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Desymmetrization of Cyclohexa-2,5-dienes through a Diastereoselective Protonation–Hydroamination Cascade

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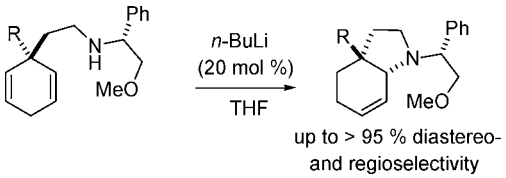
ABSTRACT

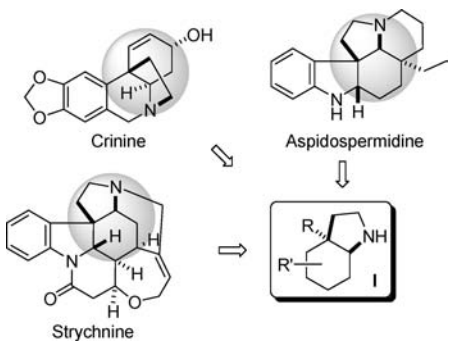


Intramolecular hydroamination of cyclohexa-2,5-dienes led with high selectivity to the corresponding bicyclic allylic amines. This study demonstrates that the reaction does not proceed through a direct hydroamination of one of the diastereotopic olefins but more likely involves a diastereoselective protonation of a pentadienyl anion, followed by addition of a lithium amide across the double bond of the resulting 1,3-diene, and is concluded by a highly regioselective protonation of the final allylic anion.

The azabicyclo[4.3.0]nonane system **I** is found in various alkaloids such as crinine, aspidospermidine, or strychnine (Scheme 1). These natural products exhibit a wide range of biological activities and are still the subject of intense synthetic studies.[1] The access to **I** includes a number of synthetic difficulties such as the introduction and the control of the stereochemistry of a quaternary center and that of a cis-ring junction. Although elegant answers to these problems have been proposed previously,[2] we have devised, in the course of our continuing interest in desymmetrization processes,[3] a simple strategy to access a target of type **I** based on a Birch reductive alkylation−desymmetrization (BRAD) sequence.

It was envisioned that the elaboration of the bicyclic core of analogues of **I** could be performed through a base-catalyzed addition of an amine N−H bond across one of the C=C bonds (hydroamination) of a symmetrical diene **III** (Scheme 2), leading to the formation of the fused five-

Scheme 1. Azabicyclo[4.3.0]nonane Core of Several Alkaloids



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(3) (a) Abd Rahman, N.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369−1395. (b) Studer, A.; Schleth, F. *Synlett* **2005**, 3033−3041.

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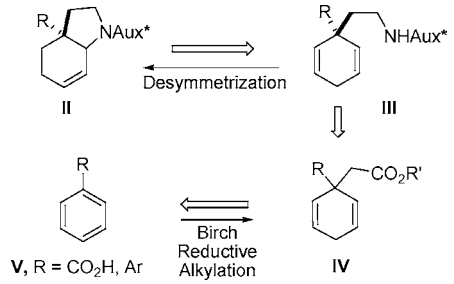
Scheme 2. BRAD Strategy

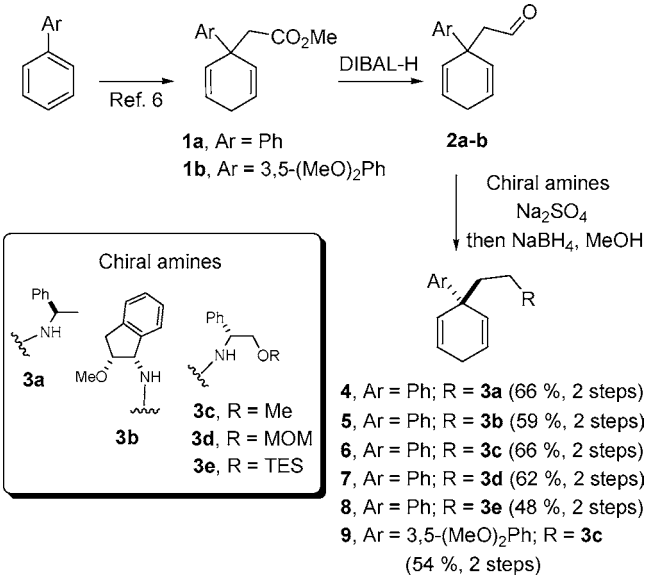


membered ring in a highly atom-economical manner.[4] Our strategy would be based on the Birch reductive alkylation of "activated" arenes **V** known to provide the corresponding cyclohexa-2,5-dienes **IV**, generally in good yield and with complete regiocontrol.[5] Various R groups can accommodate the Birch reaction conditions, and we recently showed that R can also be a substituted aryl group,[6] thus offering a general entry toward alkaloids such as those above. It was anticipated that a chiral auxiliary (Aux*) linked to the quaternary center (i.e., **III**) through an alkyl chain would be able to discriminate diastereotopic double bonds during the hydroamination process.

We thus report in this communication our preliminary studies on this approach which led to the discovery of an unprecedented tandem diastereoselective protonation−hydroamination of cyclohexa-2,5-dienes, which provides an azabicyclo[4.3.0]nonene system of type **II** with complete regio- and diastereocontrol.

A series of dienes of type **III** were thus prepared starting from readily available arenes, following the general and straightforward route below (Scheme 3). Birch reduction of biaryls[6] was followed by alkylation with methyl α-chloroacetate leading to dienes **1a**,**b** which were then reduced to

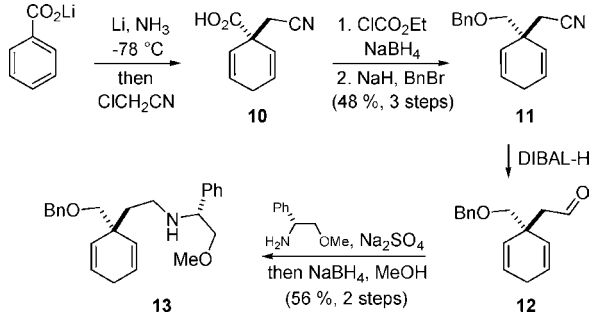
Scheme 3. Preparation of Arylcyclohexa-2,5-dienes **4**−**9**



the corresponding aldehydes **2a**,**b** using DIBAL-H. Reductive amination of **2a**,**b** starting from a range of chiral amines and amino-ethers led to the required secondary amines **4**−**9** with good overall yield over two steps. Chiral phenethylamine (i.e., **3a**), amino-indanol (i.e., **3b**), and phenylglycinol derivatives (i.e., **3c**−**e**) were designed as candidates to test the desymmetrization of our dienes.

The strategy was also applied to the preparation of cyclohexadiene **13** which was obtained through the sequence summarized in Scheme 4. Birch reductive alkylation of

Scheme 4. Preparation of Cyclohexadiene **13**



lithium benzoate led to nitrile **10**.[5a] The carboxylic acid function of **10** was then reduced through its mixed anhydride into the corresponding alcohol, which was protected as a benzyl ether **11**. The nitrile function of **11** was then converted into the aldehyde **12** using DIBAL-H, and reductive amination, as above, led to the chiral secondary amine **13**.

Preliminary investigations regarding the asymmetric hydroamination were carried out using diene **4**. Treatment of the latter with a substoichiometric amount of *n*-BuLi (0.2 equiv) at room temperature in THF led to a cyclized product **14** (not shown, see Supporting Information) in 93% isolated yield but as an inseparable 67:33 mixture of two isomers (vide infra).[7] Anticipating that an additional chelating group on the chiral auxiliary would lead to a more efficient coordination of the lithium cation and provide a better differentiation of the diastereotopic double bonds, we repeated the experiment with derivative **5**, which led to cyclized product **15**, again as a mixture of two isomers in low yield but with a more satisfying 9:1 selectivity (Scheme 5). The best results were finally obtained using phenylglycinol-derived chiral auxiliaries **3c**,**d**. Amine **6** thus led to the cyclized product **16** in excellent yield as a single isomer. Similarly, **9** and **13** led to **17** and **18**, respectively, with ^{1}H and ^{13}C NMR spectra of the crude reaction mixture showing essentially a single isomer.

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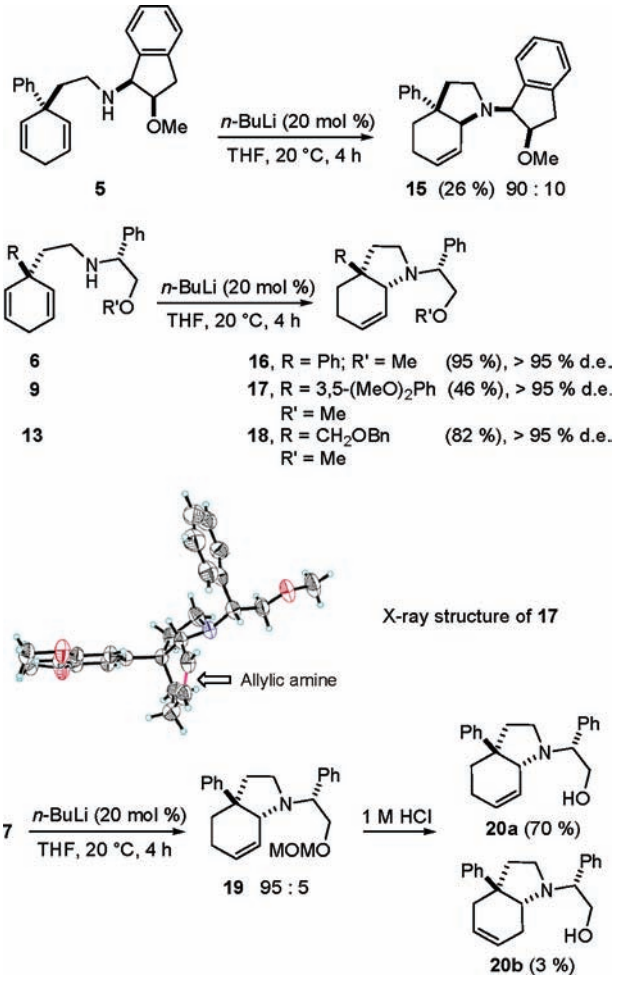
(7) NMR spectra did not allow us to determine at this stage if the two compounds were regio- (position of the double bond) or diastereomers.

Scheme 5. Cyclization of Amines **5**−**13** and X-ray Structure of **17**



Importantly, the structure of **17**, determined through X-ray structure analysis, revealed that the position of the remaining double bond of the cyclohexene moiety was unequivocally that of an allylic amine.[8] In addition, MOM-protected diene **7** produced a cyclized product **19**, again with excellent selectivity, which was then deprotected under acidic conditions to provide the corresponding alcohol **20a** along with a small amount of a second regioisomer **20b**, the structure of which was unambiguously assigned through ^{1}H and 2D NMR studies. The presence of **20b** is important as it provides some useful information regarding the mechanism of this intriguing hydroamination reaction (vide infra). This clearly points toward a more complex mechanism than that originally envisioned, i.e., a simple addition of the amine across one of the diastereotopic double bonds.[9] Finally, treatment of silyl-protected diene **8** did not lead to any cyclized product but returned the starting material.

As a summary, bicyclic amines **16**, **17**, and **19** were obtained in only four steps with excellent overall yield, complete diastereocontrol, and high regiocontrol, starting from simple biaryls. These results have been tentatively rationalized as summarized in Figure 1. The formation of

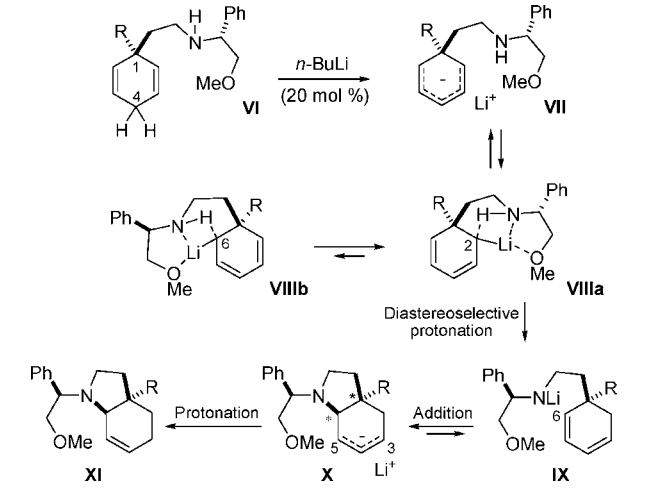


Figure 1. Tentative mechanistic rationale.

an allylic amine as the only isomer in most cases indicates that isomerization of the olefinic system must occur at some stage, i.e., either on the starting diene or on the olefin formed after hydroamination.[10] It was reasoned that isomerization of the olefin left after addition of the amine across the first double bond should be difficult under these mild reaction conditions. Isomerization of the 1,4-dienyl system prior to the hydroamination seemed in contrast more plausible. Estimation of the respective pka's of a secondary amine (pka ∼ 36 in DMSO) and that of the C4-cyclohexadienyl protons (pka ∼ 35 in DMSO)[11] reinforced the hypothesis that removal of both types of protons may take place using *n*-BuLi.[12] Therefore, treatment of dienes **VI** with this strong base may provide a stabilized pentadienyl anion **VII** which would then be protonated intramolecularly at C2 by the chiral secondary amine, with complete stereocontrol through a lithium complex such as **VIIIa** (more favorable than protonation at C6 through **VIIIb**).[13] This would explain the requirement of a coordinating group (OMe) on the chiral auxiliary to provide a tighter lithium chelate, thus ensuring a higher level of selectivity. The resulting lithium amide (**IX**) would then add selectively onto the 1,3-diene at C6 to afford an allylic anion **X**. It is noteworthy that in this hypothesis the Li amide of **IX** now adds onto a conjugated diene which

(8) **16** and **18** exhibit ^{1}H and ^{13}C NMR spectra similar to that of **17** and were thus assigned the same structure.

(9) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795−813.

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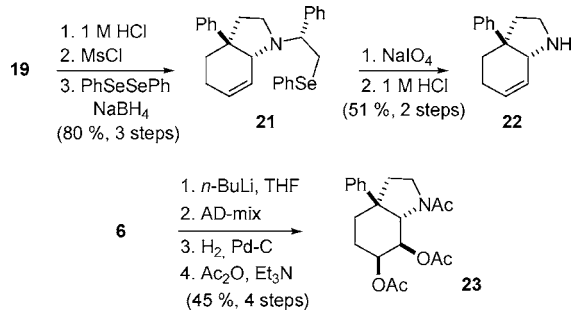
(12) Equilibration between the lithium amide (**VI**, N−Li) and **VII** would also explain the unselective deuterations when using deuterated amine **6**.

(13) An alternative intermolecular protonation through a second equivalent of amine was ruled out, as we observed that intermolecular reaction of related cyclohexadienyl anions with electrophiles (MeI, R_3SiCl, H^+) occurs exclusively at C4. See also: Bates, R. B.; Gosselink, D. W.; Kaczynski, J. A. *Tetrahedron Lett.* **1967**, *8*, 199−204.

should be more favorable under such conditions.[9,14] Hydroamination product **X** can then be protonated at both allylic sites C3 and C5, with a large predominance for the former. Support for such a scenario was provided by the isolation, in a small amount, of the second regioisomer **20b** formed during cyclization of **7** and issued from protonation at C5. The final protonation would then occur with high regioselectivity at the allylic site remote from the N−Aux* moiety, probably for steric reasons. The source of the proton in the last step remains uncertain, as it may originate from either the C4 center or the secondary amine of the starting 1,4-diene **VI** or simply from the solvent.[15]

The chiral auxiliaries may be removed before or after further functionalization of the remaining double bond (Scheme 6). For instance, the MOM protective group of **19**

Scheme 6. Functionalizations of Hydroamination Products



may be removed by an acidic treatment to provide the resulting alcohol which is then converted into the corresponding selenylated derivative **21**.[16] Oxidation of the latter with $NaIO_4$ and hydrolysis of the enamine led to the free amine **22**, albeit in moderate yield. More satisfyingly, dihydroxylation of the olefin **16** (from **6**) then hydrogenolysis of the phenylglycine residue and exhaustive acetylation led to diacetate **23** in good overall yield.[17]

In summary, we reported here on the preliminary investigations on a highly selective tandem diastereoselective protonation−hydroamination of cyclohexa-2,5-dienes. Desymmetrization of dienes **5**−**9** and **13** did not appear to result from a stereoselective addition of an amine across one of the diastereotopic double bonds but more likely from a diastereoselective protonation of a pentadienyl anion.

This series of very selective processes including a deprotonation−diastereoselective protonation−addition−protonation sequence (Figure 1), simply mediated by a substoichiometric amount of *n*-BuLi, is remarkable and affords highly functionalized substrates in excellent and reproducible yields, from easily available arenes. The BRAD strategy thus provides access to useful bicyclic amines, key fragments in various naturally occurring alkaloids. This study also underlines the utility of the atom-economical hydroamination of olefins and nonconjugated dienes. Work is now in progress to obtain a better understanding of the mechanism and the origin of the selectivity of the protonation process. Application of the method to the total synthesis of crinine-type alkaloids is also ongoing.

Acknowledgment. We gratefully acknowledge the CNRS, MENRT (grant to R.L.), the Institut Universitaire de France, and COST-D28 for financial support.

Supporting Information Available: Detailed experimental procedures and spectral and analytical data for all dienes and cyclized products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411−3414.

(17) **23** was obtained as a mixture of two conformers in solution.