Synthesis K. Koide Short Review

Mechanistic and Synthetic Studies of Biaryl Birch Reductions

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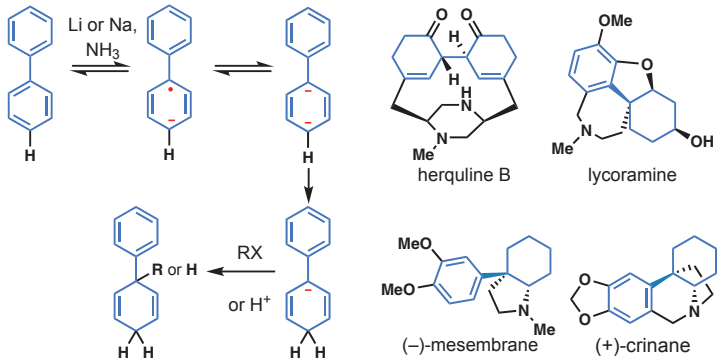

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Abstract The Birch reduction of biaryls generally converts one of the two arenes into a cyclohexa-1,4-diene. Biaryls are more reactive than monocyclic arenes under the Birch conditions. Unlike the reduction of monocyclic arenes, biaryl reduction proceeds through two consecutive electron transfer steps before the protonation of the dianion intermediate. The biaryl reductions and subsequent alkylations in one pot rapidly increase the molecular complexity and thus have been used in the synthesis of natural products and drug-like molecules.

Key words lithium, sodium, reduction, electron transfer, Birch, biphenyl, cyclohexa-1,4-diene

Kazunori Koide obtained his bachelor's and master's degrees from the Department of Pharmaceutical Sciences at the University of Tokyo (Professor Masaji Ohno's group). He then received his Ph.D. in chemistry at the University of California, San Diego (Professor K. C. Nicolaou's group). He conducted post-doctoral research in the Department of Chemistry and Chemical Biology at Harvard University (Professor Gregory Verdine's group). He has been a faculty member at The University of Pittsburgh since 2000.

1 Introduction

The Birch reduction converts arenes **A** into cyclohexa-1,4-dienes **C**, which is mediated by Li(0), Na(0), or K(0) in liquid ammonia (NH_3) (Scheme 1).[1,2] The first electron transfer to the arene substrates **A** to form radical anion $\mathbf{A}^{\bullet-}$ is reversible. Except when R = electron-withdrawing group (e.g., CO_2H), the second electron transfer to generate dianion $\mathbf{A}^{2-}$ does not take place. Instead, exogenous alcohol protonates the radical anion $\mathbf{A}^{\bullet-}$ to give the radical species **B**, which accepts the second electron to form the protonated monoanion $\mathbf{B}^{-}$. Finally, an aqueous workup, often with NH_4Cl, affords cyclohexa-1,4-dienes **C**.

The Birch reduction of biaryls proceeds through a different pathway, as detailed in Section 2, and can be a powerful platform for synthesizing complex polycyclic molecules (Section 6). Rabideau published a review article on the Birch reduction of biaryls in 1988,[3] but there has not been a follow-up review article since then. Now that various cross-coupling technologies make the biaryl substrates more readily accessible,[4–6] this may be a good time to review the subject.

2 The Physical Organic Chemistry of the Birch Reduction of Biaryls

As Scheme 2 shows, it is more thermodynamically favorable to add the first electron to biphenyl **1** than to benzene due to the resonance stabilization of the radical anion $\mathbf{1}^{\bullet-}$.[7] Notably, even the second electron transfer in the biphenyl system is more favorable (–3.18 eV versus –3.35 eV)

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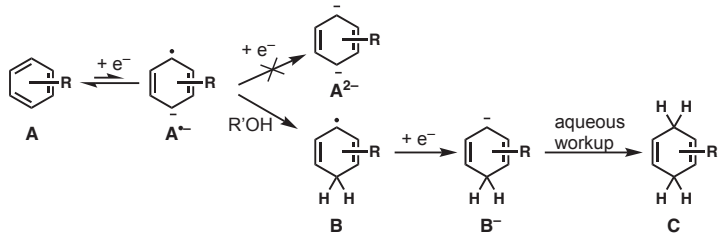
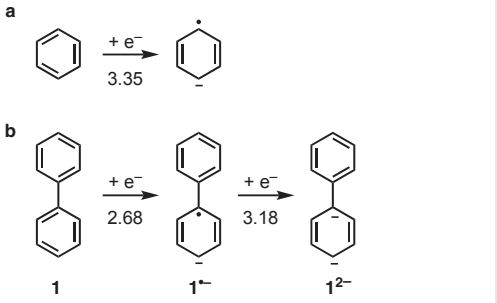
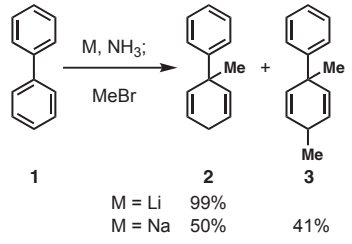


Scheme 1 General pathway for the Birch reduction of arenes



Scheme 2 Redox potentials $-E°$ (V) in $MeNH_2$ and $^nBu_4NBr$



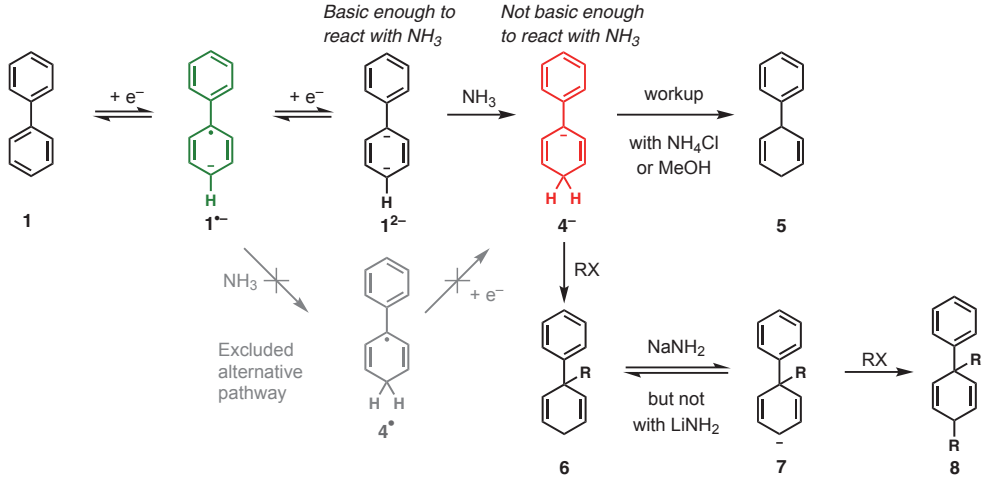
Scheme 3 Birch reductive methylation of biphenyl with Li and Na

than the first in benzene.[7] Therefore, when Li(0) or Na(0) is used in excess without alcohol, biphenyl is converted into dianion **1**$^{2-}$ during the Birch reduction.

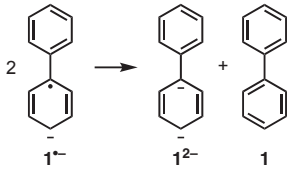
The Harvey group treated biphenyl with Li(0) in liquid ammonia followed by MeBr to afford **2** in 99% yield (Scheme 3).[8] With Na(0), the major products were **2** in 50% yield and a mixture of *cis*- and *trans*-**3** in 41% yield.

The authors proposed the pathways depicted in Scheme 4; the formation of the protonated monoanion **4**$^-$ (red solution) proceeds via the generation of the highly basic dianion **1**$^{2-}$. Radical anion **1**$^{\bullet-}$ (green solution) is not basic enough to abstract a proton from NH_3 to form the protonated radical species **4**$^\bullet$. When NH_4Cl or alcohol is added during the workup, 1,4-dihydrobiphenyl **5** is formed. When an alkyl halide (RX) is added, the *ipso*-alkylated product **6** is formed. With $NaNH_2$, this product may be deprotonated, and the resulting anion **7** may react with the alkyl halide to form dialkylated product **8**.[8] The reactivities and stabilities of radical anion **1**$^{\bullet-}$, dianion **1**$^{2-}$, and anion **4**$^-$ were inferred from studies by the Hoijtink and Argabright groups.[9,10]

The Guijarro group analyzed the spectroscopic data of $[Li^+(THP)_4][BPh^{\bullet-}]$ and suggested the disproportionation of **1**$^{\bullet-}$ into **1**$^{2-}$ and biphenyl (Scheme 5).[11] However, this experiment was performed under ammonia-free conditions.



Scheme 4 Pathways for the Birch reduction of biphenyl



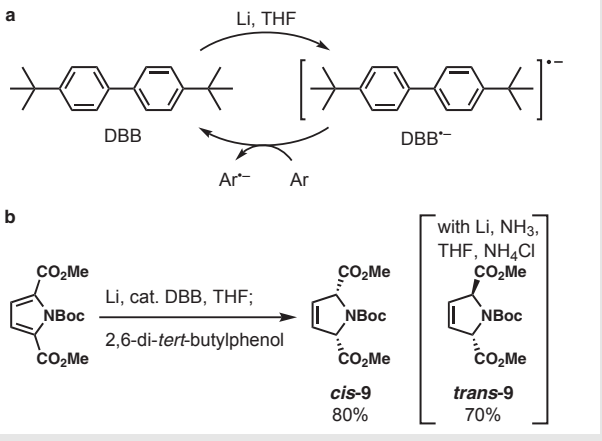
Scheme 5 Disproportionation of biphenyl radical anion

Therefore, it is unclear whether this is relevant in synthetic organic chemistry.

In summary, the mechanism for the Birch reduction of biphenyl is more complex than that of benzene. When substituted biaryls are used as substrates, the regioselectivity is poorly understood.

3 Biaryls as the Mediators of Electron Transfer

The Donohoe group employed 4,4′-di-*tert*-butylbiphenyl (DBB) as a mediator of electron transfer to perform the Birch-type reduction of electron-deficient arenes (Scheme 6a).[12] The Compton and Donohoe groups showed that the activation energy for biaryls is substantially lower than for other arenes.[13] The same two groups studied substituent effects on biaryls as mediators of electron transfer.[14] Their system implies challenges and opportunities associated with substrates that contain a biaryl and other potential electron acceptors in synthesis. One of the synthetic applications is shown in Scheme 6b; while the traditional Birch reduction of dimethyl *N*-(*tert*-butoxycarbonyl)pyrrole-2,5-dicarboxylate provided *trans*-**9**, Donohoe's method generated *cis*-**9** in 80% yield.[15]



Scheme 6 Donohoe's Birch reduction method that uses 4,4′-di-*tert*-butylbiphenyl as a mediator of electrons

4 Methods for the Dissolving-Metal Reduction of Biaryls

In 1956, Hückel and Schwen reported that the Birch reduction of biphenyl (**1**) with Na(0) in liquid ammonia produced 1,4-dihydrodiphenyl (**5**) as the major product.[16] Before more advanced NMR techniques became available, it was not trivial to distinguish between 1,4-dihydrodiphenyl (**5**) and 2,5-dihydrobiphenyl (**10**) (Figure 1). In 1968, chemists at Eastman Kodak Company established a spectroscopic method to unambiguously determine the structures of the Birch reduction products of biphenyl.[17] This was key to the structural elucidations of the biaryl Birch reduction products in the early years.

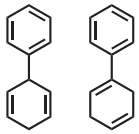
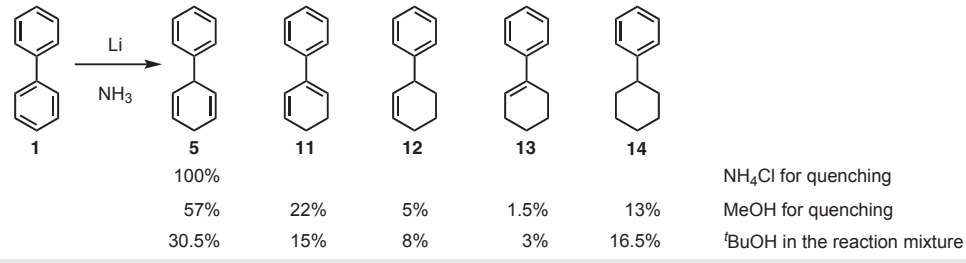


Figure 1 Structures of two dihydrobiphenyls

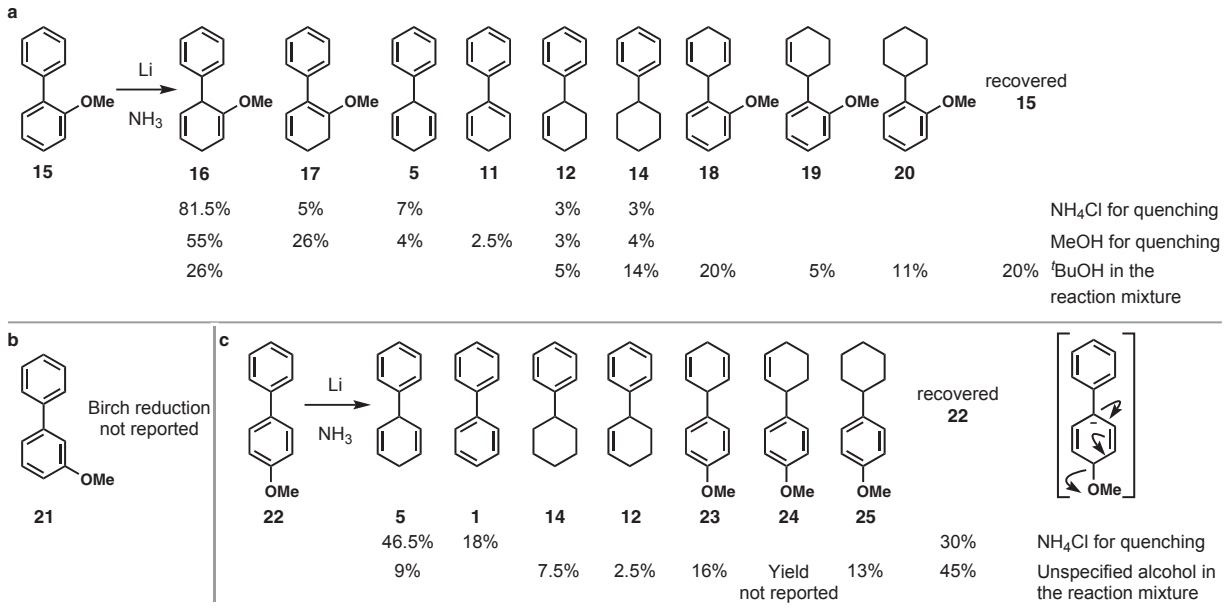
Birch and Nadamuni investigated the effects of proton sources; the conversion of biphenyl into 1,4-dihydrobiphenyl (**5**) was the most efficient when NH_4Cl was added after the substrate was consumed, yielding **5** in 100% (Scheme 7). Quenching the reaction mixture with MeOH generated **5** in 57% yield. This quenching protocol produced methoxide, which would reversibly deprotonate the allylic hydrogen to form the more stable compound 3,4-dihydrobiphenyl (**11**) in 22% yield. The conjugated diene is more prone to reduction, which accounts for the formation of tetrahydro products **12** and **13** in 5% and 1.5% yields, respectively. The latter would be further reduced to cyclohexylbenzene (**14**) in 13% yield. The presence of ^{t}BuOH in the reaction mixture produced **5** in ~31% yield.[18] As shown in Scheme 7, the distribution of byproducts was similar to quenching with MeOH.

When the Birch reduction of 2-methoxybiphenyl (**15**) was quenched with NH_4Cl or MeOH (Scheme 8a), the trend of product distribution was similar to Scheme 7.[18] For electron-rich biaryls like **15**, it is unknown whether the radical anion intermediate accepts the second electron (see Scheme 4) or is basic enough to deprotonate NH_3. The Birch reduction of 3-methoxybiphenyl (**21**) (Scheme 8b) has not been reported. The Birch reduction of 4-methoxybiphenyl (**22**) (Scheme 8c) remains challenging, with the substantial loss of the methoxy group.[18]

The Birch reduction of 2-fluorobiphenyl (**26**) has not been reported (Scheme 9a). The Rabideau group showed that the treatment of 3-fluorobiphenyl (**27**) with Na(0) in Et_2O/NH_3 could afford the corresponding Birch-type product **28** (yield not reported; Scheme 9b), whereas that of 4-fluorobiphenyl (**29**) resulted in the loss of fluoride, leading to products **1** and **5** (yields not reported; Scheme 9c).[19]



Scheme 7 The effects of quenching methods for the Birch reduction of biphenyl

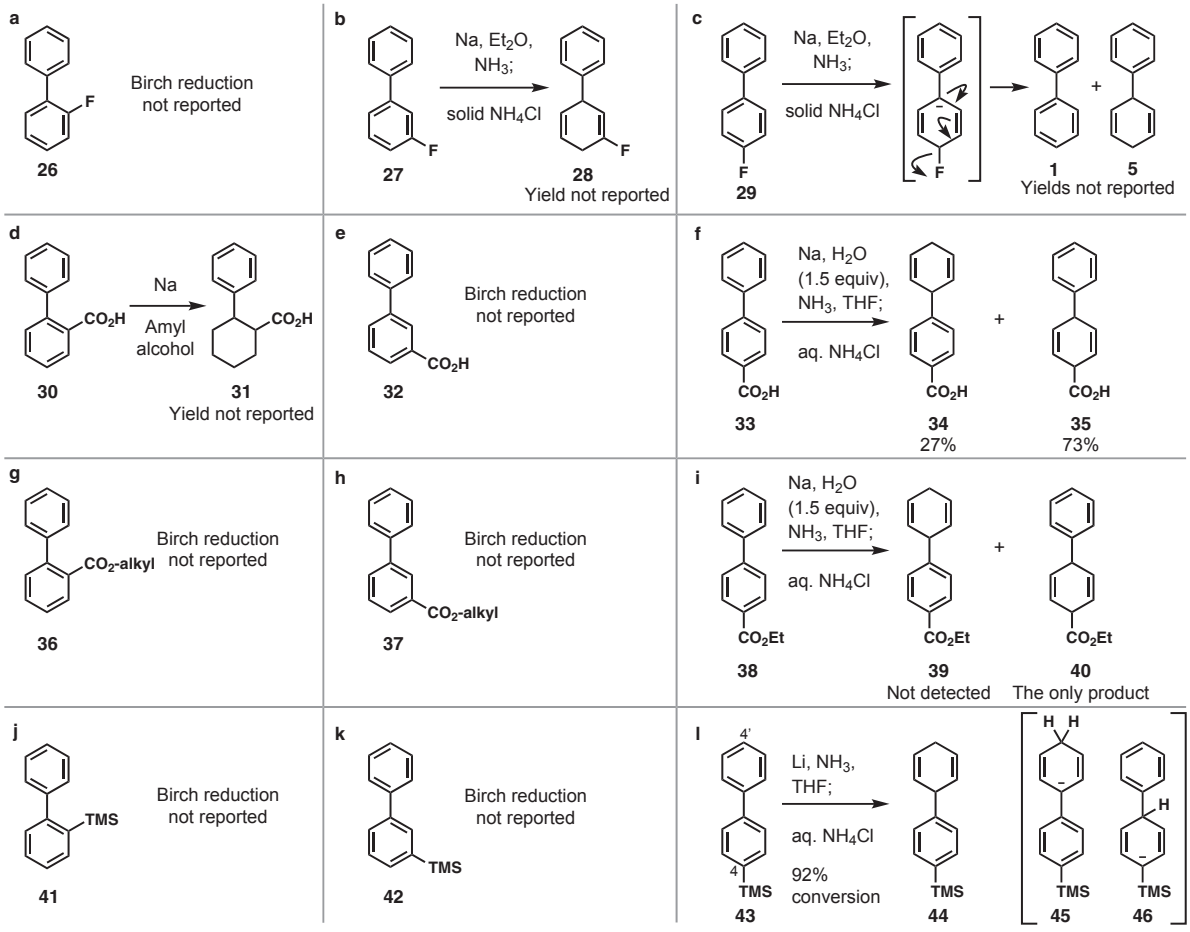


Scheme 8 The Birch reductions of 2-, 3-, and 4-methoxybiphenyls

Biphenyl-2-carboxylic acid (**30**) was treated with Na(0) in amyl alcohol (no ammonia) to produce the cyclohexyl product **31** (yield not reported; Scheme 9d).[20] The Birch reduction of biphenyl-3-carboxylic acid (**32**) (Scheme 9e) has not been reported. The Rabideau group disclosed that while the reduction of biphenyl-4-carboxylic acid (**33**) (Scheme 9f) afforded acids **34** and **35** in 27% and 73% yields, respectively, the reduction of the corresponding ethyl ester **38** generated only **40** (yield not reported; Scheme 9i).[21] It is unclear whether they obtained acid **35** and ester **40** as a mixture of 1,4-*cis* and 1,4-*trans* products. The Grossel group published somewhat contradictory results,[22] but the Rabideau group later showed that the Grossel group generated different results due to different aqueous workups.[23] The Birch reductions of esters **36** (Scheme 9g) and **37** (Scheme 9h) have not been reported, although their reductive alkylations will be discussed below (see Scheme 14).

There is no report on the Birch reductions of 2-(trimethylsilyl)biphenyl **41** (Scheme 9j) and 3-(trimethylsilyl)biphenyl (**42**) (Scheme 9k). The Rabideau group reported that when 4-(trimethylsilyl)biphenyl (**43**) was treated with Li(0) in NH_3/THF, the TMS-bearing aryl ring was intact, giving dihydrobiphenyl **44** as the sole product (Scheme 9l).[24] The authors proposed two plausible reasons; the first being the protonated anion **45** is more stable than the regioisomer **46**, leading to **44**. The second possibility is that the dianion gets protonated at the 4′-position faster than at the 4-position, generating **45**.

In summary, because the mechanism for the Birch reduction of substituted biaryls is poorly understood, it remains challenging to predict the chemo- and regioselectivity for the Birch reductions of these substrates. Scheme 8 and Scheme 9 show that many gaps exist with respect to the systematic studies on substrates to develop predictive models.



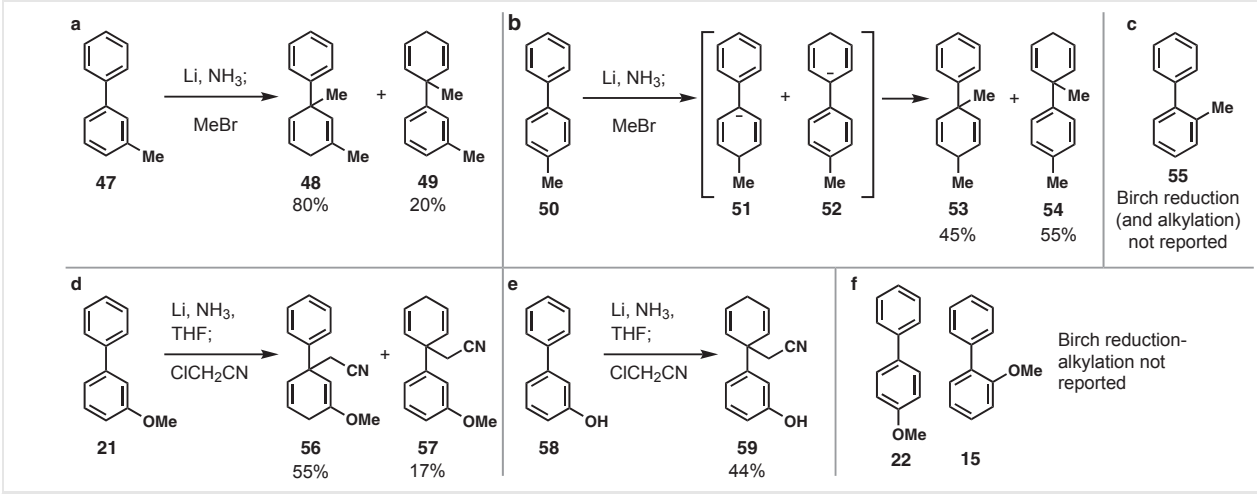
Scheme 9 The Birch reductions of monosubstituted biphenyls

5 Intercepting the Biaryl Reduction Intermediates with Electrophiles

The alkylation of biphenyl dianion $\mathbf{1}^{2-}$ (Scheme 4) under ammonia-free conditions proceeds via an S_N2 mechanism.[25] With ammonia, protonated monoanions $\mathbf{4}^{-}$ (Scheme 4) react with alkyl halides presumably via an S_N2 mechanism as well. The Rabideau group investigated the Birch reduction of methyl-substituted biphenyls and trapped intermediates with MeBr. The major product for the reductive methylation of 3-methylbiphenyl (**47**) was the *ipso*-methylation product **48** (Scheme 10a). Of particular interest was the reductive methylation of 4-methylbiphenyl (**50**) (Scheme 10b). Although the protonated anion **52** was believed to be less stable than anion **51** because the methyl group destabilizes **52**, the corresponding methylated product **54** was produced in 55% yield. The reversible formation of **51** and **52** and the higher reactivity of anion **52** might account for this result.[26] 2-Methylbiphenyl (**55**) (Scheme 10c) has not been reported as a Birch reduction substrate.

3-Methoxybiphenyl (**21**) was reductively alkylated on the anisole ring to form **56** as the major product (Scheme 10d). The corresponding hydroxy-substituted substrate **58** was alkylated on the non-substituted ring to form **59** in 44% yield (+ 23% starting material) (Scheme 10e).[27] The reductive alkylations of **22** and **15** have not been reported (Scheme 10f).

Inspired by the natural products in Figure 2, the Landais group expanded the synthetic utilities of reductive alkylations by introducing various functional groups in the biphenyls.[27] For example, after the phenolic hydroxy group of **60** (Scheme 11a) was deprotonated with ^{n}BuLi to protect the phenol ring from being reduced, the resulting phenoxy intermediate was treated with Li(0) in NH_3 and THF. The resulting anion **61** was then treated with $ClCH_2CN$ to form the corresponding alkylated compound **62** in 86% yield.[27,28] Nitrile **64** was prepared similarly and was further elaborated to afford crinine-like compound **65** in four steps (Scheme 11b).[27] Biaryl **66** could be reductively alkylated with $ClCH_2CN$ or $ClCH_2CO_2Me$ to form **67** or **68** in 88% or 77% yield (Scheme 11c). Scheme 11d shows other electrophiles examined by the same group.[28]



Scheme 10 Reductive alkylations of substituted biphenyls

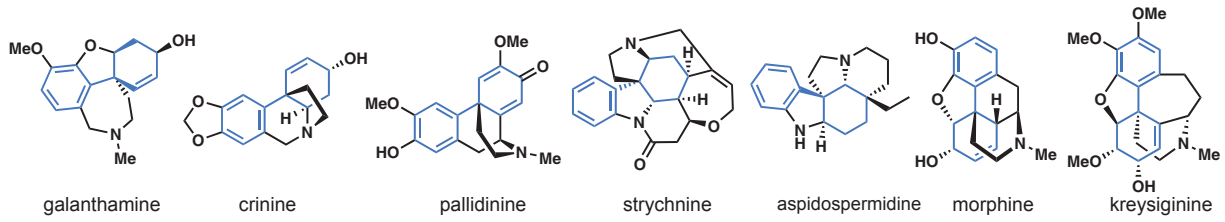
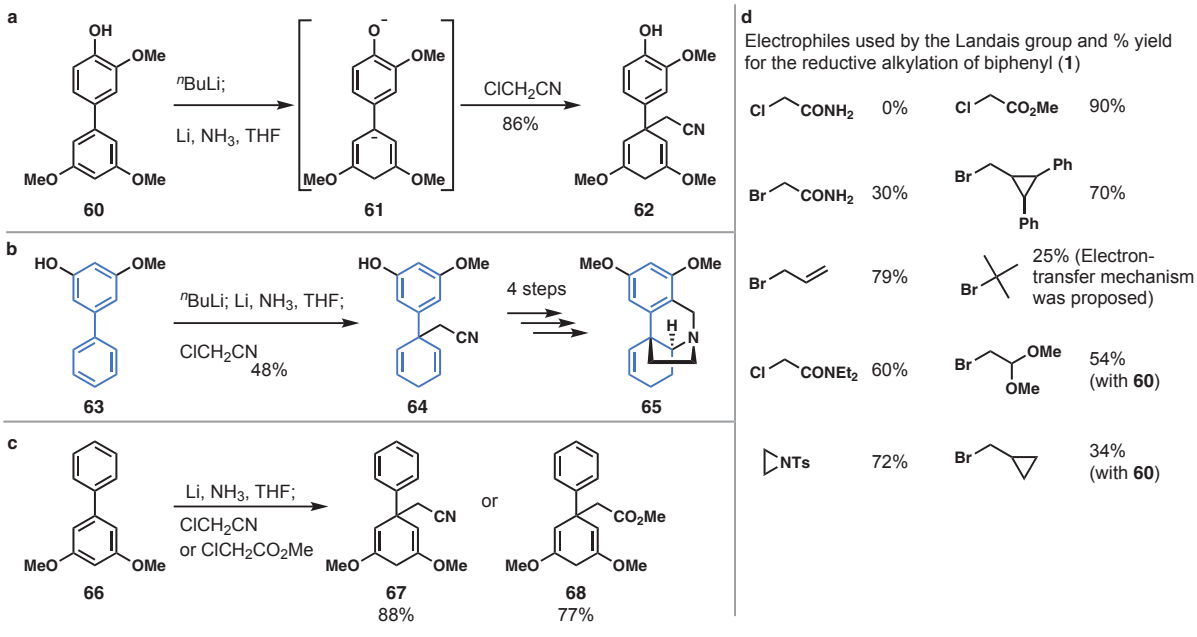
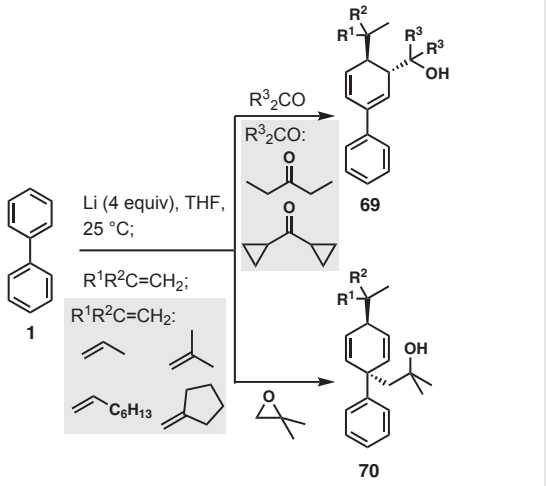


Figure 2 Structures of natural products that may be synthesized by the Birch reductions of biaryls



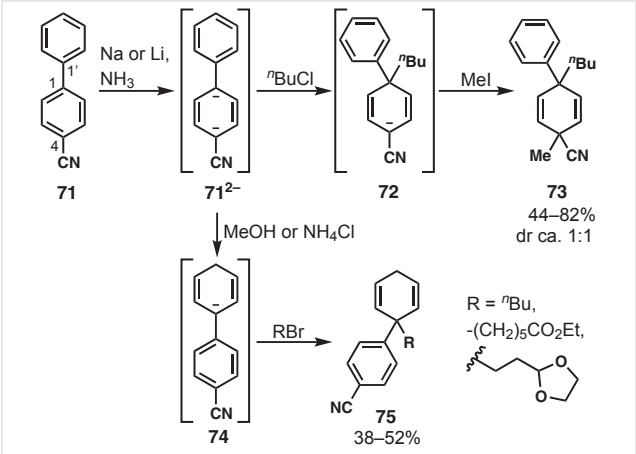
Scheme 11 Birch reductive alkylations of functionalized biphenyls with chloroacetonitrile and other electrophiles

The Yus group reported the surprising reactivity of a dianion intermediate under ammonia-free conditions; the dianion of biphenyl first reacted with terminal alkenes, and the resulting monoanion reacted with ketones or an epoxide (Scheme 12).[29,30] It should be noted that ketones reacted at the *meta* position and the epoxide at the *ipso* position to form **69** and **70**, respectively. The only biaryl substrate was biphenyl in their work, and the generality of their chemistry remains to be seen.



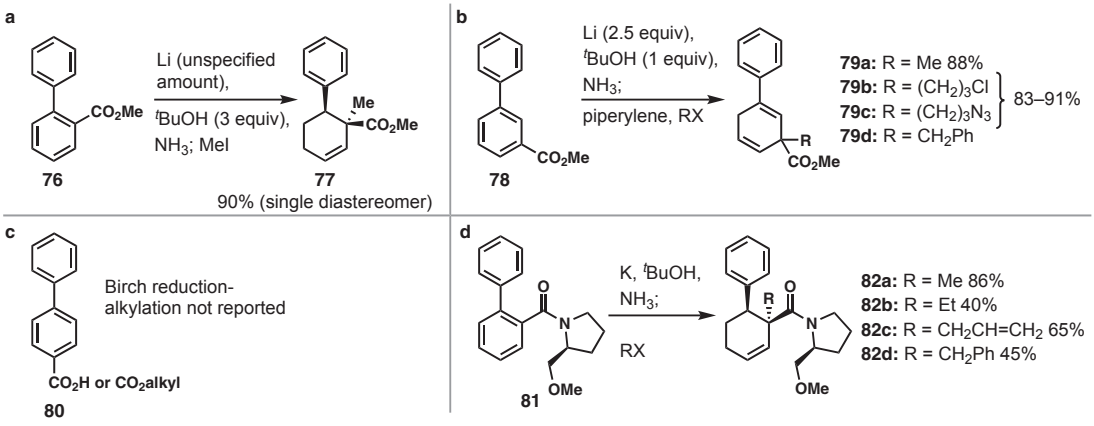
Scheme 12 Double additions of dianion prepared by the Birch-type reduction of biphenyl without ammonia

The Peshkov group studied the reductive mono- and dialkylations of biphenyl-4-carbonitrile (**71**) (Scheme 13). The dianion of biphenyl-4-carbonitrile **71**$^{2-}$ could be stored for days in the reaction mixture. The first equivalent of alkyl chloride reacted at the *ipso* position to form **72**, and the second electrophile needed to be more electrophilic because the monoanion intermediate **72** was not sufficiently nucleophilic toward alkyl chlorides. Methyl iodide reacted at the *para* position to produce the dialkylated product **73** in 44–82% yields as a mixture of diastereomers.[31] When the dianion was mono-protonated by MeOH or NH_4Cl, the resulting protonated monoanion **74** reacted with alkyl bromides at the *ipso* position of the other phenyl group to form **75** in 38–52% yields.[31]



Scheme 13 Birch reductive alkylations of biphenyl-4-carbonitrile

The Schultz group showed that methyl biphenyl-2-carboxylate (**76**) could be reductively methylated to form **77** in 90% yield as a single diastereomer (Scheme 14a).[32] Methyl biphenyl-3-carboxylate (**78**) was converted into **79a–d** when only 2.5 equiv of Li were used without reducing the cyclohexa-1,4-diene ring (Scheme 14b).[33] The Birch reduction-alkylation of *para*-substituted biaryl **80** has not been reported (Scheme 14c). Biphenyl-2-carboxamide **81** bearing a chiral auxiliary was reductively alkylated to generate **82a–d** in 40–86% yields (Scheme 14d).[32]

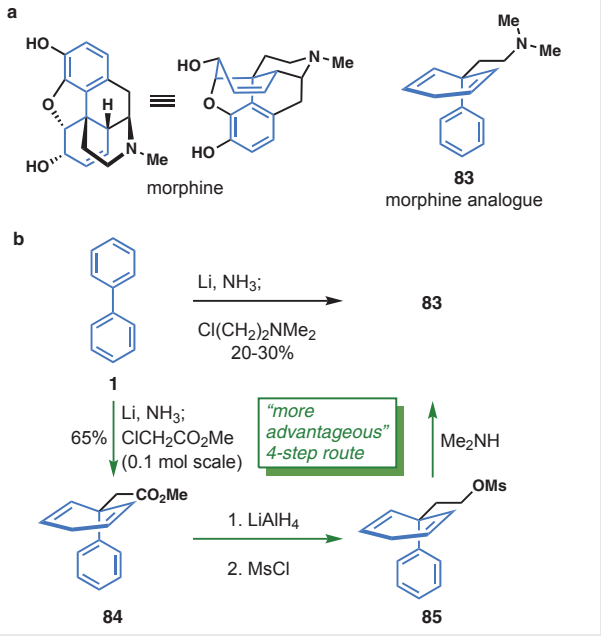


Scheme 14 Birch-reduction alkylations of biphenyls bearing carbonyl groups

In summary, for traditional Birch reductions (i.e., in liquid ammonia), the reductive alkylations of biaryls mainly occur at the *ipso* position. However, the regioselectivity often depends on reaction conditions, substituents, and electrophiles. Further studies are needed to develop a predictive model.

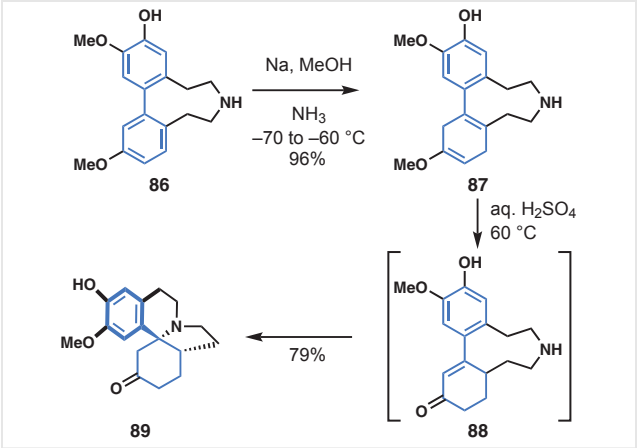
6 Synthetic Applications of the Dissolving-Metal-Mediated Reductions of Biaryls

Müller and Pfister hypothesized that amine **83** might mimic the biological effects of morphine's analgesic activity (Scheme 15a). Although the reductive alkylation of biphenyl with 2-chloro-*N*,*N*-dimethylethylamine gave the target amine **83** in one step in 20–30% yield (Scheme 15b), they stated that the alternative four-step sequence was more advantageous (the rationale was not provided).[34] The first step, the Birch reduction-alkylation reaction, was performed on a 0.1-mole scale to form ester **84** in 65% yield. The subsequent three steps shown in Scheme 15b produced the target morphine analogue.



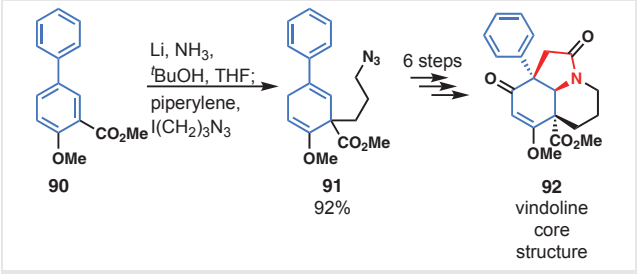
Scheme 15 (a) The similarity between morphine and analogue **83**; (b) Synthesis of morphine analogue **83**

The Tanaka group treated the biphenyl-fused cyclic amine **86** (Scheme 16) with Na(0) in NH_3 and MeOH to form vinyl ether **87** in 96% yield. After adding H_2SO_4, this amine cyclized, presumably through the enone intermediate **88**, to form the tetracyclic amine **89** in 79% yield.[35] The same group published the same strategy for different ring sizes.[36] Their examples showcase how a Birch reduction of a biphenyl system rapidly increases the structural complexity.



Scheme 16 Two-step synthesis of a tetracyclic amine from a biphenyl-fused cyclic amine

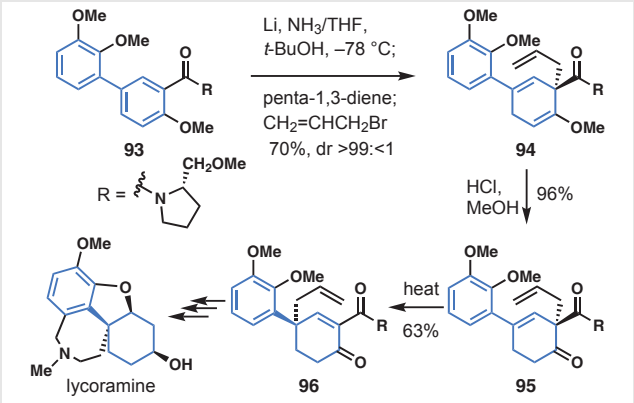
Guo and Schultz demonstrated that biaryl **90** (Scheme 17) could be regio- and chemoselectively reduced and alkylated to form **91** in 92% yield. The subsequent six-step sequence produced vindoline-like compound **92** (for the structure of vindoline, see Scheme 21a).[33,37]



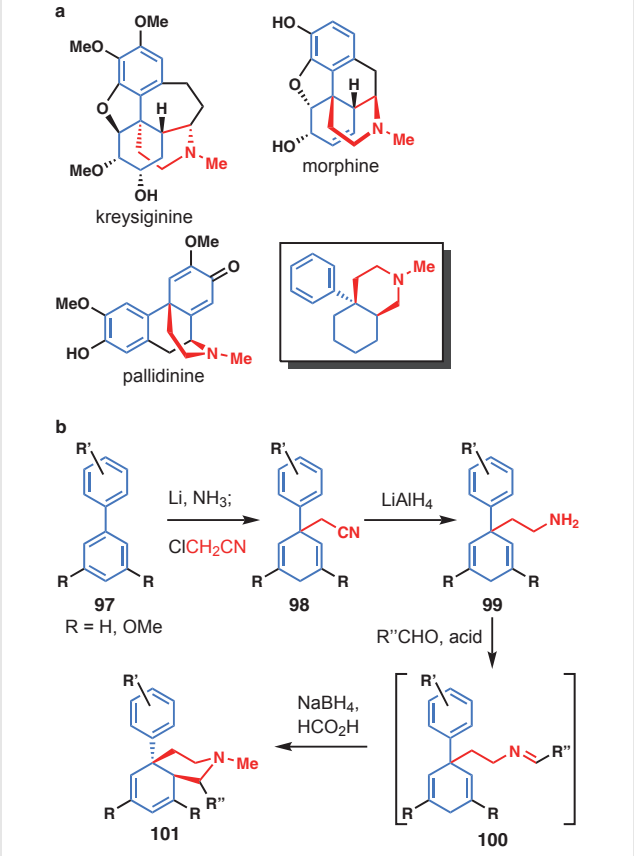
Scheme 17 Synthesis of the tricyclic core structure of vindoline

Using Schultz's chiral auxiliary strategy,[38] the Malachowski group reductively allylated biaryl **93** to form **94** with high diastereoselectivity (Scheme 18). Penta-1,3-diene (piperylene) was used to quench the remaining Li(0) before the addition of allyl bromide. Upon the hydrolysis of vinyl ether **94**, the resulting ketone **95** underwent a Cope rearrangement to create the conjugated enone **96**. Further elaboration led to the completion of the total synthesis of (–)-lycoramine.[39]

The Landais group recognized the common framework indicated in blue and red in kreysiginine, morphine, and pallidinine (Scheme 19a) and used the Birch reduction-alkylation sequence to construct the core structure quickly (Scheme 19b); specifically, biaryls **97** were treated with Li(0) in NH_3 followed by $ClCH_2CN$, and the resulting nitriles **98** were reduced to the primary amines **99** after exposure to $LiAlH_4$. The amines were converted into imines **100**, which underwent an intramolecular Mannich-type reaction and *N*-methylation to afford the tricyclic compounds **101**.[40]

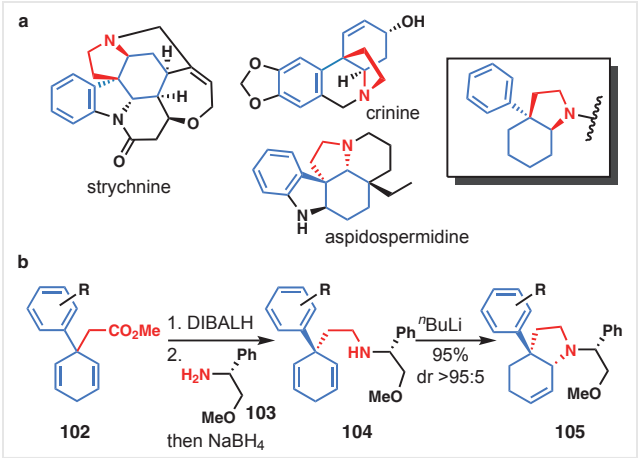


Scheme 18 Total synthesis of lycoramine



Scheme 19 Synthetic studies of the skeleton of morphine, kreysiginine, and pallidinine

The Landais group was also inspired by the connectivity shown in blue and red in strychnine, crinine, and aspidospermidine (Scheme 20a). The reductive alkylation products of biaryls **102** (Scheme 20b),[27] were reduced to the corresponding aldehydes, which underwent reductive amination with chiral primary amine **103** and $NaBH_4$ to form the secondary amines **104**. These amines were treated with ^{n}BuLi (20 mol%) to form the tricyclic system **105** with the diastereomeric ratio of >95:5.[41] The mechanism of the cyclization was discussed in detail in a separate paper.[42]

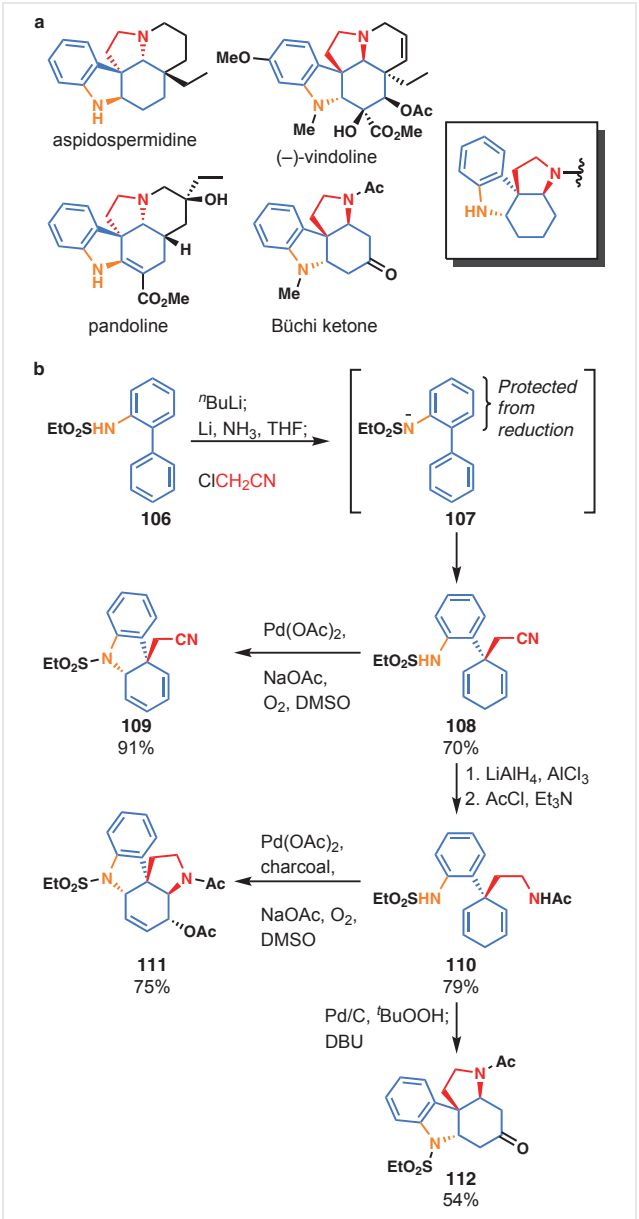


Scheme 20 Synthetic studies of the skeleton of strychnine, crinine, and aspidospermidine

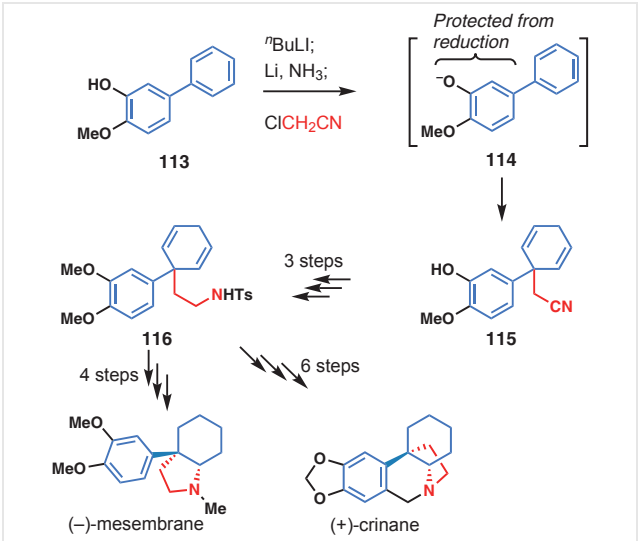
The same group also recognized the common core structure shown in the box in Scheme 21a.[43] To develop a general strategy toward the core, they treated biaryl **106** (Scheme 21b) with ^{n}BuLi to form anion **107**, protecting the N-bearing arene from being reduced. This species was reduced by Li(0), and the putative carbanion intermediate was alkylated to form **108** in 70% yield. The subsequent Pd(II)-catalyzed oxidative amination of the olefin gave tricyclic product **109** in 91% yield. Also, after the reduction of the cyano group to the N-acetylated primary amine, **110** was subjected to similar oxidative cyclization conditions to form tetracyclic product **111** in 75% yield. Amide **110** was also treated with Pd/C and *tert*-butyl hydroperoxide followed by DBU to form the N-sulfonated analogue of Büchi ketone **112** in 54% yield.

The Zhu group used Landais' chemistry[27] to prepare **115** (Scheme 22) from **113** via **114** (yield not reported).[44] After the O-methylation, $LiAlH_4$ reduction, and *N*-tosylation, compound **116** was subjected to an enantioselective aza-Wacker cyclization, and subsequent functional group transformations that yielded natural products (–)-mesembrane and (+)-crinane.

In the first total synthesis of herquline C (herquline C was also converted into herquline B in one step by base-catalyzed double-epimerization; Scheme 23a), the Baran group treated the biaryl intermediate **117** with Li(0) and 2,2,2-trifluoroethanol (TFE) in NH_3 (Scheme 23b). It was essential to use TFE because other alcohols produced a mixture of the desired product **118** and its regioisomer **119**.



Scheme 21 (a) Structures of natural products and their common structure in the box; (b) synthesis of the core structures

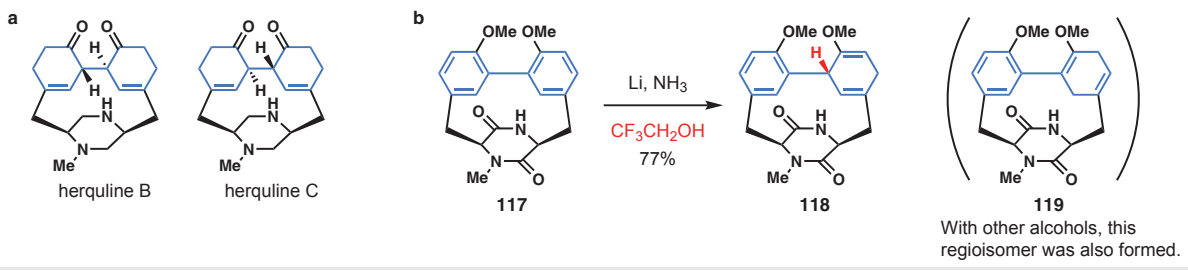


Scheme 22 Total synthesis of (–)-mesembrane and (+)-crinane

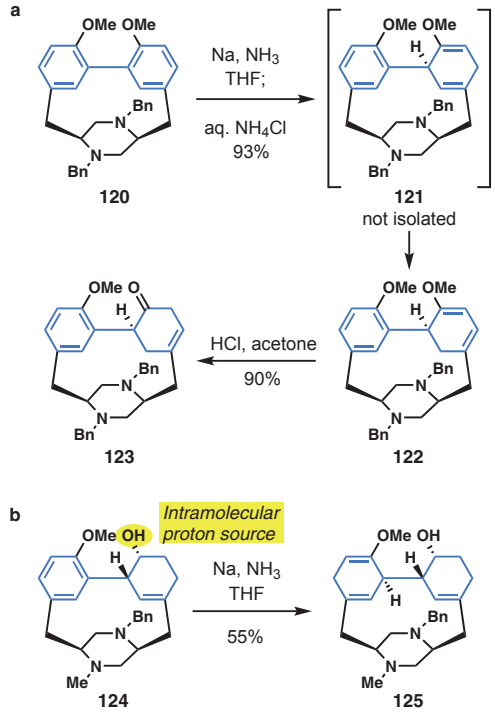
The reason for this observation remains unknown.[45] TFE is unusually acidic as the source of a proton for the Birch reduction and may apply to other Birch reductions.

The Schindler group also completed the total synthesis of herqulines B and C.[46] They reduced the biaryl intermediate **120** with Na(0) in NH_3 to afford compound **122** in 93% yield (Scheme 24a). The use of alcohols such as ^{t}BuOH resulted in the over-reduced products. Although the acid-catalyzed hydrolysis gave the desired ketone **123**, the Birch reduction of this ketone or its ketal was unsuccessful. The group prepared alcohol **124** (Scheme 24b) through an oxidative route and used the secondary hydroxy group to control the diastereoselectivity of the Birch reduction of the methoxyphenyl ring to form **125**. The insight into the hydroxy-directed stereoselective protonation of a Birch reduction intermediate may apply to other systems.

In summary, although the underlying reasons for various chemo- and regioselectivity for the Birch reductions of biaryls are incompletely understood, their synthetic applications have shown a handful of remarkable successes.



Scheme 23 The Birch reduction of a biphenyl in the total synthesis of herqulines by the Baran group



Scheme 24 The Birch reductions of a biphenyl and an arene in the total synthesis of herqulines by the Schindler group

7 Outlook

The modern variants of the Birch reduction have made it operationally easier to perform the Birch reduction in the laboratory.[47–55] Given the reactivity of biaryls discussed above[22] and the importance of biaryl reduction in natural product synthesis, the modern Birch-like reductions should be evaluated for biaryls for their scopes and limitations. Additionally, because the carbanion intermediates of biaryl reduction are more stable than those of monoarenes in general, it may be possible to expand the range of electrophiles to introduce non-hydrogen substituents to increase the complexity.

Conflict of Interest

The authors declare no conflict of interest.

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