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Rearrangement of Spirocyclic Oxindoles with Lithium Amide Bases

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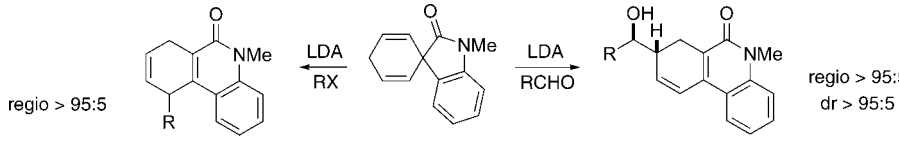
ABSTRACT

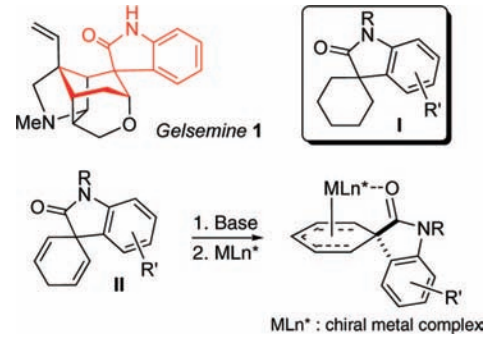


Spirocyclohexa-2,5-dienes were shown to rearrange at −40 °C, when treated with 1 equiv of LDA. Alkyl halides and aldehydes then reacted with the resulting phenanthridinone lithium enolate intermediates, with distinct regioselectivities and high diastereocontrol, to afford functionalized dearomatized phenanthridinones which were elaborated further. A mechanistic scheme involving a diisopropylamine-mediated proton transfer was proposed to rationalize the rearrangement.

Spirocyclic oxindoles (e.g., **I**, Scheme 1) constitute the core skeleton of several naturally occurring alkaloids isolated from *Gelsemium sempervirens*, including gelsemine **1**,[1] one of the most active constituents of this plant. This simple tricyclic skeleton is also present as a key fragment in various biologically relevant synthetic targets[2] and as such constitutes a versatile intermediate in organic synthesis.[3] In the course of our ongoing interest in desymmetrization processes involving 1,4-diene systems,[4] we became recently interested in the chemistry of spirocyclohexa-2,5-dienes of type **II**, containing the spirooxindole moiety.

The desymmetrization of cyclohexa-1,4-dienes (e.g., **II**) implies the differentiation of both diastereotopic faces and an enantiotopic group, a challenging task, which has recently attracted a great deal of interest.[4,5] The spiro-type structure of **II** exhibits attractive features in this context, including electronically well-differentiated diastereotopic faces with a polar amide functional group on one face and an apolar aryl substituent on the other face. It was envisioned that the propensity of the amide functional group to lead to hydrogen bonding[6] and metal binding[7] could be exploited to differentiate diastereotopic faces. The desymmetrization process could

Scheme 1. Spirocyclic Oxindole Core in *Gelsemium* Alkaloids



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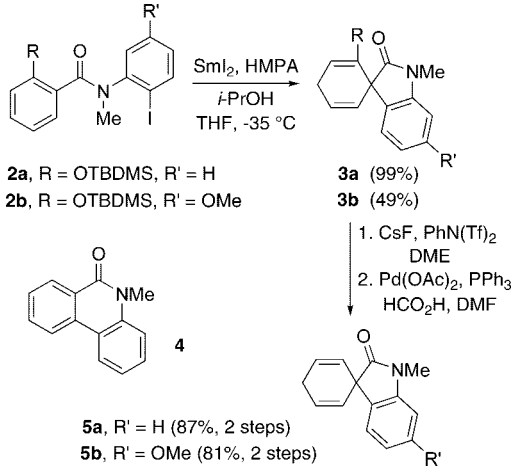
then be performed through deprotonation of the dienyl system, followed by transmetalation with a suitable chiral metal complex (e.g., ML*═Ti(OR*)$_4$,...) and reaction of the resulting pentadienyl−metal complex with various electrophiles.[5b−d]

Spirocyclic oxindoles were prepared using a methodology based on a SmI_2-mediated aryl cyclization process. Tanaka *et al.*[8] recently reported that SmI_2−HMPA was able to mediate the radical cyclization of iodoamides **2** to afford the spirocyclic skeleton of **3**, provided that an *ortho* substituent was present on the arene (Scheme 2). **2** (R = R′ = H) was

Scheme 2. Preparation of Spirocyclic Oxindoles **5a**,**b**

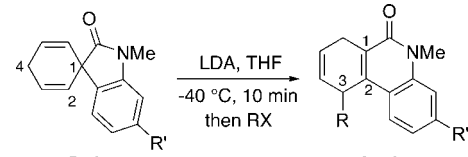


effectively shown to provide the desired oxindole **5a**, along with large amounts of the unseparable phenanthridinone **4**.

In contrast, the expected spiro compounds **3a**,**b** were obtained in reasonable to good yields from amides **2a**,**b** having a bulky silyloxy group (OTBDMS) in the *ortho* position. Silyloxycyclohexadienes **3a**,**b** were then transformed into the desired cyclohexadienes **5a**,**b** following a two-step procedure, including the conversion of **3a**,**b** into the corresponding triflates (not shown), using a fluoride source and $PhN(Tf)_2$,[9] followed by a palladium-mediated hydrogenation of the latter with formic acid.[10]

With spirocyclic oxindoles **5a**,**b** in hand, we then turned our attention toward the metalation step, varying the nature of the base. *n*-BuLi and *s*-BuLi were shown to afford a complex mixture of products, while LiHMDS, NaH, and *t*-BuOLi led to recovered starting material in essentially quantitative yield. In contrast, metalation with *t*-BuOK followed by addition of MeI led to a mixture of the C-4 methylated spiro oxindole (20%) and the 2,4-isomerized spiro oxindole (53%). More attractive results were obtained when LDA was used as a base. When **5a** was treated with LDA at −78 °C, no reaction took place. However, upon warming to −40 °C, the reaction mixture turned rapidly deep purple, a color which rapidly vanished upon addition of MeI. To our surprise, a rearranged product **6a**, possessing a new 1,4-cyclohexadienyl ring substituted at C-3, was formed without a trace of the expected methylated spiro oxindole (Table 1).

Table 1. LDA-Mediated Rearrangement of Spiro Oxindoles **5a**,**b**, Followed By Alkylation



5a-b **6a-d**

entry	spiro oxindole	R′	RX	R	diene	yield[a]
1	**5a**	H	MeI	Me	**6a**	67
2	**5a**	H	AllylBr	Allyl	**6b**	48
3	**5a**	H	MOMCl	$MeOCH_2$	**6c**	30
4	**5b**	OMe	MeI	Me	**6d**	42

[a] Isolated yield of **6a**−**d** after chromatography.

Varying the nature of the electrophile, a range of alkylated products **6a**−**d** was obtained in moderate to good isolated yields but in all cases as a single regioisomer (C3). Reactions were generally clean (crude yield >90%), the isolated yield not reflecting the efficiency of the process due to the sensitivity of dienes **6a**−**d** to rearomatization. The structure of regioisomers **6a**−**d** was assigned based on the X-ray structure determination of a derivative of **6a** (vide infra). Metalation and methylation of spiro oxindole **5b** also led to rearranged product **6d** after methylation. Other electrophiles such as aldehydes also reacted, providing alcohols **7a**−**d** with complete regiocontrol and in most cases with high diastereocontrol (Table 2). Surprisingly and in contrast with alkylation above, reaction with aldehydes took place at C-5.[11] The stereochemistry of **7a**−**d** was assigned based on X-ray diffraction studies performed on alcohol **7a**.[12] Reaction of **5a** with formaldehyde invariably led to the formation of the phenanthridinone **4** and no trace of the desired alcohol.

Interestingly, cinnamaldehyde reacted with rearranged **5a** in a 1,4-fashion to give the aldehyde **8** with complete regio-

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(6) Epoxidation of **II** (R = Me, R′ = H) using CF_3CO_3H was shown to lead exclusively to the expoxidation *syn* relative to the C═O group, likely as a result of the amide functional group directing effect: Rousseau, G.; Robert, F.; Landais, Y. unpublished results.

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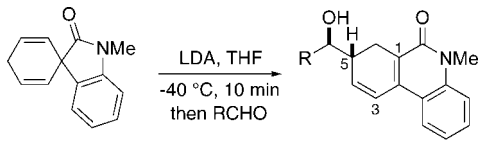
(12) The relative configuration of alcohol **7a** results from an *ul*-addition, involving the *Si*-face of the enolate and the *Re*-face of the aldehyde, through a transition state in which the aldehyde carbonyl group is likely coordinated to the lithium cation. Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654–660.

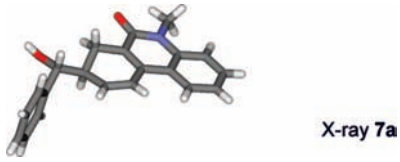
Table 2. LDA-Mediated Rearrangement of Spiro Oxindole **5a**,**b**, Followed By Addition of Aldehydes



5a **7a-d**

entry	R	alcohol	dr[a]	yield[b]
1	Ph	**7a**	>95:5	60
2	*i*-Pr	**7b**	85:15	63
3	*t*-Bu	**7c**	>95:5	61
4	4-OMePh	**7d**	>95:5	30

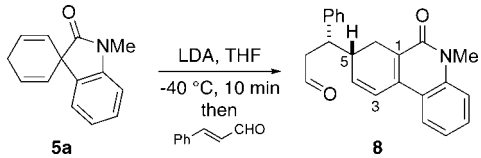
[a] Estimated from the ^{1}H NMR of the crude reaction mixture. [b] Isolated yields of **7a**−**d** after chromatography.



X-ray **7a**

and stereocontrol (Scheme 3). Its relative configuration was assigned based on the assumption that the topicity of the process is similar to that proposed above for the addition of aldehydes.[12]

Scheme 3. Synthesis of Aldehyde **8**



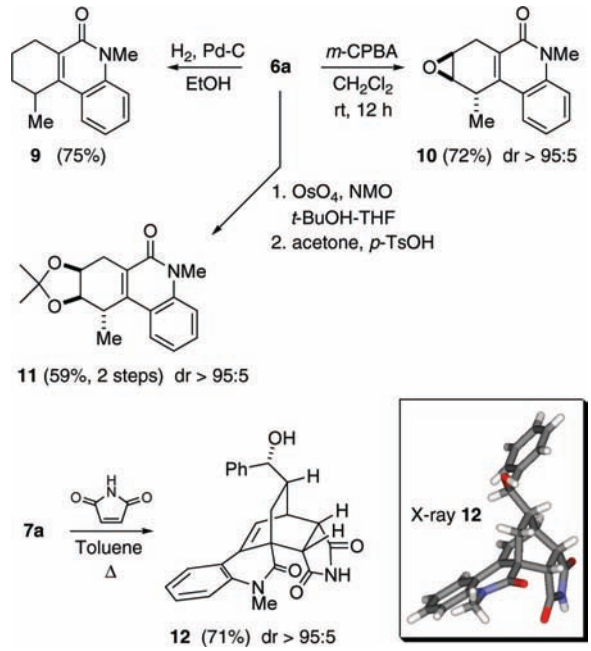
5a **8**

(51%) dr > 95:5

Dienes were then functionalized further, demonstrating that despite their sensitivity they represent valuable intermediates for organic synthesis. Hydrogenation of **6a** also occurred regioselectively on the C4−C5 double bond, leaving α,β-unsaturated amide **9** in 75% yield (Scheme 4). **6a** was shown to react selectively with *m*-CPBA, affording epoxide **10** as a single diastereomer. X-ray crystallography was used to establish the stereochemistry of **10**, indicating that approach of the peracid has occurred *anti* relative to the methyl group on the resident C3-stereogenic center. Dihydroxylation of **6a**, followed by diol protection, occurred similarly to afford acetonide **11** as a unique *anti*-diastereomer, for which stereochemistry was assigned through NMR experiments.

Finally, alcohol **7a** was shown to react with maleimide, providing, with complete diastereocontrol, Diels−Alder cycloadduct **12** having six stereogenic centers installed in only two steps. The stereochemistry of **12** was determined through NOESY experiments and confirmed by X-ray diffraction studies. This indicates that the *endo*-adduct results

Scheme 4. Functionalization of Rearranged Products **6a** and **7a**



from an approach of the dienophile *anti* relative to the benzylic alcohol moiety of the diene partner.

This unprecedented rearrangement of spirocyclo oxindoles **5a**,**b** was rationalized invoking the general pathway depicted in Figure 1. LDA abstraction of the bisallylic protons of **5a**,**b**

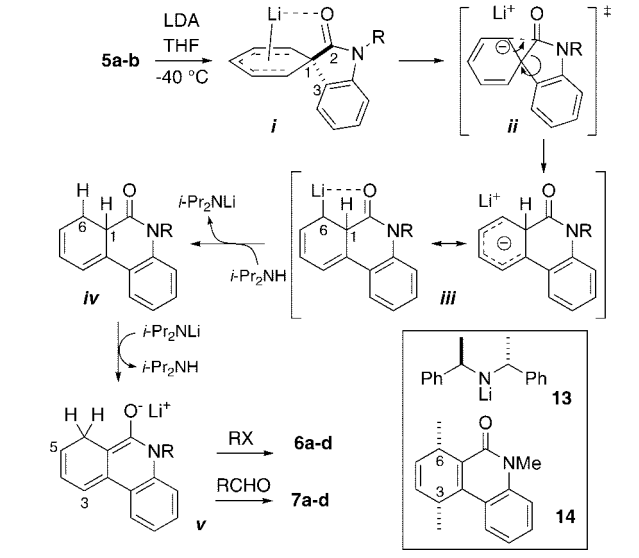


Figure 1. Tentative mechanism of the anionic rearrangement of **5a**,**b**.

likely generates a pentadienyl lithium intermediate ***i***[13] that rearranges at −40 °C into an amide-stabilized[7] lithiated

carbanion ***iii*** through transition state ***ii***.[14] The structure of products **6a**−**d** and **7a**−**d** implies that an enolate such as ***v*** is involved at a late stage of the process. Reaction of ***v*** with aldehydes occurs at C-5 and probably involves a complexation of the carbonyl group with the lithium cation of the enolate. In constrast, the alkylation reaction takes place at C-3. The origin of this regiochemical change remains presently unclear. The conversion of ***iii*** into ***v*** was rationalized, invoking an equilibrium between these two species, as a result of the presence in the medium of diisopropylamine issued from LDA. Diisopropylamine would protonate ***iii*** at C-6 to provide ***iv***. The regenerated LDA would then abstract the acidic proton at C-1 on the latter to give ***v***. Diisopropylamine would thus serve as a proton transfer agent to shift the equilibrium toward the thermodynamically more stable lithium enolate ***v***. Two observations support this hypothesis. First, when the reaction was performed in the presence of chiral amide base **13**,[15] **6a** was formed in low to modest yield (10−47%) but with significant enantiocontrol (6−20% e.e.), indicating that the secondary chiral amine is located in close proximity to the lithium enolate.[16] Second, when repeating the same experiment, but adding to the medium, a second equivalent of *n*-Buli at −78 °C before warming to −40 °C, *cis*-dimethylated product **14**,[17] was formed as the major compound in 40% yield. This indicates that when the proton transfer agent (R_2NH) is "removed" from the medium the conversion of ***iii*** into ***iv*** does not take place and ***iii*** may be alkylated at C-6. Deprotonation of 6-Me−***iii*** by LDA then generates the corresponding enolate that is alkylated at C3 to afford **14**. The role of diisopropylamine in this process is thus central and would explain the failure observed during reaction of **5a** with alkyllithium bases (*n*-BuLi and *s*-BuLi).

In summary, we have described along these lines an unprecedented LDA-mediated rearrangement of spirocyclic oxindoles. Ring strain is likely a driving force in this rearrangement, which is only observed in the presence of lithium amide bases for the reasons given above. The reaction displays a broad scope of applications, giving rise to highly functionalized phenanthridinones that represent valuable intermediates for organic synthesis. Preliminary experiments show that an enantioselective version is at hand by using chiral amide bases or chiral ligands. DFT calculations are currently carried out to get a deeper insight into the mechanism of this rearrangement and will be reported in due course.

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Involvement of anionic species such as aryllithium or acyllithium intermediates formed through C1−C3 or C1−C2 bond breaking should not be ruled out. These would then recombine to afford ***iii***.

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(17) The relative configuration of **14** was determined through X-ray diffraction analysis (see Supporting Information).