Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800548

Link to VoR: http://dx.doi.org/10.1002/adsc.201800548

10.1002/adsc.201800548

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Dual Role of Vinyl Sulfonamides as *N*-Nucleophiles and Michael Acceptors in the Enantioselective Synthesis of Bicyclic δ-Sultams

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Received: ((will be filled in by the editorial staff))

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Abstract. A new methodology for the synthesis of enantiomerically enriched bicyclic δ-sultams is described, involving an initial organocatalytic intramolecular aza-Michael reaction of vinyl sulfonamides bearing a conjugated ketone at a remote position. The resulting Michael adducts were then subjected to an intramolecular conjugate addition over the vinyl sulfone moiety, thus rendering the final bicyclic sultams containing two stereocenters. The key point of this strategy relies on the use of vinyl sulfonamides as both, nitrogen nucleophiles and Michael acceptors. The use of phosphazene-derived bases avoided the racemization of the intermediate derivatives, rendering 6-membered ring bicyclic δ-sultams in enantiomerically enriched manner with a small erosion of enantiopurity. Anyway, after recrystallization, final sultams were obtained in almost enantiomerically pure form. Nevertheless, the enantioselective synthesis of either 5-membered ring products or benzofused derivatives was found to be out of the scope of our strategy.

Keywords: vinyl sulfonamides; intramolecular Michael addition; bicyclic sultams; enantioselectivity; organocatalysis

Introduction

Since the discovery of the antibacterial activity of sulfonamides in 1932,[1] this functional group has become one of the most important pharmacophores in medicinal chemistry,[2] being a commonly found motif in drugs and agrochemicals. As mimics of the amide functionality, sulfonamides are used to replace amide groups in the design of novel peptidomimetics and small molecule inhibitors due to their better hydrolytic stability, low energy conformation and PK properties.[3] Among the pool of sulfonamides, sultams (cyclic sulfonamides) have emerged as privileged structures in drug discovery due to their diverse biological properties,[4] even though they do not occur in Nature. Several marketed drugs contain the sultam substructure such as the non-steroidal antiinflamatory agents Ampiroxicam[5] and Piroxicam,[6] the antiepileptic Sulthiame,[7] or the antidepressant Tianeptine,[8] among many others. This huge assortment of bioactivities explains the intense research activity that the synthesis of sultams has attracted in the last decades.[9] Furthermore, sultam scaffolds have been employed as chiral auxiliaries[10] and reagents to perform specific organic transformations.[11] Specifically, the applications of Oppolzer camphorsultam[12] have rapidly grown over the past few years and nowadays it is considered one of the most useful and suitable chiral auxiliaries for asymmetric synthesis.[13]

From a structural point of view, benzofused sultams are by far the most abundant ones, and a huge amount of these derivatives have been described.[14] However, fusion of the sultam scaffold with saturated carbo- or heterocycles is quite scarce in the literature.[15] Therefore, the development of convenient methods to prepare these types of sultams are highly desirable.

On the other hand, chiral sultams, beside their utility as chiral auxiliaries, have also found potent biological activities. For example, chiral sultams can be found in RORc inverse agonists as potential treatments of inflammatory diseases,[16] carbonic anhydrase inhibitors such as Brinzolamide for the treatment of glaucoma,[17] calpain I inhibitors

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implicated in neurodegenerative processes,[18] HIV-1 inhibitors,[19] or MMP-2 inhibitors mainly targeted for cancer[20] (Figure 1).

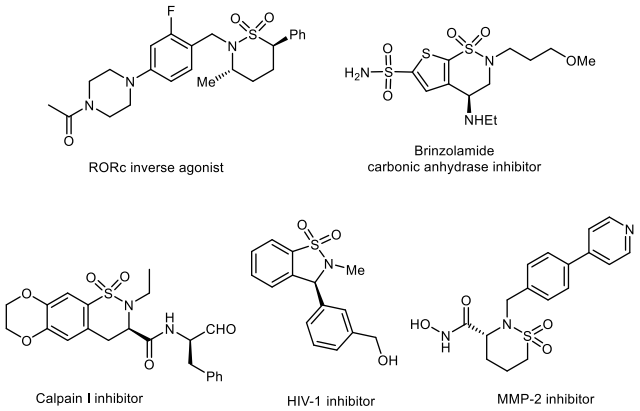
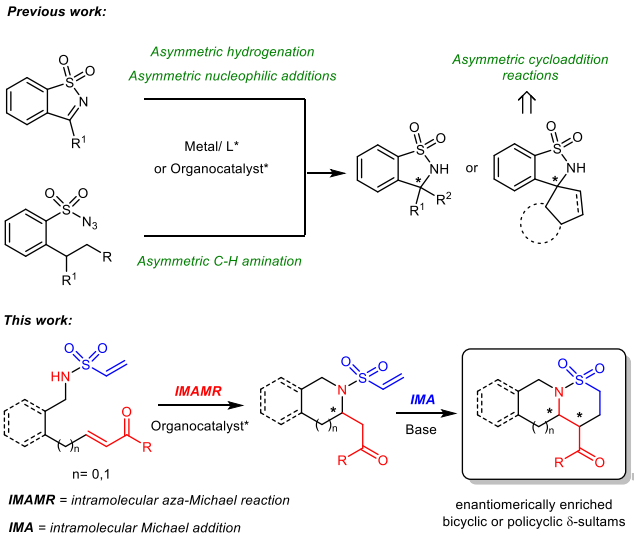


Figure 1. Biologically relevant chiral sultams.

In spite of the importance of chiral sultams in medicinal and synthetic chemistry, catalytic enantioselective procedures for the synthesis of optically active sultams are still limited and most of them allow for the construction of benzofused sultam derivatives. In this context, catalytic asymmetric nucleophilic additions to cyclic *N*-sulfonyl ketimines have been reported,[21] including transition metal-catalyzed asymmetric arylation, allylation,[22] alkenylation[23] or propargylation[24] reactions as well as organocatalyzed Mannich type processes.[25] Examples of metal-catalyzed asymmetric reductions[26] and organocatalytic asymmetric annulations of cyclic sulfonyl ketimines leading to chiral spirocyclic sultams have also been recently developed.[27] Another synthetic strategy towards chiral benzosultams involved an enantioselective intramolecular C-H bond amination reaction[28] (Scheme 1, *Previous work*). To the best of our knowledge, there are no examples to date concerning the enantioselective synthesis of non-benzofused chiral bicyclic sultams.[29] Therefore, in the present paper, a new methodology for the synthesis of enantiomerically enriched bicyclic δ-sultams is described, involving an initial organocatalytic intramolecular aza-Michael reaction (IMAMR) of vinyl sulfonamides bearing a conjugated ketone at a remote position. The resulting intermediates will be then subjected to an intramolecular conjugate addition over the vinyl sulfone moiety, thus rendering the desired δ-sultams containing two stereocenters (Scheme 1, *This work*). The key point of this strategy relies on the use of vinyl sulfonamides as both, *N*-nucleophiles in the IMAMR and Michael acceptors. Final products exemplify a very exclusive family of chiral sultams, given the position of the sulfonamide nitrogen at the ring juncture, not reported to date in an asymmetric manner.



Scheme 1. Enantioselective synthetic strategies towards chiral sultams.

Results and Discussion

Among the different cyclization protocols aimed at the construction of the sultam skeleton, intramolecular Michael-type processes have been scarcely investigated.[30] On account of our interest in the development of methodologies to perform the IMAMR in an asymmetric organocatalytic fashion,[31] we envisioned the possibility of employing conveniently functionalized vinyl sulfonamides to carry out an enantioselective synthesis of chiral nonracemic bicyclic sultams by means of an organocatalytic IMAMR as a key step. The starting materials required to carry out the projected strategy were assembled through a selective cross-metathesis (CM) reaction between vinyl sulfonamides **1**, previously synthesized according to literature procedures, and commercially available α,β-unsaturated ketones **2**.[32] Due to the presence of two different olefin moieties in compounds **1**, three possible scenarios should be considered, namely the desired CM reaction through the isolated olefin to yield compounds **3**, a CM reaction with the vinyl sulfonamide olefin, and a ring-closing metathesis (RCM) cyclization pathway (Scheme 2), although the last would be less favorable due to the slow formation rate of an 8-membered ring. According to the general model for predicting product selectivity in CM reactions proposed by Grubbs and co-workers in 2003,[33] in the presence of second generation ruthenium catalysts, we anticipated that a highly selective CM reaction would be feasible between the more reactive isolated olefin in compounds **1** (type I olefin, rapid homodimerization and very reactive homodimers) and conjugated ketones **2** (type II olefins, slower homodimerization rate than type I) just by employing an excess of the conjugated ketone in order to avoid the homodimerization of the type I

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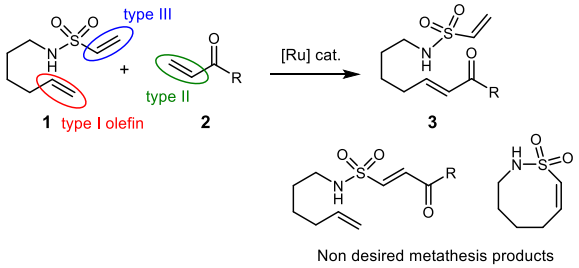
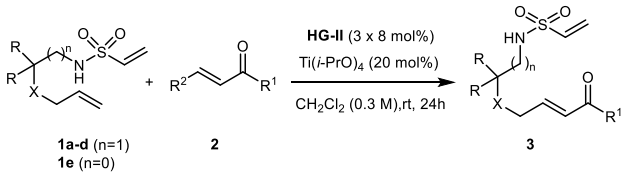
olefin counterpart. On the other hand, vinyl sulfonamide would be a type III olefin, poorly reactive in CM reactions and, therefore, unable to react with unsaturated ketones **2**.



Scheme 2. Classification of olefins and plausible metathesis reactions between substrates **1** and **2**.

Second generation Hoveyda-Grubbs catalyst [**HG-II**, Cl_2(IMes)Ru=CH(*o*-*i*PrOC_6H_4)] was chosen in order to optimize the desired transformation since it was described to facilitate cross-coupling reactions between olefins bearing electron-withdrawing groups and terminal olefins.[34] Thus, the optimal conditions to carry out the CM reaction between vinyl sulfonamides **1** and conjugated ketones **2** involved the addition of 24 mol% of catalyst **HG-II** in three portions, 5 equiv of the ketone and titanium (IV) isopropoxide (20 mol%) as a Lewis acid acid, which avoids the basicity of the sulfonamide nitrogen. Several vinyl sulfonamides **3** bearing a conjugated ketone at a remote position were obtained in moderate to good yields, as depicted in Table 1.

Table 1. Selective cross-metathesis reaction between vinyl sulfonamides **1** and conjugated ketones **2**.[a)]

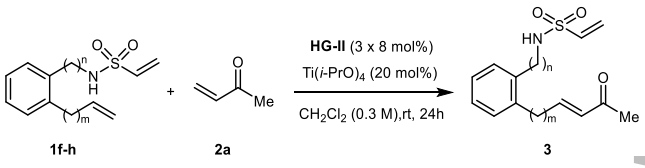


Ent.	**1**	n	R	X	**2**	R^1	R^2	**3** [%][b)]
1	**1a**	1	H	CH_2	**2a**	Me	H	**3a** [86]
2	**1a**	1	H	CH_2	**2b**	Pr	H	**3b** [81]
3	**1a**	1	H	CH_2	**2c**	Pent	H	**3c** [70]
4	**1a**	1	H	CH_2	**2d**	Ph	Me	**3d** [45]
5	**1b**	1	Me	CH_2	**2a**	Me	H	**3e** [93]
6	**1c**	1	Ph	CH_2	**2a**	Me	H	**3f** [88]
7	**1d**	1	H	O	**2a**	Me	H	**3g** [58]
8	**1e**	0	H	CH_2	**2a**	Me	H	**3h** [65]

[a)] Reactions were carried out with **1** (1 equiv) and **2** (5 equiv), catalyst **HG-II** (3 x 8 mol%) and Ti(*i*-PrO)$_4$ (20 mol%) in dichloromethane (0.3M) at room temperature for 24h.[b)] Yields of compounds **3** after purification by flash column chromatography.

In order to explore our planned strategy for the synthesis of benzofused derivatives, compounds **3i-k** were also synthesized through the CM reaction of conveniently functionalized vinyl sulfonamides **1f-h** (Table 2).

Table 2. Cross-metathesis reaction between benzofused vinyl sulfonamides **1** and methyl vinyl ketone **2a**.[a)]



Entry	**1**	n	m	**3** [%][b)]
1	**1f**	1	1	**3i** [55]
2	**1g**	2	0	**3j** [66]
3	**1h**	1	0	**3k** [60]

[a)] Reactions were carried out with **1** (1 equiv) and **2a** (5 equiv), catalyst **HG-II** (3 x 8 mol%) and Ti(*i*-PrO)$_4$ (20 mol%) in dichloromethane (0.3M) at room temperature for 24h.[b)] Yields of compounds **3** after purification by flash column chromatography.

With α,β-unsaturated ketones **3** in hand, the next step was the optimization of the organocatalytic IMAMR, taking as starting point the results previously obtained by our research group.[35] Therefore, the first attempt was performed on model compound **3a** employing 9-amino-9-deoxy-*epi*-hydroquinine (**HQ-NH$_2$**, 20 mol%) as the organocatalyst and trifluoroacetic acid (20 mol%) as a co-catalyst in chloroform at room temperature. As expected, the intramolecular conjugate addition took place in 15 hours, giving rise to piperidine **4a** in 57% yield with a good 92:8 enantiomeric ratio (Table 3, entry 1). When the reaction was carried out in THF or dichloromethane, slightly lower yield and asymmetric induction were observed (Table 3, entries 2, 3), whereas the use of a more polar solvent (CH_3CN) completely inhibited the desired transformation (Table 3, entry 4). Lowering the temperature to 0ºC led to enhanced er values (95:5 and 94:6 in $CHCl_3$ and THF, respectively) at the expense of yields (Table 3, entries 5, 6). We also tested the reaction under microwave heating at 60ºC, although both yield and enantioselectivity became negatively affected (Table 3, entry 7). Finally, the catalyst/co-catalyst loading was evaluated. Therefore, decreasing the amount of TFA from 20 to 10 mol% entailed a drastic drop in yield and enantiocontrol (Table 3, entry 8), while the use of a 1:2 ratio of catalyst/co-catalyst led to the best er value (97:3) with a good 76% yield of compound **4a** (Table 3, entry 9).

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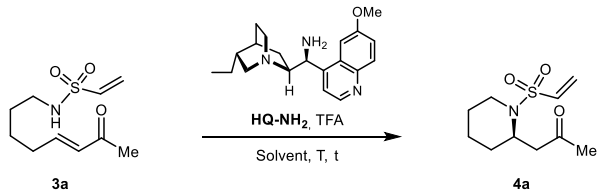
Table 3. Optimization of the organocatalytic IMAMR on α,β-unsaturated ketone **3a**.[a)]



Entry	**HQ-NH$_2$** (mol%)	TFA (mol%)	Solvent	T (°C)	t (h)	% Yield [b)]	er [c)]
1	20	20	$CHCl_3$	25	15	57	92:8
2	20	20	THF	25	15	47	88:12
3	20	20	DCM	25	15	58	90:10
4	20	20	CH_3CN	25	120	NR	---
5	20	20	$CHCl_3$	0	48	22	95:5
6	20	20	THF	0	48	50	94:6
7	20	20	$CHCl_3$	60 [d)]	2	55	87:13
8	20	10	$CHCl_3$	25	72	25	60:40
9	10	20	$CHCl_3$	25	24	76	97:3

NR= no reaction. [a)] Reactions were carried out with **3a** (0.1 mmol), catalyst **HQ-NH$_2$** and TFA as a co-catalyst in the specified solvent (1 mL), temperature and time. [b)] Yields of compound **4a** after purification by flash column chromatography. [c)] Enantiomeric ratios determined by HPLC analysis on a chiral stationary phase (see Supporting Information). [d)] Heating by means of microwave irradiation.

The optimal reaction conditions for the organocatalytic IMAMR (Table 3, entry 9) were then applied to the rest of α,β-unsaturated ketones **3**. In this manner, a small family of enantioenriched *N*-heterocycles was obtained in very good yields and excellent enantioselectivities as determined by chiral HPLC analysis (Figure 2). The assignment of the absolute configuration at the stereocenter generated in the IMAMR was made according to the mechanism commonly invoked to rationalize the conjugate additions of nitrogen nucleophiles to enones when chiral primary amines are employed as catalysts, previously described by our research group.[35] Furthermore, this stereochemical outcome was later confirmed by X-ray analysis of a crystalline sultam (see compound **5a** in Table 5)

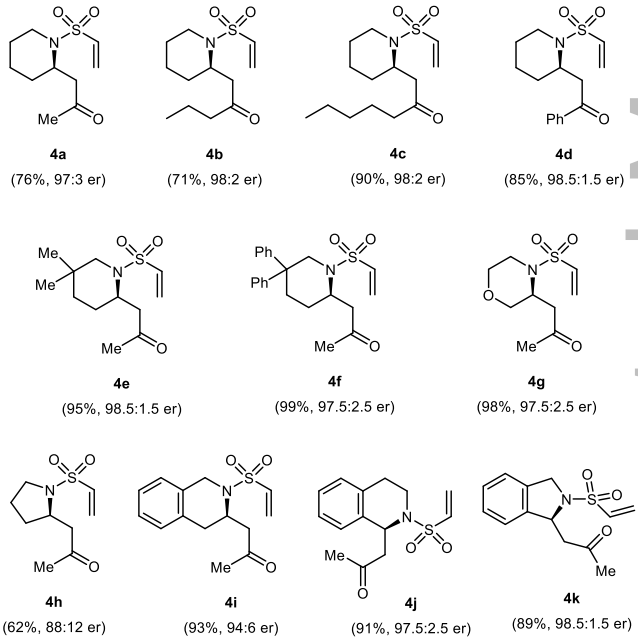


Figure 2. Scope of the organocatalytic IMAMR.

The next step in our study was the cyclization of compounds **4** by means of a diastereoselective intramolecular Michael addition (IMA) over the vinyl sulfone moiety. In this manner, the skeleton of the desired bicyclic or polycyclic δ-sultams would be assembled. Initially, the cyclization was performed under basic conditions with compound **4a** as the model substrate. The first attempt involved the use of NaH (1 equiv) in a 5:1 THF/ DMF mixture (0.03M) at

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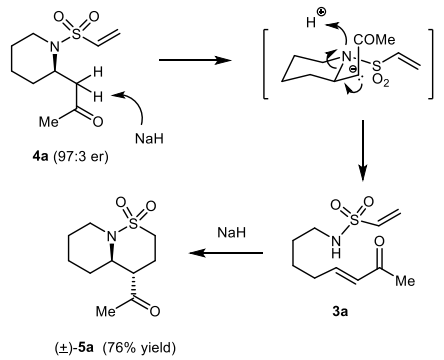
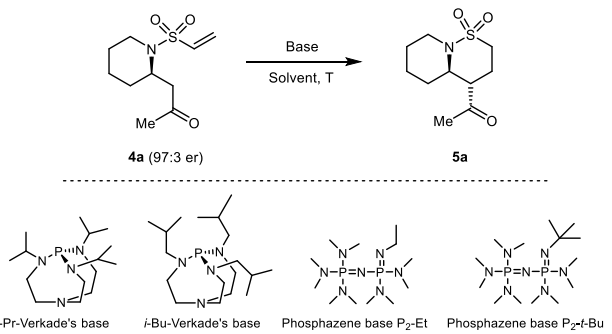
room temperature, since these conditions had been successfully employed in the racemic synthesis of our bicyclic and polycyclic sultams (see Supporting Information). Unfortunately, even though the reaction proceeded in good yield and complete diastereoselectivity, HPLC analysis showed a complete racemization of the final product **5a** (Table 4, entry 1). This disappointing result can be explained through a retro-aza-Michael reaction taking place in the presence of NaH, thereby destroying the stereochemical integrity of the stereocenter generated during the organocatalytic IMAMR step (Scheme 3).



Scheme 3. NaH-mediated retro-aza-Michael reaction. Racemic synthesis of sultam **5a**

In view of the above experiment, our next goal was to find suitable conditions in order to carry out the IMA avoiding the undesired retro-aza-Michael reaction. In this context, several bases were screened, with the results summarized in Table 4. Beside NaH, the use of *t*-BuOK afforded the desired bicyclic sultam in 80% yield as a single diastereoisomer, although again with complete racemization (Table 4, entry 2). Potassium hexamethyldisilazide led to a mixture of non-identified products (Table 4, entry 3), even at low temperature (−40ºC). Other bases such as TBAF or DBU did not promote the cyclization process and the starting piperidine **4a** was recovered (Table 4, entries 4, 5). We also tested chiral bases, namely *trans*-2,5-dimethylpiperazine and L-proline, without positive results (Table 4, entries 6, 7).[36] Fortunately, the chirality was slightly kept with the use of *i*-Pr-Verkade's base, which allowed us to isolate sultam **5a** in 93% yield as a 61:39 mixture of enantiomers (Table 4, entry 8). Lowering the temperature to −78ºC led to an enhanced er value (75:25) with an excellent 95% yield (Table 4, entry 9), whereas the *i*-Bu-Verkade's base completely inhibited the desired cyclization (Table 4, entry 10). Finally, phosphazene base P_2-Et, included in the superbases family,[37] came up with an acceptable rate of chirality and yield as bicyclic sultam **5a** was obtained in 77% yield and 93:7 er when the reaction was performed at −78ºC in the presence of 4Å MS (Table 4, entry 11). However, the bulkier phosphazene base P_2-*t*-Bu did not work under the same conditions (Table 4, entry 12).

Table 4. Optimization of the IMA on sulfonamide **4a**.[a)]



Ent.	Base	Solvent	% Yield [b)]	T (ºC)	er [c)]
1	NaH	THF/ DMF	76	25	--- [d)]
2	*t*-BuOK	THF	80	25	--- [d)]
3	KHMDS	THF	CM	25	---
4	TBAF	THF	NR	25	---
5	DBU	THF	NR	25	---
6	*trans*-2,5-DMP	DCM	CM	25	---
7	L-Pro	MeOH	NR	25	---
8	*i*-Pr-Verkade	THF	93	25	61:39
9	*i*-Pr-Verkade	THF	95	−78 to −40	75:25
10	*i*-Bu-Verkade	THF	NR	−78 to −40	---
11	P_2-Et	THF	77	−78 [e)]	93:7
12	P_2-*t*-Bu	THF	NR	−78 [e)]	---

NR= no reaction. CM= complex mixture. DMP= dimethylpiperazine. [a)] Reactions were carried out with **4a** (0.1 mmol), base (1 equiv) in the specified solvent (1 mL) and temperature for 4 hours.[b)] Yields of compound **5a** after purification by flash column chromatography. [c)] Enantiomeric ratios determined by HPLC analysis on a chiral stationary phase (see Supporting Information). [d)] Racemic product **5a** was obtained. [e)] Reactions performed in the presence of 4Å MS.

According to entry 11, the optimal conditions to perform the intramolecular Michael addition with the minimal erosion of enantiopurity were employed for the synthesis of different bicyclic δ-sultams **5**. In this manner, non-benzofused bicyclic sultams **5a-g** were obtained as single diastereoisomers, in yields ranging from 70 to 99% and high er values, as depicted in Table 5 (entries 1-7). Interestingly, a single recrystallization of these enantioenriched sultams **5a-g** from a mixture of *n*-hexanes: 2-propanol resulted in

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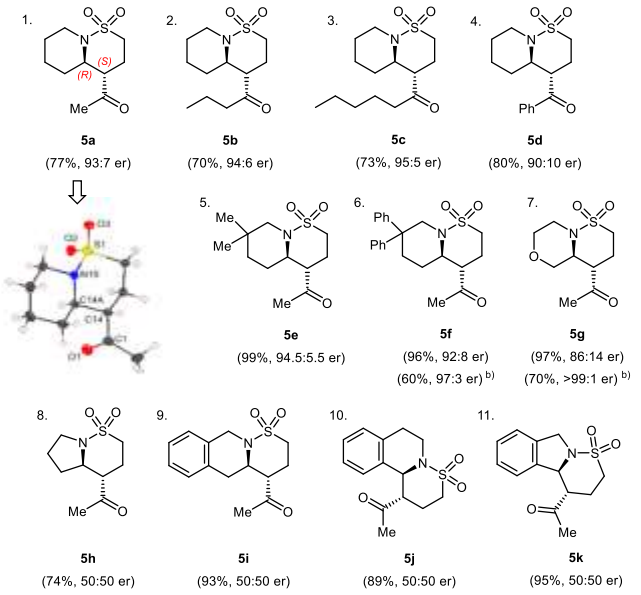
a significant enrichment in enantioselectivity, exemplified by compounds **5f** and **5g** (Table 5, entries 6, 7), which were finally obtained with excellent er values (97:3 and >99:1, respectively). Unfortunately, the P_2-Et mediated intramolecular Michael addition was found to be ineffective, in terms of enantioselectivity, for the synthesis of the pyrrolidine-fused δ-sultam **5h** (Table 5, entry 8) and the benzofused derivatives **5i-k** (Table 5, entries 9-11). Although these sultams were obtained in good yields, it seems that the retro-aza-Michael reaction is faster than the intramolecular Michael addition in these cases.

Table 5. Bicyclic and polycyclic δ-sultams **5** synthesized through the base-mediated IMA.[a)]



[a)] Reactions were carried out with **4** (1 equiv), phosphazene base P_2-Et (1 equiv) in THF (0.1M) at −78ºC with 4Å MS for 4h. [b)] Yields and enantiomeric ratios of sultams **5** after a single recrystallization from a mixture of *n*-hexane:2-propanol.

The absolute configuration of the final products was assigned by X-ray analysis. Crystals of sultam **5a** suitable for single crystal X-ray diffraction were grown from DCM/ Et_2O solution and its structure was unambiguously established (see structure in Table 5).[38] It revealed the *anti* relative configuration of the two sterocenters and confirmed the expected (*R*) configuration of the stereocenter generated in the IMAMR. Identical stereochemical outcomes were assumed for all other enantioenriched bicyclic sultams **5**.

Conclusion

In conclusion, a two-step protocol for the synthesis of chiral bicyclic δ-sultams has been developed. These products constitute interesting scaffolds in medicinal chemistry due to their diverse biological activities, and their enantioselective synthesis has almost been limited to benzofused derivatives. Our synthetic strategy entails a highly enantioselective intramolecular aza-Michael reaction (IMAMR), followed by a diastereoselective intramolecular Michael addition (IMA), taking advantage of the dual ability of vinyl sulfonamides to act as nucleophilic nitrogen sources and Michael acceptors. After careful optimization of the second conjugate addition reaction in order to avoid the epimerization of the stereocenter initially generated in the IMAMR, we were able to obtain non-benzofused bicylic δ-sultams in very good yields and excellent enantioselectivities after a single recrystallization process. However, our strategy did not work for the enantioselective synthesis of either a 5-membered-fused bicyclic δ-sultam or benzofused tricyclic sultams.

Experimental Section

General procedure for the CM reaction: synthesis of vinyl sulfonamides 3.

To a solution of vinyl sulfonamide **1** (1.0 equiv) in dry DCM (0.3M) under nitrogen atmosphere, the corresponding conjugated ketone **2** (3.0 equiv), titanium isopropoxide (20 mol%) and an initial 8 mol% loading of second generation Hoveyda-Grubbs catalyst were added. After stirring for 2-3 h at room temperature, two more portions of catalyst (2 x 8 mol%) were added as well as ketone (2.0 equiv). The resulting mixture was stirred for 20 h at room temperature and then concentrated to dryness and purified by means of flash column chromatography on silica gel using mixtures of *n*- hexane and ethyl acetate as eluents.

(*E*)-*N*-(7-oxo-5-octen-1-yl)ethenesulfonamide (3a): By means of the general procedure described above, compound **3a** (211 mg, 86% yield) was obtained as a brown oil starting from 200 mg (1.06 mmol) of **1a** after flash chromatography with 1:1 *n*-hexanes: ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50-1.63 (m, 4H), 2.21-2.28 (m, 5H), 2.99-3.06 (m, 2H), 4.58 (br s, 1H), 5.94 (d, *J* = 9.9 Hz, 1H), 6.07 (dt, *J* = 15.9, 1.4 Hz, 1H), 6.23 (d, *J* = 16.5 Hz, 1H), 6.50 (dd, *J* = 16.5, 9.8 Hz, 1H), 6.76 (dt, *J* = 15.9, 6.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 26.7, 29.1, 31.6, 42.5, 126.3, 131.3, 135.7, 147.6, 198.8. HRMS (ESI/Q-TOF) m/z: $[M^+ + H]$ calcd. for $C_{10}H_{17}NO_3S$ 232.1002; found: 232.1005.

General procedure for the intramolecular aza-Michael reaction. Synthesis of compounds 4.

In a 25 mL round bottomed flask, the corresponding vinyl sulfonamide **3** (1.0 equiv) was dissolved in chloroform (0.1 M). Catalyst **HQ-NH$_2$** (10 mol%) and trifluoroacetic acid (20 mol%) were added and the resulting solution was stirred at room temperature for 24 h. Then, the crude reaction mixture was subjected to flash column chromatography on silica gel using mixtures of *n*-hexane: ethyl acetate as eluents to afford the corresponding products **4**. The enantiomeric ratios were determined by means of HPLC analysis with an appropriate chiral column.

(*R*)-*N*-(1-vinylsulfonyl)-2-(2-oxopropyl) piperidine (4a): By means of the general procedure described above, 2-substituted piperidine **4a** (76 mg) was obtained as a colorless oil from **3a** in 76% yield and 97:3 er after flash chromatography with 2:1 *n*-hexanes: ethyl acetate. The er value was determined by HPLC analysis using a Chiralpack AD column (hexane: isopropanol 90:10); flow rate = 1.0 mL/min, t_{major}= 21.1 min, t_{minor}= 18.9 min. $[\alpha]_D^{25}$ +20.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46-1.70 (m, 6H), 2.19 (s, 3H), 2.81 (d, *J* = 7.2 Hz, 2H), 2.93-3.03 (m, 1H), 3.62 (d, *J* = 14.1 Hz, 1H), 4.39-4.45 (m, 1H), 5.89 (d, *J* = 9.6 Hz, 1H), 6.21 (d, *J* = 16.5 Hz, 1H), 6.43 (dd, *J* = 16.4, 9.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 25.3, 28.7, 30.4, 41.3, 44.7, 49.0, 126.2, 136.3, 206.1. HRMS (ESI/Q-TOF) *m/z*: $[M^+$+H] calcd. for $C_{10}H_{17}NO_3S$ 232.1002; found: 232.0996.

General procedure for the base-mediated intramolecular Michael addition. Synthesis of δ-sultams 5.

A microwave vial was filled with oven-dried 4Å MS and it was heated at 120ºC for 10 min under microwave irradiation. Then, a solution of the corresponding compound **4** (1.0 equiv) in THF (0.1M) was added into the vial. After immersing it into a −78ºC bath, phosphazene base P_2-Et (1.0 equiv) was added and the resulting mixture was stirred at that temperature for 4 hours. Then, the crude reaction mixture was hydrolyzed with 1M HCl, extracted with EtOAc and dried over anhydrous Na_2SO_4. Purification of the crude mixture by flash column chromatography on silica gel using mixtures of *n*-hexane: ethyl acetate as eluents afforded the corresponding bicyclic sultams **5**. The enantiomeric ratios were determined by means of HPLC analysis with an appropriate chiral column.

(4*S*,4a*R*)-4-(1-oxoethyl)octahydropyrido[1,2-*b*][1,2]thiazine 1,1-dioxide (5a): By means of the general procedure described above, bicyclic sultam **5a** (38.5 mg) was obtained as a white solid from **4a** in 77% yield and 93:7 er after flash chromatography with 1:1 *n*-hexanes: ethyl acetate. The er value was determined by RID-HPLC analysis using a Chiralcel OD-H column (hexane: isopropanol 85:15); flow rate = 1.0 mL/min, t_{major}= 26.0 min, t_{minor}= 24.2 min. $[\alpha]_D^{25}$ +1.9 (*c* 1.0, $CHCl_3$). Mp= 34-36ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36-1.77 (m, 6H), 2.13-2.20 (m, 4H), 2.28-2.42 (m, 1H), 2.82-2.91 (m, 1H), 2.97-3.17 (m, 3H), 3.29-3.37 (m, 1H), 3.75-3.82 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 24.5, 25.9, 20.4, 29.7, 41.9, 45.0, 49.8, 58.3, 208.0. HRMS (ESI/Q-TOF) *m/z*: $[M^+$+H] calcd. for $C_{10}H_{17}NO_3S$ 232.1002; found: 232.0996.

Acknowledgements

We gratefully thank the Spanish Ministerio de Economía y Competitividad (CTQ-2017-43310-P to C. P.). M. E. thanks the Spanish Ministerio de Educación, Cultura y Deporte for a predoctoral fellowship.

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10.1002/adsc.201800548

FULL PAPER

Dual Role of Vinyl Sulfonamides as *N*-Nucleophiles and Michael Acceptors in the Enantioselective Synthesis of Bicyclic δ-Sultams

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