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Asymmetric Synthesis of Pyrrolidine Containing Chemical Scaffolds via Tsuji-Trost Allylation of *N*-*tert*-Butanesulfinyl Imines

Rafid S. Dawood^a, Irene Georgiou^a, Ross P. Wilkie^a, William Lewis^a and Robert A. Stockman^{*a}

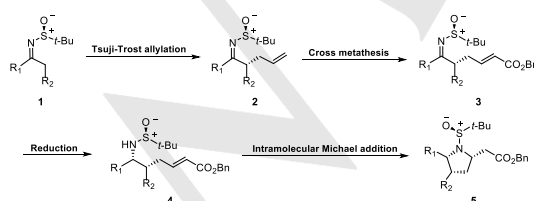
Abstract: A simple and efficient asymmetric synthesis of novel sp³-rich pyrrolidine chemical scaffolds over five steps starting from simple ketones is described. Key steps involve the use of *tert*-butanesulfinamide as a chiral auxiliary to perform an asymmetric Tsuji-Trost allylation, with subsequent cross-metathesis with an acrylate ester and reduction of the sulfinimine/cyclisation of the resulting amine giving the pyrrolidine scaffolds in high yields and diastereoselectivities. By removing the chiral auxiliary and functionalising the ester group, the resulting scaffold core can be further derivatised.

Introduction

Compounds containing a pyrrolidine ring usually possess a wide range of biological activities such as, anticancer, antitumor and anti-biotic activity.^[1] Specifically, chiral pyrrolidines constitute a large group of heterocyclic organic compounds which are useful building blocks of pharmaceuticals,^[2,3] vitamins, dyes, drug candidates, hormones, agrochemicals^[4] and alkaloid natural products.^[5,6] Furthermore, these compounds have been used as ligands for transition metals, organocatalysts,^[7-9] and effective chiral controllers in asymmetric synthesis.^[10-12]

It has been observed that there is a significant interest in the stereoselective synthesis of chiral pyrrolidines, using *N*-*tert*-butanesulfinyl imines as a chiral auxiliary. In particular, by the addition of Grignard reagents^[13] or hydride^[14] to γ -chlorinated *N*-*tert*-butanesulfinyl imines followed by cyclisation, or via Wacker-type oxidation cyclisation of alkenes with *tert*-butanesulfinamide nucleophiles^[15] or iodocyclisation of homoallylic sulfonamides.^[16]

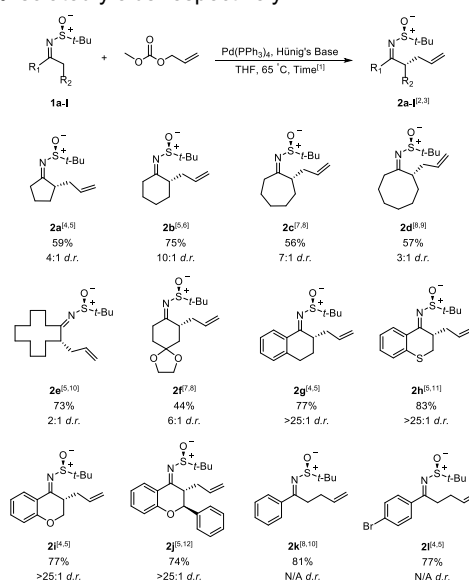
Recently, the diastereoselective α -allylation of a variety of chiral α -*N*-*tert*-butanesulfinyl imines using Tsuji-Trost reaction has been reported by Stockman and co-workers.^[17] In particular, under mild reaction conditions, compounds bearing an allyl group at the α -position of chiral *N*-*tert*-butanesulfinyl imines were obtained in high yields, with good diastereoselectivity and substrate tolerance. In a following report, the α -allylation of chiral *N*-*tert*-butanesulfinyl imines derived from symmetric cyclic ketones was reported.^[18] Hence, we envisioned taking advantage of the Tsuji-Trost allylation of *N*-*tert*-butanesulfinyl imines to access, in five steps, pyrrolidine-based chemical scaffolds as outlined in Scheme 1. We aimed to achieve this through cross metathesis of the allylated *N*-*tert*-butanesulfinyl imines, followed by reduction and finally ring cyclisation, using an intramolecular Michael addition.



Scheme 1. Outline of the asymmetric synthesis of pyrrolidine chemical scaffolds **5**.

Results and Discussion

Prior to applying the optimised reaction conditions of the allylation,^[17,18] the focus was turned on the synthesis of required starting *N*-*tert*-butanesulfinyl imines **1a-l**. This was achieved by following Ellman's protocol, in yields ranging from 57% to 92% (see SI).^[19] The optimised conditions of the Tsuji-Trost allylation were then applied on compounds **1a-l** affording the corresponding α -allyl *N*-*tert*-butanesulfinyl imines **2a-l** in good yields (44-83%) with *d.r.* up to >25:1 (Scheme 2). It was observed that symmetrical cyclic *N*-*tert*-butanesulfinyl imines **1a-e** gave a moderate to good yield (56-75%) and *d.r.* from 2:1 to 7:1. Compound **1a** containing a five membered ring gave **2a** in 59% yield with *d.r.* 4:1. Increased *d.r.* was obtained when cyclic substrates bearing six and seven membered rings **1b** and **1c** were used. The *d.r.* decreased to 3:1 and 2:1 when the substrates possessing an eight or twelve membered rings (**1d** and **1e**) were employed respectively. The allylation of *N*-*tert*-butanesulfinyl imine bearing acetal-protected carbonyl **1f** afforded **2f** in 44% yield and *d.r.* 6:1. The *N*-*tert*-butanesulfinyl imines derived from unsubstituted aromatic-cyclic aliphatic rings **1g-j** afforded **2g-j** in excellent *d.r.* (>25:1) with good yields (77-83%). Although, substrate **1j** has an extra stereocentre, the product **2j** was obtained in an excellent *d.r.* (>25:1). While, the aromatic-aliphatic system **1k** and **1l** provided **2k** and **2l** in 81% and 77% isolated yields respectively.

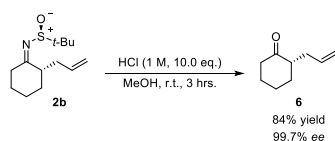


[1] Reactions were performed using 1.0 mmol of substrates **1a-l** in THF, Pd(PPh₃)₄ (2.5-5.0 mol%), allyl methyl carbonate (1.5 mmol) and Hünig's base (2.0 mmol). [2] Isolated yield. [3] The *d.r.* values were determined by ¹H-NMR. [4] 24 hrs. [5] 2.5 mol% Pd(PPh₃)₄. [6] 30 hrs. [7] 27 hrs. [8] 5.0 mol% Pd(PPh₃)₄. [9] 29 hrs. [10] 20 hrs. [11] 18 hrs. [12] 23 hrs. N.A. = not applicable.

Scheme 2. Synthesis of α -allyl *N*-*tert*-butanesulfinyl imines **2a-l** via Tsuji-Trost allylation.

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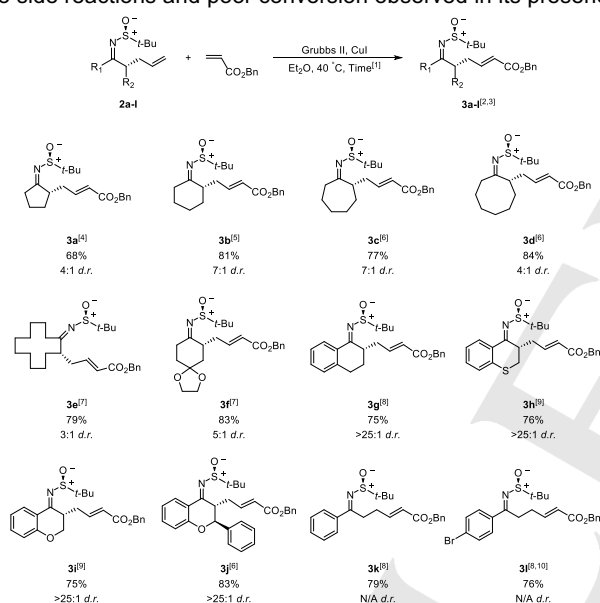
In order to determine the stereochemistry of the newly created chiral centre at **2b**, the substrate was hydrolysed resulting in the corresponding chiral ketone **6** as a single enantiomer (*ee* >99%) (Scheme 3).



Scheme 3. Hydrolysis of *N*-tert-butanesulfinyl imine **2b** to afford **6**.

The *ee* value of **6** was determined by GC analysis on a chiral stationary phase.^[20] In the literature, the specific rotation of (*S*)-**6** is $[\alpha]_D -15.8$ (*c* = 3, MeOH), which was used to compare with our recorded value ($[\alpha]_D^{23} -14.9$, *c* = 3, MeOH).^[21]

Having in hand α -allylated *N*-tert-butanesulfinyl imines **2a-l**, a literature reported procedure for the cross metathesis was applied.^[22] Hence, α -allyl derivatives **2a-l**, were treated with benzyl acrylate in the presence of Grubbs II catalyst and CuI giving the corresponding metathesis adducts **3a-l** in yields ranging from 68 to 84% with *d.r.* up to >25:1 (Scheme 4). The cross metathesis of **2l** was performed in the absence of CuI due to side reactions and poor conversion observed in its presence.



[1] Reactions were performed using 1.0 mmol of substrates **2a-l** in Et₂O, Grubbs II catalyst (2.0 mol%), benzyl acrylate (3.0 mmol) and CuI (3.0 mol%). [2] Isolated yield. [3] The *d.r.* values were determined by ¹H-NMR. [4] 3 hrs. [5] 8 hrs. [6] 7 hrs. [7] 5 hrs. [8] 6 hrs. [9] 4 hrs. [10] Reaction was carried in the absence of CuI. N.A. = not applicable.

Scheme 4. Cross metathesis coupling of **2a-l** with benzyl acrylate to provide **3a-l**.

The following step was the reduction of compounds **3a-l** to prepare the corresponding sulfinamide derivatives **4a-l**. Different reducing agents were used to explore the best results in terms of yield and diastereoselectivity. Substrate **3k** was chosen as a bench mark substrate to develop our optimised reaction conditions (Table 1). In all cases, the reaction was carried out at -78 °C and in the presence of 2.2 eq. of the reducing agent to prevent any reduction of the ester group to the undesired aldehyde or alcohol. DIBAL-H (Entry 1) was the best reducing agent examined, which gave good yield (74%) and *d.r.* >25:1. Likewise, the reduction with 9-BBN (Entry 2) afforded the desired product **4k** in >25:1 *d.r.* with 67% yield, a slightly reduced yield compared to DIBAL-H. On the other hand, the *d.r.*

dropped to 5:1 with acceptable yield (65%) when L-selectride was used (Entry 3). Unfortunately, desired chiral sulfinamide **4k** was not observed when LiAlH₄ was used (Entry 4), due to the reduction of the ester to the corresponding alcohol. Finally, NaBH₄ gave **4k** with *d.r.* (1:1) and 38% yield (Entry 5).

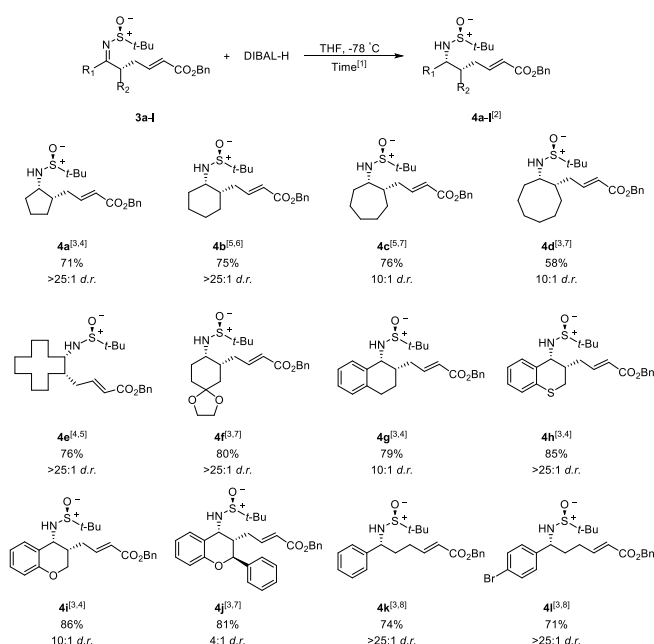
Entry	Reducing agent	Time (hrs)	Yield (%)	<i>d.r.</i>
1	DIBAL-H	3	74	>25:1
2	9-BBN	3	67	>25:1
3	L-selectride	3	65	5:1
4	LiAlH ₄	6	-	-
5	NaBH ₄	4	38	1:1

[1] Reactions were performed using 1.0 mmol of substrate **3k** in THF, reducing agent (2.2 eq.). [2] Isolated yield. [3] The *d.r.* values were determined by ¹H-NMR.

Table 1. Optimisation of reduction conditions required to afford sulfinamide **4k** from **3k**.

The optimised reduction conditions using DIBAL-H were then applied on *N*-tert-butanesulfinyl imines **3a-l** as a mixture of diastereoisomers (see Scheme 4) affording the corresponding sulfinamides **4a-l** (Scheme 5). The *d.r.* of desired sulfinamides **4a-l** was determined by ¹H-NMR (up to >25:1) and the yields ranged from 58% to 86%. *N*-tert-Butanesulfinyl imine **3a** resulted in the desired chiral sulfinamide **4a** in an excellent *d.r.* >25:1 with good yield (71%). Likewise, the reduction of **3b** furnished **4b** in 75% yield with >25:1 *d.r.* The substrates bearing seven and eight membered rings **3c** and **3d** were employed and gave products **4c** and **4d** in *d.r.* 10:1 and yield 76% and 58% respectively. In these two substrates, the spontaneous transformation to the corresponding pyrrolidines **5c** and **5d** in the absence of catalyst or base was also detected in trace amounts. Using the twelve-membered ring substrate **3e** afforded **4e** in *d.r.* >25:1 and good yield (75%), demonstrating that there is no significant effect of the ring size on the reduction. The reduction of substrate bearing acetal-protected carbonyl **3f** led to **4f** in very good yield (80%) and *d.r.* >25:1, proving its stability under these reducing conditions. Unsubstituted aromatic-cyclic aliphatic ring systems **3g-i** afforded desired chiral sulfinamides **4g-i** in *d.r.* between 10:1 to >25:1 and yields ranging from 79% to 86%. On the other hand, the substituted aromatic-cyclic aliphatic ring system **3j** gave the corresponding sulfinamide **4j** in very good yield (81%), but the *d.r.* dropped to 4:1. This is possibly due to the phenyl group on the ring, which partially blocks the top face, reducing the effect of the chiral sulfinyl directing group. Desired sulfinamides **4k** and **4l** were obtained in an excellent *d.r.* >25:1 with good yields 74% and 71% respectively, and starting material **3k** was consumed completely within 3 hrs.

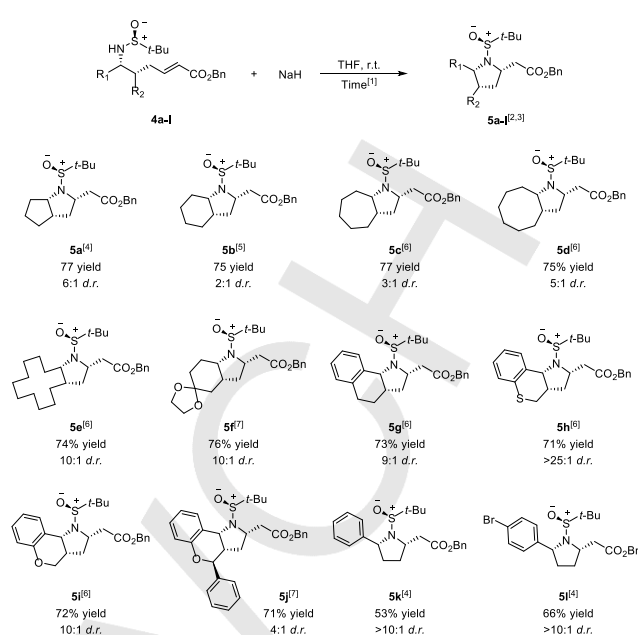
The *N*-H proton of the sulfinamides **4a-l** was observed by ¹H-NMR spectroscopy and no exchange with CDCl₃ was observed. The stereochemistry of the C-N bond has been assigned depending on Colyer's *et al.* explanation (see SI).^[23]



[1] Reactions were performed using 1.0 mmol of substrates **3a-l** in THF and DIBAL-H (2.2 mmol). [2] Isolated yield. [3] The *d.r.* values were determined by ¹H-NMR. [4] 5 hrs. [5] The *d.r.* values were determined by ¹H-NMR after purification by column chromatography due to impurities in crude mixture [6] 7 hrs. [7] 6 hrs. [8] 3 hrs.

Scheme 5. Synthesis of sulfonamides **4a-l** via reduction of **3a-l** with DIBAL-H.

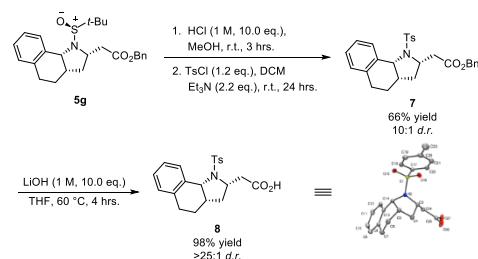
Sulfonamides **4a-l** were then used to prepare the corresponding pyrrolidine chemical scaffolds **5a-l** via an intramolecular Michael addition in the presence of NaH in THF at r.t. (Scheme 6). To our delight, all the substrates were converted into the desired pyrrolidine products in moderate to good yields (53–77%) with *d.r.* up to >25:1. Ring-formation was found to proceed with moderate to good diastereoselectivity to yield *cis*-2,5-pyrrolidines as the major diastereoisomer. The pyrrolidine derivatives **5c-e** were isolated in good yields (74–77%). In addition, the cyclisation of sulfonamide bearing acetal-protected carbonyl **4f** was achieved successfully and afforded desired pyrrolidine **5f** in good yield (76%) and 10:1 *d.r.* Unsubstituted aromatic-cyclic aliphatic rings system **4g** and **4i** afforded corresponding pyrrolidines **5g** and **5i** in yields of 73% and 72% respectively, the *d.r.* was 9:1 for **5g** and 10:1 for **5i**. On the other hand, the pyrrolidine **5h** was obtained in the best *d.r.* (>25:1) and yield (71%) when **4h** was employed. The reason for this may be the size of the sulfur atom present on the heterocycle, which improves the selectivity of the cyclisation. Substituted aromatic-cyclic aliphatic ring system **4j** gave desired pyrrolidine **5j** in 71% yield and no change in the *d.r.* was observed (4:1). This may be attributed to the phenyl substituent on **4j**, which is considered a bulky group and therefore increased the selectivity on opposite face. The aromatic-aliphatic system **4k** and **4l** provided **5k** and **5l** in *d.r.* >10:1 and yields 53% and 66% respectively. We saw no evidence of reversibility in the cyclizations, and thus presume they are under kinetic control.



[1] Reactions were performed using 1.0 mmol of substrates **4a-l** in THF and NaH (1.2 mmol). [2] Isolated yield. [3] The *d.r.* values were determined by ¹H-NMR. [4] 3 hrs. [5] 4 hrs. [6] 5 hrs. [7] 6 hrs. [8] 3 hrs.

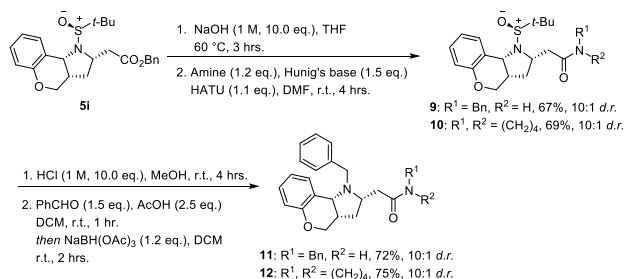
Scheme 6. Synthesis of pyrrolidine derivatives **5a-l** via cyclization of **4a-l** under basic conditions.

After achieving the synthesis of the pyrrolidine chemical scaffolds **5a-l**, our focus was then turned to further functionalise them. In particular, by taking advantage the two points of diversity that each of the pyrrolidine chemical scaffolds **5a-l** possesses. Hence, deprotection of the chiral auxiliary group of **5g** under acidic conditions afforded the corresponding amine, which was sulfonylated affording **7** in 66% yield (over 2 steps) and *d.r.* 10:1 (Scheme 7). Hydrolysis of the ester group of **7** under basic conditions afforded the desired carboxylic acid **8** in 98% yield and >25:1 *d.r.* X-ray crystallographic analysis of **8** confirmed the atoms connectivity and absolute stereochemistry.



Scheme 7. Synthesis of **8** via deprotection, sulfonylation and hydrolysis of the benzyl group of **5g**.

In addition, the synthetic route was scaled up to provide a total of 3 g of scaffold core **5i**, bearing two points of diversity which can be further functionalised. The transformation of **5i** to the corresponding carboxylic acid was carried out successfully using NaOH. The acid was then used to synthesize amides **9** and **10** via coupling with primary and secondary amines respectively (Scheme 8). The chiral auxiliary groups of amides **9** and **10** were then removed using standard conditions giving the corresponding amines. This was followed by reductive amination with benzaldehyde in the presence NaBH(OAc)₃ and AcOH in CH₂Cl₂ resulting in the corresponding substituted tertiary amines **11** and **12** in 72% and 75% yields respectively.



Scheme 8. N-alkylation and C-amidation on **5I**.

Furthermore, bromide substituted scaffold core **5I** was derivatised using Suzuki-Miyaura cross-coupling reaction (Scheme 9). In particular, **5I** was treated with pinacolboronate esters under microwave conditions (120 °C, 2 hrs.) in the presence of Pd(dppf)Cl₂ as a catalyst affording desired products **13-16** in yields 50-66%.



Scheme 9. Suzuki-Miyaura cross-coupling of **5I** with pinacolboronate esters using Microwave conditions.

Conclusions

The synthesis of novel pyrrolidine containing chemical scaffolds using chiral *N*-*tert*-butanesulfinyl imines has been investigated. The Tsuji-Trost reaction was used to obtain α-allyl *N*-*tert*-butanesulfinyl imines, followed by cross metathesis reaction to give α,β-unsaturated esters. DIBAL-H was found to be a selective reducing agent of the sulfinyl imine group of α,β-unsaturated esters to afford the corresponding sulfonamides in high d.r. in most cases (up to >25:1) in moderate to good yields ranging from 58 to 86%. The sulfonamides were then used to synthesise a range of pyrrolidine scaffolds via cyclisation in the presence of NaH. The desired pyrrolidine products were isolated in yields between 53% and 77% with d.r. up to >25:1. A range of further derivatisation such as, sulfonylation, reductive amination, amidation and Suzuki coupling leading to highly functionalised substrates has been achieved successfully.

Acknowledgment

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Conflict of interest

The authors declare no conflict of interest.

Experimental Section

The entire experimental section can be found in the supporting information, including compound characterization data and copies of NMR spectra.

Keywords: Pyrrolidine • Chiral auxiliary • Tsuji-Trost allylation.

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