

T3P® – A Benign Desulfurating Reagent in the Synthesis of Isothiocyanates

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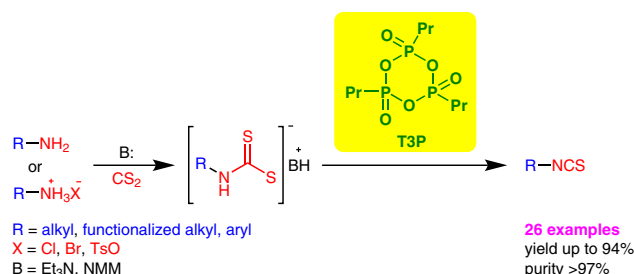
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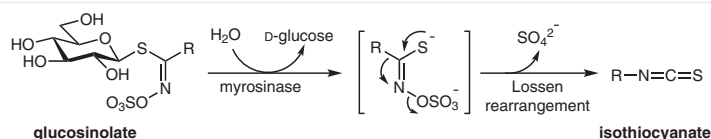
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Abstract A number of alkyl, aryl and bifunctional isothiocyanates are obtained in moderate to high yields (41–94%) in a two-step, one-pot reaction of the parent primary amines or their salts with carbon disulfide, followed by reaction of the thus formed dithiocarbamates with T3P® (propane phosphonic acid anhydride) as a new and efficient desulfurating agent.

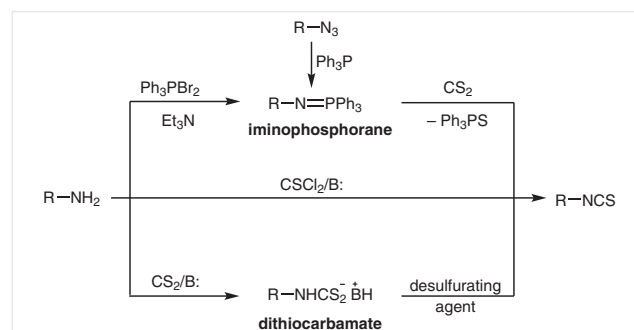
Key words isothiocyanates, desulfuration, propane phosphonic acid anhydride (T3P®), dithiocarbamates, amino acids, amines

Isothiocyanates (ITCs) belong to the group of heterocumulenes, which have been the focus of research for many years. ITCs are employed in the synthesis of sulfur-containing heterocycles,¹ thioamides,² thiourea-derived organocatalysts,^{3a,b} chiral derivatizing auxiliaries,^{3c} and thiourea receptors,⁴ whilst several natural ITCs exhibit chemopreventive and anticancer activity.⁵ Natural ITCs are an element of a plant's defense system and their task is to deter potential aggressors. In several cruciferous plants such as broccoli, cauliflower and cabbage, isothiocyanates are present in the form of inactive precursors – glucosinolates, and just after 'the aggressor's attack' they release biologically active ITCs under the action of myrosinase followed by a Lossen rearrangement (Scheme 1).⁶ Release of ITCs from glucosinolates also occurs during damage to plants or in the course of their digestion by human intestinal flora.⁷



Scheme 1 Enzymatic formation of ITCs

All these facts have resulted in interest from the scientific community in developing synthetic pathways to ITCs. The most important of these are based on primary amines or organic azides as starting materials, and the choice of the method depends on the availability of the substrates and the structure of the target isothiocyanate (Scheme 2).



Scheme 2 Selected synthetic approaches to isothiocyanates

According to Scheme 2, azides, which can be considered as convenient amine precursors, are converted upon reaction with triphenylphosphine into iminophosphoranes, which, in turn, via a reaction with carbon disulfide, afford the target ITCs under neutral conditions (the tandem Staudinger/aza-Wittig reaction⁸). Alternatively, iminophosphoranes can be formed directly from amines and triphenylphosphine dibromide⁹ (Scheme 2). The azide approach has been applied to the efficient synthesis of structurally

diverse ITCs.¹⁰ The only restriction to this approach results from the limited availability of the parent azides in some cases, or the fact that the explosive character of low-molecular-weight organic azides makes their preparation dangerous. Occasionally, separation of the target isothiocyanates from the triphenylphosphine sulfide by-product formed in these reactions can cause difficulties.

Because of their excellent availability, primary amines are the most often used starting materials in the synthesis of ITCs. Their reactions with thiophosgene, discovered by Ratke^{11a} in 1872, are still currently extensively used as a direct and efficient route to this class of compounds^{4,11b-e} (Scheme 2). The advantage of this approach is the straightforwardness and reproducibility of the reactions; its main disadvantages being the use of highly toxic thiophosgene, its low tolerance to the presence of some functional groups and thiophosgene's foul odor. As an alternative, thiophosgene surrogates such as di(2-pyridyl) thionocarbonate,¹² 1,1'-thiocarbonyldiimidazole,¹³ and 1,1'-thiocarbonyldi-2(1*H*)-pyridone¹⁴ are used.

A particularly important route to ITCs is a two-step, and usually one-pot reaction of primary amines with carbon disulfide leading to dithiocarbamic acid salts, followed by in situ desulfuration of the thus formed dithiocarbamates (Scheme 2). After its discovery by Hofmann,¹⁵ a number of reagents have been exploited as desulfurating agents. Amongst others, peptide coupling reagents,^{10a,16} tosyl chloride,¹⁷ mesyl chloride,¹⁸ hydrogen peroxide,^{16f,19} molecular iodine,²⁰ ethyl chloroformate,²¹ di-*tert*-butyl dicarbonate,²² 2,4,6-trichloro-1,3,5-triazine,²³ triphosgene,²⁴ diethyl chlorophosphate,²⁵ phenyl chlorothionoformate,²⁶ diacetoxyiodobenzene,²⁷ and 1,1'-(ethane-1,2-diyl)dipyridinium bis-tribromide²⁸ have recently been employed as desulfurating agents. However, some of these protocols suffer from difficulties in the separation of by-products or inconvenient work-up procedures.

To date, the dithiocarbamate approach to ITCs, in which propane phosphonic acid anhydride (T3P®)²⁹ (**1**) (Figure 1) is used as a desulfurating agent, has not been described. T3P® is a widely used peptide coupling reagent and dehydrating agent, which also finds applications in large-scale syntheses.³⁰ It is a stable, non-toxic, safe and user-friendly 'green' reagent. It is important from a preparative standpoint that water soluble side products are formed during reactions involving T3P®, which should be easily removable during a standard work-up.

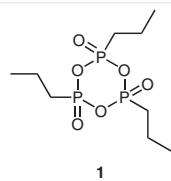


Figure 1 Propane phosphonic acid anhydride (T3P®) (**1**)

In this paper, we present the results of our investigation into the general synthesis of structurally diverse isothiocyanates from their parent amines via a one-pot dithiocarbamate approach using T3P® as a desulfurating agent.

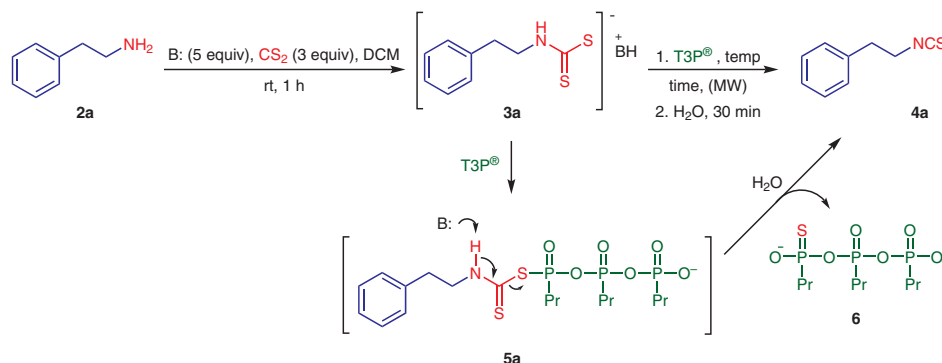
Initially, optimization of the reaction conditions was performed with phenethylamine (**2a**) as a model substrate. Treatment of **2a** with carbon disulfide in the presence of triethylamine readily afforded the intermediate dithiocarbamate **3a** after one hour at room temperature, in dichloromethane as the solvent. Next, dithiocarbamate **3a** was allowed to react in situ with T3P® (1.1 equiv) to give the target, (2-isothiocyanatoethyl)benzene (**4a**), in 77% yield after 2 hours at room temperature (Table 1, entry 1; method A). The use of 5 equivalents of Et₃N is recommended to ensure optimal conditions for both steps. We also demonstrated that increasing and decreasing the time for the desulfuration step in the presence of T3P® resulted in lower yields (72% and 71%, respectively) of **4a** [entry 1 (see footnote c) and entry 2]. In turn, desulfuration by T3P® performed in boiling DCM was complete in 15 minutes and the isothiocyanate **4a** was obtained with a yield comparable to those mentioned above [entry 3 (see footnote d); method B]. Next, other bases such as *N*-methylmorpholine (NMM), *N,N*-diisopropylethylamine (DIPEA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were tested. The reaction in the presence of NMM led to a yield comparable to that with Et₃N (entry 4), whereas the reactions with DIPEA and DBU delivered lower yields when compared to those of Et₃N and NMM (entries 1 and 4 vs entries 5 and 6). As the highest yield was obtained in the presence of Et₃N, we used this as the base and next varied the ratio of **2a** to T3P®. Decreasing the **2a**/T3P® ratio to 1:0.8 equivalents resulted in a negative impact on the yield (entry 7). An inverse effect was observed when the loading of T3P® was increased to 1.5 equivalents (entry 1 vs 8). After careful screening, we found that setting the substrate ratio (**2a**/T3P®) to 1:1.8 resulted in the best yield: 85% (entry 9). Subsequent increases in the substrate ratio had no influence on the yield [entry 9 (see footnote e)]. We also showed that desulfuration was compatible with microwave (MW) conditions. After short experimentation (see the Supporting Information, Table S1), we found that performing reactions in a pressure vial under microwave-assisted conditions for 5 minutes at 80 °C afforded the target **4a** in 83% yield [entry 10 (see footnote f); method C]. A plausible mechanistic pathway for the above transformation (Table 1) involves formation of mixed dithiocarbamate-phosphoric anhydride **5a** as a result of a reaction between **3a** and T3P® (**1**), followed by the base-mediated desulfuration of **5a** to give the target isothiocyanate **4a** and thiopyrophosphate **6** as a side product. Attempts to confirm the presence of **5a** by ³¹P NMR spectroscopy under the reaction conditions failed. However, a singlet at 96 ppm displayed in the ³¹P NMR spectrum of the reaction mixture after quenching and subsequent hydroly-

sis of intermediate **6** and unreacted T3P® (**1**), could be assigned to the propanephosphonothioic salt,³¹ which confirms in part this mechanistic hypothesis.

With optimized reaction conditions in hand, the scope of the transformation was evaluated. Structurally diverse alkyl and aryl isothiocyanates **4a–p** were obtained in high yields from the parent amines **2a–g,n–p** under the conditions shown in Table 2 (entries 1–7 and 14–16). Further studies revealed that the method was also compatible with optically active amines with a stereogenic center on the α -carbon atom. Thus, enantiopure (*R*)- and (*S*)-(1-isothiocyanatoethyl)benzene (**4b**)^{16c} and (**4c**)³² were isolated in 84% and 83% yields from their optically pure precursors (*R*)-**2b** and (*S*)-**2c**, respectively (entries 2 and 3). The protocol worked for an aromatic amine and with examples possessing electron-donating or electron-withdrawing groups. Thus, isothiocyanatobenzene (**4n**) was obtained in 92% yield from aniline (**2n**) (entry 14), whilst 1-isothiocyanato-4-methoxybenzene (**4o**) and 1-isothiocyanato-4-fluoro-

benzene (**4p**) were prepared in good yields from 4-methoxyaniline (**2o**) and 4-fluoroaniline (**2p**), respectively (entries 15 and 16). However, attempts to obtain 1-isothiocyanato-4-nitrobenzene from strongly electron-deficient 4-nitroaniline were unsuccessful. As the use of ammonium salts is often more advantageous compared with free amines, we screened several ammonium salts **2a** and **2h–m**, and proved that they were also convenient starting materials in this synthesis [entry 1 (see footnote c) and entries 8–13]. For ammonium salts, double the amount of Et₃N (10 equiv) had to be used to achieve good yields of isothiocyanates **4a** and **4h–m**. Unfortunately, volatile, low-molecular-weight isothiocyanate **4m** (entry 13) and more sterically demanding **4k** and **4l** (tertiary α -carbon) (entries 11 and 12) were isolated in low yields under the applied conditions. Pure ITCs were easily obtained after flash chromatography through a short pad of silica gel by simple elution of the products with hexane or pentane, followed by careful evaporation of the eluate.

Table 1 Optimization of the Reaction Conditions^a and a Plausible Mechanism



Entry	Base (B)	T3P® (equiv)	Time (h)	Yield (%) ^b
1	Et ₃ N	1.1	2 ^c	77
2	Et ₃ N	1.1	24	71
3	Et ₃ N	1.1	0.25 ^d	72
4	NMM	1.1	2	72
5	DIPEA	1.1	2	64
6	DBU	1.1	2	57
7	Et ₃ N	0.8	2	63
8	Et ₃ N	1.5	2	80
9	Et ₃ N	1.8 ^e	2	85
10	Et ₃ N	1.8	5 min ^f	83

^a Method A: **2a** (2 mmol), CS₂ (6 mmol, 3 equiv), base (10 mmol, 5 equiv), 1 h, r.t., then T3P® (50% w/w in EtOAc) was added at 4 °C and the reaction mixture was stirred at r.t. for the time given in Table 1.

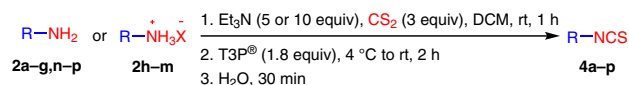
^b Yields of isolated products after flash chromatography (hexane).

^c Decreasing the reaction time with T3P® to 1 h resulted in a 72% yield.

^d Method B: reaction was carried out at reflux for 15 min.

^e Reaction with 2.1 equiv of T3P® had no influence on the yield.

^f Method C: microwave-assisted reaction, pressure vial, 5 min at 80 °C.

Table 2 Preparation of Alkyl and Aryl Isothiocyanates via T3P®-Mediated Desulfuration of Dithiocarbamates^a

R = alkyl, aryl; X = Cl, TsO

Entry	Substrate	Product	Yield (%) ^b
1 ^c			85
2			84
3			83
4			83
5			94
6			82
7			72
8			75
9			79
10			74
11			55
12			45

Table 2 (continued)

Entry	Substrate	Product	Yield (%) ^b
13			41
14 ^d			92
15			82
16 ^e			72

^a Reaction conditions: **2a–p** (2 mmol), CS₂ (6 mmol, 3 equiv), Et₃N (10 mmol, 5 equiv) for **2a–g, o–p** or Et₃N (20 mmol, 10 equiv) for ammonium salts **2h–m**, 1 h, r.t.; then, T3P® (50% w/w in EtOAc) was added at 4 °C, followed by 2 h at r.t.

^b Yields of pure products after flash chromatography (hexane or pentane).

^c Product **4a** was obtained in 77% yield starting from 2-phenylethylammonium chloride.

^d The following reaction conditions were applied: **2n** (2 mmol), CS₂ (8 mmol, 4 equiv), Et₃N (16 mmol, 8 equiv), first step 22 h at r.t. (see ref.^{17b}), then T3P® was added at 4 °C, followed by 2 h at r.t.

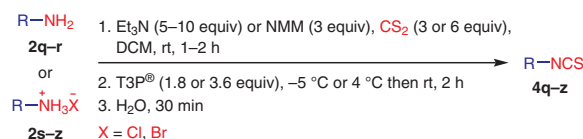
^e First step: 20 h at r.t., then T3P® was added at 4 °C, followed by 2 h at r.t.

To expand the synthetic utility of our protocol we focused on the preparation of bifunctional isothiocyanates. The results demonstrate that the established conditions allowed the reactions to proceed with a variety of bifunctional isothiocyanates and that the reaction was compatible with a variety of functional groups. 1,6-Diisothiocyanato-hexane (**4q**) was obtained in 60% yield from parent diamine **2q** (Table 3, entry 1). *N*-Boc-1,2-diaminoethane (**2r**) and 6-bromohexylammonium bromide (**2s**) were also found to be good starting materials, giving the isothiocyanates **4r** and **4s** in 60% and 55% yields, respectively (entries 2 and 3). In the light of the antiproliferative activity of some isothiocyanatoalkylphosphonates,^{10a,e,16f} diethyl aminoalkylphosphonate hydrochlorides were also examined as potential substrates. We found that aminophosphonate hydrochlorides **2t–w** afforded the corresponding products, diethyl (2-isothiocyanatoheptyl)phosphonate (**4t**), diethyl (3-cyclohexyl-2-isothiocyanatopropyl)phosphonate (**4u**), diethyl [isothiocyanato(4-methoxyphenyl)methyl]phosphonate (**4v**) and diethyl (isothiocyanatomethyl)phosphonate (**4w**) in good yields (entries 4–7). Unfortunately, when this protocol was applied to methyl (*S*)-phenylalanate, (*S*)-alanate and (*R*)-alanate hydrochlorides **2x–z** as starting materials, partly racemized (as confirmed by a substantial decrease in the specific rotation) isothiocyanates **4x–z** were obtained. Fortunately, after a short experimentation (see the Supporting Information, Table S3) we found that to ensure the

reaction was free of racemization the replacement of Et₃N by a limited amount of NMM (3 equiv) was necessary. In addition, release of the free amino esters from their hydrochlorides, the formation of the corresponding dithiocarbamates in the first step, and also the addition of T3P® to the reaction mixture should be carried out at -5 °C. Thus modified, the protocol allowed us to obtain enantiopure methyl (*S*)-2-isothiocyanato-3-phenylpropionate (**4x**), methyl (*S*)-2-isothiocyanatopropionate (**4y**), and methyl (*R*)-2-isothiocyanatopropionate (**4z**) from their optically pure amino acid counterparts in 72%, 63% and 62% yields (entries 8–10). Racemization depends on the strength of the amine used. It is highly probable that it occurs during the second step of the transformation. As proof, we subjected optically pure isothiocyanate **4y** (>99.9:0.1 er), derived from amino acid **2y**, to 5 equivalents of Et₃N or NMM under the standard reaction time/temperature (2 h, r.t.). Significant racemization was observed only when Et₃N was used (52:48 er), while almost no racemization took place on exposure to NMM (99:1 er).

Isothiocyanates derived from α-amino acids are valuable chiral building blocks, and among numerous applications, they have recently been employed in the synthesis of peptidomimetics^{17d,e,33} and chiral carboxylate receptors.⁴

Table 3 Preparation of Bifunctional Isothiocyanates via T3P®-Mediated Desulfuration of Dithiocarbamates^a



Entry	Substrate	Product ^b	Yield (%)
1 ^c			60
2			60
3			55
4			63
5			53

Entry	Substrate	Product ^b	Yield (%)
6			51
7			50
8 ^d			72
9 ^d			63
10 ^d			62

^a Reaction conditions: **2q-z** (2 mmol) [for **2q,s-w** Et₃N (20 mmol, 10 equiv) was used, for **2r** Et₃N (10 mmol, 5 equiv) was applied, for **2x-z** NMM (6 mmol, 3 equiv) was used], CS₂ (6 mmol, 3 equiv), T3P® (3.6 mmol, 1.8 equiv).

^b Yields of pure products after flash chromatography.

^c Double amounts of reagents were used: Et₃N (20 mmol, 10 equiv), CS₂ (12 mmol, 6 equiv), T3P® (7.2 mmol, 3.6 equiv).

^d CS₂, NMM and T3P® were added at -5 °C and the first step was continued for 2 h at r.t.

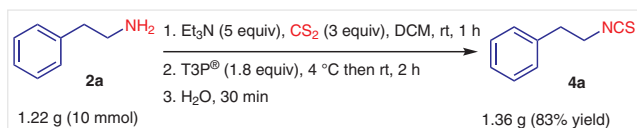
In order to compare the effectiveness of the proposed methodology with previously reported methods, the conversion of the model amine **2a** into isothiocyanate **4a** was studied using selected reagents. For this purpose, the dithiocarbamate was generated in the reaction of **2a** with carbon disulfide and then desulfurated to give **4a** using either TsCl,^{17b} Boc₂O,²² I₂,²⁰ or H₂O₂.^{16f,19} (Table 4, entries 2–5). Additionally, the reaction of **2a** with thiophosgene was carried out (entry 6). The results were compared with the T3P® protocol presented in this work (entry 1). Table 4 presents the yields of isolated, pure isothiocyanate **4a** after flash chromatography. Thiophosgene (entry 6) afforded the highest yield of (2-isothiocyanatoethyl)benzene (**4a**) (90%), but handling problems and the toxicity relevant to this reagent discouraged its use. In turn, the reaction involving H₂O₂ was the lowest yielding (77%) compared to the others (entry 5). The dithiocarbamate approach to **4a** in which either T3P® or TsCl were applied as desulfurating agents were found to be equally attractive (entries 1 and 2, 85% yields), while Boc₂O and I₂ were slightly less effective (entries 3 and 4, 82% and 81%, respectively).

Table 4 A Comparative Study of the Reagents Used for the Synthesis of **4a** from **2a**

Entry	Reagents	Yield (%)
1 ^a	CS ₂ , Et ₃ N, anhyd DCM, T3P [®]	85
2 ^{17b}	CS ₂ , Et ₃ N, THF, TsCl	85
3 ²²	CS ₂ , Et ₃ N, EtOH, cat. DMAP, Boc₂O	82
4 ²⁰	CS ₂ , Et ₃ N, MeCN, I ₂	81
5 ^{16f,19}	CS ₂ , Et ₃ N, THF, 30% H₂O₂	77
6 ^{4,11b-e}	NaHCO ₃ , CHCl ₃ /H ₂ O, CSCl₂	90

^a This work.

To illustrate the practical application of the established protocol, a gram-scale experiment was conducted (Scheme 3). We found that the reaction could be performed using 1.22 g (10 mmol) of phenethylamine (**2a**) to give 1.36 grams of isothiocyanate **4a** in 83% yield, being comparable to that of the small-scale experiment.

**Scheme 3** A gram-scale experiment

All the synthesized isothiocyanates, except for new compounds **4t** and **4u**, are described in the literature. However, full spectroscopic data have not been reported for compounds **4e**, **4g**, **4k**, **4l**, **4s**, and **4z** until now.

In conclusion, an efficient one-pot protocol for the synthesis of structurally diverse alkyl, aryl and bifunctional isothiocyanates has been developed. The reaction is broad in scope, and the target isothiocyanates are obtained in high and reproducible yields. The method is compatible with a variety of protecting groups and the reactions occur without racemization for the investigated groups of compounds. The key element of this protocol is the application of propane phosphonic acid anhydride (T3P[®]) – an easily available, green and safe reagent – for in situ desulfuration of the intermediate dithiocarbamates obtained from the parent primary amines and carbon disulfide. In our opinion, the established protocol makes a valuable contribution to those already described for the synthesis of isothiocyanates.

All reagents and solvents were purchased from Sigma-Aldrich (Poland) and used as obtained. 1-Propanephosphonic acid anhydride (50% in EtOAc) (T3P[®]) was purchased from Fluorochem. Methyl (*S*)-phenylalaninate, (*S*)-alanate and (*R*)-alanate hydrochlorides and 1,6-diaminohexane were purchased from Sigma-Aldrich. *N*-Boc-1,2-diaminoethane was prepared from 1,2-diaminoethane according to the procedure described by Famulok et al.³⁴ 6-Bromohexylammonium

bromide was prepared according to the procedure given by Obika et al.³⁵ Aminophosphonate hydrochlorides **2t–w** were obtained according to the procedure described by Zwierzak et al.³⁶ The temperatures of the reaction mixtures were measured with an external infrared sensor. Flash chromatography was performed with a glass column packed with Baker silica gel (30–60 μm). For TLC, silica gel on aluminum-backed TLC plates (Sigma-Aldrich) with indicator 254 mm were used. A monomode microwave reactor (CEM Discover SP) equipped with an IntelliVent pressure control system was used. The standard method was applied, and the maximum pressure was set to 250 psi. Melting points were obtained using a Büchi SMP-20 apparatus. Optical rotations were measured at 25 °C on a PolaAAR 3001 Polarimeter at λ = 589 nm, and are reported as follows: [α]_D²⁵ (c = g/100 mL solvent). Isothiocyanates were assessed for purity with a HPLC Gilson Prep ELS[™] II Detector, UV-VIS-156 using a reverse phase Kromasil 100-5C18 250 × 4.6 mm E64911 analytical column (detection at 254 nm), in various MeCN/H₂O gradients: A: 0–1 min 20% MeCN, 10–20 min 70% MeCN, 25–30 min 80% MeCN; B: 0–1 min 20% MeCN, 10–20 min 70% MeCN, 25–30 min 90% MeCN; C: MeCN/H₂O, 90%:10%; D: 0–1 min 20% MeCN, 5–15 min 70% MeCN, 20–30 min 80% MeCN. Samples were prepared by dissolution of 0.5–1 mg in 1 mL of eluent (H₂O/MeCN, 80:20 or H₂O/MeCN, 10:90 for **4t–w**). Flow rate: 1 mL/min. Software: Trilution. The enantiomeric ratios (er) of **4b,c** and **4x–z**, and of the reactions between compound **4y** with Et₃N and NMM were determined by chiral stationary phase HPLC using a Daicel Chiralpak ID column for compounds **4b,c** (hexane), a Daicel Chiralpak IF column for compound **4x** (hexane/*i*-PrOH, 99:1), and a Daicel Chiralpak IC column for compounds **4y,z** (hexane/*i*-PrOH, 98:2); column temperature: 30 °C; flow rate: 1.0 mL/min. IR spectra were measured on an FT-IR Alpha Bruker (ATR) instrument and are reported in cm⁻¹. NMR spectra were measured on a Bruker Avance II Plus spectrometer (700 MHz for ¹H NMR, 176 MHz for ¹³C NMR and 283 MHz for ³¹P NMR) and a Bruker Avance DPX spectrometer (250.13 MHz for ¹H NMR) in CDCl₃ solution. ¹H and ¹³C NMR spectra are referenced according to the residual peak of the solvent based on literature data. ³¹P NMR chemical shifts are reported in ppm downfield from 85% H₃PO₄ as an external standard. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. ³¹P and ¹³C NMR spectra are proton-decoupled. A Bruker MicrOTOF-Q II spectrometer (Bruker Daltonics, Germany) equipped with an Apollo II electrospray ionization source with an ion funnel was used for the acquisition of the high-resolution electrospray ionization (MS-ESI) spectra. An AutoSpec Premier (Waters) spectrometer with a HP 7890 (Agilent) gas chromatograph and an advanced autosampler was used for recording the high-resolution electron ionization (MS-EI) spectra.

Isothiocyanates **4a–w**; Method A

Et₃N (1.4 mL, 10 mmol for amines **2a–g,o–p,r**, or 2.8 mL, 20 mmol for diamine **2q** and ammonium salts **2h–m,s–w**, or 2.23 mL, 16 mmol for **2n**) and CS₂ (0.36 mL, 6 mmol for **2a–w**, or 0.72 mL, 12 mmol for **2q**, or 0.48 mL, 8 mmol for **2n**) were added in one portion to a solution of primary amine **2a–g,n–r** or ammonium salt **2h–m,s–w** (2 mmol) in anhyd DCM (10 mL) and placed in a 50 mL two-neck round-bottomed flask equipped with a magnetic stir bar, a rubber septum, and a thermometer and secured from moisture with a syringe filled with CaCl₂. The solution was stirred for 1 h at r.t. (22 h at r.t. for **2n** or 20 h at r.t. for **2p**). Next, the reaction mixture was cooled to 4 °C and T3P[®] (2.12 mL, 3.6 mmol for **2a–p** and **2r–w**, or 4.24 mL, 7.2 mmol for **2q**) was added over 5 min in three portions. Thereafter, the solution was allowed to reach r.t. and was stirred for 2 h at this temperature. Next, the mixture was hydrolyzed with H₂O (10 mL) for 30 min and diluted with DCM (50 mL). The organic layer was separated and washed suc-

cessively with H₂O (2 × 5 mL), 1 M HCl (2 × 5 mL), H₂O (2 × 5 mL), saturated NaHCO₃ (2 × 5 mL), H₂O (5 mL) and brine (5 mL) and then dried over anhydrous MgSO₄. The crude products were purified by flash chromatography on silica gel using hexane or pentane as eluents. Pure isothiocyanates **2a–w** were isolated after careful evaporation of the solvent and removal of volatile residues under reduced pressure.

Amino Acid Derived Isothiocyanates **4x–z**; Method A

N-Methylmorpholine (NMM) (0.66 mL, 6 mmol) and CS₂ (0.36 mL, 6 mmol) were added dropwise to a cooled (–5 °C) suspension of amino acid methyl ester hydrochloride **2x–z** (2 mmol) in anhyd DCM (10 mL). The solution was stirred for 2 h at r.t. and then cooled to –5 °C again. T3P® (2.12 mL, 3.6 mmol) was added over 5 min in three portions, and the solution was stirred for 2 h at r.t. The isothiocyanates **4x–z** were then isolated using the same procedure as described above for ITCs **4a–w**.

(2-Isothiocyanatoethyl)benzene (**4a**)

Colorless oil. Yield: 0.279 g, 1.7 mmol (85%) after flash chromatography (hexane). Purity determined by HPLC was 98%, gradient A, *t_R* = 18.47 min.

IR (ATR): 2180 (NCS), 2079 (NCS), 1495, 1453, 1346, 748, 698 cm⁻¹.

¹H NMR (700 MHz, CDCl₃): δ = 7.36–7.34 (m, 2 H, CH_{Ar}), 7.30–7.27 (m, 1 H, CH_{Ar}), 7.23–7.21 (m, 2 H, CH_{Ar}), 3.73 (t, *J*_{HH} = 7.0 Hz, 2 H, CH₂NCS), 3.00 (t, *J*_{HH} = 7.0 Hz, 2 H, CH₂).

¹³C NMR (176 MHz, CDCl₃): δ = 137.0 (s, C_{Ar}), 130.8 (s, NCS), 128.7 (s, C_{Ar}H), 128.6 (s, C_{Ar}H), 127.1 (s, C_{Ar}H), 46.3 (s, CH₂NCS), 36.4 (s, CH₂).

The analytical data are in agreement with those reported previously in the literature.³⁷

(*R*)-(1-Isothiocyanatoethyl)benzene (**4b**)

Colorless oil. Yield: 0.272 g, 1.68 mmol (84%) after flash chromatography (hexane). Purity determined by HPLC was 99%, gradient A, *t_R* = 20.30 min.

The er was determined by HPLC using a Chiralpak ID column (hexane); *t*_{major} = 7.40 min, *t*_{minor} = 6.82 min (>99.9:0.1 er).

[α]_D²⁵ –17.9 (c 1.0, CHCl₃); [α]_D²⁵ –5.7 (c 1.0, acetone) [Lit.^{16e} [α]_D²⁰ –4.3 (c 1.0, acetone)].

IR (ATR): 2077 (NCS), 2039 (NCS), 1493, 1452, 1306, 1020, 756, 695 cm⁻¹.

¹H NMR (700 MHz, CDCl₃): δ = 7.40–7.38 (m, 2 H, CH_{Ar}), 7.34–7.32 (m, 3 H, CH_{Ar}), 4.92 (q, *J*_{HH} = 6.8 Hz, 1 H, CHNCS), 1.68 (d, *J*_{HH} = 6.8 Hz, 3 H, CH₃).

¹³C NMR (176 MHz, CDCl₃): δ = 140.3 (s, C_{Ar}), 132.5 (s, NCS), 129.0 (s, C_{Ar}H), 128.3 (s, C_{Ar}H), 125.5 (s, C_{Ar}H), 57.1 (s, CHNCS), 25.0 (s, CH₃).

The analytical data are in agreement with those reported previously in the literature.^{16e,38}

(*S*)-(1-Isothiocyanatoethyl)benzene (**4c**)

Colorless oil. Yield: 0.270 g, 1.66 mmol (83%) after flash chromatography (hexane). Purity determined by HPLC was 98%, gradient A, *t_R* = 20.41 min.

The er was determined by HPLC using a Chiralpak ID column (hexane); *t*_{major} = 6.82 min, *t*_{minor} = 7.40 min (>99.9:0.1 er).

[α]_D²⁵ +5.4 (c 1.0, acetone); [α]_D²⁵ +17.8 (c 1.0, CHCl₃) [Lit.³² [α]_D²⁰ +16.6 (c 1.02, CHCl₃)].

IR (ATR): 2079 (NCS), 1495, 1450, 1306, 1019, 757, 696 cm⁻¹.

¹H NMR (700 MHz, CDCl₃): δ = 7.40–7.38 (m, 2 H, CH_{Ar}), 7.34–7.32 (m, 3 H, CH_{Ar}), 4.91 (q, *J*_{HH} = 6.8 Hz, 1 H, CHNCS), 1.68 (d, *J*_{HH} = 6.8 Hz, 3 H, CH₃).

¹³C NMR (176 MHz, CDCl₃): δ = 140.3 (s, C_{Ar}), 132.5 (s, NCS), 129.0 (s, C_{Ar}H), 128.3 (s, C_{Ar}H), 125.5 (s, C_{Ar}H), 57.1 (s, CHNCS), 25.0 (s, CH₃).

The analytical data are in agreement with those reported previously in the literature.³²

(Isothiocyanatomethyl)benzene (**4d**)

Colorless oil. Yield: 0.247 g, 1.66 mmol (83%) after flash chromatography (hexane). Purity determined by HPLC was 99%, gradient A, *t_R* = 17.73 min.

IR (ATR): 2163 (NCS), 2068 (NCS), 1495, 1453, 1345, 694 cm⁻¹.

¹H NMR (700 MHz, CDCl₃): δ = 7.41–7.39 (m, 2 H, CH_{Ar}), 7.36–7.34 (m, 1 H, CH_{Ar}), 7.33–7.31 (m, 2 H, CH_{Ar}), 4.71 (s, 2 H, CH₂NCS).

¹³C NMR (176 MHz, CDCl₃): δ = 134.3 (s, C_{Ar}), 132.4 (s, NCS), 129.0 (s, C_{Ar}H), 128.5 (s, C_{Ar}H), 126.9 (s, C_{Ar}H), 48.8 (s, CH₂NCS).

The analytical data are in agreement with those reported previously in the literature.^{17b,39}

2-Isothiocyanatooctane (**4e**)⁴⁰

Colorless oil. Yield: 0.320 g, 1.87 mmol (94%) after flash chromatography (pentane). Purity determined by HPLC was 98%, gradient B, *t_R* = 31.18 min.

IR (ATR): 2083 (NCS), 1456, 1378, 1334 cm⁻¹.

¹H NMR (700 MHz, CDCl₃): δ = 3.77–3.72 (m, 1 H, CHNCS), 1.65–1.60 (m, 1 H, *H* from CH₂), 1.57–1.52 (m, 1 H, *H* from CH₂), 1.48–1.43 (m, 1 H, *H* from CH₂), 1.38–1.33 (m, 1 H, *H* from CH₂, *d*, *J*_{HH} = 6.5 Hz, 3 H, CH₃CH), 1.32–1.25 (m, 6 H, 3 × CH₂), 0.89 (t, *J*_{HH} = 7.0 Hz, 3 H, CH₃).

¹³C NMR (176 MHz, CDCl₃): δ = 129.9 (s, NCS), 54.1 (s, CHNCS), 37.6 (s, CH₂), 31.6 (s, CH₂), 28.8 (s, CH₃CH), 26.0 (s, CH₂), 22.6 (s, CH₂), 21.8 (s, CH₂), 14.1 (s, CH₃).

EI-MS: *m/z* [M]⁺ calcd for C₉H₁₇NS: 171.1082; found: 171.1078.

3-Isothiocyanatopentane (**4f**)

Colorless oil. Yield: 0.211 g, 1.63 mmol (82%) after flash chromatography (pentane). Purity determined by HPLC was 100%, gradient A, *t_R* = 20.76 min.

IR (ATR): 2137 (NCS), 2088 (NCS), 2049 (NCS), 1458, 1346, 821 cm⁻¹.

¹H NMR (700 MHz, CDCl₃): δ = 3.53–3.49 (m, 1 H, CHNCS), 1.66–1.61 (m, 4 H, 2 × CH₂), 1.02 (t, *J*_{HH} = 7.4 Hz, 6 H, 2 × CH₃).

¹³C NMR (176 MHz, CDCl₃): δ = 129.9 (s, NCS), 61.9 (s, CHNCS), 28.6 (s, 2 × CH₂), 10.6 (s, 2 × CH₃).

The analytical data are in agreement with those reported previously in the literature.⁴¹

1-Isothiocyanato-2-methylpropane (**4g**)⁴²

Colorless oil. Yield: 0.166 g, 1.44 mmol (72%) after flash chromatography (pentane). Purity determined by HPLC was 99%, gradient A, *t_R* = 17.48 min.

IR (ATR): 2170 (NCS), 2074 (NCS), 1466, 1444, 1343, 690 cm⁻¹.

¹H NMR (700 MHz, CDCl₃): δ = 3.33 (d, *J*_{HH} = 6.2 Hz, 2 H, CH₂NCS), 1.99 (sept, *J*_{HH} = 6.3 Hz, 1 H, CH), 1.00 (t, *J*_{HH} = 6.7 Hz, 6 H, 2 × CH₃).

¹³C NMR (176 MHz, CDCl₃): δ = 129.8 (s, NCS), 52.5 (s, CH₂NCS), 29.7 (s, CH), 19.9 (s, 2 × CH₃).

EI-MS: m/z [M^+] calcd for C_5H_9NS : 115.0456; found: 115.0454.

(3-Isothiocyanatopropyl)benzene (4h)

Colorless oil. Yield: 0.266 g, 1.5 mmol (75%) after flash chromatography (hexane). Purity determined by HPLC was 100%, gradient A, t_R = 21.60 min.

IR (ATR): 2181 (NCS), 2084 (NCS), 1495, 1451, 1344, 743, 697 cm^{-1} .

1H NMR (700 MHz, $CDCl_3$): δ = 7.33–7.31 (m, 2 H, CH_{Ar}), 7.24–7.22 (m, 1 H, CH_{Ar}), 7.20–7.19 (m, 2 H, CH_{Ar}), 3.50 (t, J_{HH} = 6.5 Hz, 2 H, CH_2NCS), 2.77 (t, J_{HH} = 7.4 Hz, 2 H, CH_2), 2.02 (quin, J_{HH} = 7.0 Hz, 2 H, CH_2).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 140.0 (s, C_{Ar}), 130.5 (s, NCS), 128.7 (s, $C_{Ar}H$), 128.6 (s, $C_{Ar}H$), 126.5 (s, $C_{Ar}H$), 44.3 (s, CH_2NCS), 32.6 (s, CH_2), 31.5 (s, CH_2).

The analytical data are in agreement with those reported previously in the literature.^{17b}

1-Isothiocyanato-3-methylbutane (4i)

Colorless oil. Yield: 0.204 g, 1.58 mmol (79%) after flash chromatography (pentane). Purity determined by HPLC was 99%, gradient A, t_R = 20.43 min.

IR (ATR): 2173 (NCS), 2090 (NCS), 2064 (NCS), 1468, 1351, 1329 cm^{-1} .

1H NMR (700 MHz, $CDCl_3$): δ = 3.53 (t, J_{HH} = 6.8 Hz, 2 H, CH_2NCS), 1.75 (sept, J_{HH} = 7.0 Hz, 1 H, CH), 1.59 (q, J_{HH} = 6.9 Hz, 2 H, CH_2), 0.93 (d, J_{HH} = 6.7 Hz, 6 H, $2 \times CH_3$).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 129.7 (s, NCS), 43.4 (s, CH_2NCS), 38.6 (s, CH_2), 25.5 (s, CH), 22.1 (s, $2 \times CH_3$).

The analytical data are in agreement with those reported previously in the literature.⁴³

1-Isothiocyanatobutane (4j)

Colorless oil. Yield: 0.17 g, 1.48 mmol (74%) after flash chromatography (pentane). Purity determined by HPLC was 100%, gradient A, t_R = 17.72 min.

IR (ATR): 2173 (NCS), 2127 (NCS), 2089 (NCS), 1510, 1345, 771 cm^{-1} .

1H NMR (700 MHz, $CDCl_3$): δ = 3.51 (t, J_{HH} = 6.6 Hz, 2 H, CH_2NCS), 1.67 (quin, J_{HH} = 7.7 Hz, 2 H, CH_2), 1.45 (sext, J_{HH} = 7.7 Hz, 2 H, CH_2), 0.94 (t, J_{HH} = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 129.7 (s, NCS), 44.8 (s, CH_2NCS), 32.0 (s, CH_2), 19.8 (s, CH_2), 13.3 (s, CH_3).

The analytical data are in agreement with those reported previously in the literature.⁴⁴

1-Isothiocyanato-1-methylcyclohexane (4k)⁴⁵

Colorless oil. Yield: 0.169 g, 1.09 mmol (55%) after flash chromatography (pentane). Purity determined by HPLC was 99%, gradient A, t_R = 25.27 min.

IR (ATR): 2077 (NCS), 2039 (NCS), 1447, 1258, 1165, 951, 771 cm^{-1} .

1H NMR (700 MHz, $CDCl_3$): δ = 1.89–1.86 (m, 2 H, CH_2), 1.70–1.66 (m, 1 H, H from CH_2), 1.63–1.55 (m, 4 H, $2 \times CH_2$), 1.41–1.37 (m, 2 H, CH_2), 1.37 (s, 3 H, CH_3), 1.21–1.15 (m, 1 H, H from CH_2).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 130.0 (s, NCS), 61.8 (s, CNCS), 39.1 (s, $2 \times CH_2$), 29.7 (s, CH_3), 25.0 (s, CH_2), 22.4 (s, $2 \times CH_2$).

EI-MS: m/z [M^+] calcd for $C_8H_{13}NS$: 155.0769; found: 155.0776.

3-Isothiocyanato-3-methylpentane (4l)

Colorless oil. Yield: 0.128 g, 0.89 mmol (45%) after flash chromatography (pentane). Purity determined by HPLC was 100%, gradient A, t_R = 23.68 min.

IR (ATR): 2075 (NCS), 1458, 1176, 819 cm^{-1} .

1H NMR (700 MHz, $CDCl_3$): δ = 1.71–1.66 (m, 2 H, CH_2), 1.61–1.56 (m, 2 H, CH_2), 1.31 (s, 3 H, CCH_3), 0.98 (t, J_{HH} = 7.4 Hz, 6 H, $2 \times CH_3$).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 129.8 (s, NCS), 65.2 (s, C), 33.0 (s, $2 \times CH_2$), 25.2 (s, CH_3), 8.5 (s, $2 \times CH_3$).

EI-MS: m/z [M^+] calcd for $C_7H_{13}NS$: 143.0769; found: 143.0770.

3-Isothiocyanatoprop-1-ene (4m)

Colorless oil. Yield: 0.08 g, 0.81 mmol (41%) after flash chromatography (pentane). Purity determined by HPLC was 100%, gradient A, t_R = 14.55 min.

IR (ATR): 2164 (NCS), 2083 (NCS), 1435, 1416, 1341, 1324, 986, 920 cm^{-1} .

1H NMR (700 MHz, $CDCl_3$): δ = 5.84 (ddt, J_{HaHc} = 16.9 Hz, J_{HaHb} = 10.0 Hz, J_{HaHde} = 4.9 Hz, 1 H, CH_a), 5.40 (dtd, J_{HcHa} = 16.9 Hz, J_{HcHde} = 1.8 Hz, J_{HcHb} = 0.5 Hz, 1 H, CH_c), 5.28 (dtd, J_{HbHa} = 10.2 Hz, J_{HbHde} = 1.6 Hz, J_{HbHc} = 0.6 Hz, 1 H, CH_b), 4.14 (dt, J_{HdeHa} = 4.9 Hz, $J_{HdeHa,Hb}$ = 1.7 Hz, 2 H, CH_{de} , NCS). For protons (a–e) labeling see Supporting Information.

^{13}C NMR (176 MHz, $CDCl_3$): δ = 132.4 (s, NCS), 130.4 (s, CH), 117.7 (s, $CH_2=CH$), 47.2 (s, CH_2NCS).

The analytical data are in agreement with those reported previously in the literature.⁴⁶

Isothiocyanatobenzene (4n)

Colorless oil. Yield: 0.248 g, 1.83 mmol (92%) after flash chromatography (pentane). Purity determined by HPLC was 99%, gradient A, t_R = 20.45 min.

IR (ATR): 2169 (NCS), 2030 (NCS), 2019 (NCS), 1589, 1451, 924, 745, 680 cm^{-1} .

1H NMR (700 MHz, $CDCl_3$): δ = 7.36–7.34 (m, 2 H, CH_{Ar}), 7.29–7.27 (m, 1 H, CH_{Ar}), 7.23–7.22 (m, 2 H, CH_{Ar}).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 135.5 (s, NCS), 131.4 (s, C_{Ar} , NCS), 129.6 (s, $C_{Ar}H$), 127.4 (s, $C_{Ar}H$), 125.8 (s, $C_{Ar}H$).

The analytical data are in agreement with those reported previously in the literature.^{17b}

1-Isothiocyanato-4-methoxybenzene (4o)

Colorless oil. Yield: 0.270 g, 1.64 mmol (82%) after flash chromatography (pentane). Purity determined by HPLC was 100%, gradient A, t_R = 19.68 min

IR (ATR): 2174 (NCS), 2035 (NCS), 1580, 1499, 1459, 1243, 926, 826 cm^{-1} .

1H NMR (700 MHz, $CDCl_3$): δ = 7.16 (d, J_{HH} = 9.1 Hz, 2 H, CH_{Ar}), 6.85 (d, J_{HH} = 9.1 Hz, 2 H, CH_{Ar}), 3.80 (s, 3 H, CH_3O).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 158.7 (s, $C_{Ar}OCH_3$), 134.1 (s, NCS), 127.1 (s, $C_{Ar}H$), 123.7 (s, C_{Ar} , NCS), 114.9 (s, $C_{Ar}H$), 55.6 (s, CH_3O).

The analytical data are in agreement with those reported previously in the literature.^{17b}

1-Fluoro-4-isothiocyanatobenzene (4p)

Colorless oil. Yield: 0.219 g, 1.43 mmol (72%) after flash chromatography (pentane). Purity determined by HPLC was 100%, gradient A, t_R = 19.65 min.

IR (ATR): 2187 (NCS), 2029 (NCS), 1497, 1250, 930, 830 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 7.22–7.20 (m, 2 H, CH_{Ar}), 7.05–7.03 (m, 2 H, CH_{Ar}).

^{13}C NMR (176 MHz, CDCl_3): δ = 161.3 (d, J_{CF} = 249.2 Hz, $\text{C}_{\text{Ar}}\text{F}$), 136.2 (s, NCS), 127.6 (s, $\text{C}_{\text{Ar}}\text{NCS}$), 127.5 (d, J_{CF} = 8.8 Hz, $\text{C}_{\text{Ar}}\text{H}$), 116.8 (d, J_{CF} = 23.3 Hz, $\text{C}_{\text{Ar}}\text{H}$).

The analytical data are in agreement with those reported previously in the literature.^{17b}

1,6-Diisothiocyanatohexane (4q)

Colorless oil. Yield: 0.240 g, 1.2 mmol (60%) after flash chromatography (pentane). Purity determined by HPLC was 100%, gradient B, t_R = 22.06 min.

IR (ATR): 2179 (NCS), 2071 (NCS), 1448, 1344 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 3.53 (t, J_{HH} = 6.5 Hz, 4 H, $2 \times \text{CH}_2\text{NCS}$), 1.74–1.70 (m, 4 H, $2 \times \text{CH}_2$), 1.48–1.45 (m, 4 H, $2 \times \text{CH}_2$).

^{13}C NMR (176 MHz, CDCl_3): δ = 130.1 (s, NCS), 45.0 (s, $2 \times \text{CH}_2\text{NCS}$), 29.8 (s, $2 \times \text{CH}_2$), 25.9 (s, $2 \times \text{CH}_2$).

The analytical data are in agreement with those reported previously in the literature.⁴⁷

tert-Butyl (2-Isouthiocyanatoethyl)carbamate (4r)

White solid; mp 92–93 °C (Lit.⁴⁸ 63–64 °C). Yield: 0.243 g, 1.2 mmol (60%) after flash chromatography (hexane/EtOAc, 10:1). Purity determined by HPLC was 98%, gradient D, t_R = 4.91 min.

IR (ATR): 2193 (NCS), 2096 (NCS), 1688 (CO), 1528, 1436, 1278, 1165 cm^{-1} .

^1H NMR (250 MHz, CDCl_3): δ = 4.88 (br s, 1 H, NH), 3.64 (t, J_{HH} = 5.6 Hz, 2 H, CH_2NCS), 3.37 (q, J_{HH} = 5.9 Hz, 2 H, CH_2NH), 1.45 [s, 9 H, (CH_3)₃].

^{13}C NMR (176 MHz, CDCl_3): δ = 155.7 (s, CO), 132.4 (s, NCS), 80.2 [s, C(CH_3)₃], 45.5 (s, CH_2), 40.7 (s, CH_2), 28.4 [s, (CH_3)₃].

The analytical data are in agreement with those reported previously in the literature.⁴⁸

1-Bromo-6-isothiocyanatohexane (4s)⁴⁹

Colorless oil. Yield: 0.244 g, 1.1 mmol (55%) after flash chromatography (pentane). Purity determined by HPLC was 100%, gradient B, t_R = 22.29 min.

IR (ATR): 2180 (NCS), 2082 (NCS), 1451, 1345 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 3.52 (t, J_{HH} = 6.6 Hz, 2 H, CH_2NCS), 3.41 (t, J_{HH} = 6.7 Hz, 2 H, CH_2Br), 1.90–1.86 (m, 2 H, CH_2), 1.73–1.69 (m, 2 H, CH_2), 1.51–1.43 (m, 4 H, $2 \times \text{CH}_2$).

^{13}C NMR (176 MHz, CDCl_3): δ = 130.1 (s, NCS), 45.1 (s, CH_2NCS), 33.6 (s, CH_2), 32.5 (s, CH_2), 29.9 (s, CH_2), 27.4 (s, CH_2), 25.8 (s, CH_2).

ESI-MS: m/z [M^+] calcd for $\text{C}_7\text{H}_{12}\text{BrNS}$: 220.9874; found: 220.9884.

Diethyl (2-Isouthiocyanatoheptyl)phosphonate (4t)

Colorless oil. Yield: 0.366 g, 1.25 mmol (63%) after flash chromatography (hexane/EtOAc, 3:2). Purity determined by HPLC was 97%, gradient C, t_R = 5.11 min.

IR (ATR): 2078 (NCS), 1239, 1050, 1021 (P–O–C), 959 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 4.19–4.08 (m, 4 H, $2 \times \text{CH}_2\text{O}$), 4.05–4.00 (m, 1 H, CH), 2.15–2.09 (m, 1 H, H_α from PCH_2), 2.01–1.96 (m, 1 H, H_β from PCH_2), 1.74–1.70 (m, 2 H, CH_2), 1.52–1.46 (m, 1 H, H_α from CH_2), 1.43–1.37 (m, 1 H, H_β from CH_2), 1.35 (t, J_{HH} = 7.0 Hz, 3 H, $\text{CH}_3\text{CH}_2\text{O}$), 1.34 (t, J_{HH} = 7.0 Hz, 3 H, $\text{CH}_3\text{CH}_2\text{O}$), 1.33–1.26 (m, 4 H, $2 \times \text{CH}_2$), 0.89 (t, J_{HH} = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (176 MHz, CDCl_3): δ = 131.8 (s, NCS), 62.2 (d, J_{CP} = 6.5 Hz, CH_2O), 62.1 (d, J_{CP} = 6.5 Hz, CH_2O), 53.3 [s, C(2)H], 37.2 [d, J_{CP} = 11.2 Hz, C(3)H₂], 35.5 [d, J_{CP} = 142.5 Hz, PC(1)H₂], 31.1 (s, CH_2), 25.4 (s, CH_2), 22.4 (s, CH_2), 16.5 ($2 \times$ d, J_{CP} = 5.5 Hz, $2 \times \text{CH}_3\text{CH}_2\text{O}$), 14.0 (s, CH_3).

^{31}P NMR (283 MHz, CDCl_3): δ = 25.64.

ESI-MS: m/z [$\text{M} + \text{Na}$]⁺ calcd for $\text{C}_{12}\text{H}_{24}\text{NNaO}_3\text{PS}$: 316.1107; found: 316.1111.

Diethyl (3-Cyclohexyl-2-isothiocyanatopropyl)phosphonate (4u)

Yellow oil. Yield: 0.338 g, 1.06 mmol (53%) after flash chromatography (hexane/EtOAc, 3:2). Purity determined by HPLC was 97%, gradient C, t_R = 4.28 min.

IR (ATR): 2082 (NCS), 1248, 1051, 1021 (P–O–C), 960 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 4.18–4.07 (m, 5 H, $2 \times \text{CH}_2\text{O}$, CHNCS), 2.13–2.08 (m, 1 H, H_α from PCH_2), 1.99–1.94 (m, 1 H, H_β from PCH_2), 1.80–1.75 (m, 1 H, H_α from CH_2), 1.72–1.63 (m, 5 H, $5 \times H_\alpha$ from CH_2), 1.52–1.45 (m, 2 H, H_β from CH_2 , CH), 1.35 (t, 3 H, J_{HH} = 6.9 Hz, CH_3), 1.34 (t, 3 H, J_{HH} = 6.9 Hz, CH_3), 1.30–1.22 (m, 2 H, $2 \times H_\beta$ from CH_2), 1.17–1.11 (m, 1 H, H_β from CH_2), 0.98–0.93 (m, 1 H, H_β from CH_2), 0.90–0.84 (m, 1 H, H_β from CH_2).

^{13}C NMR (176 MHz, CDCl_3): δ = 131.7 (s, NCS), 62.3 (d, J_{CP} = 6.7 Hz, CH_2O), 62.2 (d, J_{CP} = 6.4 Hz, CH_2O), 51.0 (s, CHNCS), 45.0 (d, J_{CP} = 10.8 Hz, CH_2), 34.5 (s, CH), 33.6 (s, CH_2), 33.1 (d, J_{CP} = 142.6 Hz, PCH_2), 32.1 (s, CH_2), 26.4 (s, CH_2), 26.2 (s, CH_2), 25.9 (s, CH_2), 16.6 (d, J_{CP} = 6.1 Hz, CH_3), 16.5 (d, J_{CP} = 6.1 Hz, CH_3).

^{31}P NMR (283 MHz, CDCl_3): δ = 25.59.

ESI-MS: m/z [$\text{M} + \text{Na}$]⁺ calcd for $\text{C}_{14}\text{H}_{26}\text{NNaO}_3\text{PS}$: 342.1263; found: 342.1269.

Diethyl [Isothiocyanato(4-methoxyphenyl)methyl]phosphonate (4v)

Yellow oil. Yield: 0.321 g, 1.02 mmol (51%) after flash chromatography (hexane/EtOAc, 7:4). Purity determined by HPLC was 97%, gradient C, t_R = 3.44 min.

IR (ATR): 2188 (NCS), 2044 (NCS), 1511, 1305, 1012 (P–O–C), 969 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 7.35 (dd, J_{HH} = 8.5 Hz, J_{HP} = 2.2 Hz, 2 H, $2 \times \text{CH}_{\text{Ar}}$), 6.91 (d, J_{HH} = 8.5 Hz, 2 H, $2 \times \text{CH}_{\text{Ar}}$), 4.93 (d, J_{HP} = 18.9 Hz, 1 H, PCHNCS), 4.14–3.99 (m, 4 H, $2 \times \text{CH}_2\text{O}$), 3.81 (s, 3 H, CH_3O), 1.28 ($2 \times$ td, J_{HH} = 7.1 Hz, J_{HP} = 3.1 Hz, 6 H, $2 \times \text{CH}_3$).

^{13}C NMR (176 MHz, CDCl_3): δ = 160.1 (d, J_{CP} = 2.4 Hz, $\text{C}_{\text{Ar}}\text{OMe}$), 137.1 (s, NCS), 128.8 (d, J_{CP} = 5.2 Hz, $2 \times \text{C}_{\text{Ar}}\text{H}$), 123.8 (d, J_{CP} = 4.9 Hz, C_{Ar}), 114.3 (d, J_{CP} = 2.1 Hz, $2 \times \text{C}_{\text{Ar}}\text{H}$), 64.3 (d, J_{CP} = 6.7 Hz, CH_2O), 63.9 (d, J_{CP} = 6.6 Hz, CH_2O), 57.5 (d, J_{CP} = 152.2 Hz, PCHNCS), 55.4 (d, J_{CP} = 2.0 Hz, CH_3O), 16.6 (d, J_{CP} = 5.2 Hz, CH_3), 16.5 (d, J_{CP} = 5.2 Hz, CH_3).

^{31}P NMR (283 MHz, CDCl_3): δ = 15.62.

The analytical data are in agreement with those reported previously in the literature.^{10a}

Diethyl (Isothiocyanatomethyl)phosphonate (4w)

Yellow oil. Yield: 0.209 g, 1 mmol (50%) after flash chromatography (hexane/acetone, 3:1). Purity determined by HPLC was 97%, gradient C, t_R = 2.19 min.

IR (ATR): 2224 (NCS), 2071 (NCS), 1243, 1014 (P–O–C), 971 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 4.25–4.21 (m, 4 H, $2 \times \text{CH}_2\text{O}$), 3.78 (d, $J_{\text{HP}} = 14.0$ Hz, 2 H, PCH_2NCS), 1.39 (t, $J_{\text{HP}} = 7.1$ Hz, 6 H, $2 \times \text{CH}_3$).

^{13}C NMR (176 MHz, CDCl_3): δ = 135.8 (s, NCS), 63.5 (d, $J_{\text{CP}} = 6.5$ Hz, $2 \times \text{CH}_2\text{O}$), 40.5 (d, $J_{\text{CP}} = 154.0$ Hz, PCH_2NCS), 16.5 Hz (d, $J_{\text{CP}} = 5.6$ Hz, $2 \times \text{CH}_3$).

^{31}P NMR (283 MHz, CDCl_3): δ = 15.90.

The analytical data are in agreement with those reported previously in the literature.^{10a}

(S)-Methyl 2-Isothiocyanato-3-phenylpropanoate (4x)

Colorless oil. Yield: 0.319 g, 1.44 mmol (72%) after flash chromatography (hexane/EtOAc, 20:1). Purity determined by HPLC was 98%, gradient D, $t_{\text{R}} = 13.05$ min.

The er was determined by HPLC using a Chiralpak IF column (hexane/*i*-PrOH, 99:1); $t_{\text{major}} = 8.08$ min, $t_{\text{minor}} = 7.38$ min (98.5:1.5 er).

$[\alpha]_{\text{D}}^{25} -62.2$ (c 1.0, toluene) [Lit.^{16d} $[\alpha]_{\text{D}}^{20} -60.0$ (c 1.0, toluene)].

IR (ATR): 2189 (NCS), 2088 (NCS), 1600 (CO), 1484, 1253, 1117, 964 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 7.35–7.33 (m, 2 H, CH_{Ar}), 7.31–7.29 (m, 1 H, CH_{Ar}), 7.23–7.22 (m, 2 H, CH_{Ar}), 4.48 (dd, $J_{\text{HaHb}} = 8.4$ Hz, $J_{\text{HaHc}} = 4.8$ Hz, 1 H, $\text{CH}_{\text{d}}\text{NCS}$), 3.79 (s, 3 H, CH_3O), 3.25 (dd, $J_{\text{HcHb}} = 13.8$ Hz, $J_{\text{HcHa}} = 4.7$ Hz, 1 H, CH_ePh), 3.13 (dd, $J_{\text{HbHc}} = 13.8$ Hz, $J_{\text{HbHa}} = 8.4$ Hz, 1 H, CH_bPh).

^{13}C NMR (176 MHz, CDCl_3): δ = 168.4 (s, CO), 138.1 (s, NCS), 135.1 (s, C_{Ar}), 129.4 (s, $\text{C}_{\text{Ar}}\text{H}$), 128.8 (s, $\text{C}_{\text{Ar}}\text{H}$), 127.7 (s, $\text{C}_{\text{Ar}}\text{H}$), 60.8 (s, CH_3O), 53.2 (s, CHNCS), 39.8 (s, CH_2).

The analytical data are in agreement with those reported previously in the literature.^{16d}

(S)-Methyl 2-Isothiocyanatopropanoate (4y)

Colorless oil. Yield: 0.185 g, 1.27 mmol (63%) after flash chromatography (hexane/EtOAc, 20:1). Purity determined by HPLC was 100%, gradient A, $t_{\text{R}} = 13.25$ min.

The er was determined by HPLC using a Chiralpak IC column (hexane/*i*-PrOH, 98:2); $t_{\text{major}} = 7.02$ min, $t_{\text{minor}} = 6.77$ min (>99.9:0.1 er).

$[\alpha]_{\text{D}}^{25} +25.8$ (c 0.32, CHCl_3) [Lit.^{11c} $[\alpha]_{\text{D}}^{20} +23.4$ (c 0.32, CHCl_3)].

IR (ATR): 2042 (NCS), 1744 (CO), 1450, 1435, 1288, 1207, 1149, 1053 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 4.35 (q, $J_{\text{HH}} = 7.1$ Hz, 1 H, CHNCS), 3.81 (s, 3 H, CH_3O), 1.60 (d, $J_{\text{HH}} = 7.1$ Hz, 3 H, CH_3).

^{13}C NMR (176 MHz, CDCl_3): δ = 169.5 (s, CO), 137.5 (s, NCS), 54.9 (s, CH_3O), 53.3 (s, CHNCS), 19.6 (s, CH_3).

The analytical data are in agreement with those reported previously in the literature.^{11c,50}

(R)-Methyl 2-Isothiocyanatopropanoate (4z)^{11c,33}

Colorless oil. Yield: 0.180 g, 1.24 mmol (62%) after flash chromatography (hexane/EtOAc, 20:1). Purity determined by HPLC was 100%, gradient D, $t_{\text{R}} = 9.05$ min.

The er was determined by HPLC using a Chiralpak IC column (hexane/*i*-PrOH, 98:2); $t_{\text{major}} = 6.78$ min, $t_{\text{minor}} = 7.06$ min (>99.9:0.1 er).

$[\alpha]_{\text{D}}^{25} -22.8$ (c 0.32, CHCl_3) [Lit.^{11c} $[\alpha]_{\text{D}}^{25} -23.9$ (c 0.3, CHCl_3)].

IR (ATR): 2050 (NCS), 1745 (CO), 1455, 1436, 1288, 1208, 1150, 1053 cm^{-1} .

^1H NMR (700 MHz, CDCl_3): δ = 4.35 (q, $J_{\text{HH}} = 7.1$ Hz, 1 H, CHNCS), 3.79 (s, 3 H, CH_3O), 1.58 (d, $J_{\text{HH}} = 7.1$ Hz, 3 H, CH_3).

^{13}C NMR (176 MHz, CDCl_3): δ = 169.5 (s, CO), 137.5 (s, NCS), 54.9 (s, CH_3O), 53.3 (s, CHNCS), 19.6 (s, CH_3).

EI-MS: m/z [M^+] calcd for $\text{C}_5\text{H}_7\text{NO}_2\text{S}$: 145.0198; found: 145.0195.

(2-Isothiocyanatoethyl)benzene (4a); Method B

Et_3N (1.4 mL, 10 mmol, 5 equiv) and CS_2 (0.36 mL, 6 mmol, 3 equiv) were added in one portion to a solution of amine **2a** (0.242 g, 2 mmol) in anhyd DCM (10 mL). Next, the solution was stirred for 1 h at r.t. Thereafter, the mixture was cooled to 4 °C in an ice bath, T3P® (1.3 mL, 2.2 mmol, 1.1 equiv) was added over 5 min in three portions and the solution was stirred for 15 min at reflux. Pure **4a** (0.235 g) was isolated as a colorless oil in 72% yield following the work-up procedure described in Method A.

(2-Isothiocyanatoethyl)benzene (4a); Method C

Et_3N (1.4 mL, 10 mmol, 5 equiv) and CS_2 (0.36 mL, 6 mmol, 3 equiv) were added in one portion to a solution of amine **2a** (0.242 g, 2 mmol) in anhyd DCM (2 mL) in a 10 mL pressure vial equipped with a magnetic stir bar. Next, the solution was stirred for 1 h at r.t. Thereafter, the mixture was cooled to 4 °C and T3P® (2.12 mL, 3.6 mmol, 1.8 equiv) was added over 5 min in three portions. The reaction mixture was subjected to microwave (MW) irradiation (standard procedure, pressure vial, 5 min at 80 °C). Pure **4a** (0.270 g) was isolated as a colorless oil in 83% yield following the work-up procedure described in Method A.

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Supporting Information

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