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Enantioselective Synthesis of α-Amino-γ-sulfonyl Phosphonates with a Tetrasubstituted Chiral α-Carbon *via* Quinine-Squaramide-Catalyzed Michael Addition of Nitrophosphonates to Vinyl Sulfones

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Dedicated to Prof. A. M. Abdul Khader, Department of Chemistry, Mangalore University, on the occasion of his 60th birthday and superannuation from distinguished service.

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Abstract: α-Nitro-γ-sulfonyl phosphonates with a key tetrasubstituted chiral α-carbon center have been synthesized for the first time in high yield and enantioselectivity through a quinine-squaramide-catalyzed conjugate addition of α-nitro phosphonates to aryl vinyl sulfones. Representative examples presented here for the transformation of nitro-sulfonyl phosphonates to aminosulfonyl phosphonates, alkylation at the α-position of the sulfonyl group followed by desulfonation and scale-up of the conjugate addition highlight the practical applications of the methodology.

Keywords: amino phosphonates; amino sulfones; asymmetric catalysis; Michael addition; squaramides

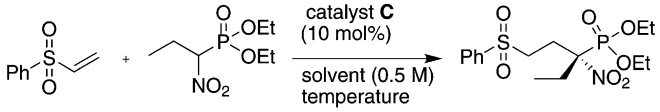
Amino phosphonates are regarded as transition state analogs of amino acids in various biological processes, for instance, in peptide bond hydrolysis.[1] The potential of amino phosphonates as synthetic intermediates and as biological agents has prompted considerable research in recent years.[2–4] α-Amino phosphonates, in particular, exhibit anti-bacterial and anti-fungal activity as well as catalytic activity in organic transformations.[5] A bioactive natural product K-26 possesses an α-amino phosphonate moiety.[6]

Introduction of reactive functional groups in the amino phosphonate chain in an asymmetric fashion appeared an attractive approach to generate novel enantioenriched amino phosphonates with enhanced or unexpected biological properties. A sulfonyl group is one such group due to its versatility as a synthetic handle and as a biological probe.[7] The role of sulfones in natural product synthesis and in functional group transformations, including those involving facile desulfonation, is well documented.[8] Various biological activities of organosulfones have also been extensively investigated.[9] For instance, the anti-prostate cancer drug Bicalutamide and the anti-leprosy drug Dapsone possess a sulfonyl group.

Although there are many reports on the catalytic asymmetric Michael addition of various nucleophiles to vinyl 1,1-bis-sulfones,[10,11] vinyl monosulfones have been seldom used in such capacity.[12–14] Only three nucleophiles, viz. α-aryl α-cyanoacetate,[12] 3-aryloxindoles[13] and α-branched aldehydes[14] have been successfully added to aryl vinyl sulfones under catalytic asymmetric conditions. Similarly, despite the fact that different approaches to enantioenriched α-amino phosphonates, which include resolution, auxiliary based and catalytic approaches, are documented in the literature,[15,16] asymmetric synthesis of α-amino phosphonates possessing a key γ-sulfonyl group remains unreported hitherto. We envisaged that this could be achieved via Michael addition of α-nitro phosphonates to vinyl sulfones in the presence of suitable chiral catalysts. This approach also generates tetrasubstituted chiral α-carbon centers in an enantioselective fashion.[17]

As part of our efforts to develop novel catalytic methods for the asymmetric synthesis of nitro/amino phosphonates,[17,18] we embarked on the idea of Michael addition of nitro phosphonate **2a** to vinyl sulfone **1a** (Table 1). Several *Cinchona*-based bifunctional organocatalysts were screened for our studies (Figure 1 and Table 1).[19] At the outset, quinine-thio-

Table 1. Catalyst screening and reaction condition optimization.



Entry	C[a]	Solvent	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**C1**	mesitylene	r.t.	12	91	87
2	**C2**	mesitylene	r.t.	12	92	83
3	**C3**	mesitylene	r.t.	15	91	85
4	**C4**	mesitylene	r.t.	15	87	88[d]
5	**C5**	mesitylene	r.t.	15	97	91
6	**C6**	mesitylene	r.t.	15	94	87
7	**C7**	mesitylene	r.t.	4	96	93
8	**C7**	toluene	r.t.	4	95	95
9	**C7**	benzene	r.t.	4	94	95
10	**C7**	xylene	r.t.	4	91	93
11	**C7**	CH_2Cl_2	r.t.	5	90	96
12	**C7**	$CHCl_3$	r.t.	5	94	96
13	**C7**	$(CH_2)_2Cl_2$	r.t.	5	95	96
14	**C7**	THF	r.t.	4	94	92
15	**C7**	MeCN	r.t.	5	91	90
16[e]	**C7**	$(CH_2)_2Cl_2$	r.t.	12	92	96
17[f]	**C7**	$(CH_2)_2Cl_2$	r.t.	48	94	96
18	**C7**	$(CH_2)_2Cl_2$	0	72	96	98

[a] Catalyst.
[b] After silica gel column chromatography.
[c] The *ee* values were determined by chiral HPLC.
[d] Opposite enantiomer.
[e] 5 mol% catalyst.
[f] 2 mol% catalyst.

urea **C1** and dihydroquinine-thiourea **C2**, recently reported from our laboratory,[17] were screened and, to our delight, the Michael adduct **3a**, with a tetrasubstituted chiral α-carbon center, α-nitro-γ-sulfonyl phosphonate, was isolated in good yield (91–92%) and enantioselectivity (83–87% *ee*, entries 1 and 2). Other catalysts such as cinchonidine-thiourea **C3**, cinchonine-thiourea **C4**, quinine-thiourea **C5** and dihydroquinine-thiourea **C6** were also quite effective (entries 3–6), but **C5** was the best giving the Michael adduct **3a** in 97% yield and 91% *ee* (entry 5). At this juncture, possible enhancement of enantioselectivity by modifying **C5** was explored. Thus, **C7** where the thiourea moiety in **C5** is replaced by a squaramide moiety with greater H-bonding capability,[20] not only decreased the reaction time from 12 h to 4 h at room temperature in mesitylene, but also improved the selectivity to 93% while maintaining excellent yield (96%, entry 7). Further solvent screening (entries 8–15) helped us identify ethylene dichloride as the best solvent (95% yield and 96% *ee*, entry 13). High yield (92–94%) and selectivity (96% *ee*) were maintained even with lower catalyst loading (2–5 mol%), albeit at the expense of reaction rate (entries 16 and 17). Finally, lowering the reaction temperature to 0 °C, though considerably decreased the reaction rate, allowed us to achieve the highest yield (96%) and selectivity (98% *ee*, entry 18).

Under the above optimized conditions, that is, in the presence of 10 mol% **C7**, in ethylene dichloride at 0 °C, phenyl vinyl sulfone **1a** was treated with a wide range of α-substituted nitro phosphonates **2a–m** (Table 2). It is noteworthy that the Michael adducts **3a–m** were isolated in excellent yields (85–99%) and selectivities (90–98% *ee*) over a period of 2–7 days. Although there was no major dependence of the yield and selectivity on the nature of α-substituent, the re-

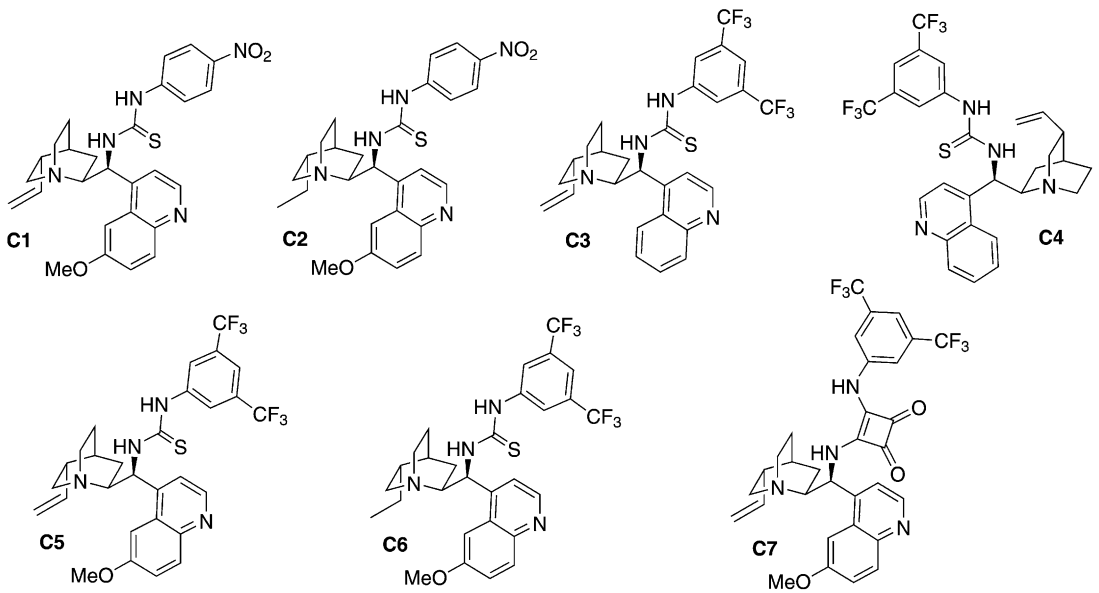
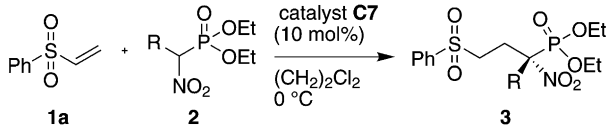


Figure 1. Bifunctional organocatalysts screened.

Table 2. Scope of nitrophosphonates **2**.

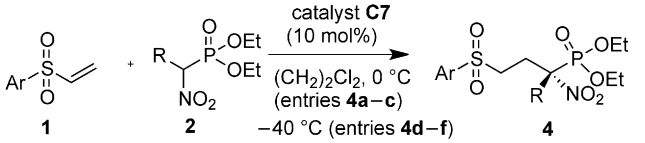


1a **2** **3**

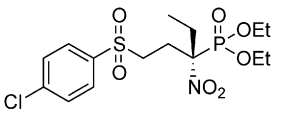
Entry	R	Time [d]	3	Yield [%][a]	*ee* [%][b]
1	Et	3	**3a**	96	98
2	Me	2	**3b**	93	97
3	*n*-Pr	5	**3c**	93	97
4	*n*Bu	6	**3d**	98	97
5[c]	*i*Bu	4	**3e**	90	90
6	*n*-C_5H_{11}	6	**3f**	99	98
7[c,d]	*c*-C_6H_{11}	7	**3g**	88	94
8[c,d]	*c*-C_3H_5	4	**3h**	85	94
9[c]	$PhCH_2$	7	**3i**	89	90
10	$PhCH_2CH_2$	7	**3j**	95	96
11	*n*-C_7H_{15}	5	**3k**	95	97
12	*n*-C_9H_{19}	5	**3l**	99	96
13	$(CH_2)_3CO_2Et$	7	**3m**	97	97

[a] After silica gel column chromatography.
[b] The *ee* values were determined by chiral HPLC.
[c] Reaction performed at room temperature.
[d] 20 mol% catalyst.

Table 3. Scope of vinyl sulfones **1**.[a–c]

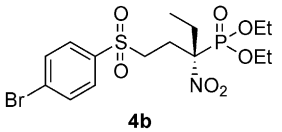


1 **2** **4**



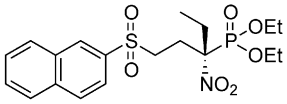
4a

36 h, 98% yield, 98% *ee*



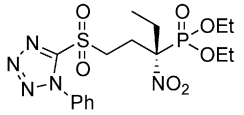
4b

36 h, 99% yield, 98% *ee*



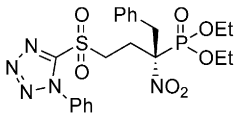
4c

60 h, 96% yield, 98% *ee*



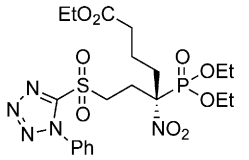
4d

40 h, 83% yield, 74% *ee*



4e

48 h, 98% yield, 74% *ee*



4f

48 h, 96% yield, 79% *ee*

[a] **1b**: Ar = 4-ClC_6H_4, **1c**: Ar = 4-BrC_6H_4, **1d**: Ar = phenyltetrazolyl.
[b] Yields after silica gel column chromatography.
[c] The *ee* value was determined by chiral HPLC.

action rate decreased with nitro phosphonates **2e** and **2g–i** bearing sterically demanding R groups (entries 5 and 7–9). Therefore, these reactions had to be conducted at room temperature. In the case of nitrophosphonates **2g** and **2h**, catalyst loading also had to be increased to 20 mol% to complete the reaction (entries 7 and 8).

Excellent yields and enantioselectivities observed in the synthesis of α-nitro-γ-sulfonylphosphonates **3** derived from phenyl vinyl sulfone **1a** and a variety nitro phosphonates **2** (Table 2) prompted us to extend the scope of this reaction to other vinyl sulfones **1b–e** (Table 3). Thus, the reaction of vinyl sulfone **1b** with nitro phosphophonate **2a** provided the desired Michael adduct **4a** in excellent yield (98%) and enantioselectivity (98% *ee*) in 36 h at 0 °C. To our delight, aryl vinyl sulfones **1b** and **1c** also reacted with nitrophosphonate **2a** to afford the Michael adducts **4b** and **4c** in similar yields and selectivity, but in longer reaction times (60 h) in the case of **1c**. The heteroaryl vinyl sulfone **1d** underwent Michael addition with nitrophosphonates **2a**, **2i** and **2m** even at −40 °C, due to the electron-withdrawing nature of tetrazole moiety, to afford the desired products **4d–f** in excellent yields, albeit in moderate selectivity (74–79% *ee*).

The absolute configuration of the Michael adducts **3** and **4** was unambiguously assigned as *S* by single crystal X-ray structure analysis of a representative compound **3c** (Figure 2, see also the Supporting Information). The proposed transition state involves activation of sulfone by the squaramide moiety and deprotonation of nitro phosphonate by the quinuclidine moiety of **C7** (Figure 2). *Si*-face addition of the nitro phosphonate anion to the activated vinyl sulfone affords nitro sulfone **3** or **4**.

Our reaction conditions are suitable for the enantioselective synthesis of nitro phosphonates **3–4** on a gram scale. This was demonstrated by the synthesis of 1.96 g of **3c** (96%) with 98% *ee via* Michael addition of 1.2 g of nitrophosphonate **2c** to 1.26 g of vinyl sulfone **1a** (Scheme 1).

Nitrosulfonyl phosphonate **3** or **4** is an excellent precursor for the enantioselective synthesis of aminosulfonyl phosphonate **5** which in turn is amenable for alkylation α to sulfonyl group and desulfonation with complete stereochemical integrity (Scheme 2). Thus, a representative nitrosulfonyl phosphonate **3c** was subjected to nitro group reduction using Zn-HCl to afford aminosulfonyl phosphonate **5** in 95% yield. *N*-Benzoylation of **5** using benzoyl chloride and Et_3N gave the amide **6** in 74% yield. Subsequent LDA mediated benzylation at the α position of sulfonyl group in **6** proceeded well to provide **7** in 75% yield. Desulfonation of **7** using Na-Hg in EtOH took place under mild conditions to deliver amidophosphonate **8** in excellent yield (81%).

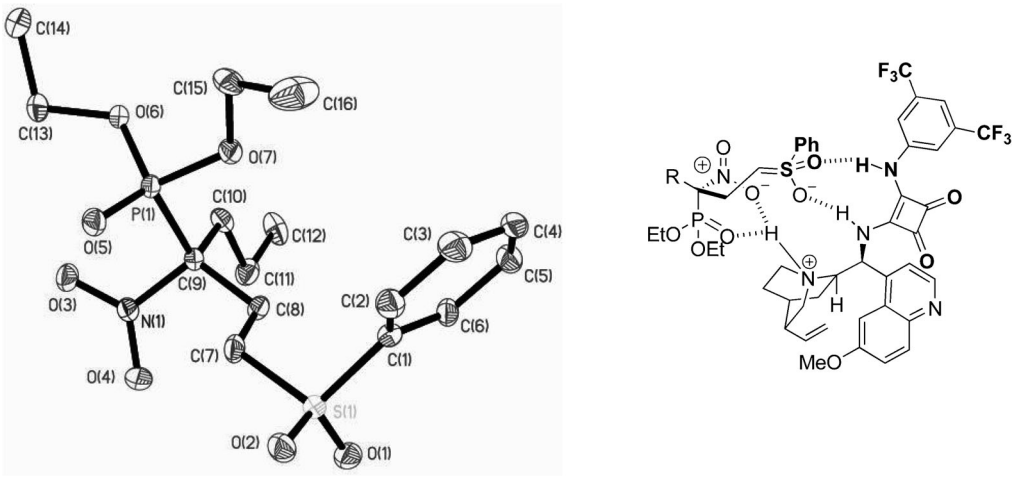
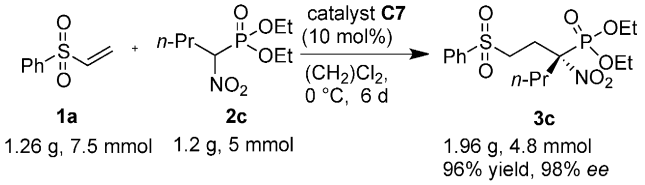
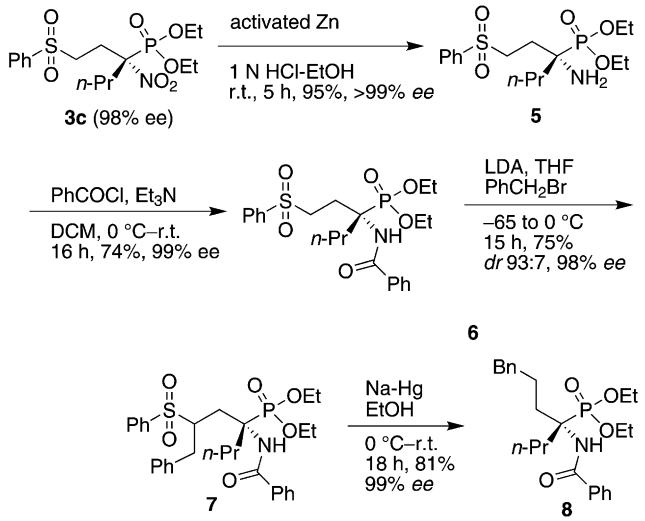


Figure 2. X-ray structure with absolute configuration of **3c** and proposed TS for the formation of **3**.



Scheme 1. Scale up of the synthesis of nitro phosphonate **3c**.



Scheme 2. Synthesis of tetrasubstituted chiral α-carbon α-amino-γ-sulfonyl phosphonate **5** and its further transformations.

In conclusion, conjugate addition of α-nitro phosphonates to aryl vinyl sulfones afforded α-nitro-γ-sulfonyl phosphonates in excellent yield (90–99%) and good to excellent enantioselectivity in the presence of a quinine-squaramide organocatalyst. The enantioselectivities were excellent (90–98%) when aryl was benzenoid and lower (74–79%) with a tetrazolyl group. Nitro group reduction and sulfonyl group assisted functionalization followed by desulfonation as well as scale up of the enantioselective conjugate addition have been successfully carried out.

Experimental Section

Michael Addition of Diethyl 1-Nitrobutylphosphonate 2c to Phenyl Vinyl Sulfone 1a

To a solution of diethyl 1-nitrobutylphosphonate **2c** (1.2 g, 5.0 mmol) and catalyst **C7** (315 mg, 0.5 mmol) in ethylene dichloride was added phenyl vinyl sulfone **1a** (1.26 g, 7.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 6 d. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using petroleum ether-EtOAc (15–55%) as eluent to afford (*S*)-diethyl 3-nitro-1-(phenylsulfonyl)hexan-3-yl-phosphonate **3c** as a colorless solid; yield: 1.96 g (4.8 mmol, 96%; 98% *ee*); mp 82–84 °C; IR (film): $\tilde{\nu}$ = 2971 (w), 2923 (m), 2851 (w), 1642 (w), 1549 (s), 1448 (w), 1305 (m), 1260 (m), 1148 (s), 1087 (m), 1045 (s), 1020 (s), 978 (m), 750 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.3 Hz, 3H), 1.13–1.27 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.33–1.43 (m, 1H), 1.93–2.04 (m, 1H), 2.19–2.30 (m, 1H), 2.33–2.44 (m, 1H), 2.59–2.73 (m, 1H), 3.40 (dd, J = 9.6, 7.2 Hz, 2H), 4.11–4.23 (m, 4H), 7.57 (t, J = 7.4 Hz, 2H), 7.65–7.70 (m, 1H), 7.91–7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 16.5 (d, J = 4.0 Hz), 16.9 (d, J = 7.0 Hz), 26.7, 37.9, 51.7 (d, J = 2.0 Hz), 64.4 (d, J = 7.0 Hz), 64.9 (d, J = 7.0 Hz), 92.1 (d, J = 149.0 Hz), 128.3, 129.6, 134.2, 138.8; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 14.9; MS (ES$^+$, Ar): m/z (%) = 409 ([MH + 1]$^+$, 22), 408 (MH$^+$, 100), 362 (40), 361 (47), 333 (45), 207 (14); HR-MS (ES$^+$, Ar): m/z = 408.1230, calcd. for $C_{16}H_{27}NO_7PS$ (M + H)$^+$: 408.1246; $[\alpha]_D^{25}$: 5.80° (c = 0.5 in $CHCl_3$); HPLC (Chiralpak IA; petroleum ether/*i*-PrOH = 80/20, flow rate 1 mL min^{-1}, λ = 216 nm): t_R (major) = 10.4 min, t_R (minor) = 9.1 min; 97% *ee*. X-ray data: $C_{16}H_{26}NO_7PS$, M = 407.41,

orthorhombic, space group $P2(1)2(1)2(1)$, $a=9.100(2)$ Å, $b=14.581(4)$ Å, $c=15.200(4)$ Å, $\alpha=90°$, $\beta=90°$, $\gamma=90°$, $V=2016.8(9)$ Å^3, $Z=4$, $\rho_{cald}=1.342$ Mg/m^3, F(000)=864, $\lambda=0.71073$ Å, $\mu=0.276$ mm^{-1}, total/unique reflections=12517/3628, Final R [$I>2\sigma(I)$]: $R1=0.0550$, $wR2=0.1265$, R (all data): $R1=0.0632$, $wR2=0.1331$, Absolute structure parameter 0.04(11). CCDC 921323 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

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