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Diastereoselective Synthesis of Chiral Oxathiazine 2-Oxide Scaffolds as Sulfinyl Transfer Agents

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Abstract: An efficient diastereoselective route for the preparation of chiral oxathiazine 2-oxide scaffolds as sulfinyl transfer agents, using *tert*-butanesulfinamide (*t*BSA) both as the source of chirality and as the precursor to the required nitrogen electron withdrawing group on the scaffold, was developed. This methodology allows the introduction of different substituents on the chiral scaffold, using commercially available reagents and standard synthetic transformations. The synthesized scaffolds were tested in the preparation of enantioenriched sulfinamides, providing results comparable to the sulfinyl transfer agents so far proposed in the literature, and opening the possibility to further elaborate these scaffolds, with the aim to support them on solid phases so to facilitate their recovery and reuse.

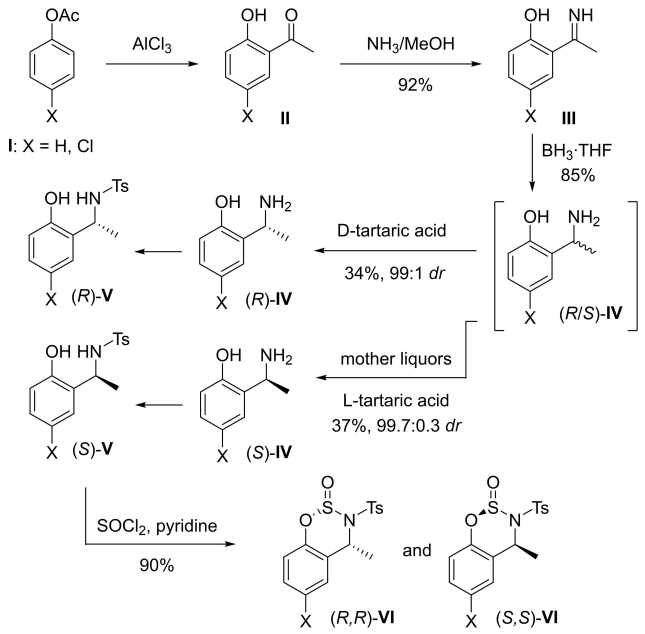
Keywords: *N*-Sulfinylimines; Oxathiazine 2-Oxides; Stereoselectivity; Sulfinamides; Sulfinyl Transfer Agents

Chiral sulfinamides are extensively used in asymmetric synthesis as efficient auxiliaries and ligands, particularly for the preparation of biologically active compounds containing chiral amine functionalities or *N*-heterocyclic frameworks.[1]

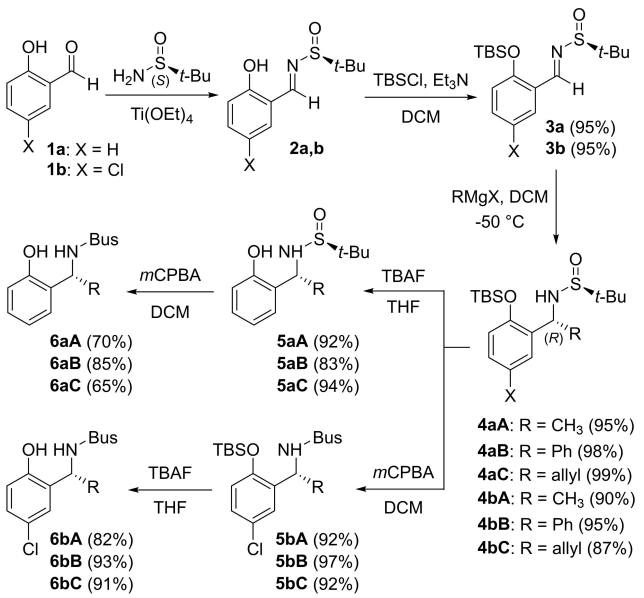
The two most commonly used chiral sulfinamide derivatives are *p*-toluensulfinamide (*p*TSA), first prepared in enantiomerically pure form by Davis in the mid-90s[2] starting from Andersen's reagent,[3] and *tert*-butanesulfinamide (*t*BSA), proposed by Ellman in the late 90s and commonly prepared starting from di-*tert*-butyl disulfide.[4] *p*TSA and *t*BSA are prepared in high optical purity with accessible methods and accordingly they are commercially available at affordable prices in both enantiomeric forms. Still, chiral sulfinamides with different substituents are much less commonly employed, due to their larger cost and to the lack of a general methodology available for their preparation.[5]

Inspired by the seminal work of Wudl on the enantioselective synthesis of chiral sulfoxides,[6] Senanayake developed in early 2000s *N*-activated 1,2,3-oxathiazolidine 2-oxide scaffolds deriving from (1*R*,2*S*)-1-*N*-tosyl-aminoindanol[7] and from *N*-tosyl-norephedrine[8] for the stereoselective synthesis of chiral sulfinyl compounds and sulfoxides, respectively. More recently, Han and Senanayake proposed a more efficient oxathiozinone sulfinyl-transfer agent (**VI**, Scheme 1) for the stereoselective synthesis of *t*BSA and of the bulkier triisopropylphenylsulfinamide (TIPPSA).[9] This practical and efficient methodology was later applied by the same authors to the stereoselective kilogram-scale preparation of *t*BSA.[10]

The precursor (**V**) to the chiral oxathiozinone scaffold (**VI**) was prepared starting from an acetylated phenol (**I**) by Fries' rearrangement to give the ketone **II**, followed by a reductive amination with ammonia and borane to give the racemic amine **IV**, that is resolved using tartaric acid affording both enantiomers in high optical yield. The precursor to the desired oxathiozinone scaffold was finally obtained by tosylation of the amine functionality (Scheme 1). Despite the remarkable results obtained, this synthetic approach presents some limitations. First, the Fries rearrange-



Scheme 1. Senanayake and Han synthesis of chiral precursors to the oxathiozinone scaffolds.



Scheme 2. Diastereoselective synthesis of chiral precursors **6** to the oxathiozinone scaffolds.

ment requires a more than stoichiometric amount of corrosive $AlCl_3$ and quite harsh conditions, limiting the possibility of functionalization of the acyl component. Second, if only one enantiomer of the chiral scaffold is required for a determined synthetic transformation, a resolution methodology may not be the most advantageous technique.

Here we propose a new, practical and efficient diastereoselective synthesis of chiral oxathiazine 2-oxide scaffolds, with the aim to i) obtain in good yield only the desired enantiomer, ii) introduce different substituents on the sidechain and to study their effect on the stereoselectivity of the sulfinyl transfer reaction, and iii) evaluate the feasibility of the preparation of more complex functionalized scaffolds for supporting them on solid phases or by tagging them with different groups, to facilitate their recovery and reuse. Our general strategy for the synthesis of the chiral precursors **6** starting from commercially available aromatic aldehydes **1a** and **1b** is depicted in Scheme 2.

Sulfinyl imines **2a** and **2b** were prepared in high yields according to reported literature procedures.[11] After protection of the phenol group with *t*butyldimethylsilyl chloride, imines **3a** and **3b** were subjected to a simple Grignard reaction, allowing the insertion of different substituents on the sidechain in fair to very high yields and the creation of a new stereocenter with an almost complete diastereoselectivity (Table 1). It is noteworthy that, to the best of our knowledge, no study on the addition of Grignard reagents to salicylaldehyde derived imines had ever been reported.[12]

Table 1. Addition of Grignard reagents to imines **3**.

Entry	3	R	t [h]	Y [%][a]	d. r.[b]
1	**3a**	CH_3	3	95	>99:1
2	**3a**	Bn	24[c]	56	97:3
3	**3a**	*i*Pr	3	4[d]	–
4	**3a**	*i*Bu	3	–[d]	–
5	**3a**	*n*Bu	24[c]	50	>99:1
6	**3a**	*n*Bu	3	60	>99:1
7	**3a**	allyl	3	99	>99:1
8	**3a**	Ph	24[c]	98	>99:1
9	**3b**	CH_3	3	90	>99:1
10	**3b**	allyl	3	87	>99:1
11	**3b**	Ph	24[c]	95	>99:1

[a] Isolated yield after purification by column chromatography (1 mmol scale).
[b] Determined by 1H NMR on crude reaction mixtures.
[c] The temperature was allowed to reach 20 °C overnight.
[d] The reduced imine was isolated as the major product.

The Grignard addition was also tested on the unprotected imine **2a**, using 2 equivalents of MeMgI. In this case, the addition proceeded again in very high yield (>90%), but with a disappointing 60:40 diastereoselectivity. Finally, starting from (*S*)-*t*BSA, the (*R*) absolute configuration of the newly formed stereogenic center was tentatively assigned, in accordance with the results reported by Ellman in the addition of Grignard reagents to benzaldehyde aldimines.[14]

The required electron-withdrawing group on nitrogen was obtained from the same chiral auxiliary used

to induce the stereoselective formation of the new stereogenic center, by oxidation of the *tert*-butylsulfinyl group to *tert*-butylsulfonyl (Bus)[15] using *m*CPBA. For compounds **4a** (X = H), first the phenol was deprotected with TBAF giving the corresponding compounds **5a** in very good yields (83–94%), then the oxidation step was carried out, to afford the desired precursors **6a** in good yields (65–85%). On the other hand, for compounds **4b** (X = Cl) the order of these last two steps was inverted, the oxidation being done before the deprotection, affording again the desired intermediates **6b** with a generally higher overall yield (Scheme 2).

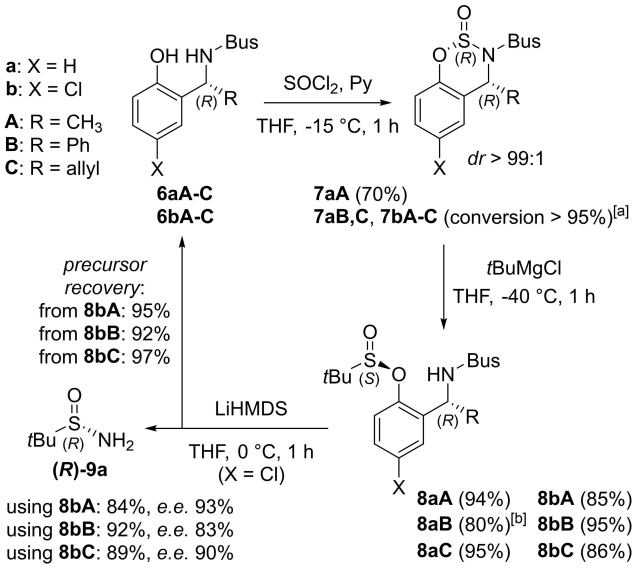
With the desired chiral precursors **6** in our hands, we studied their conversion into the corresponding oxathiazine 2-oxide scaffolds **7** and their efficiency as stereoselective sulfinyl transfer agents in the preparation of enantiomerically enriched *t*BSA, using the same protocols recently reported by Han and Senanayake (Scheme 3).[9,10] Scaffolds **7** were prepared by reaction with thionyl chloride and pyridine in THF at −15 °C, in good to high yields. Except for **7aA**, which can be isolated and purified by flash-chromatography on silica as a stable white solid, all other oxathiazine 2-oxides are unstable and easily hydrolyze back to the precursors **6** if prolonged reaction times are used, as well as during the work-up stage and during purification by flash-chromatography on silica. Thus, appropriate mild conditions must be used during the work-up (see Experimental Section) and **7** must be used as crudes in the subsequent ring-opening step. Fortunately, 1H NMR spectra showed crude reaction mixtures with high conversions and almost quantitative diastereoselectivities in all cases (*dr* > 99:1). Again, the relative stereochemistry of the major diastereoisomer of oxathiazine 2-oxides **7** was tentatively assigned in accordance with the work of Han and Senanayake.[10]

Ring-opening of oxathiazine 2-oxides was thus tested using *t*BuMgCl in THF at −40 °C and the results obtained are reported in Table 2.

We were very pleased to find that the ring-opening reaction proceeded smoothly in all cases examined, affording the desired sulfinate esters **8** in very good isolated yields. Moreover, except for **8aB** (entry 2), very high diastereoselectivities were obtained, especially when using precursors **7b** having the chlorine substituent on the aromatic ring (entries 4–6).

Surprisingly in the last step, namely the addition of LiHMDS to **8** to prepare enantioenriched *t*BSA (Table 3), only scaffolds **8b** gave good conversions to the desired product **9**, while all sulfinate esters **8a** were completely unreactive under the conditions tested, stressing the importance of the chlorine substituent of the aromatic ring in making the phenolic moiety a good enough leaving group. Sulfinate **8aB** was obtained as a hardly separable mixture of two diastereoisomers (Table 2, entry 2). Since it was not reactive in the subsequent ring opening with LiHMDS, no further attempt to separate the diastereoisomers was made.

Although the *N*-tosylated analogue to **7aA** was prepared by Senanayake, its ring-opening with



Scheme 3. Preparation of enantiomerically enriched *t*BSA. [a] The products were used in the following step without further purification. [b] Sulfinate **8aB** was obtained as a hardly separable mixture of diastereoisomers (85:15).

Table 2. Addition of *t*BuMgCl to scaffolds **7**.

Entry	7	R	8	Y [%][a]	d. r.[b]
1	**7aA**	CH_3	**8aA**	94	99:1
2	**7aB**	Ph	**8aB**	80	85:15
3	**7aC**	allyl	**8aC**	95	99:1
4	**7bA**	CH_3	**8bA**	85	99:1
5	**7bB**	Ph	**8bB**	95	99:1
6	**7bC**	allyl	**8bC**	86	99:1

[a] Isolated yield after purification by column chromatography (1 mmol scale).
[b] Determined by 1H NMR on crude reaction mixtures.

Table 3. Addition of LiHMDS to sulfinate esters **8b**.

Entry	8	R	(*R*)-9a Y [%][a]	(*R*)-9a *e.e.* [%][b]	6b Y [%][a]
1	**8bA**	CH_3	84	93	95
2	**8bB**	Ph	92	83	92
3	**8bC**	allyl	89	90	97

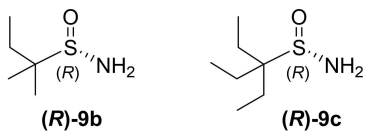
[a] Isolated yield after purification by column chromatography (1 mmol scale).
[b] Determined by chiral HPLC (see Supporting Information).

Grignard reagent was not reported. The capability of unsubstituted phenol to act as a potential leaving group was demonstrated by the same authors using the addition of LiHMDS to the corresponding structurally simpler phenylsulfinate ester.[9] Apparently, the presence of a supplementary aminoalkyl substituent on the aromatic ring of the sulfinate esters **8** is either enough to make it an unsuitable leaving group, or it actively participates in the organometallic addition by chelating LiHMDS and promoting a different reaction pathway with respect to the unsubstituted phenol.

Using scaffold **8bA** (entry 1), results comparable to the ones reported by Senanayake using the transfer agent deriving from **V** (Scheme 1, X = Cl) were obtained (mean yield and *ee* on 3 batches for the last step: 93%, 93%; overall *t*BSA yield starting from **6**: 40%).[10] While phenyl substituent gave a slightly lower enantiomeric excess, although with a very good yield (entry 2), we were very pleased to find that the allyl group (entry 3) gave comparable results to the original methyl substituent, opening the possibility of further functionalizations, for example by cross-metathesis. In all cases, the precursors **6b** were recovered in almost quantitative yields, after purification by flash-chromatography, further confirming the efficiency of the protocol. Finally, by comparing the value of absolute optical rotation with the one of an original commercial sample, we confirmed the (*R*) absolute configuration of the obtained *t*BSA, and correspondingly the correctness of all the tentatively assigned configurations of the stereogenic centers in compounds **6**–**8**.

To demonstrate the general applicability of the oxathiazine 2-oxide scaffolds **7**, we applied the proposed protocol to the synthesis of two other not commercialy available sulfinamides, namely (*R*)-2-methyl butanesulfinamide (**9b**, Figure 1) and (*R*)-3-ethyl pentanesulfinamide (**9c**, Figure 1), starting from oxathiazine **7bA**.

Ring opening of **7bA** with *tert*-pentyl magnesium chloride and (3-ethylpentan-3-yl)magnesium chloride in Et_2O at −40 °C for 1 h, afforded the corresponding sulfinates **8bD** and **8bE** as a single diasteroisomer in 90 and 95% isolated yield, respectively. We were very pleased to find that the reaction of **8bD** with LiHMDS in THF at 0 °C for 1 h proceeded smoothly to give (*R*)-**9b** in 82% isolated yield and >99% enantiomeric excess. Differently, the reaction of the more sterically hindered **8bE** proceeded only at room temperature, giving **9c** in only 43% yield, but again with a complete enantioselectivity. Finally, we also tried the ring opening of **7bA** using 2-mesitylmagnesium bromide, but in this case, we were able to isolate only the corresponding symmetrical sulfoxide, even when the reaction was carried out at −78 °C or using a two-fold excess of **7bA**. This last result was not completely unexpected, since the symmetrical sulfoxide was obtained also by Senanayake as the major product when using the more sterically hindered 1,3,5-triisopropylphenylmagnesium bromide.[9]



(*R*)-9b (*R*)-9c

Figure 1. Structure of sulfinamides (*R*)-**9b** and (*R*)-**9c**.

As last remark, it is worth noticing that starting from (*S*)-*t*BSA as a chiral auxiliary, (*R*)-sulfinamides were obtained as major enantiomers, opening the interesting possibility of synthetizing both enantiomeric forms of different chiral sulfinamides, starting from a single enantiomer of the chiral auxiliary. Finally, it should be mentioned that both (*S*)-*t*BSA and (*R*)-*t*BSA can be bought at the very reasonable price of less than 0.15 €/mmol.[16]

In conclusion, we have developed a 5-step diastereoselective route for the preparation of chiral oxathiazine 2-oxide scaffolds as sulfinyl transfer agents. This procedure allows for the introduction of different substituents on the chiral scaffold, opening the possibility of further functionalization, also for supporting it on solid phases. It should be mentioned that the relatively low overall yield of *t*BSA obtained with the currently available method (~40%)[10] is mainly due to the difficulty in its extraction after the final work-up. Here a solid supported scaffold should facilitate not only the final product recovery, but also the recovery of the chiral precursor and its recycling. Experiments to support the allyl-substituted precursor **6bC** on solid phases are currently underway and will be reported in due course.

Experimental Section

General methods. All the commercial chemicals were purchased from Sigma-Aldrich, VWR, Alfa Aesar, or TCI-Chemicals and used without additional purifications. The 1H and 13C NMR spectra were recorded on a Varian INOVA 400 NMR instrument with a 5 mm probe. All chemical shifts have been quoted relative to residue solvent signal; chemical shifts (δ) are reported in ppm and coupling constants (*J*) are reported in hertz (Hz). GC-MS (GCMS) spectra were obtained by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection; they are reported as: *m/z* (rel. intensity). High-resolution MS (HRMS) ESI analyses were performed on a Xevo G2-XS QTof (Waters) mass spectrometer. Mass spectrometric detection was performed in the full-scan mode from *m/z* 50 to 1200, with a scan time of 0.15 s in the positive ion mode, cone voltage: 40 V, collision energy: 6.00 eV. ESI: capillary: 3 kV, cone: 40 V, source temperature: 120 °C, desolvation temperature: 600 °C, cone gas flow: 50 L/h, desolvation gas flow: 1000 L/h. CSP-HPLC analyses were performed on an Agilent Technologies Series 1200 instrument using chiral

columns. The enantiomeric compositions were checked against the corresponding racemic products. Melting point (m.p.) measurements were performed on Bibby Stuart Scientific SMP3 apparatus. Optical rotation measurements were performed on a polarimeter Schmidt+Haensch UniPol L1000. Flash chromatography purifications were carried out using VWR silica gel (40–63 μm particle size). Thin-layer chromatography was performed on Merck 60 F254 plates. Compounds **2a**[11a] and **2b**[11b] were synthesized following reported literature procedures and their spectroscopical data matched the reported ones.

General procedure for the synthesis of 3. Triethylamine (7 mmol, 0.976 mL, 1.4 eq.), *N,N*-dimethylpyridin-4-amine (0.006 g, 0.01 eq.) and *tert*-butylchlorodimethylsilane (6 mmol, 0.904 g, 1.2 eq.) were added at 0 °C to a solution of the appropriate sulfinyl imine **2** (5 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL), The reaction mixture was stirred at room temperature for 4 h. After completion, monitored by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3×), the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography.

General procedure for the synthesis of 4. The desired Grignard reagent (1.5 mmol, 1.5 mL 1.5 eq., 1 M solution) was added at −50 °C to a solution of the sulfinamide **3** (1 mmol) in anhydrous CH_2Cl_2 (3 mL). The reaction mixture was stirred to completion, monitored by TLC (see Table 1). The reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with CH_2Cl_2 (3×), the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography.

General procedure for the synthesis of 5a and 6b. Tetrabutylammonium fluoride (0.314 g, 1.2 mmol, 1.2 eq.) was added at 0 °C to a solution of the sulfinamide **4a** or the sulfonamide **5b** (1 mmol, 1 eq.) in anhydrous THF (5 mL). The reaction mixture was stirred at room temperature for 1 h. After completion, monitored by TLC, the reaction was washed with water. The organic phase was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography.

General procedure for the synthesis of 5b and 6a. Fresh *meta*-chloroperoxybenzoic acid (0.269 g, 1.2 mmol, 1.2 eq., ≤77%) was added at 0 °C to a solution of the sulfinamide **4b** or the sulfonamide **5a** (1 mmol, 1 eq.) in anhydrous CH_2Cl_2 (5 mL). The reaction mixture was stirred at 0 °C for 1 h. After completion, monitored by TLC, the reaction was quenched with an aqueous solution of saturated $NaHSO_3$ and $NaHCO_3$ and stirred for 30 minutes. The mixture was extracted with CH_2Cl_2 (3×), the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography.

General procedure for the synthesis of 7. Thionyl chloride (0.150 mL, 2.04 mmol, 1.02 eq.) was added at −15 °C to a solution of the sulfonamide **6** (2 mmol, 1 eq.) in anhydrous THF, followed by the slow addition of pyridine (0.372 mL, 4.6 mmol, 2.3 eq.). The reaction mixture was stirred at −15 °C for 1 h. After completion, monitored by TLC, the reaction was quenched with water and extracted with AcOEt (3×). The organic phase was then washed with aqueous Na_2HPO_4 solution (5%, 2×), water (2×), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Except for **7aA**, compounds are too unstable to be purified or manipulated, so the crudes were checked by 1H NMR only and readily used in the following step without further purification.

General procedure for the synthesis of 8. The selected alkylmagnesium chloride (1.05 mmol, 1.05 eq.) was slowly added at −40 °C to a solution of the oxathiozinone **7** (1 mmol) in anhydrous THF (3 mL). The reaction mixture was stirred at −40 °C for 1 h. After completion, monitored by TLC, the reaction was quenched with aqueous citric acid solution (0.4 eq., 20%) and extracted with AcOEt (3×). The organic phase was then washed with aqueous Na_2HPO_4 solution (5%, 2×), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography. Compound **8aB** was obtained as a hardly separable mixture of two diastereoisomers; since the corresponding sulfinate was not reactive in the subsequent step, no further effort was made to purify the reaction mixture.

General procedure for the synthesis of 9. Lithium bis(trimethylsilyl)amide (2.3 mmol, 2.3 mL, 2.3 eq., 1 M solution in THF) was added at 0 °C to a solution of the compound **8b** (1 mmol) in anhydrous THF (3 mL). The reaction mixture was stirred at 0 °C (rt for **8bE**) for 1 h. After completion, monitored by TLC, the reaction was quenched with water (1 eq.). The solvent was removed under reduced pressure and the crude was directly purified by column chromatography.

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[16] Doug Discovery offers (*S*)-*t*BSA at 0.13 €/mmol (100 g) and (*R*)-*t*BSA at 0.09 €/mmol (500 g).

Correction added on May 27 2022 after first online publication: Correction of Funding statement.