CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200901434

Functionalization and Rearrangement of Spirocyclohexadienyl Oxindoles: Experimental and Theoretical Investigations

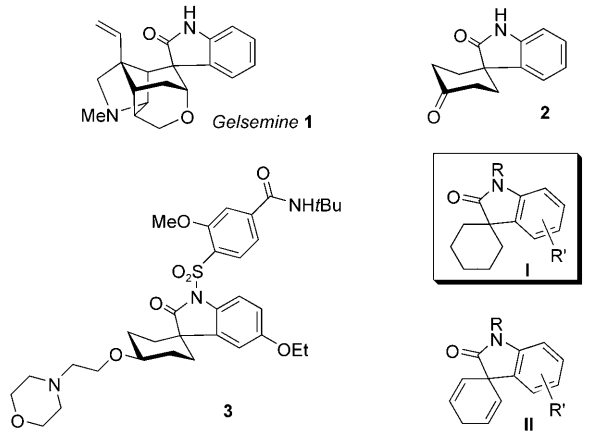
Géraldine Rousseau, Frédéric Robert,* and Yannick Landais*[a]

Abstract: The preparation and functionalization of spirocyclohexa-2,5-diene oxindoles is described. The spirocyclic core of the title compounds was installed by using a SmI_2-mediated cyclization of aryl iodobenzamides. Epoxidation with CF_3CO_3H was then carried out and was shown to occur with a high level of diastereocontrol: the reagent approaches the diene moiety *syn* to the amide group, which is likely to be as a consequence of hydrogen bonding between the amide C=O bond and the peracid hydrogen. Carbanionic functionalization of the spirocyclohexa-2,5-diene oxindoles was then examined, leading to an unprecedented rearrangement of the strained spiro system into dearomatized phenanthridinones. Upon treatment with lithium diisopropylamide (LDA) at −40 °C, the dienes rearranged to provide a phenanthridinone lithium enolate intermediate that was trapped by electrophiles including alkyl halides and aldehydes. Interestingly, alkylation and hydroxyalkylation occurred with different regiocontrol. DFT calculations were performed that rationalize the observed skeleton rearrangement, emphasizing the role of LDA/diisopropylamine in this rearrangement. The proposed mechanism thus relies on a thermodynamically driven diisopropylamine-mediated proton transfer with the cleavage of the diene–amide C=O bond as the key step.

Keywords: density functional calculations · enolates · epoxidation · lithium amides · rearrangement

Introduction

Spirocyclic oxindoles such as **I** constitute the key fragment of relevant alkaloids, including gelsemine **1**,[1] the main component of *Gelsemium sempervirens*, but also of several important synthetic targets that exhibit attractive biological activities, amongst them the ketone **2** (active against *Mycobacterium tuberculosis* H37Rv[2]) and SR 121463 A **3**, an antagonist of vasopressin receptors (Scheme 1).[3] Spirocyclic oxindoles are also versatile intermediates, as illustrated in the synthesis of complex *Alstonia* oxindole alkaloids.[4] The functionalized spirooxindole core is accessible through a wide range of methods, including Pummerer[5a] and Claisen[5b] rearrangements of tryptophan precursors, [3,3]-sigmatropic rearrangements,[5c] but also radical processes,[5d–i] or through oxidation of indoles.[5j] The challenging installation of the stereogenic spiro center in gelsemine **1** has also garnered a lot of attention.[1] This has led to the development of general approaches for the elaboration of spirooxindoles,[6] which include the intramolecular Heck reaction that provides the required spirocyclic skeleton with a high level of stereoselectivity.[7] In the course of our ongoing research on desymmetrization,[8] it was envisioned that spirocyclohexa-2,5-dienes



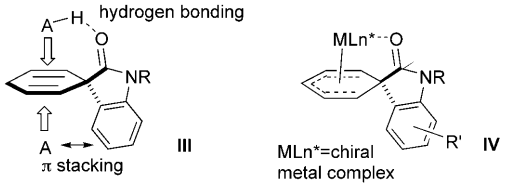
Scheme 1. The spirocyclic oxindole skeleton in natural and synthetic compounds of biological interest.

[a] Dr. G. Rousseau, Dr. F. Robert, Prof. Dr. Y. Landais
Université de Bordeaux, Institut des Sciences Moléculaires
UMR-CNRS 5255, 351 cours de la libération
33405 Talence (France)
Fax: (+33) 540-00-62-86
E-mail: f.robert@ism.u-bordeaux1.fr
y.landais@ism.u-bordeaux1.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901434.

of type **II** might be valuable precursors for chiral spirocyclic oxindoles using symmetry-breaking transformations, including enantioselective electrophilic (epoxidation, dihydroxylation) and carbanionic processes. These simple functionalizations of precursor **II** would thus offer a rapid approach to such attractive synthons that would be complementary to those described before.

Enantioselective desymmetrization of **II** implies that one is able to differentiate between the diastereo- and enantiotopic faces of the cyclohexadienyl system, a difficult task to achieve.[9] We showed previously that both faces could be efficiently distinguished providing that a large substituent (e.g., SiR_3) is present on the prochiral allylic center to shield one diastereotopic face.[8a,b,9a] We envisaged in this study that discrimination of the two faces of the dienyl system might also be carried out through electronic effects by using a polar group on one face and an apolar group on the other face (Scheme 2). Spirocyclic oxindoles **II** exhibit electronically well-differentiated diastereotopic faces with a polar amide function and an apolar aryl group, respectively, shielding each face. One can then envisage the approach of a given reagent **A** on the top face though hydrogen bonding (e.g., **III**) or complexation (**A** = metal, **IV**) by the strongly polar amide group. Conversely, π stacking might favor approach from the bottom face (**III**).

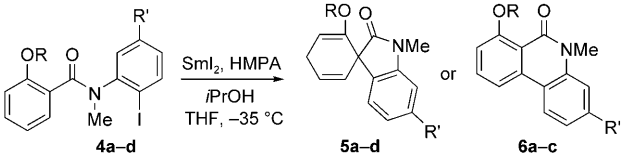


Scheme 2. Diastereotopic face differentiation in spirocyclohexadienyl oxindoles using electrophilic and organometallic reagents.

We describe below our study on functionalization of these dienes, using both electrophilic and organometallic processes. In the course of these studies, we discovered a new rearrangement mediated by lithium amide bases that provides useful and highly functionalized phenanthridinones, which are valuable intermediates for organic synthesis. We report a full account on these investigations,[8d] including our attempts at desymmetrizing dienes **II** and disclose our efforts to understand the mechanism of the above rearrangement. Ab initio calculations that support the mechanism of amide–base-mediated rearrangement of these compounds are also provided.

Results and Discussion

Synthesis of spirocyclic oxindole precursors: The spirocylic precursors were prepared by using methodology based on a SmI_2-mediated aryl cyclization of arylamides **4a–d**. Tanaka et al.[10] recently described a rapid access to spirooxindoles using a radical-mediated 5-*exo*-trig cyclization of aryl iodides. They showed that spiro compounds were formed predominantly, providing that an *ortho* substituent was located on the aromatic amide. In the absence of such a substituent, the reaction led to the corresponding phenanthridinones. Based on this premise, we tested the reaction on aryl amides **4a–d**, which have various alkoxy substituents (OR) in the *ortho* position that can then be removed to afford the desired cyclohexa-1,4-dienes (Scheme 3).



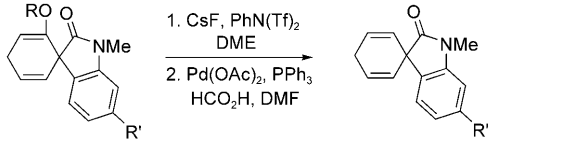
Scheme 3. SmI_2-mediated cyclization of aryliodoamides **4a–e**.

The results are summarized in Table 1. Phenol amide **4a** cyclizes to give the phenanthridinone **6a** as the sole product, albeit in modest yield (Table 1, entry 1). Surprisingly, the same compound was obtained starting from the triflate **4b** (Table 1, entry 2), a direct precursor of the desired diene (see below). Finally, the $OSiMe_2tBu$ group in amides **4c** and **4d** gave the best results with the expected spirooxindole **5c** and **5d** formed in quantitative and modest yields, respectively (Table 1, entries 3 and 4). The siloxycyclohexadienes **5c** and **5d** were then transformed into the desired nonsubstituted dienes **7a** and **7b** using a two-step sequence (Scheme 4). Compounds **5c** and **5d** were first converted, by treatment with $PhNTf_2$, into the corresponding triflates,[11] which were not isolated but directly transformed into the desired dienes through a palladium-mediated hydrogenation.[12] Compounds **7a** and **7b** were isolated in satisfying 87 and 81% overall yields, respectively.

Table 1. Synthesis of spirocyclohexadienyl oxindoles **5a–d** (Scheme 3).

Entry	Amide	R	R′	Cpd **5**	Cpd **6**	Ratio **5/6**[a]	Yield [%][b]
1	**4a**	H	H	**5a**	**6a**	0:100	55
2	**4b**	Tf	H	**5b**	**6a**	0:100	20
3	**4c**	$SiMe_2tBu$	H	**5c**	**6b**	100:0	99
4	**4d**	$SiMe_2tBu$	OMe	**5d**	**6c**	100:0	49[c]

[a] Estimated by ^1H NMR spectroscopy of the crude reaction mixture. [b] Isolated yields of **5** and **6**. [c] 60% based on recovered starting material (brsm).



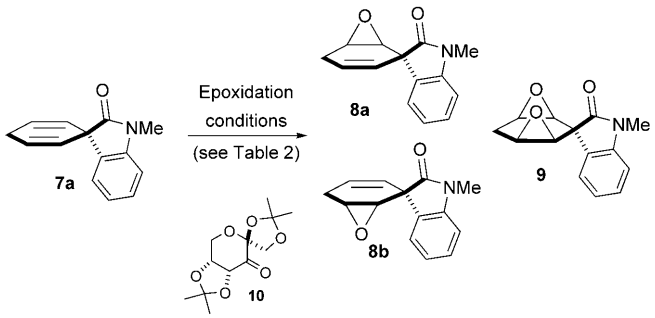
5c: R = $SiMe_2tBu$; R' = H
5d: R = $SiMe_2tBu$; R' = OMe

7a: R' = H (87%, 2 steps)
7b: R' = OMe (81%, 2 steps)

Scheme 4. Preparation of spirocyclic oxindoles **7a** and **7b**.

Epoxidation of cyclohexadienes 7a and 7b: The epoxidation reaction was first tested, since it is a well-documented process,[13] which should be helpful to reveal the electronic and steric effects at play during the functionalization of these dienes as depicted in Scheme 2. Various conditions were tested on spirocyclohexadiene **7a** (Table 2), indicating that

Table 2. Epoxidation of spirooxindole **7a**.



Entry	Conditions[a]	Product	Yield[b] [%]	d.r.[c] [%]	*ee*[d] [%]
1	*m*CPBA, CH_2Cl_2, 20 °C, 24 h	**8a/8b**	33	50:50	–
2	$(CF_3CO)_2O$ (2 equiv), H_2O_2, (1.3 equiv) CH_2Cl_2, 20 °C, 12 h	**8a/8b**	19 (59)	>95:<5	–
3	$(CF_3CO)_2O$ (13 equiv), H_2O_2 (13 equiv), CH_2Cl_2, 0 °C, 4 h	**9**	78	>95:<5	–
4	**10**, Na_2EDTA, Oxone, 0 °C, 24 h	**8a/8b**	43 (78)	<5:>95	10
5	**10**, Na_2EDTA, Oxone, 20 °C, 24 h	**8a/8b**	33 (50)	<5:>95	3

[a] EDTA = ethylenediaminetetraacetic acid. [b] Isolated yield (brsm yield). [c] Estimated from ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Estimated from HPLC analysis on WHELK-O 2 (REGIS technologies INC).

spirooxindoles are poorly reactive toward most epoxidation reagents. However, we were pleased to observe that complementary stereochemical outcomes may be obtained by changing the nature of the reagents. For instance, *meta*-chloroperbenzoic acid (*m*CPBA) was shown to be nonselective (Table 2, entry 1), whereas the much more reactive CF_3CO_3H[14] (generated in situ from $(CF_3CO)_2O$ and H_2O_2) led to a low yield of a single isomer, **8a** (Table 2, entry 2). Increasing the reaction time had a deleterious effect and led to product degradation, along with unreacted starting material. When a large excess of $(CF_3CO)_2O$ (13 equiv) was used at 0 °C, the *syn*-diepoxide **9** was formed as a single diastereomer (Table 2, entry 3), the structure of which was unambiguously determined through X-ray diffraction studies. In contrast, the chiral Shi reagent (e.g., **10**/Oxone)[15] afforded the other diastereomer, **8b**, with complete diastereocontrol, albeit with low enantioselectivity (Table 2, entries 4 and 5). The structures of both diastereomers **8a** and **8b** were also confirmed through X-ray diffraction analysis (Figure 1). Finally, Sharpless epoxidation conditions[16] (not shown) did not provide the desired epoxides.

These results were tentatively rationalized as follows: In the presence of the acidic CF_3CO_3H, the reaction occurs *syn*

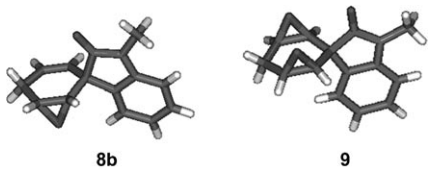
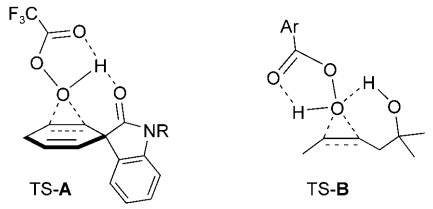


Figure 1. X-ray crystal structures of epoxides **8b** and **9**.

to the polar amide group, which is likely to be as a result of hydrogen bonding between the reagent and the amide C=O bond, following a transition state such as TS-**A** (Scheme 5).[17] The Lewis basic carbonyl group thus plays



Scheme 5. Transition state for the epoxidation of spirooxindoles.

the role of the proton acceptor and directs the epoxidation reagent, in good agreement with previous results by Ganem and McKittrick,[14b] who showed that CF_3CO_3H was able to hydrogen bond to chiral allylic and homoallylic ethers, but also to urethanes and amides. In contrast, the less acidic *m*CPBA is not able to hydrogen bond efficiently to the oxygen of the amide group, thus leading to no diastereofacial selectivity. It is interesting to notice the difference in directing effect between *m*CPBA and CF_3CO_3H, the former generally providing good level of diastereocontrol with chiral allylic and homoallylic alcohols through TS-**B** (Scheme 5). In this case, the epoxidizing reagent plays the role of the proton acceptor.[18]

Finally, epoxidation using the Shi reagent **10**/Oxone led to complementary diastereocontrol, showing that when the heteroatom directing effect cannot operate, the face *anti* to the amide group is the more accessible. As suggested by Fehr,[14a] it was envisaged that the preference for *syn* selectivity with CF_3CO_3H, could also be ascribed to electrostatic interactions. CF_3CO_3H possesses a high electrostatic potential and coulombic interactions with the π face of the olefin with the highest electron density should be favored. The estimation of electrostatic potential of each of the diastereotopic faces (carried out through semi-empirical calculations using PM6)[19a] effectively showed that the diene double bonds exhibit a more negative electrostatic field on the carbonyl face (red area in Figure 2).

Furthermore, DFT calculations were run to estimate the energy of the spirocyclic system when approaching (or not) an added positive charge (0.2 unit) on the two π faces.[19a] The charge was placed 2.0 Å from the alkene center, perpendicular to the alkene plane. Then, B3LYP 6-31G(d)

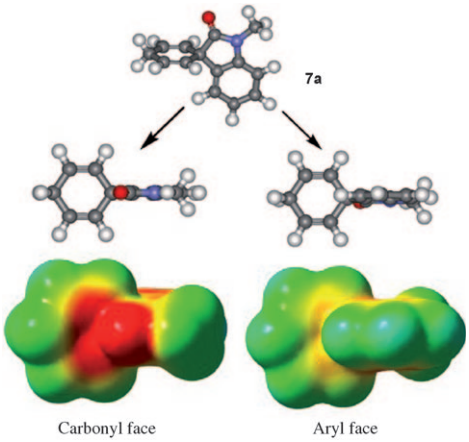
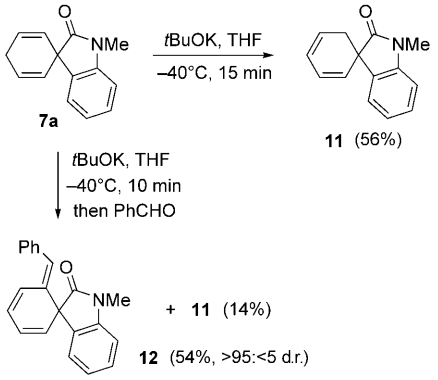


Figure 2. Optimized geometry of **7a** and electron density surface encoded by the electrostatic potential at the PM6 level.

energy calculations were performed, which showed a 6.4 kcal mol^{-1} stabilization on the carbonyl face and a 3.29 kcal mol^{-1} stabilization on the aryl face. These results are consistent with the ability of the spirocycle to stabilize a transition state close to TS-**A** (Scheme 5), in which positively charged electrophiles like CF_3CO_3H approach the face *syn* to the carbonyl group. This shows that electrostatic effects also significantly influence the stereoselectivity of the epoxidation reaction onto spirocyclohexa-2,5-diene oxindoles **II**. Such an effect was also put forward to explain the *anti* selectivity during electrophilic reactions of chiral allylsilanes.[19b] In summary, the results of these series of experiments support our assumption that highly diastereoselective reactions may be performed using the directing effect of the Lewis basic amide bond. They also show that the face *anti* to the C=O bond is accessible to bulky reagents and provides a general trend for further electrophilic functionalization of these spirocyclic oxindoles.

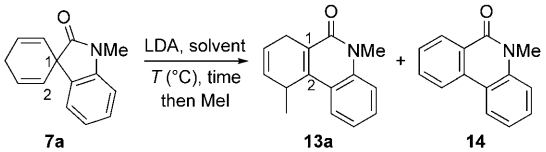
Rearrangement of spirooxindoles 7a and 7b: We then turned our attention to the desymmetrization of our substrates through metalation of the cyclohexadienyl system. Recent studies by Studer et al.[9b–d] have demonstrated that metalation of 1,4-cyclohexadiene with a strong base, followed by transmetalation using chiral titanium or boron reagents led to the corresponding useful chiral enantiopure dienylmetals, which, upon addition to aldehydes and imines, provided addition products with high levels of diastereo- and enantioselectivity. It was envisioned that extension of this strategy to our spirooxindoles should afford a chiral metal complex closely related to **IV** (Scheme 2), in which the C=O bond of the amide would coordinate to the metal[20] and thus help in the control of the diastereofacial selectivity. Various attempts at metallating precursor **7a** were thus made, leading first to disappointing results. *n*BuLi and *t*BuLi at −78 °C in THF gave complex mixtures of products, whereas lithium hexamethyldisilazide (LiHMDS), *t*BuOLi, and NaH led to recovered starting material. More interesting observations were made when treating **7a** with *t*BuOK in THF. Under these conditions, isomerization of **7a** provided 1,3-diene **11** in moderate yield, through deprotonation of **7a** with the strong base, followed by reprotonation with *t*BuOH (Scheme 6). Addition of benzaldehyde shortly after deprotonation gave rise to olefin **12** as a single *Z* isomer along with isomerized **11**.[21]



Scheme 6. Metalation of spirocyclohexadienyl oxindole **7a** with *t*BuOK.

More surprising results were obtained when treating diene **7a** with lithium diisopropylamide (LDA), followed by quenching the reaction mixture with MeI. Whereas **7a** did not react at −78 °C, a conversion was observed at −40 °C, with the formation of a rearranged product **13a**, which possesses a new 1,4-cyclohexadienyl system and a phenanthridinone skeleton. When the alkylating agent (MeI) was added after 1 h at −40 °C, about 50 % (^{1}H NMR spectroscopic analysis) of **13a** was formed along with phenanthridinone **14** and recovered starting material (Table 3, entry 1). A larger amount of **14** was obtained when MeI was added after 2 h at −40 °C (Table 3, entry 2) or at higher temperature (Table 3, entry 3), indicating that **14** is probably formed through oxidative aromatization of a lithium intermediate. Optimal yields of **13a** were obtained by adding freshly prepared LDA to the diene **7a** at −40 °C, and allowing the resulting purple solution to stir for 10 min before the addition of the alkylating agent (Table 3, entry 4). Finally, THF was shown

Table 3. Optimization of rearrangement of spirooxindole **7a** with LDA.



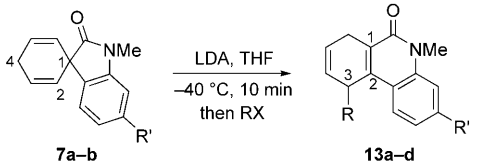
Entry	Conditions	**13a**[a] [%]	**14**[a] [%]	**7a**[b] [%]
1	THF, −40 °C, 1 h	64	15	21
2	THF, −40 °C, 2 h	48	41	11
3	THF, −20 °C, 1 h	–	75	25
4	THF, −40 °C, 10 min	>90	–	–
5	diethyl ether, −40 °C, 10 min	–	–	>95

[a] Estimated yields through ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Yield of recovered material.

to be the best solvent because no reaction occurred in diethyl ether (Table 3, entry 5).

With these conditions in hand, the process was extended to other dienes and electrophiles. Thus, spirooxindole **7b** led to rearranged product **13d** in modest yield (Table 4, entry 4). A range of electrophiles was also tested, providing alkylated products **13b** and **13c** in modest to good yields (Table 4, entries 2 and 3). These dienes are obtained as single regioisomers and as indicated in Table 3, the isolated yields do not reflect the real efficiency of the process because compounds **13a–d** tend to rearomatize.

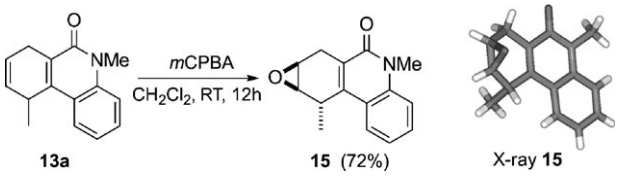
Table 4. Rearrangement of spirooxindole **7a** and **7b** in the presence of LDA, followed by the addition of alkylating agents.



Entry	Spirooxindole	R′	RX	Product	Yield [%][a]
1	**7a**	H	MeI	**13a**	67
2	**7a**	H	AllylBr	**13b**	48
3	**7a**	H	$MeOCH_2Cl$	**13c**	30
4	**7b**	OMe	MeI	**13d**	42

[a] Isolated yield after chromatography.

The structure of dienes **13a–d** was confirmed through X-ray crystallography of **15**, which was obtained from the regio- and diastereoselective epoxidation of diene **13a**; the epoxide formed *anti* relative to the resident methyl substituent (Scheme 7).

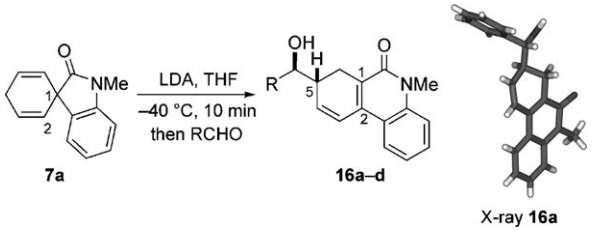


Scheme 7. Epoxidation of dearomatized phenanthridinone **13a**.

Other electrophiles, such as aldehydes, were found to react with the intermediate resulting from the rearrangement of diene **7a** (Table 5). Surprisingly, the regioselectivity was different from that observed for the alkylation and occurred at the C-5 center on the putative carbanionic intermediate. The reaction was also highly stereoselective to give the *anti*-isomer, as indicated by the structure of alcohol **16a**, which was confirmed through X-ray diffraction analysis. We assume that analogues **16b–d** possess the same relative configuration (see below).

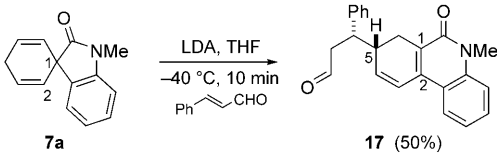
Interestingly, when cinnamaldehyde was added, a new aldehyde **17** was formed, resulting from a 1,4-addition of the putative carbanion species that is generated in the rearrangement onto the unsaturated aldehyde (Scheme 8). Alkyllithiums generally react in a 1,2-fashion, which suggests that the anionic intermediate generated through LDA rearrangement of **7a** is a soft species, likely an enolate (see below). Our attempts to obtain crystals of the oxime and hydrazone derivatives of **17** unfortunately failed, and therefore, the relative configuration of **17** was assigned based on the assumption that the topicity of the 1,4-addition was the same as that of the 1,2-addition described above.

Table 5. Rearrangement of spirooxindole **7a** followed by addition of aldehydes.



Entry	R	Product	d.r.[a]	Yield [%][b]
1	Ph	**16a**	>95:<5	60
2	*i*Pr	**16b**	85:15	63
3	*t*Bu	**16c**	>95:<5	61
4	4-OMePh	**16d**	>95:<5	30

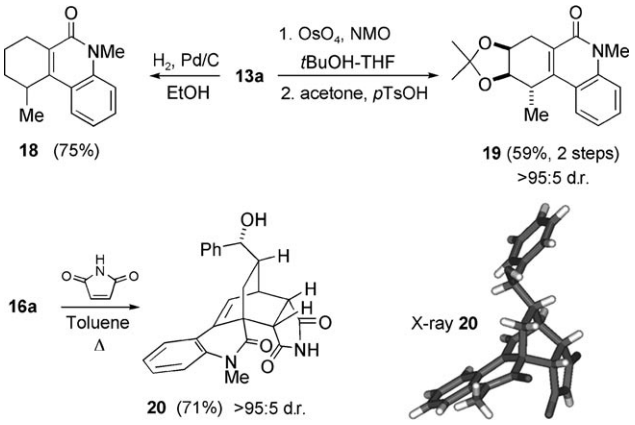
[a] Estimated from the ^{1}H NMR spectroscopy of the crude reaction mixture. [b] Isolated yield after chromatography.



Scheme 8. Addition of cinnamaldehyde and synthesis of **17**.

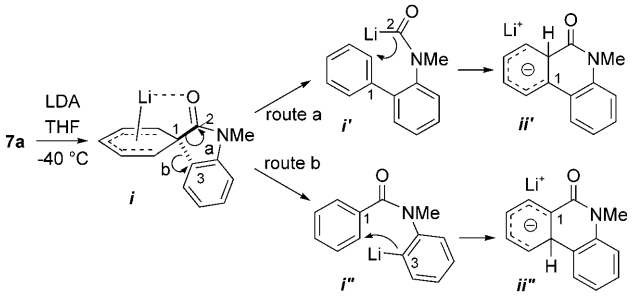
The various phenanthridinones obtained previously were also functionalized, demonstrating that despite their tendency to aromatize, they constitute valuable intermediates for organic synthesis. For instance, methylated diene **13a** was regioselectively hydrogenated into compound **18**, or epoxidized into **15** (Scheme 7), but also dihydroxylated to afford, after protection of the diol, acetonide **19** (Scheme 9). In the dihydroxylation experiment, the reaction occurred *anti* relative to the resident methyl substituent, as indicated by NMR spectroscopy. The 1,3-dienyl system of these phenanthridinones was also engaged in a Diels–Alder reaction. The highly stereoselective [4+2] cycloaddition between **16a** and maleimide afforded the complex polycyclic compound **20**, the structure of which was determined through NOESY experiments and confirmed by X-ray diffraction studies. The *endo* adduct **20** results from an approach of the dienophile *anti* relative to the benzyl alcohol moiety of **16a**.

Rearrangement mechanism: theoretical and experimental aspects: To draw a plausible picture of the whole rearrangement mechanism, a quantum chemical study, using DFT calculations, was performed along with some additional experiments, which are described as follows: First, we assumed



Scheme 9. Functionalization of phenanthridinones **13a** and **16a**.

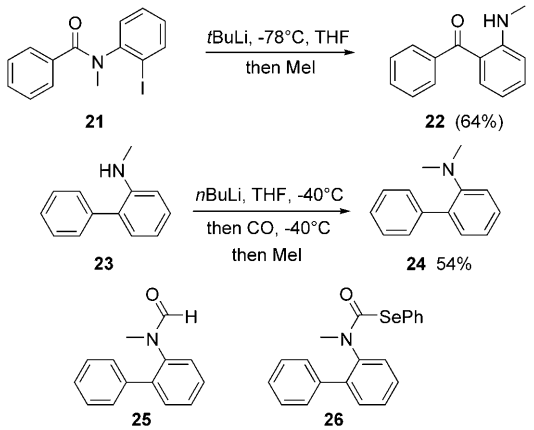
that the rearrangement of the spirocycle takes place before the reaction with electrophiles (RX or RCHO). Because deprotonation of **7a** in the presence of *t*BuOK provides isomerization product **11** and addition product **12**, it was assumed that abstraction of the bis-allylic proton by LDA,[22] would provide a pentadienyllithium species ***i***,[23] which would rearrange at −40 °C into a phenanthridinyl anion intermediate ***ii*** (Scheme 10).



Scheme 10. Bond breaking during the rearrangement process of **7a**.

The amide group is essential here because it probably coordinates the lithium ion and influences the regioselectivity of the whole process. Two different routes starting from pentadienyl lithium species ***i*** may be envisioned; the first in which the C_1–C_2=O bond is broken (route a) to provide a putative acyllithium ***i′*** and the second (route b) where the C_1–aryl bond is cleaved to give an aryllithium ***i″*** (Scheme 10). A third route might also be envisioned that would involve a concerted process without the formation of one of the lithiated intermediate species above. Although closely related pentadienyllithiums have been proposed recently as intermediates in rearrangements,[24] the ring expansion to phenanthridinones is unprecedented. A recent report by Robertson and co-workers described some radical cyclizations of aryl amides and the formation of phenanthridinones, involving a spirocyclohexadienyl radical intermediate closely related to ***i***.[25] The radical ring expansion was assumed to involve a 3-*exo*-trig cyclization of the spirocyclohexadienyl radical to form a highly strained norcaradiene-type species, which upon fragmentation led to the phenanthridinone skeleton. Such a highly energetic species was not envisaged in our rearrangement, due to excessive ring strain, a hypothesis supported by DFT calculations.

The possible pathways depicted in Scheme 10 were examined by performing two sets of experiments (Scheme 11). Iododiarylamide **21** was first submitted to iodine–lithium exchange in the presence of *t*BuLi to generate in situ the lithium species ***i″***, then MeI was added. No trace of phenanthridinone **13a** was observed, but instead product **22** issued from a Fries rearrangement was obtained, thus ruling out the participation of an aryllithium species in the conversion ***i***→***ii*** under the rearrangement conditions.[24b] The generation of an acyl anion such as ***i′*** proved to be more troublesome. Insertion of carbon monoxide into an N–Li bond has been described,[26] but was unsuccessful in our hands even under forcing conditions. For instance, carbonylation of lithiated amine **23** with CO (1 atm), followed by methylation led to the corresponding dimethylamine **24** and no trace of the expected phenanthridinone **13a**. Other methods, including the deprotonation of the *N*-formyl arylamine **25**[27] using LDA and even bulky lithium tetramethylpiperidide (LiTMP) led to the loss of the formyl group, probably through a nucleophilic attack of the lithium amide base. Therefore, these experiments did not allow us to establish or unambiguously rule out the formation of an acylanion intermediate. It is worth noting that in comparison, the corresponding acyl radical (generated from selenylated precursor **26** using Bu_3SnH, azobisisobutyronitrile (AIBN), benzene, reflux) led to phenanthridinone **14**, albeit in a modest 24% yield (60% brsm).



Scheme 11. Attempts at establishing the intermediate involved in the rearrangement of spirooxindoles.

To validate rearrangement through an anionic pathway, DFT calculations were conducted at the B3LYP 6-31++G-(d,p) level starting from the pentadienyl lithium **A**. The effect of the solvent (THF) was accounted for, by assuming two dimethyl ether (DME) ligands coordinated to the lithium[28] to keep the pentadienyl lithium coordinated to the

carbonyl group in a tetrahedral environment.[29] This complex is a plausible starting point because allyllithium species are monomeric.[30] We did not consider, at that stage, the involvement of LDA or diisopropylamine as potential ligands for Li (see below). Rearrangement through route b was rapidly ruled out, because the migration of the aryl moiety went through a single but highly energetic (31.6 kcal mol^{-1}) transition state. Exploring route a, the minimum-energy pathway was found to be stepwise. The cleavage of the C_1–C_2 bond through a first transition state (TS**1**) revealed an unexpectedly stable acyl anion **B**, which could reattack the aryl ring through TS**2** to give the phenanthridinyl anion intermediate **C** with reasonable energy barriers (Figure 3).

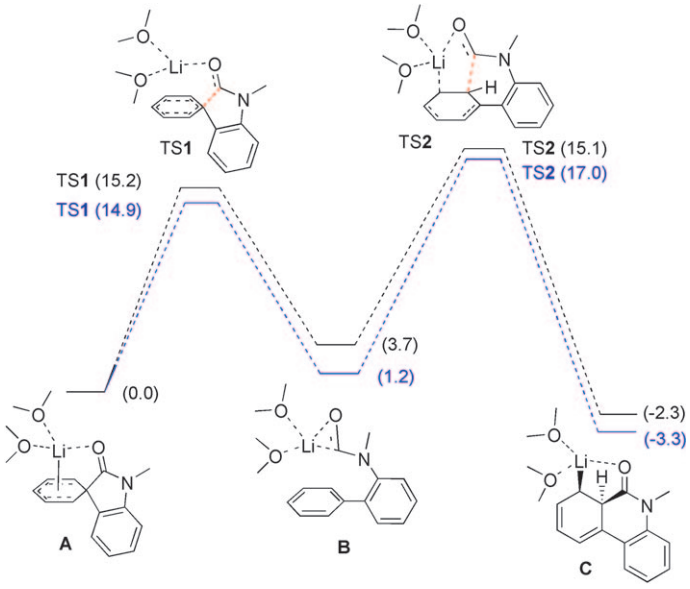
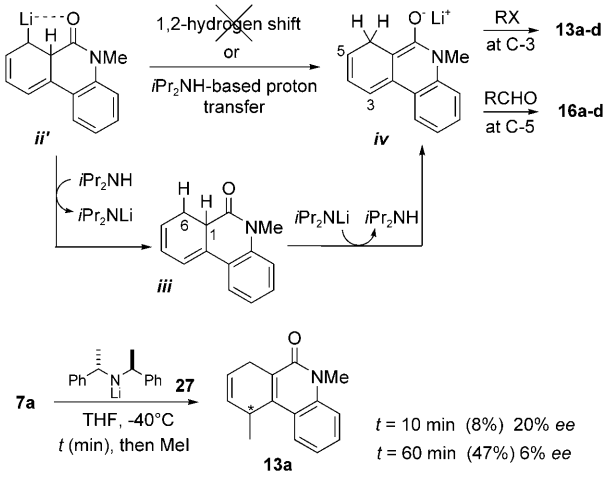


Figure 3. Energy profile [kcal mol^{-1}] reaction path at B3LYP 6-31++G-(d,p) level in gas phase (black) and with single-point calculation in THF (blue).

Single-point calculations in THF, using IEFPCM as the continuum solvation model, showed a slight decrease of the reaction energetic profile (Figure 3, blue) indicating that a full optimization in THF and with two molecules of THF as ligands[31] could lower the barrier around 12–15 kcal mol^{-1}, which are more reasonable values for a rearrangement taking place at −40 °C.

Given the nature of products **13** and **16** and the 1,4-addition product **17**, a soft nucleophile, such as enolate ***iv***, is likely to be involved in the late stage of the anionic rearrangement (Scheme 12). This would then imply a conversion of ***ii′*** into ***iv*** through a simple proton transfer. However, a direct 1,2-hydrogen transfer is forbidden by symmetry rules and a calculated pathway for this transformation showed a highly energetic transition state (around 55 kcal mol^{-1}). However, an additional experiment led to a key observation, which eventually enabled us to rationalize the hydrogen transfer from ***ii′*** to ***iv***. When an enantioselective version of the rearrangement was attempted using chiral base **27** as a



Scheme 12. Possible pathways for the generation of the reactive intermediate ***iv*** and rearrangement of **7a** in the presence of chiral amide **27**.

chiral LDA equivalent,[32] the reaction provided, under the conditions reported above for LDA and after the addition of MeI, phenanthridinone **13a** in low to moderate yield but with significant enantiomeric excess (*ee*) (Scheme 12). A lower *ee* value was measured after 1 h, probably due to a partial racemization of **13a** in the strongly basic medium. Several other chiral bases were also tested but led to lower yields of **13a** and no enantioselectivity. Similarly, the use of (−)-sparteine to bind to the lithium enolate prior to alkylation led to **13a** in 84% yield but with no enantioselectivity. This enantioselective alkylation indicates that the lithium amide and its conjugate amine are likely to be in close proximity with the lithium enolate.[33] It was thus envisioned that the proton transfer could be mediated by the diisopropylamine present in the medium. The crucial role of the latter would also explain the failure of the anionic rearrangement with other bases such as *n*BuLi, NaH, or *t*BuOK, which led instead to isomerization of **7a** into the 1,3-diene **11**. Protonation of ***ii′*** would thus give ***iii***, which upon treatment with the regenerated LDA would lead to the thermodynamically more stable enolate ***iv***, through abstraction of the acidic proton at C_1 (Scheme 12). Diisopropylamine would thus serve to shift the equilibrium towards the thermodynamic species ***iv***. The latter would then react with alkylating agents and aldehydes at C_3 or C_5, respectively, to provide **13**, **16**, and **17**. The origin of the regioselectivity remains unclear to date, but follows some precedent in the literature.[34] The relative configuration of aldehydes **16a–d** thus results from a *ul* addition, in which the *Re* face of the aldehydes approaches the *Si* face of the enolate intermediate.[35]

Following these observations, a complete reaction pathway was then computed at the B3LYP 6-31+G(d,p) level, replacing one DME ether ligand around the lithium atom by a dimethylamine or the corresponding amide (DMA) to mimic LDA/diisopropylamine behavior.[36] The enantioselective rearrangement above led us to rule out a possible intermolecular hydrogen transfer from diisopropylamine to ***ii′***, which therefore was not computed. The reaction would start

with the complexation of LDA to the amide carbonyl group and was thus modeled by the DMA equivalent **D** (Figure 4). Deprotonation and loss of a DME ligand in **E** led to the spirocycle **F**. It is interesting to notice the low energy barrier for the deprotonation of **D** (through TS**3**) as a result of a chelation-induced proximity effect (CIPE), supporting our assumption in Scheme 2.[37] However, it turned out that replacing a dimethyl ether ligand by dimethylamine rendered the lithium atom of **F** chiral. As the migration also generates a chiral center, both combinations had therefore to be computed. Chirality around the lithium was noted *R* and *S* by following the priority order: 1) carbonyl oxygen; 2) DME oxygen; 3) nitrogen atom; 4) carbanion center, and the migration studied on the same side for both complexes. Thus TS_R corresponds to a migration on the DMA side (Figure 4, green) and TS_S to a migration on the DME side (Figure 4, blue). Interestingly, the reaction pathways were quite similar and also very close to the former reaction with two DME ligands (Figure 3). The migration (from **F** to **H**) computed at the high B3LYP 6-311++G(d,p) level showed almost identical energy values, in a 1 kcal mol^{-1} range (see the Supporting Information). The proton transfer was then studied starting from **I**, obtained by addition of a DME ligand to either complex $\mathbf{H_R}$ or $\mathbf{H_S}$ (the lithium atom is no longer chiral in **I**). This addition was found to be necessary to keep the lithium constantly in a tetrahedral environment. At this stage, two transition states (TS**6**) could be drawn, depending on which side the proton is transferred (*sup*, shown in green (Figure 4), is noted for the proton transfer on the carbonyl face and *inf*, shown in red, for the transfer on the aryl face). But again, the two reaction pathways were found to be almost isoenergetic. This proton transfer regenerated a complex **J**, in which the lithium amide partner is in close proximity with the acidic proton α to the amide carbonyl group (Figure 4, red). This could explain the very low energy barrier to reach the final enolate **K** through TS**7**. The replacement of a DME ligand by a DMA did not modify the rearrangement profile, but as ligand exchanges are easier than the migration, the rearrangement could also take place with two DME ligands (**A**→**C**, Figure 3), followed by the addition of one DMA (**I**→**K**) that would finally promote the proton transfer. Additional single-point calculations in THF (using IEFPCM as the continuum solvation model and the UFF parameter for proton nucleus radius in proton transfer) were run at the B3LYP 6-31+G(d,p) level to confirm the relative stability of the different complexes. Results were almost identical, in a 1–1.5 kcal mol^{-1} range (see the Supporting Information).

The picture in Figure 4 was supported further by a final experiment as depicted in Scheme 13. During the rearrangement of **7a** mediated by chiral amide base **27**, when a second equivalent of *n*BuLi was added 10 min after the addition of **27**, but prior to MeI, a dialkylated product **28** with *syn*-stereochemistry was formed, as shown by X-ray diffraction studies. Following the calculations outlined above, this can be rationalized by the removal of the secondary amine (NR^*_2H) from the solution by the addition of the second equivalent of *n*BuLi. In the absence of this secondary amine, ***ii'*** cannot provide the protonated species ***iii*** (Scheme 12). In the energy profile depicted in Figure 4, the

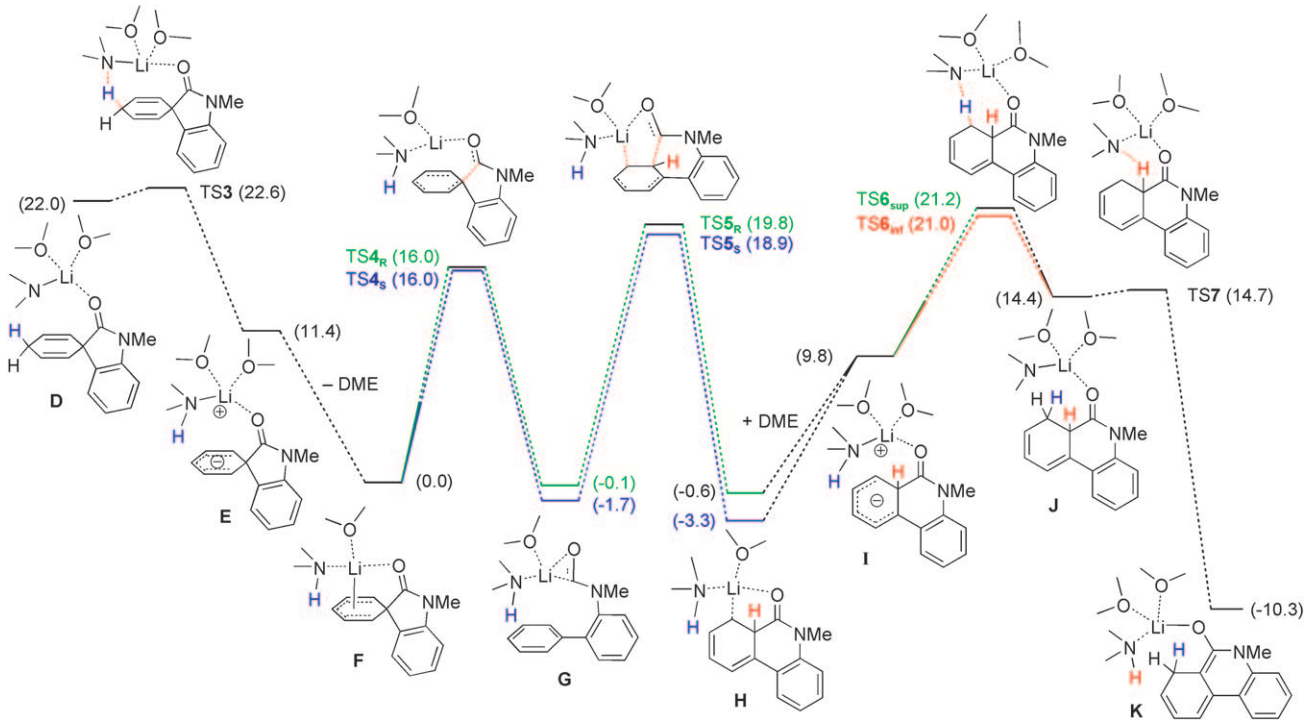
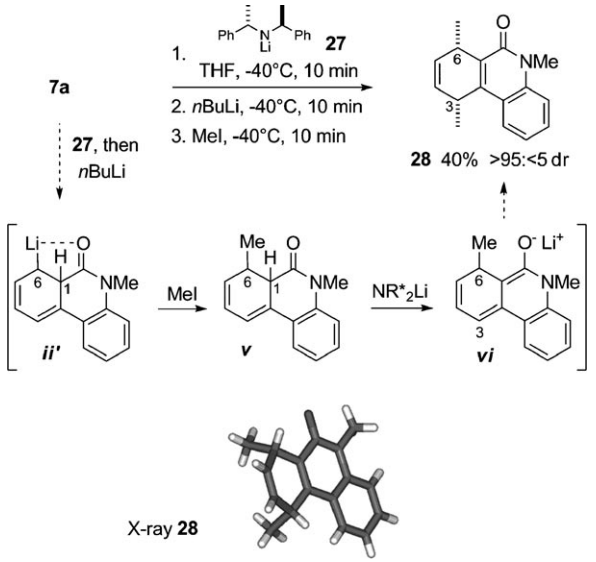


Figure 4. Computed energy profile [kcal mol^{-1}] relative to **F** at the B3LYP 6-31+G(d,p) level for a complete reaction pathway with one amino ligand and one or two ethers.



Scheme 13. Rearrangement of **7a** in the presence of chiral amide **27**-*n*BuLi.

pathway **I**→**J**→**K** would thus be interrupted (due to removal of the N–H proton in **I**). Intermediate ***ii'*** would then be methylated regioselectively at C_6 by MeI to afford intermediate ***v***. The latter would finally be deprotonated by the remaining NR^*_2Li to give the enolate ***vi***, which upon methylation would lead to **28**. These few experiments along with DFT calculations strongly support the mechanism proposed above. The complete pathway displays realistic activation barriers consistent with all of the experimental observations. Rearrangement using chiral bases also suggests that further optimization of the process with suitable chiral bases may lead to enantioenriched phenanthridinones.

Conclusion

We have described a short synthesis and the functionalization of a new class of spirocyclohexadienyl oxindoles. Epoxidation of these systems occurs diastereoselectively, depending on the nature of the oxidizing reagent. An unprecedented rearrangement of these spirooxindoles, mediated by lithium amide bases, was also observed, which led to dearomatized phenanthridinones that proved to be valuable synthons for organic synthesis. An enantioselective version of this rearrangement is possible by using chiral amide bases and is currently under study in our laboratory. During these different functionalizations, the polar amide bond plays a crucial role, notably by directing the reagents through hydrogen bonding or coordinating metal ions in anionic processes. DFT calculations were performed that rationalized the observed selectivities and established the full pathway for the spirooxindole rearrangement.

Experimental Section and Computational Details

General: ^1H and ^{13}C NMR spectra were recorded on Brüker DPX-200 FT (^1H: 200 MHz, ^{13}C: 50.2 MHz), Brüker AC-250 FT (^1H: 250 MHz, ^{13}C: 62.5 MHz), Brüker Avance-300 FT (^1H: 300 MHz, ^{13}C: 75.4 MHz), and Brüker DPX-400 FT (^1H: 400 MHz, ^{13}C: 100.2 MHz) instruments. The chemical shifts (δ) and coupling constants (J) are expressed in ppm and Hz, respectively. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FTIR spectrophotometer as neat films on NaCl windows or as KBr pellets. Mass spectra were recorded on a Nermag R10-10C instrument and high-resolution mass spectra were recorded on a Micromass ZAB-Spec TOF apparatus (for ESI). Melting points were not corrected and determined by using a Stuart Scientific apparatus (SMP3). Macherey–Nagel silica gel 60M (230–400 mesh ASTM) was used for flash chromatography. Dichloromethane, dimethoxyethane, hexamethylphosphoramide (HMPA), (iPr)$_2$NH, and iPrOH were distilled from CaH_2. THF and Et_2O were distilled from sodium and benzophenone. Commercial anhydrous DMF was used without further purification. THF was degassed by bubbling nitrogen gas through the solvent for 30 min to 1 hour or by three successive freeze–thaw–pump cycles.

Radical spirocyclization of amide (General procedure A): SmI_2 was freshly prepared from samarium powder (1.2 equiv) and iodine (1 equiv).[39] SmI_2 (5 equiv, 0.1 M in THF) was added by cannula to a stirred, degassed solution of amide (1 equiv), HMPA (16 equiv), and iPrOH (2 equiv) in THF (0.04 M) at −35 °C. After complete addition, a 10% aqueous solution of $Na_2S_2O_3$ was added until the blue mixture turned to a milky solution. The reaction mixture was then allowed to reach room temperature and the layers were separated. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography yielded the desired spirooxindoles **5** and phenanthridinones **6**.

Reduction of vinyl TBDMS ether (General procedure B): CsF (8 equiv) (previously dried for 12 h. at 300 °C in vacuo) and $PhN(Tf)_2$ (5 equiv) were added quickly (to prevent the escape of gaseous CF_3SO_2F formed during the reaction) to a solution of vinyl *tert*-butyldimethylsilyl (TBDMS) ether **5c** and **5d** (1 equiv) in dimethoxyethane (0.1 M), in a flask equipped with a screw cap (previously evacuated and flushed with nitrogen). The flask was closed and the reaction mixture was stirred at RT overnight. The flask was cooled to 0 °C and opened carefully. A phosphate buffer solution (pH 7) and Et_2O were added and the layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and the solvents concentrated in vacuo. $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), iPr$_2$NEt (6 equiv), and HCO_2H (8 equiv) were added to a solution of the crude vinyl triflate (1 equiv) in DMF (0.13 M) and the reaction mixture was stirred at 60 °C for 1 h. EtOAc and H_2O were added and the layers were separated. The aqueous layer was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvents concentrated in vacuo. Purification by flash chromatography yielded the desired dienes **7**.

Base-induced spirocyclic oxindole rearrangement (General procedure C): Freshly prepared LDA (1.1 equiv, 0.1 M in THF) was added dropwise to a solution of spirocyclic diene **7a** and **7b** (1 equiv) in THF (0.1 M) at −40 °C (temperature inside flask < −38 °C). The reaction mixture was stirred at this temperature for 10 min. The electrophile (2 equiv) was added dropwise and stirring was continued for 10 min. H_2O (2.5 mL) was added by syringe at −40 °C and the mixture was allowed to reach room temperature. Et_2O was added and the layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvents concentrated in vacuo. Purification by flash chromatography yielded the desired dienes.

Compound 5c: Synthesized according to general procedure A from **4c** (1.75 g, 3.74 mmol, 1 equiv), HMPA (10.5 mL, 59.84 mmol, 16 equiv), iPrOH (0.58 mL, 7.48 mmol, 2 equiv), and SmI_2 (187 mL, 18.72 mmol,

5 equiv) in THF (90 mL). Purification by flash chromatography (silica gel, CH_2Cl_2: 100%) afforded **5c** as a pale yellow solid (1.27 g, 99%). M.p. 63–64 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25 (td, J = 7.6, 1.6 Hz, 1H), 7.12–6.99 (m, 2H), 6.78 (d, J = 7.9 Hz, 1H), 6.04 (td, J = 9.8, 3.4 Hz, 1H), 5.34 (td, J = 9.8, 2.1 Hz, 1H), 5.08 (t, J = 3.5 Hz, 1H), 3.20 (s, 3H), 3.04–2.99 (m, 2H), 0.54 (s, 9H), 0.08 (s, 3H), −0.16 ppm (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 177.1, 146.9, 144.2, 133.0, 128.3, 126.9, 124.1, 123.9, 122.5, 107.6, 101.7, 55.6, 26.9, 26.4, 25.0, 17.4, 4.5, −5.4 ppm; IR (KBr): ν = 2930, 2857, 1723, 1611, 1491, 1471, 1345, 1242 cm^{-1}; HRMS (ESI): m/z calcd for $C_{20}H_{28}NO_2Si$ $[M+H]^+$: 342.1883; found: 342.1887.

Compound 5d: Synthesized according to general procedure A from **4d** (764 mg, 1.54 mmol, 1 equiv), HMPA (4.47 mL, 10.01 mmol, 16 equiv), *i*PrOH (0.24 mL, 3.08 mmol, 2 equiv), and SmI_2 (77 mL, 7.70 mmol, 5 equiv) in THF (36 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 9:1) afforded **5d** as a pale yellow solid (280 mg, 49%; 60% brsm). M.p. 122–125 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.98 (d, J = 8.3 Hz, 1H), 6.52 (dd, J = 8.1, 2.2 Hz, 1H), 6.37 (d, J = 2.4 Hz, 1H), 6.01 (td, J = 9.7, 3.4 Hz, 1H), 5.29 (m, 1H), 5.06 (t, J = 3.6 Hz, 1H), 3.81 (s, 3H), 3.16 (s, 3H), 3.01–2.96 (m, 2H), 0.57 (s, 9H), 0.08 (s, 3H), −0.14 ppm (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.4, 160.4, 147.0, 145.3, 126.4, 124.5, 124.3, 106.2, 101.5, 95.7, 55.4, 55.0, 26.8, 26.3, 25.0, 17.4, −4.7, −5.4 ppm; IR (KBr): ν = 2930, 2857, 1724, 1686, 1625, 1505, 1471, 1371, 1325, 1260, 1182 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{30}NO_3Si$ $[M+H^+]$: 372.1989; found: 372.1992.

Compound 6a: Synthesized according to general procedure A from **4a** (83 mg, 0.24 mmol, 1 equiv), HMPA (0.67 mL, 3.84 mmol, 16 equiv), *i*PrOH (36 μL, 0.47 mmol, 2 equiv), and SmI_2 (11.8 mL, 1.18 mmol, 5 equiv) in THF (6 mL). Purification by flash chromatography (silica gel, CH_2Cl_2: 100%) afforded **6a** as a pale yellow solid (30 mg, 55% yield). M.p. 109–113 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 13.33 (s, 1H), 8.22 (dd, J = 8.2, 1.2 Hz, 1H), 7.70–7.51 (m, 2H), 7.41–7.30 (m, 2H), 7.01 (dd, J = 7.6, 1.2 Hz, 1H), 3.75 ppm (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 165.3, 162.0, 137.0, 134.6, 134.5, 129.7, 123.8, 123.3, 119.7, 115.1, 115.0, 111.5, 110.34, 29.2 ppm; IR (neat, NaCl): ν = 2925, 1640, 1420, 1213, 1141 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{12}NO_2$ $[M+H]^+$: 226.0862; found: 226.0860.

Compound 7a: Synthesized according to general procedure B from **5c** (3.6 g, 10.56 mmol, 1 equiv), CsF (12.75 g, 84.48 mmol, 8 equiv), and $PhN(Tf)_2$ (18.84 g, 52.80 mmol, 5 equiv) in dimethoxyethane (30 mL) for the first step, and $Pd(OAc)_2$ (236 mg, 1.10 mmol, 10 mol%), PPh_3 (552 mg, 2.20 mmol, 20 mol%), *i*Pr_2NEt (11 mL, 63.36 mmol, 6 equiv), and HCO_2H (3.2 mL, 84.48 mmol, 8 equiv) in DMF (85 mL) for the second step. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 8:2) yielded **7a** as a yellow solid (1.95 g, 87% over 2 steps). M.p. 98–101 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 1H), 7.14–7.03 (m, 2H), 6.84 (d, J = 7.6 Hz, 1H), 6.02–6.01 (m, 2H), 5.41–5.36 (m, 2H), 3.23 (s, 3H), 2.96–2.88 ppm (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 177.7, 142.8, 134.0, 128.3, 127.1, 124.6, 123.7, 122.8, 107.9, 51.6, 26.5, 25.6 ppm; IR (KBr): ν = 3032, 2863, 1716, 1608, 1491, 1470, 1338 cm^{-1}; MS (ESI): m/z (%) 234 (98) $[M+Na]^+$, 212 (100) $[M+H]^+$; HRMS (ESI):): m/z calcd for $C_{14}H_{13}NONa$ $[M+Na]^+$: 234.0889; found: 234.0886.

Compound 7b: Synthesized according to general procedure B from **5d** (280 mg, 0.75 mmol, 1 equiv), CsF (0.91 g, 6 mmol, 8 equiv), and $PhN(Tf)_2$ (1.34 g, 3.75 mmol, 5 equiv) in dimethoxyethane (9 mL) for the first step, and $Pd(OAc)_2$ (17 mg, 0.08 mmol, 10 mol%), PPh_3 (42 mg, 0.16 mmol, 20 mol%), *i*Pr_2NEt (0.8 mL, 4.50 mmol, 6 equiv), and HCO_2H (0.23 mL, 6 mmol, 8 equiv) in DMF (6 mL) for the second step. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 8:2) yielded **7b** as colorless crystals (147 mg, 81% over 2 steps). M.p. 133–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (d, J = 8.1 Hz, 1H), 6.55 (dd, J = 8.1, 2.2 Hz, 1H), 6.42 (dd, J = 8.1, 2.4 Hz, 1H), 6.10 (td, J = 9.7, 3.4 Hz, 2H), 5.35 (td, J = 10.0, 1.7 Hz, 2H), 3.82 (s, 3H), 3.20 (s, 3H), 3.01–2.76 ppm (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 178.3, 160.3, 144.1, 126.9, 126.2, 125.2, 124.1, 106.5, 95.9, 55.4, 51.1, 26.5, 25.6 ppm; IR (neat, NaCl): ν = 3037, 1720, 1627, 1371, 1258, 1086 cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{15}NO_2Na$ $[M+Na]^+$: 264.0995; found: 264.0995.

Compound 8a: At 0 °C, a 35% aqueous solution of H_2O_2 (24 mL, 0.27 mmol, 1.35 equiv) was added to a solution of trifluoroacetic anhydride (56 mL, 0.4 mmol, 2 equiv) in CH_2Cl_2 (0.2 mL). The reaction mixture was stirred at 0 °C for 30 min. At −50 °C, this mixture was added to a solution of **7a** (42 mg, 0.2 mmol, 1 equiv) and Na_2CO_3 (57 mg, 0.54 mmol, 2.7 equiv) in CH_2Cl_2 (0.24 mL). The reaction mixture was stirred at −50 °C for 3 h, at −10 °C for 2 h, and overnight at RT. The reaction mixture was then poured into a saturated aqueous solution of Na_2SO_3. The aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 9:3) yielded **8a** as a yellow solid (9 mg, 19%; 59% yield brsm). M.p. 143–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 1H), 7.13–7.03 (m, 2H), 6.88 (d, J = 7.9 Hz, 1H), 5.87–5.80 (m, 1H), 5.36–5.30 (m, 1H), 3.40–3.36 (m, 1H), 3.27 (s, 3H), 3.08–3.04 (m, 1H), 2.92–2.81 (m, 1H), 2.75–2.65 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 176.3, 143.8, 129.7, 124.8, 124.2, 122.8, 122.4, 108.4, 55.2, 50.2, 48.7, 26.5, 25.1 ppm; IR (neat, NaCl): ν = 2919, 1708, 1605, 1467, 1345 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{13}NO_2Na$ $[M+Na]^+$: 250.0838; found: 250.0839.

Compound 8b: An aqueous solution of Na_2EDTA (2.5 mL, 1×10^{-4} M in H_2O, 2.5×10^{-4} mmol) and an aqueous solution of tetrabutylammonium hydroxide (0.08 mL, 40% in H_2O, 0.05 mmol, 5 mol%) were added to a solution of **7a** (53 mg, 0.25 mmol, 1 equiv) in CH_3CN (3.8 mL) at 0 °C with vigorous stirring. A mixture of Oxone (770 mg, 1.25 mmol, 5 equiv) and $NaHCO_3$ (326 mg, 3.86 mmol, 15.5 equiv) was pulverized. A small portion of this mixture was added to the reaction mixture to adjust the pH > 7. After 5 min, ketone **10** (194 mg, 0.75 mmol, 3 equiv) was added portionwise over 1 h. Simultaneously, the rest of the Oxone and $NaHCO_3$ mixture was added portionwise over 50 min. After completion of the addition of **10**, the reaction mixture was stirred at 0 °C for 24 h, diluted with water (8 mL), and extracted four times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 8:2 to 6:4) yielded **8b** as a yellow solid (25 mg, 43%; 78% yield brsm). M.p. 100–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.32 (m, 2H), 7.11 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 5.88–5.81 (m, 1H), 5.17–5.10 (m, 1H), 3.48–3.46 (m, 1H), 3.25 (s, 3H), 3.16–3.14 (m, 1H), 2.83 (dq, J = 19.6, 2.6 Hz, 1H), 2.73 ppm (dd, J = 19.6, 4.9 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.8, 143.1, 131.3, 128.9, 126.1, 125.3, 123.2, 122.5, 108.1, 55.7, 51.4, 50.8, 26.6, 24.9 ppm; IR (neat, NaCl): ν = 1702, 1610, 1347, 1260 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1019; found: 228.1018.

Compound 9: A 35% aqueous solution of H_2O_2 (0.25 mL, 2.6 mmol, 13 equiv) was added to a solution of trifluoroacetic anhydride (0.56 mL, 4 mmol, 20 equiv) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and a solution of **7a** (42 mg, 0.2 mmol, 1 equiv) in CH_2Cl_2 (0.4 mL) was added dropwise. The resulting reaction mixture was stirred at 0 °C for 4 h and poured into a saturated aqueous solution of Na_2SO_3. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford **9** as yellow crystals (38 mg, 78% yield). M.p. 217–223 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40 (td, J = 7.6, 1.1 Hz, 1H), 7.24–7.20 (m, 1H), 7.12 (td, J = 7.5, 0.8 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 3.30 (s, 3H), 3.21–3.17 (m, 2H), 3.02 (d, J = 17.0 Hz, 1H), 2.90 (d, J = 3.8 Hz, 1H), 2.46 ppm (dt, J = 17.0, 2.6 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 174.3, 143.9, 130.0, 126.5, 124.1, 122.8, 108.7, 52.4, 47.8, 47.1, 29.6, 23.1 ppm; IR (neat): ν = 1717, 1609, 1493, 1471, 1344, 1256, 2092 cm^{-1}; MS (EI): m/z: 243 (100) $[M]^+$; HRMS (ESI): m/z calcd for $C_{14}H_{13}NO_3Na$ $[M+Na]^+$: 266.0787; found: 266.0788.

Compounds 11 and 12: *t*BuOK (19 mg, 0.17 mmol, 1.1 equiv) was added to a solution of **7a** (32 mg, 0.15 mmol, 1 equiv) in THF (1.5 mL) at −40 °C. The reaction mixture was stirred at −40 °C for 10 min. PhCHO (30 mL, 0.30 mmol, 2 equiv) was added and the mixture was allowed to reach RT. H_2O and Et_2O were added and the layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, petrole-

um ether/EtOAc 9:1) yielded **11** (5 mg, 14% yield) as a yellow oil and **12** (24 mg, 54% yield) as a yellow oil. **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 7.5 Hz, 1H), 7.41–7.24 (td, J = 7.9, 1.5 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.20 (dd, J = 9.4, 5.3 Hz, 1H), 6.14–6.08 (m, 1H), 5.91–5.85 (m, 1H), 5.46 (d, J = 9.4 Hz, 1H), 3.22 (s, 3H), 3.07–3.01 (td, J = 7.7, 2.6 Hz, 1H), 2.36 ppm (dd, J = 7.7, 5.6 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 180.6, 141.7, 133.1, 128.5, 125.5, 124.7, 124.2, 123.6, 123.4, 122.7, 108.1, 48.5, 32.3, 26.5 ppm; IR (neat, NaCl): ν = 3042, 2932, 1713, 1610, 1490, 1470, 1372, 1345 cm^{-1}; MS (EI): m/z: 211 (26) $[M]^+$, 210 (100) $[M-H]^+$; HRMS (ESI): m/z calcd for $C_{14}H_{13}NONa$ $[M+Na]^+$: 234.0889; found: 234.0898. **12**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.41–7.22 (m, 6H), 7.15–7.04 (m, 3H), 6.87 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 9.8 Hz, 1H), 6.53 (s, 1H), 5.62–5.52 (m, 2H), 3.26 ppm (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 143.0, 136.7, 132.2, 131.7, 130.0, 129.4, 129.2, 128.7, 128.3, 127.9, 127.1, 125.5 125.3, 125.0, 123.1, 108.2, 55.0, 26.8 ppm; IR (neat, NaCl): ν = 3418, 3055, 2928, 1714, 1608, 1488, 1470, 1421 cm^{-1}; MS (EI): m/z: 299 (100) $[M]^+$, 284 (10) $[M-CH_3]^+$; HRMS (ESI): m/z calcd for $C_{21}H_{18}NO$ $[M+H]^+$: 300.1382; found: 300.1382.

Compound 13a: Synthesized according to general procedure C from **7a** (211 mg, 1 mmol, 1 equiv), methyl iodide (0.3 mL, 2 mmol, 2 equiv), and THF (10 mL). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc 97:3) afforded the **13a** as a yellow viscous oil (150 mg, 67%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.9 Hz, 1H), 7.54–7.52 (m, 1H), 7.40–7.38 (m, 1H), 7.28–7.24 (m, 1H), 5.95 (brs, 2H), 3.87–3.84 (m, 1H), 3.75 (s, 3H), 3.46–3.38 (m, 1H), 3.17–3.10 (m, 1H), 1.32 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (65 MHz, $CDCl_3$): δ = 161.8, 144.7, 139.1, 129.3, 125.8, 124.5, 123.7, 122.0, 119.7, 114.7, 30.6, 29.9, 26.2, 22.9 ppm; IR (neat, NaCl): ν = 3053, 2930, 1644, 1584, 1455, 1417, 1356, 1311 cm^{-1}; MS (EI): m/z: 225 (10) $[M]^+$, 210 (100) $[M-CH_3]^+$, 195 (23); HRMS (ESI): m/z calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1231; found: 226.1230.

By using (+)-bis[(*R*)-α-methylbenzyl]amine instead of diisopropylamine led to enantioenriched **13a**. Enantiomeric excess was measured by HPLC analysis using a Chiralcel AD-H column (MeOH/EtOH/Et_2NH 70:30:0.1, flow rate 0.8 mL min^{-1}, λ = 276 nm): t_{minor} = 14.3 min, t_{major} = 30.1 min).

Compound 13b: Synthesized according to general procedure C from **7a** (42 mg, 0.2 mmol, 1 equiv) and allyl bromide (35 μL, 0.4 mmol, 2 equiv) in THF (2 mL). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc 98:2) afforded **13b** as a yellow oil (24 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.3 Hz, 1H), 7.57–7.50 (m, 1H), 7.42–7.39 (m, 1H), 7.30–7.25 (m, 1H), 6.10–5.94 (m, 2H), 5.81–5.71 (m, 1H), 4.97 (m, 2H), 3.98–3.89 (m, 1H), 3.77 (s, 3H), 3.47–3.37 (m, 1H), 3.14–3.03 (m, 1H), 2.61–2.30 ppm (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 161.4, 142.6, 138.9, 134.5, 129.2, 126.9, 126.8, 125.1, 124.0, 121.9, 119.4, 117.3, 114.6, 40.6, 35.3, 29.7, 26.4 ppm; IR (neat, NaCl): ν = 3415, 2928, 1633, 1588, 1462, 1416, 1316 cm^{-1}; MS (EI): m/z: 251 (5) $[M]^+$, 210 (100) $[M-C_3H_5]^+$, 195 (42) $[M-C_4H_8]^+$; HRMS (ESI): m/z calcd for $C_{17}H_{18}N_O$ $[M+H]^+$: 252.1382; found: 252.1389.

Compound 13c: Synthesized according to general procedure C from **7a** (42 mg, 0.2 mmol, 1 equiv) and methoxymethyl chloride (MOMCl; 30 μL, 0.4 mmol, 2 equiv) in THF (2 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 1:1) afforded **13c** as a yellow oil (15 mg, 30%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.3 Hz, 1H), 7.56–7.51 (m, 1H), 7.41–7.26 (m, 2H), 6.11 (brs, 2H), 4.15–4.06 (m, 1H), 3.76 (s, 3H), 3.68 (dd, J = 9.0, 4.1 Hz, 1H), 3.53–3.44 (m, 2H), 3.32 (s, 3H), 3.19–3.09 ppm (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 161.4, 140.2, 138.8, 129.3, 127.6, 126.0, 125.7, 124.1, 121.9, 119.7, 114.5, 77.0, 59.2, 36.7, 29.7, 26.3 ppm; IR (neat, NaCl): ν = 2926, 1633, 1596, 1461, 1417, 1314, 1192, 1110 cm^{-1}; MS (ESI): m/z: 256 (100) $[M+H]^+$, 239 (14) $[M-CH_3]^+$; HRMS (ESI): m/z calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1338; found: 256.1341.

Compound 13d: Synthesized according to general procedure C from **7b** (48 mg, 0.2 mmol, 1 equiv) and methyl iodide (25 μL, 0.4 mmol, 2 equiv) in THF (2 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 8:2) afforded **13d** as a yellow oil (21 mg, 42%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.6 Hz, 1H), 6.87–6.81 (m, 2H), 5.94 (brs, 2H), 3.91 (s, 3H), 3.84–3.75 (m, 1H), 3.71 (s, 3H), 3.42–3.31 (m, 1H), 3.14–3.03 (m, 1H), 1.30 ppm (d, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.0, 160.4, 144.5, 140.5, 129.0, 125.6, 123.6, 122.5, 113.6, 109.0, 104.5, 98.9, 55.5, 30.4, 29.7, 25.7, 22.8 ppm; IR (neat, NaCl): ν = 3563, 2969, 1679, 1567 cm^{-1}; HRMS (ESI): m/z calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1332; found: 256.1330.

Compound 15: *m*CPBA (54 mg, 0.31 mmol, 1.5 equiv) was added to a solution of **13a** (45 mg, 0.2 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at 0°C. After 4 h at 0°C, the reaction mixture was stirred for 16 h at RT. A saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted three times with CH_2Cl_2.The combined organic extracts were washed with brine, dried over $MgSO_4$, and the solvent concentrated in vacuo. Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc 8:2) yielded **10** as a white solid (35 mg, 72%). M.p. 181–183°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.3 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 3.90–3.83 (m, 1H), 3.72 (s, 3H), 3.60 (d, J = 16.3 Hz, 1H), 3.54 (brs, 1H), 3.40 (brs, 1H), 2.80 (d, J = 16.3 Hz, 1H), 1.34 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 142.5, 138.9, 129.5, 123.3, 122.0, 121.7, 119.5, 114.5, 56.2, 50.5, 29.8, 29.7, 24.6, 17.4 ppm; IR (KBr): ν = 2922, 1638, 1596, 1457, 1339, 1312, 1098 cm^{-1}; MS (EI): m/z (%): 241 (34) $[M]^+$, 226 (29) $[M-CH_3]^+$, 212 (100) $[M-NCH_3]^+$, 198 (54) $[M-COCH_3]^+$; HRMS (ESI): m/z calcd for $C_{15}H_{16}NO_2$ $[M+H]^+$: 242.1175; found: 242.1178.

Compound 16a: Synthesized according to general procedure C from **7a** (42 mg, 0.2 mmol, 1 equiv) and benzaldehyde (50 μL, 0.40 mmol, 2 equiv) in THF (2 mL). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc 6:4) afforded **16a** as a pale yellow solid (38 mg, 60%). M.p. 182–183°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.3 Hz, 1H), 7.56–7.50 (m, 1H), 7.40–7.23 (m, 7H), 6.97 (dd, J = 9.8, 1.5 Hz, 1H), 6.11 (dd, J = 10.0, 4.3 Hz, 1H), 4.65 (d, J = 10.3 Hz, 1H), 3.76 (s, 3H), 3.16–2.88 ppm (m, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 162.0, 142.4, 138.8, 136.7, 136.1, 129.5, 128.3, 127.7, 126.8, 123.4, 123.3, 121.9, 121.6, 118.3, 114.4, 75.2, 40.9, 29.8, 23.0 ppm; IR (KBr): ν = 3386, 1643, 1597, 1454, 1093 cm^{-1}; MS (ESI): m/z: 340 (100) $[M+Na]^+$, 318 (23) $[M+H]^+$, 300 (15) $[M+H-H_2O]^+$; HRMS (ESI): m/z calcd for $C_{21}H_{19}NO_2Na$ $[M+Na]^+$: 340.1313; found: 340.1309.

Compound 16b: Synthesized according to general procedure C from **7a** (42 mg, 0.2 mmol, 1 equiv) and isobutyraldehyde (35 μL, 0.40 mmol, 2 equiv) in THF (2 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 1:1) afforded **16b** (36 mg, 63%) as a yellow oil (85:15 mixture of diastereomers that were assigned M for the major and m for the minor one in the NMR data). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.3 Hz , $1H_M$), 7.59 (d, J = 8.3 Hz, $1H_m$), 7.45–7.40 (m, $1H_{M+m}$), 7.27–7.24 (m, $1H_{M+m}$), 7.18–7.12 (m, $1H_{M+m}$), 6.90 (dd, J = 10.0, 1.3 Hz, $1H_M$), 6.26 (dd, J = 9.8, 4.1 Hz, $1H_{M+m}$), 5.87–5.81 (m, $1H_m$), 4.17 (m, $1H_m$), 3.65 (s, $3H_M$), 3.60 (s, $3H_m$), 3.45–3.39 (m, $1H_m$), 3.32 (t, J = 6.0 Hz, $1H_{M+m}$), 3.16–3.07 (m, $1H_m$), 2.99–2.80 (m, $2H_{M+m}$), 2.66–2.60 (m, $1H_M$), 1.85–1.74 (m, $1H_{M+m}$), 1.14 (d, J = 6.8 Hz, $3H_m$), 0.96 (d, J = 6.8 Hz, $3H_m$), 0.92 (d, J = 6.8 Hz, $3H_M$), 0.85 ppm (d, J = 6.8 Hz, $3H_M$); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 162.0 (M), 161.1 (m), 141.1 (m), 139.0 (m), 138.8 (M), 137.4 (M),136.6 (M), 129.6 (m), 129.4 (M+m), 129.2 (m), 128.3 (m), 123.6 (m), 123.4 (M), 121.8 (M), 121.5 (M), 121.4 (M+m), 119.2 (m), 118.3 (M), 114.7 (m), 114.4 (M), 80.3 (m), 77.4 (M), 38.6 (m), 36.8 (M), 32.4 (m), 30.4 (M), 29.8 (M), 29.6 (m), 27.0 (m), 21.4 (M), 20.2 (m), 19.8 (M), 19.4 (m), 17.0 (M); IR (neat, NaCl): ν = 3416, 2959, 1642, 1618, 1597, 1460 cm^{-1}; MS (ESI): m/z: 306 (100) $[M+Na]^+$, 284 (63) $[M+H]^+$; HRMS (ESI): m/z calcd for $C_{18}H_{21}NO_2Na$ $[M+Na]^+$: 306.1470; found: 310.1476.

Compound 16c: Synthesized according to general procedure C from **7a** (42 mg, 0.2 mmol, 1 equiv) and pivaladehyde (44 μL, 0.4 mmol, 2 equiv) in THF (2 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 1:1) afforded **16c** as a pale yellow solid (36 mg, 61%). M.p. 96–98°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.3 Hz, 1H), 7.51 (t, J = 8.3 Hz, 1H), 7.36–7.33 (m, 1H), 7.25–7.20 (m, 1H), 6.93 (dd, J = 9.8, 2.3 Hz, 1H), 6.30 (dd, J = 9.8, 3.8 Hz, 1H), 3.74 (s, 3H), 3.47 (d, J = 3.8 Hz, 1H), 3.10–2.91 (m, 2H), 2.83–2.75 (m, 1H), 1.01 ppm (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 161.9, 139.9, 138.8, 136.4, 129.4, 123.9, 123.3, 121.8, 121.0, 118.2, 114.3, 81.4, 36.1, 35.7, 29.8, 27.0, 21.9 ppm; IR (KBr): ν = 3424, 2954, 2868, 1645, 1616, 1598, 1460, 1414, 1364, 1315 cm^{-1}; MS (ESI): m/z: 320 (100) $[M+Na]^+$, 298 (77) $[M+H]^+$, 210

(17) $[M+H-C_5H_{12}O]^+$; HRMS (ESI): *m/z* calcd for $C_{19}H_{23}NO_2Na$ $[M+Na]^+$: 320.1626; found: 320.1624.

Compound 16d: Synthesized according to general procedure C from **7a** (42 mg, 0.2 mmol, 1 equiv) and *p*-anisaldehyde (49 μL, 0.4 mmol, 2 equiv) in THF (2 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 8:2 to 2:8) afforded **16d** as a yellow viscous oil (21 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.72$ (d, $J=7.9$ Hz, 1H), 7.46 (t, $J=7.9$ Hz, 1H), 7.31–7.27 (m, 1H), 7.20–7.15 (m, 3H), 6.87 (dd, $J=10.0$, 1.3 Hz, 1H), 6.76 (d, $J=8.7$ Hz, 2H), 6.03 (dd, $J=9.8$, 4.1 Hz, 1H), 4.51 (d, $J=7.5$ Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.05–2.88 (m, 2H), 2.85–2.75 ppm (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta=161.9$, 159.1, 138.9, 136.7, 136.0, 134.5, 129.5, 127.9, 123.4, 121.9, 121.7, 118.3, 114.4, 113.7, 75.0, 55.2, 40.9, 29.8, 23.2 ppm; IR (neat, NaCl): $\nu=3317$, 1640, 1574, 1513, 1248 cm^{-1}; MS (EI): *m/z*: 329 (34) $[M+H-H_2O]^+$, 210 (100) $[M-C_8H_{10}O_2]^+$, 137 (73) $[C_8H_{10}O_2]^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{21}NO_3Na$ $[M+Na]^+$: 370.1419; found: 370.1414.

Compound 17: Synthesized according to general procedure C from **7a** (42 mg, 0.2 mmol, 1 equiv) and cinnamaldehyde (50 μL, 0.4 mmol, 2 equiv) in THF (2 mL). Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc 9:1) afforded **17** as a pale yellow solid (34 mg, 50%). M.p. 99–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.35$ (s, 1H), 8.01 (d, $J=$ 7.9 Hz, 1H), 7.60–7.57 (m, 1H), 7.47–7.28 (m, 1H), 6.26–6.21 (m, 1H), 5.72–5.66 (m, 1H), 4.23–4.13 (m, 1H), 3.96–3.89 (m, 1H), 3.79 (s, 3H), 3.52–3.47 (m, 1H), 3.21–3.15 (m, 1H), 3.00–2.87 (m, 1H), 2.44–2.36 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=201.5$, 161.3, 141.5, 141.3, 139.4, 129.9, 129.1, 128.3, 128.1, 128.0, 127.5, 124.2, 123.5, 122.5, 119.3, 115.2, 44.4, 42.5, 41.9, 30.0, 27.3 ppm; IR (KBr): $\nu=3411$, 2958, 1721, 1631, 1593, 1460, 1416, 1316, 1265 cm^{-1}; MS (EI): *m/z*: 344 (8) $[M+H]^+$, 209 (100) $[M-C_9H_{10}O]^+$; HRMS (ESI): *m/z* calcd for $C_{23}H_{22}NO_2$ $[M+H]^+$: 344.1645; found: 344.1650.

Compound 18: H_2 gas was introduced with a balloon to a mixture of **13a** (45 mg, 0.2 mmol, 1 equiv) and palladium (10% on charcoal, 42 mg, 0.04 mmol, 20 mol%) in EtOH (5 mL) at RT. The reaction mixture was stirred at RT overnight, filtered through Celite, then the solvent was evaporated under vacuum. Purification by flash chromatography (silica gel, CH_2Cl_2/EtOAc 95:5) yielded **18** as a white solid (34 mg, 75%). M.p. 88–90 °C; IR (neat): $\nu=3050$, 2935, 1637, 1594, 1461, 1414 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.79$ (d, $J=7.9$ Hz, 1H), 7.51–7.45 (m, 1H), 7.37–7.34 (m, 1H), 7.27–7.21 (m, 1H), 3.73 (s, 3H), 3.41–3.31 (m, 1H), 2.91–2.83 (m, 1H), 2.50–2.40 (m, 1H), 1.91–1.80 (m, 4H), 1.32 ppm (d, $J=$ 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=162.2$, 146.5, 138.5, 128.8, 127.5, 124.0, 121.6, 120.2, 114.3, 29.6, 28.9, 27.8, 24.6, 21.0, 16.7 ppm; MS (EI): *m/z*: 227 (81) $[M]^+$, 212 (100) $[M-CH_3]^+$, 198 (32) $[M-NCH_3]^+$; HRMS (ESI): *m/z* calcd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1382; found: 228.1384.

Compound 19: *N*-methylmorpholine *N*-oxide (28 mg, 0.21 mmol, 1.05 equiv) and OsO_4 (90 μL, 2.5 wt% in *t*BuOH) were added sequentially to a solution of **13a** (45 mg, 0.2 mmol, 1 equiv) in THF/*t*BuOH (1:1; 3 mL) and H_2O (0.3 mL). The reaction mixture was stirred overnight at RT. Then, Na_2SO_3 (152 mg, 1.2 mmol, 6 equiv) and H_2O (1.5 mL) were added at 0 °C and stirring was continued for 30 min at RT. EtOAc and brine were added. The aqueous layer was extracted five times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent concentrated in vacuo. *p*-Toluenesulfonic acid monohydrate (cat.) was added to a solution of the crude diol (0.2 mmol, 1 equiv) and 4 Å molecular sieves (100 mg) in acetone (4 mL). The reaction mixture was stirred at RT overnight, filtered over basic alumina, washed with EtOAc, and the solvent evaporated. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 6:4) yielded **19** as a white solid (35 mg, 59%). M.p. 173–175 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.77$ (d, $J=8.3$ Hz, 1H); 7.51 (t, $J=7.9$ Hz, 1H); 7.39 (d, $J=8.3$ Hz, 1H); 7.26 (t, $J=7.2$ Hz, 1H); 4.79 (t, $J=6.0$ Hz, 1H); 4.53 (d, $J=6.4$ Hz, 1H); 3.76 (s, 3H); 3.67 (q, $J=7.5$ Hz, 1H); 3.58 (d, $J=14.8$ Hz, 1H), 2.46 (dd, $J=17.7$, 4.9 Hz, 1H), 1.31 (s, 3H), 1.57 (d, $J=7.9$ Hz, 3H), 1.10 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=161.7$, 145.3, 138.9, 129.5, 124.0, 123.3, 122.0, 119.9, 114.5, 107.8, 78.4, 72.1, 32.9, 29.8, 26.4, 25.9, 24.4, 15.4 ppm; IR (neat, NaCl): $\nu=2970$, 2925, 2889, 1640, 1595, 1568, 1460, 1382, 1310 cm^{-1}; MS (EI): *m/z*: 299 (30) $[M]^+$, 284 (29) $[M-CH_3]^+$, 224 (100) $[M-C_3H_6O_2]^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.1594; found: 300.1597.

Cycloadduct 20: Maleimide (240 mg, 2.4 mmol, 24 equiv) was added to a solution of conjugated diene **16a** (32 mg, 0.1 mmol, 1 equiv) in toluene (2.5 mL). The reaction mixture was heated at reflux overnight and the solvent evaporated in vacuo. Flash chromatography (silica gel, CH_2Cl_2/EtOAc: 6/4) afforded the cycloadduct **20** (29 mg, 71% yield) as a white powder, m.p. 254–256 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta=11.08$ (s, 1H), 7.98 (d, $J=7.9$ Hz, 1H), 7.52–7.44 (m, 5H), 7.32 (d, $J=8.4$ Hz ,1H), 7.19 (t, $J=7.9$ Hz, 1H), 7.03 (d, $J=6.5$ Hz, 1H), 5.32 (d, $J=3.9$ Hz, 1H), 3.93–3.90 (m, 1H), 3.63 (d, $J=8.4$ Hz, 1H), 3.53 (s, 3H), 3.09 (dd, $J=8.4$, 2.0 Hz, 1H), 2.74–2.72 (m, 1H), 2.39–2.29 (m, 2H), 1.63 ppm (dd, $J=$ 12.8, 3.2 Hz, 1H); ^{13}C NMR (75.4 MHz, [D$_6$]DMSO): $\delta=179.3$, 178.1, 170.2, 144.7, 137.1, 135.1, 129.5, 128.2, 127.3, 126.6, 122.7, 122.6, 120.7, 117.7, 115.4, 76.6, 48.5, 44.7, 44.5, 44.2, 35.4, 34.6, 29.3 ppm; IR (neat, NaCl): $\nu=3379$, 1715, 1649, 1598, 1472, 1374 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{22}N_2O_4Na$ $[M+Na]^+$: 437.1471; found: 437.1453.

Compound 22: *t*BuLi (0.32 mL, 0.42 mmol, 2.1 equiv) was added to a solution of benzamide **21** (68 mg, 0.2 mmol, 1 equiv) in THF (2 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h and MeI (0.08 mL, 1.2 mmol, 6 equiv) was added. A saturated aqueous solution of NH_4Cl was added after an additional hour at −78 °C, and the resulting reaction mixture was allowed to reach RT. H_2O was added and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 95:5) yielded **22** (27 mg, 64%) as a yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.56$ (br s, 1H), 7.61–7.39 (m, 5H), 6.76 (d, $J=$ 8.7 Hz, 1H), 6.54 (t, $J=7.5$ Hz, 1H), 2.98 ppm (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta=199.3$, 152.7, 140.6, 135.4, 135.0, 130.6, 128.9, 128.0, 117.1, 113.6, 111.0, 29.4 ppm; IR (neat, NaCl): $\nu=3339$, 2962, 2816, 1619, 1572, 1520, 1445, 1425, 1261 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{14}NO$ $[M+H]^+$: 212.1069; found: 212.1073.

Compound 24: A 2.34 M solution of *n*BuLi in hexane (0.47 mL, 1.1 mmol, 1.1 equiv) was added dropwise to a solution of amine **23** (0.183 g, 1 mmol) in dry THF (2 mL) at −78 °C. The yellow reaction mixture was allowed to reach −40 °C. The solution was then degassed by three successive freeze–thaw–pump cycles and dry CO was bubbled through the solvent for 0.5 h. The reaction mixture under a CO atmosphere was then stirred for 10 min at −40 °C then H_2O was added. CO was carefully eliminated by bubbling N_2 into the reaction vessel, and the reaction mixture was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvents concentrated in vacuo. Purification by flash chromatography (silica gel, petroleum ether/EtOAc: 9/1) afforded amine **24** as a colorless oil (0.107 g, 54%). Spectroscopic data were identical with those reported in the literature.[40]

Compound 26: Phosgene (0.07 mL, 20% in toluene 0.68 mmol, 2.5 equiv) was added dropwise to a solution of *N*-methylbiphenyl-2-amine (50 mg, 0.27 mmol, 1 equiv) in toluene (4 mL). The reaction mixture was heated for 2 h under reflux then cooled to RT. Toluene was then removed through distillation under a well-ventilated fume hood and CH_2Cl_2 was added. The organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. $NaBH_4$ (55 mg, 0.59 mmol, 2.02 equiv) was added portionwise to a suspension of diphenyldiselenide (84 mg, 0.27 mmol, 1 equiv) in EtOH (3.5 mL). The reaction mixture was stirred for 15 min and a solution of the above crude carbamoyl chloride (0.27 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred for 1 h at RT. EtOAc and brine were added, the layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 9:1) yielded **26** as a yellow oil (74 mg, 75% yield over 2 steps). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=7.60$–7.37 (m, 14H), 2.96 ppm (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta=165.2$, 140.9, 138.6, 138.3, 136.2, 131.6, 130.4, 129.8, 128.9, 128.6, 128.5, 128.4, 127.8, 37.6 ppm; IR (neat, NaCl): $\nu=3059$, 2930, 1682, 1479, 1276 cm^{-1}; MS (EI): *m/z*: 210 (100)

$[M\text{-}C_6H_5Se]^+$; HRMS (ESI): m/z calcd for $C_{20}H_{18}NOSe$ $[M+H]^+$: 368.0548; found: 368.0555.

Compound 28: *n*BuLi (0.11 mL, 0.44 mmol, 2 equiv) was added to a solution of (+)-bis[(*R*)-α-methylbenzyl]amine hydrochloride (58 mg, 0.22 mmol, 1 equiv) in THF (2.1 mL) at −78 °C. The reaction mixture was allowed to reach RT and cooled again to −78 °C. The resulting freshly prepared solution of chiral base **27** was added dropwise to a solution of **7a** (42 mg, 0.2 mmol, 1 equiv) in THF (2 mL) at −40 °C (temperature inside flask < −38 °C). The reaction mixture was stirred at −40 °C for 10 min. *n*BuLi (0.11 mL, 0.22 mmol, 1.1 equiv) was added and the reaction mixture was stirred for an additional 10 min at −40 °C. Methyl iodide (25 μL, 0.44 mmol, 2 equiv) was then added dropwise and stirring was continued for another 10 min. H_2O (0.55 mL) was added by syringe at −40 °C and the mixture was allowed to reach RT. Et_2O was added and the layers were separated. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel, petroleum ether/EtOAc 8:2) afforded **28** as yellow crystals (19 mg, 40 %). M.p. 132–134 °C; $R_f = 0.4$ (petroleum ether/EtOAc 8:2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.75$ (dd, $J = 8.2$, 1.22 Hz, 1H), 7.54–7.47 (m, 1H), 7.38–7.34 (m, 1H), 7.28–7.21 (m, 1H), 6.02–5.89 (m, 2H), 3.81–3.76 (m, 1H), 3.74 (s, 3H), 3.67–3.62 (m, 1H), 1.38 (d, $J = 7.0$ Hz, 3H), 1.32 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 161.2$, 144.9, 139.0, 131.1, 131.0, 129.1, 128.3, 124.3, 121.8, 119.5, 114.4, 31.2, 30.9, 29.6, 23.8, 21.9 ppm; IR (neat, NaCl): $\nu = 2961$, 1926, 1673, 1629, 1595, 1456, 1312, 1078, 1051, 743 cm^{-1}; HRMS (ESI): m/z calcd for $C_{16}H_{18}NO$ $[M+H]^+$: 240.1382; found: 240.1383.

X-ray crystallography: CCDC 731966 (**8b**), CCDC 731967 (**9**), CCDC 710659 (**15**), CCDC 710658 (**16a**), CCDC 710660 (**20**) and CCDC 710661 (**28**) contain the crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational details: All geometries of intermediates and transition states were optimized fully using the Gaussian 03 program.[38] Geometry optimizations were performed in vacuum using DFT with the three-parameter hybrid functional B3LYP as implemented in Gaussian. Frequency calculations were performed to confirm the nature of the stationary points and to obtain zero-point energies (ZPE). The connectivity between stationary points was established by intrinsic reaction coordinate computations (IRC). Every transition structure was characterized by a single imaginary frequency in the diagonalized mass-weighted Hessian matrix. The geometries of all the stationary points and TS are provided in the Supporting Information. Single-point calculations in THF were run using IEFPCM as continuum solvation model.

Acknowledgements

MNERT (grant to G.R.) and the CNRS are thanked for financial support. We gratefully acknowledge Dr. J. Maddaluno, Dr. C. Fressigné (University of Rouen), Dr. H. Gerard (University Paris-VI) and Dr. F. Castet (University Bordeaux-1, ISM) for helpful discussions about DFT calculations. We acknowledge B. Kauffmann (IECB, Bordeaux) for X-ray diffraction studies and J. C. Lartigue and N. Pinaud (ISM, University Bordeaux-1) for NMR spectroscopy experiments.

[1] H. Lin, S. Danishefsky, *Angew. Chem.* **2003**, *115*, 38–53; *Angew. Chem. Int. Ed.* **2003**, *42*, 36–51 and references cited therein.
[2] M. S. Chande, R. S. Verma, P. A. Barve, R. R. Khanwelkar, R. B. Vaidya, K. B. Ajaikumar, *Eur. J. Med. Chem.* **2005**, *40*, 1143–1148.
[3] H. Venkatesan, M. C. Davis, Y. Altas, J. P. Snyder, D. C. Liotta, *J. Org. Chem.* **2001**, *66*, 3653–3661.
[4] A. C. Peterson, J. M. Cook, *J. Org. Chem.* **1995**, *60*, 120–129.
[5] a) K. S. Feldman, D. Boneva Vidulova, A. G. Karatjas, *J. Org. Chem.* **2005**, *70*, 6429–6440; b) H. Miyamoto, Y. Okawa, A. Nakazaki, S. Kobayashi, *Tetrahedron Lett.* **2007**, *48*, 1805–1808; c) Z. Mao, S. W. Baldwin *Org. Lett.* **2004**, *6*, 2425–2428; d) S. Atarashi, J.-K. Choi, D.-C. Ha, D. J. Hart, D. Kuzmich, C.-S. Lee, S. Ramesh, S. C. Wu, *J. Am. Chem. Soc.* **1997**, *119*, 6226–6241; e) D. Kuzmich, S. C. Wu, D.-C. Ha, C.-S. Lee, S. Ramesh, S. Atarashi, J.-K. Choi, D. J. Hart, *J. Am. Chem. Soc.* **1994**, *116*, 6943–6944; f) J. K. Dutton, R. W. Steel, A. S. Tasker, V. Popsavin, A. P. Johnson, *J. Chem. Soc. Chem. Commun.* **1994**, 765–766; g) T. Fukuyama, G. Liu, *Pure Appl. Chem.* **1997**, *69*, 501–505; h) H. Tokuyama, T. Yamashita, M. T. Reding, Y. Kaburagi, T. Fukuyama, *J. Am. Chem. Soc.* **1999**, *121*, 3791 –3792; i) T. A. Khan, R. Tripoli, J. J. Crawford, C. G. Martin, J. A. Murphy, *Org. Lett.* **2003**, *5*, 2971–2974; j) X. Zang, C. S. Foote, *J. Am. Chem. Soc.* **1993**, *115*, 8867–8868.
[6] a) I. Fleming, M. A. Loreto, J. P. Michael, I. H. M. Wallace, *Tetrahedron Lett.* **1982**, *23*, 2053–2056; b) I. Fleming, M. A. Loreto, I. H. M. Wallace, *J. Chem. Soc. Perkin Trans. 1* **1986**, 349–359; c) I. Fleming, R. C. Moses, M. Tercel, J. Ziv, *J. Chem. Soc. Perkin Trans. 1* **1991**, 617–626; d) C. Clarke, I. Fleming, J. M. D. Fortunak, P. T. Gallagher, M. C. Honan, A. Mann, C. O. Nubling, P. R. Raithby, J. J. Wolff, *Tetrahedron* **1988**, *44*, 3931–3934.
[7] a) A. Ashimori, B. Bachand, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487; b) A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman, M. J. Sharp, *J. Am. Chem. Soc.* **2005**, *127*, 18054–18065; c) N. J. Newcombe, F. Ya, R. J. Vijn, H. Hiemstra, W. N. Speckamp, *J. Chem. Soc. Chem. Commun.* **1994**, 767–768.
[8] a) R. Angelaud, O. Babot, T. Charvat, Y. Landais, *J. Org. Chem.* **1999**, *64*, 9613–9624; b) Y. Landais, E. Zekri, *Eur. J. Org. Chem.* **2002**, 4037–4053; c) R. Lebeuf, F. Robert, K. Schenk, Y. Landais, *Org. Lett.* **2006**, *8*, 4755–4758; d) G. Rousseau, F. Robert, K. Schenk, Y. Landais, *Org. Lett.* **2008**, *10*, 4441–4444.
[9] a) N. Abd Rahman, Y. Landais, *Curr. Org. Chem.* **2002**, *6*, 1369–1395; b) A. Studer, F. Schleth, *Synlett* **2005**, 3033–3041; c) M. S. Maji, R. Frohlich, A. Studer, *Org. Lett.* **2008**, *10*, 1847–1850; d) R. Umeda, A. Studer, *Org. Lett.* **2007**, *9*, 2175–2178; e) M. Butters, M. C. Elliott, J. Hill-Cousins, J. S. Paine, J. K. E. Walker, *Org. Lett.* **2007**, *9*, 792–803; f) F. Schleth, T. Vogler, K. Harms, A. Studer, *Chem. Eur. J.* **2004**, *10*, 4171–4185; g) F. Schleth, A. Studer, *Angew. Chem.* **2004**, *116*, 317–319; *Angew. Chem. Int. Ed.* **2004**, *43*, 313–315.
[10] a) H. Ohno, H. Iwasaki, T. Eguchi, T. Tanaka, *Chem. Commun.* **2004**, 2228–2229; b) H. Iwasaki, T. Eguchi, N. Tsutsui, H. Ohno, T. Tanaka, *J. Org. Chem.* **2008**, *73*, 7145–7152.
[11] Y. Mi, V. Schreiber, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 11290–11291.
[12] R. Mori, M. Nakanishi, D. Kajishima, Y. Sato, *J. Am. Chem. Soc.* **2003**, *125*, 9801–9807.
[13] a) F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry*, Part B, Springer Eds, **2007** Chap. 12 and references cited therein; b) G. Sello, T. Fumagalli, F. Orsini, *Curr. Org. Synth.* **2006**, *3*, 457–476; c) K. B. Sharpless, T. R. Verhoeven, *Aldrichimica Acta* **1979**, *12*, 63–74; d) K. A. Jorgensen, *Chem. Rev.* **1989**, *89*, 431–458.
[14] a) C. Fehr, *Angew. Chem.* **1998**, *110*, 2509–2512; *Angew. Chem. Int. Ed.* **1998**, *37*, 2407–2409; b) B. A. McKittrick, B. Ganem, *Tetrahedron Lett.* **1985**, *26*, 4895–4898.
[15] a) Y. Tu, Z. X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807; b) Z. X. Wang, Y. Tu, M. Frohn, J. R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.
[16] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
[17] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307–1370.
[18] a) H. B. Henbest, R. A. L. Wilson, *J. Chem. Soc.* **1959**, 1958–1965; b) P. D. Bartlett, *Rec. Prog. Chem.* **1950**, *11*, 47–51; c) G. Berti, *Top. Stereochem.* **1973**, *7*, 93–251.
[19] a) Y.-D. Wu, Y. Li, J. Na, K. N. Houk, *J. Org. Chem.* **1993**, *58*, 4625–4628; b) S. D. Kahn, C. F. Pau, A. R. Chamberlin, W. J. Hehre, *J. Am. Chem. Soc.* **1987**, *109*, 650–663.
[20] J. Clayden, *Organolithiums: Selectivity for Synthesis*, Vol. 23, Elsevier, Oxford, **2002**.

[21] An enantioselective version of the process was attempted using potassium mentholate. This provided **12** (30% yield) and isomerized **11** (36% yield, 10% *ee*), along with starting material (11%), indicating that enantioselective desymmetrization of such spirooxindoles might be carried out through a simple isomerization.
[22] The pK_a of such bis-allylic protons in DMSO has been estimated around 30–32, see: E. M. Arnett, K. G. Venkatasubramaniam, *J. Org. Chem.* **1983**, *48*, 1569–1578.
[23] The symbols ***i***, ***ii***… are used for numbering postulated intermediates, whereas **A**, **B**, **C**, TS**1**… designate computed intermediates.
[24] a) J. Clayden, J. Dufour, D. M. Grainger, M. Helliwell, *J. Am. Chem. Soc.* **2007**, *129*, 7488–7489; b) L. Liu, Z. Wang,, F. Zhao, Z. Xi, *J. Org. Chem.* **2007**, *72*, 3484–3491.
[25] J. Robertson, M. J. Palframan, S. A. Shea, K. Tchabanenko, W. P. Unsworth, C. Winters, *Tetrahedron* **2008**, *64*, 11896–11907.
[26] a) D. G. Perez, N. S. Nudelman, *J. Org. Chem.* **1988**, *53*, 408–413; b) N. S. Nudelman, H. Schulz, G. Garcia Linares, A. Bonatti, G. Boche, *Organometallics* **1998**, *17*, 146–150; c) N. S. Nudelman, G. Garcia Linares, *J. Org. Chem.* **2000**, *65*, 1629–1635; d) T. Mizuno, I. Nishiguchi, T. Okushi, T. Hirashima, *Tetrahedron Lett.* **1991**, *32*, 6867–6868.
[27] a) B. Bánhidai, U. Schöllkopf, *Angew. Chem.* **1973**, *85*, 861–862; *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 836–837; b) K. Smith, K. Swaminathan, *J. Chem. Soc. Chem. Commun.* **1976**, 387–388.
[28] L. M. Pratt, *THEOCHEM* **2007**, *811*, 191–196.
[29] C. C. Pye, *Int. J. Quantum Chem.* **2000**, *76*, 62–76.
[30] M. Stähle, M. Schlosser, *J. Organomet. Chem.* **1981**, *220*, 277–283.
[31] Although dimethyl ether is a valuable model to replace THF when computing reaction pathways, energetic barriers may however be overestimated, see reference [28] and references therein.
[32] a) J. K. Whitesell, S. W. Felman, *J. Org. Chem.* **1980**, *45*, 755–756; b) C. M. Cain, R. P. C. Cousins, G. Coumbarides, N. S. Simpkins, *Tetrahedron* **1990**, *46*, 523–544.
[33] P. O'Brien, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1439–1457.
[34] a) B. B. Snider, G. B. Phillips, R. Cordova, *J. Org. Chem.* **1983**, *48*, 3003–3010; b) P. Ballester, A. Costa, A. Garcia-Raso, A. Gomez-Solivellas, R. Mestres, *Tetrahedron Lett.* **1985**, *26*, 3625–3628.
[35] D. Seebach, V. Prelog, *Angew. Chem.* **1982**, *94*, 696–702; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654–660.
[36] Lithium dimethylamide has recently been used as an LDA surrogate when studying reactivity, see: a) K. J. Singh, D. B. Collum, *J. Am. Chem. Soc.* **2006**, *128*, 13753–13760; b) J. C. Riggs, K. J. Singh, M. Yun, D. B. Collum, *J. Am. Chem. Soc.* **2008**, *130*, 13709–13717.
[37] a) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356–363; b) M. C. Whisler, S. McNeil, V. Snieckus, P. Beak, *Angew. Chem.* **2004**, *116*, 2256–2276; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225.
[38] Gaussian 03, Revision D.02: M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.
[39] M. J. Totleben, D. P. Curran, P. Wipf, *J. Org. Chem.* **1992**, *57*, 1740–1744.
[40] J. Broggi, H. Clavier, S. P. Nolan, *Organometallics* **2008**, *27*, 5525–5531.

Received: May 28, 2009
Published online: September 16, 2009

