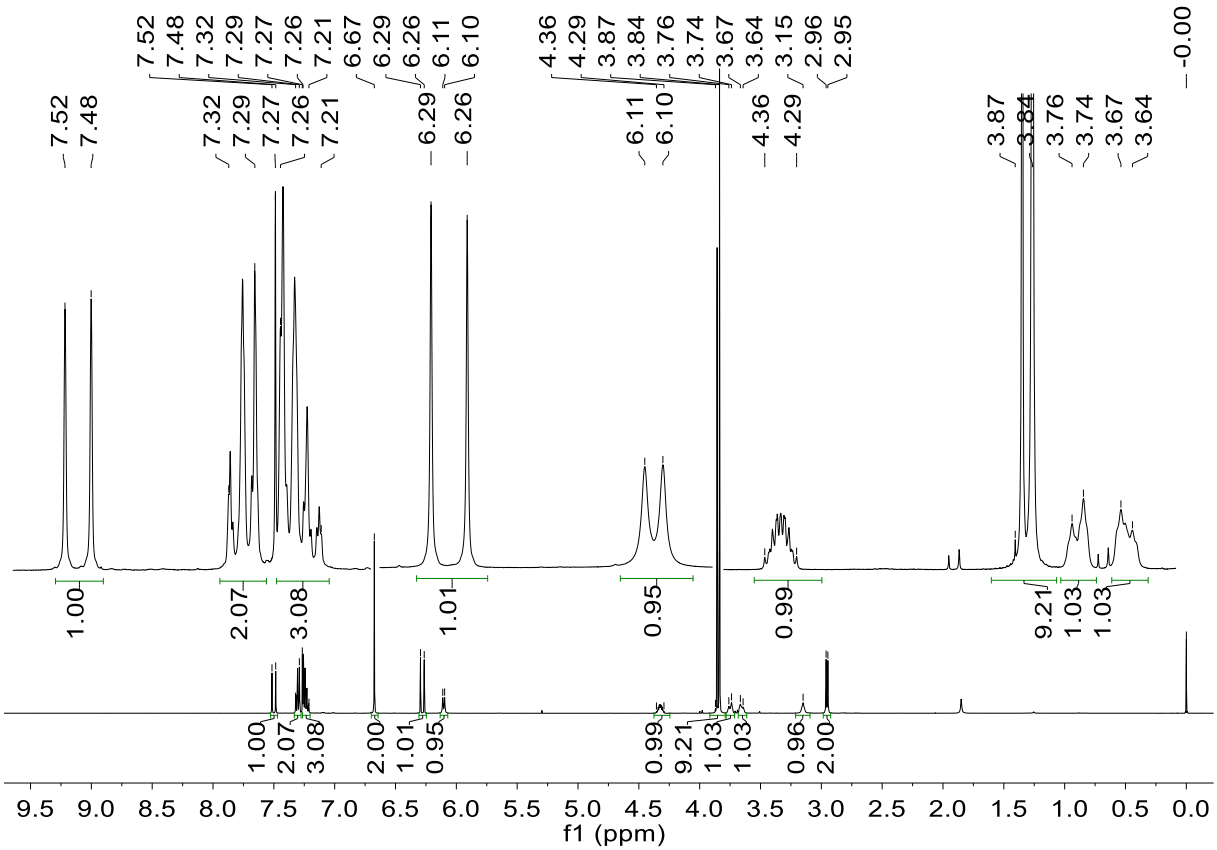


2_{17q}

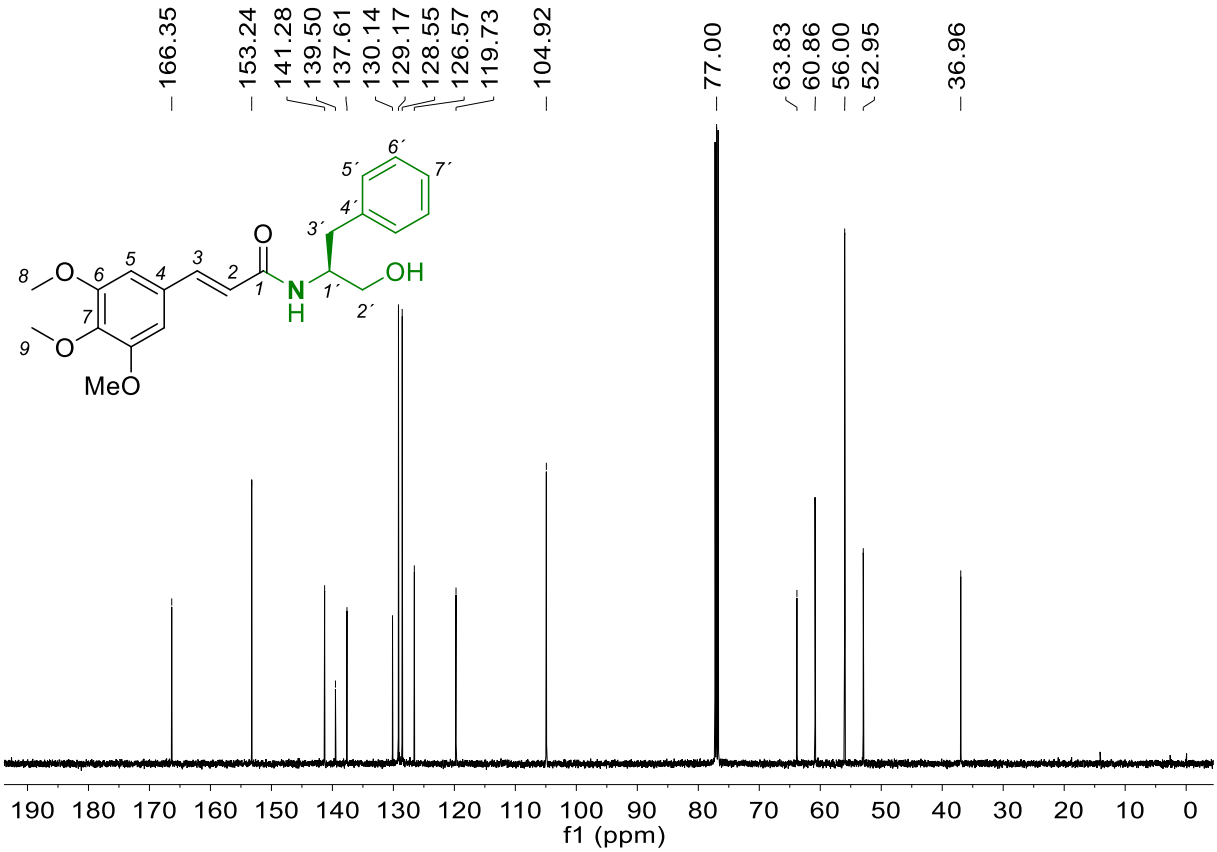
PH3412: As delineated in general protocol 4 (chapter 5.3.4, page 50) to a suspension of *E*-3-(3,4,5-trimethoxyphenyl)-2-propanoic acid (238 mg, 1.0 mmol, 1.0 equiv) and FPyr (9.8 μL, 10.2 mg, 100 μL, 10 mol%) in MeCN (0.50 mL, 2 M) was added TCT (72 mg, 0.38 mmol, 38 mol%) and the mixture was stirred for 4.5 h at 80 °C. Next, the resulting yellow suspension was cooled in an ice bath and treated dropwise with a suspension of (*S*)-phenylalaninol (314 mg, 1.1 mmol, 1.1 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) in MeCN (1.0 mL). The 4 mL glass vial, in which the suspension of phenylalaninol had been prepared, was rinsed with further MeCN (0.25 mL→0.6 M) and the reaction mixture was allowed to stir for 6 h at room temperature. Eventually, the crude material (brownish oil, 596 mg, 160%) was subjected to column chromatographic purification on silica gel (39.7 g, mass relation crude **2_{17q}**/SiO_2 1:66) with EtOAc/*n*Hex 90:10→100:0 to yield the title compound as a colourless, foamy solid (293.9 mg, 0.79 mmol, 79%) after concentration with dichloromethane (3 x 2 mL) and drying at the rotary evaporator for 15 min at 5 mbar. In order to charge the silica gel column with the crude product, it was dissolved in EtOAc (0.5 mL) under heating and applied onto the surface of the column after cooling down to ambient temperature.



M ($C_{21}H_{25}NO_5$) = 371.43 g/mol; **mp.** 54-56 °C; **r_f** (SiO_2, EtOAc/*n*Hex 90:10) = 0.34; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 7.50 (d, $^3J_{3,2}$ = 15.6 Hz, 1H, 3-H), 7.32-7.29 (m, 2H, 6´-H), 7.26-7.21 (m, 3H, 5´-H, 7´-H), 6.67 (s, 2H, 5-H), 6.28 (d $^3J_{2,3}$ = 15.6 Hz, 1H, 2-H), 6.11 (d, $^3J_{NH,1´}$= 5.8 Hz, 1H, NH), 4.36-4.29 (m, 1H, 1´-H), 3.87 (s, 3H, 9-H), 3.84 (s, 6H, 8-H), 3.76-3.74 (m, 1H, 2´-H_a), 3.67-3.64 (m 1H, 2´-H_b), 3.15 (s, 1H,OH), 2.96-2.95 (d, $^3J_{3´,1´}$ = 7.2 Hz, 2H, 3´-H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 166.35 (C-1), 153.24 (C-6), 141.28 (C-3), 139.50 (C-7), 137.61 (C-4´), 130.14 (C-4), 129.17 (C-5´), 128.55 (C-6´), 126.57 (C-7´), 119.73 (C-2), 104.92 (C-5), 63.83 (C-2´), 60.86 (C-9), 56.00 (C-8), 52.95 (C-1´), 36.96 (C-3´); **$[\alpha]_D^{20}$** = -54.8 (c = 1.075 g/100 mL, $CHCl_3$); **HR-MS** ($[C_{21}H_{25}NO_5]^+$) calc. 371.1733 u found 371.1737 u.

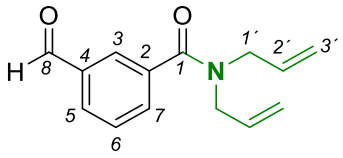


^{1}H-NMR spectrum of *E*-(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-3-(3,4,5-trimethoxy phenyl)propenoic amide (500 MHz, $CDCl_3$).



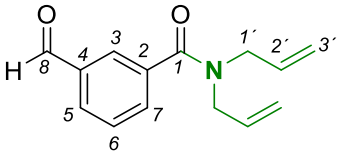
^{13}C-NMR spectrum of *E*-(*S*)-*N*-(1-hydroxy-3-phenylpropan-2-yl)-3-(3,4,5-trimethoxy phenyl)propenoic amide (125 MHz, $CDCl_3$).

5.4.2.21 Synthesis of *N,N*-Diallyl 3-formylbenzamide (2_{13s})



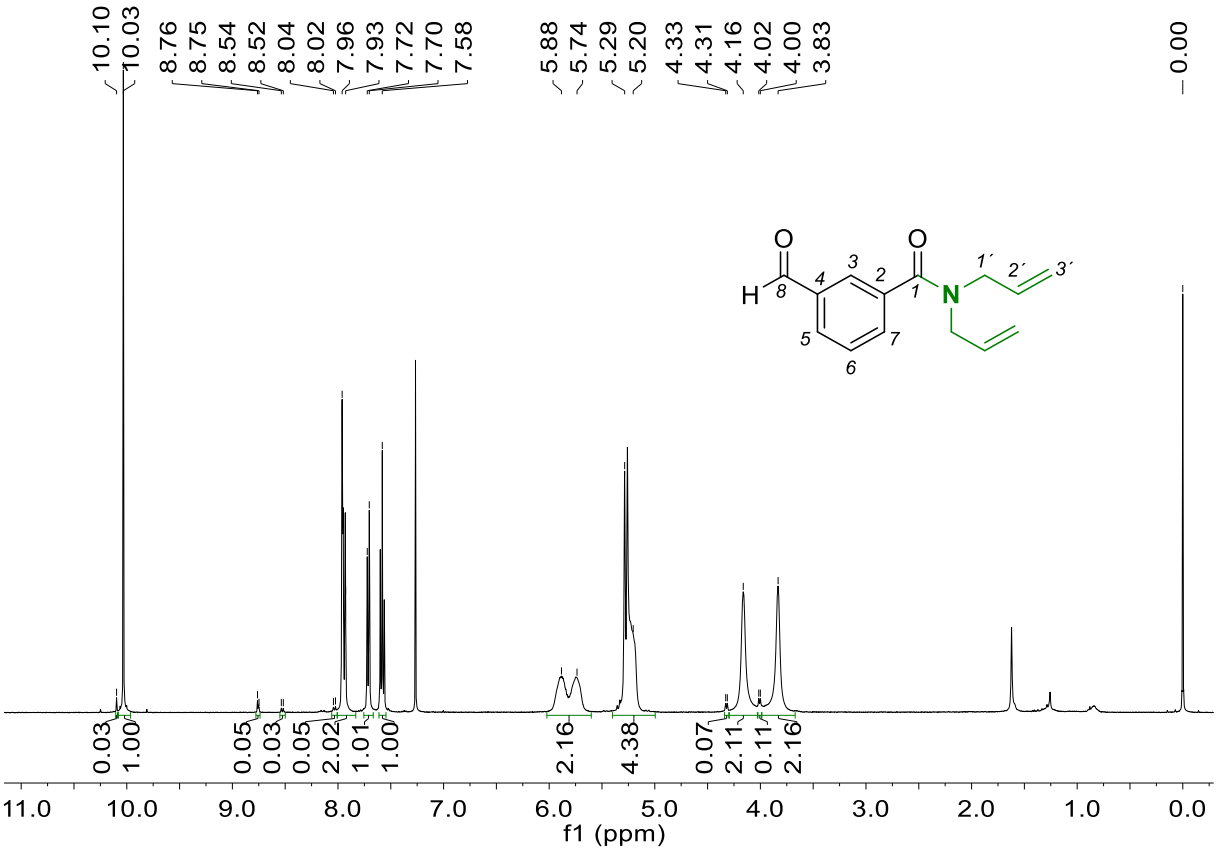
2_{13s}

PH3353: In accordance with general protocol 4 (chapter 5.3.4, page 50) 3-formyl benzoic acid (150 mg, 1.0 mmol, 1.0 equiv) was stirred with TCT (72 mg, 0.38 mmol, 38 mol%) and FPyr (9.8 μL, 10.2 mg, 100 μL, 10 mol%) in MeCN (0.50 mL, 2 M) for 4 h at 80 °C. Subsequently, the reaction suspension was diluted MeCN (0.50 mL→1 M), diallylamine (150 μL, 1.2 mmol, 1.2 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were added at 0 °C and stirring was continued for 4 h at room temperature. Finally, the crude title compound (orange, 226 mg, 99%) was purified with the aid of column chromatography on silica gel (16.0 g, mass ratio crude product in respect to SiO_2 1:71) applying EtOAc/*n*Hex 40:60 as eluent mixture, which allowed to access amide **2_{13s}** in 87% yield as a pale yellow oil (198.8 mg, 0.867 mmol) after drying at the rotary evaporator at 5 mbar for 15 min.

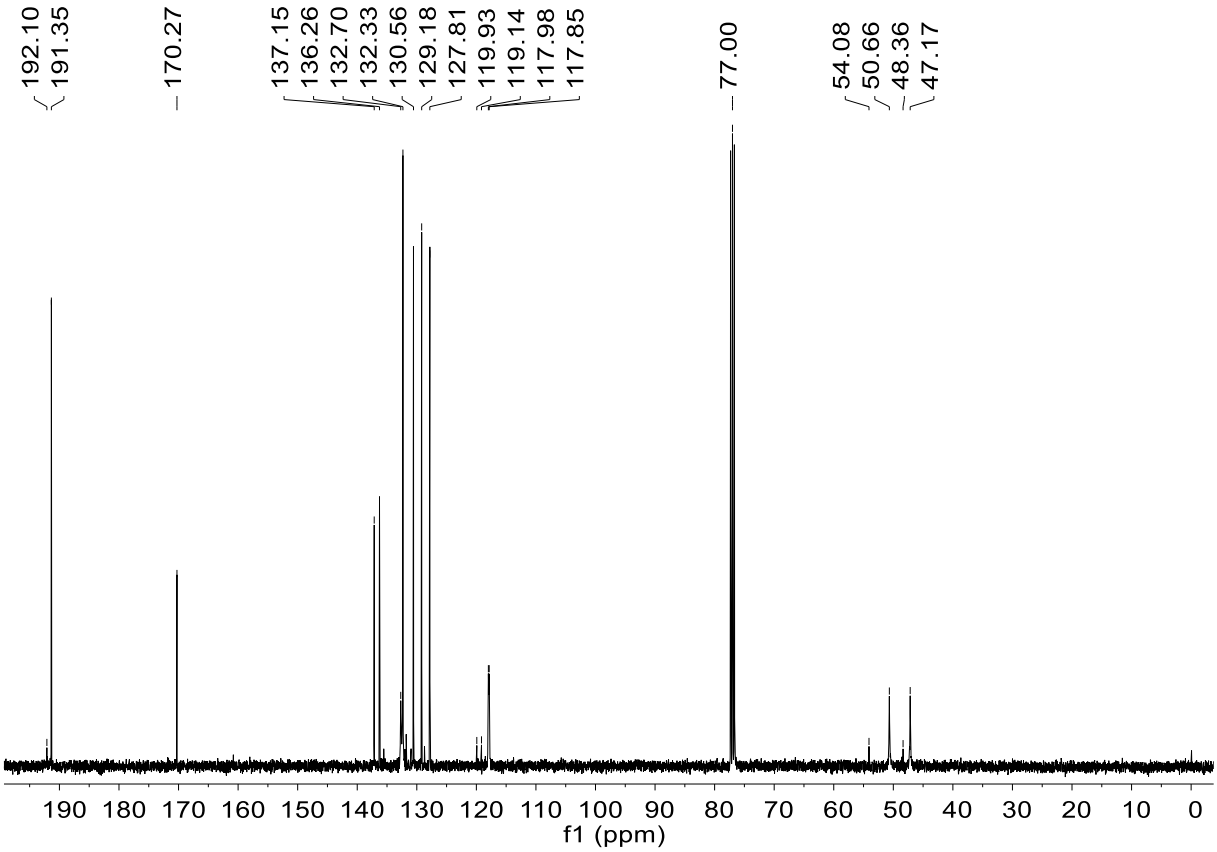


Compound **2_{13s}** shows most likely two rotational isomers in the NMR. GC-MS indicates a purity of ≥98%, because only one compound was detected.

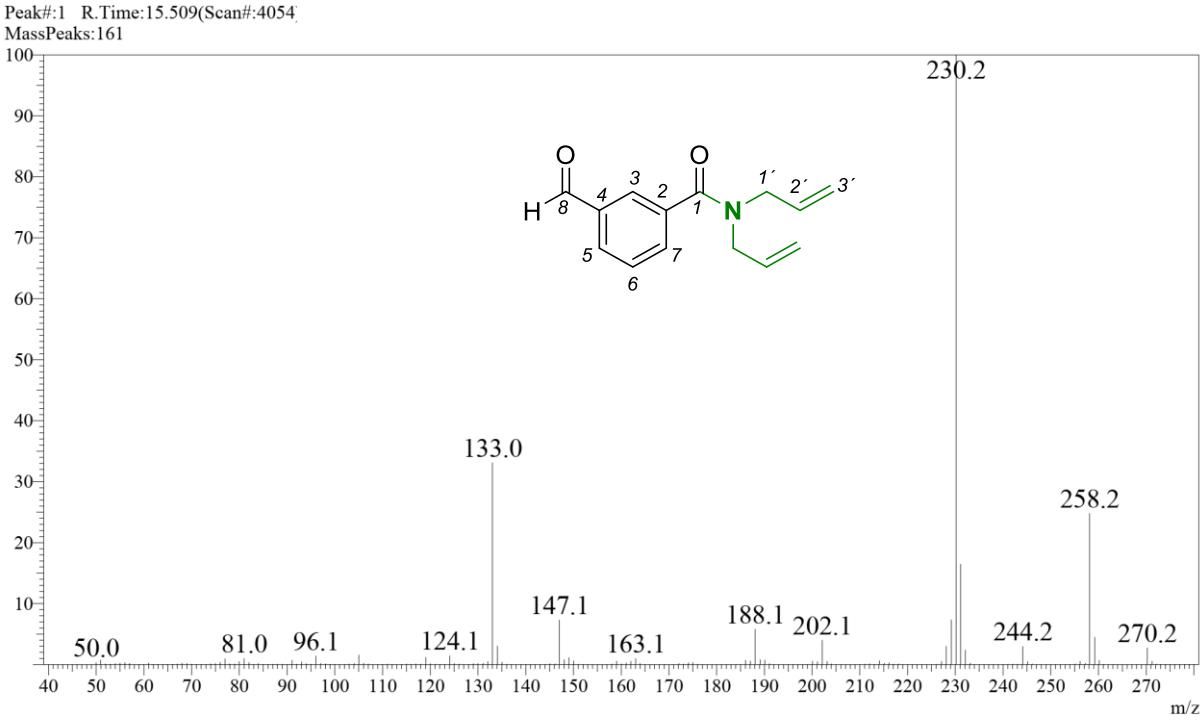
M ($C_{14}H_{15}NO_2$) = 229.28 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 40:60) = 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$, rotameric ratio = *rr* = 3:97 rotamer 1/2) δ [ppm] = 10.10 (s, 1H, 8-H_{rot1}, *rr* = 3:97), 10.03 (s, 1H, 8-H_{rot2}, *rr* = 97:3), 8.76-8.75 (m, 2H, 3-H_{rot1}, 5-H_{rot1}, *rr* = 2:98), 8.53 (ψ-tt, *J* = 7.6, 1.3 Hz, 1H, 7-H_{rot1}, *rr* = 3:97), 8.02 (ψ-tt, *J* = 7.7, 1.4 Hz, 1H, 6-H_{rot1}), 7.96-7.93 (m, 2H, 3-H_{rot1}, 5-H_{rot1}, *rr* = 98:2), 7.71 (ψ-dt, *J* = 7.7, 1.5 Hz, 1H, 7-H_{rot2}, *rr* = 97:3), 7.58 (ψ-t, *J* = 7.6 Hz, 1H, 6-H_{rot2}), 5.88-5.74 (m, 2H, 2´-H), 5.29-5.20 (m, 4H, 3´-H), 4.32 (d, $^3J_{1´,2´}$ = 6.1 Hz, 2H, 1´-$H_{a,rot1}$, *rr* = 3:97), 4.16 (br. s, 2H, 1´-$H_{a,rot2}$, *rr* = 97:3), 4.01 (d, $^3J_{1´,2´}$ = 5.9 Hz, 2H, 1´-$H_{b,rot1}$, *rr* = 5:95), 3.83 (br. s, 2H, 1´-$H_{b,rot2}$, *rr* = 95:5); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 192.10 (C_{rot2}-8), 191.35 (C_{rot1}-8), 170.27 (C_{rot2}-1), 137.15 (C_{rot2}-2), 136.26 (C_{rot2}-4), 135.55 (C_{rot1}-7), 132.70 (C_{rot2}-2´) 132.33 (C_{rot2}-7), 132.00 (C_{rot1}), 131.78 (C_{rot1}), 130.96 (C_{rot1}), 130.56 (C_{rot2}-5), 129.18 (C_{rot2}-6), 128.71 (C_{rot1}=, 127.81 (C_{rot2}-3), 119.93+119.14 (C_{rot1}-3´), 117.98+117.85 (C_{rot2}-3´), 54.08 ($C_{rot1,b}$-1´), 50.66 ($C_{rot2,b}$-1´), 48.36 ($C_{rot1.a}$-1´), 47.17 ($C_{rot2,a}$-1´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 270 (2, [M+allyl]$^+$), 258 (28, [M+Et]$^+$), 244 (2, [M+Me]$^+$), 230 (100, [M+H]$^+$), 202 (3, [M-vinyl]$^+$), 188 (5, [M-allyl]$^+$), 147 (8),133 (32, [M-Nallyl$_2$]$^+$); **HR-MS** ([$C_{14}H_{16}NO_2$]$^+$) calc. 230.1181 u found 230.1181 u.



^{1}H-NMR spectrum of *N,N*-diallyl 3-formylbenzamide (400 MHz, $CDCl_3$).

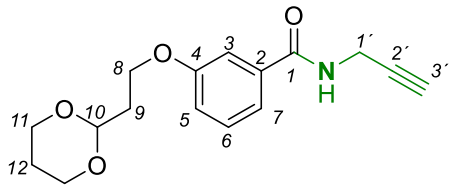


^{13}C-NMR spectrum of *N,N*-diallyl 3-formylbenzamide (100 MHz, $CDCl_3$).



Mass spectrum of *N,N*-diallyl 2-formylbenzamide (CI, 70 eV).

5.4.2.22 Synthesis of *N*-Propargyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzamide (2_{20t})

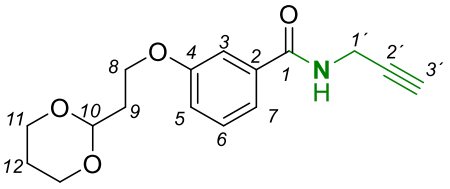


2_{20t}

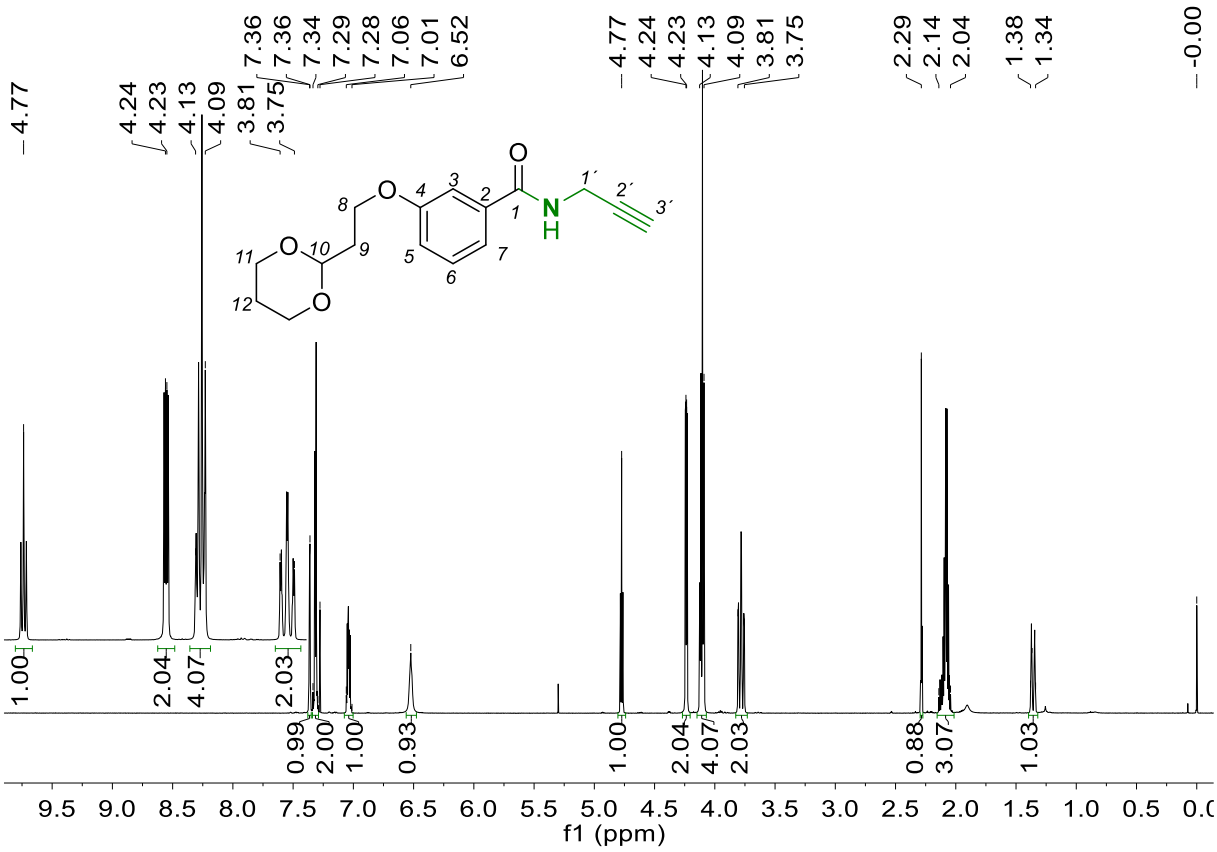
The production of 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoic acid (**1_{20}**) is described in chapter 5.4.5.2 on page 238.

PH3537: In agreement with general protocol 4 (chapter 5.3.4, page 50) the a suspension of the acid **1_{20}** (252 mg, 1.0 mmol, 1.0 equiv) and FPyr (19.8 μL, 20.4 mg, 200 μmol, 20 mol%) in MeCN (1.0 mL, 1 M) was treated with TCT (72 mg, 0.38 mmol, 38 mol%) and stirred for 18 h at **room temperature**. Subsequently, propargyl amine (100 μL, 1.5 mmol, 1.0 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were added under cooling in an ice bath and the resulting suspension was stirred for 4 h at ambient temperature. Aqueous work up gave the crude amide **2_{20t}** as a pale yellow solid (284 mg, 98%). Then, column chromatographic purification on silica gel (23.0 g, mass ratio SiO_2/crude material 81:1) with EtOAc/*n*Hex 50:50→60:40 afforded amide **2_{20t}** as a colourless solid in 87% yield (251.7 mg, 0.87 mmol). In order to charge the silica column with the crude product, it was dissolved in CH_2Cl_2(ca. 20 mL), SiO_2 was added (0.67 g, relation weight crude amide in respect to SiO_2 1:2.4) and the solvent was evaporated *in vacuo*.

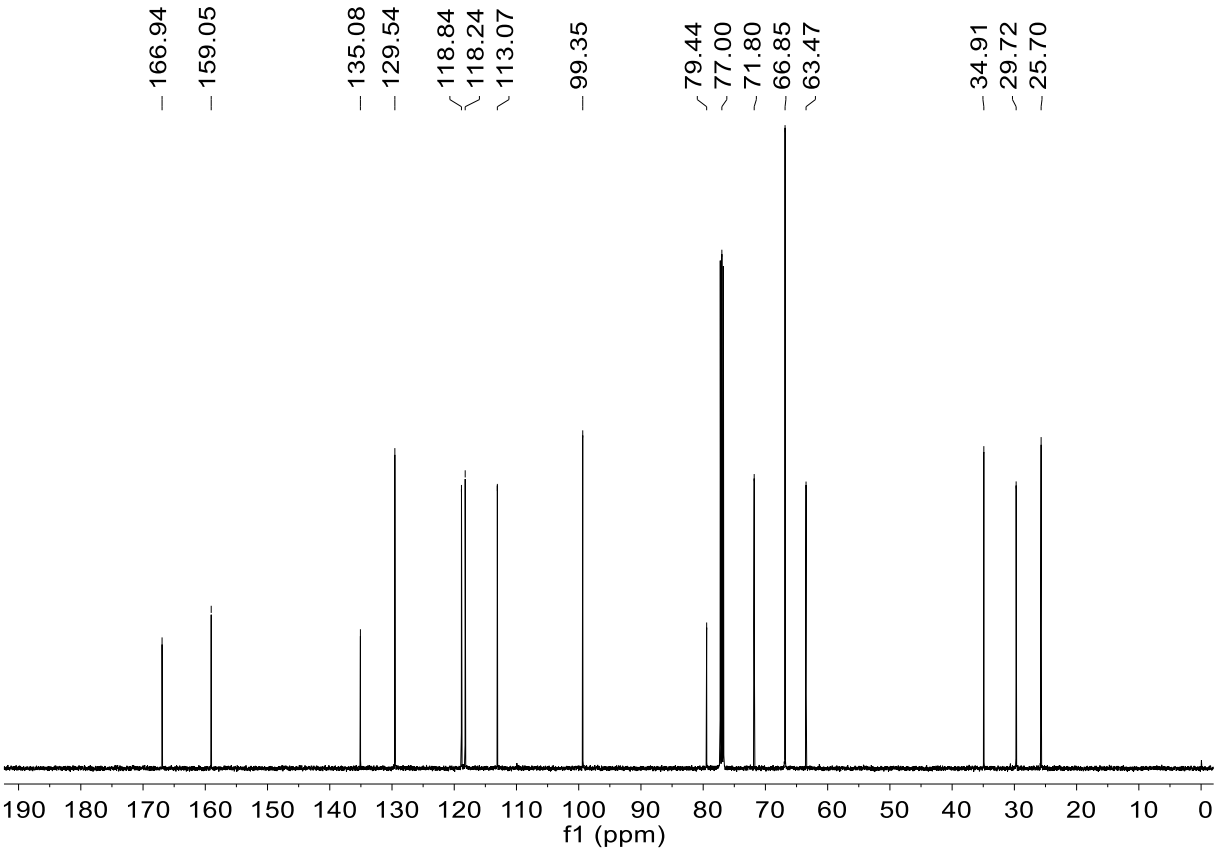
PH3566: Following general protocol 4 (chapter 5.3.4, page 50) benzoic acid **1$_{20}$** (1.00 mmol, 1.0 equiv) was allowed to react with TCT (75 mg, 0.40 mmol, 40 mol%) in the presence of FPyr (20 mol%) in MeCN (1 M) for 9 h at **40 °C**. Next, propargyl amine (1.5 equiv) and NMM (1.3 equiv) were introduced at 0 °C and the reaction suspension was stirred overnight (15 h) at room temperature. Afterwards, purification of the crude material (273 mg, 94%, pale brownish solid) by means of column chromatography on silica gel (22.8 g, mass crude product/SiO_2 1:84) using EtOAc/CH_2Cl_2 20:80) furnished the title compound as a colourless solid (242.8 mg, 0.839 mmol, 84%). Loading of the crude product onto the silica gel column was realized through adsorption on SiO_2 (0.73 g, weight crude amide **2$_{20t}$**/silica gel 1:2.7).



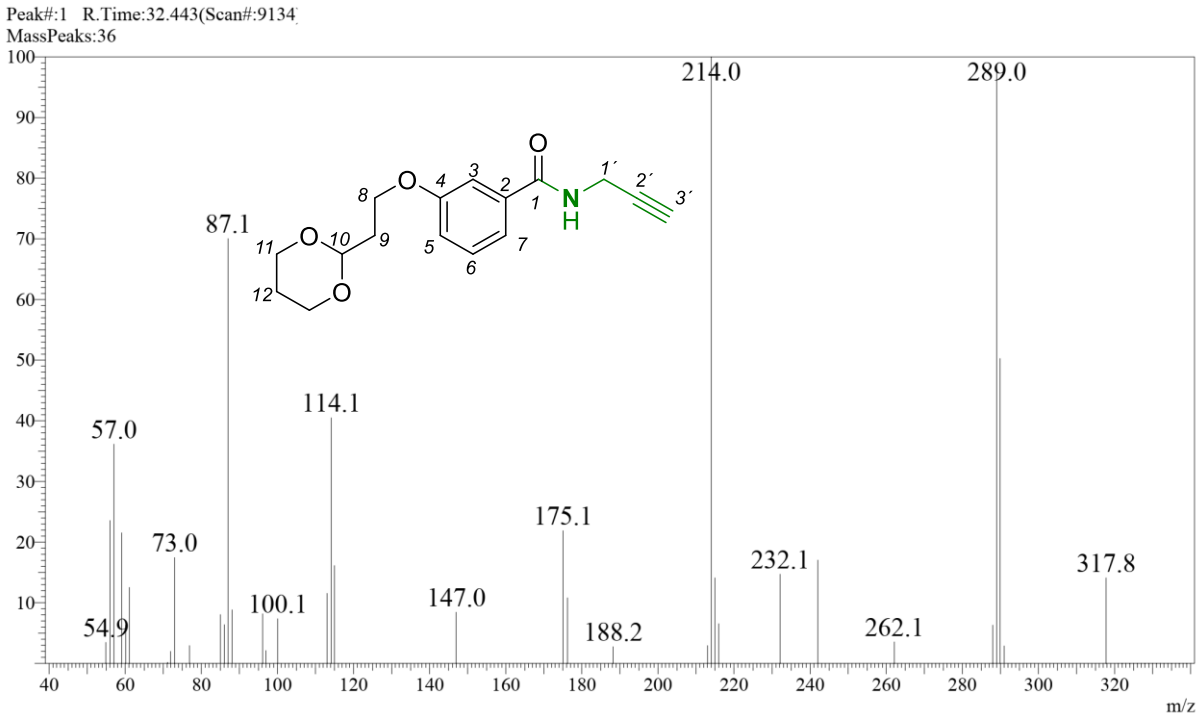
M ($C_{16}H_{19}NO_4$) = 289.33 g/mol; **mp.** = 109-111 °C ; **r$_f$** (SiO_2) = 0.34 (EtOAc/nHex 50:50), 0.34 (EtOAc/CH_2Cl_2 20:80); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 7.37-7.36 (m, 1H, 7-H), 7.34-7.29 (m, 2H, 3-H, 5-H), 7.06-7.01 (m, 1H, 5-H), 6.52 (t, $^3J_{NH,1´}$ = 4.4 Hz, 1H, NH), 4.77 (t, $^3J_{10,9}$ = 5.2 Hz, 1H, 10-H), 4.24 (dd, $^3J_{1´,NH}$ = 5.3, $^4J_{1´,3´}$ = 2.6 Hz, 2H, 1´-H), 4.13-4.09 (m, 4H, 8-H, 11-H$_a$), 3.81-3.75 (m, 2H, 11-H$_b$), 2.29 (t, $^4J_{3´,1´}$ = 2.2 Hz, 1H, 3´-H), 2.14-2.04 (m, 3H, 9-H, 12-H$_a$), 1.38-1.34 (m, 1H, 12-H$_b$); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 166.94 (C-1), 159.05 (C-4), 135.08 (C-2), 129.54 (C-3 or C-6), 118.84 (C-3 or C-6), 118.24 (C-5), 113.07 (C-7), 99.35 (C-10), 79.44, (C-2´) 71.80 (C-3´), 66.85 (C-11), 63.47 (C-8), 34.91 (C-9), 29.72 (C-1´), 25.70 (C-12); **GC-MS** (CI, 70 eV) m/z [u] (%) = 318 (15, $[M+Et]^+$), 290 (52, $[M+H]^+$), 289 (100, $[M]^+$), 262 (4), 242 (18), 232 (17), 214 (100, $[H_2CHCHO(C_6H_4)CONHCH_2CCH]$), 176 (11, $[3\text{-}HO(C_6H_4)C(OH)\ NHCH_2CCH]^+$), 175 (23, $[3\text{-}HO(C_6H_4)CONHCH_2CCH]^+$), 147 (9), 114 (41), $[(CH_2)_3O_2CHCHCH_2]^+$, 87 (71, $[(CH_2)_3O_2CH]^+$), 73 (19), 57 (38); **HR-MS** (ESI, $[C_{16}H_{20}NO_4]^+$) calc. 290.1387 u found 290.1384 u.



^{1}H-NMR spectrum of *N*-propargyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzamide (500 MHz, $CDCl_3$).



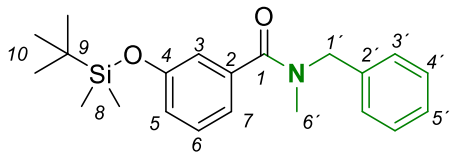
^{13}C-NMR spectrum of *N*-propargyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzamide (125 MHz, $CDCl_3$).



Mass spectrum of *N*-propargyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzamide (CI, 70 eV).

5.4.2.23 Synthesis of *N*-Benzyl-*N*-methyl 3-(*tert*-butoxydimethylsilyloxy) benzamide (2_{21u})

The preparation of the starting material 3-(*tert*-butoxydimethysiloxy) benzoic is given in chapter 5.4.5.3 on page 242.

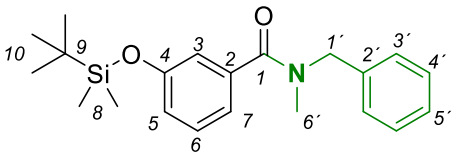


2_{21u}

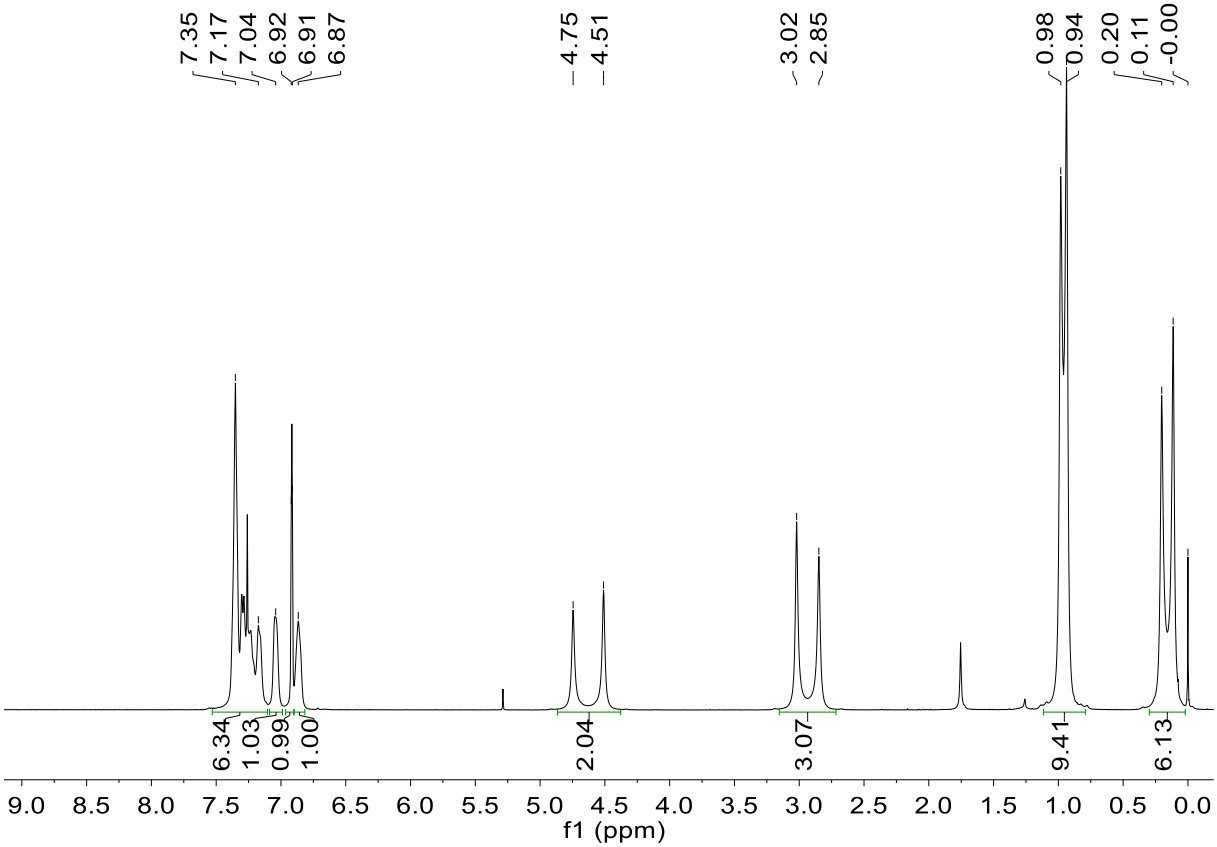
PH3492: As described general protocol 4 (chapter 5.3.4, page 50) benzoic acid **1_{21}** (252 mg, 1.0 mmol, 1.0 equiv) was successively combined with FPyr (19.6 μL, 20.4 mg, 200 μL, 20 mol%), MeCN (0.50 mL, 2 M) and TCT (72 mg, 0.38 mmol, 38 mol%) and stirred overnight (14 h) at **room temperature**. In the following, the colourless reaction suspension was diluted with more MeCN (0.50 mL→1 M), cooled to 0 °C and sequentially *N*-methylbenzylamine (140 μL, 1.1 mmol, 1.1 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were added. Due to an increase in viscosity during NMM addition, the reaction mixture was diluted with additional MeCN (0.50 mL→0.7 M). Past stirring for 4 h at ambient temperature, aqueous work without HCl-washing afforded the crude product a yellow oil (366 mg, 103 mol%). ^{1}H-NMR indicated 14 mol% of *N*-methylbenzylamine with regard to the title amide **2_{21u}**. Finally, purification by means of column chromatography with EtOAc/*n*Hex 20:80 on silica gel (21.5 g, ratio weight crude material in respect to SiO_2 1:58) delivered amide **2_{21u}** as a colourless oil (267.7 mg, 0.752 mmol, 75%).

PH3496: The title compound was prepared from acid **1_{21}** (1.0 mmol, 1.0 equiv) as described above with the deviation that in the initial activation step the reaction mixture was heated to

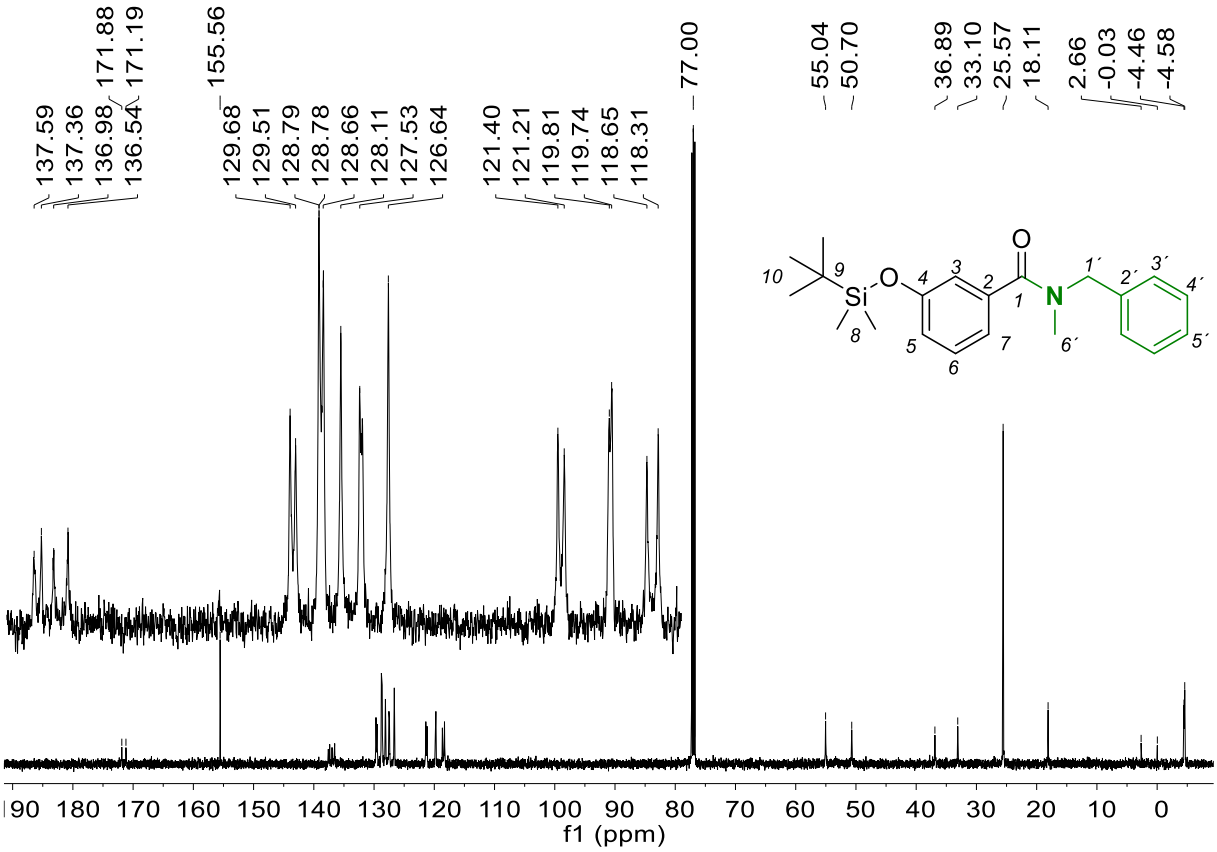
40 °C for 7 h. Eventually, the crude material (yellow oil, 356 mg, 100%) was subjected to purification with the aid of column chromatography on silica gel (19.9 g, mass relation crude product/SiO_2 1:55) using EtOAc/*n*Hex 20:80. Concentration with CH_2Cl_2 drying in high vacuum for 3 h allowed to isolate amide **2_{21u}** as a colourless oil in 70% yield (249.8 mg, 0.703 mmol).



M ($C_{21}H_{29}NO_2Si$) = 255.55 g/mol; **r_f** (SiO_2, EtOAc/CH_2Cl_2 20:80) = 0.34; **^{1}H-NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 7.35-7.17 (m, 6H, 6-H, 3´-H, 4´-H, 5´-H), 7.04 (br. s, 2H, 5-H or 7-H), 6.92-6.91 (m, 1H, 3-H), 6.87 (br. s, 1H, 5-H or 7-H), 4.75/4.51 (2 x s, 2H, 1´-H), 3.02/2.85 (2 x s, 3H, 6`-H), 0.98/0.94 (2 x s, 9H, 10-H), 0.20/0.11 (2 x s, 6H, 8-H); **^{13}C-NMR** (125 MHz, $CDCl_3$, mixture of rotamers) δ [ppm] = 171.88/171.19 (C-1), 155.56 (C-4), 137.59/137.36 (C-2), 136.98/136.54 (C-2´), 129.68/129.51 (C-6), 128.78/128.66 (C-4´), 128.11 (C_{rot1}-3´), 127.52/127.45 (C-5´), 126.64 (C_{rot2}-3´), 121.40/121.21 (C-5 or C-7), 119.81/119.74 (C-5 or C-7), 118.65/118.31 (C-3), 55.04/50.70 (C-1´), 36.89/33.10 (C-6´), 25.57 (C-10), 18.11 (C-9), -4.46/-4.58 (C-8).

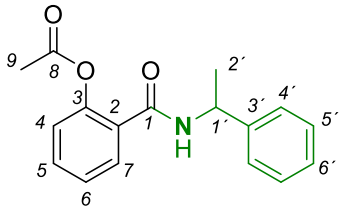


^{1}H-NMR spectrum of *N*-benzyl-*N*-methyl 3-(*tert*-butoxydimethylsilyloxy) benzamide (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *N*-benzyl-*N*-methyl 3-(*tert*-butoxydimethylsilyloxy) benzamide (125 MHz, $CDCl_3$).

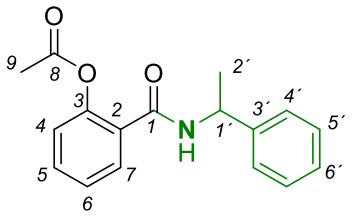
5.4.2.24 Synthesis of *rac*-*N*-(1-Phenylethyl) 2-acetoxybenzamide (2_{22v})



2_{22v}

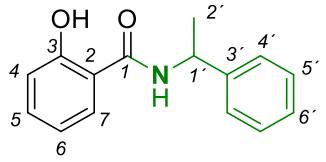
PH3409: According to general protocol 4 (chapter 5.3.4, page 50) acetyl salicylic acid (180 mg, 1.0 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 1 M) for 4 h at 80 °C. Next, the colourless reaction suspension was treated with further MeCN (0.50 mL→1 M), cooled to 0 °C and successively *rac*-1-phenylethylamine (140 μL, 1.1 mmol, 1.1 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were added. After 5 h or stirring at room temperature, aqueous work up provided the crude title compound as a pale yellow solid (301 mg, 106%). Eventually, column chromatographic purification on silica gel (21.9 g, relation of masses crude product/SiO_2 1:73) with EtOAc/*n*Hex 40:60 enabled the isolation of the title amide as a colourless solid (207.5 mg, 0.732 mmol, 73%). Aside *N*-(1-phenylethyl) 2-hydroxybenzamide was obtained as a colourless oil in 6% yield (13.8 mg, 0.057 mmol). In order to load silica gel column, the crude material was dissolved in CH_2Cl_2 (ca. 10 mL), silica gel was introduced (0.60 g, mass crude **2_{22v}**/SiO_2 1:2) and the solvent was evaporated *in vacuo*.

***N*-(1-Phenylethyl) 2-acetoxybenzamide (2_{22v})**



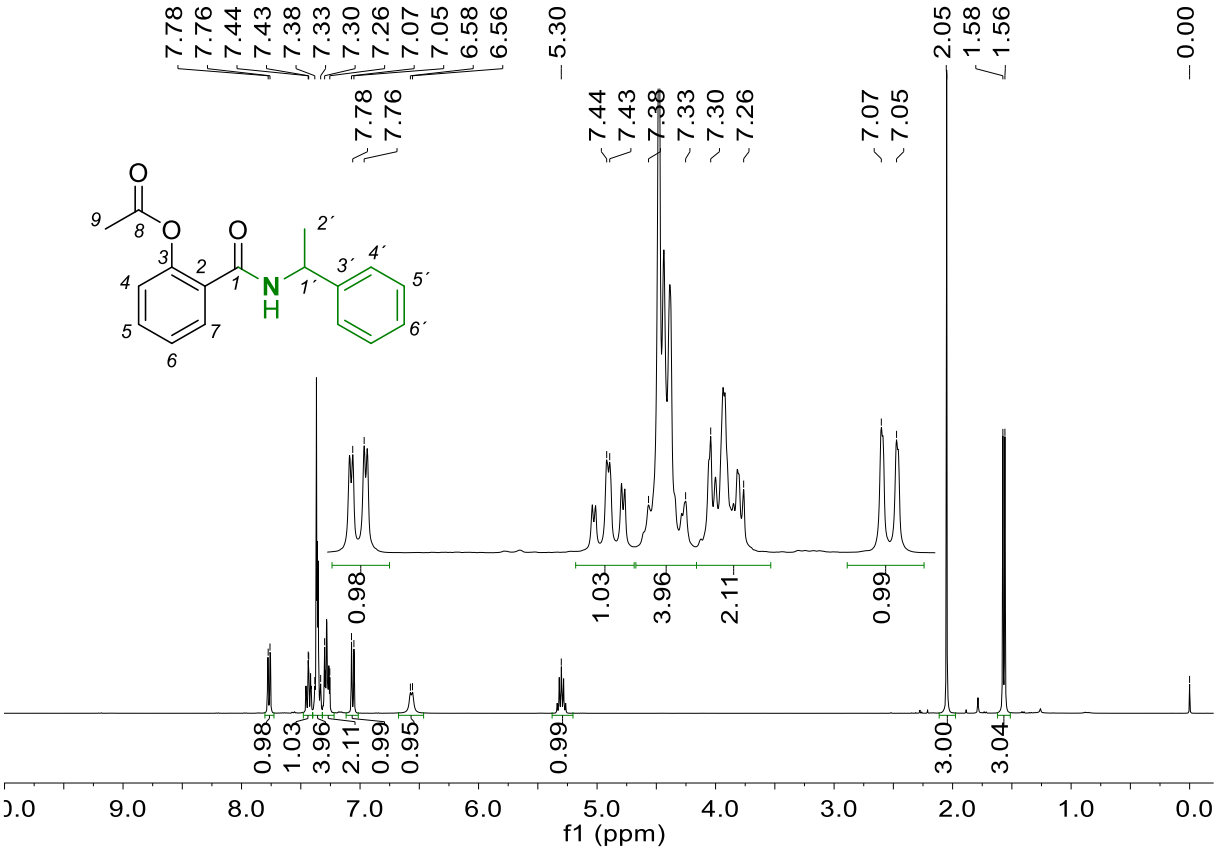
M ($C_{17}H_{17}NO_3$) = 283.32 g/mol; **mp.** = 113-114 (lit.-mp. 98 °C);[39] **r_f** (SiO_2, EtOAc/*n*Hex 40:60) = 0.42; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.78-7.76 (dd, $^3J_{7,6}$ = 7.8 Hz, $^4J_{7,5}$ = 1.6 Hz, 1H, 7-H), 7.44 (ψ-td, *J* = 7.6, 1.7 Hz, 1H, 5-H), 7.38-7.33 (m, 4H, 4´-H, 5´-H), 7.30-7.26 (m, 2H, 6´-H, 6-H), 7.06 (dd, $^3J_{4,5}$ = 8.1 Hz, $^4J_{4,6}$ = 0.8 Hz, 1H, 4-H), 6.57 (d, $^3J_{NH,1´}$ = 7.1 Hz, 1H, NH), 5.30 (qd, $^3J_{1´,2´}$ = 7.1 Hz, $^3J_{1´,NH}$ = 7.1 Hz, 1H, 1´-H), 2.05 (s, 3H, 9-H), 1.57 (d, *J* = 6.9 Hz, 3H, 2´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 169.00 (C-8), 164.45 (C-1), 147.64 (C-3), 142.77 (C-3´), 131.62 (C-5), 129.90 (C-7), 128.74 (C-5´), 128.44 (C-2), 127.51 (C-6´), 126.28 (C-6), 126.23 (C-4´), 123.02 (C-4), 49.05 (C-1´), 21.45 (C-2´), 20.62 (C-9); **GC-MS** (CI, 70 eV) m/z [u] (%) = 312 (2, $[M+Et]^+$), 284 (5, $[M+H]^+$), 283 (4, $[M]^+$), 242 (100, $[M+2\ H\text{-}MeCO]^+$), 241 (53, $[M+H\text{-}MeCO]^+$), 208 (5), 138 (29, $[2\text{-}HO(C_6H_4)C(=OH)NH_2]^+$), 137 (39, $[AcOPh+H]^+$), 121 (23, $[2\text{-}HO(C_6H_4)CO]^+$), 120 (30, $[PhC(NH_2)Me]^+$), 105 (96, $[PhCHCH_3]^+$), 61 (13); **HR-MS** ($[C_{17}H_{18}NO_3]^+$) calc. 284.1287 u found 284.1283 u.

***N*-(1-Phenylethyl) 2-hydroxybenzamide**

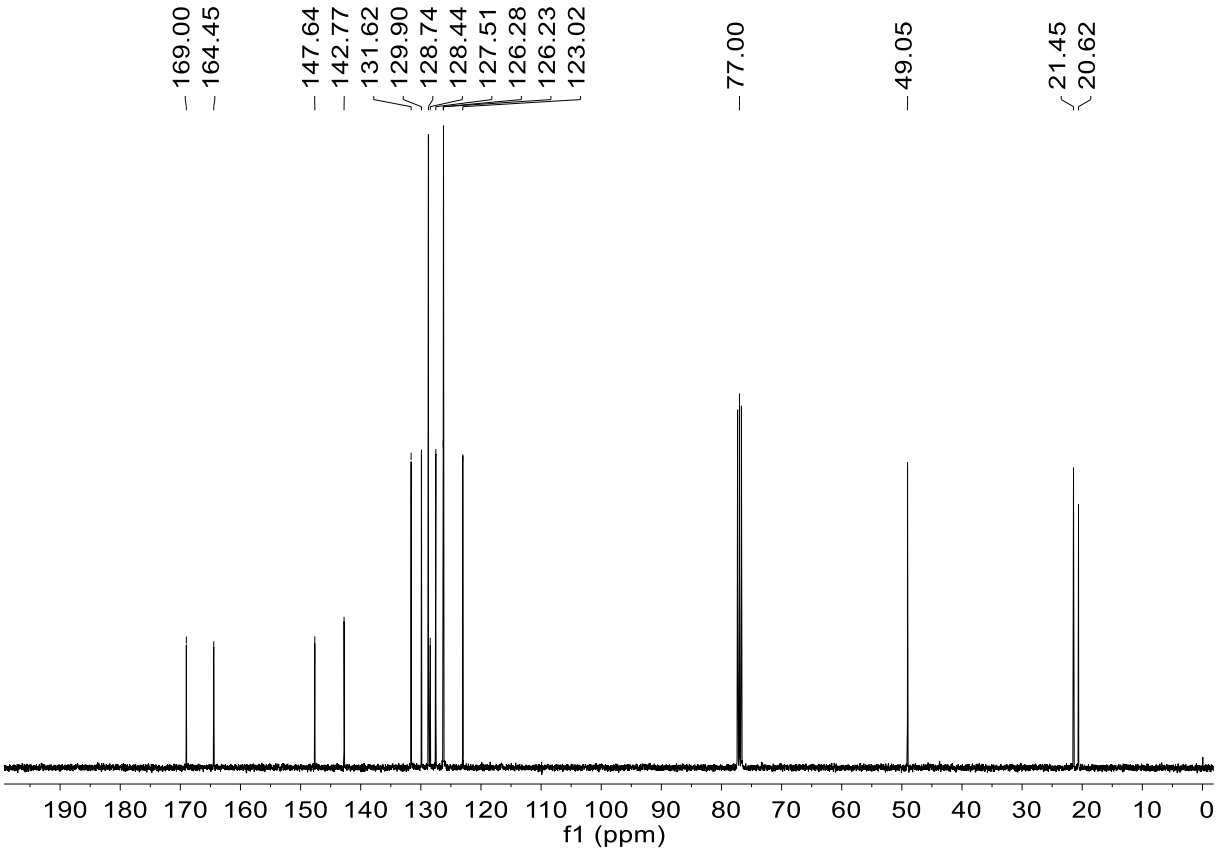


M ($C_{15}H_{15}NO_2$) = 241.29 g/mol, **mp.** = (lit.-mp. 103 °C);[39] **r_f** (SiO_2, EtOAc/*n*Hex 40:60) = 0.74; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 12.28 (s, 1H, OH), 7.40-7.33 (m, 6H, 5-H, 7-H, 4´-H, 5´-H), 7.32-7.28 (m, 1H, 6´-H), 6.98 (dd, 8.4, 0.8 Hz, 1H, 6-H), 6.85-6.81 (m, 1H, 4-H), 6.48 (br. s, 1H, NH), 5.31 (qd, $^3J_{1´,2´}$ = 7.0 Hz, $^3J_{1´,NH}$ = 7.0 Hz, 1H, 1´-H), 1.62 (d, $^3J_{2´,1´}$ = 6.9 Hz, 3H, 2´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 169.10 (C-1), 161.64 (C-3), 142.44 (C-3´), 134.24 (C-5 or C-7), 128.86 (C-5)´, 127.70 (C-6´), 126.13 (C-4´), 125.24 (C-5 or C-7), 118.66 (C-6), 118.57 (C-4), 114.15 (C-2), 49.05 (C-1´), 21.65 (C-2´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 270 (1, $[M+Et]^+$, 242 (42, $[M+H]^+$), 241 (33, $[M]^+$), 166 (8), 149 (6), 138 (38, $[2\text{-}HO(C_6H_4)C(=OH)NH_2]^+$), 137 (52, $[AcOPh+H]^+$), 121 (17, $[2\text{-}HO(C_6H_4)CO]^+$), 120 (23, $[PhC(NH_2)Me]^+$), 105 (100, $[PhCHCH_3]^+$).

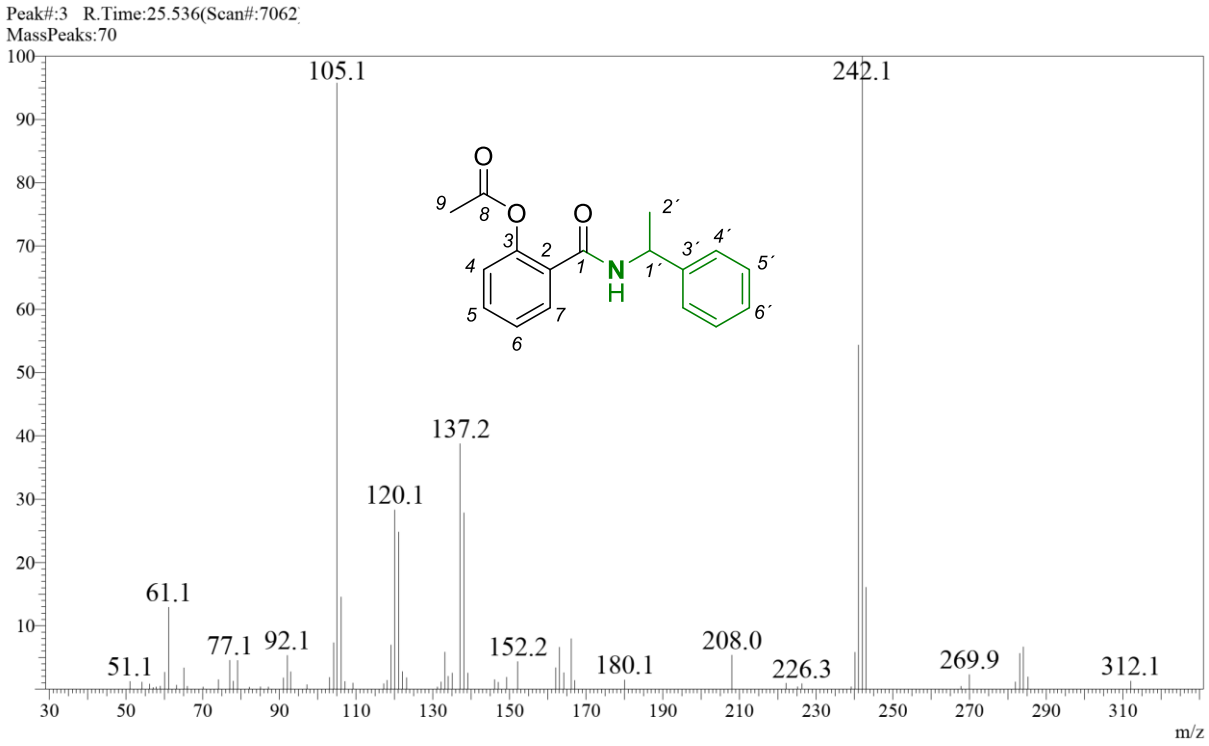
The NMR-data is in agreement with the literature of the *S*-enantiomer.[40]



^{1}H-NMR spectrum of *N*-(1-phenylethyl) 2-acetoxybenzamide (400 MHz, $CDCl_3$).

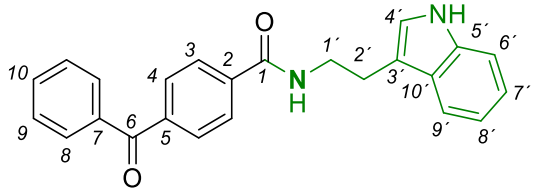


^{13}C-NMR spectrum of *N*-(1-phenylethyl) 2-acetoxybenzamide (100 MHz, $CDCl_3$).



Mass spectrum of *N*-(1-phenylethyl) 2-acetoxybenzamide (CI, 70 eV).

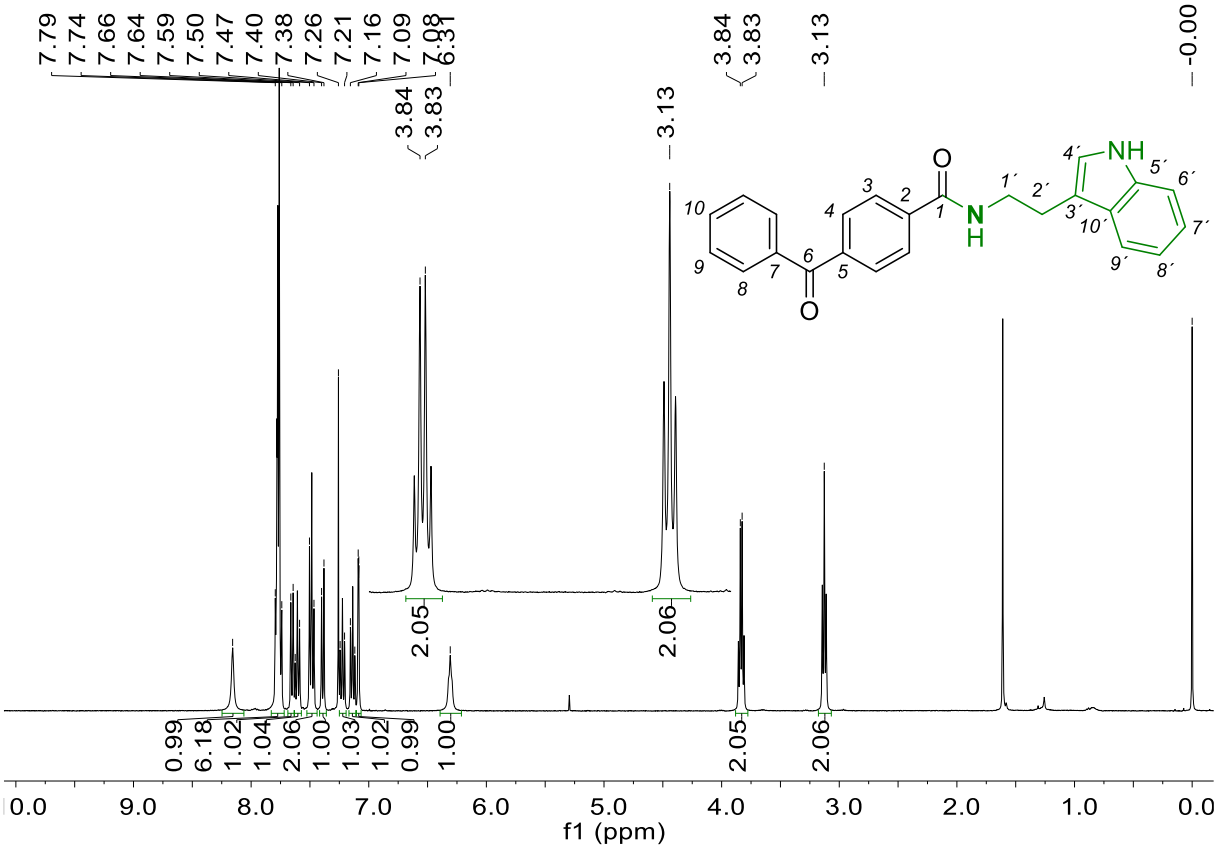
5.4.2.25 Synthesis of *N*-(2-(Indol-3-yl)ethyl) 4-benzoylbenzamide (2_{23w})



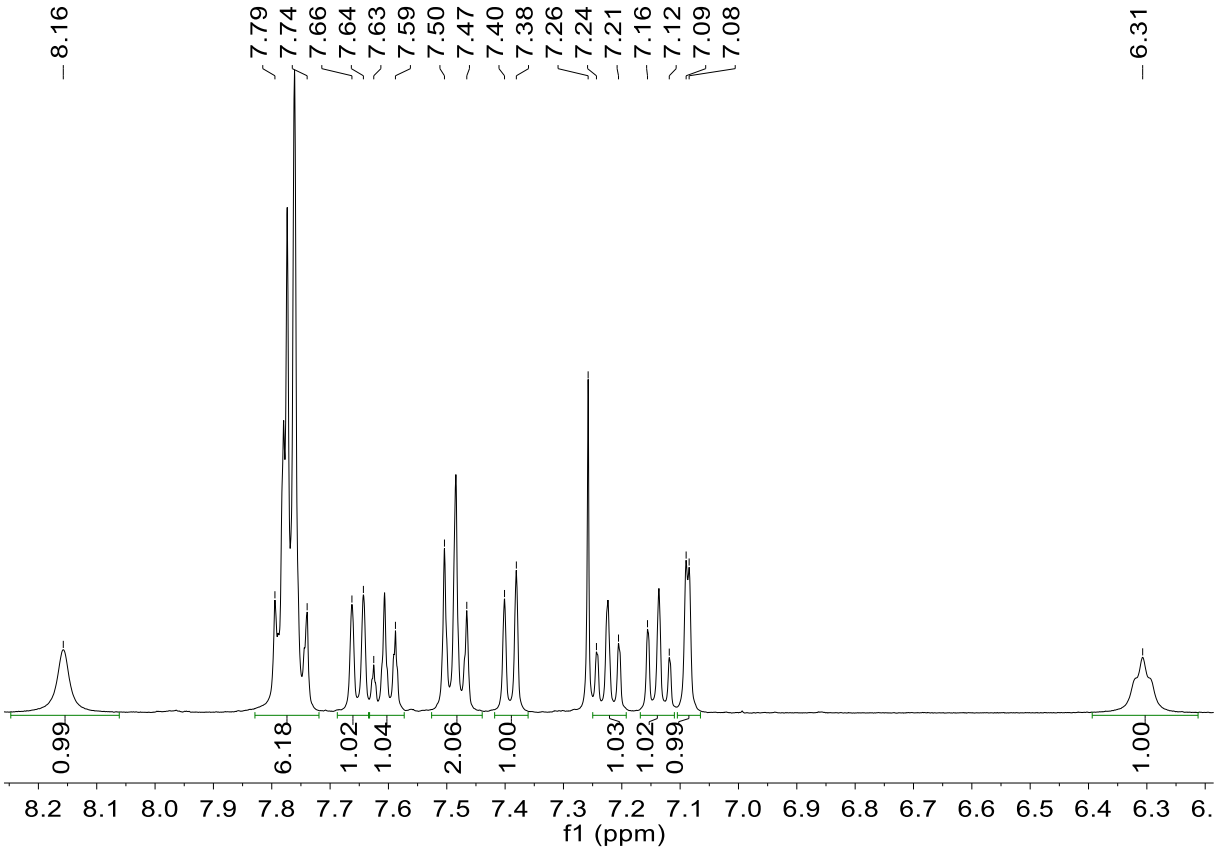
2_{23w}

PH3428: As described in general protocol 4 (chapter 5.3.4, page 50) 4-benzoyl benzoic acid (226 mg, 1.0 mmol, 1.0 equiv) was combined with FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%), MeCN (0.50 mL, 2 M) and TCT (72 mg, 0.38 mmol, 38 mol%) and heated for 5 h to 80 °C. Then, the yellow reaction suspension was diluted with more MeCN (1.0 mL→0.7 M), cooled to 0 °C and tryptamine (176 mg, 1.1 mmol, 1.1 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were added. After stirring for 4 h at room temperature and aqueous work up, the crude material was isolated as a brownish solid (356 mg, 96%). Lastly, chromatographic purification on silica gel (20.9 g, relation weight crude product/SiO_2 1:60) employing EtOAc/CH_2Cl_2 15:85 as eluent mixture afforded the title amide **2_{23w}** as a pale yellow solid (264.0 mg, 0.717 mmol, 72%). Due to low solubility in the eluent, the crude material was adsorbed on silica gel (0.82 g, mass ratio crude product/SiO_2 1:2.3). For this purpose, the crude product was dissolved under heating in acetone (ca. 20 mL), because solubility in CH_2Cl_2 and EtOAc, respectively, were too low.

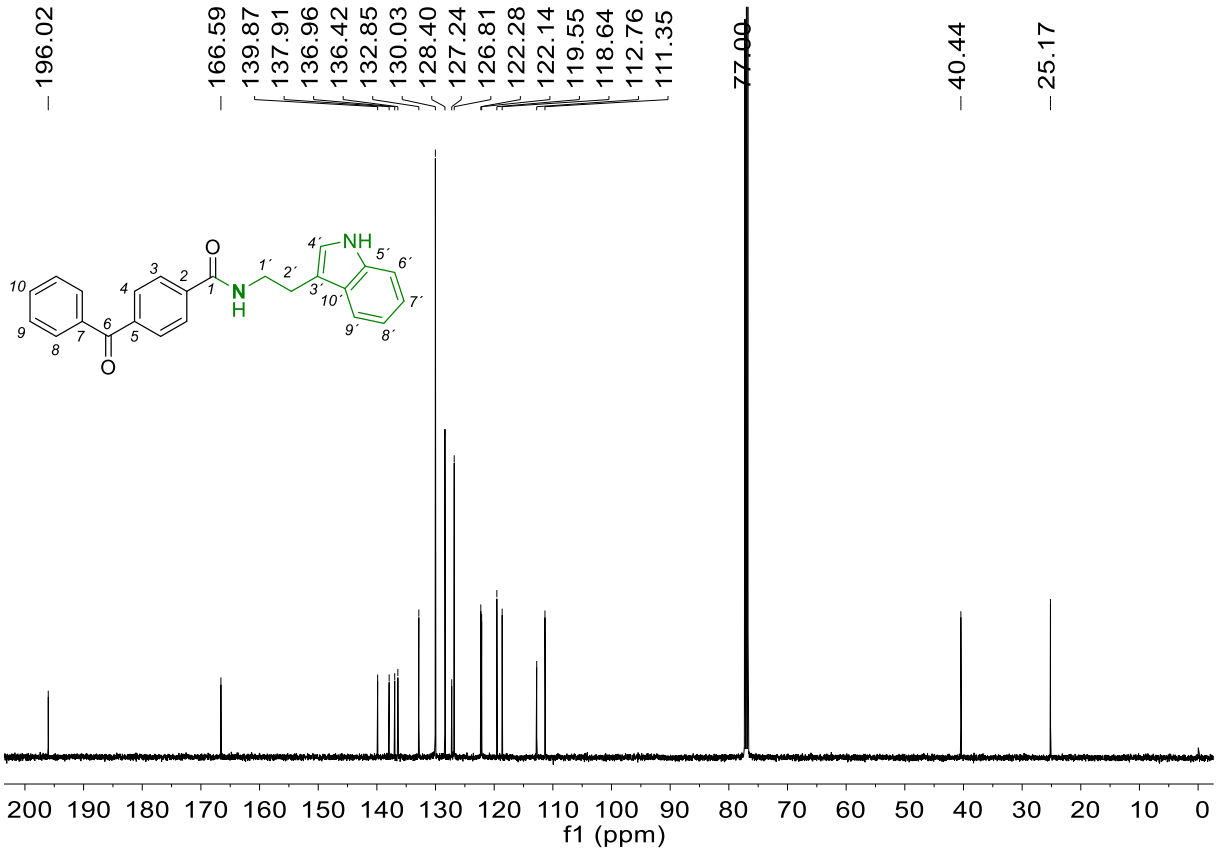
M ($C_{24}H_{20}N_2O_2$) = 368.44 g/mol; **mp.** 151-153 °C; **r_f** (SiO_2, EtOAc/CH_2Cl_2 15:85) = 0.44; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.16 (s, 1H, NH_{indole}), 7.79-7.74 (m, 6H, 3-H, 4-H, 8-H), 7.65 (d, $^3J_{9',8'}$ = 7.9 Hz, 1H, 9´-H), 7.63-7.59 (m, 1H, 10-H), 7.50-7.47 (m, 2H, 9-H), 7.39 (d, $^3J_{6',7'}$ = 8.1 Hz, 1H, 6´-H), 7.24-7.21 (m, 1H, 7´-H), 7.16-7.12 (m, 1H, 8´-H), 7.09 (d, $^3J_{4',NH'}$ = 2.1 Hz, 4´-H), 6.31 (br. t, ^3J = 4.9 Hz, 1H, NH_{amide}), 3.84 (td, $^3J_{1',2'}$ = $^3J_{1',NH}$ = 6.2 Hz, 2H, 1´-H), 3.13 (t, $^3J_{2',1'}$ = 6.6 Hz, 2H, 2´-H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 196.02 (C-6), 166.59 (C-1), 139.87 (C-2 or C-5), 137.91 (C-2 or C-5)**,** 136.96 (C-7)**,** 136.42 (C-5´), 132.85 (C-10), 130.03 (C-8 and C-3 or C-4), 128.40 (C-9), 127.24 (C-10´), 126.81 (C-3 or C-4), 122.28 (C-7´), 122.14 (C-4´), 119.55 (C-8´), 118.64 (C-9´), 112.76 (C-3´), 111.35 (C-6´), 40.44 (C-1´), 25.17 (C-2´); **HR-MS** ($[C_{24}H_{19}N_2O]^+$) calc. 351.1497 u found 351.1468 u.



^{1}H-NMR spectrum of *N*-(2-(indol-3-yl)ethyl) 4-benzoylbenzamide (400 MHz, $CDCl_3$).

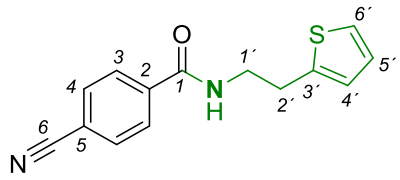


Zoom of ^{1}H-NMR spectrum of *N*-(2-(indol-3-yl)ethyl) 4-benzoylbenzamide (400 MHz, $CDCl_3$).



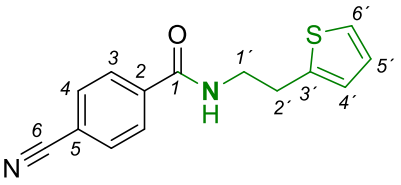
^{13}C-NMR spectrum of *N*-(2-(indol-3-yl)ethyl) 4-benzoylbenzamide (125 MHz, $CDCl_3$).

5.4.2.26 Synthesis of *N*-(2-Thiophen-2-ylethyl) 4-cyanobenzamide (2_{24x})

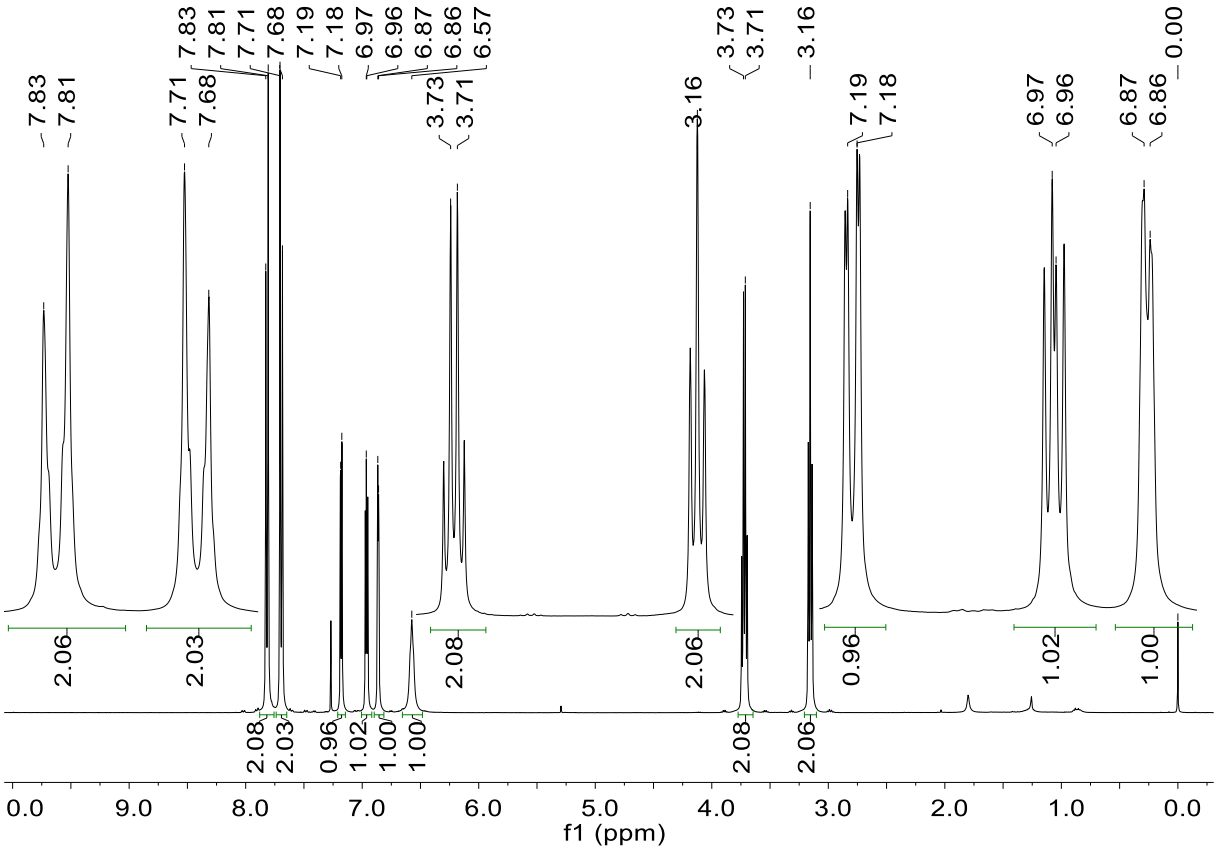


2_{24x}

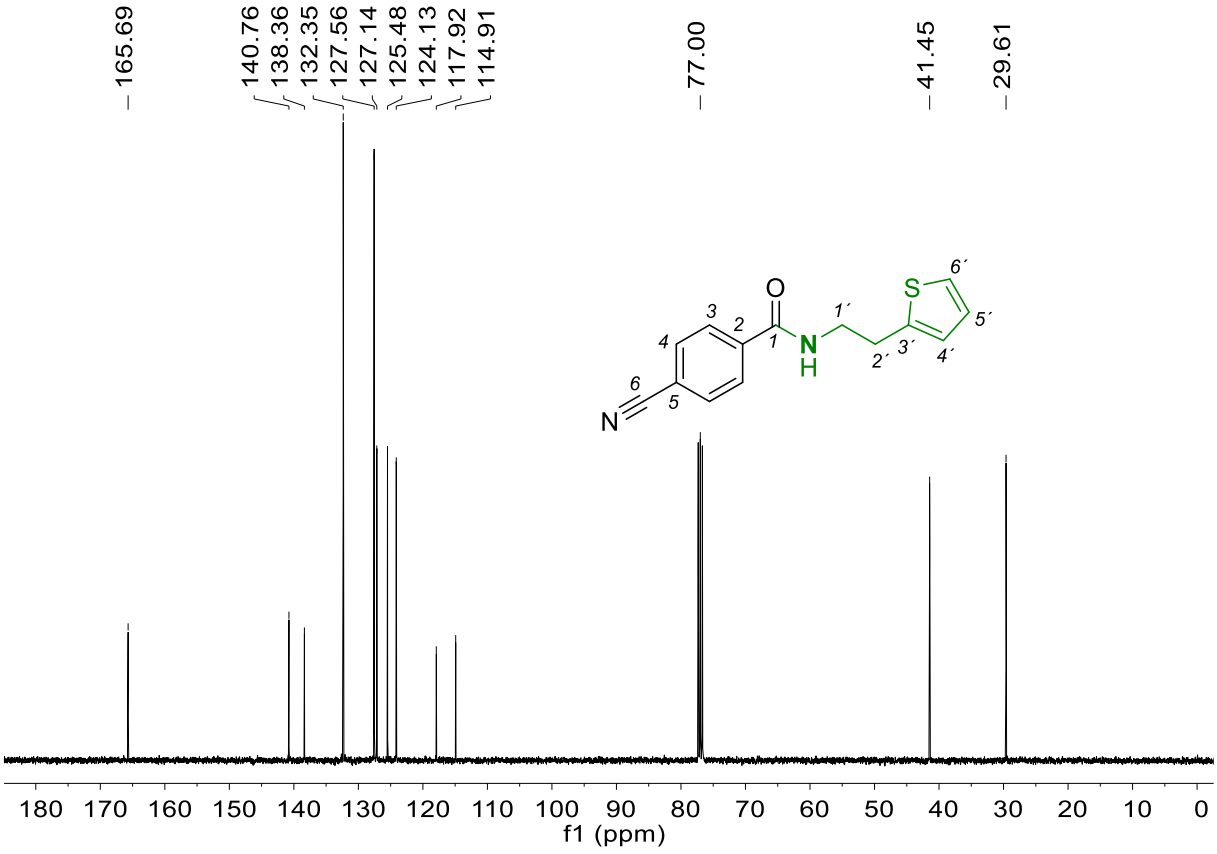
PH3358: As described in general protocol 4 (chapter 5.3.4, page 50) 4-cyanobenzoic acid (147 mg, 1.0 mmol, 1.0 equiv) was heated with TCT (72 mg, 0.38 mmol, 38 mol%) and FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) for 4 h to 80 °C. Next, the reaction suspension was diluted with further MeCN (0.50 mL→1 M), cooled in an ice bath, sequentially 2-(2-aminoethyl)thiophene (130 μL, 1.1 mmol, 1.1 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were added and the reaction suspension was stirred for 4 h at room temperature. At the end, the crude product (brownish solid, 265 mg, 103%) was purified with the aid of column chromatography on silica gel (18.1 g, ratio mass crude material with regard to SiO_2 1:70) using EtOAc/*n*Hex 45:55 as eluent system afforded the title amide as a colourless solid in 88% yield (224.3 mg, 0.875 mmol, 88%). For the purpose to load crude **2_{24x}** onto the silica gel column, it was dissolved in CH_2Cl_2 (ca. 10 mL), SiO_2 was added (0.72 g, ratio weight crude product in respect to silica gel 1:2.7) and the mixture was concentrated under reduced pressure to yield a fine powdered solid.



M ($C_{14}H_{13}N_2OS$) = 256.32 g/mol; **mp.** 111-113 °C; $\mathbf{r_f}$ (SiO_2, EtOAc/PE 45:55) = 0.34; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.83-7.81 (m, 2H, 3-H), 7.71-7.68 (m, 2H, 4-H), 7.19 (dd, $^3J_{6',5'}$ = 5.2 Hz, $^4J_{6',4'}$ = 1.1 Hz, 1H, 6´-H), 6.97 (dd, $^3J_{5',6'}$ = 5.1 Hz, $^3J_{5',4'}$ = 3.4 Hz, 1H, 5´-H), 6.87 (dd, $^3J_{4',5'}$ = 3.4 Hz, $^4J_{4',6'}$ = 0.8 Hz, 1H, 4´-H), 6.57 (t, $^3J_{NH,1'}$ = 5.1 Hz, 1H, NH), 3.73 (td, *J* = 6.4 Hz, 2H, 1´-H), 3.16 (t, $^3J_{2',1'}$= 6.6 Hz, 2H, 2´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 165.69 (C-1), 140.76 (C-3´), 138.36 (C-2), 132.35 (C-4), 127.56 (C-3), 127.14 (C-5´), 125.48 (C-4´), 124.13 (C-6´), 117.92 (C-6), 114.9 (C-5), 41.45 (C-1´), 29.61 (C-2´); **HR-MS** ($[C_{14}H_{11}NO_2{}^{32}S]^+$) calc. 257.0511 u found 257.0519 u.

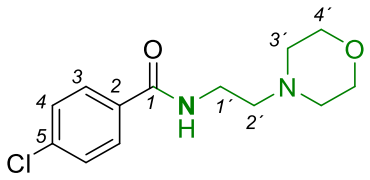


^{1}H-NMR spectrum of *N*-(2-thiophen-2-ylethyl) 4-cyanobenzamide (400 MHz, $CDCl_3$).



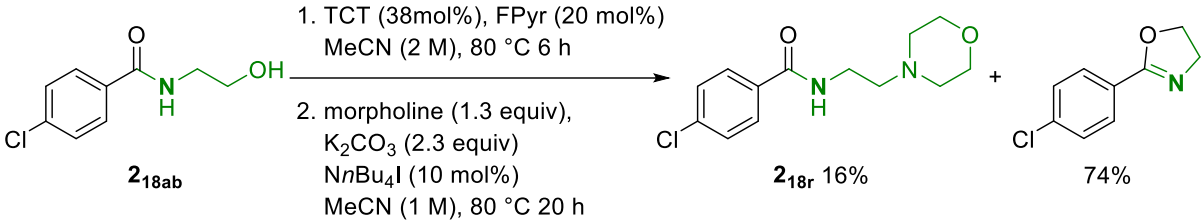
^{13}C-NMR spectrum of *N*-(2-thiophen-2-ylethyl) 4-cyanobenzamide (100 MHz, $CDCl_3$).

5.4.2.27 Synthesis of Moclobemide (2_{18r}) and 2-(4-Chlorophenyl)-1,3-oxazoline



2_{18r}

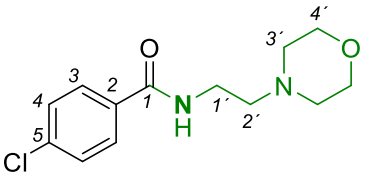
PH3450: As stated in general protocol 4 (chapter 5.3.4, page 50) 4-chloro benzoic acid (313 mg, 2.0 mmol, 1.0 equiv) was transformed into the respective benzoyl chloride derivative with the aid of TCT (144 mg, 0.76 mmol, 38 mol%) and FPyr (19.6 μL, 20.4 mg, 200 μmol, 10 mol%) in MeCN (1.0 mL, 2 M) under heating to 80 °C for 4.5 h. In the following, the colourless reaction suspension was diluted with additional MeCN (1.0 mL→1 M), cooled in an ice bath and *N*-(2-aminoethyl)morpholine (320 μL, 2.4 mmol, 1.2 equiv) and NMM (290 μL, 2.6 mmol, 1.3 equiv) were introduced. After stirring for 4 h at room temperature the reaction mixture turned solid and subsequent aqueous work up without 1 N HCl-washing delivered the crude material as a pale brownish solid (527 mg, 98%). Finally, column chromatographic purification on silica gel (23.3 g, ratio weight crude **2_{18r}**/SiO_2 1:44) with MeOH/EtOAc/NEt_3 5:95:0 (50 mL) → 93:5.2 (300 mL) yielded Moclobemide as a colourless oil (484.4 mg, 1.80 mmol, 90%). Thereby, the silica gel column was prepared with MeOH/EtOAc 5:95, and the crude material was adsorbed on silica gel by dissolution in CH_2Cl_2 (ca. 20 mL), addition of SiO_2 (1.3 g, mass ratio crude **2_{18r}**/silica gel 1:2.5) and concentration under reduced pressure.



The synthesis of compound **2_{18ab}** is described in chapter 5.4.2.32 on page 181.

PH3446: According to our previous protocol for the amination of alcohols via intermediate chlorination in ref. [20] the primary aliphatic alcohol **2_{18ab}** (200 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (19.8 μL, 20.4 mg, 200 μL, 20 mol%) in MeCN (1 mL, 1 M) for 6 h at 80 °C. After cooling down to ambient temperature the reaction suspension was diluted with more MeCN (1 mL→0.5 M), successively K_2CO_3 (320 mg, 2.3 mmol, 2.3 equiv), morpholine (110 μL, 1.2 mmol, 1.2 equiv) were added and the resulting suspension was stirred for 20 h at 80 °C. Aqueous work up following general protocol 4 (chapter 5.3.4, page 50) delivered the crude product as a brownish solid (242 mg). Finally, chromatographic purification on silica gel (20.8 g, ratio weight crude material with regard to SiO_2 1:87) using EtOAc/*n*Hex 40:60 → MeOH/EtOAc/NEt_3 5:93:2 furnished the title compound as a brownish solid in 16% yield (43.3 mg, 0.161 mmol) and a purity of ca. 90% as determined by ^{1}H-NMR and the 2-(4-chlorophenyl)-1,3-oxazoline as a colourless solid (133.4 mg, 0.735 mmol, 74%). In order to load the silica gel column with the

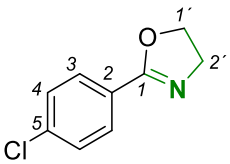
crude material, it was dissolved in CH_2Cl_2 (ca. 10 mL), SiO_2 (0.75 g, mass crude product/SiO_2 1:3.1) was added and the solvent was evaporated *in vacuo*.



Moclobemide

M ($C_{13}H_{17}ClN_2O_2$) = 268.74 g/mol; **mp.** 134-135 °C (lit.-mp. 135-137 °C).[41] $\mathbf{r_f}$ (SiO_2, MeOH/EtOAc 10:90) = 0.26; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 7.73-7.70 (m, 2H, 3-H), 7.42-7.39 (m, 2H, 4-H), 6.84 (s, 1H, NH) 3.73 (m, *J* = 4.7 Hz, 4H, 4´-H), 3.55-3.52 (m, 2H, 1´-H), 2.60 (t, ^3J = 6.0 Hz, 2H, 2´-H), 2.50 (t, *J* = 4.2 Hz, 4H, 3´-H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 166.24 (C-1), 137.51 (C-5), 132.89 (C-2), 128.71 (C-4), 128.27 (C-3), 66.90 (C-4´), 56.74 (C-2´), 53.24 (C-3´), 36.04 (C-1´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 271 (5, $[M(^{35}Cl)]^+$), 269 (14, $[M(^{35}Cl)]^+$), 212 (1), 210 (3,), 184 (4, $[M(^{37}Cl)\text{-}N(CH_2CH_2)_2O]^+$), 182 (12, $[M(^{35}Cl)\text{-}N(CH_2CH_2)_2O]^+$), 157 (3), 141 (3, $[4\text{-}^{37}Cl(C_6H_4)CO]^+$), 139 (8, $[4\text{-}^{35}Cl(C_6H_4)CO]^+$), 114 (11), 113 (13, $[O(CH_2CH_2)_2NCHCH_2]^+$), 100 (100, $[O(CH_2CH_2)_2NCH_2]^+$), 70 (4).

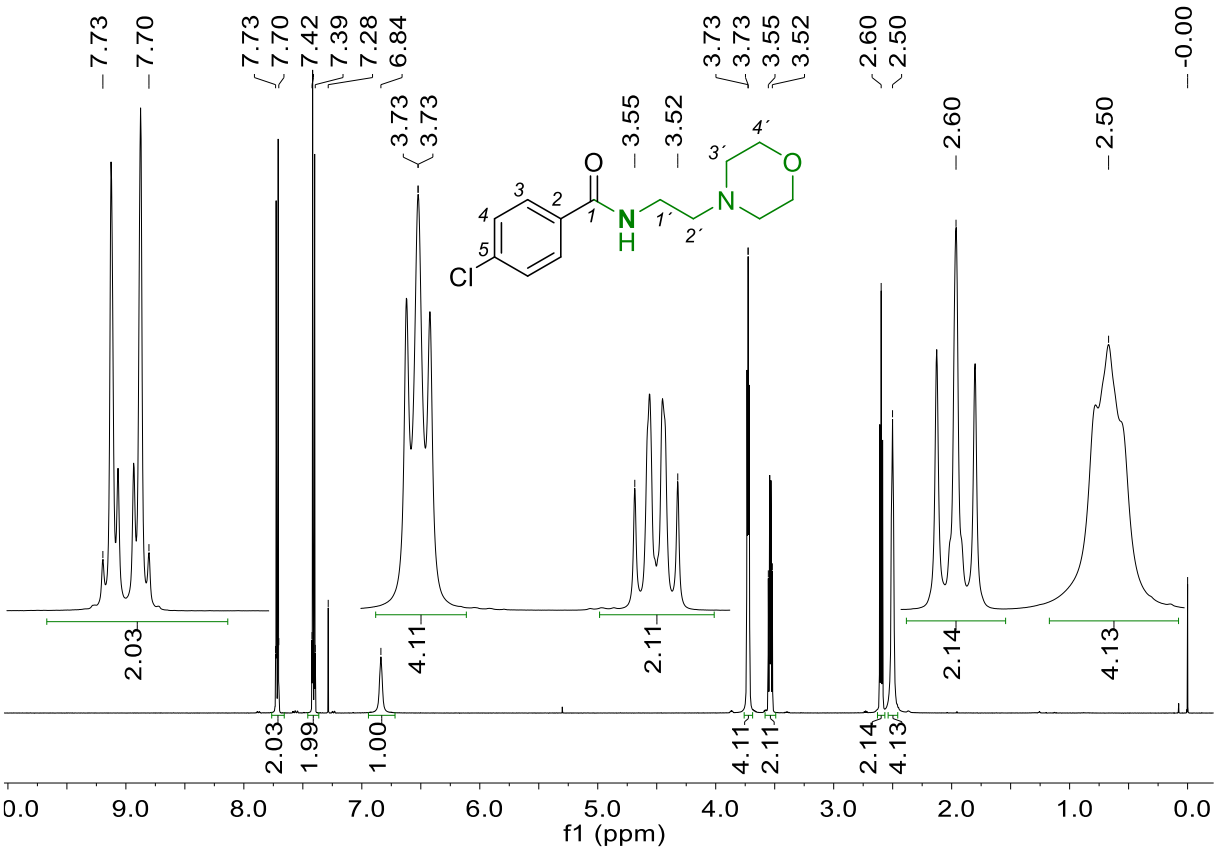
The NMR data is in agreement with reported data.[41]



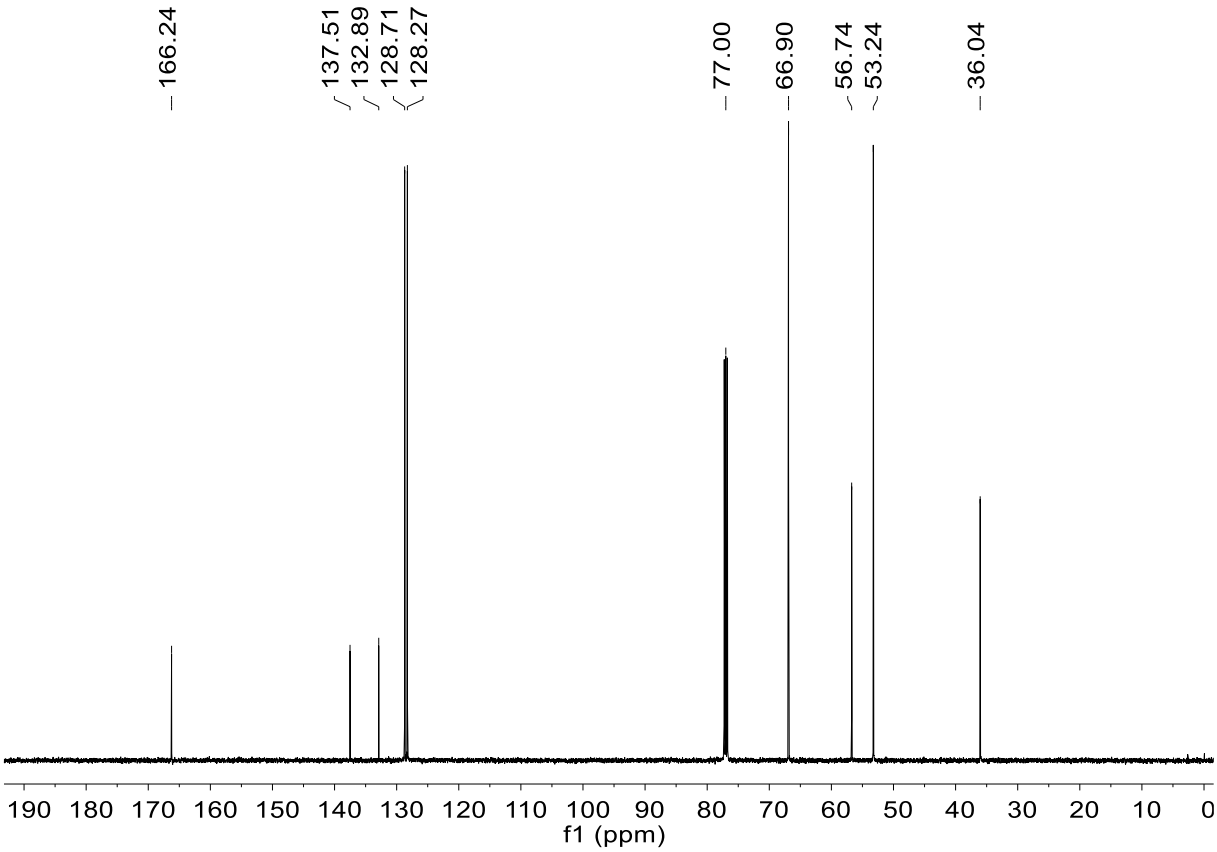
2-(4-chlorophenyl)-1,3-oxazoline

M (C_9H_8ClNO) = 181.62 g/mol; **mp.** 77-78 °C (lit-mp. 77-78 °C); $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 40:60) = 0.33; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 7.89-7.86 (m, 2H, 3-H), 7.39-7.37 (m, 2H, 4-H), 4.43 (t, ^3J = 9.6 Hz, 2H, 1´-H), 4.05 (t, ^3J = 9.5 Hz, 2H, 2´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 163.69 (C-1), 137.36 (C-5), 129.44 (C-3), 128.56 (C-4), 126.19 (C-2), 67.70 (C-1´), 54.93 (C-2´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 224 (1, $[M(^{37}Cl)+allyl]^+$), 222 (2, $[M(^{35}Cl)+allyl]^+$), 212 (13, $[M(^{37}Cl)+Et]^+$), 210 (38, $[M(^{35}Cl)+Et]^+$), 184 (34, $[M(^{37}Cl)+H]^+$), 183 (30, $[M(^{37}Cl)]^+$), 182 (100, $[M(^{35}Cl)+H]^+$), 181 (52, $[M(^{35}Cl)]^+$), 169 (1), 167 (3), 153 (11), 151 (32), 141 (4, $[4\text{-}^{37}Cl(C_6H_4)CO]$), 139 (12, $[4\text{-}^{35}Cl(C_6H_4)CO]$), 127 (2), 125 (5), 113 (1, $[^{37}ClPh]^+$), 111 (3, $[^{35}ClPh]^+$), 91 (3, $[Bn]^+$), 75 (4).

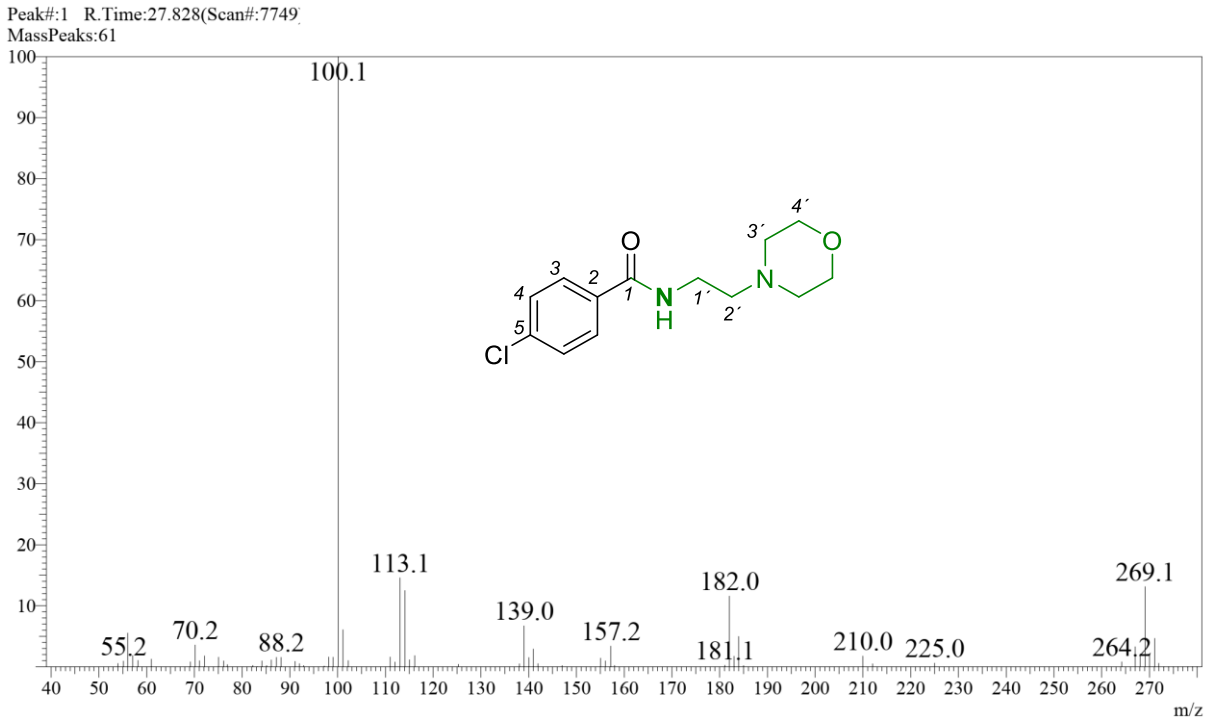
The ^{1}H-NMR data is matching reported data.[42]



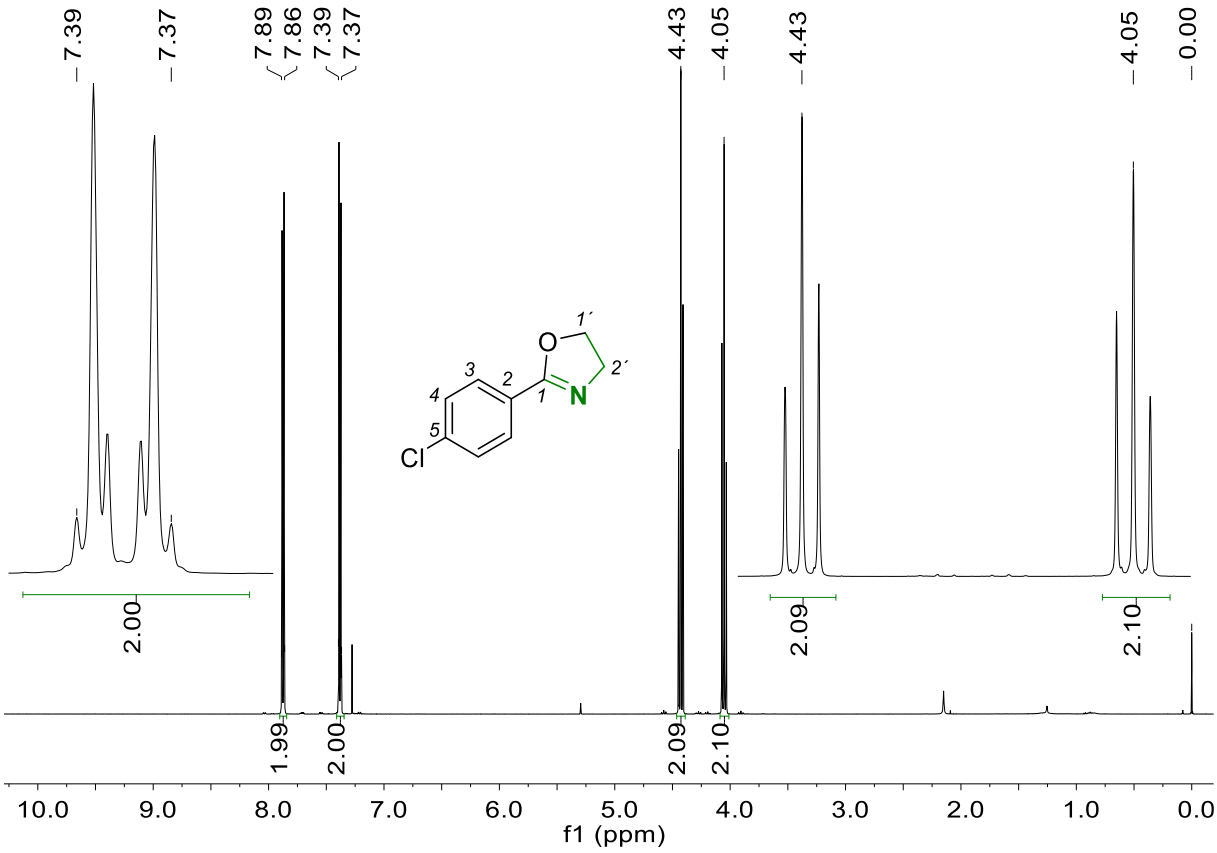
^{1}H-NMR spectrum of Moclobemide (500 MHz, $CDCl_3$).



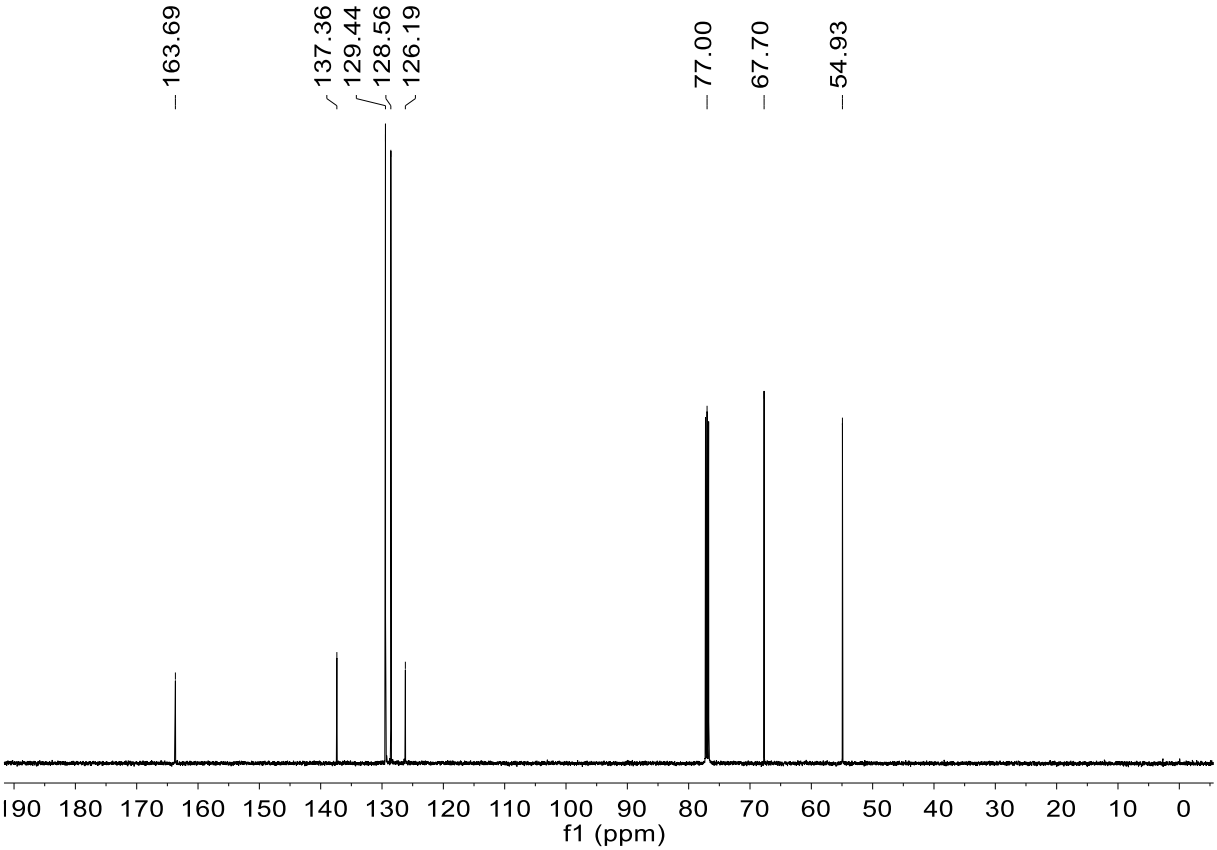
^{13}C-NMR spectrum of Moclobemide (125 MHz, $CDCl_3$).



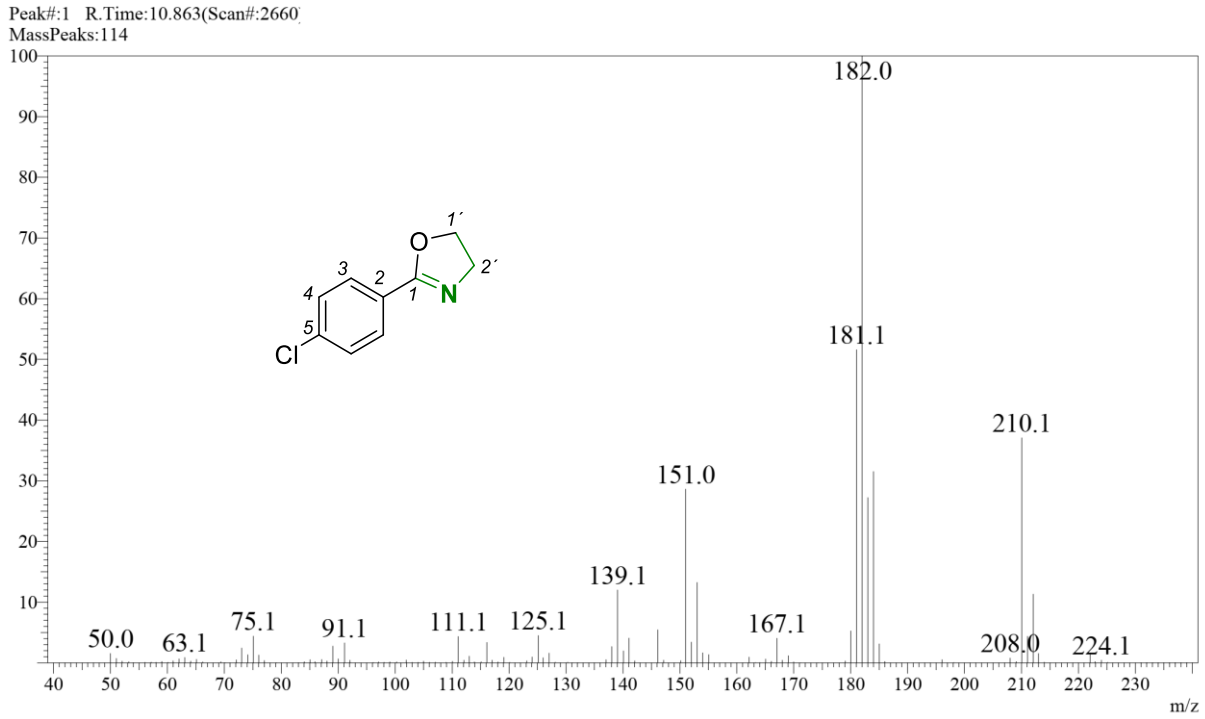
Mass spectrum of Moclobemide (CI, 70 eV).



^{1}H-NMR spectrum of 2-(4-chlorophenyl)-1,3-oxazoline (500 MHz, $CDCl_3$).

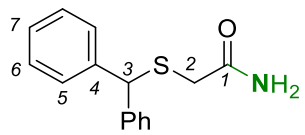


^{13}C-NMR spectrum of 2-(4-chlorophenyl)-1,3-oxazoline (125 MHz, $CDCl_3$).



Mass spectrum of 2-(4-chlorophenyl)-1,3-oxazoline (CI, 70 eV).

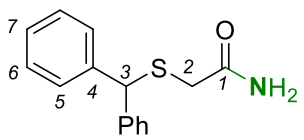
5.4.2.28 Synthesis of 2-(Diphenylmethylthio) acetamide (2_{19m})



2_{19m}

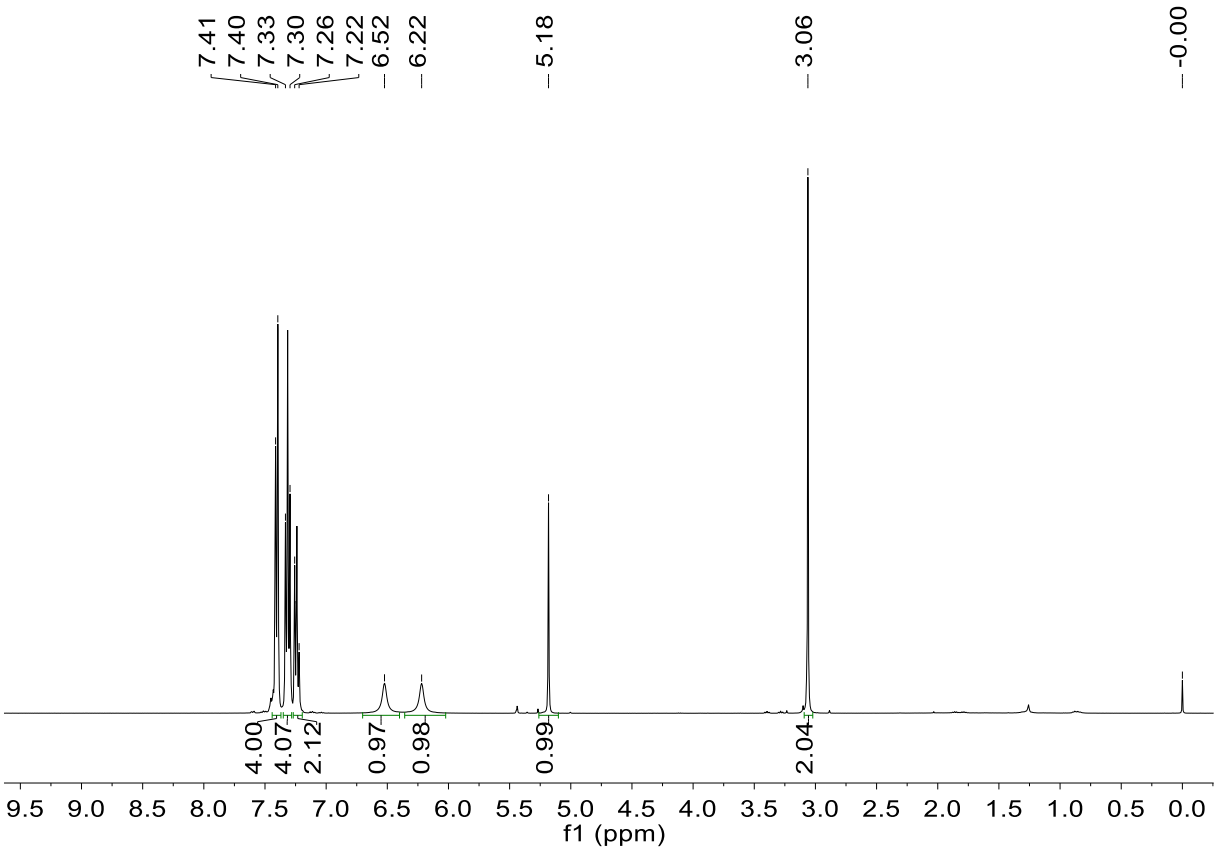
PH3407: Following general protocol 4 (chapter 5.3.4, page 50) (diphenylmethylthio) ethanoic acid (517 mg, 2.00 mmol, 1.0 equiv) was reacted with TCT (144 mg, 0.76 mmol, 38 mol%) in the presence of FPyr (19.6 μL, 20.4 mg, 0.20 mmol, 10 mol%) in MeCN (1.0 mL, 1 M) under heating to 40 °C for 4 h. Afterwards MeCN (1.0 mL→1 M) and under cooling to 0 °C 32 wt% NH_3 solution in water (290 μL, 2.3 mmol, 2.3 equiv) were added and the reaction mixture was stirred for 5 h at room temperature. An aqueous work without HCl-washing allowed to isolate the crude title compound as a yellow solid (506 mg, 98%). Subsequently, column chromatographic purification on silica gel (40.4 g, mass ratio crude **2_{19m}**/SiO_2 1:80) utilizing EtOAc/*n*Hex 75:25 gave rise to the primary amide **2_{19m}** as a colourless solid (435.2 mg, 1.69 mmol, 85%). Due to low solubility in the eluent mixture, the crude material had to be dissolved in EtOAc (20 mL) under heating, silica gel was introduced (0.99 g, mass relation crude product/$SiO_2$1:2) and the solvent was removed *in vacuo*.

PH3379: In alignment to general procedure 4 (chapter 5.3.4, page 50) to a mixture of (diphenylmethylthio) ethanoic acid (2.00 mmol, 1.0 equiv) and FPyr (10 mol%) in MeCN (2 M) was added TCT (38 mol%) and the resulting suspension was stirred for 5 h at 40 °C. Thereafter, the yellow reaction suspension was treated with further MeCN (→1 M), cooled to 0 °C and 32 wt% aqueous NH_3 solution (180 μL, 3.0 mmol, 1.5 equiv) and **K_2CO_3** (360 mg, 2.6 mmol, 1.3 equiv) were added. Past stirring at room temperature over-night (11 h), aqueous work up furnished the crude amide **2_{19m}** as a yellow solid (517 mg, 100%). In the end, column chromatographic purification on silica gel (23.2 g, weight crude material in respect to SiO_2 1:45) employing EtOAc/*n*Hex 80:20 as eluent delivered the amide **2_{19m}** as a pale yellow solid in 77% yield (396.5 mg, 1.54 mmol). In order to charge the silica gel column, the crude material was adsorbed on silica gel (1.25 g, mass relation **2_{19m}**/SiO_2 1:2.4).

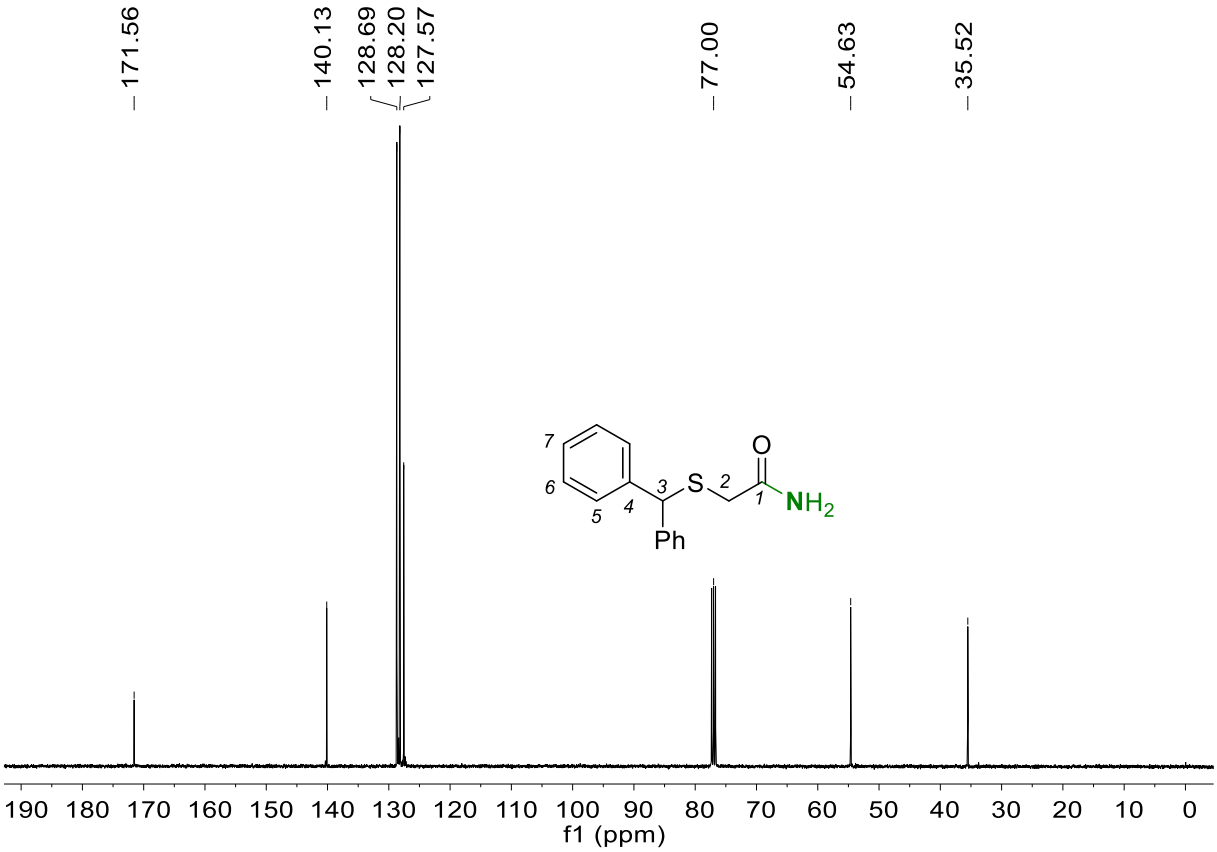


M ($C_{15}H_{15}NOS$) = 257.35 g/mol; **mp.** 105-107 °C (lit.-mp. 108-110 °C);[43] **r_f** (SiO_2, EtOAc/*n*Hex 75:25) = 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.41-7.40 (m, 4H, 5-H), 7.33-7.30 (m, 4H, 6-H), 7.26-7.22 (m, 2H, 7-H), 6.52 (s, 1H, NH), 6.22 (s, 1H, NH), 5.18 (s, 1H, 3-H), 3.06 (s, 2H, 2-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 171.56 (C-1), 140.13 (C-4), 128.69 (C-6), 128.20 (C-5), 127.57 (C-7), 54.63 (C-3), 35.52 (C-2).

The NMR data is in agreement with the literature.[43]



^{1}H-NMR spectrum of 2-(diphenylmethylthio) acetamide (400 MHz, $CDCl_3$).

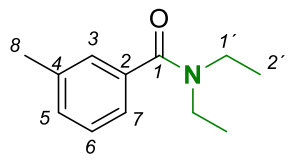


^{13}C-NMR spectrum of 2-(diphenylmethylthio) acetamide (100 MHz, $CDCl_3$).

5.4.2.29 Synthesis of *N,N*-Diethyl 3-methylbenzamide (2_{3y}, DEET)

entry	conditions	yield [%] 2_{3y}	CA
1	1. TCT (40 mol%), FPyr (10 mol%), EtOAc (1.7 M), 4 h 80 °C 2. $HNEt_2$ (1.1 equiv), NMM (1.1 equiv), 2.5 n 0 °C then 0.75 h rt	92[a] (**87 g**)	78[a]
2	1. TCT (40 mol%), FPyr (10 mol%), EtOAc (2 M), 4 h 80 °C 2. $HNEt_2$ (1.2 equiv), NMM (1.2 equiv), 1 h 0 °C then 2 h rt	89[a] (**17 g**)	61[a]
3	1. TCT (40 mol%), FPyr (10 mol%), **MeCN** (2 M), 3.5 h 80 °C 2. $HNEt_2$ (1.2 equiv), **K_2CO_3** (1.2 equiv), **MeCN** (1 M) 0.5 h 0 °C then 18 h rt	86[a] (**16 g**)	56[a]
4	1. TCT (40 mol%), FPyr (10 mol%), MeCN (2 M), 3 h 80 °C 2. **K_2CO_3** (1.2 equiv), $HNEt_2$ (1.1 equiv), MeCN (1 M) 0.5 h 0 °C then 22 h rt	84[a] (**16 g**)	n.d.
5	1. TCT (40 mol%), FPyr (10 mol%), **reused EtOAc from entry 1** (1.7 M), 4 h 80 °C 2. $HNEt_2$ (1.2 equiv), NMM (1.3 equiv), EtOAc (1 M) 0.25 n 0 °C then 2 h rt	32[b]	n.d.
6	1. TCT (40 mol%), FPyr (10 mol%), **reused MeCN from entry 3** (2 M), 4 h 80 °C 2. $HNEt_2$ (1.2 equiv), NMM (1.3 equiv), MeCN (1 M) 0.25 h 0 °C then 2 h rt	90[b]	n.d.
7	1. TCT (40 mol%), FPyr (10 mol%), **dry MeCN** (2 M), 4 h 80 °C 2. $HNEt_2$ (1.2 equiv), NMM (1.3 equiv), MeCN (1 M) 0.25 h 0 °C then 3 h rt	94[b]	n.d.
8[22]	1. TCT (33 mol%), NMM (1.3 equiv), MeCN (1 M), 15 min 0° C then **1 h rt** 2. $HNEt_2$ (1.2 equiv), 15 min 0° C then 21 h rt	50[b]	n.d.

a. Yield determined from mass of isolated material after distillation and precipitation, respectively. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of dibenzylether as internal standard. n.d. = not determined



2_{3y}

The title compound was synthesized in EtOAc on a 500 mmol scale, whereby cyanuric acid was isolated in 78% yield (entry 1). Thereby, an initial distillation furnished amide **2_{3y}** in 88%, whereas chromatographic purification of a prefraction furnished DEET (**2_{3y}**) in 4% yield. For this experiment an E-factor of 3.3 was determined under consideration of isolated **2_{3y}** after distillation and cyanuric acid and reisolated EtOAc. While reaction on a 500 mmol scale requested for mechanic stirring, magnetic stirring was sufficient on a 100 mmol scale (entry 2). Utilization of K_2CO_3 as base instead of NMM allowed for the production of amide **2_{3y}** in 84-86% yield (entries 3+4). However, full conversion of the intermediate acid chloride **6_3** required prolonged stirring overnight. Indeed, after $HNEt_3$ addition approximately 70% conversion of **6_3** are accomplished. Due to the increased reaction duration some hydrolysis to give the starting material 3-methylbenzoic acid (**1_3**) was observed, which explains the slightly decreased yield in comparison to the experiments using NMM. Noteworthy, under mechanical stirring on a 500 mmol scale even stirring overnight did not allowed full consumption of 3-methylbenzoic acid.

In a small scale experiment EtOAc, which had been reisolated form the experiment in entry 1, was reapplied (entry 5). Albeit a purity of ≥98% had been attested by ^{1}H-NMR, the title amide was obtained in a strongly depleted yield of 32%. Usage of reisolated MeCN from the

experiment in entry 3 allowed for the synthesis of **2$_{3y}$** in 90% yield (entry 6), which matched the reaction outcome employing dry MeCN (entry 7). Importantly, the literature protocol of Rayle[22] gave rise to amide **2$_{3y}$** in only 50% yield.

Entry 1, PH3532: In accordance with general procedure 4 (chapter 5.3.4, page 50) a 1 L three-necked round bottom flask was charged with 3-methylbenzoic acid (**1$_3$**, 68.08 g, 500 mmol, 1.0 equiv), FPyr (4.9 mL, 5.11 g, 50 mmol, 10 mol%) and reagent grade EtOAc (300 mL, 1.7 M), the reaction apparatus was equipped with a mechanical overhead stirrer,(50) reflux condenser and PE stopper, placed in an oil bath and stirred for 10 min at ambient temperature to result in an almost clear solution (level of stirring speed 3 out of 10). Next, TCT (37.65 g, 200 mmol, 40 mol%) was added as a single portion and the reaction apparatus was heated to 80 °C within 30 min.(51) The reaction mixture was heated to 80 °C for 2 h, whereby a precipitate occurred after 5 min and no reflux could be observed. Micro-work up and ^{1}H-NMR after 2 h implied a conversion of 80%, whereas after 4 h a consumption of **1$_3$** was accomplished of ≥92%.(52,53) The oil bath was removed, the reaction suspension was stirred for 30 min at ambient temperature and 15 min at 0 °C. In the following, the reflux condenser was replaced with a dropping funnel and a mixture of diethylamine (57 mL, 550 mmol, 1.1 equiv) and NMM (61 mL, 550 mmol, 1.1 equiv) was added over the course of 2 h via the funnel.(54) Past 15 min of further stirring the oil bath was removed and the yellow reaction suspension was stirred for 1 h at room temperature.

The **work up** was commenced with the addition of a 2 N HCl solution in water (200 mL) at room temperature and stirring for 5 min to allow dissolution of NMM and $HNEt_2$ derived ammonium salts. Subsequently, the heterogeneous mixture was filtered over a sintered funnel (porosity level 3, diameter 6 cm) by suction, which required approximately 5 min. The reaction flask was rinsed with further EtOAc (50 mL), which was also used to triturated the filter cake

(50) In an prior experiment on the same scale magnetic stirring with a strong stir bar failed in the amidation step **6$_3$**→**2$_{3y}$**.

(51) Upon addition, TCT dissolver completely. After 10 min at an oil bath temperature of 65 °C the reaction mixture became a clear solution.

(52) Since the observed multiplets in the ^{1}H-NMR spectrum in $CDCl_3$ are close to each other (s at 2.42 ppm of **1$_3$** and at 2.44 ppm of **6$_3$**), the accuracy of the determination of the conversion is relatively low. In addition, 3-methylbenzoic anhydride might show a s at 2.42 ppm, too.

(53) In order to extract the first sample after 2 h, stirring was paused. Before this interruption, cyanuric acid formed a fine precipitate. Afterwards, it precipitated in bigger pieces and partially sticked to the glass wall. Although in the described experiment this did not hamper stirring, a continuous stirring is required to prevent aggregation of cyanuric acid. The utilization of MeCN as solvent allowed for a more homogenous precipitation of cyanuric acid.

(54) Initial, addition of $HNEt_2$ caused an increased viscosity, which afforded higher solvent amounts to maintain stir-ability.

thoroughly with a spatula. The collected filtrates were poured into a 1 L extraction funnel and the reaction flask/filter cake was rinsed/triturated with further EtOAc (50 mL). The phases were separated (pH aqueous phase = 2), the organic phase was washed successively with aqueous 1 N NaOH solution (1 x 200 mL), whereby the phase separation necessitated 15 min, and brine (1 x 200 mL) and dried over $MgSO_4$ for 5 min under stirring (600 rpm). After filtration over a plug of wool, the remaining $MgSO_4$ was rinsed with EtOAc (2 x 20 mL), the collected filtrates were concentrated *in vacuo*, whereby the pressure was stepwise decreased from 200 to 100 mbar, and the residue was dried at the rotary evaporator for 10 min at 20 mbar, which afforded the crude title compound as an orange oil (95.59 g, 100%). Thereby, EtOAc was reisolated in 86% yield (380 mL) and a purity ≥98% as judged by ^{1}H-NMR. In order to avoid boiling retardation, the crude material was collected in a 1 L one-necked round bottom flask.

Eventually, **purification by means of distillation** at 0.072 mbar and a stirring level of 800 rpm initially delivered a prefraction with boiling range of 92-95 °C (717 mg, colourless oil), which consisted of the title amide in a purity of ca. 90% as determined by ^{1}H-NMR. In the following, the amide **2$_{3y}$** was isolated as a colourless liquid with a bp. of 95-98 °C in 88% yield (83.88 g, 439 mmol), of which ^{1}H-NMR and GC-MS attested a purity of ≥98%. To secure a constant distillation process, the oil bath temperature was increased from 125 to 125 °C. A further stepwise elevation of the oil bath temperature from 145 to 180 °C delivered a third fraction with a boiling range of 99-121 °C (3.16 g, colourless liquid) in a purity of approximately 90% (^{1}H-NMR).

In order to enhance the yield, the two smaller distillation fractions (combined mass 3.88 g) were subjected to a **column chromatographic purification** on silica gel (130 g, mass ratio crude title compound/SiO_2 1:34) using EtOAc/PE 35:65→40:60 as eluent mixture. Concentration with CH_2Cl_2 and drying at the rotary evaporator at 5 mbar for 10 min furnished amide **2$_{3y}$** in 4% yield as a colourless oil (3.427 g, 17.9 mmol). Thereby, the material was dissolved in the EtOAc/PE 35:65 (3 mL) and loaded onto the silica gel column.

Finally, the filter cake separated during the work up (see above) processed further as follows to obtain **cyanuric acid**. Drying at the rotary evaporator for 2 h at 5 mbar furnished a pale yellow solid (22.48 g, 87%), which was dissolved in a minimum amount of 2 N NaOH solution in water (220 mL, 440 mmol). The resulting yellow solution was cooled in an ice bath and aqueous 37 wt% HCl solution (40 mL, 490 mmol) was added by means of a dropping funnel in 20 min under vigorous stirring (800 rpm). The precipitated solid was collected by filtration over a sintered funnel by suction (porosity level 3, diameter 6 cm, pH of filtrate 2), the filter cake was triturated with water (1 x 40 mL) and acetone (2 x 40 mL) and dried at the rotary evaporator for 2 h at 5 mbar to yield cyanuric acid as a colourless solid (20.04 g, 155 mmol, 78%) in purity of ≥98% as shown by ^{1}H- and ^{13}C-NMR spectrum in DMSO-d^6.

Under consideration of isolated amide **2_{3y}** after distillation in 88% yield, isolated cyanuric acid and all chemicals used in the reaction solely an E-factor for 3.5 was determined:

$$E-factor$$
$$= \frac{m(\mathbf{1}) + m(FPyr) + m(EtOAc) + m(TCT) + m(HNEt_2) + m(NMM) - m(\mathbf{1}) - m(\boldsymbol{CA})}{m(\mathbf{1}) + m(\boldsymbol{CA})}$$
$$= \frac{68.1\ g + 5.1\ g + 271\ g + 37.7\ g + 40.3\ g + 56.1\ g - 83.9\ g - 20.0\ g}{83.9\ g + 20.0\ g} = \frac{374.4\ g}{103.9\ g} = \mathbf{3.5}$$

Taking all chemicals with the exception of the chromatographic purification and reisolated EtOAc into account the E-factor is even improved to 3.3:

$$E-factor$$
$$= \frac{m(\mathbf{1}) + m(FPyr) + m(EtOAc) + m(TCT) + m(HNEt_2) + m(NMM) + m(EtOAc) - m(\mathbf{2_{3y}}) - m(\boldsymbol{CA})}{m(\mathbf{1}) + m(\boldsymbol{CA})}$$
$$+ \frac{m(EtOAc, work\ up) + m(HCl) + m(NaOH) + m(NaCl) + m(acetone) - m(EtOAc, reisolated)}{m(\mathbf{1}) + m(\boldsymbol{CA})}$$
$$= 3.5 + \frac{128.8\ g + (14.6\ g + 14.8\ g) + (8.0\ g + 17.6\ g) + 71.8\ g + 63.3\ g - 342.8\ g}{83.9\ g + 20.0\ g}$$
$$= 3.5 + \frac{-23.9}{103.9\ g} = 3.3$$

A summary of all chemicals used and isolated can be found in the following table:

component	M [g/mol]	density [g/mL]	V [mL]	m (g)
1_3	136.2	/	/	68.08
FPyr	99.1	1.04	4.9	5.1
EtOAc (reaction)	88.1	0.902	300	271
TCT	184.41	/	/	37.65 g
$HNEt_2$	73.13	0.707	57	40.3
NMM	101.15	0.92	61	56.1
EtOAc (work up)	88.1	0.902	140	128.8
2 M HCl (aq.)	36.46	/	200	14.6
1 M NaOH (aq.)	40.0	/	200	8.0
brine	58.44	/	200	71.8
2 M NaOH (aq.)	40.0	/	220	17.6
acetone	58.08	0.791	80	63.3
HCl (37 wt%, aq.)	36.46	1.2	40	14.8
EtOAc (reisolated)	88.1	0.902	380	342.8

2_{3y}	191.3	/	/	20.04
CA	129.1	/	/	83.88

Entry 2, PH3465: In a related preparation of the title compound on a 100 mmol scale as described in general procedure 4 (chapter 5.3.4, page 50), magnetical stirring was feasible. In the beginning, a 250 mL one-necked round bottom flask with a **strong stir bar** was loaded with acid **1_3** (13.62 g, 100 mmol, 1.0 equiv), FPyr (980 μL, 1.02 g, 10 mmol, 10 mol%) and reagent-grade EtOAc (50 mL, 2 M). Next, TCT was introduced in one portion (7.51 g, 40 mmol, 40 mol%) at a stirring speed of 400 rpm and the reaction mixture was heated to 80 °C for 4 h, whereupon micro work up and ^{1}H-NMR verified a conversion of ≥97%). Subsequently, the oil bath was removed, the reaction suspension was allowed to stir at ambient temperature for 45 min and at 0 °C for 5 min. Then, a mixture of $HNEt_2$ (12.4 mL, 120 mmol, 1.2 equiv) and NMM (13.5 mL, 120 mmol, 1.2 equiv) was added within 50 min with the aid of a dropping funnel at 0 °C and under vigorous stirring (600 rpm). After 15 min the cooling bath was removed and the yellow reaction suspension was stirred for 2 h at room temperature.

Thereafter, aqueous 2 N HCl solution (50 mL) was introduced and stirring was continued for 15 min. The resulting suspension was filtered through a sintered funnel (porosity level 3, diameter 6 cm) by suction and the reaction flask/filter cake was rinsed/triturated with a spatula with further EtOAc (2 x 30 mL). The combined filtrates were transferred to a 250 mL extraction funnel, in which the phases were separated. The EtOAc-phases was washed successively with 1 N NaOH solution in water (1 x 50 mL) and brine (1 x 50 mL), dried over $MgSO_4$, $MgSO_4$ was rinsed with EtOAc (2 x 10 mL), the combined filtrates were concentrated *in vacuo* and dried at the rotary evaporator for 10 in at 20 mbar to afforded the crude product as a yellow oil (18.39 g, 96%). The evaporation fo the solvent facilitated the isolation of EtOAc in a yield of 92% (120 mL).

In the end, distillation at 0.019 mbar under vigorous stirring (800 rpm) furnished the title compound as a colourless liquid (16.97 g, 88.7 mmol, 89%) with a boiling point of 90-92 °C. In order to purity cyanuric acid, the filter cake obtained during the aqueous work up was dried at the rotary evaporator at 5 mbar for 30 min. The resulting pale yellow solid (4.11 g, 80%), of which ^{13}C-NMR in DMSO-d^6 confirmed cyanuric acid as main component, was dissolved in 2 N NaOH solution in water (40 mL, 80 mmol), the obtained clear solution was cooled in an ice bath and an aqueous 6 N HCl solution (16 mL, 96 mmol) was added by means of a dropping funnel over 15 min. The solid precipated formed was susbequently collected by filtration over a sintered funnnel by suction (porosity level 3, diameter 6 cm), washed with water (1 x 10 mL) and acetone (2 x 10 mL) under intensive trituration with a spatula and dried at the rotary evaporator for 60 min. Finally, cyanuric acid was isolated as a colourless fine-powdered solid in 61% yield (3.14 g, 24.3 mmol).

Entry 3, PH3470: In compliance with general procedure 4 (chapter 5.3.4, page 50) TCT (40 mol%) was allowed to react with substrate **1_3** (100 mmol, 1.0 equiv) in the presence of FPyr (10 mol%) in **reagent-grade MeCN** (50 mL, 2 M) at 80 °C for 3.5 h. After cooling down to ambient temperature further reagent-grade MeCN was added (50 mL), the resulting suspension was cooled in an ice bath and $HNEt_2$ (1.2 equiv) was added within 30 min through a dropping funnel under rmagnetical stirring (600 rpm). Next, fine-powdered **K_2CO_3** (16.59 g, 120 mmol, 1.2 equiv) was added in one portion, whereby a very weak gas evolution could be observed, and the cooling bath was removed after 15 min of stirring. Since after 2 h of stirring at room temperature, micro work up and ^{1}H-NMR indicated 72% conversion of intermediate **6_3** the reaction mixture was allowed to stir overnight (18 h). Thereupon, repeated reaction control verified full consumption of **6_3** under partial hydrolysis (**2_{3y}/1_3** 92:8).

In order to enable an enhanced phase separation during the subsequent aqueous work up, the reaction suspension was concentrated under reduced pressure, which afforded MeCN in 85% yield (85 mL) and a purity of ≥98% as judged by ^{1}H-NMR. After drying at the rotary evaporator at 20 mbar for 10 min, the residue was up taken with MTBE (100 mL) and aqueous 1 N NaOH solution (60 mL), the mixture was poured into a 250 mL extraction funnel and the reaction flask was rinsed with further MTBE and 1 N NaOH solution (2 x 15 mL/10 mL). Further 1 N NaOH solution was added (30 mL) in order to dissolve the remaining solid entirely. Next, the phases were separated, the organic phase was washed with 2 N HCl solution in water (1 x 50 mL) and brine (1 x 50 mL) and dried over $MgSO_4$. Rinsing of $MgSO_4$ by means of MTBE (2 x 15 mL), concentration of the collected filtrates and drying at the rotary evaporator at 20 mbar for 10 min eventually furnished the crude title compound as a yellow oil (17.54 g, 92%). The evaporation process thereby facilitated the reisolation of MTBE in 81% yield (130 mL) and a purity of ≥98% without a trace of MeCN being visible as proven by ^{1}H-NMR.

Lastly, distillation at 0.031 mbar afforded DEET with a boiling point ot 92-94 °C as a colourless liquid in 86% yield (16.45 g, 86.0 mmol, 86%). The basic NaOH-phase separated during work up (110 mmol NaOH) was cooled in an ice bath and under vigorous stirring (800 rpm) and a 37 wt% solution of HCl in water (24 mL, 295 mmol) was added by means of dropping funnel over the course of 15 min. The generated solid precipiate was collected through filtration over a sintered funnel by suction (porosity level 3, diameter 6 cm), washed with water (1 x 20 mL) and acetone (1 x 20 mL) and dried at the rotary evaporator at 5 mbar for 60 min, which gave cyanuric acid as colourless, solid fine powder in 56% yield (2.91 g, 22.5 mmol).

Entry 4, PH3477: The current experiment was performed as stated in entry 4 with the following deviations: (1) 70 mL of MeCN (1.4 M) was used from the beginning; (2) K_2CO_3 (1.2 equiv) was added to the reaction mixture before NMM (11.4 mL, 110 mmol, 1.1 equiv) and (3) the reaction mixture was stirred for 22 h at room temperature after addition of K_2CO_3 and NMM.

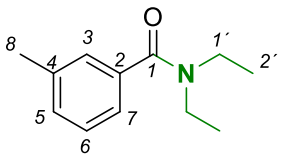
Monitoring of the reaction progress of the transformation of **6_3→2_{3y}** with the aid of micro work up and ^{1}H-NMR analysis verified 67% conversion after 3 h of stirring, 70% after 7 h and ≥98% after 21 h of stirring at ambient temperature. Distillation of the crude product (17.15 g, 90%, yellow oil) at 0.010 mbar furnished the title compound as a colourless oil (16.04 g, 83.8 mmol, 84%) with a bp. of 78-81 °C.

Entry 5, PH3550: According to general protocol 3 (chapter 5.3.3, page 49) acid **1_3** (68 mg, 0.50 mmol, 1.0 equiv) was allowed to react with TCT (38 mg, 200 μmol, 40 mol%) in the presence of FPyr (4.9 μL, 5.1 mg, 50 μmol, 10 mol%) in **reisolated EtOAc** from the experiment in entry 1 (250 μL, 2 M) for 4 h at 80 °C. Then, the reaction suspension was diluted with further reisolated EtOAc (250 μL→1 M) and $HNEt_2$ (60 mL, 0.60 mmol, 1.2 equiv) and NMM (75 μL, 0.65 mmol, 1.3 equiv) were added at 0 °C. After 2 h of stirring at room temperature and aqueous work up, ^{1}H-NMR with dibenzylether (32.0 mg) revealed the title amide in 32% yield. The same experiment using EtOAc from another large scale synthesis of DEET afforded **2_{3y}** also in a clearly depleted yield of 37% (PH3559).

Entry 6, PH3551: The title compound was synthesized using **reisolated MeCN** from the respective experiment in entry 3 (250 μL→500 μL, 2 M→1 M) from 3-methylbenzoic acid (0.50 mmol, 1.0 equiv), TCT (40 mol%), FPyr (10 mol%), $HNEt_2$ (1.2 equiv) and NMM (1.3 equiv) as delineated in general protocol 3 (chapter 5.3.3, page 49). Thereby, for the transformation **1_3→6_3** the reaction mixture was heated to 80 °C for 4 h, whereas amidation **1_3→6_3** was pursued for 2 h at room temperature. ^{1}H-NMR with dibenzylether (29.4 mg) unravelled amide **2_{3y}** in 90% yield.

Entry 7, PH3560: The current experiment was performed as given in entry 6 with the exception that **dry MeCN** was applied, which furnished the title compound in 94% as judged by ^{1}H-NMR with dibenzylether (25.1 mg) as internal standard.

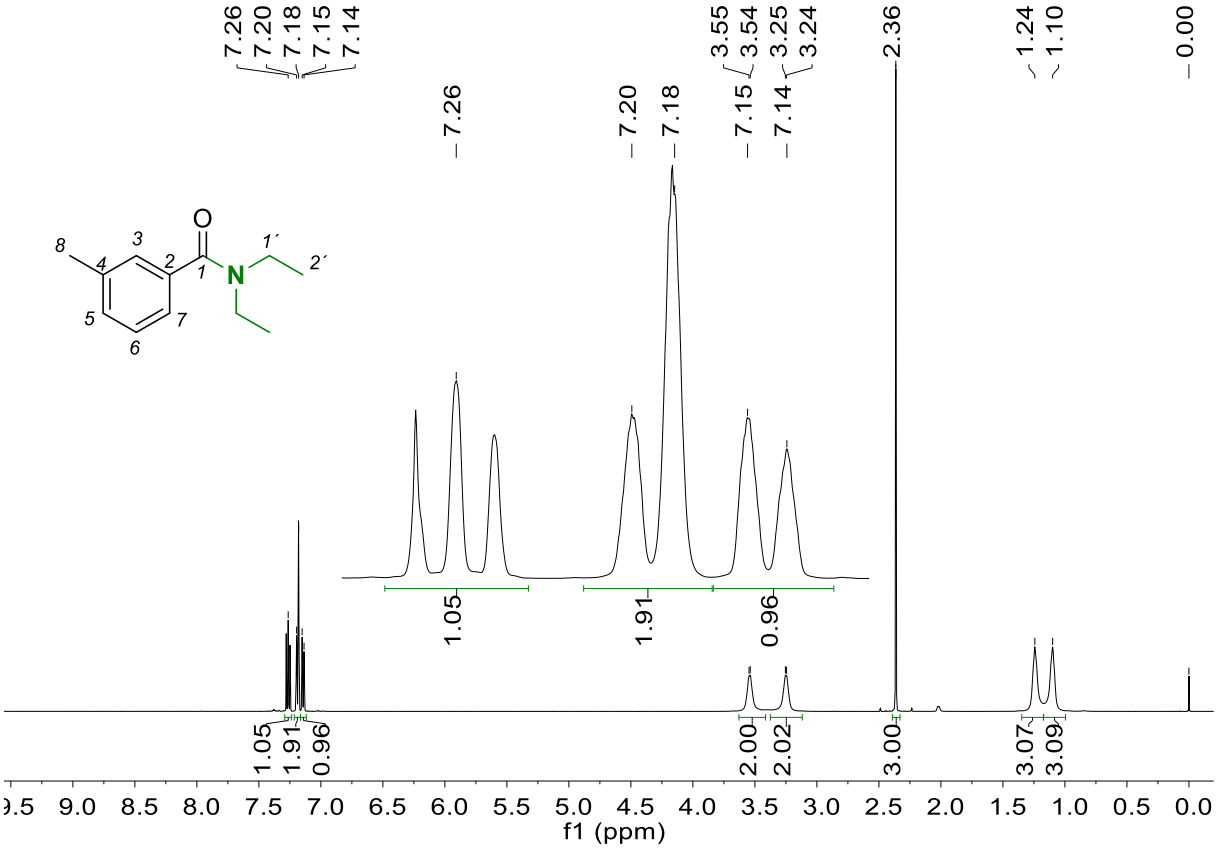
Entry 8, PH3505: In a comparison experiment according to Rayle[22] following general protocol 5 (chapter 5.3.5, page 56) 3-methylbenzoic acid (0.50 mmol, 1.0 equiv) was at the outset allowed to react with TCT (31 mg, 165 μmol, 33 mol%) and NMM (1.3 equiv) in MeCN (0.50 mL, 1 M) for 15 min at 0 °C and for 1 h at room temperature. Then, diethylamine (1.2 equiv) was added at 0 °C and the reaction suspension was stirred overnight (22 h). Therefore, the title amide could be identified in 50% yield as determined by ^{1}H-NMR with dibenzylether (31.5 mg) as internal standard.



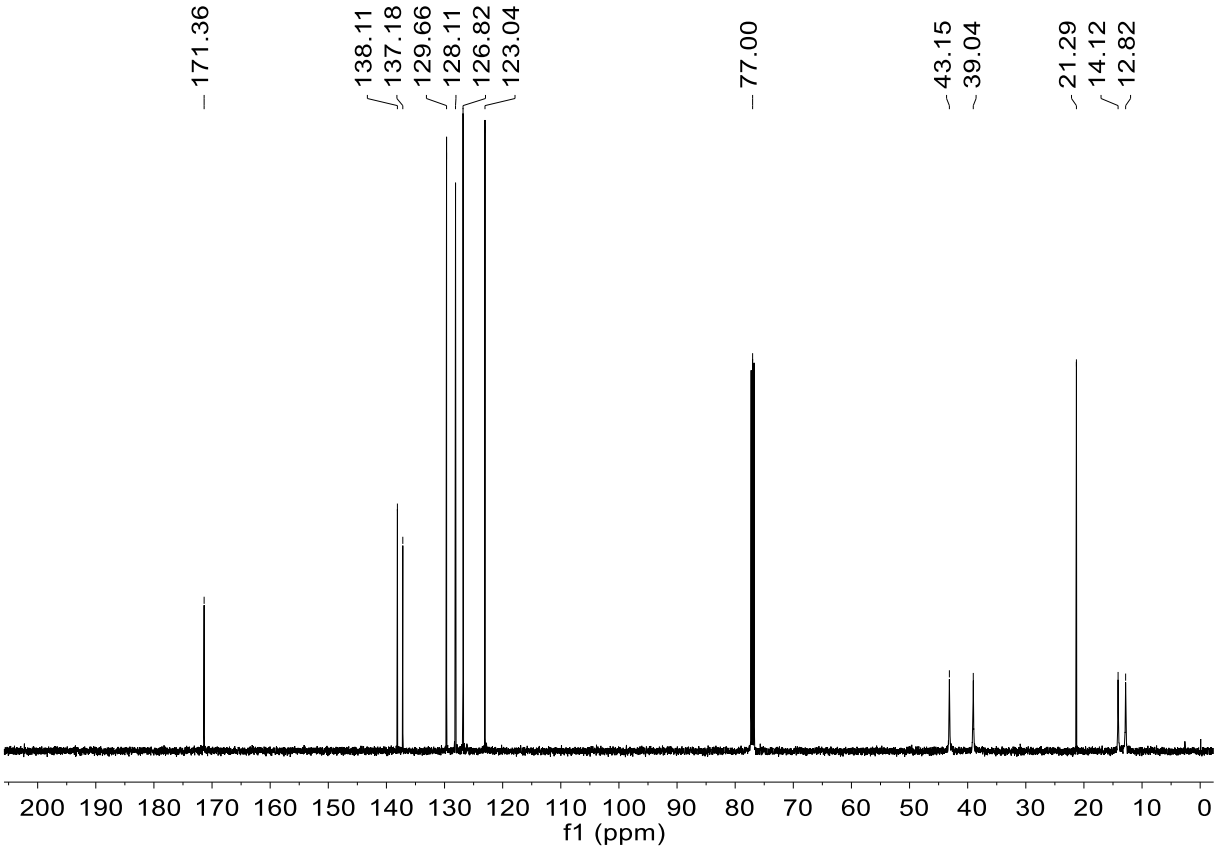
M ($C_{12}H_{17}NO$) = 191.27 g/mol; **r_f** (SiO_2, EtOAc/PE 35:65) = 0.34; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 7.26 (ψ-t, *J* = 7.6 Hz, 1H, 6-H), 7.20-7.18 (m, 2H, 3-H, 5-H), 7.15 (d, ^3J = 7.7 Hz, 1H, 7-H), 3.55 (q, $^3J_{1´,2´}$ = 4.8 Hz, 2H, 1´-H_a), 3.25 (br. q, $^3J_{1´,2´}$ = 4.6 Hz, 2H, 1´-H_b), 2.36 (s, 3H, 8-H), 1.24 (br. s, 3H, 2´-H_a), 1.10 (br. s, 3H, 2´-H_a); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 171.36 (C-1), 138.11 (C-2), 137.18 (C-4), 129.66

(C-5), 128.11 (C-6), 126.82 (C-3), 123.04 (C-7), 43.15 (C_b-1´), 39.04 (C_a-1´), 21.29 (C-8), 14.12 (C_b-2´), 12.82 (C_a-2´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 232 (1, $[M+allyl]^+$). 220 (13, $[M+Et]^+$), 206 (6, $[M+Me]^+$), 192 (100, $[M+H]^+$), 190 (47, $[M-H]^+$), 176 (3, $[M-Me]^+$), 162 (2), 119 (66, $[M-NEt_2]^+$), 100 (9, $[Et_2NCO]^+$), 91 (15, $[Bn]^+$), 65 (5, $[Cp]^+$).

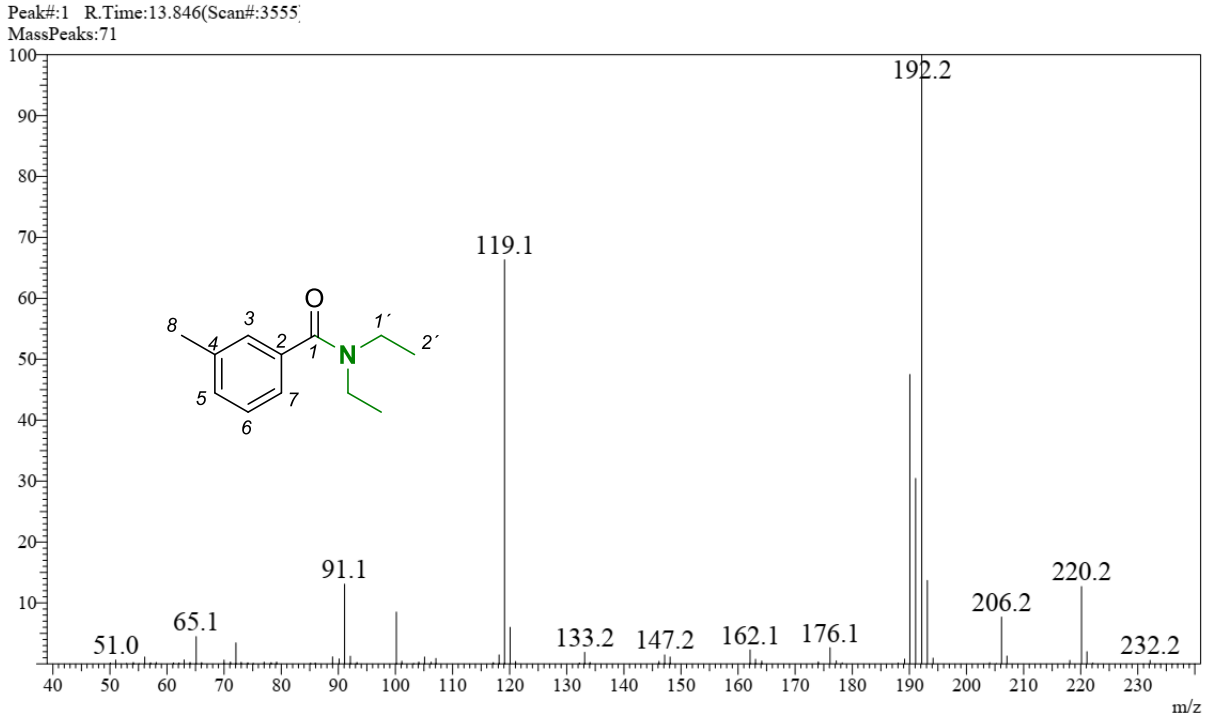
The NMR data is in match with literature values.[44]



^{1}H-NMR spectrum of *N,N*-diphenyl phenylethanoic amide (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *N,N*-diphenyl phenylethanoic amide (125 MHz, $CDCl_3$).



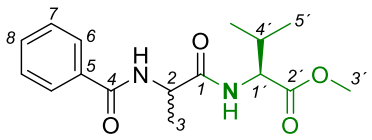
Mass spectrum of *N,N*-diphenyl phenylethanoic amide (CI, 70 eV).

5.4.2.30 Synthesis of *N*-Benzoyl-L/D-alanine-L-valine methyl ester (2_{26z})

entry	conditions	yield 2_{26z} [%][a]	*dr*[b]
1	1. TCT (40 mol%), FPyr (20 mol%), MeCN (2 M), 5 h 40 °C 2. L-Val-OMe-HCl (1.1 equiv), NMM (2.3 equiv), MeCN (0.8 M), 0.25 n 0 °C then 19 h rt	34	71:29
2	1. TCT (40 mol%), FPyr (20 mol%), MeCN (2 M), **23 h rt** 2. L-Val-OMe-HCl (1.1 equiv), NMM (2.3 equiv), MeCN (0.8 M),1 h 0 °C then 6 h rt	39	68:32
3	1. TCT (40 mol%), **FPyr (40 mol%)**, MeCN (2 M), **4.25 h rt** 2. L-Val-OMe-HCl (1.1 equiv), NMM (2.3 equiv), MeCN (0.8 M),1 h 0 °C then 3 h rt	37	67:33

a. Yield refers to isolated material after chromatographic purification. b. Determined from the ^{1}H-NMR-spectrum of the crude material.

^{1}H-NMR in DMSO-d^6 at 100 °C showed two separate set of signals, which confirmed the existence of two diastereomers. Despite different conditions tested, the chemical yield for the synthesis of dipeptide **2_{26z}** remained low, which also accounted for the diastereoisomers ratio.



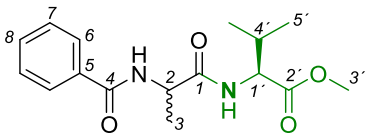
2_{26z}

Entry 1, PH3485: As given in general protocol 4 (chapter 5.3.4, page 50) L-*N*-benzoyl alanine (193 mg, 1.0 mmol, 1.0 equiv) was reacted with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (19.6 μL, 20.4 mg, 200 μmol, 20 mol%) in MeCN (0.50 mL, 2 M) for 5 h at 40 °C. Afterwards the reaction suspension was diluted with MeCN (0.75 mL→0.8 M), L-valine methyl ester (184 mg, 1.1 mmol, 1.1 equiv) and NMM (260 μL, 2.3 mmol, 2.3 equiv) were added at 0 °C and the mixture was stirred for 19 h at room temperature. After aqueous work up without 1 N HCl-washing the crude material (298 mg, 97%, yellow oil), of which no *dr* could be determined due to signal overlap in the ^{1}H-NMR spectrum, was subjected to column chromatographic purification on silica gel (24.8 g, relation weight crude product/SiO_2 1:83) with EtOAc/*n*Hex 50:50. Concentration with CH_2Cl_2 and drying at the rotary evaporator for 30 min at 5 mbar afforded the title compound as a pale yellow, viscous oil (104.1 mg, 0.34 mmol, 34%) and an *dr* of 71:29 as judged by ^{1}H-NMR.

PH3779: As described in general protocol 4 (chapter 5.3.4, page 50) L-*N*-benzoyl alanine (1.00 mmol, 1.00 equiv) was combined with FPyr (20 mol%), MeCN (2 M) and TCT (75 mg, 0.40 mmol, 40 mol%) and stirred for 23 h at room temperature. Next, the resulting colourless suspension was diluted with MeCN (→0.8 M), cooled in an ice bath and L-valine methyl ester (1.10 equiv) and NMM (2.3 equiv) were added. After 6 h of stirring at room temperature work up afforded the crude title compound as yellow oil (280 mg, 91%, yellow oil). Subsequently, purification on silica gel (27.0 g, relation of weight crude product/SiO_2 1:96) using EtOAc/*n*Hex

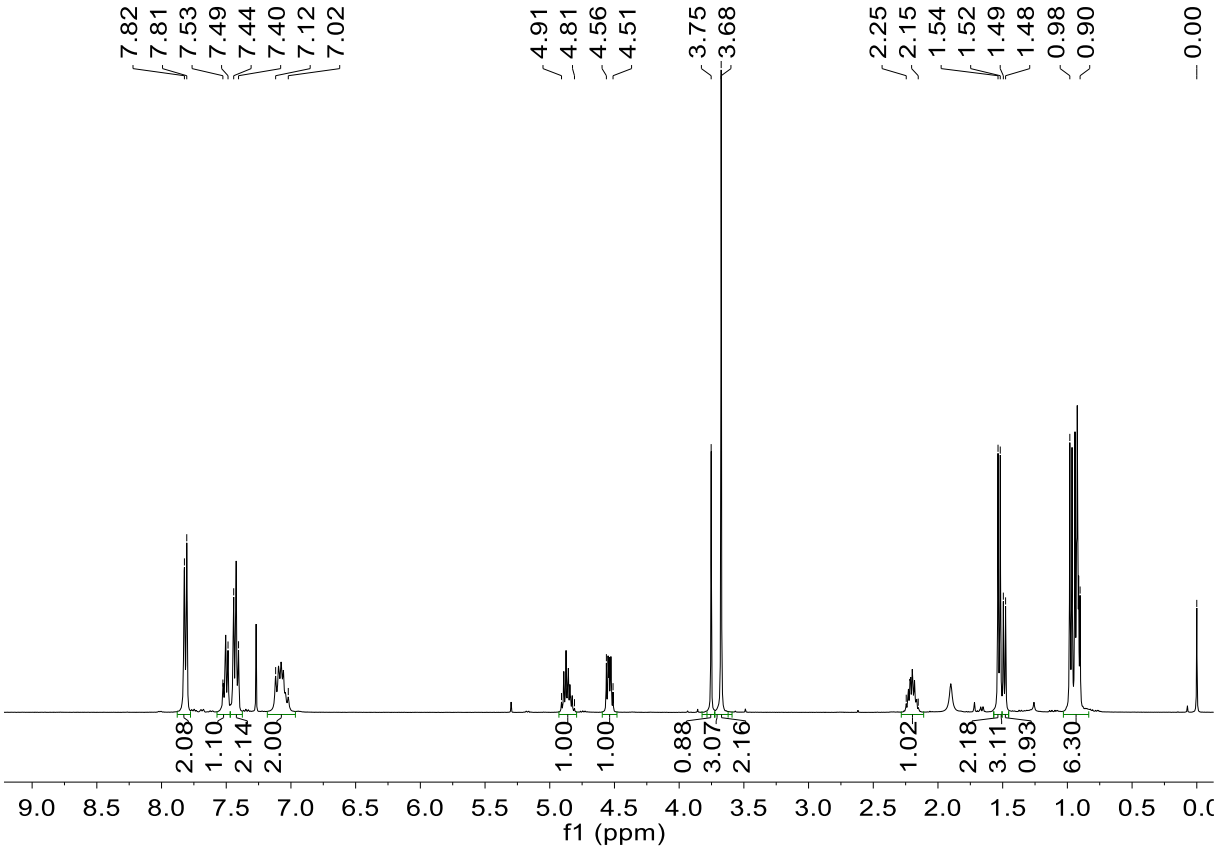
60:40 delivered the dipeptide **2_{26z}** as a pale yellow oil (118.8 mg, 0.388 mmol, 39%), of which ^{1}H-NMR confirmed a stereoisomer ratio of 68:32.

Entry 3, PH3836: In accordance with general procedure 4 (chapter 5.3.4, page 50) L-*N*-benzoyl alanine (1.00 mmol, 1.00 equiv) was reacted with TCT (40 mol%) in the presence of FPyr (39 μL, 41 mg, 0.40 mmol, 40 mol%) in MeCN (0.50 mL, 2 M) for 4.25 h at room temperature. Afterwards, the reaction suspension was treated with more MeCN (→0.8 M) and L-valine methyl ester hydrochloride (1.1 equiv). Under cooling in an ice bath NMM (2.3 equiv) was added drop wise. After 15 min of stirring at 0 °C, the cooling bath was removed and the reaction mixture was stirred for 3 h at room temperature. Aqueous work up with 2 N HCl washing gave rise of the crude title compound as a yellow solid (187 mg, 61%). Finally, purification with the aid of column chromatography on silica gel (22.8 g, mass relation crude product/SiO_2 1:120) delivered the dipeptide **2_{26z}** as a pale yellow oil in a yield of 37% (113.2 mg, 0.37 mmol) and a *dr* of 67:33 as determined by ^{1}H-NMR. In order to charge the crude material onto the chromatography column, it was dissolved in CH_2Cl_2 (ca. 10 mL), SiO_2 was added (0.58 g, mass ratio 1:3) and the mixture was concentrated under reduced pressure to dryness.

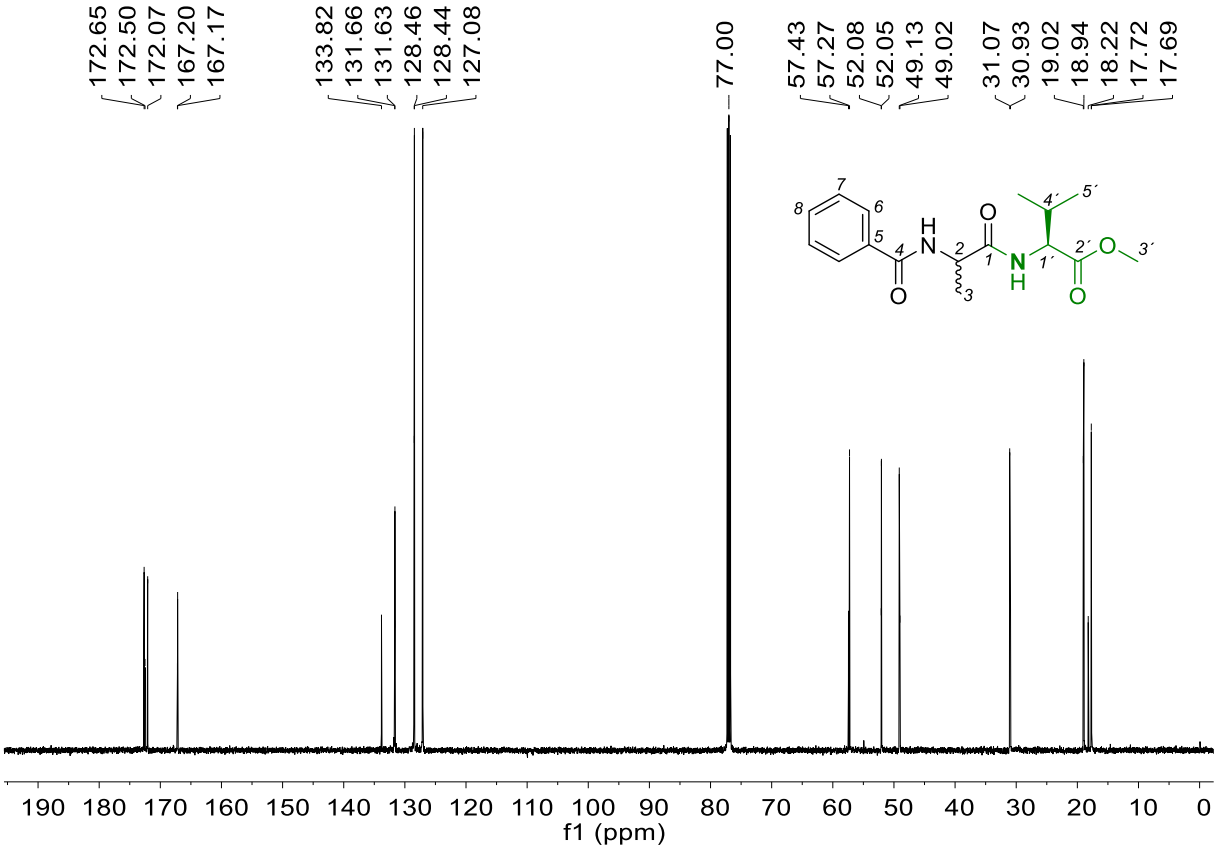


M ($C_{16}H_{22}N_2O_2$) = 306.362 g/mol; **r_f** (SiO_2, EtOAc/*n*Hex 50:50) = 0.25; **^{1}H-NMR** (400 MHz, $CDCl_3$, dia1/dia2 29:71) δ [ppm] = 7.82-7.81 (m, 2H, 6-H), 7.53-7.49 (m, 1H, 8-H), 7.44-7.40 (m, 2H, 7-H), 7.12-7.02 (m, 2H, 2 x NH), 4.91-4.81 (m, 1H, 2-H), 4.56-4.51 (m, 1H, 1´-H), 3.75 (2, 3H, 3´-H_{dia1}, *dr* = 29:71) 3.68 (s, 3H, 3´-H_{dia2}, *dr* = 71:29), 2.25-2.15 (m, 1H, 4´-H), 1.53 (d, $^{3}J_{3,2}$ = 7.0 Hz, 3H, 3-H_{dia2}, *dr* = 70:30), 1.49 (d, $^{3}J_{3,2}$ = 7.0 Hz, 3H, 3-H_{dia1}, *dr* = 30:70), 0.98-0.90 (m, 6H, 5´-H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 172.65 (C_{dia2}-1), 172.50 (C_{dia1}-1), 172.07 (C-2´), 167.20 (C_{dia1}-4), 167.17 (C_{dia2}-4), 133.82, 131.66 (C_{dia2}-8), 131.63 (C_{dia2}-8), 128.46 (C_{dia1}-7), 128.44 (C_{dia2}-7), 127.08 (C-6), 57.43 (C_{dia1}-1´), 57.27 (C_{dia2}-1´), 52.08 (C_{dia1}-3´), 52.05 (C_{dia2}-3´), 49.13 (C_{dia2}-2), 49.02 (C_{dia1}-2), 31.07 (C_{dia2}-4´), 30.93 (C_{dia1}-4´), 19.02 (C_{dia2}-5´), 18.94 (C_{dia1}-5´, C_{dia2}-3), 18.22 (C_{dia1}-3), 17.72 (C_{dia1}-5´), 17.69 (C_{dia1}-5´); **HR-MS** (ESI, $[C_{16}H_{23}N_2O_4]^+$) calc. 307.1652 u found 307.1654 u.

In the NMR data no stereoisomer dia1/dia2 is given, if both isomers are represented by the respective multiplet. In ^{13}C-NMR the signals were partially allocated to the stated stereoisomer based on relative intensities. The main epimer dia2 most likely corresponds to *N*-benzoyl-L-alanine-L-valine methyl ester, whereas dia1 should match *N*-benzoyl-D-alanine-L-valine methyl ester accordingly.



^{1}H-NMR spectrum of *N*-benzoyl-L/D-alanine-L-valine methyl ester (400 MHz, $CDCl_3$).



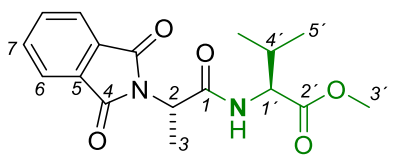
^{13}C-NMR spectrum of *N*-benzoyl-L/D-alanine-L-valine methyl ester (125 MHz, $CDCl_3$).

5.4.2.31 Synthesis of *N*-Phthaloyl-L-alanine-L-valine methyl ester (2_{27z})

entry	conditions	yield 2_{27z} [%][a]	*dr*[b]
1	1. TCT (40 mol%), FPyr (20 mol%), MeCN (2 M), 15 h rt 2. L-Val-OMe-HCl (1.1 equiv), NMM (2.3 equiv), MeCN (0.8 M), 0.25 n 0 °C then 4 h rt	83	≥97:3
2	1. TCT (40 mol%), FPyr (**40 mol%**), MeCN (2 M), 4.25 h rt 2. L-Val-OMe-HCl (1.1 equiv), NMM (2.3 equiv), MeCN (0.8 M),1 h 0 °C then 3 h rt	79	≥98:2
3	1. TCT (40 mol%), FPyr (20 mol%), **EtOAc** (2 M), 15 h rt 2. L-Val-OMe-HCl (1.1 equiv), NMM (2.3 equiv), **EtOAc** (0.8 M) 0.25 n 0 °C then 4 h rt	54	58:42

a. Yield refers to isolated material after chromatographic purification. b. Determined from the ^{1}H-NMR-spectrum of the crude material.

Phthaloyl protected alanine (**1_{27}**) could be coupled with valine methyl ester in good chemical yield (79-83%) and basically without erosion in terms of diastereomeric ratio (entries 1+2). However, utilization of EtOAc as solvent instead of MeCN resulted in both a clearly deteriorated yield and isomer ratio (entry 3).



2_{27z}

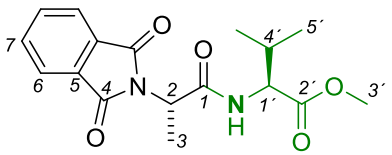
Entry 1, PH3840: According to general protocol 4 (chapter 5.3.4, page 50) a suspension of L-*N*-phthaloyl alanine (219 mg, 1.00 mmol, 1.0 equiv) and FPyr (19.6 μL,20.4 mg, 20 mol%) in dry MeCN (0.50 mL, 2 M) was treated with TCT (75 mg, 0.40 mmol, 40 mol%) and stirred overnight (15 h). In the following, to the reaction suspension were added further MeCN (0.75 mL→0.8 M) and L-valine methyl ester hydrochloride (184 mg, 1.1 mmol, 1.1 equiv). Upon cooling in an ice bath, NMM (260 μL, 2.3 mmol, 2.3 equiv) was added dropwise. After stirring for 15 min at 0 °C and 4 h at room temperature aqueous work up including 2 N HCl-washing afforded the crude dipeptide **2_{27z}** as a pale yellow oil (370 mg, 111%), of which ^{1}H-NMR verified a *dr* of ≥97:3. Column chromatographic purification on silica gel (16.7 g, mass relation crude material/SiO_2 1:45) and concentration with CH_2Cl_2 (2 x) delivered a colourless oil. Drying in high vacuum for 2.5 h finally provided the title compound as a colourless solid in 83% yield (277.3 mg, 0.83 mmol). The ^{1}H-NMR spectrum of the isolated product verified a *dr* of ≥97:3. In order to apply the crude product onto the silica gel column, it was dissolved in CH_2Cl_2 (ca. 10 mL), silica gel was introduced (1.24 g, mass ratio 1:3.3) and all volatiles were removed under reduced pressure.

Entry 2, PH3837: In the presence of **FPyr (39 μL, 41 mg, 0.40 mmol, 40 mol%)** L-*N*-phthaloyl alanine (1.00 mmol, 1.0 equiv) was allowed to react with TCT (40 mol%) in MeCN (2 M) for 4.25 h at room temperature as delineated in general protocol 4 (chapter 5.3.4, page 50). Next, the reaction suspension was treated with more MeCN (→0.8 M) and L-valine methyl ester

hydrochloride (1.1 equiv), cooled in an ice bath and NMM (2.3 equiv) was added dropwise. Past 15 min of stirring at 0 °C and 3 h at ambient temperature, aqueous work up delivered the crude title compound as a pale yellow oil (374 mg, 112%), of which ^{1}H-NMR showed a *dr* of ≥98:2). Eventually, purification by means of column chromatography on silica gel (18.8 g, mass ratio crude material/SiO_2 1:50) using EtOAc/*n*Hex 40:60 as eluent, concentration with CH_2Cl_2 *in vacuo* (3 x) and drying in high vacuum for 1 h furnished dipeptide **2_{27z}** as a colourless solid (262.8 mg, 0.79 mmol, 79%) in a *dr* ≥98:2 as judged by ^{1}H-NMR. In order to charge the silica gel column, the crude material was dissolved in CH_2Cl_2 (ca. 10 mL), silica gel was added (0.89 g, ratio weight crude **2_{27z}**/SiO_2 1:2.4) and the all volatile components were removed under reduced pressure.

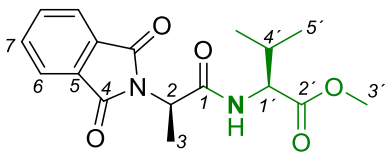
Entry 3, PH3839: In alignment to general protocol 4 (chapter 5.3.4, page 50) to a suspension of *N*-phthaloyl alanine (1.00 mmo, 1.0 equiv) and FPyr (20 mol%) in reagent-grade **EtOAc** (0.50 mL, 2 M) was added TCT (40 mol%) and the resulting mixture was stirred for 4.25 h at room temperature. Afterwards, the reaction suspension was diluted with further **EtOAc** (0.75 mL→0.8 M), L-valine methyl ester hydrochloride (1.1 equiv) was added, the mixture was chilled in an ice bath and NMM (2.3 equiv) was added dropwise., whereupon stirring was continued for 15 min at 0 °C and for 4 h at room temperature. Aqueous work up with 2 N HCl washing gave the crude title compound as a pale yellow oil (276 mg, 83%), of which ^{1}H-NMR confirmed a *dr* of 59:41. Thereafter, column chromatographic purification using silica gel (18.4 g, ratio of masses crude product/SiO_2 1:65) with EtOAc/*n*Hex 40:60, concentration with CH_2Cl_2 (2 x) and drying in high vacuum resulted in the title compound as a colourless solid in 54% yield (180.9 mg, 0.54 mmol) as a 58:42 mixture of diastereomers as determined by ^{1}H-NMR. In order to load crude **2_{27z}** onto the silica gel column, it was adsorbed on silica gel (0.77 g, mass relation 1:2.8) by dissolution in CH_2Cl_2 (approximately 10 mL) and concentration under reduced pressure.

***N*-Phthaloyl-L-alanine-L-valine methyl ester (2_{27z})**



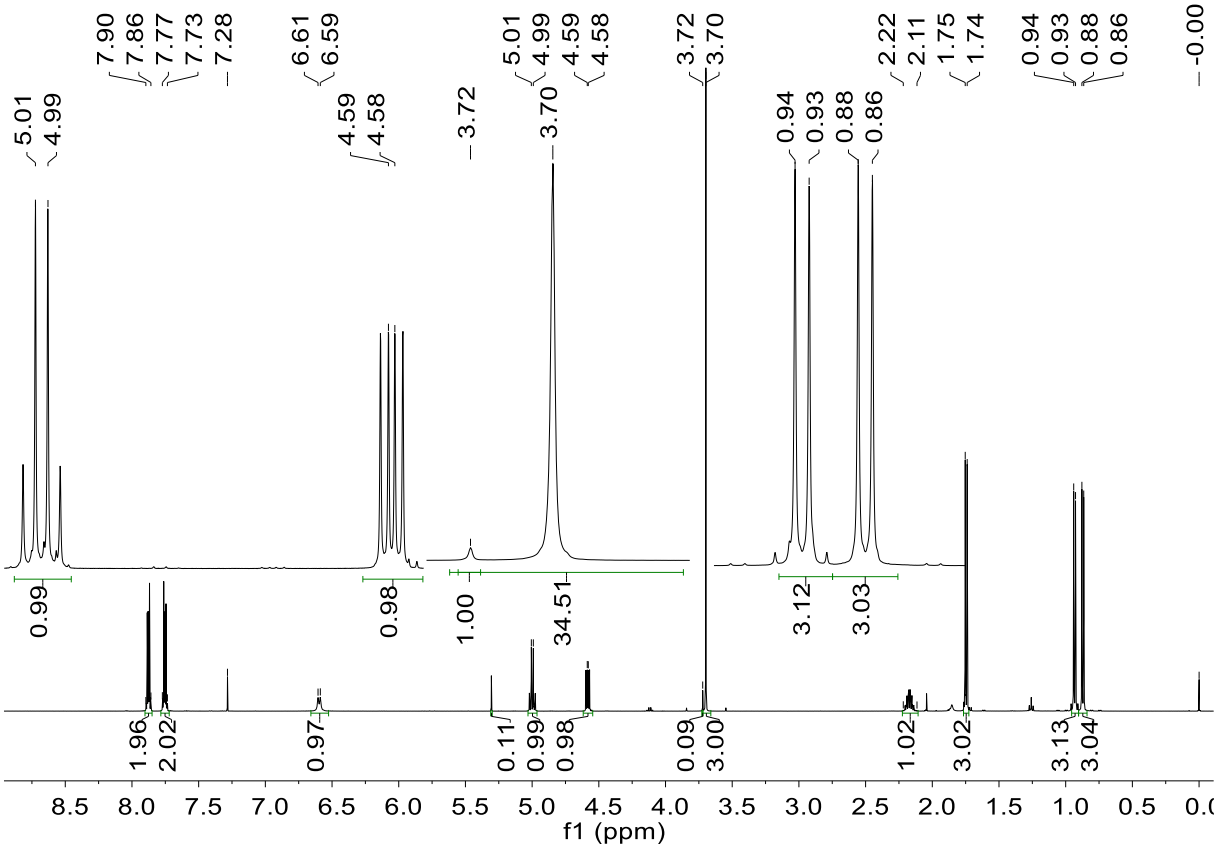
M ($C_{17}H_{20}N_2O_5$) = 332.356 g/mol; **r_f** (SiO_2, EtOAc/*n*Hex 40:60) = 0.29; **^{1}H-NMR** (400 MHz, $CDCl_3$, dia1/dia2 29:71) δ [ppm] = 7.90-7.86 (m, 2H, 6-H), 7.77-7.73 (m, 2H, 7-H), 6.61-6.59 (d, $^3J_{NH,1´}$ = 8.4 Hz, 1H, NH), 5.00 (q, ^3J = 7.4 Hz, 1H, 2-H), 4.59 (dd, ^3J = 8.6, 4.8 Hz, 1H, 1´-H), 3.70 (s, 3H, 3´-H), 2.22-2.11 (m, 1H, 4´-H), 1.75 (d, $^3J_{3,2}$ = 7.4 Hz, 3H, 3-H), 0.94 (d, $^3J_{5´,4´}$ = 6.9 Hz, 3H, 5´-H_a), 0.87 (d, $^3J_{5´,4´}$ = 7.0 Hz, 3H, 5´-H_b); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 172.18 (C-2´), 169.05 (C-1), 167.72 (C-4), 134.26 (C-7), 131.75 (C-5), 123.52 (C-6), 57.28 (C-1´), 52.13 (C-3´), 49.52 (C-2), 31.35 (C-4´), 18.80 (C_a-5´), 17.65 (C_b-5´), 15.34 (C-3); **HR-MS** (CI, $[C_{17}H_{21}N_2O_5]^+$) calc. 333.1450 u found 333.1455 u.

N-Phthaloyl-D-alanine-L-valine methyl ester (*dia*-$\mathbf{2_{27z}}$)

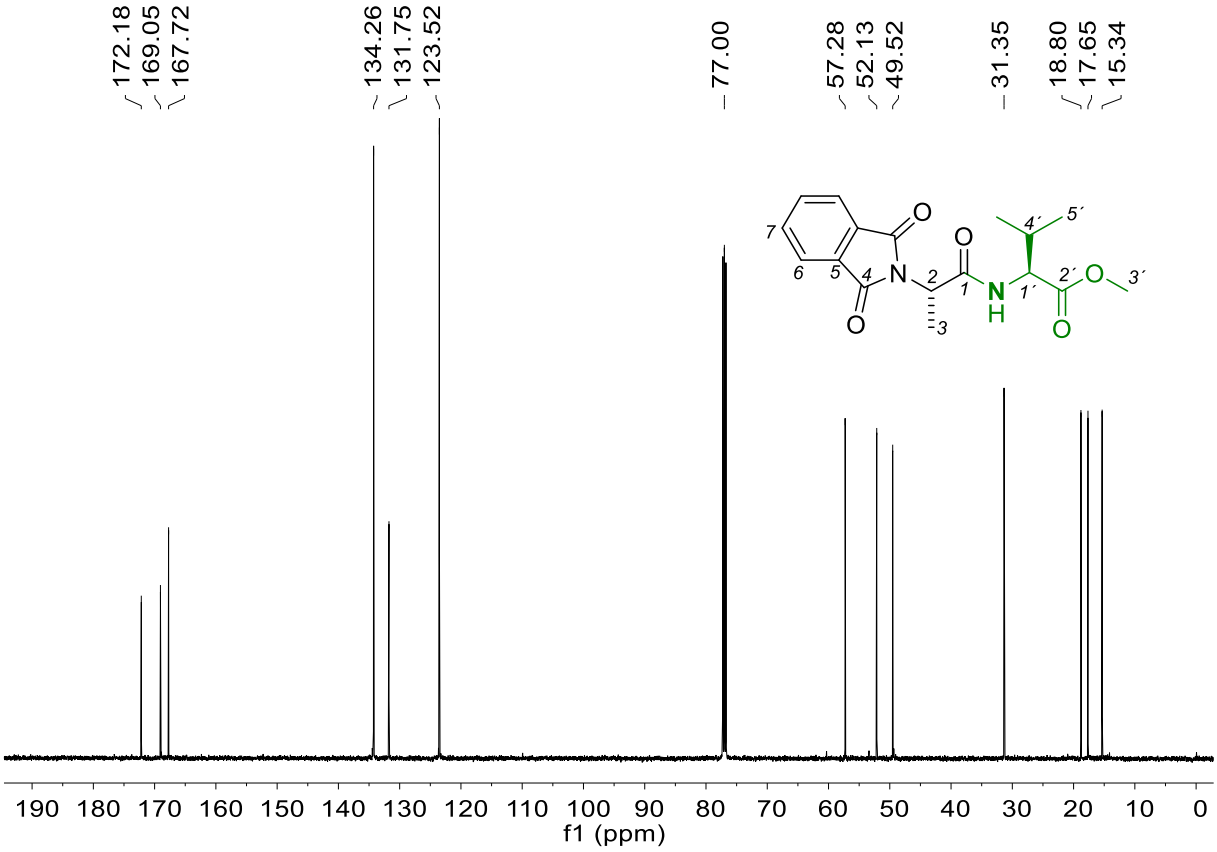


Analytical data was collected from a 58:42 $\mathbf{2_{27z}}$/*dia*-$\mathbf{2_{27z}}$ mixture of diastereomers. Therefore, only separate muliplets are reported.

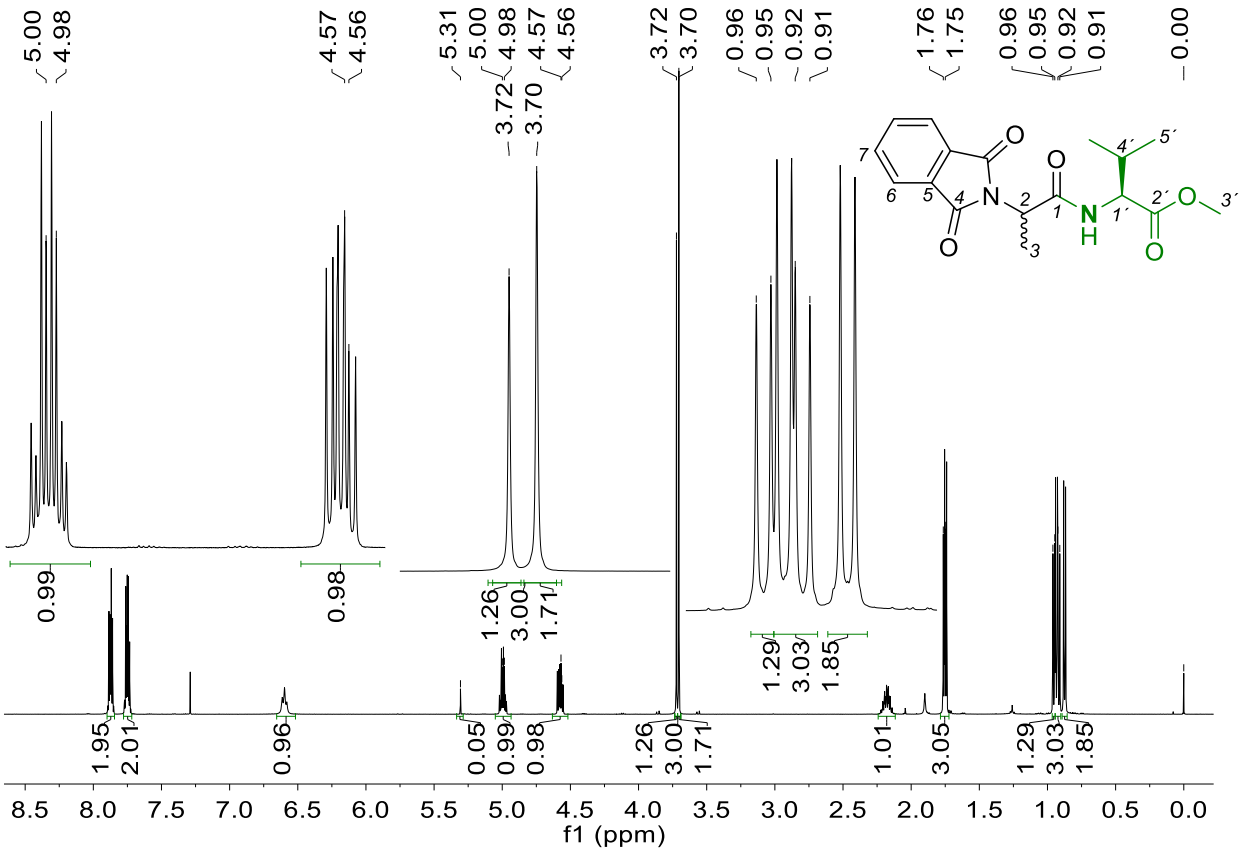
M ($C_{17}H_{20}N_2O_5$) = 332.356 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 40:60) = 0.29; **^{1}H-NMR** (400 MHz, $CDCl_3$, dia1/dia2 29:71) δ [ppm] = 4.99 (q, $^3J_{2,3}$ = 7.4 Hz, 1H, 2-H), 4.57 (dd, ^3J = 8.4, 4.8 Hz, 1H, 1´-H) 3.72 (s, 3H, 3´-H), 1.76 (d, $^3J_{3.2}$ = 7.4 Hz, 3H, 3-H), 0.96 (d, $^3J_{5´,4´}$ = 7.0 Hz, 3H, 5´-H_a), 0.92 (d, $^3J_{5´,4´}$ = 6.9 Hz, 3H, 5´-H_b); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 172.15 (C-2´), 168.92 (C-1), 134.17(C-7), 131.76, (C-5), 123.46, (C-6), 57.36 (C-1´), 52.14 (C-3´), 49.33 (C- ..... 2), 31.31 (C-4´), 18.83 (C_a-5´), 17.68 (C_b-5´), 15.16 (C-3)



^{1}H-NMR spectrum of *N*-phthaloyl-L-alanine-L-valine methyl ester (500 MHz, $CDCl_3$).

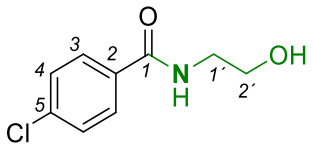


^{13}C-NMR spectrum of *N*-phthaloyl-L-alanine-L-valine methyl ester (125 MHz, $CDCl_3$).



^{1}H-NMR spectrum of a 58:42 mixture of *N*-phthaloyl-L-alanine-L-valine methyl ester and *N*-phthaloyl-D-alanine-L-valine methyl ester (500 MHz, $CDCl_3$).

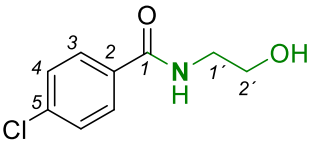
5.4.2.32 Synthesis of *N*-(2-Hydroxyethyl) 4-chlorobenzamide (2_{18ab})



2_{18ab}

PH3411: Following general protocol 4 (chapter 5.3.4, page 50) 4-chloro benzoic acid (313 mg, 2.0 mmol, 1.0 equiv) was converted into the corresponding acid chloride by means of TCT (144 mg, 0.76 mmol, 38 mol%) using FPyr (19.6 μL, 20.4 mg, 200 μmol, 10 mol%) in MeCN (1.0 mL, 2 M) under heating to 80 °C for 5 h. Subsequently, the reaction suspension was added dropwise under cooling to 0 °C to a solution of **2-ethanolamine** (280 μL, 284 mg, 4.6 mmol, **2.3 equiv**) in MeCN (0.75 mL), the reaction vial was rinsed with further MeCN (0.25 mL→1 M) and the resulting mixture was stirred for 6 h at room temperature. In the end, chromatographic purification of the crude material (pale yellow solid, 372 mg, 93%) on silica gel (31.8 g, relation weight crude product/SiO_2 1:86) with MeOH/EtOAc 2:98 gave the title amide as a colourless solid in 79% yield (315.1 mg, 1.58 mmol). In order to charge the silica gel column with crude **2_{18ab}**, it was dissolved in CH_2Cl_2 (ca. 20 mL) under heating, SiO_2 was added (3.0 g, mass crude product/SiO_2 1:8) and the solvent was evaporated *in vacuo*.

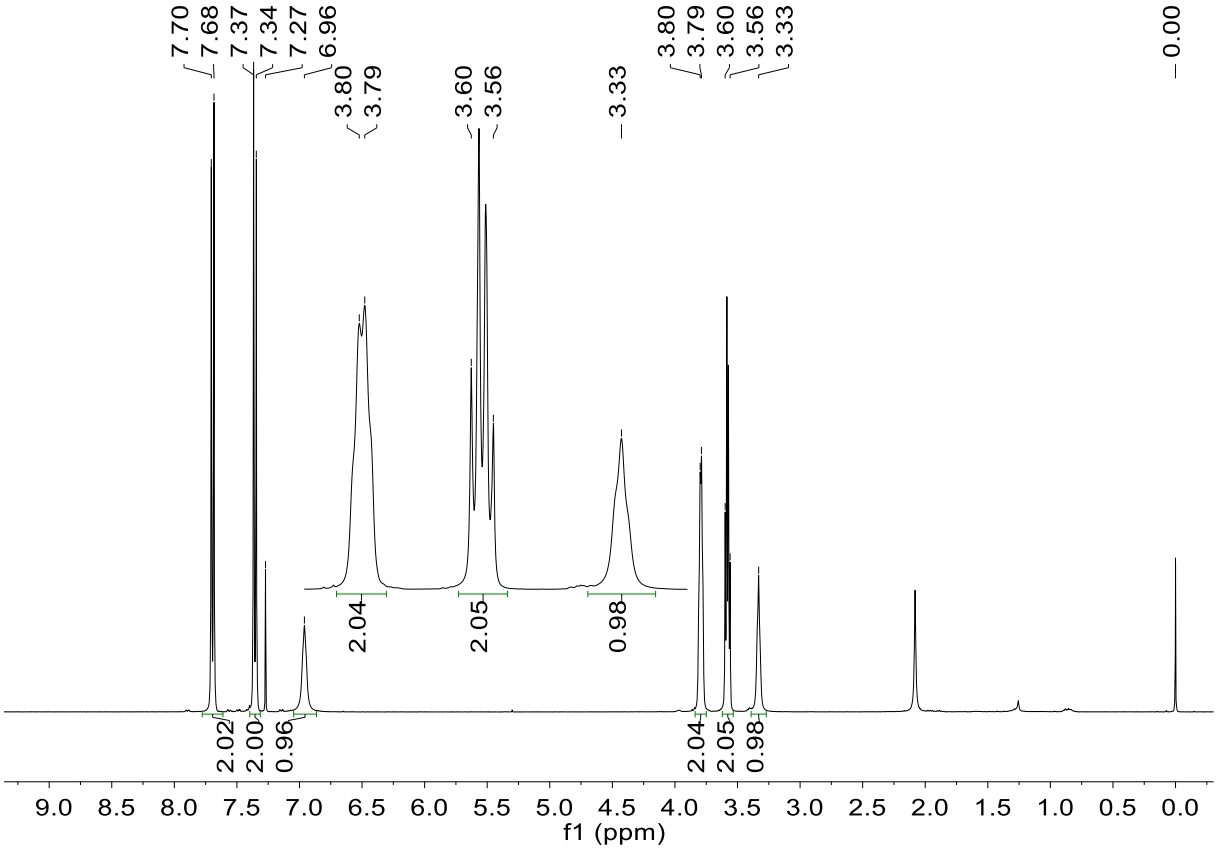
PH3403: In accordance with general procedure 4 (chapter 5.3.4, page 50) 4-chloro benzoic acid (2.0 mmol, 1.0 equiv) was combined with FPyr (10 mol%), MeCN (2 M) and TCT (38 mol%) and heated to 80 °C for 4 h. Afterwards, the yellow reaction suspension was diluted with more MeCN (1 mL→1 M) and under cooling to 0 °C **2-ethanolamine** (150 μL, 2.4 mmol, **1.2 equiv**) and **NMM** (150 μL, 2.6 mmol, 1.3 equiv) were added. After stirring for 4 h at room temperature, aqueous work up yielded the crude title compound as a pale yellow solid (374 mg, 94%). Eventually, chromatographic purification on silica gel (36.6 g, ratio weight crude material in respect to SiO_2 1:99) with MeOH/EtOAc 2:98 yielded amide **2_{18ab}** as a colourless solid in 76% yield (304.5 mg, 1.53 mmol).



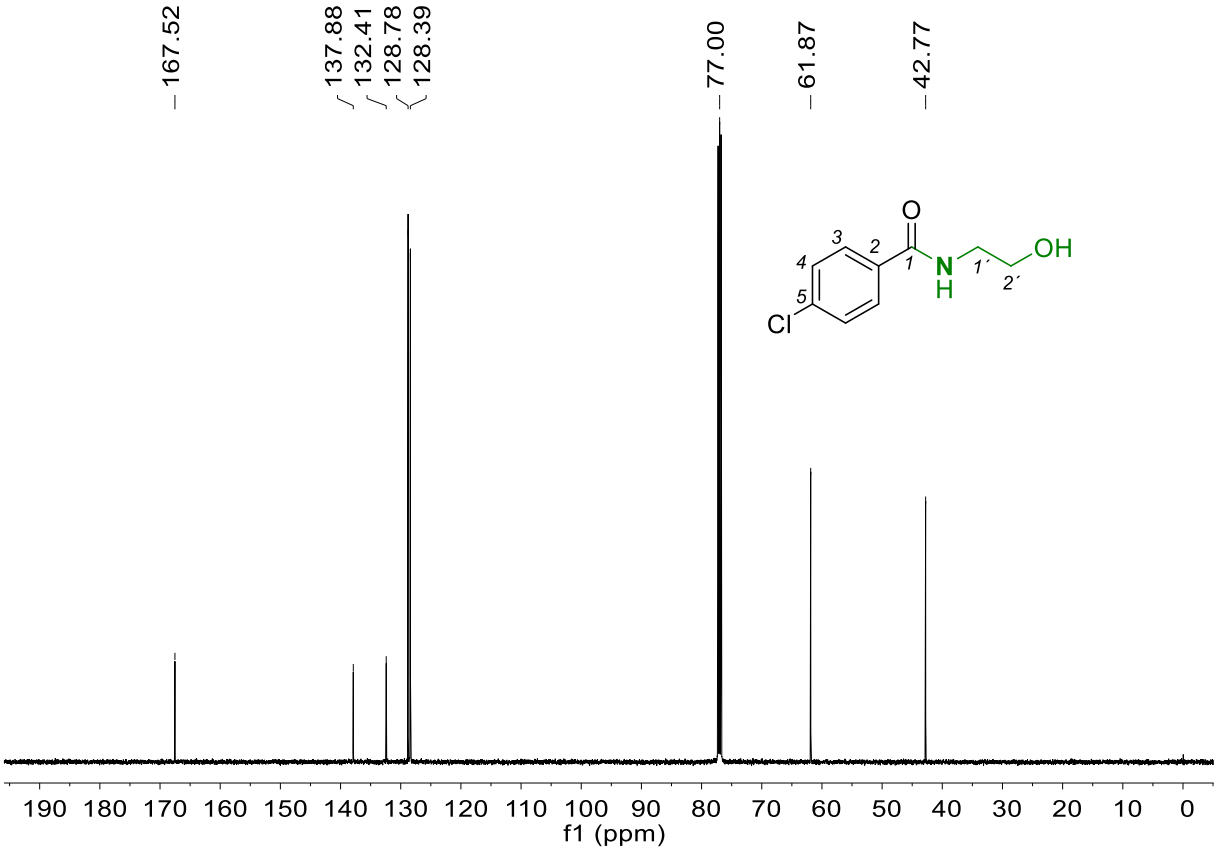
M ($C_9H_{10}ClNO_2$) = 199.63 g/mol; **mp.** = 99-101 °C (lit.-mp. 116-117 °C)[45] **r_f** (SiO_2, MeOH/EtOAc 2:98) = 0.32; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.70-7.68 (m, 2H, 3-H), 7.37-7.34 (m, 2H, 4-H), 6.96 (br. s, 1H, NH), 3.80-3.79 (m, 2H, 2´-H), 3.60-3.56 (m, 2H, 1´-H), 3.33 (s, 1H, OH); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 167.52 (C-1), 137.88 (C-5), 132.41 (C-2), 128.78 (C-4), 128.39 (C-3), 61.87 (C-2´), 42.77 (C-1´); **^{1}H-NMR** (500 MHz, DMSO-d^6) δ [ppm] = = 8.53 (t, $^3J_{NH,1´}$ = 5.4 Hz, 1H, NH), 7.89-7.86 (m, 2H, 3-H), 7.53-7.51 (m, 2H,4-H), 4.75 (t, $^3J_{OH,2´}$= 5.7 Hz, 1H, OH), 3.52 (td, $^3J_{2´,1´}$ = 6.0 Hz, $^3J_{1´,OH}$ = 6.0 Hz, 2H, 2´-H), 3.33-3.32 (td, $^3J_{1´,2´}$ = 6.0 Hz, $^3J_{1´,NH}$ = 6.0 Hz, 2H, 1´-H); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ [ppm] = 165.28 (C-1), 135.91 (C-5), 133.30 (C-2), 129.15 (C-3), 128.31 (C-4), 59.70 (C-2´), 42.27 (C-1´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 212 (9, [M(^{37}Cl)-H_2O+Me]$^+$) 210 (32, [M(^{35}Cl)-H_2O+Me]$^+$) 184 (33, [M(^{37}Cl)-

OH]$^+$) 183 (33, [M(^{37}Cl)-H_2O]$^+$), 182 (100, [M(^{35}Cl)-OH]$^+$), 181 (72, [M(^{35}Cl]-H_2O]$^+$), 153 (20), 151 (42), 141 (5, [4-^{37}Cl(C_6H_4)CO]$^+$), 139 (18, [4-^{37}Cl(C_6H_4)CO]$^+$), 125 (9)

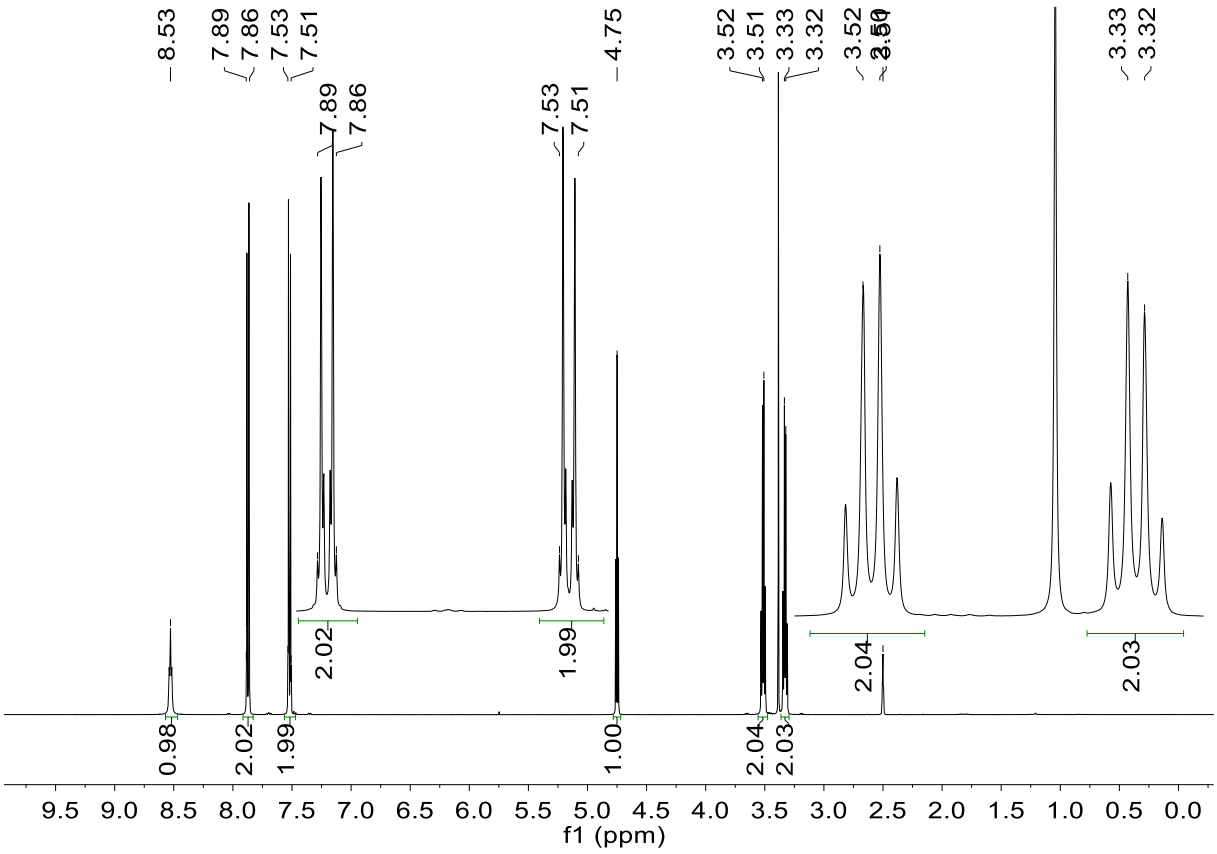
The NMR data matches reported values.[45]



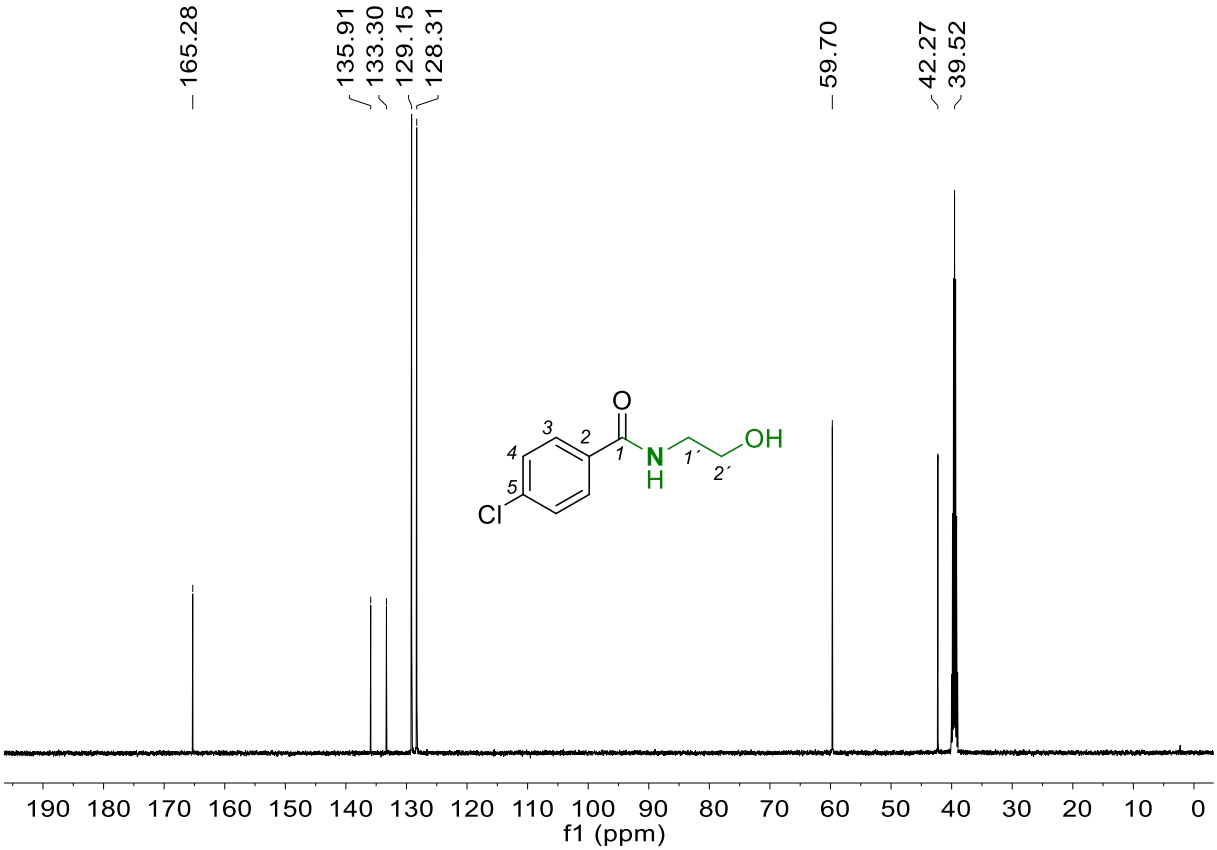
^{1}H-NMR spectrum of *N*-(2-hydroxyethyl) 4-chlorobenzamide (400 MHz, $CDCl_3$).



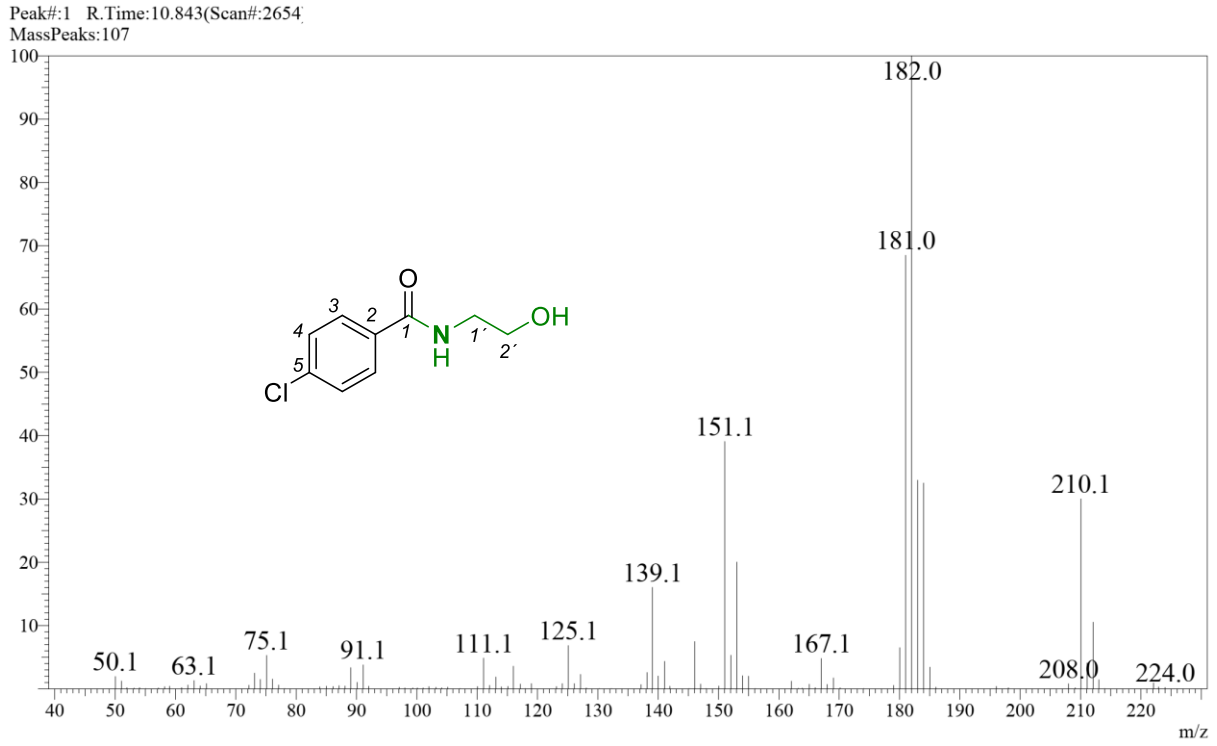
^{13}C-NMR spectrum of *N*-(2-hydroxyethyl) 4-chlorobenzamide (125 MHz, $CDCl_3$).



^{1}H-NMR spectrum of *N*-(2-hydroxyethyl) 4-chlorobenzamide (500 MHz, DMSO-d^{6}).



^{13}C-NMR spectrum of *N*-(2-hydroxyethyl) 4-chlorobenzamide (125 MHz, DMSO-d^6).

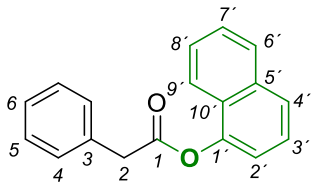


Mass spectrum of *N,N*-diphenyl phenylethanoic amide (CI, 70 eV).

5.4.3 Synthesis of Esters of Type 3 and 9 (Scheme 5)

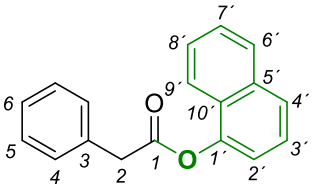
5.4.3.1 Synthesis of 1-Naphthyl 2-phenylethanoate (3_{4a})

The optimization of the reaction conditions for the preparation of the title compound can be found in chapter 3.2.3 (page 26), whereas comparison experiments with literature methods are located in chapter 4.1.3 on page 36.



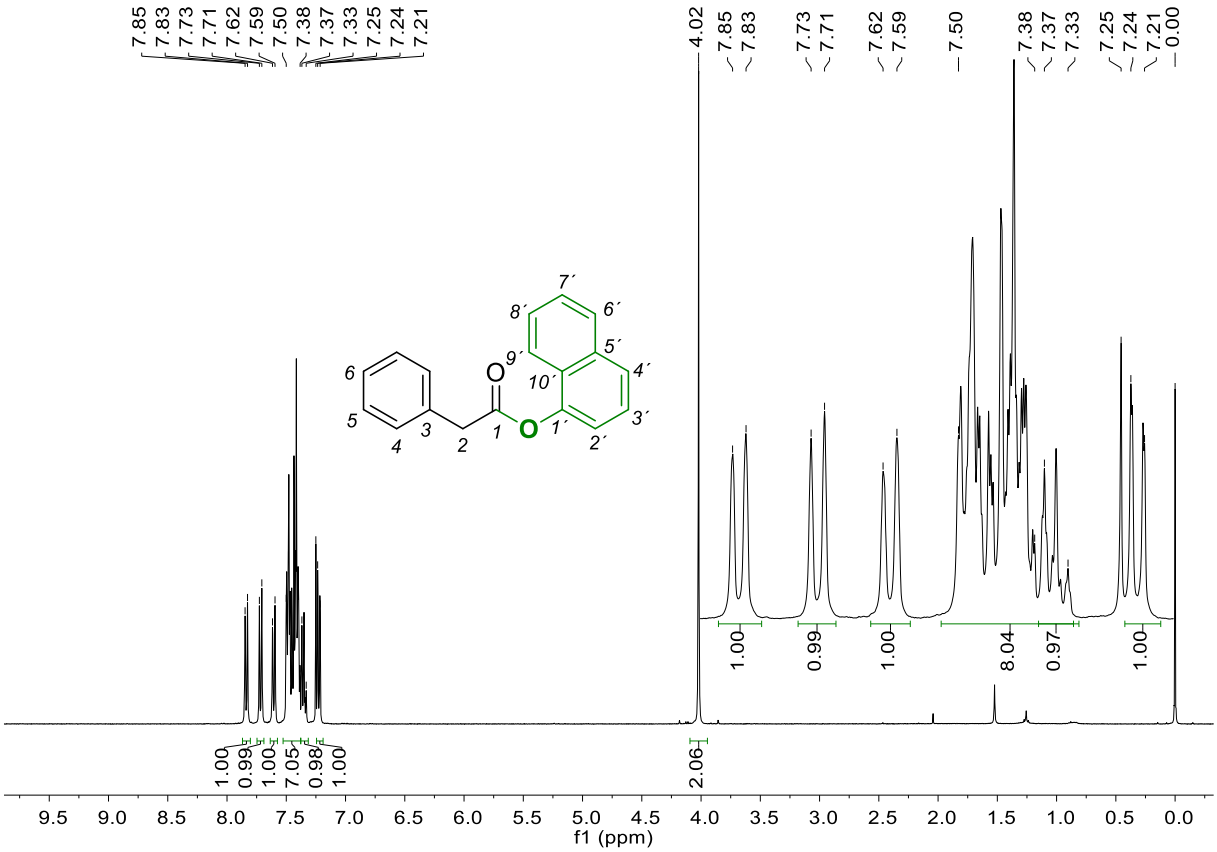
3_{4a}

PH2879: According to general protocol 4 (chapter 5.3.4, page 50) phenylethanoic acid (135 mg, 1.00 mmol, 1.0 equiv) was reacted with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (9.8 µL, 10.2 mg, 100 µL, 10 mol%) in EtOAc (0.50 mL, 2 M) at 40 °C for 8 h. Next, additional EtOAc (0.50 mL→1 M) and subsequently at 0 °C 1-naphthol (173 mg, 1.2 mmol, 1.2 equiv) and NMM (145 µL, 1.3 equiv, 1.3 mmol) were added. After stirring for 18 h at ambient temperature column chromatographic purification of the crude material (yellow oil, 263 mg, 100%) on silica gel (16.3 g, mass ratio crude $\mathbf{3_{4a}}$/SiO_2 1:62) utilizing EtOAc/*n*Hex 7:93 and drying at the rotary evaporator at 10 mbar for 10 min afforded the title ester as a pale yellow oil (232.6 mg, 0.887 mmol, 89%), which turned solid upon storage of ambient temperature overnight.

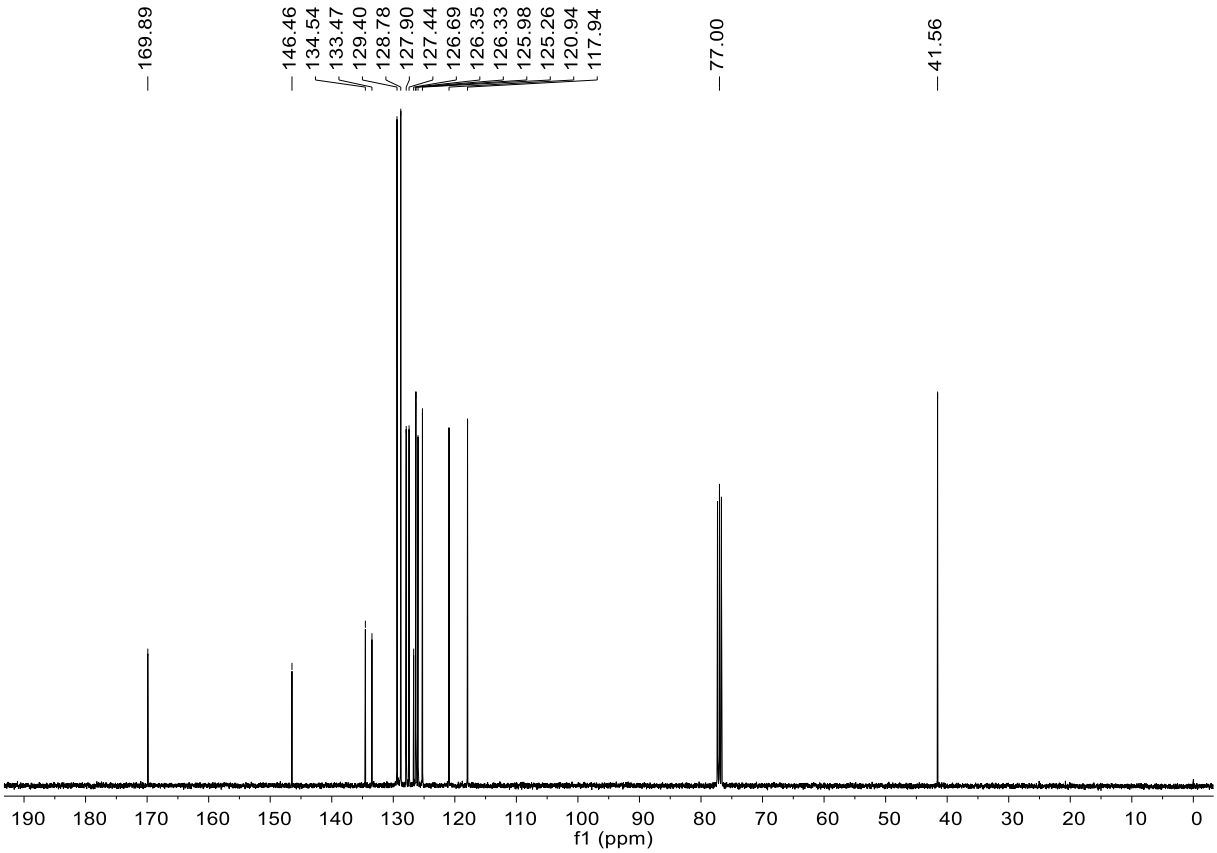


M ($C_{18}H_{14}O_2$) = 262.308 g/mol; **mp.** = 47-49 °C ; **Lit.-mp.** 52 °C;[54] **r_f** (SiO_2, EtOAc/*n*Hex 7:93) = 0.31; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.84 (d, $^3J_{9´,8´}$ = 8.3 Hz, 1H, 9´-H), 7.72 (d, $^3J_{6´,7´}$ = 8.3 Hz, 1H, 6´-H), 7.61 (d, $^3J_{2´,3´}$ = 8.6 Hz, 1H, 2´-H), 7.50-7.38 (m, 8H, 4-H, 5-H, 3´-H, 8´-H, 7´-H), 7.37-7.33 (m, 1H, 6-H) 7.24-7.21 (dd, $^3J_{4´,3´}$ = 7.5 Hz, ^4J = 0.9 Hz, 4´-H), 4.02 (s, 2H, 2-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 169.89 (C-1), 146.46 (C-1´), 134.54 (C-5´ or C-10´), 133.47 (C-3), 129.40 (C-4), 128.78 (C-5), 127.90 (C-9´), 127.44 (C-6), 126.69 (C-10´ or C-5´), 126.35 (C-3´, C-7´ or C-8´), 126.33 (C-3´, C-7´ or C-8´), 125.98 (C-6´), 125.26 (C-3´, C-7´ or C-8´), 120.94 (C-2´), 117.94 (C-4´), 41.56 (C-2); **GC-MS** (CI, 70 eV) m/z [u] (%) = 291 (2, $[M+Et]^+$), 277 (<1, $[M+Me]^+$), 263 (4, $[M+H]^+$), 262 (4, $[M]^+$), 185 (2), 173 (22), 145 (100, $[naphthol+H]^+$), 144 (49, $[naphthol]^+$), 119 (10, $[PhCH_2CO]^+$), 115 (5), 91 (19, $[Bn]^+$); **HR-MS** (CI, 70 eV, $[C_{18}H_{14}O_2]^+$) calc. 262.0994 u found 262.0991 u.

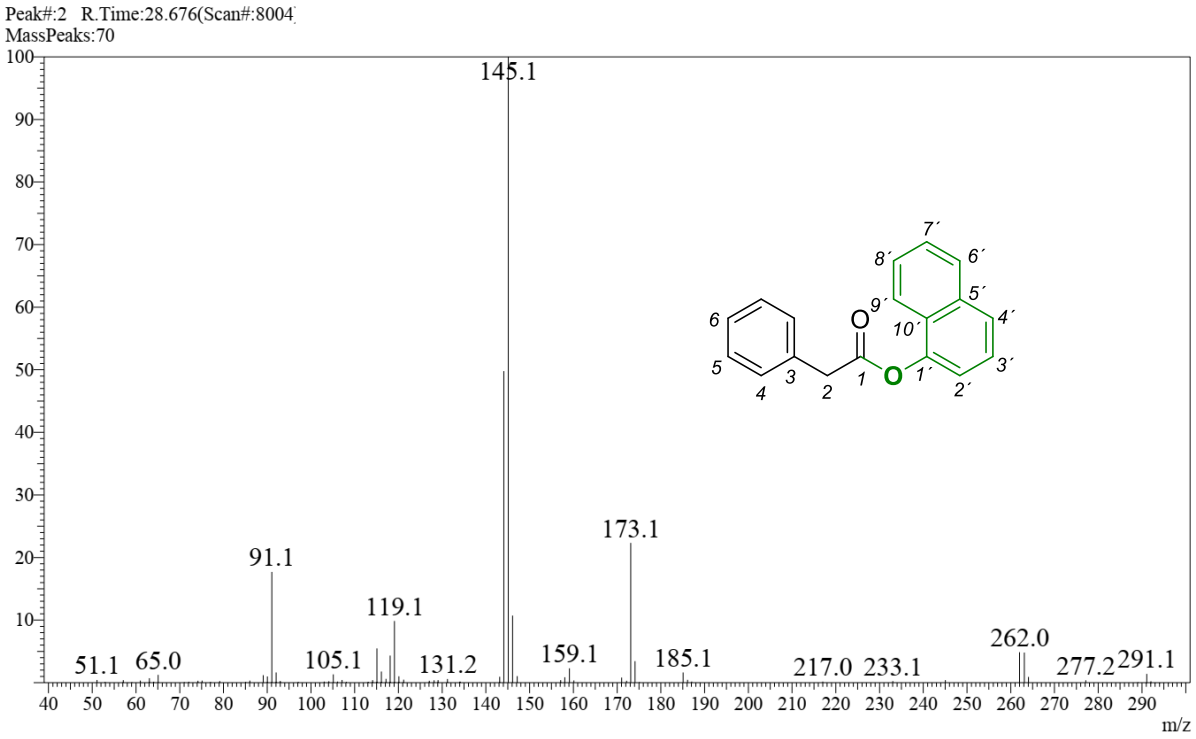
The NMR data is in agreement with the literature.[46]



^{1}H-NMR spectrum of 1-naphthyl 2-phenylethanoate (400 MHz, $CDCl_3$).



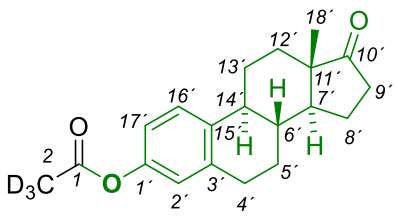
^{13}C-NMR spectrum of 1-naphthyl 2-phenylethanoate (100 MHz, $CDCl_3$).



Mass spectrum of 1-naphthyl 2-phenylethanoate (CI, 70 eV).

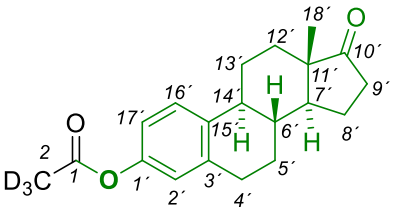
5.4.3.2 Synthesis of O-Trideuteroacetyl estrone (3_{28b})

For the synthesis of the title compound full consumption of estrone was pivotal, since the starting alcohol was difficult to separate from the product.



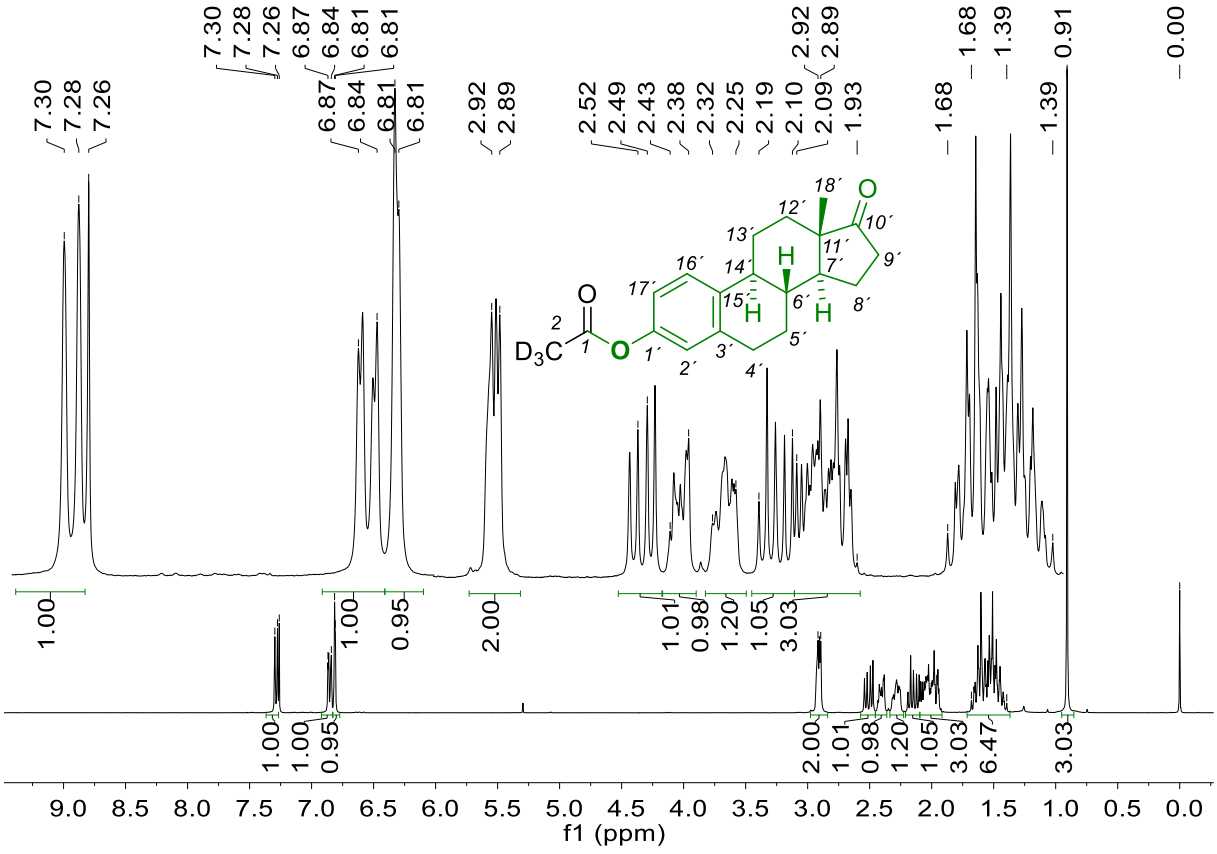
3_{28b}

PH3154: Following general procedure 4 (chapter 5.3.4, page 50) chlorination of tetradeuteroacetic acid (74 μL, 83 mg, 1.30 mmol, 1.3 equiv) was executed with TCT (92 mg, 0.49 mmol, 49 mol%) and FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in EtOAc (0.50 mL, 2 M) under heating for 5 h to 40 °C. Next, the reaction suspension was cooled in an ice bath and sequentially EtOAc (0.50 mL→1 M), estrone (273 mg, 1.00 mol, 1.0 equiv) and a solution of NMM (190 μL, 175 mg, 1.7 mmol, 1.7 equiv) in EtOAc (0.50 mL) were added. After stirring at 2 h at room temperature, DMAP (12.2 mg, 100 μmol, 10 mol%) were added and stirring was continued overnight (14 h). Finally, column chromatographic purification of the crude material (363 mg, 115%, yellow oil; full consumption of estrone as judged by ^{1}H-NMR) on silica gel (24.8 g, mass ratio SiO_2/crude product 69:1) with EtOAc/*n*Hex 25:75 and drying in high vacuum for 2 h afforded the title compound in 88% yield as a colourless solid (281.1 mg, 0.891 mmol).

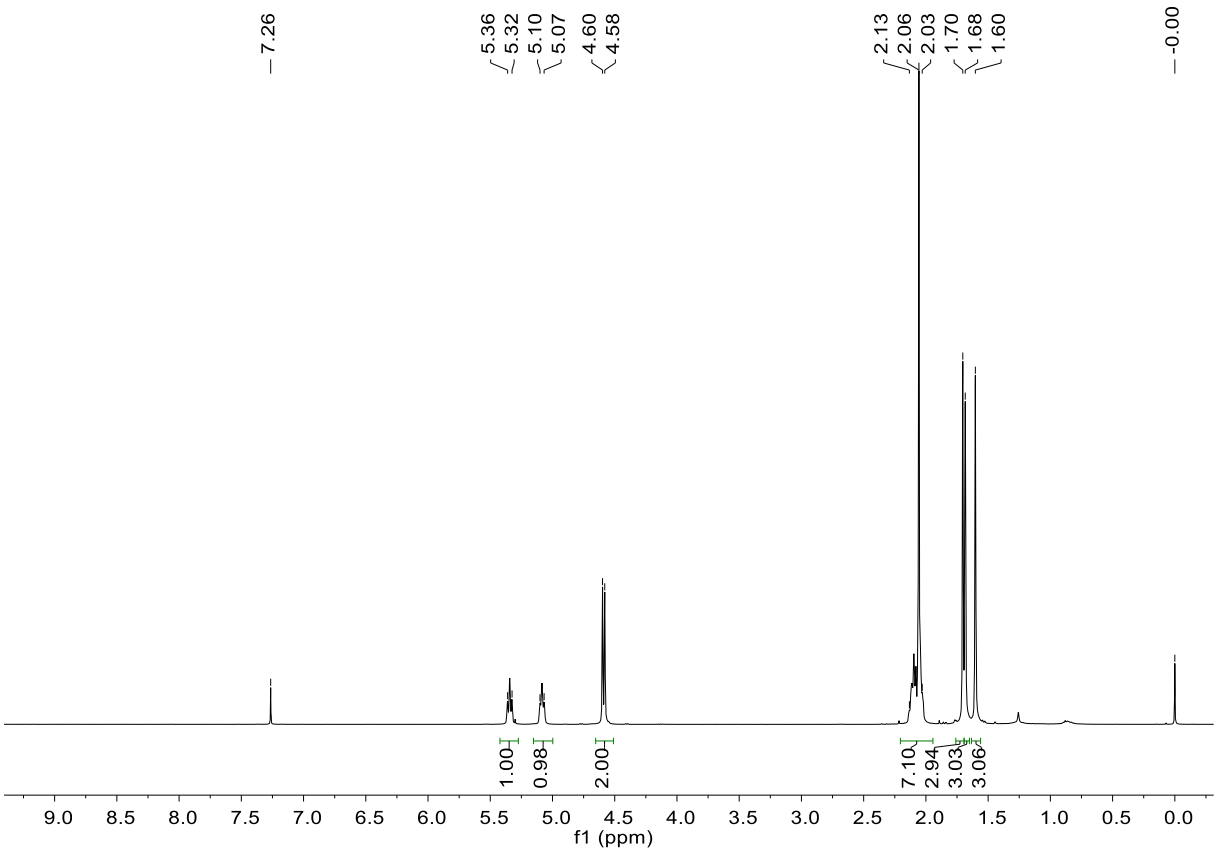


M ($C_{20}H_{21}D_3O_3$) = 315.427 g/mol; **mp**. 120-122 °C; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 25:75) = 0.28; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.29 (d, $^3J_{16',15'}$ = 8.5 Hz, 1H, 16´-H), 6.86 (dd, $^3J_{17',16'}$ = 8.5 Hz, $^4J_{17'.2'}$ = 2.4 Hz, 1H, 17´-H), 6.81-6.80 (m, 1H, 2´-H), 2.92-2.89 (m, 2H, 4´-H), 2.51 (dd, ^3J = 18.5 Hz, ^4J = 8.9 Hz, 1H, 9´-H_a), 2.43-2.38 (m, 1H, 13´-H_a), 2.32-2.25 (m, 1H, 14´-H), 2.19-2.10 (m, 1H, 9´-H_b), 2.09-1.93 (m, 3H, 5´-H_a, 8´-H_a, 12´-H_a), 1.68-1.39 (m, 6H, 5´-H_a, 6´-H, 7´-H, 8´-H_b, 13´-H_b), 0.91 (s, 3H, 18´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 220.63 (C-10´), 169.75 (C-1), 148.45 (C-1´), 137.92 (C-3´), 137.30 (C-15´), 126.32 (C-16´), 121.51 (C-2´), 118.67 (C-17´), 50.33 (C-7´), 47.85 (C-11´), 44.06 (C-14´), 37.90 (C-6´), 35.77 (C-9´), 31.47 (C-12´), 29.32 (C-4´), 26.25 (C-5´), 25.66 (C-13´), 21.51 (C-8´), 20.58 (q, $^1J_{2,D}$ = 19.8 Hz), 13.75 (C-18´); **$[\alpha]_D^{20}$** (c = 1.065 g/100 mL, $CHCl_3$) = +140.2; **HR-MS** (ESI, $[C_{20}H_{21}D_3O_3]^+$) calc. 315.1914 u found 316.1987 u.

The NMR data is in agreement with the literature.[47]

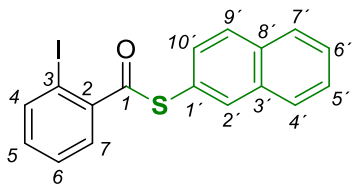


^{1}H-NMR spectrum of O-trideuteroacetyl estrone (400 MHz, $CDCl_3$).



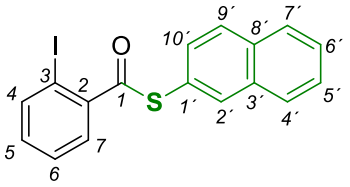
^{13}C-NMR spectrum of O-trideuteroacetyl estrone (100 MHz, $CDCl_3$).

5.4.3.3 Synthesis of *S*-(2-Naphthyl) 2-iodobenzothioate (9_{29a})

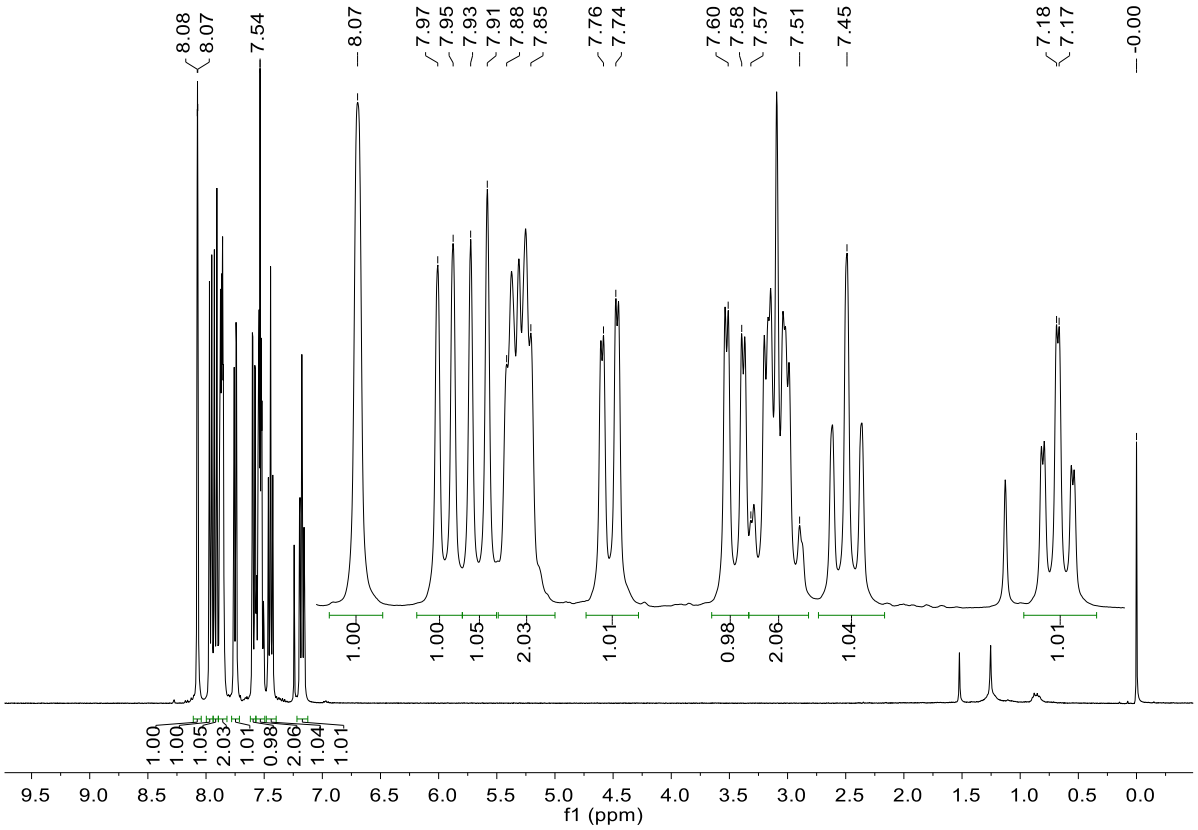


9_{29a}

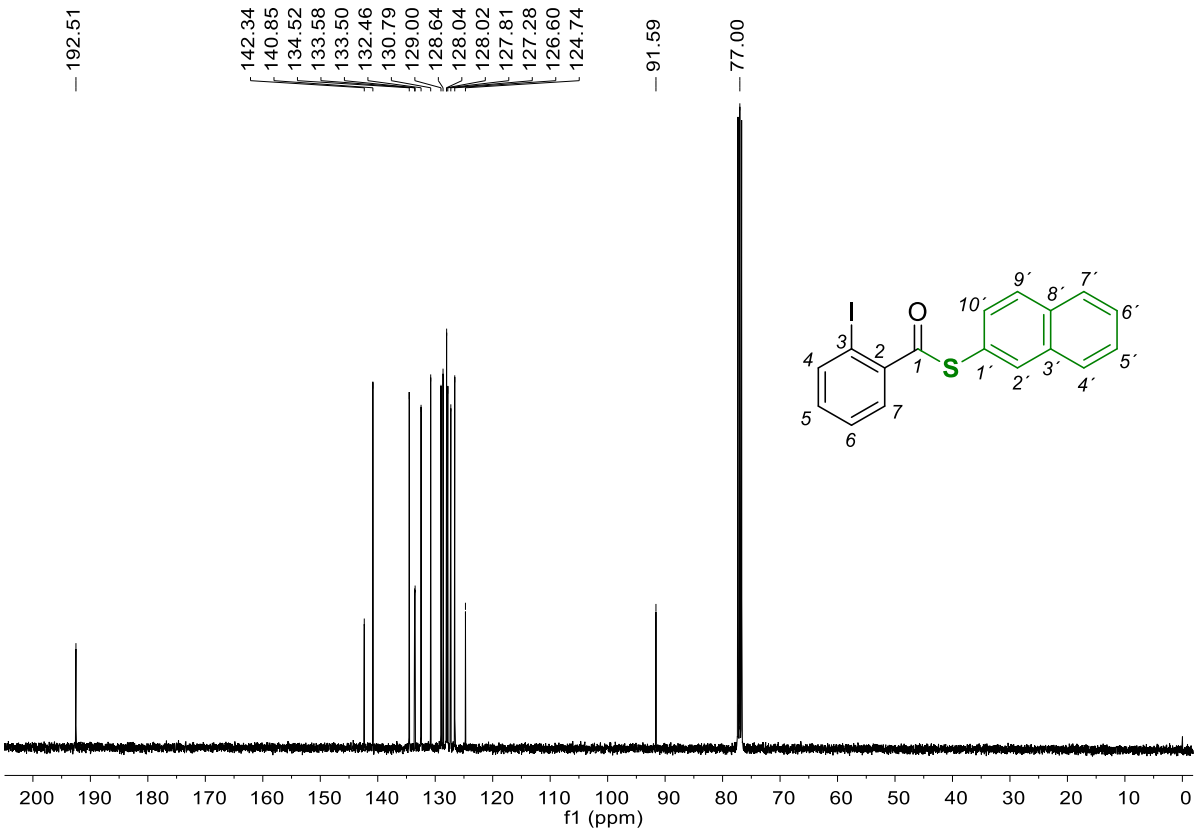
PH3016: As described in general procedure 4 (chapter 5.3.4, page 50) to a suspension of 2-iodobenzoic acid (248 mg, 1.00 mol, 1.0 equiv) and FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) was added TCT (72 mg, 0.38 mmol, 38 mol%) and the resulting mixture was stirred at 80 °C for 5 h. Next, additional MeCN (0.50 mL→1 M) and under cooling to 0 °C 2-naphthylthiol (192 mg, 1.2 mmol, 1.2 equiv) and K_2CO_3 (180 mg, 1.3 equiv) were added. During stirring overnight (14 h) the reaction mixture turned solid. In the end, purification of the crude product (405 mg, 104%, pale brownish solid) with the aid of column chromatography on silica gel (26.1 g, ratio weight crude material/SiO_2 1:64) with toluene/*n*Hex 50:50, concentration with $CHCl_3$ and drying at the rotary evaporator at 5 mbar for 40 min afforded the thioether **9_{29a}** as a pale yellow solid in 84% yield (326.4 mg, 0.837 mmol). In order to charge the silica gel column, the crude material was dissolved in toluene (0.5 mL) under gentle heating with a heat gun.



M ($C_{14}H_{13}NO_2S$) = 390.239 g/mol; **mp.** = 120-122 °C ; $\mathbf{r_f}$ (SiO_2, toluene/*n*Hex 60:40) = 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.07 (s, 1H, 2´-H), 7.96 (d, $^3J_{4,5}$ = 7.9 Hz, 1H, 4-H), 7.92 (d, $^3J_{9´,10´}$ = 8.5 Hz, 1H, 9´-H), 7.88-7.85 (m, 2H, 4´-H, 5´-H, 6´-H or 7´-H), 7.76 (dd, $^3J_{7,6}$ = 7.7 Hz, $^4J_{7,5}$ = 1.4 Hz, 1H, 7-H), 7.59 (dd, $^3J_{10´,9´}$ = 8.6 Hz, $^4J_{10´,2´}$ = 1.6 Hz, 1H, 10´-H), 7.57-7.51 (m, 2H, 4´-H, 5´-H, 6´-H or 7´-H), 7.45 (ψ-t, *J* = 7.4 Hz, 1H, 6-H), 7.18 (ψ-td, ^3J = 7.7 Hz, 1.3 Hz, 1H, 5-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 192.51 (C-1), 142.34 (C-2), 140.85 (C-4), 134.52 (C-2´), 133.58 (C-3´ or C-8´), 133.50 (C-3´ or C-8´), 132.46 (C-5), 130.79 (C-10´), 129.00 (C-9´), 128.64 (C-7), 128.04 (C-4´, C-5´, C-6´ or C-7´), 128.02 (C-4´, C-5´, C-6´ or C-7´), 127.81 (C-6), 127.28 (C-4´, C-5´, C-6´ or C-7´), 126.60 (C-4´, C-5´, C-6´ or C-7´), 124.74 (C-1´), 91.59 (C-3); **HR-MS** (CI, $[C_{17}H_{11}OIS]^+$) calc. 389.957u found 389.9579 u.



^{1}H-NMR spectrum of *S*-(2-naphthyl) 2-iodobenzothioate (400 MHz, $CDCl_3$).



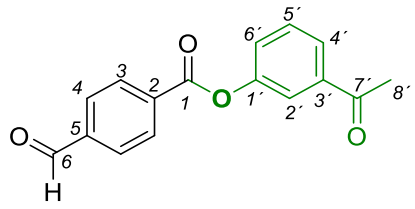
^{13}C-NMR spectrum of *S*-(2-naphthyl) 2-iodobenzothioate (100 MHz, $CDCl_3$).

5.4.3.4 Synthesis of 3-Acetylphenyl 4-formylbenzoate (3_{30c})

entry	conditions	Yield 3_{30c} [%]
1	1. TCT (40 mol%), FPyr (10 mol%), EtOAc (1 M), 1 h 40 °C, 5 h 80 °C 2. ArOH (1.05 equiv), DMAP (10 mol%), NMM (1.3 equiv), EtOAc (0.7 M), 45 min 0 °C then 17 h rt	88[a] (4.7 **g**)
2	1. TCT (40 mol%), FPyr (10 mol%), EtOAc (1 M), 1 h 40 °C, 3 h 80 °C 2. ArOH (1.05 equiv), NMM (1.3 equiv), EtOAc (0.5 M), 30 min 0 °C then 20 h rt	71[a] (**3.8 g**)
3[22]	1. TCT (33 mol%), NMM (1.3 equiv), EtOAc (0.5 M), 15 min 0° C then 1 h rt 2. ArOH (1.2 equiv), 15 min 0° C then 17 h rt	42[b]
4[22]	1. TCT (33 mol%), NMM (1.3 equiv), EtOAc (0.5 M), 15 min 0° C then 1 h rt 2. ArOH (1.2 equiv), **DMAP (10 mol%)**, 15 min 0° C then 17 h rt	36[b]

a. Yield determined from mass of isolated material after distillation and precipitation, respectively. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of dibenzylether as internal standard. ArOH = 3-Acetylphenol.

For the synthesis of the title compound in good yields DMAP (10 mol%) was crucial in the esterification step (entry 1). Without usage of DMAP the aromatic ester **3_{29c}** was isolated in a deteriorated yield of 71% (entry 2). The literature protocol [22] facilitated the preparation of ester **3_{29c}** in a reduced yield of 42% (entry 3), which could not be improved by application of DMAP (36%, entry 4).



3_{30c}

Entry 1, PH3704: As described in general procedure 4 (chapter 5.3.4, page 50) 4-formylbenzoic acid (3.00 g, 20.0 mmol, 1.0 equiv) was reacted with TCT (1.51 g, 8.0 mmol, 40 mol%) in the presence of FPyr (197 μL, 204 mg, 2.00 mmol, 10 mol%) in EtOAc (10 mL, 2 M) initially for 1 h at 40 °C and subsequently for 5 h at 80 °C. After cooling down to room temperature, the pale yellow reaction suspension was diluted with additional EtOAc (15 mL→0.8 M), cooled to 0 °C and 3-acetylphenol (2.86 g, 21.0 mmol, 1.05 equiv) and DMAP (244 mg, 2.00 mmol, 10 mol%) were added in single portions. Next, NMM (2.9 mL, 26.0 mmol, 1.3 equiv) was added under vigorous stirring by means of a syringe pump within 15 min. During stirring overnight (12 h) the reaction mixture turned solid, was hence diluted with further EtOAc (20 mL→0.7 M) and stirred for additional 5 h.

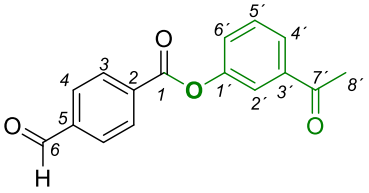
In the following, the reaction mixture was diluted with 2 N HCl solution (20 mL) and filtered over a sintered funnel (porosity level 3, diameter 6 cm) by suction and the filtrate was transferred to a 250 mL extraction funnel. The reaction flask/filter cake was rinsed/triturated with a spatula with more EtOAc/1 N HCl solution in water (20 mL/10 mL). From the collected filtrates the organic phase was separated, washed with 1 N NaOH solution (aq., 1 x 30 mL) and brine (1 x 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Eventually, the crude material (4.97 g, 93%, yellow solid) was purified by means of column chromatography on silica gel (101 g, mass ratio crude **3_{30c}**/SiO_2 1:20) using EtOAc/CH_2Cl_2 4:96 as eluent. Concentration with $CH_2Cl_2$and drying at the rotary evaporator for 30 min at 5 mbar furnished the title compound as a colourless solid in 88% yield (4.705 g, 17.5 mmol). Since the poor solubility of the title ester in the eluent, the crude material was dissolved in CH_2Cl_2 (30 mL), SiO_2 (9.4 g, relation of weight crude product/SiO_2 1:1.9) was added, all volatiles were removed *in vacuo* and the residue was loaded onto the silica gel column.

Entry 2, PH3696: The reaction was basically conducted as elaborated in entry 1 with the exception that no DMAP was used. The reaction durations were marginally varied, since for the transformation of **1_{29}** into the respective acid chloride the reaction mixture was heated to 40 °C for 1 h and then to 80 °C for 3 h and in the second step stirring was pursued for 20 h at room temperature. Eventually, column chromatographic purification of the crude material (4.53 g, 84%, yellow solid) on silica gel (101 g, ratio mass crude **3_{29c}**/SiO_2 1:22) using EtOAc/CH_2Cl_2, 3:97→5:95 furnished the title compound as a colourless solid (3.821 g, 14.2 mmol, 71%). In order to charge the silica gel column, the crude material was adsorbed on silica gel (8.8 g, relation crude title compound with respect to SiO_2 1:2),

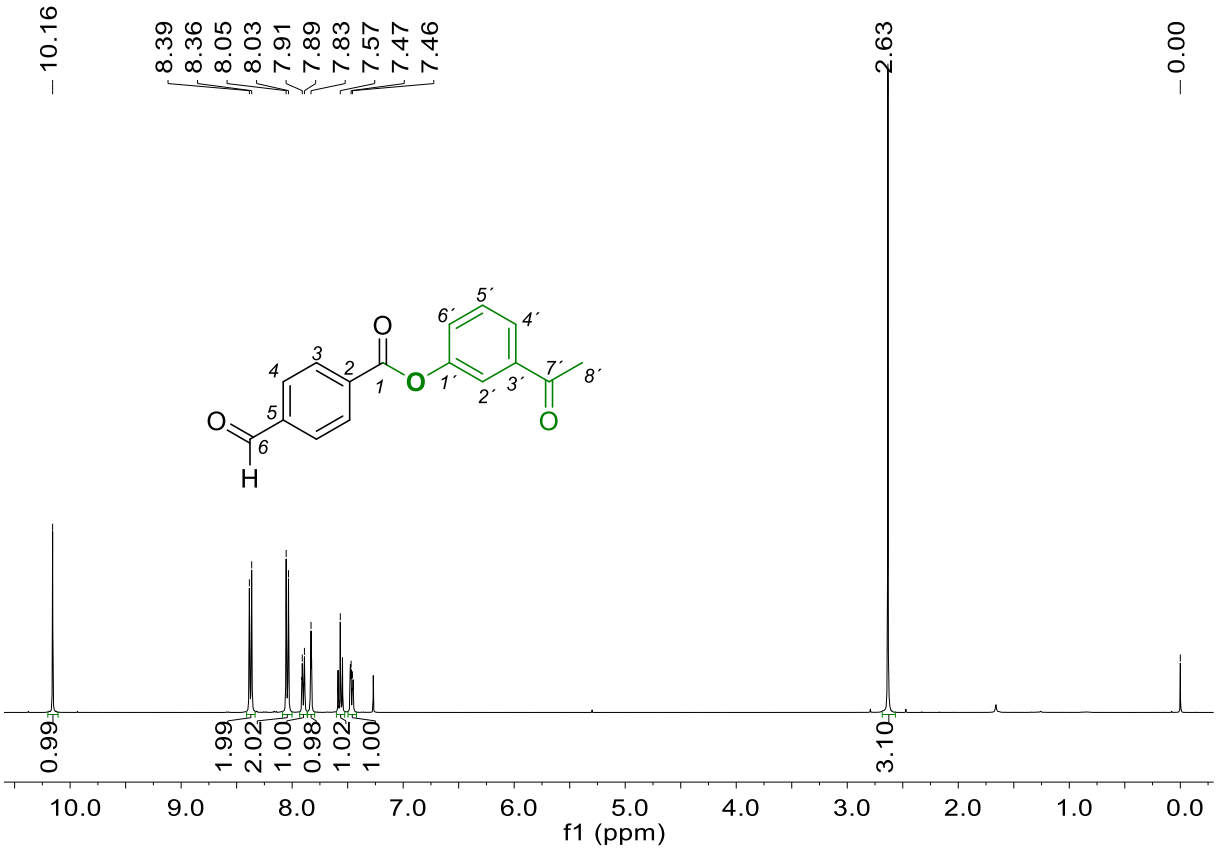
Entry 3, PH3710: According to literature protocol [22] (general procedure 5, chapter 5.3.5, page 56) 4-formylbenzoic acid (75 mg, 0.50 mmol, 1.0 equiv) was combined with EtOAc (0.50 mL, 1 M), TCT (31 mg, 0.165 mmol, 33 mol%) and under ice bath chilling with NMM

(75 μL, 0.65 mmol, 1.3 equiv), diluted with further EtOAc (0.50 mL→0.5 M) to enhance stirability and stirred for 1 h at ambient temperature. Subsequently, 3-acetylphenol (82 mg, 0.60 mmol, 1.2 equiv) was introduced at 0 °C and the resulting mixture was stride overnight at room temperature. ^{1}H-NMR after aqueous work up using dibenzylether (30.8 mg) as internal standard showed the title compound in 42% yield.

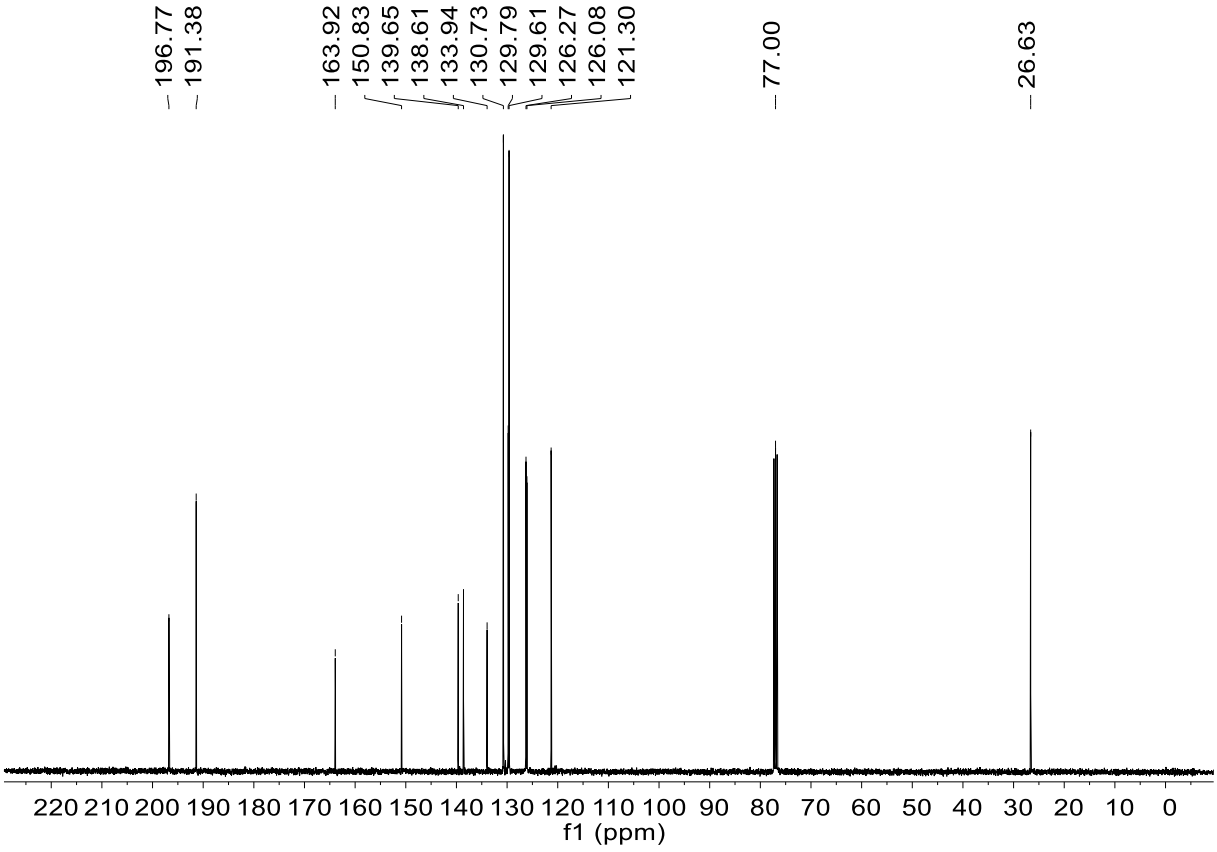
Entry 4, PH3711: This experiment was performed as stated in entry 3 with the deviation that **DMAP** (6.2 mg, 50 μmol, 10 mol%) was added at 0 °C after addition of the aromatic alcohol. After all, ^{1}H-NMR of the crude material with dibenzylether (27.6 mg) as internal standard uncovered the ester **3$_{30c}$** in a yield of 36%.



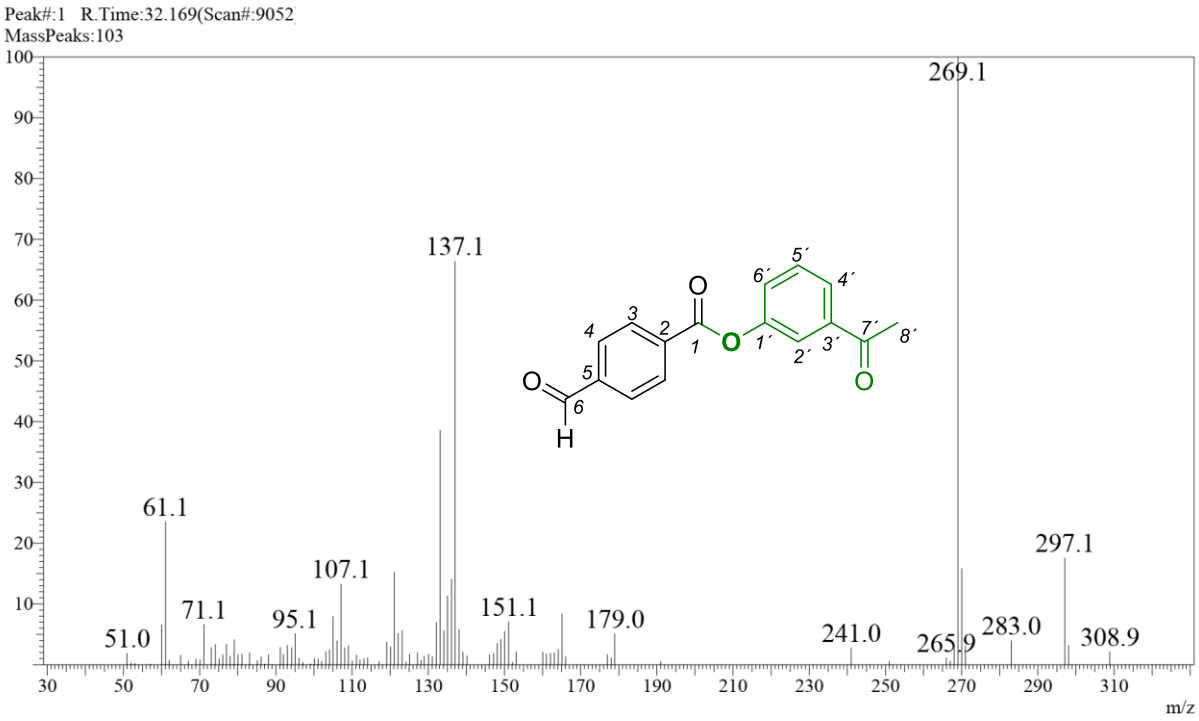
M ($C_{16}H_{12}O_4$) = 268.268 g/mol; **mp.** 108-110 °C; **r$_f$** (SiO_2, EtOAc/CH_2Cl_2 3:97) = 0.27; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 10.16 (s, 1H, 6-H), 8.39-8.36 (m, 2-H, 3-H), 8.05-8.03 (m, 2H, 4--H), 7.90 (ψ-dt, *J* = 7.8 Hz, 1.3 Hz, 1H, 4´-H), 7.83 (ψ–t, *J* = 1.8 Hz, 1H, 2´-H), 7.57 (ψ-t, *J* = 7.8 Hz, 1H, 5´-H), 7.47 (ddd, *J* = 8.1 Hz, 2.3 Hz, 1.0 Hz, 1H, 6´-H), 2.63 (s, 3H, 8´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 196.77 (C-7´), 191.38 (C-6), 163.92 (C-1), 150.83 (C-1´), 139.65 (C-5), 138.61 (C-3´), 133.94 (C-2), 130.73 (C-3), 129.79 (C-5´), 129.61 (C-4), 126.27 (C-6´), 126.08 (C-4´), 121.30 (C-2´), 26.63 (C-8´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 309 (2, $[M+allyl]^+$), 297 (19, $[M+Et]^+$), 283 (4, $[M+Me]^+$), 269 (100, $[M+H]^+$), 241 (3, $[M+H-CHO]^+$), 179 (5), 165 (10), 151 (10, $[4\text{-}OHC(C_6H_4)C(OH)_2]^+$), 137 (66, $[3\text{-}HO(C_6H_4)C(=OH)CH_3]^+$), 135 (39, $[3\text{-}O(C_6H_4)C(=O)CH_3]^+$), 116 (15), 107 (15, $[PhC(=OH)H]^+$), 61 (25); **HR-MS** (EI, $[C_{16}H_{12}O_4]^+$) calc.- 268.0736 u found 268.0710 u.



^{1}H-NMR spectrum of 3-acetylphenyl 4-formylbenzoate (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of 3-acetylphenyl 4-formylbenzoate (100 MHz, $CDCl_3$).



Mass spectrum of 3-acetylphenyl 4-formylbenzoate (CI, 70 eV).

5.4.3.5 Synthesis of *rac*-(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl hexadodecanoate (3_{31d})

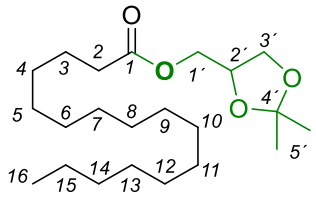
entry	equiv 1_{30}	conditions	Yield 3_{31d} [%]
1	1.1	1. TCT (44 mol%), FPyr (10 mol%), EtOAc (1 M), 1 h 40 °C, 5 h 80 °C 2. ROH (1.0 equiv), DMAP (10 mol%), NMM (2.3 equiv), EtOAc (0.5 M), 15 min 0 °C then 17 h rt	86[a] (**3.2 g**)
2	1.1	1. TCT (44 mol%), FPyr (15 mol%), EtOAc (1 M), 1 h 40 °C, 4 h 80 °C 2. ROH (1.0 equiv), DMAP (10 mol%), NMM (**1.4 equiv**), EtOAc (0.5 M), 15 min 0 °C then 17 h rt	83[a] (**3.1 g**)
3	1.1	1. TCT (44 mol%), FPyr (15 mol%), EtOAc (1 M), 1 h 40 °C, 5 h 80 °C 2. ROH (1.0 equiv), NMM (1.4 equiv), EtOAc (0.5 M), 15 min 0 °C then 1.5 h rt 3. DMAP (10 mol%), 14 h rt	84[a] (**3.1 g**)
4	1.3	1. TCT (**49 mol%**), FPyr (10 mol%), **MeCN** (1 M), 4 h 40 °C 2. ROH (1.0 equiv), NMM (**1.7 equiv**), **MeCN** (0.5 M), 15 min 0 °C then 1.5 h rt 3. DMAP (10 mol%), 16 h rt	82[a] (**3.0 g**)
5	1.3	1. TCT (49 mol%), FPyr (10 mol%), MeCN (2 M), 5 h 40 °C 2. ROH (1.0 equiv), NMM (1.7 equiv), MeCN (0.7 M), 15 min 0 °C then 15 h rt	65[a]
6	1.0	1. TCT (**38 mol%**), FPyr (10 mol%), MeCN (2 M), 5 h 40 °C 2. ROH (1.0 equiv), NMM (1.7 equiv), MeCN (0.8 M), 15 min 0 °C then 14 h rt	64[a]
7[22]	1.0	1. TCT (33 mol%), NMM (1.3 equiv), EtOAc (0.5 M), 15 min 0° C then 1 h rt 2. ROH (1.2 equiv), 15 min 0° C then 20 h rt	8[b]
8[22]	1.0	1. TCT (33 mol%), NMM (1.3 equiv), EtOAc (1 M), 15 min 0° C then 1 h rt 2. ROH (1.2 equiv), **DMAP (10 mol%)**, 15 min 0° C then 20 h rt	50[b]

a. Yield determined from mass of isolated material after distillation and precipitation, respectively. b. Yield determined from ^{1}H-NMR spectra of the crude products by means of dibenzylether as internal standard. ROH = *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol.

Using 1.1 equiv palmitic acid and DMAP (10 mol%) in EtOAc the title compound was prepared on in 86% on a multigram scale (entry 1). Thereby, addition of the intermediately formed hexanoic acid chloride to a solution of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (1.0 equiv) containing NMM and DMAP was crucial. A reduction of the amount of NMM from 2.3 to 1.4 equiv caused a slightly lower yield of 83% (entry 2). Notably, DMAP can also be added to the reaction mixture after 1-2 h of stirring, which gave rise to the title ester in 84% yield (entry 3). Addition of the base NMM to a mixture of hexadecanoyl choride and the primary alcohol also provided the palmitate **3_{31d}** in an acceptable yield of 82%, when MeCN was applied as solvent (entry 4).

That DMAP is crucial for high yields was demonstrated through two experiment in its absence, which furnished the title compound in only 64-65% yield (entries 5+6). Remarkably, a literature protocol based on TCT (33 mol%) and NMM afforded ester **3_{31d}** in only 8% yield (entry 7). Nevertheless, when DMAP was engaged, which has not been reported in the

literature, the yield could be enhanced to still moderate 50%. The work up had to be conducted with KOH instead of NaOH solution, because in the latter case a poorly soluble precipitate formed (probably sodium hexadodecanoate), which strongly hampered phase separation.



3_{31d}

Entry 1, PH3730: According to general procedure 4 (chapter 5.3.4, page 50) a suspension of hexadodecanoic acid (palmitic acid, 2.82 g, 11.0 mmol, 1.0 equiv) and FPyr (98 μL, 102 mg, 1.00 mmol, 10 mol%) in reagent-grade EtOAc (5 mL) in a 50 mL flask was treated with TCT (828 mg, 4.4 mmol, 44 mol%) in one portion and the resulting mixture was successively stirred for 1 h at 40 and 5 h at 80 °C. After cooling down to ambient temperature for 20 min, additional EtOAc (5 mL→1 M) was added and the reaction suspension was stirred in an ice bath for 5 min. Next, the suspension containing palmitoyl chloride was filtered by suction through a sintered funnel (porosity level 3, 2 cm diameter) and the filtrate was transferred to a dropping funnel.(55) The reaction flask/the filter cake was rinsed/triturated with a spatula with further EtOAc (2 x 2 mL).(56) The collected filtrates were added dropwise over 30 min under vigorous stirring to a solution of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (1.24 mL, 1.32 g, 10.0 mmol, 1.0 equiv), NMM (2.58 mL, 23.0 mmol, 2.3 equiv) and DMAP (122 mg, 1.00 mmol, 10 mol%) in EtOAc (10 mL, 1 M) in a 100 mL flask under cooling in an ice bath and stirring was continued at ambient temperature for 17 h.

Next, the colourless reaction suspension was diluted with 2 N HCl solution in water (10 mL), stirred for 10 min and filtered through a sintered funnel (porosity level 3, 2 cm diameter) by suction and the filtrate was poured into a 100 mL extraction funnel. The reaction flask/the filter cake were additionally rinsed/triturated with a spatula with EtOAc/2 N HCl solution (10 mL/5 mL). From the combined filtrates the organic phase was separated and washed with aqueous 1 N KOH solution, whereby complete phase separation required 60 min.(57) Then, the organic phase was dried over $MgSO_4$ under stirring for 5 min and filtered through sintered

(55) In related experiments attempted transfer of the acid chloride containing suspension to the reaction solution with the alcohol nucleophile, NMM and DMAP by means of a transfer cannula resulted in clogging of the cannula. Moreover, addition of the reaction suspension (without previous filtration) through a dropping funnel can also not be recommended, because the valve of the funnel gets easily blocked by the precipitated.

(56) A 40 μL aliquot of the filtrate was dried at the rotary evaporator for 5 min at 20 mbar. ^{1}H-NMR of the residue indicated ≥98% conversion of the starting material and 6 mol% residual FPyr. The conversion was determined by the ratios of the integrals of the triplets of the CH_2-groups next to the carbonyl groups of palmitic acid at 2.35 ppm, palmitoyl chloride at 2.88 and anhydride at 2.44 ppm.

(57) Washing with brine also caused a solid precipitate, which hindered phase separation. Application of saturated KCl solution in water (10 mL) resulted in a slow phase separation.

funnel (porosity level 3, diameter 2 cm) by suction.[58] Finally, removal of all volatiles *in vacuo* and drying for 5 min at 5 mbar at the rotary evaporator furnished the crude title compound as a colourless oil containing precipitate (3.54 g, 95%), of which ^{1}H-NMR verified full consumption of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol. In the end, column chromatographic purification on silica gel (118 g, relation of masses crude material/SiO_2 1:33) with EtOAc/PE 10:90 afforded the title compound as a colourless oil (3.171 g, 8.56 mmol, 86%), which turned solid upon storage at ambient temperature. In order to load the crude product on the silica gel column, it was diluted with the eluent (3 mL).[59]

Entry 2, PH3728: Initially, chlorination of palmitic acid (11.0 mmol, 1.1 equiv) was effected through heating to 40 °C for 1 h and subsequently 80 °C for 4 h with FPyr (147 μL, 153 mg, 1.50 mmol, 15 mol%) in EtOAc (5 mL, 2 M) as described in general procedure 4 (chapter 5.3.4, page 50). Then, the reaction suspension was filtered through a sintered funnel as stated in entry 1.[60] The filtrate was added under vigorous stirring and cooling to 0 °C within 20 min to a solution of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (10.0 mmol, 1.0 equiv), NMM (1.57 mL, 14.0 mmol, 1.4 equiv) and DMAP (10 mol%) and the resulting suspension was allowed to stir for 17 h at room temperature. Work up as given in entry 1 gave rise to the crude title ester as a colourless oil (3.51 g, 95%), whereby ^{1}H-NMR proved full conversion of the nucleophilic alcohol. In the end, purification by means of column chromatography on silica gel (124 g, ratio weight crude material 1:35) with EtOAc/PE 10:90 allowed to isolate the ester **3_{31d}** as a colourless oil (3.066 g, 8.27 mmol, 83%), which turned solid at ambient temperature.

Entry 3, PH3727: Applying general protocol 4 (chapter 5.3.4, page 50) chlorination of hexadecanoic acid (11.0 mmol, 1.1 equiv) was accomplished with TCT (44 mol%) and FPyr (15 mol%) in EtOAc (2 M) by means of stirring for 1 h at 40 °C and 5 h at 80 °C. In the following, the reaction suspension was filtered through a sintered funnel as stated in entry 1.[61] Then, the filtrate was added via a dropping funnel within 15 min to a solution of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (10.0 mmol, 1.0 equiv) and NMM (1.4 equiv) in EtOAc (1 M) under chilling in an ice bath and the reaction suspension was stirred for 1.5 h at room temperature. Next, DMAP (10 mol%) was added and stirring was resumed for 14 h. Work as according to

(58) During filtration through a plug of wool, a solid precipitate (likely magnesium hexadodecanoate) could not be retained.

(59) Storage of the crude material usually resulted in solidification. In this case, the crude material could not be dissolved in the eluent anymore. Instead, it had to be adsorbed on silica gel through dissolution in CH_2Cl_2, addition of silica gel and concentration in order to be loaded onto the silica column. To avoid solidification, the crude material could also store in the water bath of the rotary evaporator at 40 °C.

(60) Drying of a 40 μL aliquot at the rotary evaporator for 5 min at 20 mbar and ^{1}H-NMR of the residue confirmed a conversion of 96% and 8 mol% of remaining FPyr

(61) Drying of a 40 μL aliquot at the rotary evaporator for 5 min at 20 mbar and ^{1}H-NMR of the residue showed a conversion of ≥98% and 5 mol% residual FPyr.

entry 1 delivered the crude product as a colourless oil (3.37 g, 91%), of which ^{1}H-NMR revealed full consumption of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol. After all, purification with the aid of column chromatography on SiO_2 (112 g, mass ratio crude material/SiO_2 1:32) employing EtOAc/*n*Hex 10:90 as eluent mixture furnished the palmitate **3_{31d}** as a colourless solid upon storage at ambient temperature (3.106 g, 8.38 mmol, 84%).

Entry 4, PH3147: Based on general protocol 4 (chapter 5.3.4, page 50) hexadecanoic acid (3.33 g, 13.0 mmol, 1.3 equiv) was reacted with TCT (922 mg, 4.9 mmol, 49 mol%) in the presence of FPyr (10 mol%) in MeCN (dry, 5 mL, 2 M) at 40 °C for 4 h. After dilution with further MeCN (5 mL→1 M) and cooling in an ice bath, a solution of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (10.0 mmol, 1.0 equiv) and NMM (1.91 mL, 1.75 g, 17.0 mmol, 1.7 equiv) in MeCN (10 mL, 1 M) was added by means of a dropping funnel in 10 min under vigorous stirring. Past 1.5 h of stirring at room temperature DMAP (10 mol%) was introduced and the reaction suspension was stirred for additional 16 h. Aqueous work up as given in footnote (44) on page 54 with KOH instead of NaOH solution gave rise to the crude material as colourless, turbid oil (3.81 g, 103%). Ultimately, column chromatography on silica gel (120 g, relation of weight crude product/SiO_2 1:32) with EtOAc/PE delivered the title compound as a colourless oil (3.040 g, 8.20 mmol, 82%), whereat storage at room resulted in solidification.

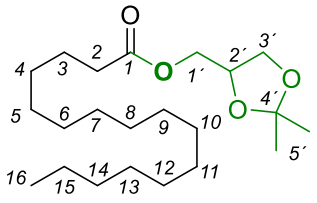
Entry 5, PH3114: Engaging on general protocol 4 (chapter 5.3.4, page 50) to a suspension of palmitic acid (333 mg, 1.30 mmol, 1.3 equiv) and FPyr (9.8 μL, 10.2 mg, 100 μL, 10 mol%) in MeCN (0.50 mL, 2 M) was added TCT (92 mg, 0.49 mmol, 49 mol%) and the mixture was stirred at 40 °C for 5 h. Next, MeCN (0.50 mL→1 M), a solution of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (132 mg, 1.00 mmol, 1.0 equiv) in MeCN (0.50 mL, 2 M) and NMM (190 μL, 1.7 mmol, 1.7 equiv) were added under cooling in an ice bath. After stirring for 15 h at room temperature aqueous work up with KOH instead of NaOH-solution and washing with 2 N HCl solution furnished the crude material as a colourless solid (452 mg, 122 %). In the end, column chromatographic purification on silica gel (22.9 g, mass ratio SiO_2/crude product (51:1) with EtOAc/*n*Hex facilitated the isolation of the title compound as a colourless solid (239.7 mg, 0.647 mmol, 65%). In order to charge the silica gel column, the crude material was adsorbed on silica gel (1.13 g, relation weight of crude material/silica gel 1:2.5).

Entry 6, PH3097: In agreement with general procedure 4 (chapter 5.3.4, page 50) carboxylic acid **1_{30}** (256 mg, 1.00 mmol, 1.0 equiv) was transformed into the corresponding acid chloride using TCT (72 mg, 0.38 mmol, 38 mol%), FPyr (10 mol%) and MeCN (2 M) through heating to 40 °C for 4 h. Subsequently, the reaction suspension was cooled in an ice bath and successively a solution of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (159 mg, 1.20 mmol, 1.2 equiv) in MeCN (0.75 mL→0.8 M) and NMM (150 μL, 1.30 mmol, 1.3 equiv) were added and the reaction mixture was stirred for 14 h at room temperature. Aqueous work up with KOH instead of NaOH-solution and washing with 2 N HCl solution furnished the crude material as a

colourless, slightly turbid oil (340 mg, 92%). Eventually, column chromatographic purification on silica gel (24.0 g, mass ratio crude **3_{31d}**/SiO_2 1:71) with EtOAc/*n*Hex 10:90 furnsihed the aliphatic ester **3_{31d}** as a colourless solid (233.9 mg, 0.631 mmol, 63%). In order to charge the SiO_2 column with the crude title compound, the crude material was dissolved in CH_2Cl_2 (0.3 mL) and diluted with the eluent (0.3 mL).

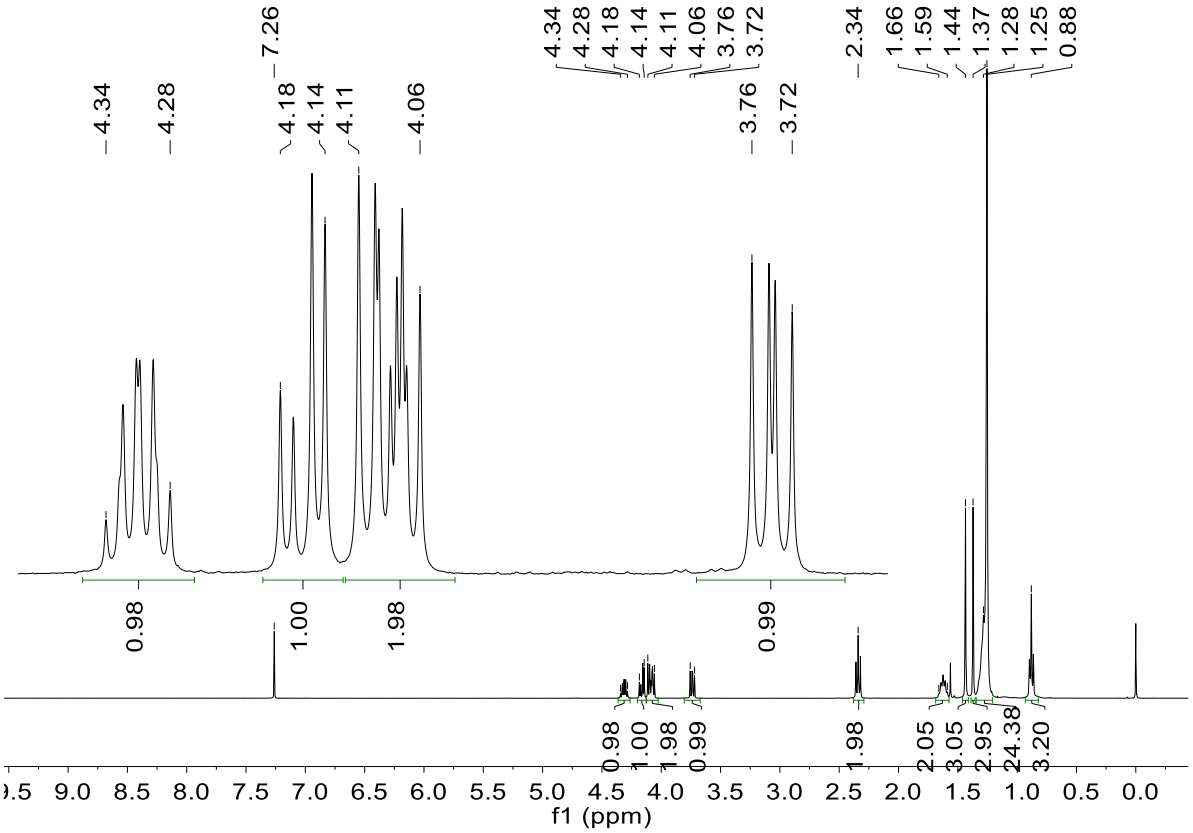
Entry 7, PH3721: Based on the procedure of Ralye [22] (general procedure 5 in chapter 5.3.5 on page 56) a mixture of palmitic acid (128 mg, 0.50 mmol, 1.0 equiv) in EtOAc (1.0 mL, 0.5 M) was treated with TCT (31 mg, 0.165 mmol, 33 mol%) and at 0 °C with NMM (75 μL, 0.65 mmol, 1.3 equiv). After 15 min of stirring at 0 °C and 1 h at room temperature, *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol (75 μL, 0.60 mmol, 1.2 equiv) was added under ice bath chilling. After 15 min the ice bath was removed and the mixture was stirred for 20 h at room temperature. Work up with KOH instead of NaOH solution and ^{1}H-NMR with dibenzylether (27.0 mg) confirmed the title compound in 8% yield. Thereby, the crude material was heated with the NMR-standard in $CDCl_3$ (1 mL) by means of a heat gun and the resulting suspension was filtered over a plug of wool with a 5 mm layer of $MgSO_4$.

Entry 8, PH3722: The present experiment was conducted as described in entry 7 with the exception that DMAP (6.1 mg, 50 μmol, 10 mol%) were added straight after treatment of the reaction mixture with *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methanol. ^{1}H-NMR with dibenzylether as internal standard (28.8 mg) revealed the title molecule in 50% yield.

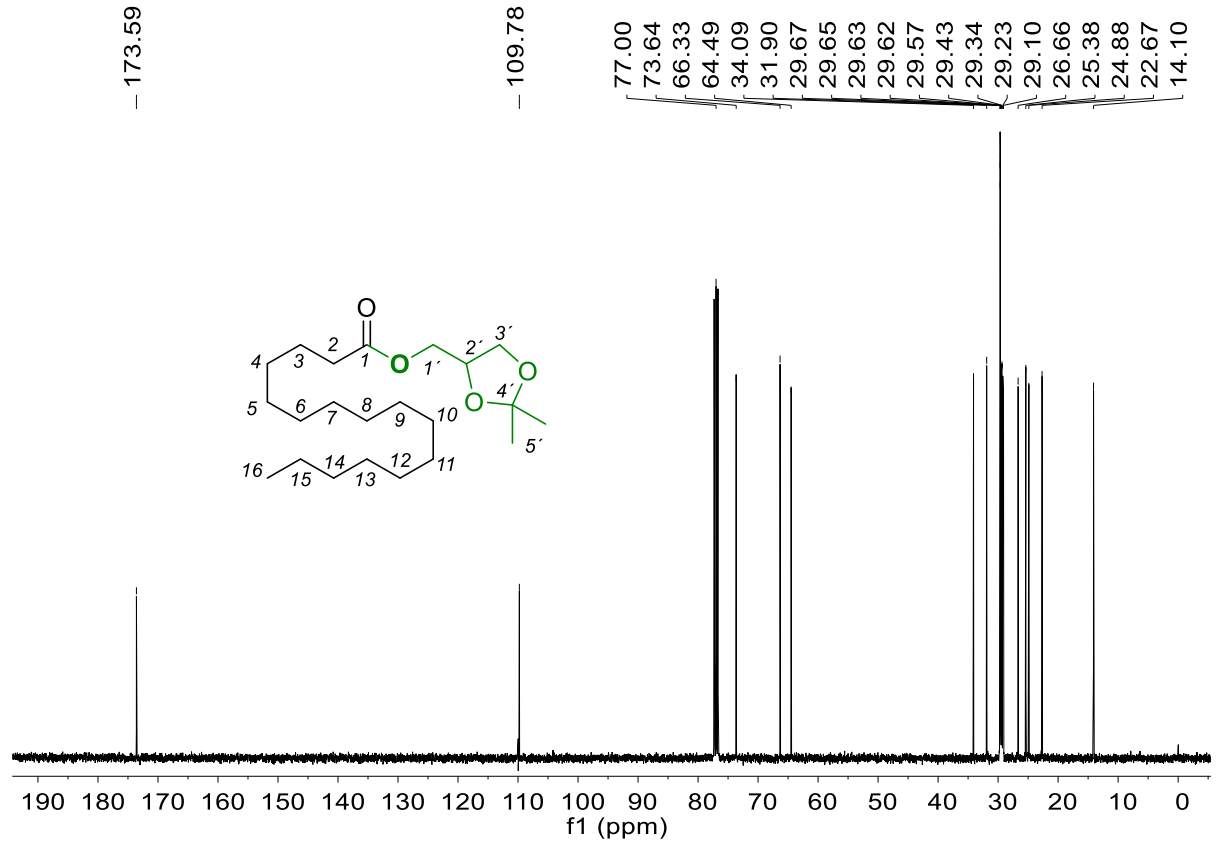


M ($C_{22}H_{42}O_2$) = 370.574 g/mol; **mp.** = 32-33 °C ; **r_f** (SiO_2, EtOAc/*n*Hex 10:90) = 0.32; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 4.34-4.28 (m, 1H, 2´-), 4.16 (dd, ^2J = 11.5, ^3J = 4.7 Hz, 1H, 1´-H_a), 4.11-4.06 (m, 2H, 1´-H_b, 3´-H_a), 3.74 (dd, ^3J = 8.4, 6.2 Hz, 1H, 3´-H_b), 2.34 (t, $^3J_{2,3}$ = 7.7 Hz, 2H, 2-H), 1.66-1.59 (m, 2H, 3-H), 1.44 (s, 3H, 5´-H), 1.37 (s, 3H, 5´-H), 1.28-1.25 (m, 24H, 4-H to 15-H), 0.88 (t, $^3J_{16,15}$ = 7.0 Hz, 3H, 16-H); **^{13}C-NMR** (100 MH z, $CDCl_3$) δ [ppm] = 173.59 (C-1), 109.78 (C-4´), 73.64 (C-2´), 66.33 (C-3´), 64.49 (C-1´), 34.09 (C-3), 31.90, 29.67, 29.65, 29.63, 29.62, 29.57, 29.43, 29.34, 29.23 (C-5 to C-15), 29.10 (C-4), 26.66 (C-5´$_a$), 25.38 (C-5´$_b$), 24.88 (C-3´), 22.67 (C-5 to C-15), 14.10 (C-16); **GC-MS** (CI, 70 eV) m/z [u] (%) = 369 (5, $[M-H]^+$), 356 (8, $[M-CH_3+H]^+$), 355 (34, $[M-CH_3]^+$), 341 (12, $[M-Et]^+$), 313 (100, $[M-Bu]^+$), 311 (72, [M-H-acetone]$^+$), 297 (5), 283 (2), 269 (2), 239 (4), 115 (26, $[CH_2(CHCH_2)O_2C(CH_3)_2]^+$), 101 (10, $[(CHCH_2)O_2C(CH_3)_2]^+$), 59 (65, [acetone+H]$^+$).

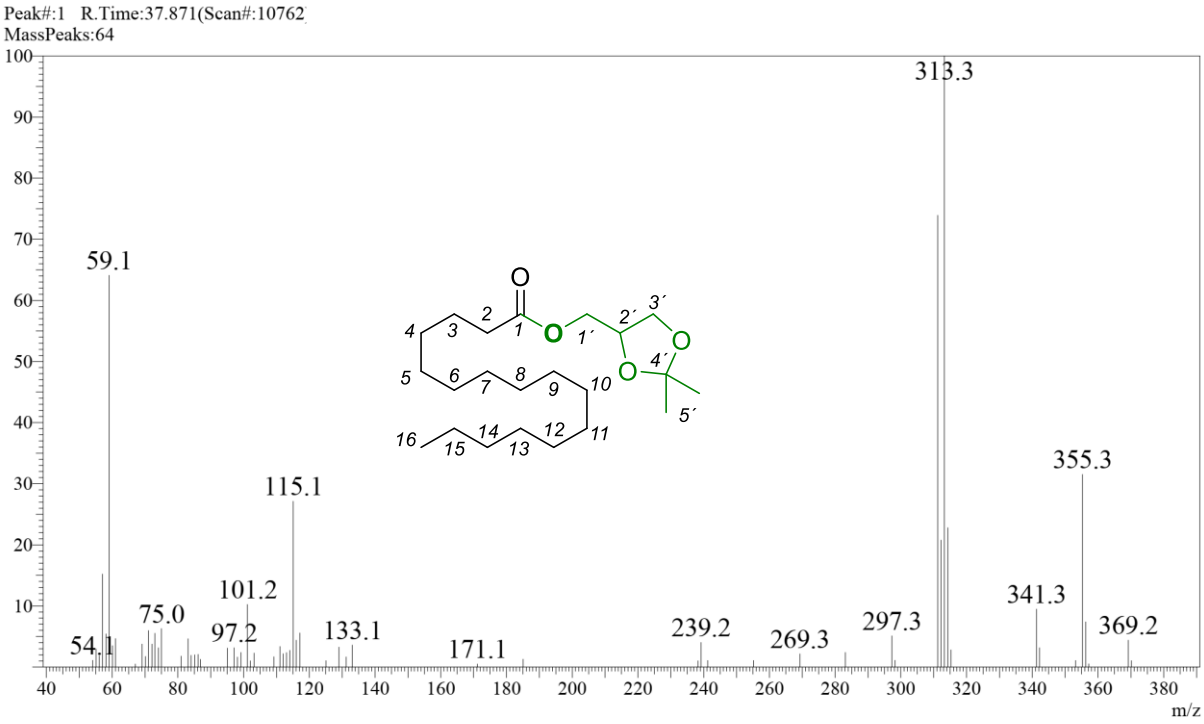
The NMR data is in agreement with the literature.[48]



^{1}H-NMR spectrum of *rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl hexadodecanoate (400 MHz, $CDCl_3$).

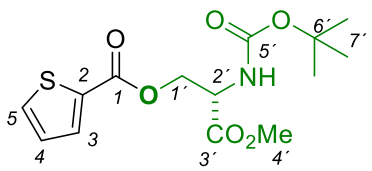


^{13}C-NMR spectrum of *rac*-(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl hexadodecanoate (125 MHz, $CDCl_3$).



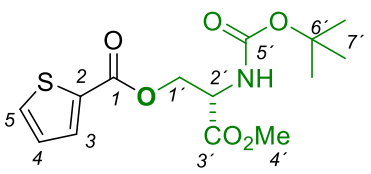
Mass spectrum of *N*-(2-(indol-3-yl)ethyl) 4-benzoylbenzamide (CI, 70 eV).

5.4.3.6 Synthesis of (S)-2-((*tert*-Butoxycarbonyl)amino)-3-methoxy-3-oxopropyl thiophene-2-carboxylate (3_{32f})

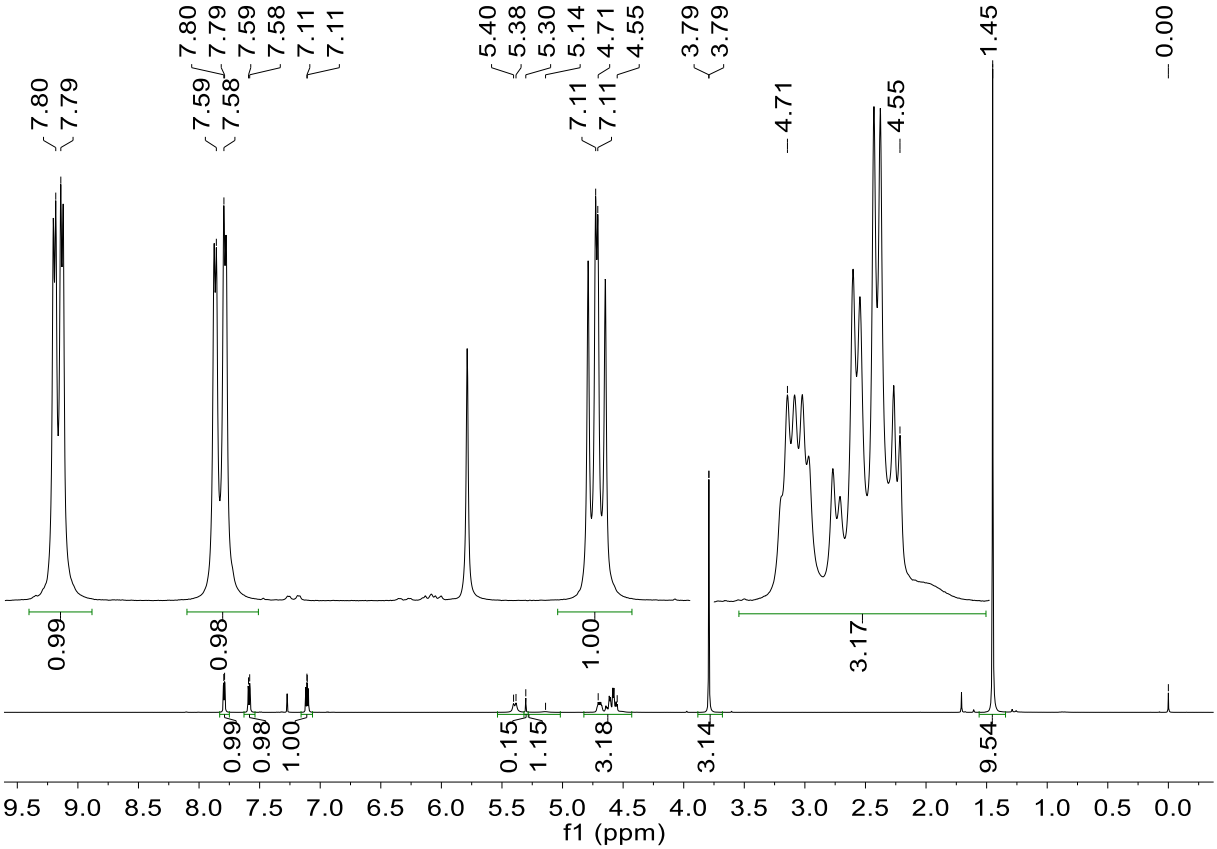


3_{32f}

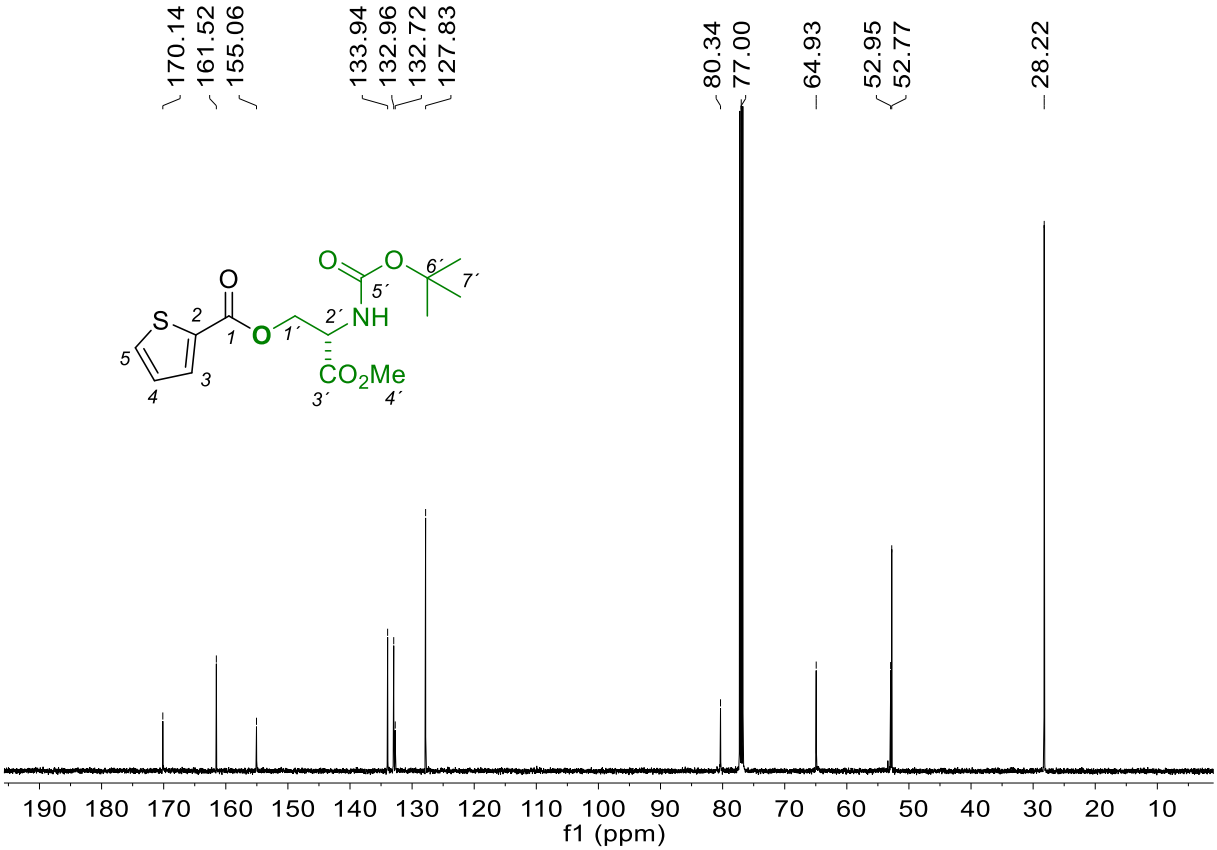
PH3233: In alignment to general procedure 4 (chapter 5.3.4, page 50) 2-thiophene carboxylic acid (167 mg, 1.30 mmol, 1.3 equiv) was allowed to react with TCT (92 mg, 0.49 mmol, 49 mol%) and FPyr (9.8 μL, 10.2 mg, 100 μL, 10 mol%) in EtOAc (0.50 mL, 2 M) for 4 h at 80 °C. Then, to the pale yellow reaction suspension was added a solution of (*S*)-*N*-Boc serine methyl ester (219 mg, 1.00 mmol, 1.0 equiv) and NMM (190 μL, 176 mg, 1.7 mmol, 1.7 equiv) in EtOAc (1.0 mL→0.7 M) under chilling in an ice bath and the vial that had contained the solution of the serine derivate was rinsed with further EtOAc (0.50 mL). After the addition of DMAP (12.2 mg, 100 μmol, 10 mol%) the reaction mixture was stirred overnight at room temperature (13 h). After all, column chromatographic purification of the crude material (313 mg, 95%, ≥98% conversion of the serine derivative as shown by ^{1}H-NMR) on silica gel (23.4 g, relation of weight crude product/SiO_2 1:76) with EtOAc/CH_2Cl_2 5:95 and drying in high vacuum for 24 h yielded the title ester as a colourless solid (291.3 mg, 0.884 mmol, 88%). In order to load the crude title compound onto the silica gel column, it was dissolved in CH_2Cl_2 (ca. 20 mL), SiO_2 was added (1.10 g, mass ratio crude **3_{32f}**/silica gel (1:3.6) and concentrated under reduced pressure.



M ($C_{14}H_{19}NO_6S$) = 329.37 g/mol; **mp.** 127-129 °C; $\mathbf{r_f}$ (SiO_2,) = 0.50 (EtOAc/CH_2Cl_2 5:95) 0.42 (EtOAc/*n*Hex 30:70); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.80 (dd, $^3J_{5,4}$ = 3.7 Hz, $^4J_{5,3}$ = 1.2 Hz, 1H, 5-H), 7.59 (dd, $^3J_{3,4}$ = 5.0 Hz, $^4J_{3,5}$ = 1.1 Hz, 1H, 3-H), 7.11 (dd, $^3J_{4,3}$ = 4.9 Hz, $^3J_{4,5}$ = 3.9 Hz), 5.39/5.14 (d/br. s, $^3J_{NH,2'}$ = 3.9 Hz, 1H, NH), 4.71-4.55 (m, 3H, 1´-H, 2´-H), 3.79 (s, 3H, 4´-H), 1.45 (s,9H, 7´-H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 170.14 (C-3´), 161.52 (C-1), 155.06 (C-5´), 133.94 (C-5), 132.96 (C-2), 132.72 (C-3), 127.83 (C-4), 80.34 (C-6´), 64.93 (C-2´), 53.39, 52.95 (C-1´), 52.77 (C-4´), 28.22 (C-7´); **HR-MS** (ESI, $[C_{14}H_{19}NNaO_6S]^+$) calc. 352.0825 u found 352.0826 u; **$[\alpha]_D^{20}$** (c = 1.120 g/100 mL, $CHCl_3$) = +47.7.



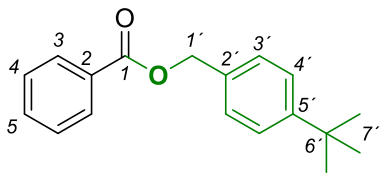
^{1}H-NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl thiophene-2-carboxylate (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl thiophene-2-carboxylate (100 MHz, $CDCl_3$).

5.4.3.7 Synthesis of 4-*tert*-Butylbenzyl benzoate (3_{2f})

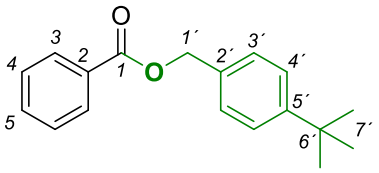
The optimization of the reaction conditions for the synthesis of the title compound can be found in chapter 3.2.4 (page 30), while comparison experiments with literature methods are located in chapter 4.1.4 on page 37.



3_{2f}

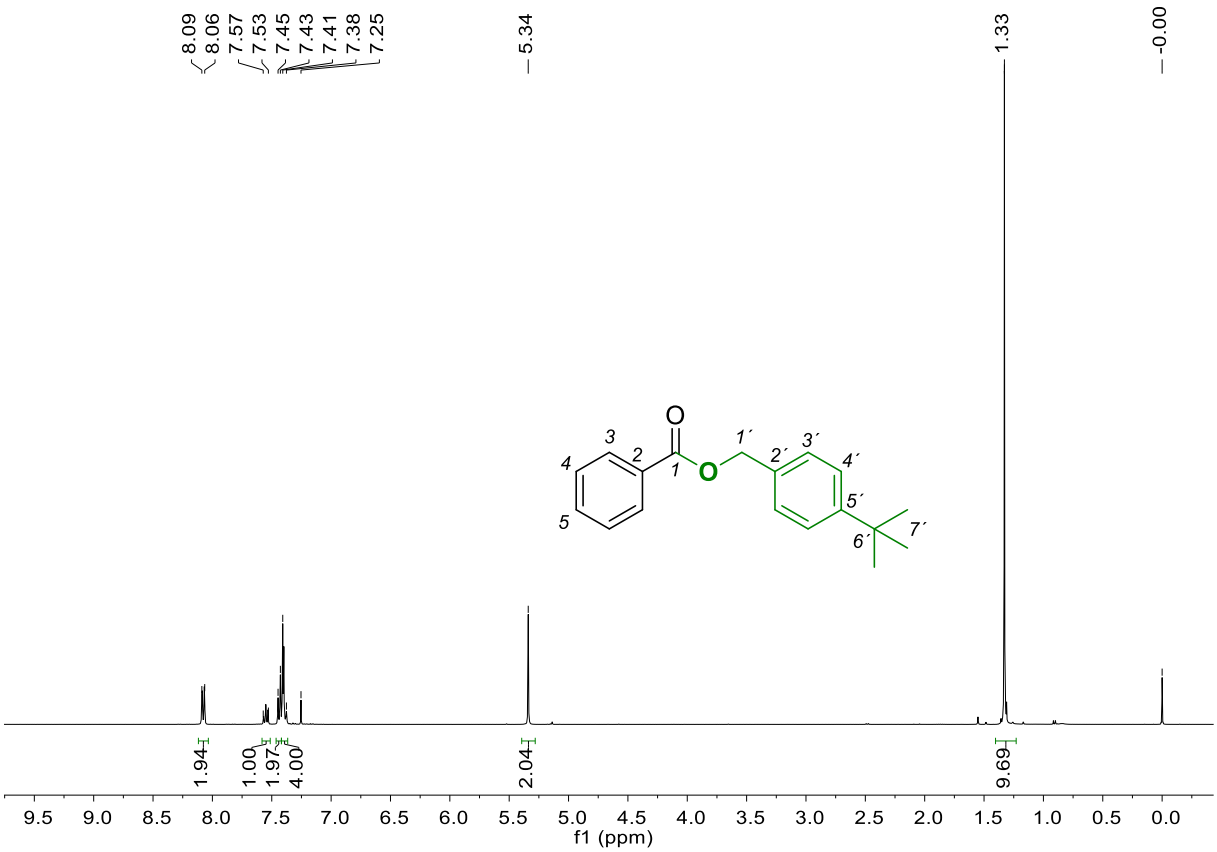
PH2886: In match with general procedure 4 (chapter 5.3.4, page 50) benzoic acid (122 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mmol, 38 mol%) using FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in EtOAc (0.50 mL, 2 M) for 4 h at 80 °C. Next, the reaction suspension, was treated with EtOAc (0.50 mL→1 M) and 4-*tert*-butylbenzyl alcohol (215 μL, 199 mg, 1.20 mmol, 1.2 equiv), cooled to 0 °C and NMM (145 μL, 1.3 mmol, 1.3 equiv) and DMAP (24.4 mg, 200 μmol, 20 mol%) were added. Finally, the reaction was stirred for 10 h at room temperature and for 7 h at **40 °C**. After aqueous work up with HCl washing, the crude product (288 mg, 107%, colourless oil) was subjected to purification by means of column chromatography on silica gel (15.5 g, mass relation crude **3_{2f}**/SiO_2 1:53) harnessing EtOAc/*n*Hex 4:96 as eluent mixture, which eventually furnished the benzoate **3_{2f}** as a pale yellow oil (235.0 mg, 0.88 mmol, 88%).

PH2827: In accordance with general procedure 4 (chapter 5.3.4, page 50) benzoic acid (244 mg, 2.00 mmol, 1.0 equiv) was converted with TCT (143 mg, 0.76 mmol, 38 mol%) in the presence of FPyr (19.7 μL, 20.4 mg, 200 μmol, 10 mol%) in EtOAc (1.0 mL, 2 M) into benzoyl chloride through heating to 40 °C for 2 h and then to 80 °C for 3 h. The resulting mixture was diluted with additional EtOAc (1.0 mL→1 M) and 4-*tert*-butylbenzyl alcohol (430 μL, 398 mg, 2.4 mmol, 1.2 equiv) was introduced. Subsequently, the reaction suspension was cooled in an ice bath, NMM (290 μL, 2.6 mmol, 1.3 equiv) and DMAP (49 mg, 0.40 mmol, 20 mol%) were added and the stirring was continued at **room temperature** for 14 h. In the following, the crude material (599 mg, 112%) was purified with the aid of column chromatography on silica gel (18.7 g, ratio crude product with regard to SiO_2 1:31) using EtOAc/*n*Hex 2:98→3:97 as eluent mixture. In the end, the title compound was obtained as a colourless oil in 85% yield (454.6 mg, 1.69 mmol) after drying for 10 min at 5 mbar at the rotary evaporator.

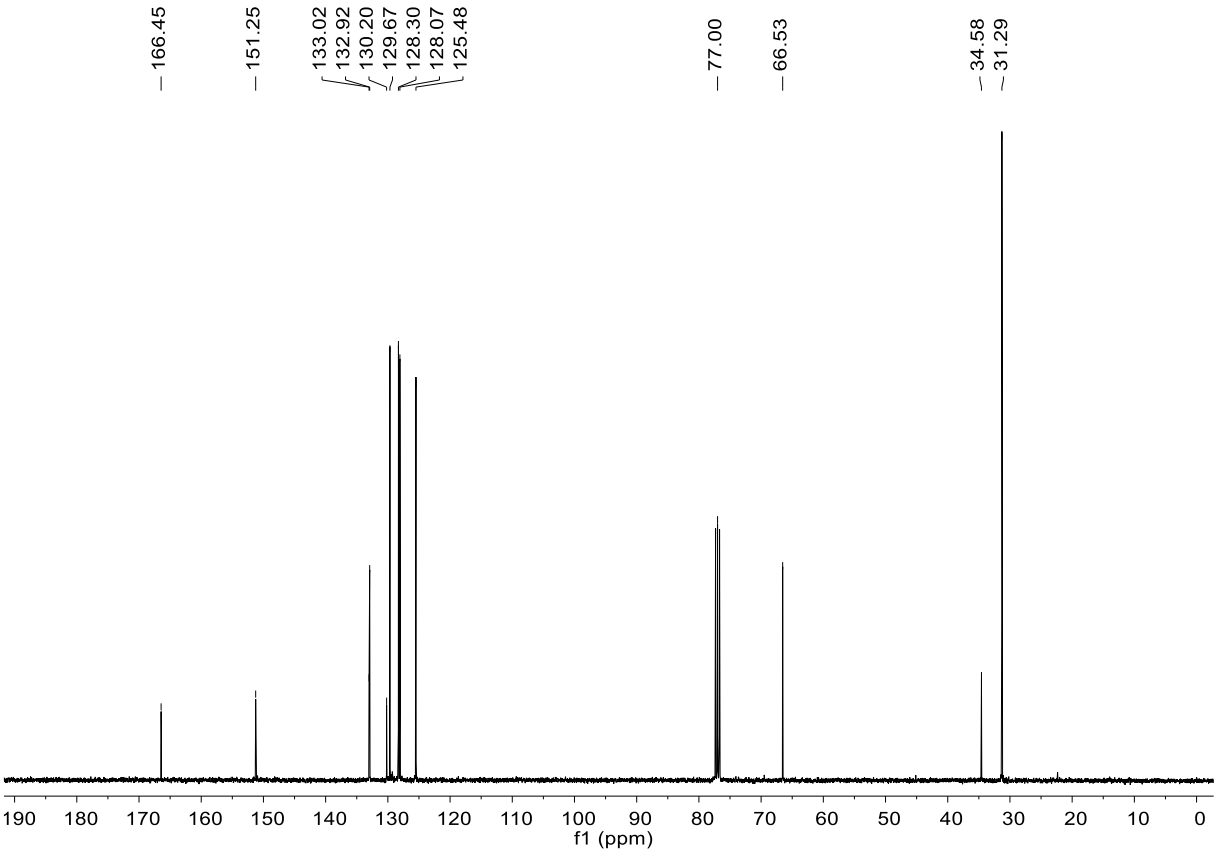


M ($C_{18}H_{20}O_2$) = 268.356 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 4:96) = 0.39; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.09-8.06 (m, 2H, 3-H), 7.57-7.53 (m, 1H, 5-H), 7.45-7.43 (m, 2H, 4´-H), 7.41-7.38 (m, 4H, 4-H, 3´-H), 5.34 (s, 2H, 1´-H), 1.33 (s, 9H, 7´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 166.45 (C-1), 151.25 (C-5´), 133.02 (C-2´), 132.92 (C-5), 130.20 (C-2), 129.67 (C-3), 128.30/128.07/125.48 (C-4, C-3´, C-4´), 66.53 (C-1´), 34.58 (C-6´), 31.29 (C-7´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 268 (12, $[M]^+$), 253 (22, $[M\text{-}Me]^+$), 175 (5), 163 (2, $[M\text{-}OCPh]^+$), 147 (100, $[M\text{-}OBz]^+$), 119 (4), 105 (18, $[PhCO]^+$), 91 (5, $[Bn]^+$), 77 (1, $[Ph]^+$), 57 (2, $[t\text{Bu}]^+$).

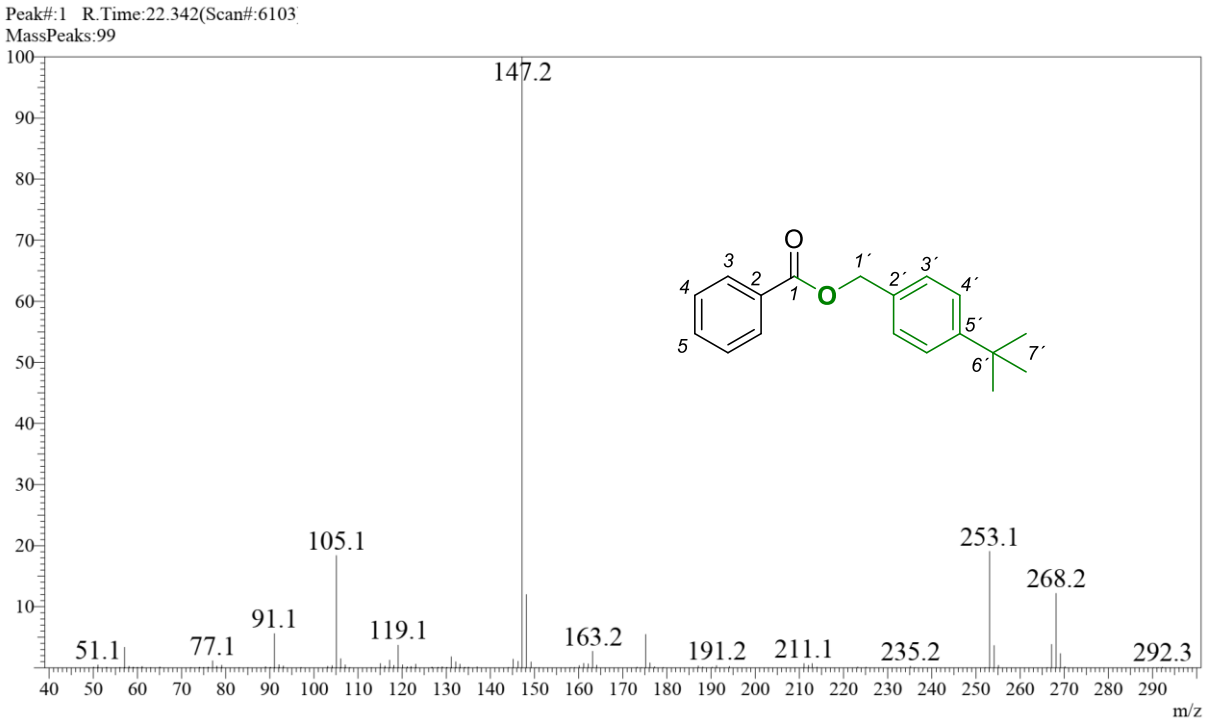
The NMR data is in agreement with the literature.[25]



^{1}H-NMR spectrum of 4-*tert*-butylbenzyl benzoate (400 MHz, $CDCl_3$).

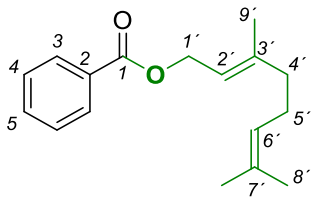


^{13}C-NMR spectrum of 4-*tert*-butylbenzyl benzoate (100 MHz, $CDCl_3$).



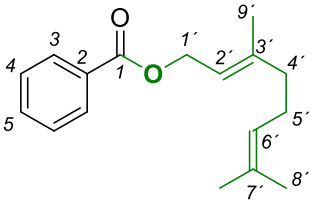
Mass spectrum of 4-*tert*-butylbenzyl benzoate (CI, 70 eV).

5.4.3.8 Synthesis of Geranyl Benzoate (3_{2g})



3_{2g}

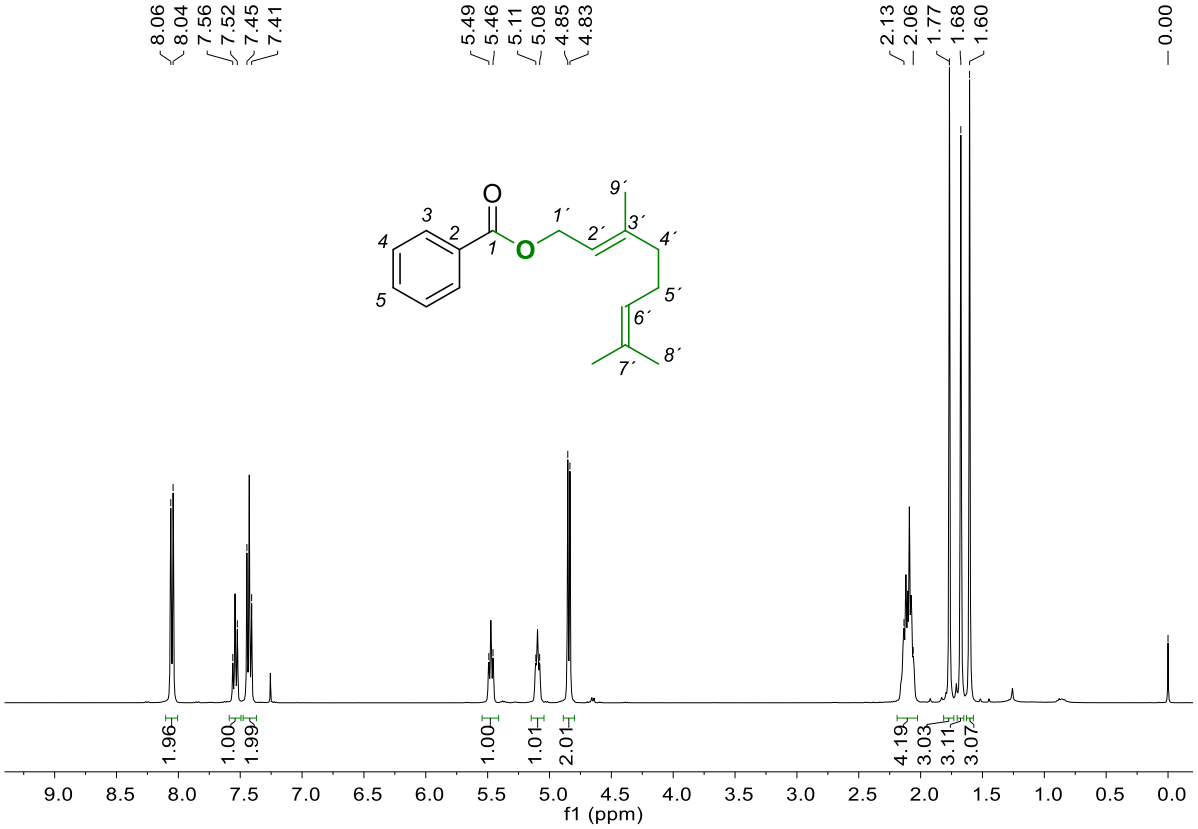
PH3037: Based on general procedure 4 (chapter 5.3.4, page 50) benzoic acid (122 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (9.8 µL, 10.2 mg, 100 µmol, 10 mol%) in EtOAc (0.50 mL, 2 M) for 4 h at 80 °C. Subsequently, the reaction suspension was diluted with further EtOAc (0.50 mL→1 M), cooled in an ice bath and successively geraniol (213 µL, 1.2 mmol, 1.2 equiv), NMM (145 µL, 1.3 mmol, 1.3 equiv) and DMAP (24 mg, 0.20 mmol, 20 mol%) were added. After 16 h of stirring at room temperature, aqueous work with HCl-washing gave rise to the crude title compound as a pale yellow solid (282 mg, 109%). In the following, column chromatographic purification on silica gel (19.2 g, mass relation crude material with respect to SiO_2 1:69) applying EtOAc/*n*Hex 3:97 furnished geranyl benzoate as a colourless oil (226.1 mg, 0.875 mmol, 88%).



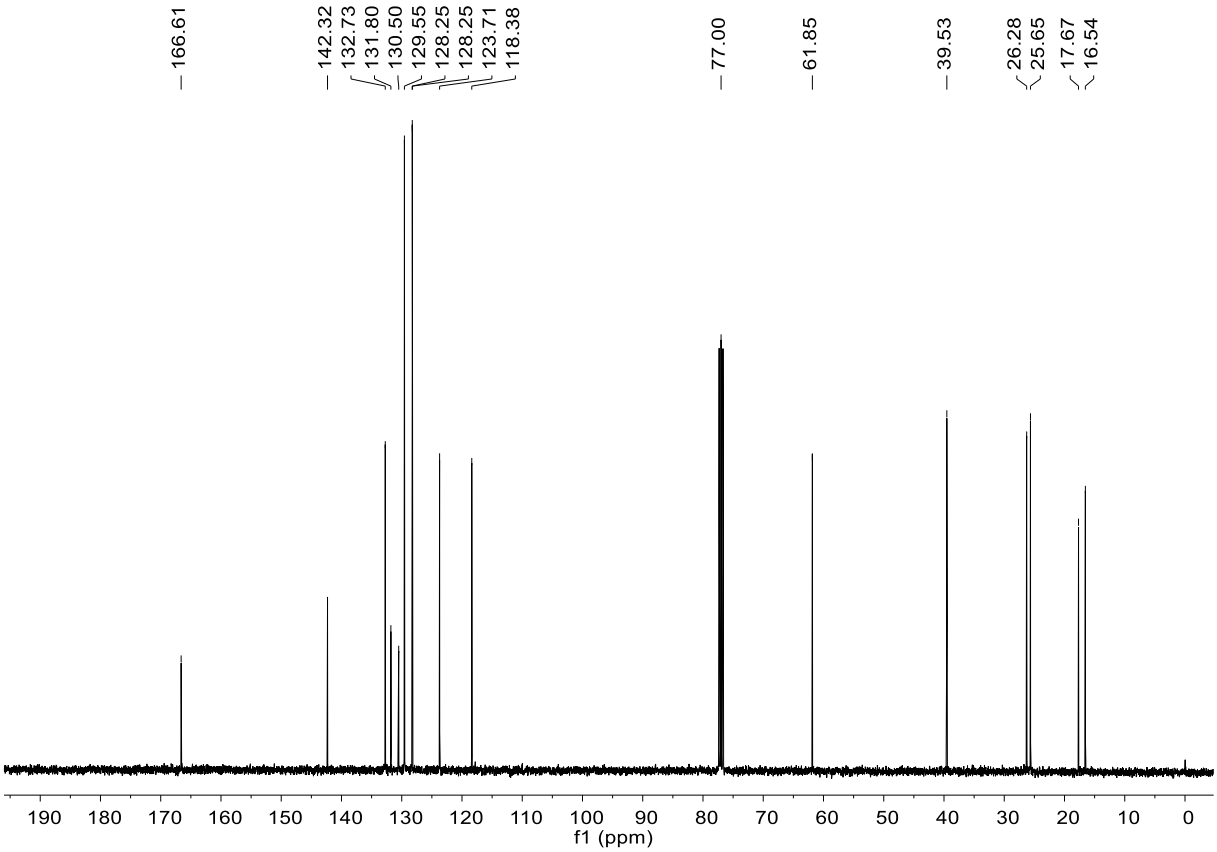
M ($C_{17}H_{22}O_2$) = 258.361 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 3:97) = 0.34; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 8.05 (m, 2H, 3-H), 7.56-7.52 (m, 1H, 5-H), 7.45-7.41 (m, 2H, 4-H), 5.49-5.46 (m 1H, 2´-H), 5.11-5.08 (m, 1H, 6´-H), 4.84 (d, $^3J_{1´,2´}$ = 7.0 Hz, 2H, 1´-H), 2.13-2.06 (m, 4H, 4´-H, 5´-H), 1.77 (s, 3H, 9´-H), 1.68 (s, 3H, 8´-H_a), 1.60 (s, 3H, 8´-H_b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 166.61 (C-1), 142.32 (C-3´), 132.73 (C-5), 131.80 (C-7´), 130.50 (C-2), 129.55, 128.25 (C-3), 128.25 (C-4), 123.71 (C-6´), 118.38 (C-2´), 61.85 (C-1´), 39.53 (C-4´),

26.28 (C-5´), 25.65 (C_a-8´), 17.67 (C_b-8´), 16.54 (C-9´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 189 (1), 165 (1), 151 (3, $[OCCHC(CH_3)CH_2CH_2CHC(CH_3)_2]^+$), 137 (53, $[M\text{-}BzO]^+$), 136 (30, $[M\text{-}BzOH]^+$), 135 (32), 123 (27, $[PhCO_2H_2]^+$), 121 (20, $[PhCO_2]^+$), 109 (23, $[CH_2C(CH_3)CHCHCH_2CH_2]^+$), 107 (21, $[CH_2C(CH_3)CHCHCHCHCH_2]^+$), 105 (13, $[PhCO]^+$), 95 (47, $[CH_2C(CH_3)CHCHCH_2CH_2]^+$), 93 (70, $[CH_2C(CH_3)CHCHCHCH]^+$), 81 (100, $[CH_2C(CH_3)CHCHCH_2]^+$), 69 (72, $[prenyl]^+$).

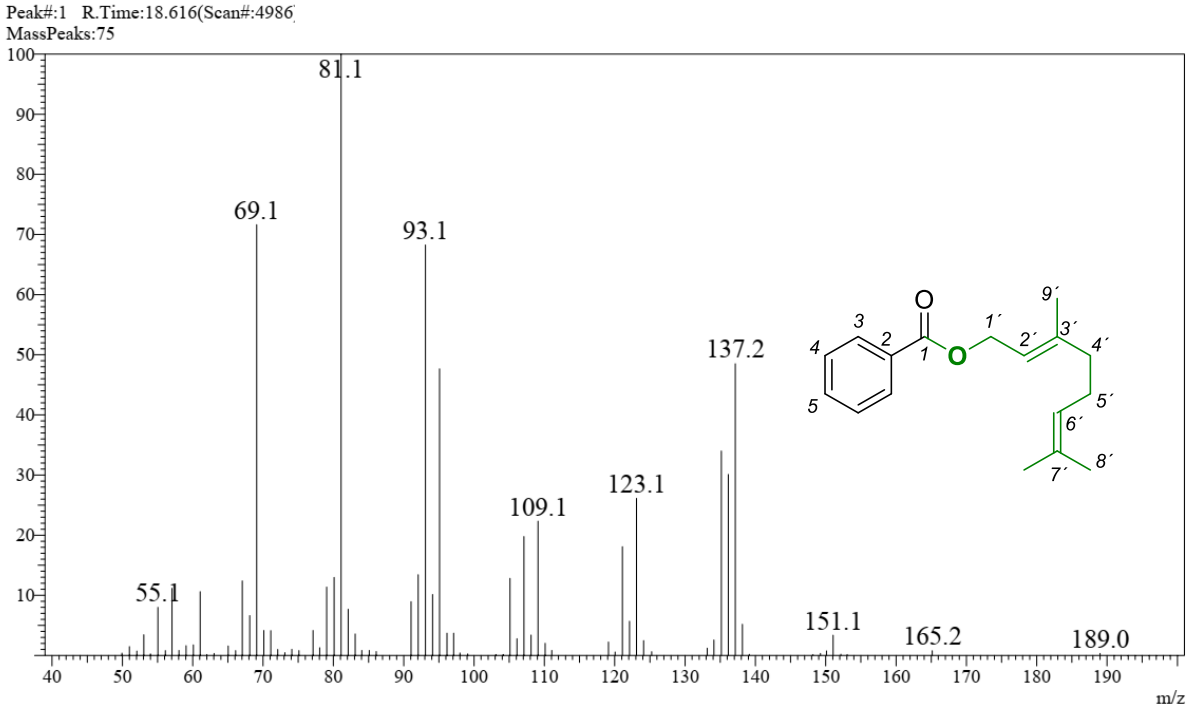
The NMR data is in agreement with the literature.[49]



^{1}H-NMR spectrum of geranyl benzoate (400 MHz, $CDCl_3$).

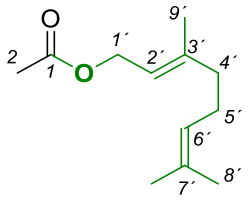


^{13}C-NMR spectrum of geranyl benzoate (100 MHz, $CDCl_3$).



Mass spectrum of geranyl benzoate (CI, 70 eV).

5.4.3.9 Synthesis of Geranyl Acetate (3_{33g})

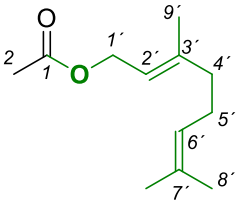


3_{33g}

PH3074: In alignment to general procedure 4 (chapter 5.3.4, page 50) acetic acid (57 μL, 60.1 mg, 1.00 mmol, 1.0 equiv) was combined with FPyr (9.8 μL, 10.2 mg, 100 μL, 10 mol%), MeCN (0.50 mL, 2 M) and TCT (72 mg, 0.38 mmol, 38 mol%) and heated for 4 h to 40 °C. To avoid evaporation of AcCl, the reaction suspension was cooled in an ice bath and successively further MeCN (0.50 mL→1 M), geraniol (215 μL, 1.2 mmol, 1.2 equiv) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were added and stirring was continued for 13 h at room temperature. Next, crude material (258 mg, 131%, yellow oil, ratio title compound/geraniol 65:35 according to ^{1}H-NMR) was further processed by means of column chromatographic purification on silica gel (17.3 g, relation weight crude product/SiO_2 1:67) employing EtOAc/*n*Hex 5:95 as eluent mixture. Eventually, concentration with CH_2Cl_2 and drying at the rotary evaporator at 20 mbar for 5 min furnished the title ester as a pale yellow oil (140.9 mg, 0.718 mmol, 72%).

PH3102: In orientation to general procedure 4 (chapter 5.3.4, page 50) a solution of **acetic acid** (74.4 μL, 78.1 mg, 1.3 mmol, **1.3 equiv**) and FPyr (10 mol%) in MeCN (2 M) was treated with **TCT** (92 mg, 0.49 mmol, **49 mol%**) and heated to 40 °C for 5 h. Next, under cooling in an ice bath a solution of **geraniol** (176 μL, 154 mg, 1.00 mmol, **1.0 equiv**) in MeCN (0.50 mL, 2 M) was added followed by NMM (190 μL, 1.7 mmol, 1.7 equiv) and the reaction suspension was stirred at ambient temperature overnight (15 h). Aqueous work up afforded the crude title compound as a pale yellow solid (181 mg, 92%, 96% conversion of geraniol as indicated by ^{1}H-NMR), which was purified with the aid of column chromatography on silica gel (15.2 g, ratio weight crude material/SiO_2 1:84) with EtOAc/*n*Hex 5:95). Concentration with CH_2Cl_2 under reduced pressure and drying at the rotary evaporator at 20 mbar for 5 min yielded geraniol acetate as a pale yellow oil (153.5 mg, 0.782 mmol, 78%).

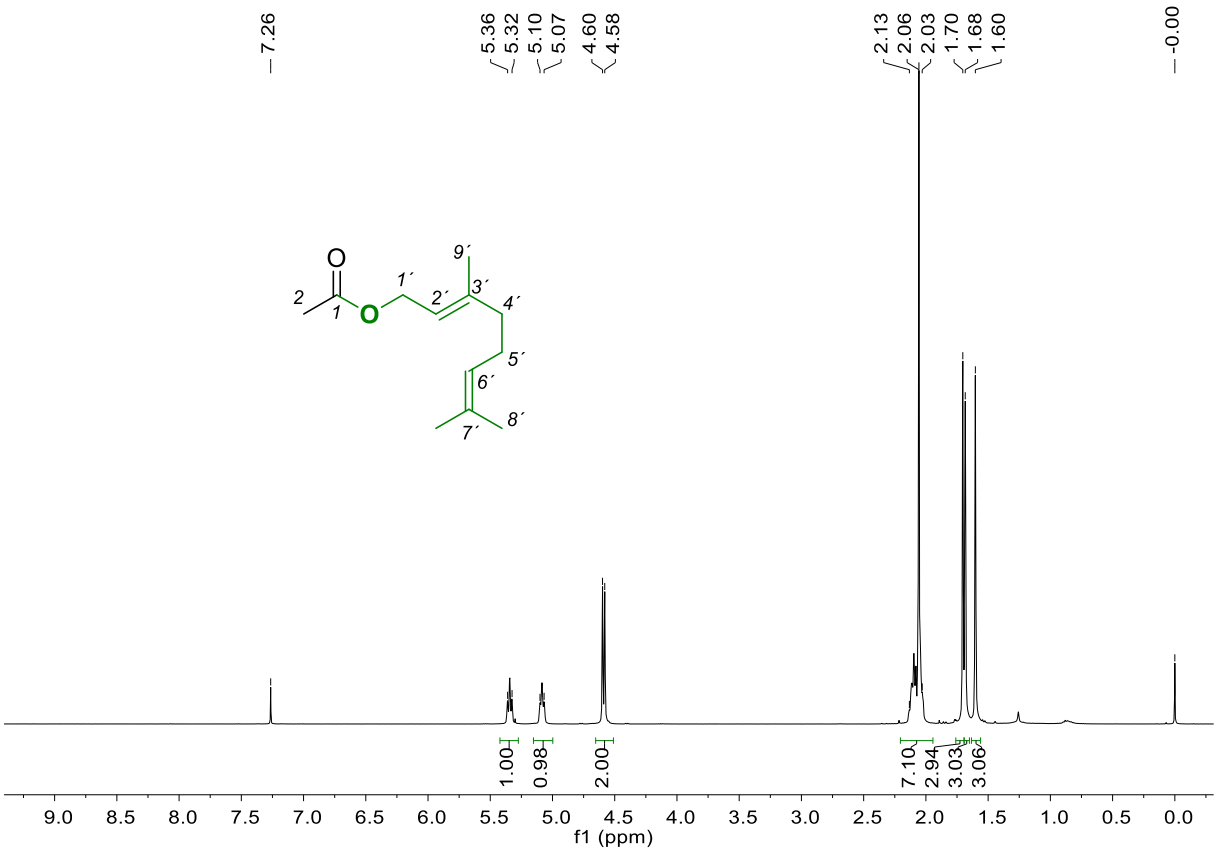
PH3025: Following general protocol 4 (chapter 5.3.4, page 50) acetic acid (1.00 mmol, 1.0 equiv) was transformed into acetyl chloride through heating with TCT (38 mol%) and FPyr (10 mol%) in MeCN (2 M) for 4 h to 40 °C. Subsequently, at 0 °C MeCN (→1 M), geraniol (1.0 equiv) and **K_2CO_3** (180 mg, 1.3 mmol, 1.3 equiv) were added and the resulting reaction suspension was stirred for 15 h at room temperature. Afterwards, the crude material (222 mg, 113%, yellow oil) was purified through column chromatography on silica gel (19.0 g, mass crude product in respect to silica gel 1:86) with EtOAc/*n*Hex 5:95, which afforded the title compound as a pale yellow oil (134 mg, 0.680 mmol, 68%)



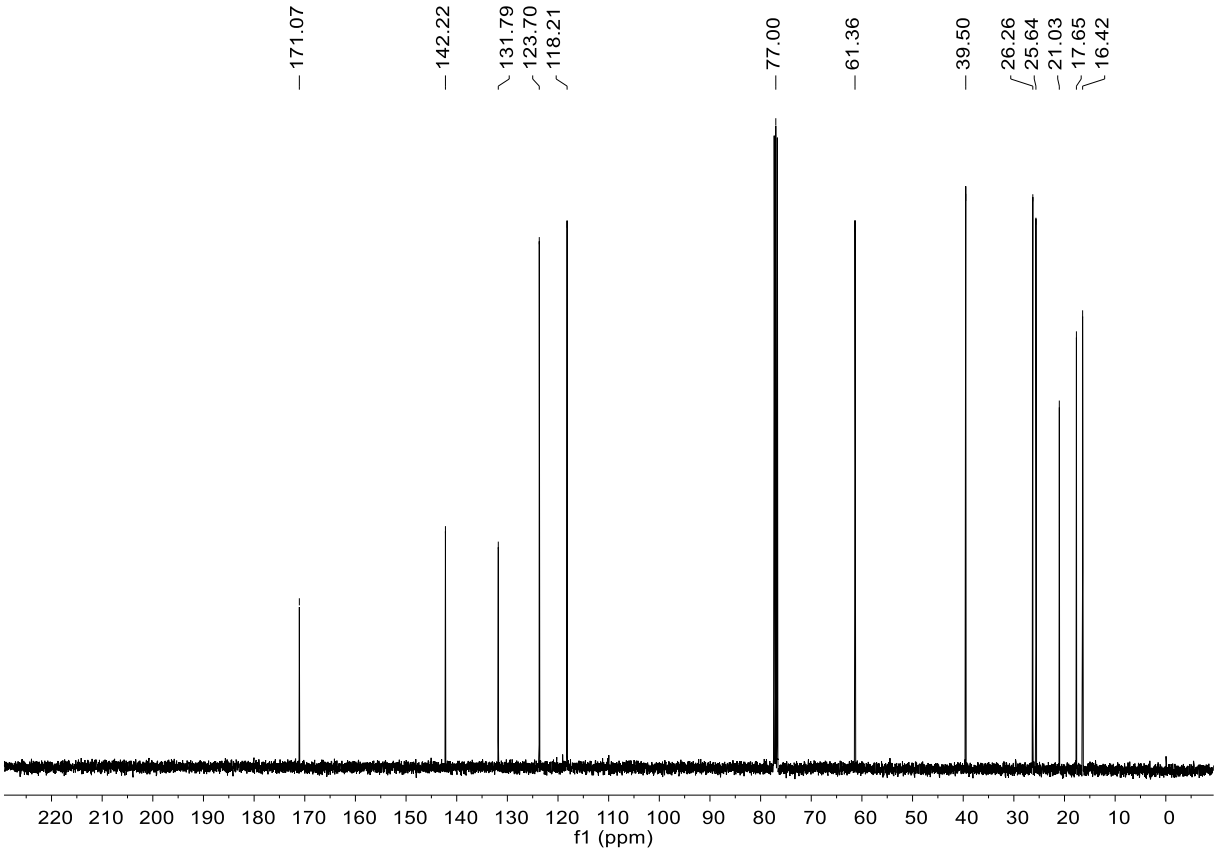
M ($C_{12}H_{20}O_2$) = 196.290 g/mol; **r_f** (SiO_2, EtOAc/*n*Hex 5:95) = 0.30; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 5.36-5.32 (m, 1H, 2´-H), 5.10-5.07 (m, 1H, 6´-H), 4.60, 4.59 (d, ^3J = 7.2 Hz, 2H, 1´-H), 2.13-2.03 (m, 7H, 2-H,

4´-H, 5´-H; amongst s at 2.06 ppm, 3H, 2-H) 1.70 (s, 3H, 9´-H), 1.68 (s, 3H, 8´-H_a), 1.60 (s, 3H, 8´-H_b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 171.07 (C-1), 142.22 (C-3´), 131.79 (C-7´), 123.70 (C-6´), 118.21 (C-2´), 61.36 (C-1´), 39.50 (C-4´), 26.26 (C-4´), 25.64 (C_a-8´), 21.03 (C-2), 17.65 (C_b-8´), 16.42 (C-9´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 165 (2), 137 (71, $[M\text{-}OAc]^+$), 135 (26, $[M\text{-}HOAc\text{-}H]^+$), 123 (5), 121 (9), 109 (16, $[CH_2C(CH_3)CHCHCH_2CH_2]^+$), 107 (9, $CH_2C(CH_3)CHCHCHCHCH_2]^+$), 95 (25, $[CH_2C(CH_3)CHCHCH_2CH_2]^+$), 93 (31, $CH_2C(CH_3)CHCHCHCH]^+$), 81 (100, $[CH_2C(CH_3)CHCHCH_2]^+$), 69 (54, $[prenyl]^+$), 61 (61, $[AcOH_2]^+$)

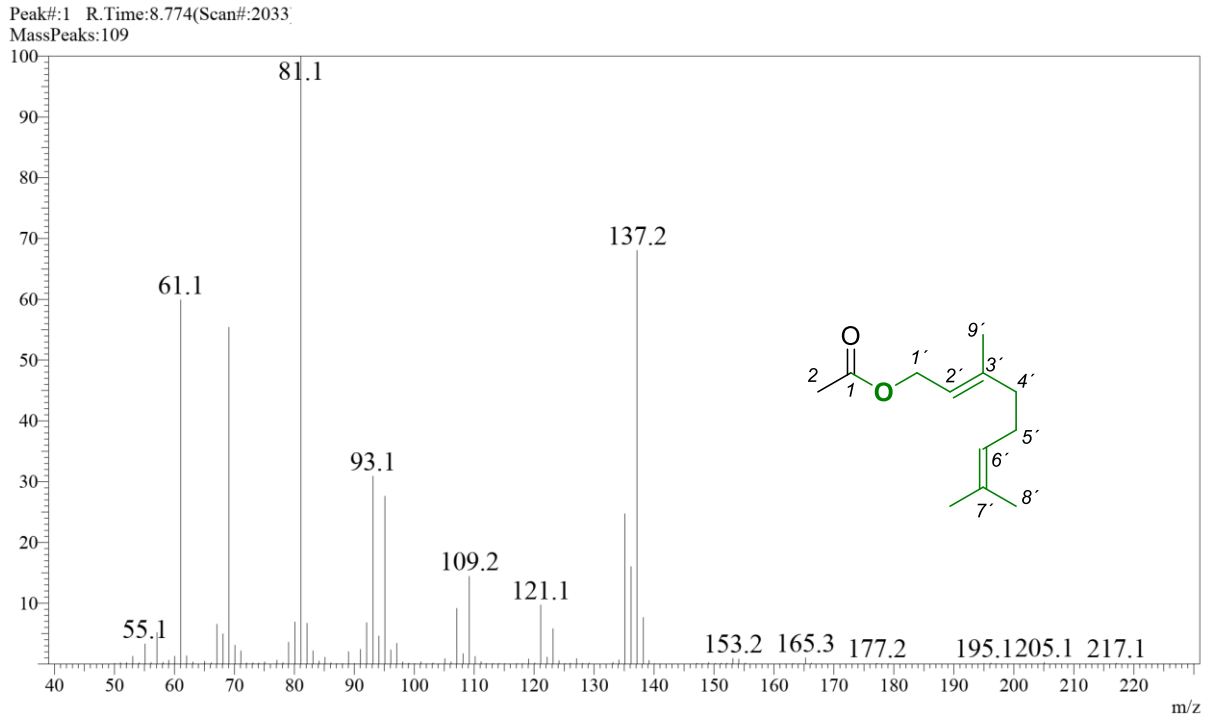
The NMR data is in agreement with the literature.[50]



^{1}H-NMR spectrum of geranyl acetate (400 MHz, $CDCl_3$).

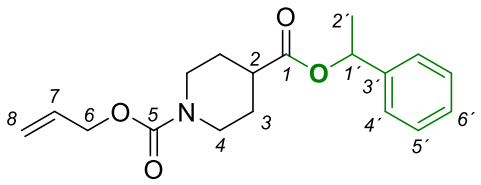


^{13}C-NMR spectrum of geranyl acetate (100 MHz, $CDCl_3$).



Mass spectrum of geranyl acetate (CI, 70 eV).

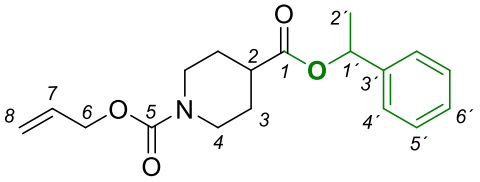
5.4.3.10 Synthesis of *rac*-1-Phenylethyl 1-(allyloxycarbonyl)piperidine-4-carboxylate (3_{34h})



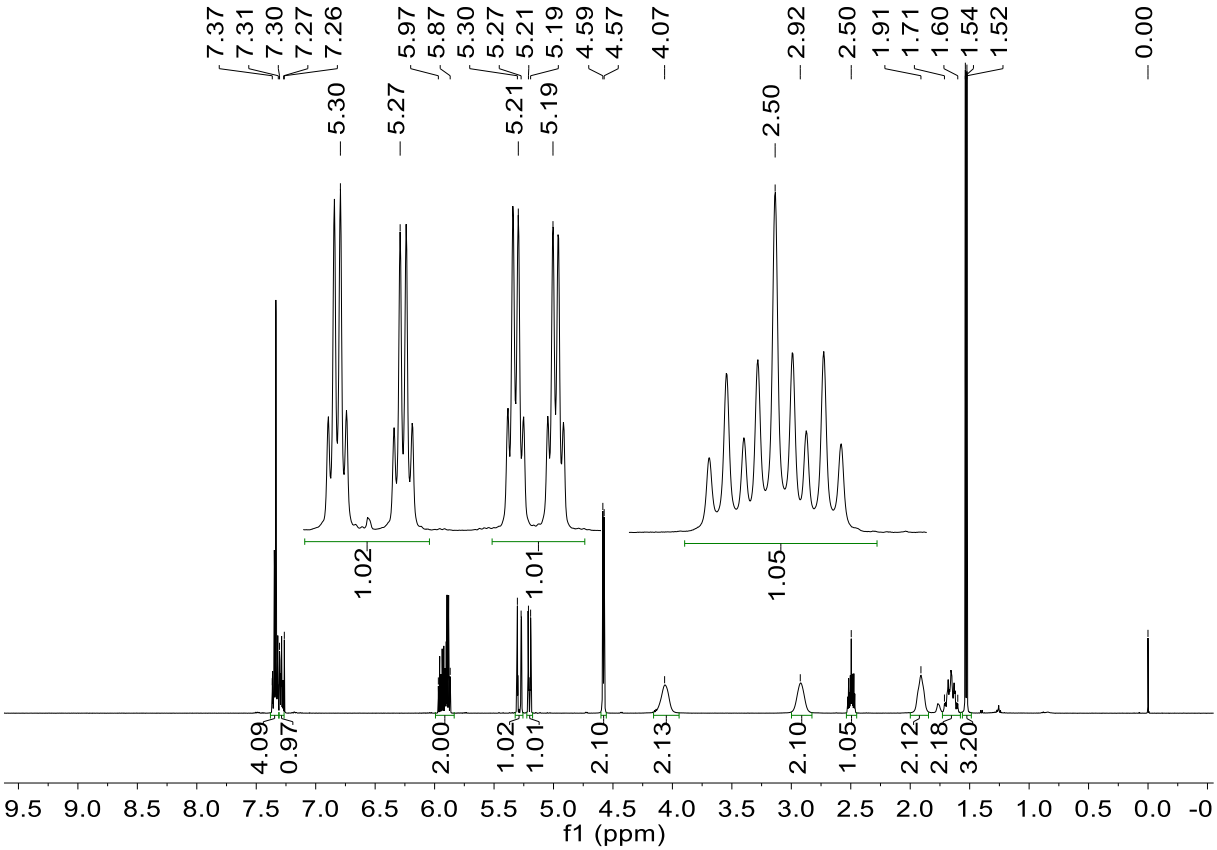
3_{34h}

1-(Allyloxycarbonyl)piperidine-4-carboxylic acid was prepared as given in chapter 5.4.5.4 (page 246). Due to similar polarities the title compound was difficult to separate from 1-phenylethanol by means of chromatography. Therefore, an excess of the acid with respect to the alcohol nucleophile was crucial. When the title compound was synthesized using EtOAc as solvent, traces of ethyl 1-(allyloxycarbonyl)piperidine-4-carboxyate were observed.

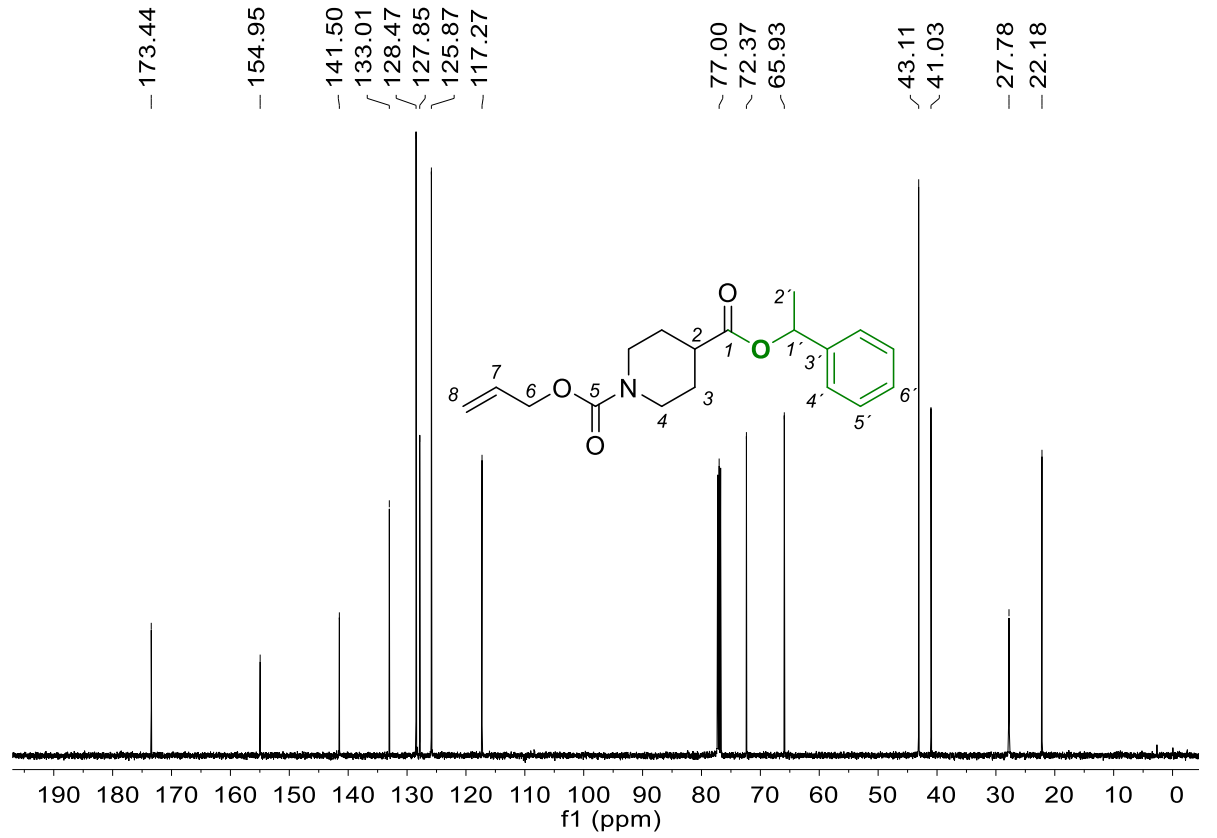
PH3480: In agreement with general procedure 4 (chapter 5.3.4, page 50), to a mixture of 1-(Allyloxycarbonyl)piperidine-4-carboxylic acid (292 mg, 1.3 mmol, 1.3 equiv) and FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) was added TCT (92 mg, 0.49 mmol, 49 mol%) and the resulting suspension was heated to 80 °C for 7 h. Next, the pale yellow reaction suspension was cooled in an ice bath and a solution of *rac*-1-phenylethanol (123 μL, 125 mg, 1.00 equiv, 1.0 equiv) in MeCN (0.5 mL→1 M). The vial, in which the solution of the alcohol had been prepared was rinsed with additional MeCN (250 μL→0.8 M) and sequentially NMM (150 μL, 1.3 mmol, 1.3 equiv) and DMAP (12.2 mg, 100 μmol, 10 mol%) were introduced. After stirring for 18 h at room temperature, work up delivered the crude title compound as pale yellow oil (340 mg, 107%), of which ^{1}H-NMR verified full consumption of phenylethanol. Eventually, column chromatographic purification on silica gel (26.6 g, ratio weight crude product/SiO_2 1:78) with EtOAc/*n*Hex 20:80 furnished the title ester as a colourless oil in 89% yield (281.9 mg, 0.888 mmol).



M ($C_{18}H_{23}NO_4$) = 317.39 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/CH_2Cl_2 7:93) = 0.32; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 7.37-7.31 (m, 4H, 4´-H, 5´-H), 7.30-7.27 (m, 1H, 6´-H), 5.97-5.87 (m, 2H, 7-H, 1´-H), 5.29 (ddt, $^{3}J_{8,7}$ = 17.2 Hz, $^{3}J_{8,8}$ = 1.6 Hz, $^{4}J_{8,6}$ = 1.6 Hz, 1H, 8-H_E), 5.20 (ddt, $^{3}J_{8,7}$ = 10.4 Hz, $^{2}J_{8,8}$ = 1.7 Hz, $^{4}J_{8,6}$ = 1.7 Hz, 1H, 8´-H_Z), 4.58 (ψ-dt, $^{3}J_{6,7}$ = 5.5 Hz, *J* = 1.4 Hz, 2H, 6-H), 4.07 (br. s, 2H, 4-H_a), 2.92 (br. s, 2H, 4´-H_b), 2.50 (tt, $^{3}J_{2,3}$ = 10.9 Hz, $^{3}J_{2,3}$ = 3.9 Hz), 1.91 (br. s, 2H, 3-H_a), 1.71-1.60 (m, 3-H_b), 1.53 (d, $^{3}J_{2´,1´}$ = 6.6 Hz, 3H, 2´-H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 173.44 (C-1), 154.95 (C-5), 141.50 (C-3´), 133.01 (C-7`), 128.47 (C-5´), 127.85 (C-6´), 125.87 (C-4´), 117.27 (C-6), 72.37 (C-1´), 65.93 (C-6), 43.11 (C-4), 41.03 (C-2), 27.78 (C-3), 22.18 (C-2´); **HR-MS** (ESI, $[C_{18}H_{24}NO_4]^+$) calc. 318.1670 u found 318.1687 u;



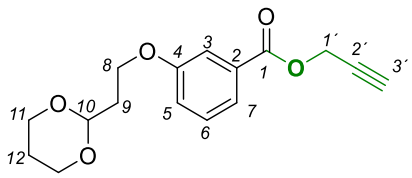
^{1}H-NMR spectrum of *rac*-1-phenylethyl 1-(allyloxycarbonyl)piperidine-4-carboxylate (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *rac*-1-phenylethyl 1-(allyloxycarbonyl)piperidine-4-carboxylate (125 MHz, $CDCl_3$).

5.4.3.11 Synthesis of Propargyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoate (3_{20i})

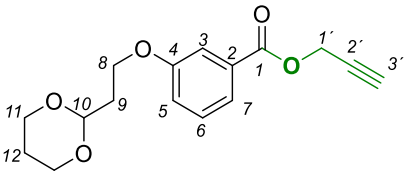
The synthesis of 3-(2-(1,3-dioxan-2-yl)ethoxy)benzoic acid is stated in chapter 5.4.5.2 on page 238.



3_{20i}

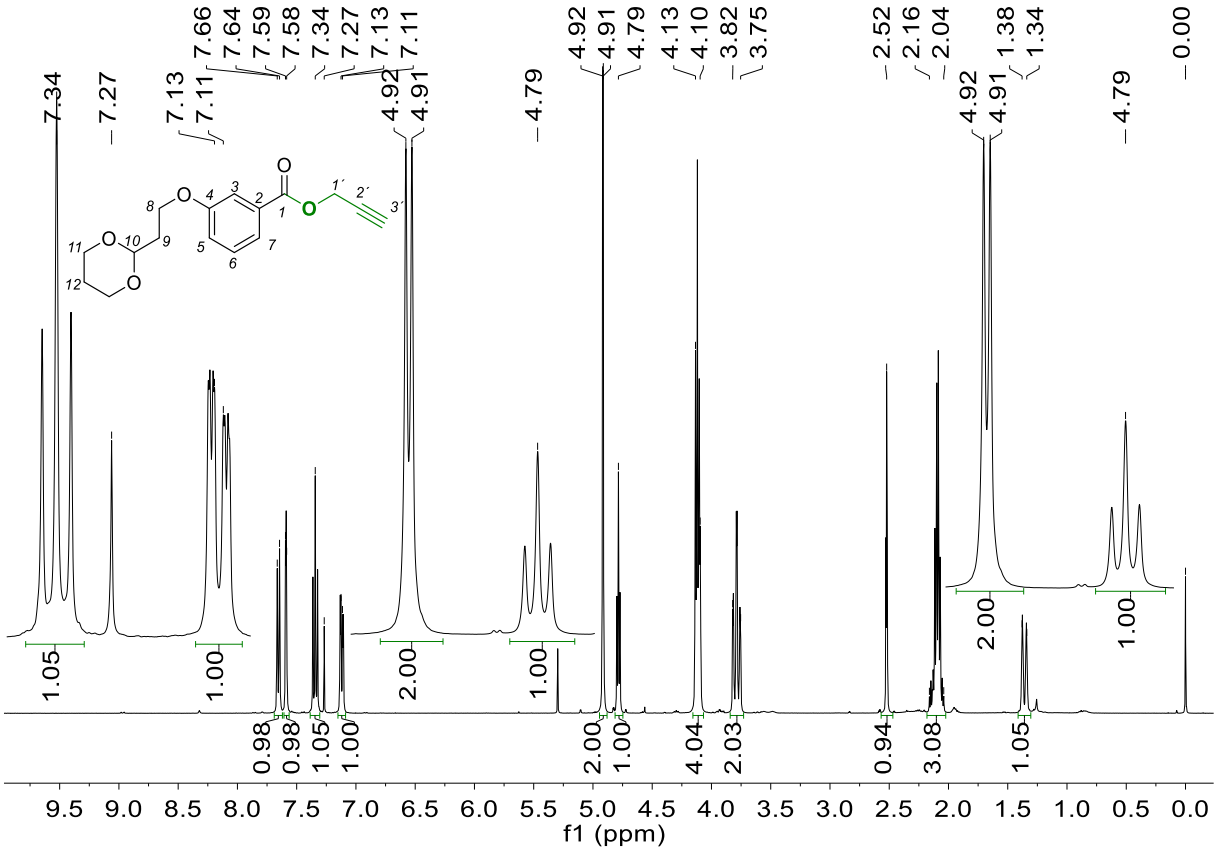
PH3536: According to general procedure 4 (chapter 5.3.4, page 50) 3-(2-(1,3-dioxan-2-yl)ethoxy)benzoic acid (252 mg, 1.00 mmol, 1.0 equiv) was reacted with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (19.8 μL, 20.4 mg, 200 μmol, 20 mol%) in MeCN (1.0 mL, 1 M) for 18 h at room temperature. Then, propargyl alcohol (90 μL, 1.5 mmol, 1.5 equiv), NMM (150 μL, 1.3 mmol, 1.3 equiv) and DMAP (12.2 mg, 100 μmol, 10 mol%) were added at 0 °C and the reaction suspension was stirred for 22 h at ambient temperature. After all, the crude material (254 mg, 87%, yellow oil) was subjected to chromatographic purification on silica gel (23.8 g, mass ratio crude product/SiO_2 1:95) employing EtOAc/*n*Hex 25:75. Concentration with CH_2Cl_2 and drying in high vacuum for 8 h finally furnished the title benzoate as a colourless oil (213.0 mg, 0.734 mmol, 73%).

PH3565: As delineated in general procedure 4 (chapter 5.3.4, page 50), to a suspension of 3-(2-(1,3-dioxan-2-yl)ethoxy)benzoic acid (1.00 mmol, 1.0 equiv) and FPyr (20 mol%) in MeCN (1 M) was added TCT (75 mg, 0.40 mmol, 40 mol%) and the resulting suspension was heated to 40 °C for 9 h. Subsequently, propargyl alcohol (1.5 equiv), NMM (1.3 equiv) and DMAP (10 mol%) were added under chilling in an ice bath and stirring as continued at room temperature for 19 h. Afterwards, column chromatographic purification of the crude material (276 mg, 95%, yellow oil) on silica gel (25.7 g, relation mass crude **3_{20i}** in regard to SiO_2 1:92) applying EtOAc/*n*Hex 25:75 and drying in high vacuum for 10 h afforded the title ester as a colourless oil (200.6 mg, 0.691 mmol, 69%).

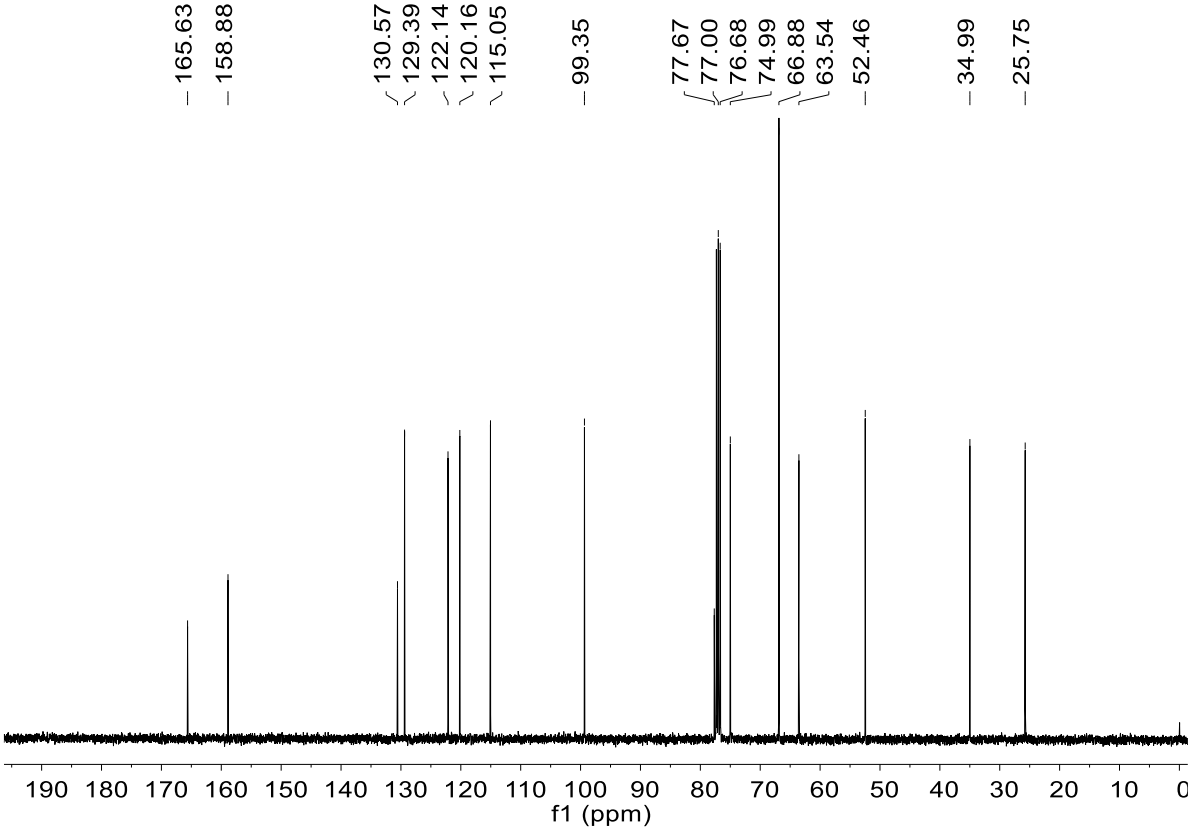


M ($C_{16}H_{18}O_5$) = 290.315 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 25:75) = 0.35; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.66-7.64 (m, 1H), 7.59-7.58 (m, 1H, 3-H), 7.34 (ψ-t, ^3J = 7.9 Hz, 1H) 7.13-7.11 (ddd, ^3J = 8.3 Hz, ^4J = 2.5 Hz, ^4J = 0.8 Hz, 1H), 4.92 (d, $^3J_{1´,3´}$ = 2.5 Hz, 2H, 1´-H), 4.79 (t, $^4J_{10,9}$ = 5.3 Hz, 1H, 10-H), 4.13-4.10 (m, 4H, 8-H, 11-H_a), 3.82-3.75 (m, 2H, 11-H_b), 2.52 (t, $^4J_{3´,1´}$ = 2.4 Hz, 1H, 3´-H), 2.16-2.04 (m, 3H, 9-H, 12-H_a), 1.38-1.34 (m, 1H, 12-H_b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 165.63 (C-1), 158.88 (C-4), 130.57 (C-2), 129.39 (C-6), 122.14 (C-5), 120.16 (C-7), 115.05 (C-3), 99.35 (C-10), 77.67 (C-2´), 76.68 (C-3´), 74.99, 66.88 (C-11), 63.54 (C-8), 52.46 (C-1´), 34.99 (C-9), 25.75 (C-12); **GC-MS** (CI, 70 eV) m/z [u] (%) = 290 (27, $[M]^+$), 243 (10), 235 (32, $[M\text{-}OCH_2CCH]^+$), 215 (100, $[3\text{-}H_2CCHCHO(C_6H_4)CO_2CH_2CCH]^+$), 177 (11, $[3\text{-}HO(C_6H_4)CO(OH)CH_2CCH]^+$), 159 (9), 114 (41,

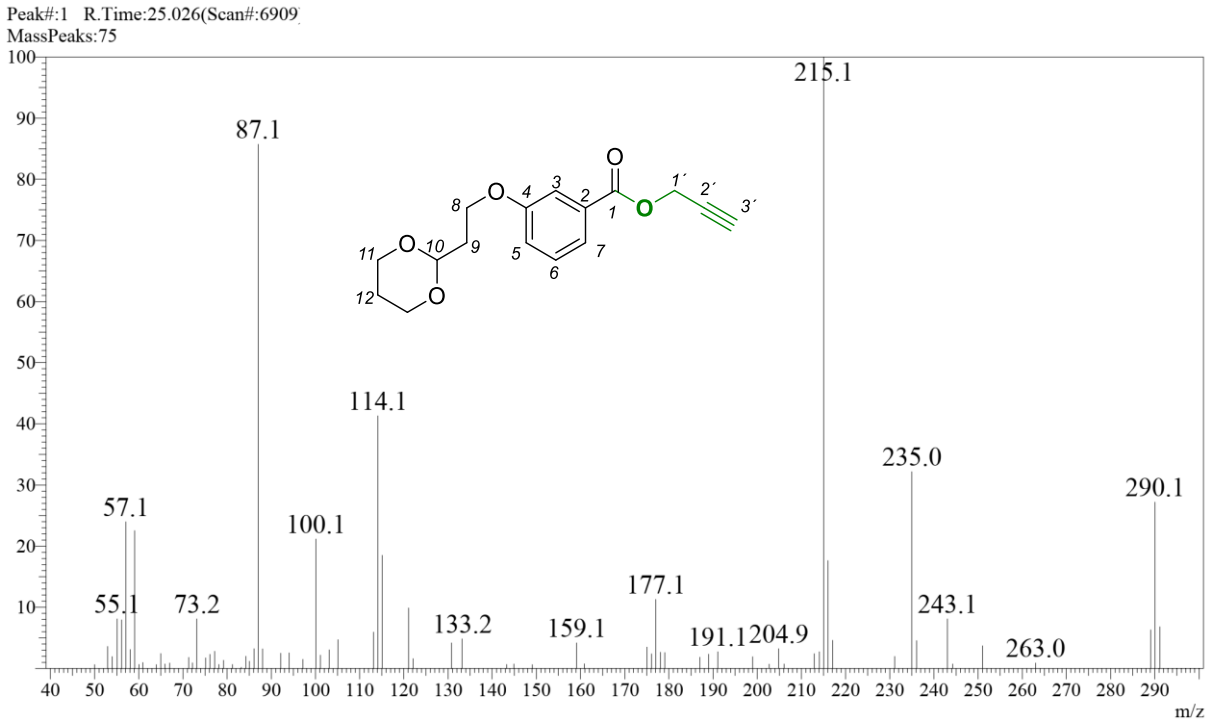
$[(CH_2)_3O_2CCHCH_2]^+$), 100 (21, $[(CH_2)_3O_2CCH_2]^+$), 87 (86, $[(CH_2)_3O_2CH]^+$), 73 (7), 59 (21), 57 (22); **HR-MS** (ESI, $[C_{16}H_{19}O_5]^+$) calc. 291.1227 u found 291.1230 u.



^{1}H-NMR spectrum of propargyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoate (400 MHz, $CDCl_3$).

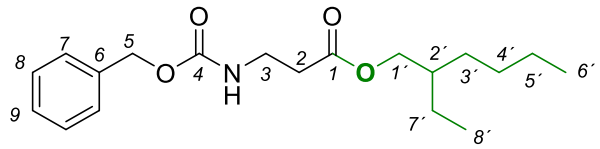


^{13}C-NMR spectrum of propargyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoate (125 MHz, $CDCl_3$).



Mass spectrum of propargyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoate (CI, 70 eV).

5.4.3.12 Synthesis of 2-Ethylhex-1-yl 3-(benzyloxycarbonylamino) propanoate (3_{35j})

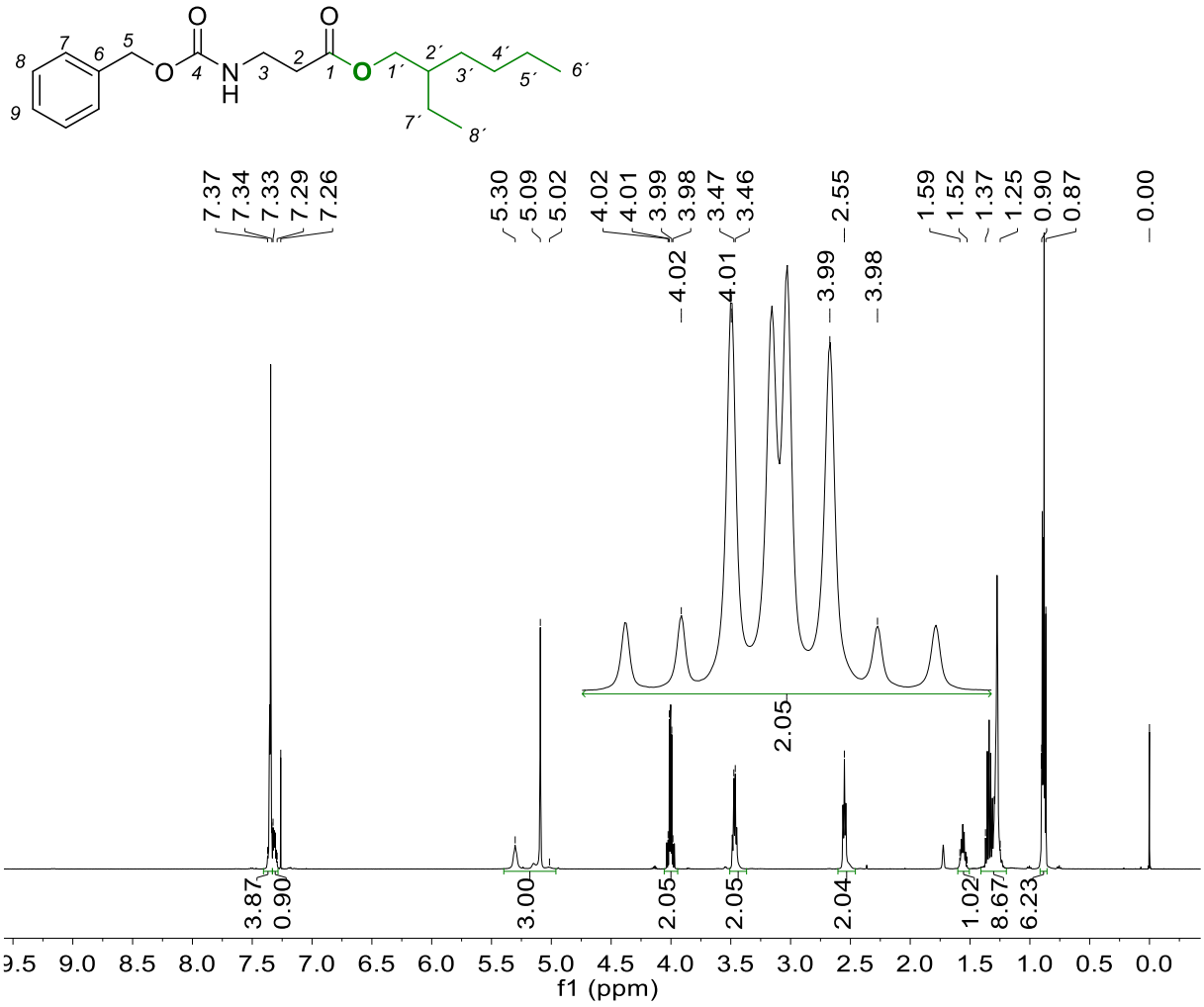


3_{35k}

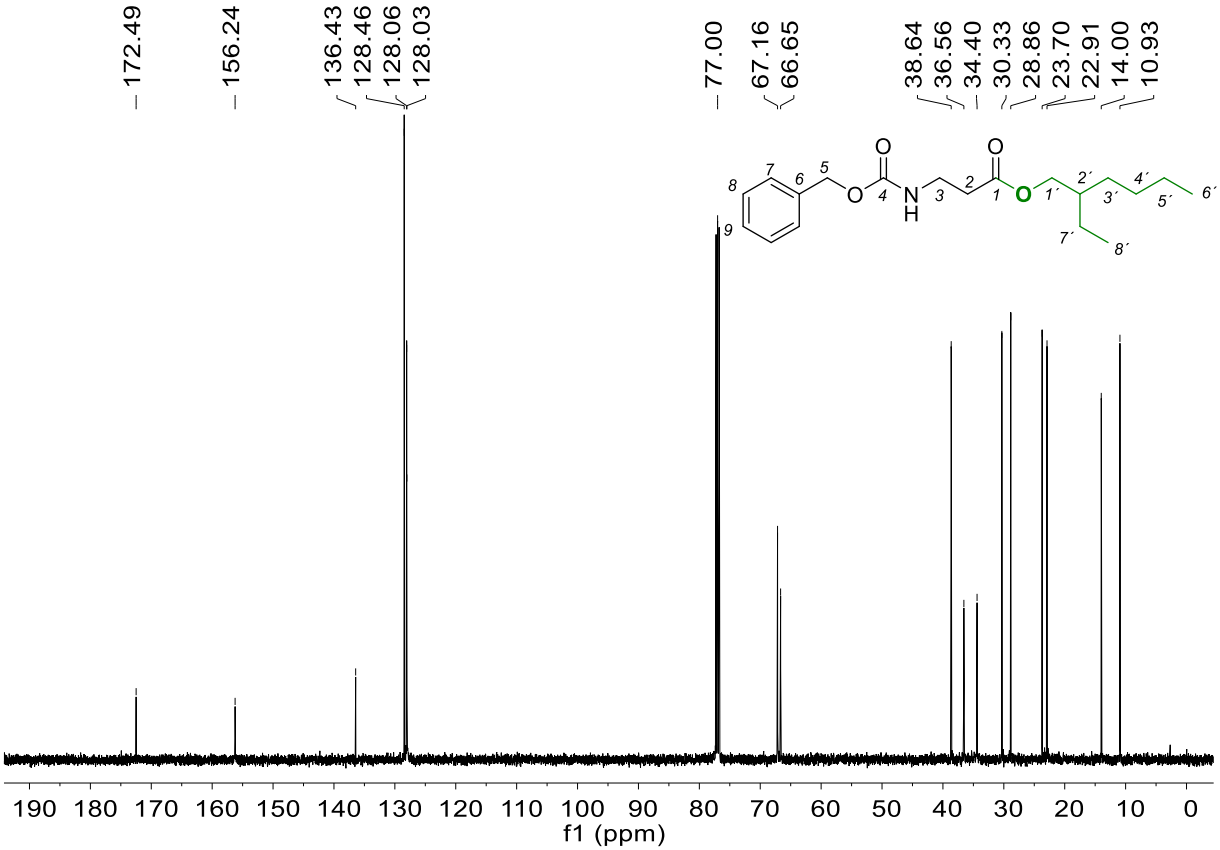
PH3483: As delineated in general procedure 4 (chapter 5.3.4, page 50), a suspension of 3-(benzyloxycarbonylamino) propanoic acid (290 mg, 1.30 mmol, 1.3 equiv) and FPyr (19.6 μL, 20.4 mg, 200 μmol, 20 mol%) in MeCN (0.50 mL) was treated with TCT (92 mg, 0.49 mmol, 49 mol%) and the resulting mixture was stirred at 40 °C for 5 h. Then, a solution of 2-ethyl-1-hexanol (158 μL, 132 mg, 1.00 mmol, 1.0 equiv) in MeCN (0.50 mL→1 M) was added under cooling in an ice bath, the vial, in which the solution of the alcohol had been prepared was rinsed with MeCN (250 μL→0.8 M) and NMM (190 μL, 1.7 mmol, 1.7 equiv) was added. After stirring for 3 h at room temperature DMAP (12.2 mg, 100 μmol, 10 mol%) was added and stirring was continued for further 16 h. ^{1}H-NMR of the crude material (356 mg, 106%, pale yellow oil) after aqueous work up confirmed a conversion of 2-ethyl-1-hexanol of 96%. Ultimately, column chromatographic purification on silica gel (25.4 g) with EtOAc/*n*Hex of 15:85 furnished the title compound as a colourless oil (251.3 mg, 0.749 mmol, 75%).

M ($C_{19}H_{29}NO_4$) = 335.44 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 15:85) = 0.33; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.37-7.34 (m, 4-H, 7-H, 8-H), 7.33-7.29 (m, 1H, 9-H), 5.30-5.02(m, 3H, 5-H, NH; amongst s at 5.09 ppm), 4.02/3.99 (2 x dd, $^2J_{1'a,1'b}$ = 9.3 Hz, $^3J_{1'a,\,2'}$ = 5.7 Hz, $^2J_{1'b,1'a}$ = 9.3 Hz, $^3J_{1'b,\,2'}$ = 6.0 Hz, 2H, 2´-H), 3.47 (dt, $^3J_{3,NH}$ = $^3J_{3,2}$ = 6.1 Hz, 2H, 3-H), 2.55 (t, $^3J_{2,3}$ = 5.9 Hz, 2H,

2-H), 1.59-1.52 (m, 1H, 2´-H, 1.37-1.25 (m, 8H, 3´-H, 4´-H, 5´-H, 6´-H, 7´´-H), 0.90-0.87 (m, 6H; 6´-H, 8´-H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 172.49 (C-1), 156.24 (C-4), 136.43 (C-6), 128.46 (C-8), 128.06 (C-7), 128.03 (C-9), 67.16 (C-1´), 66.65 (C-5), 38.64 (C-2´), 36.56 (C-3), 34.40 (C-2), 30.33, (C-3´) 28.86 (C-4´ or C-5´), 23.70 (C-7´), 22.91 (C-4´ or C-5´), 14.00 (C-6´), 10.93 (C-8´); **HR-MS** (ESI, $[C_{19}H_{33}N_2O_4]^+$, PH34832) calc. 353.2435 u found 353.2429 u.

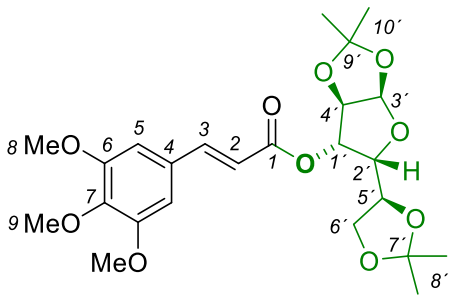


^{1}H-NMR spectrum of 2-ethylhex-1-yl 3-(benzyloxycarbonylamino) propanoate (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of 2-ethylhex-1-yl 3-(benzyloxycarbonylamino) propanoate (125 MHz, $CDCl_3$).

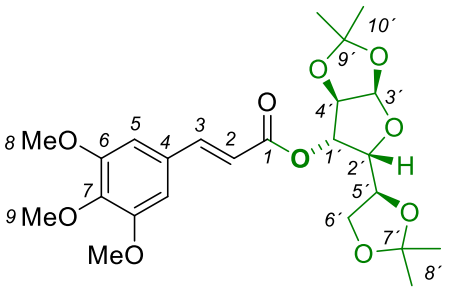
5.4.3.13 Synthesis of 3-O-(3,4,5-Trimethoxyphenyl)propenoyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (3_{17k})



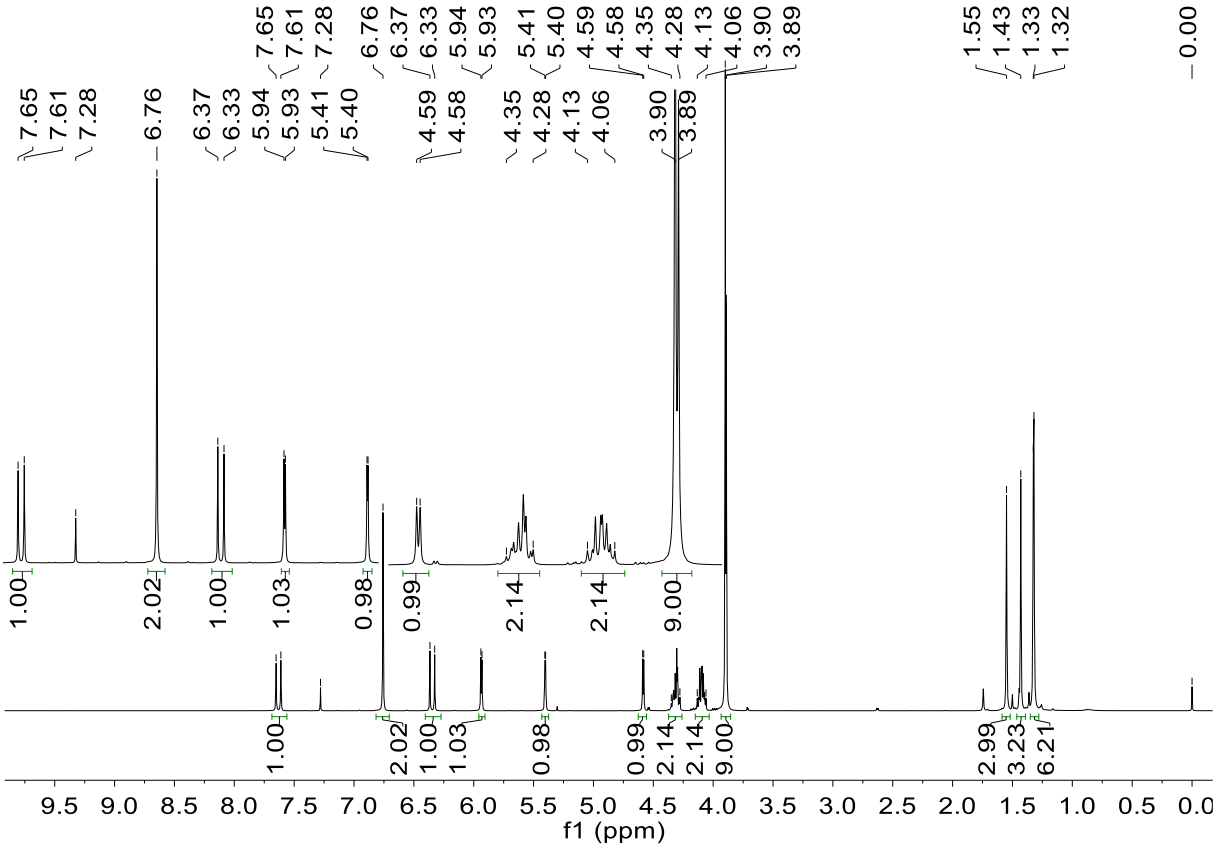
3_{17k}

PH3369: According to general procedure 4 (chapter 5.3.4, page 50), *trans*-3-(3,4,5-trimethoxphenyl)-2-propenoic acid (238 mg, 1.00 mmol, 1.0 equiv) was allowed to react with TCT (72 mg, 0.38 mmol, 38 mol%) using FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) for 4 h at 80 °C. Subsequently, the reaction suspension was diluted with MeCN (1.0 mL→0.7 M) and under cooling to 0 °C successively 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (273 mg, 1.05 mmol, 1.05 equiv), NMM (150 μL, 1.3 mmol, 1.3 equiv) and DMAP (24.4 mg, 200 μmol, 20 mol%) were added. After stirring for 21 h at room temperature and aqueous work up with HCl-washing, the crude material was obtained as yellow, foamy oil (463 mg, 96%), of which ^{1}H-NMR confirmed as composition of title compound with respect to the sugar derivative of 64:36. Next chromatographic purification on silica gel (23.2 g, mass ratio crude **3_{17k}**/SiO_2 1:50) with EtOAc/*n*Hex 30:70, concentration with $CHCl_3$ (3 x 2 mL) and drying for 18 h in high vacuum afforded the title ester as a colourless solid (239.3 mg, 0.498 mmol, 50%). In order to apply

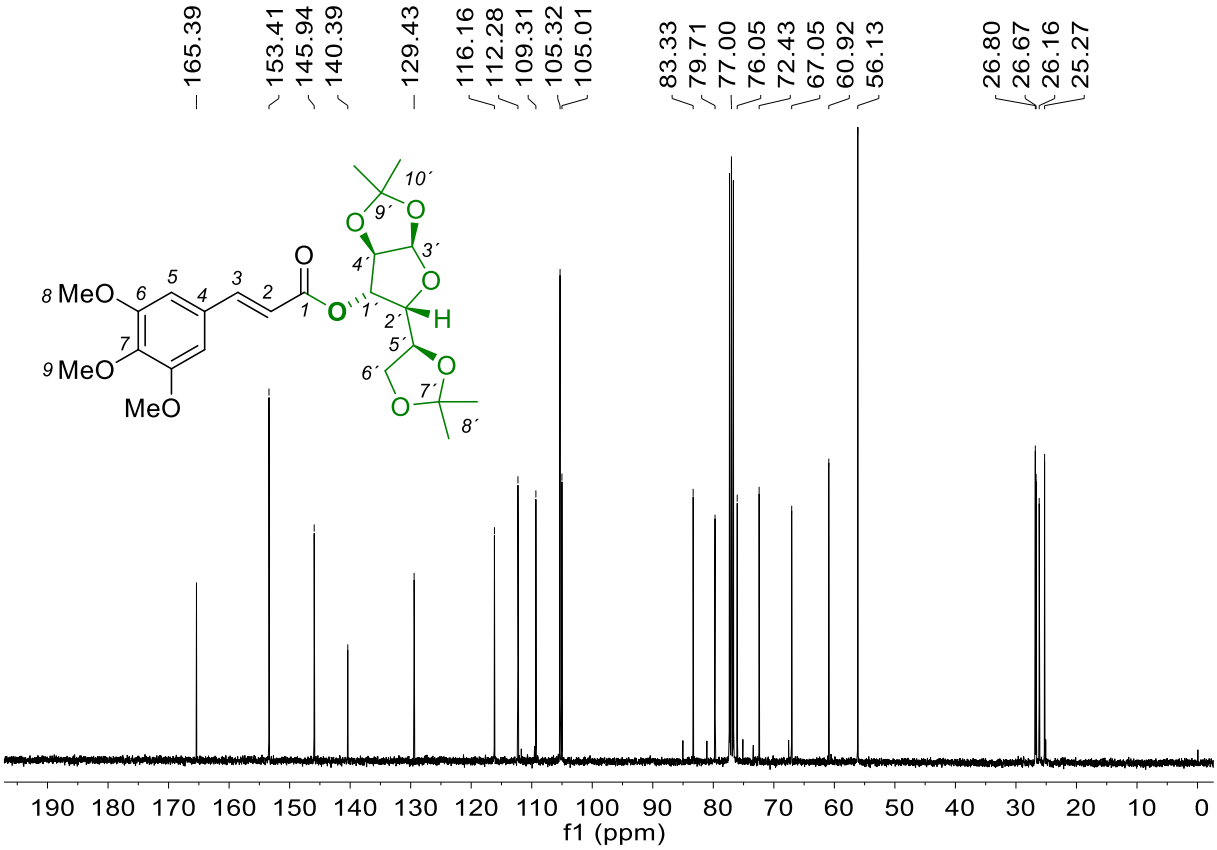
the crude product onto the SiO_2-column, it was dissolved in CH_2Cl_2 (ca. 10 mL), SiO_2 was added (0.97 g, ratio 1:2.1) and the all volatiles were removed in *vacuo*.



M ($C_{24}H_{32}O_{10}$) = 480.51 g/mol; **mp.** 57-60 °C ; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 30:70) = 0.22; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.63 (d, $^3J_{3,2}$ = 15.9 Hz, 1H, 3-H), 6.76 (s, 2H, 5-H), 6.35 (d, $^3J_{2,3}$ = 15.9 Hz, 1H, 2-H), 5.94 (d, ^3J = 3.7 Hz, 1H, C-3´), 5.41 (d, ^3J = 2.6 Hz, 1H, 1´-H), 4.59 (d, ^3J = 3.7 Hz, 1H, C-4´), 4.35-4.28 (m, 2H, 2´-H, 5´-H), 4.13-4.06 (m, 2H, 6´-H), 3.90/3.89 (2 x s, 9H, 8-H, 9-H), 1.55 (s, 3H, 10´-H_a), 1.43 (s,3H, 8´-H_a), 1.33/1.32 (2 x s, 6H, 8´-H_b, 10´-H_b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 165.39 (C-1), 153.41 (C-6), 145.94 (C-3), 140.39 (C-7), 129.43 (C-4), 116.16 (C-2), 112.28 (C-9´), 109.31 (C-7´), 105.32 (C-5), 105.01 (C-3´), 83.33 (C-4´), 79.71 (C-2´), 76.05 (C-1´), 72.43 (C-5´), 67.05 (C-6´), 60.92 (C-9), 56.13 (C-8), 26.80 (C_a-8´), 26.67 (C_a-10´), 26.16 (C_b-8´ or C-10$_b$´), 25.27 (C_b-8´ or C_b-10´); **HR-MS** (CI, $[C_{20}H_{23}O_{10}]^+$) calc. 423.2191 u found 423.1256 u; ($[C_{24}H_{33}O_{10}]^+$) calc. 481.2068 u found 481.2082 u; **$[\alpha]_D^{20}$** (c = 1.025 g/100 mL, $CHCl_3$) = -37.5.

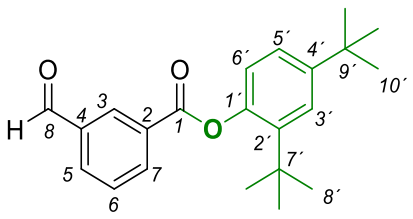


1H-NMR spectrum of 3-O-(3,4,5-trimethoxyphenyl)propenoyl-1,2:5,6-di-O-isopropyl-idene-α-D-glucofuranose (400 MHz, CDCl3).



13C-NMR spectrum of 3-O-(3,4,5-trimethoxyphenyl)propenoyl-1,2:5,6-di-O-isopropyl-idene-α-D-glucofuranose (125 MHz, CDCl3).

5.4.3.14 Synthesis of 2,4-Di-*tert*-butylphenyl 3-formylbenzoate (3_{14l})



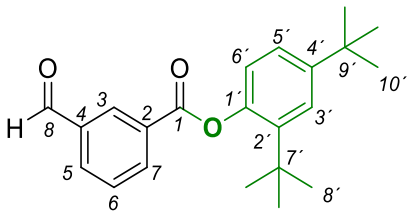
3_{14l}

PH3331: As given in general procedure 4 (chapter 5.3.4, page 50), TCT (92 mg, 0.49 mmol, 49 mol%) was added to a mixture of 3-formyl benzoic acid (195 mg, 1.3 mmol, 1.3 equiv) and FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) and the resulting reaction mixture was heated to 80 °C for 4 h. Next, a solution of 2,4-di-*tert*-butylphenol (206 mg, 1.00 mmol, 1.0 equiv) in MeCN (0.50 mL) and NMM (190 μL, 1.7 mmol, 1.7 equiv) was added under cooling to 0 °C. The vial used for the preparation of the solution of the phenol derivative was rinsed with more MeCN (0.50 mL→0.7 M) and DMAP (24.2 mg, 200 μmol, 20 mol%) was added. Finally, the reaction mixture was stirred for 1 h at room temperature and 19 h at 40 °C.

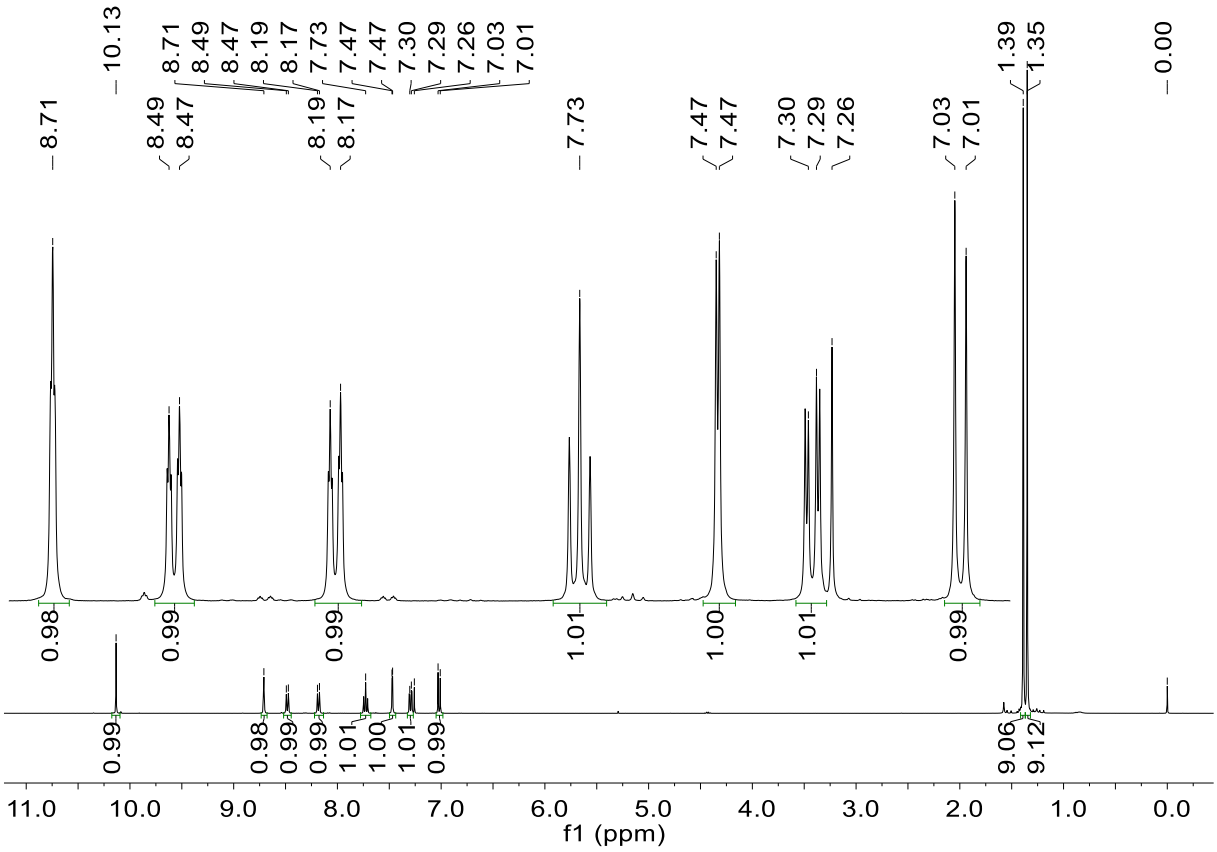
Aqueous work up furnished the crude material as yellow oil (333.7 mg, 99%), whereat ^{1}H-NMR verified a ratio of the title compound with respect to di-*tert*-butylphenol of 56:45. Then, column chromatographic purification on silica gel (35.0 g, ratio weight of crude **3_{14l}**/SiO_2 1:105) with EtOAc/*n*Hex 10:90 as eluent delivered the title compound as a colourless solid (163.8 mg, 0.484 mmol, 48%). Due to low solubility of the crude material in the eluent, it was adsorbed on

silica gel (0.89 g, mass crude product/SiO_2 1:2.7) through dissolution in CH_2Cl_2, addition of SiO_2 and evaporation of all volatile components under reduced pressure.

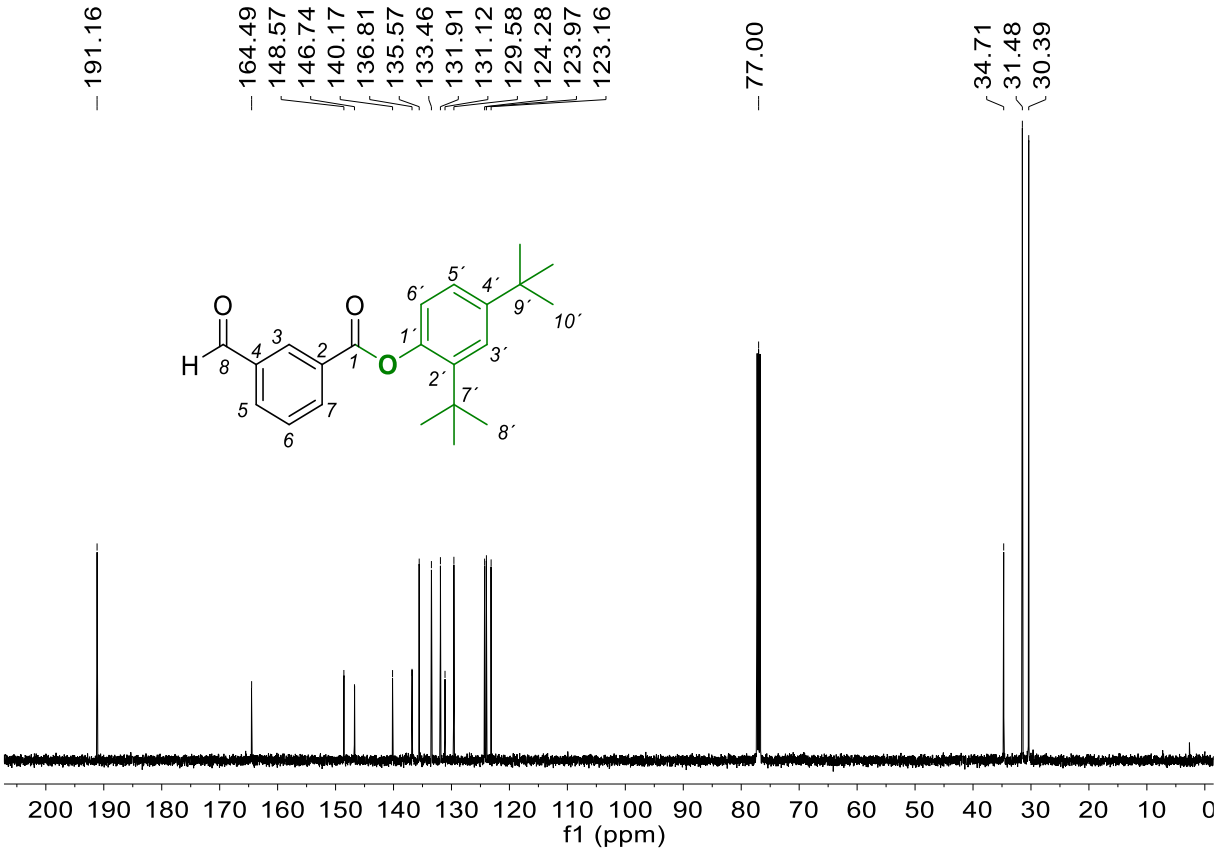
PH3317: As described in general procedure 4 (chapter 5.3.4, page 50), **3-formyl benzoic acid** (150 mg, 1.00 mmol, **1.0 equiv**) was converted to the respective acid chloride using **TCT** (72 mg, 0.38 mmol, **38 mol%**) and **FPyr** (19.6 μL, 20.4 mg, 200 μmol, **20 mol%**) in MeCN (2 M) under heating to **40 °C** for 12 h. In the following, successively a solution of **2,4-di-*tert*-butylphenol** (227 mg, 1.1 mmol, 1.1 equiv) in MeCN (0.50 mL) and NMM (150 μL, 1.3 mmol, 1.3 equiv) were added under cooling in an ice bath. Subsequently, the vial, in which the solution of the aromatic alcohol had been prepared, was rinsed with further MeCN (0.25 mL, 0.8 M) and DMAP (12.2 mg, 100 μmol, 10 mol%) was added. After stirring for 24 h at room temperature, aqueous work resulted in the crude product as a yellow oil (346.6 mg,102%). Purification by means of column chromatography on silica gel (32.8 g, mass relation crude $\mathbf{3_{14l}}$/SiO_2 1:94) with EtOAc/*n*Hex 10:90. Thereby, the crude material was adsorbed on silica gel (0.89 g, crude product/SiO_2 1:2.5).



M ($C_{22}H_{26}O_3$) = 338.45 g/mol; **mp.** 110-111 °C; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 10:90) = 0.36; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 10.13 (s, 1H, 8-H), 8.71 (ψ-t, *J* = 1.4 Hz, 1H, 3-H), 8.48 (ψ-dt, *J* = 7.8 Hz, 1.5 Hz, 1H, 7-H), 8.18 (ψ-dt, *J* = 7.7 Hz, 1.4 Hz, 1H, 5-H), 7.73 (ψ-t, *J* = 7.7 Hz, 1H, 6-H), 7.47 (d, $^3J_{3´,5´}$ = 2.3 Hz, 1H, 3´-H), 7.30 (dd, $^3J_{5´,6´}$ = 8.5, $^3J_{5´,3´}$ = 2.4 Hz, 1H, 5´-H), 7.02 (d, $^3J_{6´,5´}$ = 8.4 Hz, 1H, 6´-H), 1.39 (s, 9H, H-10´), 1.35, (s, 9H, H-8´); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 191.16 (C-8), 164.49 (C-1), 148.57 (C-4´), 146.74 (C-1´), 140.17 (C-2´), 136.81 (C-2 or C-4), 135.57 (C-7), 133.46 (C-5), 131.91 (C-3), 131.12 (C-2 or C-4), 129.58 (C-6), 124.28 (C-3´), 123.97 (C-5´), 123.16 (C-6´), 34.71 (C-7´ and C-9´), 31.48 (C-8´), 30.39 (C-10´); **HR-MS** ($[C_{22}H_{26}O_3]^+$) calc. 338.1882 u found 338.1890 u.

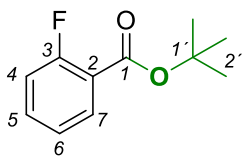


^{1}H-NMR spectrum of 2,4-di-*tert*-butylphenyl 3-formylbenzoate (400 MHz, $CDCl_3$).



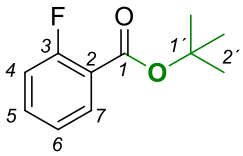
^{13}C-NMR spectrum of 2,4-di-*tert*-butylphenyl 3-formylbenzoate (125 MHz, $CDCl_3$).

5.4.3.15 Synthesis of *tert*-Butyl 2-fluorobenzoate (3_{15m})

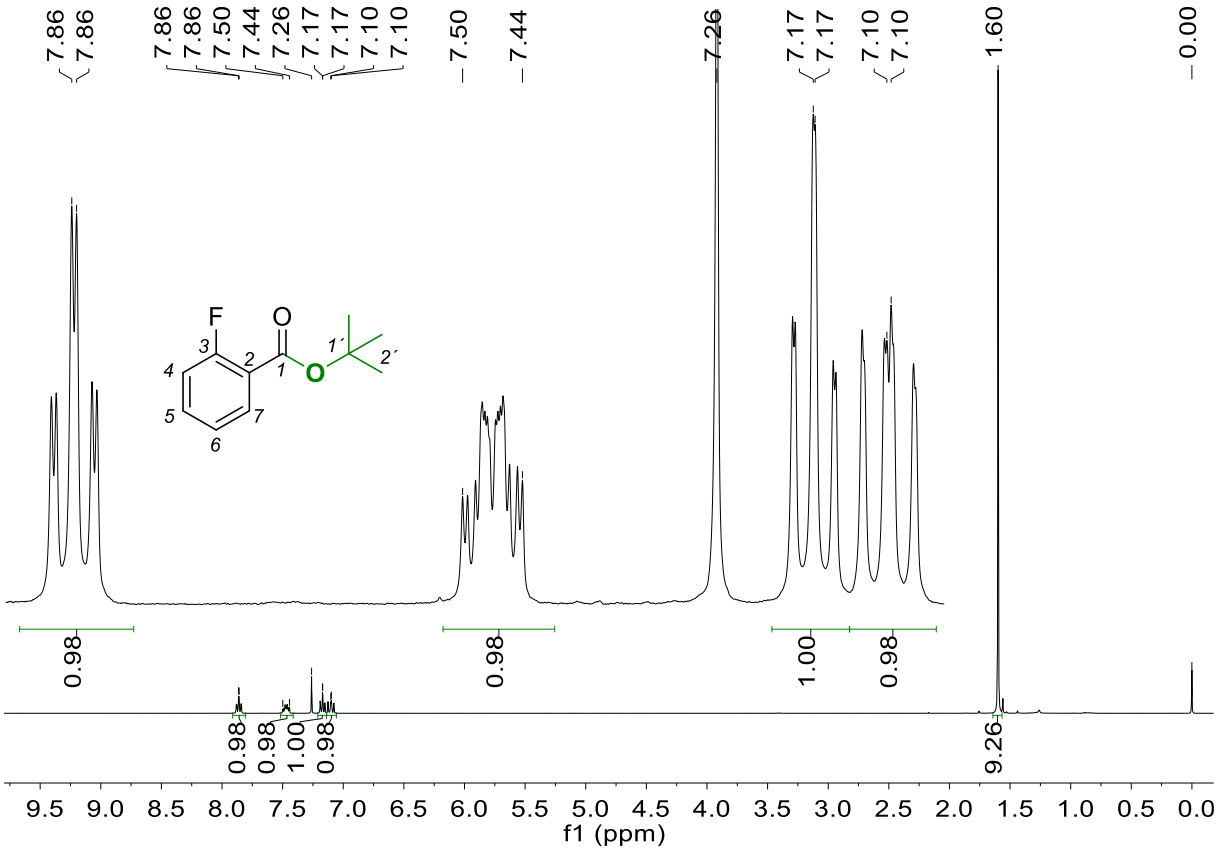


3_{15m}

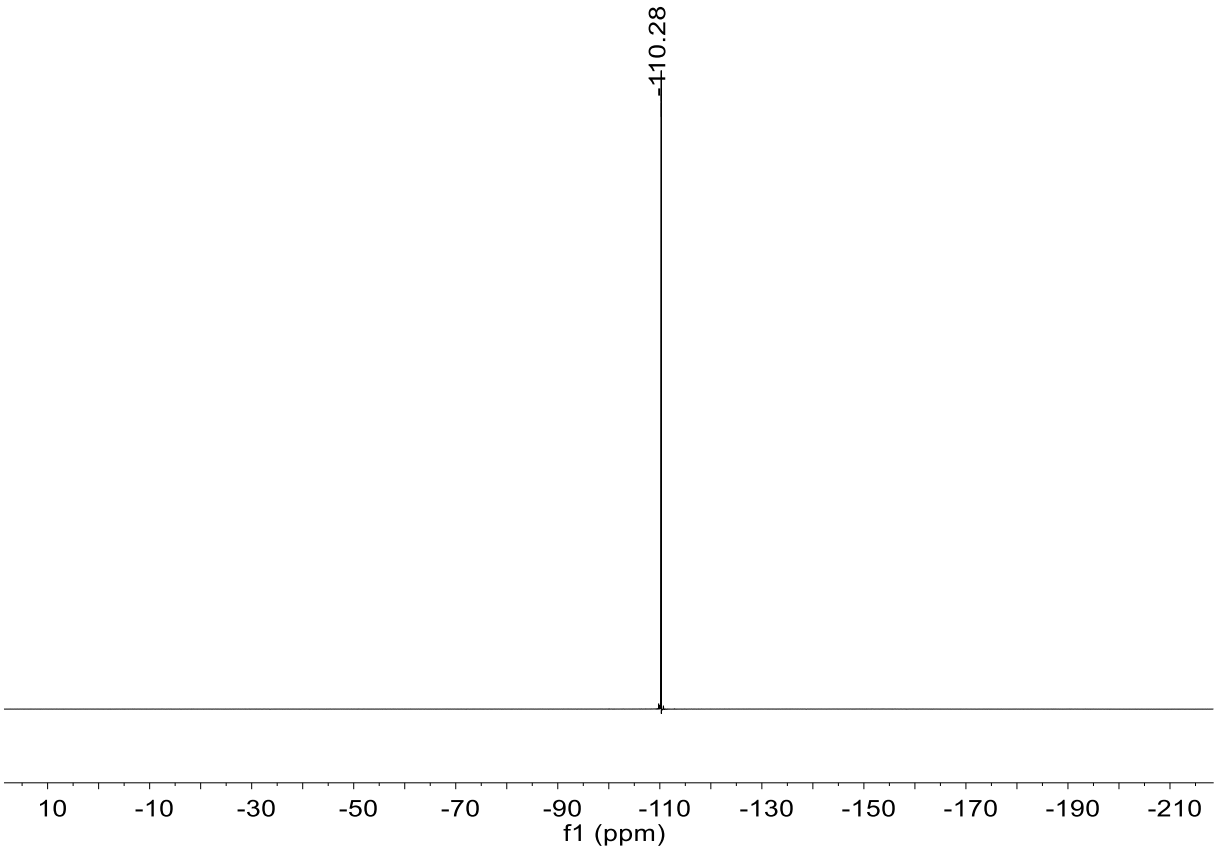
PH3322: In agreement with general procedure 4 (chapter 5.3.4, page 50), 2-fluoro benzoic acid (140 mg, 1.00 mmol, 1.0 equiv) was reacted with TCT (72 mg, 0.38 mmol, 38 mol%) in the presence of FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) in MeCN (0.50 mL, 2 M) for 5 h at 80 °C. Then, a solution of *t*BuOH (142 μL, 111 mg, 1.5 mmol, 1.5 equiv), NMM (260 μL, 2.3 mmol, 2.3 equiv) in MeCN (0.50 mL→1 M) and subsequently DMAP (24.4 mg, 200 μmol, 20 mol%) were added under cooling to 0 °C. In the following the reaction mixture was stirred for 15 min at ambient temperature and for 24 h at 40 °C. Finally, purification of the crude material (107 mg, 55%) by means of column chromatography on silica gel (9.0 g, mass ratio crude product/SiO_2 1:82) engaging EtOAc/*n*Hex 3:97 as eluent, drying at the rotary evaporator at 20 mbar for 15 min furnished the title compound as a colourless oil (91.3 mg, 0.465 mmol, 47%). In order to load the crude material onto the column, it was dissolved in EtOAc (0.2 mL) and diluted with the less polar eluent (0.3 mL).



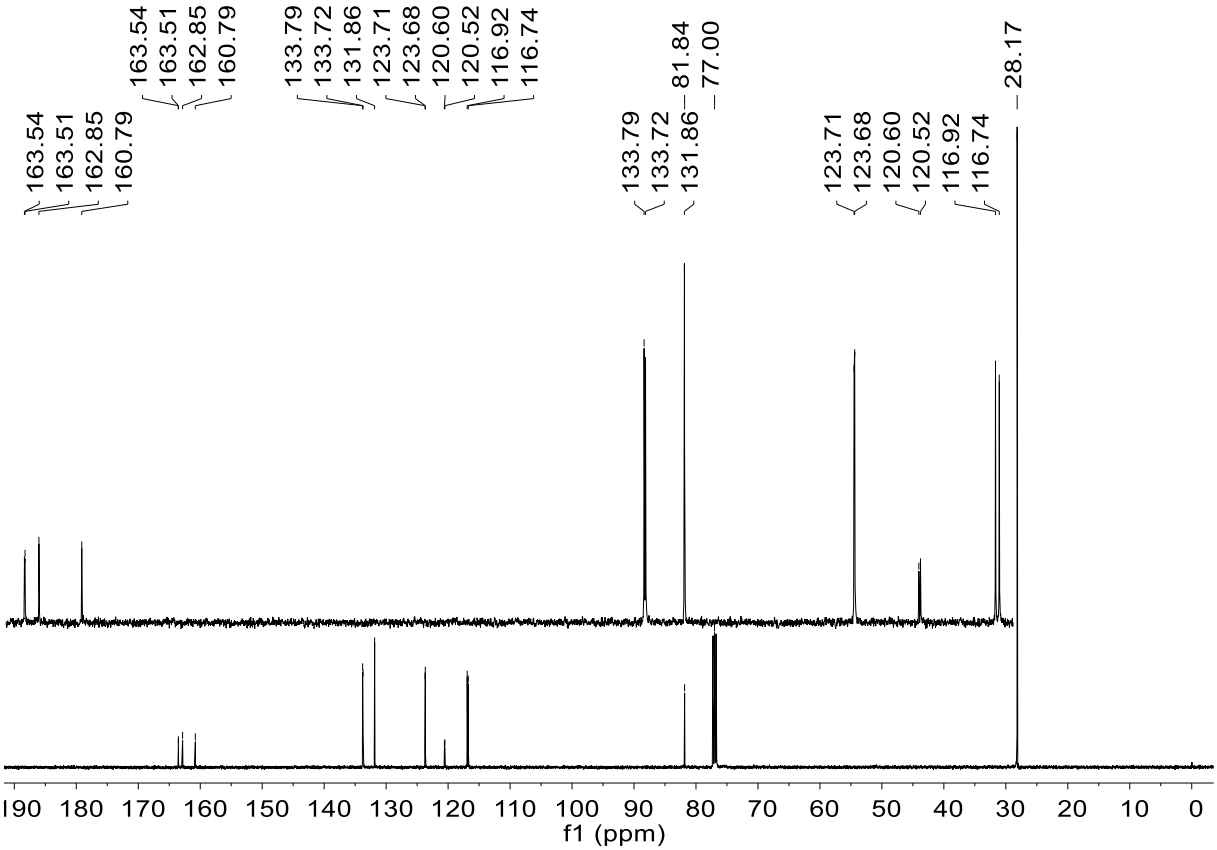
M ($C_{11}H_{13}FO_2$) = 196.22 g/mol; **r_f** (SiO_2, EtOAc/CH_2Cl_2 7:93) = 0.36; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.86 (ψ-td, *J* = 7.6 Hz, 1.8 Hz, 1H, 7-H), 7.50-7.44 (m, 1H, 5-H), 7.17 (ψ-td, *J* = 7.7, 0.7 Hz, 1H, 6-H), 7.10 (ddd, $^3J_{4,F}$ = 10.8 Hz, $^3J_{4,5}$ = 8.4 Hz, $^4J_{4,6}$ = 0.9 Hz, 1H, 4-H), 1.60 (s, 9H, 2´-H); **^{19}F-NMR** (375 MHz, $CDCl_3$) δ [ppm] = -110.28; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 163.53 (d, $^3J_{1,F}$ = 4 Hz, C-1), 161.82 (d, $^1J_{3,F}$ = 260 Hz, C-3), 133.77 (d, $^3J_{5,F}$ = 9 Hz, C-5), 131.86 (C-7), 123.70 (d, $^4J_{6,F}$ = 4 Hz, 6-H), 120.56 (d, *J* = 10 Hz, C-2), 116.83 (d, $^2J_{4,F}$ = 23 Hz, C-4), 81.84 (C-1´), 28.17 (C-2´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 197 (<1, $[M+H]^+$), 169 (11, $[M-(H_2CCH_2]^+$), 155 (2), 141 (100, $[M-H_2CC(CH_3)_2]^+$), 123 (12, $[M-O$*t*$Bu]^+$), 109 (1), 57 (59, $[Bu]^+$). The NMR data is in agreement with reported data.[51]



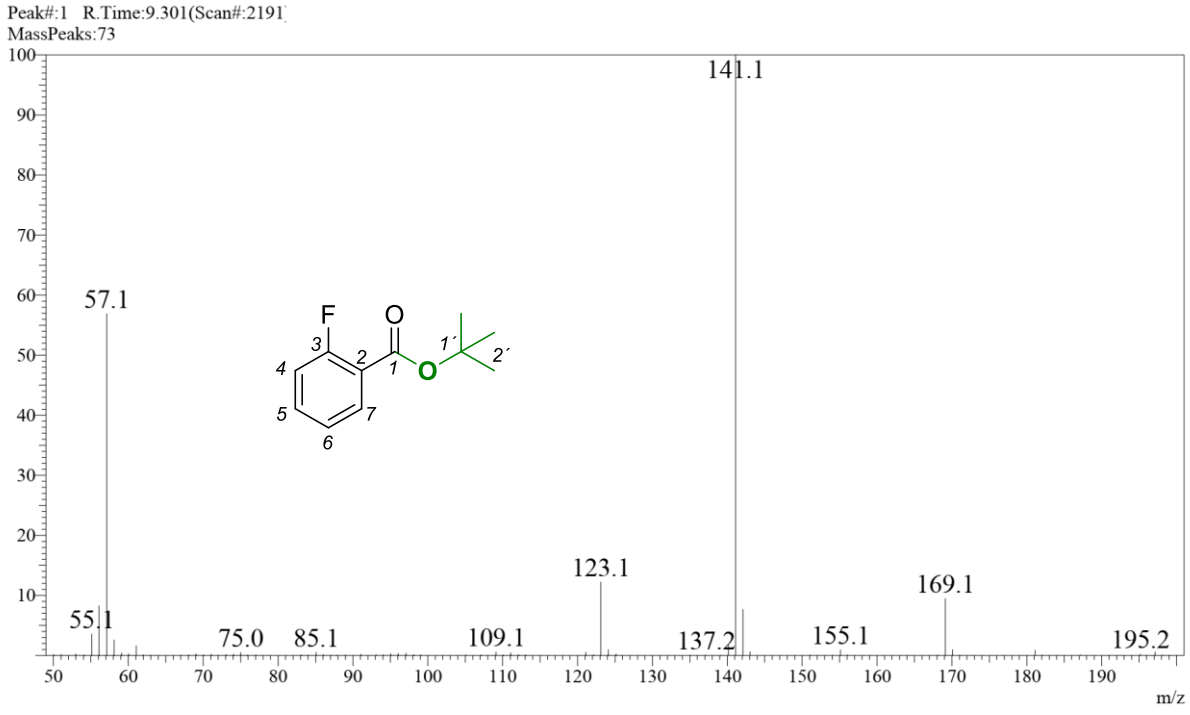
^{1}H-NMR spectrum of *tert*-butyl 2-Fluorobenzoate (400 MHz, $CDCl_3$).



^{19}F-NMR spectrum of *tert*-butyl 2-Fluorobenzoate (375 MHz, $CDCl_3$).

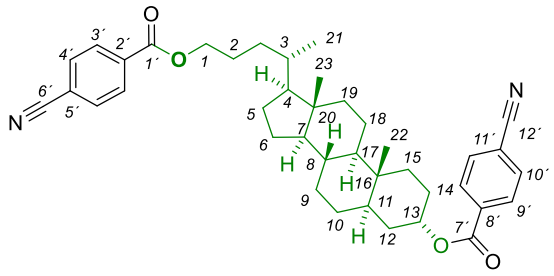


^{13}C-NMR spectrum of *tert*-butyl 2-Fluorobenzoate (125 MHz, $CDCl_3$).



Mass spectrum of *N*-(2-(indol-3-yl)ethyl) 4-benzoylbenzamide (CI, 70 eV).

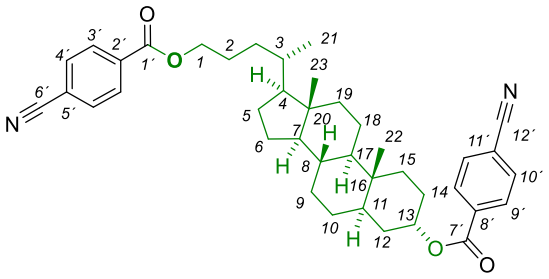
5.4.3.16 Synthesis of α,24-Di(4-cyanobenzoyloxy) cholane (3_{24n})



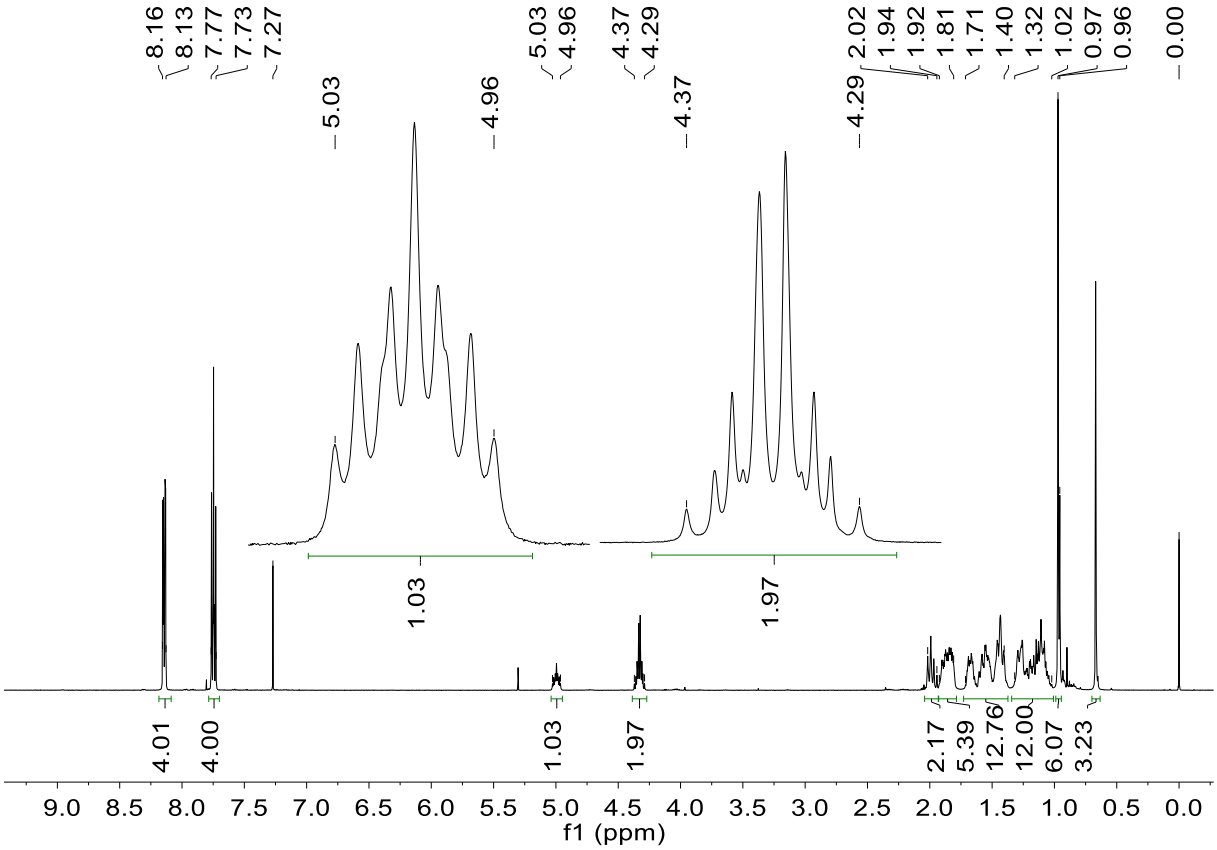
3_{24n}

Attempted monoacylation of cholane proceeded in very poor chemoselectivity, which is most likely reasoned by the poor solubility of this starting material in organic solvents and a probably strongly improved solubility of cyanobenzoyloxy cholane.

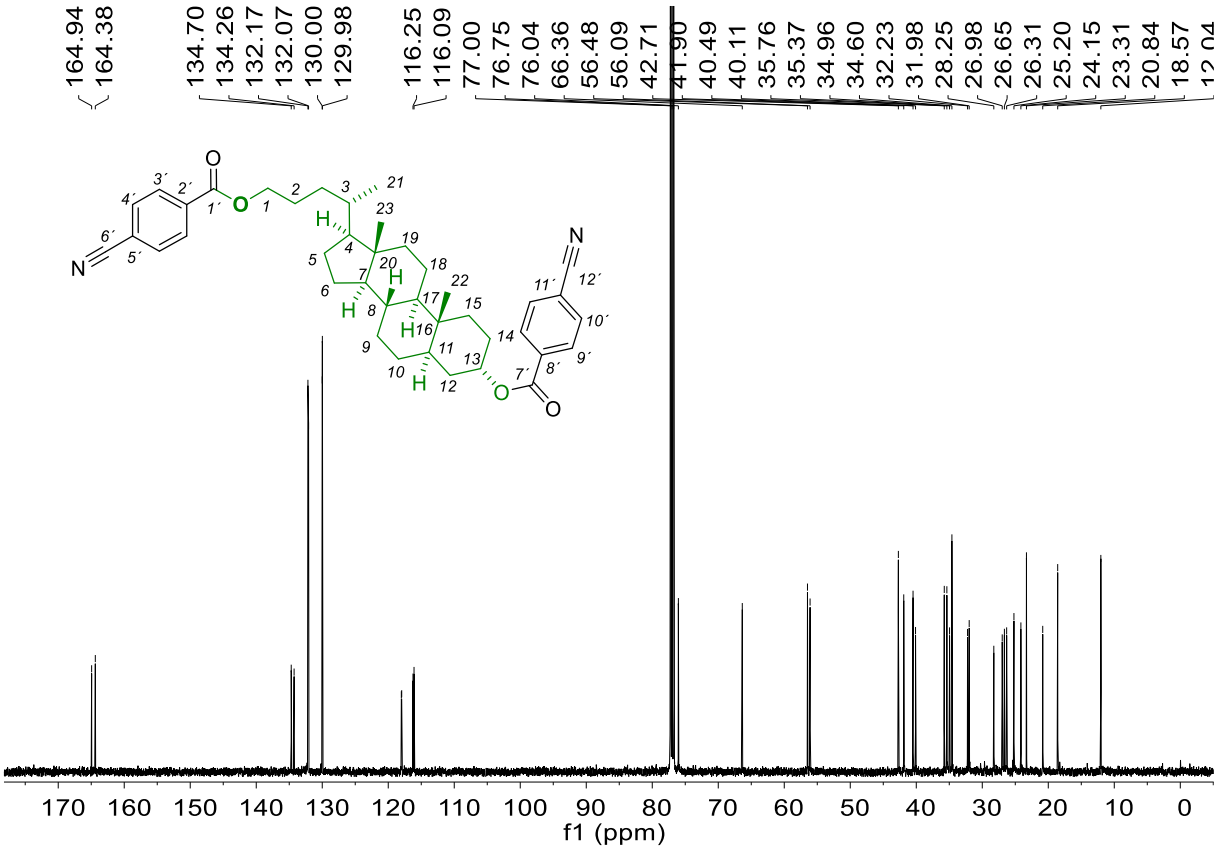
PH3408: In agreement with general protocol 4 (chapter 5.3.4, page 50), TCT (79 mg, 0.42 mmol, 84 mol%) was added to a suspension of 4-cyanobenzoic acid (162 mg, 1.10 mmol, 2.2 equiv) and FPyr (9.8 μL, 10.2 mg, 100 μL, 20 mol%) in MeCN (0.50 mL, 1 M) and the reaction mixture was heated to 80 °C for 4 h. Then, under chilling in an ice bath the reaction suspension was added to a suspension of cholane (182 mg, 0.50 mmol, 1.0 equiv), NMM (160 μL, 1.45 mmol, 2.9 equiv) and DMAP (12.2 mg, 100 μmol, 20 mol%) in MeCN (1.0 mL→0.3 M) and the reaction vial was rinsed with further MeCN (2 x 0.25 mL→0.25 M). After stirring at room temperature for 20 h, aqueous work up delivered the crude material as a colourless, foamy solid (279 mg, 90%). Eventually, the purification with the aid of column chromatography on silica gel (22.2 g, mass ratio crude product/SiO_2 1:79) with EtOAc/*n*Hex 15:85 afforded the title benzoate as a colourless foamy solid in 60% yield (186.8 mg, 0.301 mmol, 60%). Reasoned by a poor solubility, the crude material was dissolved in CH_2Cl_2 (ca. 20 mL), SiO_2 was introduced (0.82 g, mass ratio 1:3), volatile compounds were removed under reduced pressure and the residue was loaded onto the silica gel column.



M ($C_{40}H_{48}N_2O_4$) = 620.83 g/mol; **mp.** = 78-80 °C; $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 15:85) = 0.38; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 8.16-8.13 (m, 4H, 3´-H, 9´-H), 7.77-7.73 (m, 4-H, 4´-H, 10´-H), 5.03-4.96 (m, 1H, 13-H), 4.37-4.29 (m, 2H, 1-H), 2.02-1.94 (m, 2H), 1.92-1.81 (m, 5H), 1.71-1.40 (m, 12H), 1.32-1.02 (m, 12H), 0.97-0.96 (m, 6H, 2 x C*H*$_3$), 0.67 (s, 3H, C*H*$_3$); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 164.94 (C-1´), 164.38 (C-7´), 134.70+134.26 (C-2´+C-8´), 132.17+132.07 (C-4´+C-10´), 130.00+129.98 (C-3´+C-9´), 118.02+117.96 (C-6´+C-12´), 116.25+116.09 (C-5´+C-11´), 76.75, 76.04 (C-13), 66.36, 56.48, 56.09, 42.71, 41.90, 40.49, 40.11, 35.76, 35.37, 34.96, 34.60, 32.23, 31.98, 28.25, 26.98, 26.65, 26.31, 25.20, 24.15, 23.31 (*C*H$_3$), 20.84, 18.57 (*C*H$_3$), 12.04 (*C*H$_3$); **CHN-analysis**) calc. C: 77.39% H: 7.79% N: 4.51% found C: 77.25% H: 7.89% N: 4.38%; **$[\alpha]_D^{20}$** = +33.2 (c = 1.005 g/100 mL, $CHCl_3$).

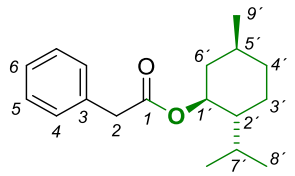


^{1}H-NMR spectrum α,24-Di(4-cyanobenzoyloxy) cholane (500 MHz, $CDCl_3$).



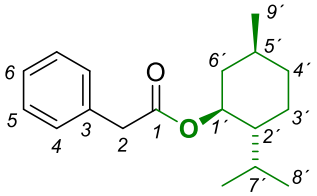
^{13}C-NMR spectrum of α,24-Di(4-cyanobenzoyloxy) cholane (125 MHz, $CDCl_3$).

5.4.3.17 Synthesis of (*1S,2R,5S*)-3-Methyl-6-*iso*-propylcyclohexyl 2-phenyl ethanoate (3_{4m})



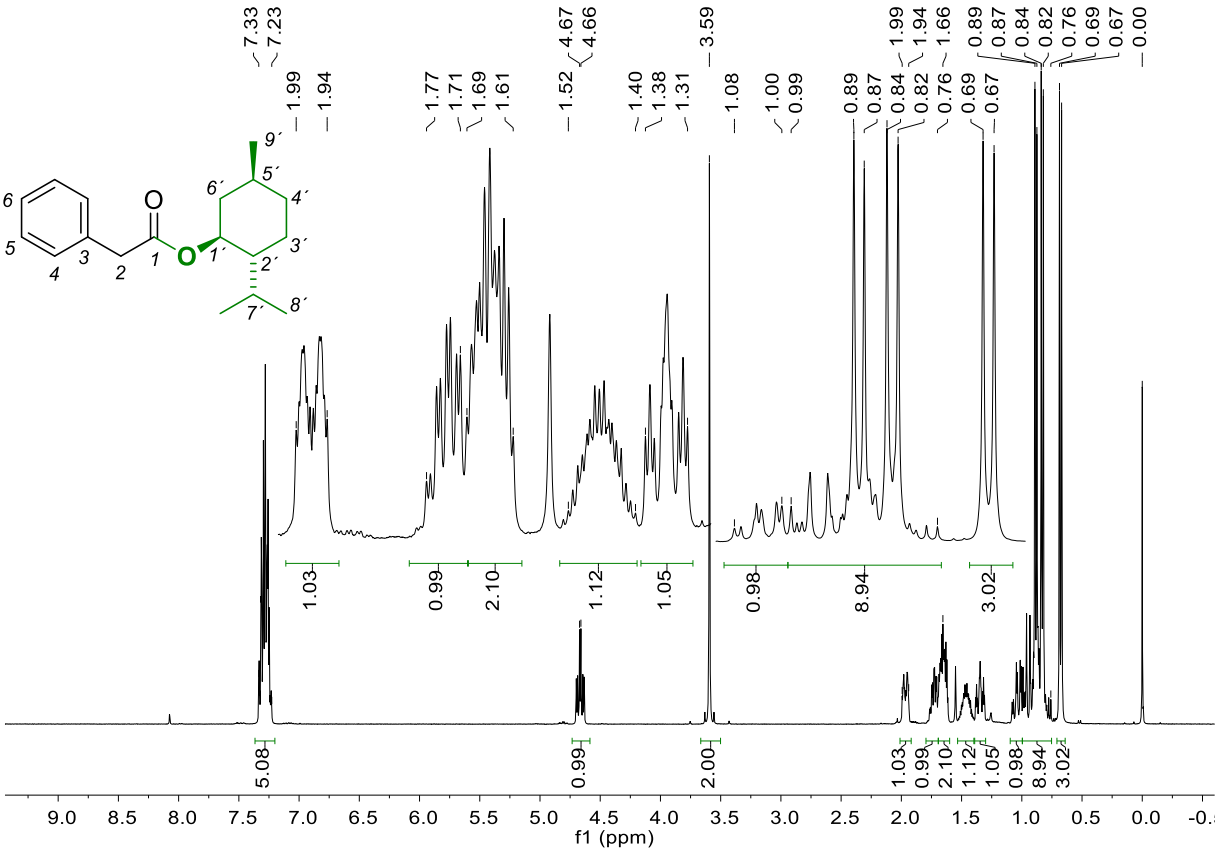
3_{4m}

PH2958: Following general procedure 4 (chapter 5.3.4, page 50) phenylacetic acid (136 mg, 1.00 mmol, 1.0 equiv) was transformed into the respective acid chloride using TCT (72 mg, 0.38 mmol, 38 mol%) and FPyr (9.8 μL, 10.2 mg, 1.00 mmol, 1.0 equiv) through heating to 40 °C for 4 h in MeCN (0.50 mL, 2 M). Then, further MeCN (0.50 mL→1 M) and D-menthol (187 mg, 1.2 mmol, 1.2 equiv) were added, the reaction suspension was cooled to 0 °C and K_2CO_3 (180 mg, 1.3 mmol, 1.3 equiv) was added. Past stirring for 19 h at room temperature aqueous work up afforded the crude product as a pale yellow oil (272 mg, 99%), of which ^{1}H-NMR verified a ratio of the title compound with regard to menthol of 54:46. Eventually, chromatographic purification on silica gel (27.1 g, crude $\mathbf{3_{4m}}$/SiO_2 1:100) with EtOAc/*n*Hex 3:97 and drying at the rotary evaporator at 10 mbar for 15 min delivered the ester $\mathbf{3_{4m}}$ as a colourless oil (166.2 mg, 0.606 mmol, 61%). The isolated product contained small traces ≤2 mol% of formyl menthol.

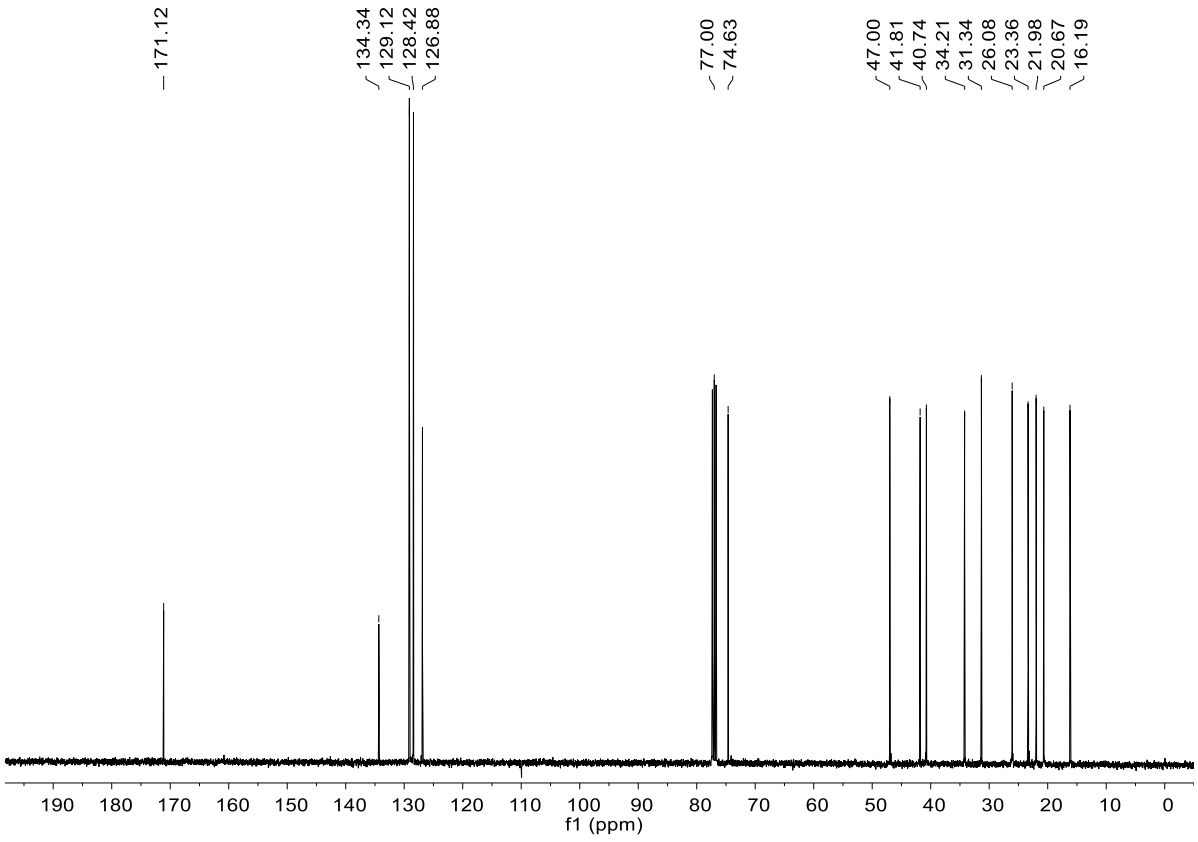


M ($C_{18}H_{26}O_2$) = 274.404 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/CH_2Cl_2 15:85) = 0.28; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.33-7.23 (m, 5H, 4-H, 5-H, 6-H), 4.67 (ψ-td, ^3J = 10.8 Hz, 4.4 Hz, 1H, 1´-H), 3.59 (s, 2H, 2-H), 1.99-1.94 (m, 1H, 6´-H_a), 1.77-1.71 (m, 1H, 7´-H), 1.69-1.61 (m, 2H, 3´-H_a, 4´-H_a), 1.52-1.40 (m, 1H, 5´-H), 1.38-1.31 (m, 1H´, 2´-H), 1.08-1.00 (m, 1H, 3´-H_b), 0.99-0.76 (m, 8H, 4´-H_b, 6´-H_b, 8´-H_a, 9´-H; amongst d at 0.88 ppm, $^3J_{9´,5´}$ = 6.6 Hz, 9´-H; and d at 0.83, $^3J_{8´,7´}$ = 7.0 Hz, 8´-H_a), 0.68 (m, $^3J_{8´,7´}$ = 7.0 Hz, 3H, 8´-H_b); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ [ppm] = 171.12 (C-1), 134.34 (C-3), 129.12 (C-4), 128.42 (C-3), 126.88 (C-6), 74.63 (C-1´), 47.00 (C-2´), 41.81 (C-2), 40.74 (C-6´), 34.21 (C-4´), 31.34 (C-5´), 26.08 (C-7´), 23.36 (C-3´), 21.98 (C-9´), 20.67 (C-8´$_a$), 16.19 (C$_b$-8´); **GC-MS** (CI, 70 eV) m/z [u] (%) = 273 (4, $[M-H]^+$), 259 (4, $[M-Me]^+$), 177 (2), 165 (22), 155 (7, $[M-BnCO]^+$), 139 (100, $[M-BnCO_2]^+$); 123 (8), 119 (7, $[BnCO]^+$), 97 (11, $[(C_6H_{10})CH_3)]^+$, 91 (10, $[Bn]^+$), 83 (71, [*c*Hex]$^+$), 69 (11, [pentenyl]$^+$), 57 (20, $[Bu]^+$); **HR-MS** (CI, $[C_{18}H_{27}O_2]^+$) calc. 275.20061 u found 275.2020 u; **$[\alpha]_D^{20}$** (c = 0.80g/100 mL, $CHCl_3$) = +75.8; **Lit-$[\alpha]_D^{25}$** of (*1R,2S,5R*) enantiomer (c = 0.62 g/100 mL, $CHCl_3$) = -65.0.[52]

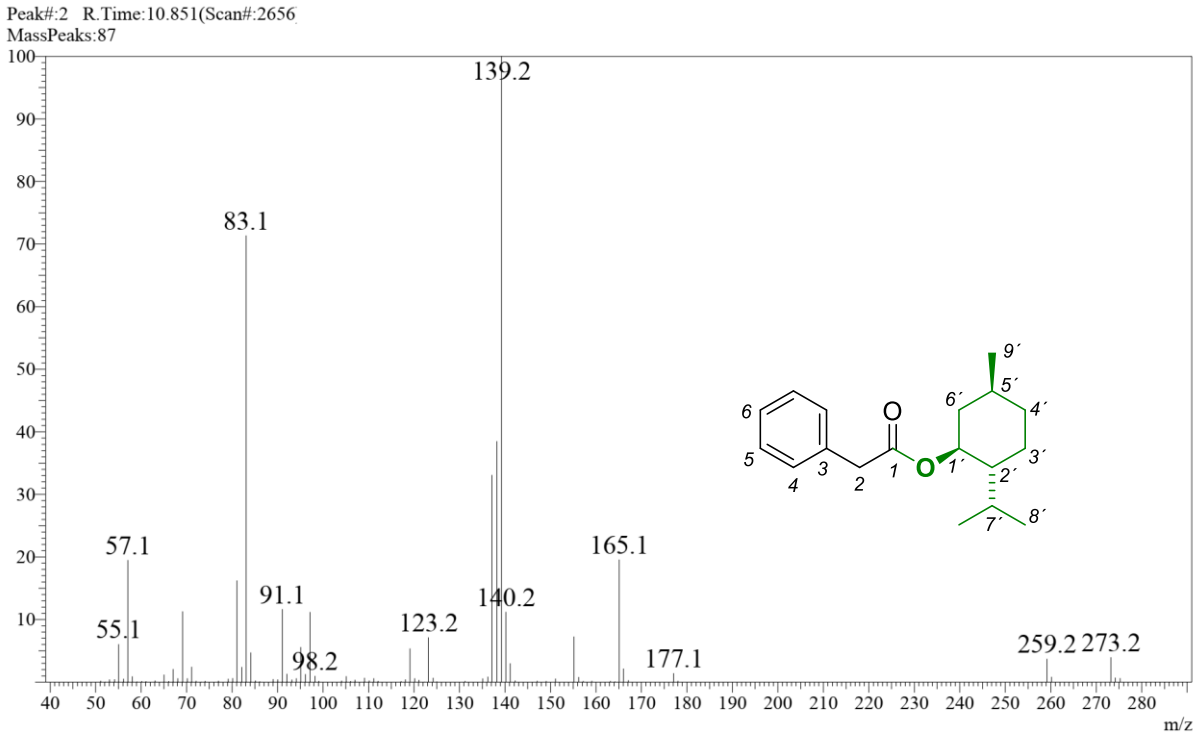
The NMR data is in agreement with the literature.[52]



^{1}H-NMR spectrum of (*1S,2R,5S*)-3-Methyl-6-*iso*-propylcyclohexyl 2-phenyl ethanoate (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of (*1S,2R,5S*)-3-Methyl-6-*iso*-propylcyclohexyl 2-phenyl ethanoate (100 MHz, $CDCl_3$).

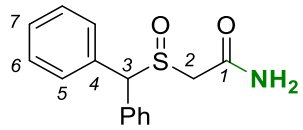


Mass spectrum of (*1S,2R,5S*)-3-Methyl-6-*iso*-propylcyclohexyl 2-phenyl ethanoate (CI, 70 eV).

5.4.4 Miscellaneous Synthesis (Scheme 3 + 4)

5.4.4.1 Synthesis of *Modafinil*

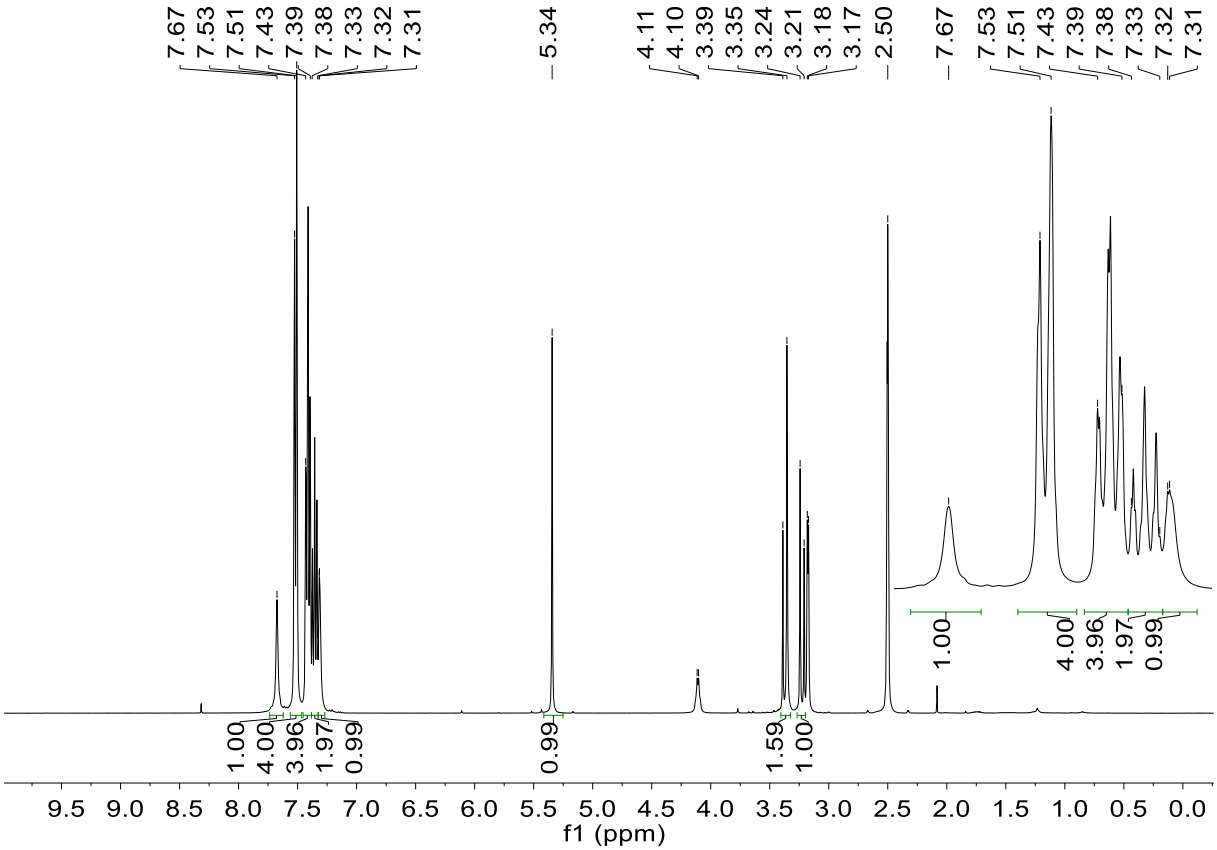
The synthesis of 2-(diphenylmethylthio) acetamide can be found in chapter on 5.4.2.28 page 163.



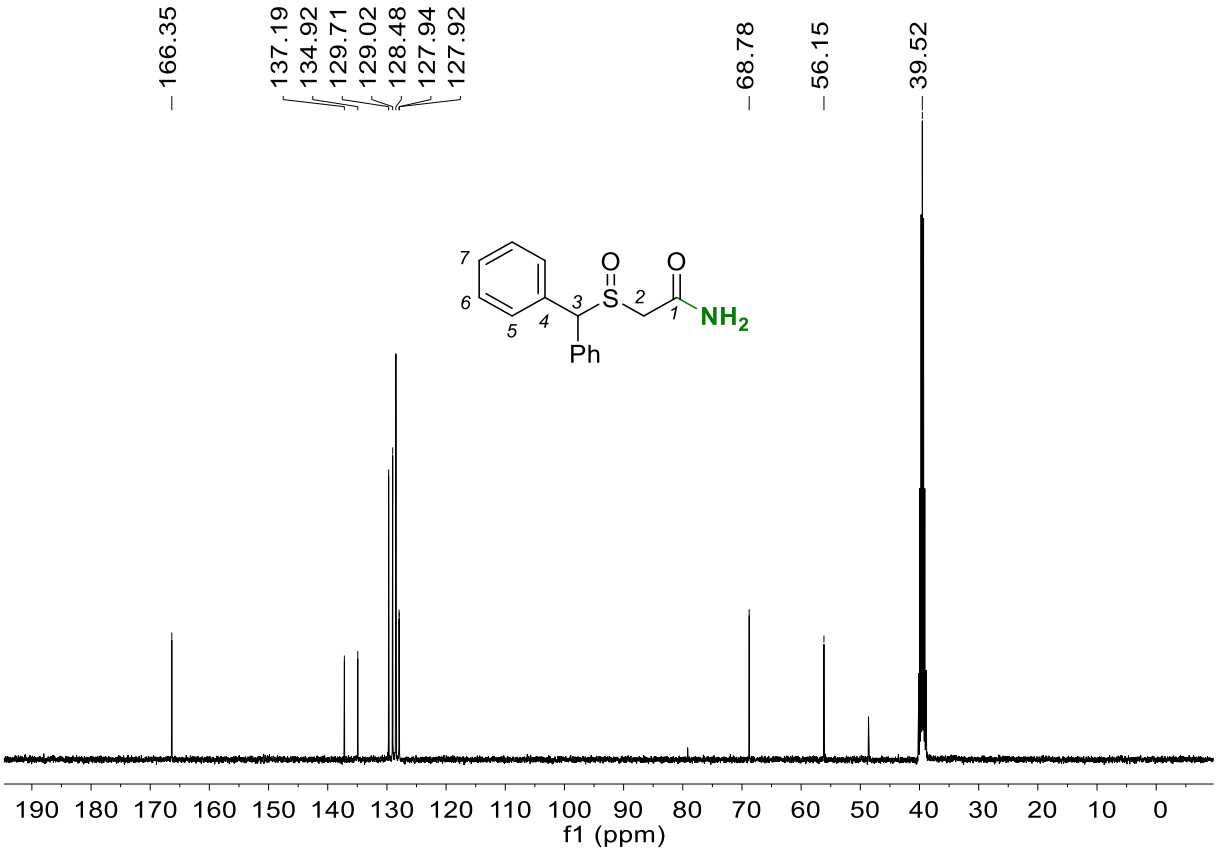
PH3417: A solution of 2-(diphenylmethylthio) acetamide (257 mg, 1.00 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL, 0.25 M) in a 10 mL flask was chilled in an ice bath. Next, MCPBA (263 mg, 1.05 mmol, 1.05 equiv) was added in three portions over 15 min and the reaction mixture was stirred for 15 min at 0 °C and for 8 h at room temperature. Then, the reaction suspension was treated with aqueous 1 N NaOH solution (3 mL) and saturated $Na_2S_2O_3$ solution in water (1 mL) and stirred for further 15 min at ambient temperature. In order to allow dissolution of the title compound the reaction mixture was diluted with additional CH_2Cl_2 (10 mL), the organic phase was washed with 1 N NaOH solution (1 x 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure, which delivered the crude material as a colourless solid (280 mg, 102%, full conversion as determined by ^{1}H-NMR). Eventually, the crude product was purified with the aid of column chromatography on silica gel (27.7 g, mass ratio crude modafinil/SiO_2 1:99) employing MeOH/EtOAc 4:96. Concentration with MeOH and drying at the rotary evaporator at 5 mbar for 20 min furnished the title compound as a colourless solid (191.5 mg, 0.700 mmol, 70%). Thereby, the crude product was dissolved in MeOH (ca. 20 mL), SiO_2 was added (0.98 g, relation of weight of crude material in respect to SiO_2 1:3.5), all volatiles were removed under reduced pressure and the residue was loaded onto the silica gel column.

M ($C_{15}H_{15}NO_2S$) = 273.35 g/mol; **mp.** 149-150 (lit-mp. 120-122 °C);[53] $\mathbf{r_f}$ (SiO_2) = 0.34 (acetone/*n*Hex 60:40), 0.45 (MeOH/EtOAc 4:96); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.67 (br. s, 1H, NH), 7.53-7.51 (m, 4H, 5-H), 7.43-7.39 (m, 4H, 6-H), 7.38-7.33 (m, 2H, 7-H), 7.32-7.31 (m, 1H, NH), 5.34 (s, 1H, 3-H), 3.37 (d, $^2J_{2a,2b}$ = 13.6 Hz, 1H, 2-H_a), 3.23 (d, $^2J_{2b,2a}$ = 13.7 Hz, 1H, 2-H_b); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 166.35 (C-1), 137.19 (C-4), 134.92 (C-4), 129.71 (C-5), 129.02 + 128.48 (C-4 + C-5), 127.94 + 127.92 (C-7), 68.78 (C-3), 56.15 (C-1), 48.62, 39.52.

The NMR data is in match with literature data.[53]

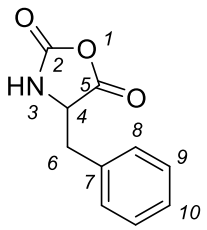


^{1}H-NMR spectrum of Modafinil (400 MHz, $CDCl_3$).



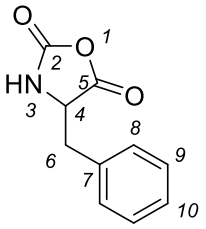
^{13}C-NMR spectrum of Modafinil (125 MHz, $CDCl_3$).

5.4.4.2 Synthesis of 4-Benzyloxazolidin-2,5-dione (10_{25})



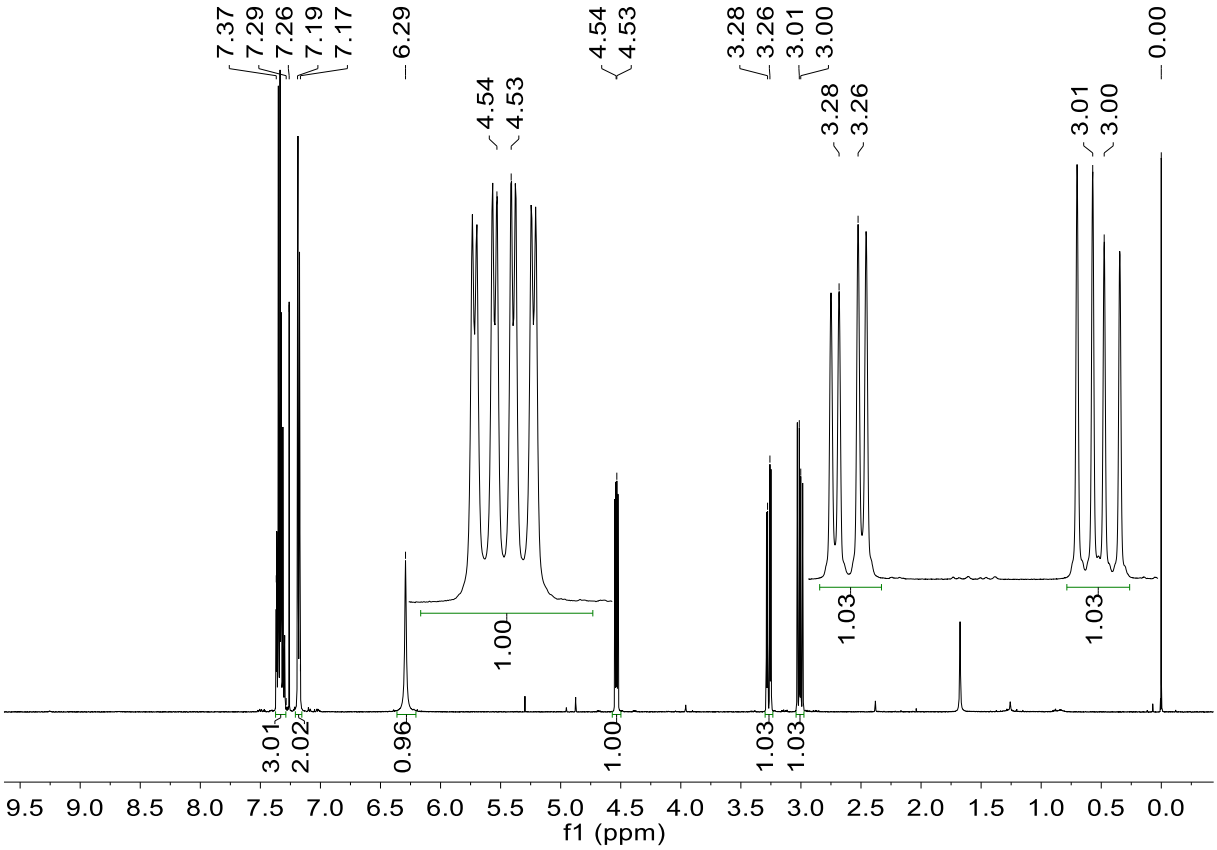
10_{25}

PH3487: *(S)*-*N*-Benzyloxycarbonyl phenylalanine (299 mg, 1.00 mmol, 1.0 equiv) and FPyr (9.8 μL, 10.2 mg, 100 μmol, 10 mol%) were dissolved in MeCN (1.0 mL, 1 M) in a 4 mL glass vial, TCT (72 mg, 0.38 mmol, 38 mol%) was added and the resulting suspension was stirred for 8 h at room temperature. Next, the reaction suspension was diluted with EtOAc (3 mL) and poured into a 10 mL flask, the reaction vial was rinsed with further EtOAc (2 x 2 mL) and the combined EtOAc-phases were filtered over a sintered funnel (porosity level 3, diameter 2 cm) with a ca. 1 cm layer of $MgSO_4$ by suction. The filter cake was rinsed with additional EtOAc (2 x 4 mL) and the combined filtrates were concentrated under reduced pressure to yield the crude material as a colourless turbid oil (370.8 mg, 193%). ^{1}H-NMR indicated full consumption of the starting material and 50 mol% BnCl with regard to the title compound. Finally, chromatographic purification on silica gel (20.8 g, relation of mass SiO_2 in regard to crude material 56:1) with EtOAc/*n*Hex 50:50 gave the title compound in a yield of 69% (132.6 mg, 0.692 mmol). Upon storage at room temperature polymerization occurred, which was indicated by a significantly decrease solubility in organic solvents. In order to charge the chromatography column, the crude material had to be dissolved in CH_2Cl_2 (0.5 mL).

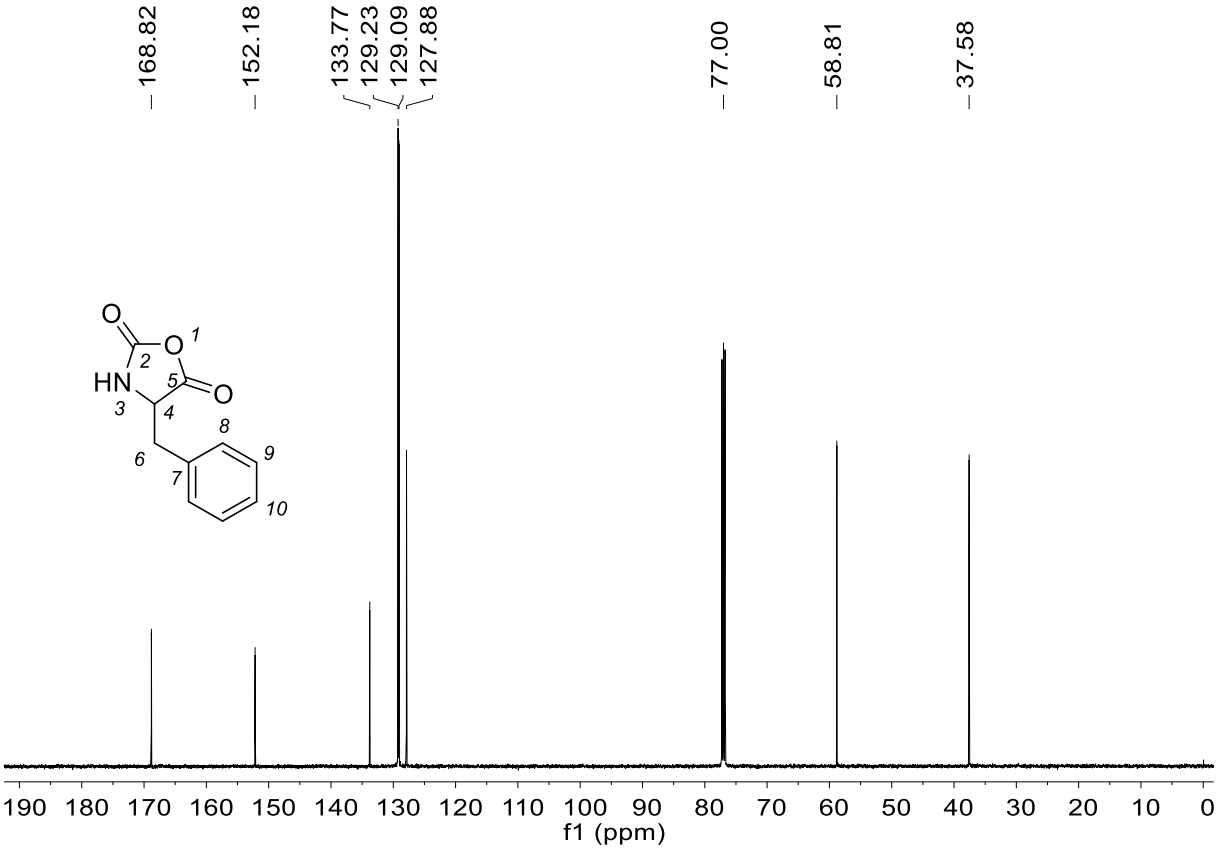


M ($C_{10}H_9NO_3$) = 191.19 g/mol;] $\mathbf{r_f}$ (SiO_2, EtOAc/*n*Hex 50:50) = 0.44; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 7.37-7.29 (m, 3H, 8-H, 10-H), 7.19-7.17 (m, 2H, 9-H), 6.29 (br. s, 1H, NH), 4.54 (ddd, $^3J_{4,6b}$ = 8.1 Hz, $^3J_{4,6a}$ = 4.2 Hz, $^3J_{4,NH}$ = 0.9 Hz, 1H, 4-H), 3.27 (dd, $^2J_{6a,6b}$ = 14.2 Hz, $^3J_{6,4}$ = 4.2 Hz, 1h, 6-H_a), 3.01 (dd, $^2J_{6b,6a}$ = 14.2 Hz, $^3J_{6,4}$ = 8.1 Hz, 1h, 6-H_b); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 168.82 (C-5), 152.18 (C-2), 133.77 (C-7), 129.23 (C-9), 129.09 (C-8), 127.88 (C-10), 58.81 (C-4), 37.58 (C-6).

The ^{1}H-NMR-data is in agreement with reported data.[54]



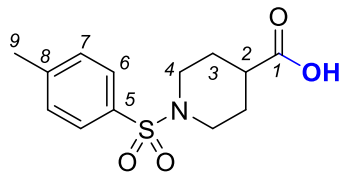
^{1}H-NMR spectrum of 4-benzyloxazolidin-2,5-dione (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of 4-benzyloxazolidin-2,5-dione (125 MHz, $CDCl_3$).

5.4.5 Synthesis of Carboxylic Acid Starting Materials 1

5.4.5.1 Synthesis of 4-Carboxy-1-(4-methylphenylsulfonyl) piperidine (1_{11})

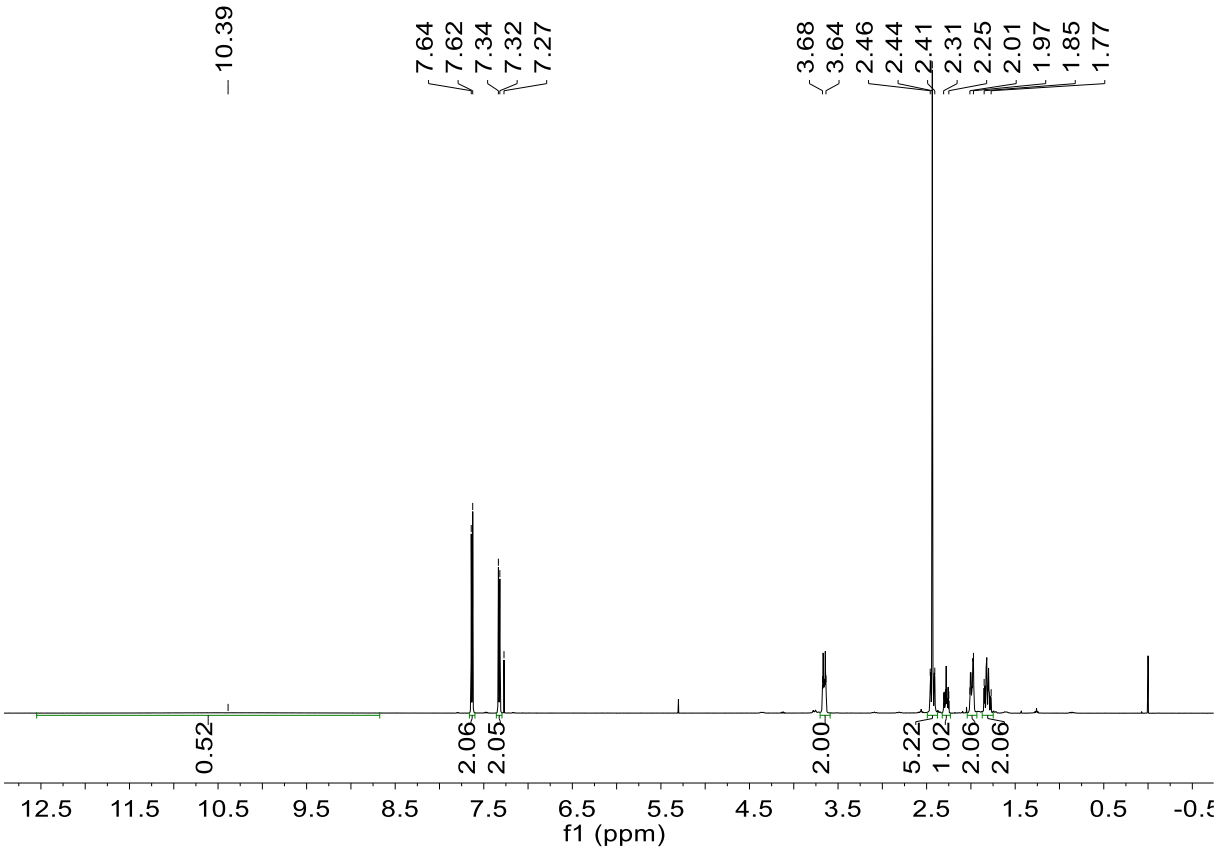


1_{11}

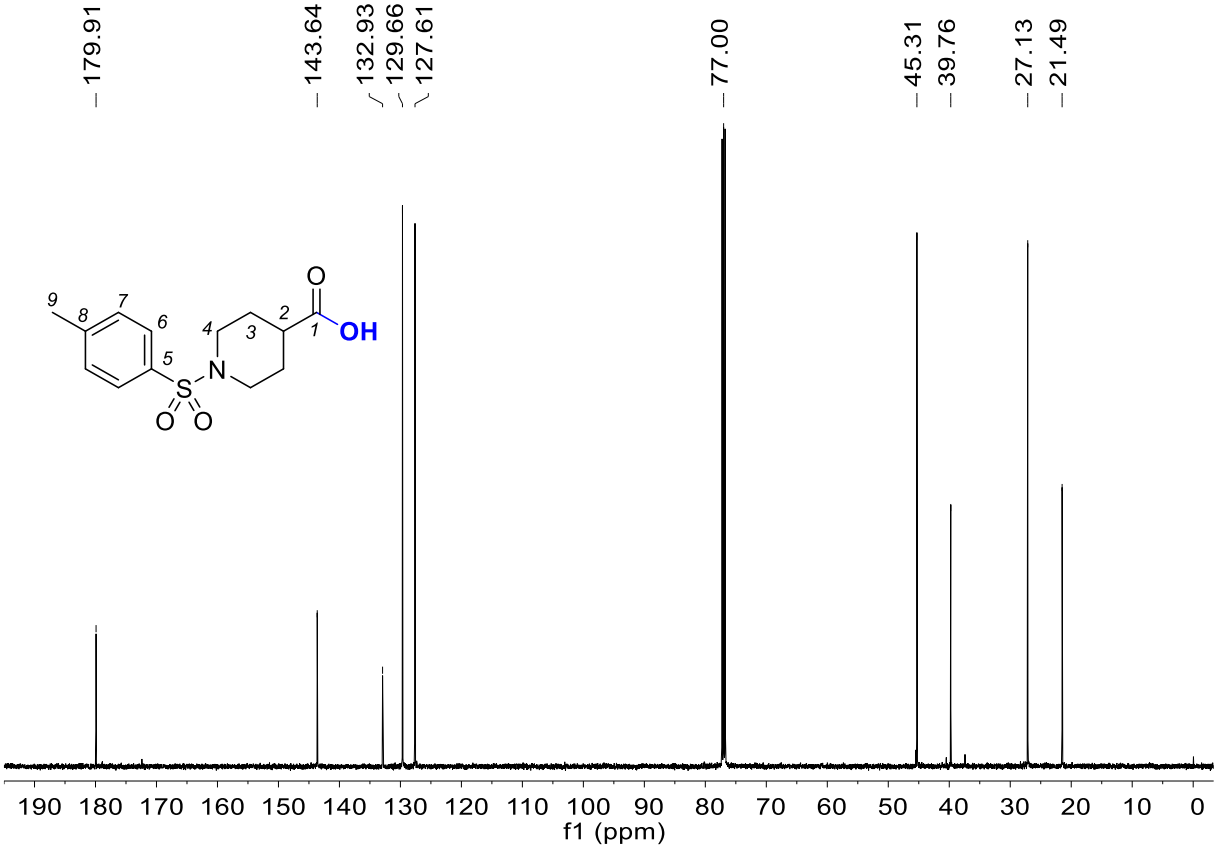
PH3250: Piperdine-4-carboxylic acid (646 mg, 5.00 mmol, 1.0 equiv) was stirred with K_2CO_3 (970 mg, 7.0 mmol, 1.4 equiv) in water (5 mL, 1 M) in a 50 mL flask at room temperature until a clear solution was obtained after 5 min. Subsequently, the reaction solution was chilled in an ice bath and a solution of TsCl (1.24 g, 6.5 mmol, 1.3 equiv) in THF (5 mL→0.25 M, H_2O/THF 1:1) was added with the aid of a dropping funnel within 15 min. After 15 min of stirring, the cooling bath was removed and the reaction mixture was allowed to stir for 24 h. Next, the reaction mixture was diluted with EtOAc (20 mL) and aqueous 2 N HCl solution (20 mL) and stirred for 5 min at ambient temperature until CO_2 evolution had ceased. Then, the mixture was poured into a 100 mL extraction funnel, the reaction flask was rinsed with EtOAc (1 x 20 mL), the organic phase was washed with brine (1 x 20 mL), dried over $MgSO_4$ und concentrated under reduced pressure. Concentration with CH_2Cl_2 (2 x 20 mL) *in vacuo* to remove EtOAc and drying in high vacuum for 4 h provided the title compound as a colourless solid (1.082 g.3.82 mmol, 76%).

M ($C_{13}H_{17}NO_4S$) = 283.34 g/mol; **mp.** 159-161 °C (lit-mp. 169-171 °C);[55] **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 10.39 (br. s., 1H, OH), 7.64-7.62 (m, 2H, 6-H), 7.34-7.32 (m, 2H, 7-H), 3.68-3.64 (m, 2H, 4-H_a), 2.46-2.41 (m, 5H, 4-H_b, 9-H; amongst s at 2.44 ppm), 2.31-2.25 (m, 1H, 2-H), 2.01-1.97 (m, 2H, 3-H_a), 1.85-1.77 (m, 3-H_b); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 179.91 (C-1), 143.64 (C-8), 132.93 (C-5), 129.66 (C-7), 127.61 (C-6), 45.31 (C-4), 39.76 (C-2), 27.13 (C-3), 21.49 (C-9).

The NMR data matches literature data.[55]

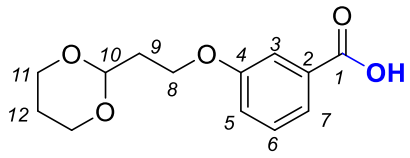


^{1}H-NMR spectrum of 4-carboxy-1-(4-methylphenylsulfonyl) piperidine (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of 4-carboxy-1-(4-methylphenylsulfonyl) piperidine (125 MHz, $CDCl_3$).

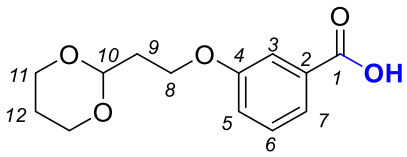
5.4.5.2 Synthesis of 3-(2-(1,3-Dioxan-2-yl)ethoxy) benzoic acid (1_{20})



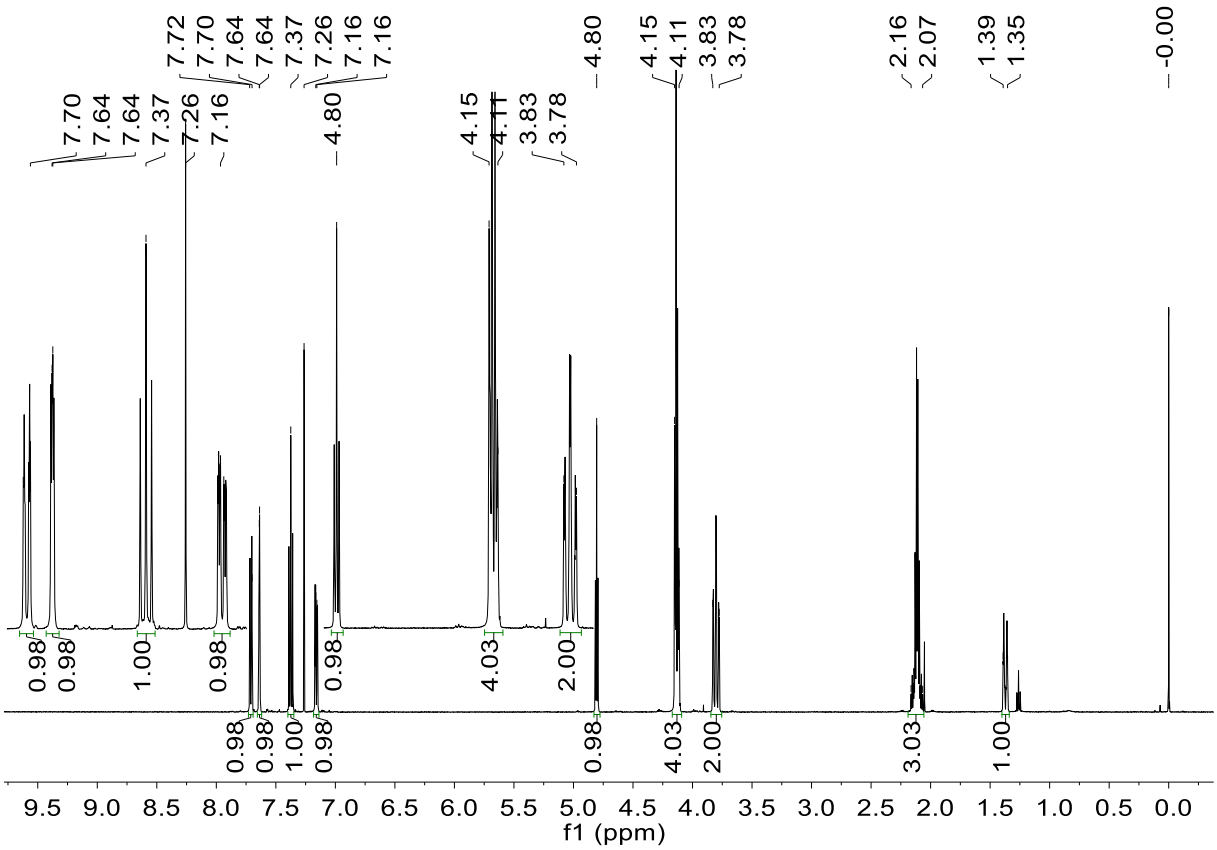
1_{20}

PH3489: Methyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoate (1.33 g, 5.00 mmol, 1.0 equiv) was dissolved in MeOH (5 mL, 1 M) in a 50 mL flask and 2 N KOH solution in MeOH (3.0 mL, 6.0 mmol, 1.2 equiv) was added. Since TLC after 4 h of stirring at room temperature revealed remaining starting material, additional 2 N KOH solution in MeOH (2.0 mL, 4.0 mmol, 0.8 equiv) was added. After stirring for 15 h at room temperature TLC control still verified incomplete conversion, the reaction flask was equipped with a reflux condenser and heated for 2.5 h at 80 °C, whereupon TLC proved full consumption of the starting material. Then, the reaction mixture was sequentially diluted with EtOAc (20 mL) and 2 N HCl solution with water (15 mL) and transferred to a 100 mL extraction funnel. The reaction flask was rinsed with EtOAc (10 mL), the combined EtOAc-phases were washed with brine (1 x 10 mL), dried over $MgSO_4$and concentrated under reduced pressure. Drying at the rotary evaporator at 5 mbar for 15 min resulted in the title compound as a colourless solid in 93% yield (1.177 g, 4.67 mmol).

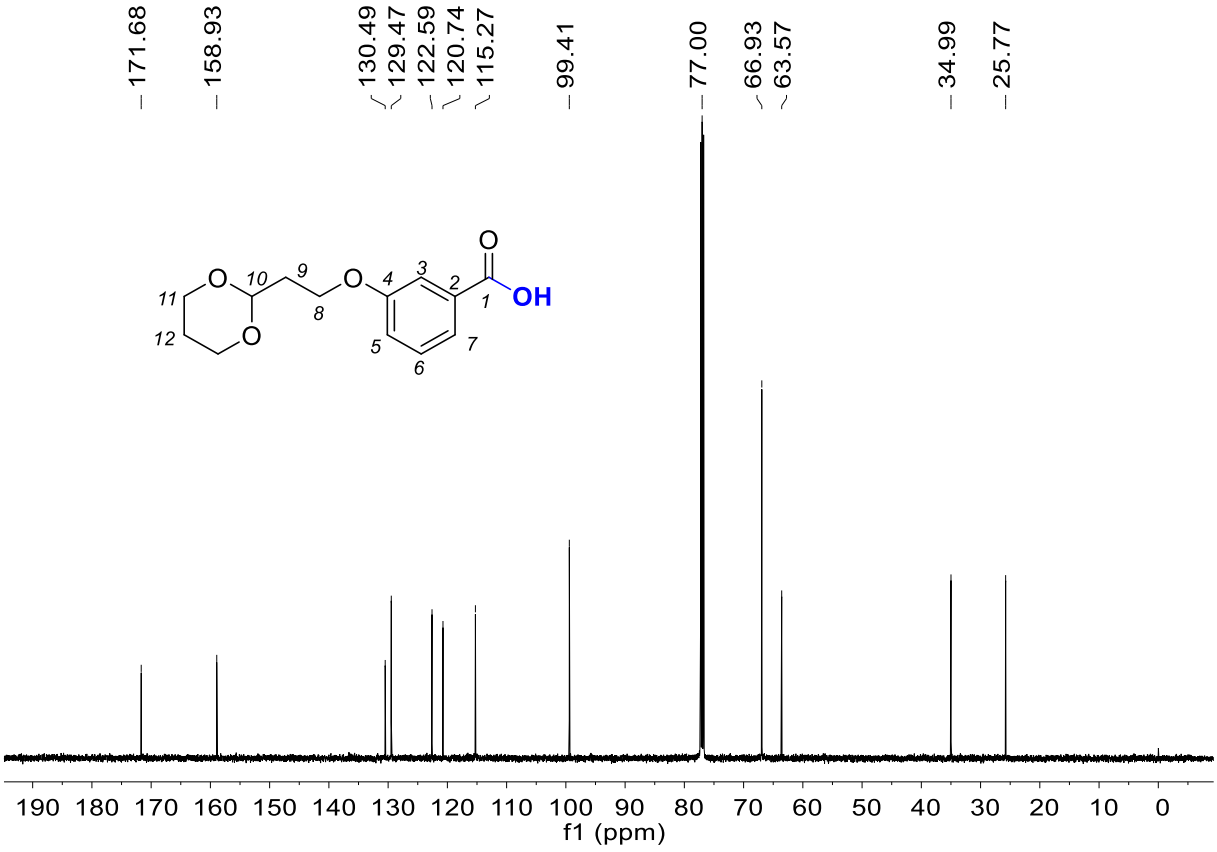
PH3530: Methyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoate (0.950 g, 3.56 mmol, 1.0 equiv) was dissolved in MeOH (4 mL, 1 M) in a 25 mL flask and 2 N KOH solution in MeOH (2.7 mL, 5.4 mmol, 1.5 equiv) was added. The reaction apparatus was equipped with a reflux condenser and heated to 80 °C until TLC control unravelled full conversion after 6 h. Work up as described in the previous procedure finally furnished the title compound as a colourless solid (3.54 mmol, *quant*.).



M ($C_{13}H_{16}O_5$) = 252.27 g/mol; **mp.** 143-145 °C; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 7.72-7.70 (m, 1H, 7-H), 7.64 (dd, $^4J_{3,5}$ = 2.6 Hz, $^4J_{3,7}$ = 1.6 Hz, 1H, 3-H), 7.37 (ψ-t, J = 7.9 Hz, 1H, 6-H), 7.16 (ddd, $^3J_{5,6}$ = 8.2 Hz, $^4J_{5,3}$ = 2.7 Hz, 0.9 Hz, 1H, 5-H), 4.80 (t, $^3J_{10,9}$ = 5.3 Hz, 1H, 10-H), 4.15-4.11 (m, 4H, 8-H, 11-H_a), 3.83-3.78 (m, 2H, 11-H_b), 2.16-2.07 (m, 3H, 9-H, 12-H_a), 1.39-1.35 (m 1H, 12-H_b); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 171.68 (C-1), 158.93 (C-4), 130.49 (C-2), 129.47 (C-6), 122.59 (C-7), 120.74 (C-5, 115.27 (C-3), 99.41 (C-10), 66.93 (C-11), 63.57 (C-8), 34.99 (C-9), 25.77 (C-12); **HR-MS** (ESI, $[C_{13}H_{15}O_5]^-$,) calc. 251.0925 u found 251.0917 u

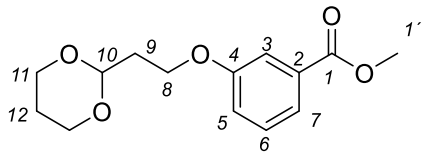


^{1}H-NMR spectrum of 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoic acid (500 MHz, $CDCl_3$).



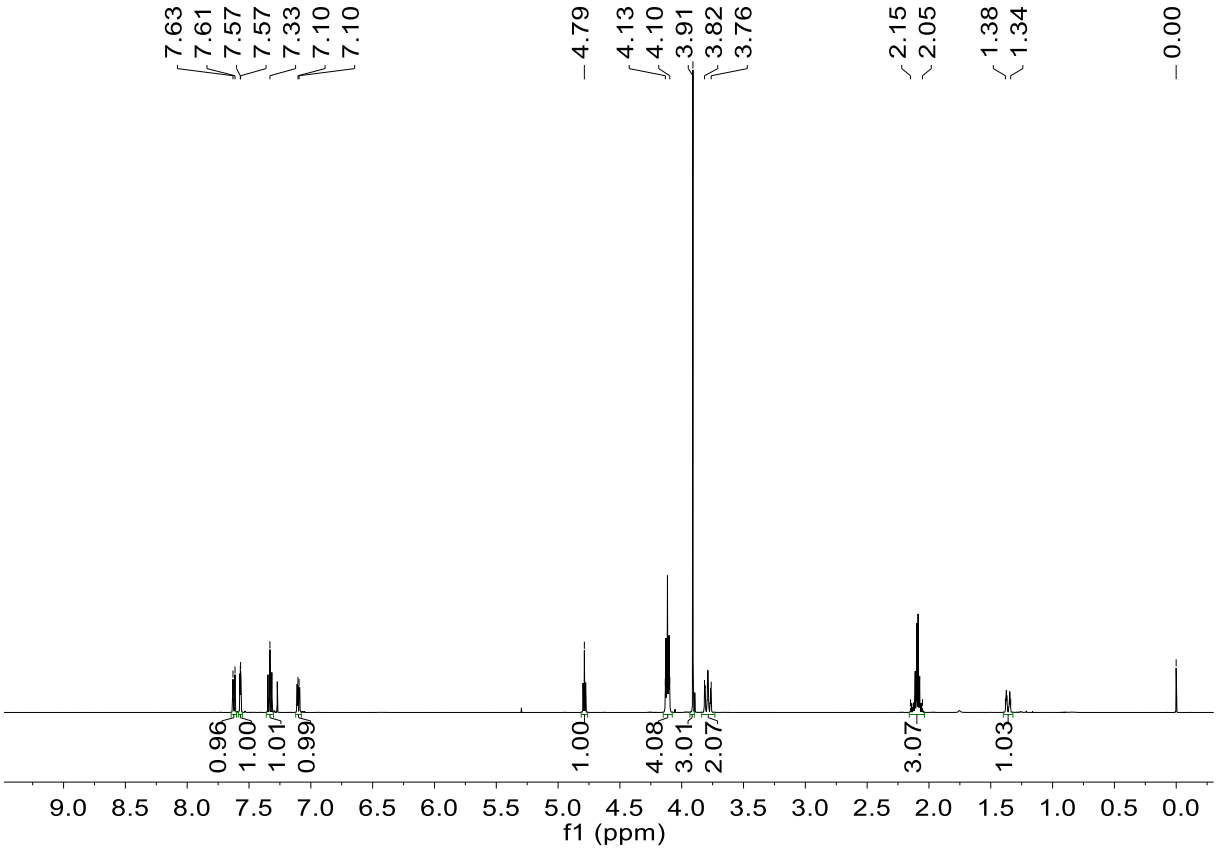
^{13}C-NMR spectrum of 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoic acid (125 MHz, $CDCl_3$).

Methyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoate

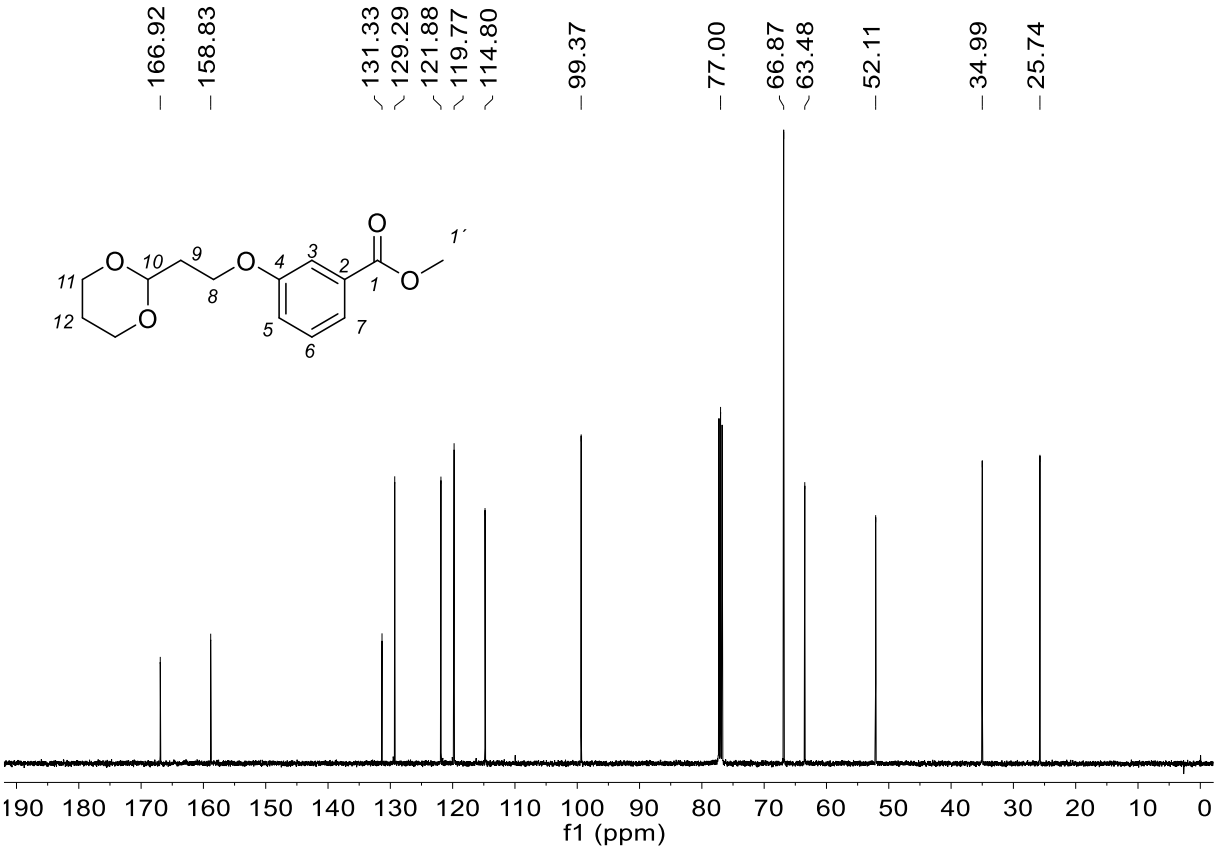


PH3484: A mixture of methyl 3-hydroxybenzoate (1.52 g, 10.0 mmol, 1.0 equiv) in MeCN (10 mL, 1 M) in a 50 mL flask was treated with K_2CO_3 (1.93 g, 14.0 mmol, 1.4 equiv) and 2-(2-bromoethyl)-1,3-dioxane (1.77 mL, 13.0 mmol, 1.3 equiv). The reaction apparatus was equipped with a reflux condenser and heated to 80 °C overnight (12 h). Subsequently, to the colourless reaction suspension were added EtOAc (20 mL) and 1 N NaOH solution in water (10 mL) and the mixture was poured into a 100 mL extraction funnel. The reaction flask was rinsed with further EtOAc/1 N NaOH solution (10 mL/5 mL), the organic phase was washed with brine (1 x 15 mL), dried over $MgSO_4$, concentrated *in vacuo* and dried at the rotary evaporator at 5 mbar for 15 min to yield the crude material as a colourless solid (3.15 g, 118%). Ultimately, purification by means of column chromatography on silica gel (46.4 g, relation weight crude product/SiO_2 1:15) using EtOAc/PE 15:85-20:80 afforded the desired ester as a colourless oil in a yield of 89% (2.368 g, 8.89 mmol).

M ($C_{14}H_{18}O_5$) = 266.29 g/mol; $\mathbf{r_f}$ (SiO_2, EtOAc/PE 20:80) = 0.37; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 7.62 (dd, $^3J_{7,6}$ = 7.6 Hz, ^4J = 1.4 Hz, 1.1 Hz, 1H, 7-H), 7.57 (dd, $^4J_{3,5}$ = 2.6 Hz, $^4J_{3,7}$ = 1.5 Hz, 1H, 3-H), 7.33 (ψ-t, J = 7.7 Hz, 1H, 6-H), 7.1o (ddd, $^3J_{5,6}$ = 8.3 Hz, $^4J_{5,3}$ = 2.7 Hz, 1.0 Hz, 1H, 5-H), 4.79 (t, $^3J_{10,9}$ = 5.3 Hz, 1H, 10-H), 4.13-4.10 (m, 4H, 8-H, 11-H_a), 3.91 (s, 3H, 1´-H), 3.82-3.76 (m, 2H, 11-H_b), 2.15-2.05 (m, 3H, 9-H, 12-H_a), 1.38-1.34 (m 1H, 12-H_b); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 166.92 (C-1), 158.83 (C-4), 131.33, (C-2), 129.29 (C-6), 121.88 (C-7), 119.77 (C-5, 114.80 (C-3), 99.37 (C-10), 66.87 (C-11), 63.48 (C-8), 52.11 (C-1´), 34.99 (C-9), 25.74 (C-12); **HR-MS** (ESI, $[C_{14}H_{19}O_5]^+$) calc. 267.1227 u found 267.1227 u.

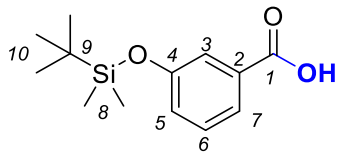


^{1}H-NMR spectrum of methyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoate (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of methyl 3-(2-(1,3-dioxan-2-yl)ethoxy) benzoate (125 MHz, $CDCl_3$).

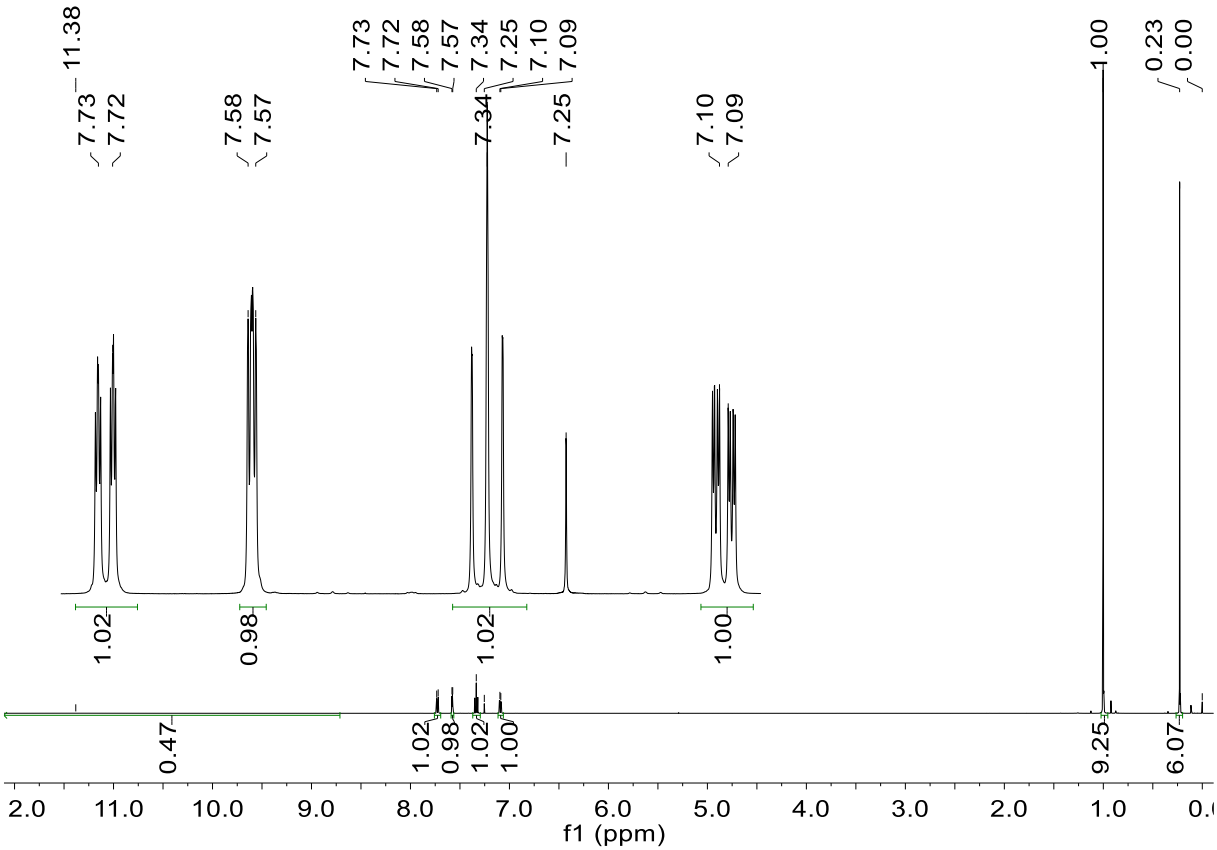
5.4.5.3 Synthesis of 3-(*tert*-Butoxydimethyloxysilyl) benzoic acid (1_{21})



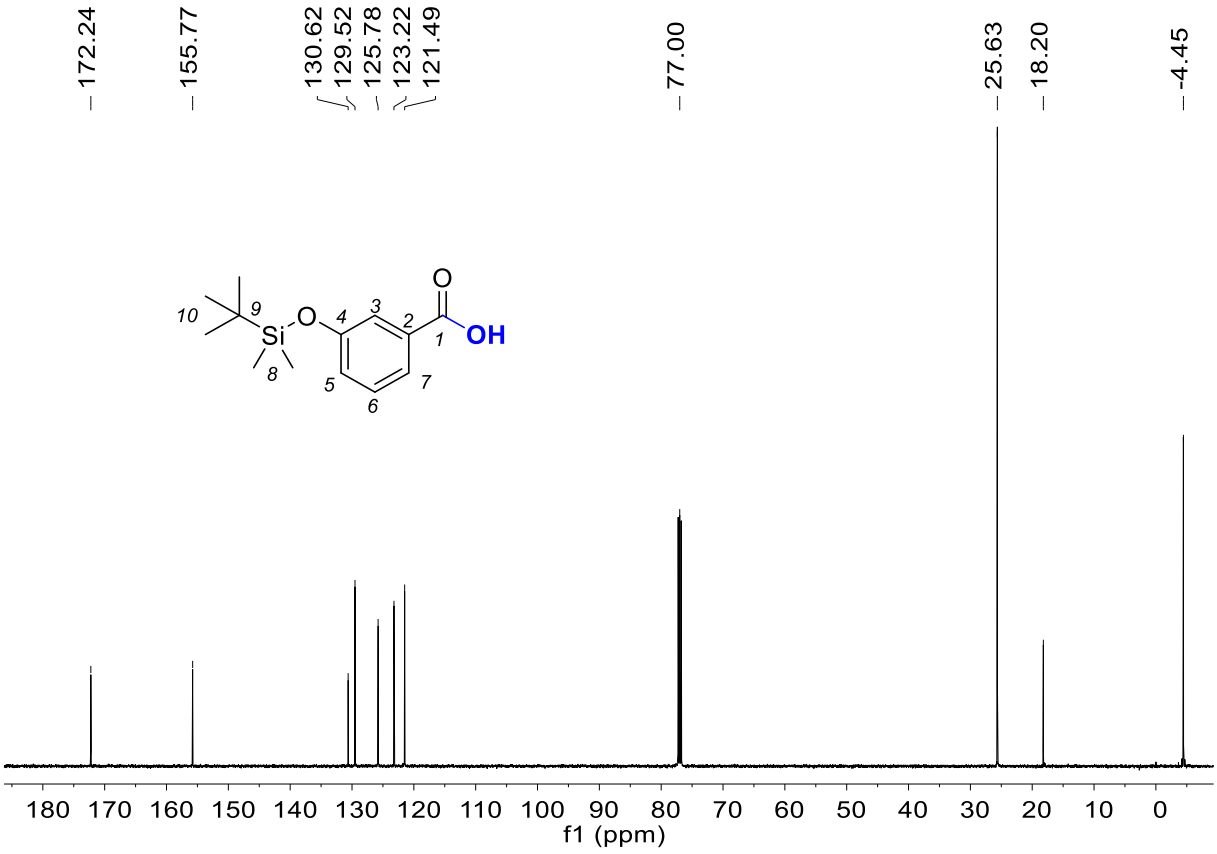
1_{21}

PH3475:[56] *Tert*-Butyldimethylsilyl 3-(*tert*-butoxydimethyl oxysilyl) benzoate (1.83 g, 5.00 mmol, 1.0 equiv) was dissolved in THF (5.0 mL,1 M) in a 50 mL flask, water (1.0 mL) and HOAc were added (4.0 mL→0.5 M, THF/H_2O/HOAc 5:1:4) and the resulting clear solution was stirred for 19 h at room temperature. In the following, Et_2O (20 mL) and aqueous 1 N HCl solution were added (10 mL) and the mixture was poured into a 50 mL extraction funnel. The organic phase was washed with further 1 N HCl solution (2 x 10 mL) and brine (1 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield crude **1_{21}** as a colourless oil (1.43 g, 113%), of which ^{1}H-NMR verified full consumption of the starting silylester. Next, the crude product was purified with the aid of column chromatography using EtOAc/PE 20:80 on silica gel (40.4 g, mass relation crude material with respect to SiO_2 1:28), concentrated with CH_2Cl_2 and dried at the rotary evaporator for 15 min at 5 mbar, which enabled the isolation of the title compound as a colourless solid in 89% yield (1.123 g, 4.45 mmol). Thereby, the crude product was dissolved in CH_2Cl_2 (ca-20 mL), silica gel was added (3.0 g, ratio weight of crude **1_{21}**/SiO_2 1:2.1.), volatile compounds were evaporated under reduced pressure and the residue was loaded onto the silica gel column.

M ($C_{13}H_{20}O_3$) = 252.39 g/mol; **mp.**) = 91-93 °C; **r_f** (SiO_2, EtOAc/PE 20:80) = 0.39; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 11.38 (br. s, 1H, OH), 7.73 (ddd, ^3J = 7.8 Hz, 1.5 Hz, 1.1 Hz, 1H, 7-H), 7.58 (dd, ^3J = 2.4 Hz, 1.6 Hz, 1H, 3-H), 7.34 (ψ-t, J = 7.8 Hz, 1H, 6-H), 7.10 (ddd, ^3J = 8.1 Hz, ^4J = 2.6 Hz, 1.1 Hz, 5-H), 1.00 (s, 9H, 10-H), 0.23 (s, 6H, 8-H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 172.24 (C-1), 155.77 (C-4), 130.62 (C-2), 129.52 (C-6), 125.78 (C-5), 123.22 (C-7), 121.49 (C-3), 25.63 (C-10), 18.20 (C-9), -4.45 (C-8).
The NMR data is in match with literature values.[56]

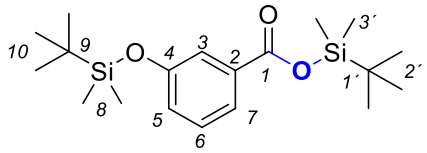


^{1}H-NMR spectrum of 4-(*tert*-butoxydimethyloxysilyl) benzoic acid (400 MHz, $CDCl_3$).



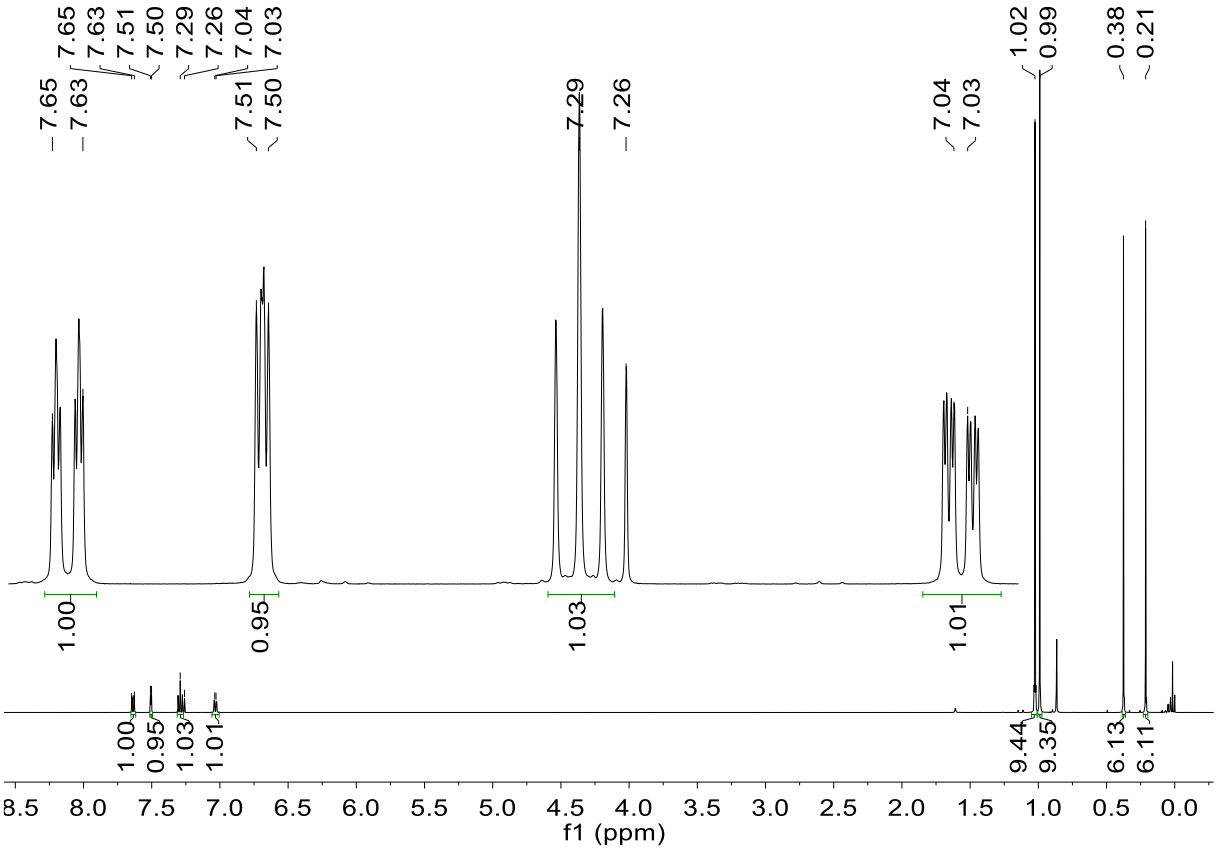
^{13}C-NMR spectrum of 4-(*tert*-butoxydimethyloxysilyl) benzoic acid (125 MHz, $CDCl_3$).

***tert*-Butyldimethylsilyl 3-(*tert*-butoxydimethyloxysilyl) benzoate**

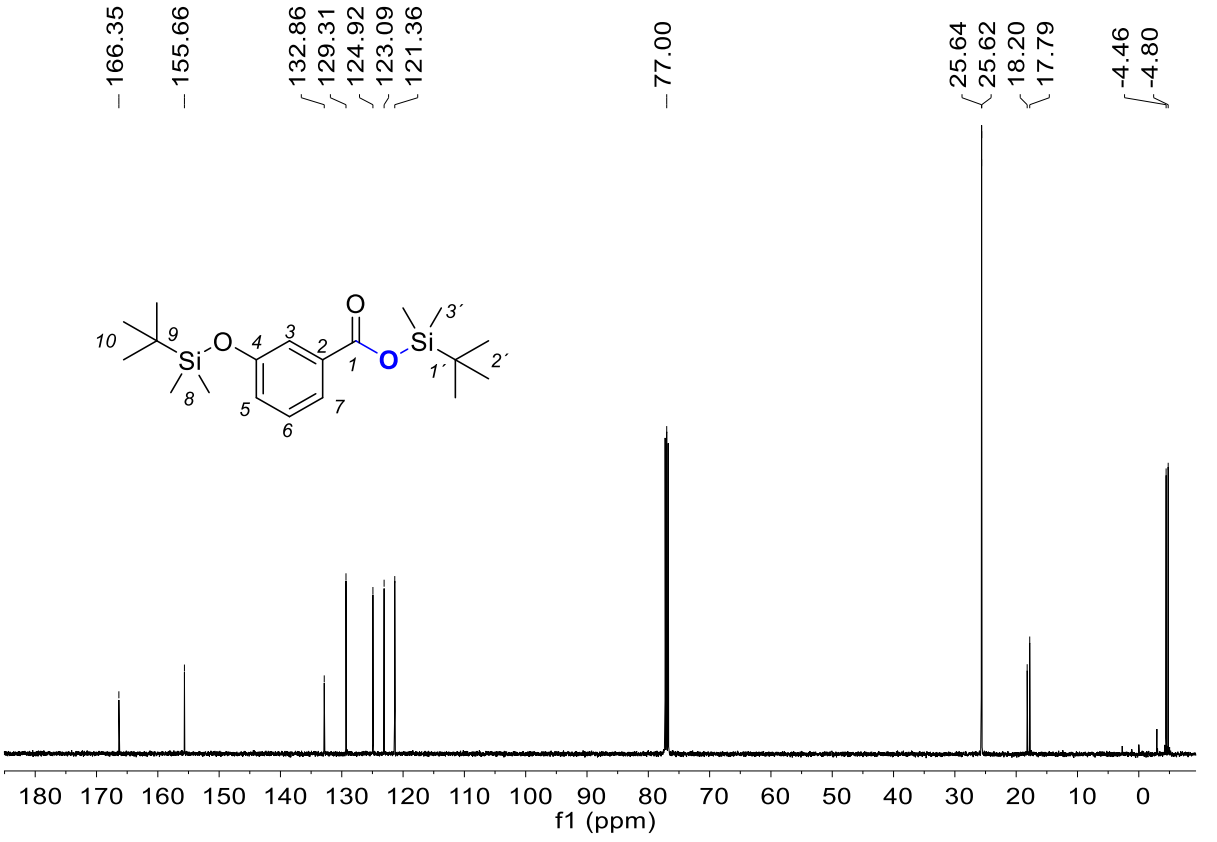


PH3471:[56] 3-Hydroxybenzoic acid (1.38 g, 10.0 mmol, 1.0 equiv) was dissolved in a 50 mL flask in DMF (dry, 10 mL, 1 M) and successively TBDMSCl (3.78 g, 25.0 mmol, 2.5 equiv) and imidazole (1.77 g, 26.0 mmol, 2.6 equiv) were added at room temperature. After stirring for 22 h at ambient temperature, the yellow reaction solution was poured in a 100 mL extraction funnel containing Et_2O (30 mL) and water (20 mL) and the reaction flask was rinsed with further Et_2O (10 mL). The organic phase was washed with brine (1 x 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield crude *tert*-butyldimethylsilyl 3-(*tert*-butyldimethylsiloxy) benzoate as a colourless oil (4.13 g, 113%). Eventually, chromatographic purification on silica gel (38.4 g, mass relation crude product/SiO_2 1:9) with EtOAc/PE 3:97, concentration with PE and drying at the rotary evaporator at 5 mbar for 15 min furnished the desired silyl compound as a colourless oil in 97% yield (3.570 g, 9.74 mmol). In order to charge the silica gel column, the crude material was dissolved in the eluent (2 mL).

M ($C_{19}H_{34}O_3Si_2$) = 366.65 g/mol; $\mathbf{r_f}$ (SiO_2 EtOAc/PE 3:97) = 0.60; **^{1}H-NMR** (500 MHz, $CDCl_3$) δ [ppm] = 7.65-7.63 (m, 1H, 7-H), 7.51-7.50 (m, 1H, 3-H), 7.29 (ψ-t, *J* = 7.9 Hz, 1H, 6-H), 7.04, 7.03 (ddd, $^3J_{5,6}$ = 8.2 Hz, ^4J = 2.5 Hz, 0.9 Hz, 1H, 5-H), 1.02 (s, 9H), 0.99 (s, 9H), 0.38 (s, 6H), 0.21 (s, 6H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 166.35 (C-1), 155.66 (C-4), 132.86 (C-2), 129.31 (C-6), 124.92 (C-5), 123.09 (C-7), 121.36 (C-3), 25.64+25.62 (C-10 + C-2´), 18.20 + 17.79 (C-9 + C-1´), -4.46 + -4.80 (C-8 + C-2´).

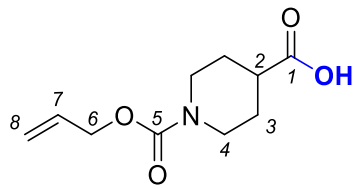


^{1}H-NMR spectrum of *tert*-butyldimethylsilyl 3-(*tert*-butyldimethylsiloxy) benzoate (500 MHz, $CDCl_3$).



^{13}C-NMR spectrum of *tert*-butyldimethylsilyl 3-(*tert*-butyldimethylsiloxy) benzoate (125 MHz, $CDCl_3$).

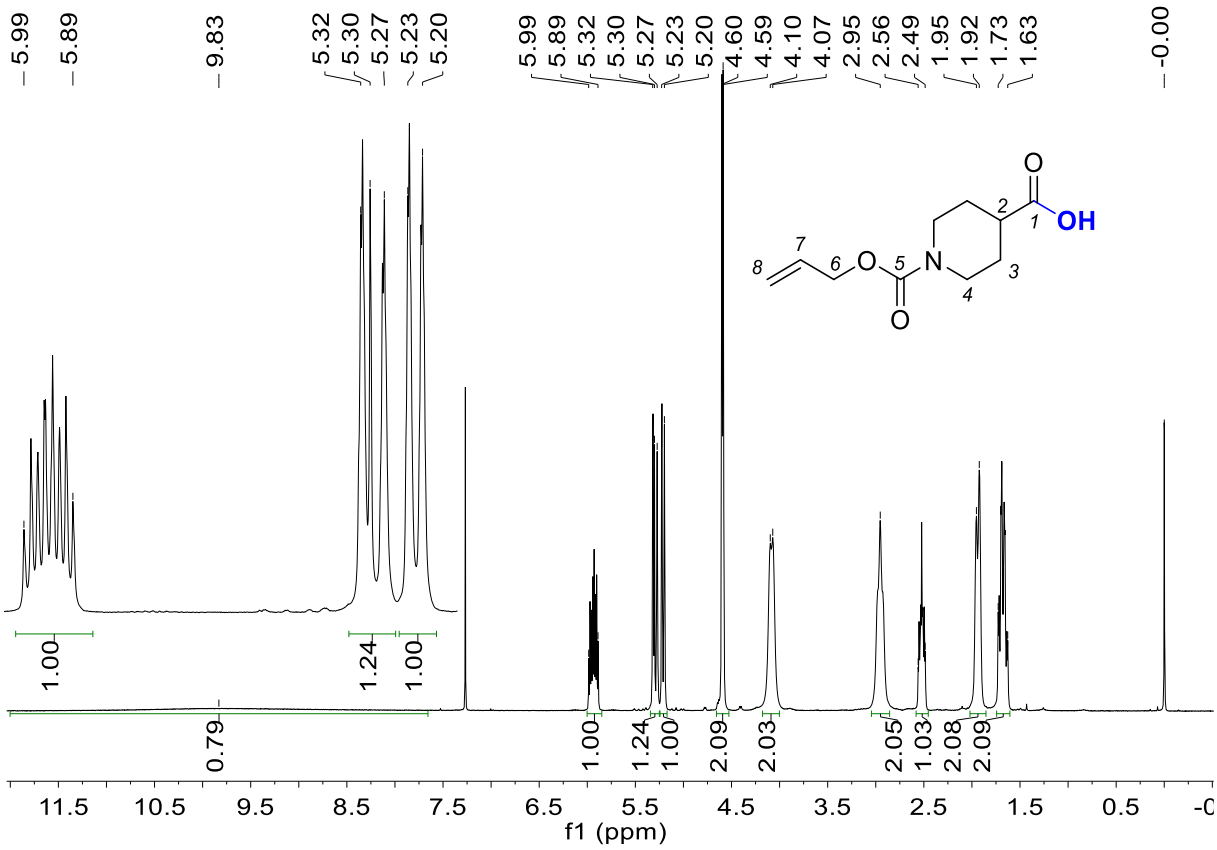
5.4.5.4 Synthesis of 1-(Allyloxycarbonyl)piperidine-4-carboxylic acid (1_{34})



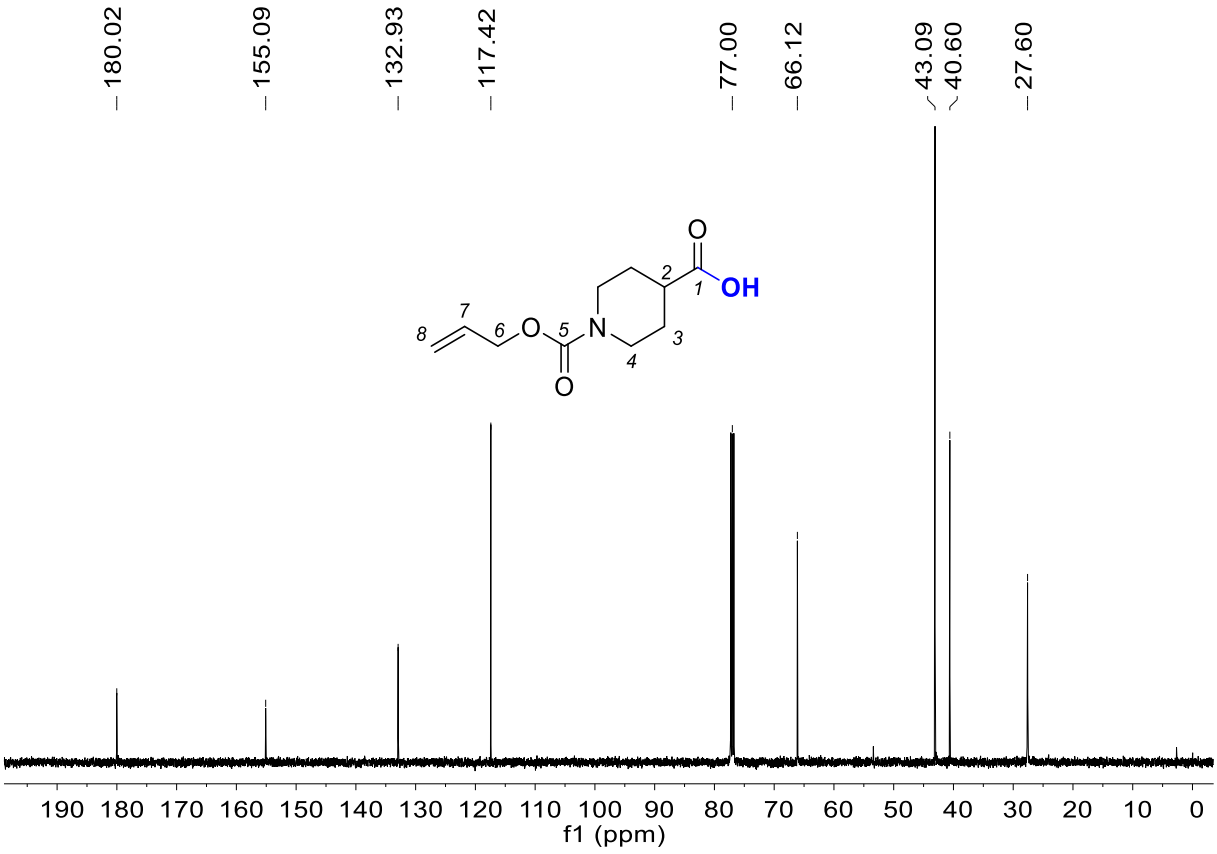
1_{34}

PH3463: Piperidine-4-carboxylic acid (1.29 g, 10.0 mmol, 1.0 equiv) was suspended in water (5 mL, 2 M) in a 50 mL flask and K_2CO_3 (1.93 g, 14.0 mmol, 1.4 equiv) was added. After 5 min of stirring at ambient temperature a clear solution was obtained, to which a solution of AllocCl (1.38 mL, 13.0 mmol, 1.3 equiv) in THF (5 mL→1 M, H_2O/THF 1:1) was added via dropping funnel within 15 min under vigorous stirring under cooling in an ice bath. The resulting emulsion was stirred for 15 min at 0 °C and for 17 h room temperature. Afterwards, the reaction mixture was diluted successively with EtOAc (20 mL) and aqueous 2 N HCl solution (10 mL), whereby a weak CO_2 generation occurred. Past 5 min of stirring, the organic phase was washed with brine (1 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. To remove EtOAc, the residue was concentrated with CH_2Cl_2 (3 x 5 mL) and dried at the rotary evaporator at 5 mbar for 40 min, which afforded the title compound as a colourless oil (2.147 g). Under consideration of 13 mol% residual CH_2Cl_2 as visualized through ^{1}H-NMR the acid **1_{34}** was isolated in a yield of 96% (9.58 mmol).

M ($C_{10}H_{15}NO_4$) = 213.23 g/mol; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ [ppm] = 9.83 (br. s, OH), 5.99-5.89 (m, 1H, C-7), 5.32-5.27 (m, 1H, 8´-H_E), 5.23-5.20 (m, 1H, 8´-H_Z), 4.60-4.59 (m 2h, 6-H), 4.10-4.07 (m, 2H, 4-H_a), 2.95 (ψ-t, *J* = 10.5 Hz, 2H, 4-H_b), 2.56-2.49 (m, 1H, 2-H), 1.95-1.92 (m, 2H, 3-H_a), 1.73-1.63 (m, 2H, 3-H_b); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ [ppm] = 180.02 (C-1), 155.09 (C-5), 132.93 (C-7), 117.42 (C-8), 66.12 (C-6), 43.09 (C-4), 40.60 (C-2), 27.60 (C-3).



^{1}H-NMR spectrum 1-(allyloxycarbonyl)piperidine-4-carboxylic acid (400 MHz, $CDCl_3$).



^{13}C-NMR spectrum of 1-(allyloxycarbonyl)piperidine-4-carboxylic acid (125 MHz, $CDCl_3$).

6 List of Abbreviations

2-MeTHF = 2-methyltetrahydrofurane

Alloc = allyloxycarbonyl

aq. = aqueous

bp. = boiling point

BzCl = benzoyl chloride

Cbz = benzyloxycarbonyl

conv. = conversion

DCE = 1,2-dichloroethane

DCM = dichloromethane

dioxane = 1,4-dioxane

DMA = *N,N*-dimethylacetamide

DME = 1,2-dimethoxyethane

DMF = dimethylformamide

ee = enantiomeric excess

equiv = equivalents

er = enantiomeric ratio

FPyr = 1-formylpyrrolidine

HMPTA = hexamethylphosphoric acid triamide

MeCN = acetonitrile

MF = methylformamide

MsCl = Methylsulfonyl chloride

MTBE = methyl-*tert*-butylether

NCS = *N*-chlorosuccinimide

NMR = nuclear magnetic resonance

PivCl = pivaloyl chloride

PMP = *para*-methoxyphenyl

Py = pyridine

TBAI = tetrabutylammonium iodide

TCT = 2,4,6-trichloro-1,3,4-triazine

TFA = trifluoroacetyl

THF = tetrahydrofurane

TMSCl = trimethylchlorosilane

TPS = *tert*-butyldiphenylsilyl

Ts = *para*-tolylsulfonyl

TsCl = *para*-tolylsulfonyl chloride

7 References

[1] (a) A. Devos, J. Remion, A. M. Frisque-Hesbain, A. Colens, and L. Ghosez, *J. Chem. Soc., Chem. Commun.* **1979**, 1180-1181; (b) B. Haveaux, A. Dekoker, M. Rens, A. R. Sidani, J. Toye, L. Ghosez, M. Murakami, M. Yoshioka, W. Nagata, *Org. Synth.* **1979**, *59*, 26.

[2] (a) H. H. Bosshard, R. Mory, M. Schmid, H. Zollinger, *Helv. Chim. Acta* **1959**, *59*, 1653-1658; (b) Y. Kimura, D. Matsuura, T. Hanawa, Y. Kobayashi, *Tetrahedron Lett.* **2012**, *53*, 1116-1118.

[3] C.-H. Lee, S.-M. Lee, B. H. Min, D.-S. Kim, C.-H. Jun, *Org. Lett.* **2018**, *20*, 2468-2471.

[4] S. G. Nelson in *Science of Synthesis*, Vol. 20a (Ed. S. G. Nelson), Georg Thieme: Stuttgart, **2006**, pp. 29-41.

[5] G. Cade, *J. Chem. Soc.* **1954**, 2030-2034

[6] D. J. Hardee, L. Kovalchuke, T. H. Lambert, *J. Am. Chem. Soc.* **2010**, *132*, 5002-5003.

[7] (a) T. V. Nguyen, A. Bekensir, *Org. Lett.* **2014**, *16*, 1720−1723; (b) T. V. Nguyen, D. J. M. Lyons, *Chem. Commun.* **2015**, *51*, 3131-3134.

[8] N. Kriebitzsch, H. Klenk in *Ullmann´s Encyclopedia of Industrial Chemistry, Vol. A8* (Eds. Gerhartz, W. et al.) VCH: Weinheim, **1987**, pp. 191-200.

[9] Seminal contributions: (a) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196-4197; (b) K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith, A. Whiting, *Adv. Synth. Catal.* **2006**, *348*, 813-820; (c) R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed.* **2008**, *47*, 2876-2879; (d) K. Ishihara, Y. Lu, *Chem. Sci.* **2016**, *7*, 1276-1280; (e) H. Noda, M. Furutachi, Y. Asada, M. Shibasaki, N. Kumagai, *Nature Chem.* **2017**, 9, 471-577; (f) M. T. Sabatini, L. T. Boulton, T. D. Sheppard, *Sci. Adv.* **2017**, *3*, e1701028; (g) S. Arkhipenko, M. T. Sabatini, A. S. Batsanov, V. Karaluka, T. D. Sheppard, H. S. Rzepa, A. Whiting, *Chem. Sci.* **2018**, *9*, 1058-1071; (h) K. Wang, Y. Lu, K. Ishihara, *Chem. Commun.* **2018**, 54, 5410-5496.

[10] (a) H. Lundberg, H. Adolfsson, *ACS Catal.* **2015**, *5*, 3271−3277, (b) H. Lundberg, F. Tinnis, J. Zhang, A. G. Algarra, F. Himo, H. Adolfsson, *J. Am. Chem. Soc.* **2017**, *139*, 2286−2295.

[11] F. Albericio, M. Cases, J. Alsina, S. A. Triolo, L. A. Carpino, S. Kates, *Tetrahedron Lett.* **1997**, *38*, 4853-4856.

[12] J. Coste, D. Le-Nguyen, B. Castro, *Tetrahedron Lett*. **1990**, *31*, 205-208.

[13] (a) M. Kunishima, C. Kawachi, F. Iwasaki, K. Terao, S. Tani, *Tetrahedron Lett.* **1990**, *40*, 5327-5330; (b) M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki, S. Tani, *Tetrahedron* **1999**, *55*, 13159-13170

[14] J. Sheehan, P. Cruickshank, G. Boshart, *J. Org. Chem.* **1961**, *26*, 2525-2528.

[15] (a) H. Wissmann, H.-J. Kleiner, *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 133-134; (b) R. Escher, P. Bünning, *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 277-278.

[16] (a) D. K. Mohapatra, A. Datta, *J. Org. Chem.* **1999**, *64*, 6879-6880; (b) K. Takeda, A. Akiyama, H. Nakamura, S.-i. Takizawa, Y. Mizuno, H. Takayanagi, Y. Harigaya, *Synthesis* **1994**, 1063-1066; (c) L. J. Gooßen, A. Döhring, *Adv. Synth. Catal.* **2003**, *345*, 943-947; (d) L. J. Gooßen, A. Döhring, *Synlett* **2004**, 263–266; (d) I. Held, P. von den Hoff, D. S. Stephenson, H. Zipse, *Adv. Synth. Catal.* **2008**, *350*, 1891-1900.

[17] D. C. Braddock, P. D. Lickiss, B. C. Rowley, D. Pugh, T. Purnomo, G. Santhakumar, S. J. Fussell, *Org. Lett.* **2018**, *20*, 950-953.

[18] (a) F. Zetzsche, *Chem. Ber.* **1939**, *72*, 1735-1738; (b) H. G. Khorana, *J. Chem. Soc.* **1952**, 2081-2088; (c) B. Neises, W. Steglich, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522-524.

[19] (a) J. R. Vaughan, R. L. Osato, *J. Am. Chem. Soc.* **1951**, *73*, 5553-5555; (b) J. R. Vaughan, R. L. Osato, *J. Am. Chem. Soc.* **1951**, *73*, 3547; (c) R. A. Boissonnas, *Helv. Chim. Acta* **1951**, *34*, 874-879; (d) J. Vaughan, R. L. Osato, *J. Am. Chem. Soc*. **1952**, *74*, 676-678; (d) J. R. Vaughan, J. A. Eichler, *J*. Am. Chem. Soc. **1953**, *75*, 5556-5560; (e) J. R. Vaughan, *J. Am. Chem. Soc*. **1952**, *74*, 6137-6139.

[20] P. H. Huy, I. Filbrich, *Chem. Eur. J*. **2018**, *24*, 7410-7416.

[21] J. Burés, *Angew. Chem. Int. Ed.* **2016**, *55*, 2028.

[22] Rayle, H. L.; Fellmeth, L. *Org. Process Res. Dev.* **1999**, 3, 172–176.

[23] Venkataraman, K.; Wagle, D. R., *Tetrahedron Lett.* **1979**, *20*, 3037-3040.

[24] (a) Forbes, D. C.; Barrett, E. J.; Lewis, D. L.; Smith, M. C. *Tetrahedron Lett*. **2000**, *41*, 9943–9947; (b) Bandgar, B. P.; Pandit, S. S*. Tetrahedron Lett.* **2002**, *43*, 3413–3414; (c) Giacomelli, G.; Porcheddu, A.; Salaris, M. *Org. Lett.* **2003**, *5*, 2715-2717.

[25] P. H. Huy, S. Motsch, S. M. Kappler, *Angew. Chem. Int. Ed.* **2016**, *55*, 10145-10149.

[26] J. S. Quesnel, Arndtsen, B. A., *J. Am. Chem. Soc.* **2013**, *135*, 16841-16844.

[27] F.-R. Gou, X. H. Wang, P.-F. Huo, H.-P. Bi, Z.-H. Guan, Y.-M. Liang, *Org. Lett.* **2009**, *11*, 5726-5729.

[28] T. Mitsudome, K. Miyagawa, Z. Maeno, T. Mizugaki, K. Jitsukawa, J. Yamasaki, Y. Kitagawa, K. Kaneda, *Angew. Chem. Int. Ed.* **2017**, *56*, 9381-9385; *Angew. Chem.* **2017**, *129*, 9509-9513.

[29] S. Chanthamath, S. Takaki, K. Shibatomi, S. Iwasa, *Angew. Chem. Int. Ed.* **2013**, *52*, 5818-5821; *Angew. Chem.* **2013**, *125*, 5930-5933.

[30] B. Song, S. Wang, C. Sun, H.; Deng, B. Xu, *Tetrahedron Lett.* **2007**, *48*, 8982-8986.

[31] S. L. Zultanski, J. Zhao, S. S. Stahl, *J. Am. Chem. Soc.* **2016**, *138*, 6416-6419.

[32] Z. Wu, S. D. Laffoon, T. T. Nguyen, J.D. McAlpin, K. L. Hull, Kami L., *Angew. Chem. Int. Ed.* **2017**, *56*, 1371-1375; *Angew. Chem.* **2017**, *129*, 1391-1395.

[33] N. Wang, X. Zou, J. Ma, F. Li, *Chem. Commun.* **2014**, *50*, 8303-8305.

[34] M: Jokic, V. Caplar, T. Portada, J. Makarevic, N. S. Vujicic, M. Sijakovic, *Tetrahedron Lett.* **2009**, *50*, 509-513.

[35] J. S. Quesnel, B. A. Arndtsen, *J. Am. Chem. Soc.* **2013**, *135*, 16841-16844.

[36] N. Ambreen, T. Wirth, *Eur. J. Org. Chem.* **2014**, *34*, 7590-7593.

[37] A. B. Eldrup, F. Soleymanzadeh, S. J. Taylor, I. Muegge, N. A. Farrow, D. Joseph, K. McKellop, C. C. Man, A. Kukulka, S. De Lombaert, *J. Med. Chem.* **2009**, *52*, 5880-5895.

[38] H. Cheng, M.-Q. Xiong, C.-X. Cheng, H.-J. Wang, Q. Lu, H.-F. Liu, F.-B. Yao, C. Chen, F. Verpoort, *Chem. Asian. J.* **2018**,*13*, 440-448.

[39] H. Mustafa, A. Eldin, A. A. Hassan, *J. Am. Chem. Soc.* **1957**, *79*, 3846-3849.

[40] W. Lu, G. Du, K. Liu, L. Jiang, J. Ling, Z. Shen*, J. Phys. Chem. A* **2014**, *118*, 283-292.

[41] G. N. Papadopoulos, C. G. Kokotos, *J. Org. Chem.* **2016**, *81*, 7023-7028

[42] M. C. Mollo, L. R. Orelli, *Org. Lett.* **2016**, *18*, 6116-6119.

[43] S. Maurya, D. Yadav, K. Pratap, A. Kumar, *Green Chem.* **2017**, *19*, 629-633.

[44] O. F. Smetanina; A. N. Yurchenko; E. V. Ivanets; A. V. Gerasimenko; P. T. H. Trinh; V. Nhut; B. M. Ly, S. S. Afiyatullov, *Chem. Nat. Comp.* **2017**, *53*, 600-602

[45] V. R. Chintareddy, H.-A. Ho, A. D. Sadow, J. G. Verkade, *Tetrahedron Lett.* **2011**, *52*, 6523–6529.

[46] K. Thalluri, K. C. Nadimpally, M. P. Chakravarty, A. Paul, B. Mandal, *Adv. Synth, Catal.* **2013**, *355*, 448-462.

[47] P. Purushottamachar, A. K. Kwegyir-Afful, M. S. Martin, V. P. Ramamurthy, S. Ramalingam, V. C. O. Njar, *ACS Med. Chem. Lett*. **2016**, *7*, 708−713

[48] A. Perosa, A. Moraschini, M. Selva, M. Noè *Molecules* **2016**, *21*, 170.

[49] M. J. Durán-Peña, J. M. Botubol-Ares, J. R. Hanson, R. Hernández-Galán, I. G. Collado, *Eur. J. Org. Chem.* **2016**, 3584-3591.

[50] S. A. Snyder, D. S. Treitler, *Angew. Chem. Int. Ed.* **2009**, *48*, 7899-7903.

[51] Y. Wu, X. Li, D. Zou, H. Zhu, Y. Wang, J. Li, Y. Wu, *Org. Lett.* **2014**, *16*, 1836-1839.

[52] I. Kim, C. Lee, *Angew. Chem. Int. Ed.* **2013**, *52*, 10023-10026; *Angew. Chem.* **2013**, *125*, 10207-10210

[53] A. V. Bogolubsky, Y. S. Moroz, P. K. Mykhailiuk, E. N. Ostapchuk, A. V. Rudnichenko, Y. V. Dmytriv, A. Bondar, O. A. Zaporozhets, S. E. Pipko, R. A. Doroschuk, L. N. Babichenko, A. I. Konovets, A. Tolmachev, *ACS Comb. Sci.* **2015**, *17*, 348−354

[54] W. H. Daly, D. Poché, *Tetrahedron Lett.* **1988**, *29*, 5859-5862.

[55] M. Winkler, D. Meischler, N, Klempier, *Adv. Synth. Catal.* **2007**, *349*, 1475-1480.

[56] M. Suzuki, J. F. K. Kotyk, S. I. Khan, Y. Rubin, *J. Am. Chem. Soc.* **2016**, *138*, 5939-5956.