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Concise asymmetric synthesis of a (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid-derived sulfonamide and ethyl ester†

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The development and demonstration of short, robust and chromatography-free sequences for the preparation of a (1*R*,2*S*)-1-amino-2-vinylcyclopropane-carboxylic acid-derived sulfonamide and ethyl ester in ≥99% ee are described. Both compounds are common building blocks in multiple preparations of potent HCV NS3 protease inhibitors. The robustness of the asymmetric cyclopropanation of (*E*)-*N*-benzylideneglycine ethyl ester under phase transfer catalysis conditions is significantly improved based on a detailed mechanistic investigation that included an analysis of the catalyst decomposition pathway, a postulated model for the stereo-selectivity that was guided by calculations and rigorous quality control of the starting materials and reagents. Wet milling has been demonstrated to dramatically accelerate this phase transfer reaction. A bench stable benzylidene-protected primary 1-amino-2-vinylcyclopropane amide intermediate was isolated and its reliable enantiomeric enrichment was achieved by a controlled crystallization process. A chemical resolution procedure was identified using di-*p*-toluoyl-D-tartaric acid to access (1*R*,2*S*)-1-amino-2-vinyl-cyclopropanecarboxylic ester in high ee.

Introduction

Hepatitis C virus (HCV) is estimated to affect more than 175 million people worldwide and is a frequent cause of liver failure and hepatocellular carcinoma.[1] In the United States, more people now die from hepatitis each year than from AIDS, according to a news report from the Centers for Disease Control and Prevention.[2] Eleven different genotypes of the virus have been identified and genotype 1 (subtypes 1a and 1b) is by far the most frequent worldwide.[3a] The current standard of care for chronic hepatitis C infection is based on a combination of a pegylated form of interferon (IFN)-α and ribavirin. This combination cures approximately 80% of infections in patients infected with HCV genotype 2 or 3, but only 40%–50% in patients infected with genotypes 1 or 4.[3] To improve the overall cure rate and broaden the spectrum of antiviral activities against HCV genotypes, several potent HCV NS3/4a protease inhibitors have recently been developed (Fig. 1), including asunaprevir (BMS-650032),[4] vaniprevir (MK-7009),[5]

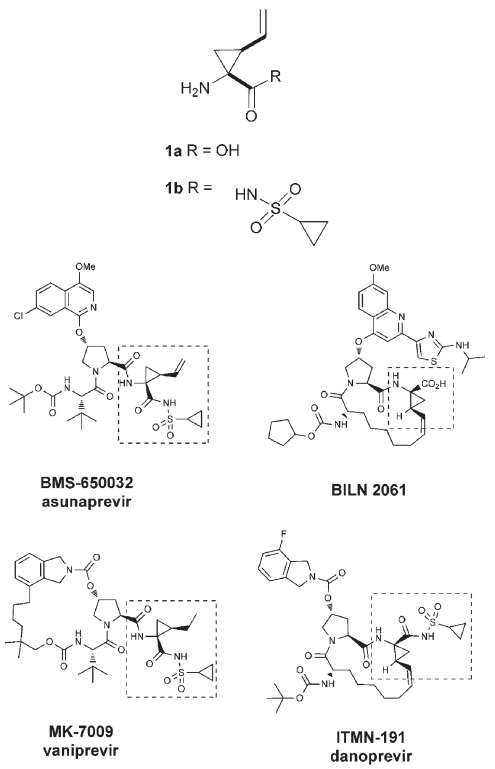

Fig. 1 Selected HCV NS3 protease inhibitors.

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†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for compounds **1b**, **2**, **3**, **4a** and **8**, and chiral HPLC chromatograms for **1b**, **2**, **3** and **4a**. See DOI: 10.1039/c3ob41394b

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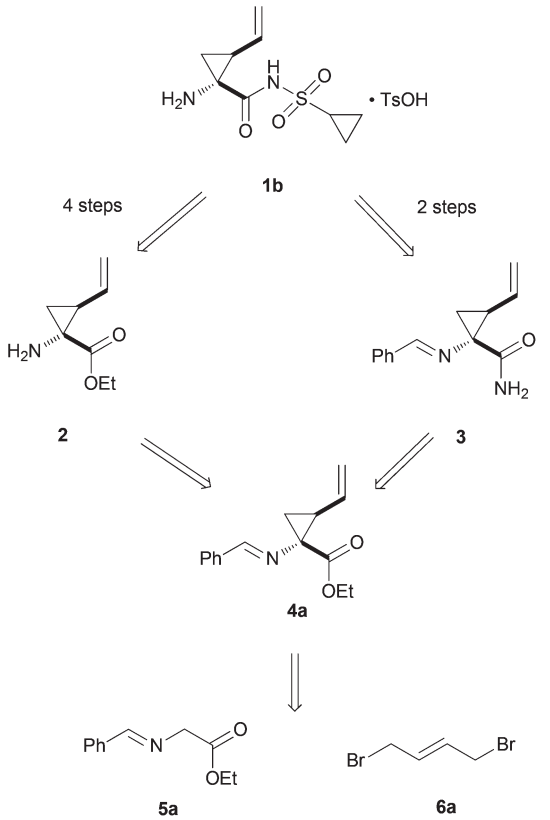
macrocyclic BILN 2061,[6] and danoprevir (ITMN-191).[7] Common structural motifs present in these NS3 protease inhibitors are (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid (vinyl-ACCA **1a**) and its corresponding sulfonamide **1b**. The pendant vinyl group of vinyl-ACCA can be elaborated *via* ring-closing metathesis to form a macrocyclic series or further functionalized for structure–activity relationship studies.

For this reason, the synthesis of chiral vinyl-ACCA derivatives has drawn considerable attention both from academic and pharmaceutical industrial labs. Synthetic routes leading to enantioenriched vinyl-ACCA *via* the enzymatic resolution of a Boc-protected 1-amino-2-vinylcyclopropanecarboxylic ester were recently reported by Bristol-Myers Squibb[4f] and Boehringer-Ingelheim.[5b] Although these processes have been successfully executed on a kilogram scale, a significant drawback of this approach is the loss of 50% of the input material in the enzymatic resolution. To overcome this issue, transition metal-catalyzed asymmetric syntheses of vinyl-ACCA derivatives have been reported, including Pd-catalyzed ring opening of 3,4-epoxy-1-butene with glycine equivalents,[8] Pd-catalyzed allylic alkylation of 1,4-dichlorobut-2-ene with α-aminoacetonitriles,[9] along with Cu(I)-catalyzed cyclopropanation of methyl nitroacetate-derived phenyliodonium ylides with 1,3-butadiene.[10] However, these approaches present several challenges for implementation on the preparation scale to supply clinical studies due to the formation of side products, moderate selectivity, high cost and limited commercial availability of the raw materials. An enantioenriched vinylcyclopropane dicarboxylic ester can also be prepared starting from (*S*)-1,2,4-butanetriol which is elaborated *via* a Curtius rearrangement to generate vinyl-ACCA.[11] Despite all these advances, a short and concise asymmetric synthesis of vinyl-ACCA is still highly desirable. Herein, we report our results on the identification, development and optimization of a route to vinyl-ACCA ester and its corresponding sulfonamide. We believe that this will facilitate the preparation of potential next-generation HCV NS3 protease inhibitors and enable the investigation of their pharmaceutical potency, safety and bioavailabilities.

Retrosynthetically sulfonamide **1b** could be prepared from its ester analog **2** in four steps involving Boc protection, saponification, coupling of the corresponding Boc-protected amino acid with cyclopropanesulfonamide and Boc deprotection (Scheme 1).[4f] Intermediate **2** could be obtained directly *via* hydrolysis of ethyl 1-((*E*)-benzylideneamino)-2-vinylcyclopropane-carboxylate **4a**. An alternate approach to **1b** would also utilize **4a**; however, the benzylidene protecting group would be retained to generate primary amide **3**. Primary amide **3** could then be converted to the target compound **1b** in only 2 steps (coupling with cyclopropanesulfonamide followed by hydrolysis of the benzylidene). This alternate approach would reduce the number of steps for accessing sulfonamide **1b** by avoiding the additional protecting group manipulations.

The synthesis of vinyl-ACCA ester **4a** *via* an asymmetric phase-transfer catalyzed dialkylation of the inexpensive and readily available (*E*)-*N*-benzylideneglycine ethyl ester **5a** with *trans*-1,4-dibromo-2-butene **6a** was recently reported.[12,13]



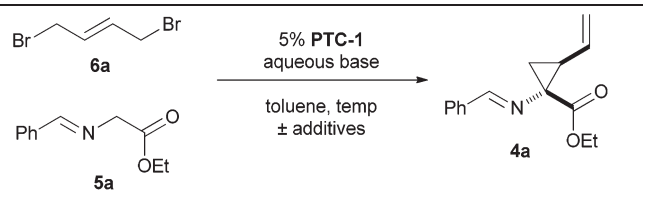
Scheme 1 Retrosynthesis of (1*R*,2*S*)-1-amino-2-vinyl-cyclopropane-carboxylic acid-derived sulfonamide **1b**.

However, the experimental procedure required a specific particle size of solid NaOH in the alkylation step and chiral preparative SFC (supercritical fluid chromatography) to isolate the desired enantiomer of vinyl-ACCA ester **4a**. Commercially available powdered NaOH is very hygroscopic and difficult to handle, therefore freshly milled NaOH had to be prepared before each use. In our hands, selectivity of the phase-transfer catalyzed reaction fluctuated quite significantly using the reported procedure.[12] Thus, we describe a short and robust synthetic sequence run on a 10 g scale using modified phase transfer conditions to prepare optically active vinyl-ACCA ethyl ester **2** and vinyl-ACCA derived sulfonamide **1b**. The route circumvents chiral column chromatography and protecting group manipulations and results in an increased overall yield.

Results and discussion

We chose to start the investigation of the phase transfer catalyzed alkylation of **5a** to improve its robustness (the reported results are shown in entry 1, Table 1).[12] The reaction conditions were modified with aqueous (50 wt%) NaOH used in place of solid NaOH to circumvent the particle size control and potential agglomeration during the course of the reaction. The reaction temperature was raised to 10 °C in order to achieve an acceptable reaction rate so that the reaction could be complete within 17 h. *trans*-1,4-Dibromo-2-butene **6a** was

Table 1 Experimental investigation of asymmetric phase transfer cyclopropanation of **5a** with **6a**



Entry[a]	Experimental	Yield[b] (%)	ee[c] (%)
1	Pin-milled NaOH and water at 0 °C (22 h)[12]	78	77
2	$NaOH_{aq}$ (50 wt%) at 10 °C (17 h)	88	77–81
3	$NaOH_{aq}$ (30 wt%)	48	55
4	KOH_{aq} (50 wt%)	84	73
5	$CsOH_{aq}$ (50 wt%)	53	51
6	Cs_2CO_3 (70 wt%)	<2	—
7	2% Et_3N in **5a**	65	37
8	5% PhCHO in **5a**	84	34
9	**PTC-1** with 1.4% cinchonidine	77	60
10	PhCl as the solvent	93	80
11	Turrax wet milling (1.5 h)	87	70

[a] Except entry 1, the reactions were carried out using **6a** as the limiting reagent, 1.20 equiv. of **5a**, solvent (16 g per g-LR), and base (15 g per g-LR). [b] Determined by reverse phase HPLC analysis. [c] Determined by normal-phase chiral HPLC analysis.

set as the limiting reagent and its complete consumption was required to preclude unselective cyclopropanation of residue 1,4-dibromo-2-butene in a crude mixture with glycine imine **5a** in the amidation step under basic conditions (see eqn (2)). With these changes in place, an optimized yield of 88% was obtained with a range of enantioselectivities from 77% to 81% (entry 2). Using less concentrated NaOH or LiOH (the result is not shown) led to a slower reaction, increased formation of saponification by-products and diminished selectivity (entry 3). Other aqueous alkaline bases, for example KOH and CsOH, were not as effective as NaOH in promoting the cyclopropanation reaction with good selectivity (entries 4 & 5). Weaker carbonate bases, such as Cs_2CO_3, were not able to mediate the double alkylation process (entry 6). During the investigation of the phase transfer reaction, the purity of (*E*)-*N*-benzylideneglycine ethyl ester **5a** was found to be a key factor impacting the enantioselectivity of the reaction. As little as 2 mol% residual Et_3N, a contaminant from the preparation of the Schiff base **5a** was detrimental to the cyclopropanation stereoselectivity and promoted significant unselective alkylation (entry 7). Residual benzaldehyde (5 mol%) in **5a** reduced the selectivity (entry 8) and we speculated that benzaldehyde may competitively bind with the catalyst.[14] The purity of the phase transfer catalyst was an additional factor which needed to be controlled to achieve high enantioselectivity. Contamination of catalyst **PTC-1** with cinchonidine led to the production of **4a** in only moderate ee (entry 9). Toluene, a hydrophobic non-polar solvent, was selected as the solvent considering its inexpensive cost, and the good enantioselectivity observed during a solvent screen. However, additional rounds of solvent screening consistently showed that the reactions in chlorobenzene generally gave better yield with shorter reaction times (entry 10). A significant improvement in reaction rate was observed when applying a wet milling process using an Ultra-Turrax in-line disperser/homogenizer (IKa UTL 25), reducing the reaction time from 17 h to 1.5 h presumably due to the remarkably improved mixing of the biphasic mixture (entry 11). Such a strong dependence on the stirring rate and mixing suggested that the **PTC-1**-catalyzed reaction is governed by the interfacial mechanism where the quaternary ammonium ion mainly resides in the organic phase and the reaction rate is limited by the rate of hydroxide extraction.[15]

After the set of conditions to give reproducible ee were determined, we established purity control of all inputs and began tuning the catalyst structure to further enhance the selectivity of the process (Fig. 2 & Table 2). A series of cinchonidine-based phase transfer catalysts were prepared. We found that the 2,5-substitution pattern on the aromatic ring of the benzyl group and the electron withdrawing character of the substituents were primary factors for obtaining good enantioselectivity (entries 1–4). For instance, a subtle change from a CF_3 group to a CH_3 group on the aromatic C5 position resulted in a decrease in selectivity of the phase-transfer cyclopropanation (entry 4). Catalysts with different substitution patterns, for instance 3,5-substitutions (entries 5–7) and 4-NO_2-aryl analogue (entry 8), varying the steric bulk of their substituent (entries 9–11) or changing their electronic character (entries 5–11) did not provide a meaningful improvement in enantioselectivity under the optimized phase transfer conditions. Interestingly the use of the *O*-allylated catalyst in the reaction afforded the product with negligible enantioselectivity in poor yield which suggested that the hydrogen bonding ability of the catalyst was a critical attribute in promoting the reaction stereoselectively (entry 12). In contrast to **PTC-1**, the Maruoka catalyst **PTC-13** was not suitable for this phase transfer

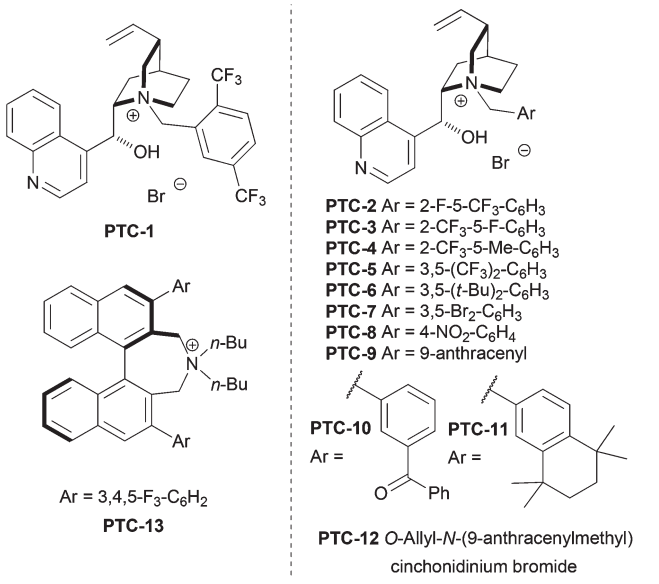
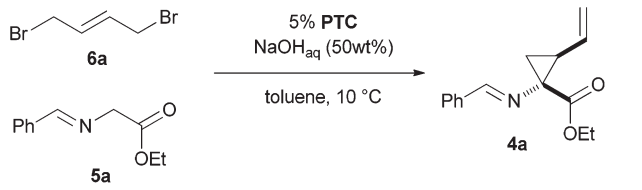


Fig. 2 Phase transfer catalysts.

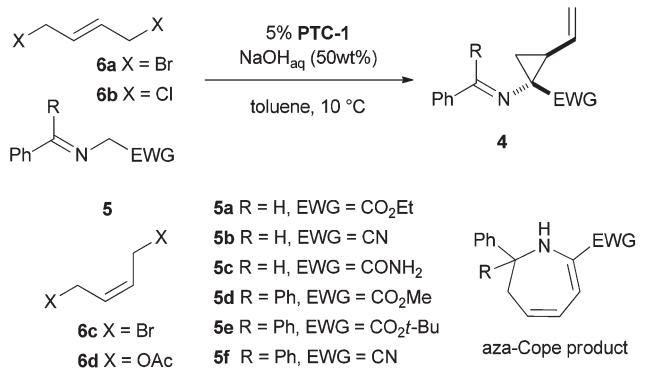
Table 2 Catalyst survey for asymmetric phase transfer cyclopropanation of **5a** with **6a**



Entry[a]	Catalyst	Yield[b] (%)	ee[c] (%)
1	**PTC-1**	88	80
2	**PTC-2**	79	60
3	**PTC-3**	91	35
4	**PTC-4**	79	11
5	**PTC-5**	84	51
6	**PTC-6**	80	29
7	**PTC-7**	82	20
8	**PTC-8**	25	35
9	**PTC-9**	81	72
10	**PTC-10**	77	10
11	**PTC-11**	52	17
12	**PTC-12**	15	<2
13	**PTC-13**	14	33

[a] The reactions were carried out using **6a** as the limiting reagent, 1.20 equiv. of **5a**, toluene (16 g per g-LR), and NaOH (15 g per g-LR). [b] Determined by reverse phase HPLC analysis. [c] Determined by normal-phase chiral HPLC analysis.

Table 3 Substrate survey for asymmetric phase transfer cyclopropanation of **5** with **6**



Entry[a]	5	6	Yield[b] (%)	ee[c] (%)	dr[d]
1	**5a**	**6a**	88	80	>20 : 1
2	**5a**	**6b**	33	64	>20 : 1
3	**5a**	**6c**	<5	—	—
4	**5a**	**6d**	<5	—	—
5	**5b**	**6a**	51	10	7 : 1
6	**5c**	**6a**	82	<5	>20 : 1
7	**5d**	**6a**	<5	—	—
8	**5e**	**6a**	15	—	—
9	**5f**	**6a**	27	<5	10 : 1

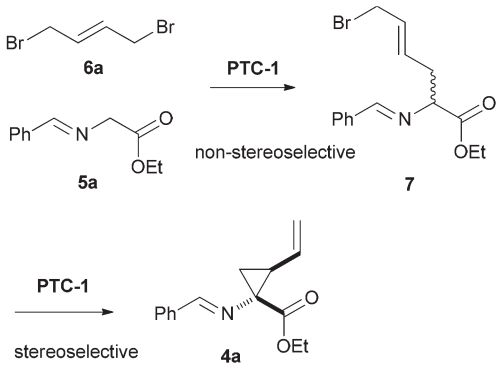
[a] The reactions were carried out using **6** as the limiting reagent, 1.20 equiv. of **5**, toluene (16 g per g-LR), and NaOH (15 g per g-LR). [b] Determined by reverse phase HPLC analysis. [c] Determined by normal-phase chiral HPLC analysis. [d] Determined by ^{1}H-NMR.

reaction and promoted the reaction in low yield and selectivity (entry 13).[13]

In an effort to attain a better enantioselectivity, we investigated the scope of both electrophiles and nucleophiles (Table 3). Under our optimized conditions, cyclopropanation product **4a** was always obtained in high dr (entry 1). Its diastereomer underwent an aza-Cope rearrangement and its derived by-product could be purged in the next step. Commercially available *trans*-1,4-dichloro-2-butene **6b** was not as competitively reactive as dibromo butene **6a** (entry 2). *cis*-1,4-Dibromo-2-butene was not a suitable electrophile giving primarily cyclopentene cyclization product (entry 3) and *cis*-1,4-diacetoxy-2-butene was completely unreactive (entry 4). Phase transfer alkylation of α-aminoacetonitrile-derived imine **5b** afforded the corresponding product in poor ee but good dr (entry 5). We also synthesized the benzylidene-protected glycinamide **5c**, a bench stable solid compound, and under **PTC-1**-catalyzed conditions cyclopropanation did occur and generated amide **3** in good yield (82%) and high dr (>20 : 1) but with low enantioselectivity. Benzophenone-derived glycine imines (**5d**, **5e** and **5f**) are relatively stable solids. However the cyclopropanation reactions of these sterically hindered imines were very slow and often led to stalled reactions at the mono-alkylation stage or a competing side reaction occurred where the mono-alkylation intermediate reacted with another equivalent of glycine imine to form a 2-butene-bridged dimer (entries 7–9).

A representative reaction progression profile of the phase transfer reaction is shown in Fig. 3.[16] A relatively rapid accumulation of mono-alkylation intermediate **7** was observed, accompanied by its slower conversion to the desired product **4a**. It was determined that intermediate **7** was a racemic compound during the course of the reaction suggesting that the first alkylation is either not enantioselective or intermediate **7** is easily racemized. Under the phase transfer conditions, cyclization of isolated racemate **7** produced **4a** in 70% yield and 77% ee, which supports the hypothesis that the second alkylation is both an enantio- and diastereo-defining step.

The degree of diastereoselectivity and enantioselectivity observed in the phase transfer reaction of **5a** with **6a** suggests a catalyst–enolate associated complex with specific steric requirements. We have developed a model that accounts for the sense of stereoinduction. We first executed a conformation search of the catalyst **PTC-1** and identified its lowest-energy conformer which featured a sterically shielded ammonium functionality (Fig. 4a).[17] In addition, we considered the enolates of mono-alkylated intermediate **7** as reactive species in the second alkylation. Both *Z*- and *E*-enolates of **7** were modelled in a reactive conformation with **PTC-1** docked by hydrogen bonding.[18] An MMFF conformation search identified the lowest-energy conformer of the enolates of **7** complexed with **PTC-1**. Upon optimization of the complex structures with DFT (B3LYP/6-31G*), the *E*-enolate/**PTC-1** complex was significantly lower in energy than the *Z*-enolate/**PTC-1** complex. According to this model (Fig. 4b), an orthogonal orientation of the *N*-benzylidene moiety relative to the enolate plane would alleviate the allylic strain imposed by the alkyl chain on the enolate α-carbon. The Br-substituted 2-butenyl group rotated away



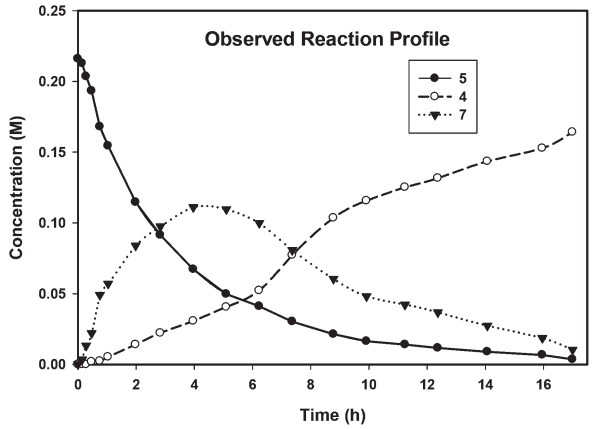


Fig. 3 Reaction profile of the phase transfer alkylation of **5a**.

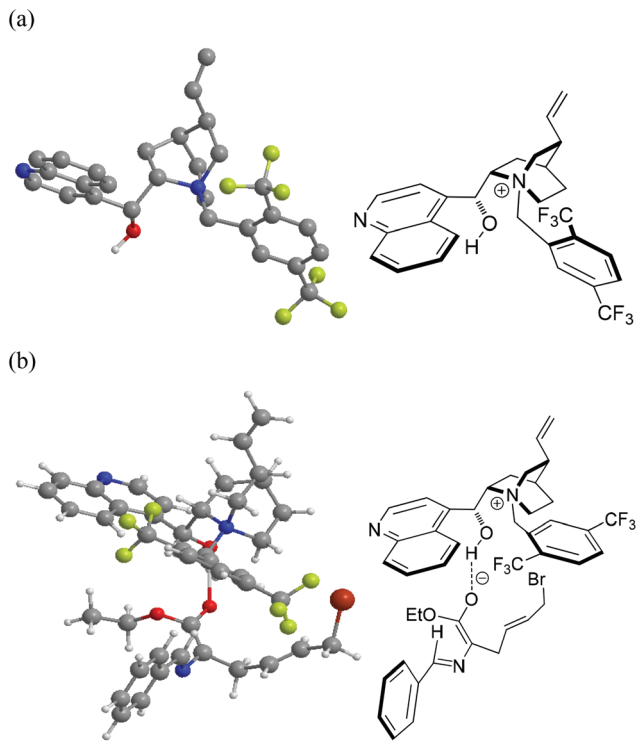
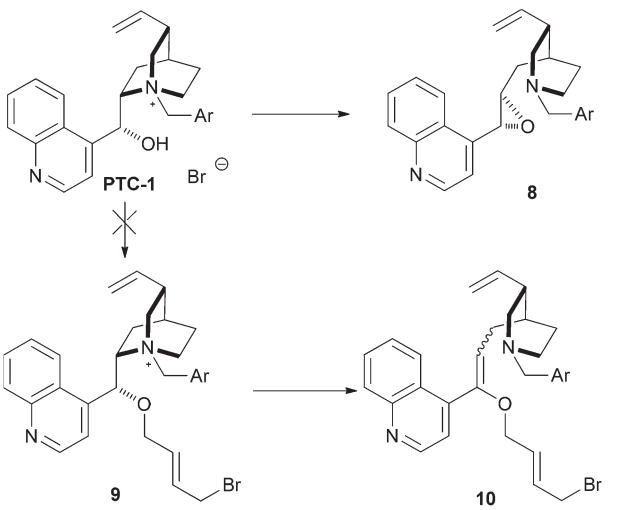


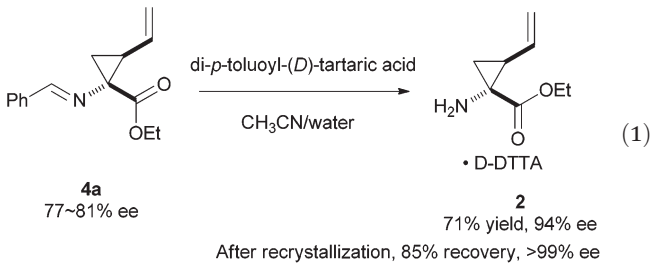
Fig. 4 Calculated ground state conformations of catalyst **PTC-1** and the **PTC-1**/enolate of **7** complex.

from the quinoline ring of the catalyst and the leaving group bromine atom was pointing towards the positive charge on the ammonium moiety. Thus, C–C bond formation to generate the cyclopropane ring favored an attack on the *si* face of the C=C double bond of the α-alkyl chain. Our proposed model is consistent with the solution structures of ion pairs formed by cinchona alkaloid-derived ammonium with small anions studied by intermolecular NOE correlations in which the preferred anion occupancy site was determined to be near the hydroxyl group.[19] Although further calculations may be warranted, we suspect that ion pairing may promote subtle conformational changes in the phase transfer catalyst. **PTC-1** with a 2,5-substitution pattern on the aryl ring may have lower activation energy to form the enolate/**PTC-1** complex from two free ions than the catalysts with other substitution patterns.

Although the catalyst **PTC-1** is not commercially available, its precursor 2,5-bis(trifluoromethyl)benzyl bromide is readily available and synthesis of **PTC-1** in high purity has been demonstrated on a 10 g scale (see the Experimental section).[20] In our optimized phase transfer procedure, premixing the catalyst with glycinate Schiff base **5a** to minimize the exposure time of free catalyst to NaOH in the interface appeared to be an important factor to achieve good enantioselectivity. We reasoned that such a procedure mitigated catalyst degradation. Indeed formation of **8** (70%) occurred when **PTC-1** was subjected to aqueous NaOH for 3–5 hours. Epoxide **8** was isolated after holding the phase transfer reaction stream for an extended period (Scheme 2)[21] and its formation appears to be the major decomposition pathway of the PTC catalyst. Neither allyl ether **9** that could be generated from a reaction of the catalyst **PTC-1** with 1,4-dibromo-2-butene **6a** nor its subsequent Hoffman elimination product **10** was observed.[22] Albeit epoxide **8** lacks the ammonium moiety to form an ion pair with the enolate, it is an organic base that proves to be a competent catalyst that promotes an unselective alkylation of **5a** to generate racemic **4a**.



Scheme 2 Plausible catalyst degradation pathways.

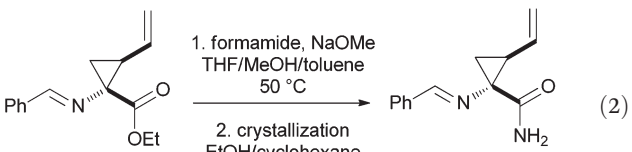


(1)

4a
77~81% ee

2
71% yield, 94% ee
After recrystallization, 85% recovery, >99% ee

With enantioenriched Schiff base **4a** in hand, we first considered accessing vinyl-ACCA sulfonamide **1b** through its ester analog **2** given the known synthetic sequence.[4f] In order to prepare material of the required purity (>90% ee), a robust chemical resolution strategy to further upgrade the chiral purity of vinyl-ACCA ethyl ester **2** was developed (eqn (1)). Upon a survey of a range of chiral acids and solvents, we were delighted to find that di-*p*-toluoyl-(D)-tartaric acid (D-DTTA) was a suitable acid for the hydrolysis of Schiff base **4a** in a mixture of acetonitrile–water resulting in the formation of the **2**/D-DTTA salt which exhibited the desired low solubility in this solvent system. By careful control of solvent composition (CH_3CN–water = 9 : 1), the **2**/D-DTTA salt was reproducibly isolated in high enantiomeric purity (94% ee). An additional recrystallization afforded **2**/D-DTTA in >99% ee with good material recovery. As described earlier (see Scheme 1), **2** can be converted to **1b** in 4 steps.[4f] This process suffers from lower throughput yield, low overall yield and long cycle time due to additional Boc protection–deprotection steps. In addition, multiple isolations involving acid–base salt formation to isolate the corresponding Boc-protected carboxylic acid and salt breaking for the peptide coupling step are necessary.



(2)

4a
77-81% ee

3
70% yield, >99% ee

Having vinyl-ACCA sulfonamide **1b** as our final target, we set out to identify and develop a shorter sequence that allowed the use of the *N*-benzylidene protecting group and thus avoid extra protection–deprotection steps. Vinyl-ACCA ester **4a** is not a stable intermediate and was not isolated. Instead, the process stream containing **4a** was subjected to amidation with a mixture of formamide and sodium methoxide in MeOH (MeOH is required) to form a stable and isolable primary amide **3** in 70% yield and >99% ee upon crystallization from ethanol and cyclohexane (eqn (2)).[23] To test the efficiency of this process in upgrading optical purity, primary amide **3** with a range of ee values was subjected to the EtOH–cyclohexane crystallization conditions. Impressively, input **3** with ≥70% ee could be recrystallized under controlled conditions to provide >99% ee material. A conglomerate phase diagram was determined for primary amide **3** (Fig. 5). In fact only 5 to 10% of the compounds have a conglomerate forming property which

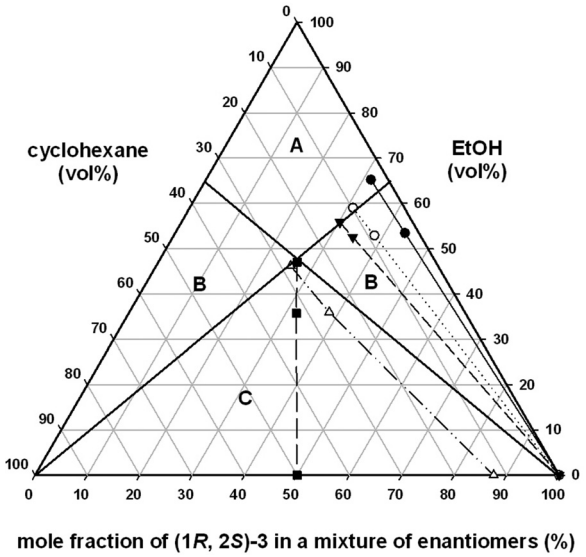
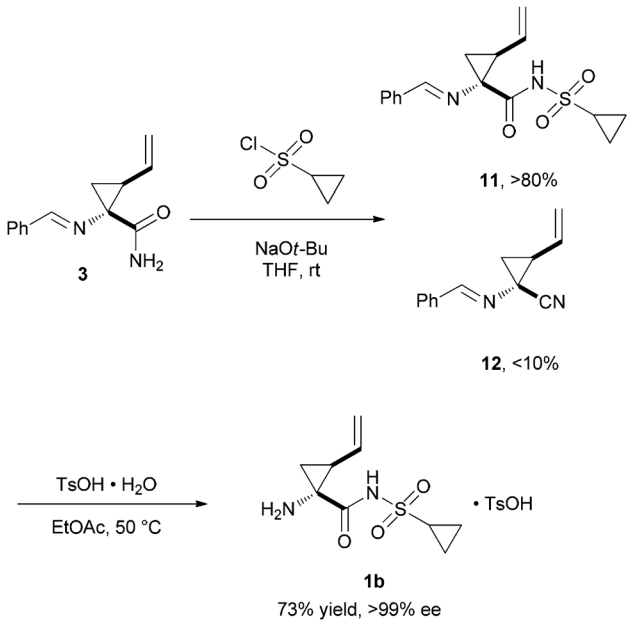


Fig. 5 Conglomerate phase diagram of amide **3** at rt.

is most favorable for achieving a successful enantiomeric enrichment by fractional crystallization from a non-racemic mixture. Such a conglomerate phase diagram generally suggests that only two crystal solid forms are present in solution,[24] one being (1*R*,2*S*)-**3** and the other being its enantiomer, (1*S*,2*R*)-**3**. The triangle edges are given in vol% of solvents (EtOH and cyclohexane) and mole fractions of (*R*)/(*S*) enantiomers.[25] Each point inside the triangle describes a ternary mixture consisting of all three components. For conglomerates, the diagram consists of three region types: a single undersaturated liquid phase region (A) close to the top vertex, two two-phase regions (B) on each side which contain an enantiopure solid phase and a saturated liquid phase with one or both enantiomers, and a three-phase region (C) where under equilibrium conditions the liquid phase is a saturated solution of a racemic mixture and the solid phase is a mixture of two enantiomeric crystal forms. The diagram depicted in Fig. 4 suggests that to ensure isolation of enantiopure **3**, the isolation needs to be conducted above the solubility of the racemic fraction of the enantioenriched mixture present in the process stream and that the isolation yield can be improved by increasing the anti-solvent volume percentage, cyclohexane in this case, within the B-phase regions.

The final two steps in the improved route to **1b** were relatively straightforward (Scheme 3). The sulfonylation to furnish **11** was carried out by treating amide **3** with cyclopropanesulfonyl chloride in the presence of a strong base. The main impurity in this step is the α-aminonitrile derivative, a dehydration product of the primary amide **3**. Typically 7–10 mol% of this side product was formed and its downstream hydrolysis product was successfully purged during the crystallization of **1b**. It was found that using lithium *tert*-butoxide as a base significantly mitigated the formation of α-aminonitrile. However, lithium tosylate formed in the hydrolysis step has higher solubility in EtOAc and could not be effectively purged by filtration



Scheme 3 Synthesis of **1b** from **3**.

prior to crystallization of **1b.** The presence of LiOTs in the reaction stream either resulted in a low isolated yield or **1b** contaminated with LiOTs. Reactions using other strong bases, such as organolithium reagents, lithium bis(trimethylsilyl)-amide, Grignard reagents, and DBU, did not afford **1b** in comparable yield. Finally, sodium *tert*-butoxide was chosen for the sulfonylation step and the resulting insoluble NaOTs were efficiently removed by filtration. Hydrolysis of the *N*-benzylidene Schiff base with TsOH·H_2O yielded sulfonamide **5** as a shelf-stable TsOH salt in high purity.

Conclusions

In summary, a 4-step chromatography-free sequence to rapidly access (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic sulfonamide **1b** in ≥99% ee and 51% overall yield has been developed. The robustness of the asymmetric cyclopropanation under phase transfer catalysis conditions was significantly improved from the previously reported process by a deliberate procedure design based upon mechanistic investigations and understanding the quality of the starting materials and the catalyst. Amidation of the vinylcyclopropanecarboxylic ester **4a** with sodium formamide afforded a bench stable benzylidene-protected primary amide **3** and its excellent optical purity enrichment to ≥99% ee was achieved by controlled crystallization conditions. In addition, a robust chemical resolution using D-DTTA following the asymmetric phase transfer reaction was developed to access (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic ester **2** in ≥94% ee and ≥99% ee upon recrystallization. Both chiral vinylcyclopropanecarboxylic sulfonamide and ester are valuable synthons for the preparation of HCV protease inhibitors.

Experimental section

General information

The following reagents were purchased and used without further purification: cinchonidine (Aldrich), 2,5-bis(trifluoromethyl)benzyl bromide (SynQuest), benzaldehyde (Aldrich), glycine ester hydrochloride (Aldrich), *trans*-1,4-dibromo-2-butene (AK Scientific), NaOH (50 wt% aq., Alfa Aesar), toluene (J. T. Baker), formamide (Aldrich), NaOMe (25 wt% in MeOH, Aldrich), cyclopropanesulfonyl chloride (AK Scientific) and TsOH monohydrate (Aldrich). (*E*)-*N*-Benzylideneglycine ethyl ester was prepared according to a literature procedure[6,25] and the spectral data are in agreement with reported values.[6] HPLC analysis was carried out using a Shimadzu Prominence system. Daicel CHIRALCEL® columns or Daicel CHIRALPAK® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μm) were used for chiral HPLC analysis. All reactions were carried out in oven-dried glassware or a clean and nitrogen-dried Chemglass jacketed 1 L process reactor under an atmosphere of nitrogen.

***N*-[2,5-Bis(trifluoromethyl)benzyl]cinchonidinium bromide (PTC-1).** The title compound was prepared according to a reported procedure[12] with an additional reslurry process to upgrade its purity. To a 3-neck RBF equipped with a thermocouple and a condenser were added cinchonidine (10.0 g [limiting reagent]; 1.0 equiv.; 34.0 mmoles) and toluene (15.0 mL per g-bulk-LR; 150 mL). 2,5-Bis(trifluoromethyl)benzyl bromide (1.20 equiv.; 40.8 mmoles; 7.48 mL; 12.5 g) was added to the RBF *via* a syringe. The solution was heated to 110 °C (internal solution temperature) and stirred for 4.0 h. The reaction was monitored by HPLC until <5.0 RAP cinchonidine was reached. The reaction mixture was cooled to rt over 2.0 h and stirred at rt for 1.0 h. The resulting white solid was filtered and washed with toluene (60.0 mL). The cake was air-dried for 5.0 min. Its purity was determined by HPLC and contained 3.50 RAP cinchonidine. The purity of the catalyst was further upgraded by a reslurry procedure: 20.1 g was treated with EtOH–MTBE (10.0 mL g^{-1}, 100 mL, 1 : 1). The resulting slurry was stirred overnight and filtered. The cake was washed with EtOH–MTBE (1.0 mL g^{-1}, 10.0 mL, 1 : 1) and MTBE (2.0 mL g^{-1}, 20.0 mL). The resulting cake was dried in a vacuum oven at 50 °C and 25.0 inHg for 2.0 h. *N*-[2,5-Bis(trifluoromethyl)-benzyl]cinchonidinium bromide was obtained as a white solid (15.4 g, 77% yield, purity >99% with <0.05 RAP of cinchonidine). Reverse phase HPLC analysis: Phenomenex Luna 3 μm 100AC18, 4.6 × 50 mm; solvent pair: A = 0.05% TFA in water–MeOH 80 : 20, B = 0.05% TFA in CH_3CN–MeOH–water 75 : 20 : 5; gradient: start % B = 0, 0.5 Min. 0%, 5 Min. 10%, 10 Min. 100%, 12 Min. 100%; flow rate = 2 ml min^{-1}; wavelength = 254 nm; retention time: 1.45 min (cinchonidine), 7.58 min (PTC-1), 7.80 min (dihydro-PTC-1); sampling: about 10 mg solid was dissolved in 10 mL MeOH in a volumetric flask; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (d, J = 4.4 Hz, 1H), 8.60 (s, 1H), 8.37 (d, J = 8.2 Hz, 1H), 8.25 (s, 2H), 8.11 (dd, J = 8.4, 1.1 Hz, 1H), 7.85 (td, J = 7.6, 0.9 Hz, 1H), 7.81 (d, J = 4.4 Hz, 1H), 7.74 (ddd, J = 8.4, 6.9, 1.1 Hz, 1H), 6.88 (d,

J = 3.2 Hz, 1H), 6.57 (br. s., 1H), 5.66 (ddd, J = 17.2, 10.9, 6.0 Hz, 1H), 5.57–5.50 (m, 1H), 5.49–5.41 (m, 1H), 5.25 (d, J = 17.3 Hz, 1H), 4.94 (d, J = 10.4 Hz, 1H), 4.37 (m, 1H), 4.14–4.02 (m, 2H), 3.51 (t, J = 11.2 Hz, 1H), 3.25–3.13 (m, 1H), 2.67 (br. s., 1H), 2.17–2.03 (m, 2H), 2.01 (br. s., 1H), 1.81–1.70 (m, 1H), 1.23–1.13 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 150.2, 147.6, 145.0, 137.9, 134.50–133.80 (q, J = 31.25 Hz), 133.7 (d, J = 3.7 Hz), 132.99–132.10 (q, J = 32.5 Hz), 129.9, 129.6 (q, J = 5.5 Hz), 129.5, 128.2 (q, J = 3.7 Hz), 127.4, 127.1, 124.2, 123.5, 123.4 (q, J = 275 Hz), 123.2 (q, J = 275 Hz), 119.9, 116.4, 68.0, 64.7, 59.2, 58.3, 51.2, 37.3, 25.3, 24.4, 21.2; Analytical data are in agreement with reported values.[12]

(1*R*,2*S*)-Ethyl 1-((*E*)-benzylideneamino)-2-vinylcyclopropane carboxylate (4a). To a 1 L reactor was charged toluene (16.0 g per g-bulk-LR; 1.73 moles; 178 mL; 160 g) and *N*-[2,5-bis(trifluoromethyl)benzyl]cinchonidinium bromide (0.050 equiv.; 2.34 mmoles; 1.41 g). The catalyst solution was cooled to 5 °C and (*E*)-*N*-benzylideneglycine ethyl ester (1.20 equiv.; 56.1 mmoles; 35.8 g, 30.0 wt% in toluene) was charged *via* a syringe. The mixture was agitated for 15.0 min. A solution of *trans*-1,4-dibromo-2-butene (10.0 g [limiting reagent]; 1.0 equiv.; 46.75 mmoles) in toluene (4.0 g per g-bulk-LR; 1.95 moles; 46.0 mL; 40.0 g) was charged *via* a syringe. Sodium hydroxide (15 g per g-bulk-LR; 1.875 moles; 98.3 mL; 150 g; 50 wt%) was added *via* an addition funnel over a period of 1 h and the reaction solution temperature was maintained at ≤5 °C. After the $NaOH_{(aq)}$ charge, the reaction mixture was warmed to 10 °C and agitated (800–1000 rpm) for 15–17 h. Upon complete consumption of monoalkylation intermediate 7 (<2.0% RAP relative to product determined by reverse phase HPLC), agitation was stopped and the biphasic reaction mixture was allowed to separate for 30 min. The aqueous phase was removed and the organic phase was filtered through a Celite® bed to remove any precipitates. The filtrate was used in the next step without further purification. The solution yield (88%) was determined by obtaining the wt% of the product in the stream according to the standard linear calibration curve. An analytical sample was obtained by column chromatography (silica gel, eluted with EtOAc in hexanes (5–30% gradient)). Appropriate fractions were combined, concentrated and dried under high vacuum. Reverse phase HPLC analysis: Waters XTerra Phenyl Column, 3.5 μm, 4.6 × 100 mm; solvent pair: A = 0.05% NH_4OH in water–MeOH 80 : 20, B = 0.05% NH_4OH in CH_3CN–MeOH 80 : 20; gradient: start % B = 0, 0.5 Min. 0%, 2 Min. 40%, 10 Min. 60%, 14 Min. 100%; flow rate = 1 ml min^{-1}; wavelength = 254 nm; retention time: 7.36 min ((*E*)-*N*-benzylideneglycine ethyl ester), 9.63 min (product **3**), 10.58 (monoalkylation intermediate); chiral HPLC analysis: Daicel CHIRALPAK AS-H column, 5 μm, 4.6 × 150 mm; solvent system: 2% IPA in heptanes (0.05% Et_2NH); 1.0 mL min^{-1}; retention times: 4.39 min (major), 5.44 min (minor); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.80–7.72 (m, 2H), 7.51–7.41 (m, 3H), 5.67 (ddd, J = 17.1, 10.3, 8.8 Hz, 1H), 5.30 (dd, J = 17.2, 1.4 Hz, 1H), 5.11 (dd, J = 10.4, 1.9 Hz, 1H), 4.21–4.12 (m, 2H), 2.36 (q, J = 8.7 Hz, 1H), 1.87 (dd, J = 7.9, 5.4 Hz, 1H), 1.76 (dd, J = 9.5, 5.4 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.2, 159.4, 135.9, 134.3, 130.8, 128.6 (2C), 127.9 (2C), 117.4, 60.7, 53.5, 35.3, 21.5, 14.1; IR (KBr) 3419, 2990, 1717, 1635, 1577, 1462, 1368, 1291, 1174, 1144, 1025, 916, 758, 702 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{18}NO_2$ (M + 1$^+$) 244.13321, found 244.13292.

(1*R*,2*S*)-1-((*E*)-Benzylideneamino)-2-vinylcyclopropane carboxamide (3). All reagent stoichiometries were calculated based on *trans*-1,4-dibromo-2-butene (10.0 g [limiting reagent]; 1.0 equiv.; 46.75 mmoles). A solution of **4a** was concentrated to ~2 mL g^{-1}. Tetrahydrofuran (5.0 mL per g-bulk-LR; 614 mmoles; 50.0 mL; 44.3 g) and formamide (6.0 equiv.; 281 mmoles; 11.2 mL; 12.6 g) were charged followed by a slow addition of sodium methoxide (2.50 equiv.; 117 mmoles; 27.2 mL; 25.3 g) *via* a syringe. The reaction solution was heated to 50 °C and stirred for 4.0 h. The reaction was monitored by HPLC until 100% conversion was observed. The reaction mixture was cooled to rt and was quenched with water (5.0 mL per g-bulk-LR; 50.0 mL; 50.0 g). The solution pH was adjusted from pH ~ 11 to pH ~ 9 by adding a saturated aqueous NH_4Cl solution. Methyl *t*-butyl ether (10.0 mL per g-bulk-LR; 100 mL; 74.2 g) was charged and the bottom aqueous layer was separated. The organic layer was washed with water (5.0 mL per g-bulk-LR; 50.0 mL; 50.0 g) twice and concentrated to ~50 mL (5.0 mL per g-bulk-LR). The solution was subjected to a constant volume distillation by adding methyl *t*-butyl ether (200 mL) over 1 h *via* an addition funnel until the water content reached <0.10 wt% (determined by Karl Fischer titration). The solvent was then exchanged to cyclohexane by adding cyclohexane (200 mL) at such a rate as to maintain the solvent volume at 50 mL (5.0 mL per g-bulk-LR) at 30 °C. Ethanol (1 mL per g-bulk-LR; 171.76 mmoles; 10.0 mL; 7.91 g) was charged. The resulting solution was heated to 60 °C to obtain a homogeneous solution. The solution was cooled to 45 °C and seeded with (1*R*,2*S*)-1-((*E*)-benzylideneamino)-2-vinyl-cyclopropanecarboxamide **3** (0.005 g per g-bulk-LR; 50 mg). After aging at 45 °C for 30 min the slurry was cooled to 20 °C over 2 h and aged at 20 °C for 1 h. The resulting crystallized product was filtered, washed with EtOH–cyclohexane (1 : 5, 10 mL) and cyclohexane (10 mL). The wet cake was dried in the vacuum oven at 50 °C and 25 inHg for 4.0 h. (1*R*,2*S*)-1-((*E*)-Benzylideneamino)-2-vinylcyclopropane carboxamide **3** was obtained as an off-white solid (7.03 g, 70.1% yield, >99% ee, and >98 wt% potency). Reverse phase HPLC analysis: Waters XTerra Phenyl Column, 3.5 μm, 4.6 × 100 mm; solvent pair: A = 0.05% NH_4OH in water–MeOH 80 : 20, B = 0.05% NH_4OH in CH_3CN–MeOH 80 : 20; gradient: start % B = 0, 0.5 Min. 0%, 2 Min. 40%, 10 Min. 60%, 14 Min. 100%; flow rate = 1 ml min^{-1}; wavelength = 254 nm; retention time: 7.79 min (product **3**), 9.63 min (starting material **4a**); sampling: about 250 mg reaction organic stream was diluted to 25 mL in a volumetric flask with acetonitrile–water = 1 : 1; chiral HPLC analysis: Daicel CHIRALPAK AD-H column, 5 μm, 4.6 × 150 mm; solvent system: 15% IPA in heptane; 1.0 mL min^{-1}; retention times: 4.39 min (minor), 6.16 min (major); ^{1}H NMR (major diastereomer only, 500 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.92–7.87 (m, 2H), 7.82 (br. s., 1H), 7.48–7.41 (m, 4H),

5.90 (ddd, J = 17.3, 10.1, 8.8 Hz, 1H), 5.20 (dd, J = 17.3, 1.9 Hz, 1H), 5.01 (dd, J = 10.4, 1.9 Hz, 1H), 2.07–1.95 (m, 2H), 1.92–1.87 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.5, 154.6, 135.9, 135.7, 130.7, 128.5 (2C), 128.3 (2C), 116.2, 52.3, 20.4; IR (KBr) 3455, 3282, 2885, 1691, 1578, 1404, 1364, 1210, 1166, 1001, 914, 904, 777, 765, 698, 636 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}N_2O$ (M + 1$^+$) 215.11789, found 215.11765.

(1*R*,2*S*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-vinyl cyclopropanecarboxamide tosylate salt (1a). To a 3-neck RBF equipped with a thermocouple was charged (1*R*,2*S*)-1-((*E*)-benzylideneamino)-2-vinylcyclopropane carboxamide **3** (10.0 g [limiting reagent]; 1.0 equiv.; 46.7 mmoles; 1.00 g) and tetrahydrofuran (6.0 mL per g-bulk-LR; 73.7 mmoles; 60.0 mL; 53.2 g) and the solution was cooled to 2 °C in an ice/water bath. Sodium *t*-butoxide (2.20 equiv.; 102.7 mmoles; 9.87 g) in 30.0 mL THF was charged over 15 min *via* a syringe to control the temperature to <5 °C. The resulting brown slurry was stirred for 10 min. Cyclopropanesulfonyl chloride (1.10 equiv.; 51.3 mmoles; 5.23 mL; 7.22 g) in tetrahydrofuran (4.0 mL per g-bulk-LR; 492 mmoles; 40.0 mL; 35.4 g) was charged over 10 min at 0–6 °C. The slurry was stirred at 2 °C for 2.0 h and at 20 °C for 2.0 h until the reaction was deemed to be complete by HPLC. *p*-Toluenesulfonic acid monohydrate (2.20 equiv.; 102.7 mmoles; 19.5 g) was charged at 20 °C. The resulting mixture was warmed to 50 °C over 15 min and stirred at 50 °C for 3.0 h. The reaction solution was cooled to 20 °C and ethyl acetate (10.0 mL per g-bulk-LR; 100.0 mL; 90.0 g) was charged. The resulting solid (NaCl and NaOTs) was removed by filtration. The filtrate was concentrated to ~5 mL per g-bulk-LR and subjected to a constant volume distillation with ethyl acetate (10.0 mL per g-bulk-LR; 100 mL; 90.0 g) at 50 °C until the water content was <0.10 wt% (determined by Karl Fischer titration). The stream was cooled to 30 °C and seeded with **1** (0.005 g per g-bulk-LR; 50 mg), cooled to 10 °C over 2.0 h and aged at 10 °C for 1.0 h. The resulting crystals were filtered and washed twice with ethyl acetate (1.50 mL per g-bulk-LR; 15.0 mL; 13.5 g). The wet cake was dried in a vacuum oven at 50 °C and 25 inHg for 4.0 h to give (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide tosylate salt (13.7 g; 73% yield, >99% ee) as a white solid. Reverse phase HPLC analysis: Waters XTerra Phenyl Column, 3.5 μm, 4.6 × 100 mm; solvent pair: A = 0.05% NH_4OH in water–MeOH 80 : 20, B = 0.05% NH_4OH in CH_3CN–MeOH 80 : 20; gradient: start % B = 0, 0.5 Min. 0%, 2 Min. 40%, 10 Min. 60%, 14 Min. 100%; flow rate = 1 ml min^{-1}; wavelength = 254 nm; retention time: 7.79 min (**4a**); sampling: about 250 mg reaction organic stream was diluted to 25 mL in a volumetric flask with acetonitrile–water = 1 : 1; chiral HPLC analysis: Daicel CHIRALCEL OJ-H column, 5 μm, 4.6 × 150 mm; solvent system: 20% EtOH in heptane (0.1% TFA); 1.0 mL min^{-1}; retention times: 6.17 min (minor), 8.53 min (major); ^{1}H NMR (major diastereomer only, 500 MHz, DMSO-d_6) δ 8.69 (br. s., 2H), 7.55–7.33 (m, 2H), 7.12 (d, J = 7.9 Hz, 2H), 5.68–5.51 (m, 1H), 5.35 (d, J = 17.0 Hz, 1H), 5.27–5.14 (m, 1H), 3.05–2.90 (m, 1H), 2.35–2.23 (m, 4H), 2.15 (t, J = 7.4 Hz, 1H), 1.59 (dd, J = 9.8, 7.3 Hz, 1H), 1.17–1.01 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.9, 145.4, 137.8, 131.2, 128.1 (2C), 125.4 (2C), 119.7, 41.4, 30.8, 28.9, 20.7, 16.3, 5.7. IR (KBr) 3428, 3192, 2921, 2832, 2650, 2575, 1707, 1699, 1599, 1518, 1479, 1360, 1329, 1190, 1136, 1036, 1010, 882, 815, 783, 686 cm^{-1}; HRMS (EI) calcd for $C_9H_{15}N_2O_3S$ (M + 1$^+$) 231.07979, found 231.07951.

(1*R*,2*S*)-Ethyl 1-amino-2-vinylcyclopropanecarboxylate di-*p*-toluoyl-D-tartaric acid salt (2). A (1*R*,2*S*)-ethyl 1-((*E*)-benzylideneamino)-2-vinylcyclopropane carboxylate (**4a**) solution in toluene was concentrated to about 84 wt% (determined by H-NMR). In a 250 mL RBF was charged **4a** (10.0 g [limiting reagent]; 1.0 equiv.; 34.52 mmoles), acetonitrile (18.0 mL per g-bulk-LR; 190 mL), water (2.0 mL per g-bulk-LR; 20.0 mL) and (+)-di-1,4-toluoyl-D-tartaric acid monohydrate (1.0 equiv.; 34.5 mmoles; 13.5 g). The solution was heated to 75 °C and stirred for 2.0 h until complete conversion of **4** was observed by HPLC. The solution was cooled to rt over 3 h and aged at rt for 1 h. The resulting white solid was filtered and washed with acetonitrile–water (18 : 2, 20 mL) and acetonitrile (20 mL). The wet cake was dried in a vacuum oven at 50 °C and 25 inHg for 5 h. The desired product **2** was obtained as a white solid (13.2 g, 71% yield and 94% ee). Reverse phase HPLC analysis: Waters XTerra Phenyl Column, 3.5 μm, 4.6 × 100 mm; solvent pair: A = 0.05% NH_4OH in water–MeOH 80 : 20, B = 0.05% NH_4OH in CH_3CN–MeOH 80 : 20; gradient: start % B = 0, 0.5 Min. 0%, 2 Min. 40%, 10 Min. 60%, 14 Min. 100%; flow rate = 1 ml min^{-1}; wavelength = 220 nm; retention time: 1.18 min (di-1,4-toluoyl-D-tartaric acid), 6.31 min (2), 6.50 min (benzaldehyde), 9.63 min (3); sampling: about 250 mg reaction organic stream was diluted to 25 mL in a volumetric flask with acetonitrile; chiral HPLC analysis: Daicel Chiralpak AD-3R, 3 μm, 4.6 × 150 mm; solvent A = 0.01 M NH_4OAc in MeOH–water (20 : 80), solvent B = B2 = 0.01 M NH_4OAc in MeOH–water–CH_3CN (20 : 5 : 75); gradient: start % B = 0%, 25% (10 min), 35% (20 min), 100% (25 min); 0.8 mL min^{-1}; retention times: 13.83 min (major), 14.96 min (minor); ^{1}H NMR (major diastereomer only, 500 MHz, DMSO-d_6) δ 7.86 (d, J = 7.9 Hz, 4H), 7.34 (d, J = 8.2 Hz, 4H), 5.69 (s, 2H), 5.57 (dt, J = 17.2, 9.7 Hz, 1H), 5.22 (dd, J = 17.0, 1.6 Hz, 1H), 5.06 (dd, J = 10.2, 1.7 Hz, 1H), 4.19–4.06 (m, 2H), 2.38 (s, 6H), 2.16 (q, J = 10.0 Hz, 1H), 1.52 (dd, J = 9.5, 5.4 Hz, 1H), 1.46 (dd, J = 7.7, 5.5 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.8, 167.8 (2C), 164.8 (2C), 144.0 (2C), 133.5, 129.34 (4C), 129.31 (4C), 126.5 (2C), 117.7, 71.7, 61.2, 40.6, 31.7, 21.2 (2C), 20.1, 14.1; IR (KBr) 3432, 3176, 2945, 1728, 1707, 1612, 1269, 1178, 1110, 750, 694 cm^{-1}; LRMS (EI) calcd for $C_8H_{14}NO_2$ (M + 1$^+$) 156.10184, found 156.10191.

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