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Organocatalytic asymmetric synthesis of trisubstituted pyrrolidines via a cascade reaction

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ABSTRACT

A new bifunctional thiourea **II** catalyzed methodology was developed for the synthesis of chiral trisubstituted pyrrolidines using 4-aminocrotonate **1a/1b** and nitroolefins **2a–g** as starting materials. Two different N-protected 4-aminocrotonates **1a** and **1b** were tested for the reaction with **1a** giving the desired product **3a** with a high diastereomeric ratio (>20:1) but with low enantioselectivity (ee up to 7%). *N*-Tosyl-4-aminocrotonate **1b**, however, yielded the product with moderate dr (up to 68:32) but with high ee in the case of the major *trans–trans*-isomers **4a–g** (ee from 92% to 98%) and modest enantiomeric excess for the minor *trans–cis*-isomers **4a′–g′** (ee up to 57%). This methodology was also successfully applied when (*E*)-β-methyl-*trans*-β-nitrostyrene **2h** was used as the starting nitroalkene to provide the product with dr 70/30 and with ee of 63% and 67%, respectively. The absolute configuration of both isomers was established using chiral derivatization with Mosher's and mandelic acids, with the relative stereochemistry being determined via NMR analysis.

1. Introduction

Cascade reactions represent a set of new efficient tools for the synthesis of complex chiral compounds in one step.[1] Combining cascade reactions with an asymmetric organocatalysis allows enantiomerically enriched target molecules to be obtained. The primarily generated stereogenic center acts as a chiral auxiliary in the following steps of the cascade. This opens up a route to the stereodirected synthesis of compounds with multiple stereocenters. Changing one or more starting compounds under at the same reaction conditions yields a large variety of products.

Substituted chiral pyrrolidines are the structural components of numerous biologically active synthetic and naturally occurring substances.[2–5] They have also found use as efficient organocatalysts in a wide variety of reactions proceeding via an iminium or an enamine intermediate.[6,7]

Over the course of our ongoing research on organocatalysis,[8–11] we recently developed a novel multicomponent reaction of α,β-unsaturated aldehydes with *N*-benzyl-4-aminocrotonate **1a**, which enabled us to synthesize new nitrogen containing bicyclic compounds.[12] The multicomponent reaction is based on an intermolecular addition of *N*-nucleophiles to an activated C–C double bond. We envisioned that one of the starting materials employed in this research, *N*-Bn-amino crotonate **1a**, could also be used as a building block for the construction of substituted monocyclic pyrrolidines. Aminocrotonates are multifunctional compounds that contain both a nucleophilic Michael donor (amino group) and an electrophilic Michael acceptor (an activated double bond) groups. When the amino group reacts first (intermolecularly) with the other Michael acceptor (nitrostyrene **2a**), a new Michael donor (nitronate anion **3′**) is generated. The following intramolecular reaction leads to the formation of the pyrrolidine framework **3** (Scheme 1). We hypothesized that using either *Cinchona* alkaloids or enantiomeric bifunctional thioureas (Fig. 1) as catalysts could result in enantioriched products. It is known that bifunctional catalysts with both hydrogen donor and acceptor moieties are more efficient in organocatalytic reactions, providing activation of the nitroolefin and increasing the nucleophilicity of the amino group via the formation of hydrogen bonds.[13] We were also inspired by the literature data in which a synthesis of similar compounds as racemates was described.[14]

2. Results and discussion

2.1. Reactions with *N*-Bn-4-aminocrotonate

For the initial screening of catalysts, a model reaction between *N*-Bn-4-aminocrotonate **1a** and β-nitrostyrene **2a** was chosen. Our initial attempts to find a suitable catalyst concentrated on taking advantage of the use of chiral thioureas **I** and **II** that had previously been reported in the literature. These catalysts are known to have high activity in nucleophilic addition reactions to nitroalkenes.[15] Although thioureas **I** and **II** were highly active in the reaction,

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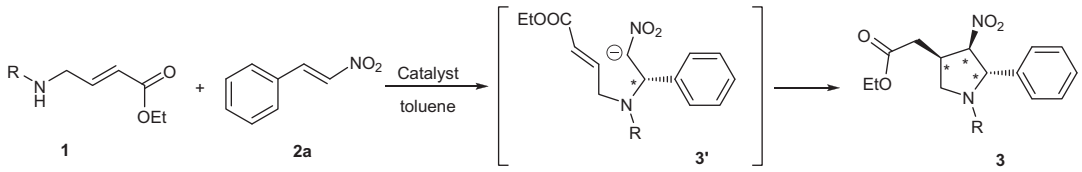


Scheme 1. Synthesis of trisubstituted chiral pyrrolidines.

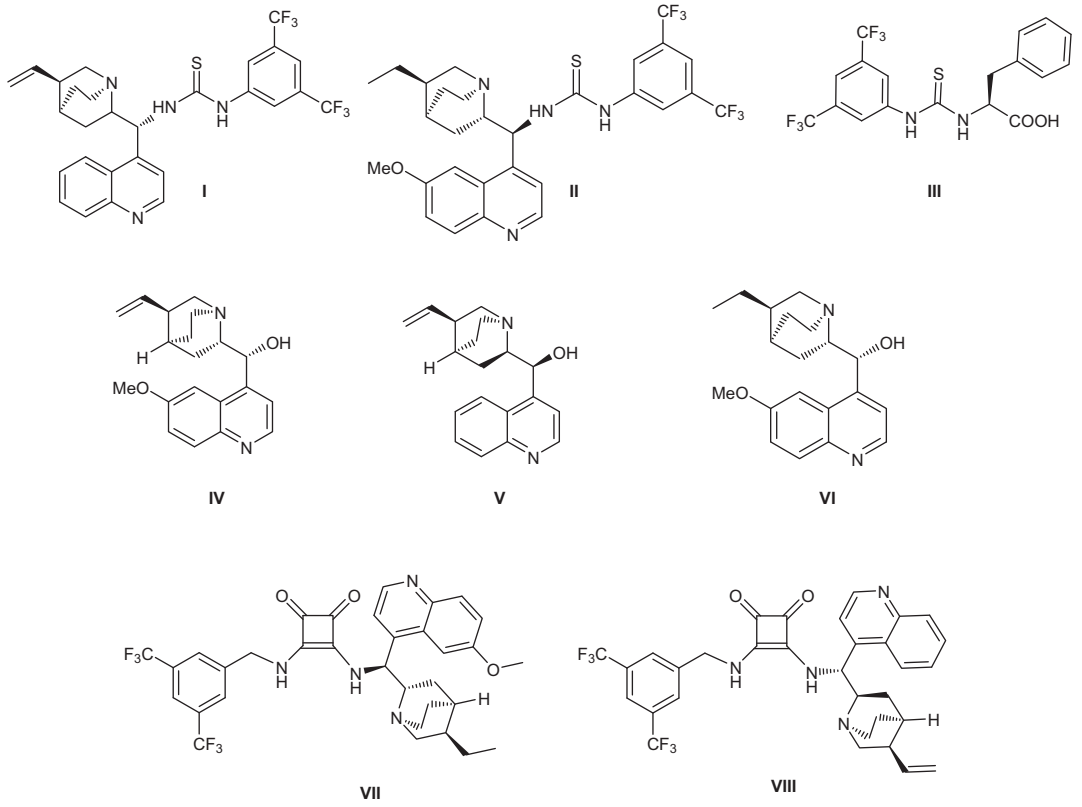
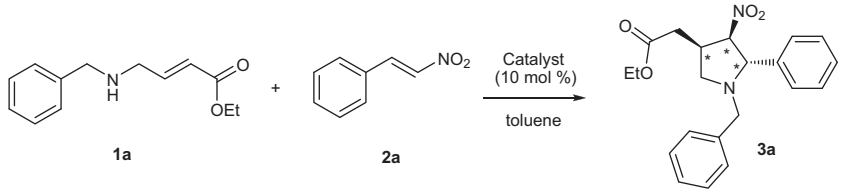


Figure 1. Catalysts used in the synthesis of chiral pyrrolidines.

Table 1
Catalyst screening with *N*-benzyl-4-aminocrotonate **1a**[a]



Entry	Catalyst	Temp (°C)	Time (h)	Yield (%)	ee[b] (%)
1	**I**	rt	2	89	7
2	**I**	−25	15	79	*rac*
3	**II**	rt	2	69	*rac*
4	**III**	rt	3	88	*rac*
5	**IV**	rt	4	77	*rac*
6	**V**	rt	4	91	2

[a] Only relative configuration of **4a** was determined.
[b] Determined by chiral HPLC.

yielding the products with good yields and diastereoselectivities, the enantioselectivities remained very low in our model reaction (Table 1, entries 1–3).

Thiourea **III** derived from L-phenylalanine did not improve the selectivity although the product was isolated in an 88% yield (Table 1, entry 4). Employing *Cinchona* alkaloids as catalysts gave

only racemic (or nearly racemic) products (Table 1, entries 5 and 6). All reactions with *N*-Bn-crotonate were diastereoselective (dr >20:1) predominantly affording a single diastereoisomer **3a** in a *trans–cis* configuration. This relative configuration was assigned on the basis of the published data on ethyl 3-pyrrolidineacetate, where the carbon from the **C**H_2CO gives a signal at 37.2 ppm[16] and in *trans*-4-nitro-1-(phenylmethyl)-3-pyrrolidineacetic acid ethyl ester **C**H_2CO at 36.2 ppm.[17] In **3a**, this carbon resonates at 32.5 ppm, pointing to a mutual *cis*-orientation of the CH_2 and NO_2 groups. A mutual *trans* orientation of nitro and phenyl substituents was confirmed by the NMR data of *trans*-*N*-benzyl-3-nitro-2-phenylpyrrolidine.[18]

2.2. Reactions with *N*-Ts-4-aminocrotonate

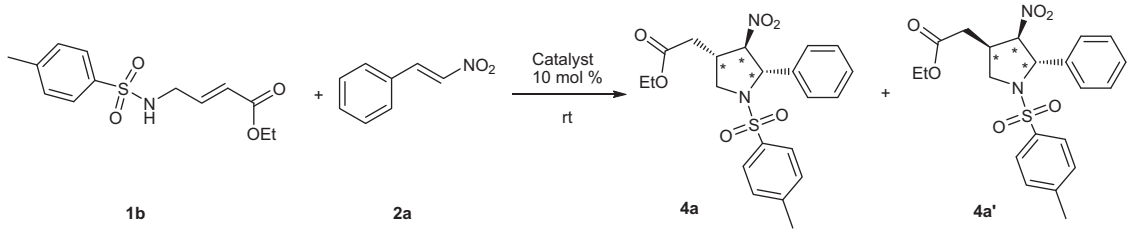
We supposed that the decrease of the nucleophilicity of the nitrogen atom might slow down the reaction and improve the stereoselectivity. Hence we decided to replace the Bn-group with a tosyl group at the nitrogen atom. Changing the protecting group in the aminocrotonate greatly influenced the reaction. When *N*-tosyl 4-aminocrotonate **1b** was reacted with nitrostyrene in the presence of 10 mol % of catalyst **I**, a 3:2 mixture of diastereoisomeric trisubstituted pyrrolidines **4a** and **4a**′ was obtained. Instead of the racemic product that was formed with *N*-Bn-crotonate **1a**, one isomer was obtained in high enantiomeric purity (ee 98%, Table 2, entry 1). The diastereoisomeric pyrrolidines **4a** and **4a**′ differed with regard to the relative configuration of the carboxymethylene substituent. This was in the *trans*-configuration with the nitro group in the isomer **4a** (**C**H_2CO at 35.2 ppm) and in the *cis*-configuration in **4a**′ (**C**H_2CO at 31.7 ppm). The nitro and phenyl groups were always in the *trans*-configuration. The yield of the first reaction was low. When thiourea **II** (which has shown higher activities compared to other thioureas derived from the *Cinchona* alkaloids[15]) was used under the same reaction conditions, the diastereoselectivity remained low but the reaction rate was considerably increased but with the same enantioselectivity (Table 2, entry 2). Switching the solvent from dichloromethane to toluene improved the yields of the reaction, although only moderate changes in diastereoselectivities and enantioselectivities were observed (Table 2, entries 3 and 4). When the reaction was performed at 80 °C, the product was isolated in an almost quantitative yield after 1.5 h although the selectivity of both isomers was lower than at the ambient temperature (Table 2, entry 5). At −25 °C, the reaction rate was significantly decreased, although the enantioselectivity of the minor isomer improved (Table 2, entry 6).

By using NaOAc as the co-catalyst, the reaction proceeded faster but with lower selectivity (Table 2, entry 7). The reaction catalyzed by the *Cinchona* alkaloid **VI** and 1,3-diethylthiourea as a co-catalyst provided products with good diastereoselectivities but low enantioselectivities. Squaramides **VII** and **VIII**, which have been noted to have high activity were also tested for the reaction.[19] However, in the present case slightly inferior results compared to thiourea **II** were obtained (Table 2, entries 9 and 10).

Next, the scope of the reaction was investigated under the best conditions found in the catalyst screening experiments (Table 2, entry 4). A cascade reaction was carried out employing different nitroolefins for the reaction. The phenyl ring with an electronegative substituent **2b** gave the product with a high yield and similar selectivity to nitrostyrene **2a** (Table 3, entry 2). The best diastereoselectivity with aromatic substrates was obtained with *p*-methoxy derivative **2c** (Table 3, entry 3). Both *p*-trifluoromethyl and thiophene-substituted derivatives **2d** and **2e** showed high reactivity (Table 3, entries 4 and 5) and diastereoselectivity and enantioselectivity values compared to the previous examples. The naphthyl-substituted starting material **2f**, although the bulkiest, reacted smoothly, yielding the product with a 93% yield (Table 3, entry 6). The aliphatic substrate **2g** also underwent the conversion with almost a quantitative yield (96%) and with the highest diastereoselectivity so far (Table 3, entry 7).

Based on these results, it can be deduced that the electronic nature of the nitroalkenes has a limited effect on the reactivity and selectivity of the reaction. In all cases, the diastereoselectivity was low, varying from 52/48 to 68/32 with minor variations. The enantioselectivities were generally very high for the major diastereoisomer but lower for the minor diastereoisomer.

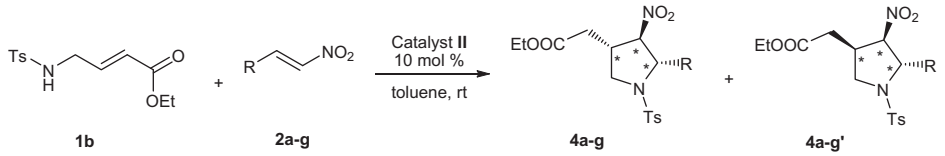
Table 2
Catalyst screening with *N*-tosyl 4-aminocrotonate **1b**



Entry	Catalyst	Solvent	Time (h)	Yield (%)	dr[a] (%)	ee[a] (%)
1	**I**	CH_2Cl_2	21	36	61/39	98/48
2	**II**	CH_2Cl_2	20	76	47/53	99/48
3	**I**	Toluene	21	76	60/40	98/43
4	**II**	Toluene	22	99	54/46	96/46
5	**II**	Toluene	1.5	99[b]	58/42	92/30
6	**II**	Toluene	6 days	62[c]	46/54	99/62
7	**II**[d]	Toluene	6	81	48/52	95/37
8	**VI**[e]	CH_2Cl_2	27	65	8/92	47/11
9	**VII**	Toluene	22	72[f]	60/40	94/32
10	**VIII**	Toluene	26	Traces	nd	nd

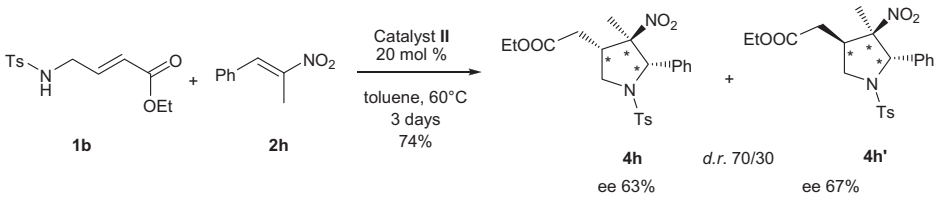
[a] Determined by chiral HPLC on a Chiralcel AD-H column.
[b] Reaction at 80 °C.
[c] Reaction at −20 °C.
[d] 1 equiv NaOAc was used as an additive.
[e] 20 mol % diethylthiourea was used as an additive.
[f] Reaction performed using 5 mol % of the catalyst.

Table 3
Substrate screening under the optimal conditions



Entry	R	Time (h)	Yield[a,b] (%)	dr[c]	ee[d] (%)
1	**a**: Phenyl	22	99	54/46	96/46
2	**b**: *p*-Br-phenyl	17	90	55/45	98/45
3	**c**: *p*-MeO-phenyl	19	91	60/40	97/51
4	**d**: *p*-CF_3O-phenyl	6	93	56/44	97/43
5	**e**: Thiophen-2-yl	8	80	52/48	97/57
6	**f**: 2-Naphthyl	20	93	58/42	95/44
7	**g**: *c*-Hexyl	22	96	68/32	92/36

[a] Reaction conditions: 1 equiv of **1a**, 3 equiv of **2a–g** were used.
[b] As a mixture of diastereoisomers.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis.



Scheme 2. Reaction with (*E*)-β-methyl-*trans*-β-nitrostyrene.

The formation of quaternary stereogenic centers is one of the most important challenges in modern asymmetric synthesis.[20] Since quaternary centers are present in many bioactive natural products, new methods for their formation are of great significance. In order to expand upon our methodology in the synthesis of chiral pyrrolidines, we decided to test β-methyl-*trans*-β-nitrostyrene **2h** as a substrate for the reaction. Since it is a less reactive starting material, 20 mol % of thiourea **II** was used instead of 10 mol % and the reaction was carried out at an elevated temperature (Scheme 2).

After three days, the product was isolated as a mixture of two diastereoisomers (in a 70:30 ratio) with good enantioselectivities for both isomers (ee 63% and 67%, respectively). For the determination of the relative configuration of the isomers, their ^{13}C chemical shifts were compared. The most remarkable difference was observed in the methyl carbon geminal to the nitro group shieldings; in **4h** it was 3.7 ppm less shielded. The reason for this is one less vicinal gauche interaction with the *cis*-substituent. At the same time, the difference in the chemical shifts of the carboxymethylene carbons is less than 0.5 ppm because in both isomers, these carbons have one vicinal *cis*-interaction: in **4h** with the methyl group and in **4h**′ with the nitro group. The similarity of methyl and nitro groups on the nonbonded effects on the ^{13}C chemical shifts was illustrated by the close chemical shifts of C-2,6 of the *cis*-isomers of 1-*tert*-butyl-4-nitrocyclohexane (22.2 ppm),[21] and 1-*tert*-butyl-4-methylcyclohexane (21.4 ppm).[22] Further confirmation of the relative configuration of the isomers **4h/4h**′ was established by NOE experiments (Fig. 2). Both isomers have nitro and phenyl groups in the *trans*-configuration, but in the major isomer, the ester substituent was *cis* to the phenyl group and in the minor isomer was *trans* to the phenyl group.

The absolute configuration of both isomers (*trans–trans* and *trans–cis*) was determined by their derivatization with Mosher's[23,24] and mandelic acid[25,26] and a comparison of the

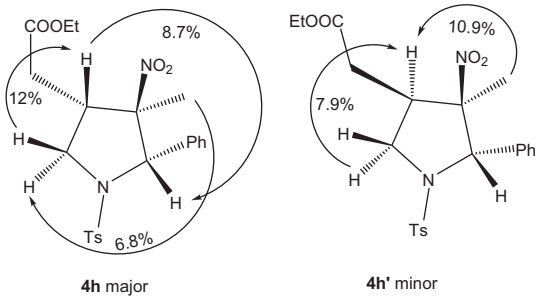
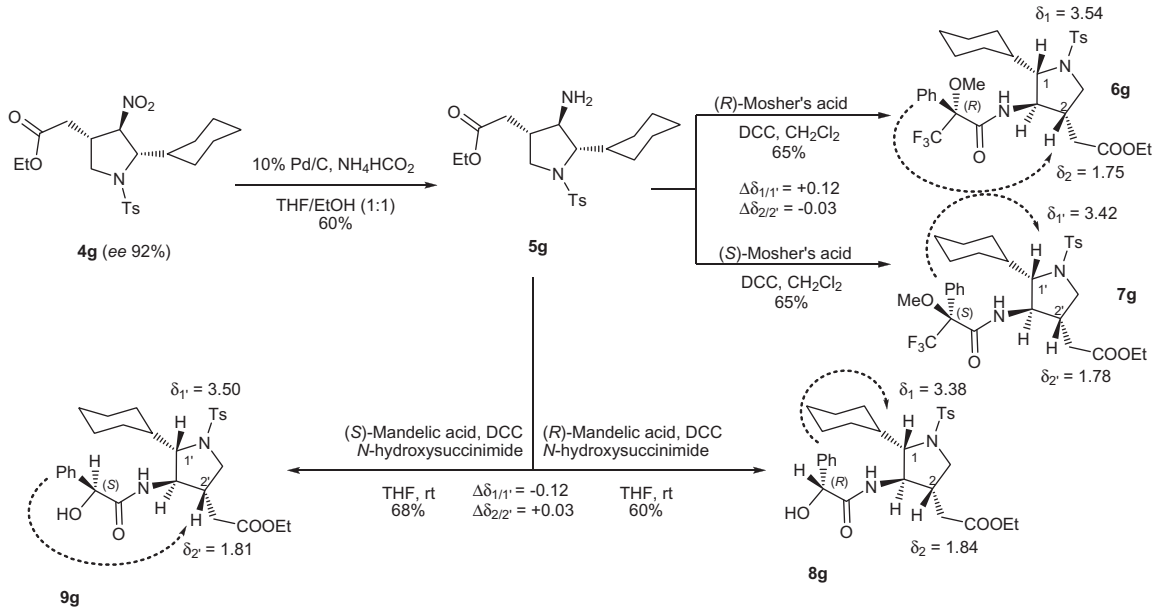


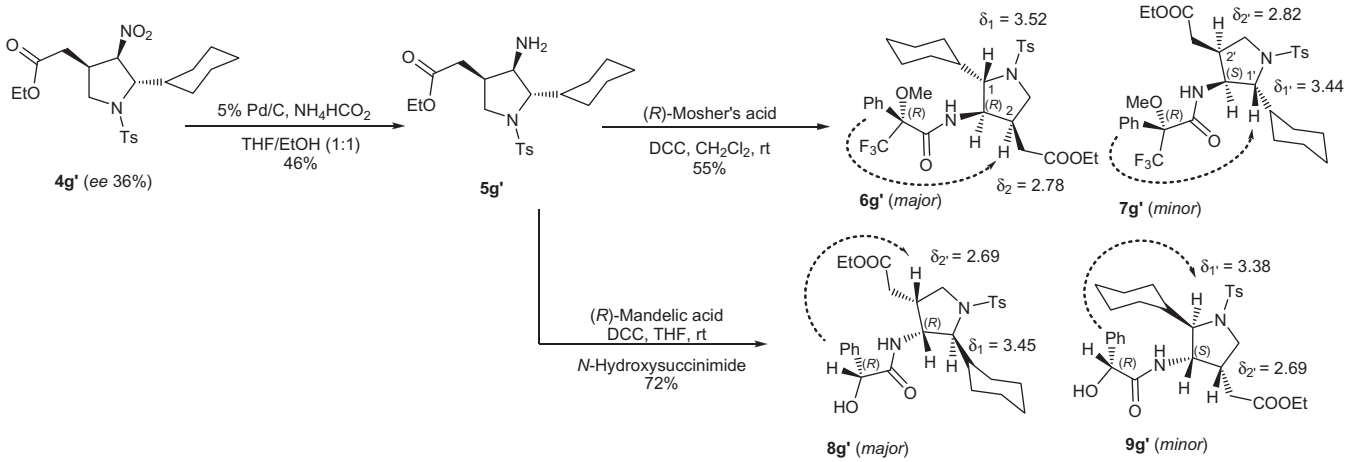
Figure 2. NOE results of pyrrolidines **4h** and **4h**′.

chemical shifts of the corresponding to the α-protons depending on both ligands surrounding the stereogenic center bearing the nitro group. The derivatizations were carried out by first reducing the nitro group to an amine, and then reacted with Mosher's and mandelic acids to form the corresponding amides (Schemes 3 and 4). Pyrrolidines **4g** and **4g**′ were used as model substrates because they could be easily separated by silica gel column chromatography.

For *trans–trans* pyrrolidine **4g**, having a high ee value (92%), a classic double derivatization was performed. After palladium-catalytic hydrogenation of the nitro group in pyrrolidine **4g**, the corresponding amine **5g** was first reacted with (*R*)- and (*S*)-Mosher's acid to form amides **6g** and **7g**. A comparison of the chemical shifts of the α-protons (Scheme 3) showed that the stereogenic center had an (*R*)-configuration. The absolute configuration of the adjacent centers can be determined from the relative configuration of the pyrrolidine. Although derivatization with only one agent (both enantiomers needed) is usually necessary, we decided to repeat the process with mandelic acid for the sake of comparison. Preliminary



Scheme 3. Determination of the absolute configuration of pyrrolidine **4g**.



Scheme 4. Determination of the absolute configuration of pyrrolidine **4g′**.

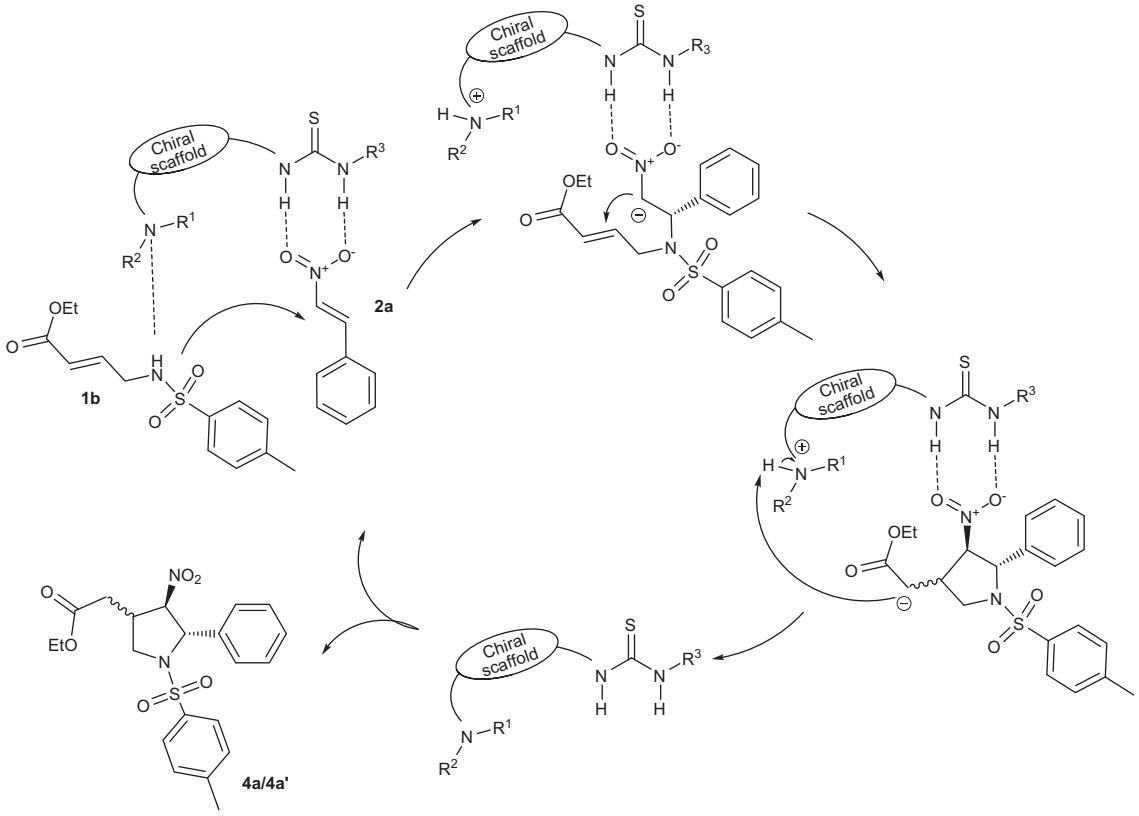
molecular mechanic optimization[27] of the amides **6g** and **7g** showed that there could be deviations from the expected preferred conformation where the trifluoromethyl, the carbonyl group of the amide and the proton at the stereogenic center would align on the same plane.

In the case of mandelic acid, the formation of a possible hydrogen bond between the hydroxyl and carbonyl groups of the amide should ensure a more rigid configuration and therefore the shielding effect exhibited by the phenyl group should be more pronounced. Molecular mechanics optimization[27] of amides **8g** and **9g** was in agreement with the expected conformation (see Scheme 3). The results obtained from the derivatization with mandelic acid were compatible with the results attained with Mosher's acid (the sign of the chemical shifts changes due to the different preferred conformation).

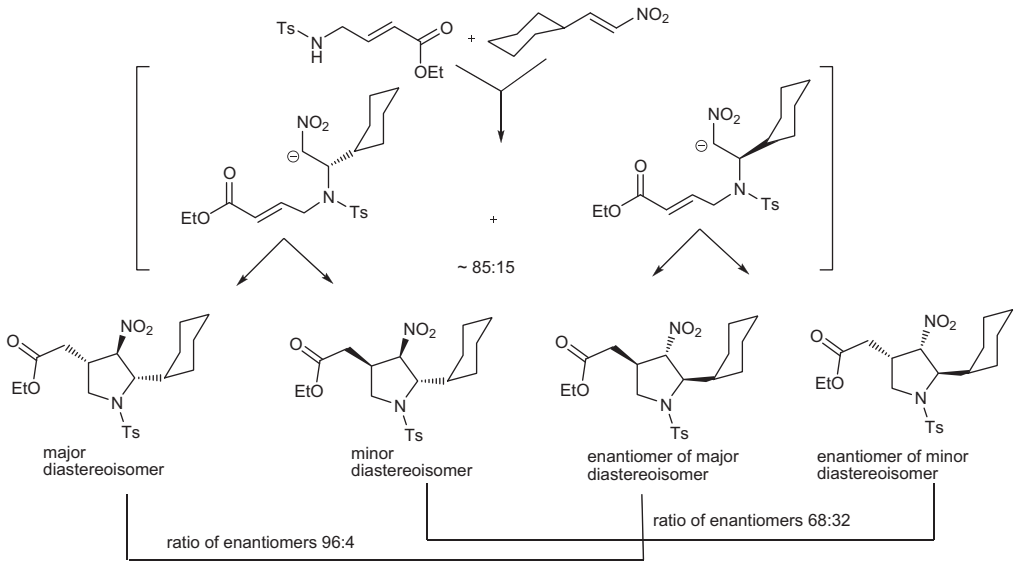
Since pyrrolidine **4g′** was formed with relatively low enantiomeric purity (ee 36%), derivatization with only (*R*)-Mosher's or (*R*)-mandelic acid was necessary (Scheme 4). The absolute configuration of *trans–cis* isomer **4g′** was assigned based on a comparison of the chemical shifts of the α-protons in the corresponding amides. The changes in chemical shifts coalesced when the derivatization was carried out with Mosher's and mandelic acid. Therefore, the absolute configuration of the center bearing the nitro group was assigned as (*R*). The adjacent centers were assigned based on the relative stereochemistry. It is assumed that the absolute configurations of the other pyrrolidines are the same as in pyrrolidines **4g** and **4g′**.

In order to elucidate the reasons for the low diastereoselectivity and high enantioselectivity of the major isomer, the following reaction mechanism was proposed (Scheme 5). The first step in the cascade involves the activation of nitroolefin **2a** by hydrogen bonding with the thiourea fragment of the catalyst and tosylamide **1b** by the tertiary amine of the catalyst. Activated substrates give the aza-Michael addition to form the nitrogen–carbon bond and the first stereogenic center.

The next step in the cascade involves the formation of a carbon–carbon bond to form the desired pyrrolidine ring. It is believed that based on the absolute configuration studies and the different enantioselectivities of the diastereoisomers, the catalyst will preferably form a *trans–trans* isomer from the major enantiomer from the first step. This control is not absolute since the enantiomeric excess of the *trans–cis* isomer is significantly lower than that of



Scheme 5. Proposed mechanism of the thiourea catalyzed formation of chiral substituted pyrrolidines.



Scheme 6. Distribution of the stereoisomers in the formation of pyrrolidines **4g** and **4g'**.

the *trans–trans* isomer. The second factor influencing the diastereoselectivity of the reaction is the conformational flexibility of the conjugated ester moiety. According to the proposed mechanism of the reaction, the ester group will remain flexible in the transition state due to the methylene unit and attack to the double bond can occur from both sides. It is evident from the experimental results that the second step of the cascade is under diastereoselective control, with the catalyst forming a more rigid transition state complex with one enantiomer from the first addition step, which results in the formation of a *trans–trans* isomer with high ee, and a *trans–cis* isomer with moderate ee. Taking into account that both isomers have the same absolute configuration at the C-2 and C-3 stereogenic centers and they are formed in a 2:1 ratio (in the case of **4g**), the ratio of the enantiomers formed in the first step of the cascade should be approximately 85:15, which corresponds to 70% ee (Scheme 6).

3. Conclusion

In conclusion we have developed a new organocatalytic cascade reaction for obtaining trisubstituted pyrrolidines. The selectivity of the reaction is highly dependent on the substituent at the nitrogen atom of the amino crotonate. The reaction with *N*-benzyl substituted reagent proceeds in high diastereoselectivity since *N*-tosyl crotonate affords products with moderate diastereoselectivity but with high enantioselectivity in the case of the major isomer and moderate enantioselectivity for the minor product. Attempts to improve the diastereoselectivity with catalyst design are currently in progress.

4. Experimental

4.1. General

The full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a Bruker Avance^{III} 400 and Avance^{III} 800 instruments. Internal standard (TMS $\delta = 0.00$) and solvent peak ($CHCl_3$ $\delta = 77.16$) were used as chemical shift references. Mass spectra were recorded by using Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS spectrometer by using AJ-ESI ionization. Chiral HPLC was performed using Chiralpak AD-H (250 × 4.6 mm) or Chiralcel OJ-H (250 × 4.6 mm) column. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP500. IR spectra were measured on a Perkin–Elmer Spectrum BX FTIR spectrometer. Toluene was dried by distillation over Na and stored over 4 Å MS. Precoated Silica Gel 60 F_{254} plates were used for TLC, whereas for column chromatography, silica gel KSK407100 μm was used. Commercial reagents were generally used as received. The petroleum ether used had a bp 40–60 °C.

4.2. Synthesis of starting materials

(*E*)-(2-Nitrovinyl)benzene **2a**, (*E*)-1-bromo-4-(2-nitrovinyl)benzene **2b**, (*E*)-1-methoxy-4-(2-nitrovinyl)benzene **2c** and (*E*)-1-(trifluoromethoxy)-4-(2-nitrovinyl)benzene **2d** were commercially available and purchased from Aldrich or Alfa-Aesar. (*E*)-2-(2-Nitrovinyl)thiophene **2e**, (*E*)-2-(2-nitrovinyl)naphthalene **2f**, (*E*)-(2-nitrovinyl)cyclohexane **2g** and (*E*)-(2-nitroprop-1-en-1-yl)benzene **2h** were prepared according to literature procedures and spectroscopic data matched literature values.[28–30]

4.2.1. (*E*)-2-(2-Nitrovinyl)thiophene 2e

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 13.4 Hz, 1H), 7.57 (d, J = 5.1 Hz, 1H), 7.48 (d, J = 13.5 Hz, 1H), 7.46 (d, J = 4.1 Hz, 1H), 7.15 (dd, J = 5.1, 3.7 Hz, 1H).

4.2.2. (*E*)-2-(2-Nitrovinyl)naphthalene 2f

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 13.6 Hz, 1H), 8.03 (s, 1H), 7.92–7.85 (m, 3H), 7.71 (d, J = 13.6 Hz, 1H), 7.63–7.54 (m, 3H).

4.2.3. (*E*)-(2-Nitrovinyl)cyclohexane 2g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 13.5, 7.2 Hz, 1H), 6.93 (dd, J = 13.5, 1.4 Hz, 1H), 2.32–2.20 (m, 1H), 1.86–1.76 (m, 4H), 1.75–1.67 (m, 1H), 1.41–1.13 (m, 5H).

4.2.4. (*E*)-(2-Nitroprop-1-en-1-yl)benzene 2h

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.55–7.33 (m, 5H), 2.46 (d, J = 1.0 Hz, 3H).

4.2.5. (*E*)-Ethyl-4-(benzylamino)but-2-enoate 1a

(*E*)-Ethyl-4-bromobut-2-enoate (5.51 mL, 30 mmol) was dissolved in CH_2Cl_2 (75 mL) and benzylamine (6.55 mL, 60.0 mmol) was added. The mixture was stirred at ambient temperature until TLC showed full conversion. The mixture was concentrated and washed with petroleum ether, and concentrated and purified by silica gel column chromatography (CH_2Cl_2–MeOH/NH_3 1%) to yield 4.27 g of product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 5H), 7.01 (dt, J = 15.7, 5.4 Hz, 1H), 6.02 (dt, J = 15.7, 1.8 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.81 (s, 2H), 3.43 (dd, J = 5.4, 1.8 Hz, 2H), 1.58–1.37 (s, 1H), 1.29 (t, J = 7.1 Hz, 3H).

4.2.6. (*E*)-Ethyl-4-(*N*-(*tert*-butoxycarbonyl)-4-methylphenylsulfonamido)but-2-enoate 1b

(*E*)-Ethyl-4-bromobut-2-enoate (1.86 mL, 10.14 mmol) was dissolved in DMF (20 mL) under argon. Sodium iodide (0.30 g, 2.03 mmol), potassium carbonate (2.80 g, 20.27 mmol) and *tert*-butyl-tosylcarbamate (2.75 g, 10.14 mmol) were then added and the mixture was heated to 60 °C. After TLC showed full conversion, the excess DMF was removed by rotary evaporation. The mixture was filtered and washed with CH_2Cl_2, and concentrated and purified by silica gel column chromatography (petroleum ether/EtOAc 10:1–5:1) to yield 3.08 g of product as a light yellow solid, mp 94–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.76 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.94 (dt, J = 15.7, 5.4 Hz, 1H), 6.01 (dt, J = 15.7, 1.6 Hz, 1H), 4.59 (dd, J = 5.4, 1.7 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.36 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 150.6, 144.7, 142.6, 136.9, 129.5 (2), 128.3 (2), 123.4, 85.0, 60.7, 47.2, 28.0 (3), 21.8, 14.4. HRMS (ESI): calcd for $[M+Na]^+$ ($C_{18}H_{25}NO_6SNa)^+$ requires m/z 406.1295, found 406.1300.

4.2.7. (*E*)-Ethyl-4-(4-methylphenylsulfonamido)but-2-enoate 1b

Compound **1b′** (3.07 g, 8.01 mmol) was dissolved in CH_2Cl_2 (20 mL) under Ar, cooled in an ice bath and trifluoroacetic acid (3.7 mL, 48.0 mmol) was then added dropwise. After the addition was complete, the stirring was continued at ambient temperature until TLC showed full conversion. The mixture was concentrated and the product recrystallized from the mixture of petroleum ether and EtOAc to yield 2.02 g of the product as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.76 (dt, J = 15.7, 5.3 Hz, 1H), 5.93 (dt, J = 15.7, 1.8 Hz, 1H), 4.87 (t, J = 6.3 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.75 (ddd, J = 6.9, 5.4, 1.8 Hz, 2H), 2.43 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 144.0, 142.4, 136.8, 130.0 (2), 127.3, (2) 123.1, 60.7, 43.9, 21.7, 14.3.

4.3. Synthesis of catalysts

Catalysts **IV**, **V** and **VI** were commercially available from Aldrich and were used as received. Catalyst **I**,[31] **II**,[32] **III**,[33] **VII**[34] and **VIII**[35] were synthesized according to literature procedures and spectral data matched those of the literature.

4.4. General procedure for the synthesis of chiral pyrrolidines 3a and 4a–g/4a′–g′

At first, *E*-nitrovinyl alkene **2a**–**g** (0.3 mmol) and (*E*)-ethyl 4-(4-methylphenylsulfonamido)but-2-enoate **1b** (28 mg, 0.1 mmol) were dissolved in toluene (0.5 mL). Next, 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*S*)-((2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)thiourea **II** (6 mg, 10 mol %) was added and the mixture was stirred at ambient temperature until TLC showed the full disappearance of *N*-tosyl crotonate **1b**. The mixture was directly purified by silica gel column chromatography using a mixture of petroleum ether and EtOAc as eluent.

4.4.1. Ethyl 2-(3S*,4S*,5R*)-1-benzyl-4-nitro-5-phenylpyrrolidin-3-yl)acetate 3a (Table 1)

At first, (*E*)-(2-nitrovinyl)benzene **2a** (82 mg, 0.55 mmol) and the catalyst (10 mol %, 0.05 mmol) were dissolved in toluene (1.25 mL). Next, (*E*)-ethyl-4-(benzylamino)but-2-enoate (0.11 g, 0.5 mmol) was added as a solution in toluene (1.25 mL) and the mixture was stirred at ambient temperature until TLC showed full conversion. The mixture was directly purified by silica gel column chromatography using petroleum ether/EtOAc as an eluent to yield product as a light yellow oil. The enantiomeric excess of the product was determined using chiral HPLC (Chiralpak AD-H column, 1 mL/min, 5% *i*PrOH in hexane, 230 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 2H), 7.33 (dt, J = 5.2, 2.1 Hz, 1H), 7.31–7.21 (m, 6H), 4.98 (dd, J = 8.5, 4.6 Hz, 1H), 4.30 (d, J = 4.5 Hz, 1H), 4.16–4.02 (m, 2H), 3.89 (d, J = 13.1 Hz, 1H), 3.39 (d, J = 13.1 Hz, 1H), 3.25 (dd, J = 8.8, 6.4 Hz, 1H), 3.17–3.04 (m, 1H), 2.52 (dd, J = 10.9, 8.9 Hz, 1H), 2.45–2.33 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.12, 139.99, 138.51, 129.10 (2), 128.73 (2), 128.57, 128.46 (2), 127.51 (2), 127.35, 95.47, 73.19, 61.07, 57.63, 56.66, 37.88, 32.51, 14.20. HRMS (ESI): calcd for $[M-NO_2]^+$ $(C_{21}H_{25}N_1O_2)^+$ requires m/z 322.1807, found 322.1791.

4.4.2. Ethyl-2-(4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)acetates 4a/4a′

Compounds **4a/4a′** (Table 3, entry 1) were synthesized according to the general procedure from (*E*)-(2-nitrovinyl)benzene **2a** (45 mg) and (*E*)-ethyl 4-(4-methylphenylsulfonamido)but-2-enoate **1b** (28 mg, 0.1 mmol) to yield 43 mg of product (99% yield) as a mixture of diastereoisomers. The diastereomeric ratio was determined by ^{1}H NMR (dr 54/46), and the enantiomeric excess by chiral HPLC (Chiralpak AD-H column, 1 mL/min, 30% EtOH in hexane, 230 nm). For **4a** 96% ee: t_R = 12.79 (major) and t_R = 18.86 (minor). For **4a′** 46% ee: t_R = 27.31 (minor) and t_R = 32.04 (major). IR ν = 1733, 1598, 1555, 1352, 1163, 1097, 816, 760, 668, 587 cm^{-1}. For **4a**:^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 6.6, 1.6 Hz, 2H), 7.43–7.29 (m, 7H), 5.30 (d, J = 5.1 Hz, 1H), 4.76 (dd, J = 6.9, 5.1 Hz, 1H), 4.28–3.88 (m, 3H), 3.47 (dd, J = 11.5, 8.0 Hz, 2H), 2.85 (td, J = 15.0, 8.0 Hz, 2H), 2.53–2.38 (m, 3H), 1.24–1.18 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.21, 144.52, 138.56, 133.90, 130.06 (2), 129.17 (2), 128.67, 127.82 (2), 126.34 (2), 96.04, 67.19, 61.35, 52.96, 40.05, 35.20, 21.77, 14.19. For **4a′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.41–7.36 (m, 5H), 7.36–7.31 (m, 2H), 5.25 (s, 1H), 4.90 (d, J = 5.8 Hz, 1H), 4.28–3.88 (m, 3H), 3.22 (dd, J = 11.4, 8.6 Hz, 1H), 3.18–3.08 (m, 1H), 2.46 (s, 3H), 2.32 (dd, J = 7.3, 2.5 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.22, 144.25, 138.84, 133.67, 129.84 (2), 129.17 (2), 128.70, 127.96 (2), 126.25 (2), 93.90, 67.56, 61.42, 51.35, 36.69, 31.68, 21.77, 14.19. HRMS (ESI): calcd for $[M+H]^+$ $(C_{21}H_{25}N_2O_6S)^+$ requires m/z 433.1433, found 433.1439.

4.4.3. Ethyl-2-(5-(4-bromophenyl)-4-nitro-1-tosylpyrrolidin-3-yl)acetates 4b/4b′

Compounds **4b/4b′** (Table 3, entry 2) were synthesized according to the general procedure from (*E*)-1-bromo-4-(2-nitrovinyl)-benzene **2b** (68 mg) and (*E*)-ethyl 4-(4-methylphenylsulfonamido)but-2-enoate **1b** (28 mg, 0.1 mmol) to yield 46 mg of product (99% yield) as a mixture of diastereoisomers. The diastereomeric ratio was determined by ^{1}H NMR (dr 55/45), and the enantiomeric excess by chiral HPLC (Chiralpak AD-H column, 1 mL/min, 30% EtOH in hexane, 230 nm). For **4b** 98% ee: t_R = 16.30 (major) and t_R = 37.21 (minor). For **4b′** 45% ee: t_R = 33.34 (major) and t_R = 45.02 (minor). IR ν = 1733, 1555, 1352, 1164, 1099, 1015, 817, 733, 668, 586 cm^{-1}. For **4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.5 Hz, 1H), 7.34 (m, 2H), 7.31–7.24 (m, 2H), 5.21 (d, J = 5.3 Hz, 1H), 4.73 (dd, J = 7.1, 5.4 Hz, 1H), 4.15–4.08 (m, 2H), 4.04 (m, 1H), 3.47 (dd, J = 11.5, 8.1 Hz, 1H), 2.90–2.79 (m, 1H), 2.53–2.39 (m, 5H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.13, 144.75,, 137.61, 133.63, 132.29 (2), 130.12 (2), 128.17 (2), 127.79 (2), 122.78, 95.52, 66.62, 61.40, 52.85, 39.88, 34.94, 21.79, 14.18. For **4b′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.68 (d, J = 8.3 Hz, 2H), 7.54–7.50 (d, J = 8.5 Hz, 2H), 7.37–7.33 (d, J = 8.0 Hz, 2H), 7.31–7.27 (d, J = 8.3 Hz, 2H), 5.20–5.17 (s, 1H), 4.89–4.85 (d, J = 5.9 Hz, 1H), 4.15–4.06 (m, 2H), 4.06–4.01 (dd, J = 8.7, 7.3 Hz, 1H), 3.23–3.16 (dd, J = 11.4, 8.8 Hz, 1H), 3.14–3.03 (m, 1H), 2.48–2.44 (s, 3H), 2.38–2.24 (m, 2H), 1.24–1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.13, 144.48, 137.96, 133.33, 132.29 (2), 129.92 (2), 128.01 (2), 127.95 (2), 122.78, 93.56, 66.92, 61.47, 51.29, 36.74, 31.54, 21.78, 14.18. HRMS (ESI): calcd for $[M+H]^+$ $(C_{21}H_{23}BrN_2O_6S)^+$ requires m/z 511.0538, found 511.0533.

4.4.4. Ethyl-2-(5-(4-methoxyphenyl)-4-nitro-1-tosylpyrrolidin-3-yl)acetates 4c/4c′

Compounds **4c/4c′** (Table 3, entry 3) were synthesized according to the general procedure from (*E*)-1-methoxy-4-(2-nitrovinyl)benzene **2c** (54 mg) and (*E*)-ethyl 4-(4-methylphenylsulfonamido)but-2-enoate **1b** (28 mg, 0.1 mmol) to yield 42 mg of product (91% yield) as a mixture of diastereoisomers. The diastereomeric ratio was determined by ^{1}H NMR (dr 60/40), and the enantiomeric excess by chiral HPLC (Chiralpak AD-H column, 1 mL/min, 30% EtOH in hexane, 230 nm). For **4c** 97% ee: t_R = 20.79 (major) and t_R = 30.81 (minor). For **4c′** 51% ee: t_R = 37.00 (minor) and t_R = 52.75 (major). IR ν = 1733, 1555, 1513, 1349, 1252, 1163, 1027, 819 cm^{-1}. For **4c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 7.2 Hz, 2H), 7.32–7.26 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.19 (s, 1H), 4.74 (dd, J = 7.1, 5.4 Hz, 1H), 4.13–4.06 (m, 2H), 4.06–4.01 (m, 1H), 3.80 (s, 3H), 3.46 (dd, J = 11.4, 8.0 Hz, 1H), 2.91–2.79 (m, 1H), 2.49–2.46 (m, 2H), 2.44 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.22, 159.78, 144.39, 133.91, 130.30, 129.97 (2), 127.76 (2), 127.71 (2), 114.46 (2), 95.98, 66.94, 61.30, 55.43, 52.82, 39.74, 35.17, 21.72, 14.16. For **4c′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.19 (s, 1H), 4.87 (d, J = 5.7 Hz, 1H), 4.10 (qd, J = 7.2, 2.2 Hz, 2H), 4.04 (dd, J = 8.3, 7.0 Hz, 1H), 3.81 (s, 3H), 3.21 (dd, J = 11.3, 8.5 Hz, 1H), 3.18–3.07 (m, 1H), 2.45 (s, 3H), 2.31 (dd, J = 7.2, 3.0 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.22, 159.80, 144.16, 133.69, 130.90, 129.78 (2), 127.90 (2), 127.44 (2), 114.48 (2), 94.00, 67.10, 61.36, 55.47, 51.28, 36.62, 31.64, 21.73, 14.16. HRMS (ESI): calcd For $[M+Na]^+$ $(C_{22}H_{26}N_2O_7SNa)^+$ requires m/z 485.1358, found 485.1353.

4.4.5. Ethyl-2-(4-nitro-1-tosyl-5-(4-(trifluoromethoxy)phenyl)pyrrolidin-3-yl)acetates 4d/4d′

Compounds **4d/4d′** (Table 3, entry 4) were synthesized according to the general procedure from (*E*)-1-(2-nitrovinyl)-4-(trifluoromethoxy)benzene **2d** (70 mg) and (*E*)-ethyl 4-(4-methylphenylsulfonamido)but-2-enoate **1b** (28 mg, 0.1 mmol) to yield 48 mg of product (93% yield) as a mixture of diastereoisomers. The diastereomeric ratio was determined by ^{1}H NMR (dr 56/44), and the enantiomeric excess by chiral HPLC (Chiralpak AD-H column, 1 mL/min, 30% EtOH in hexane, 230 nm). For **4d** 97% ee: t_R = 8.59 (major) and t_R = 15.86 (minor). For **4d′** 43% ee: t_R = 18.16 (major) and t_R = 23.01 (minor). IR ν = 1733, 1557, 1353, 1262, 1220, 1164, 1101, 1022, 758, 669 cm^{-1}; For **4d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.22 (d, J = 5.5 Hz, 1H), 4.69 (dd, J = 7.4, 5.5 Hz, 1H), 4.08–3.95 (m, 3H), 3.40 (dd, J = 11.6, 8.4 Hz, 1H), 2.78 (pd, J = 7.9, 6.0 Hz, 1H), 2.48–2.40 (m, 2H), 2.37 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.15, 149.35, 144.76, 137.19, 133.82, 130.11 (2), 128.08 (2), 127.75, (2) 121.55 (2), 119.22, 95.53, 66.40, 61.42, 52.79, 39.97, 34.81, 21.77, 14.17.

For **4d′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 5.18 (s, 1H), 4.82 (d, J = 5.8 Hz, 1H), 4.08–3.95 (m, 3H), 3.14 (dd, J = 11.4, 8.8 Hz, 1H), 3.08–2.97 (m, 1H), 2.39 (s, 3H), 2.32–2.18 (m, 2H), 1.14 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.18, 149.35, 144.53, 137.49, 133.36, 129.92 (2), 127.96 (2), 127.88 (2), 121.62 (2), 119.22, 93.61, 66.78, 61.50, 51.32, 36.75, 31.55, 21.74, 14.17. HRMS (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}F_3N_2O_7S)^+$ requires m/z 517.1256, found 517.1257.

4.4.6. Ethyl-2-(4-nitro-5-(thiophen-2-yl)-1-tosylpyrrolidin-3-yl)-acetates 4e/4e′

Compounds **4e/4e′** (Table 3, entry 5) were synthesized according to the general procedure from (*E*)-2-(2-nitrovinyl)thiophene **2e** (47 mg) and (*E*)-ethyl 4-(4-methylphenylsulfonamido)but-2-enoate **1b** (28 mg, 0.1 mmol) to yield 35 mg of product (80% yield) as a mixture of diastereoisomers. The diastereomeric ratio was determined by ^{1}H NMR (dr 52/48), and the enantiomeric excess by chiral HPLC (Chiralpak AD-H column, 1 mL/min, 20% *i*PrOH in hexane, 230 nm). For **4e** 97% ee: t_R = 20.27 (major) and t_R = 26.16 (minor). For **4e′** 57% ee: t_R = 27.66 (minor) and t_R = 43.01 (major). IR ν = 1732, 1555, 1354, 1165, 1098, 1028, 817, 711, 668 cm^{-1}; For **4e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.35–7.30 (m, 2H), 7.29–7.24 (m, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 5.61 (d, J = 4.7 Hz, 1H), 4.85 (dd, J = 7.0, 4.8 Hz, 1H), 4.20–4.07 (m, 2H), 4.05 (dd, J = 11.6, 7.8 Hz, 1H), 3.42 (dd, J = 11.6, 8.3 Hz, 1H), 2.88 (dq, J = 15.1, 8.0 Hz, 1H), 2.62–2.46 (m, 2H), 2.44 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.20, 144.58, 142.98, 134.00, 130.06 (2), 127.96 (2), 127.43, 126.27, 126.21, 95.89, 63.38, 61.38, 52.50, 40.26, 35.30, 21.77, 14.20. For **4e′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.35–7.30 (m, 2H), 7.29–7.24 (m, 1H), 7.09 (m, 1H), 6.98 (m, 1H), 5.51 (s, 1H), 5.02 (d, J = 5.9 Hz, 1H), 4.20–4.07 (m, 2H), 3.97 (dd, J = 8.6, 7.4 Hz, 1H), 3.30 (tt, J = 14.1, 7.6 Hz, 1H), 3.17 (dd, J = 11.3, 8.9 Hz, 1H), 2.45 (s, 3H), 2.34 (dd, J = 7.3, 5.5 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.15, 144.32, 142.39, 133.74, 129.83 (2), 127.81 (2), 127.50, 126.07, 125.65, 93.47, 63.32, 61.45, 50.91, 37.28, 31.66, 21.77, 14.20. HRMS (ESI): calcd for $[M+H]^+$ $(C_{19}H_{23}N_2O_6S_2)^+$ requires m/z 439.0998, found 439.0996.

4.4.7. Ethyl 2-(5-(naphthalen-2-yl)-4-nitro-1-tosylpyrrolidin-3-yl)acetates 4f/4f′

Compounds **4f/4f′** (Table 3, entry 6) were synthesized according to the general procedure from (*E*)-2-(2-nitrovinyl)naphthalene **2f** (60 mg) and (*E*)-ethyl 4-(4-methylphenylsulfonamido)but-2-enoate **1b** (28 mg, 0.1 mmol) to yield 45 mg of product (93% yield) as a mixture of diastereoisomers. The diastereomeric ratio was determined by ^{1}H NMR (dr 58/42), and the enantiomeric excess by chiral HPLC (Chiralpak AD-H column, 1 mL/min, 30% EtOH in hexane, 230 nm). For **4f** 95% ee: t_R = 19.50 (major) and t_R = 24.20 (minor). For **4f′** 44% ee: t_R = 30.53 (minor) and t_R = 42.01 (major). IR ν = 1732, 1555, 1352, 1165, 1098, 1025, 910, 819, 735, 666 cm^{-1}. For **4f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.80 (m, 4H), 7.67 (d, J = 8.3 Hz, 2H), 7.54–7.47 (m, 2H), 7.43 (dd, J = 3.6, 1.7 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 5.44 (d, J = 5.2 Hz, 1H), 4.85 (dd, J = 7.0, 5.3 Hz, 1H), 4.17–4.04 (m, 3H), 3.55 (dd, J = 11.5, 8.0 Hz, 1H), 2.92 (dq, J = 15.0, 7.9 Hz, 1H), 2.49–2.44 (m, 2H), 2.41 (s, 3H), 1.20 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.19, 144.51, 135.62, 133.93, 133.32, 133.21, 130.00 (2), 129.32, 128.28, 127.95, 127.80 (2), 126.75, 126.69, 125.87, 123.56, 95.81, 67.44, 61.33, 53.02, 39.99, 35.22, 21.71, 14.15. For **4f′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.80 (m, 4H), 7.73 (d, J = 8.2 Hz, 2H), 7.53–7.49 (m, 2H), 7.42 (dd, J = 8.5, 1.8 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 5.42 (s, 1H), 4.98 (d, J = 5.8 Hz, 1H), 4.16–4.05 (m, 3H), 3.30 (dd, J = 11.3, 8.9 Hz, 1H), 3.24–3.11 (m, 1H), 2.44 (s, 3H), 2.33 (dd, J = 7.4, 3.5 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.21, 144.27, 136.02, 133.74, 133.33, 133.26, 129.83 (2), 129.22, 128.30, 127.95, 127.80 (2), 126.82, 126.69, 125.74, 123.56, 93.70, 67.71, 61.39, 51.46, 36.73, 31.65, 21.74, 14.15. HRMS (ESI): calcd for $[M+H]^+$ $(C_{25}H_{27}N_2O_6S)^+$ requires m/z 483.1590, found 483.1590.

4.4.8. Ethyl-2-(5-cyclohexyl-4-nitro-1-tosylpyrrolidin-3-yl)-acetate 4g/4g′

Compounds **4g/4g′** (Table 3, entry 7) were synthesized according to the general procedure from (*E*)-(2-nitrovinyl)cyclohexane **2g** (47 mg) and (*E*)-ethyl 4-(4-methylphenylsulfonamido)but-2-enoate **1b** (28 mg, 0.1 mmol) to yield 42 mg of product (96% yield) as a mixture of diastereoisomers (isomers were later separated via silica gel column chromatography to obtain analytical data). The diastereomeric ratio was determined by ^{1}H NMR (dr 68/32), and the enantiomeric excess by chiral HPLC (Chiralpak AD-H column, 1 mL/min, 15% *i*PrOH in hexane, 230 nm). For **4g** 92% ee: t_R = 14.15 (major) and t_R = 20.52 (minor); $[\alpha]_D^{25} = -62$ (*c* 0.10, $CHCl_3$). For **4g′** 36% ee: t_R = 15.17 (minor) and t_R = 31.59 (major); $[\alpha]_D^{25} = -40$ (*c* 0.07, $CHCl_3$). IR ν = 2931, 2857, 1734, 1554, 1346, 1163, 1096, 1025, 818, 759, 668 cm^{-1}. For **4g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.59 (dd, J = 8.4, 5.1 Hz, 1H), 4.27 (t, J = 5.6 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.02 (dd, J = 12.8, 7.4 Hz, 1H), 3.04 (dd, J = 12.9, 11.0 Hz, 1H), 2.56–2.49 (m, 1H), 2.45 (s, 3H), 2.39–2.32 (m, 1H), 2.32–2.18 (m, 1H), 1.88–1.67 (m, 6H), 1.34–1.26 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.19–1.13 (m, 1H), 1.10–0.97 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.20, 144.43, 134.92, 130.16 (2), 127.83 (2), 91.23, 68.76, 61.27, 52.90, 42.83, 41.29, 34.55, 29.42, 27.95, 26.25, 26.02, 25.94, 21.77, 14.22. For **4g′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.94 (d, J = 5.8 Hz, 1H), 4.14 (qt, J = 6.9, 3.6 Hz, 2H), 3.82 (d, J = 4.0 Hz, 1H), 3.81–3.77 (m, 1H), 3.01 (dd, J = 11.6, 8.1 Hz, 1H), 2.98–2.89 (m, 1H), 2.46 (s, 3H), 2.32 (dd, J = 17.4, 5.9 Hz, 1H), 2.20 (d, J = 8.2 Hz, 1H), 2.18–2.12 (m, 1H), 1.96 (d, J = 12.0 Hz, 1H), 1.86–1.77 (m, 1H), 1.71 (t, J = 13.9 Hz, 2H), 1.43–1.28 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.16 (m, 1H), 1.02 (m, 1H), 0.76 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.47, 144.22, 132.68, 129.84 (2), 128.17 (2), 88.60, 69.99, 61.43, 51.73, 41.96, 38.05, 31.81, 30.54, 27.02, 26.43, 26.20, 26.06, 21.78, 14.23. HRMS (ESI): calcd for $[M+H]^+$ $(C_{21}H_{31}N_2O_6S)^+$ requires m/z 439.1903, found 439.1897.

4.4.9. (Ethyl-2-((3*S*,4*R*,5*S*)-4-methyl-4-nitro-5-phenyl-1-tosyl-pyrrolidin-3-yl)acetate 4h and ethyl-2-((3*R*,4*R*,5*S*)-4-methyl-4-nitro-5-phenyl-1-tosylpyrrolidin-3-yl)acetate 4h′

At first, (*E*)-(2-nitroprop-1-en-1-yl)benzene **2h** (49 mg, 0.3 mmol) and (*E*)-ethyl-4-(4-methylphenylsulfonamido)but-2-enoate **1b** (28 g, 0.1 mmol) were dissolved in toluene (0.5 mL). Next, 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*S*)-((2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)thiourea **II** (12 mg, 20 mol %) was added and the mixture was stirred at 60 °C for 3 days. The mixture was purified directly by silica gel column chromatography using a mixture of heptane and EtOAc as eluent to yield 33 mg (74%) of product as a mixture of diastereoisomers. The diastereomeric ratio was determined by ^{1}H NMR (dr 70/30), and the enantiomeric excess by chiral HPLC (Chiralpak AD-H column, 1 mL/min, 30% EtOH in hexane, 230 nm). For **4h** 63% ee: t_R = 10.45 (major) and t_R = 20.14 (minor); IR ν = 1732, 1599, 1555, 1351, 1161, 1097, 815 cm^{-1}. For **4h′** 67% ee: t_R = 14.95 (major) and t_R = 51.24 (minor). For **4h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.41–7.23 (m, 7H), 5.35 (s, 1H), 4.19–4.08 (m, 3H), 3.33 (dd, J = 11.9, 10.3 Hz, 1H), 2.92 (tdd, J = 10.1, 8.0, 4.7 Hz, 1H), 2.47 (s, 3H), 2.38 (dd, J = 16.5, 4.7 Hz, 1H), 2.26 (dd, J = 16.5, 10.0 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.24, 144.65, 136.09, 133.00, 130.15 (2), 128.80, 128.59 (2), 128.07 (2), 127.56 (2), 96.50, 70.97, 61.36,

52.56, 43.06, 32.43, 21.81, 16.59, 14.22. For **4h′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.3 Hz, 2H), 7.40–7.24 (m, 7H), 5.19 (s, 1H), 4.15 (q, J = 7.2 Hz, 3H), 3.23 (dd, J = 10.9, 9.1 Hz, 1H), 2.88 (tdd, J = 10.9, 7.7, 3.4 Hz, 1H), 2.51–2.45 (m, 1H), 2.44 (s, 3H), 2.13 (dd, J = 16.8, 10.4 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 1.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.83, 143.95, 138.56, 134.21, 129.69 (2), 128.99 (2), 128.83, 127.82 (2), 127.47 (2), 98.11, 71.14, 61.50, 51.43, 42.70, 31.97, 21.76, 20.29, 14.26. HRMS (ESI): calcd for $[M+H]^+$ ($C_{22}H_{27}N_2O_6S$)$^+$ requires m/z 447.1590, found 447.1588.

4.5. Assignment of the absolute configuration of the *trans–trans*-isomer via Mosher's amide and mandelic amide synthesis

4.5.1. Ethyl-2-((3*S*,4*R*,5*S*)-4-amino-5-cyclohexyl-1-tosylpyrrolidin-3-yl)acetate 5g

Ethyl-2-((3*S*,4*R*,5*S*)-5-cyclohexyl-4-nitro-1-tosylpyrrolidin-3-yl)acetate **4g** (70 mg, 0.16 mmol) was dissolved in a mixture of THF (1.6 mL) and EtOH (1.6 mL) under argon. Next, 10% Pd/C (14 mg) and ammonium formate (50 mg, 0.8 mmol) were added and the mixture was stirred at ambient temperature until the complete disappearance of the starting material. The mixture was diluted with Et_2O, filtered, concentrated and purified by silica gel column chromatography (CH_2Cl_2/EtOAc 10/1) to yield 39 mg of product as a colorless solid. IR ν = 3498, 2927, 2855, 1730, 1452, 1341, 1158, 1093, 1025, 813, 666, 588 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.84 (dd, J = 12.5, 7.9 Hz, 1H), 3.64–3.60 (m, 1H), 3.09 (dd, J = 7.2, 4.6 Hz, 1H), 2.91 (dd, J = 12.4, 10.7 Hz, 1H), 2.51 (dd, J = 16.3, 6.0 Hz, 1H), 2.43 (s, 3H), 2.25 (dd, J = 16.3, 8.2 Hz, 1H), 2.00–1.85 (m, 1H), 1.85–1.59 (m, 6H), 1.29–0.98 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 143.6, 136.1, 129.7 (2), 127.8 (2), 70.1, 66.9, 60.9, 53.1, 42.2, 38.2, 36.4, 29.7, 28.7, 26.5, 26.4, 26.2, 21.7, 14.3. $[\alpha]_D^{25} = -34$ (c 0.51, $CHCl_3$). HRMS (ESI): calcd for $[M+H]^+$ ($C_{21}H_{33}N_2O_4S$)$^+$ requires m/z 409.2161, found 409.2155.

4.5.2. Ethyl-2-((3*S*,4*R*,5*S*)-5-cyclohexyl-1-tosyl-4-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)pyrrolidin-3-yl)acetate 6g

Ethyl-2-((3*S*,4*R*,5*S*)-4-amino-5-cyclohexyl-1-tosylpyrrolidin-3-yl)acetate **5g** (10 mg, 0.024 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). DCC (7.6 mg, 0.037 mmol) and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (8.6 mg, 0.037 mmol) were added and the mixture was stirred at ambient temperature until TLC showed full conversion. The mixture was filtered through Celite and concentrated, purified directly by silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/EtOAc) to yield 10 mg of the product as a colorless solid. $[\alpha]_D^{25} = -51.5$ (c 0.20, $CHCl_3$); IR ν = 3239, 2930, 2855, 1734, 1451, 1344, 1163, 1017, 914, 813 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.49–7.39 (m, 5H), 7.32 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.1 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.89 (dd, J = 12.9, 8.2 Hz, 1H), 3.54 (dd, J = 6.8, 3.3 Hz, 1H), 3.52–3.50 (m, 3H), 3.28 (td, J = 6.7, 3.3 Hz, 1H), 2.91 (dd, J = 12.9, 10.3 Hz, 1H), 2.44 (s, 3H), 2.36 (dd, J = 16.8, 6.4 Hz, 1H), 2.22 (dd, J = 16.8, 8.2 Hz, 1H), 1.76 (dd, J = 9.3, 5.5 Hz, 1H), 1.71–1.51 (m, 5H), 1.51–1.39 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.19–0.80 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 165.8, 144.1, 135.9, 131.7, 130.0 (2), 130.0, 128.7 (2), 127.7 (2), 127.4 (2), 69.2, 69.1, 61.1, 55.7, 52.9, 41.8, 39.4, 36.3, 29.5, 29.4, 26.3 (2), 26.2, 21.7, 14.3. HRMS (ESI): calcd for $[M-H]^-$ ($C_{31}H_{38}F_3N_2O_6S$)$^-$ requires m/z 623.2408, found 623.2418.

4.5.3. Ethyl-2-((3*S*,4*R*,5*S*)-5-cyclohexyl-1-tosyl-4-((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)pyrrolidin-3-yl)acetate 7g

Ethyl-2-((3*S*,4*R*,5*S*)-4-amino-5-cyclohexyl-1-tosylpyrrolidin-3-yl)acetate **5g** (10 mg, 0.024 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL). DCC (7.6 mg, 0.037 mmol) and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (8.6 mg, 0.037 mmol) were added and the mixture was stirred at ambient temperature until TLC showed full conversion. The mixture was filtered through Celite, concentrated, and purified by silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/EtOAc) to yield 10 mg of the product as a colorless solid. $[\alpha]_D^{25} = -57.9$ (c 0.20, $CHCl_3$); IR ν = 3240, 2931, 2855, 1735, 1344, 1269, 1165, 1116, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.51–7.40 (m, 5H), 7.32 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 7.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.87 (dd, J = 12.8, 8.2 Hz, 1H), 3.51–3.48 (m, 3H), 3.42 (dd, J = 6.7, 3.3 Hz, 1H), 3.30 (td, J = 7.0, 3.4 Hz, 1H), 2.92 (dd, J = 12.8, 10.3 Hz, 1H), 2.42 (s, 3H), 2.38 (d, J = 6.0 Hz, 1H), 2.20 (dd, J = 16.7, 8.5 Hz, 1H), 1.83–1.76 (m, 1H), 1.75–1.59 (m, 5H), 1.51–1.39 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.20–0.74 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 165.8, 144.1, 135.8, 131.7, 130.10, 130.05 (2), 128.8 (2), 127.8 (2), 127.4 (2), 69.1, 69.0, 61.0, 55.7, 52.9, 41.7, 39.4, 36.3, 29.5, 29.2, 26.3, 26.3, 26.2, 21.7, 14.3. HRMS (ESI): calcd for $[M-H]^-$ ($C_{31}H_{38}F_3N_2O_6S$)$^-$ requires m/z 623.2408, found 623.2417.

4.5.4. Ethyl-2-((3*S*,4*R*,5*S*)-5-cyclohexyl-4-((*R*)-2-hydroxy-2-phenylacetamido)-1-tosylpyrrolidin-3-yl)acetate 8g

Ethyl-2-((3*S*,4*R*,5*S*)-4-amino-5-cyclohexyl-1-tosylpyrrolidin-3-yl)acetate **5g** (10 mg, 0.02 mmol), (*R*)-(−)-mandelic acid (4.5 mg, 0.03 mmol), DCC (6.6 mg, 0.03 mmol) and 1-hydroxypyrrolidine-2,5-dione (3.7 mg, 0.03 mmol) were dissolved in THF (0.5 mL) and the mixture was stirred at ambient temperature until TLC showed full conversion. The mixture was directly purified by silica gel column chromatography using a mixture of heptane–EtOAc as eluent to yield 8 mg of product. $[\alpha]_D^{25} = -101.3$ (c 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2H), 7.44–7.34 (m, 5H), 7.25 (d, J = 7.6 Hz, 2H), 7.02 (d, J = 6.4 Hz, 1H), 5.14 (d, J = 5.5 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.81 (dd, J = 12.6, 8.1 Hz, 1H), 3.43 (d, J = 5.7 Hz, 1H), 3.38 (dd, J = 6.7, 3.4 Hz, 1H), 3.18 (td, J = 6.3, 3.5 Hz, 1H), 2.89 (dd, J = 12.6, 10.0 Hz, 1H), 2.40 (s, 3H), 2.29 (dd, J = 16.6, 6.6 Hz, 1H), 2.17 (dd, J = 16.6, 7.9 Hz, 1H), 1.90–1.80 (m, 1H), 1.80–1.57 (m, 6H), 1.52–1.40 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.20–1.06 (m, 2H), 1.01–0.92 (m, 1H), 0.91–0.74 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.93, 171.67, 143.99, 137.60, 135.65, 129.93 (2), 129.12 (2), 129.01 (2), 127.76 (2), 126.70, 72.47, 69.07, 68.52, 61.06, 52.80, 41.63, 38.85, 36.20, 29.59, 28.99, 26.29, 26.26, 26.17, 21.72, 14.29.

4.5.5. Ethyl-2-((3*S*,4*R*,5*S*)-5-cyclohexyl-4-((*S*)-2-hydroxy-2-phenylacetamido)-1-tosylpyrrolidin-3-yl)acetate 9g

Ethyl-2-((3*S*,4*R*,5*S*)-4-amino-5-cyclohexyl-1-tosylpyrrolidin-3-yl)acetate **5g** (10 mg, 0.02 mmol), (*S*)-(−)-mandelic acid (4.5 mg, 0.03 mmol), DCC (6.6 mg, 0.03 mmol) and 1-hydroxypyrrolidine-2,5-dione (3.7 mg, 0.03 mmol) were dissolved in THF (0.5 mL) and the mixture was stirred at ambient temperature until TLC showed full conversion. The mixture was directly purified by silica gel column chromatography using a mixture of heptane–EtOAc as eluent to yield 9 mg of product. $[\alpha]_D^{25} = -28.5$ (c 0.22, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2H), 7.41–7.34 (m, 5H), 7.32 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 6.5 Hz, 1H), 5.17 (d, J = 5.4 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.79 (dd, J = 12.7, 8.1 Hz, 1H), 3.49 (dd, J = 6.7, 3.4 Hz, 1H), 3.39 (d, J = 5.5 Hz, 1H), 3.18 (td, J = 6.4, 3.5 Hz, 1H), 2.89 (dd, J = 12.7, 10.0 Hz, 1H), 2.43 (s, 3H), 2.33 (dd, J = 16.7, 6.6 Hz, 1H), 2.21 (dd, J = 16.6, 7.9 Hz, 1H), 1.87–1.77 (m, 1H), 1.77–1.52 (m, 6H), 1.42 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.20–1.03 (m, 2H), 1.02–0.92 (m, 1H), 0.92–0.77 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.97, 171.56, 144.04, 137.49, 135.68, 129.94 (2), 129.02, 128.93 (2), 127.84 (2), 126.73 (2), 72.45, 69.09, 68.74, 61.08, 52.74, 41.64, 38.88, 36.24, 29.59, 29.05, 26.28, 26.23, 26.14, 21.74, 14.29.

4.6. Assignment of the absolute configuration of the *trans–cis* isomer via Mosher's and mandelic amide synthesis

4.6.1. Ethyl-2-((3*R*,4*R*,5*S*)-4-amino-5-cyclohexyl-1-tosylpyrrolidin-3-yl)acetate 5g′

Ethyl-2-((3*R*,4*R*,5*S*)-5-cyclohexyl-4-nitro-1-tosylpyrrolidin-3-yl)-acetate **4g′** (28 mg, 0.06 mmol) was dissolved in a mixture of THF (1.6 mL) and EtOH (1.6 mL) under argon. Next, 5% Pd/C(7 mg) and ammonium formate (20 mg, 0.3 mmol) were added and the mixture was stirred at ambient temperature until the complete disappearance of the starting material. The mixture was diluted with Et_2O, filtered, concentrated and purified by silica gel column chromatography (CH_2Cl_2/EtOAc 20/1) to yield 12 mg of product as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.57 (m, 1H), 3.54 (m, 1H), 3.38 (d, J = 5.8 Hz, 1H), 2.92 (dd, J = 10.7, 9.2 Hz, 1H), 2.74–2.61 (m, 1H), 2.43 (s, 3H), 2.41–2.24 (m, 2H), 1.90–1.63 (m, 6H), 1.24 (t, J = 6.9 Hz, 3H), 1.10 (m, 5H), 0.96–0.82 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.25, 143.66, 134.31, 129.59 (2), 127.99 (2), 68.71, 63.82, 61.00, 52.89, 41.87, 37.13, 32.32, 30.58, 28.23, 26.62, 26.49, 26.32, 21.71, 14.31. HRMS (ESI): calcd for $[M+H]^+$ ($C_{21}H_{33}N_2O_4S$)$^+$ requires m/z 409.2161, found 409.2157.

Ethyl-2-((3*R*,4*R*,5*S*)-5-cyclohexyl-1-tosyl-4-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)pyrrolidin-3-yl)acetate **6g′** (major) and ethyl-2-((3*S*,4*S*,5*R*)-5-cyclohexyl-1-tosyl-4-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanamido)pyrrolidin-3-yl)acetate **7g′** (minor). Ethyl-2-(4-amino-5-cyclohexyl-1-tosylpyrrolidin-3-yl)acetate **5g′** (12 mg, 0.029 mmol) was dissolved in anhydrous CH_2Cl_2 (1.2 mL). Next, DCC (9.1 mg, 0.044 mmol) and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (10.3 mg, 0.044 mmol) were added and the mixture was stirred at ambient temperature until TLC showed full conversion. The mixture was filtered through Celite and concentrated, purified directly by silica gel column chromatography (CH_2Cl_2 and CH_2Cl_2/EtOAc) to yield 10 mg of product as a colorless solid. For the mixture of **6g′** and **7g′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 3H), 7.50–7.38 (m, 7.5H), 7.25 (m, 3H), 7.07 (d, J = 5.7 Hz, 1H), 7.02 (d, J = 6.2 Hz, 0.5H), 4.17–4.06 (m, 3H), 3.58 (dd, J = 8.6, 7.4 Hz, 1.5H), 3.53 (d, J = 5.7 Hz, 1H), 3.49 (s, 4.5H), 3.47 (s, 1H), 3.45 (d, J = 4.1 Hz, 0.5H), 2.85 (m, 1.5H), 2.81–2.71 (m, 1.5H), 2.41 (s, 3H), 2.41 (s, 1.5H), 2.37 (dd, J = 7.7, 3.4 Hz, 1.5H), 2.32–2.24 (m, 1.5H), 1.78–1.59 (m, 9H), 1.31–0.70 (m, 13H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.59, 171.51, 166.29, 143.81, 133.86, 133.74, 131.52, 130.14, 130.09, 129.75, 129.69, 128.77, 128.71, 128.00, 127.91, 127.48, 127.41, 84.40, 69.63, 63.28, 61.15, 61.07, 55.68, 55.62, 51.71, 41.86, 37.14, 37.11, 31.88, 31.84, 30.35, 30.30, 28.76, 28.69, 26.47, 26.42, 26.32, 26.30, 21.71, 21.69, 14.26.

4.6.2. Ethyl-2-((3*R*,4*R*,5*S*)-5-cyclohexyl-4-((*R*)-2-hydroxy-2-phenylacetamido)-1-tosylpyrrolidin-3-yl)acetate 8g′ (major) and ethyl-2-((3*S*,4*S*,5*R*)-5-cyclohexyl-4-((*R*)-2-hydroxy-2-phenylacetamido)-1-tosylpyrrolidin-3-yl)acetate 9g′ (minor)

Ethyl-2-(4-amino-5-cyclohexyl-1-tosylpyrrolidin-3-yl)acetate **5g′** (24 mg, 0.06 mmol), (*R*)-(−)-mandelic acid (13 mg, 0.09 mmol), DCC (19 mg, 0.09 mmol) and 1-hydroxypyrrolidine-2,5-dione (10.8 mg, 0.09 mmol) were dissolved in THF (1.2 mL) and the mixture was stirred at ambient temperature until TLC showed full conversion. The mixture was directly purified by silica gel column chromatography using a mixture of heptane–EtOAc as eluent to yield 23 mg of product as a mixture of diastereomers. For the mixture of **8g′** and **9g′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.49–7.33 (m, 7H), 7.29 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 4.8 Hz, 0.4H), 6.75 (d, J = 5.4 Hz, 1H), 5.14 (d, J = 5.6 Hz, 0.4H), 5.09 (d, J = 5.5 Hz, 1H), 4.12 (m, 3H), 3.51 (ddd, J = 11.9, 8.8, 7.7 Hz, 1.4H), 3.45 (d, J = 6.3 Hz, 1.4H), 3.42–3.36 (m, 1H), 2.89 (dd, J = 11.3, 9.1 Hz, 0.4H), 2.80 (dd, J = 11.4, 8.9 Hz, 1H), 2.74–2.63 (m, 1.4H), 2.42 (s, 1.4H), 2.36 (s, 3H), 2.32–2.18 (m, 3H), 1.80–1.46 (m, 11H), 1.34–0.59 (m, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.94, 172.71, 171.83, 171.79, 143.94, 143.87, 137.54, 137.39, 133.88, 133.63, 129.65, 129.64, 129.12, 128.99, 128.91, 127.97, 127.82, 126.68, 126.60, 72.50, 72.45, 69.40, 69.10, 62.99, 61.09, 52.04, 51.83, 41.74, 41.60, 37.20, 37.12, 32.01, 31.89, 31.87, 30.44, 30.25, 29.16, 28.28, 26.57, 26.49, 26.45, 26.41, 26.38, 26.24, 21.72, 21.66, 14.28.

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