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Homo- and heterogeneous organocatalysis: enantioselective Mannich addition of ketones to endocyclic carbon–nitrogen double bonds

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ABSTRACT

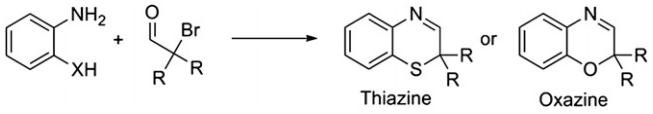
The proline-catalyzed Mannich addition of ketones to chalkogenazines is reported. Yields and enantioselectivities of the corresponding products were good to excellent, using different types of organocatalysts. Furthermore the immobilization of hydroxyproline into a readily synthesized polystyrene-copolymer was accomplished. The catalytic performance of this heterogeneous catalyst was successfully demonstrated in the discussed Mannich reaction.

1. Introduction

Over the last ten years the field of asymmetric organocatalysis rapidly emerged, becoming a key area in modern organic synthetic chemistry.[1] Among the most powerful organocatalysts proline and its derivatives were identified already in the early 1970s, however the real breakthrough followed around the millennium break.[2] Since then organocatalysis, and enamine catalysis in particular, underwent an impressive progression, mainly focusing on the development of new organocatalytic reactions, more active catalysts and new accessible products.[3]

Within the reactions known to be catalyzed under metal-free conditions, the Mannich reaction plays a key role, giving easy access to nitrogen containing compounds. After the very first organocatalytic Mannich reaction of imines and ketones was reported in the year 2000,[4] various catalytic systems have been developed, giving rise to different Mannich products.[5] However the focus has mainly been set on imines with exocyclic reactive C,N-double bonds. Organocatalytic reports utilizing cyclic imines are to the best of our knowledge only scarce.[6]

Within the species of cyclic imines, the readily available chalkogenazines (Scheme 1) play an important role.[7] These subunits occur in an array of different biologically active compounds and are ideally suited for further chemical manipulations.[8] Since these structures bear an internal C,N-double bond, they are likewise potential electrophiles for organocatalytic Mannich additions.



Scheme 1. Thiazines and oxazines.

Furthermore the development of heterogeneous catalysts for organic syntheses is an important task.[9] The easy immobilization of organocatalytically active molecules into heterogeneous systems can provide various possibilities for the connection and comparison of homogeneous and heterogeneous catalysis.[10] Due to the high versatility of proline as a rather general organocatalyst, even applications in synthesis machines can be imagined.[11]

This work is supposed to deal with both, the homo- and heterogeneously catalyzed Mannich addition of ketones to chalkogenazines.

2. Results and discussion

The class of chalkogenazines was chosen as a new motif of preformed imine substrates for the indirect Mannich addition with carbonyl compounds like ketones. This so far unknown transformation initially was carried out with 2,2-dimethyl-2*H*-benzo[1,4]thiazine **1** as acceptor in acetone as solvent and donor with

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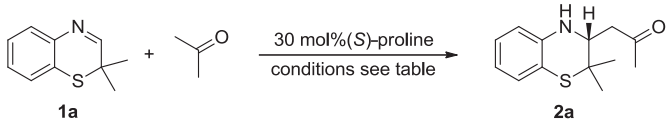
30 mol % of (*S*)-proline as the catalyst. The desired product **2a** was obtained in 61% yield with an excellent er of 99:1. With this first result in hand a solvent screening using different polar solvent systems was carried out (see Table 1).

Table 1
Screening of the reaction conditions for the Mannich reaction of the benzothiazine **1** and acetone

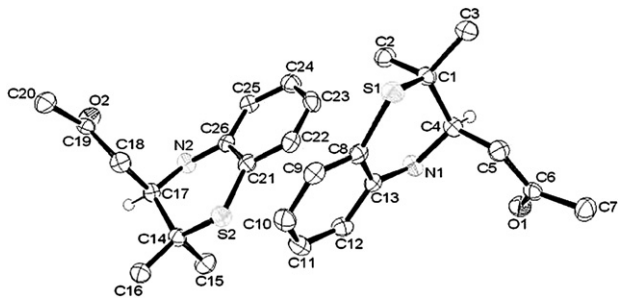


1a **2a**

Entry	Solvent	Time	Temperature [°C]	Yield[a] (%)	er[b]
1	Acetone	1 day	20	61	98.5:1.5
2	DMF	1 day	20	56	99:1
3	Acetonitrile	1 day	20	80	99:1
4	DMSO	7 days	20	83	99:1
5	DMSO/water	1 day	20	85	99:1
6	DMSO/water	7 days	20	99	99:1
7	DMSO/water	24 h	0	40	>99.5:0.5
8	DMSO/water	24 h	40	98	99:1
9	DMSO/water	24 h	60	89	98.5:1.5

[a] Isolated yield.
[b] er was determined by chiral HPLC with Daicel Chiralpak AS.

The solvent system tested for the Mannich reaction of a cyclic dihydro-β-carboline by Ohsawa et al., DMSO with water as co-solvent, furnished remarkable results for the present reaction of benzothiazine **1** with acetone as well.[12] The corresponding aminoketone **2a** was obtained in 85% yield and an excellent er of 99:1 after 1 day at room temperature (Table 1, entry 5). Among the solvents investigated, namely acetone, DMSO, DMF and MeCN the results in DMSO were superior. The yield of the reaction was increased by longer reaction time, after 7 days almost quantitative amounts of product were isolated (Table 1, entry 6). However, the enantioselectivity was not significantly solvent-dependent. The following investigation of the temperature-dependance was carried out in DMSO/water. In the tested temperature range between 0 °C and 60 °C (Table 1, entries 7–9) the reactivity was influenced considerably, whereas the er only dropped slightly. This underlined the generally high enantioselective character of Mannich transformations, in particular involving thiazine **1** as an electrophile. The product **2a** was demonstrated being (*R*)-configured using X-ray analysis of a single crystal (see Scheme 2).[13]

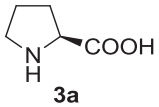
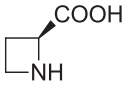
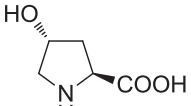
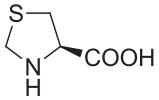
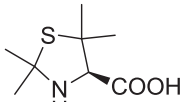
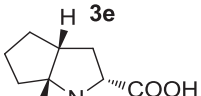


Scheme 2. X-ray structure of product **2a**.

After having these initial promising results, the influence of different amino acid based catalysts was investigated (see Table 2). In this study unbranched, small, cyclic amino acids proved to be very effective.

Proline **3a** and its four-membered analogue, the naturally available non-proteinogenic (*S*)-azetidine-2-carboxylic acid **3b** provided the product in high yields and excellent enantioselectivities.[14] Changes on the pyrrolidine framework influenced the catalytic performance considerably. Whereas hydroxyproline **3c** only showed

Table 2
Reaction of compound **1a** with acetone using different catalysts (50 mol %)

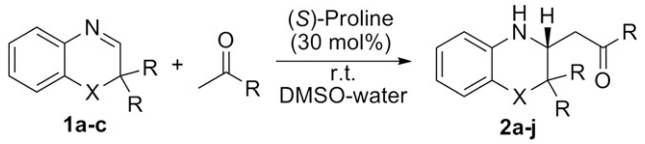
Entry	Catalyst	Yield[a] (%)	er[b]
1	 **3a**	85	99:1
2	 **3b**	92	98.5:1.5
3	 **3c**	55	99:1
4	 **3d**	32	97.5:2.5
5	 **3e**	—	—
6	 **3f**	9	63.5:36.5[c]

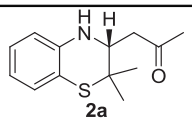
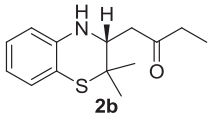
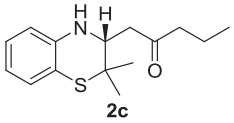
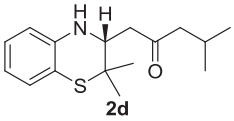
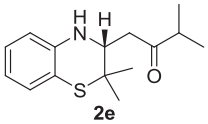
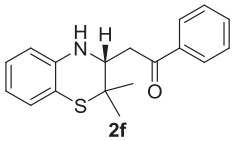
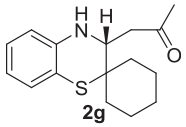
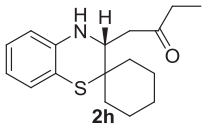
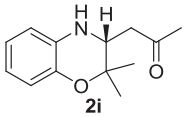
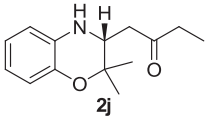
[a] Isolated yields.
[b] er was determined by chiral HPLC with Daicel Chiralpak AS.
[c] Opposite enantiomer detected.

decreased reactivity, further introduction of complexity had dramatic influence. Utilization of thiaproline **3d**, first reported as ligand in copper-catalyzed allylic oxidations and an efficient organocatalyst for domino reactions, exhibited further decreased reactivity.[15] The appearance of double *gem*-substitution, like in catalyst **3e**, gave no activity at all. Bicyclic catalyst **3f**, a building block in the synthesis of the angiotensin-converting enzyme-(ACE)-inhibitor Ramipril, proved to be active, but showed only slight enantioselectivity, however leading to the other enantiomer, presumably due to its inverted configuration on the carboxylic acid moiety.[16] From this catalyst screening, proline was suggested as the catalyst of choice for further investigation of the reported transformation.

The scope of the reaction was investigated involving differently bulky 2-ketones and other acceptors (Table 3). The reactions took place exclusively at the methyl group of the 2-ketones (products **2a**–**f**), presumably because the corresponding methyl–enamine intermediate formed between ketone and catalyst is more reactive and susceptible. The other isomer was not isolated in any case. Remarkably reactions involving cyclohexanone as donor could not be accomplished. This suggests, that the *gem*-substitution in the thiazine-moiety exhibits a high steric demand, prohibiting reactions with enamine-intermediates exceeding the size of a methyl group. Furthermore it was observed, that the increase of size on the second substituent on the ketone led to dramatically decreased yields. The change of *gem*-dimethyl substitution on the thiazine to the corresponding spiro-substituent was tolerated (products **2g**,**h**), but led to diminished reactivity, strengthening the aforementioned observation. Oxazine derivatives reacted as well, following the

Table 3
Reaction scope incorporating different ketones and chalkogenazines

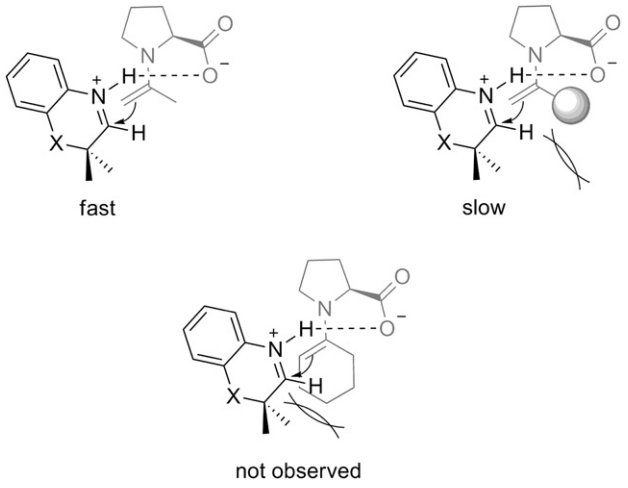


Entry	Product	Yield[a]	er[b]
1	 2a	99	99:1
2	 2b	52	99:1
3	 2c	32	98.5:1.5
4	 2d	16	98:2
5	 2e	5	—[c]
6	 2f	10	—[c]
7	 2g	61	99.5:0.5
8	 2h	43	97.5:2.5
9	 2i	69	99.5:0.5
10	 2j	16	99.5:0.5

[a] Isolated yield after 7 days.
[b] er was determined by chiral HPLC with Daicel Chiralpak AS.
[c] Determination of er not possible.

trends regarding the size of the ketone substrates, however with decreased activity (products **2i,j**).

The observation, that the corresponding products showed excellent enantiomeric purities in all cases indicates, that the bicyclic *gem*-substituted chalkogenazines are sterically demanding reactants. Since proline-catalyzed Mannich reactions usually follow an enamine intermediate, a highly congested transition state with strongly convergent interactions of the *gem*-substituents and the active enamine-intermediate seems likely. Especially the low reactivity of 2-ketones with bigger substituents support this observation (see Scheme 3).

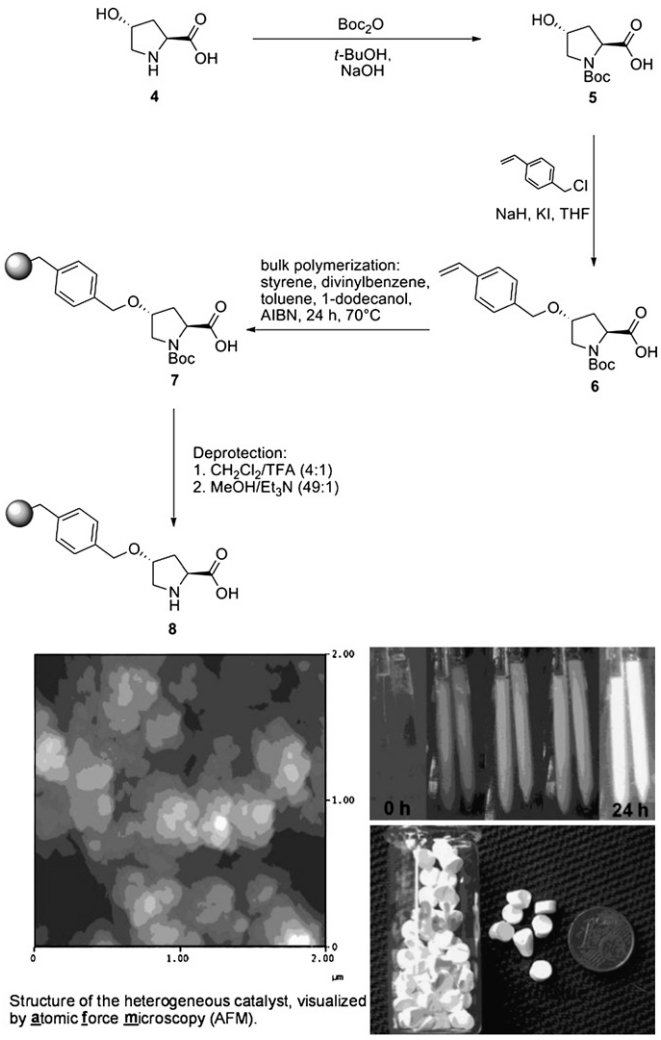


Scheme 3. Steric congestion between the enamine intermediate and the substrate.

The positive results from this homogeneous organocatalytic transformation led to the decision to use it as a model reaction for investigations on heterogeneous organocatalysis. The field of heterogeneous catalysis is in terms of ecology and sustainability extremely important. Heterogeneous catalysts have a high potential of reusability and can therefore support 'Green Chemistry'.[17] Within heterogeneous catalysis the metal-free catalysis plays a relatively new role, wherein most developments were conducted in recent years.[18] The transfer of the described homogeneous method was envisaged by immobilization of (*S*)-proline in a heterogenous, macroporous carrier phase.[19]

As polymeric host system polystyrene was selected, involving crosslinking units and porogenic agents to obtain macroporous polymeric templates (see Scheme 4). Therefore the catalytically active molecule, in this case a (*S*)-proline-scaffold had to be inserted in this heterogeneous system. For that purpose, the natural product (2*S*,4*R*)-4-hydroxyproline showed the most convenient structure, as the hydroxyl function is an easily modifyable group, as already shown previously. In order to insert the chosen (2*S*,4*R*)-4-hydroxyproline **4** in a polymer, the Boc-protected monomer, bearing a polymerizable styrene-sidechain, was synthesized in two steps via protection with Boc_2O, leading to **5**, followed by a classical Williamson etherification with 4-vinyl-benzylchloride, furnishing compound **6**.

For the heterogenisation purpose the bulk polymerisation method was chosen.[20] In this technique the monomer is dissolved in the main monomer styrene and a specific amount of divinylbenzene as crosslinking agent. A macrostructure can be disposed by the addition of porogenic solvents, in this case toluene and 1-dodecanol, which cause the formation of a three-dimensional structure and provide channels inside of the polymer. These macroporous channel structures are a necessary condition for a successful performance in the polymer, they can be visualized with microspcopic techniques (see Scheme 4). They ideally have to enable an unhindered transport of educts and products through the heterogeneous catalyst. To give a form to the polymeric mixture, a shape, in the current work easily prepared pipet-moulds, were used. The start of the polymerisation process using bulk polymerisation is initiated by the addition of a small and defined amount of a radical starter, here AIBN (see

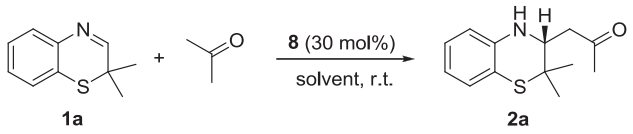


Scheme 4. Preparation of the catalytically active polymer and visualization.

polymerisation monitoring Scheme 4). The deprotection of the Boc-group on the proline-moiety was conducted inside of the polymerized macromolecular catalyst template **7**, involving trifluoroacetic acid in dichloromethane and successive treatment with triethylamine in methanol, liberating heterogeneous catalyst **8**. The cleaning of the monolithic column formed solids from porogenic solvents and deprotective agents was performed by Soxhlet-extraction with THF. Cutting the monoliths into discs resulted in bench-stable templates as catalytic additives for the Mannich reaction (see picture in Scheme 4). The analytic of the obtained polymer was conducted via IR-spectroscopy and qualitative elemental analysis (see Experimental section).

The most important property was the reactivity in the two component Mannich reaction between chalkogenazines and ketones. Therefore a specific amount of the polymer was added to an otherwise identically prepared reaction mixture. The reaction conditions were chosen with water as a main part of the sole solvent. Circumventing column chromatography was a major goal in the heterogeneous catalysis part of this work, mainly to reach a high level of 'Green Chemistry' and applicability in a sense of mixing, filtering and evaporating.[21] Indeed the reaction was catalyzed successfully in different organic solvents after 66–96 h (see Table 4). The organic solvents were in all cases mixed with an equal amount of water. The best results were achieved in acetone and water. In the cases of organic solvents which provided superior results for the homogeneously catalyzed reaction, such as DMSO and DMF, the mix, filter and evaporate strategy failed. The products were, however with similarly high enantioselectivities, impure. For the products obtained from the solvents acetone/water, MeCN/water and neat acetone no further purification steps were necessary.

Table 4
Mannich-reaction catalysed with **8** in different solvents

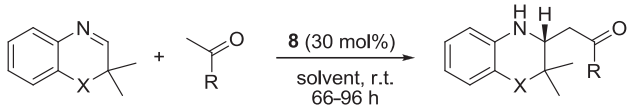


Entry	Solvent	Time (h)	Yield (%)	er[a]
1	Acetone	96	86	93:7
2	DMSO	96	91[b]	90:10
3	DMF	96	62[b]	88.5:11.5
4	MeCN	96	47	93:7
5	Acetone[c]	66	83	85:15

[a] Detected by chiral HPLC (Chiralpak AS column).
[b] Yield uncorrected (impurity shown by ^{1}H NMR and HPLC).
[c] Used as neat solvent without addition of water.

To proof the reusability of the heterogeneous catalyst, another important goal in terms of 'Green chemistry', the identical polymer was used in 10 successive reaction cycles. After 10 cycles **2a** was still obtained with an er of 85:15. However, to allow a higher level of comparison with the homogeneously catalyzed reaction system, the catalyst **8** was tested with varying substrates as well (see Table 5). However the tendencies in reactivity of the keto-components proved to be similar, and could be therefore considered as support for the mechanistic discussion.

Table 5
Mannich-reaction catalysed with **8** using different donors and acceptors



Entry	Product	Yield[a] (%)	er[b]
1	**2a**	86	93:7
2	**2c**	93	90:10
3	**2d**	95	81.5:18.5
4	**2f**	20	–[c]
5	**2i**	62	91:9

[a] Isolated yields.
[b] er was determined by chiral HPLC with Daicel Chiralpak AS.
[c] Determination of er not possible.

Obviously the yields for conversions of ketones with chalkogenazines are equal or even higher than those obtained from homogeneously catalyzed reactions. This may be due to the easy reaction handling and the loss-less workup. However the enantiomeric excesses are in all cases lower. The reasoning for this phenomenon can be found in the fact, that in the polymer the catalysts lie in gaps in the connecting channels. This topological property may prohibit the reaction to occur from the preferred sites at some of the catalytically active sites.

However, the results achieved by the polymerically supported proline in the three component Mannich reaction were auspicious. The high versatility of this catalyst is underlined by the easy way of preparing this reactive catalyst template, as well as by the straightforward application during the catalysis.

3. Conclusion

In summary the first example of an organocatalytic synthesis of 3-ketosubstituted chalkogenazines, potential building blocks for

biologically active compounds was achieved. The organocatalysts involved, proline and analogues, delivered the corresponding products in good yields and enantiomeric ratios.

A transfer of the reaction strategy from homogeneously catalyzed Mannich reactions to heterogeneous polystyrene-supported catalysis was accomplished. The results of the homogeneously catalyzed reaction were supported. The interesting facilities of polymer-supported catalysts using polystyrene templates were shown. The macroporous properties of the polymeric templates could be visualized via atomic force microscopy. Further investigations on the reported Mannich reaction and additional applications of the heterogeneous catalysts are future tasks.

4. Experimental section

4.1. General information

Synthetic procedures, performed under argon atmosphere were performed on a vacuum line using standard Schlenck techniques. All reagents and solvents were commercial grade and were purified prior to use when necessary. Preparative column chromatography was carried out using Grace SiO_2 (0.035–0.070 mm, type KG 60). TLC was performed on Merck SiO_2 F_{254} plates on aluminium sheets. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance DRX 500 and Avance DPX 300 spectrometers. Assignments of the signals in the ^{13}C NMR spectrum were supported by measurements applying DEPT and COSY techniques. EIMS, CIMS and HRMS spectra were obtained with a Finnigan MAT 95 spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a 'GoldenGate' diamond-ATR unit. The enantiomeric excess was determined by chiral HPLC (column: Chiralpak AS). Microscopy experiments were obtained with a Nanoscope IIIA Controller with Dimension 3100, BioScope and Enviroscope by Veeco.

4.2. Syntheses of chalkogenazines

The preparations and analytic properties for the 2,2-dimethyl-2*H*-1,4-benzothiazine (starting material for **2a**–**f**) and the 2,2-dimethyl-2*H*-1,4-benzoxazine (starting material for **2i**,**j**) were described in the literature by our lab before.[7]

*4.2.1. Spiro[benzo[b][1,4]thiazine-2,1′-cyclohexane] (starting material for **2g**,**h**).* To a suspension of NaH (60% in oil, 50 mmol, 2.0 g) in dry THF (20 mL) was added aminothiophenol (48 mmol, 6.00 g) dissolved in 20 mL dry THF at 0 °C under vigorous stirring. To maintain the mixture miscible, 50 mL dry THF were added additionally and the resulting reaction mixture was stirred for 2 h at room temperature. After this time 1-bromocyclohexanecarbaldehyde (50.5 mmol, 9.65 g) dissolved in 15 mL dry THF were added dropwise to the foamy reaction mixture and stirred overnight at room temperature. Subsequently 4 Å-molecular sieves were added to the reaction mixture and stirring is continued for another 2 h. The mixture was filtered through a pad of Celite and the solvent removed in vacuo. Column chromatography (solvent: MTBE/hexanes 1:1 with an R_f=0.63) afforded the product as an off-white solid (6.20 g, 29.00 mmol, 57%), mp 100–102 °C. IR: ν=2939, 2924, 2854, 1616, 1446, 1073, 769 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.50–1.80 [m, 10H, $5CH_2$], 7.11 [dd, 1H, CH_{Ar} ^3J=7.9, 7.9 Hz], 7.18 [dd, 1H, CH_{Ar} ^3J=7.9, 7.9 Hz], 7.24 [d, 1H, CH_{Ar}, ^3J=7.9 Hz], 7.39 [d, 1H, CH_{Ar}, ^3J=7.9 Hz], 7.58 [s, 1H, N=CH] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=21.0, 25.5, 33.1, 42.1, 122.9, 126.2, 127.2, 127.6, 127.7, 141.7, 160.7 ppm. MS (CI, *iso*-butane): *m*/*z*(%)=218.0 (100) $[MH]^+$. HRMS (CI, *iso*-butane): calcd for $[C_{13}H_{16}NS]^+$: 218.1004; found 218.1004.

4.3. General procedure homogenous phase (GP A)

To a solution of corresponding chalkogenazine in a mixture of DMSO and water were given 20 mol % (*S*)-proline and the described ketone and stirred for 7 days at room temperature. The reaction mixture was quenched with methylene chloride. The organic phase was washed with a saturated sodium hydrogencarbonate solution and water. The solution was dried over magnesium sulfate. The solvent was removed in vacuum. The crude product was purified by flash-column chromatography (methylene chloride). The enantiomeric excess was determined by chiral HPLC.

4.4. General procedure heterogenous phase

The corresponding chalkogenazine **1** was dissolved in the particular solvent. Then the amount of heterogeneous catalyst **9**, which by calculation contained 30 mol % of the catalyst in respect to the thiazine was added. Subsequently the mixture was stirred for the given reaction time. The reaction workup could be performed either following the GP A procedure or by simple filtration and evaporation in high vacuum. In both ways, the product was obtained in equally high purities. The obtained yields can be found in Table 3.

*4.4.1. (R)-1-(2,2-Dimethyl-3,4-dihydro-2H-benzo[1,4]thiazine-3-yl)-propan-2-one (**2a**).* Following GP A the corresponding benzothiazine (0.226 mmol, 40 mg), DMSO (3.2 mL), water (0.3 mL), (*S*)-proline (0.068 mmol, 7.8 mg) and acetone (0.8 mL) were used. The product was isolated as nearly colourless crystals, mp 57 °C. TLC: R_f=0.73 (solvent: methylene chloride). The enantiomeric excess was determined by chiral HPLC [column: Chiralpak AS, solvent: EtOH/*n*-hexane (1:9), flow: 1.0 mL min^{-1}; t_R=5.0 min (major enantiomer), t_R=13.1 min (minor enantiomer)]. IR: ν=3409, 3049, 2991, 2897, 1708, 1587, 1485, 743 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=6.95 (d, $^3J_{H,H}$=7.8 Hz, 1H, H_{Ar}), 6.89 (dd, $^3J_{H,H}$=7.6, 7.6 Hz, 1H, H_{Ar}), 6.62 (dd, $^3J_{H,H}$=7.5, 7.5 Hz, 1H, H_{Ar}), 6.48 (d, $^3J_{H,H}$=8.0 Hz, 1H, H_{Ar}), 4.68 (br s, 1H, NH), 3.61 (m, $^3J_{H,H}$=9.3 Hz, 1H, NCH), 2.78 (dd, $^2J_{H,H}$=17.9 Hz, $^3J_{H,H}$=2.9 Hz, 1H, CH_2), 2.72 (dd, $^2J_{H,H}$=17.9 Hz, $^3J_{H,H}$=9.3 Hz, 1H, CH_2), 2.14 (s, 1H, $COCH_3$), 1.41 (s, 1H, CH_3), 1.30 (s, 1H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=208.5, 139.0, 127.5, 125.5, 117.8, 115.3, 115.0, 54.9, 46.2, 41.9, 30.8, 29.7, 25.8 ppm. MS (CI, *iso*-butane): *m*/*z*(%)=236.1 (100) $[MH]^+$. HRMS (CI, *iso*-butane): calcd for $[C_{13}H_{18}NOS]^+$ 236.1109; found 236.1109.

*4.4.2. (R)-1-(2,2-Dimethyl-3,4-dihydro-2H-benzo[1,4]thiazine-3-yl) butan-2-one (**2b**).* Following GP A the corresponding benzothiazine (0.564 mmol, 100 mg), DMSO (6 mL), water (0.5 mL), (*S*)-proline (0.169 mmol, 20.0 mg) and butan-2-one (1.22 g) were used. The product was isolated as colourless oil (77 mg, 0.293 mmol, 52%). TLC: R_f=0.76 (solvent: methylene chloride). The enantiomeric excess was determined by chiral HPLC [column: Chiralpak AS, solvent: EtOH/*n*-hexane (1:9), flow: 1.0 mL min^{-1}; t_R=4.2 min (major enantiomer), t_R=6.9 min (minor enantiomer)] ee: 98%. IR: ν=3399, 2974, 2934, 1705, 1590, 1481, 742 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=6.95 (dd, $^3J_{H,H}$=7.5 Hz, $^4J_{H,H}$=1.1 Hz, 1H, *o*-$CH_{Ar}S$), 6.89 (ddd, $^3J_{H,H}$=7.5 Hz, $^3J_{H,H}$=7.9 Hz, $^4J_{H,H}$=1.1 Hz, 1H, *p*-$CH_{Ar}S$), 6.62 (dd, $^3J_{H,H}$=7.5, 7.5 Hz, 1H, *p*-$CH_{Ar}N$), 6.49 (d, $^3J_{H,H}$=7.9 Hz, 1H, *o*-$CH_{Ar}N$), 3.64 (dd, $^3J_{H,H}$=9.4 Hz, $^3J_{H,H}$=2.9 Hz, 1H, C*H*CH_2), 2.75 (dd, $^2J_{H,H}$=17.6 Hz, $^3J_{H,H}$=2.9 Hz, 1H, C*H*$_2$CO), 2.69 (dd, $^2J_{H,H}$=17.6 Hz, $^3J_{H,H}$=9.4 Hz, 1H, C*H*$_2$CO), 2.33–2.49 (m, 2H, C*H*$_2$$CH_3$), 1.41 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.04 (dd, $^3J_{H,H}$=7.3, 7.3 Hz, 3H, CH_2C*H*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=211.25, 138.88, 127.47, 125.47, 117.88, 115.42, 115.25, 55.06, 44.84, 41.99, 36.76, 29.63, 25.75, 7.63 ppm. MS (CI, *iso*-butane): *m*/*z*(%)=250.1

(100) $[MH]^+$. HRMS (EI): calcd for $[C_{14}H_{19}NOS]$ 249.1187; found 249.1187.

*4.4.3. (R)-1-(2,2-Dimethyl-3,4-dihydro-2H-benzo[1,4]thiazine-3-yl) pentan-2-one (**2c**).* Following GP A the corresponding benzothiazine (0.282 mmol, 50 mg), DMSO (3.2 mL), water (0.3 mL), (*S*)-proline (0.056 mmol, 6.5 mg) and pentan-2-one (0.8 mL) were used. The product was isolated as colourless oil (23.4 mg, 0.089 mmol, 32%). TLC: R_f=0.80 (solvent: methylene chloride). The enantiomeric excess was determined by chiral HPLC [column: Chiralpak AS, solvent: *iso*-propanol/*n*-hexane (3:97), flow: 1.0 mL min^{-1}; t_R=5.9 min (major enantiomer), t_R=13.6 min (minor enantiomer)] ee 98%. IR: ν=3400, 2962, 2931, 1705, 1592, 1483, 1306, 744, 631 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=6.94 (d, $^3J_{H,H}$=7.6 Hz, 1H, *o*-$CH_{Ar}S$), 6.89 (dd, $^3J_{H,H}$=7.5 Hz, $^3J_{H,H}$=7.8 Hz, 1H, *p*-$CH_{Ar}S$), 6.61 (dd, $^3J_{H,H}$=7.5 Hz, $^3J_{H,H}$=7.6 Hz, 1H, *p*-$CH_{Ar}N$), 6.47 (d, $^3J_{H,H}$=7.8 Hz, $^3J_{H,H}$=7.8 Hz, 1H, *o*-$CH_{Ar}N$), 3.62 (dd, $^3J_{H,H}$=9.3 Hz, $^3J_{H,H}$=3.1 Hz, 1H, NCH), 2.74 (dd, $^2J_{H,H}$=17.6 Hz, $^3J_{H,H}$=3.1 Hz, 1H, NCHCH_2CO), 2.68 (dd, $^2J_{H,H}$=17.6 Hz, $^3J_{H,H}$=9.3 Hz, 1H, NCHCH_2CO), 2.29–2.44 (m, 2H, C$H_2$$CH_2CH_3$), 1.63–1.52 (m, 2H, C$H_2CH_3$), 1.41 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 0.89 (dd, $^3J_{H,H}$=7.4, 7.4 Hz, 3H, CH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=210.93, 139.03, 127.45, 125.46, 117.77, 115.30, 115.13, 55.01, 45.56, 45.25, 41.99, 29.65, 25.76, 17.15, 13.62 ppm. MS (CI, *iso*-butane): *m*/*z*(%)=264.2 (100) $[MH]^+$. HRMS (CI, *iso*-butane): calcd for $[C_{15}H_{22}NOS]^+$ 264.1422; found 264.1422.

*4.4.4. (R)-1-(2,2-Dimethyl-3,4-dihydro-2H-benzo[1,4]thiazine-3-yl)-4-methylpentan-2-one (**2d**).* Following GP A the corresponding benzothiazine (0.282 mmol, 50 mg), DMSO (3.2 mL), water (0.3 mL), (*S*)-proline (0.056 mmol, 6.5 mg) and 4-methylpentan-2-one (0.8 mL) were used. The product was isolated as colourless oil (12.4 mg, 0.045 mmol, 16%). TLC: R_f=0.82 (solvent: methylene chloride). The enantiomeric excess was determined by chiral HPLC [column: Chiralpak AS, solvent: *iso*-propanol/*n*-hexane (1:99), flow: 1.0 mL min^{-1}; t_R=5.6 min (major enantiomer), t_R=10.2 min (minor enantiomer)] ee: 96%. IR: ν=3400, 2958, 2870, 1704, 1591, 1482, 1366, 1305, 743, 630 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=6.94 (dd, $^3J_{H,H}$=7.7 Hz, $^4J_{H,H}$=1.3 Hz, 1H, *o*-$CH_{Ar}S$), 6.89 (ddd, $^3J_{H,H}$=7.7, 7.9 Hz, $^4J_{H,H}$=1.3 Hz, 1H, *p*-$CH_{Ar}S$), 6.61 (ddd, $^3J_{H,H}$=7.7, 7.7 Hz, $^4J_{H,H}$=1.2 Hz, 1H, *p*-$CH_{Ar}N$), 6.47 (dd, $^3J_{H,H}$=7.9 Hz, $^4J_{H,H}$=1.2 Hz, 1H, *o*-$CH_{Ar}N$), 3.62 (dd, $^3J_{H,H}$=8.6, 3.7 Hz, 1H, CH), 2.72 (dd, $^2J_{H,H}$=17.1 Hz, $^3J_{H,H}$=3.7 Hz, 1H, CHCH_2CO), 2.67 (dd, $^2J_{H,H}$=17.1 Hz, $^3J_{H,H}$=8.6 Hz, 1H, CHCH_2CO), 2.25 (dd, $^2J_{H,H}$=16.3 Hz, $^3J_{H,H}$=7.2 Hz, 1H, C$H_2$$CH(CH_3)_2$), 2.25 (dd, $^2J_{H,H}$=16.3 Hz, $^3J_{H,H}$=6.9 Hz, 1H,CH_2CH$(CH_3)_2$), 2.15–2.04 (m, 1H, C$H(CH_3)_2$), 1.41 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 0.89–0.87 (m, 6H, CH(C$H_3)_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=210.72, 138.98, 127.45, 125.48, 117.83, 115.35, 115.19, 54.97, 52.64, 45.74, 42.01, 29.69, 25.78, 24.61, 22.52, 22.45 ppm. MS (CI, *iso*-butane): *m*/*z*(%)=278.3 (100) $[MH]^+$. HRMS (CI, *iso*-butane): calcd for $[C_{16}H_{24}NOS]^+$ 278.1579; found 278.1579.

*4.4.5. (R)-1-(2,2-Dimethyl-3,4-dihydro-2H-benzo[1,4]thiazine-3-yl)-3-methylbutan-2-one (**2e**).* Following GP A the corresponding benzothiazine (0.282 mmol, 50 mg), DMSO (3.2 mL), water (0.3 mL), (*S*)-proline (0.056 mmol, 6.5 mg) and 3-methylbutan-2-one (0.8 mL) were used. The product was isolated as colourless oil (3.7 mg, 0.014 mmol, 5%). TLC: R_f=0.78 (solvent: methylene chloride). The enantiomeric excess could not be determined. IR: ν=3401, 2964, 2924, 1706, 1592, 1483, 1366, 743, 631 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ=6.94 (dd, $^3J_{H,H}$=7.6 Hz, $^4J_{H,H}$=1.3 Hz, 1H, *o*-$CH_{Ar}S$), 6.88 (ddd, $^3J_{H,H}$=7.5, 7.9 Hz, $^4J_{H,H}$=1.3 Hz, 1H, *p*-$CH_{Ar}S$), 6.61 (ddd, $^3J_{H,H}$=7.5, 7.6 Hz, $^4J_{H,H}$=0.9 Hz, 1H, *p*-$CH_{Ar}N$), 6.46 (dd, $^3J_{H,H}$=7.9 Hz, $^4J_{H,H}$=0.9 Hz, 1H, *o*-$CH_{Ar}N$), 3.61 (dd, $^3J_{H,H}$=7.4, 4.2 Hz, 1H, CH), 2.77 (dd, $^2J_{H,H}$=17.0 Hz, $^3J_{H,H}$=4.2 Hz, 1H, CHCH_2), 2.73 (dd, $^2J_{H,H}$=17.0 Hz, $^3J_{H,H}$=7.4 Hz, 1H, CHCH_2), 2.60–2.51 (m, 1H, CH $(CH_3)_2$), 1.42 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.07 (d, $^3J_{H,H}$=7.0 Hz, 3H, CH(C$H_3)_2$), 1.02 (d, $^3J_{H,H}$=7.0 Hz, 3H, CH(C$H_3)_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ=214.73, 139.00, 127.43, 125.45, 117.78, 115.32, 115.16, 55.05, 43.03, 42.18, 41.61, 29.80, 29.68, 25.83, 18.07 ppm. MS (CI, *iso*-butane): *m*/*z*(%)=264.1 (40) $[MH]^+$. HRMS (EI): calcd for $[C_{15}H_{22}NOS]$ 264.1421; found 264.1421.

*4.4.6. (R)-2-(2,2-Dimethyl-3,4-dihydro-2H-benzo[1,4]thiazine-3-yl)-1-phenyl-ethanone (**2f**).* Following GP A the corresponding benzothiazine (0.282 mmol, 50 mg), DMSO (3.2 mL), water (0.3 mL), (*S*)-proline (0.056 mmol, 6.5 mg) and acetophenone (0.8 mL) were used. The excess of acetophenone was removed by distillation before performing the purification by chromatography. The product was isolated as colourless oil (8.4 mg, 0.028 mmol, 10%). TLC: R_f=0.81 (solvent: methylene chloride). The enantiomeric excess could not be determined. IR: ν=3402, 2962, 2918, 1678, 1593, 1483, 1306, 744, 632 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=7.92–7.89 (m, 1H, *p*-CH_{Ph}), 7.60–7.40 (m, 4H, *o*+*m*-CH_{Ph}), 6.96 (dd, $^3J_{H,H}$=7.8 Hz, $^4J_{H,H}$=1.3 Hz, 1H, *o*-$CH_{Ar}S$), 6.86 (ddd, $^3J_{H,H}$=8.1, 7.7 Hz, $^4J_{H,H}$=1.3 Hz, 1H, *p*-CHS), 6.60 (ddd, $^3J_{H,H}$=7.7, 7.8 Hz, $^4J_{H,H}$=1.1 Hz, 1H, *p*-CN), 6.45 (dd, $^3J_{H,H}$=8.1, 1.0 Hz, 1H, *o*-C N), 4.78 (br s, 1H, NH), 3.82 (dd, $^3J_{H,H}$=3.7, 8.3 Hz, 1H, CH), 3.32–3.23 (m, 2H, CH_2), 1.48 (s, 3H, CH_3), 1.38 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=199.61, 139.05, 136.78, 133.43, 128.62, 128.08, 127.52, 125.51, 117.70, 115.36, 114.93, 55.29, 42.26, 41.59, 29.92, 26.02 ppm. MS (CI, *iso*-butane): *m*/*z*(%)=298.3 (100) $[MH]^+$. HRMS (CI, *iso*-butane): calcd for $[C_{18}H_{20}NOS]^+$ 298.1264; found 298.1264.

*4.4.7. (R)-1-(3,4-Dihydrospiro[benzo[b][1,4]thiazine-2,1′-cyclohexan]-3-yl)propan-2-one (**2g**).* Following GP A the corresponding spiro-thiazine (0.37 mmol, 80 mg), DMSO (3.0 mL), water (0.3 mL), (*S*)-proline (0.11 mmol, 13.0 mg) and acetone (0.9 mL) were used. The reaction was performed for 3 days at 0 °C before purification by column chromatography. The product was isolated as colourless oil (61.6 mg, 0.22 mmol, 61%). TLC: R_f=0.73 (solvent: methylene chloride). The enantiomeric excess was determined by chiral HPLC [column: Chiralpak AS, solvent: *iso*-propanol/*n*-hexane (10:90), flow: 1.0 mL min^{-1}; t_R=6.0 min (major enantiomer), t_R=10.5 min (minor enantiomer)] ee: 99%. IR: ν=3425, 2961, 2918, 2848, 1702, 1590, 1486, 1306, 756, 629 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.19–1.32, 1.37–1.49, 1.50–1.84, 1.86–1.94 [m, 10H, $5CH_2$], 2.12 [s, 3H, CH_3], 2.75 [dd, 1H, CH_2CO, ^2J=18.2 Hz, ^3J=9.5 Hz], 2.85 [dd, 1H, CH_2CO, ^2J=18.2 Hz, ^3J=9.5 Hz], 3.60–3.65 [m, 1H, NCH], 4.76 [br s, 1H, NH], 6.47 [d, 1H, *o*-$CH_{Ar}N$, ^3J=7.7 Hz], 6.62 [dd, 1H, *p*-$CH_{Ar}N$, ^3J=7.4, 7.4 Hz], 6.89 [dd, 1H, *p*-$CH_{Ar}S$, ^3J=7.4, 7.4 Hz], 6.98 [d, 1H, *o*-$CH_{Ar}S$, ^3J=7.7 Hz] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=21.41, 21.92, 25.70, 30.93, 36.41, 34.83, 45.65, 47.02, 54.16, 114.95, 115.65, 117.83, 125.41, 127.72, 139.01, 208.77 ppm. MS (CI, *iso*-butane): *m*/*z*(%)=276.0 (100) $[MH]^+$.

*4.4.8. (R)-1-(3,4-Dihydrospiro[benzo[b][1,4]thiazine-2,1′-cyclohexan]-3-yl)butan-2-one (**2h**).* Following GP A the corresponding spiro-thiazine (1.38 mmol, 300 mg), DMSO (9.0 mL), water (1.5 mL), (*S*)-proline (0.42 mmol, 47.7 mg) and ethylmethylketone (2.99 g) were used. The reaction was performed for 3 days at room temperature before performing the purification by chromatography. The product was isolated as colourless oil (170.0 mg, 0.587 mmol, 43%). TLC: R_f=0.79 (solvent: methylene chloride). The enantiomeric excess was determined by chiral HPLC [column: Chiralpak AS, solvent: *iso*-propanol/*n*-hexane (10:90), flow: 1.0 mL min^{-1}; t_R=4.8 min (major enantiomer), t_R=6.8 min (minor enantiomer)] ee: 95%. IR: ν=3425, 2928, 2850, 1704, 1588, 1485, 1311, 751, 674 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ=1.02 [dd, 3H, CH_2CH_3, ^3J=7.3, 7.3 Hz], 1.20–1.31, 1.38–1.49, 1.50–1.84, 1.87–1.94 [m, 10H, $5CH_2$], 2.30–2.46 [m, 2H, CH_2CH_3], 2.71 [dd, 1H, CH_2CO, ^2J=17.8 Hz, ^3J=2.5 Hz], 2.85 [dd, 1H, CH_2CO, ^2J=17.8 Hz, ^3J=9.7 Hz], 3.64 [dd, 1H,

NCH, ^3J=2.5, 9.7 Hz], 4.62 [br s, 1H, NH], 6.44 [d, 1H, *o*-$CH_{Ar}N$, ^3J=7.7 Hz], 6.60 [dd, 1H, *p*-$CH_{Ar}N$, ^3J=7.4, 7.7 Hz], 6.88 [ddd, 1H, *p*-$CH_{Ar}S$, ^3J=7.4, 7.7 Hz, ^4J=1.0 Hz], 6.97 [dd, 1H, *o*-$CH_{Ar}S$, ^3J=7.7 Hz, ^4J=1.0 Hz] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=7.64, 21.44, 21.99, 25.77, 34.81, 36.48, 36.87, 44.34, 47.13, 54.25, 114.70, 115.35, 117.61, 125.37, 127.65, 139.23, 211.66 ppm. MS (CI, *iso*-butane): *m*/*z*(%)= 290.1 (100) $[MH]^+$. HRMS (CI, *iso*-butane): calcd for $[C_{18}H_{20}NOS]^+$ 290.1579; found 290.1577.

*4.4.9. (R)-1-(2,2-Dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl) propan-2-one (**2i**).* Following GP A the corresponding oxazine (0.31 mmol, 50.2 mg), DMSO (3.2 mL), water (0.28 mL), (*S*)-proline (0.06 mmol, 7.3 mg) and acetone (0.8 mL) were used. The reaction was conducted at 0 °C for 7 days before performing the purification by chromatography. The product was isolated as colourless oil (46.6 mg, 0.21 mmol, 69%). TLC: R_f=0.80 (solvent: methylene chloride). The enantiomeric excess was determined by chiral HPLC [column: Chiralpak AS, solvent: ethanol/*n*-hexane (10:90), flow: 1.0 mL min^{-1}; t_R=5.3 min (major enantiomer), t_R=15.4 min (minor enantiomer)] ee: 99%. IR: ν=3382, 2979, 2925, 1653, 1479, 1385, 755 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.24 [s, 3H, CH_3], 1.33 [s, 3H, CH_3], 2.17 [s, 3H, $COCH_3$], 2.53 [dd, 1H, CH_2, ^2J=17.8 Hz, ^3J=10.5 Hz], 2.73 [dd, 1H, CH_2, ^2J=17.8 Hz, ^3J=2.2 Hz], 3.50 [dd, 1H, NCH, ^3J=10.5 Hz, ^3J=2.2 Hz], 4.47 [br s, 1H, NH], 6.55–6.58 [m, 1H, *o*-$CH_{Ar}N$], 6.65 [ddd, 1H, *p*-$CH_{Ar}N$, ^3J=7.6, 7.5 Hz, ^4J=1.1 Hz], 6.72–6.77 [m, 2H, *p*-$CH_{Ar}O$, *o*-$CH_{Ar}O$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=22.51, 25.46, 30.65, 44.23, 52.79, 74.45, 115.23, 116.83, 118.74, 120.99, 131.76, 142.23, 208.05 ppm. MS (CI, *iso*-butane): *m*/*z* (%)=220.2 (100) $[MH]^+$. HRMS (CI, *iso*-butane): calcd for $[C_{18}H_{20}NOS]^+$ 220.1338; found 220.1338.

*4.4.10. (R)-1-(2,2-Dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)butan-2-one (**2j**).* Following GP A the corresponding oxazine (0.31 mmol, 50.2 mg), DMSO (3.2 mL), water (0.28 mL), (*S*)-proline (0.06 mmol, 7.3 mg) and acetone (0.8 mL) were used. The reaction was conducted at 0 °C for 7 days before performing the purification by chromatography. The product was isolated as colourless oil (11.4 mg, 0.05 mmol, 16%). TLC: R_f=0.75 (solvent: methylene chloride). The enantiomeric excess was determined by chiral HPLC [column: Chiralpak AS, solvent: ethanol/*n*-hexane (2:98), flow: 1.0 mL min^{-1}; t_R=6.4 min (major enantiomer), t_R=19.0 min (minor enantiomer)] ee: 99%. IR: ν=3383, 2977, 2935, 1710, 1500, 1306, 744 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.07 [dd, 3H, CH_2CH_3, ^3J=7.3, 7.3 Hz], 1.25 [s, 3H, CH_3], 1.34 [s, 3H, CH_3], 2.38–2.54 [m, 3H, CH_2CH_3, CH_2CO], 2.71 [dd, 1H, CH_2CO, ^2J=17.6 Hz, ^3J=2.2 Hz], 3.51 [dd, 1H, CH, ^3J=10.6, 2.2 Hz], 4.51 [br s, 1H, NH], 6.58 [dd, 1H, *o*-$CH_{Ar}N$, ^3J=8.1 Hz, ^4J=1.3 Hz], 6.66 [ddd, 1H, *p*-$CH_{Ar}N$, ^3J=7.7, 7.6 Hz, ^4J=1.3 Hz], 6.73–6.78 [m, 2H, *p*-$CH_{Ar}O$, *o*-$CH_{Ar}O$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=7.62, 22.51, 25.52, 36.68, 42.95, 52.96, 74.58, 115.27, 116.88, 118.79, 121.03, 131.81, 142.30, 210.92 ppm. MS (CI, *iso*-butane): *m*/*z*(%)=234.2 (100) $[MH]^+$. HRMS (CI, *iso*-butane): calcd for $[C_{18}H_{20}NOS]^+$ 234.1494; found 234.1495.

*4.4.11. (2S,4R)-1-(tert-Butoxycarbonyl)-4-(4-vinylbenzyloxy)pyrrolidine-2-carboxylic acid (**7**).* To a solution of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (12.9 mmol, 3.00 g,) in dry THF (90 mL) was added NaH (26.4 mmol, 1.00 g, 60% suspension in oil) in dried THF (20 mL) at 0 °C under argon atmosphere. The mixture was stirred for 1.5 h. Then *p*-vinyl-benzyl-chloride (19.4 mmol, 3.04 mL) was added dropwise via syringe at 0 °C, subsequently a spatula tip potassium iodide was added. The reaction mixture was heated to 50 °C for 66 h. The reaction was quenched with ice water. The resulting yellow liquid was washed twice with hexanes, the aqueous phase was acidified to pH 2 with $KHSO_4$-solution (10%) under ice cooling. The aqueous phase was extracted with ethyl acetate four times, the organic phase was washed with water and brine, dried over $MgSO_4$ and dried in vacuo. The product was obtained as a yellow oil (2.68 g, 7.7 mmol, 60%). The analytical data was in accordance to that reported in the literature.[22]

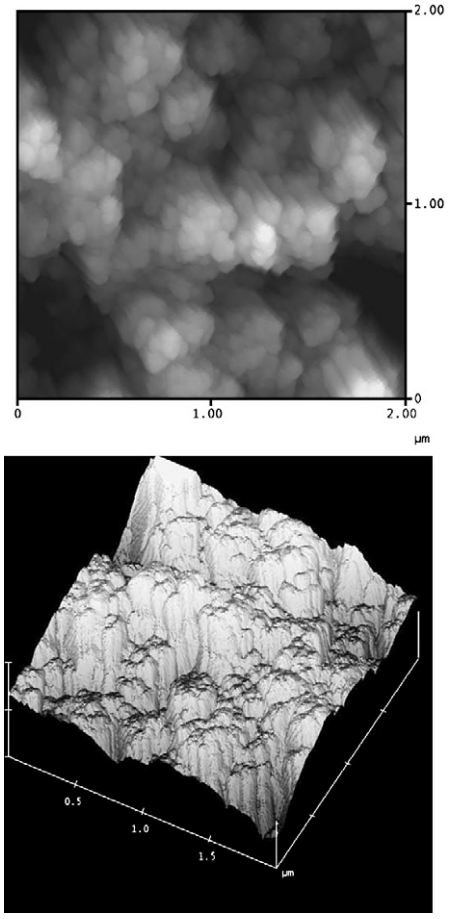


Fig. 1. Atomic force microscopy (AFM) images of a monolithic polymer disc. Both items show the identical region in 2D-picture (left side) and relief modellation (right) on identical scale.

*4.4.12. Polystyrene-supported (S)-proline (**8**).* The polymeric mixture contained 40 mol % of the polymerizable compounds: (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid **7**, styrene, divinylbenzene and 60 mol % of the porogenic agents: toluene and 1-dodecanol, the radical initiator AIBN was added in 1 wt % (related to polymerizable compounds). The 40 mol % polymerizable compounds were composed of: 7.5 mol % of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid, 72.0 mol % of styrene and 20.5 mol % of divinylbenzene (80%, technical grade). The 60 mol % porogenic agents were composed of: 70 mol % 1-dodecanol and 30 mol % toluene. The components were mixed in the following order: 1. monomer; 2. styrene; 3. toluene; 4. divinylbenzene; 5. 1-dodecanol; 6. AIBN. After addition of all components, the mixture was thoroughly homogenized. Afterwards the slightly yellow liquid was filled into column formed moulds, the moulds were capped and placed in an oil bath which was tempered to 70 °C for 24 h. After this time the moulds were broken and the column formed polymer was cut into discs, washed in a Soxhlet-extractor with THF for 3 h and oven-dried at 60 °C. Deprotection step: 0.5 g of the polymer were given into 15 mL of a mixture of CH_2Cl_2/trifluoracetic acid (4:1) and mixed for 2 h in an ice bath. The reaction mixture was stirred for an additional hour while warming to room temperature. After this 25 mL MeOH/NEt_3 (49:1) were added and the mixture was stirred for 2 h.

Subsequently the polymer was washed in a Soxhlet-extractor with THF for 3 h and oven-dried at 60 °C, to afford the polymer templates which were subjected to the reaction conditions. IR (cm^{-1}): Background polymer without catalyst: 3026, 2923, 1602, 1493, 1452, 905, 758; Loaded Polymer: 3026, 2923, *1705*, 1602, 1452, *1180*, 905, 758 (Fig. 1).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.10.079.

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