CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200903025

Enantioselective Organocatalytic Addition of Oxazolones to 1,1-Bis(phenylsulfonyl)ethylene: A Convenient Asymmetric Synthesis of Quaternary α-Amino Acids

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Dedicated to Professor Josep M. Ribó on the occasion of his 70th birthday

Abstract: A new, easy, and highly enantioselective method for the synthesis of quaternary α-alkyl-α-amino acids based on organocatalysis is reported. The addition of oxazolones to 1,1-bis(phenylsulfonyl)ethylene is efficiently catalyzed by simple chiral bases or thioureas. The reaction affords α,α-disubstituted α-amino acid derivatives with complete C4 regioselectivity and with excellent yields and enantioselectivities. This methodology is complementary to previously reported enantioselective approaches to quaternary α-amino acids and allows the synthesis of α-phenyl-α-alkyl-α-amino acids and α-*tert*-butyl-α-alkyl-α-amino acids. It has distinct advantages in terms of operational simplicity, enviromentally friendly conditions, and suitability for large-scale reactions.

Keywords: amino acids · Michael addition · organocatalysis · oxazolones · stereoselectivity

Introduction

The asymmetric synthesis of nonproteinogenic quaternary α-amino acids is a topic of growing interest. In particular, α-alkyl-α-amino acids have proven to be extremely useful building blocks for the design and construction of new peptides or proteins with improved pharmacological properties, due to the restricted conformational mobility that these amino acids are able to impart to the peptide backbone[1,2] and also due to the enhanced resistance to enzymatic degradation exhibited by the products.[3] Quaternary α-amino acids have also been found in some natural antibiotics[4] and, more recently, in some carbonaceous meteorites,[5] where their presence in the optically active form (up to 15% *ee* for L-isovaline) has led to interesting speculations on their possible contribution to terrestrial chemical evolution and the origin of biological homochirality.[6]

There are several synthetic methods for the enantioselective preparation of quaternary amino acids.[7] One of the most classical approaches is based on the principle of "self-regeneration of stereocenters",[8] developed by Seebach et al., in which the stereogenic center of an α-amino acid generates a temporary center of chirality on a suitable derivative (such as the 5-oxazolidinone in the procedure described by Seebach et al.); this, in turn, is used to introduce diastereoselectively a new substituent at the original stereogenic center.[9] A related strategy, based on the principle of "memory of chirality",[10] has been recently used for the enantioselective quaternization of α-amino acid derivatives.[11] The asymmetric alkylation of amino acid derived Schiff bases by using chiral phase-transfer organocatalysts, pioneered by O'Donnell et al.[12] and further improved by Lygo,[13] Corey,[14] Maruoka,[15] and their respective co-workers, has become one of the most reliable procedures for the enantioselective preparation of α-amino acids.[16] However, its application to the asymmetric synthesis of α-alkyl-α-amino acids is not straightforward and still presents important limitations, both in scope and in enantioselectivity.[17] Very recently, Jørgensen and co-workers have reported on the use of 5-oxazolones (azalactones) in the synthesis of

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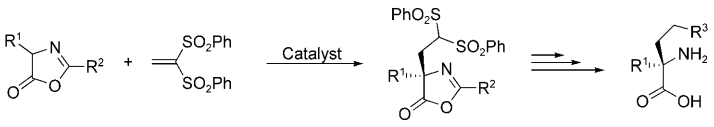
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903025.

quaternary α-amino acids by asymmetric organocatalytic Michael addition[18] to α,β-unsaturated aldehydes[19] and nitroalkenes,[20] whereas Terada and co-workers have described an efficient access to β-hydroxy-α-amino acid derivatives with a quaternary stereocenter at the α-carbon atom.[21] These reactions afforded the desired amino acids with excellent yields and enantioselectivities. However, one of the drawbacks of these methodologies is the presence of several functional groups in the final amino acid, which makes the synthesis of α,α-dialkylamino acids difficult.

The use of sulfones and vinyl sulfones in enantioselective synthesis is receiving much attention. Between the pioneering work of Mossé and Alexakis concerning the asymmetric addition of aldehydes to vinyl sulfones[22] and the recent addition of 2-fluoromethylenedisulfones and methylenedisulfones to α,β-unsaturated aldehydes developed in our research group,[23] the use of sulfones has grown exponentially in the last few years, due to their easy modification or removal by reduction.[24] These characteristics make sulfones synthetically versatile groups that can be introduced in either nucleophilic or electrophilic synthons.

Results and Discussion

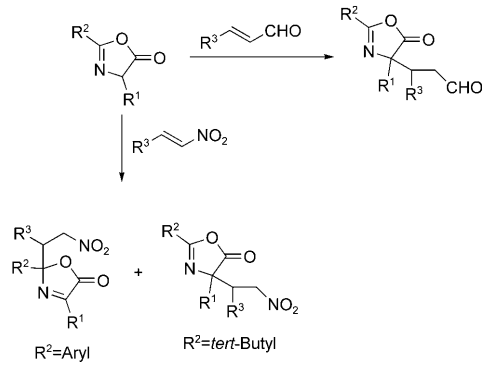
With this information in mind, and based on our previous experience in asymmetric organocatalysis,[23,25] we became interested in studying the unprecedented addition of 5-oxazolones to vinyl sulfones catalyzed by chiral bases, in order to synthesize quaternary α-amino acids (Scheme 1). This



Scheme 1. The proposed reaction.

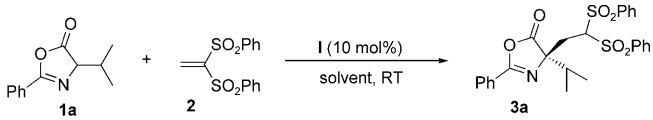
strategy would allow some of the limitations shown by the methodologies cited above to be avoided. Another concern was the possible regioselectivity in the reaction of the oxazolones. As previously reported, the regioselectivity of oxazolone additions is strongly dependent on both the nature of the substituents of the oxazolone and on the Michael acceptor. Thus, when unsaturated aldehydes were used as the Michael acceptors, only C4 addition on the oxazolone ring was observed.[19] However, when nitrostyrenes were used as the Michael acceptors, the regioselectivity could be totally reversed depending on the substituent at the C2 position, as shown in Scheme 2.[20,26]

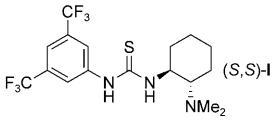
To our delight, when 2-phenyl-4-isopropyl-5-oxazolone (**1a**) was treated with 1,1-bis(phenylsulphonyl)ethene (**2**) in several solvents and in the presence of the thiourea-based catalyst of Takemoto and co-workers,[27] (*S*,*S*)-**I** (Table 1), the addition product **3a** was obtained with complete C4 regioselectivity and in moderate enantioselectivity (up to



Scheme 2. Regioselectivity of oxazolone addition.

Table 1. Solvent screening in the addition of oxazolone **1a** to vinylsulfone **2**.[a]





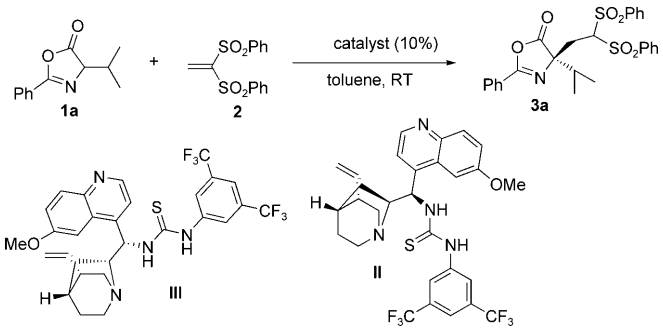
Entry	Solvent	Conversion [%][b]	e.r.[c]
1	CH_2Cl_2	100	85:15
2[d]	$CHCl_3$	100	15.5:84.5
3	toluene	100	86:14
4	AcOEt	100	83:17
5	DMF[e]	100	racemic
6	EtOH	100	72:28
7	hexane	20	77:23

[a] In all cases, 1,1-bis(phenylsulfonyl)ethene (**2**; 1.0 equiv) was added to a mixture of **1a** (1.5 equiv) and catalyst **I** (0.1 equiv) in the appropriate solvent at room temperature. [b] Determined by NMR spectroscopy after 1 h. [c] Determined by chiral HPLC analysis. [d] (*R*,*R*)-**I** was used as the catalyst. [e] DMF: *N*,*N*-dimethylformamide.

86:14 enantiomeric ratio (e.r.)). The reaction took place with excellent conversion in all solvents except hexane (Table 1, entry 7). Dichloromethane, chloroform, toluene, and ethyl acetate (Table 1, entries 1–4, respectively) afforded very similar enantioselectivities. The enantiomeric ratio of the adduct decreased with the use of ethanol as the solvent (Table 1, entry 6), and the racemic product was obtained in *N*,*N*-dimethylformamide (Table 1, entry 5).

Next, we decided to optimize the nature of the catalyst, by testing several chiral thioureas and bases derived from *Cinchona* alkaloids (**II**–**XII**) in the benchmark addition of **1a** to **2** (Table 2) with toluene as the solvent. The reaction was efficiently catalyzed (100% conversion after 1 h at room temperature) by all of the catalysts; remarkably, when the Sharpless ligands $(DHQD)_2AQN$ (**IV**) or $(DHQD)_2PHAL$ (**V**) were used (Table 2, entries 1 and 2), we obtained good enantioselectivities, at the same level as

Table 2. Catalyst screening in the addition of oxazolone **1a** to vinylsulfone **2**.[a]



Entry	Catalyst[b]	Conversion [%][c]	e.r.[d]
1	$(DHQD)_2AQN$ (**IV**)	100	87:13
2	$(DHQD)_2PHAL$ (**V**)	100	87:13
3	$(DHQD)_2PYR$ (**VI**)	100	61:39
4	$(DHQ)_2AQN$ (**VII**)	100	24:76
5	$(DHQ)_2PHAL$ (**VIII**)	100	30:70
6	$(DHQ)_2PYR$ (**IX**)	100	28:72
7	(*S*,*S*)-**I**	100	86:14
8	**II**	100	9:91
9	**III**	100	86:14
10	quinine (**XI**)	100	52:48
11	quinidine (**XII**)	100	47:53

[a] In all cases, 1,1-bis(phenylsulfonyl)ethene (**2**) (1.0 equiv) was added to a mixture of **1a** (1.5 equiv) and of the catalyst **I-XII** (0.1 equiv) in toluene at room temperature. [b] $(DHQD)_2AQN$: hydroquinidine(anthraquinone-1,4-diyl) diether; $(DHQD)_2PHAL$: 1,4-bis(dihydroquinidinyl)-phthalazine; $(DHQD)_2PYR$: hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether. The DHQ catalysts are the equivalent dihydroquininyl compounds. [c] Determined by NMR spectroscopy after 1 h. [d] Determined by chiral HPLC analysis.

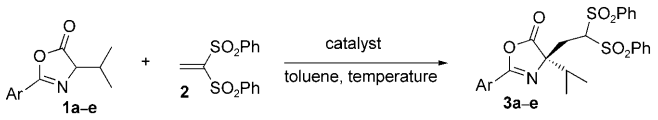
those provided by the Takemoto thiourea **I** (Table 2, entry 7). The best results were obtained with the quinidine-derived thiourea catalyst **II** (Table 2, entry 8). The pseudoenantiomeric catalyst **III**, derived from quinine, gave the opposite enantiomer as expected, albeit with somewhat lower enantioselectivity (Table 2, entry 9). When we used pseudoenantiomers of the Sharpless catalysts (Table 2, entries 4 and 5) or alkaloids such as quinine or quinidine (Table 2, entries 10 and 11), the enantioselectivities dropped dramatically. It is worth noting that both the quinidine-derived Sharpless ligands **IV**–**VI** and the quinine-derived bifunctional thiourea catalyst **III** gave the same sense of asymmetric induction as that obtained with the Takemoto catalyst (*S*,*S*)-**I**.

In order to improve the overall results of the reaction, we also investigated the effect of temperature. Rather unexpectedly, if the reaction was catalyzed by thioureas, the enantioselectivity did not improve upon a decrease in the temperature. On the other hand, the Sharpless ligands produced better enantioselectivities at lower temperatures, at the expense of a reduced reaction rate. Gratifyingly, the use of $(DHQD)_2AQN$ (**IV**) afforded the final quaternary amino acid derivative **3a** with excellent yield (84%) and enantioselectivity (96.5:3.5 e.r.) after 3 days at −40°C (Table 3, entry 1).

With these results on hand, we decided to study the effect of the aromatic C2 substituent of the oxazolone derived from valine. As previously noticed by Jørgensen and coworkers,[20] the presence of halogens (F, Cl) in the *ortho* and/or *para* positions of the phenyl ring increased the enantioselectivity of the reaction with the thiourea-derived catalysts **I**–**III**. In Table 3, we summarize the best conditions (catalyst, reaction temperature) finally achieved for each of the studied compounds **1a**–**e** (see the Supporting Information for additional screening results). As expected, when there are halogenated substituents in the aromatic ring, the enantioselectivity increases to 95:5 e.r. at room temperature upon catalysis with the Takemoto thiourea **I** (Table 3, entry 4). This opens a new door to achieve high enantioselectivities by only changing the nature of the aromatic ring substituents.

To further examine the scope of the reaction, we prepared a library of oxazolones bearing different substituents in positions 2 and 4 (Tables 4–7). The reaction is strongly dependent on the oxazolone substitution pattern, so in order to achieve good enantioselectivities, we optimized the reaction

Table 3. Effect of the substitution pattern of the C2 aromatic substituent on the addition of valine-derived oxazolones **1a**–**e** to vinylsulfone **2**.[a]



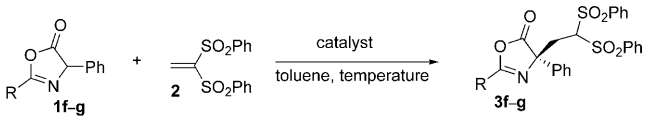
Entry	Ar	Product	Catalyst	*T*	*t*	Yield [%][b]	e.r.[c]
1		**3a**	$(DHQD)_2AQN$ (**IV**)	−40°C	3 days	84	96.5:3.5
2		**3b**	(*S*,*S*)-**I**	−20°C	1 day	96	96:4
3		**3c**	(*S*,*S*)-**I**	RT	14 h	78	94:6
4		**3d**	(*S*,*S*)-**I**	RT	14 h	82	95:5
5		**3e**	(*S*,*S*)-**I**	RT	14 h	93	92:8
6		**3a**	(*S*,*S*)-**I**	RT	14 h	79	86:14

[a] In all cases, 1,1-bis(phenylsulfonyl)ethene (**2**; 1.0 equiv) was added to **1a**–**e** (1.5 equiv) and the catalyst (0.1 equiv) in toluene at the specified temperature. [b] Determined after isolation by column chromatography. [c] Determined by chiral HPLC analysis.

temperature, catalyst, and C2 substituent for each initial amino acid.

When the oxazolones derived from phenylglycine were used (Table 4), the best results were obtained with phenyl (**1f**) or *tert*-butyl (**1g**) substituents at the C2 position and

Table 4. Addition of oxazolones derived from phenylglycine to vinylsulfone **2**.[a]



Entry	R	Product	Catalyst	T [°C]	t [days]	Yield [%][b]	e.r.[c]
1		**3f**	(*S*,*S*)-**I**	−80	3	72	90:10
2	*t*Bu	**3g**	**II**	−40	3	82	9:91
3		**3f**	(*S*,*S*)-**I**	−40	2	78	85:15
4		**3f**	**IV**	−40	2	67	68:32
5	*t*Bu	**3g**	(*S*,*S*)-**I**	−40	2	77	88:12

[a] In all cases, 1,1-bis(phenylsulfonyl)ethene (**2**; 1.0 equiv) was added to **1f** or **1g** (1.5 equiv) and the catalyst (0.1 equiv) in toluene at the specified temperature. [b] Determined after isolation by column chromatography. [c] Determined by chiral HPLC analysis.

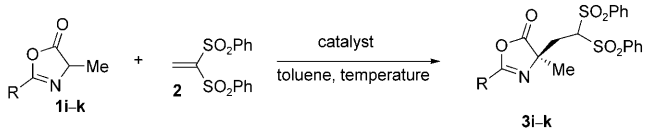
the Takemoto catalyst **I** or quinidine-derived bifunctional thiourea catalyst **II**, respectively, to afford the final quaternary amino acid derivatives with 90:10 e.r. and 72% yield (**3f**; Table 4, entry 1) and 9:91 e.r. and 82% yield (**3g**; Table 4, entry 2). It should be highlighted that, in both cases, the corresponding amino acids cannot be synthesized with the methodology of Maruoka and co-workers.[15]

The oxazolone **1h**, derived from *tert*-leucine, reacted with vinylsulfone **2** to afford the corresponding quaternary amino acid derivative **3h** with moderate yield (76%) and enantioselectivity (85:15 e.r.) when the Takemoto thiourea **I** was used as the catalyst at room temperature (Table 5, entry 1). A decrease in the temperature to 4°C (Table 5, entry 4) marginally improved the enantioselectivity but brought about a substantial decrease in the yield. Moreover, the reaction, probably due to the steric bulk of the *tert*-butyl C4 substituent, afforded the product in only moderate yields when other catalysts were used (Table 5, entries 2 and 3) and did not proceed at all when run at low temperatures (Table 5, entry 5). It is worth noting, however, that the quaternary amino acid obtained from **3h** cannot be obtained by any of the previously described enantioselective methodologies.

When oxazolones derived from alanine, **1i–k**, were used (Table 6), the effect of fluorine substitution on the aromatic C2 substituent was evident, and we could obtain high yields (up to 98%) and enantioselectivities (up to 93:7 er; Table 6, entry 7) for compound **3k**.

With oxazolone **1l**, derived from leucine (Table 7), high enantioselectivities and good yields were obtained at room temperature either with Takemoto catalyst **I** (Table 7, entry 1) or with the quinidine-derived thiourea catalyst **II**

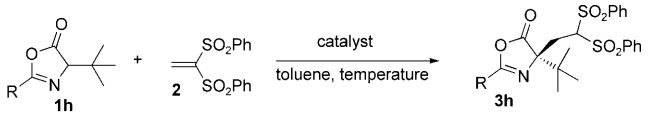
Table 6. Addition of oxazolones derived from alanine to vinylsulfone **2**.[a]



Entry	R	Product	Catalyst	T [°C]	t	Yield [%][b]	e.r.[c]
1		**3i**	(*S*,*S*)-**I**	RT	14 h	86	75:25
2		**3i**	**II**	RT	14 h	85	24:76
3		**3i**	**IV**	−40	2 days	68	83:17
4		**3i**	**IV**	RT	14 h	67	68:32
5		**3j**	(*S*,*S*)-**I**	−40	2 days	0	–
6		**3k**	(*S*,*S*)-**I**	−40	2 days	77	88:12
7[d]		**3k**	(*S*,*S*)-**I**	−40	2 days	98	93:7

[a] In all cases, 1,1-bis(phenylsulfonyl)ethene (**2**; 1.0 equiv) was added to **1i–k** (1.5 equiv) and the catalyst (0.1 equiv) in toluene at the specified temperature. [b] Determined after isolation by column chromatography. [c] Determined by chiral HPLC analysis. [d] CH_2Cl_2 was used as the solvent.

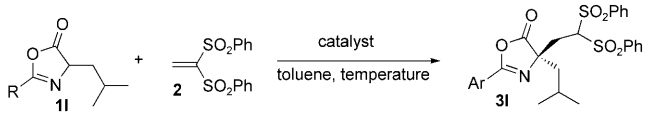
Table 5. Addition of the oxazolone derived from *tert*-leucine, **1h**, to vinylsulfone **2**.[a]



Entry	R	Product	Catalyst	T [°C]	t	Yield [%][b]	e.r.[c]
1		**3h**	(*S*,*S*)-**I**	RT	14 h	76	85:15
2		**3h**	**II**	RT	14 h	73	30:70
3		**3h**	**IV**	RT	14 h	68	65:35
4		**3h**	(*S*,*S*)-**I**	4	14 h	66	86:14
5		**3h**	(*S*,*S*)-**I**	−40	2 days	0	–

[a] In all cases, 1,1-bis(phenylsulfonyl)ethene (**2**; 1.0 equiv) was added to **1h** (1.5 equiv) and the catalyst (0.1 equiv) in toluene at the specified temperature. [b] Determined after isolation by column chromatography. [c] Determined by chiral HPLC analysis.

Table 7. Addition of oxazolone **1l**, derived from leucine, to vinylsulfone **2**.[a]



Entry	R	Product	Catalyst	T [°C]	t [h]	Yield [%][b]	e.r.[c]
1		**3l**	(*S*,*S*)-**I**	RT	14	77	92:8
2		**3l**	**II**	RT	14	75	7:93
3		**3l**	**II**	4	14	35	25:75
4[d]		**3l**	**II**	4	14	67	30:70

[a] In all cases, 1,1-bis(phenylsulfonyl)ethene (**2**; 1.0 equiv) was added to **1l** (1.5 equiv) and the catalyst (0.1 equiv) in toluene at the specified temperature. [b] Determined after isolation by column chromatography. [c] Determined by chiral HPLC analysis. [d] CH_2Cl_2 was used as the solvent.

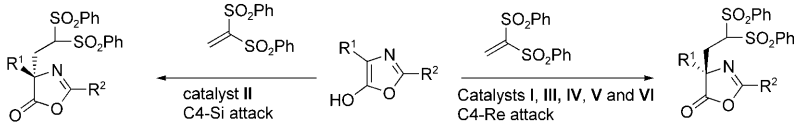
(Table 7, entry 2). However, at lower temperatures, the reaction became sluggish and afforded the addition product in low yield and, surprisingly, with poor enantioselectivity (Table 7, entries 3 and 4).

In summary, with the appropriate choice of C2 substituent, catalyst, and reaction temperature, the addition of oxazolones **1** to 1,1-bis(phenylsulfonyl)ethene (**2**) can take place with good to excellent yields and good enantioselectivities. The best catalysts are, in general, the Takemoto thiourea **I** (both enantiomers of which are commercially available) and the quinidine thiourea derivative **II**, although Sharpless ligand **IV** proved to be the catalyst of choice for the addition of oxazolone **1a**. The scope of the reaction is very broad and enantiomeric ratios higher than 90:10 can be achieved for several amino acid derived oxazolones. Only in the case of *tert*-leucine derived oxazolones was the enantiomeric ratio of the addition product not greater than 86:14; however, this result stands out as the only successful example of catalytic asymmetric α-alkylation of a *tert*-leucine derivative.

The obtained adducts could be easily derivatized into *N*-protected α-amino acids or *N*-protected α-amino esters. Moreover, the resulting adducts can also be derivatized by addition of different electrophiles to the disulfone moiety or even by reductive removal of the sulfone groups with Mg in MeOH to afford the naked alkyl chain.[23] In all cases, the final compounds were obtained in excellent yields, as illustrated in Scheme 3.

Comparison of the optical rotation of **6i** with that reported in the literature for the same compound, which gives (*R*)-(−)-isovaline upon hydrolysis of the amide,[28] allowed us to determine the absolute configuration as *R*. We conclude that the stereochemical outcome of the reaction, in accordance with the results shown in Table 2 and Tables 4–7, is that depicted in Scheme 4.

Based on this absolute configuration result, we decided to further investigate the possible mechanism of the reaction.



Scheme 4. Stereochemical outcome of the reaction

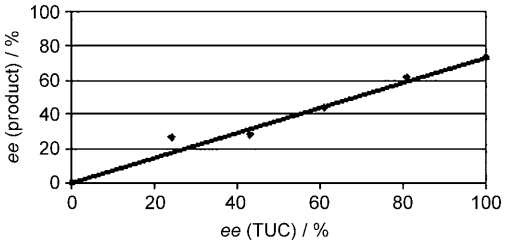
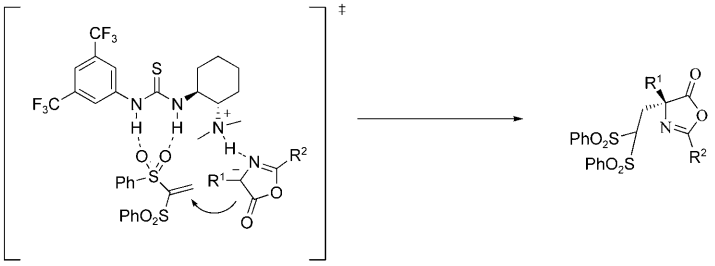


Figure 1. Representation of nonlinear effects on the reaction between **1a** and **2** catalyzed by thiourea **I**.



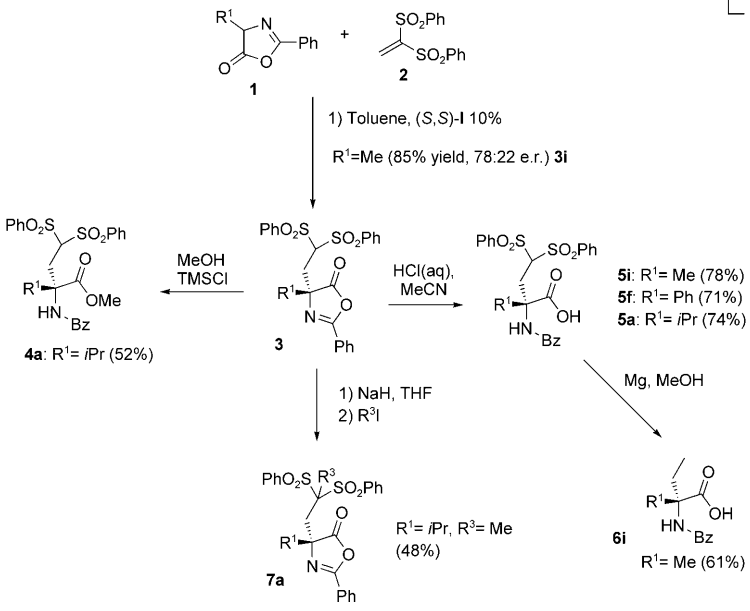
Scheme 5. Proposed transition state for the reaction.

In order to see whether only one molecule of the Takemoto catalyst or two were involved in the reaction, we performed the addition of oxazolone **1a** to vinylsulfone **2** in toluene at room temperature with the Takemoto thiourea catalyst in different enantiomeric purities. As illustrated in Figure 1, no nonlinear effects were observed, which suggests that only one molecule of the catalyst was involved in the transition state.[29]

With these data to hand, we tentatively propose a transition state in which the tertiary amine deprotonates the oxazolone while the thiourea moiety activates the vinylsulfone, as shown in Scheme 5.[30]

Conclusion

In conclusion, we have reported a new, easy, and highly enantioselective method for the synthesis of quaternary α-



Scheme 3. Derivatization of products **3**. Bz: benzoyl; THF: tetrahydrofuran; TMS: trimethylsilyl.

alkyl-α-amino acids based on organocatalysis. The addition of oxazolones to bis(phenylsulfonyl)ethylene (**2**) is efficiently catalyzed by chiral bases or thioureas with complete C4 regioselectivity[26] and with good yields and enantioselectivities. Moreover, this methodology is complementary to previously reported enantioselective approaches to quaternary α-amino acids and allows the synthesis of α-phenyl-α-alkyl-α-amino acids and of α-*tert*-butyl-α-alkyl-α-amino acids. Therefore, the procedure presented here has distinct advantages in terms of operational simplicity, enviromentally friendly conditions, and suitability for large-scale reactions for practical industrial preparations.[31]

Experimental Section

General procedure for oxazolone addition to 1,1-bis(phenylsulfonyl)ethylene (2): 1,1-Bis(phenylsulfonyl)ethylene (16 mg, 0.052 mmol, 1 equiv) was added in one portion to a flask containing a solution of the oxazol-5-one (0.078 mmol, 1.5 equiv) and the corresponding catalyst (0.0052 mmol, 0.1 equiv) at the desired temperature in toluene (0.5 mL). The reaction mixture was stirred overnight at this temperature. The crude residue was purified by column chromatography to afford compound **3**.

(4*S*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-4-isopropyl-2-phenyloxazol-5(4*H*)-one (3a): This was prepared according to the general procedure from 4-isopropyl-2-phenyl-oxazol-5(4*H*)-one (**1a**; 16 mg, 0.078 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **IV** at −40 °C: Colorless oil; yield: 22 mg (84 %); ^{1}H NMR (300 MHz, $CDCl_3$, tetramethylsilane as the internal standard (TMS_{int})): δ = 8.08–8.05 (m, 2H), 8.01–7.98 (m, 2H), 7.83–7.81 (m, 2H), 7.64–7.51 (m, 6H), 7.44–7.39 (m, 2H), 5.05 (dd, J = 8.2, J' = 2.6 Hz, 1H), 2.89 (dd, J = 16.4, J' = 2.3 Hz, 1H), 2.74 (dd, J = 16.1, J' = 7.9 Hz, 1H), 2.08 (h, J = 6.7 Hz, 1H), 0.98 (d, J = 6.7 Hz, 1H), 0.95 ppm (d, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.9, 162.0, 137.3, 136.9, 134.7, 134.6, 133.1, 130.0, 129.7, 129.1, 128.8, 128.2, 79.3, 72.3, 37.4, 30.9, 29.5, 16.4 ppm; HRMS (ESI): m/z calcd for $[M+H]^+$ ($C_{26}H_{26}NO_6S_2$): 512.1196; found: 512.1198; HPLC (Chiralpak IA, *n*-hexane/*i*PrOH = 80:20, λ = 254 nm, 1.0 mL min^{-1}): t_R = 9.5, 12.4 min; $[\alpha]_D^{25}$ = −11.2 (c = 0.77, $CHCl_3$, 93 % *ee*).

(4*S*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-2-(2,6-difluorophenyl)-4-isopropyloxazol-5(4*H*)-one (3b): This was prepared according to the general procedure from 4-isopropyl-2-(2,6-difluorophenyl)-oxazol-5(4*H*)-one (**1b**; 19 mg, 0.078 mmol,1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **I** at −20 °C: Colorless oil; yield: 28 mg (98 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 8.01–7.93 (m, 4H), 7.73–7.66 (m, 2H), 7.61–7.50 (m, 5H), 7.10–7.02 (m, 2H), 5.01 (dd, J^1 = 2.3, J^2 = 7.9 Hz, 1H), 2.95 (dd, J^1 = 2.5, J^2 = 16.4 Hz, 1H), 2.76 (dd, J^1 = 7.8, J^2 = 16.3 Hz, 1H), 2.15–2.03 (m, 1H), 0.97 ppm (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −107.6, −107.7 ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 162.5 (d, J = 5.4 Hz), 159.9 (d, J = 5.4 Hz), 155.5, 137.8, 136.1, 134.8, 134.6, 134.1, 134.0, 133.9, 130.6, 129.3, 129.2, 129.0, 112.3 (dd, J^1 = 3.1, J^2 = 21.9 Hz), 78.7, 72.3, 37.1, 28.9, 16.4, 16.1 ppm; HRMS (ESI): m/z calcd for $[2M+K]^+$ ($C_{52}H_{46}F_4N_2KO_{12}S_4$): 1133.1501; found: 1133.1503; HPLC (Chiralpak IA, hexane/*i*PrOH = 90:10, λ = 254 nm, 1 mL min^{-1}): t_R = 25.7 (major), 27.3 min; $[\alpha]_D^{25}$ = −12.7 (c = 0.9, $CHCl_3$, 92 % *ee*).

(4*S*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-2-(2,4-difluorophenyl)-4-isopropyloxazol-5(4*H*)-one (3c): This was prepared according to the general procedure from 4-isopropyl-2-(2,4-difluorophenyl)-oxazol-5(4*H*)-one (**1c**; 19 mg, 0.078 mmol,1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **I** at room temperature: Colorless oil; yield: 22 mg (78 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 7.99–7.89 (m, 5H), 7.74–7.48 (m, 6H), 7.06–6.96 (m, 2H), 5.05 (dd, J^1 = 2.6, J^2 = 7.9 Hz, 1H), 2.89 (dd, J^1 = 2.6, J^2 = 16.4 Hz, 1H), 2.73 (dd, J^1 = 7.9, J^2 = 16.4 Hz, 1H), 2.15–2.00 (m, 1H), 0.95 ppm (d, J = 6.7 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −100.9, −103.0 ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3, 166.9 (d, J = 11.9 Hz), 164.4 (d, J = 11.5 Hz), 163.6 (d, J = 12.3 Hz), 161.0 (d, J = 12.7 Hz), 157.9 (d, J = 6.5 Hz), 140.3, 137.5, 136.5, 134.7 (d, J = 9.2 Hz), 132.5 (dd, J^1 = 2.3, J^2 = 10.4 Hz), 130.2, 129.8, 129.5, 128.9, 128.5, 112.2 (dd, J^1 = 3.8, J^2 = 21.9 Hz), 105.6 (t, J = 25.1 Hz), 79.0, 72.3, 37.4, 29.2, 16.4, 16.2 ppm; HRMS (ESI): m/z calcd for $[2M+Na]^+$ ($C_{52}H_{46}F_4N_2NaO_{12}S_4$): 1117.1762; found: 1117.1756; HPLC (Chiralpak IA, hexane/IPA = 80:20, λ = 254 nm, 1 mL min^{-1}): t_R = 11.3, 13.6 min (major); $[\alpha]_D^{25}$ = −10.3 (c = 1.1, $CHCl_3$, 88 % *ee*).

(4*R*)-4-(2,2-Bisphenylsulfonyl)ethyl)-2-(2-fluorophenyl)-4-isopropyloxazol-5(4*H*)-one (3d): This was prepared according to the general procedure from 4-isopropyl-2-(2-fluorophenyl)-oxazol-5(4*H*)-one (**1d**; 17 mg, 0.078 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **I** at room temperature: Colorless oil; yield: 23 mg (82 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 7.99–7.88 (m, 5H), 7.69–7.55 (m, 5H), 7.51–7.46 (m, 2H), 7.31–7.28 (m, 2H), 7.25–7.22 (m, 2H), 5.08 (dd, J = 7.9, J' = 2.6 Hz, 1H), 2.90 (dd, J = 16.4, J' = 2,6 Hz, 1H), 2.76 (dd, J = 16.4, J' = 7.9 Hz, 1H), 2.09 (h, J = 6.7 Hz, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.95 ppm (d, J = 6.7 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −108.0 ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS_{int}): δ = 178.6, 161.4 (d, J = 261.5 Hz), 158.6 (d, J = 5.7 Hz), 136.1 (d, J = 90.1 Hz), 134.7 (d, J = 4.6 Hz), 134.5 (d, J = 8.8 Hz), 130.9, 130.2, 129.5, 129.2, 128.9, 124.5 (d, J = 3.8 Hz), 117.1 (d, J = 20.7 Hz), 78.9, 72.3, 37.4, 29.3, 16.4, 16.2 ppm; HRMS (ESI): m/z calcd for $[2M+Na]^+$ ($C_{52}H_{48}F_2N_2NaO_{12}S_4$): 1081.1950; found: 1081.1935; HPLC (Chiralpak IA, *n*-hexane/*i*PrOH = 90:10, λ = 254 nm, 1.0 mL min^{-1}): t_R = 11.6, 14.2 min; $[\alpha]_D^{25}$ = −9.6 (c = 0.86, $CHCl_3$, 92 % *ee*).

(4*S*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-2-(2-chlorophenyl)-4-isopropyloxazol-5(4*H*)-one (3e): This was prepared according to the general procedure from 4-isopropyl-2-(2-chlorophenyl)-oxazol-5(4*H*)-one (**1e**; 19 mg, 0.078 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **I** at room temperature: Colorless oil; yield: 26 mg (93 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 8.00–7.85 (m, 5H), 7.76–7.45 (m, 8H), 7.44–7.35 (m, 1H), 5.11 (dd, J^1 = 2.3, J^2 = 8.2 Hz, 1H), 2.92 (dd, J^1 = 2.3, J^2 = 16.4 Hz, 1H), 2.76 (dd, J^1 = 8.2, J^2 = 16.4 Hz, 1H), 2.15–2.02 (m, 1H), 0.97 (d, J = 6.7 Hz, 3H), 0.96 ppm (d, J = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 160.0, 140.3, 137.6, 136.5, 134.9, 134.7, 134.7, 133.9, 133.0, 131.7, 131.4, 130.3, 129.8, 129.4, 129.2, 128.9, 128.4, 127.0, 124.7, 79.1, 73.0, 37.5, 29.1, 16.4, 16.3 ppm; HRMS (ESI): m/z calcd for $[M+H]^+$ ($C_{26}H_{25}ClNO_6S_2$): 546.0806; found: 546.0795; HPLC (Chiralpak IA, hexane/*i*PrOH = 90:10, λ = 254 nm, 1 mL min^{-1}): t_R = 21.9, 25.4 min (major); $[\alpha]_D^{25}$ = −5.6 (c = 0.9, $CHCl_3$, 84 % *ee*).

(4*S*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-2,4-diphenyloxazol-5(4*H*)-one (3f): This was prepared according to the general procedure from 2,4-diphenyloxazol-5(4*H*)-one (**1f**; 19 mg, 0.078 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **I** at −40 °C: Colorless oil; yield: 20 mg (72 %); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, J = 7.3 Hz, 2H), 7.88–7.82 (m, 5H), 7.32–7.11 (m, 18H), 5.08 (dd, J = 6.4, J' = 4.1 Hz, 1H), 3.16–3.14 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3, 162.1, 138.8, 137.4, 137.1, 134.6, 133.3, 133.0, 129.9, 129.6, 129.2, 129.1, 129.1, 128.9, 128.9, 128.9, 128.8, 128.7, 128.3, 127.8, 125.3, 79.4, 70.5, 35.1 ppm; HRMS (ESI): m/z calcd for $[M+H]^+$ ($C_{29}H_{24}NO_6S_2$): 546.1040; found: 546.1037; HPLC (Chiralpak IA, *n*-hexane/*i*PrOH = 80:20, λ = 254 nm, 1.0 mL min^{-1}): t_R = 15.5, 18.7 min; $[\alpha]_D^{25}$ = −12.3 (c = 0.95, $CHCl_3$, 80 % *ee*).

(4*S*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-2-*tert*-butyl-4-phenyloxazol-5(4*H*)-one (3g): This was prepared according to the general procedure from 2-*tert*-butyl-4-phenyloxazol-5(4*H*)-one (**1g**; 17 mg, 0.078 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **II** at −40 °C: Colorless oil; yield: 22 mg (82 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 8.04–7.99 (m, 2H), 7.82–7.48 (m, 8H), 7.46–7.40 (m, 2H), 7.33–7.28 (m, 1H), 4.99–4.94 (m, 1H), 3.02–2.97 (m, 2H), 1.36 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3, 172.3, 138.4, 137.7, 136.9, 134.5, 130.3, 129.4, 129.4, 129.1, 129.0, 128.9, 128.7, 125.2, 79.2, 69.8, 34.4, 29.7, 26.8 ppm; HRMS (ESI): m/z calcd for $[2M+Na]^+$ ($C_{54}H_{54}N_2NaO_{12}S_4$): 1073.2452; found: 1073.245; HPLC (Chiralpak IA, hexane/IPA = 80:20, λ = 254 nm, 1 mL min^{-1}): t_R = 7.9, 9.7 min (major); $[\alpha]_D^{25}$ = +10.3 (c = 0.6, $CHCl_3$, 82 % *ee*).

(4*S*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-4-*tert*-butyl-2-phenyloxazol-5(4*H*)-one (3h): This was prepared according to the general procedure from 4-*tert*-butyl-2-phenyloxazol-5(4*H*)-one (**1h**; 17 mg, 0.078 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **I** at 4 °C: Colorless oil; yield: 18 mg (66 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 8.08–7.98 (m, 4H), 7.79–7.76 (m, 2H), 7.71–7.52 (m, 7H), 7.41–7.36 (m, 2H), 5.03 (d, J = 8.8 Hz, 1H), 2.99 (d, J = 16.4 Hz, 1H), 2.68–2.59 (m, 1H), 0.98 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS_{int}): δ = 178.7, 162.1, 137.3, 137.2, 134.7, 134.5, 133.1, 129.9, 129.7, 129.2, 128.9, 128.8, 128.2, 125.7, 79.6, 73.9, 40.2, 28.0, 23.9 ppm; HRMS (ESI): m/z calcd for $[2M+Na]^+$ ($C_{54}H_{54}N_2NaO_{12}S_4$): 1073.2452; found: 1073.2447; HPLC (Chiralpak IA, *n*-hexane/*i*PrOH = 90:10, λ = 254 nm, 1.0 mL min^{-1}): t_R = 7.8, 11.1 min; $[\alpha]_D^{25} = -5.2$ (c = 0.9, $CHCl_3$, 72 % *ee*).

(4*R*)-4-(2,2-bis(phenylsulfonyl)ethyl)-4-methyl-2-phenyloxazol-5(4*H*)-one (3i): This was prepared according to the general procedure from 4-methyl-2-phenyloxazol-5(4*H*)-one (**1i**; 15 mg, 0.078 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **IV** at −40 °C: Colorless oil; yield: 18 mg (68 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 8.05–7.96 (m, 4H), 7.88–7.85 (m, 2H), 7.74–7.69 (m, 1H), 7.64–7.56 (m, 4H), 7.52–7.42 (m, 4H), 5.04 (dd, J^1 = 6.0, J^2 = 4.2 Hz, 1H), 2.81–2.77 (m, 2H), 1.51 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS_{int}): δ = 179.4, 161.5, 137.5, 136.8, 134.7, 134.7, 133.2, 130.0, 129.8, 129.1, 129.0, 128.8, 128.1, 125.5, 78.9, 66.2, 32.2, 25.8 ppm; HRMS (ESI): m/z calcd for $[M+H]^+$ ($C_{24}H_{22}NO_6S_2$): 484.0885; found: 484.0885; HPLC (Chiralpack IA, hexane/*i*PrOH = 80:20, λ = 254 nm, 1 mL min^{-1}): t_R = 12.1, 15.0 min; $[\alpha]_D^{25} = -2.2$ (c = 0.9, $CHCl_3$, 66 % *ee*).

(4*R*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-2-(2,6-difluorophenyl)-4-methyloxazol-5(4*H*)-one (3k): This was prepared according to the general procedure from 4-methyl-2-(2,6-difluorophenyl)oxazol-5(4*H*)-one (**1j**; 17 mg, 0.078 mmol, 1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **I** at −40 °C: Colorless oil; yield: 26 mg (98 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 8.01–7.95 (m, 4H), 7.75–7.48 (m, 7H), 7.09–7.01 (m, 2H), 5.01 (dd, J^1 = 3.5, J^2 = 6.4 Hz, 1H), 2.86–2.80 (m, 2H), 1.55 ppm (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −107.2, −107.4 ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6, 162.5 (d, J = 5.0 Hz), 159.9 (d, J = 5.4 Hz), 155.2, 137.7, 136.3, 134.8, 134.7, 134.3, 134.2, 134.1, 130.4, 129.7, 129.5, 129.3, 129.2, 129.0, 112.4 (dd, J^1 = 3.4, J^2 = 21.5 Hz), 78.7, 65.9, 31.7, 25.9 ppm; HRMS (ESI): m/z calcd for $[2M+Na]^+$ ($C_{48}H_{38}F_4N_2NaO_{12}S_4$): 1061.1136; found: 1061.1130; HPLC (Chiralpak IC, hexane/*i*PrOH = 60:40, λ = 254 nm, 0.8 mL min^{-1}): t_R = 47.8, 52.6 min (major); $[\alpha]_D^{25} = -7.2$ (c = 0.9, $CHCl_3$, 86 % *ee*).

(4*S*)-4-(2,2-Bis(phenylsulfonyl)ethyl)-4-isobutyl-2-(2-fluorophenyl)oxazol-5(4*H*)-one (3l): This was prepared according to the general procedure from 4-isobutyl-2-(2-fluorophenyl)oxazol-5(4*H*)-one (**1k**; 18 mg, 0.078 mmol,1.5 equiv), 1,1-bis(phenylsulfonyl)ethylene (**2**; 16 mg, 0.052 mmol, 1 equiv), and catalyst **II** at room temperature: Colorless oil; yield: 21 mg (75 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 8.05–7.88 (m, 5H), 7.76–7.47 (m, 7H), 7.32–7.20 (m, 3H), 5.10–5.03 (m, 1H), 2.80–2.74 (m, 2H), 1.81 (dd, J^1 = 5.6, J^2 = 14.1 Hz, 1H), 1.70 (dd, J^1 = 6.4, J^2 = 14.1 Hz, 1H), 1.55–1.45 (m, 1H), 0.85 (d, J = 6.4 Hz, 3H), 0.83 ppm (d, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −107.9, −108.0 ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.3, 161.4 (d, J = 261.5 Hz), 158.0 (d, J = 6.1 Hz), 137.7, 136.8, 134.7, 134.7, 134.6, 130.9, 130.1, 129.8, 129.2, 129.0, 124.5 (d, J = 3.8 Hz), 117.1 (d, J = 21.1 Hz), 114.1 (d, J = 10.0 Hz), 78.7, 69.7, 47.2, 32.2, 24.6, 24.1, 23.4 ppm; HRMS (ESI): m/z calcd for $[M+H]^+$ ($C_{27}H_{27}FNO_6S_2$): 544.1258; found: 544.1248; HPLC (Chiralpak IA, hexane/*i*PrOH = 80:20, λ = 254 nm, 0.9 mL min^{-1}): t_R = 12.2, 13.1 min (major); $[\alpha]_D^{25} = +6.5$ (c = 1.05, $CHCl_3$, 83 % *ee*).

(4*S*)-Methyl 2-benzamido-2-isopropyl-4,4-bis(phenylsulfonyl)butanoate (4a): An ordinary vial equipped with a magnetic stirring bar was charged with MeOH (0.8 mL) and product **3a**. TMSCl (0.05 mL) was then added in one portion. Stirring was maintained at room temperature until consumption of the starting materials was complete. The solvent was then evaporated, and the product was purified by flash chromatography with mixtures of hexane and ethyl acetate as the eluent, to obtain compound **4a** in 52 % yield: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 7.91–7.80 (m, 6H), 7.68–7.55 (m, 2H), 7.55–7.40 (m, 7H), 5.25–5.19 (m, 1H), 3.82 (s, 3H), 3.10–2.90 (m, 3H), 1.28–1.24 (m, 1H), 1.07 (d, J = 7.0 Hz, 3H), 1.03 ppm (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 166.4, 137.9, 136.7, 134.7, 134.3, 133.4, 131.8, 129.7, 129.4, 129.0, 128.9, 127.0, 79.1, 63.9, 52.9, 32.7, 27.3, 18.4, 18.0 ppm; HRMS (ESI): m/z calcd for $[2M+Na]^+$ ($C_{54}H_{58}N_2NaO_{14}S_4$): 1109.2663; found: 1109.2656; $[\alpha]_D^{25} = +13.7$ (c = 1.4, $CHCl_3$, 73 % *ee*).

(4*R*)-4-(2,2-Bis(phenylsulfonyl)propyl)-4-isopropyl-2-phenyloxazol-5(4*H*)-one (7a): A suspension of sodium hydride (60 %) in mineral oil (6 mg, 1.1 equiv) was added to a round-bottomed flask under an argon atmosphere. Anhydrous THF and compound **3a** (75 mg, 1 equiv) were added at 0 °C. The temperature was raised to room temperature, and the reaction mixture was stirred for 1 h. The reaction mixture was cooled to 0 °C and methyl iodide (0.03 mL, 3 equiv) was added. The reaction mixture was stirred at room temperature overnight. The reaction was quenched by addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with dichloromethane, and the combined organic layers were cleaned with an aqueous solution of NaOH (1 M) and dried over $MgSO_4$. The solvent was evaporated. The crude residue was purified by flash chromatography with mixtures of hexane and ethyl acetate as the eluent, to obtain compound **7a** in 48 % yield: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ = 8.10–7.40 (m, 15H), 3.04 (d, J = 15.6 Hz, 1H), 2.74 (d, J = 15.6 Hz, 1H), 1.99 (h, J = 6.7 Hz, 1H), 1.85 (s, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.92 ppm (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 154.9, 134.8, 134.6, 132.8, 131.5, 131.2, 129.4, 129.2, 128.9, 128.9, 128.8, 128.7, 128.6, 128.1, 127.3, 87.8, 73.5, 39.2, 35.2, 19.3, 16.6, 16.2 ppm; HRMS (ESI): m/z calcd for $[2M+Na]^+$ ($C_{54}H_{54}N_2NaO_{12}S_4$): 1073.2452; found: 1073.2442; $[\alpha]_D^{25} = -7.2$ (c = 0.6, $CHCl_3$, 73 % *ee*).

(4*S*)-2-Benzamido-2-methyl-4,4-bis(phenylsulfonyl)butanoic acid (5i): An ordinary vial equipped with a magnetic stirring bar was charged with compound **3i** (400 mg, 1 equiv) and acetonitrile (5 mL). Concentrated HCl (0.34 mL, 5 equiv) was then added in one portion. Stirring was maintained at room temperature until consumption of the starting materials was complete. A solution of 1 N NaOH was added until the pH value reached 12. The aqueous layer was then washed three times with dichloromethane. Next, the pH value of the solution was adjusted to 1 with concentrated HCl. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The pure product was obtained without further purification (78 % yield): Colorless oil; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.99 (s, 1H), 7.83 (m, 5H), 7.47 (m, 10H), 5.34 (m, 1H), 2.96 (dd, J^1 = 16.4, J^2 = 3.5 Hz, 1H), 2.73 (dd, J^1 = 16.4, J^2 = 4.1 Hz, 1H), 1.17 ppm (s, 3H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 173.7, 166.5, 136.3, 134.1, 134.0, 130.7, 129.7, 129.1, 128.5, 128.3, 127.6, 127.1, 56.9, 28.8, 22.5 ppm; HRMS (ESI): m/z calcd for $[M+H]^+$ ($C_{24}H_{24}NO_7S_2$): 502.0989; found: 502.0993.

(4*R*)-2-Benzamido-2-phenyl-4,4-bis(phenylsulfonyl)butanoic acid (5f): This was prepared by a similar procedure to that described above: Colorless oil; ^{1}H NMR (300 MHz, [D$_6$]DMSO, TMS_{int}): δ = 7.96 (s, 1H), 7.75–7.20 (m, 20H), 5.25 (m, 1H), 2.92 ppm (m, 2H); ^{13}C NMR (75 MHz, [D$_6$]DMSO, TMS_{int}): δ = 177.3, 162.1, 138.8, 137.4, 137.1, 134.6, 133.3, 133.0, 129.9, 129.6, 129.2, 129.1, 129.1, 128.9, 128.9, 128.9, 128.8, 128.7, 128.3, 127.8, 125.3, 79.4, 70.5, 35.1 ppm; HRMS (ESI): m/z calcd for $[M+H]^+$ ($C_{29}H_{25}NNaO_7S_2$): 586.0965; found: 586.0972.

(4*R*)-2-Benzamido-2-isopropyl-4,4-bis(phenylsulfonyl)butanoic acid (5a): This was prepared by a similar procedure to that described above: ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ = 7.96 (s, 1H), 7.74 (m, 5H), 7.43 (m, 10H), 5.18 (m, 1H), 2.92 (m, 2H), 2.11 (m, 1H), 0.95 ppm (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS_{int}): δ = 173.5, 167.2, 137.4, 134.6, 133.05, 131.9, 129.6, 129.3, 128.9, 128.5, 127.0, 79.6, 64.0, 32.4, 18.0, 17.5 ppm; HRMS (ESI): m/z calcd for $[M+H]^+$ ($C_{26}H_{28}NO_7S_2$): 530.1302; found: 530.1300.

(4*R*)-2-Benzamido-2-methylbutanoic acid (6i): A Schlenk apparatus equipped with a magnetic stirring bar under a nitrogen atmosphere was charged with previously activated magnesium (188 mg, 30 equiv). A solution of product **5i** in MeOH (2 mL) was added, and stirring was maintained at room temperature until consumption of the starting material was complete. A solution of 1 N NaOH was added until the pH reached 12. The aqueous layer was then washed three times with dichlorome-

thane. Next, the pH value of the solution was adjusted to 1 with concentrated HCl. The aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The pure product was obtained without further purification (61% yield): Colorless oil; NMR: matched with literature data;[28] HRMS (ESI): *m/z* calcd for $[M+Na]^+$ ($C_{12}H_{15}NO_3Na$): 244.0944; found: 244.0948; $[\alpha]_D^{25} = -5.1$ ($c = 1.75$, MeOH, 55% *ee*).

Acknowledgements

We thank the Spanish Ministry of Science and Innovation (MICINN) for financial support (Project AYA2009-13920-C02-02). A.-N.R.A. is also grateful to the MICINN for a predoctoral fellowship.

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Received: November 2, 2009
Published online: March 5, 2010

