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

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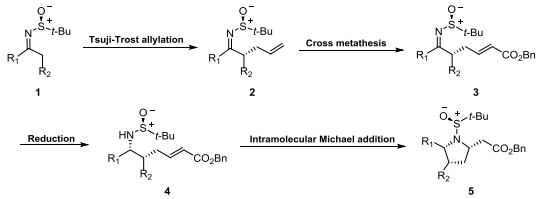
Abstract: A simple and efficient asymmetric synthesis of novel sp3-rich pyrrolidine chemical scaffolds over five steps starting from simple ketones is described. Key steps involve the use of tert-butanesulfinamide as a chiral auxiliary to perform an asymmetric Tsuji-Trost allylation, with subsequent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

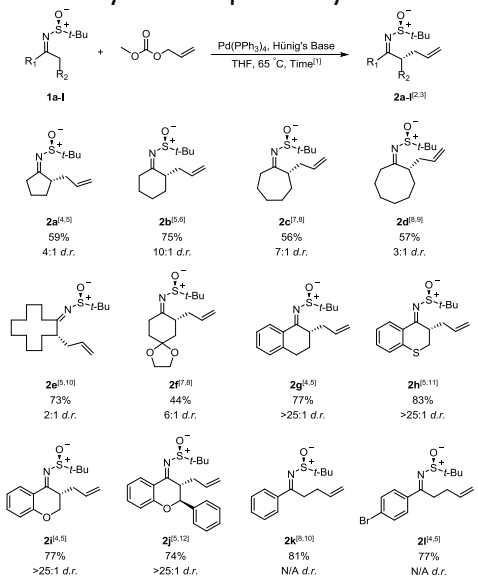
It has been observed that there is a significant interest in the stereoselective synthesis of chiral pyrrolidines, using N-tert-butanesulfinyl imines as a chiral auxiliary. In particular, by the addition of Grignard reagents[13] or hydride[14] to γ-chlorinated N-tert-butanesulfinyl imines followed by 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 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

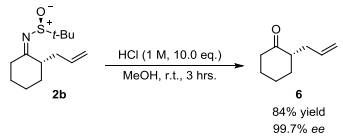
Prior to applying the optimised reaction conditions of the allylation,[17,18] the focus was turned on the synthesis of required starting N-tert-butanesulfinyl imines 1a-l. This was achieved by following Ellman's protocol, in yields ranging from 57% to 92% (see SI).[19] The optimised conditions of the 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.

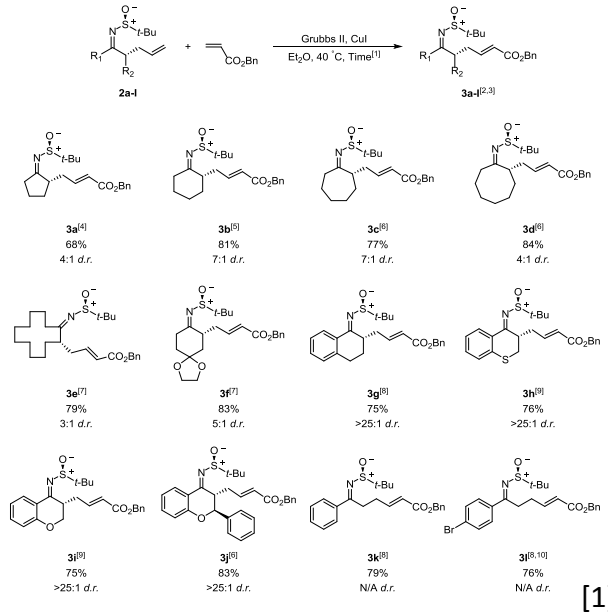
Scheme 2. Synthesis of α-allyl N-tert-butanesulfinyl imines 2a-l via Tsuji-Trost allylation.

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).

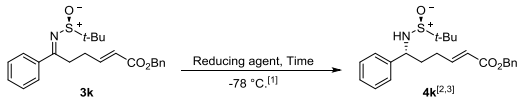


Scheme 3. Hydrolysis of N-tert-butanesulfinyl imine 2b to afford 6.

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 [α]D -15.8 (c = 3, MeOH), which was used to compare with our recorded value ([α]D23 -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).



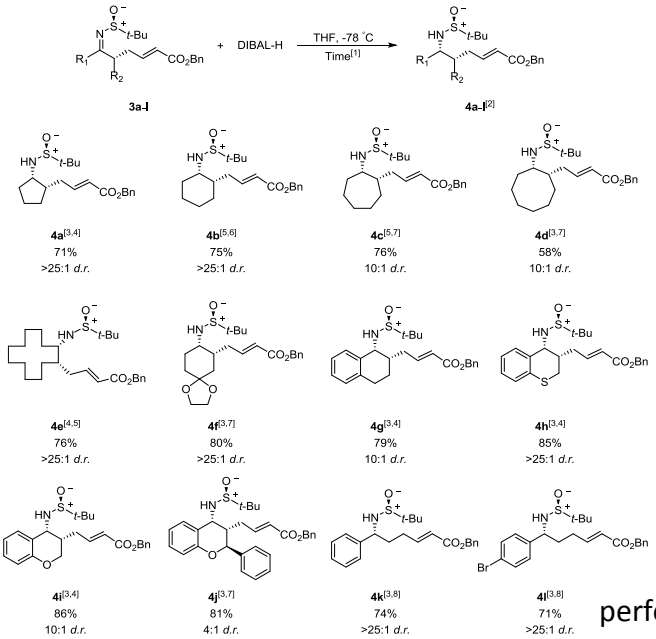
Entry	Reducing agent	Time (hrs)	Yield (%)	d.r.
1	DIBAL-H	3	74	>25:1
2	9-BBN	3	67	>25:1
3	L-selectride	3	65	5:1
4	LiAlH4	6	-	-
5	NaBH4	4	38	1:1

[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.

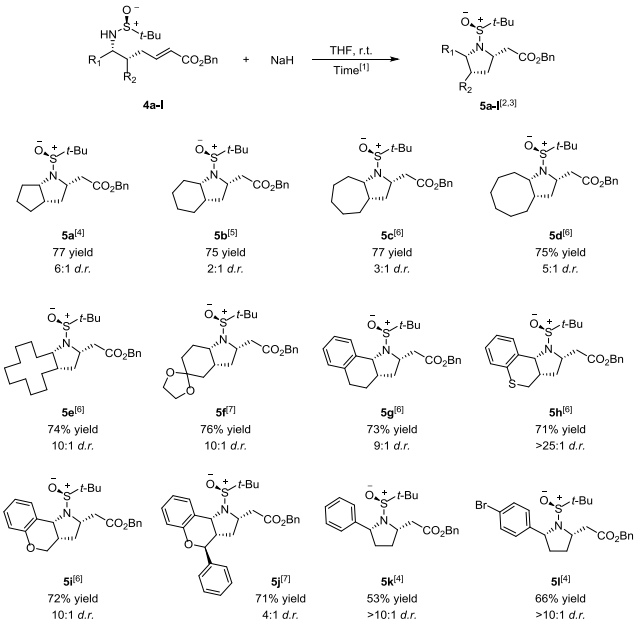
The N-H proton of the sulfinamides 4a-l was observed by 1H-NMR spectroscopy and no exchange with $CDCl_3$ was observed. The stereochemistry of the C-N bond has been assigned depending on Colyer's et al. explanation (see SI).[23]



[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 sulfinamides 4a-l via reduction of 3a-l with DIBAL-H.

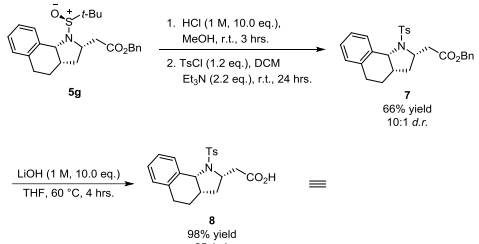
Sulfinamides 4a-l were then used to prepare the corresponding pyrrolidine chemical scaffolds 5a-l via an intramolecular Michael addition in the presence of NaH in THF at r.t. (Scheme 6). To our delight, all the substrates were converted into the desired pyrrolidine products in moderate to good yields (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 sulfinamide 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.

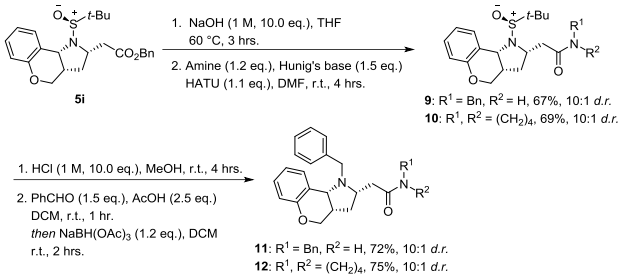
Scheme 6. Synthesis of pyrrolidine derivatives 5a-l via cyclization of 4a-l under basic conditions.

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.



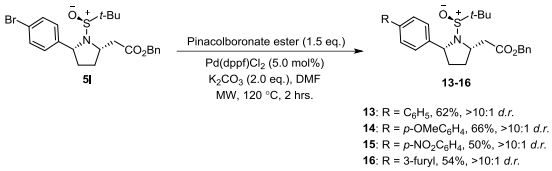
Scheme 7. Synthesis of 8 via deprotection, sulfonylation and hydrolysis of the benzyl group of 5g.

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 5l was derivatised using Suzuki-Miyaura cross-coupling reaction (Scheme 9). In particular, 5l 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 5l 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 seteroselective reducing agent of the sulfinyl imine group of α,β-unsaturated esters to afford the corresponding sulfinamides in high d.r. in most cases (up to >25:1) in moderate to good yields ranging from 58 to 86%. The sulfinamides 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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