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Enantioselective Synthesis of γ-Tetrasubstituted Nitrosulfonyl Carboxylates and Amides *via* L-*tert*-Leucine-Derived-Squaramide Catalyzed Conjugate Addition of Nitrosulfones to Acrylates and Acrylamides

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Michael addition of α-nitrosulfones to aryl- and alkyl acrylates and acrylamides proceeds in the presence of 5-10 mol % of an amino acid derived new organocatalyst to provide γ-tetrasubstituted γ-nitro-γ-sulfonyl carboxylates and amides in excellent yields and enantioselectivities. Scale-up of the reaction to multi-grams, convenient recovery of the catalyst and its recyclability without any drop in yield and selectivity are attractive features of this methodology.

Introduction

Asymmetric organocatalysis has emerged in the last decade as a powerful platform for the synthesis of enantioenriched molecules.[1] Among various substrate activation strategies, H-bonding involving chiral alcohol,[2] amide,[3] urea,[4] thiourea,[3-4] and guanidine[5] have proven to be extremely effective. Recently, Rawal et al reported cinchonine[6] and cyclohexanediamine-derived[7] squaramides as superior H-bond donors paving the way for introduction of new squaramides derived from other chiral sources such as cinchona alkaloids[8] and various chiral 1,2-diamines[9] into the realm of H-bond assisted asymmetric organocatalysis.[10] However, besides a recent report on a Michael addition catalyzed by an amino acid-derived squaramide,[11] there has been no development, to our knowledge, in the possible application of relatively inexpensive and easily available amino acids as chiral source for the preparation of squaramide catalysts.

From the point of view of substrates and products, sulfones belong to a unique class of compounds with versatile reactivity as nucleophiles, electrophiles and as an activating/stabilizing group for functional group interconversion.[12] Organosulfones also possess a prominent pharmacological profile[13] among which chiral organosulfones received particular attention.[14-16] For instance, sulfones attached to a tetrasubstituted chiral center exhibit activities against Alzheimer's[14] and glaucoma.[16] Enantiopure β-alkyl-β-sulfonylhydroxamates are superior MMP (matrix metalloprotease) and PDE (phosphodiesterase) inhibitors as compared to their racemic counterparts.[17] The pivotal role of organosulfones in synthesis and biology prompted stereoselective synthesis of organic compounds with a key sulfone functionality.[18-28] Michael addition to vinyl sulfones,[18-19] nucleophilic addition of active methylene/methine sulfones,[20-22] hydrogenation/reduction,[23-24] allylation,[25-26] cyclopropanation[27] and [3+2] cycloaddition[28] of various sulfones are the methods of choice for the diastereo- and enantioselective synthesis of organosulfones. However, catalytic asymmetric synthesis of sulfones attached to a chiral center has received only limited attention.[22, 25-28] In particular, catalytic asymmetric approaches to sulfones attached to a tetrasubstituted chiral center are rare,[22,26-27] and there are only three reports for such approaches via Michael addition.[22]

In this context, we have recently reported the synthesis of enantioenriched α-nitro-δ-ketosulfones via a quinine-squaramide catalyzed conjugate addition of α-nitrosulfones to enones which were further transformed to γ-tetrasubstituted γ-sulfonylhydroxamic acid in two steps.[29] Herein we describe the first enantioselective synthesis of γ-tetrasubstituted γ-nitro-γ-sulfonyl carboxylates and amides via conjugate addition of α-nitrosulfones to acrylates and acrylamides in the presence of a new L-*tert*-leucine derived squaramide catalyst.

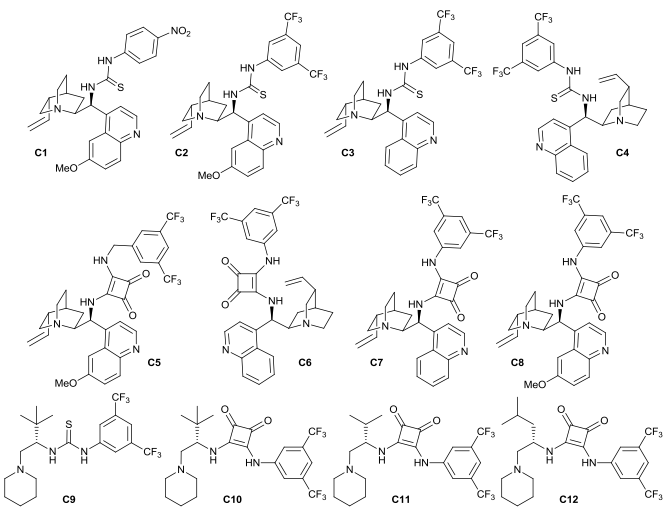
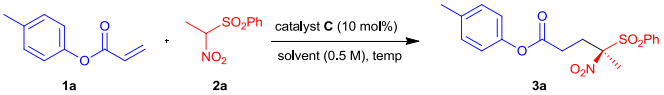


Fig. 1 Catalysts screened.

Results and discussion

In order to identify the suitable reaction conditions, we commenced our studies by evaluating the catalytic activity of cinchona alkaloid and amino acid derived bifunctional catalysts in the reaction between *p*-tolyl acrylate **1a** and (1-nitroethylsulfonyl)benzene **2a** in mesitylene at room temperature (Figure 1 and Table 1). At the outset, quinine-thiourea **C1**, recently reported from our laboratory,[31] was employed in the Michael addition, and gratifyingly, the Michael adduct, γ-nitro-γ-sulfonyl ester **3a** was obtained in excellent yield (96%) albeit with poor enantioselectivity (48% ee, entry 1). Although the use of other bifunctional catalysts such as quinine-thiourea **C2**, cinchonidine-thiourea **C3**, cinchonine-thiourea **C4** and quinine-squaramide **C5** provided Michael adduct **3a** in similar yields, the enantioselectivity remained low (entries 2-5). However, cinchonine-squaramide **C6**, cinchonidine-squaramide **C7** and quinine-squaramide **C8** provided Michael adduct **3a** with better selectivities (61-79% ee, entries 6-8) when compared to their thiourea derivatives (entries 1-4). At this juncture, further improvement in the selectivity was explored by employing amino acid-derived bifunctional catalysts. Thus, although there was no substantial improvement in the yield and the selectivity with L-*tert*-leucine-derived-thiourea **C9** (entry 9), the performance of the new squaramides **C10**-**12** derived from different L-amino acids appeared very promising. To our delight, the reaction of nitrosulfone **2a** with vinyl ester **1a** in mesitylene at room temperature took place in the presence of squaramide **C10** to afford the Michael adduct **3a** in excellent yield and enantioselectivity (97%, 93% ee, entry 10). However, other amino acid derived squaramides **C11** and **C12** did not improve the selectivity (entries 11 and 12). Further solvent screening confirmed that mesitylene was the best (entries 13-20) which furnished the Michael adduct **3a** in 97% yield and 93% ee (entry 10). Though lowering the reaction temperature to 0 °C caused marginal increase in the selectivity (93% ee to 94% ee), the rate of the reaction decreased drastically (12 to 48 h, entries 10 and 21). More importantly, a comparable result (98% yield and 92% ee) was still obtained even when the catalyst loading was reduced to 5 mol % at room temperature (entry 22).

Table 1 Catalyst screening and optimization of reaction conditions

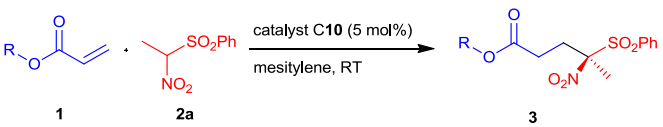


Entry	C[a]	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	*ee*[c] (%)
1	**C1**	mesitylene	rt	12	96	48
2	**C2**	mesitylene	rt	12	94	50
3	**C3**	mesitylene	rt	12	95	52
4	**C4**	mesitylene	rt	12	93	45[d]
5	**C5**	mesitylene	rt	12	98	39
6	**C6**	mesitylene	rt	12	95	61[d]
7	**C7**	mesitylene	rt	12	95	79
8	**C8**	mesitylene	rt	12	98	78
9	**C9**	mesitylene	rt	12	97	80
10	**C10**	mesitylene	rt	12	97	93
11	**C11**	mesitylene	rt	12	95	89
12	**C12**	mesitylene	rt	12	96	90
13	**C10**	toluene	rt	12	96	90
14	**C10**	xylene	rt	12	96	91
15	**C10**	$PhCF_3$	rt	12	95	84
16	**C10**	CH_2Cl_2	rt	16	86	82
17	**C10**	$CHCl_3$	rt	16	93	85
18	**C10**	$(CH_2)_2Cl_2$	rt	16	97	81
19	**C10**	THF	rt	16	91	83
20	**C10**	MeCN	rt	12	92	53
21	**C10**	mesitylene	0	48	98	94
22[e]	**C10**	**mesitylene**	**rt**	**16**	**98**	**92**

[a]Catalyst. [b]after silica gel column chromatography. [c]determined by chiral HPLC. [d]opposite enantiomer. [e]5 mol % catalyst.

Having optimized the reaction conditions (i.e. 5 mol % of catalyst **C10**, in mesitylene at room temperature), we explored the scope of the aforementioned method by treating a variety of substituted acrylates **1** with nitrosulfone **2a** and the results are summarized in Table 2. Thus, the reaction of nitrosulfone **2a** with a variety of *para*-substituted aryl acrylates such as **1a**, **1c** and **1g-i** showed that although the substitution doesn't have any appreciable influence on the yield (94-99%), the selectivities are higher for acrylates with electron donating substituents **1a** and **1c** (91-92% ee, entries 1 and 3) as opposed to those with electron withdrawing substituents **1g-i** (84-86% ee, entries 7-9). As for *ortho*-substituted aryl acrylates, the selectivities were higher for those with electron withdrawing substituents on the aromatic ring **1k** and **1l** (91-94% ee, entries 11-12) as compared to the one with electron donating substituent **1e** (84% ee, entry 5). Acrylates with multiple electron donating aryl groups **1b** and **1d** also gave the products **3b** and **3d**, respectively, in excellent yield and selectivity (97-99%, 90-91% ee, entries 2 and 4). While the yields and selectivities were high for 1-naphthyl acrylate **3n** and alkyl acrylates **3o-p** (91-99%, 93-95% ee, entries 14-16), slightly lower selectivities were encountered for phenyl- and 2-naphthyl acrylates **1f** and **1m**, respectively (89% and 86% ee, respectively, entries 6 and 13).

Table 2 Scope of acrylates **1**

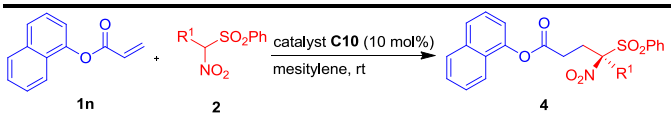


Entry	R	Time (h)	3	Yield[a] (%)	ee[b] (%)
1	4-MeC_6H_4	16	**3a**	98	92
2	3,5-$(Me)_2C_6H_3$	16	**3b**	97	91
3	4-$OMeC_6H_4$	16	**3c**	94	91
4	3,4-$(OCH_2O)C_6H_3$	24	**3d**	99	90
5	2-MeC_6H_4	16	**3e**	98	84
6	C_6H_5	16	**3f**	97	89
7	4-FC_6H_4	9	**3g**	97	86
8	4-ClC_6H_4	10	**3h**	96	85
9	4-BrC_6H_4	10	**3i**	99	84
10	3-$NO_2C_6H_4$	12	**3j**	86	92
11	2-ClC_6H_4	14	**3k**	94	94
12	2-BrC_6H_4	12	**3l**	94	91
13	2-naphthyl	16	**3m**	90	86
14	1-naphthyl	16	**3n**	94	93
15	Me	24	**3o**	91	94
16	Et	24	**3p**	99	95

[a]After silica gel column chromatography. [b]determined by chiral HPLC.

The high yields and enantioselectivities observed for α-nitrosulfones **3** derived from nitrosulfone **2a** and a variety of acrylates **1** (Table 2), prompted us to investigate the scope of the reaction further with other sterically and electronically different nitrosulfones **2b-g** (Table 3). Thus, a number of alkyl, allyl and benzyl substituted nitrosulfones **2b-g** were treated with a representative 1-naphthyl acrylate **1n** in the presence of 10 mol % of catalyst **C10**. Generally, the Michael adducts **4a-f** were obtained in excellent yields and high enantioselectivities (entries 1-5) except in the case of benzyl nitrosulfone **2g** where the selectivity dropped to 83% (entry 6).

Table 3 Scope of nitrosulfones **2**[a]



1n 2 4

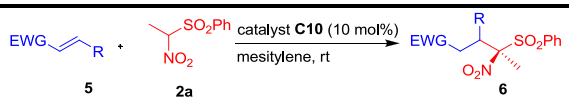
Entry	2, R^1	Time (h)	4	Yield[b] (%)	ee[c] (%)
1	**2b**, Et	20	**4a**	99	92
2	**2c**, allyl	16	**4b**	99	93
3	**2d**, *n*-Bu	36	**4c**	97	92
4	**2e**, *n*-C_5H_{11}	36	**4d**	95	92
5	**2f**, *n*-C_7H_{15}	36	**4e**	93	92
6	**2g**, benzyl	36	**4f**	98	83

[a]Due to slow reaction rate, 10 mol % catalyst was used. [b]after silica gel column chromatography. [c]determined by chiral HPLC.

The scope of our methodology was further extended to other electron deficient alkenes (Table 4). First of all, our recently reported quinine-squaramide **C8** catalyzed reaction of nitrosulfones **2** with vinyl ketones[29] was revisited using our new *tert*-leucine-derived squaramide **C10**. Accordingly, nitrosulfone **2a** was treated with vinyl ketone **5a** under our optimized conditions to afford α-nitro-δ-ketosulfone **6a** in excellent yield (98%) and enantioselectivity (96%) in short reaction time (1 h, entry 1) which were comparable to those reported with **C8** (99% yield, 96% ee).[29] This shows that while both catalysts are equally efficient for vinyl ketones, *tert*-leucine-derived squaramide **C10** is clearly superior for acrylate (see Table 1 and also *vide infra*).

Subsequently, other Michael acceptors such as crotonate **5b**, amides **5c-f**, sulfone **5g** and nitrile **5h** were screened. While a β-substituted acceptor such as **5b** remained unreactive even after 72 h (entry 2), we were pleased to note the formation of adduct **6c** from Weinreb amide **5c** in excellent yield (91%) and selectivity (92% ee) in 48 h (entry 3). Tertiary amide **5d** also reacted satisfactorily with nitrosulfone **2a** to afford adduct **6d** in moderate yield (53%) and excellent selectivity (96%, entry 4). However, secondary and primary amides, **5e** and **5f**, respectively, were not amenable for Michael addition of nitrosulfone **2a** under our experimental conditions (entries 5-6). Further scope of our methodology investigated with vinyl sulfone **5g** and acrylonitrile **5h** led to the formation of adducts **6g** and **6h** in in 91% and 51% yields, respectively, and in low, but measurable, enantioselectivities (10-14% ee, entries 7-8).

Table 4 Scope of electron deficient olefins **5**



5 2a 6

Entry	5, EWG, R	Time (h)	6	Yield[a] (%)	ee[b] (%)
1	**5a**, 4-MeC_6H_4CO, H	1	**6a**	98	96
2	**5b**, CO_2Me, Me	72	**6b**	-[c]	-[d]
3	**5c**, CONMe(OMe), H	48	**6c**	91	92
4[e]	**5d**, CONPh(Me), H	72	**6d**	53	96
5	**5e**, 4-$NO_2C_6H_4NHCO$, H	72	**6e**	-[c]	-[d]
6	**5f**, $CONH_2$, H	72	**6f**	-[c]	-[d]
7	**5g**, SO_2Ph, H	24	**6g**	91	10
8[e,f]	**5h**, CN, H	72	**6h**	51	14

[a]After silica gel column chromatography. [b]determined by chiral HPLC. [c]no reaction. [d]not determined. [e]~20% of **2a** was recovered. [f]due to slow reaction rate, 20 mol % catalyst was used.

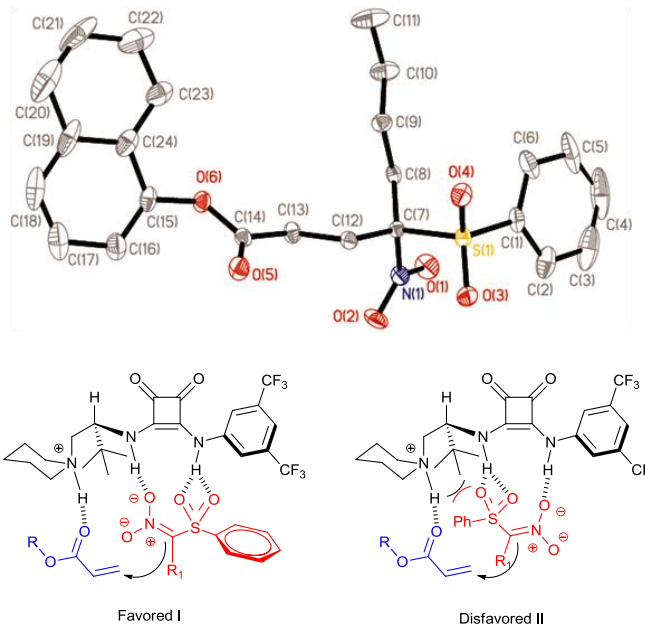
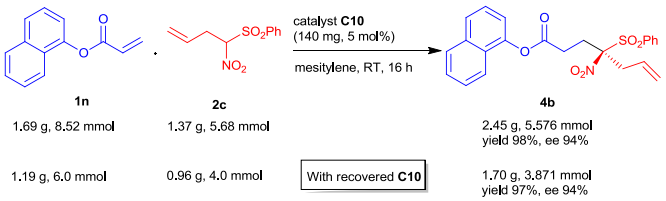


Fig. 2 X-ray structure of **4c** and proposed mechanistic model.

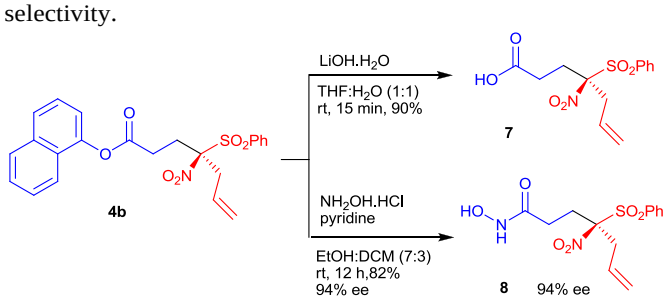
The absolute configuration of the Michael adduct **4c** was unambiguously assigned as *R* from its single crystal X-ray analysis (Figure 2) and that of other Michael adducts **3**, **4** and **6** was assigned by analogy. The proposed mechanism based on model studies involves deprotonation of nitrosulfone **2** by the piperidine moiety, stabilization of the nitronate by the squaramide moiety of catalyst **C10** and activation of ester **1** by the protonated piperidine moiety (Figure 2). This is consistent with a recent report by Pedrosa et al.[30] who suggested similar mechanism for addition of nitromethane to vinyl ketones through DFT calculations that amino acid derived thiourea catalyst stabilizes the nitronate nucleophile by hydrogen bonding while the protonated tertiary amine activates the carbonyl group. Although in both models **I** and **II**, the squaramide moiety co-ordinates with the nitro and the sulfone

groups, and the piperidinium moiety with the ester group, model **I** that enables nucleophilic addition of nitrosulfone anion from the *Re*-face to the acrylate ester **1** affording (*R*)-nitrosulfone **3**, **4** or **6** appears favored. This is because there are no severe steric interactions in this approach and there exists the possibility of a favorable π–π interaction between the phenyl group of sulfone **2** and the aryl group of catalyst **C10**. On the other hand, the alternative model **II** appears disfavored due to severe steric interactions between the phenyl group of the sulfone and the *tert*-butyl group of catalyst **C10** as well as due to the absence of the above mentioned π–π interaction. It may be noted that a mechanism in which activation of the ester carbonyl group by the squaramide moiety and stabilization of the nitronate by the protonated amine was not considered. This is due to poor Michael acceptor ability of acrylate and its activation by squaramide moiety did not appear sufficient for the reaction to proceed well and provide high selectivity. The reason for lower ee's observed with catalysts **C1**-**C8** (the best being 79% with **C7**, entry 7, Table 1) is attributable to insufficient activation of the ester carbonyl in the sterically crowded TS.



Scheme 1 Scale-up reaction.

A practical synthetic utility of our method was demonstrated by the synthesis of 2.45 g of γ-tetrasubstituted γ-nitro-γ-sulfonyl ester **4b** in 98% yield and 94% ee via Michael addition of 1.37 g of nitrosulfone **2c** to 1.69 g of 1-naphthyl acrylate **1n** in the presence of 5 mol % (140 mg) of catalyst **C10** (Scheme 1). Notably, in the reaction mixture, the catalyst **C10** existed in the form of a suspension and was completely precipitated out from the mixture on addition of petroleum ether and then was recovered (upto 80%, 112 mg) by filtration. Further use of the recovered catalyst **C10** in a gram scale reaction, gratifyingly, provided nitrosulfonyl ester **4b** in 97% yield (1.7 g) and 94% selectivity.



Scheme 2 Synthetic applications of nitrosulfone **4b**.

The synthetic applications of nitrosulfonylesters **3** and **4** were demonstrated by the transformation of a representative substrate **4b** to carboxylic acid **7** and hydroxamic acid **8** (Scheme 2). Thus, lithium hydroxide mediated hydrolysis of **4b** afforded quaternary γ-nitro-γ-sulfonyl carboxylic acid **7** in 90% yield. Similarly, hydroxamic acid **8** was synthesized in 82% yield by treating **4b** with hydroxylamine hydrochloride. In our previous work with vinyl ketones,[29] an additional step, Baeyer-Villiger oxidation of the Michael adducts, was necessary to obtain the same carboxylate derivatives.

Conclusions

Conjugate addition of α-nitrosulfones to aryl and alkyl acrylates as well as unsaturated amides in the presence of 5-10 mol % of an L-*tert*-leucine-derived squaramide organocatalyst afforded quaternary α-nitrosulfones in good to excellent yields and enantioselectivities. Similar additions to vinyl sulfone and acrylonitrile, though afforded the products in moderate to excellent yields, encountered poor selectivity. The feasibility of scale up of the enantioselective conjugate addition, recovery of the catalyst by simple filtration and subsequent use of the recovered catalyst in multi-gram scale reaction have been successfully demonstrated without any drop in yield and selectivity. Furthermore, the conjugate adduct was successfully converted into corresponding carboxylic and hydroxamic acid derivatives.

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Experimental

General Experimental Details. The melting points recorded are uncorrected. NMR spectra (^{1}H and ^{1}H decoupled ^{13}C) were recorded with TMS as the internal standard. The coupling constants (*J* values) are given in Hz. High resolution mass spectra were recorded under ESI Q-TOF conditions. Enantioselectivities were determined using a chiral HPLC equipped with a PDA-detector. Specific rotations were measured for solutions of samples of known concentrations in $CHCl_3$ using a polarimeter equipped with a sodium vapor lamp. X-ray data were collected on a diffractometer equipped with Mo Kα radiation. The structure was solved by direct methods shelxs97 and refined by full-matrix least squares against F^2 using shelxl97 software. General procedures and representative characterization data are given below. For complete characterization data, see the ESI.

General procedure for the synthesis of catalysts C10-12. To a solution of 3-methoxy-4-(arylamino)cyclobut-3-ene-1,2-dione (678 mg, 2.00 mmol) in dry DCM (10 ml) was slowly added a solution of diamine[32] (2.00 mmol) in dry DCM (10 ml) at rt. The reaction mixture was stirred for 4 h and the resulting precipitate was isolated by filtration. The residue was washed with ether (10 ml) and dried in vacuo to afford catalyst **C** as a white solid.

(*S*)-3-(3,5-Bis(trifluoromethyl)phenylamino)-4-(3,3-dimethyl-1-(piperidin-1-yl)butan-2-ylamino)cyclobut-3-ene-1,2-dione (C10). Colorless solid; Yield 736 mg, 75%; mp 257-259 °C; ν_{max}(film)/cm^{-1} 3205m, 3149m, 2942m, 1796m, 1662m, 1576vs, 1464s, 1376vs, 1275vs, 1196m, 1174m, 1127vs, 940w, 882w, 749w, 683w; δ_H(400 MHz; DMSO-d_6) 0.84 (9H, s), 1.15-1.42 (6H, m), 2.06-2.20 (2H, m), 2.25 (1H, t, *J* 11.8 Hz), 2.32-2.50 (3H, m), 3.92 (1H, t, *J* 8.6 Hz), 7.50-7.58 (2H, br unresolved), 7.99 (2H, s), 9.99 (1H, br s); δ_C(100 MHz; DMSO-d_6) 23.9, 25.7, 26.1, 33.8, 54.2, 58.9, 60.5, 114.6, 117.9, 123.2 (q, J_{C-F} 271.0 Hz), 131.4 (q, J_{C-F} 33.0 Hz), 141.2, 161.6, 170.7, 180.1, 184.6; HRMS (ES$^+$, Ar) calcd for

$C_{23}H_{27}F_6N_3O_2Na$ (MNa^+, 100), 514.1900, found 514.1890; $[\alpha]^{26}_D$ +49.47 (c 0.5 in DMSO).

General procedure for the addition of nitrosulfone 2 to acrylate 1 and other electron deficient alkenes 5. To a solution of nitrosulfone **2** (0.4 mmol) and catalyst **C10** (0.02 mmol, 9.9 mg) in mesitylene (0.8 ml) was added **1** or **5** (0.6 mmol) at rt. The reaction mixture was stirred at rt and monitored by TLC. The residue was purified by silica gel column chromatography using pet ether-EtOAc (18-40%) as eluent.

***(R)*-Naphthalen-1-yl 4-nitro-4-(phenylsulfonyl)octanoate (4c).** Colorless solid; Yield 176 mg, 97%; mp 108-109 °C; ν_{max}(film)/cm^{-1} 2961w, 2935w, 2873w, 1760s, 1646w, 1553s, 1509vw, 1448w, 1385w, 1331s, 1314m, 1259vw, 1225w, 1150vs, 1079w, 798m, 775m, 756m, 775s, 756s, 738s, 688m, 619w, 550w; δ_H(400 MHz; $CDCl_3$) 0.93 (3H, t, *J* 7.3 Hz), 1.16-1.27 (1H, m), 1.31-1.43 (2H, m), 1.54-1.65 (1H, m), 2.33 (2H, ABqdd, *J* 14.7, 11.6, 4.8 Hz), 2.72-2.85 (1H, m), 3.02-3.12 (2H, m), 3.25-3.39 (1H, m), 7.29 (1H, dd, *J* 7.8, 0.9 Hz), 7.48 (1H, t, *J* 7.8 Hz), 7.53 (1H, td, *J* 6.9, 1.9 Hz), 7.55 (1H, td, *J* 6.9, 2.0 Hz), 7.62 (2H, t, *J* 8.1 Hz), 7.77 (1H, tt overlap with dd, *J* 8.1, 1.1 Hz), 7.77 (1H, dd overlap with tt, *J* 7.8, 0.9 Hz) 7.84-7.91 (2H, m), 7.93 (2H, dd, *J* 8.1, 1.1 Hz), confirmed by ^{1}H-^{1}H-COSY spectrum; δ_C(100 MHz; $CDCl_3$) 13.8, 22.8, 25.8, 26.3, 29.3, 32.5, 109.0, 118.2, 121.2, 125.5, 126.4, 126.7, 126.8 (× 2), 128.3, 129.4, 131.2, 133.4, 134.8, 135.6, 146.5, 170.5; HRMS (ES^+, Ar) calcd for $C_{24}H_{25}NO_6SNa$ (MNa^+) 478.1295, found 478.1308; $[\alpha]^{25}_D$ +19.98 (c 1.0 in $CHCl_3$); HPLC: Lux Cellulose-1 (pet ether/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 250 nm), t_R (major) = 18.7 min, t_R (minor) = 16.6 min; 92% ee; Selected X-ray data: C_{24} H_{25} N O_6 S, M = 455.51, Orthorhombic, Space group *P*2(1)2(1)2(1), *a* = 10.600(4) Å, *b* = 12.434(5) Å, *c* = 16.898(6) Å, α = 90°, β = 90°, γ = 90°, *V* = 2227.2(15) Å^3, Z = 4, ρ_{cald} = 1.358 Mg/m^3, F(000) = 960, λ = 0.71073 Å, μ = 0.186 mm^{-1}, total/unique reflections = 17141/4049, Final R [I>2σ(I)]: *R*1 = 0.0381, *wR*2 = 0.0867, R (all data): *R*1 = 0.0419, *wR*2 = 0.0885 Absolute structure parameter 0.01(7).

(*S*)-4-Nitro-4-(phenylsulfonyl)hept-6-enoic acid (7). To a solution of **4b** (220 mg, 0.50 mmol) in THF (5.0 ml) and H_2O (5.0 ml) was added LiOH·H_2O (42 mg, 1.0 mmol) and the mixture was stirred at room temperature for 15 min. The mixture was acidified with 1 N HCl and extracted with Et_2O (3 × 15 ml). The combined extract was dried over anhydrous sodium sulfate. The organic layer was concentrated in vacuo and the residue was purified by silica gel column chromatography using EtOAc-pet ether (90%) as eluent to afford the acid **7.** Red oil; Yield 141 mg, 90%; ν_{max}(neat)/cm^{-1} 3069brs, 2987brs, 1716vs, 1582m, 1554vs, 1441s, 1334vs, 1315s, 1230vw, 1151vs, 1082m, 999w, 937m, 854w, 758w, 721w, 688w, 608m, 565w, 545w; δ_H(400 MHz; $CDCl_3$) 2.57-2.69 (2H, m), 2.77-2.96 (2H, m), 2.98-3.12 (2H, m), 5.27 (1H, dd, *J* 16.8, 1.2 Hz), 5.30 (1H, dd, *J* 10.1 1.2 Hz), 5.67 (1H, ddt, *J* 16.8, 10.1, 7.0 Hz), 7.62 (2H, t, *J* 7.9 Hz), 7.78 (1H, tt, *J* 7.9, 1.2 Hz), 7.88 (2H, dd, *J* 7.9, 1.2 Hz); δ_C(100 MHz; $CDCl_3$) 26.0, 28.5, 36.9, 107.8, 123.0, 128.2, 129.5, 131.2, 133.1, 135.7, 177.4; HRMS (ES^+, Ar) calcd for $C_{13}H_{15}NO_6SNa$ (MNa^+) 336.0512, found 336.0514; $[\alpha]^{25}_D$ +25.00 (c 1.0 in $CHCl_3$).

(*S*)-*N*-hydroxy-4-nitro-4-(phenylsulfonyl)hept-6-enamide (8). To a solution of **4b** (317 mg, 0.72 mmol) in EtOH-DCM (10.5:4.5, 15.0 ml) was added $HONH_2$·HCl (187 mg, 2.89 mmol) and pyridine (233 µl, 2.89 mmol) and the mixture was stirred at room temperature for 12 h. The mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography using EtOAc-pet ether (60:40) as eluent to afford pure amide **8**. Colorless sticky liquid; Yield 194 mg, 82%; ν_{max}(neat)/cm^{-1} 3235brvs, 1662vs, 1583m, 1554s, 1448m, 1332s, 1315s, 1268m, 1150vs, 1081m, 999m, 937m, 894w, 853m, 757m, 739m, 689m, 607m, 543m; δ_H(500 MHz; $CDCl_3$) 2.40-2.52 (1H, m), 2.61-2.74 (2H, m), 2.81-2.90 (1H, m), 2.97, 3.05 (2H, ABqd, *J* 15.0, 7.1 Hz), 5.22 (1H, d, *J* 15.1 Hz), 5.23 (1H, d, *J* 12.3 Hz), 5.60-5.70 (1H, m), 7.61 (2H, t, *J* 7.6 Hz), 7.76 (1H, t, *J* 7.6 Hz), 7.88 (2H, d, *J* 7.6 Hz); δ_C(125 MHz; $CDCl_3$) 26.7, 27.3, 36.8, 108.4, 123.1, 128.0, 129.5, 131.2, 133.1, 135.7, 169.8; HRMS (ES^+, Ar) calcd for $C_{13}H_{16}N_2O_6SNa$ (MNa^+) 351.0621, found 351.0626; $[\alpha]^{25}_D$ +26.19 (c 1.0 in $CHCl_3$); HPLC: Chiralpak IC (pet ether/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 216 nm), t_R (major) = 11.4 min, t_R (minor) = 13.5 min; 94% ee.

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