Chiral Bifunctional Thioureas and Squaramides and their Copolymers as Recoverable Organocatalysts. Stereoselective Synthesis of 2-Substituted-4-amino-3-nitro-Benzopyrans and 3-Functionalyzed-3,4-diamino-4*H*-Chromenes.

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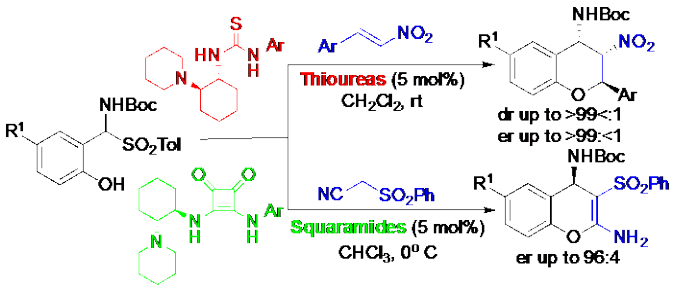


Abstract.

Novel styryl-substituted thioureas and squaramides were obtained in three steps from commercially available 4-hydroxy-3,5-dichloroaniline. These organocatalysts promote cascade reactions in high yields and excellent stereoselection. By using only 5 mol% loading of catalyst it is possible to obtain 2,3,4-trisubtituted benzopyrans by reaction of α-amidosulfones derived from salicyladehydes and nitrostyrenes, or 2,3,4-trisubstituted 4*H*-chromenes by reaction of the same α-amidosulfones with phenylsulfonylacetonitrile in excellent diastereo- and enantioselectivities. Two polymeric thiourea and squaramide were prepared by copolymerization of the best monomeric catalysts with styrene and divinylbenzene and used for the same transformations. These polymers behave also as excellent stereoselective catalysts that can be recovered and reused for five cycles.

Key words: Aminochromenes. Aminobenzopyranes. Supported squaramides. Squaramides. Supported thioureas. Thioureas

INTRODUCTION

The cascade or domino stereoselective organocatalytic reactions are one of the most interesting processes because they allow the construction of cyclic compounds with several stereocenters with atom and steps economy.[1]

4-Aminochromanes is a family of natural and synthetic products with important biological activity, and their synthesis has attracted considerable interest. In general, the organocatalyzed synthesis involves cascade reactions of imines derived from salicylaldehyde and different electrophiles. Aryl prolinol derivatives have been used as catalysts for the synthesis of 4-amino-4*H*-chromenes in a tandem oxa-Michael aza-Baylis-Hillman reaction.[2] 3-Nitro-2*H*-chromenes with a single stereocenter was first prepared by domino oxa-Michael-aza-Henry reaction of *N*-tosylaldimines with nitrostyrene catalyzed by a bifunctional thiourea derived from quinidine.[3] The same starting materials lead to trisubstituted 3,4-diaminochromanes when the reaction was carried out at low temperature by using chiral thioureas derived from *trans* 1,2-cyclohexanediamine.[4] Later, the same authors synthesized 4-aminochromanes with three contiguous stereocenters from α–amido sulfones and nitrostyrene catalyzed by chiral squaramides.[5]

Enantioenriched 4-aminobenzopyrans have been also prepared by sequential Mannich-ketalization reactions promoted by *N*-triflylphosphoramides,[6] and by cycloaddition of salicylaldimines and electron-rich alkenes catalyzed by binol-derived phosphoric acids.[7] 4-Amino-4*H*-chromenes with a single stereocenter are also formed by cycloaddition of salicylaldimines with allenic esters catalyzed by quinine-derived thioureas.[8] 4-Aminobenzopyrans with three contiguous stereocenters have been obtained in a different aza-Michael-Michael approach catalyzed by bifunctional chiral thioureas.[9] All these transformations have been done under homogeneous conditions,

and the recovering of the catalysts is a problem associated with chromatography. Interestingly, no antecedents appear on the use of easily recoverable supported organocatalysts in that type of cascade reactions.

The most popular thioureas[10] and squaramides[11] are mixed compounds derived from chiral diamines and 3,5-bis(trifluoromethyl)aniline. The presence of electron-withdrawing groups in the aniline substituent is important because they are responsible for the increasing the acidity, and consequently the activity of the catalysts.[12]

As an extension of our interest in the synthesis of supported bifunctional squaramides[13] and thioureas in both synthetic[14] and natural[15] polymers we summarize here the bottom-up preparation of monomeric and polymeric novel catalysts and their use and recovering in a cascade oxa-Michael aza-Henry process directed to the synthesis of trisubstituted benzopyrane and 4*H*-chromene derivatives with up to three contiguous stereocenters.

RESULTS AND DISCUSSION

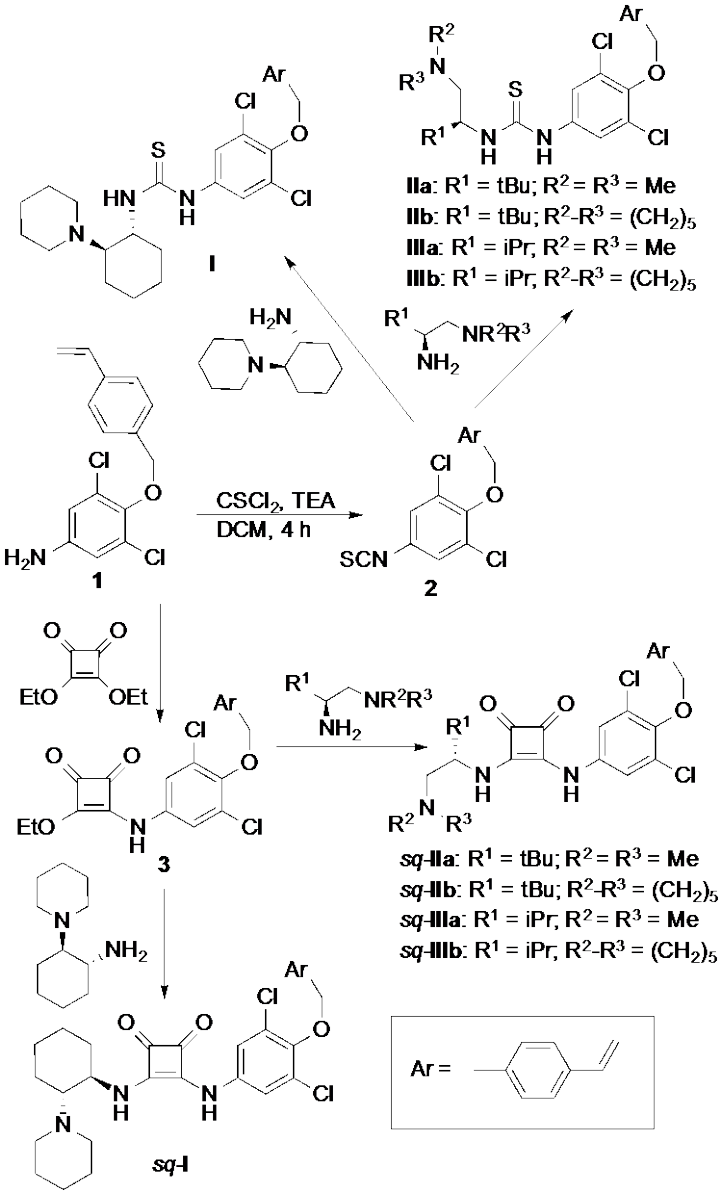
Monomeric thioureas (**I-III**) and squaramides (sq-**I**-sq-**III**) were prepared (Scheme 1), in two steps from **1**, easily obtained by reaction of commercially available 4-amino-2,6-dichlorophenol with 4-vinylbenzyl chloride and t-BuOK in DMF at 0 ^{o}C.[16]

The reaction of **1** with thiophosgene at room temperature in the presence of triethylamine yielded isothiocyanate **2** in near quantitative yield.[17] In a second step, thioureas **I**, **IIa-b**, and **IIIa-b** were obtained by reaction of **2** with the piperidine substituted (1*R*, 2*R*)-cyclohexanediamine,[18] and L-*tert*-Leucine or L-valine derived diamines,[19] respectively.

It is well known that the difference in spacing between the two donor hydrogen atoms of thioureas and squaramides[20] could modify their reactivity. To see these differences we also prepare squaramides sq-**I**, sq-**IIa-b**, and sq-**IIIa-b**, with the same chiral environment than thioureas. Scheme 1 summarizes the two-steps synthesis of squaramides from **1** by reaction with diethyl squarate to semisquaramide **3**. The condensation of **3** with the piperidine substituted (1*R*, 2*R*)-cyclohexane diamine, and

L-*tert*-Leucine or L-valine derived diamines lead to sq-**I**, sq-**IIa-b**, and sq-**IIIa-b**, respectively.

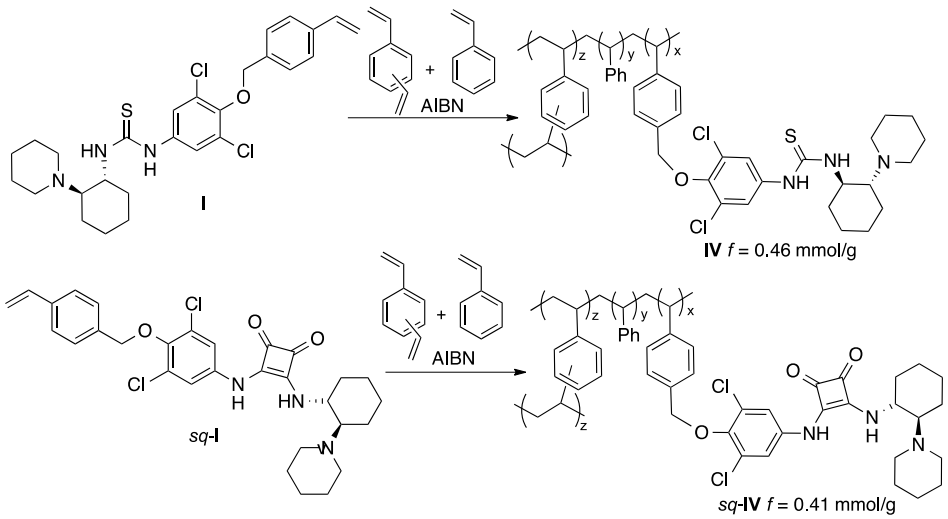
Scheme 1. Synthesis of monomeric thioureas and squaramides.



Because the most active catalysts showed to be **I** and sq-**I**, we prepared supported thiourea **IV**, and squaramide sq-**IV** by copolymerization of the corresponding monomers (Scheme 2). A modified previously reported protocol[21] allowed the synthesis of **IV** and sq-**IV** from **I** and sq-**I**, respectively by heating at 70 ^{o}C for 24h a mixture of monomers with styrene (10 equiv) and divinyl benzene (0.2 equiv) in the presence of AIBN as radical initiator and toluene and 1-dodecanol as porogenic solvents. The polymers were isolated, washed with methanol and dried under vacuum.

The effective functionalization of these materials was calculated on the basis of the contents of sulfur and nitrogen atoms in the final products.

Scheme 2. Bottom-up synthesis of polymeric thiourea and squaramide.

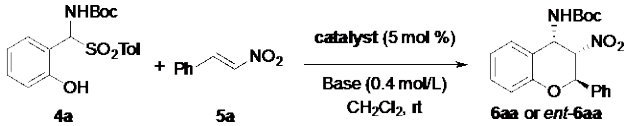


We tested the ability of all these catalysts to promote the stereoselective synthesis of enantioenriched 2,3,4-trisubstituted benzopyrans by using 2-hydroxy *N*-Boc-α-amidosulfone (**4a**), a bench stable precursor of 2-hydroxy *N*-Boc imine,[22] and *trans*-β-nitrostyrene (**5a**) as model compounds (Table 1). First, we studied different aqueous solutions of bases able to generate the *N*-Boc imine in the presence of thiourea **I** (entries 1-4 in Table 1). All the bases tested provided excellent er, but Cs_2CO_3 and Na_2CO_3 decreased the dr to very low or moderate, respectively. A balance of yields, dr and er leaded us to consider the aqueous solution of K_2CO_3 (entry 4 in Table 1) as the standard basic media of choice for all reactions. A slight enhancement on both the enantioselection, and diastereoselection, was observed when the reaction was carried out at 0 ºC (entry 5), and the use of only 2 mol% of catalyst decreased the stereoselection, although maintaining very good level (94:6 dr; 94:6 er, entry 6 in Table 1). The absolute configuration of the reaction product was established by comparison of the sign of the specific rotation with that of the previously described *ent*-**6aa**.[5]

Under the described reaction conditions, we screened the reminder catalysts (Table 1, entries 7-19). All thioureas promoted the process with good diastereo- and

enantioselectivities, but thiourea **I**, derived from (1*R*, 2*R*)-cyclohexane diamine, provided much better stereoselection than **IIa-b** or **IIIa-b** obtained from L-*tert*-leucine or L-valine derived diamines, respectively (compare entry 4 *versus* entries 7-10). *Sq*-**I**, homologous of thiourea **I**, also promotes the reaction with good enantioselectivity, but moderate diastereoselectivity (entry 11), but *sq*-**IIa-b** and sq-**IIIa-b** provided the final product in moderate enantioselection, and very low diastereoselection (entries 12-15 in Table 1). Fortunately, both the polymeric thiourea **IV** (entry 16), and squaramide *sq*-**IV** (entry 19) were able to catalyze the reaction with high degree of enantioselection although slighting decreasing the diastereoselection with respect to the monomeric analogs. The most important fact for the polymeric catalysts refers to their easy recovering and reusing, and in our case, both **IV** and sq-**IV** were easily recovered by filtration, and reused for five cycles maintaining their activity (Table S-1 in SI).[23] The reaction can be scale up by using 1g (2.9 mmol) of **4a** in the described conditions, and the result is collected in entry 20 (Table 1). Both the yield, and stereoselection is maintained for the process (compare entries 16 and 20 in Table 1).

Table 1. Evaluation of different catalysts and conditions in the cascade process.



Entry[a]	Catalyst	Base	t (h)	Product Yield[b] (%)	dr[c]	er[c]
1	**I**	$LiOH.H_2O$	12	**6aa** (84)	92:8	99:1
2	**I**	Cs_2CO_3	12	**6aa** (70)	57:43	92:8
3	**I**	Na_2CO_3	12	**6aa** (87)	86:14	99:1
4	**I**	K_2CO_3	12	**6aa** (88)	98:2[e]	97:3[e]
5[d]	**I**	K_2CO_3	12	**6aa** (91)	99:1	99:1
6[f]	**I**	K_2CO_3	18	**6aa** (85)	94:6	94:6
7	**IIa**	K_2CO_3	6	*ent*-**6aa** (90)	95:5	93:7
8	**IIb**	K_2CO_3	12	*ent*-**6aa** (83)	94:6	94:6
9	**IIIa**	K_2CO_3	12	*ent*-**6aa** (75)	91:9	90:10
10	**IIIb**	K_2CO_3	12	*ent*-**6aa** (86)	92:8	95:5
11	*sq*-**I**	K_2CO_3	12	**6aa** (91)	82:18	98:2
12	*sq*-**IIa**	K_2CO_3	16	*ent*-**6aa** (67)	59:41	88:12
13	*sq*-**IIb**	K_2CO_3	16	*ent*-**6aa** (74)	60:40	95:5
14	*sq*-**IIIa**	K_2CO_3	12	*ent*-**6aa** (84)	64:36	87:13
15	*sq*-**IIIb**	K_2CO_3	12	*ent*-**6aa** (91)	67:33	93:7
16	**IV**	K_2CO_3	12	**6aa** (87)	87:13	97:3

17[f]	**IV**	K_2CO_3	20	**6aa** (81)	84:16	97:3
18[d]	**IV**	K_2CO_3	48	**6aa** (70)	76:24	99:1
19	*sq*-**IV**	K_2CO_3	12	**6aa** (84)	84:16	95:5
20	**IV**	K_2CO_3	15	**6aa** (87)	85:15	97:3

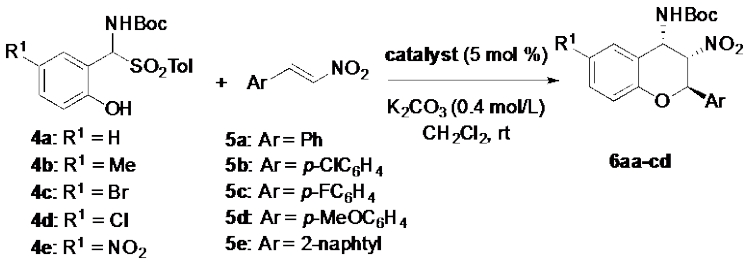
[a] The reactions were carried out with **4a** (0.2 mmol), **5a** (0.24 mmol), catalyst (5 mol%) in CH_2Cl_2 (0.6 mL) and 0.6 mL of K_2CO_3 in water (0.4 mol/L, 0.24 mmol) at rt. [b] Isolated yield after purification by flash chromatography. [c] Determined by chiral HPLC analysis. [d] Reaction performed at 0 ºC. [e] Dr and er were improved to 100:0 after recrystallization. [f] Reaction performed with 2 mol% catalyst.

The results summarized in Table 1 showed that the best reaction conditions correspond to the use of potassium carbonate as a base, and thiourea **I**, squaramide sq-**I**, and polymeric thiourea **IV** as catalysts. All these catalysts provided better stereoselection than that previously described for the same reaction.[5] Under these conditions, the reaction was extended to a series of 5-substituted 2-hydroxy *N*-Boc aldimines, in situ generated from *N*-Boc-α-amidosulfones **4a-e**, and nitrostyrene derivatives **5a-e** (Table 2). The process accepted nucleophiles and electrophiles with both electron-donating and electron-withdrawing substituents, leading to the cyclization products in good yields and stereoselectivities.

The influence of the electronic character of the substituents at the amido sulfone was studied in the reactions of **4a-e** with nitrostyrene **5a** (entries 1-7 in Table 2). The best stereoselection was obtained for the chloro derivative **4d** (entry 6), but the presence of a high electron-withdrawing group at the amido sulfone (**4e**) increased the rate of the reaction at expense to decrease the enantioselection (entry 7 in Table 2). On the contrary, the electronic character of the substituent at the nitrostyrene has limited influence in the diastereoselection (entries 8-30 in Table 2), although the best results were obtained for the *p*-methoxyphenyl (**5d**) and 2-naphthyl (**5e**) derivatives (entries 25 and 27 in Table 2, respectively). Generally, thiourea **I** was a more stereoselective catalyst than squaramide sq-**I**, for this transformation (compare entries 1, 9, 13, 15, and 19 *versus* 3, 12, 14, 18, and 20 in Table 2). Interestingly, when the processes were carried out at 0^o C, the reaction time increased, and the diastereoselectivity slight diminished (compare entries 1, 4, 7, 9, 15, 21, and 27 *versus* 2, 5, 8, 10, 16, 22, and 28, respectively), except for the reaction of **4a** with **5a** catalyzed by thiourea **I**

(compare entries 4 and 5 in Table 1). To our delight, polymeric thiourea **IV** was also an excellent organocatalyst for the proposed transformation, maintaining the high yields and degree of stereoselection (entries 11, 17, 23, and 29 in Table 2).

Table 2. Scope of the cascade process.



Entry[a]	R^1	Ar	Catalyst	t (h)	Product (%)[b]	dr[c]	er[c]
1	CH_3	Ph	**I**	16	**6ba** (90)	92:8	>99:<1[d]
2[e]	CH_3	Ph	**I**	16	**6ba** (88)	94:6	94:6
3	CH_3	Ph	*sq*-**I**	16	**6ba** (84)	89:11	97:3
4	Br	Ph	**I**	8	**6ca** (79)	89:11	90:10
5[e]	Br	Ph	**I**	12	**6ca** (81)	81:19	89:11
6	Cl	Ph	**I**	6	**6da** (87)	100:0	98:2
7	NO_2	Ph	**I**	6	**6ea** (88)	90:10	85:15
8[e]	NO_2	Ph	**I**	6	**6ea** (88)	85:15	82:18
9	H	*p*-ClC_6H_4	**I**	6	**6ab** (91)	95:5	95:5
10[e]	H	*p*-ClC_6H_4	**I**	12	**6ab** (93)	93:7	97:3
11	H	*p*-ClC_6H_4	**IV**	12	**6ab** (96)	92:8	95:5
12	H	*p*-ClC_6H_4	*sq*-**I**	12	**6ab** (86)	92:8	85:15
13	CH_3	*p*-ClC_6H_4	**I**	12	**6bb** (95)	81:19	98:2
14	CH_3	*p*-ClC_6H_4	*sq*-**I**	12	**6bb** (79)	82:18	96:4
15	H	*p*-FC_6H_4	**I**	12	**6ac** (93)	97:3	95:5
16[e]	H	*p*-FC_6H_4	**I**	16	**6ac** (86)	96:4	95:5
17	H	*p*-FC_6H_4	**IV**	12	**6ac** (92)	82:18	96:4
18	H	*p*-FC_6H_4	*sq*-**I**	12	**6ac** (87)	93:7	98:2
19	CH_3	*p*-FC_6H_4	**I**	12	**6bc** (88)	96:4	96:4
20	CH_3	*p*-FC_6H_4	*sq*-**I**	12	**6bc** (83)	86:14	97:3
21	H	*p*-$MeOC_6H_4$	**I**	20	**6ad** (96)	96:4	92:8
22[e]	H	*p*-$MeOC_6H_4$	**I**	24	**6ad** (80)	92:8	95:5
23	H	*p*-$MeOC_6H_4$	**IV**	24	**6ad** (91)	95:5	93:7
24	H	*p*-$MeOC_6H_4$	*sq*-**I**	16	**6ad** (95)	99:1	92:8
25	CH_3	*p*-$MeOC_6H_4$	**I**	24	**6bd** (88)	99:1	98:2
26	CH_3	*p*-$MeOC_6H_4$	*sq*-**I**	16	**6bd** (88)	99:1	92:8
27	H	2-naphthyl	**I**	12	**6ae** (94)	99:1	>99:<1[d]
28[e]	H	2-naphthyl	**I**	16	**6ae** (97)	99:1	>99:<1[d]
29	H	2-naphthyl	**IV**	12	**6ae** (91)	99:1	>99:<1[d]
30	H	2-naphthyl	*sq*- **I**	24	**6ae** (72)	100:0	93:7

[a] The reactions were carried out with **4a-e** (0.2 mmol), **5a-e** (0.24 mmol), catalyst (5 mol%) in CH_2Cl_2 (0.6 mL) and 0.6 mL of K_2CO_3 in water (0.4 mol/L, 0.24 mmol) at

rt. [b]Isolated yield after purification by flash chromatography. [c]Determined by chiral HPLC analysis. [d] Only one enantiomer was detected by HPLC. [e] Reaction performed at 0 ºC.

The good results obtained in the described cascade process, and the interest of 2-amino-4-substituted-4*H*-chromenes as natural and biological active substances,[24] led us to consider the organocatalyzed enantioselective synthesis of that kind of substrates. Organocatalysis has been previously applied for the synthesis of alkyl- or aryl-substituted 4*H*-chromenes by sequential Michael addition-cyclization of different substrates,[25] but to the best of our knowledge only one case has been described for the synthesis of 2,4-diamino-3-cyano-4*H*-chromenes catalyzed by chiral thioureas with good to moderate enantioselectivity.[26]

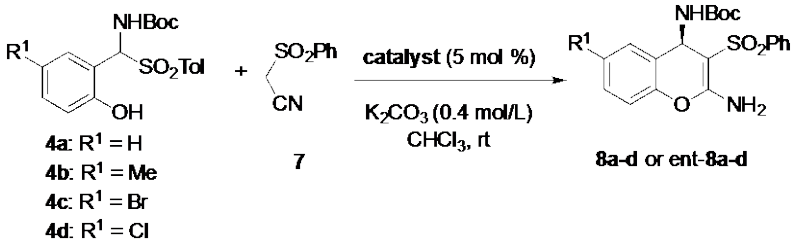
We were interested in the unprecedented synthesis of enantioenriched 3-phenylsulfonyl-substituted 2,4-diamino-4*H*-chromenes through a Mannich cyclization–tautomerization cascade sequence, and then we reacted amido sulfones (**4a-d**) with phenylsulfonylacetonitrile **7** in the presence of our catalysts. The reactions were carried out in a mixture of chloroform and aqueous solution of K_2CO_3 as the base able to promote the formation of the aldimine, and 5 mol% of the corresponding catalyst (Table 3). First, we studied the efficiency of different monomeric catalysts taken the reaction of **4a** with **7** as a model (entries 1-9 in Table 3). The addition-cyclization products **8a** or *ent*-**8a** were obtained with good yields, but the stereoselection varies with the nature of the catalyst. The absolute stereochemistry of the products were determined by X-ray analysis of a single crystal of *ent*-**8a** (Figure 1).[27] Thioureas **IIa-b** and **IIIa-b** provided low enantiomeric excess (entries 2-5 in Table 3), whereas (1*R*,2*R*)-cyclohexanediamine derived thiourea **I** promotes more enantioselective reaction (80:20 er, entry 1). Polymeric thiourea **IV** and, specially, *sq*-**IV** worked very well as catalysts (entries 10-13 in Table 3), although in longer reaction time, and they can be recovered and reused for five cycles maintaining their activity (Table S-2 in SI).[23] No modification were observed in the recovered catalysts because the identity of their IR spectral data with respect to the freshly prepared ones.

Contrary to the fact observed for the intermolecular oxa-Michael-aza-Henry process described above, squaramides were much more efficient catalysts in this process than their homologous thioureas did (compare entries 1, 5, and 10 *versus* 6, 8, and 11 in

Table 3). Both monomeric *sq*-**I**, and *sq*-**IIIb**, and polymeric *sq*-**IV** lead to the final product with very good enantioselectivities, and the loading for the polymeric squaramide *sq*-**IV** can be diminished to 2 mol% with slight decrease in the enantioselection (compare entries 11 and 13). The temperature played an important role in this process because the rate of the reaction slow down, but the enantioselection increased when the reactions were carried out at 0 ºC (compare entries 6, 8, 11, 14, 16, 20, 22, 26, and 28 *versus* 7, 9, 12, 15, 17, 21, 23, 27, and 29, respectively in Table 3). The described squaramides improve the enantioselection with respect to previously thioureas used in a related process.[26]

The cascade reaction was extended to amido sulfones **4b-d** with different substituents by using the best monomeric *sq*-**I**, *sq*-**IIIb**, and polymeric s*q*-**IV** squaramides, and polymeric thiourea **IV** as catalysts (entries 14-31 in Table 3). Substrate **4b**, with a electron-donating substituent, showed a good enantioselectivity (entries 14-19), but better enantioselection was observed for electron-withdrawing substituted substrates, especially for chloro-derivative **4d** (entries 26-31 in Table 3). Once again, thiourea **IV** has been shown to be much less efficient than the squaramide sq-**IV** (compare entries 18, 24, and 30 *versus* 19, 25, and 31, respectively in Table 3).

Table 3. Cascade Mannich-cyclization process to enantioenriched 2,4-diamino-3-phenylsulfonyl- 4*H*-chromenes.

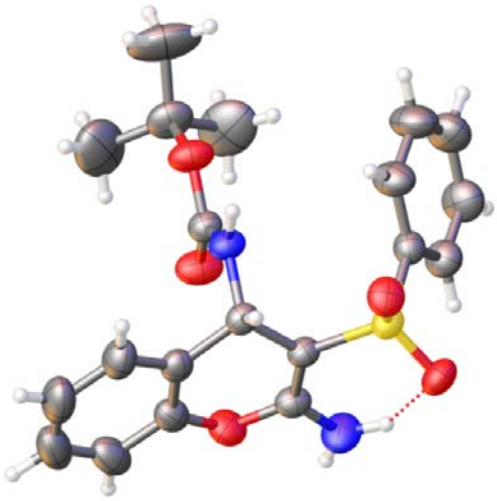


Entry[a]	R^1	Catalyst	t (h)	Product (%)[b]	er[c]
1	H	**I**	6	**8a** (85)	80:20
2	H	**IIa**	6	*ent*-**8a** (74)	66:34
3	H	**IIb**	6	*ent*-**8a** (76)	74:26
4	H	**IIIa**	6	*ent*-**8a** (82)	74:26
5	H	**IIIb**	6	*ent*-**8a** (90)	82:18
6	H	*sq*-**I**	8	**8a** (83)	91:9
7[d]	H	*sq*-**I**	12	**8a** (87)	93:7
8	H	*sq*-**IIIb**	12	*ent*-**8a** (88)	93:7[e]
9[d]	H	*sq*-**IIIb**	16	*ent*-**8a** (87)	96:4
10	H	**IV**	12	**8a** (87)	79:21

11	H	*sq*-**IV**	12	**8a** (84)	90:10
12[d]	H	*sq*-**IV**	50	**8a** (68)	92:8
13[f]	H	*sq*-**IV**	20	**8a** (79)	87:13
14	CH_3	*sq*-**I**	16	**8b** (89)	94:6
15[d]	CH_3	*sq*-**I**	22	**8b** (81)	95:5
16	CH_3	*sq*-**IIIb**	16	*ent*-**8b** (90)	90:10
17[d]	CH_3	*sq*-**IIIb**	21	*ent*-**8b** (91)	94:6
18	CH_3	**IV**	16	**8b** (85)	78:22
19	CH_3	*sq*-**IV**	16	**8b** (82)	89:11
20	Br	*sq*-**I**	12	**8c** (89)	93:7
21[d]	Br	*sq*-**I**	16	**8c** (85)	94:6
22	Br	*sq*-**IIIb**	6	*ent*-**8c** (95)	91:9
23[d]	Br	*sq*-**IIIb**	12	*ent*-**8c** (89)	93:7
24	Br	**IV**	12	**8c** (80)	79:21
25	Br	*sq*-**IV**	12	**8c** (78)	91:9
26	Cl	*sq*-**I**	12	**8d** (84)	94:6
27[d]	Cl	*sq*-**I**	16	**8d** (82)	94:6
28	Cl	*sq*-**IIIb**	6	*ent*-**8d** (91)	95:5
29[d]	Cl	*sq*-**IIIb**	12	*ent*-**8d** (96)	97:3
30	Cl	**IV**	12	**8d** (84)	75:25
31	Cl	*sq*-**IV**	12	**8d** (80)	94:6

[a] The reactions were carried out with **4a-d** (0.2 mmol), phenylsulfonylacetonitrile (0.24 mmol), catalyst (5 mol%) in $CHCl_3$ (0.6 mL) and 0.6 mL of K_2CO_3 in water (0.4 mol/L, 0.24 mmol) at rt. [b] Isolated yield after purification by flash chromatography. [c] Determined by chiral HPLC analysis. [d] Reaction performed at 0 ºC. [e] Er was improved to 99:1 after recrystallization. [f] Only 2 mol% of catalyst was used.

Figure 1. X-ray crystal structure of *ent*-**8a** (50% probability ellipsoids).

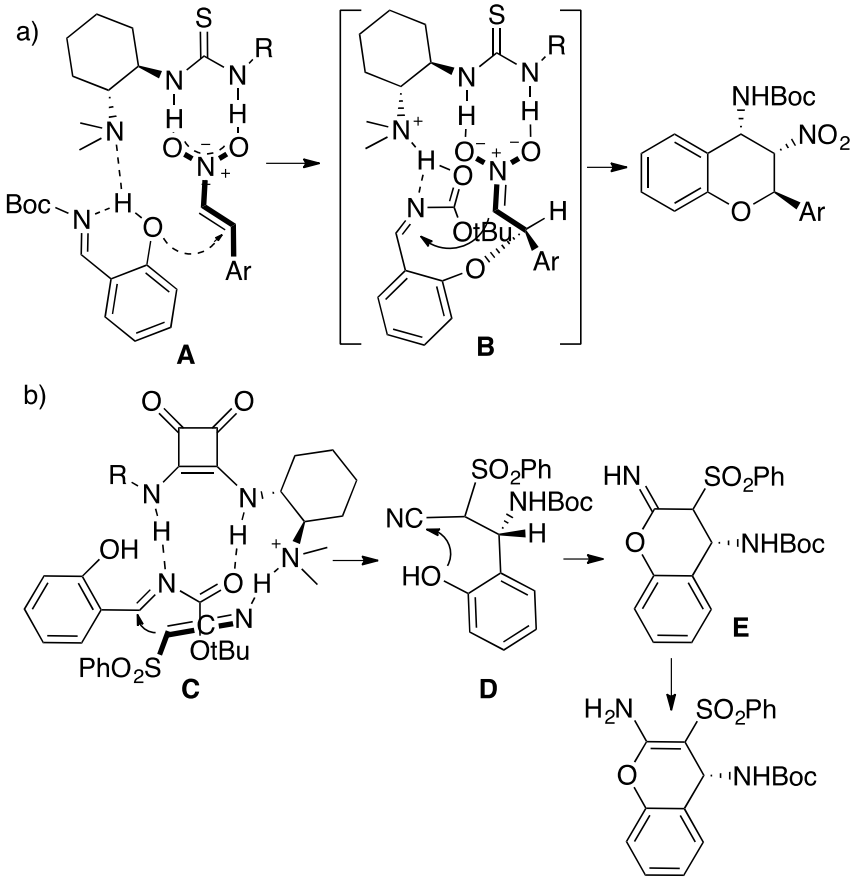


It is interesting to note the different ability as organocatalyst showed by the thioureas and squaramides used in this work. Thioureas are more efficient catalysts for the cascade oxa-Michael-aza-Henry reactions, whereas thioureas worked better in the Michael-addition-cyclization processes. An important difference between squaramides and thioureas refers to the relative spacing and distance of the two hydrogen atoms able to activate the electrophilic reagent. Then, a plausible explanation could be related with the better accommodation by thioureas of the nitro group in the first process, while the acyl imine functionality used in the second reaction fits better in the squaramide appendage.

The absolute stereochemistry of the final products and the excellent stereoselectivity obtained in the described cascade processes can be explained as summarizes in Scheme 3. The intermediate 2-hydroxy benzaldimine derivative will be formed by elimination on 2-hydroxy *N*-Boc-α-amidosulfone promoted by K_2CO_3. Bifunctional thiourea, which is the best catalyst for the oxa-Michael-aza-Henry process, will form ternary complex **A**. The thiourea, acting as a Brönsted acid, is able to activate the electrophilic nitroalkene through hydrogen bonding, and the tertiary amine helps to deprotonate the phenolic group, increasing its nucleophilicity (Scheme 3a). The attack to the β-position of the nitroalkene is the responsible of the formation of the stereogenic center at C-2, and it occurs to the *re* face of the double bond, leading to nitronate **B**. This intermediate immediately cyclized by addition of the *si* face of the nitronate to the *re* face of the Boc-imine double bond.

Scheme 3b summarizes the plausible formation of the ternary complex **C** responsible for the stereochemistry in the reaction of 2-hydroxybenzaldimines with phenylsulfonylacetonitrile. In that case, the *N*-Boc imine previously formed was activated by hydrogen bonding with the squaramide, and the tertiary amine deprotonates the acidic hydrogen of the pronucleophile. Mannich addition of the *re* face of the nucleophile to the *si* face of the imine double bond yielded compound **D**. This compound, never detected, leads to the imino ether **E** by intramolecular nucleophilic addition of the phenolic OH to the nitrile group. The tautomerization of the imine yields the final 4*H*-chromenes.

Scheme 3. Plausible ternary complexes responsible for the stereochemistry of the processes.



CONCLUSIONS

In summary, a series of novel bifunctional chiral styryl-substituted thioureas and squaramides, and their copolymers, has been prepared and used as catalysts in two different transformations. All the catalysts were able to promote the oxa-Michael-aza-Henry cascade reaction of α-amidosulfones of salicylaldehyde derivatives and different nitrostyrenes with only 5 mol% loading. The final 4-amino-2-aryl-3-nitrobenzopyrans were obtained in good yields and excellent stereoselectivities. Thioureas have been shown to be better catalysts than squaramides for those transformations. The same catalysts were used in the cascade Mannich-cyclization processes yielding enantioenriched 2,4-diamino-3-phenylsulfonyl-4*H*-chromenes by reaction of the same α-amidosulfones with phenylsulfonylacetonitrile. The best catalysts for that transformation were squaramides instead thioureas.

Polymeric urea **IV**, and squaramide sq-**IV** were prepared from the best monomeric catalysts **I**, and sq-**I** by copolymerization with styrene and divinylbenzene, and used in the same transformations. Both polymeric catalysts have been shown very efficient, and recoverable and reusable for five cycles without loss of activity.

EXPERIMENTAL

General

^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts for protons and carbons are reported in ppm from TMS with the residual $CHCl_3$ or the solvent resonances as internal reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants in Hertz, and integration. Specific rotations were measured on a digital polarimeter using a sodium lamp, on a 5-mL cell with a 1-dm path length. Concentration is given in g per 100 mL. FT–IR absorptions are reported in frequencies (only the structurally most important peaks are provided). Flash chromatography was carried out using silica gel (230–240 mesh). Melting points were obtained with open capillary tubes and are uncorrected. TLC analysis was performed on glass-backed plates coated with silica gel 60, and visualized by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed by using Daicel Chiralcel OD, Chiralpak AS-H, ADH, and IA or Lux-amylose-1 analytical columns (250 x 4.6 mm). UV detection was monitored at 220 or at 254 nm. Elemental analyses were carried out at the Elemental Analysis Center of the Complutense University of Madrid.

Commercially available compounds were used without further purification. Solvents were dried and stored over microwave–activated 4 Å molecular sieves. L-valine and L-tert-leucine derived diamines,[19] and α-amido sulfones **4a-d**[5] were prepared according to literature procedures. Nitroolefins **5a-d** are commercially available, and **5e**[28] was synthesis as previously reported. Racemic reference samples were prepared by using achiral bifunctional thiourea derived from N^1,N^1-dimethylethane-1,2-diamine[29] (5 mol%) following the same reaction conditions as for the asymmetric reaction.

3,5-Dichloro-4-(4-vinylbenzyloxy)aniline (1). To a stirred solution of 4-amino-2,6-dichlorophenol (890 mg, 5 mmol) in dry DMF (50 mL) at 0 °C, KO^{t}Bu was added (600 mg, 5.5 mmol, 1.1 equiv). After 15 min, 4-vinylbenzyl chloride (0.8 mL, 5.5 mmol, 1.1 equiv) was added dropwise and the reaction left to stir overnight before quenching with H_2O (40 mL). The solution was then repeatedly extracted with EtOAc (3 x 10 mL) and the organics were combined. The organics were then washed with H_2O and brine, dried over $MgSO_4$ and concentrated in *vacuo*. The resulting residue was purified by column chromatography on silica gel (eluent: hexane/ EtOAc: 10/1) to yield **1**: 1.12 g (3.8 mmol, 76%). Colorless solid, mp 73-74 ºC. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.65 (br s, 2H), 4.94 (s, 2H), 5.28 (dd, J = 10.9, 0.9 Hz, 1H), 5.79 (dd, J = 17.6, 0.9 Hz, 1H), 6.58 (m, 2H), 6.75 (dd, J = 17.6, 10.9 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 74.9, 114.1, 115.0, 126.3, 128.7, 129.7, 136.3, 136.5, 137.6, 142.8, 143.7. IR (ATR): 3469, 3375, 1480, 1224, 988, 827, 799 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+H] Calcd for $C_{15}H_{14}Cl_2NO$ 294.0479; found 294.0448.

4-Isothiocyanato-2,6-(dichloro)-1-(4-vinylbenzyloxy)benzene (2). To a solution of amine **1** (882 mg, 3 mmol) in CH_2Cl_2 (30 mL), triethylamine (1.7 mL, 12 mmol, 4 equiv) and thiophosgene (0.28 mL, 3.6 mmol, 1.2 equiv) were added dropwise at rt. After 3 h, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate: 20/1) to obtain isothiocyanate **2**: 888 mg (2.64 mmol 88%). Brownish solid, mp 126-128 ºC. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.03 (s, 2H), 5.28 (dd, J = 10.9, 0.9 Hz, 1H), 5.78 (dd, J = 17.6, 0.9 Hz, 1H), 6.74 (dd, J = 17.6, 10.9 Hz, 1H), 7.19 (s, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 75.0, 114.4, 126.0, 126.4, 128.3, 128.8, 130.5, 135.2, 136.4, 137.9, 138.8, 150.3. IR (ATR): 2977, 2050, 1452, 1279, 1200, 811 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{16}H_{11}Cl_2NOSNa$ 357.9837; found 357.9830.

3-((3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)amino)-4-ethoxycyclobut-3-ene-1,2-dione (3). To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (0.3 mL, 2 mmol) in MeOH (5 mL) amine **1** (588 mg, 2 mmol, 1 equiv) was added at room temperature and the reaction mixture stirred overnight. The formed yellow precipitate was filtered and dried in vacuo to give **3**: 810 mg (1.94 mmol, 97%). Colorless solid, mp 161-163 ^{o}C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.39 (t, J = 7.1 Hz, 3H), 2.74 (q, J

= 7.1 Hz, 2H), 4.93 (s, 2H), 5.25 (d, J= 10.9 Hz, 1H), 5.83 (d, J = 17.6 Hz, 1H), 6.72 (dd, J = 17.7, 10.9 Hz, 1H), 7.42-7.48 (m, 6H), 10.83 (s, 1H). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 15.9, 70.3, 75.0, 115.2, 120.1, 123.6, 123.7, 129.2, 135.9, 136.0, 136.7, 137.6, 169.6, 179.2, 184.4, 187.8. IR (ATR): 3232, 3073, 1796, 1720, 1596, 1551, 1409, 800 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+H] Calcd for $C_{21}H_{18}Cl_2NO_4$ 418.0614; found 418.0613.

1-(3,5-Dichloro-4-(4-vinylbenzyloxy)phenyl)-3-((1R,2R)-2-(piperidin-1-yl) cyclohexyl)thiourea (I). To a solution of 1-((1*R*,2*R*)-2-aminociclohexyl)piperidine (182 mg, 1 mmol) in anhydrous CH_2Cl_2 (4 mL), isothiocyanate **2** (370 mg, 1.1 mmol, 1.1 equiv) in CH_2Cl_2 (1 mL) was added at 0 °C, under nitrogen atmosphere. The resulting solution was stirred overnight at room temperature. The reaction was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (eluent: DCM/MeOH: 20/1) to afford **I** as a colorless oil: 373 mg (0.72 mmol, 72%). $[\alpha]_D^{23}$ = -9.8 (c = 0.4, MeOH). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.23-1.40 (m, 6H), 1.56 (m, 2H), 1.78 (m, 3H), 1.93 (m, 1H), 2.03 (m, 2H), 2.41 (m, 1H), 2.80 (m, 2H), 3.11 (m, 3H), 4.48 (br s, 1H), 4.96 (s, 2H), 5.24 (dd, J = 10.9, 0.9 Hz, 1H), 5.74 (dd, J = 17.6, 0.9 Hz, 1H), 6.71 (dd, J = 17.6, 10.9 Hz, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.59 (s, 2H), 9.22 (br s, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 22.4, 23.6, 24.0, 24.6, 32.4, 53.2, 68.9, 74.7, 114.2, 123.4, 126.2, 128.7, 129.0, 135.9, 136.1, 136.5, 137.6, 147.7, 180.5. IR (ATR): 2931, 1535, 1474, 1225, 988, 862, 747 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+H] Calcd for $C_{27}H_{34}Cl_2N_3OS$ 518.1800; found 518.1793.

(*S*)-1-(3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)-3-(1-(dimethylamino)-3,3-dimethylbutan-2-yl)thiourea (IIa). This compound was obtained from isothiocyanate **2** (407 mg, 1.21 mmol) by reaction with (*S*)-N^1,N^1,3,3-tetramethylbutane-1,2-diamine (159 mg, 1.10 mmol) in CH_2Cl_2 (5 mL) as described for **I** and purified by flash chromatography (DCM/MeOH: 20/1): 370 mg (0.77 mmol, 70%). Colorless oil. $[\alpha]_D^{23}$ = -56.2 (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.02 (s, 9H), 2.40 (s, 6H), 2.61 (m, 2H), 3.31 (m, 1H), 4.99 (s, 2H), 5.25 (dd, J = 10.9, 3.0 Hz, 1H), 5.77 (dd, J = 17.6, 3.0 Hz, 1H), 6.17 (br s, 1H), 6.73 (ddd, J = 17.6, 10.9, 3.0 Hz, 1H), 7.43 (m, 2H), 7.51 (m, 4H), 12.77 (br s, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.6, 33.5, 45.2, 63.2, 63.9, 74.8, 114.2, 123.3, 126.3, 128.7, 129.1, 135.9, 136.5, 137.6, 137.7, 147.6, 182.9. IR (ATR): 2931, 1470, 1372, 1229, 960, 772, 670

cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+H] Calcd for $C_{24}H_{31}Cl_2N_3OS$ 480.1644; found 480.1641.

(*S*)-1-(3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)-3-(3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)thiourea (IIb). This compound was obtained from isothiocyanate **2** (361 mg, 1.07 mmol) by reaction with (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine (180 mg, 0.97 mmol) in CH_2Cl_2 (5 mL) as described for **I** and purified by flash chromatography (DCM/MeOH: 20/1): 439 mg (0.84 mmol, 87%). Colorless oil. $[\alpha]_D^{23}$ = -87.1 (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.98 (s, 9H), 1.46 (m, 6H), 2.39 (m, 3H), 2.59 (m, 3H), 3.31 (m, 1H), 4.98 (s, 2H), 5.21 (br s, 1H), 5.23 (d, J = 10.9 Hz, 1H), 5.73 (d, J = 17.6 Hz, 1H), 6.26 (br s, 1H), 6.69 (dd, J = 17.6, 10.9 Hz, 1H), 7.40 (m, 2H), 7.46 (m, 4H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 23.5, 25.8, 26.6, 33.6, 54.7, 62.6, 63.5, 74.7, 114.1, 125.8, 126.2, 128.6, 128.9, 135.9, 136.5, 137.1, 137.6, 148.2, 183.5. IR (ATR): 2959, 1527, 1470, 1368, 1217, 988, 821 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+H] Calcd for $C_{27}H_{36}Cl_2N_3OS$ 520.1956; found 520.1951.

(*S*)-1-(3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)-3-(1-(dimethylamino)-3-methylbutan-2-yl)thiourea (IIIa). This compound was obtained from isothiocyanate **2** (406 mg, 1.2 mmol) by reaction with (*S*)-N^1,N^1,3-trimethylbutane-1,2-diamine (143 mg, 1.09 mmol) in CH_2Cl_2 (5 mL) as described for **I** and purified by flash chromatography (DCM/MeOH: 20/1): 428 mg (0.92 mmol, 84%). Colorless oil. $[\alpha]_D^{23}$ = -45.0 (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.96 (m, 6H), 1.90 (m, 1H), 2.35 (s, 6H), 2.43 (m, 1H), 2.61 (m, 1H), 3.46 (m, 1H), 4.98 (s, 2H), 5.25 (d, J = 10.9 Hz, 1H), 5.77 (d, J = 17.6 Hz, 1H), 6.32 (br s, 1H), 6.73 (dd, J = 17.6, 10.9 Hz, 1H); 7.36-7.52 (m, 6H), 8.95 (br s, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 18.3, 19.4, 31.5, 45.2, 59.9, 64.0, 74.8, 114.2, 123.7, 124.5, 126.3, 128.7, 135.9, 136.4, 136.5, 137.7, 147.8, 182.5. IR (ATR): 2935, 1474, 1371, 907, 719 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+H] Calcd for $C_{23}H_{30}Cl_2N_3OS$ 466.1489; found 466.1482.

(*S*)-1-(3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)-3-(3-methyl-1-(piperidin-1-yl)butan-2-yl)thiourea (IIIb). This compound was obtained from isothiocyanate **2** (336 mg, 1 mmol) by reaction with (*S*)-3-methyl-1-(piperidin-1-yl)butan-2-amine (155 mg, 0.91 mmol) in CH_2Cl_2 (5 mL) as described for **I** and purified by flash chromatography (DCM/MeOH: 20/1): 420 mg (0.83 mmol, 91%). Yellow oil, $[\alpha]_D^{23}$

= -32.3 (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.00 (d, J = 6.9 Hz, 6H), 1.46-1.53 (m, 6H), 1.90 (m, 1H), 2.32-2.60 (m, 4H), 2.67 (m, 2H), 3.52 (m, 1H), 5.02 (s, 2H), 5.26 (dd, J = 10.9, 0.9 Hz, 1H), 5.76 (dd, J = 17.6, 0.9 Hz, 1H), 6.19 (br s, 1H), 6.73 (dd, J = 17.6, 10.9 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.46 (s, 2H), 7.51 (d, J = 8.2 Hz, 2H), 12.51 (br s, 1H).^{13}C-NMR (126 MHz, $CDCl_3$): δ 18.2, 18.3, 23.6, 25.7, 31.7, 54.7, 59.4, 63.4, 74.7, 114.2, 126.0, 126.2, 128.1, 128.6, 135.9, 136.5, 137.0, 137.6, 148.4, 183.5. IR (ATR): 2959, 1527, 1474, 1225, 988, 829 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+H] Calcd for $C_{26}H_{34}Cl_2N_3OS$ 506.1799; found 506.1794.

3-((3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)amino)-4-(((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (*sq*-I). To a solution of squaric ester monoamide **3** (486 mg, 1.16 mmol) in MeOH (8 mL) was 1-((1*R*,2*R*)-2-aminociclohexyl)piperidine (212 mg, 1.16 mmol, 1 equiv) and then was stirred 72 h at room temperature. The reaction was concentrated in *vacuo* and the residue was purified by flash chromatography (DCM/MeOH: 20/1) to afford *sq*-**I**: 470 mg (0.85 mmol, 73%). Yellow oil. $[\alpha]_D^{23}$ = -31.0 (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.23 (m, 2H);); 1.35 (m, 3H); 1.55 (m, 3H); 1.78 (m, 2H); 2.01 (m, 3H); 2.18 (m, 1H); 2.91 (m, 2H), 3.20 (m, 3H), 4.21 (m, 1H), 4.95 (s, 2H); 5.24 (d, J = 10.8 Hz, 1H), 5.73 (d, J = 17.7 Hz, 1H), 6.68 (dd, J = 17.7, 10.8, 1H), 7.39 (d, J = 7.8 Hz, 2H), 7.47 (d, J = 7.8 Hz, 2H), 7.55 (s, 2H), 9.20 (s, 1H), 10.27 (s, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 23.6, 23.7, 24.1, 24.4, 24.8, 34.7, 53.6, 60.3, 67.9, 74.8, 114.0, 118.5, 126.2, 128.6, 129.8, 136.1, 136.5, 137.5, 146.5, 164.8, 168.9, 180.7, 183.5. IR (ATR): 2931, 1788, 1682, 1576, 1437, 800, 723 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{30}H_{33}Cl_2N_3O_3Na$ 576.1797; found 576.1804.

(*S*)-3-((3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)amino)-4-((1-(dimethylamino)-3,3-dimethylbutan-2-yl)amino)cyclobut-3-ene-1,2-dione (*sq*-IIa). This compound was obtained from squaric ester monoamide **3** (548 mg, 1.31 mmol) by reaction with (*S*)-*N*^{1},*N*^{1},3,3-tetramethylbutane-1,2-diamine (189 mg, 1.31 mmol) in MeOH (9 mL) as described for *sq*-**I** and purified by flash chromatography (DCM/MeOH: 20/1) to afford *sq*-**IIa**: 440 mg (0.85 mmol, 65%). Yellow oil. $[\alpha]_D^{23}$ = -15.5 (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.99 (s, 9H), 2.51 (s, 7H); 2.64 (m, 1H), 3.04 (m, 1H), 4.23 (br s, 1H), 4.85 (s, 2H), 5.25 (d, J = 10.9 Hz, 1H), 5.74 (dd, J = 17.6 Hz, 1H), 6.70 (dd, J = 17.6, 10.9 Hz, 1H), 7.35-7.43 (m, 6H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 26.3, 34.7, 45.4, 59.2, 61.2, 74.8, 114.1, 118.8, 126.2, 128.6, 129.9, 135.8, 136.5,

137.6, 146.8, 162.5, 170.5, 180.9. IR (ATR): 2930, 1794, 1696, 1597, 1524, 1425 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{27}H_{31}Cl_2N_3O_3Na$ 538.1639 ; found 538.1642.

(*S*)-3-((3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)amino)-4-((3,3-dimethyl-1-(piperidin-1-yl)butan-2-yl)amino)cyclobut-3-ene-1,2-dione (*sq*-IIb). This compound was obtained from monoamide **3** (88 mg, 0.21 mmol) by reaction with (*S*)-3,3-dimethyl-1-(piperidin-1-yl)butan-2-amine (43 mg, 0.21 mmol) in MeOH (2 mL) as described for *sq*-**I** and purified by flash chromatography (DCM/MeOH: 20/1): 84 mg (0.15 mmol, 72%). Yellow oil. $[\alpha]_D^{23}$ = -13.1 (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.99 (m, 9H), 1.49 (m, 2H), 1.69 (m, 4H), 2.80 (m, 4H), 2.98 (m, 3H), 4.31 (br s, 1H), 4.88 (s, 2H), 5.23 (d, J = 10.9 Hz, 1H), 5.73 (d, J = 17.6 Hz, 1H), 6.70 (dd, J = 17.6, 10.9 Hz, 1H), 7.32-7.50 (m, 6H, Har). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 22.9, 24.2, 26.2, 34.9, 54.8, 58.2, 59.6, 74.8, 114.1, 118.7, 126.2, 128.6, 130.0, 135.8, 135.9, 136.5, 137.6, 146.7, 163.2, 170.2, 180.7, 183.2. IR (ATR): 2962, 1790, 1675, 1577, 1524, 1425, 802 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+H] Calcd for $C_{30}H_{36}Cl_2N_3O_3$ 556.2134; found 556.2142.

(*S*)-3-((3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)amino)-4-((1-(dimethylamino)-3-methylbutan-2-yl)amino)cyclobut-3-ene-1,2-dione (*sq*-IIIa). This compound was obtained from **3** (418 mg, 1 mmol) by reaction with (*S*)-N^1,N^1,3-trimethylbutane-1,2-diamine (130 mg, 1 mmol) in MeOH (7 mL) as described for *sq*-**I** and purified by flash chromatography (DCM/MeOH: 20/1): 398 g (0.79 mmol, 79%). Yellow oil. $[\alpha]_D^{23}$ = -51.8 (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 0.95 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.90 (m, 1H), 2.22 (m, 1H), 2.43 (s, 6H), 2.52 (m, 1H), 2.94 (m, 1H), 4.29 (br s, 1H), 4.84 (s, 2H), 5.23 (dd, J = 10.9, 0.9 Hz, 1H), 5.72 (d, J = 17.6 Hz, 1H), 6.68 (dd, J = 17.6, 10.9 Hz, 1H), 7.33-7.43 (m, 6H), 8.42 (br s, 1H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 17.4, 19.4, 31.7, 45.3, 58.4, 61.3, 74.7, 114.1, 119.2, 126.2, 128.5, 129.8, 135.6, 135.9, 136.5, 137.6, 146.8, 162.4, 170.5, 180.7, 183.2. IR (ATR): 2959, 1792, 1678, 1568, 1437, 825 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{26}H_{29}Cl_2N_3O_3Na$ 524.1483; found 524.1482.

(*S*)-3-((3,5-Dichloro-4-((4-vinylbenzyl)oxy)phenyl)amino)-4-((3-methyl-1-(piperidin-1-yl)butan-2-yl)amino)cyclobut-3-ene-1,2-dione (*sq*-IIIb). This compound was obtained from squaric ester monoamide **3** (657 mg, 1.57 mmol) by

reaction with (*S*)-3-methyl-1-(piperidin-1-yl)butan-2-amine (266 mg, 1.57 mmol) in MeOH (11 mL) as described for *sq*-**I** and purified by flash chromatography (DCM/MeOH: 20/1): 707 mg (1.30 mmol, 83%). Yellowish oil. $[\alpha]_D^{23}$ = -25.2 (c = 1.0, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.98 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 1.58 (m, 2H), 1.84 (m, 2H), 1.93 (m, 3H), 2.95 (m, 1H), 3.00-3.30 (m, 5H), 2.85 (m, 1H), 3.35 (m, 1H), 4.36 (br s, 1H), 4.94 (s, 2H), 5.24 (dd, J = 10.9, 0.9 Hz, 1H), 5.74 (dd, J = 17.6, 0.9 Hz, 1H), 6.70 (dd, J = 17.6, 10.9 Hz, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.56 (s, 2H), 8.72 (br s, 1H).^{13}C-NMR (126 MHz, $CDCl_3$): δ 17.7, 19.0, 22.1, 23.1, 32.6, 54.6, 55.4, 59.4, 74.8, 114.1, 118.3, 126.2, 128.7, 130.0, 135.8, 136.1, 136.5, 137.5, 146.6, 164.2, 169.6, 176.3, 180.5, 183.0. IR (ATR): 2935, 1796, 1690, 1600, 1523, 1425, 800 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{29}H_{33}Cl_2N_3O_3Na$ 564.1796; found 564.1792.

Preparation of polymeric thiourea IV. Compound **I** (335 mg, 0.65 mmol) was placed in a sealed tube and dissolved in a mixture of 1-dodecanol/dry toluene 3:1 (2.4 mL). To this solution were successively added styrene (0.74 mL, 6.5 mmol), divinylbenzene (19 µL, 0.13 mmol) and azobisisobutyronitrile (42 mg, 0.26 mmol). The resulting mixture was deoxygenated by purging with nitrogen atmosphere for at least 15 minutes at room temperature. Then, the tube was heated with an oil bath at 70 °C and stirred for 24 hours. After reaction time the polymer was cooled to rt, removed from the tube, crushed, suspended in methanol (15 mL) and stirred for 10 minutes at room temperature. Then the resin was filtered and washed with methanol (3 x 15 mL). The solid was recovered and dried under vacuum to give 881 mg of polymer **IV** as a brown solid (86% yield). IR (ATR): 3028, 2926, 1596, 1494, 1025, 756 cm^{-1}. An effective functionalization, f = 0.46 mmol g^{-1}, was calculated on the basis of sulfur elemental analysis. Found: C, 80.40; H, 7.98; N, 2.15; S, 1.47.

Preparation of polymeric squaramide *sq*-**IV.** Compound *sq*-**I** (319 mg, 0.58 mmol) was placed in a sealed tube and dissolved in a mixture of 1-dodecanol/dry toluene 3:1 (2.2 mL). To this solution were successively added styrene (0.65 mL, 5.8 mmol), divinylbenzene (18 µL, 0.11 mmol) and azobisisobutyronitrile (17 mg, 0.23 mmol). The resulting mixture was deoxygenated by purging with nitrogen atmosphere for at least 15 minutes at room temperature. Then, the tube was heated with an oil bath at 70 °C and stirred for 24 hours followed by the same work-up procedures as for **IV** to afford 824 mg of polymer *sq*-**IV** as a brown solid (89% yield). IR (ATR): 3028, 2926,

1600, 1494, 1025, 756 cm^{-1}. An effective functionalization, f = 0.41 mmol g^{-1}, was calculated on the basis of nitrogen elemental analysis. Found: C, 85.21; H, 7.36; N, 1.73.

***tert*-Butyl ((2-hydroxy-5-nitrophenyl)(tosyl)methyl)carbamate (4e).** This compound was obtained by the method described in the literature[5] from *tert*-butyl carbamate (2.9 g, 25 mmol, 1 equiv) sodium *p*-tolylsulfinate (8.9 g, 50 mmol, 2 equiv) and 5-nitrosalicylaldehyde (6.26 g, 37.5 mmol, 1.5 equiv) to yield compound **4e** (4.78 g, 17.9 mmol, 72%). Colorless solid, mp 240-242 ºC. ^{1}H-NMR (500 MHz, acetone-d): δ 1.25 (s, 9H), 2.42 (s, 3H), 6.60 (d, J = 10.5 Hz, 1H), 7.12 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 7.9 Hz, 2H), 7.75 (d, J = 7.9 Hz, 2H); 8.12 (d, J = 9.1 Hz, 1H), 8.64 (s, 1H). ^{13}C-NMR (126 MHz, acetone-d): δ 20.6, 27.3, 67.7, 79.6, 115.7, 119.3, 126.3, 126.6, 129.4, 129.5, 134.8, 140.5, 144.8, 154.1, 161.8. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{12}H_{15}N_2O_5Na$ 290.0877; found 290.0879.

General procedure for the oxa-Michael-aza-Henry cascade reaction of 2-hydroxyaryl substituted α-amido sulfones with nitroolefins. *α*-Amido sulfone **4** (0.2 mmol, 1 equiv) and bifunctional catalyst (0.01 mmol, 0.05 equiv) was dissolved in CH_2Cl_2 (0.6 mL), and the resulting solution was stirred for 15 min at room temperature. A 0.4 mol/L aqueous solution of K_2CO_3 (0.6 mL) was then added to the reaction followed by nitroolefin **5** (0.24 mmol, 1.2 equiv), and the resulting mixture was stirred at 0 ºC or room temperature and monitored by ^{1}H-NMR until the *α*-amido sulfone had completely disappeared. A saturated aqueous NH_4Cl solution was then added to the reaction, and the resulting mixture was extracted with DCM. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give a residue, which was purified by flash column chromatography on silica gel (hexane/ethyl acetate mixtures) to give the desired product. The diastereomeric and enantiomeric ratios were determined by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent.

General procedure for the oxa-Michael-aza-Henry cascade reaction of 2-hydroxyaryl substituted α-amido sulfones with nitroolefins catalyzed by polymeric catalysts, and their recovering.

The reactions were carried out as described for unsupported catalyst until the reactions were finished. Then, the catalyst was recovered by filtration, washed with

MeOH, dried under vacuum, and reused in the next cycle without further purification. The filtrate was worked up as described above.

The catalyst was recovered without apparent modification, because the IR of the material after five cycles is coincident with that of the starting material (Compare the IR spectra in page S-28 in SI).

***tert*-Butyl ((2*R*,3*S*,4*S*)-3-nitro-2-phenylchroman-4-yl)carbamate (6aa).** Obtained according to the general procedure, using α-amido sulfone **4a** (74 mg, 0.2 mmol), *trans*-β-nitrostyrene (36 mg, 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol) at 0 ºC. The solvent was eliminated by evaporation, and the reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6a** (67 mg, 0.18 mmol, 91%). Colorless solid, mp 144-145 °C. [Lit.[5] mp 143-146 ºC]. $[\alpha]_D^{23}$ = +9.7 (c = 0.5, $CHCl_3$). [Lit.[5] $[\alpha]_D^{23}$ = -13.5 (c = 1.0, $CHCl_3$, for ent-**6aa**, dr 91:9, er 97:3)].^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 5.22 (m, 2H), 5.34 (m, 1H), 5.83 (d, *J* = 4.9 Hz, 1H), 7.02 (m, 2H), 7.37 (m, 7H). HPLC: (Chiralpak AD-H, *n*-hexane/2-propanol = 95:5, 0.8 mL/min, λ = 210 nm) *major (*2*S*,3*R*,4*R)*: t_R = 18.6 min (major), t_R = 30.4 min (minor). (dr 99:1; er 99:1).

***tert*-Butyl ((2*R*,3*S*,4*S*)-6-methyl-3-nitro-2-phenylchroman-4-yl)carbamate (6ba).** Obtained according to the general procedure using α-amido sulfone **4b** (78 mg, 0.2 mmol), *trans*-β-nitrostyrene (36 mg, 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6ba** (69 mg, 0.18 mmol, 90%). Colorless solid, mp 68-71 ºC. [Lit[5] mp 66-69 ºC]. $[\alpha]_D^{23}$ = +6.1 (c = 0.3, $CHCl_3$). [Lit.[5] $[\alpha]_D^{23}$= -6.38 (c = 1.0, $CHCl_3$), for ent-**6ba**, *dr* = 91:9, *er* = 97.5:2.5)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.34 (s, 3H), 5.18 (m, 2H), 5.27 (m, 1H), 5.77 (d, J = 4.9 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 8.9 Hz, 2H), 7.37 (m, 5H). HPLC: (Chiralpak IA, *n*-hexane/2-propanol = 96:4, 0.5 mL/min, λ = 254 nm) *major (*2*S*,3*R*,4*R)*: t_R = 26.4 min (major), t_R = 46.1 min (minor). (dr 92:8; er 100:0).

***tert*-Butyl ((2*R*,3*S*,4*S*)-6-bromo-3-nitro-2-phenylchroman-4-yl)carbamate (6ca).** Obtained according to the general procedure using α-amido sulfone **4c** (91 mg, 0.2 mmol), *trans*-β-nitrostyrene (36 mg, 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol). When the reaction was finished, was purified by column chromatography on silica gel

(eluent: hexane/ethyl acetate 20:1) to yield compound **6ca** (71 mg, 0.16 mmol, 79%). Colorless solid, mp 83-84 °C. $[\alpha]_D^{23}$ = +13.2 (c = 0.3, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9H), 5.12 (m, 1H), 5.19 (d, J = 9.5 Hz, 1H), 5.31 (m, 1H), 5.90 (d, J= 4.0 Hz, 1H), 6.89 (d, J = 9.1 Hz, 1H), 7.30-7.41 (m, 7H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.2, 44.2, 77.2, 81.2, 84.5, 114.3, 118.7, 122.1, 125.3, 127.2, 129.2, 129.3, 129.5, 133.7, 135.5, 151.7, 155.1. IR (ATR): 2924, 1701, 1554, 1477, 1236, 1155, 694 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{20}H_{21}BrN_2O_5Na$ 471.0531; found 471.0536. HPLC: (Chiralpak AS-H, *n*-hexane/2-propanol = 95:5, 0.5 mL/min, λ = 210 nm) *major (2S,3R,4R)*: t_R = 17.3 min (major), t_R = 21.7 min (minor). (dr 89:11; er 90:10).

***tert*-Butyl ((2*R*,3*S*,4*S*)-6-chloro-3-nitro-2-phenylchroman-4-yl)carbamate (6da).** From α-amido sulfone **4d** (84 mg, 0.2 mmol), *trans*-β-nitrostyrene (36 mg, 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol). When the reaction was finished, the mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6da** (69 mg, 0.17 mmol, 87%). Colorless solid, mp 233-235 °C. $[\alpha]_D^{23}$ = +26.0 (c = 0.5, $CHCl_3$).^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.46 (s, 9H), 5.14 (m, 1H), 5.21 (m, 1H), 5.34 (m, 1H), 5.91 (d, J= 5.7 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 7.25 (m, 2H), 7.32-7.42 (m, 5H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.2, 44.3, 77.1, 81.1, 84.5, 118.3, 121.7, 125.3, 126.6, 127.0, 129.2, 129.3, 129.8, 135.5, 151.1, 155.1. IR (ATR): 3290, 1668, 1554, 1477, 763, 694 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{20}H_{21}ClN_2O_5Na$ 427.1036; found 427.1035. HPLC: (Lux-amilose-1, *n*-hexane/2-propanol = 95:5, 0.8 mL/min, λ = 254 nm). *major (2S,3R,4R)*: t_R = 16.8 min (major), t_R = 25.8 min (minor). (dr 100:0; er 98:2).

***tert*-Butyl ((2*R*,3*S*,4*S*)-3,6-dinitro-2-phenylchroman-4-yl)carbamate (6ea).** From *tert*-butyl α-amido sulfone **4e** (82 mg, 0.2 mmol), *trans*-β-nitrostyrene (36 mg 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol). The mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6ea** (71 mg, 0.17 mmol, 88%). Yellow solid, mp 275-278 °C. $[\alpha]_D^{23}$ = +7.6 (c = 0.5, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.47 (s, 9H), 5.17 (m, 1H), 5.27 (m, 1H), 5.38 (m, 1H), 6.11 (d, J = 2.9 Hz, 1H), 7.38 (m, 3H), 7.38 (m, 3H), 8.20 (m, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.2, 43.8, 78.2, 81.6, 83.9, 117.6, 123.0, 124.8, 125.6, 127.2, 129.5, 129.6, 134.8, 142.5, 157.5, 159.0. IR (ATR): 3319, 2975, 1704, 1556,

1515, 732, 700 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{20}H_{21}N_3O_7Na$ 438.1277; found 438.1279. HPLC: (Lux Amilose-1, *n*-hexane/2-propanol = 95:5, 0.5 mL/min, λ = 254 nm). *major (2S,3R,4R)*: t_R = 47.3 min (major), t_R = 60.0 min (minor). (dr 90:10; er 85:15).

***tert*-Butyl ((2*R*,3*S*,4*S*)-2-(4-Chlorophenyl)-3-nitrochroman-4-ylcarbamate (6ab).** From α-amido sulfone **4a** (74 mg, 0.2 mmol), *trans*-4-chloro-β-nitrostyrene (44 mg, 0.24 mmol), and catalyst **I** (5 mg, 0.01 mmol) at 0 ºC. The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6ab** (75 mg, 0.19 mmol, 93%). Colorless solid, mp 119-122 °C. $[\alpha]_D^{23}$ = +4.7 (c = 0.5, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.46 (s, 9H), 5.22 (m, 2H), 5.28 (m, 1H), 5.78 (d, J = 4.7 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H, Har), 7.27-7.40 (m, 6H, Har). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.2, 45.1, 75.7, 81.0, 85.0, 116.9, 122.3, 127.1, 127.4, 129.4, 129.9, 134.3, 135.1, 152.3, 155.1. IR (ATR): 3326, 1670, 1555, 1009, 833, 760 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{20}H_{21}ClN_2O_5Na$ 427.1037; found: 427.1031. HPLC: (Chiralpak IA, *n*-hexane/2-propanol = 95:5, 0.5 mL/min, λ = 210 nm). *major (2S,3R,4R)*: t_R = 34.1 min (major), t_R = 53.0 min (minor).(dr 93:7; er 97:3).

***tert*-Butyl ((2*R*,3*S*,4*S*)-2-(4-chlorophenyl)-6-methyl-3-nitrochroman-4-yl)carbamate (6bb).** From α-amido sulfone **4b** (78 mg, 0.2 mmol), *trans*-4-chloro-β-nitrostyrene (44 mg, 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **4bb** (79 mg, 0.19 mmol, 95%). Colorless solid, mp 88-90° C. $[\alpha]_D^{23}$ = +7.0 (c = 0.4, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.31 (s, 3H), 5.17 (m, 2H), 5.27 (m, 1H), 5.75 (d, J = 5.2 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 7.08 (m, 2H), 7.33 (m, 4H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 20.6, 28.2, 45.2, 75.6, 80.9, 85.0, 116.7, 119.1, 127.4, 127.5, 129.4, 130.7, 131.8, 134.5, 135.1, 150.2, 155.2. IR (ATR): 3299, 2981, 1701, 1554, 1493, 1367, 1159, 816 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{21}H_{23}ClN_2O_5Na$ 441.1192; found 441.1196. HPLC: (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, 1 mL/min, λ = 254 nm). *major (2S,3R,4R)*: t_R = 19.0 min (major), t_R = 37.8 min (minor).(dr 81:19; er 98:2).

***tert*-Butyl ((2*R*,3*S*,4*S*)-2-(4-fluorophenyl)-3-nitrochroman-4-yl)carbamate (6ac).** From α-amido sulfone **4a** (74 mg, 0.2 mmol), 4-fluoro-β-nitrostyrene (40 mg, 0.24

mmol), and catalyst *sq*-**I** (5 mg, 0.01 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6ac** (73 mg, 0.17 mmol, 87%). Colorless solid, mp 54 -56 °C. [Lit.[5] mp 50-55 ºC]. $[\alpha]_D^{23}$ = +15.9 (c = 0.9, $CHCl_3$). [Lit.[5] $[\alpha]_D^{23}$ = -18.3 (c = 1.0, $CHCl_3$, for ent-**6ac**, dr 84:16, er 96.5: 3.5)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 5.27 (m, 3H), 5.76 (d, J = 3.7 Hz, 1H), 7.06 (m, 4H), 7.32 (d, J = 7.3 Hz, 2H), 7.41 (m, 2H). HPLC: (Lux amylose-1, *n*-hexane/2-propanol = 96:4, 0.5 mL/min, λ = 254 nm). *major (2S,3R,4R)*: t_R = 29.9 min (minor), t_R = 40.0 min (major). (dr 93:7; er 98:2).

***tert*-Butyl ((2*R*,3*S*,4*S*)-2-(4-fluorophenyl)-6-methyl-3-nitrochroman-4-yl)carbamate (6bc).** Obtained from α-amido sulfone **4b** (78 mg, 0.2 mmol), 4-fluoro-β-nitrostyrene (40 mg, 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6bc** (76 mg, 0.17 mmol, 88%). Colorless solid, mp 65-67 °C. $[\alpha]_D^{23}$ = +30.7 (c = 0.4, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.46 (s, 9H), 2.31 (s, 3H), 5.17 (m, 1H), 5.21 (m, 1H), 5.26 (m, 1H), 5.72 (d, J = 5.5 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 7.03-7.09 (m, 4H), 7.37 (m, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 20.6, 28.2, 45.3, 75.5, 80.9, 85.2, 110.0, 116.1 (d, J = 21.7 Hz), 116.7, 119.3, 127.7, 128.0 (d, J = 8.7 Hz), 130.7, 131.7, 150.3, 155.2, 162.9 (d, J = 248.5 Hz). IR (ATR): 3278, 2981, 1672, 1554, 1497, 1159, 837, 816 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{21}H_{23}FN_2O_5Na$ 425.1488; found 425.1493. HPLC: (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, 1 mL/min, λ = 254 nm). *major (2S,3R,4R)*: t_R = 17.8 min (major), t_R = 36.4 min (minor). (dr 86:14; er 97:3).

***tert*-Butyl ((2*R*,3*S*,4*S*)-2-(4-methoxyphenyl)-3-nitrochroman-4-yl)carbamate (6ad).** From α-amido sulfone **4a** (75 mg, 0.2 mmol), *trans*-4-methoxy-β-nitrostyrene (43 mg, 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol). When the reaction was finished, was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6ad** (77 mg, 0.19 mmol, 96%). Colorless solid, mp 117 -120 °C. [Lit.[5] mp 116-119 ºC]. $[\alpha]_D^{23}$ = +31.1 (c = 0.4, $CHCl_3$). [Lit.[5] $[\alpha]_D^{23}$ = -35.9 (c = 1.0, $CHCl_3$, for ent-**6ad**, dr 93:7, er 96.5: 3.5)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.78 (s, 3H), 5.19 (m, 1H), 5.28 (m, 2H), 5.74 (d, J = 4.7 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.3 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 7.29 (m, 4H). HPLC: (Chiralpak IA, *n*-hexane/2-propanol = 85:15, 0.3 mL/min, λ = 254

nm). *major (2S,3R,4R)*: t_R = 38.9 min (major), t_R = 42.1 min (minor) (dr 92:8; er 95:5).

***tert*-Butyl ((2*R*,3*S*,4*S*)-2-(4-methoxyphenyl)-6-methyl-3-nitrochroman-4-yl)carbamate (6bd).** From α-amido sulfone **4b** (78 mg, 0.2 mmol), *trans*-4-methoxy-β-nitrostyrene (43 mg, 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol). The reaction mixture was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6bd** (76 mg, 0.17mmol, 88%). Colorless solid, mp 111-113 °C. [Lit.[5] mp 110-113°C]. $[\alpha]_D^{23}$ = +37.8 (c = 0.8, $CHCl_3$). [Lit.[5] $[\alpha]_D^{23}$ = -35.3 (c = 1.0, $CHCl_3$, for ent-**6bd**, dr 88:12, er 98:2) for (2*S*,3*R*,4*R*) stereoisomer]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.29 (s, 3H), 3.77 (s, 3H), 5.24 (m, 2H), 5.31 (m, 1H), 5.69 (d, J = 4.6 Hz, 1H), 6.86 (m, 3H), 7.05 (m, 2H), 7.31 (m, 2H). HPLC: (Chiralpak AD-H, *n*-hexane/2-propanol = 90:10, 0.5 mL/min, λ = 254 nm). *major (2S,3R,4R)*: t_R = 27.6 min (major), t_R = 45.1 min (minor). (dr 99:1; er 98:2).

***tert*-Butyl ((2*R*,3*S*,4*S*)-2-(naphthalen-2-yl)-3-nitrochroman-4-yl)carbamate (6ae).** From α-amido sulfone **4a** (75 mg, 0.2 mmol), (*E*)-2-(2-nitroethenyl)-naphthalene[28] (48 mg, 0.24 mmol) and catalyst **I** (5 mg, 0.01 mmol). When the reaction was finished, was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to yield compound **6ae** (79 mg, 0.19 mmol, 94%). Colorless solid, mp 160-161 °C. [Lit.[5] mp 150-154 ºC]. $[\alpha]_D^{23}$ = +33.4 (c = 0.5, $CHCl_3$). [Lit.[5] $[\alpha]_D^{23}$ = -32.6 (c = 1.0, $CHCl_3$, for ent-**6ae**, dr 88:12, er 96.5:3.5)]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 5.24 (m, 2H), 5.45 (m, 1H), 5.99 (d, J = 5.0 Hz, 1H), 7.06 (m, 2H), 7.31 (m, 2H), 7.49 (m, 3H), 7.83-7.89 (m, 4H). HPLC: (Chiralcel OD, *n*-hexane/2-propanol = 80:20, 1 mL/min, λ = 254 nm). *major (2S,3R,4R)*: t_R = 14.9 min (minor), t_R = 19.9 min (major). (dr 99:1; er 100:0).

General procedure for the Mannich-cyclization–tautomerization cascade reaction of 2-hydroxyaryl substituted α-amido sulfones with phenylsulfonylacetonitrile. *α*-Amido sulfone **4** (75 mg, 0.2 mmol, 1 equiv) and bifunctional catalyst (0.01 mmol, 0.05 equiv) was dissolved in $CHCl_3$ (0.6 mL), and the resulting solution was stirred for 15 min at 0 ºC. A 0.4 mol/L aqueous solution of K_2CO_3 (0.6 mL) was then added to the reaction followed by (phenylsulfonyl)acetonitrile (43 mg, 0.24 mmol), and the resulting mixture was stirred at 0 °C and monitoring by ^{1}H-NMR. A saturated aqueous NH_4Cl solution was

then added to the reaction, and the resulting mixture was extracted with DCM. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give a residue, which was purified by flash column chromatography on silica gel (hexane/ethyl acetate mixtures) to give the desired product. The enantiomeric ratio were determined by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent.

General procedure for the Mannich-cyclization–tautomerization cascade reaction of 2-hydroxyaryl substituted α-amido sulfones with phenylsulfonylacetonitrile with supported catalysts. The reactions were carried out as described for unsupported catalyst until the reactions were finished. Then, the catalyst was recovered by filtration, washed with MeOH, dried under vacuum, and reused in the next cycle without further purification. The filtrate was worked up as described above.

The catalyst was recovered without apparent modification, because the IR of the material after five cycles is coincident with that of the starting material (Compare the IR spectra in page S-29 in SI).

***tert*-Butyl (*S*)-(2-amino-3-(phenylsulfonyl)-4*H*-chromen-4-yl)carbamate (*ent*-8a).** This compound was obtained from α-amido sulfone **4a** (75 mg, 0.2 mmol), (phenylsulfonyl)acetonitrile (43 mg, 0.24 mmol) and ***sq*-IIIb** (5 mg, 0.01 mmol) as catalyst. The product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 4:1) to yield compound *ent*-**8a** (71 mg, 0.17 mmol, 87%). Colorless solid, mp 77-79 °C. $[\alpha]_D^{23}$ = +23.5 (c = 1.0, $(CH_3)_2CO$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 9H), 4.77 (m, 1H), 5.57 (d, J = 8.2 Hz, 1H), 6.04 (br s, 2H), 6.93 (d, J = 8.2 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.46-7.55 (m, 4H), 7.95 (d, J = 7.3 Hz, 2H, Har). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.3, 44.1, 79.5, 83.1, 115.6, 123.5, 125.1, 126.6, 128.7, 129.0, 132.6, 143.2, 148.6, 154.7, 158.3. IR (ATR): 3331, 1697, 1632, 1395, 1134, 723 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{20}H_{22}N_2O_5SNa$ 425.1146; found 425.1153. HPLC: (Chiralpak IA, *n*-hexane/2-propanol = 80:20, 1 mL/min, λ = 254 nm) t_R = 10.6 min (major), t_R = 15.4 min (minor). (er 96:4).

***tert*-Butyl (*R*)-(2-amino-6-methyl-3-(phenylsulfonyl)-4*H*-chromen-4-yl)carbamate (8b).** This compound was obtained from α-amido sulfone **4b** (75 mg, 0.2 mmol),

(phenylsulfonyl)acetonitrile (43 mg, 0.24 mmol) and catalyst ***sq*-I** (5 mg, 0.01 mmol) as described for **8a**. The product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 4:1) to yield **8b** (46 mg, 0.16 mmol, 81%). Colorless solid, mp 97-100 °C. $[\alpha]_D^{23}$ = -86.5 (c = 1.0, $(CH_3)_2CO$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.26 (s, 3H), 4.75 (m, 1H), 5.51 (d, J = 8.3 Hz, 1H), 5.98 (br s, 2H), 6.82 (d, J = 8.3 Hz, 1H), 7.00 (dd, J = 8.3 Hz, 2.2 Hz, 1H), 7.22 (m, 1H), 7.46-7.53 (m, 3H), 7.95 (m, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): ^{13}C-NMR (126 MHz, $CDCl_3$): δ 20.7 ($\underline{C}H_3$); 28.4, 44.2, 79.5, 81.1, 115.3, 123.1, 126.6, 129.0, 129.1, 129.4, 132.6, 134.8, 143.1, 146.6, 154.8, 158.3. IR (ATR): 3335, 1693, 1636, 1387, 1224, 1089, 723 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{21}H_{24}N_2O_5SNa$ 439.1303; found 439.1303. HPLC: (Lux amylose-1, *n*-hexane/2-propanol = 80:20, 1 mL/min, λ = 254 nm) t_R = 30.4 min (minor), t_R = 34.6 min (major). (er 95:5)

***tert*-Butyl (*R*)-(2-amino-6-bromo-3-(phenylsulfonyl)-4*H*-chromen-4-yl)carbamate (8c).** This compound was obtained from α-amido sulfone **4c** (91 mg, 0.2 mmol), (phenylsulfonyl)acetonitrile (43 mg, 0.24 mmol) and catalyst ***sq*-I** (5 mg, 0.01 mmol) as described for **8a**. The product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 4:1) to yield **8c** (85 mg, 0.18 mmol, 85%). Colorless solid, mp 139-141°C. $[\alpha]_D^{23}$ = -11.8 (c = 1.0, $(CH_3)_2CO$). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 9H), 4.77 (m, 1H), 5.45 (d, J = 7.9 Hz, 1H), 5.98 (br s, 2H), 6.82 (d, J = 8.8 Hz, 1H), 7.30 (dd, J = 8.7 Hz, 2.4 Hz, 1H), 7.45-7.60 (m, 4H), 7.92 (d, J = 8.0 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.3, 43.9, 77.9, 83.0, 117.4, 125.3, 126.6, 129.1, 131.7, 131.8, 132.8, 142.9, 147.8, 154.6, 158.0. IR (ATR): 3339, 1697, 1632, 1387, 1085, 723 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{20}H_{21}BrN_2O_5SNa$ 503.0252; found 503.0258. HPLC: (Chiralpak IA, *n*-hexane/2-propanol = 80:20, 1 mL/min, λ = 254 nm) t_R = 18.3 min (minor), t_R = 23.1 min (major). (er 94:6)

***tert*-Butyl (*R*)-(2-amino-6-chloro-3-(phenylsulfonyl)-4*H*-chromen-4-yl)carbamate (8d).** Obtained from α-amido sulfone **4d** (84 mg, 0.2 mmol), (phenylsulfonyl)acetonitrile (43 mg, 0.24 mmol) and catalyst ***sq*-I** (5 mg, 0.01 mmol) as described for **8a**. The product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 4:1) to yield compound **8d** (81 mg, 0.17 mmol, 82%). Colorless solid, mp 175-177 °C. $[\alpha]_D^{23}$ = -45.1 (c = 1.0, $(CH_3)_2CO$). ^{1}H-NMR (500

MHz, $CDCl_3$): δ 1.39 (s, 9H), 4.78 (br s, 1H), 5.47 (d, J = 7.9 Hz, 1H), 5.98 (br s, 2H), 6.89 (d, J = 8.8 Hz, 1H), 7.18 (dd, J = 8.8, 2.5 Hz, 1H), 7.44 (br s, 1H), 7.50 (m, 2H); 7.56 (m, 1H), 7.94 (d, J = 7.1 Hz, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 28.3, 44.1, 79.9, 83.0, 117.1, 124.9, 126.6, 128.7, 128.9, 129.1, 130.0, 132.8, 142.9, 147.2, 154.6, 158.0. IR (ATR): 3339, 1697, 1640, 1342, 1089, 727 cm^{-1}. HRMS (ESI-QTOF) *m/z*: [M+Na] Calcd for $C_{20}H_{21}ClN_2O_5SNa$ 459.0757; found 459.0754. HPLC: (Chiralpak IA, *n*-hexane/2-propanol = 80:20, 1 mL/min, λ = 254 nm) t_R = 16.9 min (minor), t_R = 21.9 min (major). (er 94:6).

Supporting Information Available: Recyclability of the supported catalysts. Copies of ^{1}H-NMR and ^{13}C-NMR spectra for all new compounds, and X-ray crystallographic data for compound *ent*-**8a**. IR (ATR) for supported thioureas and squaramides, and copies of the HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org

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