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Regioselectivity of Birch Reductive Alkylation of Biaryls†

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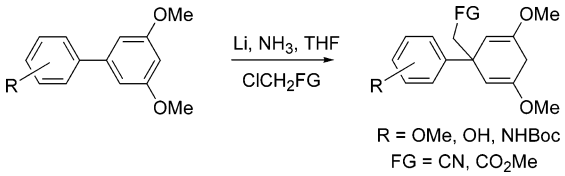
ABSTRACT

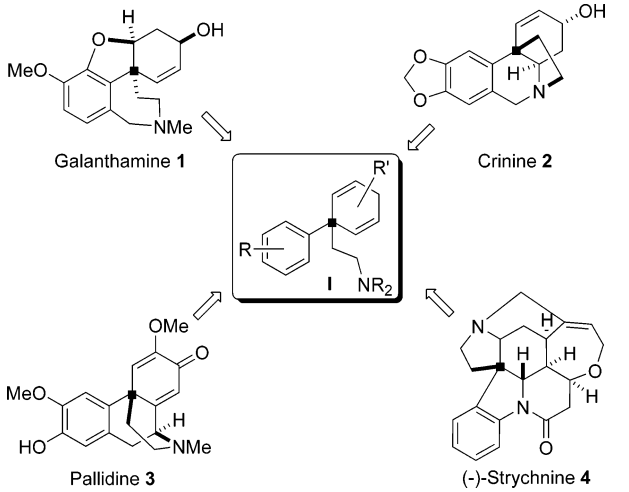


The regioselectivity of the Birch reductive alkylation of polysubstituted biaryls has been investigated. Results indicate that regioselectivity is affected by the electronic nature of substituents on both aromatic rings. The electron-rich 3,5-dimethoxyphenyl moiety is selectively reduced and then alkylated, while phenols and aniline are not dearomatized under these conditions. Biaryls possessing a phenol moiety are alkylated on the second ring, providing that the acidic proton has been removed prior to the Li/NH_3 reduction.

Galanthamine and crinine alkaloids **1** and **2** isolated from Amaryllidaceae[1] and morphine alkaloids such as **3**[2] or strychnine **4**[3] are all made up of an arylcyclohexane moiety connected to an ethylamino chain through a quaternary stereocenter (marked ■) (Scheme 1). These natural products possess a wide range of biological activity and have been the subject of intense research for many years. In the course of our continuing interest in desymmetrization processes,[4] we envisaged a general strategy to access these different classes of alkaloids on the basis of the desymmetrization of arylcyclohexa-2,5-dienes of type **I**.[5]

It was anticipated that these building blocks could be prepared through a Birch reductive alkylation[6] of a suitably substituted biaryl precursor. While the Birch reduction of biaryl compounds has been well studied,[7] the corresponding Birch reductive alkylation has been relatively unexplored.[8] This probably stems from the lack of regioselectivity that could be predicted from Li/NH_3 reduction of unsymmetrical biaryls and by the difficulty in controlling alkylation vs protonation of the resulting carbanion. We thus carefully

Scheme 1. Arylcyclohexa-2,5-diene Core of Several Alkaloids



† Dedicated to Prof. Michel Pereyre on the occasion of his 65th birthday.

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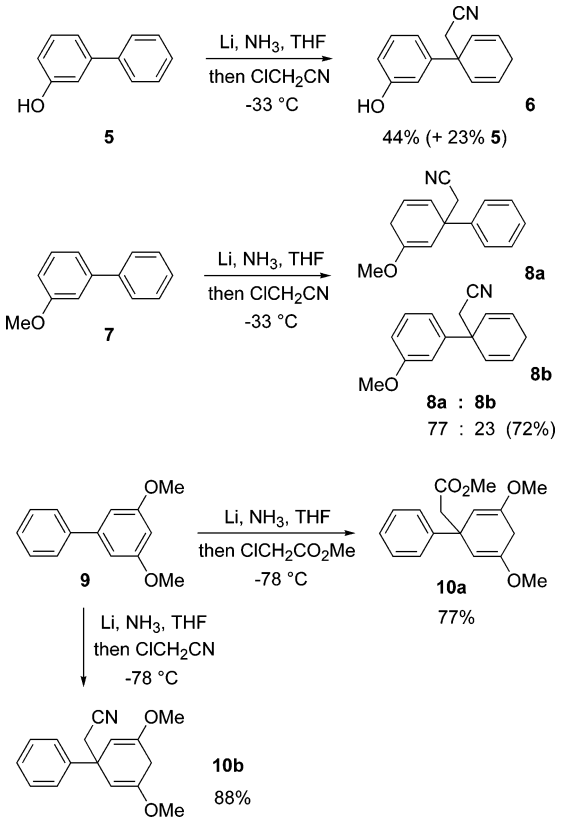
examined the scope of such reductive alkylations through a general survey of the conditions that could allow for both a control of the alkylation vs protonation processes and the regioselectivity of the reduction. We report here our preliminary studies on this regioselective Birch alkylation of biaryls and the utility of this strategy to access alkaloids of the crinine family.

We envisioned that a careful choice of the nature of R and R′ substituents on the biarylic precursor of **I** (Scheme 1) would allow the regioselective reduction of one arene over the other. We thus investigated first the reduction of biaryls having only one substituted arene (Scheme 2). Reduction of

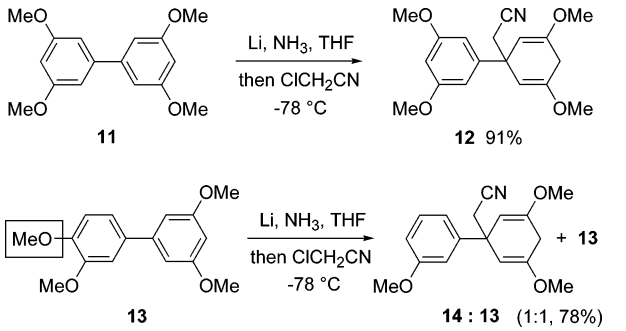
Scheme 2. Birch Reductive Alkylation of Biaryls with One Substituted Arene



commercially available biphenyl **5** was carried out in Li/NH_3 at −33 °C. Reduction occurred regioselectively on the unsubstituted ring to provide the alkylated product **6**, albeit in a moderate 44% yield (along with 23% recovered **5** and some polymeric byproducts). The same reaction carried out on the methylated analogue **7** led to a 77:23 mixture of alkylated products **8a**,**b**, with the reduction and alkylation occurring predominantly on the methoxy-substituted ring. It is interesting to note that these results are in line with the relative reduction rates of simple monosubstituted arenes, which follow the order ArOMe > ArH > ArOH.[6a,9] We then carried out the reduction on biaryl **9**[10] bearing two methoxy groups and found that reduction occurred in high yield with complete regiocontrol, leading to symmetrical diene **10a**,**b**, irrespective of the nature of the electrophile.

The above studies were then extended to the reduction/alkylation of biaryls having a 3,5-dimethoxyphenyl group, the other aromatic ring being substituted with hydroxy and methoxy groups (Scheme 3). As expected, Birch reduction

Scheme 3. Birch Reductive Alkylation of Polysubstituted Biaryls



of biaryl **11** led to the alkylated product **12** in high yield. In comparison, biaryl **13** produced an inseparable mixture of alkylated product **14** (which also lost a methoxy group) and starting material in a 1:1 ratio (^{1}H NMR). This indicates that electron transfer followed by protonation is not regioselective in this case, occurring both on 3,4- and 3,5-dimethoxyphenyl rings.

Methoxy groups ortho or para to an activating group (here the second arene) are known to be good leaving groups under such reaction conditions. It was thus decided to replace the *p*-OMe group in **13** by a OH group, which should be a poorer leaving group.[6] This proved to be the case since phenols **15** and **17** led to exclusive reduction on the 3,5-dimethoxyphenyl ring, but with no or only partial alkylation (Scheme 4). For instance, **15** led to 38% of alkylated product **16**, along with 51% of the reduced diene (not shown), while **17** led only to the reduced product in 51% yield and recovered starting material (21%). The large amount of reduced product is attributed to the protonation of the carbanionic intermediate by the acidic phenolic proton, protonation thus competing with alkylation (*vide infra*).[11] This problem was eventually solved by performing Li/NH_3 reduction on biaryls **15** and **17**, after prior deprotonation of the phenol with *n*-BuLi (1.1 equiv). Under these conditions, Birch reductive alkylation

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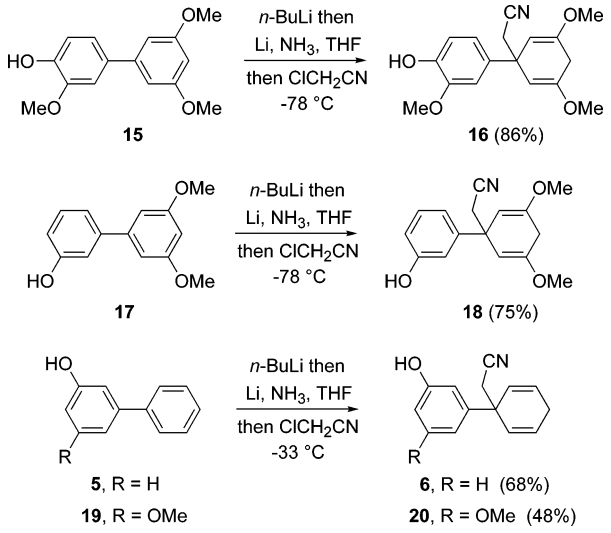
(9) The relative rates of reduction of two separate arenes may differ from the order observed if these arenes were conjugated.

(10) Biaryls **13** and **23** were prepared using a Suzuki coupling. Biaryls **15**, **17**, **21a**,**b** having a 3,5-dimethoxyphenyl moiety are more conveniently prepared on a large scale using a four-step one-pot sequence (see the Supporting Information).

(11) Addition of excess lithium (3.3 equiv) led to the same result.

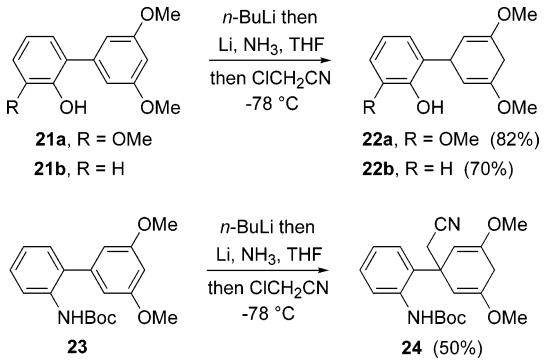
Scheme 4. Birch Reductive Alkylation of Biaryls with a *m*- or *p*-Phenol Group



occurred smoothly at −78 °C, producing the desired dienes **16** and **18** in excellent yields (Scheme 4). Interestingly, under these conditions, phenol **19** also led to alkylated product **20**, albeit in a modest 48% yield. This last example demonstrates that it is possible, through a careful tuning of the nature of the substituents on the aromatic ring, to alkylate selectively the substituted arene (as in **10b**) or the unsubstituted one (as in **20**), starting from closely related biaryls **9** and **19**, respectively. This simple protocol is also of interest as it provides a ready access to dienes such as **16**, which are precursors of pallidine **3** and other morphine analogues.

While this protocol was found efficient and reproducible with phenol in meta and para positions relative to the biaryl linkage, such was not the case with *o*-phenols, which were reduced in good yields but were reluctant to undergo further alkylation (Scheme 5). For instance, *o*-phenol **21a** and **21b**

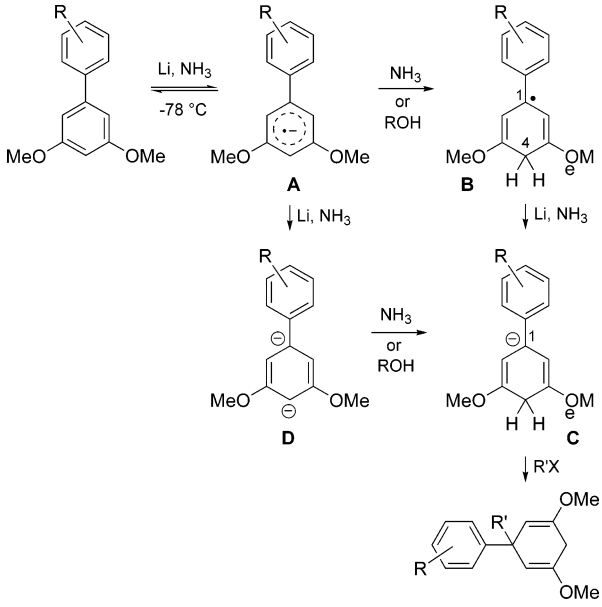
Scheme 5. Birch Reductive Alkylation of Biaryls with *o*-Phenol or Amino Groups



led to the reduced diene **22a** and **22b** in excellent yield after deprotonation with 1.1 equiv of *n*-BuLi. In sharp contrast, *N*-Boc-protected *o*-aminobiaryl **23** led, under the same conditions, to the alkylated diene **24** in reasonable yield, along with some reduced product (∼20%).

These results may be rationalized following the mechanism summarized in Scheme 6. Regioselectivity in Birch reduction

Scheme 6. Tentative Mechanistic Rationale of the Birch Reductive Alkylation of Biaryls



is determined during the first step, involving protonation of the radical anion **A**, formed through electron transfer from Li to the biaryl system, and during the second protonation of the cyclohexadienyl anion **C**. In line with kinetic studies and calculations by Zimmerman et al.,[12] we propose that protonation occurs first at the site of highest electron density (C4) to provide the most stable radical species **B**. This would explain the tendency to transfer electrons regioselectively to the most electron-rich arene, which is also more proficient at stabilizing a radical species. A second transfer of electron onto **B** would then lead to carbanion **C**, which may then be alkylated. In the presence of a better source of proton than NH_3 (i.e., phenol or NHR), protonation of **C** contends with alkylation to provide reduced products (R′ = H). Without any proton source, ammonia is too weak an acid to protonate the benzylic carbanion and alkylation may ensue. Formation of a dianion intermediate **D** has also been proposed in the Birch reduction of biaryls and should not be ruled out.[13] In this case, protonation of **D** could also occur at (C4) to provide the most stable anion **C**.

Finally, reduction during Birch reduction of biaryls possessing an *o*-phenol substituent (i.e., **21a**,**b**) may result from an increase in the basicity of carbanion **C** due to an oxanion−carbanion repulsion.[14] Successful reductive alkylation of

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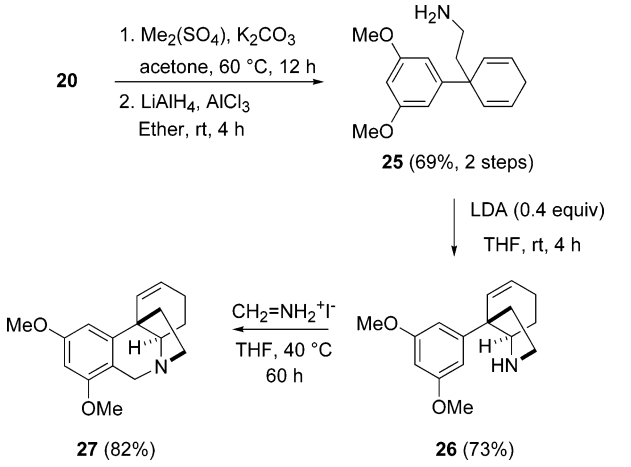
Scheme 7. Access to Crinine-Type Alkaloids



biaryl **23** would support such a hypothesis as, in this case, delocalization of the nitrogen negative charge on the Boc carbonyl function would reduce this repulsion and thus allow the alkylation. A subtle change in the structure of the starting biaryl (ortho vs meta OH group) thus makes the anion **C** resistant (or not) to protonation by NH_3. Our attempts to carry out Birch reductive alkylation on **21a**,**b** without ammonia have so far been unsuccessful.

We finally established the utility of this strategy for the synthesis of alkaloids such as those depicted above (Scheme 1) through a rapid access to a crinine analogue **27**, starting from diene **20** (Scheme 7). The phenol group of **20** was first protected and the cyano group reduced using $LiAlH_4-AlCl_3$ to produce **25** in good overall yield. The piperidine ring of the crinine skeleton was easily assembled through olefin hydroamination using a catalytic amount of LDA.[15] This produced the desired intermediate **26** as a single isomer, which was then directly submitted to Pictet−Spengler cyclization using Echenmoser's salt,[16] affording **27** in five steps and 20% overall yield from biaryl **19**.

In summary, we report here on the preliminary investigations on regioselective Birch reductive alkylation of biaryls. The reactivity profile of a series of biarylic systems has thus been established, demonstrating that reduction of poorly activated arenes can be followed by alkylation through a careful choice of substituents. This is to our knowledge the first Birch reductive alkylations of polysubstituted biaryls. This complements nicely the well-known Birch reductive alkylation of benzoic and heterocyclic esters and amides.[17] The process is applicable to a large variety of biarylic systems and is readily amenable to large scale synthesis. This strategy can offer a rapid entry toward useful building blocks for the synthesis of alkaloids. Desymmetrization of these dienes is actively pursued in our laboratory and will be reported in due course.

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

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(14) A loss of conjugation between the benzylic carbanion at C1 and the neighboring arene due to a non planarity of the system may also increase the basicity of the carbanion.

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