Use of samarium diiodide in the field of asymmetric synthesis†

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Samarium diiodide may be a useful reagent in a step of an asymmetric synthesis process. It can release a blocking group in mild conditions, as described in several examples. SmI_2 has been used as electron donor in many C–C bond formations in presence of a chiral auxiliary. It can also generate samarium enolates which were subjected to asymmetric protonation. The examples selected in this review of SmI_2 methodology concern only the cases where the chiral auxiliary is not retained in the final product.

1. Introduction

Thirty years ago a paper was published at the beginning of the first issue of *Nouveau Journal de Chimie* (ancestor of the present *New Journal of Chemistry*) a note entitled "A new preparation of some divalent lanthanide iodides and their usefulness in organic synthesis" with J. L. Namy, P. Girard and H. B. Kagan as co-authors.[1] The first full paper was published three years later,[2] including many results obtained by P. Girard in his PhD work. Samarium diiodide was a salt already mentioned in 1906 and of interest for inorganic chemists.[3] It has never been studied for applications in organic chemistry. It has the potential to act as a reducing agent (one electron donor) since Sm^{3+} is the stable oxidation state. Moreover the solubility of SmI_2 in THF ($\sim$0.1 M) and change of colour from deep green (Sm^{2+}) to yellow (Sm^{3+}) allowed to readily screen various organic transformations. In the paper which was published in 1977, we reported the possibility to perform samarium Barbier reactions, selective reduction of aldehydes in the presence of ketones, and Meerwein–Ponndorf–Verley (MPV) reductions.[1] The scope of the transformations induced by SmI_2 quickly enlarged, many reviews are devoted to this reagent.[4–16] The application in total synthesis of complex natural products have been reported.[13,17] Reactions which are *catalytic in SmI_2* thanks to a stoichiometric amount of a co-reducing agent (zinc,[18] magnesium,[19] and mischmetall[20]) are also possible. Some of the reactions of SmI_2 are surprisingly fast in mild conditions, allowing to work on polyfunctional systems. The influence of simple additives (water, alcohols, amines, HMPA *etc.*) can modulate the reactivity of SmI_2 and induce specific reactions.[16] Interestingly, many C–C bond formations, especially in polyfunctional molecules, were achieved with a high degree of diastereoselectivity, because of chelating effects involving Sm^{2+} or Sm^{3+} ions.[6]

The SmI_2 technologies developed during the last thirty years and became an important tool in organic synthesis. This review is intended to highlight the use of samarium diiodide in the field of *asymmetric synthesis* from several points of view. We will show that SmI_2 is now an established and mild reagent to remove some protecting groups after a process of asymmetric synthesis. Then will be discussed the use of SmI_2 in the creation of a chiral unit under the influence of a removable chiral auxiliary either linked to a substrate or to a reagent. These two classes will be categorized for simplicity as enantioselective asymmetric synthesis and diastereoselective asym-

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† Dedicated to the memory of Professor A. I. Meyers who died in October 2007.

Kovuru Gopalaiah

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metric synthesis, although in both cases diastereomeric transition states are involved. Catalytic reactions by respect to the chiral auxiliary will be also discussed.

2. Release of protecting groups

In the devise of an asymmetric synthesis it is often necessary to introduce protecting groups close to the prochiral center or to a remote position. After the stereogenic center has been created it is needed to selectively remove the protecting group. In that purpose samarium diiodide appeared to be very useful for cleavage of *N–N*, *N–S*, *C–O* and *C–S* bonds in mild conditions. Some examples will illustrated below this methodology.

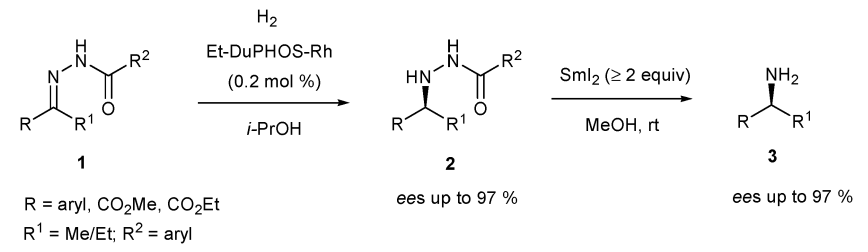
2.1 N–N bond cleavage

The creation of a stereogenic center vicinal to a NH_2 group may be performed by reduction or addition of a nucleophilic agent to a C=N–N′ precursor, where N′ is a group which has to be released in a final step. Samarium diiodide is now commonly used for that purpose.

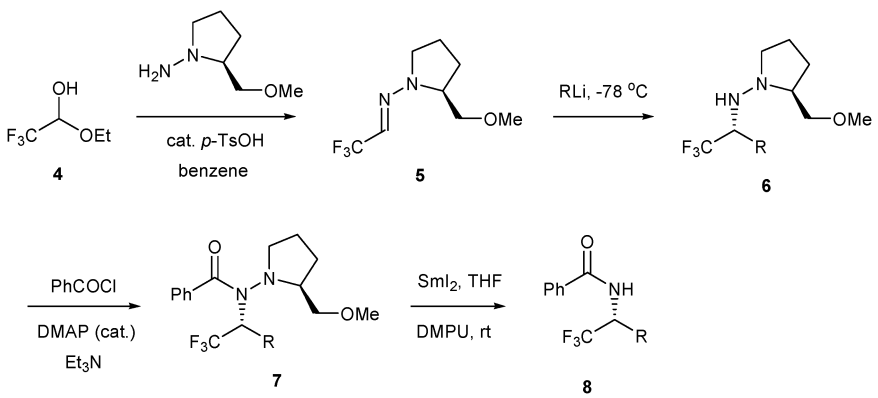
Burk *et al.* have reported a catalytic asymmetric hydrogenation of the C=N group of *N*-aroylhydrazones **1** using rhodium/DUPHOS catalyst, and transformation of the resulting *N*-aroylhydrazines **2** into chiral amines **3** (Scheme 1).[21a,b] Cleavage of the *N–N* bond of **2** with SmI_2, resulted amines **3** in 75–90% yield with no loss of enantiomeric purity.

Enders *et al.* have described the asymmetric synthesis of α-trifluoromethyl-substituted primary amines *via* nucleophilic 1,2-addition of alkyllithium reagents to trifluoroacetaldehyde SAMP- or RAMP-hydrazone **5** followed by benzoylation and SmI_2-promoted nitrogen–nitrogen single bond cleavage (Scheme 2).[22] Reaction of hydrazone **5** derived from trifluoroacetaldehyde ethyl hemiacetal **4** and SAMP, with alkyllithiums (*n*-BuLi, EtLi, *n*-PrLi, *n*-HexLi) led to the corresponding trifluoromethylated hydrazides **6** in 68–79% yields with excellent diastereoselectivity (>96%). After benzoylation of **6**, the chiral auxiliary was easily cleaved by treatment of **7** with 3 equiv. of SmI_2 in the presence of 1,3-dimethyltetrahydro-2(1*H*)-pyrimidone (DMPU), it afforded the (*R*)-α-trifluoromethylated amines **8** without detectable racemization. Similarly, cleavage of various SAMP- or RAMP-hydrazides **7** (R = *n*-Bu, *n*-Pr, *n*-Hex, *t*-Bu, Ph), provided the corresponding amides **8** in 71–90% yields with excellent *ee*s (up to >99%).

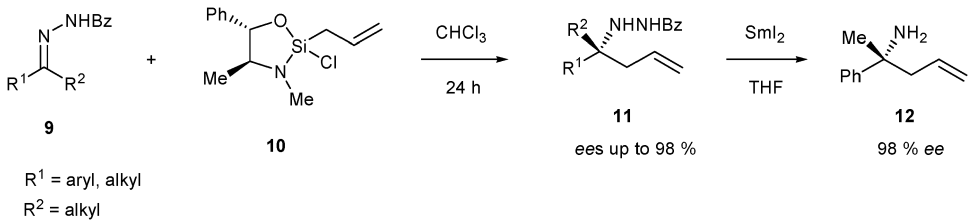
The enantioselective synthesis of tertiary carbinamine **12** *via* asymmetric allylation of ketone-derived benzoylhydrazones **9** have been reported by Leighton and co-workers (Scheme 3).[23] Reaction of **9** with allylsilane **10**, gave the corresponding



Scheme 1



Scheme 2



Scheme 3

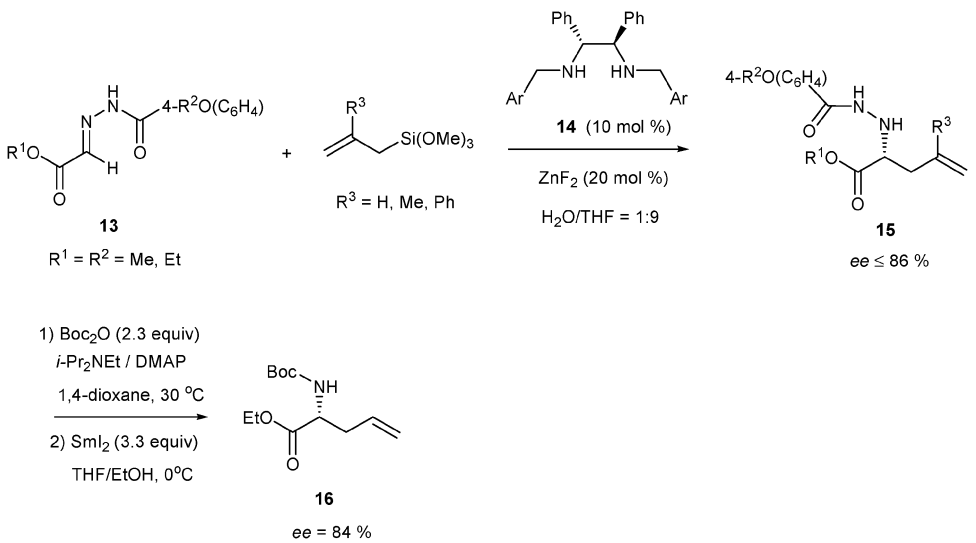
hydrazide **11** in good yields (64–95%) and high enantioselectivities. Cleavage of the *N–N* bond of the hydrazide **11** (R^1 = Ph, R^2 = Me) was accomplished using SmI_2, it led to the free amine **12** in 86% yield.

Kobayashi *et al.* have reported a catalytic asymmetric allylation of hydrazonoester **13** derived from ethyl glyoxylate, with allyltrimethoxysilane in aqueous media by using ZnF_2 and a chiral diamine **14** (Scheme 4).[24] It furnished hydrazine **15** in good yields (up to 99%) and enantioselectivities. Hydrazine **15** was converted into synthetically important *N*-Boc α-amino acid ester **16**. *N*-Boc protection of **15** (R^1 = Et, R^2 = Me, R^3 = H, 82% yield) and subsequent cleavage of *N–N* bond of the hydrazine with SmI_2, afforded **16** in 91% yield without significant loss of the enantiomeric purity.

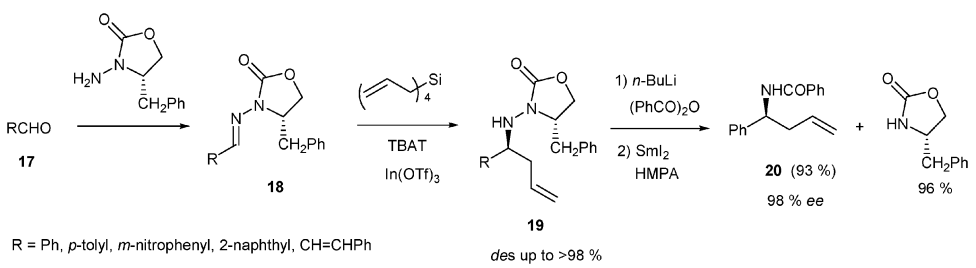
Reaction of hydrazones **18** derived from the aldehydes **17**, with tetraallylsilane gave allyl adducts **19** in 51–94% yields with excellent stereoselectivity in the presence of tetrabutylammonium triphenyldifluorosilicate (TBAT) and $In(OTf)_3$ (Scheme 5).[25] Removal of the auxiliary in **19** (R = Ph) was accomplished by benzoylation of the *NH*-group followed by treatment of SmI_2, affording the chiral amide **20**.

The trifluoroacetyl-activated nitrogen–nitrogen bond cleavage of hydrazines by samarium(II) iodide have also been studied.[26] The comparative studies focused on the effect of trifluoroacetyl and benzoyl groups in the *N–N* bond activation, and on the effect of additives on the *N–N* bond cleavage, in the cases of **22** and **23** (Scheme 6, eqn (1); Table 1). Substrates **22** and **23** were prepared by lithiation of **21** and reaction with benzoic anhydride or trifluoroacetic anhydride (TFAA), respectively. The *N*-benzoyl hydrazine **22** was exposed to SmI_2 in the presence of either HMPA or MeOH as an additive, afforded benzamide **24** in high yield (entries 1 and 2). Unfortunately, hydrolysis of the benzamide **24** to the corresponding primary amine required harsh conditions that ultimately caused decomposition. The *N*-TFA hydrazine **23** treated with samarium(II) iodide in the presence of HMPA gave good yield of trifluoroacetamide **25** (entry 4). Replacing HMPA with MeOH improved the results (entry 5). In the absence of additive yields decreased (entries 3 and 6) due to some side reactions. The scope of the reaction was explored by cleavage of various types of hydrazines **26** with SmI_2, afforded the corresponding trifluoroacetamides **27** in excellent yields (91–96%) without racemization (Scheme 6, eqn (2)).[26] Finally, removal of the TFA protecting group from **27** (R^1 = 3,4-$(OMe)_2C_6H_3$, R^2 = allyl) was accomplished under mild conditions.

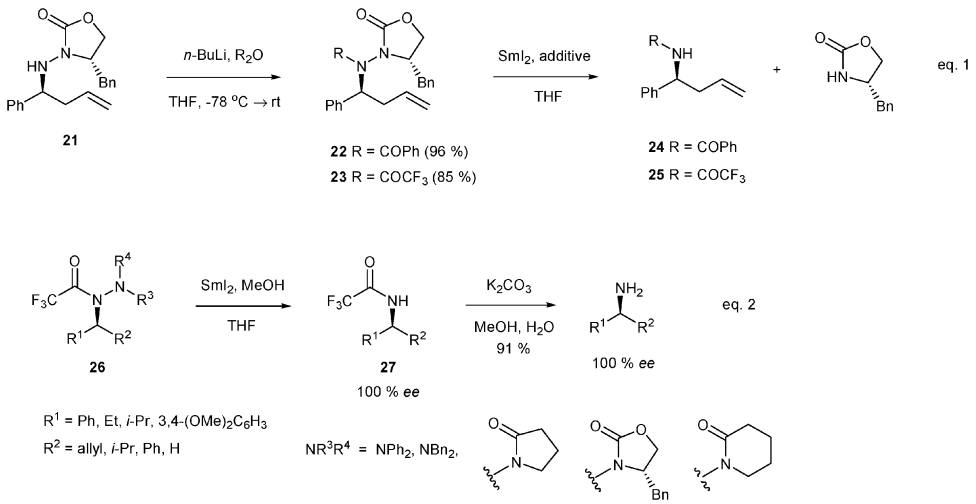
Jørgensen *et al.* have reported organocatalytic asymmetric amination of α-substituted α-cyanoacetates **28**, with di-*tert*-butyl azodicarboxylate **29**, catalyzed by quinidine-derived alkaloid β-isocupreidine **30** (Scheme 7).[27] It gave the corresponding hydrazine adducts **31** in quantitative yields with excellent enantioselectivities. The substrate generality was further explored by the reaction of various β-keto esters **32a–c** and a β-diketone **32d** with azodicarboxylate **29**. The desired amination products were obtained in excellent yields (86–99%) with enantioselectivities ranging from 83 to 90% *ee*.



Scheme 4



Scheme 5



Scheme 6

Table 1

Entry	Hydrazine	Additive	Product (yield %)
1	**22**	HMPA	**24** (96)
2	**22**	MeOH	**24** (94)
3	**22**	None	**24** (68)
4	**23**	HMPA	**25** (83)
5	**23**	MeOH	**25** (95)
6	**23**	None	**25** (67)

Hydrazine *N–N* bond in **31** was cleaved to access to quaternary α-amino acid derivatives. Substrate **31** (Ar = Ph) in the presence TFAA followed by reaction with SmI_2 gave **33** in 46% yield without any loss of enantiomeric excess.

Barbas III *et al.* have reported an enantioselective total synthesis of cell adhesion inhibitor **BIRT-377**, a potent inhibitor of the interaction between intercellular adhesion molecular-1 and lymphocyte function-associated antigen-1, *via* tetrazole-catalyzed asymmetric α-amination of aldehyde **34** with dibenzyl azodicarboxylate (Scheme 8).[28] The amination product **35** was obtained in 95% yield with 80% *ee*, it was then transformed into trifluoroacetyl derivative **36** by several steps. The *N–N* bond of **36** was cleaved by treatment of SmI_2, it provided the Cbz-protected quaternary amino acid methyl ester **37**. It was further transformed by several steps into BIRT-377.

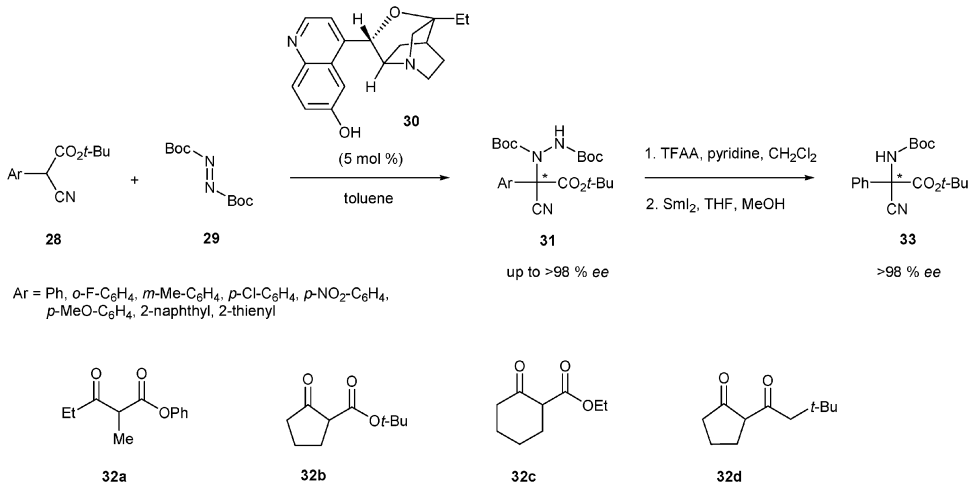
2.2 N–S Bond cleavage

Tomioka *et al.* have developed a catalytic asymmetric arylation of *N*-tosylarylimines **38** with arylboroxines **39** by using a chiral amidomonophosphane rhodium(I) catalyst (Scheme 9).[29] It gave the corresponding *N*-tosyl-diarylmethylamides **40** in 83–99% yield and enantioselectivities up to 94%. Substrate **40** (Ar^1 = Ph, Ar^2 = 4-Ph–C_6H_4) was exposed to samarium iodide in THF-HMPA, and transformed into the corresponding detosylated (*R*)-**41** in 98% yield without any loss of enantiomeric purity.

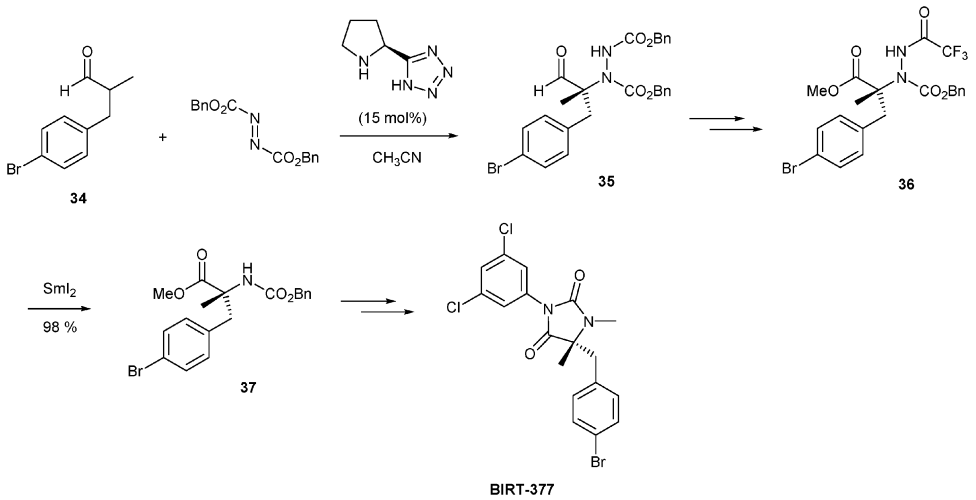
2.3 C–O Cleavage

The alcohol functionality may be released by reductive cleavage of an ether if there is a vicinal carbonyl, samarium diiodide has been used for this purpose in some asymmetric syntheses.

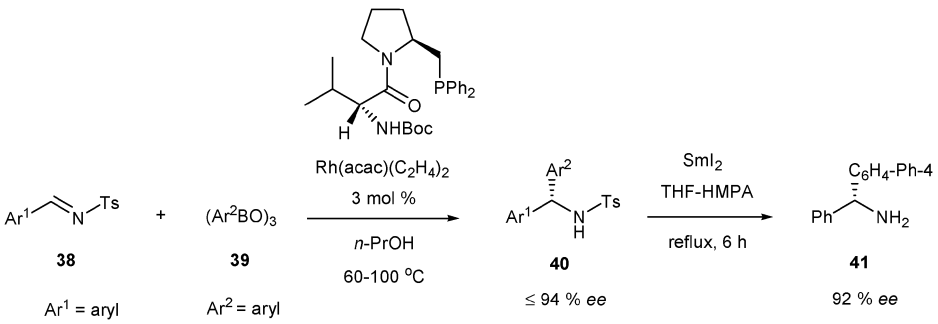
Guindon *et al.* have studied the asymmetric synthesis of secondary alcohols from tartrate acetals.[30] Addition of Me_2BBr



Scheme 7



Scheme 8

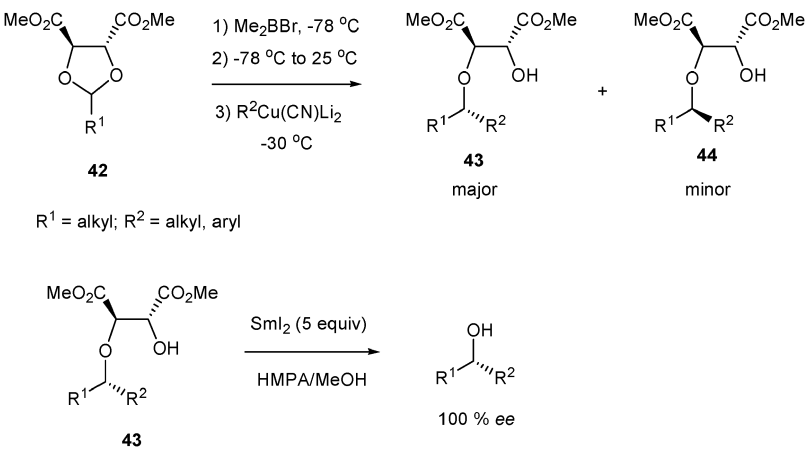


Scheme 9

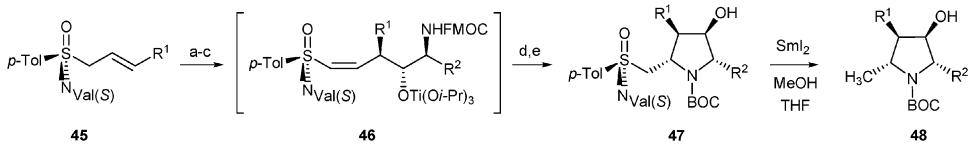
to acetal **42** at −78 °C followed by the introduction of $Me_2Cu(CN)Li_2$ gave a mixture of diastereomers **43** and **44** in 60–80% yields with high diastereoselection (up to 34 : 1) (Scheme 10). The major isomer **43** was isolated, and the tartrate auxiliary was cleaved by using SmI_2 in the presence of HMPA.

2.4 C–S Cleavage

Reggelin *et al.* have reported the stereoselective synthesis of enantiomerically pure pyrrolidine derivatives **48** from chiral titanated 2-alkenylsulfoximides **46** (Scheme 11).[31] Reaction of sulfoximides **45** with chlorotris(isopropoxy)titanium and FMOC-protected α-aminoaldehydes in the presence of *n*-BuLi, formed *O*-titanated intermediate **46** (not isolated). Removal of the FMOC group in **46** results a free NH_2 group, which attacks the acceptor-substituted double bond of the vinylsulfoximide, it afforded the 5-sulfonimidoylmethyl-substituted heterocycle **47** after treatment with Boc_2O. Cleavage of the auxiliary in **47** was accomplished with samarium diiodide, it led to enantiopure pyrrolidine derivative **48** in moderate yields (21–63%) with excellent enantioselectivity



Scheme 10



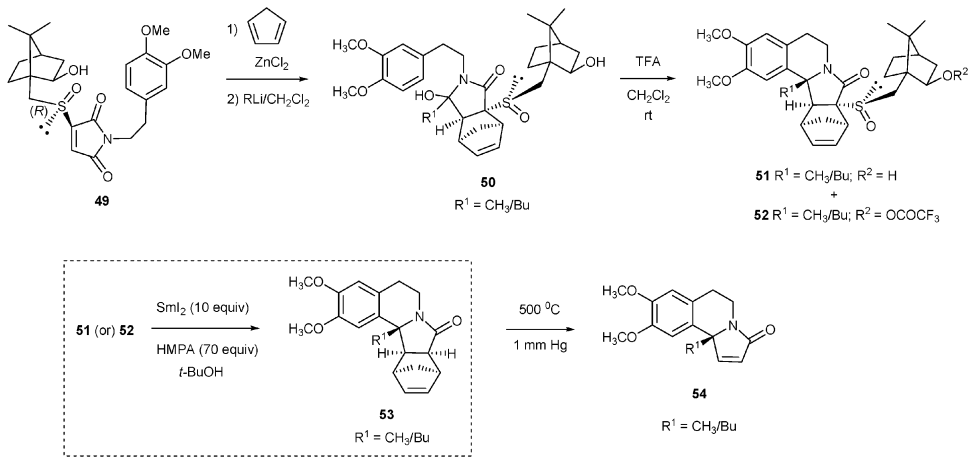
45 46 47 48

R^1 = H, Me

R^2 = Bn, *i*-Bu, *i*-BuOCH$_2$

a) *n*-BuLi, -78 °C, b) Chlorotris(isopropoxy)titanium, 0 °C, c) (*R*)-R_2CH(NHFMOC)CHO/THF, d) Piperidine, 20 °C; $(NH_4)_2CO_3$, NH_4Cl; e) K_2CO_3, MeOH; Boc_2O, $NaHCO_3$

Scheme 11



49 50 51 (or) 52 53 54

R^1 = CH_3/Bu

51 R^1 = CH_3/Bu; R^2 = H + 52 R^1 = CH_3/Bu; R^2 = $OCOCF_3$

Scheme 12

(≥ 96%). Similar transformations have been performed for the enantiomer of **45** affording the *ent*-**48**.

These transformations are strictly speaking not in the framework of the asymmetric synthesis as we defined it in the introduction, since the chiral auxiliary is not released. However the *C*—*S* cleavage in sulfoximides realized here gives good features for asymmetric synthesis.

Lete *et al*. have reported the asymmetric synthesis of pyrrolo[2,1-*a*]isoquinolines **54** starting from enantiopure sulfinylmaleimide **49** (Scheme 12).[32] Reaction of **49** with cyclopentadiene followed by alkyl lithium, afforded α-hydroxylactams **50** in quantitative yields as single diastereoisomers. Treatment of **50** with an excess of TFA at room temperature furnished isoquinolines **51**, together with their derivatives **52**, in which trifluoroacetylation of the hydroxyl group of the auxiliary had occurred. Mixtures were separated, and reductive desulfinylation was performed separately with SmI_2, afforded **53** in 83–96% yields and >99% *ee*'s. Retro-Diels–Alder reaction of **53** using a FVP technique produced the α,β-unsaturated pyrroloisoquinolines **54** in 80–85% yields and >99% *ee*.

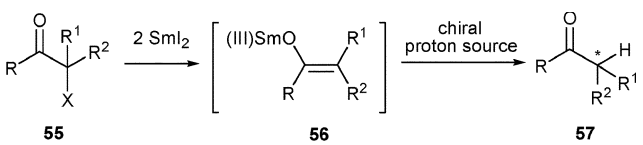
3. Enantioselective asymmetric synthesis

One important class of asymmetric reactions involves the formation of a stereogenic unit in an achiral substrate under the influence of an external chiral auxiliary (part of the reagent or catalyst). This section will present cases where samarium diiodide is one of the reactants.

3.1 Protonation of samarium enolates

Enantioselective protonation of samarium enolates with chiral proton sources is a process for the preparation of carbonyl compounds or carboxylic acid derivatives bearing a stereogenic carbon at the α-position. Samarium enolates **56** are usually generated from α-heterosubstituted carbonyl compounds **55** with SmI_2 in mild conditions (Scheme 13).[33] The following enantioselective protonation of this enolate by chiral agent gives chiral ketone **57**.

Mikami *et al*. have reported the enantioselective protonation of samarium enolates which are regioselectively generated by SmI_2-mediated reaction of α-hetero-substituted cyclohexanones bearing an α-aryl substituent, using chiral diol proton sources derived from achiral diamine or *pro*-atropisomeric biphenol.[34] Screening of several chiral agents in the reaction of **58** (R = Ph, X = OMe) to obtain ketone **59** (R = Ph), provided the best enantioselectivities with alcohols **60** (*ee* = 73%), **61** (*ee* = 85%), and **62** (*ee* = 87%) (Scheme 14). The enantioselectivity with **60** was accounted based on the co-operative effect of the sterically demanding *N*-benzyl

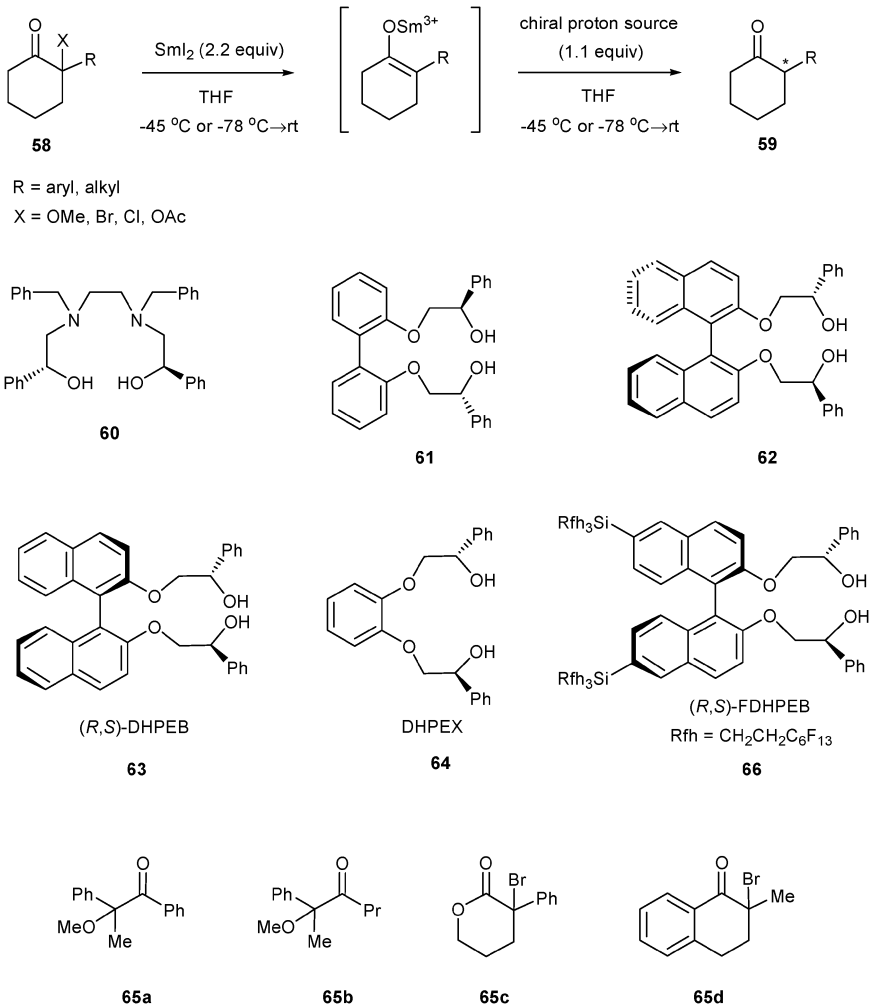


55 56 57

R = R^1 = R^2 = alkyl or aryl

X = halide, OMe, SPh

Scheme 13



Scheme 14

group and the phenyl substituent at the carbinol carbon (Fig. 1; **A** over **B**).

Subsequently, Takeuchi *et al.* have investigated the reaction on many substrates using different chiral proton sources.[35,36] A variety of C_2-symmetric chiral diols were synthesized and screened in the reaction of **58** (R = Ph, X = OMe) to obtain **59** (R = Ph) (Scheme 14). The highest enantioselectivity (89%) was obtained with **63** at −45 °C. The generality of the reaction was studied with a variety of 2-aryl- and 2-alkylcyclohexanones bearing different α-heterosubstitutions, using **63**. High enantiomeric excesses (up to 94%) were obtained in most of the cases. Reaction for acyclic 2-heterosubstituted ketones

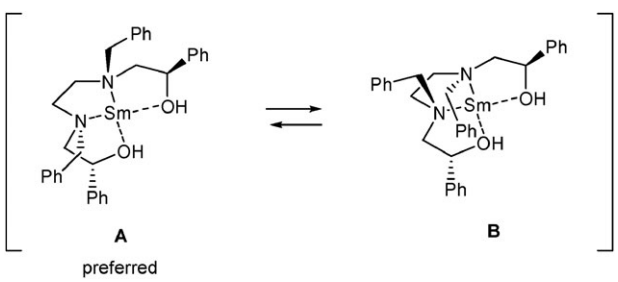


Fig. 1

(**65a** and **65b**), valerolactone (**65c**), and 2-heterosubstituted tetralone (**65d**) was also examined using reagents **63** and **64** at −45 °C.[36] Ketones **65a** and **65b** gave low enantiomeric excesses probably because of low *E*/*Z* selectivities of the samarium enolates. The valerolactone **65c** afforded high enantiomeric excess (72%) when **64** was the protonating agent, and tetralone **65d** provided low *ee* (24%). Furthermore, an enantioselective protonation of a samarium enolate derived from 2-methoxy-2-phenylcyclohexanone, was investigated using a fluorous chiral BINOL derivative.[37] The enolate of **58** (R = Ph, X = OMe) formed by reductive cleavage of SmI_2, was protonated by (*R*,*S*)-FDHPEB (**66**), afforded the ketone **59** in 89% *ee*. The ligand **66** was easily recovered by a simple filtration through a fluorous reverse phase silica gel and was recycled.

The first enantioselective reaction mediated by SmI_2 was reported by Takeuchi *et al.* for the reduction of benzil to benzoin in the presence of quinidine.[38a] It involves an enantioselective protonation of samarium enolate intermediate, and the *ee* of the reaction reached up to 56% when HMPA was used an additive. Subsequently, asymmetric synthesis of ketones by SmI_2-mediated allylation or benzylation of ketenes followed by enantioselective protonation was studied (Scheme 15).[38b] The allylation and benzylation of

various alkylarylketenes **67** in the presence of SmI_2 and HMPA using DHPEX (Scheme 16) as a proton source, afforded the corresponding ketones **68** in good yields (51–68%) and high enantioselectivities (up to 91% *ee*).

A similar reaction was performed on dialkylketenes **69** in the presence of trityl alcohol as an achiral proton source for regenerating the catalyst DHPEX (Scheme 16).[39a] The allyl products **70** were obtained in 55–72% yields and enantioselectivities up to 95% when trityl alcohol was added very slowly to the reaction mixture over a period of 26 h at −45 °C.

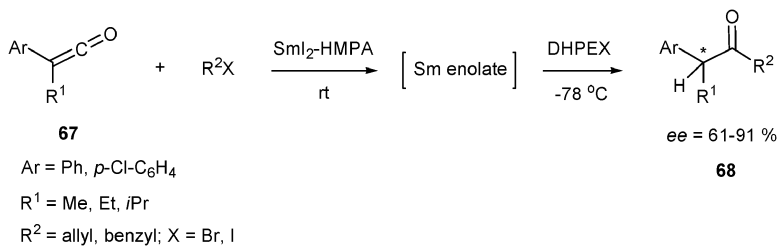
Authors have studied the above catalytic enantioselective protonation of a samarium enolate with fluorous chiral proton donor in the presence of achiral proton sources in fluorous biphasic systems (Scheme 17).[39b] Reaction of ketene **71** with allyl halide and Rfh_2–MPE in the presence of Rfh_3C–OH in THF and THF/FC-72 systems, furnished allyl adduct **72** with 52 and 60% *ee*, respectively. The effect of the fluorous side chain of Rfh_2–MPE in the biphasic system was also checked using DHPEX as the catalyst. High enantioselectivity (90% *ee*) was obtained in both the THF and THF/FC-72 systems.

3.2 Reduction of ketones

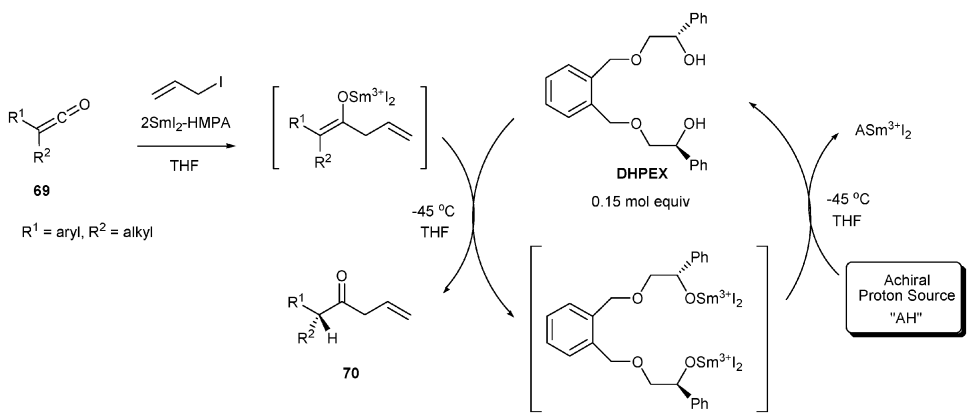
Xu, Lin *et al.* have discovered the enantioselective SmI_2-induced ketone reduction followed by lactonization of 2-acylarylcarbonylates **73** into phthalides **74** using a chiral oxazolidinone catalyst **75** (Scheme 18).[40] The authors initially studied the reaction of **73** (R^1 = Ph, R^2 = H) with samarium diiodide in the presence of stoichiometric amount of **75**, which furnished the corresponding phthalide product **74** in 88% yield with 98% *ee*. It was then turned out that the enantioselective process might be accomplished using a catalytic amount of **75** in the presence of a stoichiometric amount of an appropriate achiral protonating agent. Several achiral alcohol, phenol, and amine compounds were screened in the reaction of **73** (R^1 = Ph, R^2 = H) with SmI_2 in the presence of **75** (0.1 equiv.). The best result (product **74** in 80% yield with 96% *ee*) was obtained with 1 equivalent of **76**. The generality of the catalytic system was evaluated to a wide variety of 2-acylarylcarbonylates. Gratifyingly, all the reactions afforded phthalide products **74** in good yields (62–85%) and excellent enantioselectivities (92–99% *ee*). It is noteworthy that the enantioselectivity of the reaction is generally not affected by the substitution pattern of **73**. R^1 could be a broad range of aromatic substituents. Substrates with either electron-donating or electron-withdrawing groups (R^2) were found to be efficient. The absolute configurations of the phthalides were determined to be *S*.

3.3 Homo-coupling of conjugated amides

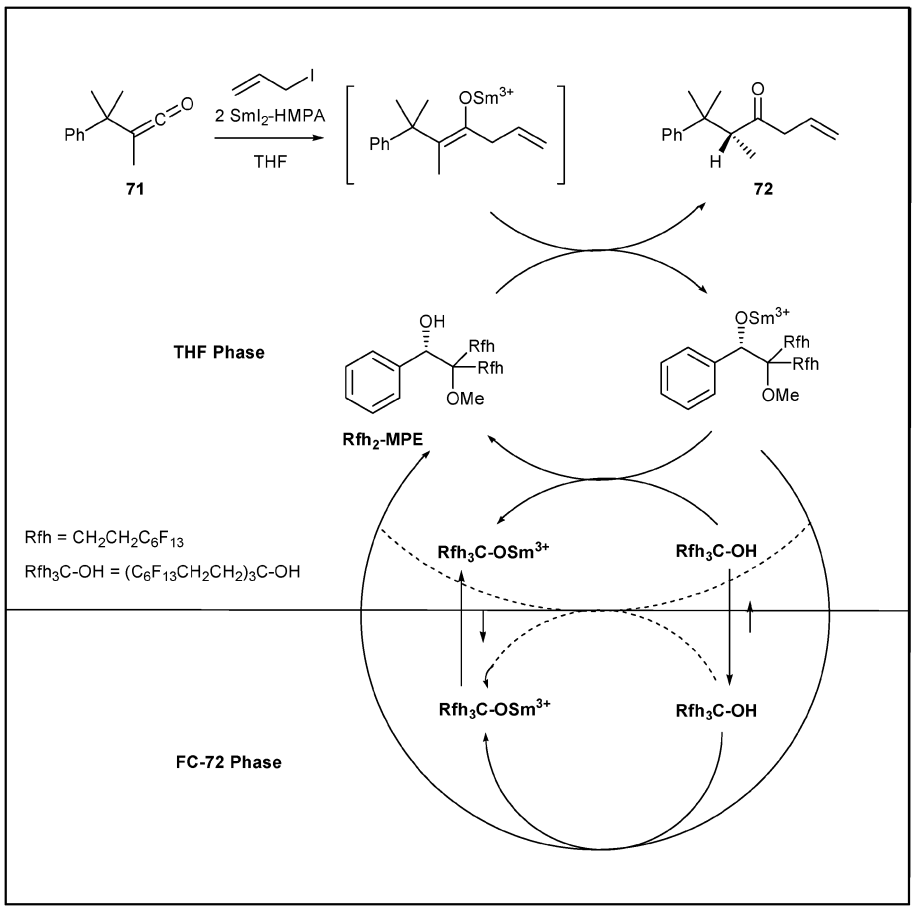
Inanaga *et al.* have studied the enantioselective reductive homo-coupling reaction of β-monosubstituted acrylic acid amides by using chiral samarium(II) complex prepared from SmI_2, (*R*)-BINOL, and an achiral tertiary amine.[41] A variety of amines as a component of the chiral samarium complexes were screened for the reaction of acrylic amide **77** (R = Me; R^1 = Bn) (Scheme 19). The best result was obtained with TMEDA, providing the corresponding 3,4-*trans*-disubstituted adipamide **78** in 70% yield with 71% *ee*, along with the saturated amide **79** (20% yield). Then the reaction was applied to a variety of amides **77** using SmI_2 (8 equiv.), (*R*)-BINOL (16 equiv.) and TMEDA (32 equiv.). It furnished the corresponding coupling product **78** (yield = 20–55%, *ee* = 44–85%) and saturated amides **79**



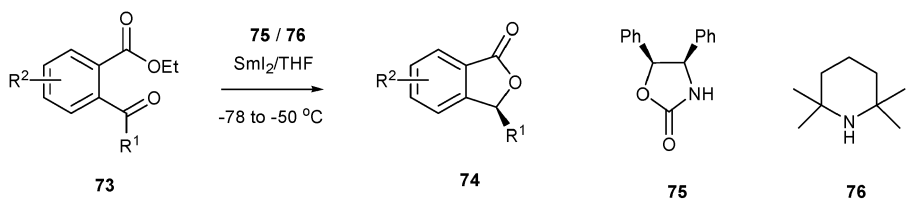
Scheme 15



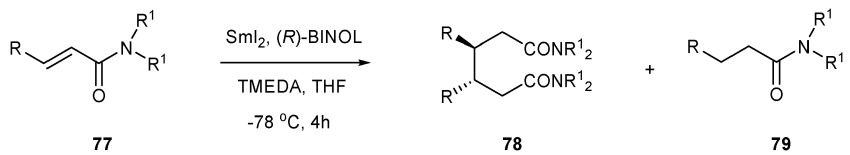
Scheme 16



Scheme 17



Scheme 18



Scheme 19

(42–52%). The authors proposed a possible nine-membered chelate transition state as shown in Fig. 2, in which the conjugated ketyl radical and the ligated crotonamide are arranged in a *cis*-relationship on the chiral coordination sphere of samarium.

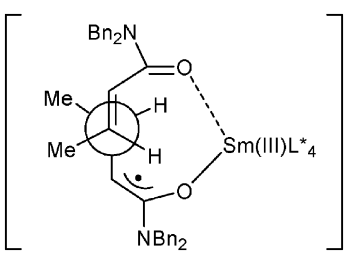
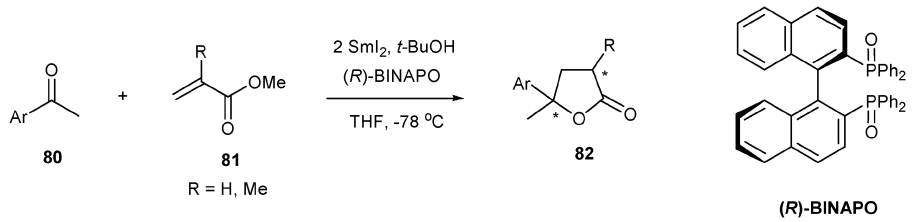


Fig. 2

3.4 Coupling between ketones and conjugated esters

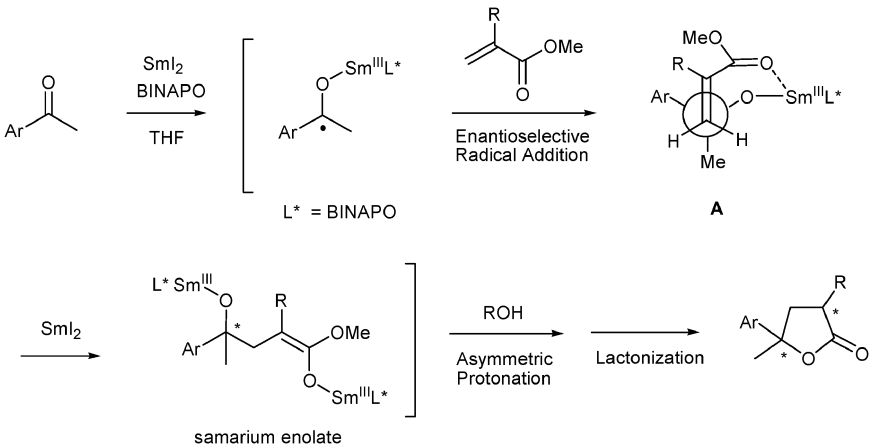
Mikami *et al.* have studied the asymmetric synthesis of enantiopure butyrolactones **82** by samarium diiodide-mediated reductive coupling of ketones with α,β-unsaturated



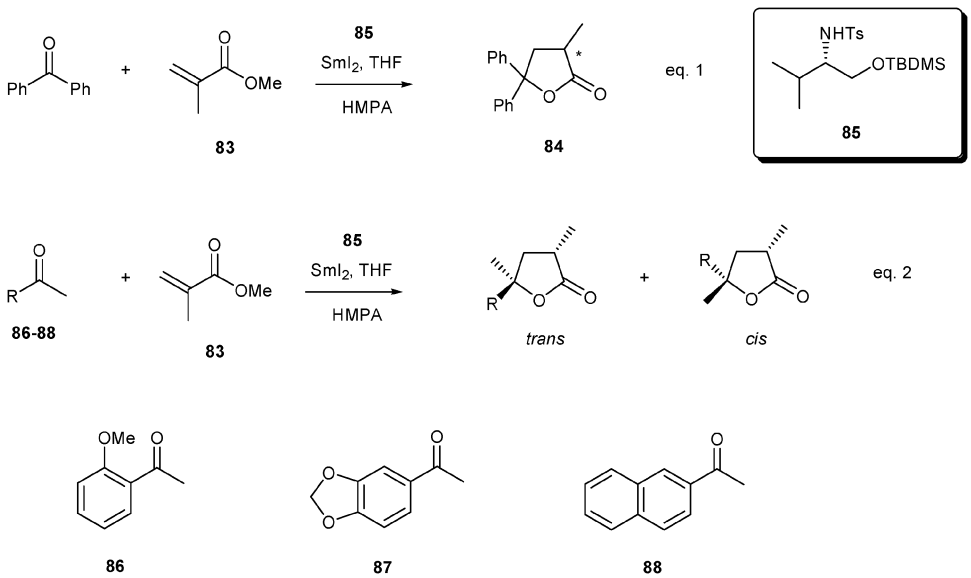
Scheme 20

esters in presence of (*R*)-BINAPO (Scheme 20).[42] Reaction of **81** with a variety of aromatic ketones **80**, afforded the corresponding lactones **82** in high enantioselectivity (up to 89% *ee* for *cis* isomer) and with a moderate level of diastereoselectivity. The mechanism of enantioselective reductive coupling is shown in Scheme 21. The ketylsamarium intermediate can be trapped by α,β-unsaturated esters through medium ring cyclic chelate (**A**) to form new carbon–carbon bonds. Asymmetric protonation of the resulting samarium enolate takes place to control the second stereogenic center of the α-substituted butyrolactone by the assistance of BINAPO ligated to the samarium enolate.

A similar transformation has been studied by Lin *et al*. by a variation of chiral proton source.[43] Screening of several chiral proton sources in the reaction of benzophenone with acrylate **83**, gave the best result with amino alcohol **85** (Scheme 22, eqn (1)). The lactone **84** was obtained in 65% yield with 84% *ee* of unknown configuration. The reaction system was extended to the preparation of butyrolactones with two chiral centers. Coupling of prochiral ketones **86–88** with **83** in the presence



Scheme 21



Scheme 22

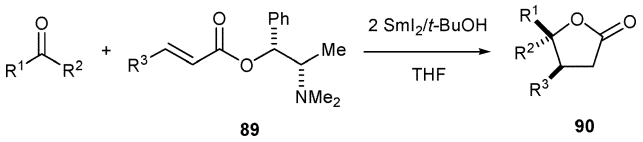
of **85** as the chiral proton source, afforded the corresponding isomeric products *trans* (*ee*'s up to 63%) and *cis* (*ee*'s up to 28%) butyrolactones, which were separated by column chromatography (Scheme 22, eqn (2)).

4. Diastereoselective asymmetric synthesis

In many asymmetric syntheses a prochiral substrate is transformed into a chiral molecule by temporary bonding to a chiral auxiliary, which will act as controller in the reaction. In the final step the chiral auxiliary is released, generating the desired enantioenriched product. This strategy is developed in the present section with the use of SmI_2.

4.1 Coupling reactions

4.1.1 Ketones or aldehydes and conjugated esters. Fukuzawa *et al.* have reported stereoselective synthesis of butyrolactones **90** by the reaction of acrylates and crotonates derived from chiral *N*-methylephedrine with ketones or aldehydes.[44] Screening of various couplings between acetophenone and acrylates derived from chiral *sec*-alcohols, afforded the best result with acrylate derivative of (1*R*,2*S*)-*N*-methylephedrine **89** (R^3 = H) (Scheme 23). The corresponding lactone **90** yielded in 86% with 90% *ee*. Reaction of various ketones and aldehydes with (1*R*,2*S*)- and (1*S*,2*R*)-*N*-methylephedrinyl acrylate **89** (R^3 = H), resulted in the corresponding chiral butyrolactones **90** with high *ee* values, the highest *ee* (>99%) was achieved with 3-phenylpropanal. With crotonates derived from *N*-methylephedrine, the *cis*-isomer of the 3,4-disubstituted-butyrolactone **90** was produced predominantly (*cis*/*trans* = 97/3 to 99/1) with 83–97% *ee* for most aldehydes. The reaction with cyclohexanecarboxaldehyde gave the highest diastereo- (*cis*/*trans* = >99/<1) and enantioselectivities



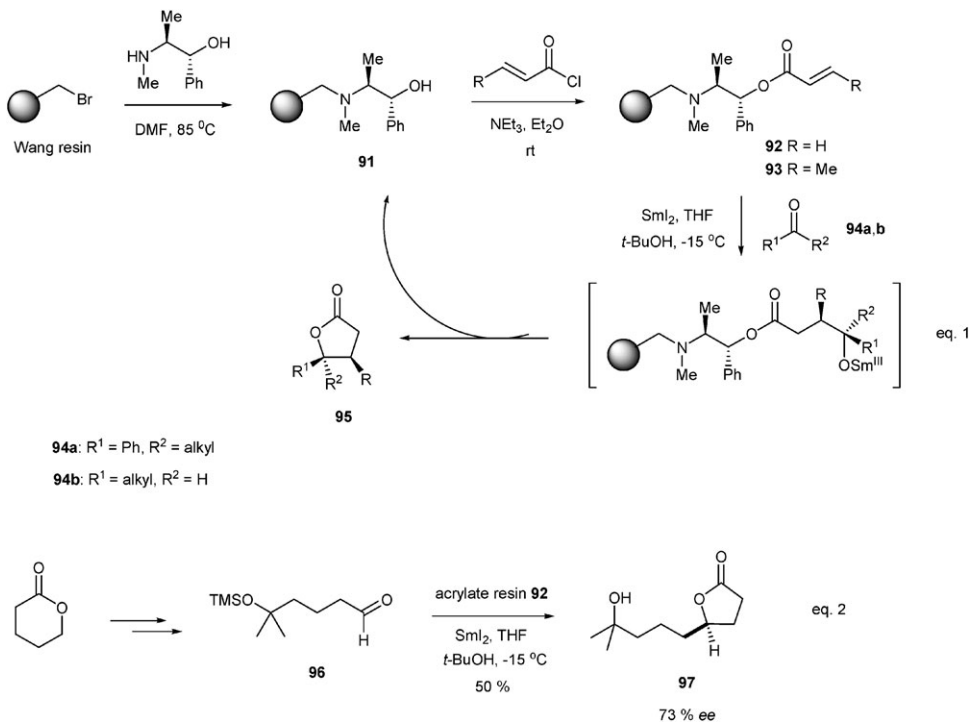
R^1 = alkyl, aryl

R^2 = H, Me, Et; R^3 = H, Me

Scheme 23

(>97% *ee*). The lactonization step allows to regenerate the *N*-methylephedrine, which has been used to prepare **89**. We placed these reactions in the present section because the lactone formation involves the *in situ* diastereoselective formation of a samarium intermediate with a new stereogenic center.

By adaptation of Fukuzawa's methodology, Procter *et al.* have developed a solid phase asymmetric version with a catch-release approach to butyrolactones using acrylates and crotonates linked to resin through an ephedrine linker.[45a,b] Resins **92** and **93** were synthesized by esterification of ephedrine-resin **91** (Scheme 24, eqn (1)). Reaction of acrylate resin **92** with a variety of ketones **94a** or aldehydes **94b**, furnished the corresponding lactones **95** in moderate yield (37–73%) and enantiomeric excess (66–81% *ee*). Reaction of the analogous crotonate resin **93** with aldehydes **94b** gave the corresponding butyrolactones **95** in 43–66% yield and high enantiomeric excess (88–96%). The chiral resin **91** was recovered and reused. The observed enantioselectivity of the reaction was rationalized by proposal of the transition structure shown in Fig. 3. The samarium(III) was coordinated to both the auxiliary and to the incoming ketyl-radical anion, this gives rise to a well-ordered transition structure.



Scheme 24

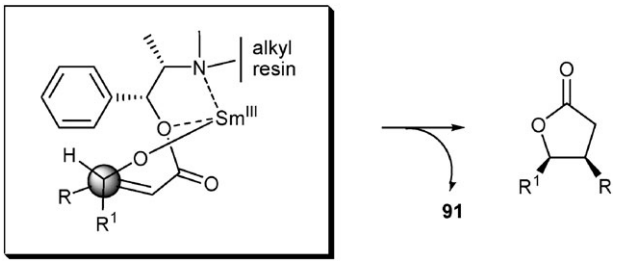


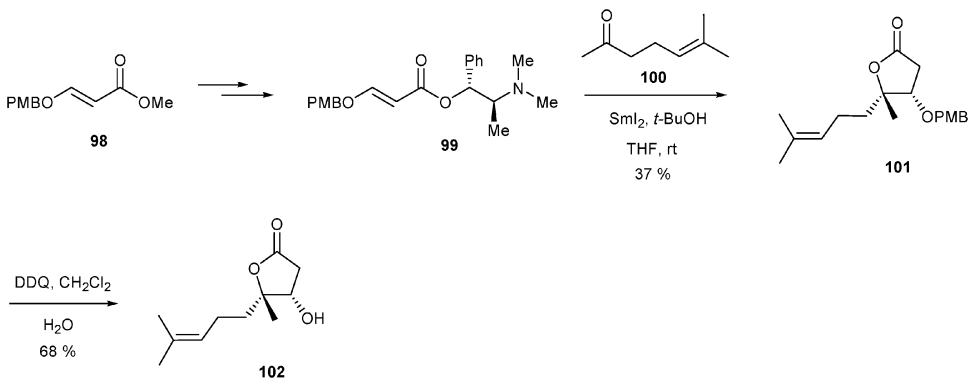
Fig. 3

The chelation not only orders the transition structure but also leads to Lewis acid activation of the aldehyde towards radical addition. The utility of asymmetric resin-capture–release process has been illustrated for the synthesis of biologically active compound **97**, a moderate DNA-binding metabolite (Scheme 24, eqn (2)).

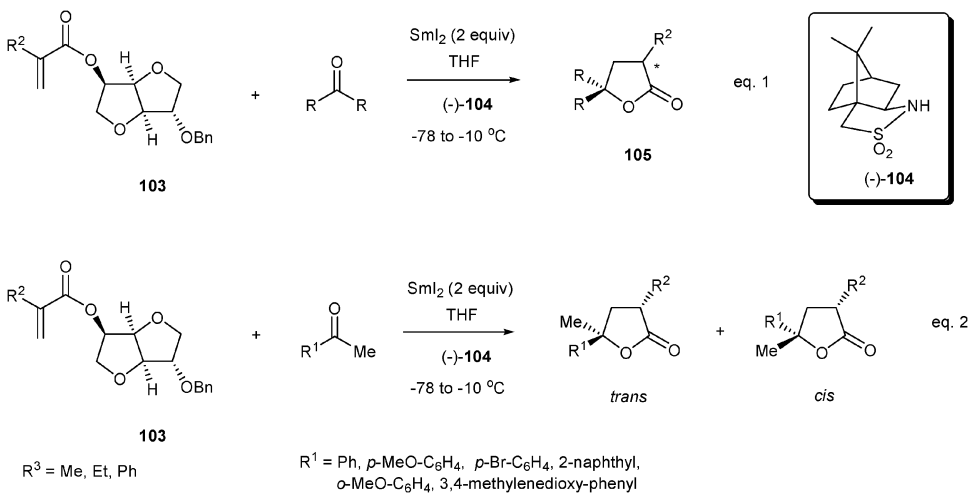
Asymmetric synthesis of antifungal furanone (**102**) has been reported using Fukuzawa reductive coupling methodology (Scheme 25).[45c] Reaction of ephedrinyl acrylate **99** derived from ester **98**, with ketone **100** afforded **101** as a separable 5 : 1 mixture (*cis* : *trans*) of diastereoisomers. Removal of the PMB protection gave the furanone **102** in 97% *ee*.

Lin *et al*. have reported in a series of papers the asymmetric synthesis of α,γ-substituted-butyrolactones by SmI_2-mediated reductive coupling of ketones with α,β-unsaturated carbonyl compounds.[46a–d] Reaction of chiral 2-alkyl acrylate **103** (R^2 = Me) derived from isosorbide, with symmetrical ketones (benzophenone, cyclohexanone, *etc*.) in the presence of (1*S*)-(−)-2,10-camphorsultam (−)-**104** as a proton source, gave the corresponding lactones **105** in 66–99% yields with up to 95% *ee* (Scheme 26, eqn (1)).[46a,b] Extension of the reaction system to the preparation of butyrolactones with two stereogenic centers was explored. Reaction of methacrylate **103** (R^2 = Me) with unsymmetrical ketones, afforded the diastereomeric *trans* and *cis* lactones (Scheme 26, eqn (2)).[46a,b] The *trans* products are predominant with *trans*/*cis* ratios up to 79 : 21. The *trans* isomers were obtained with excellent *ee* values (93–99%). In contrast, much lower enantioselectivities were observed for the *cis* products (< 50% *ee*), except in the case of α-tetralone (75% *ee*). The scope of the reaction was further extended to the substrates **103** (R^2 = Et, Ph) with a variety of ketones in the presence of (−)-**104**. The corresponding *trans*/*cis* lactones were obtained with *trans* being the major isomer (56/44 to 80/20). The enantioselectivies of *trans* could be very high (*ee* = 89–96%), however lower *ee*s for *cis* were reported (14–46%).

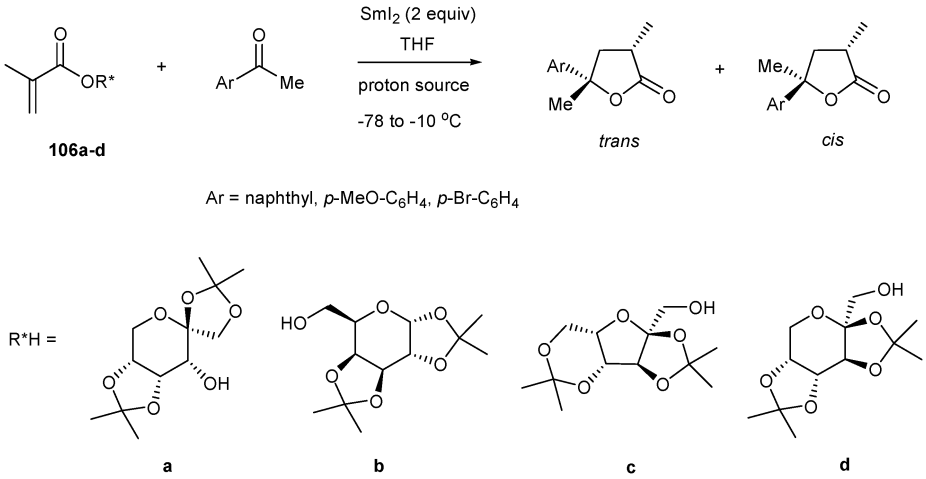
The reaction was then studied using a variety of carbohydrates based chiral auxiliaries, some are indicated (**106a–d**) in Scheme 27.[46c] Reaction of acrylate **106a** and *ent*-**106a**



Scheme 25



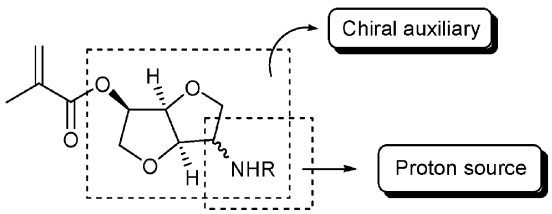
Scheme 26



Scheme 27

with several ketones in the presence of triphenylmethanol or (−)-**104** or (+)-**104** as sterically hindered proton sources, afforded the diastereomeric *trans*/*cis* products in good yields (58–75%). The *cis* products were obtained as the major products in high enantiomeric excess (77 to >99%). Reaction of acrylates **106b–d** with 2′-acetonaphthone in the presence of (−)-**104**, resulted in the formation of the *trans* isomers predominantly in all cases. The enantioselectivity of the *trans* isomers was generally excellent (61–92%). Substrate scope was broaden by using acrylate **106d** with a variety of ketones, affording *trans* products (*ee* = 90–93%).

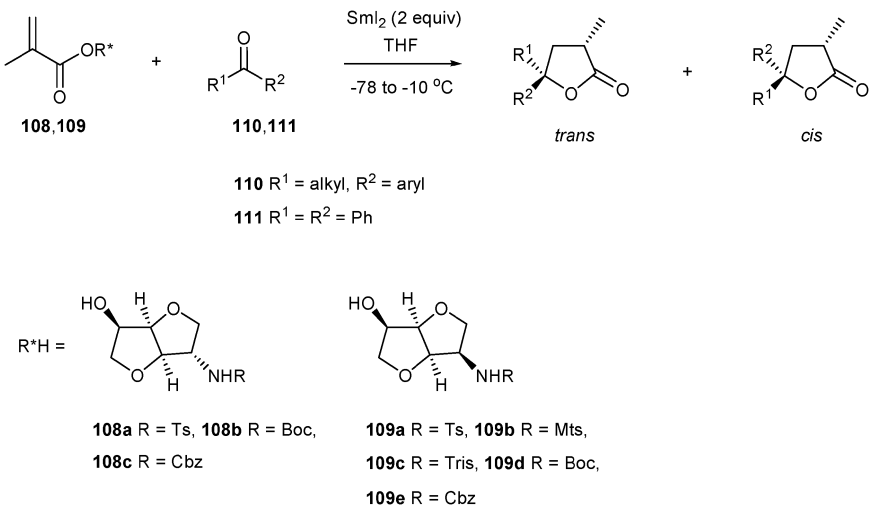
A new entry to the asymmetric synthesis of α,γ-substituted butyrolactones was explored by using a carbohydrate-derived amide **107** acting both as a chiral auxiliary and as a protonating agent (Fig. 4).[46d] Novel methacrylate compounds **108a–c** and **109a–e** were synthesized from carbohydrate derivative isomannide (Scheme 28). Reaction of acrylates **108a–c** with a variety of ketones **110** in THF in the presence of SmI_2 afforded the corresponding diastereomeric *trans*- and *cis*-butyrolactones in 53–90% yields, with the *trans* isomer being the major one (*trans*/*cis* = 60/40 to >99/1). The enantioselectivity of the *trans* isomers was excellent (75 to >99%). Ketone **111** with



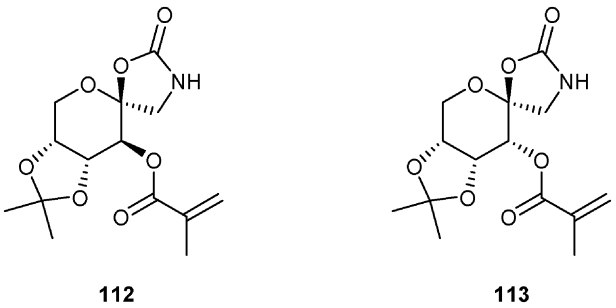
107

Fig. 4

acrylates **108a,c** gave only *trans* isomer in 40% yield with 75–86% *ee*. Interestingly, when the NHR group *endo*-oriented acrylates **109a–c** reacts with ketones **110** the corresponding diastereomeric *trans*- and *cis*-butyrolactones were obtained in 56–91% yields, with *cis* diastereomer as the major product (*ee*s of *cis* = 23 to >99% and *ee*s of *trans* = 70 to 97%). Reaction of acrylates **109d** and **109e** with **110** (R^1 = Me, R^2 = *p*-anisyl), generated predominantly the *trans* isomer in ratio of *trans*/*cis* = 67/33 and 75/25, respectively (*ee* of *trans* = 71–99% and *ee* of *cis* = 79–81%). It has also been synthesized two novel chiral methacrylates **112** and **113** bearing a *NH*-amide group



Scheme 28



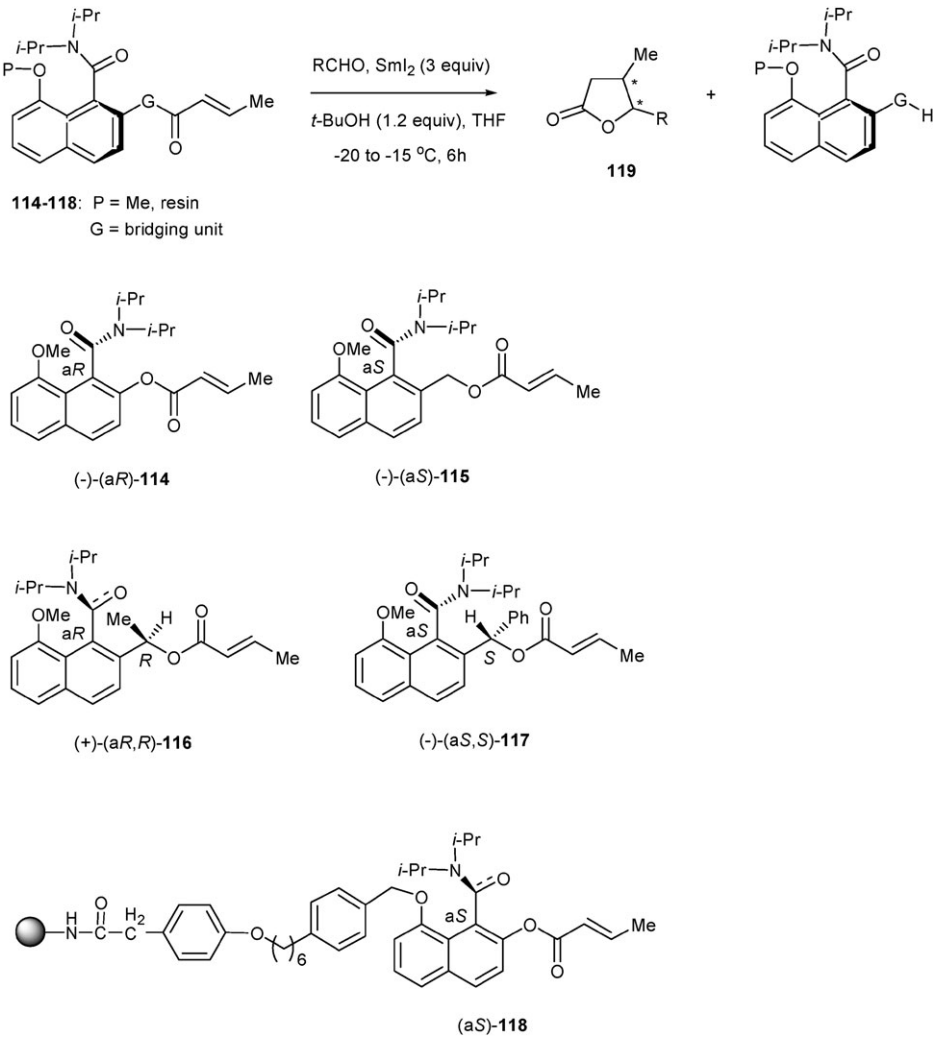
112 113

Fig. 5

(Fig. 5).[46d] Reaction of **112** or **113** with **110** resulted the desired butyrolactones. In most cases, *cis* isomers were indeed obtained as major products and relatively high *ee* values (80–99%) when **113** was used. It was noteworthy that the reaction of **113** with 4′-methoxyacetophenone afforded a 50 : 50 (*trans* : *cis*) diastereomeric ratio and extremely high enantiomeric excess (99%) for both isomers.

Dai *et al*. have studied the stereoselective coupling between aldehydes and crotonates **114–118** with axial chirality, it led to the lactones **119** (Scheme 29).[47] The results are summarized in Table 2. The bridging group "G" [–O–, $–CH_2O–$, –CH(Me)O–, or –CH(Ph)O–] in the crotonates (**114–118**) significantly influences the efficiency of asymmetric induction. Among the four crotonates, the one derived from 2-hydroxy-8-methoxy-1-naphthamide (**114**) reacted with pentanal afforded the highest *ee* of >99% for the *cis*-butyrolactone and in 90% combined yield with a *cis*/*trans* ratio of 90 : 10 (entry 1). A chelation-control model shown in Fig. 6 was proposed for the reaction of (+)-(a*S*)-**114** with aldehydes, leading to the formation of (3*S*,4*S*)-**119** as the major products. Chelation of both carbonyl oxygen atoms of the atropisomeric naphthamide unit and the crotonate moiety within the substrate forms an eight-membered ring complex, which seems to play a key role for the asymmetric induction as depicted in **I**. The ketyl radical generated from the reduction of aldehydes can coordinate with the Sm(III) cation only from the same side of the amide unit, which results a cage-like complex.

Uemura *et al*. have reported the reaction of planar chiral chromium complexes **120** (R^1 = Me, OMe; R^2 = Me) with methyl acrylate afforded the corresponding butyrolactone chromium complexes **121** as single diastereomer in 71–75% yields (Scheme 30).[48] Similarly, *o*-substituted benzaldehyde



Scheme 29

Table 2

Entry	Crotonate	RCHO	Yield **119** (%)	*cis*/*trans*	*ee* (%, *cis*; *trans*)
1	(−)-(*aR*)-**114**	*n*-BuCHO	90	90 : 10	>99; 96
2	(+)-(*aS*)-**114**	*n*-BuCHO	90	90 : 10	>99; 95
3	(+)-(*aS*)-**114**	*i*-PrCHO	81	91 : 9	>99; 75
4	(+)-(*aS*)-**114**	*t*-BuCHO	85	72 : 28	96; 61
5	(−)-(*aR*)-**114**	CyCHO	87	88 : 12	80
6	(−)-(*aS*)-**115**	*n*-BuCHO	55	95 : 5	32; 46
7	(−)-(*aS*)-**115**	*t*-BuCHO	67	100 : 0	5
8	(+)-(*aR*,*R*)-**116**	*n*-BuCHO	48	84 : 16	63; 76
9	(+)-(*aR*,*R*)-**116**	*t*-BuCHO	45	84 : 16	36; >95
10	(−)-(*aS*,*S*)-**117**	*n*-BuCHO	40	83 : 17	14; 83
11	(*aS*)-**118**	*t*-BuCHO	58	71 : 29	94; 89
12	(*aR*)-**118**	CyCHO	66	89 : 11	88

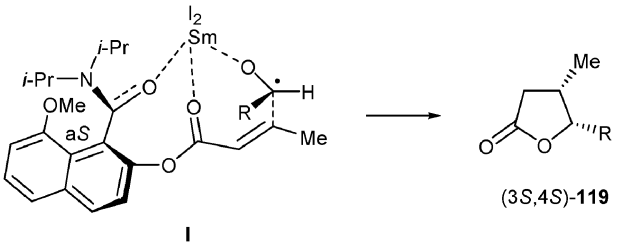


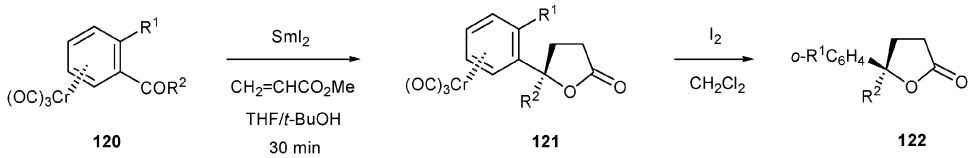
Fig. 6

chromium complexes **120** (R^1 = Me, OMe, Br; R^2 = H) were coupled with methyl acrylate at lower reaction temperature (0 to −78 °C) provided the corresponding chromium complexes **121** as single diastereomer in 53–75% yields. The proposed mechanism for the stereoselective radical coupling is described as follows (Fig. 7). The ketyl radical intermediate **124**, which possesses a substantial exocyclic double bond character **125** with a limitation of the C_α–C_{ipso} bond rotation, is trapped by the acrylate from *exo*-side leading to the product **121**.

Similar transformations have been studied by Merlic *et al.* for the synthesis of enantiopure lactones **128** and **131** (Scheme 31).[49] Reaction of enantiopure ketone (*S*)-**126** with samarium diiodide, methyl acrylate, and *t*-BuOH in THF gave *endo*-lactone complex (*S*,*S*)-**127** in 81% yield in 100% *de*. Oxidative decomplexation of (*S*,*S*)-**127** afforded enantiopure lactone (*S*)-**128**. A Lewis acid-mediated cationic rearrangement of (*S*,*S*)-**127** allows novel access to its diastereomer, and hence the enantiomer of (*R*)-**128**. The methodology was also applied to the synthesis of enantiopure lactones (*R*)-**131** and (*S*)-**131** from enantiopure aryl aldehyde chromium complex (*S*)-**129** as shown in Scheme 32.

4.1.2 Nitrones and conjugated esters. Py *et al.* have studied the SmI_2-mediated reductive conjugate addition of chiral nitrones **132** to α,β-unsaturated esters, leading to diastereomeric γ-*N*-hydroxyamino esters **133** (Scheme 33).[50a] Reaction of a variety of nitrones bearing a chiral auxiliary at the nitrogen center, with ethyl or methyl acrylate afforded the addition products **133** in good yields with different diastereomeric ratios (Scheme 33, Table 3). When the 1-(triisopropylphenyl)ethyl auxiliary was used, an excellent diastereoselectivity (>95 : 5) was observed (Table 3, entry 6). Relative stereochemistry of the addition products **133** were determined by converting them into the γ-amino acid derivative **134**.

Subsequently, the SmI_2-induced reductive coupling of nitrone **135** with a variety of α,β-unsaturated esters was performed, which led to γ-*N*-hydroxyamino esters **136–139** (Scheme 34).[50b] Reaction of a variety of nitrones **135** (R = Me, Et, *i*-Bu, *i*-Pr, *c*-Hex) with ethyl acrylate in the presence of SmI_2 and H_2O furnished the amino esters **136** in high yields (71–94%) and excellent diastereoselection (>95 : 5). Reductive coupling of **135** (R = *i*-Pr) with various other unsaturated esters furnished the amino esters **137–139** with *dr* = >95 : 5 in all the cases. The coupling adducts **136** were



Scheme 30

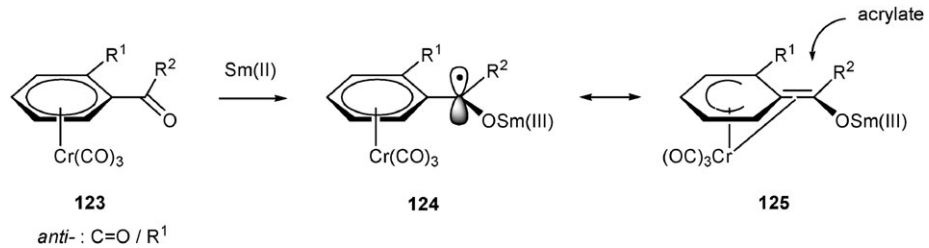
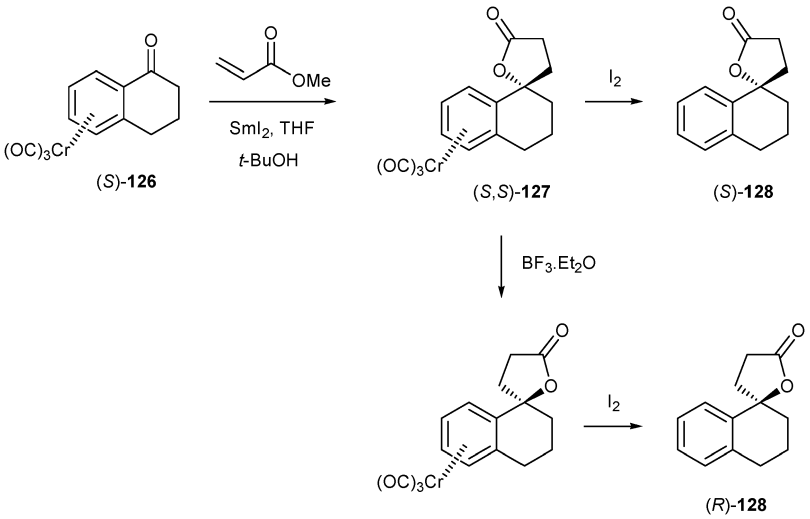
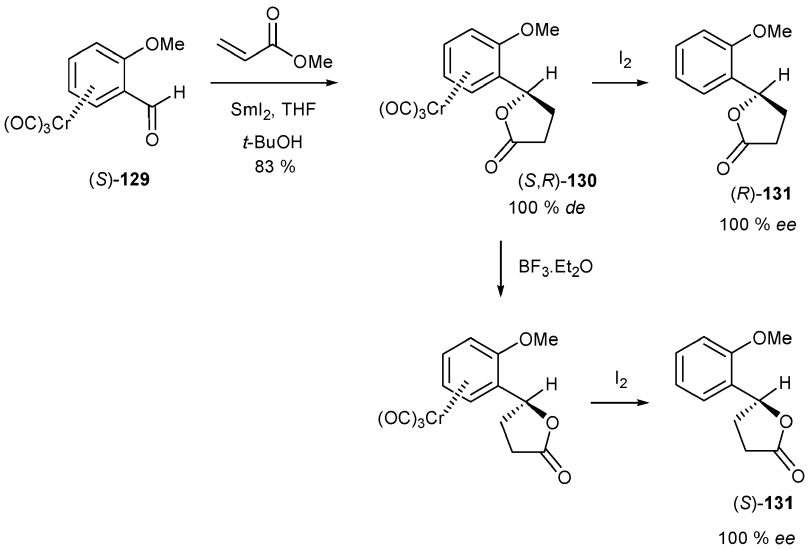


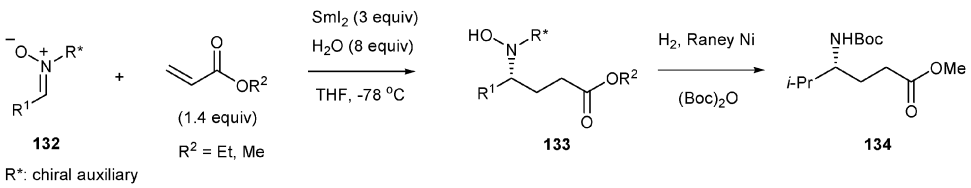
Fig. 7



Scheme 31



Scheme 32



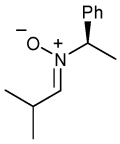
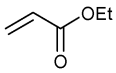
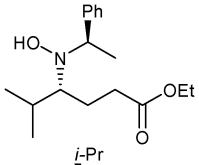
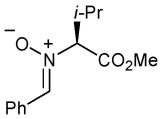
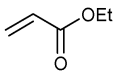
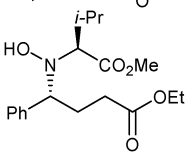
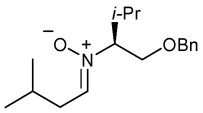
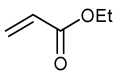
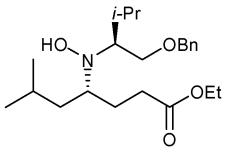
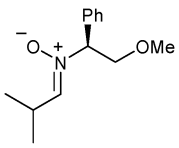
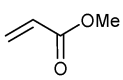
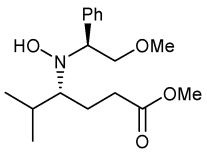
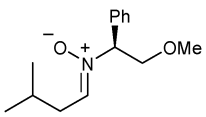
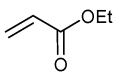
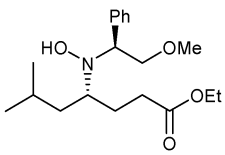
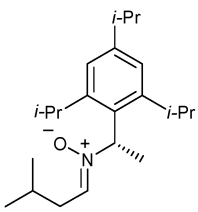
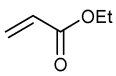
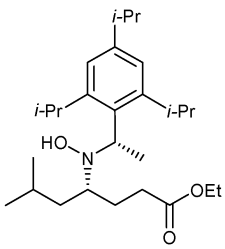
Scheme 33

transformed into potentially useful γ-amino acid derivatives **140** and γ-lactams **141** with excellent enantioselection (>98% *ee*) (Scheme 35).

A formal synthesis of (*S*)-vigabatrin was reported *via* a samarium diiodide-induced reductive coupling of chiral nitrone **143** derived from aldehyde **142**, with alkyl acrylates as a key step (Scheme 36).[50c] Esters **144a,b** were obtained in 70–77% yields with a 90 : 10 (*anti* : *syn*) diastereomeric ratio. Addition of water (8 equiv.) as a proton source to the reaction mixture shortens the reaction time (1 h) and increasing the yield (84%), but slightly lowers diastereoselectivity (75 : 25). It was explained that the major *anti* isomer is consistent with a β-chelated transition state (Fig. 8), a competition of water with the β-oxygen in the substrate for coordination with samarium lowers the diastereomeric ratio. The major *anti* isomer **144a** was isolated and further transformed to compound **145**, which is a known intermediate in Pericas' synthesis of (*S*)-vigabatrin.[50d]

Skrydstrup *et al*. have studied the SmI_2-promoted reductive coupling of nitrones **146** and **147** with α,β-unsaturated esters **148a–c** possessing various chiral auxiliaries, leading to γ-*N*-

Table 3

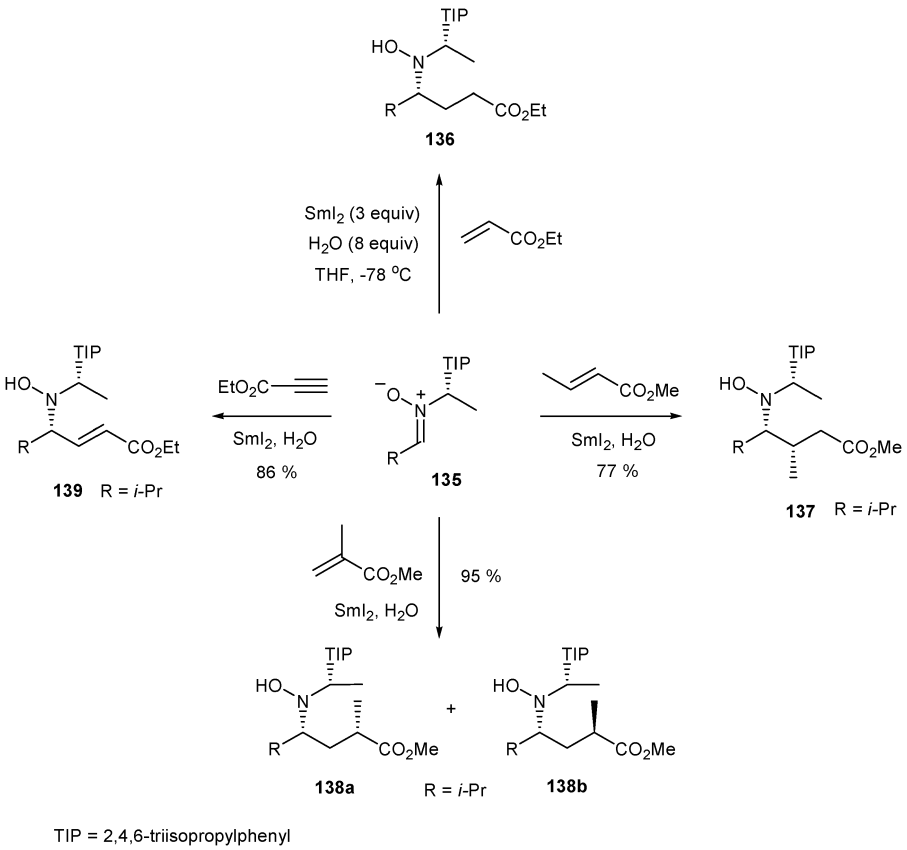
Entry	Nitrone **132**	Electrophile	Major diastereomer **133**	Yield (%)	*dr*
1				78	75 : 25
2				36	70 : 30
3				56	60 : 40
4				96	85 : 15
5				84	85 : 15
6				73	>95 : 5

hydroxyamino acid derivatives **149a–c** and **150**, respectively, in good yields and diastereoselection (Scheme 37).[51a] The highest diastereoselectivity (9 : 1) was obtained with the acrylate **148c** of (1*R*,2*S*)-*N*-methylephedrine. Compound **150** underwent spontaneous loss of the chiral auxiliary upon chromatography, then provided the Boc-protected γ-amino acid derivative **151** in high *ee*.

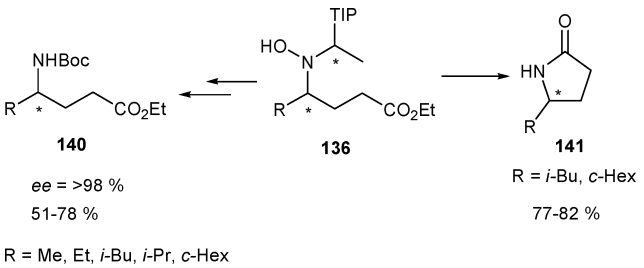
Authors have also studied the asymmetric synthesis of γ-amino acids by SmI_2-mediated radical addition of alkyl nitrones bearing carbohydrate-based chiral auxiliaries to the *n*-butyl acrylate (Scheme 38).[51b] The *N*-D-mannose substituted nitrones **152a** provided the γ-amino acid derivatives **152b** with high diastereoselectivities and with (*R*)-configuration at the newly created stereogenic center. Interestingly, the sugar residue had ring-opened under the reaction conditions, affording a new nitrone as depicted in Scheme 38. Removal of the sugar auxiliary in **152b** (R = isopropyl) by acidic hydrolysis furnished the *N*-hydroxyl γ-amino acid **152c**. Reaction of nitrones **153a** bearing C5-deoxy-D-ribose auxiliary, with *n*-butyl acrylate afforded the addition products **153b** with high diastereoselectivities and with (*S*)-configuration at the new stereogenic center. The stereochemical outcomes of these reactions are proposed by a schematic model as shown in Fig. 9. Addition of the carbon centered radical to the electrophilic alkene occurs from its least hindered face.

4.1.3 Nitrones and ketones or aldehydes. The SmI_2-induced cross-coupling of enantiopure $Cr(CO)_3$-complexed *ortho*-substituted nitrones **154** with a variety of carbonyl compounds led to the corresponding complexes **155** in 65–96% yield and >95 : 5 *dr* (Scheme 39).[52] Interestingly, the use of an excess of SmI_2 (6 equiv.) could directly produces β-amino alcohol complex **157** in 81% yield in a one-pot sequence, by reduction of the *in situ* generated hydroxylamine. Decomplexation of **155** (R = R^1 = R^2 = Me) gave β-*N*-hydroxyamino alcohol **156** in quantitative yield.

4.1.4 Nitrones and imines. Lin *et al.* have developed the synthesis of unsymmetrical chiral vicinal diamines by SmI_2-induced reductive cross-coupling of nitrones **158** with chiral *N*-*tert*-butanesulfinyl imines **159** (Scheme 40).[53] After optimization, the best result was obtained with the use of 3 equiv. of



Scheme 34



Scheme 35

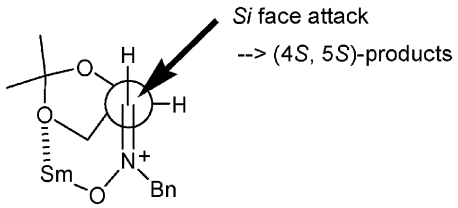
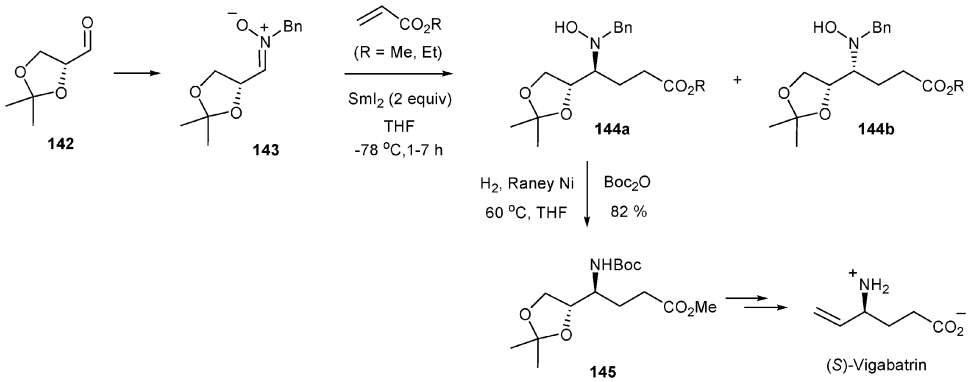
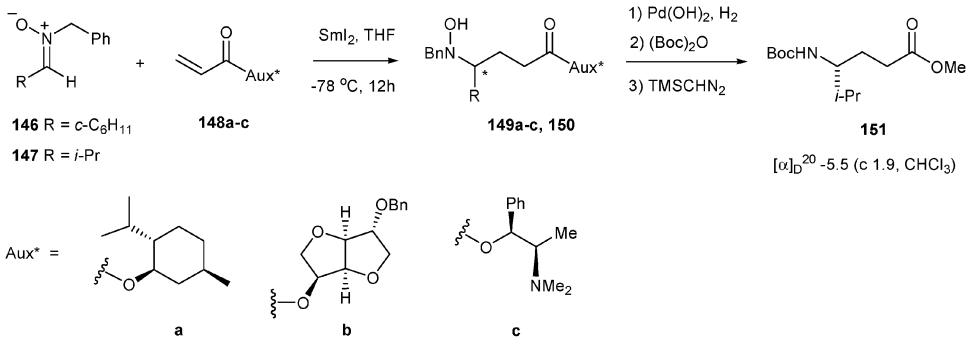


Fig. 8

SmI_2 in the presence of 2 equiv. of *tert*-butyl alcohol. The 1,2-diamine **160** (R^1 = *i*-Pr, R^2 = Ph) resulting from the reductive cross-coupling was isolated as a single diastereomer in 75% yield. The scope of the reaction was studied by cross-coupling of various nitrones **158** with *N*-*tert*-butanesulfinyl imines **159**. A less hindered nitrone (R^1 = *n*-hexyl) gave the best yield of 85%. However, when R^1 substituent became bulky, the yield of the coupling product decreased, and only 22% of the

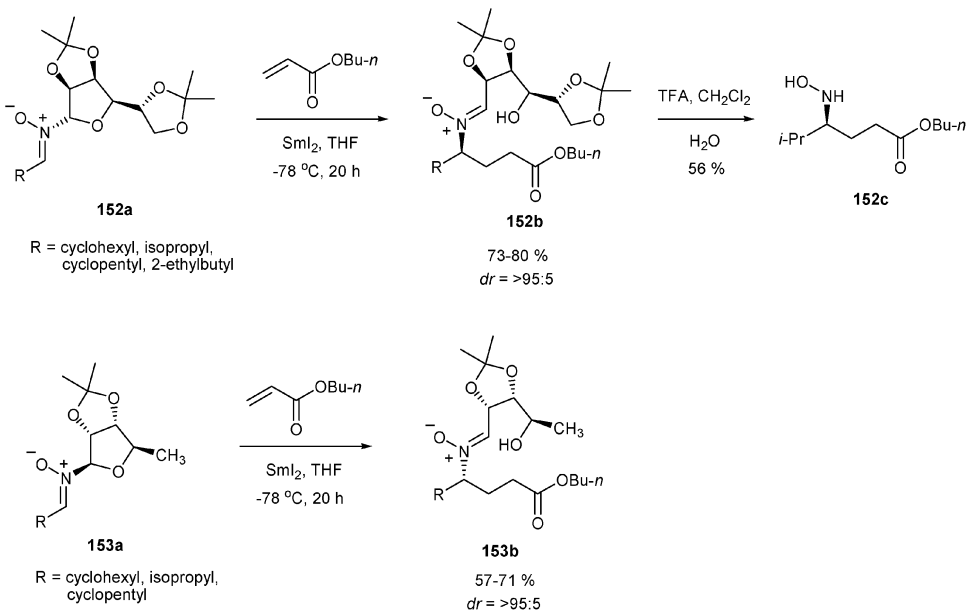


Scheme 36



nitrone	acrylate	product	yield (*dr*)
146	**148a**	**149a**	78 % (4:1)
146	**148b**	**149b**	43 % (8:1)
146	**148c**	**149c**	70 % (9:1)
147	**148c**	**150**	54 % (9:1)

Scheme 37



Scheme 38

product was produced in case of substituent R^1 = *tert*-butyl. Excellent diastereoselectivities were reported in most of the cases, and extremely high diastereoselectivities were obtained when isopropyl-, cyclohexyl-, and *tert*-butyl-substituted nitrones were employed. It was also investigated the reactions of nitrone **158** (R^1 = *i*-Pr) with a variety of aromatic *N*-*tert*-butanesulfinyl imines containing electron-donating or electron-withdrawing substituents at the para position. Reactions were facile in both the cases and gave the corresponding diamines **160** in good yields. Cross-coupling reaction was also effective for a variety of different substituted long-chain aliphatic nitrones **158** with imine **159** (R^2 = Ph), provided good yields and high diastereoselectivity (7 : 1 to >10 : 1). The cross-coupling product **160** (R^1 = *i*-Pr, R^2 = Ph) was easily converted to the corresponding enantiopure diamine **161** in 87% overall yield in a three-step reaction sequence as shown in

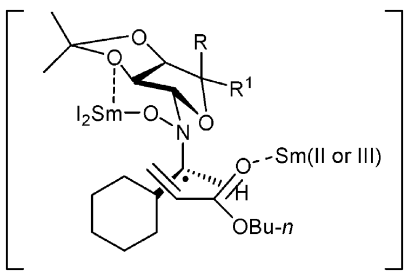
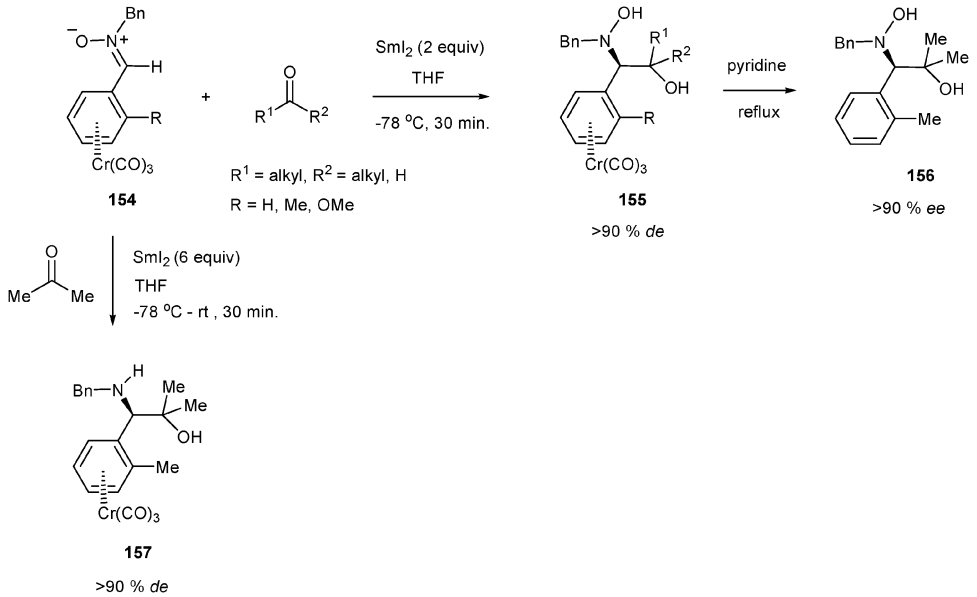
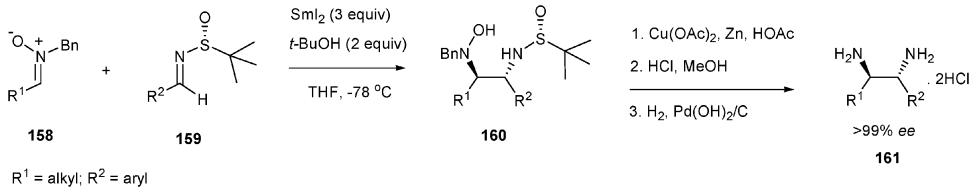


Fig. 9



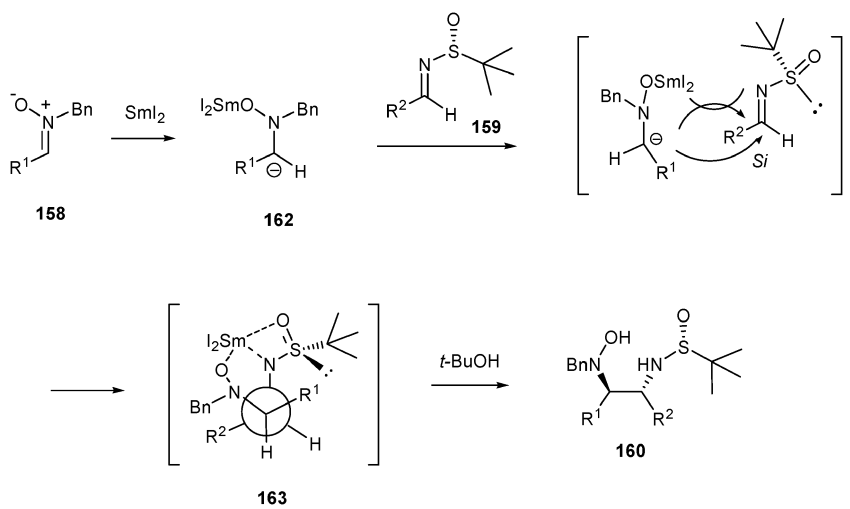
Scheme 39



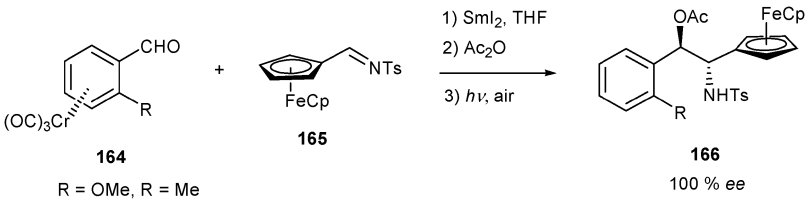
Scheme 40

Scheme 40. A mechanism for the observed stereoselective cross-coupling process was proposed, which is depicted in Scheme 41.[53] The nitrone **158** with SmI_2 is first reduced to generate probably an α-aza-nucleophilic anion (**162**), which then adds intermolecularly to the C=N bond of the *N-tert*-butanesulfinyl imine. The *tert*-butanesulfinyl group serves as a chiral directing group in the reaction. Due to its steric bulkiness, the nitrone anion **162** approaches preferably from the *Si*-face of the C=N bond, and formation of transition state **163** could be explained by chelation control and steric repulsion between R^1 and R^2.

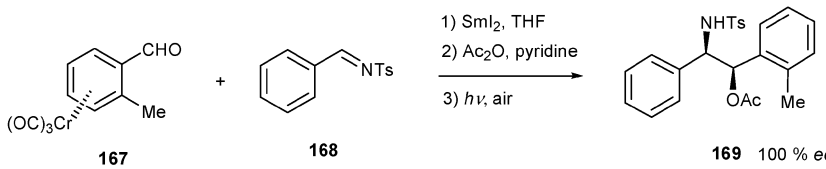
4.1.5 Aldehydes and imines. Uemura *et al*. have reported the asymmetric synthesis of *anti*- and *syn*-β-amino alcohols by reductive cross-coupling of chromium complexed planar chiral benzaldehydes with aldimines.[54] Reaction of enantiopure *o*-substituted benzaldehyde chromium complex (**164**) with imine **165** produced the *anti*-β-amino alcohols **166** in 90–94% yields

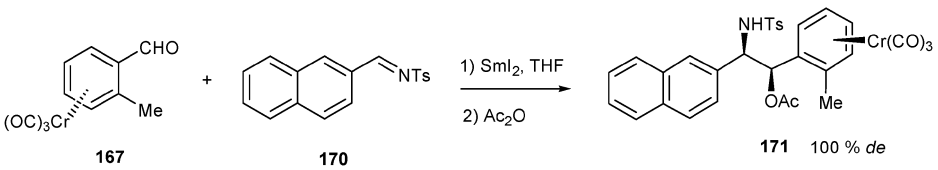


Scheme 41



Scheme 42





Scheme 43

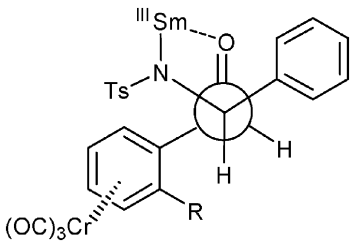


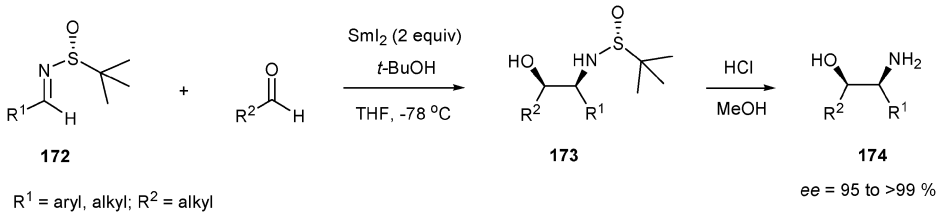
Fig. 10

without formation of any stereoisomers (Scheme 42). Reaction with enantiomers of **164** has been also performed, which allowed to prepare the enantiomers of **166**.

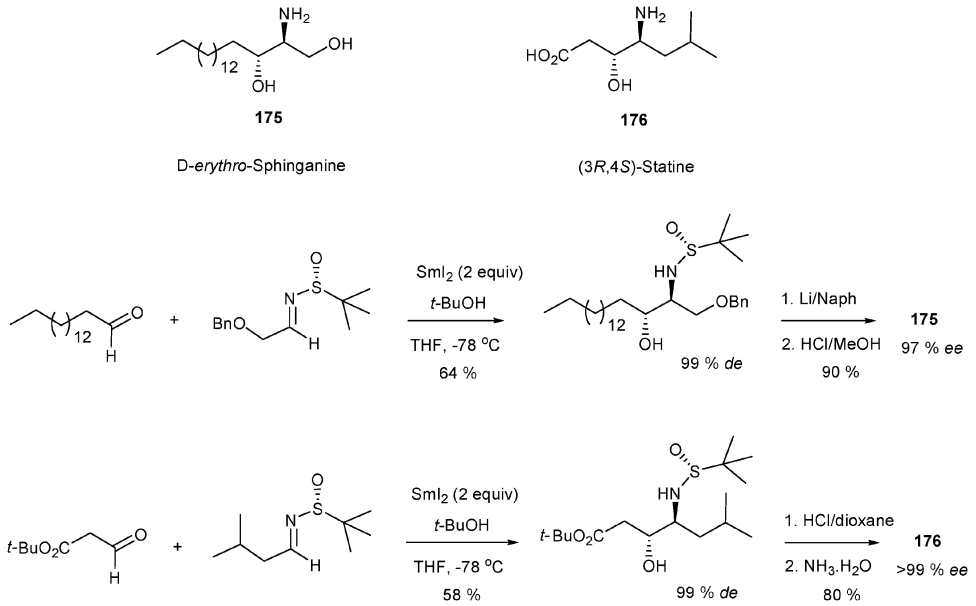
The enantiomerically active *syn*-β-amino alcohols were synthesized by coupling of planar chiral chromium complexes with *N*-tosyl arylideneamines.[54] Reaction of **167** and *ent*-**167** with imine **168** gave both enantiomers of the corresponding *syn*-β-amino alcohols **169** and *ent*-**169**, respectively (Scheme 43). Similarly, the cross-coupling of *N*-tosyl β-naphthylimine **170** with chromium complexes **167** and *ent*-**167** gave the *syn*-β-amino alcohols **171** and *ent*-**171**, respectively, depending on the planar chirality. A reaction mechanism of the cross-coupling of *N*-tosyl aldimines **168** or **170** with chromium complexes **167** or *ent*-**167** has been postulated to rationalize the observed *syn* stereoselectivity (Fig. 10).

Lin *et al*. have developed asymmetric synthesis of enantiopure β-amino alcohols by cross-coupling of chiral *N*-*tert*-butanesulfinyl imines with aldehydes.[55] Coupling of *N*-sulfinyl imine **172** (R^1 = *p*-tolyl) with isobutyraldehyde was initially examined for optimization of the reaction conditions (Scheme 44). High yields (92%) and extremely high diastereoselectivity (>99%) was accomplished by using 1.5 equiv. of aldehyde in the presence of SmI_2 and of *tert*-butyl alcohol. The general scope of the process was explored by performing the cross-coupling of a series of *N*-sulfinyl imines **172** with various aliphatic aldehydes including isobutyraldehyde. The desired cross-coupling products **173** were obtained in 70–95% yield and diastereomeric ratios up to >99 : 1. Subsequently, sulfinyl group of **173** was cleaved under acidic conditions, afforded the corresponding β-amino alcohols **174** in good yields with >95% *ee*s. The synthetic value of the reaction was further demonstrated by carrying out the preparation of two biologically active compounds D-*erythro*-sphinganine (**175**) and (3*R*,4*S*)-statine (**176**) as shown in Scheme 45.[55]

4.1.6 Homo-coupling of imines or ketones. Xu *et al*. have synthesized enantiopure C_2-symmetrical vicinal diamines by reductive homocoupling of aromatic *N*-*tert*-butanesulfinyl imines in the presence of SmI_2 and HMPA.[56] Imine **177a** was used for optimization of the reaction conditions in the presence of SmI_2 and a variety of additives (Scheme 46, eqn



Scheme 44



Scheme 45

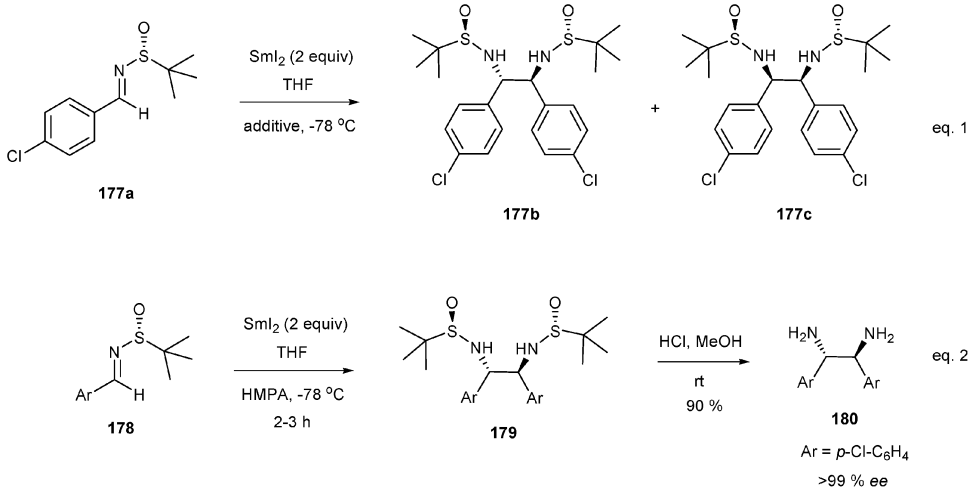
(1); Table 4). Reaction proceeded with 2 equiv. of SmI_2 in THF at −78 °C, produced both *d*/*l* (**177b**) and pseudo-*meso*-adduct (**177c**) in overall 81% of yield (Table 4, entry 1). When 2 equiv. of HMPA was added, the coupling reaction proceeded smoothly gave only diastereomer **177b**in an almost quantitative yield (Table 4, entry 4). Imines **178** containing either electron-withdrawing or electron-donating substituents were all successfully stereoselectively coupled into diamines **179** as the only products in moderate to excellent yields (52–99%), except for imine (R = Ph), which provided 25% yield of **179** (Scheme 46, eqn (2)). The homocoupling products **179** were easily converted to the corresponding free amines **180** by removal of the *N*-*tert*-butanesulfinyl group under acidic conditions. The *ee* of **180** (R = *p*-Cl–C_6H_4) was showed to be >99%. The proposed mechanism for the homocoupling reaction is shown in Scheme 47.

Kim *et al*. have studied the diastereoselective pinacol coupling of chiral α-ketoamides.[57] Ketoamides **181a** in

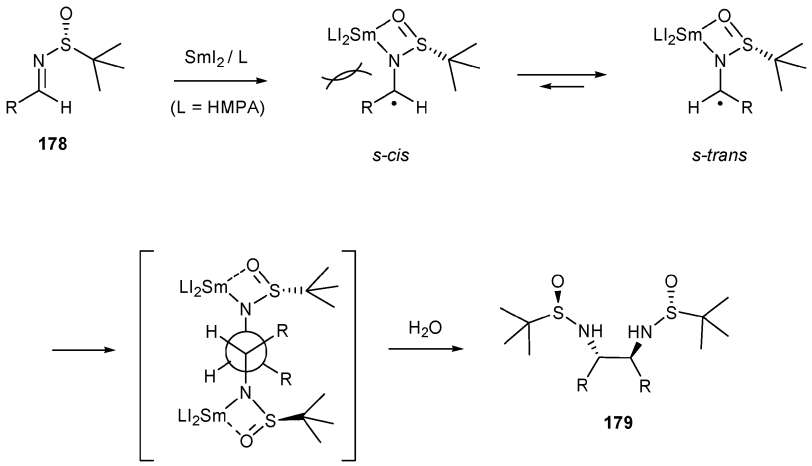
Table 4

Entry	Additive	Yield (%)	**177b** : **177c**
1	—	81	1.4 : 1
2	*t*-BuOH (2.0 equiv.)	77	1.7 : 1
3	NiI_2 (2 %)	72	1.7 : 1
4	HMPA (2.0 equiv.)	99	Only **177b**
5	HMPA (1.2 equiv.)	96	6 : 1

the presence of SmI_2, HMPA and *t*-BuOH gave the corresponding pinacols **182a** with high diastereoselectivity (**182a** : **183a** : **184a** up to 95 : 0 : 5) (Scheme 48). Acidic hydrolysis of **182a** (R = R^1 Me) gave (*S*,*S*)-2,3-dimethyltartaric acid **185** in 85% yield together with recovery of chiral auxiliary (*S*)-2-methoxymethylindolinone, with no loss of chirality. Similarly, the ketoamides **181b** afforded the corresponding pinacols **182b** with diastereoselectivity **182b** : **183b** : **184b** up to >99 : 0 : 1 under the same



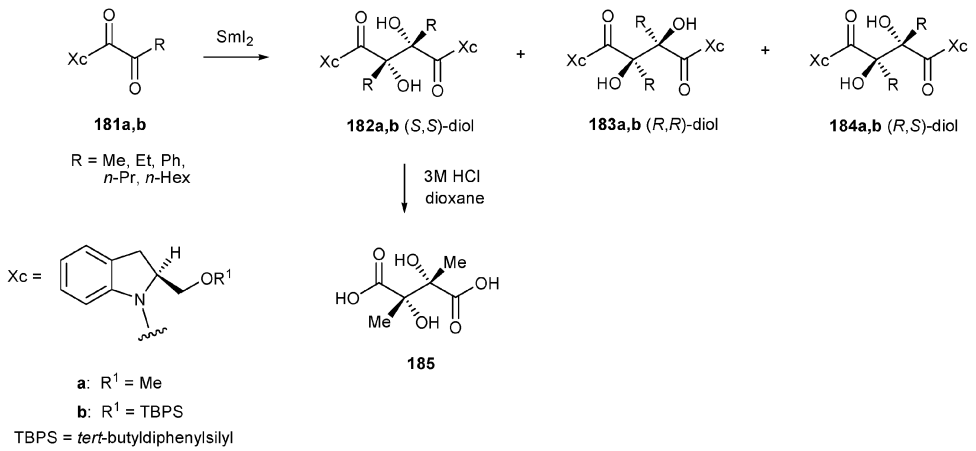
Scheme 46



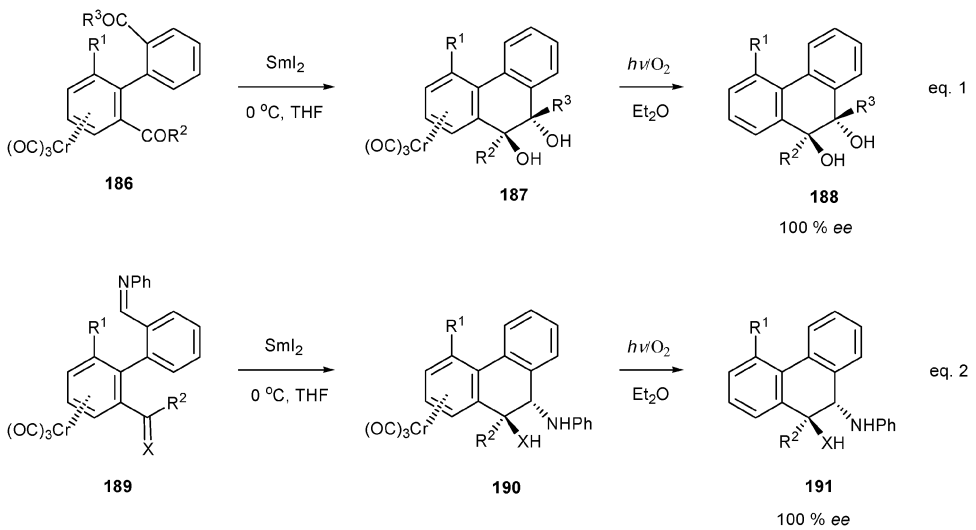
Scheme 47

conditions, which is probably due to the steric effect of the bulky TBPS moiety.

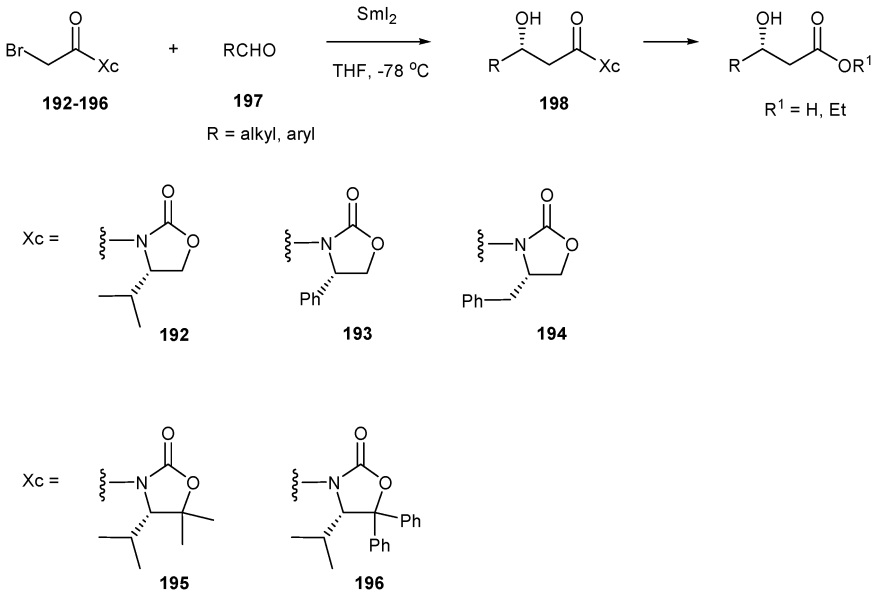
The SmI_2-mediated intramolecular pinacol coupling of planar chiral mono-$Cr(CO)_3$ complexes of biphenyls bearing dicarbonyl, diimino, or iminocarbonyl groups at the 2- and 2′-positions, led to the cyclic *trans*-1,2-diols, diamines, and amino alcohols in enantiomerically pure form.[58] Reaction of dialdehyde **186** ($R^1 = R^2 = R^3 = H$) with samarium diiodide



Scheme 48



Scheme 49



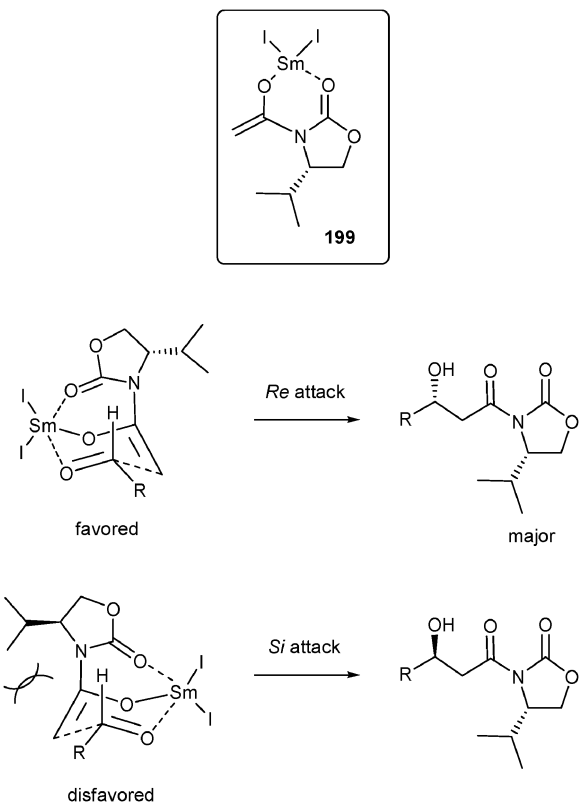
Scheme 50

in THF at 0 °C afforded the diol **187** in 81% yield without any formation of stereoisomers (Scheme 49, eqn (1)). Photo-oxidative demetalation of **187** gave (−)-(*S*,*S*)-diol **188** (R^1 = R^2 = R^3 = H) in a quantitative yield. Similarly, the mono-$Cr(CO)_3$-complexed biphenyls with keto-aldehyde functionality at the 2- and 2′-positions produced stereoselectively the corresponding cyclic *trans*-diols **188** (R^1 = H, OMe; R^2 = R^3 = H, Me). An intramolecular pinacol coupling of mono-$Cr(CO)_3$ complex of diiminobiphenyl **189** (R^1 = R^2 = H, X = NPh) produced a single *trans*-1,2-diamine derivative **190** under the same conditions (Scheme 49, eqn (2)). The diamino complex **190** exposed to sunlight gave the *trans*-1,2-diamine **191** (R^1 = R^2 = H, X = NPh). Similarly, the chromium complexes **189** (R^1 = H, OMe, R^2 = Me, X = O) produced stereoselectively the corresponding chromium-free *trans*-1,2-amino alcohols **191** under the same reaction conditions.

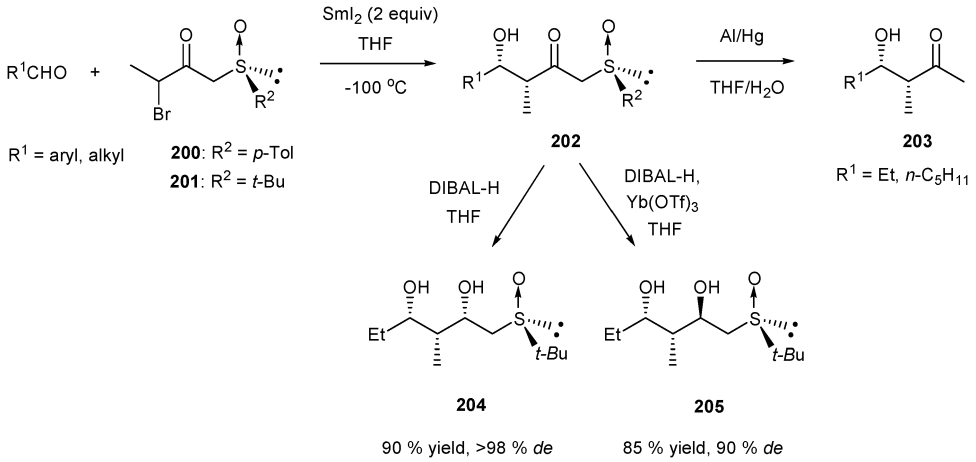
4.2 Reformatsky reaction

Fukuzawa *et al*. have investigated the asymmetric Reformatsky-type reaction between chiral α-bromoacetyl-2-oxazolidinones and aldehydes, which led to β-hydroxy carboximides (Scheme 50).[59] Reaction of a series of Evans' chiral 3-(2-bromoacetyl)-2-oxazolidinones **192–194** with several aldehydes **197**, furnished the corresponding β-hydroxy carboximides **198** in good to excellent yields (67–95%) and *de* values (64 to >99). The *de* value is highest with hindered aldehydes such as pivalaldehyde. It is interesting to point out that the diastereoselectivities is much higher here than that in the classical aldol reaction promoted by boron enolates of *N*-acetyl oxazolidinone. Additionally, reaction of SuperQuat chiral auxiliaries attached α-bromoacetyl substrates (**195** and **196**) with a variety of aldehydes was screened. Though the yield of the products were lower (32–87%) than those with **192–194**, stereoselectivities were improved. The relative stereochemistry of the β-hydroxy carboximides **198** was determined by converting them into the corresponding acids or ethyl esters. It was presumed that the reaction involved the samarium imide enolate **199**, which subsequently attacked the aldehyde. The stereochemistry of the reaction was explained by the chair transition structure model as shown in Scheme 51.

Colobert *et al*. have studied the intermolecular diastereoselective Reformatsky reaction of nonracemic α-bromo-α′-sulfinyl ketones (**200**, **201**) with various aldehydes in the presence of samarium diiodide (Scheme 52).[60a,b] Screening of different



Scheme 51



Scheme 52

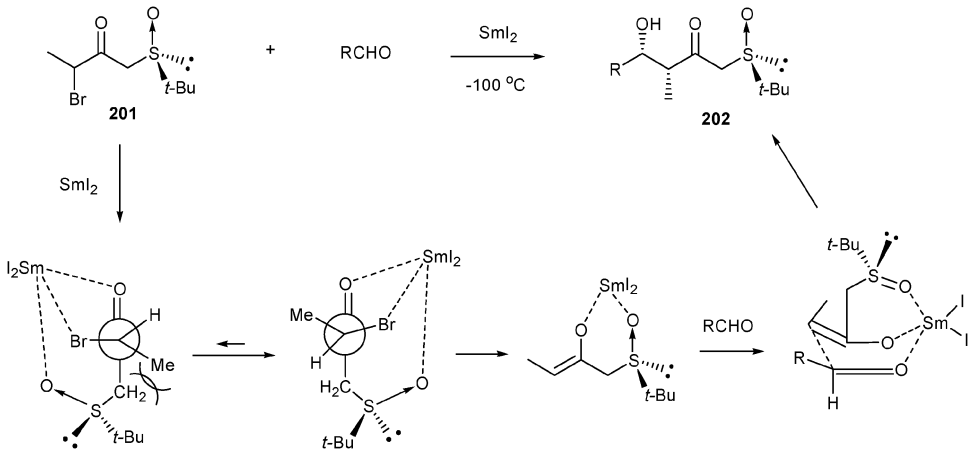
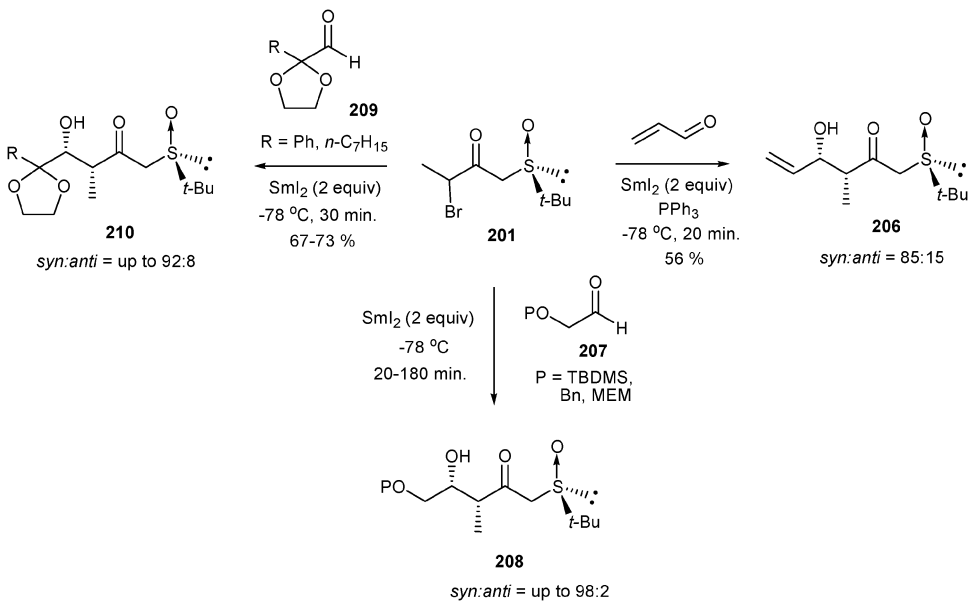
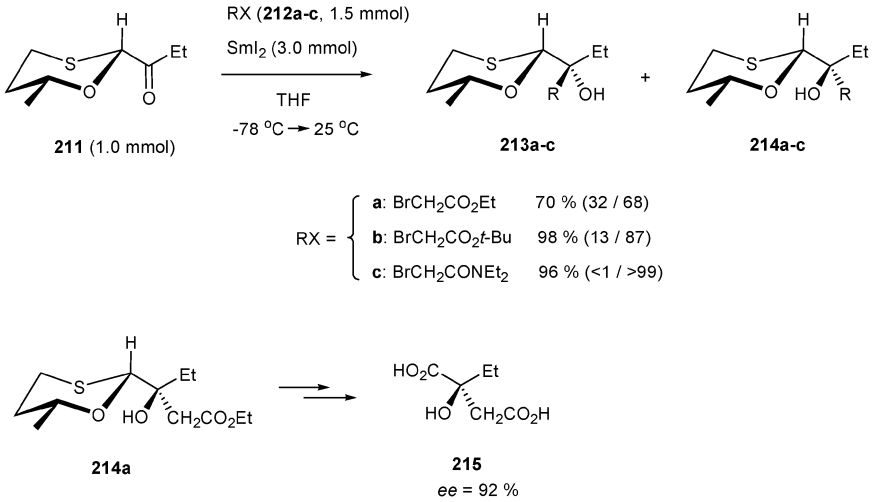


Fig. 11



Scheme 53

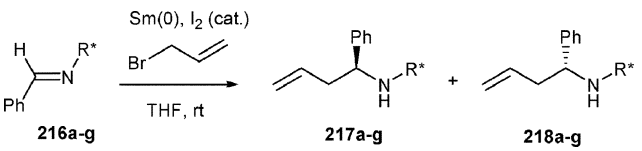


Scheme 54

Lewis acids in the reaction of **200** with benzaldehyde furnished the best *syn* diastereoselectivity (85/15) using SmI_2 in THF at −100 °C. The selectivity was further improved (96/4) with a more hindered substituent on the sulfur (**201**). Generality of the reaction was studied in the addition of **201** to various aromatic and aliphatic aldehydes at −100 °C. Linear aliphatic aldehydes afforded Reformatsky adducts **202** in good yields (65–79%) with diastereoselectivities as high as 95 : 5 for the *syn* product. The absolute stereochemistry of **202** (R^1 = Et, *n*-C_5H_{11}) was determined after reductive cleavage of the sulfoxide with aluminum amalgam giving the corresponding methyl ketones **203**. Reduction of the Reformatsky adduct **202** (R^1 = Et, R^2 = *t*-Bu) either with only DIBALH or with DIBALH in the presence of $Yb(OTf)_3$ furnished the corresponding 2-methyl-1,3-*syn* and *anti* diols **204** and **205**, respectively.

The stereochemical outcome was rationalized by proposal of the transition-state models involving coordination of bromine, carbonyl and sulfinyl oxygens on Sm(III) as shown in Fig. 11.[60b]

Table 5 Allylation of chiral imines



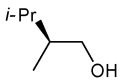
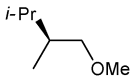
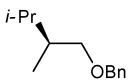
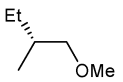
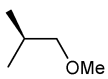
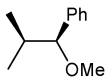
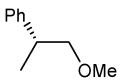
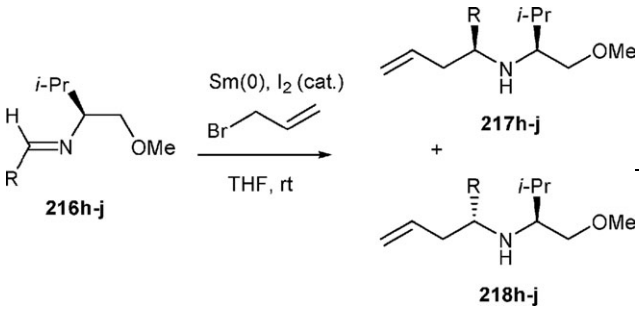
Imine	R*	Products	Yield (%) **217** + **218**	Ratio **217** : **218**
216a		**217a**, **218a**	47	62 : 38
216b		**217b**, **218b**	85	96 : 4
216c		**217c**, **218c**	79	97 : 3
216d		**217d**, **218d**	73	7 : 93
216e		**217e**, **218e**	74	90 : 10
216f		**217f**, **218f**	75	91 : 9
216g		**217g**, **218g**	77	<1 : >99

Table 6 Allylation of chiral imines



Entry	Imine	R	Products	Yield (%) 217 + 218	Ratio 217 : 218
1	**216h**	4-MeO–C_6H_4	**217h**, **218h**	93	97 : 3
2	**216i**	2-MeO–C_6H_4	**217i**, **218i**	77	99 : 1
3	**216j**	1-Naphthyl	**217j**, **218j**	62	92 : 8

The scope of the Reformatsky-type reaction was extended to a variety of functionalized aldehydes (Scheme 53).[60b] The reductive cleavage of the sulfoxide component in adducts **206**, **208** and **210** should generate almost enantiopure β-ketols.

Matsubara *et al*. have studied the samarium(II) Reformatsky reaction on ketone **211** containing (*R*)-6-methyl-1,3-oxathiane moiety as a chiral auxiliary (Scheme 54).[61] The oxathiane group of adduct **214a** was transformed into enantioenriched carboxylic acid **215**.

4.3 Barbier-type allylation

Yanada *et al*. have reported the diastereoselective Barbier-type allylation of chiral imines with metallic samarium, a catalytic amount of iodine, and allyl bromide.[62] A variety of imines

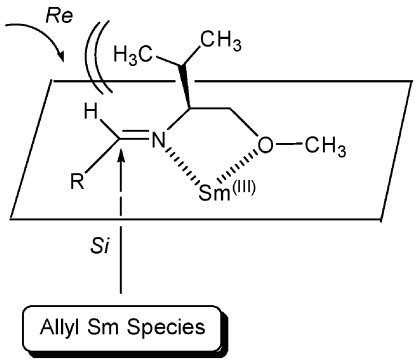
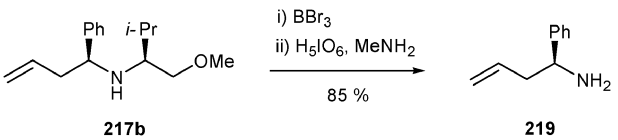
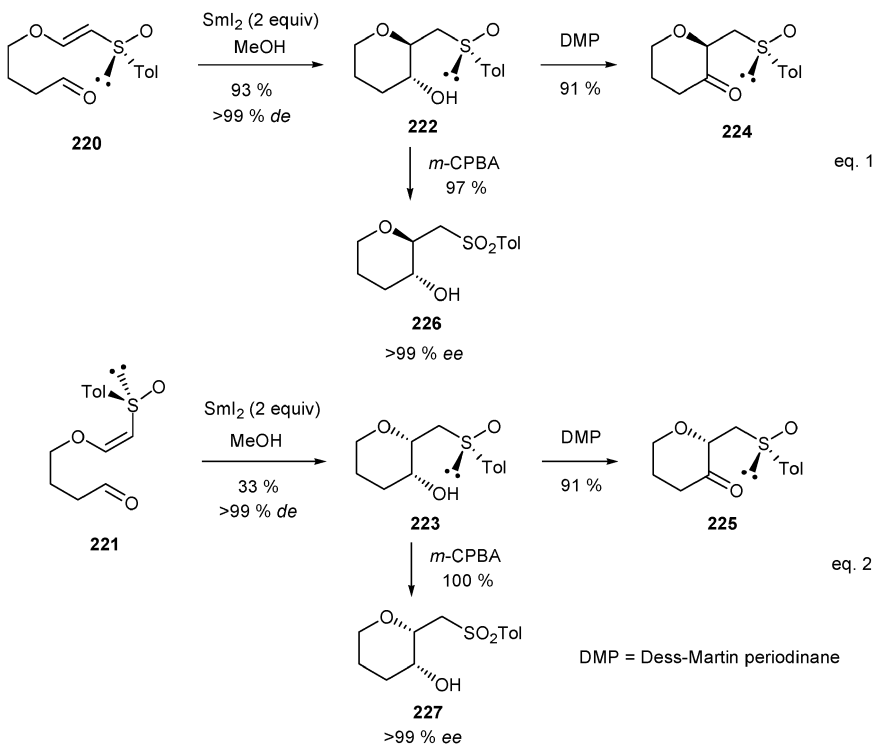


Fig. 12

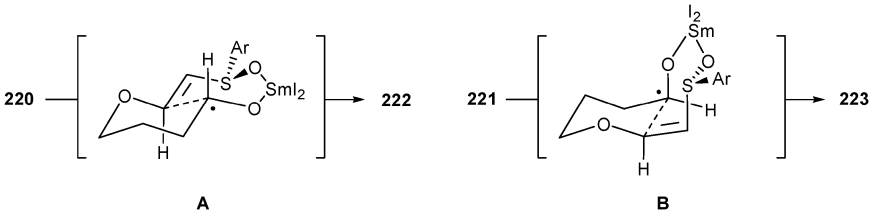


Scheme 55

216a–g produced the allylation products **217a–g** and **218a–g** in excellent diastereoselectivities (Table 5). The allylation of (*S*)-valinol methyl ether type imines **216h–j** which has substituents in the aldehyde side of imine, afforded the allylation products **217h–j** and **218h–j** (Table 6). The products **217a–j** or **218a–j** should be readily transformed into the corresponding enantiomerically enriched homoallylic amines. For example, **217b** was converted into (*S*)-**219** by demethylation followed by oxidative cleavage of the *C*–*N* bond (Scheme 55). The scheme of asymmetric induction in Fig. 12 has been proposed by the authors.



Scheme 56



Scheme 57

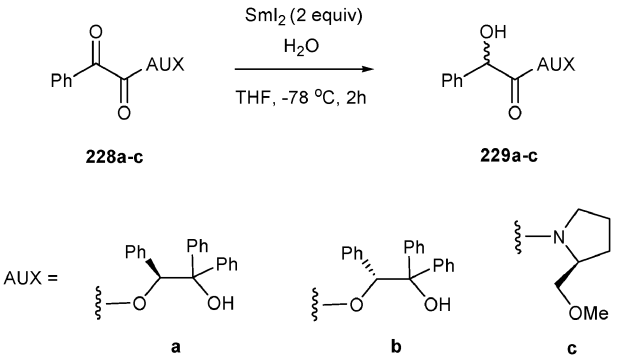
4.4 Reductive cyclizations

The SmI_2-mediated cyclization of sulfoxides **220** and **221** have been reported by Lee *et al.*, which led to the stereoselective synthesis of 3-hydroxyoxanes **222** and **223**, respectively (Scheme 56).[63] The stereochemistry of **222** and **223** were deduced by Dess–Martin oxidation, which produced **224** and **225**, respectively. Subsequently, *m*-CPBA oxidation of **222** and **223** gave sulfones **226** and **227**, respectively. The observed stereoselectivity was explained by proposing the ''eclipsed lone pair'' transition states **A** and **B**, in which the sulfoxide oxygen-coordinated samarium ketyl group necessarily approaches the double bond opposite from the bulky aryl group (Scheme 57). Similarly, the SmI_2-mediated cyclizations of various β-alkoxy-vinyl sulfoxides have been studied, the oxacyclic products were obtained as sole product in each case.[63]

4.5 Reduction of ketones

Fukuzawa *et al.* have investigated the diastereoselective reduction of chiral α-keto esters/amides **228** bound to a variety of auxiliaries (Scheme 58).[64] In the reduction of benzoylformic acid esters or amides which are derived from several classes of chiral auxiliaries, it was found that **228a–c** were efficiently reduced to products **229a–c** with 63, 60 and 75% *de*, respectively. In section 3.1, a case of enantioselective reduction of benzil to benzoin has been mentioned. The similar mechanism applies to the reduction of **228**.

Subsequently, the SmI_2-mediated reductive intermolecular coupling of benzoylformate and pyruvate of **228a** with allyl iodide, α-bromo ester and α,β-unsaturated ester has been studied (Scheme 59).[64] The allylation of **228a**, **228c**, and **230a** gave the corresponding 2-hydroxy-4-pentenoic acid esters with 57, 35 and 54% *de*, respectively. The Reformatsky-type reaction of **228a** and **228c** with methyl α-bromoacetate

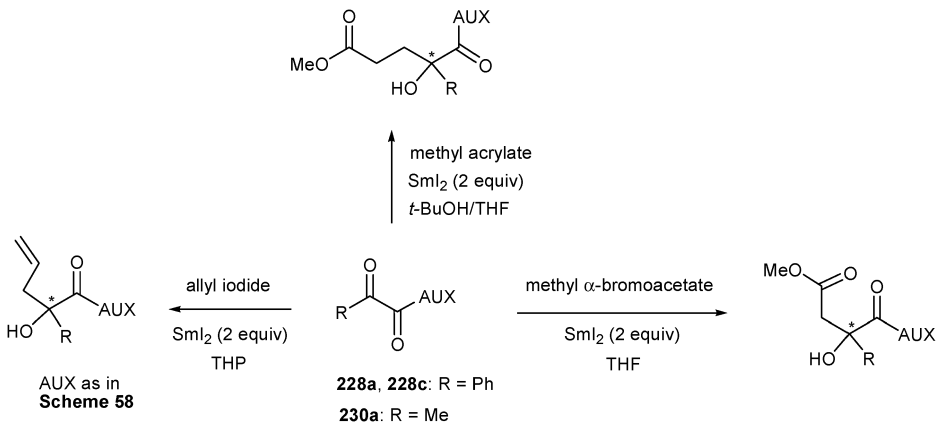


Scheme 58

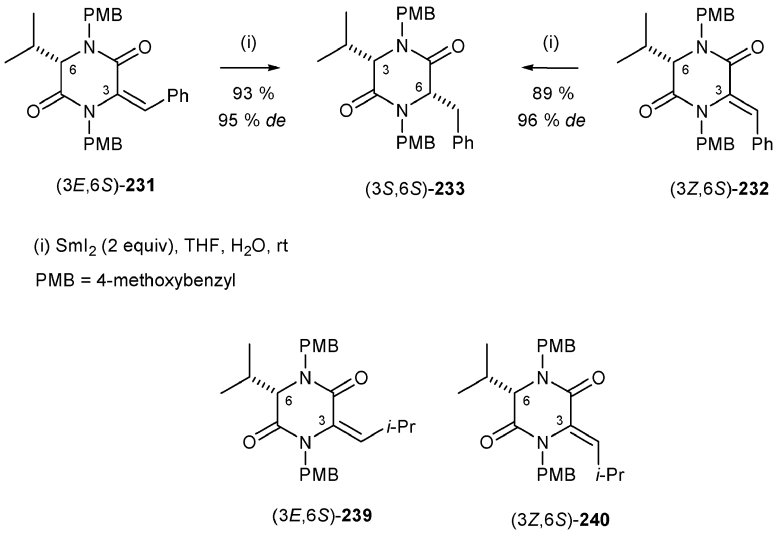
afforded the corresponding 1,4-diesters in 80–90% yields with 72 and 60% *de*, respectively. The coupling of methyl acrylate with **228a** gave the corresponding 1,5-diester in 91% yield with 78% *de*, while the reaction with **228c** resulted in 47% yield with 86% *de*. The chiral auxiliary group (AUX) can be deblocked by a hydrolytic treatment, leading to the enantio-enriched α-hydroxy acids.

4.6 Reduction of conjugated C=C double bonds

Davies *et al.* have studied the samarium diiodide-promoted reduction of enantiopure (*E*)-**231**,**239** and (*Z*)-**232**,**240** in the presence of H_2O (Scheme 60).[65a,b] Reduction of (3*E*,6*S*)-**231** or (3*Z*,6*S*)-**232** with SmI_2, led to the generation of a *C*-3 stereogenic centre afforded *cis*-(3*S*,6*S*)-**233** in excellent yield (89–93%) and diastereoselectivity (~95% *de*) (Scheme 61). The high levels of *cis*-stereoselectivity in both these reductions are consistent with the formation of a common samarium enolate intermediate which undergoes stereoselective

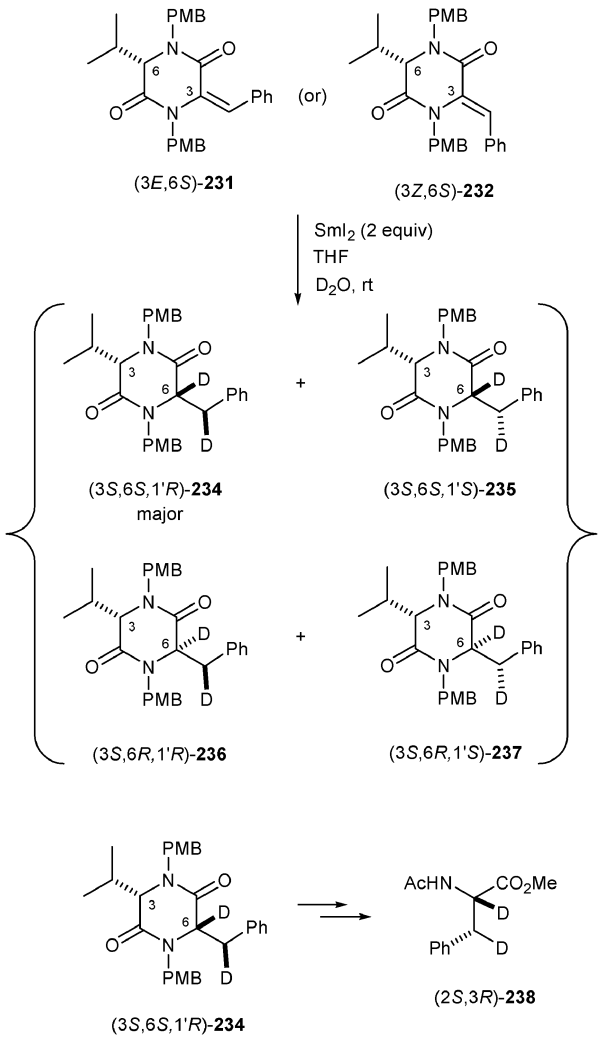


Scheme 59



Scheme 60

protonation *anti* to the isopropyl group. The high levels of diastereofacial selectivity in the generation of a single stereogenic centre was established by dideuteration of these enamides templates, a process which has the potential to stereoselectively generate simultaneously two stereogenic centers at *C*-6 and *C*-1′ (Scheme 61). Reduction of either (3*E*,6*S*)-**231**, (3*Z*,6*S*)-**232**, or a 7 : 1 mixture of (3*E*,6*S*)-**231** : (3*Z*,6*S*)-**232** with a solution of SmI_2 in THF and D_2O gave *C*-1′,*C*-3-dideuterated-diketopiperazine (3*S*,6*S*,1′*R*)-**234** (as a ~92 : 8 mixture of **234** and minor diastereoisomers **235–237**) in 96% yield. The (3*S*,6*S*,1′*R*)-configuration within dideuterio **234** was established by conversion to the known bis-deuterated aminoester **238**.



Scheme 61

Similar dideuteration studies were performed for (*E*)- and (*Z*)-isobutylidene diketopiperazines (*E*)-**239** and (*Z*)-**240** with SmI_2 and D_2O, afforded the corresponding dideuteriated products in excellent yields and diastereoselection.[65b]

5. Conclusion and perspectives

Samarium diiodide found a place as reducing agent in the tool box of practitioners of asymmetric synthesis for the mild release of some protecting groups or of chiral auxiliaries. Another application of samarium diiodide is its ability to produce highly diastereoselective couplings which can lead to enantioenriched products after the proper synthetic manipulations. The *in situ* formation of samarium enolates followed by asymmetric protonation (stoichiometric or catalytic by respect to the chiral auxiliary) is also a promising area. Up to now there is no report in asymmetric synthesis where samarium diiodide was used in catalytic amount (thanks to a co-reducing agent). In conclusion there are many utilizations of samarium diiodide in organic synthesis connected to asymmetric synthesis. May be this review will encourage more chemists involved in synthesis of chiral compounds to consider the use of this reagent in the context of enantioselective or diastereoselective reactions connected to asymmetric synthesis.

Acknowledgements

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