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PAPER

Exploiting Sm(II) and Sm(III) in SmI_2-initiated reaction cascades: application in a tag removal–cyclisation approach to spirooxindole scaffolds†

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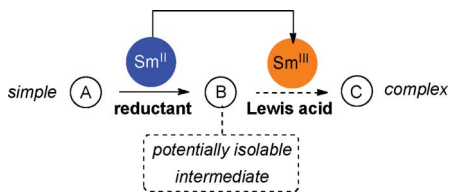
A tag removal–cyclisation sequence is described that is initiated by reduction using a Sm(II) species and completed by a Sm(III) Lewis acid that is formed in an earlier stage. Therefore, the reaction cascade utilises both oxidation states of a samarium reagent in discrete steps and allows access to privileged, pyrrolidinyl-spirooxindole scaffolds and analogues inspired by the anti-cancer natural product spirotryprostatin A.

Introduction

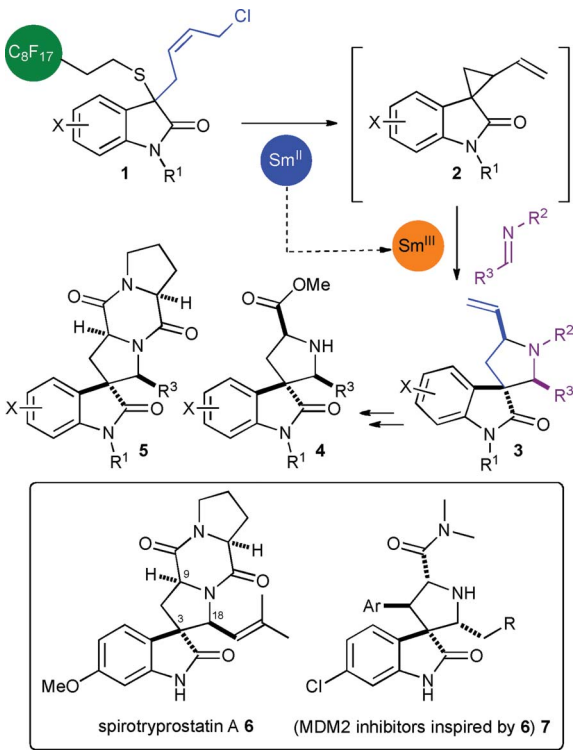
Cascade reactions in which multiple synthetic tasks are carried out selectively in a single reaction flask represent the holy grail for the synthetic chemist. The lanthanide reagent, samarium diiodide (SmI_2),[1] is one of the most important chemical reductants and is often the reagent of choice for the orchestration of reductive reaction cascades due to the high chemo-, regio- and stereoselectivity it exhibits.[2]

Here we describe an example of a sequence that utilises both oxidation states of a samarium reagent in discrete steps. In contrast to reduction-only cascades, the exploitation of additional Lewis acid-mediated processes to terminate reaction sequences, mediated by Sm(III) species formed in earlier reductive steps, greatly expands the chemical space that can be accessed. In the new reaction cascades, Sm(II)-mediated reduction of A generates an otherwise stable product B that is then transformed by the Lewis acidic Sm(III) by-product to give C (Scheme 1).



Scheme 1 Exploiting Sm(II) and Sm(III) in SmI_2-initiated cascades.

To evaluate the feasibility of exploiting both oxidation states of a samarium reagent in cascade reactions we designed a phase tag removal–cyclisation sequence initiated by reduction of tagged oxindoles **1** using a Sm(II) species and completed by a Sm(III) Lewis acid that is formed in an earlier step. The fluorous[3] approach would allow access to the biologically significant pyrrolidinyl-spirooxindoles **3**, with purification being conveniently carried out using fluorous solid-phase extraction (FSPE)[4] (Scheme 2). The pyrrolidinyl-spirooxindole unit forms the core of an extensive family of alkaloid natural products, many of whose members possess bioactivity.[5] For example, spirotryprostatins A and B[6]



Scheme 2 A Sm(II)/Sm(III)-mediated approach to the pyrrolidinyl-spirooxindole scaffold.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data and ^{1}H and ^{13}C spectra, X-ray crystallographic data. CCDC reference numbers 780379–780382 and 791298. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05710c

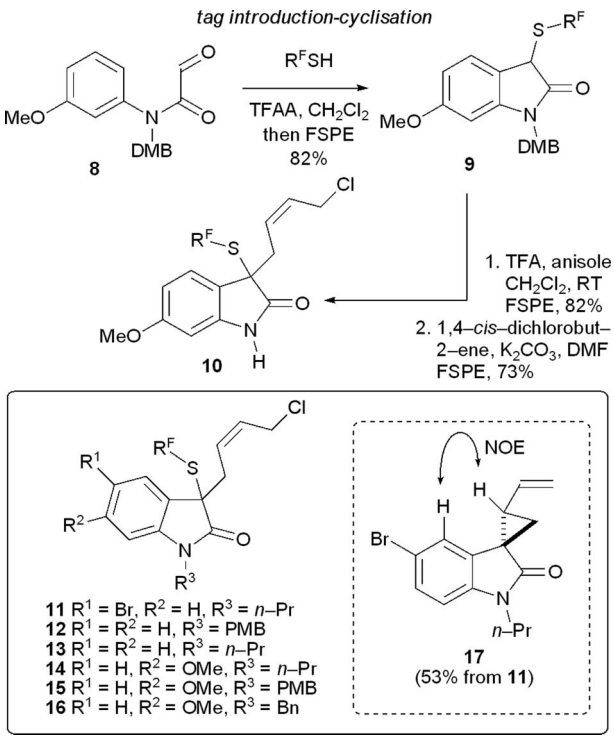
exhibit anti-cancer activity and analogues of spirotryprostatin A **6** have improved activity against breast cancer cell lines.[6b] Furthermore, simplified analogues such as **7** are promising MDM2 inhibitors.[7] We proposed that manipulation of **3** could give natural product analogues **5** *via* intermediates **4**, which are related to MDM2 inhibitors **7** (Scheme 2).

New tagging strategies[8] continue to play a key role in the quest for more efficient synthesis. In particular, the use of fluorous tags and associated purification technologies[3] now enjoys widespread use in chemistry and chemical biology. In addition to the development of new Sm-mediated cascade processes, our studies will show how the unavoidable tag introduction and tag removal steps can be used to trigger important synthetic events in a route and thus the use of a phase tag to assist purification need not lengthen a synthesis.

Results and discussion

Development and scope of Sm(II)/Sm(III)-mediated reaction cascades

To investigate our proposal to exploit a Sm(II)/Sm(III)-mediated reaction cascade, tagged oxindoles **10–16** were prepared using a modification of our tag introduction–cyclisation process based on a Pummerer-type[9] reaction, and were purified conveniently using fluorous solid-phase extraction (FSPE).[4] For example, tag introduction–cyclisation[10,11] involving glyoxamide **8** followed by removal of the DMB protection and alkylation with *cis*-1,4-dichlorobut-2-ene gave **10**. *N*-Alkyl substrates **11–16** were prepared in two steps from substrates analogous to **8**. FSPE was used to purify products in all steps *en route* to **10–16** (Scheme 3). Pleasingly, treatment of tagged substrate **11** with SmI_2[12] triggered

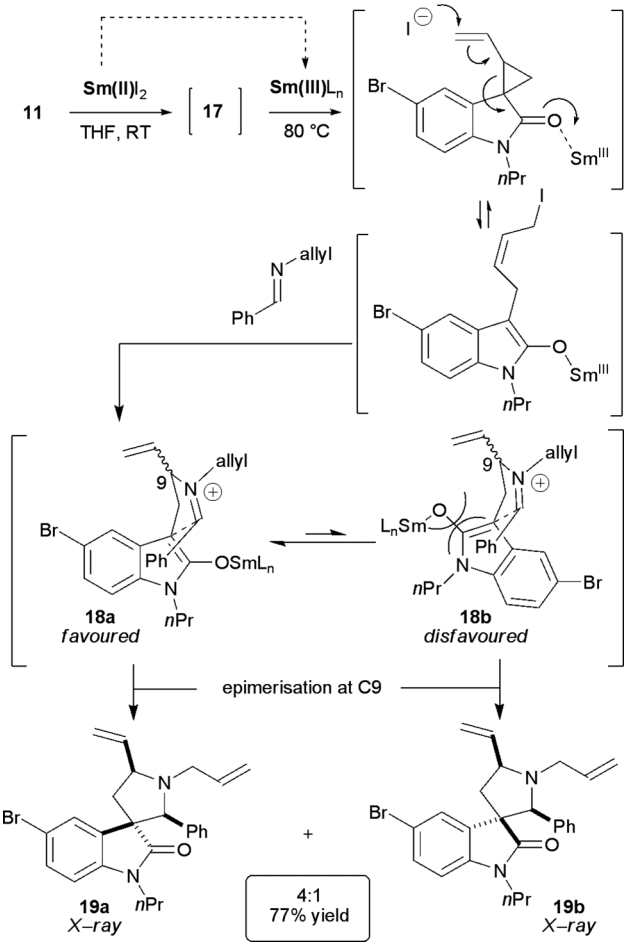


Scheme 3 Substrates for Sm(II)/Sm(III)-mediated cascades (R^F = $-CH_2CH_2C_8F_{17}$).

expulsion of the fluorous tag and intramolecular Sm(III)-enolate[13] alkylation to give vinylcyclopropane **17** (*cf.* **2**) in 53% isolated yield as a single diastereoisomer (Scheme 3).

We postulated that **17** would react with an imine in the presence of a Sm(III) Lewis acid, formed during tag removal, to give an iminium ion intermediate (*cf.* **18**) that would undergo subsequent Mannich-type cyclisation. Carreira has previously employed oxindole cyclopropanes in analogous cycloadditions mediated by MgX_2.[6h,6j,14]

We were pleased to find that treatment of **11** with SmI_2 in THF (2 equiv) at room temperature followed by addition of *N*-allylphenylimine and heating to 80 °C resulted in removal of the fluorous tag and cyclisation to give pyrrolidinyl-spirooxindole **19** as a separable 4 : 1 mixture of diastereoisomers in 77% yield after purification by FSPE. The relative stereochemistry of diastereoisomers **19a** and **19b** was confirmed by X-ray crystallographic analysis[15] (Scheme 4).



Scheme 4 Mechanism and proposed origin of diastereoselectivity in the Sm(II)/Sm(III)-mediated reaction cascade.

The intermediacy of spirocyclopropyloxindole **17** was confirmed by monitoring the reaction by ^{1}H NMR spectroscopy and by the observation that heating **17** at 80 °C with *N*-allylphenylimine in the presence of SmI_3 gave **19** in 68% yield and a similar diastereoisomeric ratio to that obtained from the sequential reaction. The evolution of the reagent was crucial to

the success of the cascade, as heating **17** with the imine in the absence of Sm(III) led to the recovery of starting materials.

The diastereoselectivity observed in the reaction cascade to give **19** can be explained by considering transition structures **18** (Scheme 4).[16] Transition structure **18b** is disfavoured due to steric interactions arising from the *syn* relationship between the Sm(III)-enolate and its associated ligands and the substituent on the imine. The *syn* relationship between the substituents α to nitrogen in the pyrrolidine ring in both products appears to result from rapid epimerisation of the stereocentre α to nitrogen bearing the vinyl group (C9 in Scheme 4), post cyclisation.

The approach to oxindole cyclopropanes embedded in our new cascade reaction has several advantages over literature routes: mild, reductive conditions are used, thereby avoiding the use of strong bases and low temperatures or diazocompounds.[6h,6j,14] In addition, the *in situ* generation of these relatively unstable species renders their isolation and purification unnecessary.

The scope of the Sm(II)/Sm(III)-mediated reaction cascade was explored using oxindole substrates **10–16** and a range of imines. Pyrrolidinyl-spirooxindoles **19–30** were obtained in good overall yield (58–77%) (Fig. 1). The moderate to good diastereoselectivity (3 : 1 dr to 11 : 1 dr) observed is comparable to that reported for the related stepwise process mediated by Mg(II).[17] The process is compatible with some imines bearing α-hydrogens (*e.g.* preparation of **27** and **28**) and oxindoles bearing a free N–H (*e.g.* preparation of **29** and **30**). In all cases, FSPE can be used to purify products by removing any unreacted starting material and the fluorous disulfide by-product resulting from removal of the fluorous tag. Pleasingly, the fluorous disulfide can be recovered from these cascades in ~70% yield using FSPE and can be reduced to the fluorous thiol (nBu$_3$P, H$_2$O, THF, 70%) and reused.[18]

Manipulation of products from the Sm(II)/Sm(III)-mediated reaction cascades

In our route to pyrrolidinyl-spirooxindoles, the introduction (see **8** to **9** in Scheme 3) and removal of the tag are used to trigger key cyclisation events in the fluorous synthesis and no additional steps result from the use of a tag as a purification handle.

The products of the Sm(II)/Sm(III)-mediated reaction cascade can be readily converted to compounds related to MDM2 inhibitors **7** and spirotryprostatin A **6**. In the latter case, Danishefsky has shown that analogues of spirotryprostatin A bearing different sidechains at C18 can have activity greater than that exhibited by the natural products.[6b] Attractively, our approach allows the synthesis of a wide range of analogues by introducing diversity at C18 and on the oxindole ring, and by manipulation of the terminal alkene in the pyrrolidinyl-spirooxindoles.

Oxidative cleavage of the alkenes in pyrrolidinyl-spirooxindoles **25**/**29** gave aldehydes **31**/**32** in good yield (Scheme 5). Subsequent oxidation, esterification and debenzylation gave methyl esters **35**/**36** (*cf.* MDM2 inhibitors **7**). The relative stereochemistry of **35** was confirmed by X-ray crystallographic analysis.[15] Coupling with Troc-(*S*)-proline chloride allowed a late-stage resolution to be exploited for the introduction of stereochemical diversity in our library approach. Removal of the Troc protecting group from **37**/**38** triggered cyclisation to give **39**/**40a**,**b** (Scheme 5). The stereochemistry of the four analogues was confirmed by X-ray crystallographic analysis of **40b**[15] and NOE studies on **39a**,**b**.

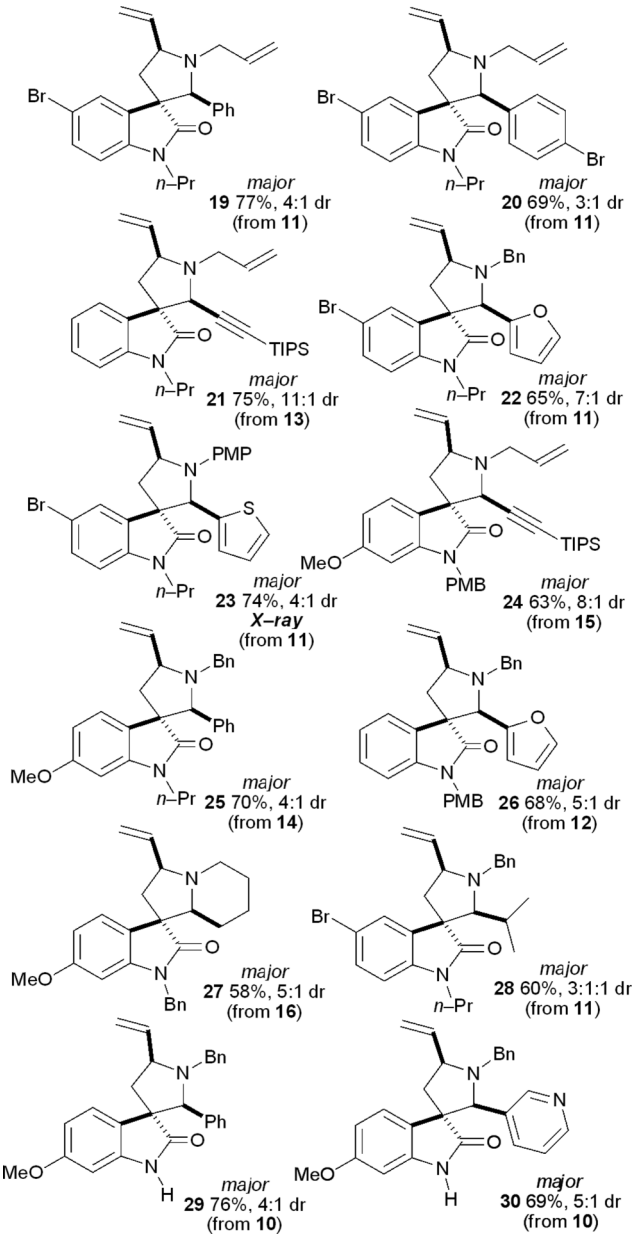
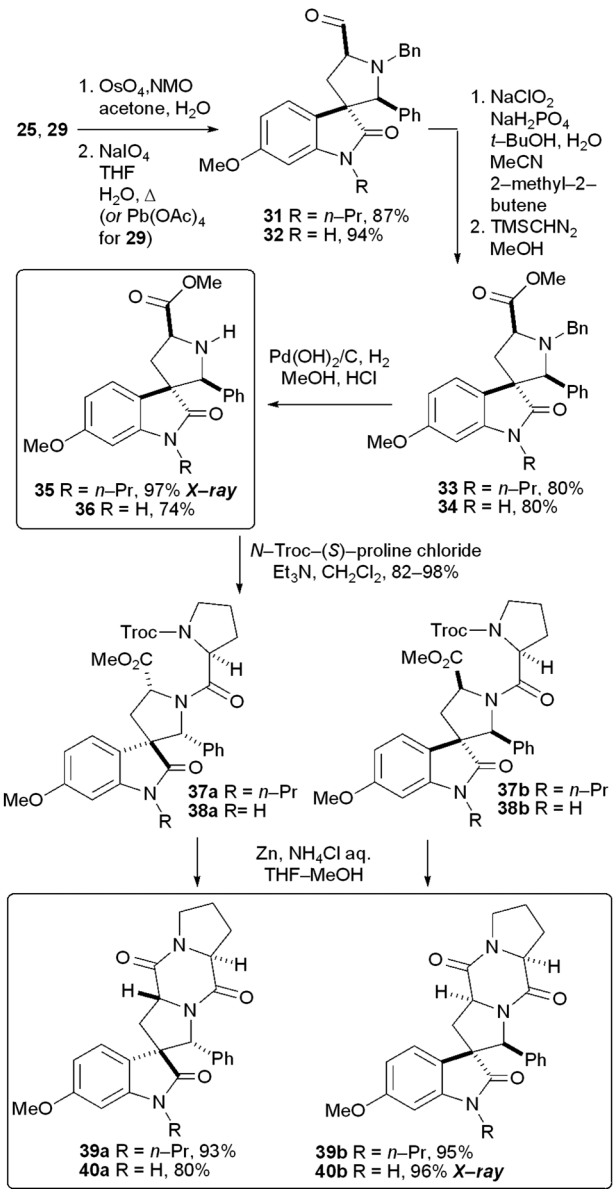
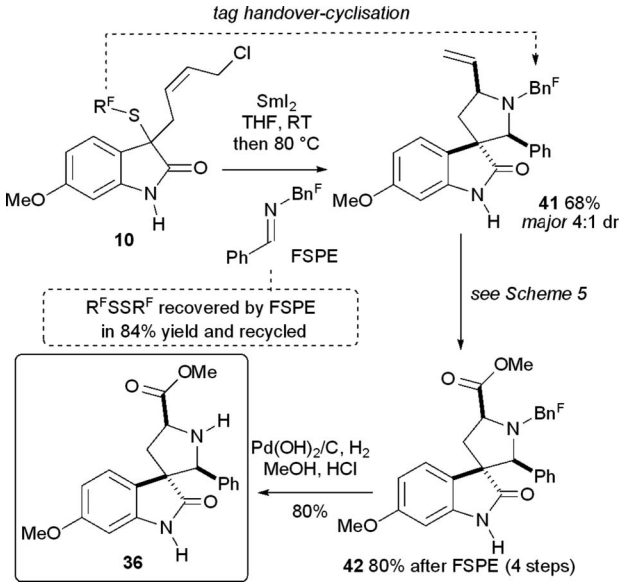


Fig. 1 Scope of the Sm(II)/Sm(III)-mediated reaction cascade.

The Sm(II)/Sm(III)-mediated reaction cascade has also been exploited in a tag handover–cyclisation strategy for the preparation of compounds related to MDM2 inhibitors **7** and spirotryprostatin A **6**. A reaction cascade employing tagged oxindole **10** and an imine bearing a fluorous benzyl protecting group[19] allowed tags to be exchanged during the cascade to generate **41** thus avoiding the need to remove an old tag and introduce a new tag in a stepwise fashion. The fluorous tag that is removed can be recovered and recycled as before (*vide supra*) as the R^{F}SSR^F elutes more slowly than **41** on fluorous silica gel due to its higher fluorine content.[18] Straightforward manipulation of **41** gave **42**, after purification by FSPE. Finally, removal of the fluorous benzyl group under acidic hydrogenolysis conditions gave **36** (Scheme 6). The conversion of **36** to **40a**,**b** has been illustrated in Scheme 5.



Scheme 5 Manipulation of pyrrolidinyl-spirooxindoles.



Scheme 6 A tag handover–cyclisation strategy (Bn^F = –CH_2(4-$C_6H_4CH_2$-$CH_2C_8F_{17}$).

Conclusions

SmI_2-initiated reaction cascades have been developed in which the samarium reagent's change from reductant to Lewis acid is exploited. The concept has been exemplified in a phase tag removal–cyclisation process which is initiated by reduction using a Sm(II) species and completed by a Sm(III) Lewis acid formed during the reductive step. Thus, the sequence utilises both oxidation states of a samarium reagent in discrete steps. The sequence has been exploited in a fluorous synthesis of pyrrolidinyl-spirooxindoles in which the introduction and removal of the fluorous tag are used to trigger key cyclisation events and thus no additional steps result from the use of a tag as a purification handle. The route has been extended to prepare analogues inspired by the anti-cancer natural product spirotryprostatin A. The biological evaluation of these compounds is underway and preliminary studies have shown that analogues such as **36** display levels of activity similar to that of spirotryprostatin A.[20]

Acknowledgements

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15 See the Supporting Information for CCDC numbers and X-ray crystallographic data†.
16 The ratio of the product diastereoisomers **19a** and **19b** remains constant throughout the course of the reaction, suggesting epimerisation at the quaternary stereocentre in the products is not taking place. The epimerisation of pyrrolidinyl–spirooxindoles through a retro–Mannich/Mannich pathway is well known. See ref. 6j and references therein.
17 Carreira obtained several diastereoisomers from his stepwise cyclisation process in a ratio of 8 : 1 : 8 (major : minor : other diastereoisomers). Epimerisation gave improved ratios of 5 : 1 to 7 : 1. See ref. 6j.
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