EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202200264

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

Samarium(II)-Promoted Cyclizations of Nonactivated Indolyl Sulfinyl Imines to Polycyclic Tertiary Carbinamines

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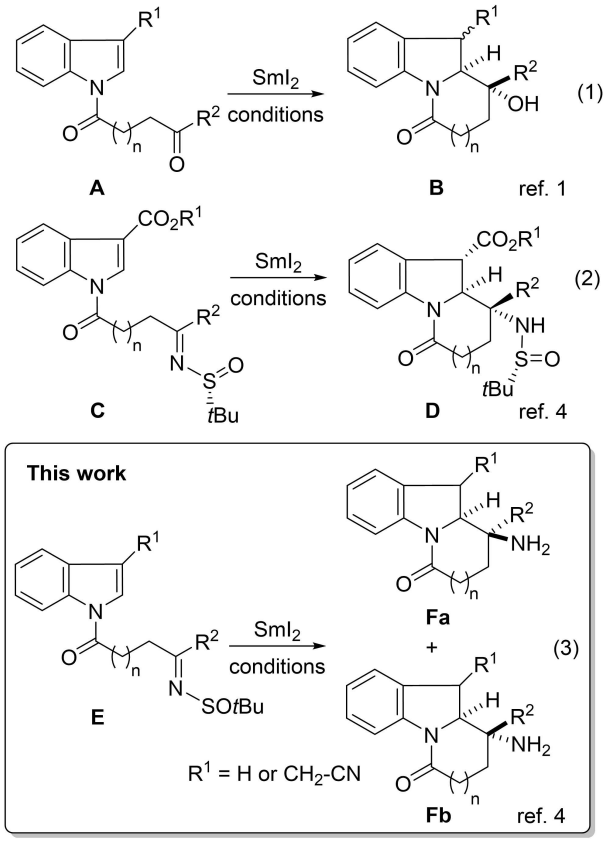
Dedicated to Professor Dr. Akihiro Ohta (Tokyo) on the occasion of his 88th birthday

Samarium(II)-promoted cyclizations of *N*-acylated indolyl sulfinyl imines without electron-withdrawing groups at C-3 furnished tertiary carbinamines in good yield. Screening of the reaction conditions revealed that application of an excess of samarium diiodide in the presence of water and lithium bromide provided the cleanest reactions and the highest yields. The most striking observation during this investigation was the reductive detachment of the sulfur functional group, which most likely precedes the cyclization step. As consequence no enantioselectivity could be observed if enantiopure sulfinyl imines were employed. The mechanisms of the N–S cleavage and of the cyclization of the intermediate imines as well as the role of the additives are discussed. The presented method generates interesting polycyclic indoline derivatives; a cascade reaction involving an ethoxycarbonyl-substituted side-chain provided unique tetracyclic spiro-γ-lactams.

Introduction

In several publications we described samarium diiodide-promoted cyclizations of *N*-alkylated and *N*-acylated indolyl ketones such as **A** which furnished indolines **B** in high yield and excellent stereoselectivity [Scheme 1, Reaction (1)].[1] This dearomatization reaction[2] was subsequently employed as key step of our short cascade route to strychnos alkaloids.[3] The analogous reaction of *N*-acylated indolyl sulfinyl imines **C** or **E** led under suitable conditions to tricyclic tertiary carbinamines [Scheme 1, Reactions (2) and (3)].[4] If precursors **C** with electron-withdrawing alkoxycarbonyl groups at C-3 are employed this process occurs under the influence of the chiral auxiliary at the sulfur moiety and products **D** are formed in high diastereoselectivity and enantioselectivity. However, if these activating electron-withdrawing groups are missing the reactions took a slightly different course. In the preliminary report we showed that *N*-acylated indolyl sulfinyl imines such as **E** undergo the cyclization under simultaneous detachment of the sulfur functional group. Products **Fa**/**Fb** were formed as mixture of diastereomers and – most significantly from a mechanistic point of view – as racemic compounds [Scheme 1, Reaction (3)].[4] We concluded from these observations that the transformations sketched in reactions (1–3) proceed via different mechanisms. In the present full account, we show examples of the reactions



Scheme 1. Samarium diiodide-promoted reductive dearomatization of *N*-acylated indolyl ketones **A** leading to indolines **B**, related reactions of activated indolyl sulfinyl imines **C** to tertiary carbinamines **D** and of nonactivated indolyl sulfinyl imines **E** giving **Fa**/**Fb**.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202200264

Research Article
doi.org/10.1002/ejoc.202200264

of nonactivated *N*-acylated indolyl sulfinyl imines **E**, including details of the optimization of the conditions and a discussion of the involved mechanisms.

Results and Discussion

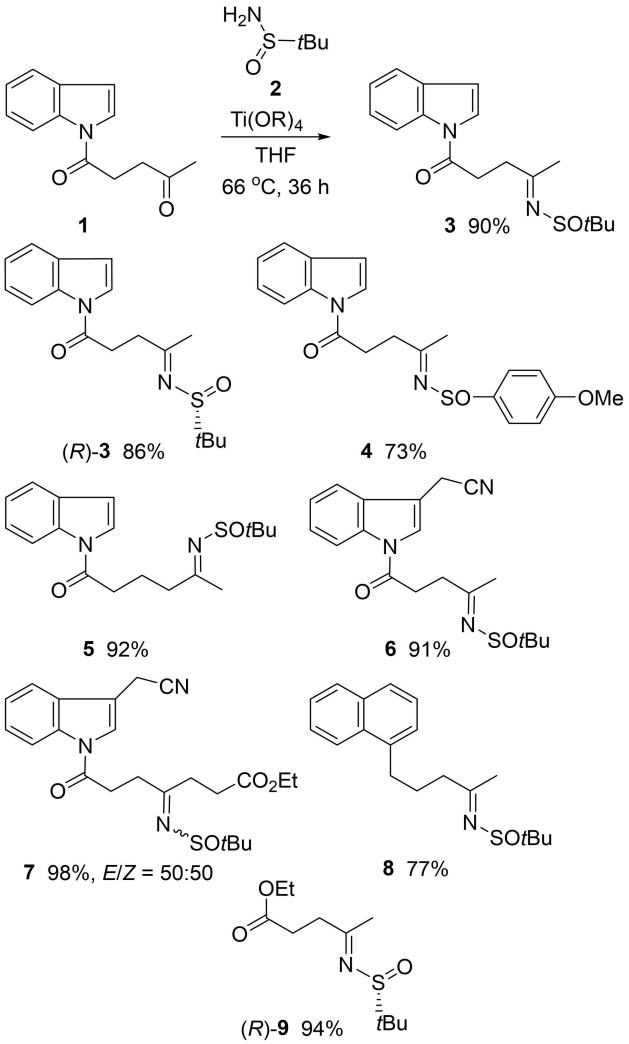
Starting from the corresponding ketones we prepared cyclization precursors **3**–**9** (Scheme 2). Among the examined literature known methods,[5] the protocol of Ellman et al. proved to be most suitably.[6] Employing an excess of titanium alkoxides as mild Lewis acidic condensation reagent converted *N*-acylated indolyl ketone **1** and racemic *tert*-butylsulfinamide **2** into the desired *N*-acylated indolyl sulfinyl imine **3** in 90% yield.[4] We did not try to speed up this slow reaction by employing microwave.[7] Alternative methods employing copper sulfate,[6] pyridinium *p*-toluenesulfonate/$MgSO_4$[6,8] or cesium carbonate[8] as reagents resulted in partial deacylation of **1** or complete failure. Similar to racemic **3**, we also prepared (*R*)-**3** in 86% yield from **1** and its condensation with enantiopure *tert*-butylsulfinamide (*R*)-**2**.

The other racemic *N*-acylated indolyl sulfinyl imines **4**–**7** shown in Scheme 2 and compounds **8** and (*R*)-**9** were analogously prepared from the corresponding ketones in good to excellent yields. The sulfinyl imines **3**–**6**, **8** and (*R*)-**9** were formed as single isomers; we assume that the sulfinyl groups generally points to the smaller methyl group resulting in *E*-configuration of these compounds. In contrast, sulfinyl imine **7** which bears to similarly sized alkyl substituents, was formed as a 50:50 mixture of isomers.

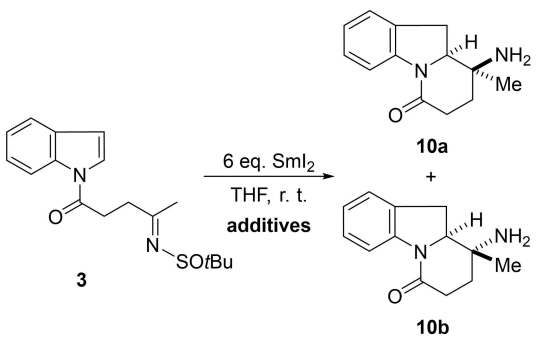
In order to achieve high conversions, samarium diiodide-promoted dearomative cyclizations[9] of aryl- or heteroaryl-substituted ketones usually require an excess of this reducing agent, a proton source and a strong Lewis base. Hexamethylphosphortriamide (HMPA) is traditionally employed[10] but this reagent is known to be carcinogenic and teratogenic. Although it can be replaced in many cases by easily available tripyrrolidinophosphoramide (TPPA)[11] or by related Lewis bases,[12] alternative reaction conditions are still very desirable. Lithium bromide/1,3-dimethyl-2-imidazolidinone[13] or a LiBr/water system,[14] were found to be suitable in a few cases.

We studied the model reaction of *N*-acylated indolyl sulfinyl imine **3** to the diastereomeric tertiary carbinamines **10a**/**10b** under different conditions (Scheme 3) and initial experiments showed that more than two equivalents of samarium diiodide are required to achieve reasonable conversions. Therefore, in all small scale experiments six equivalents of samarium diiodide in tetrahydrofuran as solvent were used and the reactions were performed at room temperature. The consumption of samarium(II) can easily be observed by naked eye due to the decolorization of the purple solution, providing a beige-brownish suspension of samarium(III) species. The resulting cyclization products **10a**/**10b** were analyzed as crude products to determine the diastereoselectivity; for the applied NMR analysis an error of approximately ±3% can be assumed.

The standard conditions for samarium ketyl-aryl cyclizations, employing HMPA as Lewis base and *t*-butanol as proton source, resulted in a slow reaction (7 h) and provided only very low quantities of products **10a**/**10b** (Table 1, entry 1). Mainly decomposition of precursor **3** (probably by deacylation and/or



Scheme 2. Synthesis of sulfinyl imines **3**–**9** starting from the corresponding ketones and sulfinamides employing titanium(IV) alkoxides (R = Et or *i*-Pr) as condensation reagent.



Scheme 3. Samarium(II)-promoted reductive cyclization of model compound **3** under different conditions (see Table 1 for details) providing diastereomeric tertiary carbinamines **10a**/**10b**.

Table 1. Samarium(II)-promoted reaction of *N*-acylated indolyl sulfinyl imine **3** to tertiary carbinamines **10a**/**10b** under different conditions according to Scheme 3.

Entry	Additives	Time	Yield of **10**[a]	**10a**:**10b**[b]
1	HMPA (10 eq.) *t*-BuOH (10 eq.)	7 h	~5%	~75:25
2	HMPA (10 eq.) H_2O (10 eq.)	5 min	70%	57:43
3	HMPA (10 eq.) H_2O (10 eq.) LiBr (60 eq.)	5 min	73%	62:38
4	H_2O (10 eq.) LiBr (60 eq.)[c]	5 min	90%	67:33
5	LiBr (60 eq.)	19 h	67%	72:28
6	H_2O (10 eq.)	5 min	60%	64:36
7	MeOH (12 eq.) LiBr (60 eq.)	5 min	67%	65:35
8	PhOH (18 eq.) LiBr (60 eq.)	2 h	88%	64:36
9	CF_3CH_2OH (10 eq.) LiBr (60 eq.)	10 h	81%	45:55

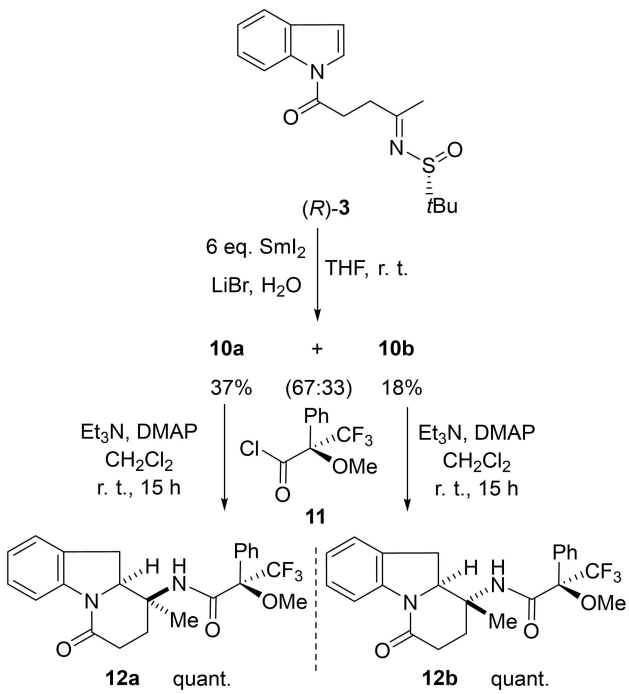
[a] Yield of isolated and purified products. [b] Ratio determined for the crude product. [c] In a larger scale experiment 72 eq. of lithium bromide and 72 eq. of water were employed (see Supporting information).

imine cleavage) was observed in this and additional control experiments in the presence of HMPA/*t*-butanol. In sharp contrast, replacement of tertiary alcohol by water induced a very fast reaction and work up after 5 minutes allowed the isolation of 70% of **10a**/**10b** (d. r. = 57:43) (entry 2). Addition of lithium bromide (entry 3) did not change the reaction outcome too much, but the reaction without HMPA, just using 10 equivalents of water and of 60 equivalents of lithium bromide (entry 4) afforded the highest yield of **10a**/**10b** and also a slightly improved diastereoselectivity (d. r. = 67:33). The relative configuration of the major diastereomer **10a** was determined by an X-ray analysis of its *N*-acetylated derivative.[4]

After having found excellent conditions for the cyclization of **3** to **10a**/**10b** (entry 4), additional experiments were performed in order to identify the essential requirements of the reaction (Table 1, entries 5–9). The two cyclization reactions employing either only lithium bromide (entry 5) or only water (entry 6) as additives, respectively, were quite instructive. They demonstrate that it is the addition of water which induces the high reactivity of samarium diiodide. The strong influence of water as unique proton donor on reactivity and selectivity of samarium(II) is known for many years. Due to recent synthetic and mechanistic studies mainly of the groups of Procter,[15] Flowers II[16] and Szostak[17] much is known about its potential in synthetic processes and about mechanistic details. With lithium bromide the reaction required 19 h for completion (entry 5), whereas in the presence of water samarium(II) was consumed within 5 minutes (entry 6) providing **10a**/**10b** in 60% yield and with a reasonable diastereoselectivity. The experiments summarized in entries 7–9 should examine the influence of alternative proton sources. Entry 7 shows that methanol can replace water without too much change. The more acidic proton sources phenol (entry 8) and 2,2,2-trifluoroethanol (entry 9) are suitable additives, however, they do cause an improvement since longer reaction times are required. The efficiency of water in terms of reactivity and diastereoselectivity remains superior. In summary, the conditions of entry 4 seem to be the most appropriate for the cyclizations of compounds such as **3**. This was confirmed in a larger scale experiment for the synthesis of **10a**/**10b** and the conditions were also applied to the other substrates studied (see below).

We also tried to induce the reductive cyclization of *N*-acylated indolyl sulfinyl imine **3** by employing zinc dust in tetrahydrofuran without or with HMPA.[18] No cyclization products could be isolated, instead, partial desulfinylation of the imine moiety was observed and the starting material was re-isolated. When *N*-acylated indolyl sulfinyl imine **4** (Scheme 2) bearing an anisyl group at the sulfur was examined its reductive cyclization under standard conditions (compare entry 4 of Table 1) provided **10a** in 26% yield and trace amounts of **10b**. The inferior behavior of substrate **4** caused us to stay generally with *tert*-butyl-substituted sulfinyl imines.

Under all conditions summarized in Table 1 we observed the formation of desulfinated products **10a**/**10b**. The cleavage of the N–S bond could occur before or after the reductive cyclization forming the new ring. In order to answer this mechanistically relevant question we executed an experiment with (*R*)-**3** (Scheme 4). As expected, its reductive cyclization under standard conditions provided diastereomers **10a** and **10b** in similar efficiency and stereoselectivity (d. r. = 67:33), fully comparable to the experiment employing racemic **3**. The separated isomers **10a** and **10b** were subsequently converted with the enantiopure Mosher carboxylic acid chloride **11** into the two amides **12a** and **12b**, respectively, under standard



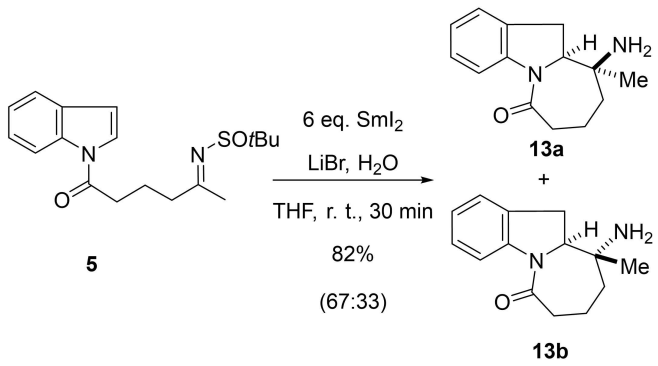
Scheme 4. Samarium(II)-promoted reaction of *N*-acylated indolyl sulfinyl imine (*R*)-**3** to **10a**/**10b**, their separation and conversion into Mosher amides **12a** and **12b**.

conditions.[19] NMR analysis of these samples revealed that both compounds were essentially racemic, which is strong evidence that the cyclization event occurs in the absence of the chiral auxiliary. For a discussion of this fact see the mechanistic section below.

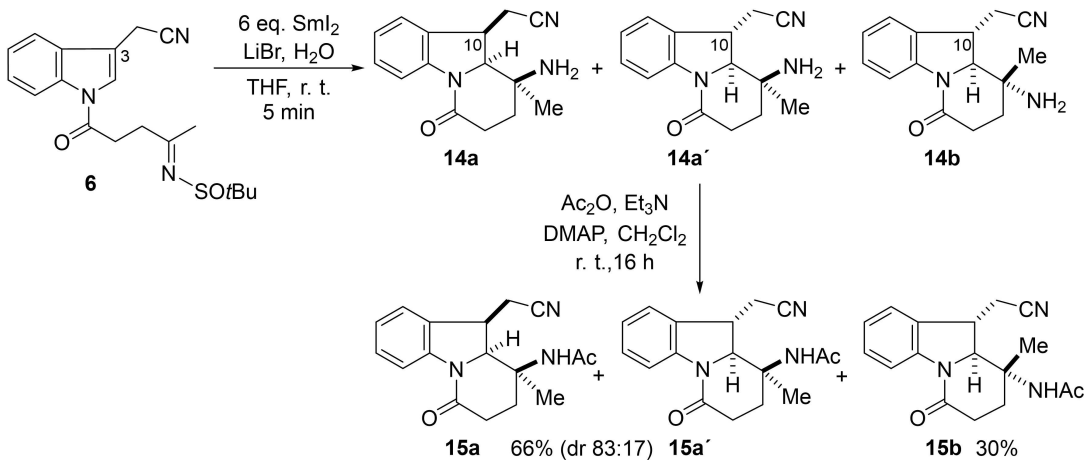
The samarium(II)-promoted cyclization of sulfinyl imines could be extended to a homolog of precursor **3**. Under the approved reaction conditions compound **5** furnished the tricyclic azepinone derivatives **13a** and **13b** as an unseparated mixture of two diastereomers (d. r. 67:33) in 82% yield (Scheme 5).[4] This example nicely demonstrates that seven-membered rings are also accessible via this route. Precursors leading to larger ring sizes were not investigated, however, considering the related samarium diiodide-promoted cyclizations of *N*-acylated and *N*-alkylated indolyl ketone derivatives, which give eight-membered ring compounds at least in moderate yields, this seems to be feasible.[1e]

The 3-cyanomethyl group of *N*-acylated indolyl ketones played a key role in our route to strychnos alkaloids.[3] We therefore included also imines with this substituent in the current study. Under the approved conditions with lithium bromide and water as additives, sulfinyl imine **6** and samarium diiodide rapidly delivered a mixture of the three diastereomeric cyclization products **14a**/**14a'**/**14b** (Scheme 6). A separation and full characterization at this stage was not possible, however, it should already be mentioned that **14a** and **14a'** have the identical relative configuration at the amino-substituted carbon and the bridge-head carbon, but have different configuration at C-10. The stereochemistry at this position is not determined during the key cyclization step but by the protonation of a carbanionic intermediate (or less likely by hydrogen acceptance of a radical intermediate) formed later in the multi-step sequence (see discussion below). The unpurified mixture of **14a**/**14a'**/**14b** was subsequently *N*-acetylated with acetic anhydride to give **15a**/**15a'**/**15b** in excellent overall yield. A partial separation by column chromatography provided the pair of diastereomers **15a**/**15a'** (66%, d. r. 83:17) and pure **15b** (30%). By recrystallization **15a** could be separated from **15a'**. All these operations allowed spectroscopic analyses and configurational assignments of all three isomers as shown in Scheme 6, also by comparison with related compounds.

N-Acylated indolyl ketone **16** bearing a functionalized side chain was employed as easily available starting material in our short route to strychnine.[3] The samarium diiodide-promoted cascade ketyl-cyclization/Dieckmann-condensation provided the tetracyclic product **17** in up to 77% yield as single diastereomer together with small amounts of the *exo*-methylene compound **18** (Scheme 7). For success of this process it was essential to use HMPA (or TPPA)[3b] as Lewis base and no proton sources should be present to avoid quenching of the intermediate carbanion. The side-product **18** is generated by cyanide elimination from this intermediate and γ-lactone formation of the tertiary hydroxyl group with the ethoxycarbonyl substituent. It was very tempting to examine imine **7** (readily prepared from **16** according to the procedure depicted in Scheme 2) in an analogous cyclization process since this starting material would easily allow to install a chiral auxiliary at the imine nitrogen. If successful, the samarium(II)-promoted cyclization might deliver the desired product **19** with high diastereoselectivity (and in the presence of the chiral auxiliary



Scheme 5. Samarium(II)-promoted reaction of *N*-acylated indolyl sulfinyl imine **5** to azepinone derivatives **13a**/**13b**.



Scheme 6. Samarium(II)-promoted reaction of *N*-acylated indolyl sulfinyl imine **6** to tricyclic compounds **14a**/**14a'**/**14b** and subsequent *N*-acetylation to amides **15a**/**15a'**/**15b**.

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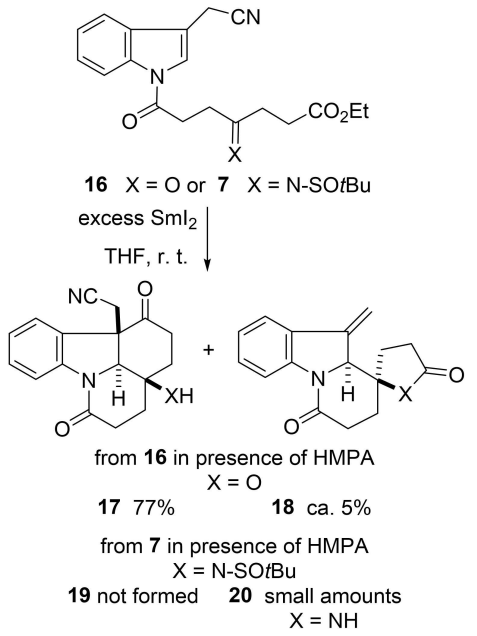


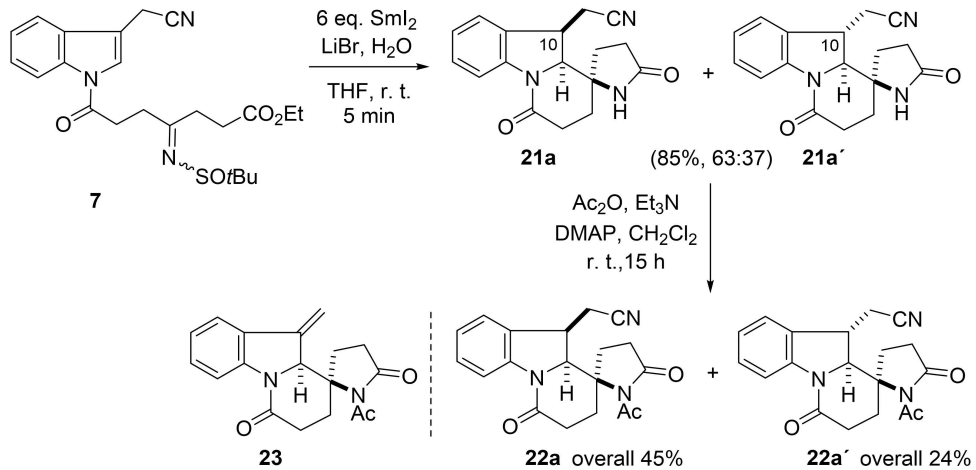
Scheme 7. Samarium diiodide-promoted cascade reaction of *N*-acylated indolyl ketone **16** leading to tetracyclic strychnine precursor **17** and *exo*-methylene compound **18** and the attempted analogous reaction of imine **7** to carbinamine **19**.

with enantioselectivity). Unfortunately, sulfinyl imine **7**, used as 50:50 mixture of *E*/*Z* isomers, belongs to the class of non-activated indole derivatives and hence all conditions employing HMPA as Lewis base were unsuccessful. Unconsumed starting material was isolated together with 3-cyanomethylindole (as a result of deacylation of **7**), compound **16** (as a result of imine cleavage) and a few undefined decomposition products. Variation of the reaction conditions, e.g. employing HMPA in the presence of lithium bromide or employing HMPA, LiBr and NiI_2,[20] induced partial conversion into cyclization products **21** together with small amounts of *exo*-methylene γ-lactam **20**, but we never observed a cascade reaction generating the tetracyclic product **19**. Unfortunately, we have to conclude that imine **7** is very likely an unsuitable precursor for cascade reactions which are easily possible with its oxygen analog **16**.

Gratifyingly, sulfinyl imine **7** cyclized under the approved conditions in the presence of water and lithium bromide and furnished the isomeric spiro γ-lactams **21 a** and **21 a'** (Scheme 8) which are formed by spontaneous intramolecular acylation of the amino group (85% yield, d. r. = 63:37). The two isomers are difficult to separate and their configurational assignment was not possible at this stage. Hence the mixture was *N*-acetylated to provide compounds **22 a** and **22 a'** which could be separated by HPLC. The two tetracyclic spiro γ-lactams were isolated in pure form and in good overall yield and the NMR analyses revealed that they have different configuration at C-10. An isomer with different relative configuration at the amino-substituted carbon and the bridge-head carbon (analogous to **15 b**) was not found in this case.

It is apparent that the cyclization of imine **7** in the presence of water cannot result in a cascade reaction delivering products of structure **19** since an intramolecular acylation of the carbanion at C-10 is required for this process (see mechanistic discussion below). In the presence of an excess of a proton source this intermediate is certainly very rapidly quenched. Instead, under these reaction conditions the ethoxycarbonyl group undergoes a condensation with the amino group forming the γ-lactam subunit. Having now clearly identified the major products **22 a** and **22 a'** it was now possible to elucidate the structure of *N*-acetylated *exo*-methylene compound **23** (Scheme 8, left hand side) which was formed in the absence of water in 4–10% yield in above mentioned experiments.

The investigations of samarium diiodide-promoted cyclizations of *N*-acylated and *N*-alkylated indole derivatives had been based on our earlier discovery of dearomatizing cyclizations of γ-aryl-substituted ketones.[9] Among these compounds γ-naphthyl-substituted ketones provided the expected tricyclic products with particular efficiency.[21] It was therefore obvious to examine the possibility of cyclizations of related γ-aryl-substituted *N*-sulfinyl imines with a naphthalene derivative.



Scheme 8. Samarium(II)-promoted cyclization of *N*-acylated indolyl imine **7** leading to tetracyclic spiro γ-lactams **21 a** and **21 a'** as primary products and subsequent *N*-acetylation to compounds **22 a** and **22 a'**.

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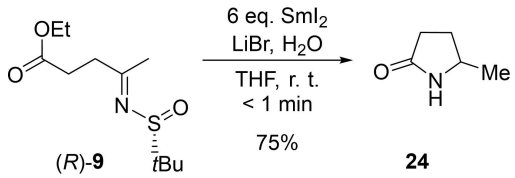
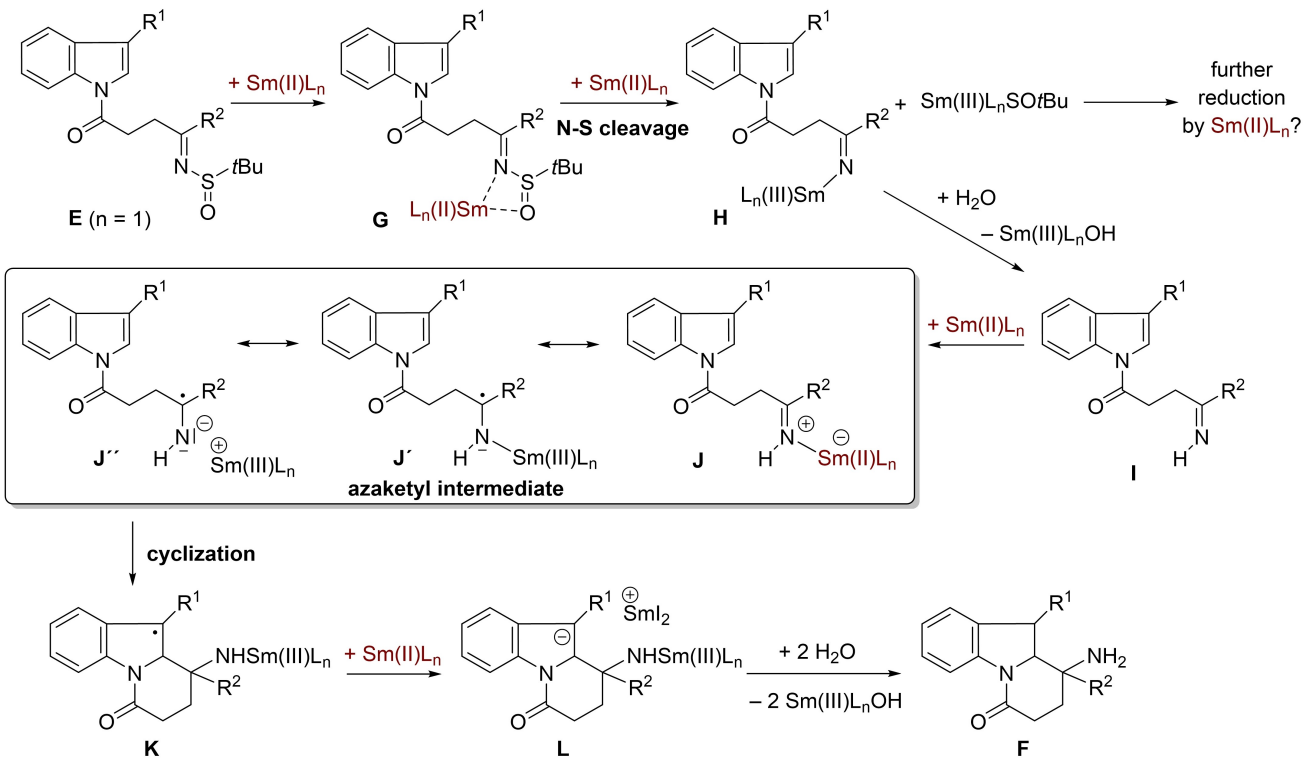
Unfortunately, the cyclization of imine **8** (Scheme 2) failed under the approved reaction conditions, only starting material and undefined decomposition products could be isolated. This has to be compared with the smooth cyclization of the precursor ketone of imine **8** which furnished a tricyclic product in high yield.[21b]

One of the striking observations of all samarium(II)-promoted cyclizations of nonactivated *N*-acylated sulfinyl imines is the fact that all are accompanied by a desulfination process delivering cyclization products with NH_2 groups. This is the reason why a larger excess of samarium diiodide is required for good conversion. The fast desulfination reaction of imines was confirmed by employing the model compound **9** which very rapidly reacted under standard conditions in the presence of water and lithium bromide to furnish γ-lactam **24** in good yield (Scheme 9). Regardless whether racemic **9** or enantiopure (*R*)-**9** was used as precursor, both reactions afforded only racemic product.[22] This observation corroborates that the desulfination occurs *before* reduction of the imine moiety and cyclization to the lactam. Most literature reported coupling reactions of (chiral) sulfinyl imines are performed under different conditions (without addition of water) and generally at much lower temperatures.[23] Due to the very fast reaction with the substrate, the N–S bond of the imine moiety was not cleaved in these cases. Remarkably, the resulting *N*-sulfinyl amine moieties were stable under the reaction conditions and no cleavage of the N–S bond was observed at this stage. This behavior was confirmed in our study when activated *N*-acylated indolyl sulfinyl imines **C** were employed [see Reaction (2) of Scheme 1].[4]



Scheme 9. Samarium(II)-promoted reduction and cyclization of model compound (*R*)-**9** to provide racemic 5-methylpyrrolidin-2-one (**24**).

The possible steps of the desulfination process of **E** and the cyclization to product **F** are represented in Scheme 10. Due to the large excess of bromide ions and water it is very likely that these ligands have replaced iodide and THF ligands at the samarium(II) center. It is known that samarium dibromide as well as the complexes of samarium(II) with water are stronger reducing agents.[15,16,17,24] The presence of an excess of water may also lead to a very fast or even concerted substitution of samarium(III) at the respective donor centers. Nevertheless, the simplified mechanistic Scheme 10 generally shows samarium(III) at these centers without specifying its ligands. We have put forward strong arguments above that the multi-step reaction of nonactivated indole derivative **E** starts with the detachment of the *N*-sulfinyl group. Precursor **E** and the first equivalent of the samarium(II) species form a Lewis-base/Lewis-acid complex **G**. It is likely that a first electron transfer occurs already within this



Scheme 10. Mechanistic scenario of the samarium(II)-promoted multi-step reaction of precursor compound **E** to cyclization product **F** (the drawn lines between samarium(II) or samarium(III) centers and the adjacent nitrogen atoms do not reflect the bonding situation but only the proximity of these centers; for clarity no specific ligands at Sm(II) and Sm(III) are shown; lone pairs at hetero atoms are only shown for the azaketyl moiety of intermediate **J**/**J'**/**J"**).

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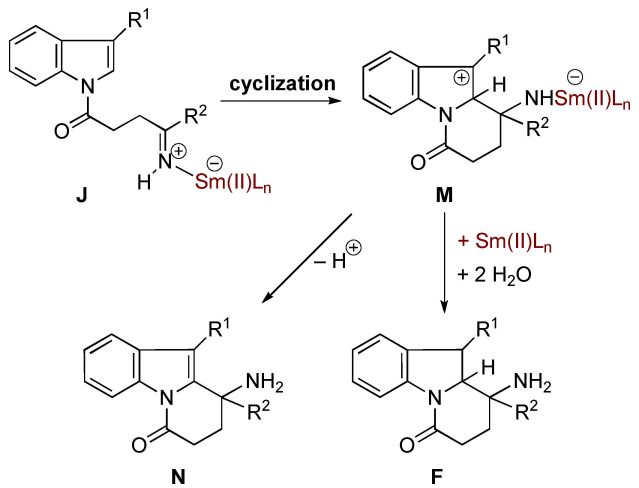
complex; the highly electron-deficient nature of the sulfinyl imine moiety should easily allow the acceptance of an electron.[25] Reaction of **G** with a second equivalent of samarium(II) reductively cleaves the N–S bond to furnish a samarium(III)-ketimine complex **H** and a samarium(III) sulfinate. This sulfur species may be further reduced by the excess of samarium(II), but no compounds defining the final product could be isolated. It is known that sulfones are reduced by samarium(II) to give thioethers.[26] As a related reaction of the observed desulfination of *N*-sulfinyl imines the smooth desulfonylation of *N*-tosyl amines and similar compounds should be mentioned.[27] Finally, protonation of **H** affords ketimine **I** which undergoes the subsequent cyclization to **F**.[28]

The cyclization to **F** starts with the reaction of ketimine **I** with a third equivalent of samarium(II) to generate an azaketyl intermediate as key species of the process. The central box of Scheme 10 depicts three formulas for this intermediate, shown as Lewis-base/Lewis-acid complex **J**, as radical **J'** after a full electron transfer and as radical anion **J''**. The exact nature of this intermediate must remain speculative.[29] The crucial cyclization step to stabilized radical **K** proceeds only with moderate diastereoselectivity (see discussion below). A forth electron transfer provides carbanion **L** which is stabilized by the adjacent aryl moiety. By protonations the final product **F** is formed. It should be mentioned again that all electron-transfer steps may occur as proton coupled processes (PCET).[30]

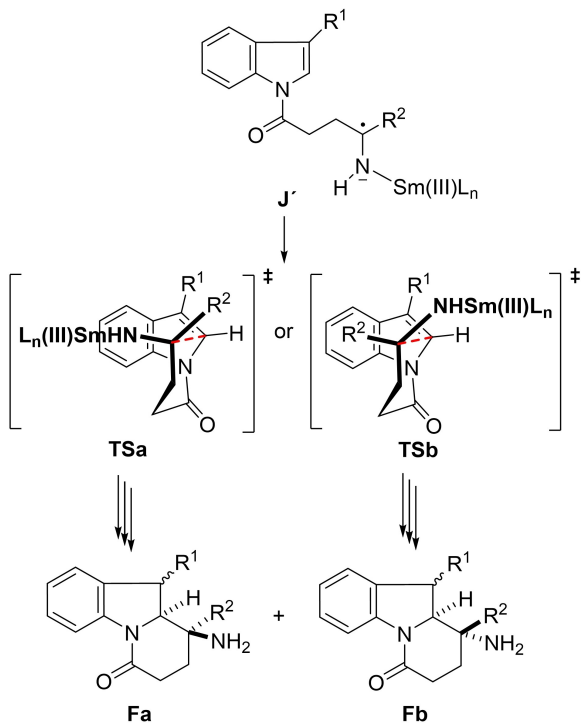
If the species generated by the interaction of ketimine **I** with samarium(II) is regarded as Lewis-base/Lewis-acid complex as represented by formula **J**, the cyclization of this species to **F** might alternatively occur as electrophilic addition to the indole moiety (Scheme 11). The resulting stabilized carbenium ion **M** is subsequently reduced by two equivalents of samarium(II) and reaction with water gives the final product **F**. We regard this pathway as less likely, since in no case the expected "normal" electrophilic substitution product **N** was detected, which should be easily formed by deprotonation of **M**.[31]

The cyclizations of precursor compounds **3** and **5** ($R^1 = H$, $R^2 = Me$) provide mixtures of diastereomers (ratio ca. 2:1). If R^1 is a cyanomethyl group as for substrates **6** and **7** an additional stereogenic center at the carbon adjacent to this substituent is generated by protonation of the intermediate carbanion (see **L** in Scheme 10), which is independent of the cyclization step. For compound **6** ($R^1 = CH_2CN$, $R^2 = Me$) again a ca. 2:1 selectivity concerning the two relevant centers was found. Remarkably, the cyclization of **7** [$R^1 = CH_2CN$, $R^2 = (CH_2)_2CO_2Et$] furnished two lactams **21** (Scheme 8) which have identical relative configuration of these key centers. Although the mass balance was slightly lower in this experiment, it can be concluded that the diastereoselectivity is higher in this case.

The usually moderate diastereoselectivity of the cyclizations of *N*-acylated indolyl imines **E** has to be compared with the excellent selectivity of the related indolyl ketones **A** [Reaction (1) of Scheme 1] which generally afforded only the shown stereoisomer **B**.[1] In Scheme 12 we suggest a rationale proposing a chair-like folding of the transition states **TSa** and **TSb** with minimized steric interactions of substituents and ligands.[32] The samarium azaketyl intermediate is just represented by formula **J'**. One major difference is certainly the ligand sphere of samarium due to different additives. In the case of the cyclizations of ketones **A** the samarium ketyl involved bears probably four very bulky HMPA ligands whereas the corresponding samarium azaketyl **J'** derived from imine **E** is probably surrounded by water molecules. Furthermore, the interaction of the oxygen with the oxophilic samarium(II) center of the ketyl may be different than that in the corresponding azaketyls.[33,34] These differences may lead to less steric compression at the



Scheme 11. Alternative electrophilic cyclization of intermediate **J** to **F** via stabilized cation **M** followed by two electron transfers.



Scheme 12. Rationale for the low diastereoselectivity of the cyclizations of intermediate **J'** to **Fa** and **Fb** via proposed transition states **TSa** and **TSb**.

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doi.org/10.1002/ejoc.202200264

nitrogen making R^2 and the NHSm(III)L_n moiety similar in size in most cases. Hence, the two diastereomorphic transition states **TSa** and **TSb** are comparable in energy. For the ketone cyclizations our major argument was that transition states analogous to **TSa** are strongly disfavored due to the interaction of the bulky samarium-alkoxy unit of the ketyl with the arene moiety. This is apparently not the case for the sterically less demanding samarium azaketyl intermediates. Interestingly, for compound **7** [$R^1 = CH_2CN$, $R^2 = (CH_2)_2CO_2Et$], a substrate bearing a larger substituent R^2, a higher selectivity was found which indicates that **TSa** is now clearly favored over **TSb**. We admit that our interpretation may be oversimplified since it is mainly based on steric effects and neglects possible electronic effects or other important factors. Experiments with additional substrates are desirable for its confirmation.

Conclusion

We could demonstrate that nonactivated *N*-acylated indolyl sulfinyl imines of type **E** are easily generated from the corresponding ketones and that they undergo smooth samarium(II)-promoted cyclizations to tertiary carbinamines **F** formed with low diastereoselectivity in most cases. This transformation is interesting from a mechanistic point of view and also synthetically relevant. Among the examined reaction conditions, the addition of water and lithium bromide replacing the iodide ligands of the reagent samarium diiodide[35] gave the best yield. It was shown that a reductive N–S bond cleavage is preceding the cyclization step resulting in an overall consumption of at least four equivalents of the samarium(II) species. This fact and other mechanistic details of these reductive processes are discussed. As crucial intermediate of the cyclization step a samarium azaketyl intermediate is proposed, represented by formulas **J**/**J'**/**J"**. The presence of water and the preceding N–S bond cleavage do not allow to convert compound **7** into tetracyclic indoline derivative **19** (Scheme 7) which should be a suitable precursor for the synthesis of enantiopure strychnine. Nevertheless, unique structures are generated by the dearomatizing cyclization of indole derivatives **E** to indolines **F**[36] which incorporate a tertiary carbinamine moiety – α,α-dibranched primary amines. Not many efficient alternative methods are known to generate this functional group.[37] The skeleton of tetracyclic spiro-indoline **22** is particularly interesting.

Experimental Section

For general information, all experimental and analytical details see Supporting Information.

Typical experimental procedure[6] for the preparation of indole-derived sulfinyl imines (GP1), (*E*)-*N*-[1'-(1*H*-Indol-1-yl)-1'-oxopentan-4'-ylidene]-*tert*-butylsulfinamide (3): To an oven dried round bottom flask charged with ketone **1**[1e] (400 mg, 1.84 mmol) in tetrahydrofuran (5 mL) were added racemic *t*-butylsulfinamide **2** (201 mg, 1.66 mmol) and $Ti(OEt)_4$ (840 mg, 3.68 mmol). The mixture was heated under reflux for 36 h, then cooled to room temperature, quenched with saturated $NaHCO_3$ solution (3 mL), stirred for 5 min with celite and the solids were filtered off. The filtrate was concentrated under reduced pressure and the resulting crude product was purified by chromatography (silica gel, ethyl acetate/hexanes **3**:2). Pure 3 (476 mg, 90%) was obtained as colorless crystals.

M. p. 69–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (s, 9 H, *t*-Bu), 2.42 (s, 3 H, Me), 2.88, 3.04, 3.09, 3.40 (ABXY system, $J_{AB} = 15.7$ Hz, $J_{AX} = 4.8$ Hz, $J_{AY} = 6.6$ Hz, $J_{BX} = 2.9$ Hz, $J_{BY} = 7.2$ Hz, $J_{XY} = 13.8$ Hz, 1 H each, 3'-H, 2'-H), 6.64 (d, $J = 3.1$ Hz, 1 H, 3-H), 7.24 (t, $J \approx 7.4$ Hz, 1 H, Ar), 7.31 (t, $J \approx 7.6$ Hz, 1 H, Ar), 7.49 (d, $J = 3.1$ Hz, 1 H, 2-H), 7.54 (d, $J = 7.6$ Hz, 1 H, 4-H), 8.38 (d, $J = 8.0$ Hz, 1 H, 7-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 21.8$ (q, *t*-Bu), 23.5 (q, Me), 30.6, 36.7 (2 t, C-2', C-3'), 56.4 (s, *t*-Bu), 109.4 (d, C-3), 116.6, 120.9, 123.7, 124.5 (4 d, Ar), 125.2 (d, C-2), 130.4, 135.7 (2 s, Ar), 170.4 (s, C=O), 183.3 (s, C=N) ppm; IR (ATR): $\nu = 3050$ (=C–H), 2950–28556 (C–H), 1710 (C=O), 1620 (C=N), 1540 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd. for $C_{17}H_{22}N_2NaO_2S$: 341.1300; found: 341.1297; $C_{17}H_{22}N_2NaO_2S$ (318.4): calcd. C 64.12, H 6.96, N 8.80, S 10.07; found: C 64.03, H 6.96, N 8.45, S 9.77.

Enantiopure (*R*)-**3** was obtained in 86% yield employing (*R*)-*t*-butylsulfinamide.

M. p. 73–74 °C (colorless solid); $[\alpha]_D^{25} = +4.7$ ($c = 0.02$, $CHCl_3$); the other analytical data agree with those of racemic **3**.

Typical experimental procedure for the SmI_2-promoted cyclization of sulfinyl imines in presence of LiBr and H_2O (GP2): Synthesis of (9*S,9a*S**)- and (9*R**,9a*S**)-9-Amino-9-methyl-8,9,9a,10-tetrahydropyrido[1,2-a]-indol-6(7*H*)-one (10a) and (10b)**: Under an atmosphere of argon, a freshly prepared solution of samarium diiodide (761 mg, 1.88 mmol, 18.8 mL) in THF (ca. 0.1 M) was transferred to an oven dried round bottom flask charged with anhydrous lithium bromide (1.96 g, 22.6 mmol). The solution was stirred for 30 min at room temperature. In a second flask, sulfinyl imine **3** (100 mg, 0.314 mmol) and water (410 mg, 22.8 mmol, 0.41 mL) were dissolved in THF (3 mL), and this solution was transferred via syringe to the THF solution of SmI_2/LiBr in a single portion. The mixture was stirred at room temperature and after decolorization of the solution the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution ($\approx$10 mL). The separated aqueous layer was washed with ethyl acetate and the combined organic layers were washed with brine and dried with Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, ethyl acetate/methanol 95:5) to obtain **10a** (42 mg, 62%) as colorless solid and **10b** (19 mg, 28%) as pale yellow liquid.

Data of diastereomer **10a**: M. p. 120–121 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.24$ (s, 3 H, 9-Me), 1.38 (s, 2 H, 9-NH_2), 1.84, 1.90, 2.58, 2.67 (ABXY system, $J_{AB} = 13.7$ Hz, $J_{AX} = 2.3$ Hz, $J_{AY} = 7.8$ Hz, $J_{BX} = 7.2$ Hz, $J_{BY} = 11.5$ Hz, $J_{XY} = 18.8$ Hz, 1 H each, 8-H, 7-H), 2.96 (dd, $J = 15.5$, 8.6 Hz, 1 H, 10-H), 3.15 (dd, $J = 15.5$, 11.2 Hz, 1 H, 10-H), 4.14 (dd, $J = 11.2$, 8.6 Hz, 1 H, 9a-H), 7.02 (d, $J = 7.5$ Hz, 1 H, 1-H), 7.19 (t, $J \approx 7.5$ Hz, 2 H, 2-H, 3-H), 8.18 (d, $J = 7.9$ Hz, 1 H, 4-H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 27.0$ (q, 9-Me), 29.5, 29.8, 36.2 (3 t, C-8, C-10, C-7), 48.9 (s, C-9), 68.8 (d, C-9a), 117.1, 124.2, 124.6, 127.7 (4 d, Ar), 129.7, 143.0 (2 s, Ar), 168.1 (s, C=O) ppm; IR (ATR): $\nu = 3390$ (N–H), 3050 (=C–H), 2995–2845 (C–H), 1730, 1645 (C=O), 1590 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{17}N_2O$: 217.1341; found: 217.1332; $C_{13}H_{16}N_2O$ (216.2): calcd. C 72.19, H 7.46, N 12.95; found: C 72.21, H 7.49, N 12.98.

Data of diastereomer **10b**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.17$ (s, 3 H, 9-Me), 1.80–1.90 (m, 2 H, 8-H), 2.04 (s, 2 H, 9-NH_2), 2.53–2.63 (m, 2 H, 7-H), 3.07 (d, $J = 9.6$ Hz, 2 H, 10-H), 4.11 (t, $J = 9.6$ Hz, 1 H, 9a-H), 7.04 (d, $J = 7.4$ Hz, 1 H, 1-H), 7.19 (t, $J \approx 7.5$ Hz, 2 H, 2-H, 3-H), 8.17 (d, $J = 8.2$ Hz, 1 H, 4-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 29.8$ (q, 9-

Me), 30.2, 31.1, 37.6 (3 t, C-8, C-10, C-7), 50.3 (s, C-9), 69.3 (d, C-9a), 117.0, 124.2, 124.7, 127.7 (4 d, Ar), 129.4, 142.9 (2 s, Ar), 167.7 (s, C=O) ppm; IR (ATR): ν = 3350 (N–H), 3060 (=C–H), 2955–2850 (C–H), 1730, 1650 (C=O) 1595 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{17}N_2O$: 217.1341; found: 217.1284. $C_{13}H_{16}N_2O$ (216.2): calcd. C 72.19, H 7.46, N 12.95; found: C 72.23, H 7.02, N 12.97.

(9*R,9a*S**,10*R**)- and (9*R**,9a*S**,10*S**)-2-[1'-Acetyl-5',6-dioxo-7,8,9a,10-tetrahydro-6*H*-spiro(pyrido[1,2-a]indole-9,2'-pyrrolidin)-10-yl]acetonitrile 22a and 22a'**: Following GP2, sulfinyl imine **7** (70 mg, 0.16 mmol) was reacted with SmI_2 (383 mg, 1.44 mmol), LiBr (395 mg, 4.55 mmol) and H_2O (82 mg, 4.55 mmol) (reaction time 5 min) to afford after column chromatography (silica gel, ethyl acetate/methanol 95:5) compounds **21a** and **21a'** (40 mg, 85%; d. r. = 63:37) as an inseparable mixture. This mixture was *N*-acetylated analogously to the procedure above (15 h, r. t.) to provide after column chromatography (silica gel, ethyl acetate/hexanes 1:1) compounds **22a**/**22a'** (43 mg, 80% overall yield). Separation by HPLC (nucleosil 50–5, dichloromethane/methanol, 99:1) afforded pure **22a** (24 mg, 45%) and **22a'** (13 mg, 24%) as colorless solids.

Data of **22a**: M. p. 221–222 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (dd, *J* = 10.7, 6.3 Hz, 2 H, 10-CH_2), 1.90 (dt, *J* = 12.3, 7.4 Hz, 1 H, 4'-H), 2.40–2.56 (m, 2 H, 3'-H, 4'-H), 2.57 (s, 3 H, Ac), 2.58–2.70 (m, 4 H, 7-H, 8-H, 3'-H), 2.92 (ddd, *J* = 18.4, 11.5, 6.7 Hz, 1 H, 7-H), 3.45 (dd, *J* = 10.7, 5.1 Hz, 1 H, 10-H), 5.17 (d, *J* = 5.1 Hz, 1 H, 9a-H), 7.09 (t, *J* ≈ 7.5 Hz, 1 H, Ar), 7.29 (t, *J* ≈ 7.7 Hz, 1 H, Ar), 7.38 (d, *J* = 7.6 Hz, 1 H, 1-H), 8.14 (d, *J* = 8.1 Hz, 1 H, 4-H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.9 (q, Ac), 24.8, 27.2, 28.8, 29.6, 31.0 (5 t, C-8, C-4', C-3', C-7, 10-CH_2), 38.8 (d, C-10), 66.1 (s, C-9), 67.0 (d, C-9a), 116.4 (d, Ar), 117.4 (s, CN), 124.3, 124.7, 129.2 (3 d, Ar), 129.9, 142.7 (2 s, Ar), 168.0, 173.5, 175.8 (3 s, C=O) ppm; IR (ATR): ν = 3300 (N–H), 3045 (=C–H), 2955–2845 (C–H), 2245 (CN), 1725, 1685, 1650 (C=O), 1600 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{19}N_3NaO_3$: 360.1324; found: 360.1318; $C_{19}H_{19}N_3O_3$ (337.1): calcd. C 67.64, H 5.68, N 12.46; found: C 67.64, H 5.70, N 12.72.

Data of **22a'**: M. p. 188–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (ddd, *J* = 13.3, 8.5, 4.7 Hz, 1 H, 4'-H), 1.91–2.05 (m, 2 H, 8-H, 4'-H), 2.53–2.59 (m, 1 H, 8-H), 2.60 (s, 3 H, Ac), 2.61–2.72 (m, 4 H, 7-H, 3'-H), 2.76 (dd, *J* = 16.8, 6.0 Hz, 1 H, 10-CH_2), 2.87 (ddd, *J* = 16.8, 9.7, 6.0 Hz, 1 H, 10-H), 3.87 (dd, *J* = 16.8, 6.0 Hz, 1 H, 10-CH_2), 5.60 (d, *J* = 9.7 Hz, 1 H, 9a-H), 7.11 (t, *J* ≈ 7.5 Hz, 1 H, Ar), 7.30 (t, *J* ≈ 7.8 Hz, 1 H, Ar), 7.41 (d, *J* = 7.6 Hz, 1 H, Ar), 8.22 (d, *J* = 8.1 Hz, 1 H, Ar) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 19.0 (q, Ac), 24.4, 27.2, 29.3, 30.3, 30.7 (5 t, C-7, C-3', C-8, C-4', 10-CH_2), 39.9 (d, C-10), 62.6 (s, C-9), 66.6 (d, C-9a), 116.4 (d, Ar), 117.9 (s, CN), 129.6, 124.8, 123.8 (3 d, Ar), 142.1, 129.7 (2 s, Ar), 168.3, 173.3, 175.6 (3 s, C=O) ppm; IR (ATR): ν = 3305 (N–H), 3065 (=C–H), 2950–2850 (C–H), 2250 (CN), 1750, 1690, 1650 (C=O), 1595 (C=C) cm^{-1}; HRMS (ESI-TOF): *m/z* $[M+Na]^+$ calcd. for $C_{19}H_{19}N_3NaO_3$: 360.1324; found: 360.1316; $C_{19}H_{19}N_3O_3$ (337.1): calcd. C 67.64, H 5.68, N 12.46; found C 67.66, H 5.74, N 12.56.

Acknowledgements

This work was supported by the Alexander von Humboldt Foundation (fellowship for C. N. Rao), the Deutsche Forschungsgemeinschaft and Bayer HealthCare. We thank Dr. Reinhold Zimmer for help during preparation of this manuscript. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Amine · Cyclization · Electron transfer · Indole · Samarium diiodide

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Manuscript received: March 3, 2022
Revised manuscript received: March 16, 2022
Accepted manuscript online: March 18, 2022