Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5021

www.rsc.org/obc

PERSPECTIVE

Synthesis and applications of masked oxo-sulfinamides in asymmetric synthesis

Ramakrishna Edupuganti and Franklin A. Davis*

Received 17th February 2012, Accepted 17th April 2012
DOI: 10.1039/c2ob25345c

This short perspective reports on the synthesis and applications of a class of chiral amino carbonyl compounds, masked oxo-sulfinamides where the amine is protected with an *N*-sulfinyl moiety and the carbonyl group is protected as the ketal or 1,3-dithiane. These polyfunctionalized chiral building blocks are prepared by addition of organometallic reagents to masked oxo-sulfinimines (*N*-sulfinyl imines) or the addition of oxo-organometallic reagents and lithio-1,3-dithianes to sulfinimines. Because unmasking of the amino and carbonyl groups results in cyclic imines, these chiral building blocks are particularly useful for the asymmetric synthesis of functionalized nitrogen heterocycles, including prolines, pipecolic acids, pyrrolidines, homotropinones, tropinones, and tropane alkaloids such as cocaine and C-1 cocaine analogues.

1. Introduction

Polyfunctionalized or densely functionalized chiral building blocks, defined as molecules having at least one stereogenic center and more than one chemically differentiated functional group, have played significant roles in the asymmetric synthesis of structurally complex biologically and pharmacologically active molecules. Examples include amino acids, carbohydrates, hydroxy acids, and terpenes. Since they are often obtained from the "chiral pool", access to both enantiomers is limited, and extensive manipulation and protecting group chemistry is often necessary to transform them into the target molecule. Designing chiral molecules that have the necessary functionality and protecting groups built in for further elaboration can circumvent these limitations.[1]

Sulfinimine (*N*-sulfinyl imine)-derived chiral building blocks have been introduced to access structurally diverse polyfunctionalized nitrogen heterocycles, key structural units found in a broad range of natural products, drugs and drug candidates.[2] The 1,2-addition of organometallic reagents to the C=N bond of enantiopure sulfinimines (*N*-sulfinyl imines), first reported by Davis *et al.*[1,3] and subsequently by Ellman *et al.*,[4] is currently the best and most reliable method for the asymmetric synthesis of amines and amine derivatives.[5] The sulfinyl auxiliary not only activates the C=N bond for nucleophilic addition but exerts powerful and predictable stereodirecting effects resulting in high diastereomeric ratios in the sulfinamide product. Epimerization of newly created carbon stereocenters is prevented because the sulfinyl auxiliary stabilizes anions at nitrogen. In addition, this auxiliary is an excellent amine-protecting group and is easily removed under mild acid conditions.

Enantiopure amino carbonyl compounds are examples of important polyfunctionalized chiral building blocks for the asymmetric synthesis of natural products, nitrogen heterocycles, and pharmaceuticals.[6,7] However, suitable protecting groups are necessary to prevent racemization and undesired self-condensation reactions. For this purpose enantiopure *N*-sulfinyl α-amino 1,3-dithianes **1** were introduced to synthesize the notoriously unstable α-amino aldehydes and ketones (Fig. 1). These compounds have been employed in the asymmetric synthesis of functionalized pyrrolidines, including (−)-3-hydroxy-3-methyl proline[8] and (−)-2,3-*trans*-3,4-*cis*-dihydroxyproline,[9a] and the 2,3-disubstituted piperidine (+)-L-733,060.[9b] Optically enriched β-amino-α-keto amides which can be elaborated into peptide structures and deprotected under oxidative conditions without racemization have also utilized this methodology.[10]

One of the best methods to synthesize β-amino ketones is the addition of Grignard and lithium reagents to enantiopure β-amino Weinreb amides **2** (Fig. 1).[11] These amides are prepared by addition of Weinreb amide enolates to sulfinimines. Enantiopure β-amino carbonyl compounds are found as structural units of natural products and are valuable for the synthesis of nitrogen heterocycles.[12] α-Amino, β-amino, γ-amino and δ-amino ketones are also available from enantiopure *N*-sulfinyl masked oxo-sulfinamides **3**, which are derived from masked oxo-sulfinimines **4**. These compounds are particularly useful for the asymmetric synthesis of nitrogen heterocycles because unmasking of the oxo and amino groups results in cyclization to imines, which

Department of Chemistry, Temple University, Philadelphia, PA 19122, USA. E-mail: fdavis@temple.edu

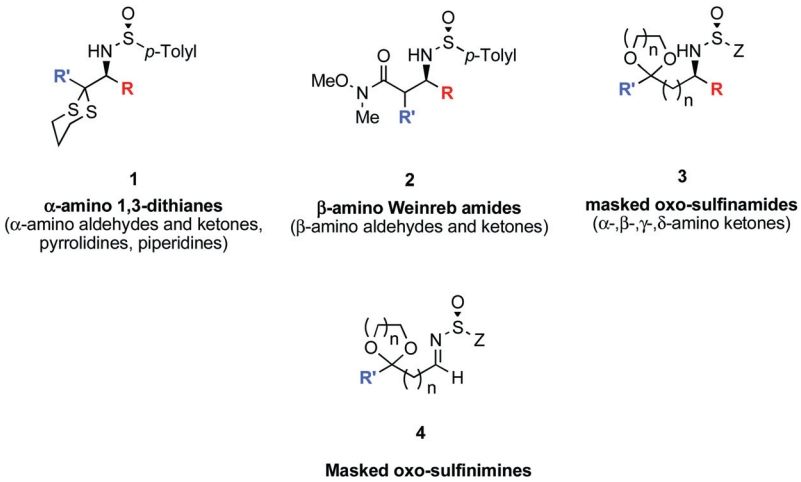


Fig. 1 Amino carbonyl compounds.

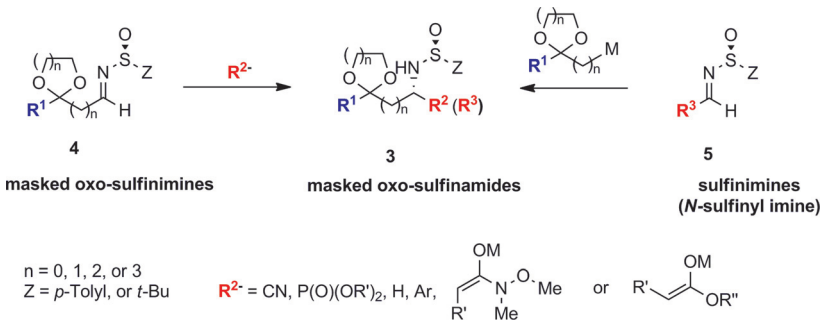


Fig. 2 Synthesis of masked oxo-sulfinamides.

on reduction give pyrrolidines and piperidine derivatives. The focus of this perspective is the synthesis of masked oxo-sulfinamides **3** and their applications in the asymmetric synthesis of amine derivatives and functionalized nitrogen heterocycles.

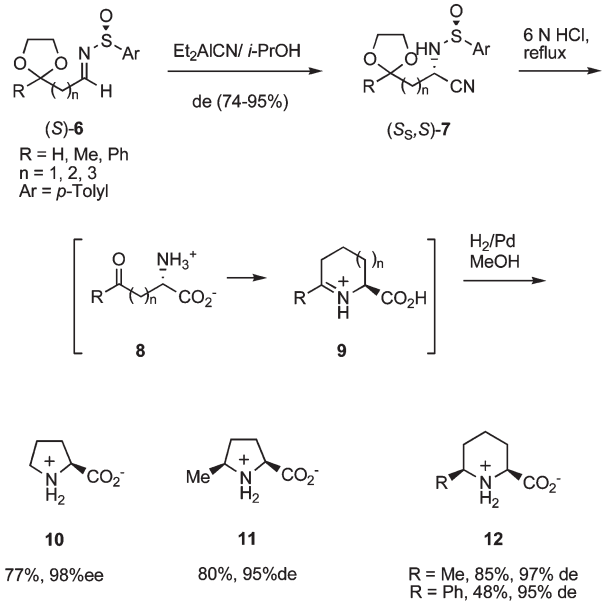
2. Synthesis and applications of enantiopure masked oxo-sulfinamides

2.1 Synthesis of masked oxo-sulfinamides

Chiral non-racemic masked oxo-sulfinamides, stable amino carbonyl compounds, can be prepared by 1,2-nucleophilic addition of organometallic reagents to the C–N double bond of enantiopure sulfinimines. These additions can be classified in two ways (Fig. 2): (i) diastereoselective addition of nucleophiles including cyanide,[13] metal phosphonates,[14] ester enolates,[15] and Weinreb amide enolates[16] to masked oxo-sulfinimines **4**; and (ii) diastereoselective addition of masked oxo organometallic reagents to sulfinimines **5**.[8,17] The requisite chiral sulfinimines **4** and **5** are prepared by the condensation of enantiopure (*R*)- and (*S*)-sulfinamides ($RS(O)NH_2$), many of which are commercially available, with carbonyl compounds. The asymmetric synthesis and applications of sulfinimines as amine building blocks have been reviewed by Davis *et al.*,[1a,5f,5h] Ellman *et al.*,[5a,g] Morton and Stockman,[5c] Senanayake,[5e] and others.[5b]

2.2 Asymmetric synthesis of proline and pipecolic acid derivatives

A strategy for the preparation of cyclic α-amino acids is cyclization/reduction of oxo α-amino acids. Lubell *et al.*[18] and Rapoport *et al.*[19] utilized this approach for the synthesis of *cis*-5-substituted prolines **11** and *cis*-6-substituted pipecolate acid derivatives **12**. However, this method is limited because most oxo α-amino acids are derived from proteinogenic amino acids, the syntheses are lengthy, and access to both enantiomers is problematic. A more efficient method for the asymmetric synthesis of oxo α-amino acids was introduced by Davis and co-workers involving masked oxo-sulfinimine (*S*)-**6** and the sulfinimine-derived asymmetric Strecker synthesis (Scheme 1).[13] Here treatment of (*S*)-**6** with Et_2AlCN:i-PrOH afford the corresponding cyano masked oxo-sulfinamide (S_S,*S*)-**7** in good yield and good to excellent diastereoselectivity (74–95% de). Hydrolysis of the diastereomerically pure sulfinamides (S_S,*S*)-**7** with 6 N HCl accomplishes four operations in a single pot (Scheme 1). Hydrolysis removes the *N*-sulfinyl auxiliary with concomitant conversion of the nitrile to the acid. The ketal is unmasked to give the intermediate oxo α-amino acids **8** which cyclizes to iminium ions **9**. Hydrogenolysis (H_2/Pd) of iminium ions **9** leads to the cyclic α-amino acids, prolines **10** and **11** and pipecolic acids **12** in good to excellent yields (48–85%) and excellent stereoselectivity (95–98% de or ee) (Scheme 1).



Scheme 1

2.3 Asymmetric synthesis of cyclic α-amino phosphonates

In a similar manner, cyclic α-amino phosphonic acids were prepared by the diastereoselective addition of lithium diethylphosphite (2 equiv.) to sulfinimines (*S*)-**13** in good to excellent de (Scheme 2).[14] Hydrolysis of the α-amino phosphonates (S_S,*R*)-**14** using 3 N aqueous HCl in THF gives the amino carbonyl intermediates that cyclize to the cyclic imino phosphonates **15** in 69–82% yields. Reduction with Adam's catalyst (PtO_2) in ethanol afforded the corresponding cyclic α-amino phosphonates **16** to **18** in 49–87% yields without loss of enantiopurity.

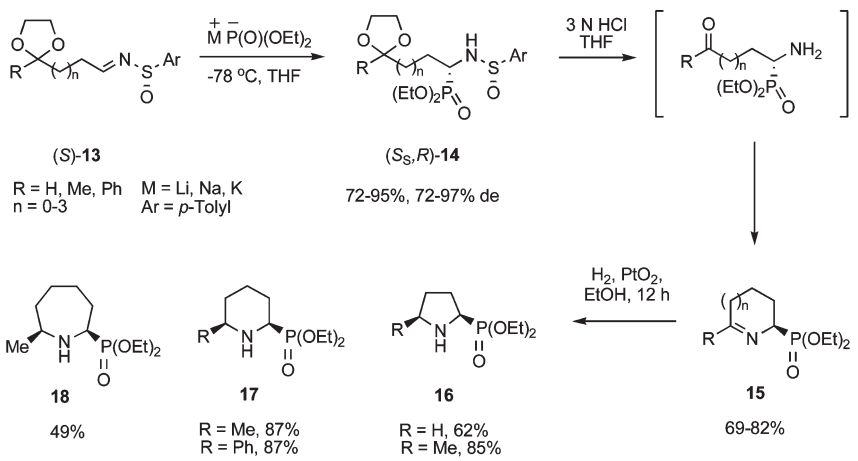
Davis and co-workers also reported the synthesis of cyclic quaternary α-amino phosphonates using masked oxo ketimines such as (*S*)-**19** (Scheme 3).[13] Because the oxo ketimine (*S*)-**19** are formed as inseparable *E*,*Z* mixtures, modest selectivity, 50% ee, was observed for α-amino phosphonates **22**.

2.4 Asymmetric synthesis of 2-substituted pyrrolidines

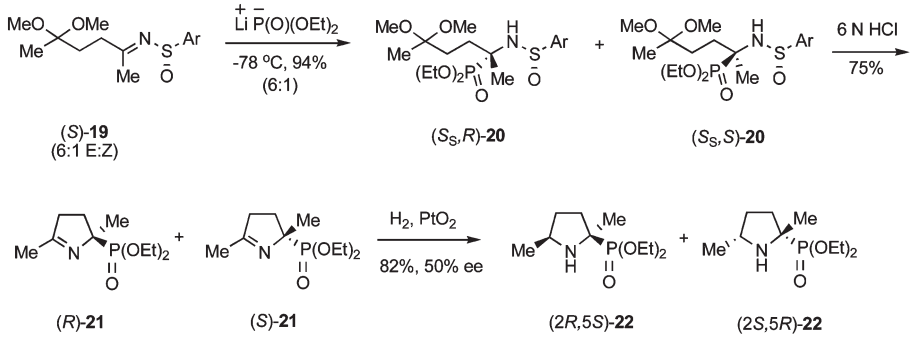
In a related study Brinner and Ellman reported the diastereoselective synthesis of 2-substituted pyrrolidines (*R*)-**27** (Scheme 4).[17] In this method the sulfinamide (R_s,*R*)-**25** was prepared by addition of masked oxo Grignard reagent **24**, prepared from 2-(2-bromoethyl)-1,3-dioxane, to *tert*-butanesulfinimines (*R*)-**23** with moderate diastereoselectivity. On treatment with TFA-H_2O followed by addition of Et_3SiH to reduce the intermediate dehydropyrrolidine **26**, 2-substituted pyrrolidines (*R*)-**27** were prepared in good to excellent yields.

2.5 Asymmetric synthesis of β-amino acids and β-lactams

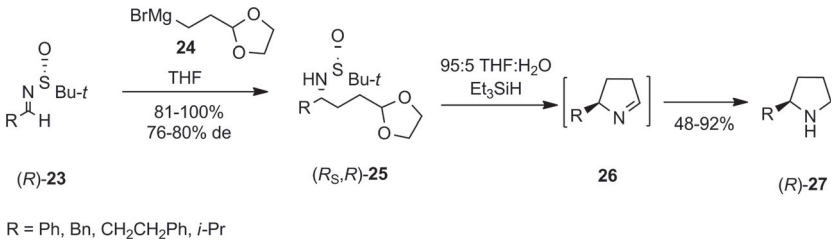
β-Amino acids are important in the synthesis of β-peptides and β-lactams and are readily prepared by the diastereoselective



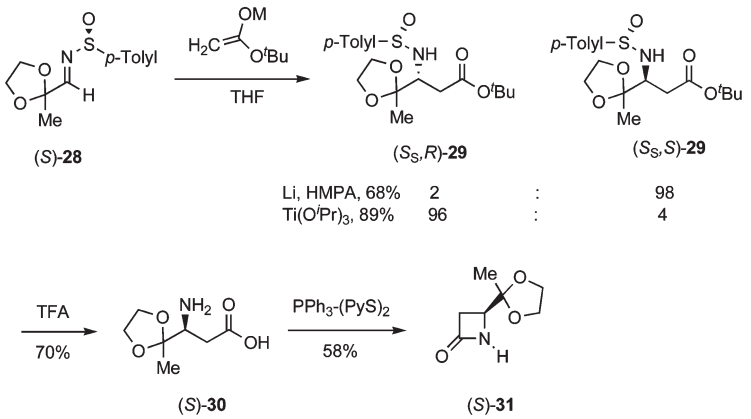
Scheme 2



Scheme 3



Scheme 4



Scheme 5

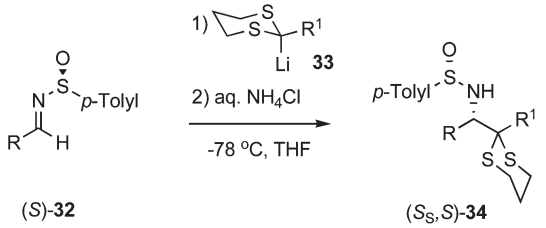
addition of metal enolates to sulfinimines.[5,20] In their synthesis of β-lactams, Fujisawa and co-workers prepared β-amino ester (*S*)-**29** by addition of the preformed enolate of *tert*-butyl acetate to sulfinimine (*S*)-**28** (Scheme 5).[15] In this study the authors observed an interesting switchover of the diastereofacial selectivity by changing the metal ion from lithium to titanium (Scheme 5). Hydrolysis of ester (S_S,*S*)-**29** with TFA followed by cyclization of β-amino acid **30** with PPh_3-$(PyS)_2$ afforded β-lactam **31**. It is noteworthy that under these hydrolysis conditions the ketal remained intact.

2.6 Asymmetric synthesis of α-amino carbonyl compounds

Enantiopure α-amino aldehydes and ketones are key chiral building blocks in the asymmetric synthesis of α-amino acids, α-amino alcohols, 1,2-diamines, allylic amines and many natural products.[6,21] In order to be useful, suitable *N*-protecting groups are necessary to prevent racemization and self-condensation. Furthermore, since most enantiopure α-amino carbonyl compounds are derived from *N*-protected α-amino acids access to both enantiomers is limited. *N*-Sulfinyl α-amino-1,3-dithianes (S_S,*S*)-**34**, masked oxo-sulfinamides, offer a general solution to both of these problems and are readily prepared by the diastereoselective addition of lithio-1,3-dithianes **33** to sulfinimines (*S*)-**32** (Table 1).[8,9]

Acid hydrolysis or treatment with the Dess–Martin periodinane (DMP) reagent selectively removes the *N*-sulfinyl group in **34e** (R = Ph) and **34f** (R = i-Pr) affording the enantiopure free amines **35** in good yield, leaving the keto group protected as the thioketal (Scheme 6).[8] While traditional thioketal hydrolysis methods would also remove the *N*-sulfinyl group, the Stork

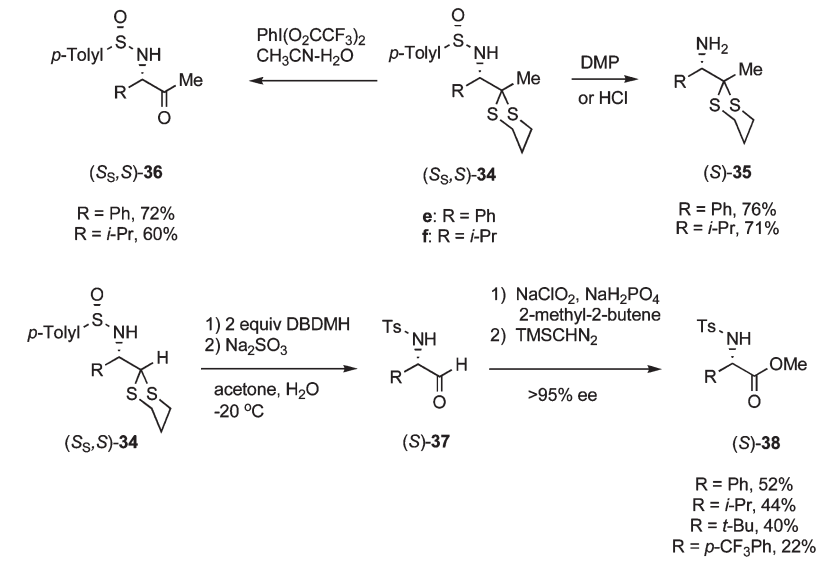
Table 1 Synthesis of *N*-sulfinyl α-amino-1,3-dithianes (S_S,*S*)-**34**[8,9]



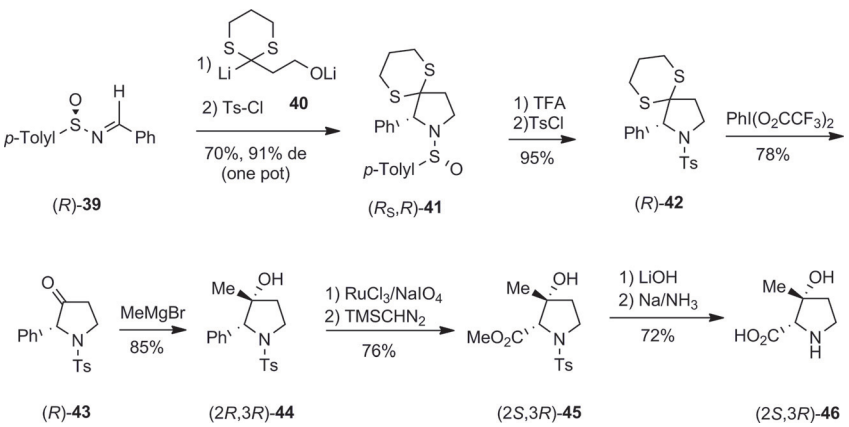
34	R	R^1	% de	% yield
a	Ph	H	82	73
b	i-Pr	H	72	70
c	*t*-Bu	H	96	72
d	*p*-CF_3Ph	H	80	75
e	Ph	Me	92	76
f	i-Pr	Me	>97	84

reagent, bis(trifluoroacetoxy)iodobenzene [$PhI(O_2CCF_3)_2$], was found to selectively give the stable *N*-sulfinyl α-amino methyl ketone (S_S,*S*)-**36**.[8] Hydrolysis of thioketals **34** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) produces *N*-tosyl α-amino aldehydes (*S*)-**37** and ketones (Scheme 6).[9c,d] The crude aldehydes **37** were transformed into *N*-tosyl α-amino acids **38** by a Pinnick-type oxidation without epimerization in >95% enantioselectivity.[9c] These transformations of *N*-sulfinyl α-amino-1,3-dithianes **34** illustrates the many opportunities for functional group manipulation not previously available for *N*-protected α-amino carbonyl compounds.

An example of the utility of *N*-sulfinyl α-amino 1,3-dithianes is the asymmetric synthesis of (2*S*,3*R*)-3-hydroxy-3-



Scheme 6



Scheme 7

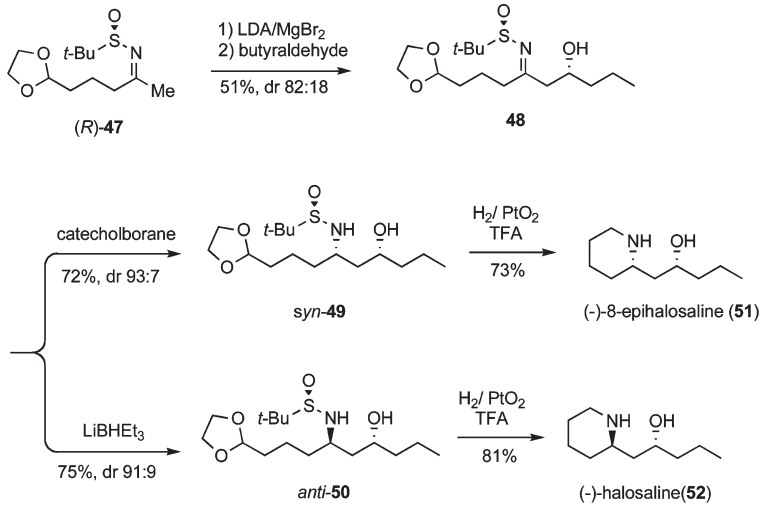
methylproline (**46**), a key component of the polyoxypeptins, a 19-member cyclic hexadepsipepatide antibiotic.[8] Here the benzaldehyde derived sulfinimine (*R*)-**39** was treated with dilithio species **40** and on treatment with Ts-Cl cyclized to pyrrolidine (R_S,*R*)-**41** in 91% de and 70% yield, all in one pot (Scheme 7). The *N*-sulfinyl was replaced with a tosyl group and hydrolysis of (*R*)-**42** with $PhI(O_2CCF_3)_2$ afforded the 3-oxo pyrrolidine **43** in 78% yield. Reaction of ketone **43** with excess methylmagnesium bromide afforded tertiary alcohol (2*R*,3*R*)-**44** as a single isomer in 85% yield. The C-2 phenyl group in **44** was oxidized with $RuCl_3/NaIO_4$ to give the acid and formation of the methyl ester gave hydroxy pyrrolidine (2*S*,3*R*)-**45** which was transformed in two steps to the target proline (2*S*,3*R*)-**46** (Scheme 7).

2.7 Asymmetric synthesis of 1,3-amino alcohols

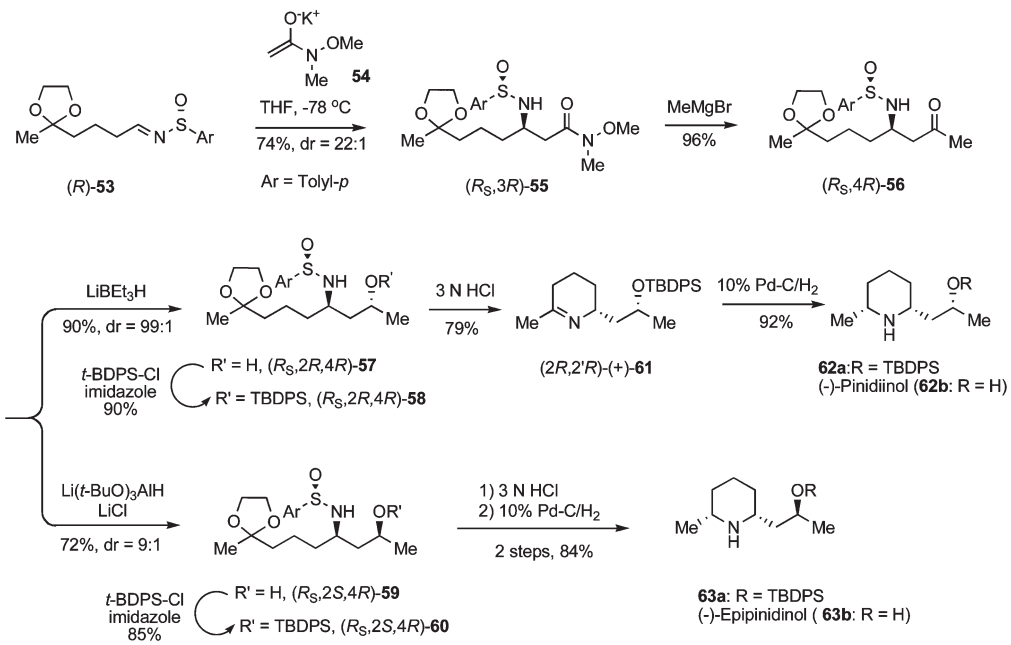
1,3-Amino alcohols are key structural components of pharmaceutically active molecules such as HIV protease inhibitors[22] and serotonin reuptake inhibitor antidepressants.[23] A number of natural products, including the sedum alkaloids, contain this moiety.[24] 1,3-Amino alcohols are also useful as chiral ligands and auxiliaries in asymmetric synthesis.[25] However, despite the importance of these amino alcohols there are few general methods for their preparation.

Ellman and co-workers devised a method for the asymmetric synthesis of both *syn*- and *anti*-1,3-amino alcohols from sulfinimine-derived β-hydroxy *N*-sulfinyl imines that were reduced to give either the *syn*- or *anti*-1,3-amino alcohol in high de.[26] In one example hydroxy imine **48** was prepared by addition of the metalloenamine derived from oxo-sulfinimine (*R*)-**47**, to butyraldehyde (Scheme 8). Reduction of **48** with catecholborane afforded sulfinamide *syn*-**49** in 72% yield and 93 : 7 dr. With $LiBHEt_3$ **48** gave the *anti*-sulfinamide **50** in 75% yield and 91 : 9 dr. These amino alcohols were transformed into alkaloids (−)-8-epihalosaline (**51**) and (−)-halosaline (**52**) in 73% and 81% yield, respectively, by treatment of amino alcohols **49** and **50** with TFA in the presence of PtO_2/H_2 (1 atm).

A more general method for the asymmetric synthesis of acyclic *syn*- and *anti*-1,3-amino alcohols was recently introduced by Davis *et al.* and involves the stereoselective reduction of



Scheme 8



Scheme 9

N-sulfinyl β-amino ketones.[16] The β-amino ketones are readily prepared by the addition of methyl ketone enolates to sulfinimines[27] or Grignard reagents to sulfinimine-derived β-amino Weinreb amides.[11] This methodology was highlighted in a formal asymmetric synthesis of two piperidine alkaloids, (−)-pinidinol (**62b**) and (+)-epipinidinol (**63b**) from a common masked oxo-sulfinamide **56** (Scheme 9).[16] Addition of enantiopure sulfinimine (*R*)-**53** to the preformed potassium Weinreb amide enolate **54** at −78 °C afforded *N*-sulfinyl β-amino Weinreb amide (R_S,3*R*)-**55** in 74% yield and 22 : 1 dr. With excess methylmagnesium bromide **55** gave β-amino ketone ketal (R_S,4*R*)-**56** in 96% yield, which is the key intermediate in the synthesis of alkaloids **62b** and **63b** (Scheme 9).

Reduction of β-amino ketone (R_S,*R*)-**56** with $LiBEt_3H$ gave the *anti*-1,3-amino alcohol (−)-**57** in 90% yield. By changing the reducing agent to Li(*t*-OBu)$_3$AlH in combination with LiCl the *syn*-1,3-amino alcohol **59** was obtained. The hydroxy groups were protected as the *tert*-butyldiphenylsilyl ethers to give **58** and **60** and hydrolysis gave the cyclic imine **61** in good yield. Hydrogenation of **61** with 10% Pd–C at 60 psi H_2 gave **62a** and is a formal synthesis of pinidinol (−)-**62b** (Scheme 9).

2.8 Asymmetric synthesis of substituted tropinones and homotropinones

An important method for the asymmetric synthesis of stereodefined piperidines is the acid-catalyzed intramolecular Mannich cyclization reaction of an *N*-sulfinyl β-amino ketone and an aldehyde.[28] In 2009, Davis and co-workers extended this methodology to the asymmetric synthesis of substituted tropinones

using *N*-sulfinyl β-amino ketone ketals.[29] In this synthesis, the objective was that hydrolysis of the ketone ketal would result in cyclization to give a dehydropyrrolidine ketone that under the acid conditions would undergo an intramolecular Mannich reaction to give the tropinone (Fig. 3).

N-Sulfinyl *δ*-amino β-ketoester ketal (S_S,*S*)-**65** was prepared in 69% yield by treating masked oxo-sulfinimine (*S*)-**64** with an excess of the sodium enolate of methyl acetate (Scheme 10).[29] However, hydrolysis with HCl-MeOH failed to give the tropinone, but resulted in dehydropyrrolidine (*S*)-**66** in 80% yield. When (*S*)-**66** was treated with $(Boc)_2O$, to generate the more reactive intermediate acyl iminium ion, the intramolecular Mannich reaction resulted in a 70 : 30 mixture of inseparable C-2 epimeric tropinones (1*R*,2*R*,5*S*)-**67** in 90% yield.

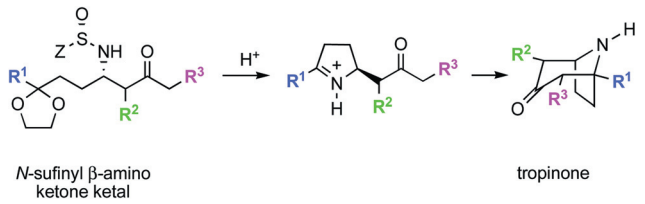
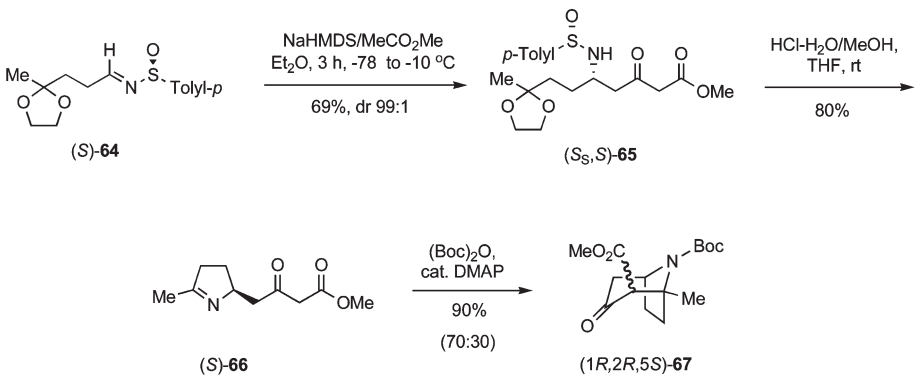


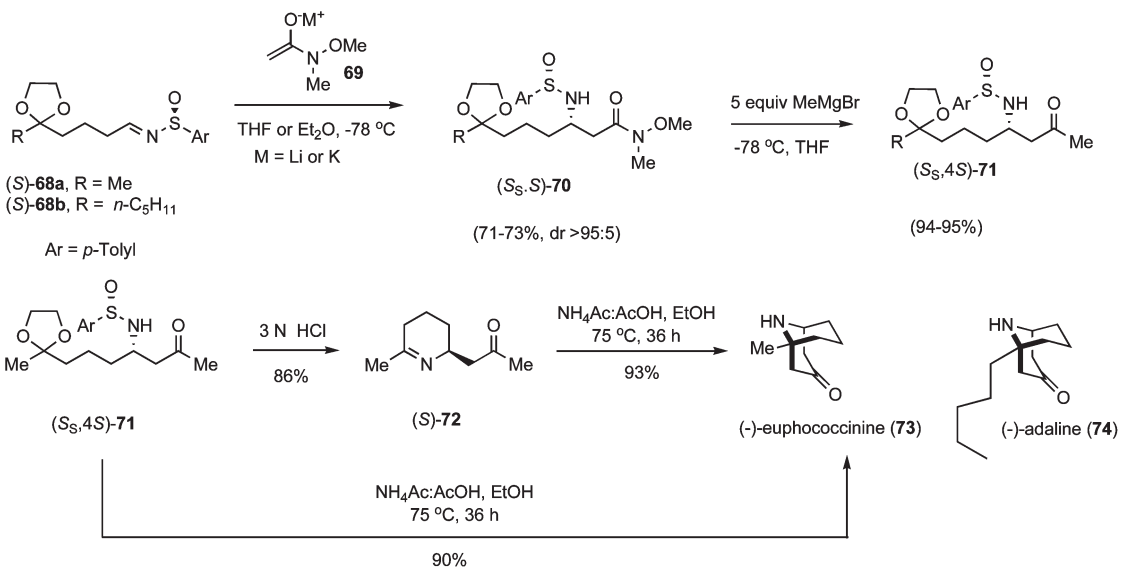
Fig. 3 Intramolecular Mannich cyclization to form tropinones.

Davis and Edupuganti reported an application of masked oxo-sulfinamides, *N*-sulfinyl β-amino ketone ketals, in the asymmetric synthesis of the homotropinones (−)-euphococcinine (**73**) and (−)-adaline (**74**) (Scheme 11).[30] These alkaloids are found in the secretions of the Coccinellid beetles (lady bugs) and are powerful deterrents to both spiders and ants. The requisite *N*-sulfinyl β-amino ketone ketals (S_S,*S*)-**71** were prepared in good yield by addition of MeMgBr to β-amino Weinreb amides (S_S,*S*)-**70**, which were prepared by the diastereoselective addition of the lithium or potassium enolate of **69** to sulfinimine (*S*)-**68** (Scheme 11).

On treatment with 3 N aqueous HCl in MeOH–THF β-amino ketone ketal (S_S,*S*)-**70a** (R = Me) did not produce homotropinone (−)-**73**, but afforded the corresponding piperideine ketone (*S*)-**72** in 86% yield.[30] However, heating ketone (*S*)-**72** at 75 °C with 10 equiv. of the buffer solution NH_4OAc : AcOH in ethanol for 36 h initiated the Mannich cyclization affording (−)-euphococcinine (**73**) in 93% yield (Scheme 11). Significantly, when the β-amino ketone ketal (S_S,*S*)-**71** was heated with NH_4OAc : AcOH for 36 h at 75 °C (−)-euphococcinine (**73**) was obtained



Scheme 10



Scheme 11

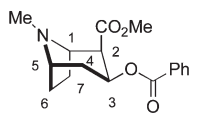
in 90% yield. Under similar conditions, but for 3.5 days, (S_S,*S*)-**71** (R = *n*-C_5H_{11}) gave (−)-adaline (**74**) in 85% yield. This four-step intramolecular Mannich cyclization reaction of *N*-sulfinyl β-amino ketone ketals (S_S,*S*)-**71** represents the most efficient method reported to date for the asymmetric synthesis of substituted homotropinone alkaloids.

2.9 Asymmetric total synthesis of cocaine and cocaine C-1 analogues

The relatively few enantioselective syntheses of (*R*)-(−)-cocaine (**75**) and cocaine analogues is due to the fact that the C-2 and C-3 substituents require a *cis*-relationship for biological activity (Fig. 4).[31] Furthermore, of cocaine's eight stereoisomers only the (*R*)-isomer (−)-(**75**) is a powerful stimulant and addictive. As a consequence most nonracemic cocaine analogs are derived from (*R*)-(−)-**75** and are modifications of the C-2 and C-3 substituents.[32]

In 2010 Davis, Theddu and Edupuganti described an enantioselective method, employing a masked oxo-sulfinamide, for the synthesis of (*S*)-(+)-cocaine (**83**) the enantiomer of (*R*)-(−)-**75**.[33] This procedure is related to Tufariello's racemic cocaine synthesis where a stereospecific [3 + 2] nitrone cycloaddition reaction was used to control the stereochemistry at C-2 and C-3 in **75**.[34] Here masked oxo-sulfinamide β-amino ester (R_S,*R*)-**76** was reduced and the aldehyde treated with trimethylphosphonoacetate in a Horner–Wadsworth–Emmons olefination reaction to give ketal sulfinamide (R_S*R*)-**78** in excellent yield (Scheme 12). Hydrolysis of **78** resulted in dehydropyrrolidine (*R*)-**79** and chemoselective oxidation with urea hydrogen peroxide (UHP) catalyzed by methyltrioxorhenium (MTO) afforded intermediate nitrone **80**. On heating, the nitrone underwent an intramolecular [3 + 2] cycloaddition to a tricyclic isoxazolidine, which on treatment with $MeSO_3Me$ gave isoxazolidine mesylate salt **81**. The salt was transformed in two steps, in excellent yield, to (*S*)-(+)-cocaine (**83**).[33]

The first examples of cocaine analogues to have substituents, Me, Et, *n*-Pr, *n*-C_5H_{11}, Ph, at the cocaine C-1 or bridgehead position were prepared in a similar manner.[31,33] Dehydropyrrolidines (*S*)-**84**, prepared by hydrolysis of the corresponding *N*-sulfinyl amino ketals, were selectively oxidized to nitrones **85** and on heating with the Lewis acid Al(O-*t*-Bu)$_3$ at 110 °C for 96 h gave the corresponding tricyclic isoxazolidines **86** in moderate yields. In three-steps the isoxazolidines were transformed into the C-1 cocaine analogues (1*R*,2*R*,3*S*,5*S*)-**87**. In the absence of the Lewis acid the nitrones **85** (R = Et, *n*-Pr, *n*-C_5H_{11}, Ph) gave oxaziridine intermediates **88** that rearranged under the reaction conditions to lactams (*S*)-**89** (Scheme 13).[31,33]

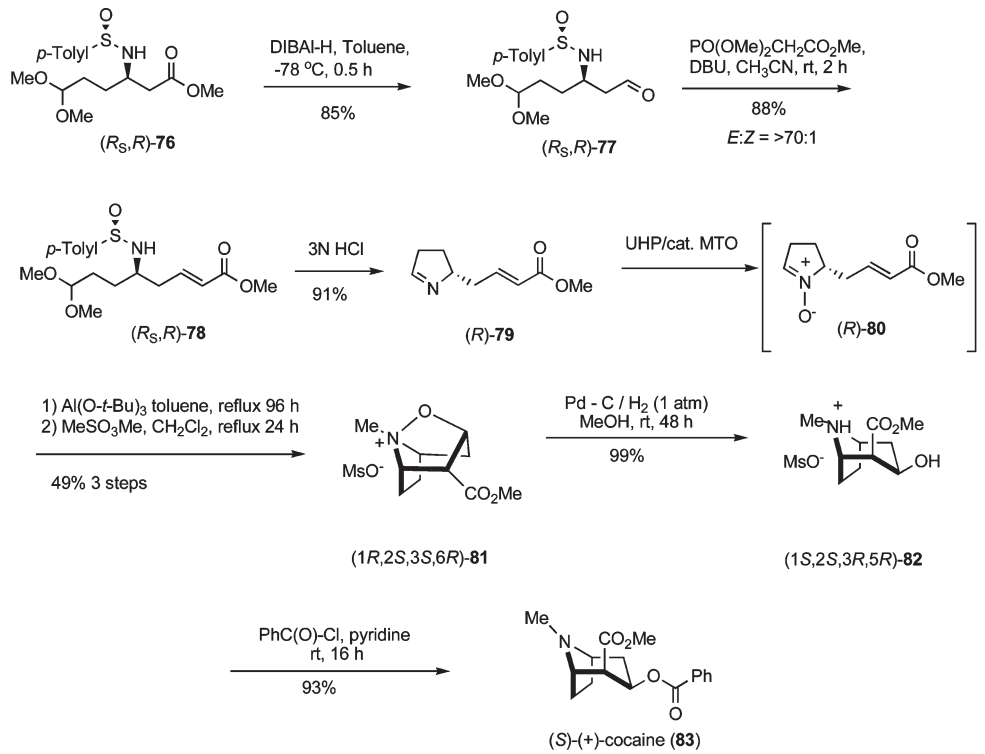


(*R*)-(-)-Cocaine (**75**)

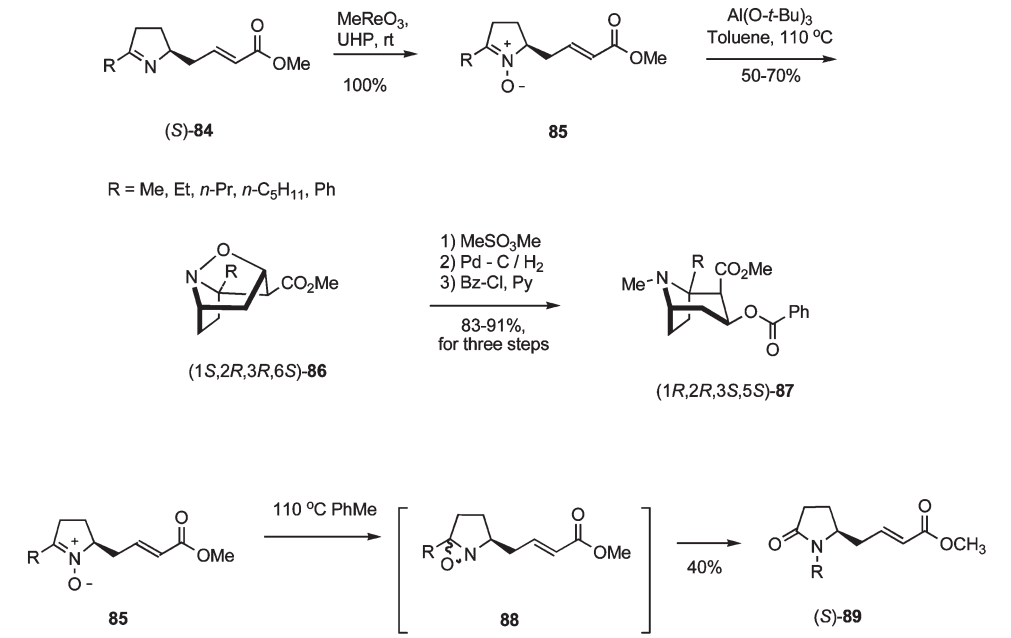
Fig. 4 (*R*)-(−)-Cocaine (**75**).

2.10 Asymmetric synthesis of other biologically significant molecules

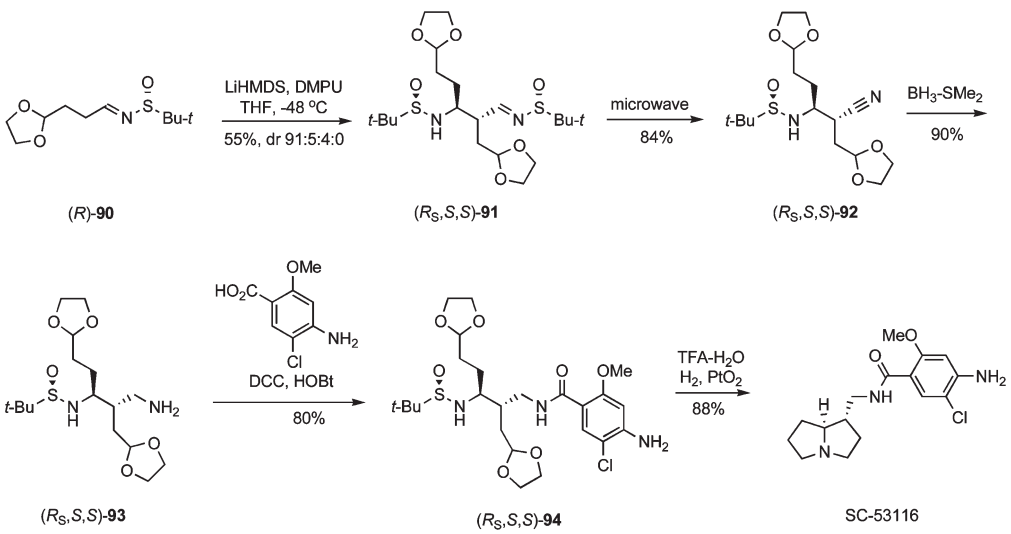
The pyrrolizidine alkaloid SC-53116, a serotonin 5-HT$_4$ receptor agonist, was prepared by Schenkel and Ellman from oxo-



Scheme 12



Scheme 13



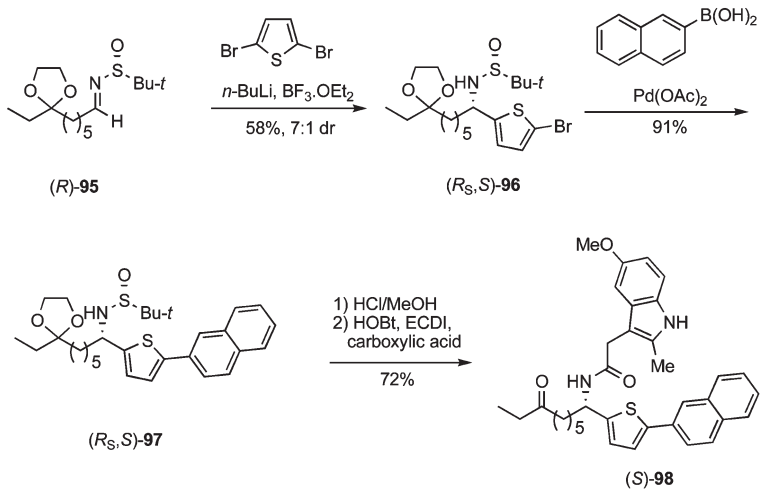
Scheme 14

sulfinamide (R_S,*S*,*S*)-**91**.[35] On treatment with LiHMDS in THF at −48 °C, sulfinimine (*R*)-**90**, underwent an intramolecular self-condensation reaction to give (R_S,*S*,*S*)-**91** in 55% yield as a 91 : 5 : 4 : 0 mixture of isomers (Scheme 14). Reduction of nitrile (R_S,*S*,*S*)-**92**, obtained on microwave irradiation of sulfinamide **91**, gave amine **93** which was transformed into amide **94**. The bis-ketal amide (R_S,*S*,*S*)-**94** was transformed in three-steps to pyrrolizidine SC-53116 (Scheme 14).

In efforts directed at developing a more general synthesis of histone deacetylase inhibitors (HDACi) for analog development, Kinzel and co-workers utilized masked oxo-sulfinamide bromothiophene (R_S,*S*)-**96** as a key intermediate.[36] Diastereoselective addition of 2-lithiobromothiophene to sulfinimine (*R*)-**95** afforded sulfinamide (R_S,*S*)-**96** which was cross-coupled with 2-naphthyl boronic acid using the Suzuki–Miyaura reaction affording sulfinamide (R_S,*S*)-**97** in 91% yield (Scheme 15). Hydrolysis and amide formation with (5-methoxy-2-methyl-1*H* indol-3yl) acetic acid gave the HDACi analog (*S*)-**98** in 72% yield.

3. Summary and conclusions

Enantiopure amino aldehydes and ketones continue to play key roles in the synthesis of biologically important natural products and pharmaceuticals, but require suitable carbonyl and/or amine protecting groups to be synthetically useful. Masked oxo-sulfinamides where the amino and carbonyl groups are both protected have emerged as important chiral building blocks for the asymmetric synthesis of diverse amine derivatives. These sulfinimine-



Scheme 15

derived polyfunctionalized chiral building blocks are particularly useful for the synthesis of nitrogen heterocycles because unmasking the amino and carbonyl groups results in intramolecular cyclization leading to cyclic imines, which are elaborated to proline and pipecolic acid derivatives, pyrrolidines, tropinone and homotropinones, and tropane alkaloids such as cocaine and its analogues. In addition to the synthesis of nitrogen heterocycles these amino carbonyl compounds have found applications in the synthesis of *syn*- and *anti*-1,3-amino alcohols and α-amino aldehydes and ketones. Masked oxo-sulfinamides are easily prepared by addition of organometallic reagents to masked-oxo sulfinimines or the addition of oxo-organometallic and lithio-1,3-dithianes to sulfinimines. It is hope that this brief perspective on oxo-sulfinamide chemistry will stimulate new applications for these versatile polyfunctionalized chiral building blocks.

Acknowledgements

We thank Dr Naresh Theddu, Department of Chemistry, University of Michigan for helpful discussions and comments.

Notes and references

1 For leading references see: (*a*) F. A. Davis, *J. Org. Chem.*, 2006, **71**, 8993–9003; (*b*) F. A. Davis, B. Chao, T. Fang and J. M. Szewczyk, *Org. Lett.*, 2000, **2**, 1041–1043.
2 For leading references to sulfinimine-derived chiral building blocks see: (*a*) F. A. Davis, J. Zhang and Y. Wu, *Tetrahedron Lett.*, 2011, **52**, 2054–2057; (*b*) F. A. Davis, B. Yang, J. Deng and J. Zhang, *ARKIVOC*, 2006, 120–128; (*c*) F. A. Davis, B. Chao, Y. W. Andemichael, P. K. Mohanty, T. Fang, D. M. Burns, A. Rao and J. M. Szewczyl, *Heteroat. Chem.*, 2002, **13**, 486–492.
3 F. A. Davis, A. J. Friedman and E. W. Kluger, *J. Am. Chem. Soc.*, 1974, **96**, 5000–5001.
4 G. Liu, D. A. Coogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1997, **119**, 9913–9914.
5 For reviews on sulfinimine chemistry see: (*a*) M. T. Robak, M. A. Herbage and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 3600–3740; (*b*) F. Ferreira, C. Botuha, F. Chemla and A. Pérez-Luna, *Chem. Soc. Rev.*, 2009, **38**, 1162–1186; (*c*) D. Morton and R. A. Stockman, *Tetrahedron*, 2006, **62**, 8869–8905; (*d*) Ref. 3 (*e*) C. H. Senanayake, D. Krishnamurthy, Z.-H. Lu, Z. Hau and I. Gallou, *Aldrichimica Acta*, 2005, **38**, 93–104; (*f*) P. Zhou, B.-C. Chen and F. A. Davis, *Tetrahedron*, 2004, **60**, 8003–8030; (*g*) J. A. Ellman, T. D. Owens and T. P. Tang, *Acc. Chem. Res.*, 2002, **35**, 984–995; (*h*) F. A. Davis, P. Zhou and B.-C. Chen, *Chem. Soc. Rev.*, 1998, **27**, 13–18.
6 For a review on amino carbonyl compounds see: S. Baktharaman, R. Hili and A. K. Yudin, *Aldrichimica Acta*, 2008, **41**, 109–119.
7 For leading references see: C. B. Jacobsen, L. Lykke, D. Monge, M. Nielsen, L. K. Ransborg and K. A. Jorgensen, *Chem. Commun.*, 2009, 6554–6556.
8 F. A. Davis, T. Ramachandar and H. Liu, *Org. Lett.*, 2004, **6**, 3393–3395.
9 (*a*) F. A. Davis, T. Ramachandar, J. Chai and E. Skucas, *Tetrahedron Lett.*, 2006, **47**, 2743–2746; (*b*) F. A. Davis and T. Ramachandar, *Tetrahedron Lett.*, 2008, **49**, 870–872; (*c*) F. A. Davis, T. Ramachandar, J. Chai and H. Qiu, *ARKIVOC*, 2010, 17–26; (*d*) F. A. Davis and J. Chai, *ARKIVOC*, 2008, 190–203.
10 C. L. Harrison, M. Krawiec, R. E. Forslund and W. A. Nugent, *Tetrahedron*, 2011, **67**, 41–57.
11 (*a*) F. A. Davis, M. B. Nolt, Y. Wu, K. R. Prasad, D. Li, B. Yang, K. Bowen, S. H. Lee and J. H. Erdley, *J. Org. Chem.*, 2005, **70**, 2184–2190; (*b*) F. A. Davis and P. Xu, *J. Org. Chem.*, 2011, **76**, 3329–3337.
12 For leading references see: F. A. Davis and N. Theddu, *J. Org. Chem.*, 2010, **75**, 3814–3820.
13 F. A. Davis, H. Zhang and S. H. Lee, *Org. Lett.*, 2001, **3**, 759–762.
14 F. A. Davis, S. H. Lee and H. Xu, *J. Org. Chem.*, 2004, **69**, 3774–3781.
15 T. Fujisawa, Y. Kooriyama and M. Shimizu, *Tetrahedron Lett.*, 1996, **37**, 3881–3884.
16 F. A. Davis, P. M. Gaspari, B. Nolt and P. Xu, *J. Org. Chem.*, 2008, **73**, 9619–9626.
17 K. M. Brinner and J. A. Ellman, *Org. Biomol. Chem.*, 2005, **3**, 2109–2113.
18 (*a*) Y. N. Belokon, A. G. Bulychev, V. A. Pavolov, E. B. Fedorova, V. A. Tsyryapkin, V. A. Bakhmutov and V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2075–2083; (*b*) M. E. Swarbrick, F. Gosselin and W. D. Lubell, *J. Org. Chem.*, 1999, **64**, 1993–2002.
19 S. C. Turner, H. Zhai and H. Rapoport, *J. Org. Chem.*, 2000, **65**, 861–870.
20 F. A. Davis, R. E. Reddy and J. M. Szewczyk, *J. Org. Chem.*, 1995, **60**, 7037–7039.
21 (*a*) J. Jurczak and A. Golebiowski, *Chem. Rev.*, 1989, **89**, 149–164; (*b*) M. T. Reetz, *Chem. Rev.*, 1999, **99**, 1121–1162; (*c*) M. R. Paleo, M. I. Calaza and F. J. Sardina, *J. Org. Chem.*, 1997, **62**, 6862–6869.
22 (*a*) D. J. Kempf, K. C. Marsh, J. F. Denissen, E. McDonald, S. Vasavanonda, C. A. Flentge, B. E. Green, L. Fino, C. H. Park, X.-P. Kong, N. E. Wideburg, A. Saldivar, L. Ruiz, W. M. Kati, H. L. Sham, T. Robins, K. D. Stewart, A. Hsu, J. J. Plattner, J. M. Leonard and D. W. Norbeck, *Proc. Natl. Acad. Sci. U. S. A.*, 1995, **92**, 2484–2488; (*b*) H. L. Sham, C. Zhao, L. Li, D. A. Betebenner, A. Saldivar, S. Vasavanonda, D. J. Kempf, J. J. Plattner and D. W. Norbeck, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3101–3103.
23 (*a*) P. R. Carlier, M. M.-C. Lo, P. C.-K. Lo, E. Richelson, M. Tatsumi, I. J. Reynolds and T. A. Sharma, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 487–492.

24 R. W. Bates and K. Sa-Ei, *Tetrahedron*, 2002, **58**, 5957–5978.
25 S. M. Lait, D. A. Rankic and B. A. Keay, *Chem. Rev.*, 2007, **107**, 767–796.
26 (*a*) T. Kochi, T. P. Tang and J. A. Ellman, *J. Am. Chem. Soc.*, 2002, **124**, 6518–6519; (*b*) T. Kochi, T. P. Tang and J. A. Ellman, *J. Am. Chem. Soc.*, 2003, **125**, 11276–11282.
27 F. A. Davis and B. Yang, *Org. Lett.*, 2003, **5**, 5011–5014.
28 For leading references see ref. 1*a*.
29 F. A. Davis, N. Theddu and P. M. Gaspari, *Org. Lett.*, 2009, **11**, 1647–1650.
30 F. A. Davis and R. Edupuganti, *Org. Lett.*, 2010, **12**, 848–851.
31 F. A. Davis, N. V. Gaddiraju, N. Theddu, J. R. Hummel, S. K. Kondaveeti and M. J. Zdilla, *J. Org. Chem.*, 2012, **77**, 2345–2359 and references cited therein.
32 S. Singh, *Chem. Rev.*, 2000, **100**, 925–1024.
33 F. A. Davis, N. Theddu and R. Edupuganti, *Org. Lett.*, 2010, **12**, 4118–4121.
34 J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong and S. A. Ali, *J. Am. Chem. Soc.*, 1979, **101**, 2435–2442.
35 L. B. Schenkel and J. A. Ellman, *Org. Lett.*, 2004, **6**, 3621–3624.
36 C. Schultz-Fademrecht, O. Kinzel, I. E. Marko, T. Pospisil, S. Pesci, M. Rowley and P. Jones, *Tetrahedron*, 2009, **65**, 9487–9493.