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Birch Reductive Alkylation of Biaryls: Scope and Limitations

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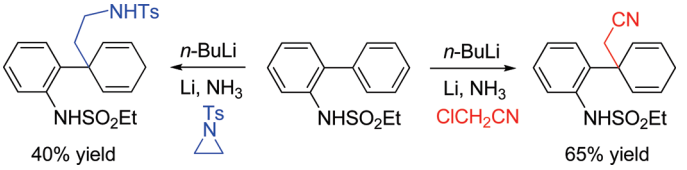

Birch reductive alkylation of biaryls has been carried out by varying the nature of the substituents on the aromatic rings. Our investigations have focused on electron-rich substituents such as OMe, OH, and NR_2 groups as they are present on the skeleton of targeted alkaloids. The regioselectivity is strongly affected by the electronic nature of these substituents on both rings. The 3,5-dimethoxyphenyl moiety is selectively reduced and then alkylated, while phenols and anilines do not react under these conditions. A biaryl possessing both a 3,5-dimethoxyphenyl moiety and a phenol ring may, however, be reduced and alkylated provided the acidic phenolic proton is removed prior to the treatment with Li in NH_3. Similarly, biaryls possessing a *o*-sulfonamide group are reduced regioselectively and alkylated with α-chloroacetonitrile or *N*-tosylaziridine to provide the corresponding dienes in reasonable to good yields. A survey of the alkylating agents was also performed showing that various functional groups may be introduced at the benzylic position, including esters, primary and tertiary amides, nitriles, epoxides, and acetals and also unfunctionalized sterically hindered *t*-Bu groups and cyclopropyl substituents. The introduction of the latter indicates that both a S_N2 and a SET mechanism may take place during the alkylating step.

Introduction

The alkaloids isolated from Amaryllidaceae, strychnos, and also morphinans have attracted considerable interest[1] and still today constitute a source of inspiration for synthetic chemists[2] and valuable targets for biological evaluation. The polycyclic nature of these complex natural products induces many synthetic problems, including the stereocontrol of all stereogenic centers and particularly that of the quaternary center[3] present in most representative members of these families. Although these alkaloids are biogenetically unrelated, it was possible to identify in most of them, a common substructure, incorporating a substituted aryl group linked to a functionalized cyclohexane moiety (in blue, Figure 1). In addition, an ethylamino group on a stereogenic quaternary center (in red, Figure 1) is present in certain cases (morphine, strychnine, crinine). Owing to our long-standing interest in desymmetrization processes,[4] it occurred to us that a symmetrical arylcyclohexadiene bearing (or not) an ethylamino group at the benzylic center (e.g., **I**, Figure 1) would constitute a common building block for all of these alkaloids. Suitable functionalization would provide a somewhat unified

(1) Hesse, M. *Alkaloids—Nature's Curse or Blessing?*; Wiley-VHCA: Zürich, 2002; 413 pp, ISBN 3-906390-24-1.

(2) (a) Hoshino, O. The Amaryllidaceae Alkaloids. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, pp 323−424. (b) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365–387. (c) Zezula, J.; Hudlicky, T. *Synlett* **2005**, 388–405. (d) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455–3482. (d) Creasey, W. A. Monoterpenoid Indole Alkaloids; Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: New York, 1994; Supplement to Vol. 25, part 4, pp 715−754.

(3) For reviews on methodologies to install quaternary centers, see: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105–10146. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. (d) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943–11948.

(4) (a) Angelaud, R.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, *64*, 9613–9624. (b) Abd. Rahman, N.; Landais, Y. *Curr. Org. Chem.* **2002**, *6*, 1369–1395. (c) Landais, Y.; Zekri, E. *Eur. J. Org. Chem.* **2002**, 4037–4053. (d) Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755–4558. (e) Rousseau, G.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2008**, *10*, 4441–4444.

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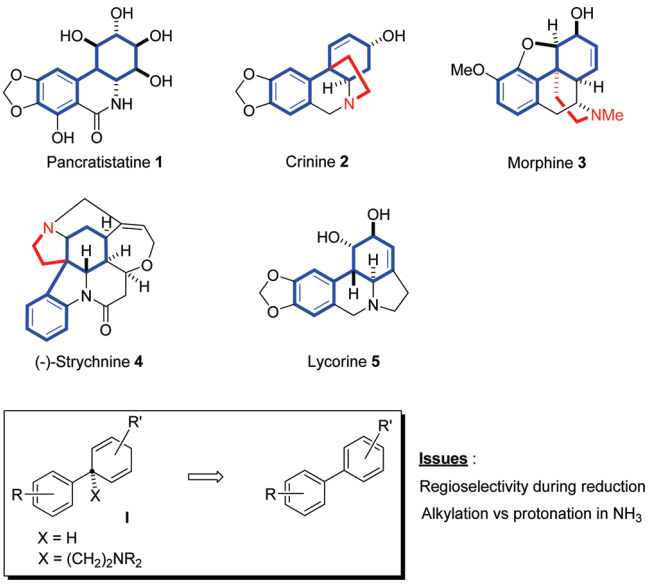


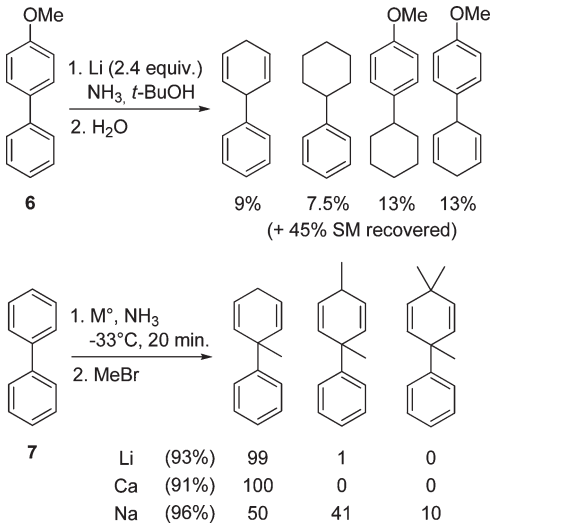
FIGURE 1. Arylcyclohexadienes **I** as precursors of various classes of alkaloids.

strategy toward the total synthesis of representative members **1**−**5** of these distinct families of alkaloids.

We recently showed that arylcyclohexadienes of type **I** could be prepared through a straightforward but multistep synthesis including the generation of the diene moiety from the corresponding silyl enol ethers.[4e,5] A simpler approach would involve the regioselective Birch reduction of a suitably substituted biaryl precursor followed by a regioselective protonation or alkylation of the resulting anion. This Birch reductive alkylation (BRA) strategy brings up two main problems: (i) the regioselectivity issue during the reduction of aryl moieties and (ii) the competition between alkylation and protonation of the resulting anion, which may either lead to the diene (**I**, X = H)[6] or to the alkylated product (**I**, X ≠ H). The first issue will mainly depend on the nature of the substituents on both aromatic groups, while the second relies on the basicity vs nucleophilicity of the last formed anion in ammonia, the medium in which the Birch reduction is generally performed. While the Birch reductive alkylation on simple arenes has been studied intensively,[7] its extension to biaryls has been so far little explored.[8] The influence of substituents on the aromatic rings of the biaryl system on the course of the Birch reduction was mainly studied by Rabideau and co-workers,[9] who showed that the introduction of an aryl substituent on a substituted arene modifies to a large extent the regioselectivity of the reduction as compared to the reduction of the same arene lacking the aryl substituent. Birch reduction of biaryls bearing various substituents including Me, $SiMe_3$, F, CO_2H, CO_2R was thus investigated. Interestingly, few studies have been performed on Birch reduction of electron-rich biaryls (substituted only by OMe, NR_2, etc.).[10] As shown in the examples above, reduction of a *p*-methoxybiphenyl **6** leads to various regioisomers and over-reduced products, indicating that regioselectivity may not be so easy to predict in this case (Scheme 1).[10a] We found no investigation on Birch reductive alkylation of electron-rich biaryls (substituted with OMe groups for instance). Harvey first reported on the Birch reductive alkylation of biaryls.[11] Its studies on the Birch reductive methylation of biphenyl **7** revealed that alkylation mainly takes place at the benzylic position as well as at the bis-allylic position when Na is used as a reducing agent (Scheme 1).[12] Dialkylation is also observed in this case, which was attributed to further deprotonation of the bis-allylic position by the highly basic sodium amide formed upon reaction.

Owing to the lack of information on the regioselectivity of such reductions and the scarce results on the Birch reductive alkylation of biaryls, it was decided to examine the scope and limitations of the Birch reductive alkylation of diversely substituted biaryls (with electron-rich substituents). We thus engaged on a systematic study, varying the nature of the

SCHEME 1. Birch Reduction and Birch Reductive Alkylation of Biaryls



(5) (a) Rousseau, G. Ph.D. Thesis dissertation, November 13, 2008. (b) Bräse, S. *Synlett* **1999**, 1654–1656.

(6) Such arylcyclohexadienes may also be prepared by addition of an aryl radical onto benzene, see: (a) Crich, D.; Grant, D.; Wink, D. J. *J. Org. Chem.* **2006**, *71*, 4521–4524. (b) Crich, D.; Rumthao, S. *Tetrahedron* **2004**, *60*, 1513–1516. (c) Crich, D.; Krishnamurthy, V. *Tetrahedron* **2006**, *62*, 6830–6840.

(7) For exhaustive reviews on Birch reductive alkylation, see: (a) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1−334 and references therein. (b) Schultz, A. G. *Chem. Commun.* **1999**, 1263–1271. (c) Rabideau, P. W. *Tetrahedron* **1989**, *45*, 1579–1603.

(8) (a) Müller, P. M.; Pfister, R. *Helv. Chim. Acta* **1983**, *66*, 771–779. (b) Müller, P. M.; Pfister, R.; Urban, R. European Patent 12801 **1980**; *Chem. Abstr.* **1980**, *93*, 185839s. (c) Rabideau, P. W.; Peters, N. K.; Huser, D. L. *J. Org. Chem.* **1981**, *46*, 1593–1597. (d) Guo, Z.; Schultz, A. G. *Org. Lett.* **2001**, *3*, 1177–1180. (e) Casimiro-Garcia, A.; Schultz, A. G. *Tetrahedron Lett.* **2006**, *47*, 2739–2742. (f) Tapas, P.; Malachowski, W. P.; Lee, J. *Org. Lett.* **2006**, *8*, 4007–4010. (g) Tapas, P.; Malachowski, W. P.; Lee, J. *J. Org. Chem.* **2007**, *72*, 930–937. (h) Malachowski, W. P.; Tapas, P.; Phounsavath, S. *J. Org. Chem.* **2007**, *72*, 6792–6796.

(9) (a) Rabideau, P. W.; Huser, D. L.; Nyikos, S. J. *Tetrahedron Lett.* **1980**, *21*, 1401−1404. (b) Rabideau, P. W.; Nyikos, S. J.; Huser, D. L.; Burkholder, E. G. *J. Chem. Soc., Chem. Commun.* **1980**, 210–211. (c) Marcinow, Z.; Clawson, D. K.; Rabideau, P. W. *Tetrahedron* **1989**, *45*, 5441–5448. (d) Harvey, R. G.; Lindow, F.; Rabideau, P. W. *J. Am. Chem. Soc.* **1972**, *94*, 5412–5420. (e) Jessup, D. W.; Paschal, J. W.; Rabideau, P. W. *J. Org. chem.* **1977**, *42*, 2620–2621. (f) Harvey, R. G. *Synthesis* **1970**, 161–172.

(10) (a) Birch, A. J.; Nadamuni, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 545–552. (b) Tanaka, H.; Shibata, M.; Ito, K. *Chem. Pharm. Bull.* **1984**, *32*, 3271–3272. (c) Tanaka, H.; Takamura, Y.; Shibata, M.; Ito, K. *Chem. Pharm. Bull.* **1986**, *34*, 24–29.

(11) (a) Lindow, D. F.; Cortez, C. N.; Harvey, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 5406–5412. (b) Lindow, D. F.; Harvey, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 3786–3787.

(12) Rabideau, P. W.; Peters, N. K.; Huser, D. L. *J. Org. Chem.* **1981**, *46*, 1593–1597.

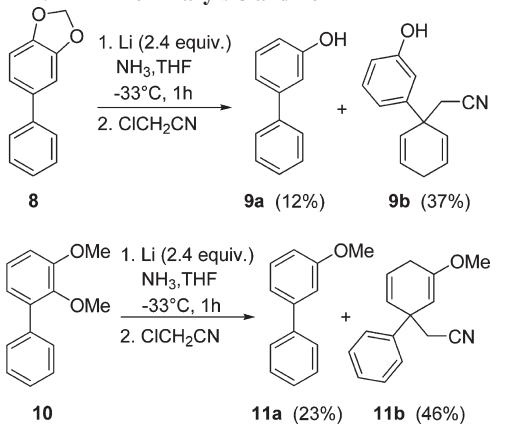
biaryl and that of the electrophile. Preliminary results have shown that the process is applicable to a variety of biarylic systems and is readily amenable to large-scale synthesis.[13] This process which is part of a methodology called the BRAD strategy (for Birch Reductive Alkylation−Desymmetrization)[4d,e,14] offers a rapid entry toward useful building blocks for the synthesis of alkaloids such as those depicted in Figure 1. We provide here a full account of these investigations, focusing on various aspects of this study, including (1) the regiocontrol as a function of the nature of the biaryl system; (2) the variation of the nature of the electrophile; and (3) some mechanistical aspects of the BRA.

Results and Discussion

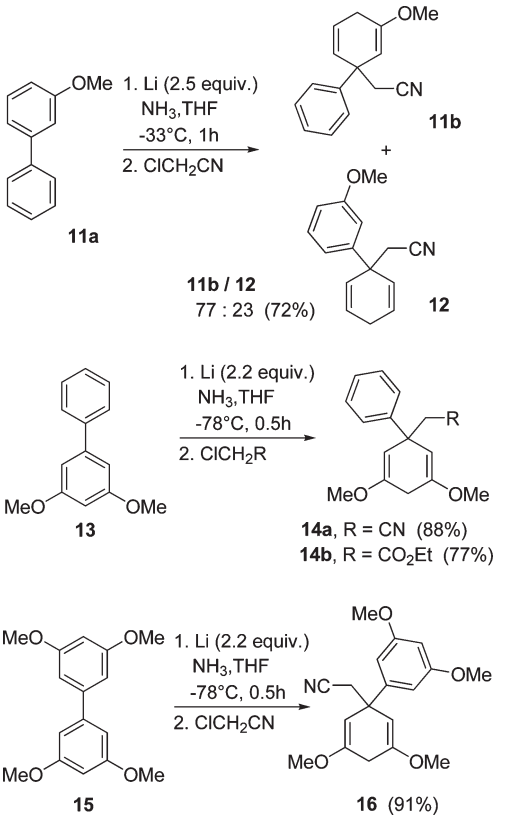
Birch Reductive Alkylation of Biaryls with Electron-Rich Substituents. The investigations started with various biaryls bearing electron-rich substituents including methoxy and methylenedioxy groups frequently found on naturally occurring alkaloids (Figure 1). Our first attempt on biaryl **8** was encouraging, producing with 2.4 equiv of lithium in ammonia under reflux the alkylated arylcyclohexadiene **9b** along with phenol **9a** (Scheme 2). Similarly, biaryl **10** afforded alkylated product **11b** and the demethylated biaryl **11a**, along with some recovered starting material (17%). In both cases, a *para* (in **8**) or an *ortho* (in **10**) substituent was lost during the process, a well-precedented observation on simple arenes.[7a,15] This can be explained by the formation of a radical anion on the most electron-rich arene, which would then decompose into an alkoxide and a phenyl radical.[16] The latter would then be reduced further into the corresponding anion which would be protonated by NH_3, leading to biaryls **9a** and **11a**. Consequently, it was deduced that **9b** and **11b** were probably generated in a second phase through BRA of **9a** and **11a**, respectively (vide infra).

The reductive alkylation was then attempted on biaryl **11a** and led to the formation of two inseparable regioisomers **11b** and **12** in a good overall yield (Scheme 3). The formation of **11b** as the major isomer indicates that the reduction occurs on the most electron-rich aromatic ring, in good agreement with the observed relative reduction rates on simple arenes, which follow the order ArOMe > ArH > ArOH.[7a,17] This suggests that the relative rates of reduction of biaryls (conjugated arenes) do not differ from the order observed for the reduction of isolated (nonconjugated) arenes. It also confirms the hypothesis of the formation of **11b** from **10** via **11a** (Scheme 2). Birch reductive alkylation of **13** having two methoxy groups *meta* to the biaryl linkage led to arylcyclohexadienes **14a**,**b** in good yield and complete regiocontrol. Likewise, symmetrical biaryl **15** provided diene **16** in excellent yield.

SCHEME 2. BRA of Biaryls 8 and 10



SCHEME 3. BRA of Biaryls Bearing *m*-OMe Groups



The previous experiments thus demonstrate that the preparation of arylcyclohexadienes of type **I**, using Birch reductive alkylation of biaryls, is a viable route but still limited in scope to biaryls having the OMe group *meta* to the biaryl linkage. As illustrated below, when the reaction was carried out on a tetrasubstituted but unsymmetrical biaryl such as **17**, the reaction provided a diene **18** and recovered starting material (Scheme 4). This can be rationalized by invoking a selective reduction of the 3,4-dimethoxyphenyl leading, after the loss of a OMe group, to a trimethoxy-substituted biaryl (with consumption of 2 equiv of Li per trimethoxy-substituted biaryl formed), which upon further reduction and alkylation afforded diene **18**. Direct reduction of the 3,5-dimethoxyphenyl fragment apparently did not occur as the

(13) (a) Lebeuf, R.; Robert, F.; Landais, Y. *Org. Lett.* **2005**, *7*, 4557–4560. (b) Lebeuf, R.; Berlande, M.; Robert, F.; Landais, Y. *Org. Synth.* **2009**, *86*, 1–10.

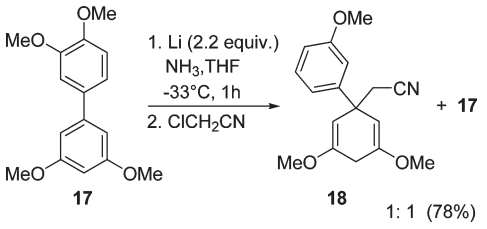
(14) Beniazza, R.; Dunet, J.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2007**, *9*, 3913–3916.

(15) Kuehne, M. E.; Lambert, B. F. *J. Am. Chem. Soc.* **1959**, *81*, 4278–4287.

(16) (a) Thornton, T. A.; Woolsey, N. F.; Bartak, D. E. *J. Am. Chem. Soc.* **1986**, *108*, 6497–6502. (b) Dewald, R. R.; Conlon, N. J; Song, W. M. *J. Org. Chem.* **1989**, *54*, 261–262.

(17) For instance, anisole is reduced 3.3 times faster than benzene; see: Krapcho, A. P.; Bothner-By, A. A. *J. Am. Chem. Soc.* **1959**, *81*, 3658–3666.

SCHEME 4. BRA of Biaryls Bearing *m*-OMe Groups

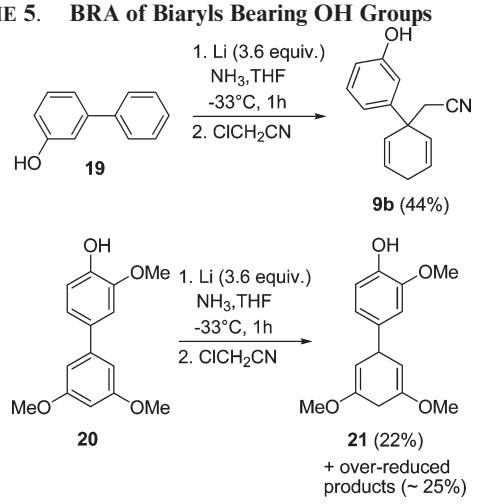


expected alkylated tetramethoxydiene was not observed in the crude reaction mixture.

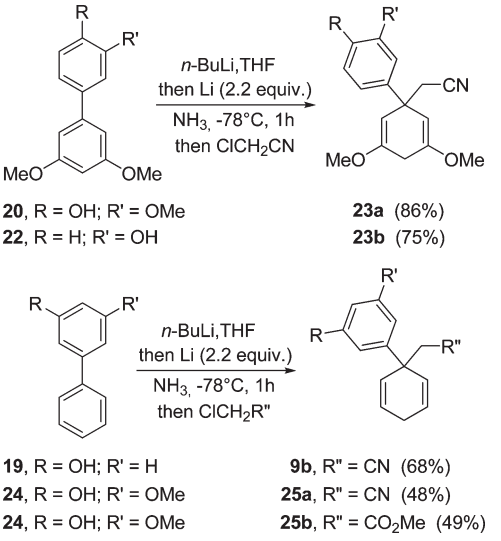
Birch Reductive Alkylation of Biaryls with Phenol Substituents (*Meta* and *Para* Positions). In order to overcome the limitation mentioned above, we then focused our attention on precursors bearing a phenol moiety as it is well-known that phenols are generally inert under Birch reduction conditions.[7,18] As a consequence, it was foreseen that the presence of a phenol fragment would direct the reduction onto the other aromatic ring, therefore circumventing the problem of regioselectivity and the loss of *o*- and *p*-OMe substituents. This proved to be partially correct as illustrated by the examples below (Scheme 5). We observed that the reaction carried out on biaryls **19** and **20** afforded modest yields of the alkylated product **9b** or only the reduced product **21**, accompanied by over-reduced byproducts that could not be purified. It is, however, worthy of note that in biaryl **19**, the alkylation takes place on the "non-phenolic" ring, leaving a cyclohexadiene without resident methyl enol ethers, which proved to be useful for the subsequent developments of the BRAD strategy.[4d] Although the amount of lithium was raised to 3.6 equiv, the presence of over-reduced products seems to indicate that either the phenol is not deprotonated under the present conditions or more likely that the ammonium phenolate (formed by reaction between the phenol and NH_3) acts as a proton source, eventually competing with the alkylation process.

The involvement of the phenol as a proton source could be easily prevented by performing the Birch reduction after prior deprotonation of the phenol with *n*-BuLi. Under these conditions, we were pleased to find that phenol **19** could now be transformed into the diene **9b** in an improved 68% yield (Scheme 6). Polysubstituted biaryls **20** and **22** led to the corresponding dienes **23a**,**b** in excellent yields indicating that a careful tuning of the nature of the substituents on the aromatic ring allowed the alkylation to take place selectively on the substituted arene (as in **14a**−**b**, Scheme 3) or on the unsubstituted one (as in **9b**, **25a** and **25b**, Scheme 6). It is important to add that the temperature is a crucial parameter in this reaction. When the temperature was raised above −50 °C, a large amount of the reduced product was formed at the expense of the desired alkylated compound, indicating that at higher temperature, protonation is favored over alkylation. In addition, we have observed that the attempt to scale up the reaction (reduction of **20** to **23a**) led to a drop in yield (from 80% to 50%), further suggesting that local raising of the temperature (for instance during addition of the alkylating agent) affects the reduced/alkylated product ratio (vide infra).

SCHEME 5. BRA of Biaryls Bearing OH Groups



SCHEME 6. BRA with Added Base of Biaryls Bearing OH Groups

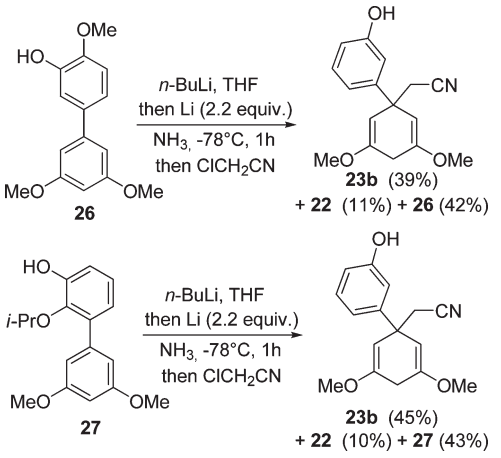


Based on these results, we then focused our attention on the Birch reductive alkylation of biaryls bearing a phenol and OMe groups in the *ortho* and *para* positions. Arylcyclohexadienes with an *ortho*-oxygenated substituent would be particularly attractive as in our general strategy, they are potent precursors of morphine alkaloids and analogues. The first attempts were unfortunately not successful. As above, BRA on precursors **26** and **27**, bearing both a phenol and a *p*-OMe or an *o*-O-*i*-Pr substituent, invariably led to loss of these substituents (Scheme 7). In the case of **26**, demethoxylation likely occurred first leaving the resulting phenol **22** which was then partially reduced and alkylated into **23b** as indicated by the presence of these two compounds in the mixture, along with recovered starting material in large quantities. Similarly, biaryl **27** bearing the bulkier O-*i*-Pr substituent in the *ortho* position, which was suggested to slow down the elimination,[19] led to an even larger amount of the elimination product **23b**.

(18) Birch, A. J.; Subba Rao, G. S. R. *Tetrahedron Lett.* **1967**, 857–858.

(19) Cambie, R. C.; Missen, A. W. *Aust. J. Chem.* **1972**, *25*, 973–983.

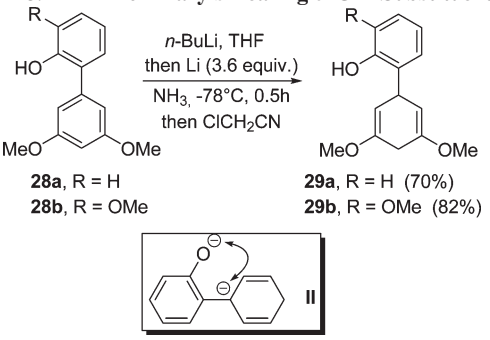
SCHEME 7. BRA of Biaryls Bearing *m*-OH Groups and *Ortho* and *Para* Substituents



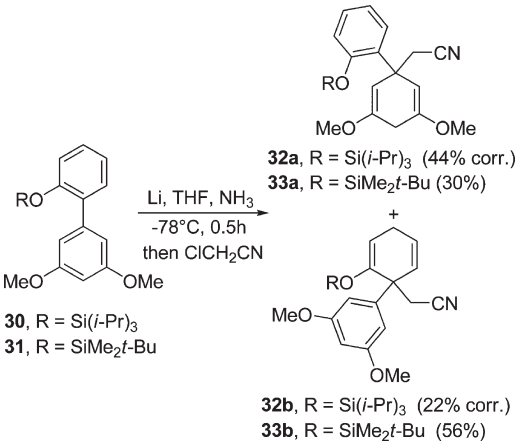
Birch Reductive Alkylation of Biaryls with Phenol Substituents (*Ortho* Position). The results above indicate that OR groups *ortho* to the biaryl linkage are labile even in the presence of a lithium phenolate moiety on the same ring. We therefore attempted a series of Birch reductive alkylation on precursors **28a**,**b** having a OH group *ortho* to the biaryl bond, using as above the *n*-BuLi procedure, as it was anticipated that OLi would be a poor leaving group (Scheme 8). Surprisingly, while the reduction proved to be very efficient under these conditions, affording dienes **29a** and **29b**, no alkylation was observed. The regioselectivity of the reduction is high, but apparently the protonation of the resulting anion is too fast, preventing the alkylation from occurring. This was attributed to electrostatic repulsion between the lithium phenolate and the benzylic carbanion species resulting from the Birch reduction (e.g., **II**, Scheme 8). This repulsion leads to an increase of the basicity of the carbanion which is then protonated by ammonia, thus preventing the alkylation. The presence of the *ortho* phenolate substituent may also prevent the conjugation of the benzylic carbanion with the neighboring aromatic ring thus raising its basicity.

Our attempts to metalate (with *n*-BuLi in THF at 0 °C) and alkylate the benzylic position of **29a**,**b** after protection of the OH group (as a OMe) having failed, we turned our attention to the reductive alkylation of various O-protected analogues of **28a**,**b**. While *o*-acetate (OCH_2CO_2Me) and *o*-amide (OCH_2CONMe_2) substituents were cleaved under the reductive conditions, more encouraging results were obtained with silylated analogues **30** and **31** (R = TIPS and TBDMS, respectively) (Scheme 9).[19] TIPS-protected phenol **30** thus afforded a separable 2/1 mixture of the desired alkylated diene **32a** and its regioisomer **32b** (66% corrected overall yield). Similarly, the TBDMS analogue **31** led to the formation of a 3/7 mixture of regioisomers **33a**,**b** (86% overall yield). In contrast with OMe substituents, $OSiR_3$ groups are thus poor leaving groups under Birch reaction conditions. They also induce much lower regioselectivity. The higher stability of *o*-$OSiR_3$ substituents as well as their influence on the regioselectivity of the process under the above conditions remain unclear but follow previous observations reported by Cambie et al. on related bulky ether groups.[19] Silyl ethers are known to be less basic than their carbon analogues due to

SCHEME 8. BRA of Biaryls Bearing *o*-OH Substituents



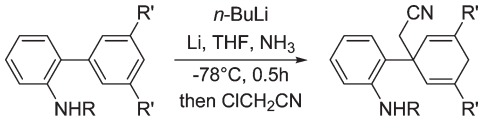
SCHEME 9. BRA of Biaryls Bearing *o*-$OSiR_3$ Substituents



oxygen lone pairs overlapping with silicon, which is a good π-acceptor. The unexpected amount of dienes **32b** and **33b** formed might then be tentatively explained by the better stabilization of the radical anion generated in the preliminary stage of the process by the siloxy substituent, as compared to the OMe group.

Birch Reductive Alkylation of Biaryls with Amino Substituents (*Ortho* Position). Referring again to the nature of the alkaloid targets depicted in Figure 1, it came into view that an access to arylcyclohexadiene **I** having an *ortho* amino group on the remaining arene would be particularly helpful in the context of the synthesis of strychnos (e.g., strychnine **4**) and aspidosperma alkaloids. The first study in this direction was carried out starting from precursor **34a**, having a 3,5-dimethoxyphenyl group and a Boc protected aniline moiety, which afforded, following the *n*-BuLi procedure, the desired diene **35a** in a satisfying 60% yield, along with over-reduced products (Table 1, entry 1). It is worth noting that in contrast with the phenolic analogue **28a**, the presence of the Boc substituent probably reduces (through delocalization) some of the anionic repulsion illustrated above (e.g., **II**, Scheme 8), allowing the alkylation to compete with the protonation by NH_3. Reduction−alkylation was then tested on precursor **34b**, having a simple phenyl group and a Boc-protected amino group on the second arene (entry 2). Deprotonation with *n*-BuLi and reduction with lithium led, after alkylation, to the desired diene **35b**, albeit in modest yield, due to the formation of over-reduced products which could not be purified. Based on the above hypothesis, it was reasoned that better acceptors on nitrogen might improve the yield of

TABLE 1. BRA of Biaryls Bearing *o*-Amino Substituents



34a-f **35a-f**

entry	biaryl	R	R′	diene	yield (%)
1	**34a**	Boc	OMe	**35a**	60[a]
2	**34b**	Boc	H	**35b**	26[a]
3	**34c**	H	H	**35c**	[b]
4	**34d**	Piv	H	**35d**	40[c]
5	**34e**	$EtSO_2$	H	**35e**	70[d]
6	**34f**	$EtSO_2$	Me	**35f**	75

[a]Over-reduced products were also observed. [b]Only over-reduced products were formed. [c]Reduction and alkylation on the aniline ring was formed in ~20% yield. [d]1,3-Cyclohexadiene **38** is also formed (8%).

the alkylation by limiting the N−Li-carbanion repulsion. This was also supported by the absence of alkylated products when starting from the unprotected amine **34c** (entry 3), whose reduction only afforded a complex mixture of reduced products. Amide **34d** and sulfonamide **34e** (entries 4−5) were subjected to the *n*-BuLi procedure, giving improved yields of the corresponding dienes **35d**−**e**, supporting the above reasoning. Biaryl **34f** possessing a 3,5-dimethylphenyl ring (entry 6) was also converted into the desired alkylated product **35f** in a satisfying 75% yield.

We also extended the reduction to more electron-rich analogues such as **36** having an additional OMe group in the *meta* position. Surprisingly, we observed the formation of diene **37** as the sole product, resulting from the reduction and alkylation of the aminophenyl ring (Scheme 10). This result is indicative of the strong electronic effect of the *m*-OMe group on the regioselectivity of the process (vide infra). Finally, we observed in several cases a mixture of over-reduced products (cyclohexenes) and 1,3-cyclohexadienes which were obtained along with the desired 1,4-dienes. For instance, Birch reductive alkylation of biaryl **34e** with ethyl α-bromoacetate afforded no trace of the alkylated product, but a quantitative yield of 1,3-diene **38**, whose structure was tentatively assigned through iodo amination (under kinetic control),[20] affording sensitive allylic iodide **39** in modest yield (Scheme 10). This surprising result suggests that ethyl α-bromoacetate may act as a better proton source than NH_3, providing the 1,3-diene upon protonation at C2 instead of the usually favored 1,4-cyclohexadiene.[21] Isomerization of the "kinetic" 1,4-diene isomer by $LiNH_2$, present in the medium under the above conditions, was ruled out on the basis of observations made by Rabideau and Harvey who showed that deprotonation of a 1,4-cyclohexadiene by $LiNH_2$ in NH_3 at −50 °C does not occur.[11a,22] Therefore, this result may simply reflect the relative protonation rate at C2 and C4 in this precursor **34e**, suggesting an implication of

SCHEME 10. Isomerized 1,3-Dienes in Birch Reductive Alkylation of Biaryls

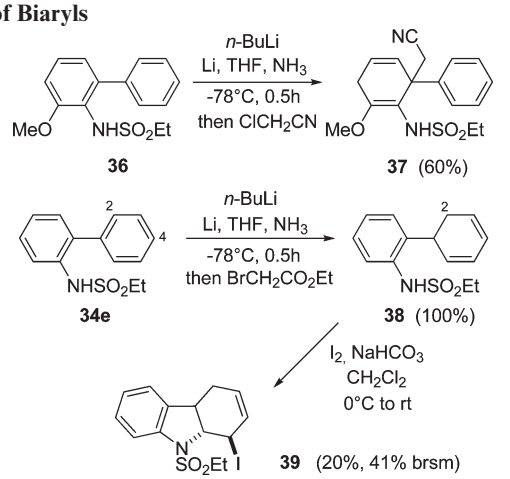
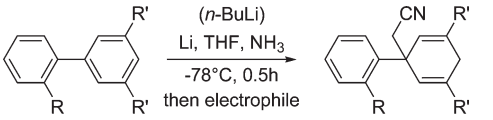


TABLE 2. BRA of Biaryls Varying the Nature of the Electrophiles



40a-j

entry	Biaryl	R	R'	Electrophile	Product	Yield
1	**7**	H	H	Cl $CONH_2$	**40a**	0%[a]
2	**7**	H	H	Br $CONH_2$	**40b**	30%
3	**7**	H	H	Br	**40c**	79%
4	**7**	H	H	Cl $CONEt_2$	**40d**	60%
5	**7**	H	H	Cl CO_2Me Ph	**40e**	90%
6	**7**	H	H	Br	**40f**	70%
7	**7**	H	H	*t*-BuBr Ph	**40g**	25%[b]
8	**13**	H	OMe	Br O	**40h**	59%[c]
9	**34e**	$NHSO_2Et$	H	Br	**40i**	47%[d,e]
10	**34e**	$NHSO_2Et$	H	Br $CH(OMe)_2$	**40j**	60%[d,f]

[a]Cyclohexa-2,5-dienylbenzene was formed exclusively. [b]Yield estimated by ^1H NMR. Starting biaryl **7** was the only other product present in the crude reaction mixture. [c]84% based on recovered starting material. [d]*n*-BuLi is used to deprotonate the sulfonamide [e]Over-reduced products were also observed. [f]1,3-Cyclohexadiene **38** is also formed (15%).

the $NLiSO_2Et$ group in the regiocontrol. Finally, the easy formation of 1,3-cyclohexadiene **38** also explains the presence of over-reduced products in certain cases as conjugated 1,3-dienes are more easily reduced than the nonconjugated ones in Li/NH_3 medium.

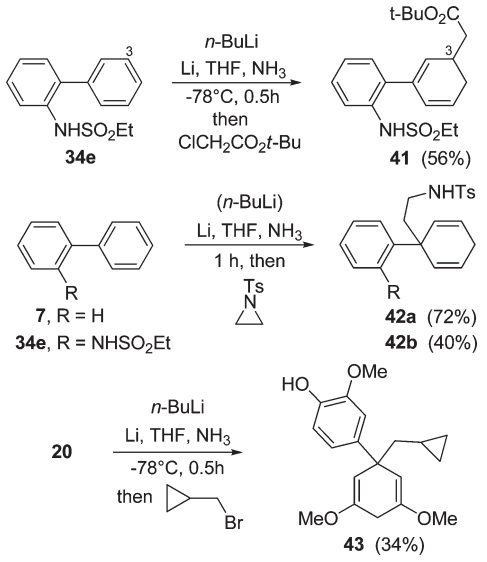
Birch Reductive Alkylation of Biaryls: Nature of the Electrophile. In the above studies, α-chloro-nitrile and esters were used as electrophiles, providing a straightforward manner to install the ethylamino group found in alkaloids **2**−**4** (Figure 1). We generalized the approach to other useful electrophiles, as summarized in Table 2 and Scheme 11. Birch reductive alkylation was carried out first with biphenyl **7** and then extended to substituted biaryls. It is worthy of note that the nature of the leaving group on the electrophile may have a strong effect on the reaction outcome as suggested by the alkylation of **7** with α-haloacetamide (Table 1, entries 1 and 2).

(20) (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408. (b) Fiorelli, C.; Marchioro, C.; Martelli, G.; Monari, M.; Savoia, D. *Eur. J. Org. Chem.* **2005**, 3987–3993.

(21) The conjugation in 1,3-diene provides little stabilization (0.41 kcal/mol) as compared to the 1,4-diene: (a) Bates, R. B.; Carnighan, R. H.; Staples, C. E. *J. Am. Chem. Soc.* **1963**, *85*, 3032–3033. (b) Turner, R. B.; Mallon, B. J.; Tichy, M.; Doering, W. V. E.; Roth, W. R.; Schröder, G. *J. Am. Chem. Soc.* **1973**, *95*, 8605–8610.

(22) Rabideau, P. W.; Huser, D. L. *J. Org. Chem.* **1983**, *48*, 4266–4271.

SCHEME 11. BRA with Esters and Aziridines As Electrophiles



The better leaving group ability of bromine relative to chlorine but also the higher acidity of α-chloroacetamide may explain these results. Birch reduction of **7** then alkylation with α-chloroacetate led to diene **40e** in an improved yield as compared to that reported in the literature[8a,b] (entry 5, Table 2). In contrast, the same reaction carried out on biaryl **34e** did not provide the corresponding alkylated product but instead the reduced product **38** in high yield, indicating that α-chloro- and α-bromoacetates may also behave as protonating agent in this context, depending on the nature of the starting biaryl (Scheme 10). Other electrophiles including allyl bromide (entries 3 and 9) and α-chloroamide (entry 4) provided the desired alkylated products in satisfying yields. Epoxides and acetals are also valuable electrophiles in the Birch reductive alkylation (entries 8 and 10). We also observed that increasing the steric bulk on the electrophile modified the regioselectivity of the alkylation process. For instance, alkylation of biaryls **34e**, using *tert*-butyl α-chloroacetate led to the alkylated product at the 3-position, as indicated by the formation of **41** (Scheme 11). Finally, aziridines were found to be potent electrophiles under the Birch conditions as shown by the reduction−alkylation of biaryls **7** and **34e**. These led respectively to dienes **42a** and **42b** having two orthogonally protected amino groups. This one-pot formation of a precursor of aspidosperma alkaloids is worthy of note and shortens to a significant extent the access to this class of alkaloids.[14] Interestingly, it was also possible to introduce a *t*ert-butyl group at the benzylic position (entry 7). Nucleophilic substitution at a tertiary center in *t*-BuBr seems inconsistent with a S_N2 process and is probably better interpreted as an electron-transfer (ET) mechanism,[23] occurring from a benzylic anion intermediate to *tert*-butyl bromide. The occurrence during the process of a radical species issued from the alkylating agent may be assessed by the use of radical clock agents such as cyclopropyl containing alkylating agents. However, the attempts to establish unambiguously the mode of alkylation of our substrates led to contrasting results, as shown by the alkylation of biaryl **7** in the presence of a diphenylcyclopropane (entry 6, Table 2), which led to the alkylated diene **40f** in a satisfying yield, without a trace of the cyclopropane ring-opening product. Similarly, Birch reductive alkylation of **20** followed by alkylation with cyclopropylmethyl bromide led to **43**, albeit in moderate yield (Scheme 11). This was intriguing as cyclopropyl bromide is frequently used as a radical clock, with cyclopropyl ring-opening rate constant as high as 6.7×10^7 M^{-1} s^{-1}.[24] Cyclopropane from bromomethyl-2,3-diphenylcyclopropane (entry 6, Table 2) exhibits an even higher ring-opening rate constant, e.g., $> 2 \times 10^{10}$ M^{-1} s^{-1}.[25] Cyclopropylmethyl bromides may thus react through an S_N2-type mechanism, while tertiary alkyl electrophiles react through a radical mechanism as the polar mechanism is not accessible due to steric hindrance. A single electron transfer followed by radical recombination in a solvent cage may also be envisioned as an alternative pathway to explain the formation of **40f** and **43**.[26]

Birch Reductive Alkylation of Biaryls: Mechanistic Considerations. A mechanism is finally proposed (Figure 2) that tentatively rationalizes the observations made during our investigations. The Birch reductive alkylation of arenes involves an initial electron-transfer process from the metal to the arene followed by the alkylation of the resulting anion.[27] The first electron transfer from Li in NH_3 to the biaryl provides the radical anion **A**.[28] At this stage, two different pathways may be envisioned. Protonation may occur at the site of highest electron density (C4) as to provide radical **B**. It is well described that the cyclohexadienyl anion is kinetically more reactive at the central position, leading to the radical intermediate **B** which is both benzylic and bisallylic. In precursors **13**, **15**, **20**, **22**, **28a**,**b**, and **36**, this radical would be further stabilized by OMe substituents in *meta* positions, rationalizing the high regioselectivity of the process in these cases, with the predominant reduction of the methoxy-substituted arene in good agreement with literature precedent on simple arenes,[17] as well as with kinetic studies and calculations.[29] A second electron transfer from lithium to **B** may then provide the benzylic anion **C** which is finally protonated by NH_3 (at C1) or alkylated depending on its basicity. This second protonation (or alkylation) generally occurs at the benzylic position leading to the 1,4-cyclohexadienyl system, thus controlling the regioselectivity of the whole process. Subtle substituent effects were shown to alter

(23) (a) Garst, J. F. *Acc. Chem. Res.* **1971**, *4*, 400–406. (b) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344–3350. (b) Hazimeh, H.; Mattalia, J. M.; Marchi-Delapierre, C.; Barone, R.; Nudelman, N. S.; Chanon, M. *J. Phys. Org. Chem.* **2005**, *18*, 1145–1160.

(24) (a) Newcomb, M. In *Radical in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1; pp 317−336. (b) Newcomb, M.; Choi, S. Y.; Horner, J. H. *J. Org. Chem.* **1999**, *64*, 1225–1231.

(25) (a) Castellino, A. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1988**, *110*, 1313–1315. (b) Castellino, A. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1988**, *110*, 7512–7519. (c) Adam, W.; Heil, M.; Castellino, A. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 1730–1736.

(26) (a) Ashby, E. C. *Acc. Chem. Res.* **1988**, *21*, 414–421. (b) Houmam, A. *Chem. Rev.* **2008**, *108*, 2180–2237.

(27) (a) Harvey, R. G. *Synthesis* **1970**, *2*, 161–172. (b) Harvey, R. G.; Arzadon, L. *Tetrahedron* **1969**, *25*, 4887–4894. (c) Rabideau, P. W.; Burkholder, E. *G. J. Org. Chem.* **1978**, *43*, 4283–4288. (d) Rossi, R. A.; Camusso, C. C.; Madoery, O. D. *J. Org. Chem.* **1974**, *39*, 3254–3258. (e) Rabideau, P. W.; Harvey, R. G. *J. Org. Chem.* **1970**, *35*, 25–30.

(28) (a) Müllen, K.; Huber, W.; Neumann, G.; Schnieders, C.; Unterberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 801–807. (b) Müllen, K. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 204–217.

(29) Zimmerman, H. E.; Wang, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 2205–2216 and references cited therein.

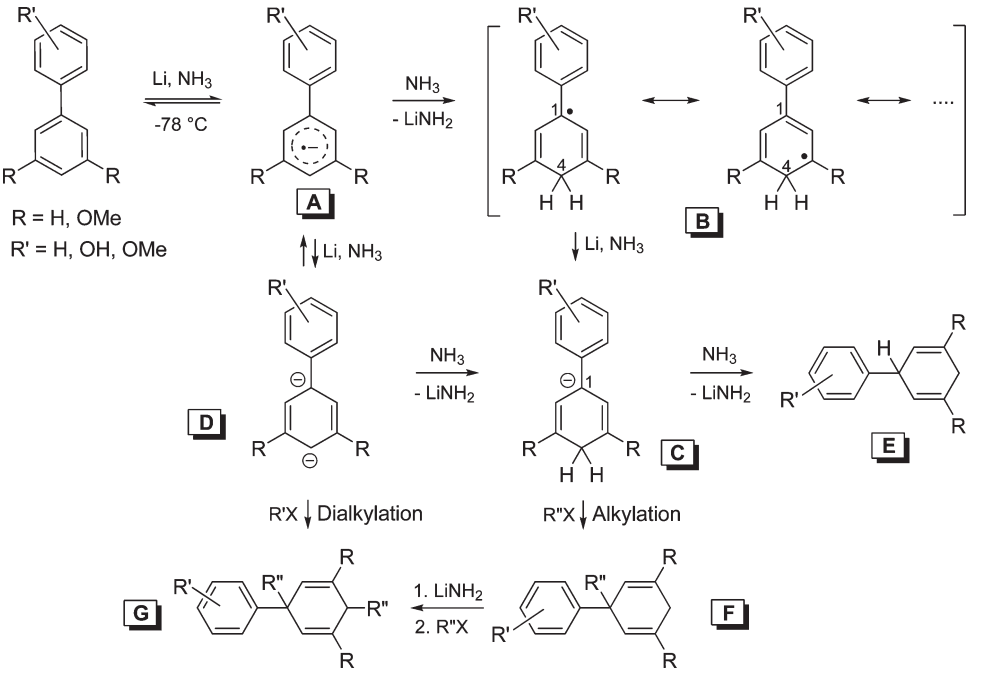
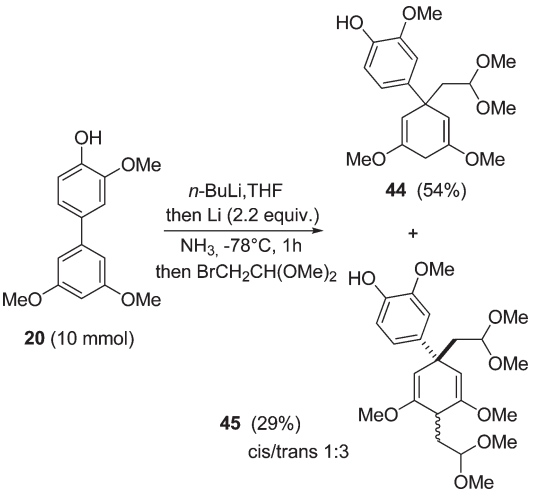


FIGURE 2. Mechanism of the Birch reductive alkylation of biaryls.

the basicity of **C** (vide supra) and modify its long lifetime in the medium, leading in certain cases to larger amount of reduced products **E** through protonation of **C** by ammonia, but also ammonium phenolate or alkylating agents such as α-haloesters. Among the alternative pathway, the occurrence of a dianion has been proposed several times for the reduction of biaryls under Birch-type conditions (NH_3) or during lithium reduction in THF.[9d,22] A second electron transfer from Li to radical-anion **A** may thus provide dianion **D**. Protonation of **D** at C-4 would then return monoanion **C** that can be protonated or alkylated as above. Deeply colored solutions are observed upon mixing the biaryl with Li and NH_3. For instance, in our hands, reduction of **34e** led to a solution having a green coloration during addition of lithium wire, which turned deep red after 2−3 min. This coloration rapidly vanished after several minutes, the alkylating agent being generally added after 5 min at −78 °C. We noticed that addition of the alkylating agent after the deep red coloration had disappeared resulted in a higher amount of reduced products. Literature precedent[9d] suggests that in our case the green coloration is due to the radical anion **A**, a stable intermediate in the medium when only 1 equiv of lithium is added, which may give rise, upon addition of 2−2.5 equiv of Li, to dianion **D** or radical **B**. Both **B** and **D** are nonpersistent species in the medium and thus are readily transformed into the monoanion **C** which is then protonated or alkylated. The red solution may thus be attributed to anion **C**, whose coloration vanishes as a result of the protonation by NH_3. The persistence of **C** in the medium may thus be qualitatively assessed by rapid changes in the coloration of the solution prior to addition of the electrophile. During our attempt to scale up the Birch reductive alkylation

SCHEME 12. Dialkylation of Biaryl 20

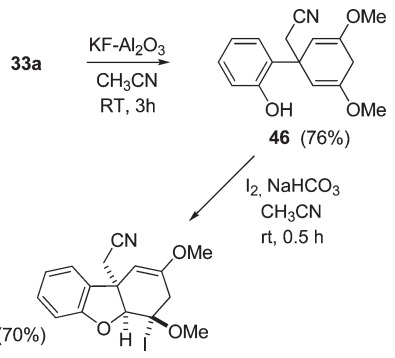


of biaryl **20**, we have observed the formation of the dialkylated product **45** as a 1:3 cis/trans[30] mixture of two diastereomers[27b] (along with the desired product **44**, Scheme 12). Compound **45** might result from a regioselective 1,4-dialkylation of dianion such as **D**. Dialkylation of lithium dianion of biphenyl **7** has been observed by Yus et al.[31] during their studies on lithiation of polyaromatic compounds in THF. High concentration of strongly basic dianion **D**, however, seems incompatible with the presence of NH_3 as a solvent. Dianion **D** is rapidly protonated in NH_3 leading to **C**, which is likely the only stable intermediate species in this media.[9b]

(30) The 1:3 cis/trans mixture could be partially separated with the first eluting cis isomer isolated pure. The relative stereochemistry of each isomer was assigned on the basis of 2D ^{1}H NMR experiments.

(31) (a) Melero, C.; Guijarro, A.; Yus, M. *Tetrahedron Lett*. **2006**, *47*, 6267–6271. (b) Melero, C.; Guijarro, A.; Baumann, V.; Jimenez, A. J. P.; Yus, M. *Eur. J. Org. Chem*. **2007**, 5514–5526. (c) Melero, C.; Pérez, H.; Guijarro, A.; Yus, M. *Tetrahedron Lett*. **2007**, *48*, 4105–4109 and references cited therein.

SCHEME 13. Iodoetherification of Dienylphenol 46



The formation of dialkylated product **45** was only observed during large-scale synthesis where temperature is more difficult to control due to the exothermicity of the process and when the amount of $LiNH_2$ present in the medium would be sufficient to deprotonate **F**, allowing the alkylation in the presence of an excess of electrophile. This is in good agreement with the observations of Harvey,[9d] who reported a higher amount of polyalkylated products when reactant concentration was high and attributed that to a larger amount of lithium amide and cyclohexadiene in the medium.

Conclusion

In summary, we described a procedure for rapid access to symmetrical arylcyclohexadienes through a regioselective Birch reductive alkylation of biaryls. Reduction of a series of biaryl precursors bearing electron-donating substituents, followed by alkylation of the resulting anion with various electrophiles, has been investigated, demonstrating that high levels of regiocontrol could be attained through a careful choice of substituents on the arene moieties. Biaryls having an aromatic ring with two methoxy groups in the *meta* position relative to the biaryl linkage were reduced selectively. Arenes with OH and NHR substituents were not reduced if deprotonation (with *n*-BuLi) of these functions was carried out prior to the reaction with Li/NH_3. We also observed that a slight modification of the position and the nature of substituents on the arenes profoundly modified the protonation vs alkylation ratio. This study establishes the scope and limitation of the Birch reductive alkylation of biaryls and demonstrates that it may be a valuable tool for organic synthesis, offering a straightforward entry toward cyclohexa-2,5-dienyl arene systems bearing a quaternary center. These dienes are valuable synthons that can be elaborated further into highly functionalized intermediates. For instance, removal of the silyl protecting group from *ortho*-substituted diene **33a** led to phenol **46**, which was then engaged in a iodoetherification process,[6,32] affording, in good yield, a benzofuran **47**, having two quaternary stereogenic centers set up in a single step (Scheme 13). Such a synthon should find utility en route to morphinan and Amaryllidaceae alkaloids. Some utilization of these dienyl precursors have been reported recently[4d,14] and other methodologies relying on this approach are currently under scrutiny in our laboratories and will be reported in due course. Finally, our regioselective Li/NH_3 reduction of biaryls complements the well-known Birch reductive alkylation of benzoic acid and heterocyclic esters and amides, which is central to many total syntheses.[33]

Experimental Section

General Procedure for Birch Reductive Alkylation with Deprotonation. A dried, three-necked, round-bottomed flask was fitted with a coldfinger condenser connected to a vacuum-nitrogen line. Another neck was fitted with a gas inlet valve connected to an ammonia tank. A solution of biaryl in anhydrous THF (0.3 M) was introduced under nitrogen. The flask and the coldfinger condenser were cooled −20 °C, *n*-BuLi (2.5 M solution in hexane, 1.1 equiv) was added dropwise, and the solution was stirred for 10 min. Then ammonia was condensed (twice more than THF) at −78 °C. Finely cut lithium (2.2 equiv) was added portionwise at −78 °C under nitrogen pressure. The solution turned rapidly blue during lithium addition, then brown, and finally brick red. After 45 min of stirring at this temperature, a cold solution of electrophile (3 equiv) in anhydrous THF (4 M) was added dropwise over 5 min keeping the temperature below −78 °C. The mixture turned immediately brown. After 20 min of stirring, the reaction was quenched by addition of solid ammonium chloride (5 equiv). The cooling bath and condenser were removed, and ammonia was allowed to evaporate under air. When the reaction mixture reached room temperature, a 1:1 solution of aqueous saturated ammonium chloride and water was added. The aqueous phase was extracted three times with ether or ethyl acetate. The combined organic phases were washed with brine and dried over sodium sulfate. The brown paste, obtained after filtration and removal of the solvents, was purified by flash chromatography (petroleum ether/EtOAc mixtures).

[1-(3-Hydroxy-5-methoxyphenyl)cyclohexa-2,5-dienyl]acetic Acid Methyl Ester (25b). Compound **25b** was synthesized according to the general procedure from 3-hydroxy-5-methoxybiphenyl **24** (2.25 g, 11.25 mmol, 1 equiv), THF (50 mL), *n*-BuLi (2.5 M in hexane, 5.0 mL, 12.5 mmol, 1.1 equiv), ammonia (approximately 100 mL), lithium (0.173 g, 24.71 mmol, 2.2 equiv), methyl chloroacetate (3.1 mL, 34 mmol, 3 equiv), and THF (10 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 75/25) afforded **25b** as a yellow oil (1.51 g, 49%): IR (film, NaCl) ν_{max} (cm^{-1}) 3404, 2952, 1715, 158, 1434, 1195, 1159, 1059, 967; ^1H NMR ($CDCl_3$, 300 MHz) δ = 6.45−6.44 (m, 1H), 6.42−6.41 (m, 1H), 6.27−6.25 (m, 1H), 5.87−5.76 (m, 4H), 3.73(s, 3H), 3.59 (s, 3H), 2.81 (s, 2H), 2.63 (broad s, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 172.0, 160.9, 157.1, 149.4, 131.1, 124.2, 106.2, 105.1, 99.2, 55.4, 51.7, 45.6, 42.7, 25.9; HRMS (EI) $[M]^{+\bullet}$ $C_{16}H_{18}O_4$ calcd 274.1205, found 274.1212 (2 ppm).

***N*-(2-(1-(Cyanomethyl)cyclohexa-2,5-dienyl)phenyl)ethanesulfonamide (35e).** Compound **35e** was synthesized according to the general procedure from biaryl **34e** (3 g, 11.5 mmol, 1 equiv), THF (60 mL), *n*-BuLi (5.06 mL, 12.65 mmol, 1.1 equiv), ammonia (approximately 120 mL), lithium (200 mg, 28.7 mmol, 2.5 equiv), chloroacetonitrile (2.2 mL, 34.5 mmol, 3 equiv), and THF (15 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 80/20) afforded **35e** as a yellow solid (2.4 g, 70%): mp 124.5−125.1 °C; IR (solid, KBr) ν_{max} (cm^{-1}) 2953, 1718, 1522, 1431, 1346, 1196, 975; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.60−7.49 (m, 1H), 7.35−7.25 (m, 1H),

(32) Butters, M.; Elliott, M. C.; Hill-Cousins, J.; Paine, J. S.; Walker, J. K. E. *Org. Lett.* **2007**, *9*, 3635–3638.

(33) (a) Schultz, A. G. *Chem. Commun.* **1999**, 1263–1271 and references cited therein. (b) Donohoe, T. J.; House, D. *J. Org. Chem.* **2002**, *67*, 5015–5018. (c) Donohoe, T. J.; Johnson, D. J.; Mace, L. H.; Bamford, M. J.; Ichihara, O. *Org. Lett.* **2005**, *7*, 435–437. (d) Gopalan, A.; Magnus, P. *J. Org. Chem.* **1984**, *49*, 2317–2321.

7.18−7.12 (m, 3H), 6.31−6.18 (m, 2H), 5.70−5.58 (m, 2H), 3.13 (q, J = 7.5 Hz, 2H), 3.01−2.95 (m, 2H), 2.93 (s, 2H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) 137.2, 130.1, 129.3, 128.8, 128.3, 125.3, 124.2, 119.8, 117.0, 46.9, 41.2, 30.6, 26.0, 8.1; MS (ESI) m/z 325 $[M + Na]^+$ (100); HRMS (ESI) calcd for $C_{16}H_{18}N_2O_2NaS$ $[M + Na]^+$ 325.0987, found 325.0977. Anal. Calcd for $C_{16}H_{18}N_2O_2S$ (302.1): C, 63.55; H, 6.00; N, 9.26; S, 10.60. Found: C, 63.56; H, 6.03; N, 9.12; S, 10.24.

Ethanesulfonic Acid (6-Cyanomethyl-2-methoxy-6-phenyl-cyclohexa-1,4-dienyl)amide (37). Compound **37** was synthesized according to the general procedure from biaryl **36** (0.5 g, 1.71 mmol, 1 equiv), THF (10 mL), *n*-BuLi (1 mL, 1.881 mmol, 1.1 equiv), ammonia (approximately 20 mL), lithium (29.8 mg, 4.27 mmol, 2.5 equiv), chloroacetonitrile (387 mg, 5.13 mmol, 3 equiv), and THF (5 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 80/20) afforded **37** as a yellow oil (0.349 g, 60%): IR (film, NaCl) ν_{max} (cm^{-1}) 3263, 2941, 2361, 1687, 1494, 1415, 1316, 1238, 1135, 1038, 888; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38−7.28 (m, 2H), 7.23−7.19 (m, 2H), 6.89−6.85 (m, 1H), 5.94−5.88 (m, 1H), 5.64−5.61(m, 1H), 3.62 (s, 3H), 3.27−3.10 (m, 2H), 3−2.91 (m, 2H), 2,48 (q, J = 4.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) 149.9, 141.1, 130.8, 129.1, 127.9, 127.3, 122.50, 117.9, 112.8, 55.1, 48.5, 48.4, 27.2, 26.7, 8.4; MS (ESI) m/z 355 (100) $[M + Na]^+$, 200 (20) $[C_{13}H_{13}NO + H]^+$; HRMS (ESI) calcd for $C_{17}H_{20}N_2O_3NaS$ $[M + Na]^+$ 355.1086, found 355.1082.

1-(*tert*-Butylcyclohexa-2,5-dienyl)benzene (40g). Compound **40g** was synthesized according to the general procedure from biaryl **7** (2 g, 12.97 mmol, 1 equiv), THF (40 mL), ammonia (approximately 80 mL), lithium (209 mg, 29.83 mmol, 2.3 equiv), *tert*-butyl bromide (3.6 mL, 32.42 mmol, 2.5 equiv), and THF (18 mL). Purification by flash chromatography (silica gel petroleum ether 100%) afforded an analytic sample of **40g** as a colorless oil: IR (film, NaCl) ν_{max} (cm^{-1}) 3034, 2965, 2873, 1597, 1495, 1391, 1362, 948. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.41−7.17 (m, 5H), 6.47 (d, J = 10.72 Hz, 2H), 5.95 (dd, J = 3.16, 7.32 Hz, 2H), 2.61 (AB, J_{ab} = 36 Hz, 2H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 146.2, 130.1, 128.2, 127.4, 125.5, 124.8, 47.4, 37.7, 26.6, 26.4; MS (ESI) m/z 319.06 (100) $[M + Ag]^+$; HRMS (ESI) calcd for $C_{16}H_{20}Ag$ $[M + Ag]^+$ 319.0610, found 319.0615.

***N*-(2-(1-(2,2-Dimethoxyethyl)cyclohexa-2,5-dienyl)phenyl)-ethanesulfonamide (40j).** Compound **40j** was synthesized according to the general procedure from biaryl **34e** (3 g, 11.5 mmol, 1 equiv), THF (60 mL), *n*-BuLi (6.02 mL, 12.65 mmol, 1.1 equiv), ammonia (approximately 120 mL), lithium (200 mg, 28.7 mmol, 2.5 equiv), 2-bromo-1,1-dimethoxyethane (5.83 mg, 34.5 mmol, 3 equiv), and THF (15 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 90/10) afforded **40j** as a yellow oil (2.45 g, 60%): IR (solid, KBr) ν_{max} (cm^{-1}) 2940, 1718, 1664, 1486, 1342, 1153, 996; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.58−7.56 (m, 1H), 7.55−7.50 (m, 1H),7.36−7.33 (m, 1H), 7.25−7.22 (m, 1H), 7.11−7.08 (m, 1H), 6.09−6.02 (m, 2H), 5.56−5.53 (m, 2H), 4.41 (t, J = 4.5 Hz, 1H), 3.30 (s, 6H), 3.10 (q, J = 7.5 Hz, 2H), 2.95−2.87 (m, 2H), 2.23 (d, J = 4.1 Hz, 2H), 1.29 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) 137.8, 132.5, 131.0, 128.5, 126.3, 125.3, 124.0, 119.3, 102.7, 53.1, 46.4, 43.6, 41.1, 25.7, 8.1; MS (ESI) m/z 374 $[M + Na]^+$ (100); HRMS (ESI) calcd for $C_{18}H_{25}NO_4NaS$ $[M + Na]^+$ 374.1402, found 374.1399.

***N*-(2-(1-(2-(Ethylsulfonamido)phenyl)cyclohexa-2,5-dienyl)-ethyl)-4-methylbenzenesulfonamide (42b).** Compound **42b** was synthesized according to the general procedure from biaryl **34e** (500 mg, 1.91 mmol, 1 equiv), THF (7 mL), *n*-BuLi (0.95 mL, 2.1 mmol, 1.1 equiv), ammonia (approximately 14 mL), lithium (33 mg, 4.77 mmol, 2.5 equiv), 1-tosylaziridine (942 mg, 4.77 mmol, 2.5 equiv), and THF (4 mL). Purification by flash chromatography (silica gel, petroleum ether/EtOAc 80/20) afforded **42b** as a pale pinky solid (341 mg, 40%): mp 140.3−141.6 °C; IR (film, NaCl) ν_{max} (cm^{-1}) 3283, 1598, 1441, 1318, 1145, 1084, 894, 809; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.74 (d, J=7.14 Hz, 2H), 7.52 (d, J=7.89 Hz, 1H), 7.32−7.20 (m, 4H), 7.04 (t, J=7.71 Hz,1H), 6.02 (d, J=8.47 Hz, 2H), 5.39 (d, J = 9.78 Hz, 2H), 3.11−3.01 (m, 4H), 2.76 (q, J_{ab} = 4.20 Hz, 2H), 2.42 (s, 3H), 2.06 (t, J=7.53 Hz, 2H), 1.27 (t, J= 7.33 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 143.6, 137.6, 137.1, 132.3, 130.1, 129.9, 128.6, 127.2, 126.8, 126.1, 124.0, 119.3, 46.5, 41.6, 39.6, 39.0, 25.8, 21.6, 8.1; MSMS (ESI) m/z 183 (39), 192 (32) $[M + Na - CH_2CH_2NHTs\text{-}SO_2Et]^+$, 206 (43), 235 (52) $[M + Na - Ts\text{-}SO_2Et]^+$, 284 (100) $[M + Na - CH_2CH_2NHTs]^+$, 352 (19) $[M - SO_2Et]^+$, 389 (65) $[M + Na - HSO_2Et]^+$, 483 (59) $[M + Na]^+$; HRMS (ESI) calcd for $C_{23}H_{28}N_2O_4S_2Na$ $[M + Na^+]$ 483.1382, found 483.1394.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds not described in the Experimental Section and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.