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Cinchona Alkaloid Catalyzed Sulfa-Michael Addition Reactions Leading to Enantiopure β-Functionalized Cysteines

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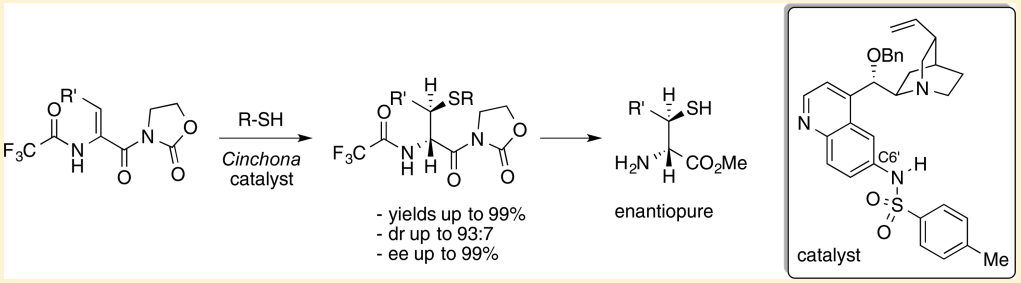
Supporting Information



ABSTRACT: Sulfa-Michael additions to α,β-unsaturated *N*-acylated oxazolidin-2-ones and related α,β-unsaturated α-amino acid derivatives have been enantioselectively catalyzed by *Cinchona* alkaloids functionalized with a hydrogen bond donating group at the C6′ position. The series of *Cinchona* alkaloids includes known C6′ (thio)urea and sulfonamide derivatives and several novel species with a benzimidazole, squaramide or a benzamide group at the C6′ position. The sulfonamides were especially suited as bifunctional organocatalysts as they gave the products in very good diastereoselectivity and high enantioselectivity. In particular, the C6′ sulfonamides catalyzed the reaction with the α,β-unsaturated α-amino acid derivatives to afford the products in a diastereomeric ratio as good as 93:7, with the major isomer being formed in an ee of up to 99%. The products of the organocatalytic sulfa-Michael addition to α,β-unsaturated α-amino acid derivatives were subsequently converted in high yields to enantiopure β-functionalized cysteines suitable for native chemical ligation.

INTRODUCTION

Catalysis with enantiopure organic molecules (organocatalysis) is widely recognized as highly valuable in asymmetric synthesis of compounds of pharmaceutical importance.[1] This is manifested in the increasing number of successful studies that have been reported for a large variety of organic reactions, such as the Henry reaction,[2] Michael additions,[3] Mannich reactions,[4] Morita−Baylis−Hillman reactions,[5] cycloadditions[6] and multicomponent cascade reactions.[7] In most of the reported studies, the reactions are performed with organocatalysts derived from a limited number of privileged structures, e.g., the natural *Cinchona* alkaloids,[1a,g,8] BINOL (1,1′-bi-2-naphthol)[9] and proline.[1f,10] In particular, *Cinchona* alkaloids have been applied in numerous studies concerned with enantioselective reactions owing to their availability, the presence of five stereogenic centers and distinct sites that can be modified with a range of hydrogen bond donating groups. In most studies the hydrogen bonding moiety is a thiourea,[11,12] a urea,[13] a squaramide,[14] a sulfonamide[15] or a guanidine[16] group situated at the C9 position. Relatively few studies have been concerned with *Cinchona* alkaloid derivatives with a hydrogen bonding group located at one of the sites of the quinoline moiety. Recently, Palacio and Connon reported that *Cinchona* alkaloids with a urea moiety at the C5′ position are efficient catalysts for asymmetric sulfa-Michael addition (SMA)[17] to nitro-styrenes.[18] Previously we showed that a C6′ thiourea derivative of quinidine is a highly efficient catalysts for the Henry reaction[2] and later Deng and co-workers reported that a C6′ thiourea with a C9-methylanthracyl ether group is well suited as a catalyst for SMA reactions with α,β-unsaturated *N*-acetylated oxazolidin-2-ones (Scheme 1).[19] More recently, we reported that the same C6′ thiourea derivative operates as an enantioselective catalysts in the SMA reaction with *N*-acylated oxazolidin-2-one derivatives of α,β-unsaturated amino acids (Scheme 1) and obtained the products in fair to good diastereoselectivity with the major diastereomer being obtained in good to high ee.[20] However, we noticed that the C9-methylanthracyl ether bond is also cleaved during the step involving demethylation of the methoxygroup at the quinoline moiety thus giving a low overall yield of this particular *Cinchona* alkaloid derivative. In other studies we have introduced a benzyl ether group at the C9 position and observed this to give a robust C6′ thiourea derivative in high yield.[2] Unfortunately, in our previous work we noted that the combination of a C9 benzyl ether and a C6′ thiourea leads to low diastereoselectivity

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Scheme 1. SMA Reaction with α,β-Unsaturated *N*-Acetylated Oxazolidin-2-ones as Described by Deng and Coworkers[19] and with *N*-Acylated Oxazolidin-2-one Derivatives of α,β-Unsaturated α-Amino Acids as Described in Our Earlier Work[20]

in the SMA reaction with α,β-unsaturated α-amino acid derivatives.[20]

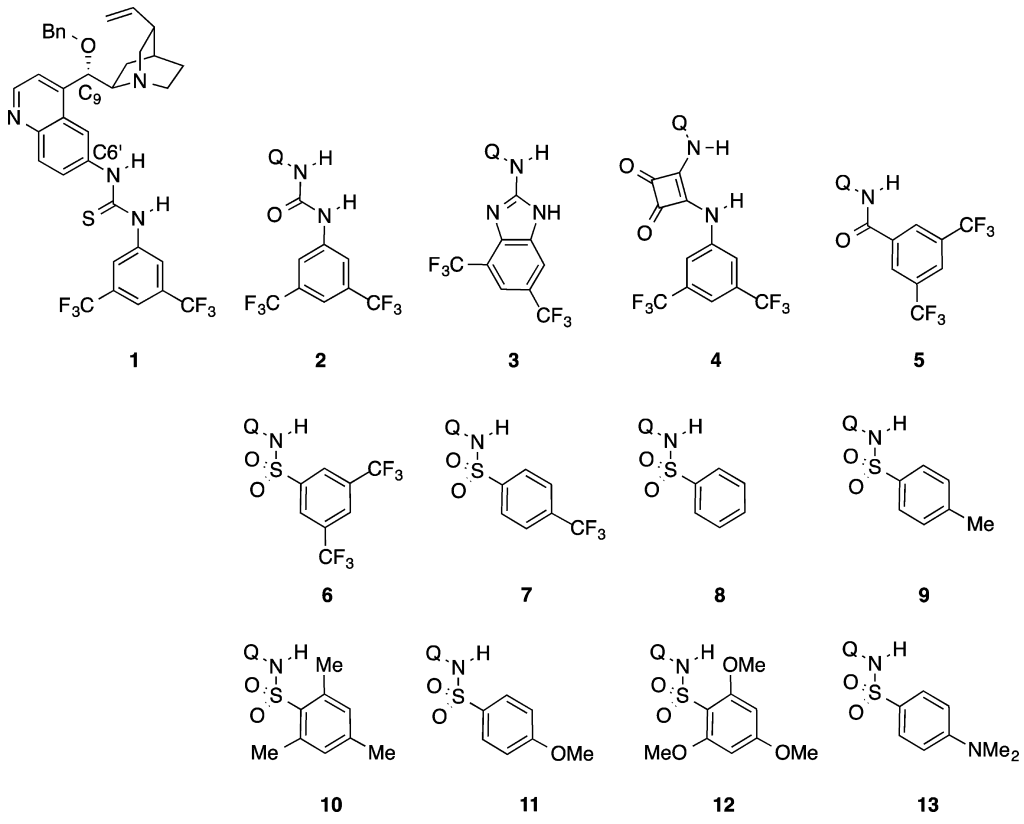
In order to optimize the organocatalyzed SMA reactions with unsaturated α-amino acid derivatives we decided to prepare an extended series of C6′ substituted *Cinchona* bases with a C9 benzyl ether group. The present series of catalysts includes the known thiourea,[2] sulfonamide[21] and urea[22] derivatives together with novel benzimidazole, squaramide and benzamide C6′ substituted *Cinchona* alkaloid derivatives (Scheme 2). The major objectives of the present study are to (i) examine the efficiency of C6′ substituted *Cinchona* derivatives as catalyst for the SMA reactions shown in Scheme 1, (ii) optimize and broaden the scope of the SMA reactions with the α,β-unsaturated α-amino acid derivatives, (iii) explore the use of benzylic thiols that can be easily removed under mild conditions, e.g., Ph_2CHSH (DPM),[23] thus forming enantiopure β-functionalized cysteines for applications in peptide chemistry.

RESULTS AND DISCUSSION

Catalyst Synthesis. The C6′ urea compound **2** was prepared similarly to the C6′ thiourea **1**[2] by coupling of the C6′ amino derivative **14** (shown in Scheme 3) with commercially available 1-isocyanato-3,5-bis(trifluoromethyl)-benzene.[2] The synthesis of the C6′ benzimidazole derivative **3** was less straightforward, but realized by a Buchwald-Hartwig coupling[24] between **14** and 2-chloro-4,6-bis(trifluoromethyl)-1*H*-benzo[*d*]imidazole[16] protected with a (trimethylsilyl)-ethoxymethyl (SEM) group at one of the nitrogen atoms (**15** in Scheme 3).[25] The benzimidazole derivative **3** was obtained in 36% overall yield from **15** after removal of the SEM group through treatment with $BF_3{\cdot}OEt_2$ in CH_2Cl_2.[26]

The novel C6′ squaramide derivative **4** also appeared to be a challenge. First we reacted amine **14** with dimethyl squarate and obtained the expected product, but the subsequent coupling with 3,5-bis(trifluoromethyl)aniline proved unsuccessful. The strategy used for the synthesis of the known C9 squaramide derivative also failed,[27] that is, the coupling of 3,5-bis(trifluoromethyl)aniline with dimethyl squarate to form **16** in Scheme 4 was facile, but no reaction occurred between **16** and C6′ amine **14** in neat methanol. Following a recent study by Taylor and co-workers concerning the synthesis of *N*,*N*-diarylsquaramides[28] we then reacted **16** with **14** in toluene/DMF in the presence of $Zn(OTf)_2$. With 0.2 or 1.0 equiv of $Zn(OTf)_2$ no reaction occurred, but the addition of 3 equiv of the zinc salt gave the desired C6′ squaramide **4** in a moderate

Scheme 2. *Cinchona* Derivatives with a Hydrogen Bonding Group at C6′ and a Benzyl Ether Function at C9[a]



[a]Q is the quinidine moiety as shown in **1**.

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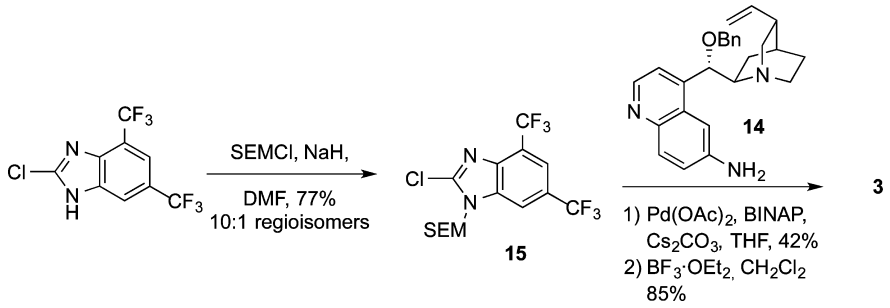
Scheme 3. Synthesis of the C6′ Guanidine *Cinchona* Derivative



Scheme 4. Synthesis of the C6′ Squaramide *Cinchona* Alkaloid Derivative

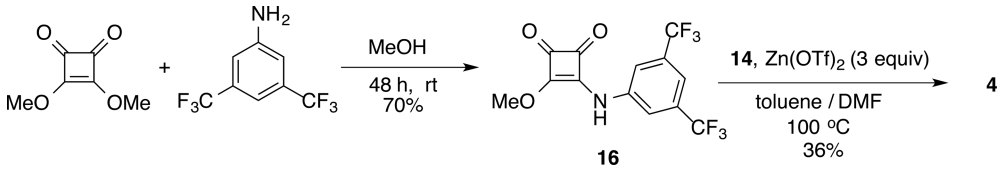
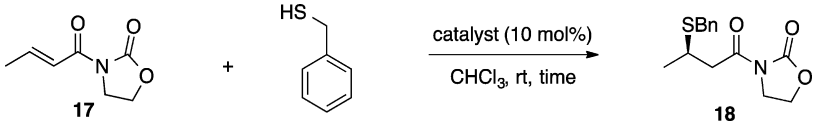


Table 1. SMA of Phenylmethanethiol onto Substrate 17[a]



entry	catalyst	reaction time (h)	conversion (%)[b]	ee (%)[c]
1	**1**	6	100	68 (*R*)
2	**2**	6	100	59 (*R*)
3	**3**	4	100	10 (*R*)
4	**4**	–	0	–
5	**5**	16	100	20 (*R*)
6	**6**	16	90	−50 (*S*)
7	**7**	72	81	−65 (*S*)
8	**8**	16	100	−84 (*S*)
9	**9**	16	100	−81 (*S*)
10	**10**	16	100	−81 (*S*)
11	**11**	6	100	−85 (*S*)
12	**12**	16	100	−86 (*S*)
13	**13**	16	100	−87 (*S*)

[a]Reaction conditions: 0.2 M in substrate, 3 equiv of BnSH, rt, $CHCl_3$. [b]Conversion determined by ^1H NMR. [c]ee determined by chiral HPLC analysis (AD column).

yield of 36%. The C6′ benzamide **5** and the series of sulfonamide derivatives **6**-**13** were prepared in high yields by the reaction of **14** with the appropriate acid chlorides.[14,29]

Catalysts Screening. The efficiency of the C6′ derivatives as catalysts was first examined on the basis of the enantioselectivity in the known SMA reaction between phenylmethanethiol and the *α,β*-unsaturated *N*-acetylated oxazolidin-2-one **17** (Table 1). In line with the results reported by Deng and co-workers the C6′ thiourea **1** gave the product in 68% ee with the major isomer being formed in the *R* configuration (entry 1, Table 1).[19] The C6′ urea derivative **2** catalyzed the reaction (entry 2) as efficiently as the related thiourea; that is, both reactions were complete within 6 h. However, the enantioselectivety was not more than 59% with **2** as the catalyst and thus somewhat lower than with the thiourea **1** (68% ee). With the C6′ benzimidazole **3** full conversion was obtained within 4 h but the product was formed in an ee of only 10% (entry 3). Unfortunately, the novel C6′ squaramide **4** did not catalyze the SMA reaction of phenylmethanethiol with **17** (entry 4).[30] With the C6′ benzamide **5** the reaction was complete after 16 h yielding the product in poor enantioselectivity (20% *ee*, entry 5). In the reactions catalyzed by **1**−**3** and **5** the major isomer was consistently formed in the *R* configuration. However, in the slow reaction catalyzed by C6′ sulfonamide **6**, chiral HPLC analysis in combination with determination of the optical rotation (see Experimental Section and Supporting Information) revealed that the major isomer is now formed in the *S* configuration, that is, an ee of −50% was obtained (entry 6).

The sulfonamide substituted with a single CF_3-group at the 4-position of the phenyl ring **7** (entry 7) gave rise to a somewhat less efficient reaction than catalyst **6** containing two CF_3- groups (entry 5). The ee was slightly better than with **6** as the catalyst, that is −65%. The C6′ sulfonamide with an unsubstituted phenyl group **8** led to a more efficient reaction than the catalysts with CF_3- substituents and also to a very good

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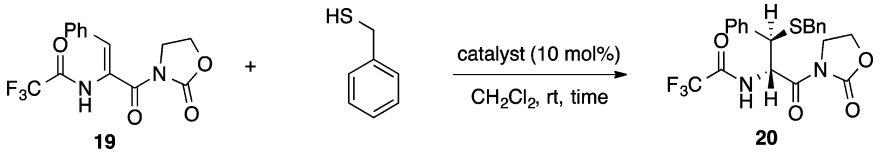
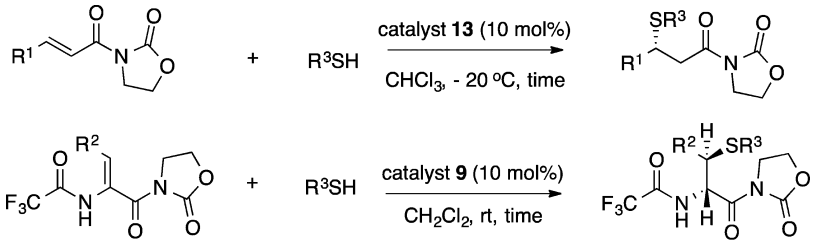
Table 2. SMA of Phenylmethanethiol onto Substrate 19[a]



entry	catalyst	reaction time (h)	conversion (%)[b]	*anti*/*syn*[c]	ee (%)[d]
1	**1**	6	100	64:36	93/55
2	**2**	8	100	29:71	13/−4
3	**3**	24	100	33:67	31/32
4	**5**	40	100	42:58	61/65
5	**6**	160	100	71:29	92/75
6	**7**	160	60	80:20	nd
7	**8**	60	100	81:19	98/12
8	**9**	60	100	84:16	99/8
9	**10**	60	100	67:33	98/−24
10	**11**	60	100	78:22	94/4
11	**12**	60	100	38:62	88/45
12	**13**	60	100	81:19	98/12

[a]Reaction conditions: 0.2 M in substrate, 3 equiv of BnSH, rt, CH_2Cl_2. [b]Conversion as determined by ^{1}H NMR. [c]Diastereomeric ratios, dr, determined by ^{1}H NMR. The assignment of the *anti* and *syn* configuration is based on our previously work (ref 20) and the results in the Supporting Information. [d]ee determined by chiral HPLC analysis (AD column).

Table 3. Substrate and Nucleophile Scope of the SMA Reactions



entry	substrate	R^1	R^2	R^3	reaction time (h)	product	yield (%)	*anti*/*syn*[a]	ee (%)[b]
1	**17**	Me	–	CH_2=CHCH	84	**25**	97	–	91 (*S*)
2	**17**	Me	–	Bn	84	**18**	97	–	93 (*S*)
3	**17**	Me	–	4-MeOBn	84	**26**	98	–	92 (*S*)
4	**17**	Me	–	Ph_2CH	84	**27**	99	–	85 (*S*)
5	**21**	*n*-Pr	–	Bn	84	**28**	99	–	92 (*S*)
6	**21**	*n*-Pr	–	4-MeOBn	84	**29**	96	–	91 (*S*)
7	**21**	*n*-Pr	–	Ph_2CH	84	**30**	97	–	92 (*S*)
8	**22**	Ph	–	Ph_2CH	140	**31**	90	–	94 (*R*)
9	**19**	–	Ph	CH_2=CHCH	24	**32**	93	73:27	99/3
10	**19**	–	Ph	Bn	16	**20**	95	84:16	99/8
11	**19**	–	Ph	4-MeOBn	16	**33**	97	83:17	96/52
12	**19**	–	Ph	Ph_2CH	16	**34**	97[c]	93:7	>99/33
13	**23**	–	4-MeOPh	Bn	16	**35**	99	80:20	98/3
14	**23**	–	4-MeOPh	4-MeOBn	16	**36**	96	80:20	97/6
15	**23**	–	4-MeOPh	Ph_2CH	16	**37**	96	90:10	98/17
16	**24**	–	Et	Bn	24	**38**	96	82:18	97/29
17	**24**	–	Et	4-MeOBn	24	**39**	99	80:20	96/26
18	**24**	–	Et	Ph_2CH	16	**40**	96	93:7	98/3

[a]Diastereomeric ratios, dr, determined by ^{1}H NMR. The assignment of the *anti* and *syn* configuration is based on our previously published results (see ref 20). [b]ee determined by chiral HPLC analysis (AD column). [c]80% yield and >99.5% ee after recrystallization of the major isomer.

ee of −84% (entry 8). A similar ee (−81%) was obtained with the 4-methyl-substituted catalyst **9** (entry 9) and the same result was obtained with the 2,4,6-trimethyl substituted C6′ sulfonamide **10** (entry 10). The sulfonamide with a methoxy at the 4-position **11** gave −85% ee and full conversion in only 6 h (entry 11). With three methoxy groups at the phenyl ring **12** the ee was −86% (entry 12). Finally, catalyst **13** containing the strongly electron donating dimethylamino group was examined and observed to yield the product in −87% ee (entry 13).

Next we explored the reactions of phenylmethanethiol with the α,β-unsaturated α-amino acid derivative **19** (Table 2). With the C6′-thiourea **1** (entry 1) the diastereomeric ratio was 64:36

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with the major diastereomer being formed in an ee of 93%. The dr is slightly better than the ratio of 52:48 reported earlier if this reaction is catalyzed by the C9-methylanthracyl ether analogue of **1**.[20] In our previous work,[20] we reported the X-ray crystal structure of the product of the addition of 4-methoxyphenylmethanethiol to **19** as catalyzed by the C6′-thiourea quinidine with a C9-methylanthracyl ether group. The X-ray analysis revealed that the major isomer formed in this reaction has the *anti* stereochemistry with the *S* configuration at the *α*-carbon and the *R*-configuration at the *β*-carbon atom. On the basis of this X-ray structure in combination with chiral HPLC and NMR analysis (see Supporting Information), we have assigned the present products as having the *anti* or *syn* stereochemistry as indicated in Table 2.

The C6′ urea **2** gave a remarkable result; that is, we observed an inversion of the *anti*:*syn* ratio as compared to the thiourea catalyst **1** (entry 1) and almost complete loss of the enantioselectivity (entry 2). The benzimidazole species **3** gave a slow reaction (entry 3) and also a reversal of the *anti*:*syn* ratio as compared to the thiourea **1**. The squaramide **4** was not examined for this reaction in view of the results obtained for **17** as substrate.[31] With the C6′ benzamide **5** catalyst a slight preference for the *syn* diastereoisomer was observed and both diastereoisomers were formed in reasonable ee's (entry 4). With the C6′ sulfonamide **6** as catalyst full conversion was obtained only after 160 h (entry 5). Significantly, the major diastereoisomer was now formed in an ee of 92%. Subsequently, we examined the series of C6′ sulfonamides **7**−**13** as catalysts in order to optimize the SMA reaction with substrate **17**. The presence of a single electron withdrawing CF_3 group at the 4-position (**7**) led to a very slow reaction as only 60% conversion was obtained after 160 h (entry 6). In addition, we were unable to separate the starting materials from the product of the reaction. Nevertheless, the diastereoselectivity was improved to 80:20 as compared to ratio of 71:29 obtained with the 3,5-$(CF_3)_2$ substituted catalyst (**6**, entry 5).

With the C6′ sulfonamides, **8**−**13**, full conversion occurred within 60 h (Table 2). The catalyst with an unsubstituted phenyl group in the sulfonamide moiety (**8**, entry 7) formed the product in a *anti*:*syn* ratio of 81:19. Notably, a very high enantioselectivity of 98% was obtained for the *anti* diastereoisomer. The introduction of a methyl group at the 4-position (**9**) caused a further improvement of the diastereoselectivity to 84:16 and with this particular sulfonamide we obtained the major *anti* diastereoisomer in an excellent ee of 99% (entry 8). With the trimethyl substituted catalyst **10** the diastereoselectivity was only 67:33 even though the *anti* diastereoisomer was again formed in a very high ee (98%, entry 9). The diastereoselectivity was moderate, 78:22, if an electron donating methoxy group was introduced at the 4-position (**11**, entry 10) and with the 2,4,6-trimethoxy substituted catalyst (**12**) the diastereoselectivity was reversed to 38:62 (entry 11). The ee of the *anti* isomer was slightly lower for the species with three methoxy groups (88%) as compared to the 4-methoxy substituted as catalysts (94%). With the sulfonamide containing a dimethylamino group at the 4-position (**13**) we obtained a *anti*:*syn* ratio of 81:19 and a high ee (98%) for the *anti* diastereoisomer (entry 12).

Scope of the Reactions. On the basis of the results of the catalyst screening we decided to explore the scope of the SMA reactions. For the reaction with the *N*-acylated oxazolidin-2-ones **17**, **21** and **22** we focused on the C6′ sulfonamide catalyst **13** containing a dimethylamino at the 4-position and performed the reactions at a temperature of −20 °C in order to optimize the ee's (Table 3).

The addition of prop-2-ene-1-thiol to **17** yielded the product in a very good ee of 91% and an excellent yield of 97% (entry 1). With phenylmethanethiol as the nucleophile, performing the reaction with **17** at −20 °C improved the ee to 93% from 87% at rt (entry 2, Table 3 and entry 1, Table 2) and gave a yield of 97% after 84 h. The addition of 4-methoxyphenylmethanethiol to **17** gave an ee (92%) and a high yield of 98% (entry 3). With the sterically hindered Ph_2CHSH as the nucleophile we obtained an ee of 85% but a very high yield of 99% after 84 h (entry 4). Excellent results were also obtained for *n*-propyl substituted **21** even with Ph_2CHSH as nucleophile (entries 5−7). The phenyl-substituted substrate **22** appeared to have a poor solubility in $CHCl_3$ and, as a result, the reaction with Ph_2CHSH was performed at low concentration leading to a reaction time of 140 h. Nevertheless, the product of the reaction was formed in a high yield and also a high ee of 94% (entry 8).

The optimal conditions for the SMA reactions with the *α*,*β*-unsaturated *α*-amino acid derivatives **19**, **23**, and **24** involved the C6′-sulfonamide **9** with a methyl group at the 4-position as catalyst, rt and CH_2Cl_2 as solvent. With prop-2-ene-1-thiol as nucleophile, the diastereoselectivity of the reaction was not more than 73:27 but the ee of the *anti* isomer was excellent, 98% (entry 9). The reaction of phenylmethanethiol with **19** gave a diastereomeric ratio of 84:16 and excellent ee for the *anti* isomer (entry 10) and similar results were obtained 4-methoxyphenylmethanethiol as the nucleophile (entry 11). The *syn* isomer was formed with a very low enantioselectivity (8%) in the former reaction (entry 9), while the reaction with the 4-methoxy-substituted thiol gave the *syn* diastereomer in a moderate ee of 52% (entry 11). The diastereoselectivity was 93:7 with Ph_2CHSH and again an excellent enantioselectivity (>99%) was obtained for the major isomer (entry 12). After purification the major isomer was recrystallized as a single enantiomer in 80% yield (see also Experimental Section).

In the reaction of the tyrosine derivate **23** with phenylmethanethiol as well as the 4-methoxy substituted thiol an 80:20 mixture of diastereoisomers was formed with excellent ee for the major isomers (entries 13 and 14). Again the best diastereoselectivity was obtained with the bulky Ph_2CHSH thiol, that is 90:10 (entry 15) and also the ee of the major isomer was very high, 98%. With the ethyl-substituted *α*,*β*-unsaturated *α*-amino acid **24** the same trend in stereoselectivity was observed as with the tyrosine derivative **23** (entries 16−18), in particular, Ph_2CHSH gave the best dr (93:7) and an excellent ee (98%) for the major diastereomer.

***β*-Thiol-Functionalized Oxazolidinones and Cysteines.** Highly enantioenriched or enantiopure compounds with a free thiol group could be obtained in a single step from the products of the SMA with Ph_2CHSH. For the product **30** from the reaction with the *n*-Pr substituted *N*-acylated oxazolidin-2-one **21**, the Ph_2CH-group was easily removed at rt with TFA and triisopropylsilane in CH_2Cl_2 (Scheme 5).

With the purpose of converting the products of the SMA reactions into derivatives suitable for peptide chemistry we developed the procedure shown in Scheme 6. First, the trifluoroacetyl group was removed with HCl in methanol at reflux[31] and then the amino group was Boc protected prior to replacing the oxazolidone group with a methyl ester to form **41** (Scheme 6). Simultaneous removal of the Ph_2CH- and the Boc group appeared less facile than shown in Scheme 5, but could

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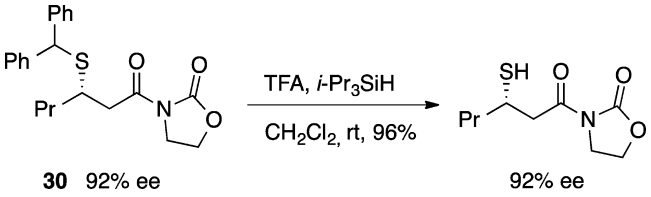
Scheme 5. Removal of the Ph_2CH-Group



30 92% ee 92% ee

be achieved at an elevated temperature (50 °C) with TFA and triisopropylsilane in CH_2Cl_2[23] giving **43** in 95% yield without loss of ee. Saponification of the methyl ester was realized with Tesser's base[32] and gave the β-functionalized cysteine **42** in 88% yield with no loss in stereochemical integrity.

β-Thiol-functionalized α-amino acids have been applied previously in native chemical ligation studies.[33] For example, Crich and Banerjee applied this strategy with a β-thiol-functionalized phenylalanine for the synthesis of decapeptides.[33a] Recently, our group reported an epimerization-free synthesis of activated aryl ester of small peptides (e.g., 4-(methylsulfonyl)phenyl esters) via the Chan–Lam coupling.[34] These esters were successfully applied in native chemical ligation thus avoiding the addition of thiophenol to the reaction mixture for the in situ generation of a thiol ester as in the more common procedure. Here, we first coupled compound **42** with a free acid group to the tripeptide, H_2N-Ala-Val-Phe-CO_2Me, with HATU, HOAt and DIPEA giving the tetrapeptide **44** in 73% yield (Scheme 7). Subsequently the Ph_2CH-group was removed from the tetrapeptide prior to purification by preparative HPLC giving a mixture of the thiol and the related disulfide. Subsequently, the tetrapeptide with a free thiol group was effectively subjected to native chemical ligation with a dipeptide containing an activated 4-(methylsulfonyl)phenyl ester group thus leading to hexapeptide **46** (Scheme 7) with a β-functionalized cysteine incorporated.

CONCLUSION

A extended series of *Cinchona* organocatalysts with a hydrogen bonding group at C6′ was prepared and applied in sulfa-Michael additions to *N*-acetylated oxazolidin-2-ones and related α,β-unsaturated α-amino acid derivatives. In the reactions with the *N*-acetylated oxazolidin-2-ones the C6′ sulfonamides gave the main enantiomer in the (*S*)-configuration while, for example, the C6′-(thio)urea gave rise to the (*R*)-enantiomer. The C6′-sulfonamides proved to give the highest ee in the SMA reaction with the α,β-unsaturated α-amino acid derivatives, up to 99% for the major *anti* isomer. The dr was up to 93:7 in the reactions with the congested nucleophile Ph_2CHSH. Facile removal of the Ph_2CH-group afforded unnatural cysteines that could be easily converted into suitable substrates for peptide chemistry.

EXPERIMENTAL SECTION

General Methods. The ^1H NMR and ^{13}C NMR spectra (APT) were recorded (^1H 400 MHz, ^{13}C 100 MHz) at room temperature with $CDCl_3$ as the solvent. Accurate mass measurements were performed with high resolution mass spectrometry (HRMS) and fast atom bombardment (FAB) or electrospray (ESI) as the ionization method. The FAB measurements were performed with a four sector tandem mass spectrometer, whereas a qTOF (quadrupole time-of-flight) instruments was used for the ESI measurements. Low resolution mass spectra were recorded with a ESI LC Ion Trap instrument. All reactions were carried out in oven-dried glassware with magnetic stirring. Tetrahydrofuran (THF) was freshly distilled from Na and benzophenone. Toluene was distilled over CaH_2 and stored over 4 Å mol sieves. DMF was dried over mol sieves. Other solvents were also distilled prior to use.

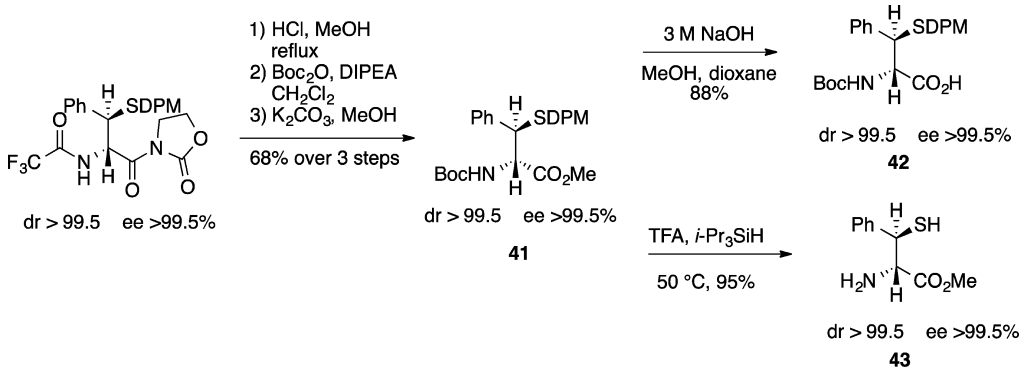
Synthesis of the Unsaturated *N*-Acylated Oxazolidinones. The oxazolidin-2-ones **17**, **21** and **22** were prepared in good yields by reacting the corresponding acid chlorides with the sodium salt of 1,3-oxazolidin-2-one generated with sodium hydride as described in the literature.[35] The α,β-unsaturated α-amino acid derivatives **19**, **23** and **24** were synthesized as described in our earlier work,[20] analogous to published procedures.[36] This methodology involved reaction of the amino acids phenylalanine, 4-methoxyphenylalanine and norvaline, respectively, with TFAA to give the corresponding pseudoazlactones, followed by bromination and treatment with excess of the sodium salt of 1,3-oxazolidin-2-one.

General Procedure for the Synthesis of the Pseudoazlactones. A mixture of an amino acid and TFAA (2.3 equiv) was refluxed for 1 h. After removing the excess reagent the product was distilled under reduced pressure.

4-(4-Methoxybenzyl)-2-(trifluoromethyl)oxazol-5(2H)-one. According to the general procedure, 4-methoxyphenylalanine (5.0 g, 25.6 mmol) was reacted with TFAA (8.3 mL, 58.9 mmol) to afford the title compound (5.7 g, 21.0 mmol, 82%) as a colorless oil after distillation under reduced pressure (0.06 mbar, 200 °C). IR (neat, cm^{-1}) ν 1808, 1606, 1157, 1018, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 2H, J = 8.7 Hz), 6.90 (d, 2H, J = 8.7 Hz), 6.10 (m, 1H), 3.99 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 163.3, 159.0, 130.3, 124.1, 120.0 (q, J = 280.0 Hz), 114.3, 92.8 (q, J = 34.9 Hz), 55.1, 33.5.

4-Propyl-2-(trifluoromethyl)oxazol-5(2H)-one. According to the general procedure, norvaline (11.7 g, 100 mmol) was reacted with TFAA (32 mL, 230 mmol) to afford the title compound (19.0 g, 97.4 mmol, 97%) as a colorless oil after distillation under reduced pressure (0.8 mbar, 81 °C). IR (neat, cm^{-1}) ν 2972, 1802,1648, 1153, 1008, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 6.13 (m, 1H), 2.70 (t, 2H, J = 5.2

Scheme 6. Formation of β-Functionalized Cysteines (DPM = Ph_2CH)



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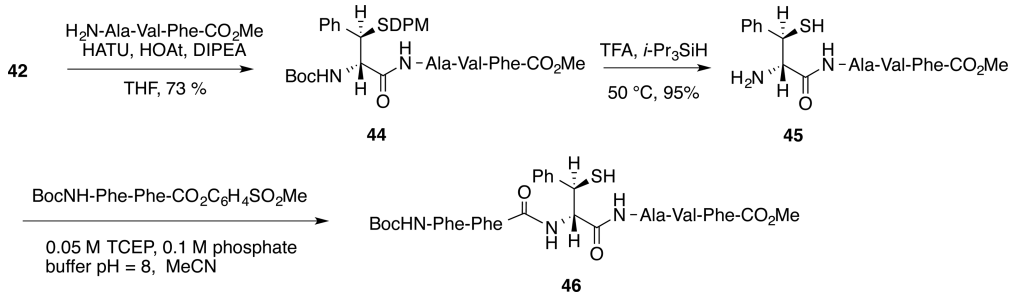
Scheme 7. Native Chemical Ligation with a Peptide Containing a β-Functionalized Cysteine



Hz), 1.83 (m, 2H), 1.04 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.8, 120.2 (q, J = 279.8 Hz) 93.1 (q, J = 34.9 Hz), 30.0, 18.6, 13.2; HRMS (FAB) for $C_7H_9F_3NO_2$ calculated $[M + H]^+$: 196.0585, found $[M + H]^+$: 196.0591.

General Procedure for Bromination of Pseudoazlactones. The pseudoazlactone was dissolved in 1,2-dichloroethane and cooled to 0 °C and then treated with a small portion of a solution of bromine (1 equiv) in 1,2-dichloroethane. A small sample was withdrawn and gently heated until it became colorless and then returned to the flask. This procedure was repeated until the mixture in the flask became colorless. Next the rest of the bromine solution was added. The mixture was allowed to warm up to rt and stirred until all the starting material had disappeared according to TLC. The product was concentrated under reduced pressure and purified as specified hereafter.

4-(Bromo(4-methoxyphenyl)methyl)-2-(trifluoromethyl)oxazol-5(2H)-one. According the general procedure, the methoxybenzyl pseudoazlactone (5.2 g, 19.0 mmol) was dissolved in 50 mL 1,2-dichloroethane and reacted with bromine (0.97 mL, 19.0 mmol) in 20 mL 1,2-dichloroethane to afford the title compound (5.9 g, 16.7 mmol, 88%) as a greenish oil after column chromatography (PE/EtOAc 30:1). This product was contaminated with a byproduct, but this appeared no problem in the next step. IR (neat, cm^{-1}) ν 1808, 1608, 1513, 1257, 1157; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 1H, J = 8.8 Hz), 7.53 (d, 1H, J = 8.8 Hz), 6.94 (m, 2H), 6.27 (q, 0.5H, J = 2.9 Hz), 6.18 (q, 0.5H, J = 3.1 Hz), 6.00 (s, 0.5H), 5.98 (s, 0.5H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.5, 163.8, 161.0, 160.7, 130.6, 130.4, 125.5, 120.0 (q, J = 280.0 Hz), 119.9 (q, J = 280.0 Hz), 114.6, 114.5, 92.7 (q, J = 35.4 Hz), 92.7 (q, J = 35.5 Hz), 55.3, 41.4, 40.6.

4-(1-Bromopropyl)-2-(trifluoromethyl)oxazol-5(2H)-one. According to the general procedure, the propyl pseudoazlactone (5.85 g, 30 mmol) was dissolved in 60 mL 1,2-dichloroethane and reacted with bromine (1.54 mL, 30 mmol) in 20 mL 1,2-dichloroethane to afford the title compound (7.25 g, 26.7 mmol, 89%) as a colorless oil after distillation under reduced pressure (0.4 mbar, 110 °C). IR (neat, cm^{-1}) ν 2978, 1806, 1643, 1366, 1305, 1154, 1016, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (m, 1H), 4.81 (m, 1H), 2.33 (m, 2H), 1.14 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 116.2, 161.3, 161.2, 120.0, (q, J = 280.1 Hz) 92.4 (q, J = 34.9 Hz), 42.2, 42.0, 27.4, 27.3, 11.9, 11.7.

General Procedure for the Formation of the Sulfa-Michael Addition Substrates. 1,3-Oxazolidin-2-one (2.3 equiv) was dissolved in THF. Sodium hydride (2.2 equiv) was added in portions and the resulting mixture was stirred for 45 min. Next, a solution of the bromopseudoazlactone in THF was added dropwise. The resulting mixture was stirred for 30 min and then quenched with saturated NH_4Cl. The layers were separated and the water layer was extracted twice with EtOAc. The organic layers were combined, washed with brine and dried with $MgSO_4$. The crude was concentrated and purified by column chromatography and if possible the product was recrystallized to obtain the pure Z-isomer.

*(Z)-2,2,2-Trifluoro-N-(3-oxo-3-(2-oxooxazolidin-3-yl)-1-phenylprop-1-en-2-yl)-acetamide (**19**).* According to the general procedure, to a solution of oxazolidinone (5.0 g, 57.4 mmol) in 250 mL THF was added NaH (60% in mineral oil, 1.3 g, 55 mmol), followed by the brominated pseudoazlactone from phenylalanine[36] (8.0 g, 25 mmol) in 50 mL THF. The reaction gave a mixture of isomers (Z/E 10:1) of compound **19** (5.3 g, 15.5 mmol, 62%) as a white solid after column chromatography (PE/EtOAc 2:1). The Z-isomer could be obtained by recrystallization from PE/EtOAc. IR (neat, cm^{-1}) ν 3253, 1617, 1717, 1685, 1529, 1388, 1209, 1184, 1155; Z-isomer: mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.47−7.40 (m, 5H), 6.94 (s, 1H), 4.44 (t, 2H, J = 7.6 Hz), 4.05 (t, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 155.5 (q, J = 38.0 Hz), 152.9, 132.2, 131.6, 128.8, 129.4, 129.0, 125.6, 115.4 (q, J = 286.0 Hz) 63.0, 42.9; E-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.49−7.42 (m, 5H), 6.65 (s, 1H), 4.43 (t, 2H, J = 8.0 Hz), 4.07 (t, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 155.7 (q, J = 38.0 Hz), 151.9, 132.0, 130.1, 129.7, 129.5, 129.1, 125.9, 115.4 (q, J = 286.0 Hz), 62.5, 42.0; HRMS (FAB) for $C_{14}H_{12}F_3N_2O_4$ calculated $[M + H]^+$: 329.0749, found $[M + H]^+$: 329.0746; Elemental analysis for $C_{14}H_{11}F_3N_2O_4$: calculated: C 51.23%, H 3.38%, F 17.36%, N 8.53% found: C 51.33%, H 3.38%, F 17.22% N 8.48%.

*(Z)-2,2,2-Trifluoro-N-(1-(4-methoxyphenyl)-3-oxo-3-(2-oxooxazolidin-3-yl)-prop-1-en-2-yl)acetamide (**23**).* According to the general procedure, to oxazolidinone (3.1 g, 35.2 mmol) in 200 mL THF was added sodium hydride (1.35 g, 33.8 mmol, 60% in mineral oil), followed by the bromo pseudoazlactone (5.4, 15.3 mmol) in 60 mL THF. The reaction gave a mixture of isomers (Z/E 10:1) as a white solid after column chromatography (PE/EtOAc 2:1). The Z-isomer **23** (3.7 g, 10.4 mmol, 68%) could be obtained by recrystallization from PE/EtOAc. Z-isomer: mp 176−178 °C; IR (neat, cm^{-1}) ν 3248, 1763, 1717, 1678, 1213, 1176, 1157,1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.45 (d, 2H, J = 9.8 Hz), 7.10 (s, 1H), 6.96 (d, 2H, J = 9.8 Hz), 4.49 (t, 2H, J = 7.9 Hz), 4.12 (t, 2H, J = 7.9 Hz), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 161.2, 155.6 (q, J = 38.0 Hz), 134.1, 131.6, 124.7, 123.0, 115.5 (q, J = 286.0 Hz), 114.1, 63.1, 55.4, 43.2; For the E-isomer no good NMR data could be obtained. HRMS (ESI) for $C_{15}H_{13}F_3N_2O_5Na$ calculated $[M + Na]^+$: 381.0669, found $[M + Na]^+$: 381.0656; Elemental analysis for $C_{15}H_{13}F_3N_2O_5$: calculated: C 50.29%, H 3.66%, F 15.91%, N 7.82% found: C 49.54%, H 3.67%, F 15.61% N 7.61%.

*(Z)-2,2,2-Trifluoro-N-(1-oxo-1-(2-oxooxazolidin-3-yl)pent-2-en-2-yl)-acetamide (**24**).* According to the general procedure, to a solution of oxazolidinone (1.47 g, 16.9 mmol) in 100 mL THF was added sodium hydride (60% in mineral oil, 387 mg, 16.2 mmol), followed by the brominated pseudoazlactone from norvaline (2.0 g, 7.3 mmol) in 30 mL THF. The reaction gave a mixture of isomers (Z/E 2:1) of compound **24** (603 mg, 2.2 mmol, 29%) as oil. The isomers were purified and separated by column chromatography (PE/Et_2O 1:1). IR (neat, cm^{-1}) ν 3286, 1766, 1718, 1691, 1532, 1388, 1322, 1192, 1157; Z-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 6.54 (t, 1H J = 7.6 Hz), 4.51 (t, 2H, J = 8.0 Hz), 4.09 (t, 2H, J = 8.0 Hz), 2.24 (m, 2H), 1.33 (dt, 3H, J = 7.6, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 155.6 (q, J = 37.8 Hz), 153.8, 142.2, 125.6, 115.5 (q, J = 286.0 Hz), 63.2, 43.2, 21.1, 12.3; E-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 5.92 (t, 1H, J = 8.0 Hz), 4.56 (t, 2H, J = 8.0 Hz), 4.13 (t, 2H, J = 8.0 Hz), 2.62 (m, 2H), 1.09 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 154.8 (q, J = 38.1 Hz), 152.7, 131.2, 125.9, 115.3 (q, J = 285.6 Hz), 62.8, 42.2, 20.8, 13.2; HRMS (FAB) for

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$C_{10}H_{12}F_3N_2O_4$ calculated $[M + H]^+$: 281.0749, found $[M + H]^+$: 281.0747.

Catalyst Syntheses. *1-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-yl)-3-(3,5-bis(trifluoromethyl)phenyl)urea (**2**).* To a solution of amine **14** (500 mg, 1.25 mmol)[2] in 15 mL dry THF was added 3,5-bistrifluoromethylphenyl isocyanate (216 μL, 1.25 mmol) and the mixture was stirred at rt for 1 h under an inert atmosphere. The THF was removed and the product purified with flash chromatography (EtOAc/MeOH 95:5) to give urea **13** (752 mg, 1.15 mmol, 93%) as a white powder: mp 133 °C; $[\alpha]_D^{20}$ = +65.0 (c = 1.0, CH_2Cl_2); IR (neat, cm^{-1}) ν 3235, 3089, 2944, 1714, 1560, 1473, 1364, 1176, 1125, 1057, 1027, 952, 851, 833, 728, 701; ^1H NMR (500 MHz, $CDCl_3$) δ 10.0 (s, 1H), 9.47 (s, 1H), 8.70 (d, 1H, J = 4.0 Hz), 8.33 (s, 1H), 7.96 (s, 2H), 7.57 (m, 3H), 7.48 (m, 5H), 7.23 (s, 1H), 6.35 (br, 1H), 5.29 (m, 1H), 5.10 (d, 1H, J = 10.5 Hz), 5.02 (d, 1H, J = 17.5 Hz), 4.92 (d, 1H, J = 10.0 Hz), 4.77 (d, 1H, J = 10.0 Hz), 4.09 (m, 2H), 3.96 (m, 1H), 3.44 (m, 1H), 3.20 (m, 1H), 2.61 (m, 1H), 2.35 (t, 1H, J = 12.0 Hz), 2.00 (s, 1H), 1.93 (m, 1H), 1.84 (m, 1H), 1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 153.4, 148.1, 144.4, 141.0, 140.6, 137.0, 136.7, 136.2, 131.4 (q, J = 32.8 Hz), 130.1, 128.8, 128.5, 128.3, 125.1, 124.9, 123.2 (q, J = 271.1 Hz), 122.9, 117.5, 117.3, 114.9, 111.4, 72.4, 60.2, 48.7, 37.4, 27.4, 25.4, 24.4, 23.5, 18.4; HRMS (FAB) for $C_{35}H_{33}F_6N_4O_2$ calculated $[M + H]^+$: 655.2508, found $[M + H]^+$: 655.2501.

*2-Chloro-4,6-bis(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)-methyl)-1H-benzo-[d]-imidazole (**15**).* 2-Chloro-4,6-bis-(trifluoromethyl)-1*H*-benzo-[*d*]-imidazole (2.0 g, 6.9 mmol)[16] was dissolved in 70 mL dry DMF and cooled to −20 °C. SEMCl (1.24 mL, 6.94 mmol) was added dropwise. After 15 min NaH (560 mg, 14 mmol, 60% dispersion in mineral oil) was added portion wise. The mixture was allowed to warm up to rt and stirred overnight. The 30 mL water was carefully added together with 45 mL EtOAc. The layers were separated, the organic phase was washed with 30 mL of water and dried with Na_2SO_4. The crude was concentrated and the product was purified with flash chromatography (PE/EtOAc 9:1) yielding protected benzimidazole **15** (2.25 g, 5.4 mmol, 77%) as a colorless liquid, which solidified upon standing: mp 44 °C; IR (neat, cm^{-1}) ν 2956, 2899, 1741, 1636, 1502, 1440, 1280, 1251, 1160, 1089, 885, 835, 789, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.86 (s, 1H), 5.69 (s, 2H), 3.64−3.60 (m, 2H), 0.97−0.93 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 140.5, 135.4, 125.8 (q, J = 33.5 Hz), 123.9 (q, J = 270 Hz), 123.0 (q, J = 270 Hz), 121.7 (q, J = 34 Hz), 117.7, 111.7, 73.7, δ 67.2, δ 17.7, − 1.81; HRMS (FAB) for $C_{15}H_{18}ClF_6N_2OSi$ calculated $[M + H]^+$: 419.0781, found $[M + H]^+$: 419.0778.

4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-N-(5,7-bis(trifluoro-methyl)-1-((2-(trimethylsilyl)-ethoxy)-methyl)-1H-benzo[d]imidazole-2-yl)-quinolin-6-amine. Amine **14** (2.31 g, 5.8 mmol)[2] was dissolved in 24 mL of dry THF. To the solution were added protected benzimidazole **15** (2.2 g, 5.3 mmol), $Pd(OAc)_2$ (118 mg, 0.53 mmol), *rac*-BINAP (327 mg, 0.53 mmol), and Cs_2CO_3 (2.4 g, 7.4 mmol). Prior to heating to reflux, argon was bubbled through the mixture for 30 min. After 4 h full consumption of the starting material was observed. The mixture was allowed to cool to rt and filtered over Celite. The solvents were removed and the residue was purified with flash chromatography (EtOAc/MeOH 95:5 to 90:10) to give the title compound (1.74 g, 2.23 mmol, 42%) as a yellow powder: mp 92−95 °C; $[\alpha]_D^{20}$ = +89.3 (c = 0.7, CH_2Cl_2); IR (neat, cm^{-1}) ν 3068, 2950, 2873, 1735, 1599, 1456, 1348, 1286, 1273, 1260, 1161, 1122, 992, 859, 778, 728; ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, 1H, J = 4.4 Hz), 8.80 (br, 1H), 8.21 (br, 1H), 8.19 (s, 1H), 8.16 (br, 1H), 7.77 (s, 1H), 7.63 (s, 1H), 7.51 (br, 1H), 7.37−7.28 (m, 5H), 5.95 (m, 1H), 5.61 (s, 2H), 5.29 (m, 1H) 4.93 (m, 2H), 4.49 (m, 2H), 3.71−3.69 (t, 2H, J = 8.4 Hz), 3.28 (br, 1H), 3.20 (br, 1H), 2.89 (m, 2H), 2.72 (m, 1H), 2.24 (m, 1H), 2.06 (m, 1H), 1.82 (br, 1H), 1.62−1.57 (m, 3H), 1.06−1.02 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 153.3, 148.8, 146.2, 145.5, 142.4, 140.4 138.0, 137.1, 134.5, 131.5, 128.4, 128.0, 127.8, 124.4 (q, J = 270.0 Hz), 123.7 (q, J = 271.0 Hz), 122.6, 122.2, 121.9, 120.4, 118.7 (q, J = 33.0 Hz), 116.8, 116.8, 114.6, 110.4, 107.9, 72.6, 71.8, 67.2, 60.8, 50.5, 49.8, 40.2, 29.8, 28.2, 26.5, 25.0, 17.7, − 1.6; HRMS (FAB) for $C_{41}H_{46}F_6N_5O_2Si$ calculated $[M + H]^+$: 782.3325, found $[M + H]^+$: 782.3336.

*4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-N-(5,7-bis(trifluoro-methyl)-1H-benzo[d]imidazole-2-yl)quinolin-6-amine (**3**).* Protected 2-aminobenzimidazole (1.7 g, 2.2 mmol) was dissolved in 90 mL of dry CH_2Cl_2. Then $BF_3{\cdot}Et_2O$ (2.66 mL, 21.7 mmol) was added dropwise at 0 °C. The mixture was stirred for 2 h under a nitrogen atmosphere. After removal of the solvent, the product was purified with flash chromatography (EtOAc/MeOH 9:1) to give **3** (1.2 g, 1.84 mmol, 85%) as a yellow powder: mp 95 °C; $[\alpha]_D^{20}$ = +33.0 (c = 0.2, CH_2Cl_2); IR (neat, cm^{-1}) ν 3065, 2926, 2870, 1575, 1510, 1455, 1366, 1335, 1273, 1261, 1165, 1120, 908, 848; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, 1H, J = 4.0 Hz), 8.43 (br, 2H), 7.93−7.80 (br m, 2H), 7.69 (br, 1H), 4.57 (br, 2H), 7.30 (m, 5H), 5.91 (m, 1H), 5.70 (br, 1H), 5.08 (d, 1H, J = 10.5 Hz), 5.04 (d, 1H, J = 17.0 Hz), 4.55 (d, 1H, J = 16.5 Hz), 4.43 (d, 1H, J = 16.5 Hz), 3.69 (br, 1H), 3.45 (br, 1H), 3.22 (br, 1H), 3.12 (m, 1H), 2.92 (m, 1H), 2.41 (m, 1H), 2.24 (br, 1H), 1.93 (br, 1H), 1.71 (br, 2H), 1.48 (br, 1H) (N−H signal is missing); ^{13}C NMR (125 MHz, $CDCl_3$): 153.1, 148.0, 147.8, 144.6, 144.0, 138.0, 137.0, 130.7, 130.6, 128.7, 128.4, 128.2, 127.7, 127.5, 127.0, 124.8 (q, J = 270.1 Hz), 123.7 (q, J = 270.2 Hz), 123.2, 12.1.0, 120.5, 118.9, 116.1, 115.1, 113.4, 108.0, 71.5, 60.7, 49.6, 49.1, 38.7, 27.5, 24.9, 21.4 (C-9 carbon is missing; broad and double signals due to hindered rotation); HRMS (FAB) for $C_{35}H_{32}F_6N_5O$ calculated $[M + H]^+$: 652.2511, found $[M + H]^+$: 652.2507.

*N-[3,5-Bis(trifluoromethyl)phenyl]-N-(9-O-benzylcinchon-6′-yl)-squaramide (**4**).* Amine **14** (300 mg, 0.75 mmol) was dissolved in toluene/DMF (5:1, 12 mL) prior to addition of $Zn(OTf)_2$ (818 mg, 2.25 mmol). The solution was stirred at rt for 10 min and then 3-(3,5-bis(trifluoromethyl)phenylamino)-4-methoxycyclobut-3-ene-1,2-dione (**16**, 280 mg, 0.83 mmol)[27] was added. The resulting mixture was stirred for 2 days at 100 °C and cooled to rt. EtOAc (20 mL) and Na_2CO_3 (20 mL) were added to the reaction mixture during the cooling to rt. The water layer was separated and washed with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude was purified by flash chromatography (CH_2Cl_2/MeOH 30/1 to 10/1) giving **4** as yellow crystals (193 mg, 0.27 mmol), 36%): mp 234 °C; $[\alpha]_D^{20}$ = −92 (c = 0.5, CH_2Cl_2). IR (neat, cm^{-1}) ν 3325, 3171, 2962, 1789, 1700, 1610, 1556, 1472, 1372, 1330, 1237, 1169, 1052, 1025. ^1H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.96 (s, 1H), 8.89 (d, 1H J = 4.4 Hz), 8.37 (s, 1H), 8.33 (s, 1H), 8.13 (t, 2H, J = 4.5 Hz), 7.84−7.59 (m, 3H), 7.40−7.35 (m, 5H), 5.95−5.79 (m, 2H), 5.08−4.91 (m, 2H), 4.47 (m, 2H), 3.85 (br, 3H), 3.42 (br, 1H), 2.63 (m, 1H), 2.12 (m, 1H), 1.98−1.78 (m, 3H), 1.23 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 182.7, 181.7, 166.3, 166.1, 149.2, 145.2, 141.1, 137.4, 136.8, 131.5 (q, J = 33.9 Hz), 131.3, 128.7, 128.4, 128.3, 128.20, 127.4, 126.2, 123.4 (q, J = 271.1 Hz), 122.5, 118.5, 116.4, 115.8, 71.6, 58.9, 48.8, 26.7 (broad and double signals due to hindered rotation). HRMS (ESI) for $C_{38}H_{33}F_6N_4O_3$, calculated $[M + H]^+$: 707.2451, found $[M + H]^+$: 707.2405.

*N-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)-methyl)quinolin-6-yl)-3,5-bis(trifluoromethyl)benzamide (**5**).* Amine **14** (200 mg, 0.5 mmol) was dissolved in 10 mL CH_2Cl_2. Et_3N (74 μL, 0.55 mmol), 3,5-*bis*-(trifluoromethyl)benzoyl chloride (99 μL, 0.55 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was washed with $NaHCO_3$ and brine. The organic layers were combined and dried with Na_2SO_4 and then concentrated. The product was purified with flash chromatography (EtOAc/MeOH 20:1) giving amide **5** (207 mg, 0.33 mmol, 65%) as a white solid: mp 101−103 °C; $[\alpha]_D^{20}$ = +33.9 (c = 0.35, CH_2Cl_2); IR (neat, cm^{-1}) ν 2936, 1626, 1504, 1276, 1127, 794, 753; ^1H NMR (500 MHz, $CDCl_3$) δ 10.32 (br, 1H), 8.87 (d, 1H, J = 4.5 Hz), 8.65 (s, 2H), 8.57 (s, 1H), 8.18 (m, 2H), 8.03 (s, 1H), 7.56 (d, 1H, J = 2.8 Hz), 7.41−7.30 (m, 5H), 5.96 (m, 1H), 5.79 (br, 1H), 5.06 (m, 2H), 4.61 (d, 1H, J = 11.0 Hz), 4.51 (d, 1H, J = 11.0 Hz), 3.69 (br, 1H), 3.42 (br, 2H), 3.16 (m, 1H), 2.92 (m, 1H), 2.44 (br, 1H), 2.36 (br, 1H), 1.93 (s, 1H), 1.77 (br, 1H), 1.68 (br, 1H), 1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 163.5, 149.2, 145.9, 143.6, 139.5, 138.7, 137.8, 137.1, 136.9, 132.1 (q, J = 33.9 Hz), 131.3, 131.0 (q, J = 33.9 Hz), 129.4, 128.5, 128.2, 126.0, 125.3, 124.3, 123.6, 123.0 (q, J = 271.5 Hz), 118.5, 116.4,

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112.4, 77.3, 71.9, 60.0, 49.3, 48.8, 38.8, 27.8, 25.0, 20.0 (broad signals due to hindered rotation); HRMS (ESI) for $C_{35}H_{32}F_6N_3O_2$ calculated $[M + H]^+$: 640.2393, found $[M + H]^+$: 640.2365.

General Procedure for the Synthesis of Sulfonamide Catalysts. Amine **14** was dissolved in pyridine (0.2 M), followed by the addition of a sulfonyl chloride (1.2 equiv). The resulting mixture was stirred at 110 °C for 16 h. The crude was concentrated under reduced pressure and the product was purified with flash column chromatography. First a column with a mixture of CH_2Cl_2/MeOH/Et_3N as the eluent was applied. The product was concentrated and a second column was performed to remove Et_3N using EtOAc/MeOH (10:1) (Et_3N formed a complex with the sulfonamide catalysts) yielding the sulfonamide catalyst.

*N-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)-methyl)quinolin-6-yl)-3,5-bis(trifluoromethyl)benzenesulfonamide (**6**).* According to the general procedure, amine **14** (160 mg, 0.4 mmol) was reacted with 3,5-*bis*-(trifluoromethyl)benzenesulfonyl chloride (150 mg, 0.48 mmol) in 2 mL of pyridine at 110 °C. The product was purified with column chromatography using as eluant CH_2Cl_2/MeOH/Et_3N (100:2:1), followed by EtOAc/MeOH (10:1), yielding sulfonamide **6** (230 mg, 0.34 mmol, 86%) as a yellowish powder: mp 103−106 °C; $[\alpha]_D^{20}$ = +66.7 (*c* = 1.00, MeOH); IR (neat, cm^{-1}) ν 2955, 1624, 1494, 1277, 1239, 1166, 1125, 1038, 902, 843, 731, 698, 681, 621; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (br, 2H), 8.43 (s, 2H), 8.08 (d, 1H, *J* = 4.0 Hz), 7.91 (s, 1H), 7.89 (m, 2H), 7.38 (m, 1H), 7.30 (m, 3H), 7.11 (m, 2H), 5.82 (m, 1H), 5.77 (br, 1H), 5.04 (d, 1H, *J* = 10.0 Hz), 4.98 (d, 1H, *J* = 17.5 Hz), 3.90 (br, 2H), 3.61 (br, 2H), 3.40 (br, 3H), 2.60 (br, 1H), 2.38 (br, 1H), 1.99 (m, 1H), 1.90 (br, 1H). 1.64 (br, 1H) 1.21 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 146.5, 145.7, 143.5, 140.8, 136.6, 131.8 (q, *J* = 33.9 Hz), 131.7, 129.0, 128.6, 128.5 128.2, 127.7, 127.1, 126.2, 124.1, 122.9 (q, *J* = 271.6 Hz), 119.7, 118.0, 117.0, 115.8, 76.4, 70.9, 59.5, 49.8, 48.7, 37.6, 27.5, 23.8, 18.9 (broad signals due to hindered rotation); HRMS (FAB) for $C_{34}H_{32}F_6N_3O_3S$ calculated $[M + H]^+$: 676.2069, found $[M + H]^+$: 676.2064.

*N-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)-methyl)quinolin-6-yl)-4-(trifluoromethyl)benzenesulfonamide (**7**).* According to the general procedure, amine **14** (400 mg, 1 mmol) was reacted with *p*-trifluoromethylbenzenesulfonyl chloride (291 mg, 1.2 mmol) in 5 mL of pyridine at 110 °C. The product was purified with column chromatography using as eluant CH_2Cl_2/MeOH/Et_3N (100:2:1), followed by EtOAc/MeOH (10:1), yielding sulfonamide **7** (588 mg, 0.97 mmol, 97%) as a yellowish powder: mp 122−126 °C; $[\alpha]_D^{20}$ = +91.2 (*c* = 1.00, CH_2Cl_2 IR (neat, cm^{-1}) ν 2938, 1623, 1484, 1370, 1323, 1240, 1166, 1128, 1062, 1008, 841, 716, 633; ^1H NMR (500 MHz, $CDCl_3$) δ 9.10 (br, 1H), 8.83 (d, 1H, *J* = 4.0 Hz), 8.20 (d, 2H, *J* = 8.0 Hz), 8.16 (s, 1H), 8.12 (m, 1H), 8.03 (m, 1H), 7.71 (d, 2H, *J* = 8.0 Hz), 7.53 (d, 1H, *J* = 4.5 Hz), 7.31 (m, 5H), 6.22 (br, 1H), 5.82 (m, 1H), 5.05 (d, 1H, *J* = 10.0 Hz), 5.02 (d, 1H, *J* = 17.0 Hz), 4.48 (d, 1H, *J* = 10.5 Hz), 4.41 (d, 1H, *J* = 10.5 Hz), 4.04 (br, 1H), 3.77 (br, 1H), 3.58 (m, 1H), 3.43 (t, 1H, *J* = 9.5 Hz), 3.31 (m, 1H), 2.61 (m, 1H), 2.42 (t, 1H, *J* = 10.5 Hz), 2.00 (s, 1H), 1.95 (m, 1H), 1.71 (m, 1H), 1.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 147.7, 145.8, 143.9, 141.2, 138.4, 136.6, 136.3, 133.8 (q, *J* = 32.6 Hz), 131.7, 128.5, 128.5, 128.1, 128.1, 128.0, 127.9, 126.7, 126.1, 125.7, 124.2, 123.3 (q, *J* = 271.5 Hz), 120.1, 118.4, 112.9, 71.9, 59.8, 49.6, 48.6, 37.1, 27.3, 23.3, 18.6 (broad signals due to hindered rotation); HRMS (FAB) for $C_{33}H_{33}F_3N_3O_3S$ calculated $[M + H]^+$: 608.2195, found $[M + H]^+$: 608.2197.

*N-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)-methyl)quinolin-6-yl)-benzenesulfonamide (**8**).* According to the general procedure, amine **14** (200 mg, 0.5 mmol) was reacted with benzenesulfonyl chloride (115 mg, 0.6 mmol) in 3 mL of pyridine at 110 °C. The product was purified with column chromatography using as eluant CH_2Cl_2/MeOH/Et_3N (100:1:1), followed by EtOAc/MeOH (10:1), yielding sulfonamide **8** (189 mg, 0.35 mmol, 70%) as a yellowish powder: mp 98−101 °C; $[\alpha]_D^{20}$ = +66.9 (*c* = 0.35, MeOH); IR (neat, cm^{-1}) ν 2935, 1518, 1495, 1328, 1164, 1092, 580; ^1H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, 1H, *J* = 4.0 Hz), 8.36 (br, 1H), 8.06 (m, 2H), 7.93 (d, 2H, *J* = 7.5 Hz), 7.81 (br, 1H), 7.48−7.39 (m, 4H), 7.29 (m, 3H), 7.17 (d, 2H, *J* = 6.0 Hz), 5.89 (m, 1H), 5.34 (br, 1H), 5.01 (s, 1H), 4.99 (d, 1H, *J* = 9.5 Hz), 4.24 (d, 1H, *J* = 11.0 Hz), 4.01 (d, 1H, *J* = 11.0 Hz), 3.32 (m, 1H), 3.13 (m, 1H), 3.00 (m, 2H), 2.82 (m, 1H), 2.31 (m, 1H), 2.09 (m, 1H), 1.80 (s, 1H), 1.59 (m, 1H), 1.45 (m, 1H), 1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 146.0, 144.3, 140.6, 138.2, 137.3, 132.3, 131.6, 129.1, 128.9, 128.5, 127.8, 127.4, 126.8, 125.5, 119.4, 115.4, 114.2, 79.4, 71.3, 59.8, 49.7, 49.1, 39.3, 29.7, 28.0, 25.7, 21.7 (broad signals due to hindered rotation); HRMS (FAB) for $C_{32}H_{34}N_3O_3S$ calculated $[M + H]^+$: 540.2321, found $[M + H]^+$: 540.2317.

*N-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)-methyl)quinolin-6-yl)-4-methylbenzenesulfonamide (**9**).* According to the general procedure, amine **14** (400 mg, 0.1 mmol) was reacted with tosyl chloride (268 mg, 1.2 mmol) in 5 mL of pyridine at 110 °C. The product was purified with column chromatography using as eluant CH_2Cl_2/MeOH/Et_3N (100:1:1), followed by EtOAc/MeOH (10:1), yielding sulfonamide **9** (484 mg, 0.87 mmol, 87%) as a yellowish powder: mp 136−140 °C; $[\alpha]_D^{20}$ = +153.6 (*c* = 1.00, CH_2Cl_2); IR (neat) ν cm^{-1} 3375, 3031, 2931, 2804, 2545, 1622, 1483, 1326, 1159, 1091, 909, 728; ^1H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, 1H, *J* = 4.5 Hz), 8.05 (d, 1H, *J* = 9.0 Hz), 7.93 (br s, 1H), 7.83 (d, 3H, *J* = 8.0 Hz), 7.46 (s, 1H), 7.31 (m, 3H), 7.22 (m, 2H), 7.18 (d, 2H, *J* = 8.0 Hz), 5.92 (m, 1H), 5.57 (m, 2H), 5.02 (d, 1H, *J* = 2.5 Hz), 5.00 (d, 1H, *J* = 10.5 Hz), 4.35 (d, 1H, *J* = 11.0 Hz), 4.27 (d, 1H, *J* = 11.0 Hz), 3.45 (br, 1H), 3.09 (m, 3H), 2.87 (br, 1H), 2.32 (s, 4H), 2.13 (m, 1H), 1.81 (s, 1H), 1.62 (m, 1H), 1.49 (m, 1H), 1.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 145.8, 144.1, 143.2, 139.2, 137.3, 137.1, 131.4, 129.9, 129.5, 129.0, 128.4, 127.9, 127.3, 126.6, 126.1, 124.4, 119.6, 115.4, 113.2, 78.6, 71.4, 59.6, 49.6, 49.0, 39.1, 27.9, 25.4, 21.5, 21.4 (broad signals due to hindered rotation); HRMS (FAB) for $C_{33}H_{36}N_3O_3S$ calculated $[M + H]^+$: 554.2477, found $[M + H]^+$: 554.2469.

*N-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)-methyl)quinolin-6-yl)-2,4,6-trimethylbenzenesulfonamide (**10**).* According to the general procedure, amine **14** (200 mg, 0.5 mmol) was reacted with mesitylsulfonyl chloride (130 mg, 0.6 mmol) in 3 mL of pyridine at 110 °C. The product was purified with column chromatography by using as eluant CH_2Cl_2/MeOH/Et_3N (100:1:1), followed by EtOAc/MeOH (10:1), yielding sulfonamide **10** (93 mg, 0.16 mmol, 32%) as yellowish solid: mp 104−108 °C; $[\alpha]_D^{20}$ = +105.2 (*c* = 1.00, CH_2Cl_2); IR (neat, cm^{-1}) ν 3030, 2937, 2871, 1623, 1454, 1324, 1153, 1056, 958, 832, 736, 654; ^1H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, 1H, *J* = 4.5 Hz), 8.65 (br, 1H), 8.09 (s, 1H), 8.01 (d, 1H, *J* = 9.0 Hz), 7.65 (d, 1H, *J* = 9.0 Hz), 7.49 (br, 1H), 7.35 (m, 5H), 6.90 (s, 2H), 5.85 (m, 1H), 5.02 (d, 1H, *J* = 10.5 Hz), 4.99 (d, 1H, *J* = 17.5 Hz), 4.47 (d, 1H, *J* = 10.5 Hz), 4.41 (d, 1H, *J* = 10.5 Hz), 3.72 (br, 1H), 3.31 (br, 2H), 3.05 (br, 1H), 2.76 (m, 7H), 2.45 (br, 1H), 2.23 (m, 4H), 1.89 (s, 1H), 1.76 (br, 1H), 1.63 (m, 1H), 1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 145.3, 142.9, 142.2, 139.4, 138.9, 138.0, 137.2, 137.0, 134.3, 132.0, 131.4, 130.9, 128.5, 128.3, 127.8, 127.3, 126.5, 122.4, 118.7, 116.5, 111.5, 71.6, 59.7, 49.7, 48.7, 38.3, 27.7, 24.6, 23.3, 23.2, 20.9 (broad signals due to hindered rotation); HRMS (FAB) for $C_{35}H_{40}N_3O_3S$ calculated $[M + H]^+$: 582.2790, found $[M + H]^+$: 582.2798.

*N-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)-methyl)quinolin-6-yl)-4-methoxybenzenesulfonamide (**11**).* According to the general procedure, amine **14** (100 mg, 0.25 mmol) was reacted with *p*-methoxybenzenesulfonyl chloride (62 mg, 0.3 mmol) in 1 mL of pyridine at 110 °C. The product was purified with column chromatography using as eluant CH_2Cl_2/MeOH/Et_3N (100:1:1), followed by EtOAc/MeOH (10:1), yielding sulfonamide **11** (114 mg, 0.2 mmol, 80%) as a yellowish powder: mp 96−99 °C; $[\alpha]_D^{20}$ = +73.8 (*c* = 1.00, CH_2Cl_2); IR (neat, cm^{-1}) ν 2936, 1623, 1497, 1455, 1327, 1260, 1157, 1093, 1027, 833, 734; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, 1H, *J* = 4.5 Hz), 8.05 (d, 1H, *J* = 9.0 Hz), 8.00 (br, 1H), 7.89 (d, 2H, *J* = 9.0 Hz), 7.81 (d, 1H, *J* = 8.0 Hz), 7.71 (br, 1H), 7.44 (br, 1H), 7.29 (m, 3H), 7.20 (m, 2H), 6.85 (d, 2H, *J* = 9.0 Hz), 5.90 (m, 1H), 5.38 (br, 1H), 5.02 (s, 1H), 4.99 (d, 1H, *J* = 8.5 Hz), 4.28 (d, 1H, *J* = 11.5 Hz), 4.11 (d, 1H, *J* = 11.5 Hz), 3.76 (s, 3H), 3.31 (br, 1H), 3.18 (br, 1H), 3.01 (br, 2H), 2.82 (br, 1H), 2.30 (q, 1H, *J* = 8.0 Hz), 2.07

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(br, 1H), 1.79 (s, 1H), 1.59 (m, 1H), 1.46 (m, 1H), 1.28 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 149.0, 146.0, 144.6, 139.7, 137.4, 137.3, 131.7, 131.5, 129.5, 128.4, 127.8, 127.8, 126.8, 124.8, 119.2, 115.2, 114.1, 113.7, 79.5, 71.3, 59.8, 55.5, 49.8, 49.1, 39.5, 28.0, 25.7, 21.8; HRMS (FAB) for $C_{33}H_{36}N_3O_4S$ calculated $[M + H]^+$: 570.2427, found $[M + H]^+$: 570.2429.

*N-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)-methyl)quinolin-6-yl)-2,4,6−trimethoxybenzenesulfonamide (**12**).* According to the general procedure, amine **14** (200 mg, 0.5 mmol) was reacted with 2,4,6-methoxybenzenesulfonyl chloride (160 mg, 0.6 mmol) in 2.5 mL of pyridine at 110 °C. The product was purified with column chromatography by using as eluant CH_2Cl_2/MeOH/Et_3N (100:1:1), followed by EtOAc/MeOH (10:1), yielding sulfonamide **12** (296 mg, 0.47 mmol, 78%) as a yellowish powder: mp 99−102 °C; $[\alpha]_D^{20}$ = +175.0 (c = 0.32, CH_2Cl_2); IR (neat, cm^{-1}) ν 2934, 1622, 1515, 1454, 1344, 1322, 1152, 1122, 1086; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, 1H, J = 4.0 Hz), 8.02 (d, 1H, J = 9.0 Hz), 7.90 (br, 1H), 7.69 (dd, 1H, J = 9.0, 1.5 Hz), 7.42 (br, 1H), 7.37 (m, 2H), 7.30 (m, 3H), 6.05 (s, 2H), 5.94 (m, 1H), 5.18 (br, 1H), 5.05 (d, 1H, J = 9.0 Hz), 5.03 (s, 1H), 4.35 (d, 1H, J = 11.5 Hz), 4.30 (d, 1H, J = 11.5 Hz), 3.88 (s, 6H), 3.74 (s, 3H), 3.20 (br, 1H), 3.11 (br, 1H), 2.88 (m, 1H), 2.84 (br, 1H), 2.70 (br, 1H), 2.24 (m, 1H), 2.00 (br, 1H), 1.78 (s, 1H), 1.46 (m, 2H), 1.41 (br, 1H) (NH of the sulfonamide is missing); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 160.6, 148.9, 146.0, 145.5, 140.4, 137.7, 136.4, 131.4, 128.4, 127.9, 127.8, 127.0, 123.4, 119.7, 114.7, 111.8, 108.5, 91.5, 80.0, 71.3, 60.1, 56.7, 55.4, 49.7, 49.0, 39.8, 28.0, 26.3, 22.7 (broad signals due to hindered rotation); HRMS (ESI) for $C_{35}H_{40}N_3O_6S$ calculated $[M + H]^+$: 630.2638, found $[M + H]^+$: 630.2640.

*N-(4-((S)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)-methyl)quinolin-6-yl)-4-(dimethylamino)-benzenesulfonamide (**13**).* According to the general procedure, amine **14** (400 mg, 1.0 mmol) was reacted with *p*-(dimethylamino)benzenesulfonyl chloride (263 mg, 1.2 mmol) in 5 mL of pyridine at 110 °C. The product was purified with column chromatography by using as eluant CH_2Cl_2/MeOH/Et_3N (100:2:1), followed by EtOAc/MeOH (10:1), yielding sulfonamide **13** (582 mg, 0.8 mmol, 80%) as a yellowish powder: mp 105−107 °C; $[\alpha]_D^{20}$ = +91.6 (c = 0.57, CH_2Cl_2); IR (neat, cm^{-1}) ν 2931, 2864, 1594, 1514, 1363, 1314, 1164, 1091, 646; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, 1H, J = 4.5 Hz), 8.04 (d, 1H, J = 9.0 Hz), 7.97 (br, 1H), 7.32 (d, 3H, J = 9.0 Hz), 7.43 (br, 1H), 7.31 (m, 3H), 7.23 (d, 2H, J = 6.5 Hz), 7.10 (br, 1H) 6.53 (d, 2H, J = 9.0 Hz), 5.93 (m, 1H), 5.19 (br, 1H), 5.03 (d, 1H, J = 4.0 Hz), 5.00 (s, 1H), 4.31 (d, 1H, J = 11.5 Hz), 4.16 (d, 1H, J = 11.5 Hz), 3.19 (br, 1H), 3.10 (br, 1H), 2.93 (s, 6H), 2.89 (br, 1H), 2.71 (br, 1H), 2.23 (m, 1H), 2.02 (br, 1H), 1.76 (br, 1H). 1.50 (m, 1H), 1.44 (m, 1H), 1.33 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 149.0, 146.0, 145.5, 140.4, 137.7, 136.5, 131.4, 129.2, 128.4, 127.8, 127.7, 127.0, 124.7, 124.2, 119.6, 114.7, 113.2, 110.8, 80.4, 71.3, 60.0, 49.8, 49.3, 39.9, 29.9, 28.1, 26.3, 22.7; HRMS for $C_{34}H_{39}N_4O_3S$ calculated $[M + H]^+$: 583.2743, found $[M + H]^+$: 583.2745.

General Procedure for the *Cinchona* alkaloid Catalyzed 1,4-Addition to *N*-Acetylated Oxazolidinones. *N*-Acetylated oxazolidinone (0.5 M)[19] and sulfonamide catalyst **13** (10 mol %) were dissolved in $CHCl_3$ and the resulting mixture was cooled to −20 °C. Subsequently a thiol (3 equiv) was added and the resulting mixture was stirred until full consumption of the starting material. The mixture was directed put on silica gel and the product was purified with column chromatography.

Preparation of the Racemates. All racemic compounds were prepared according to the general procedure for the *Cinchona* alkaloid catalyzed 1,4-addition to *N*-acetylated oxazolidinones, with the only difference that Et_3N was used instead of the chiral catalyst.

*(S)-3-(3-(Benzhydrylthio)butanoyl)oxazolidin-2-one (**27**).* According to the general procedure, **17** (31 mg, 0.2 mmol), sulfonamide catalyst **13** (11 mg, 0.02 mmol) and diphenylmethanethiol (110 μL, 0.6 mmol) were dissolved in 400 μL $CHCl_3$. Stirring at −20 °C for 84 h gave full conversion. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **27** (71 mg, 0.2 mmol, 99%) as colorless oil (ee = 85%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 10: (1.0 mL, λ = 220 nm), t_r major 20.5 min and t_r minor 22.4 min). $[\alpha]_D^{20}$ = +10.9 (c = 0.28, CH_2Cl_2); IR (neat, cm^{-1}) ν 2867, 1775, 1698, 1386, 1318, 703;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 4H, J = 7.9 Hz), 7.32 (dd, 4H, J = 7.9, 7.3 Hz), 7.23 (t, 2H, J = 7.3 Hz), 5.33 (s, 1H), 4.39 (t, 2H, J = 8.0 Hz), 3.98 (t, 2H, J = 8.0 Hz), 3.31 (dd, 1H, J = 16.5, 6.7), 3.19 (m, 1H), 3.05 (dd, 1H, J = 16.5, 6.6 Hz), 1.32 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 153.2, 141.6, 141.4, 128.4, 128.2, 128.2, 127.0, 127.0, 61.9, 53.6, 42.3, 42.3, 36.2, 21.5; HRMS (ESI) for $C_{20}H_{21}NO_3SNa$ calculated $[M + Na]^+$: 378.1134, found $[M + Na]^+$: 378.1111.

*(S)-3-(3-(Benzylthio)hexanoyl)oxazolidin-2-one (**28**).* According to the general procedure, **21** (37 mg, 0.2 mmol), sulfonamide catalyst **13** (11 mg, 0.02 mmol) and phenylmethanethiol (71 μL, 0.6 mmol) were dissolved in 400 μL $CHCl_3$. Stirring at −20 °C for 84 h gave full conversion. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **28** (61 mg, 0.2 mmol, 99%) as colorless oil (ee = 92%, determined by HPLC Daicel chiralcel ODH, *i*-PrOH/heptane 30:70 (0.5 mL, λ = 220 nm), t_r major 20.6 min and t_r minor 29.6 min). $[\alpha]_D^{20}$ = +21.6 (c = 0.25, CH_2Cl_2); IR (neat, cm^{-1}) ν 2027, 2957, 2927, 1773, 1695, 1384, 1221, 1183, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 4.01 (t, 2H, J = 8.4 Hz), 4.00 (m, 2H), 3.80 (m, 2H), 3.30 (m, 1H), 3.13 (m, 2H), 1.58 (m, 2H), 1.51 (m, 1H), 1.41 (m, 1H), 0.87 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 153.3, 138.6, 128.9, 128.4, 126.8, 62.0, 45.0, 42.4, 41.1, 40.8, 37.4, 35.3, 19.9, 13.7; HRMS (ESI) for $C_{16}H_{21}NO_3SNa$ calculated $[M + Na]^+$: 330.1134, found $[M + Na]^+$: 330.1115.

*(S)-3-(3-(Benzhydrylthio)hexanoyl)oxazolidin-2-one (**30**).* According to the general procedure, **21** (37 mg, 0.2 mmol), sulfonamide catalyst **13** (11 mg, 0.02 mmol) and diphenylmethanethiol (110 μL, 0.6 mmol) were dissolved in 400 μL $CHCl_3$. Stirring at −20 °C for 84 h gave full conversion. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **30** (75 mg, 0.19 mmol, 97%) as colorless oil (ee = 92%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 10:90 (1.0 mL, λ = 220 nm), t_r major 14.1 min and t_r minor 15.7 min). $[\alpha]_D^{20}$ = +22.6 (c = 0.81, CH_2Cl_2); IR (neat, cm^{-1}) ν 2958, 2927, 1778, 1698, 1386, 1222;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 4H), 7.30 (m, 4H), 7.22 (m, 2H), 5.30 (s, 1H), 4.37 (t, 2H, J = 8.1 Hz), 3.97 (t, 2H, J = 8.1 Hz), 3.29 (m, 1H), 3.11 (m, 2H), 1.57 (m, 2H), 1.40 (m, 2H), 0.82 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 153.2, 141.8, 141.7, 128.4, 128.3, 128.2, 127.0, 126.9, 61.9, 53.8, 42.4, 41.3, 41.0, 37.4, 19.7, 13.7. HRMS (ESI) for $C_{22}H_{25}NO_3SNa$ calculated $[M + Na]^+$: 406.1447, found $[M + Na]^+$: 406.1429.

*(R)-3-(3-(Benzhydrylthio)-3-phenylpropanoyl)oxazolidin-2-one (**31**).* According to the general procedure, **22** (17 mg, 0.2 mmol), sulfonamide catalyst **13** (5 mg, 0.02 mmol) and diphenylmethanethiol (110 μL, 0.6 mmol) were dissolved in 1 mL $CHCl_3$. Stirring at −20 °C for 140 h gave full conversion, the product was purified with column chromatography (PE/EtOAc 2:1), yielding **31** (75 mg, 0.18 mmol, 90%) as a colorless oil (ee = 94%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 10:90 (1.0 mL, λ = 220 nm), t_r major 12.4 min and t_r minor 15.0 min). $[\alpha]_D^{20}$ = −85.5 (c = 0.33, CH_2Cl_2); IR (neat, cm^{-1}) ν 2957, 2853, 1778, 1701, 1387, 675;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.38 (m, 3H), 7.37−7.26 (m, 7H), 7.25−7.17 (m, 5H), 4.80 (s, 1H), 4.38−4.31 (m, 2H), 4.16 (t, 1H, J = 7.4 Hz), 3.96−3.88 (m, 2H), 3.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 153.2, 141.1, 140.9, 140.6, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.4, 127.2, 127.0, 61.9, 53.6, 44.9, 42.3, 41.4; HRMS (ESI) for $C_{25}H_{23}NO_3SNa$ calculated $[M + Na]^+$: 440.1291, found $[M + Na]^+$: 440.1272.

General Procedure for the *Cinchona* Alkaloid Catalyzed 1,4-Addition to *α,β*-Unsaturated *α*-Amino Acid Derivatives. Alkene (0.2 M) and *Cinchona* alkaloid derived catalyst **9** (10 mol %) were dissolved in CH_2Cl_2. A thiol (3 equiv) was added and the resulting mixture was stirred until all the starting material had reacted. The mixture was directly put on silica gel and the product was purified with column chromatography.

Preparation of the Racemates. All racemic compounds were prepared according to the general procedure for the *Cinchona* alkaloid catalyzed 1,4-addition to *α,β*-unsaturated *α*-amino acid derivatives,

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with the only difference that Et_3N was used instead of the chiral catalyst.

*N-((1R,2S)-1-(Benzylthio)-3-oxo-3-(2-oxooxazolidin-3-yl)-1-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (**20**).* According to the general procedure, **19** (26 mg, 0.08 mmol), catalyst **9** (4 mg, 0.008 mmol) and phenylmethanethiol (28 μL, 0.24 mmol) were dissolved in 400 μL CH_2Cl_2 and the resulting mixture was stirred for 16 h. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **20** (34 mg, 0.076 mmol, 95%) as a white powder and as an inseparable mixture of diastereoisomers (*anti*/*syn* 84:16) (ee *anti* = 99% and *syn* 8%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 10:90 (1.0 mL, λ = 220 nm), t_r *anti*-diastereoisomer 92.3 min (major) and 22.1 min (minor), t_r *syn*-diastereoisomer 27.4 min (major) and 18.7 min (major/minor)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, 1H, *J* = 6.8, 0.32 Hz), 7.19−7.31 (m, 9H), 6.95 (d, 0.16H, *J* = 6.8 Hz), 6.88 (d, 0.84H *J* = 8.8 Hz), 6.25 (t, 0.84H, *J* = 8.4 Hz), 5.94 (dd, 0.16H, *J* = 8.4, 5.6 Hz), 4.37 (t, 1.68H, *J* = 8.0 Hz), 4.25 (m, 0.16H), 4.20 (m, 0.16H), 4.17 (d, 0.84H, *J* = 4.4 Hz), 4.04 (m, 0.16H), 3.96 (m, 0.84H), 3.87 (m, 1H), 3.68 (d, 0.84H, *J* = 12.8 Hz), 3.57 (d, 0.84H, *J* = 12.8 Hz), 3.55 (d, 0.16H, *J* = 13.6 Hz), 3.52 (m, 0.16H), 3.28 (d, 0.16H, *J* = 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.2, (q, *J* = 38 Hz), 157.5 (q, *J* = 38 Hz), 152.9, 152.4, 137.4, 136.8, 136.5, 136.2, 129.9, 129.7, 129.6, 129.5, 129.3, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 128.0, 120.4, 120.3, 116.6, (q, *J* = 287 Hz), 62.6, 62.4, 56.2, 54.1, 50.8, 49.7, 42.6, 41.3, 36.0, 35.1; HRMS (FAB) for $C_{21}H_{20}F_3N_2O_4S$ calculated $[M + H]^+$: 453.1096, found $[M + H]^+$: 453.1101.

*N-((1R,2S)-1-(Allylthio)-3-oxo-3-(2-oxooxazolidin-3-yl)-1-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (**32**).* According to the general procedure, **19** (26 mg, 0.08 mmol), catalyst **9** (4 mg, 0.008 mmol) and 2-propene-1-thiol (20 μL, 0.24 mmol) were dissolved in 400 μL CH_2Cl_2 and the resulting mixture was stirred for 24 h. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **32** (30 mg, 0.074 mmol, 93%) as a white powder and as an inseparable mixture of diastereoisomers (*anti*/*syn* 73:27) (ee *anti* = 99% and *syn* 3%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 3:97 (0−60 min) then 10:90 (60−90 min) (1.0 mL, λ = 220 nm), t_r *anti*-diastereoisomer 80.9 min (major) and 42.3 min (minor), t_r *syn*-diastereoisomer 39.1 min (major) and 53.0 min (minor)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 0.73H), 7.36−7.19 (m, 4.27H), 7.09 (d, 0.27H, *J* = 9.6 Hz), 6.86 (d, 0.73H, *J* = 8.4 Hz), 6.27 (t, 0.73H, *J* = 7.6 Hz), 6.03 (dd, 0.27H, *J* = 7.9, 6.4 Hz), 5.70−5.58 (m, 1H), 5.04 (d, 1.54H, *J* = 10.4 Hz), 4.98 (d, 0.27H, *J* = 1.1 Hz), 4.87 (dd, 0.27H, *J* = 17.1, 1.1 Hz), 4.43−433 (m, 2H), 4.21−4.17 (m, 1H), 4.03−3.98 (m, 1H), 3.93−3.87 (m, 0.73H), 3.76−3.70 (m, 0.27), 3.10 (dd, 0.73H, *J* = 13.8, 6.2 Hz), 3.00−2.90 (m, 1H), 2.80 (dd, 0.27H, *J* = 13.8, 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.5, 156.6 (q, *J* = 38 Hz) 156.5 (q, *J* = 38 Hz), 152.9, 152.7, 136.5, 136.4, 133.2, 133.0, 128.9, 128.7, 128.6, 128.4, 128.3, 128.0, 118.5, 118.3, 115.6, (q, *J* = 287 Hz), 62.7, 62.6, 55.7, 55.4, 54.1, 50.2, 49.8, 42.6, 42.5, 34.4, 34.0; HRMS (FAB) for $C_{17}H_{18}F_3N_2O_4S$ calculated $[M + H]^+$: 403.0939, found $[M + H]^+$: 403.0945.

*N-((1R,2S)-1-(Benzhydrylthio)-3-oxo-3-(2-oxooxazolidin-3-yl)-1-phenyl-propan-2-yl)-2,2,2-trifluoroacetamide (**34**).* According to the general procedure, **19** (1.05 g, 3.2 mmol), catalyst **9** (177 mg, 0.32 mmol) and diphenylmethanethiol (1.76 mL, 9.6 mmol) were dissolved in 16 mL CH_2Cl_2 and the resulting mixture was stirred for 16 h. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **34** (1.63 g, 3.1 mmol, 97%) as a white powder and as an inseparable mixture of diastereoisomers (*anti*/*syn* 93:7) (ee *anti* = 99% and *syn* 33%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 10:90 (1.0 mL, λ = 220 nm), t_r *anti* diastereoisomer 53.9 min (major) and 19.0 (minor), t_r *syn* diastereoisomer 16.5 min (major) and 23.7 (minor)). IR (neat, cm^{-1}) ν 3412, 3329, 3028, 1782, 1731, 1699, 1391, 1216, 1168, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.20 (m, 15H), 7.10 (d, 0.07H, *J* = 8.2 Hz), 6.92 (d, 0.93H, *J* = 8.6 Hz), 6.34 (t, 0.93H, *J* = 8.3 Hz), 6.03 (dd, 0.07H, *J* = 8.2, 5.3 Hz), 4.93 (s, 0.93H), 4.81 (s, 0.07H), 4.45−4.34 (m, 2H), 4.19 (m, 0.07H), 4.06 (m, 0.93H), 3.97 (m, 1.93H), 3.73 (m, 0.07H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 168.1, 156.1 (q, *J* = 37.6 Hz), 140.5, 140.0, 139.8, 139.6, 136.7, 136.3, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 127.9, 127.8, 127.6, 127.5, 127.3, 127.0, 115.4 (q, *J* = 286.3 Hz), 62.4, 56.0, 54.1, 53.9, 53.3, 51.5, 51.1, 42.4. HRMS (ESI) for $C_{27}H_{23}F_3N_2O_4SNa$ calculated $[M + Na]^+$: 551.1223, found $[M + Na]^+$: 551.1205. Recrystallization of the product (PE/EtOAc) gave the *anti*-isomer as a single enantiomer (1.35 g, 2.56 mmol, 80%): mp 198 °C; $[\alpha]_D^{20}$ = −196.0 (*c* = 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.20 (m, 15H), 6.92 (d, 1H, *J* = 8.6 Hz), 6.34 (t, 1H, *J* = 8.3 Hz), 4.93 (s, 1H), 4.47−4.37 (m, 2H), 4.06 (m, 1H), 3.97 (d, 1H, *J* = 11.3 Hz), 3.94 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 156.1 (q, *J* = 37.6 Hz), 152.6, 140.0, 139.7, 136.3, 128.7, 128.6, 128.6, 128.4, 128.4, 128.3, 128.3, 127.6, 127.3, 115.4 (q, *J* = 286.3 Hz), 62.4, 54.1, 53.9, 51.5, 42.4.

*N-((1R,2S)-1-(Benzylthio)-1-(4-methoxyphenyl)-3-oxo-3-(2-oxooxazolidin-3-yl)-propan-2-yl)-2,2,2-trifluoroacetamide (**35**).* According to the general procedure, **23** (29 mg, 0.08 mmol), catalyst **9** (4 mg, 0.008 mmol) and phenylmethanethiol (28 μL, 0.24 mmol) were dissolved in 400 μL CH_2Cl_2 and the resulting mixture was stirred for 16 h. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **35** (36 mg, 0.079 mmol, 99%) as a white powder and as an inseparable mixture of diastereoisomers (*anti*/*syn* 80:20) (ee *anti* = 98% and *syn* 3%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 30:70 (1.0 mL, λ = 220 nm), t_r *anti* diastereoisomer 23.3 min (major) and 9.8 min (minor), t_r *syn* diastereoisomer 8.2 min (major) and 12.8 min (minor)). IR (neat, cm^{-1}) ν 3323, 2929, 1779, 1728, 1699, 1495, 1251, 1175; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.17 (m, 5H), 7.15 (m, 2H), 6.95 (d, 0.2H, *J* = 10.0 Hz), 6.87 (d, 0.8H, *J* = 8.3 Hz), 6.81 (m, 2H), 6.21 (t, 0.8H, *J* = 7.7 Hz), 5.91 (dd, 0.2H, *J* = 8.3, 5.6 Hz), 4.38 (t, 1.6H, *J* = 8.1 Hz), 4.28 (m, 0.2H), 4.14 (d, 0.2H, *J* = 5.6 Hz), 4.12 (d, 0.8H, *J* = 7.3 Hz), 4.03 (m, 0.4H), 3.96 (m, 0.8H), 3.86 (m, 0.8H), 3.74 (s, 0.6H), 3.73 (s, 2.4H), 3.67 (d, 0.8H, *J* = 12.9 Hz), 3.57−3.50 (m, 1.2H), 3.28 (d, 0.2H, *J* = 13.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.4, 159.7, 159.6, 156.5 (q, *J* = 38.0 Hz), 152.9, 152.5, 137.5, 136.9, 129.7, 129.4, 129.1, 129.0, 128.8, 128.6, 128.5, 128.3, 127.9, 127.4, 127.3, 115.5 (q, *J* = 286.0 Hz), 114.3, 114.1,62.6, 62.4, 56.3, 55.3, 50.2, 49.2, 42.7, 42.6, 35.9, 35.1. HRMS (ESI) for $C_{22}H_{21}F_3N_2O_5SNa$ calculated $[M + Na]^+$: 505.1015, found $[M + Na]^+$: 505.0998.

*2,2,2-Trifluoro-N-((1R,2S)-1-((4-methoxybenzyl)thio)-1-(4-methoxyphenyl)-3-oxo-3-(2-oxooxazolidin-3-yl)-propan-2-yl)-acetamide (**36**).* According to the general procedure, **23** (29 mg, 0.08 mmol), catalyst **9** (4 mg, 0.008 mmol) and 4-MeO-phenylmethanethiol (34 μL, 0.24 mmol) were dissolved in 400 μL CH_2Cl_2 and the resulting mixture was stirred for 16 h. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **36** (37 mg, 0.077 mmol, 96%) as a white powder and as an inseparable mixture of diastereoisomers (*anti*/*syn* 80:20) (ee *anti* = 96% and *syn* 52%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 30:70 (1.0 mL, λ = 220 nm), t_r *anti* diastereoisomer 78.5 min (major) and 13.9 min (minor), t_r *syn* diastereoisomer 16.7 min (major) and 9.3 min (minor)). IR (neat, cm^{-1}) ν 3321, 2925, 1779, 1728, 1699, 1583, 1510, 1391, 1249, 1215, 1174, 1033; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 0.4H, *J* = 8.7 Hz), 7.20−7.14 (m, 3.2H), 7.09 (d, 0.4H, *J* = 8.6 Hz), 7.01 (d, 0.2H, *J* = 8.3 Hz), 6.97 (d, 0.8H, *J* = 7.5 Hz), 6.89−6.81 (m, 4H), 6.29 (t, 0.8H, *J* = 7.8 Hz), 5.98 (dd, 0.2H, *J* = 8.3, 5.3 Hz), 4.47 (t, 1.6H, *J* = 8.1 Hz), 4.37 (m, 0.2H), 4.23 (m, 1H), 4.06 (m, 0.8H), 3.98 (m, 1H), 3.84 (s, 0.6H), 3.84 (s, 0.6H), 3.82 (s, 2.4H), 3.81 (s, 2.4H), 3.71 (d, 0.8H, *J* = 12.8 Hz), 3.66−3.58 (m, 1.2H), 3.33 (d, 0.2H, *J* = 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.2, 159.6, 159.5, 158.8, 158.8, 156, 156.4 (q, *J* = 37.5 Hz), 130.2, 130.1, 129.7, 129.4, 128.7, 128.5, 127.9, 115.5 (q, *J* = 286.0 Hz), 114.2, 114.1, 114.0, 113.9, 62.6, 62.4, 56.5, 55.3, 55.2, 54.2, 50.0, 48.8, 42.5, 42.5, 35.3, 34.5. HRMS for $C_{23}H_{23}F_3N_2O_6SNa$ calculated $[M + Na]^+$: 535.1121, found $[M + Na]^+$: 535.1101.

*N-((1R,2S)-1-(Benzhydrylthio)-1-(4-methoxyphenyl)-3-oxo-3-(2-oxo-oxazolidin-3-yl)-propan-2-yl)-2,2,2-trifluoroacetamide (**37**).* According to the general procedure, **23** (29 mg, 0.08 mmol), catalyst **9** (4 mg, 0.008 mmol) and diphenylmethanethiol (44 μL, 0.24 mmol) were dissolved in 400 μL CH_2Cl_2 and the resulting mixture was stirred for 16 h. The product was purified with column chromatography (PE/

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EtOAc 2:1), yielding **37** (43 mg, 0.077 mmol, 96%) as a white powder and as an inseparable mixture of diastereoisomers (*anti*/*syn* 90:10) (ee *anti* = 98% and *syn* 17%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 10:90 (1.0 mL, λ = 220 nm), t_r *anti* diastereoisomer 91.2 min (major) and 27.1 min (minor), t_r *syn* diastereoisomer 30.7 min (major) and 36.3 min (minor)). IR (neat, cm^{-1}) ν 3323, 1779, 1729, 1698, 1510, 1390, 1211, 1165, 730, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (m, 10H), 7.14 (m, 2.1H), 6.91−6.86 (m, 2.9H), 6.30 (t, 0.9H, J = 8.2 Hz), 6.00 (dd, 0.1H, J = 8.4, 5.4 Hz), 4.91 (s, 0.9H), 4.79 (s, 0.1H), 4.43 (m, 1.8H, 4.20 (m, 0.1H), 4.09 (m, 0.1H), 4.06 (m, 1H), 3.92 (m, 1.9H), 3.84 (s, 3H), 3.73 (m, 0.1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.4, 159.7, 159.6, 156.3 (q, J = 38.0 Hz), 140.7, 140.2, 139.9, 139.7, 129.7, 129.6, 128.7, 128.6, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 115.5 (q, J = 287.0 Hz), 114.2, 114.1, 62.5, 60.4, 56.2, 55.3, 54.3, 53.9, 53.3, 51.0, 50.5, 42.5. HRMS (ESI) for $C_{28}H_{25}F_3N_2O_5SNa$ calculated $[M + Na]^+$: 581.1328, found $[M + Na]^+$: 581.1307.

*N-((2S,3R)-3-(Benzylthio)-1-oxo-1-(2-oxooxazolidin-3-yl)pentan-2-yl)-2,2,2-trifluoroacetamide (**38**).* According to the general procedure, **24** (22 mg, 0.08 mmol), catalyst **9** (4 mg, 0.008 mmol) and phenylmethanethiol (28 μL, 0.24 mmol) were dissolved in 400 μL CH_2Cl_2 and the resulting mixture was stirred for 24 h. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **38** (32 mg, 0.078 mmol, 98%) as a white powder and as an inseparable mixture of diastereoisomers (*anti*/*syn* 82:18) (ee *anti* = 97% and *syn* 29%, determined by HPLC Daicel chiralcel ADH, *i*-PrOH/heptane 3:97 (1.0 mL, λ = 220 nm), t_r *anti* diastereoisomer 112.2 min (major) and 63.4 min (minor), t_r *syn* diastereoisomer 55.5 min (major) and 51.5 (minor)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.12 (m, 5.18H), 6.95 (d, 0.82H, J = 8.6 Hz), 6.00 (dd, 0.82H, J = 8.6, 5.8), 5.70 (dd, 0.18H, J = 9.0, 2.2 Hz), 4.43 (t, 1.64H, J = 16.2 Hz), 4.35 (m, 0.18H), 4.12 (m, 0.82H), 4.02 (m, 1H) 3.87 (s, 1.64H), 3.63 (m, 0.54H), 3.09 (m, 1H), 1.82 (m, 0.18H), 1.65 (m, 1H), 1.36 (m, 0.82H), 1.08 (t, 0.54H, J = 7.4 Hz), 0.99 (t, 2.46H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 169.0, 157 (q, J = 37.0 Hz), 137.9, 137.7, 129.8, 129.1, 128.6, 127.3, 115.7 (q, J = 287.0 Hz), 115.3 (q, J = 287.0 Hz), 62.6, 62.6, 54.9, 54.0, 48.6, 48.1, 42.6, 42.4, 36.0, 35.8, 27.8, 23.0, 11.7, 11.6. HRMS (ESI) for $C_{17}H_{19}F_3N_2O_4SNa$ calculated $[M + Na]^+$: 427.0910, found $[M + Na]^+$: 427.0905.

*2,2,2-Trifluoro-N-((2S,3R)-3-((4-methoxybenzyl)thio)-1-oxo-1-(2-oxooxazolidin-3-yl)pentan-2-yl)acetamide (**39**).* According to the general procedure, **24** (22 mg, 0.08 mmol), catalyst **9** (4 mg, 0.008 mmol) and 4-MeO-phenylmethanethiol (34 μL, 0.24 mmol) were dissolved in 400 μL CH_2Cl_2 and the resulting mixture was stirred for 24 h. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **39** (34 mg, 0.078 mmol, 98%) as a white powder and as an inseparable mixture of diastereoisomers (*anti*/*syn* 80:20) (ee *anti* = 96% and *syn* 26%, determined by HPLC Daicel chiralcel ADH, *i*-PrOH/heptane 8:92 (1.0 mL, λ = 220 nm), t_r *anti*-diastereoisomer 71.4 min (major) and 32.5 min (minor), t_r *syn*-diastereoisomer 28.7 min (major) and 23.4 min (minor)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 1.6H, J = 8.8 Hz), 7.18 (d, 0.2H, J = 8.0 Hz), 7.16 (d, 0.4H, J = 8.8 Hz), 7.06 (d, 0.8H, J = 8.3 Hz), 6.87 (m, 2H), 6.08 (dd, 0.8H, J = 8.8, 5.8 Hz), 5.77 (dd, 0.2H, J = 9.2, 2.4 Hz), 4.50 (t, 1.6, J = 8.0 Hz), 4.44−4.39 (m, 0.2H), 4.30 (q, 0.2H, J = 7.2 Hz), 4.14−4.09 (m, 0.8H), 3.92 (m, 1H), 3.73 (s, 1.6H) 3.82 (s, 0.6H), 3.80 (s, 2.4H), 3.68−3.57 (m, 0.6H), 3.09−3.01 (m, 1H), 1.86−1.79 (m, 0.2H), 1.74−1.63 (m, 1H), 1.28 (m, 0.8H) 1.11 (t, 1.59H, J = 7.2 Hz), 0.99 (t, 1.41H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.9, 158.8, 158.7, 156.6 (q, J = 38 Hz), 156.5 (q, J = 38 Hz), 152.9, 152.5, 130.2, 130.2, 129.8, 129.5, 115.5 (q, J = 286 Hz), 114.2, 62.6, 62.5, 55.3, 55.2, 55.0, 54.0, 48.4, 47.7, 42.6, 42.5, 35.4, 35.2, 27.9, 23.05, 11.8, 11.6; HRMS (FAB) for $C_{18}H_{22}F_3N_2O_5S$ calculated $[M + H]^+$: 435.1202, found $[M + H]^+$: 435,1201.

*N-((2S,3R)-3-(Benzhydrylthio)-1-oxo-1-(2-oxooxazolidin-3-yl)-pentan-2-yl)-2,2,2-trifluoroacetamide (**40**).* According to the general procedure, **24** (22 mg, 0.08 mmol), catalyst **9** (4 mg, 0.008 mmol) and diphenylmethanethiol (44 μL, 0.24 mmol) were dissolved in 400 μL CH_2Cl_2 and the resulting mixture was stirred for 16 h. The product was purified with column chromatography (PE/EtOAc 2:1), yielding **40** (37 mg, 0.077 mmol, 96%) as a white powder and as an inseparable mixture of diastereoisomers (*anti*/*syn* 93:7) (ee *anti* = 98% and *syn* 3%, determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 10:90 (1.0 mL, λ = 220 nm), t_r *anti* diastereoisomer 20.2 min (major) and 17.9 min (minor), t_r *syn* diastereoisomer 11.7 min (major) and 10.1 min (minor)). IR (neat, cm^{-1}) ν 3328, 1781, 1727, 1697, 1538, 1390, 1207, 1171, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 1.86H, J = 7.6 Hz), 7.42−7.24 (m, 8.21H), 6.97 (d, 0.93H, J = 8.3 Hz), 6.16 (dd, 0.93H, J = 8.3, 5.8 Hz), 5.74 (d, 0.07H, J = 9.2 Hz), 5.35 (s, 0.93H), 5.14 (s, 0.07H), 4.48−4.36 (m, 1.86H), 4.23 (m, 0.14H), 4.08 (m, 0.93H), 3.95 (m, 1H), 3.70 (m, 0.07H), 3.05 (m, 0.07H), 2.95 (m, 0.93H), 1.85 (m, 0.07H), 1.62 (m, 1H), 1.38 (m, 0.93H), 1.12 (t, 0.21H, J = 7.4 Hz), 0.99 (t, 2.79H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 156.9 (q, J = 37.0 Hz), 152.7, 141.0, 140.9, 128.8, 128.8, 128.6, 128.4, 128.4, 128.2, 128.1, 127.8, 127.6, 127.4, 127.3, 115.6 (q, J = 286.0 Hz), 62.5, 62.4, 54.8, 54.1, 53.9, 53.7, 48.9, 42.5, 28.1, 23.3, 11.7, 11.3. HRMS (ESI) for $C_{23}H_{23}F_3N_2O_4SNa$ calculated $[M + Na]^+$: 503.1223, found $[M + Na]^+$: 503.1208.

*(2S,3R)-Methyl-3-(benzhydrylthio)-2-((tert-butoxycarbonyl)-amino)-3-phenylpropanoate (**41**).* Compound **34** (2.1 g, 3.9 mmol) was dissolved in 120 mL of HCl (0.33 M) in methanol (made through addition of acetyl chloride to methanol). The mixture was stirred overnight at reflux temperature. The solvent was evaporated and the residue was dissolved in 70 mL of CH_2Cl_2. Then Boc_2O (1.03 g, 4.7 mmol) was added followed by DIPEA (1.03 mL, 5.9 mmol). The resulting mixture was stirred for 6 h and then quenched with saturated $NaHCO_3$. The layers were separated, dried with $MgSO_4$ and the crude was concentrated. Next the crude product was dissolved in 75 mL methanol and cooled to 0 °C. K_2CO_3 (2.2 g, 15.9 mmol) was slowly added and stirring was continued for 5 min. The mixture was quenched with saturated NH_4Cl and the resulting mixture was extracted three times with EtOAc. The organic layers were combined and dried with $MgSO_4$. The product was purified with flash column chromatography (PE/EtOAc 8:1) yielding **41** (1.28 g, 2.7 mmol, 68%) as a colorless oil and single isomer (determined by HPLC Daicel chiralcel AD, *i*-PrOH/heptane 5:95 (1.0 mL, λ = 220 nm), t_r *anti* diastereoisomer 6.6 (major) and 12.4 min (minor), t_r *syn* diastereoisomer 8.2 min (major) and 9.2 min (minor)). $[\alpha]_D^{20}$ = −134.4 (c = 1.0, CH_2Cl_2); IR (neat, cm^{-1}) ν 3435, 1746, 1714, 1492, 1162, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 15H), 5.01 (m, 2H), 4.83 (t, 1H, J = 5.9 Hz), 3.96 (d, 1H, J = 5.6 Hz), 3.64 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 155.1, 140.4, 140.3, 137.0, 128.6, 128.5, 128.5, 128.3, 128.1, 127.3, 127.2, 80.0, 57.0, 53.5, 52.1, 51.9, 28.2. HRMS (ESI) for $C_{28}H_{31}NO_4SNa$ calculated $[M + Na]^+$: 500.1866, found $[M + Na]^+$: 500.1849.

*(2S,3R)-3-(Benzhydrylthio)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanoic acid (**42**).* Compound **41** (900 mg, 1.9 mmol) was dissolved in a mixture of dioxane (9.4 mL) and methanol (2.5 mL). Next 0.63 mL of 3 M aq NaOH was added and the mixture was stirred overnight. The solution was acidified with 1 M $KHSO_4$ to pH 1 and extracted three times with EtOAc. The organic layers were combined and dried with $MgSO_4$. The product was purified with column chromatography (PE/EtOAc/AcOH 8:1:0.2) yielding acid **42** (770 mg, 1.66 mmol, 88%) as a white solid: mp 61−63 °C; $[\alpha]_D^{20}$ = −83.6 (c = 0.67, MeOH); IR (neat, cm^{-1}) ν 1706, 1491, 1155, 747; ^{1}H NMR (400 MHz, DMSO, 363 K) (3:1 mixture of rotamers in ^{1}H NMR) δ 7.62 (d, 1H, J = 7.1 Hz), 7.41−7.13 (m, 14H), 6.38 (br, 0.25H), 6.20 (br, 0.75H), 5.00 (s, 0.75H), 4.92 (s, 0.25H), 4.49 (t, 0.75H, J = 8.2 Hz), 4.44 (t, 0.25H, J = 9.1 Hz), 4.08 (d, 0.25H, J = 7.2 Hz), 4.00 (d, 0.75, J = 8.0 Hz), 1.38 (s, 4H), 1.29 (s, 5H); ^{13}C NMR (100 MHz, DMSO, 363 K) (mixture of rotamers): δ 170.7, 140.6, 140.3, 137.8, 133.7, 130.3, 129.2, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.8, 126.6, 126.6, 126.5, 78.5, and 78.2 (rotamers), 53.2, 51.6, 50.4, 27.7, and 27.6 (rotamers); HRMS (ESI) for $C_{27}H_{29}NO_4SNa$ calculated $[M + Na]^+$: 486.1710, found $[M + Na]^+$: 486.1695.

*(2S,3R)-Methyl 2-amino-3-mercapto-3-phenylpropanoate (**43**).* Compound **41** (53 mg, 22 mmol) was dissolved in 1 mL TFA. This solution was treated with 0.1 mL of iPr_3SiH. The resulting mixture was stirred for 1 h at 50 °C and then concentrated. The residue was dissolved in EtOAc. Saturated K_2CO_3 was added and the layers were

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separated. The water layer was extracted twice with EtOAc. The organic layers were combined, dried with Na_2SO_4 and then concentrated. The product was purified with column chromatography (EtOAc) yielding **43** as the disulfide (22, mg, 0.052 mmol, 95%) as oil. $[\alpha]_D^{20}$ = −102.6 (c = 0.35, MeOH). IR (neat, cm^{-1}) ν 3382, 2951, 1740, 1267, 757; ^1H NMR (400 MHz, MeOD) δ 7.26 (m, 3H), 7.10 (m, 2H), 3.95 (d, 1H, J = 6.4 Hz), 3.87 (d, 1H, J = 6.4 Hz), 3.57 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 173.9, 137.8, 130.0, 129.9, 129.7, 129.6, 59.2, 58.1, 52.7. HRMS (ESI) for $C_{20}H_{25}N_2O_4S_2$ calculated $[M + H]^+$: 421.1250, found $[M + H]^+$: 421.1237.

Tetrapeptide ***44***. Acid **42** (172 mg, 0.37) was dissolved in 7 mL THF. Then HOAt (50 mg, 0.37 mmol), HATU (140 mg, 0.37 mmol) and DIPEA (129 μL, 0.74 mmol) were added. Next H_2N−Ala−Val−Phe−CO_2Me (130 mg, 0.37 mmol) in 1 mL THF was added and the mixture was stirred for 6 h. The reaction mixture was acidified with 1 M $KHSO_4$ to pH 1 and extracted three times with EtOAc. The organic layers were combined, dried with $MgSO_4$ and concentrated. The product was purified with column chromatography (PE/EtOAc 1:1), yielding tetrapeptide **44** (214 mg, 0.27 mmol, 73%) as a white solid: mp 188−190 °C; IR (neat, cm^{-1}) ν 3645, 3272, 2968, 1737, 1714, 1632, 1159, 838; ^1H NMR (400 MHz, DMSO, 363 K) δ 8.00 (br, 1H), 7.94 (br, 1H), 7.44 (br, 1H), 7.30−7.21 (m, 18H), 7.11 (d, 2H, J = 7.3 Hz), 6.19 (br, 1H), 4.89 (s, 1H), 4.56 (m, 2H), 4.45 (m, 1H), 4.17 (t, 1H, J = 8.2 Hz), 3.90 (d, 1H, J = 8.2 Hz), 3.60 (s, 3H), 3.0 (m, 1H), 2.97 (m, 1H), 1.97 (m, 1H), 1.37 (d, 3H, J = 4.8 Hz), 1.22 (s, 9H), 0.83 (m, 6H); ^{13}C NMR (100 MHz, DMSO): 171.8, 171.7, 171.1, 169.7, 154.5, 141.4, 140.7, 139.4, 137.1, 129.0, 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 128.1, 127.9, 127.1, 127.0, 126.6, 77.9, 58.3, 57.4, 53.5, 53.5, 51.8, 50.5, 48.5, 36.5, 30.7, 28.0, 19.1, 18.1, 18.0; HRMS (ESI) for $C_{45}H_{54}N_4O_7SNa$ calculated $[M + Na]^+$: 817.3605, found $[M + Na]^+$: 817.3566.

Tetrapeptide ***45***. Protected tetrapeptide **44** (50 mg, 0.063 mmol) was dissolved in 5 mL of TFA and 0.25 mL of iPr$_3$SiH. The resulting mixture was heated for 2 h at 50 °C. The solvent was removed and the peptide was purified by preparative HPLC (BESTA preparative system, Inerstsill ODS C18 column 10 × 250 mm, gradient H_2O/ACN 0.1% TFA 60:40 to 30:70, 30 min) yielding **45** as a TFA salt and as a mixture of free thiol and disulfide. Low resolution LCMS for free thiol $C_{27}H_{37}N_4O_5S$ calculated $[M + H]^+$: 529.2, found $[M + H]^+$: 529.2 and for disulfide $C_{54}H_{71}N_8O_{10}S$ calculated $[M + H]^+$: 1055.5, found $[M + H]^+$: 1055.4.

Hexapeptide ***46***. Tetrapeptide **45** (5 mg, 0.008 mmol) was dissolved in 1 mL of 0.1 M phosphate buffer containing 0.05 M TCEP. The pH was adjusted to pH 8 with 0.1 M NaOH. Next 3 mL of a degassed solution of acetonitrile containing the activated ester (5.3 mg, 0.009 mmol) was added and the resulting mixture was stirred overnight. The hexapeptide **46** was purified by preparative HPLC (BESTA preparative system, Inerstsill ODS C18 column 10 × 250 mm, gradient H_2O/ACN 0.1% TFA 60:40 to 20:80, 30 min). Low resolution LCMS for $C_{50}H_{63}N_6O_9S$ calculated $[M + H]^+$: 923.4, found $[M + H]^+$: 923.1.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01660.

Copies of the ^1H and ^{13}C NMR spectra and HPLC chromatograms for ee determinations. (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Reviews include: (a) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, *2010*, 1229−1279. (b) Li, H.; Chen, Y.; Deng, L. In *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, 2011; Chapter 10, pp 361−408. (c) Yeboah, E. M. O.; Yeboah, S. O.; Singh, G. S. *Tetrahedron* **2011**, *67*, 1725−1762. (d) Bhanushali, M.; Zhao, C.-G. *Synthesis* **2011**, *2011*, 1815−1830. (e) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632−649. (f) Melchiorri, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748−9770. (g) Ingemann, S.; Hiemstra, H. *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2013; pp 119−160. (h) Fang, X.; Wang, C.-F. *Chem. Commun.* **2015**, *51*, 1185−1197. (i) Holland, M. C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 3862−3871.

(2) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929−931.

(3) See for example ref 1h and (a) Bahlinger, A.; Fritz, S. P.; Wennemers, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8779−8783. (b) Kótai, B.; Kardos, G.; Hamza, A.; Farkas, V.; Pápai, S. T. *Chem. - Eur. J.* **2014**, *20*, 5631−5639.

(4) For a recent example, see Koley, D.; Krishna, Y.; Srinivas, K.; Khan, A. A.; Kant, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 13196−13200.

(5) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659−6690.

(6) (a) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703−4832. (b) For a recent theoretical study, see Krenske, E. H.; Houk, K. N.; Harmata, M. *J. Org. Chem.* **2015**, *80*, 744−750.

(7) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390−2431.

(8) *Cinchona Alkaloids in Synthesis & Catalysis: Ligands, Immobilization and Organo- catalysis*; Song, C. E., Ed.; Wiley-VCH: Weinheim, 2009.

(9) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047−9153.

(10) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471−5569.

(11) Connon, S. J. *Chem. Commun.* **2008**, 2499−2510.

(12) (a) Li, B−J.; Jiang, L.; Liu, M.; Chen, L.−S.; Wu, Y. *Synlett* **2005**, 603−606. (b) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967−1969. (c) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367−6370. (d) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, *35*, 4481−4483.

(13) See for an example Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089−2091.

(14) For a recent review, see Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253−281.

(15) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 7872−7875.

(16) Zhang, L.; Lee, M.-M.; Lee, S.-M.; Lee, J.; Cheng, M.; Jeong, B.-S.; Park, H.-G.; Jew, S.-S. *Adv. Synth. Catal.* **2009**, *351*, 3063−3066.

(17) For a review on sulfa-Michael additions, see: Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807−8864.

(18) Palacio, C.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 2849−2851.

(19) Liu, Y.; Sun, B. F.; Wang, B. M.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418−419. See also Zhao, F.; Zhang, W.; Yang,

DOI: 10.1021/acs.joc.5b01660
J. Org. Chem. 2015, 80, 10561−10574

Y.; Pan, Y.; Chen, W.; Liu, H.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2011**, *353*, 2624−2630. In addition C9-squaramide derivatives of quinine have been reported to be efficient catalysts for the SMA reaction of α,β-unsaturated *N*-acylated oxazolidin-2-ones Dai, L.; Yang, H.; Chen, F. *Eur. J. Org. Chem.* **2011**, *2011*, 5071−5076. and β-substituted-β-trifluoromethyl oxazolidin-2-ones Chen, W.; Jing, Z.; Chin, K. F.; Qiao, B.; Zhao, Y.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2014**, *356*, 1292−1300.

(20) Breman, A. C.; Smits, J. M. M.; de Gelder, R.; van Maarseveen, J. H.; Ingemann, S.; Hiemstra, H. *Synlett* **2012**, *23*, 2195−2200.

(21) Xiao, X.; Liu, M.; Rong, C.; Xue, F.; Li, S.; Xie, Y.; Shi, Y. *Org. Lett.* **2012**, *14*, 5270−5273.

(22) Guang, J.; Larson, A. J.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2015**, *357*, 523−529.

(23) Góngora-Benítez, M.; Mendive-Tapia, L.; Ramos-Tomillero, I.; Breman, A. C.; Tulla-Puche, J.; Albericio, F. *Org. Lett.* **2012**, *14*, 5472−5475.

(24) (a) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211−3214. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.

(25) Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891−1894.

(26) Palmer, A. M.; Chiesa, V.; Schmid, A.; Münch, G.; Grobbel, B.; Zimmermann, P. J.; Brehm, C.; Buhr, W.; Simon, W.-A.; Kromer, W.; Postius, S.; Volz, J.; Hess, D. *J. Med. Chem.* **2010**, *53*, 3645−3674.

(27) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416−14417.

(28) Rostami, A.; Colin, A.; Li, X. Y.; Chudzinski, M. G.; Lough, A. J.; Taylor, M. S. *J. Org. Chem.* **2010**, *75*, 3983−3992.

(29) (a) Cui, Y.-M.; Yasutomi, E.; Otani, Y.; Yoshinaga, T.; Ido, K.; Sawada, K.; Ohwada, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5201−5205. (b) Kilpatrick, B.; Heller, M.; Arns, S. *Chem. Commun.* **2013**, *49*, 514−516.

(30) The novel C6′ squaramide derivative of quinidine catalyzed the Henry reaction between nitromethane and benzaldehyde to give the product in 74% ee after 99% conversion (catalyst (20 mol%), THF, rt, 48 h). In the reaction between dimethyl malonate and *trans*-β-nitrostyrene the product was formed in 84% ee (catalyst (10 mol%), CH_2Cl_2, rt, 16 h): Scott, J. I.; Breman, A. C.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. unpublished results.

(31) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562−570.

(32) Tesser, G. I.; Balvert-Geers, I. C. *Int. J. Pept. Protein Res.* **1975**, *7*, 295−305.

(33) (a) Crich, D.; Banerjee, A. *J. Am. Chem. Soc.* **2007**, *129*, 10064−10065. (b) Thompson, R. E.; Chan, B.; Radom, L.; Jolliffe, K. A.; Payne, R. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9723−9727.

(34) Popovic, S.; Bieräugel, H.; Detz, R. J.; Kluwer, A. M.; Koole, J. A. A.; Streefkerk, D. E.; Hiemstra, H.; van Maarseveen, J. H. *Chem. - Eur. J.* **2013**, *19*, 16934−16937.

(35) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340−5345.

(36) Breitholle, E. G.; Stammer, C. H. *J. Org. Chem.* **1976**, *41*, 1344−1349.

DOI: 10.1021/acs.joc.5b01660
J. Org. Chem. 2015, 80, 10561−10574