

A Practical and Chemoselective Ammonia-Free Birch Reduction

Peng Lei,[‡][©] Yuxuan Ding,[‡] Xiaohe Zhang, Adila Adijiang, Hengzhao Li, Yun Ling, and Jie An^{*}[©]

College of Science, China Agricultural University, No. 2 Yuanmingyuan West Road, Beijing 100193, China

Supporting Information

ABSTRACT: A novel protocol for a significantly improved, practical, and chemoselective ammonia-free Birch reduction mediated by bench-stable sodium dispersions and recoverable 15-crown-5 ether is reported. A broad range of aromatic and heteroaromatic compounds is reduced with excellent yields.



The reduction and dearomatization of aromatic compounds to produce unconjugated cyclohexadienes is a key synthetic transformation in organic synthesis, with wide application and scope. Despite being developed over 70 years ago, the classic Birch reduction, involving dissolving metal in liquid ammonia, is still the most common method available¹ (Scheme 1, eq 1). Recently, the venerable Birch reduction has

Scheme 1. Single Electron Reduction of Benzenoid Compounds



been applied in the functionalization of carbon-based materials, such as graphene and carbon nanotubes.² Nevertheless, the use of liquid ammonia, poor chemoselectivity, and tedious experimental procedures are obvious disadvantages of this classic reaction. In a typical Birch reduction, careful purification of ammonia and all starting materials is critical. Dilute conditions (0.1-0.5 g/100 mL ammonia) are often required, which makes the scaleup nontrivial.¹

Although liquid ammonia can be replaced by low molecular weight amines (Benkeser reduction), over-reduced byproducts are always formed under these conditions (Scheme 1, eq 2).³ Catalytic hydrogenation of aromatic rings is challenging and typically leads to more saturated products with low predictability.⁴ Recent advances in single electron transfer reductants, including alkali metals and alloys in silica gel (Na-SG(I) and Na₂K-SG(I)) developed by Dye,⁵ a lithium di-*tert*-butylbiphenyl (LiDBB)/bis(methoxyethyl)amine (BMEA) sys-

tem developed by Donohoe,⁶ SmI₂/Et₃N/H₂O⁷ complexes, etc., have provided better alternatives for ammonia-free dearomatization processes. However, the reduction of benzene and electron-rich benzenoid aromatic compounds under ammonia and amine-free conditions is still a formidable challenge.

Herein, we address this challenge and report the development of a new electride-based Birch reduction that is practical, green, and wide in scope. This ammonia-free system is amenable to scale-up, using only bench-stable and commercially available sodium dispersions, recoverable 15-crown-5, and *i*PrOH (Scheme 1, eq 3).

Dye demonstrated that crown ethers and cryptand improve the solubility of alkali metals in organic solvents, affording solutions of electride salts.⁸ This discovery has attracted significant interest from organic chemists.⁹ However, to the best of our knowledge, aromatic compound reduction mediated by Na/crown ether remains unknown.

Electride salts are typically prepared using freshly distilled sodium, a potassium mirror or highly pyrophoric potassium sodium alloy, and a suitable complexant under rigorous oxygenand moisture-free conditions.^{8a,9} The reaction between a freshly prepared sodium lump and a complexant is extremely slow. Undoubtedly, the tedious procedures required for the preparation of electride salts have restricted their application in organic synthesis.

Recently, bench-stable sodium dispersions with high specific surface area have been developed as useful deprotonating reagents, and we have previously demonstrated the application of such reagents as a practical electron transfer reagent.¹⁰

In this study, we found that sodium dispersions (particle size $5-10 \ \mu\text{m}$) react rapidly with 15-crown-5 at room temperature to form the corresponding electride salt, even without the use of rigorously dried reagents and Schlenk conditions (Scheme 2).

Given the preferred outer sphere reduction mechanism of the electride, we hypothesized that this reagent might be suitable for the challenging reduction of unactivated aromatics. To test our hypothesis, we chose **1a** as model, since it comprises both a

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Scheme 2. Formation of Electride Salt



phenyl ring and alkyl amide. Upon exposure of 1a to the Na/ 15-crown-5/*i*PrOH system at 0 °C, the corresponding dearomatized product 2a was obtained in 68% yield (Scheme 3). It is worth noting that the aliphatic tertiary amide that is

Scheme 3. Reduction via Inner or Outer Sphere Electron Transfer Process



readily reduced by Na/NH₃ is stable under these conditions.¹¹ As expected, the control reaction without crown ether afforded only alcohol **2a'** (Scheme 3). The above results demonstrate that crown ether can effectively switch the electron transfer mediated by sodium from an inner to an outer sphere electron transfer process.^{7a-c}

After careful investigation of the reaction (see the Supporting Information (SI)), a 91% yield of 2a was obtained by using 6 equiv of Na/*i*PrOH/15-crown-5 in THF at 0 °C.

A stable and strong complexant for the sodium cations is the key to generating the electride; therefore, different complexants were screened (Scheme 4). Cyclic polyethers are in general



^{*a*}Conditions: **1b** (0.50 mmol, 1.0 equiv), Na (6.0 equiv), *i*PrOH (6.0 equiv), ligand (6.0 equiv), THF (3.0 mL), 0 $^{\circ}$ C, 15 min. Yield of **2b** determined by ¹H NMR.

suitable for this reaction, although, as expected, the yield is sensitive to the size of the crown ether. A higher yield was achieved with 15-crown-5, which is the most complementary crown ether to the sodium cation. Aza-analogs of crown ethers (**3e**, **3f**, and **3h**) are much less effective for this reaction,^{8b} while the alkylated aza-crown ether **3g** afforded a similar result. Acyclic polyether **3j** and primary amine **3k** were determined to be unsuitable complexants for this reaction. While it is noteworthy that the reaction with cryptand **3i** afforded the highest yield of **2b**, given the high price of **3i**, 15-crown-5 **3c** is still recommended as the complexant of choice. Importantly, 15-crown-5 is not consumed under our conditions, and about 95% of the crown ether can be recovered using a simple protocol (see the SI).

Next, the substrate scope was investigated. In general, this method is amenable to a broad range of benzenoid aromatic and heteroaromatic compounds, with excellent regioselectivity and yields (Tables 1 and 2). Benzene derivatives with electrondonating substituents (1b, 1h, 1p) are reduced using 9.0 equiv of Na/15-crown-5/iPrOH, indicating that the reducing power of Na/15-crown-5/iPrOH is comparable to that of sodium in liquid ammonia. In the case of aryl ethers 1h and 1p, partial loss of the alkoxy or methyl groups was not observed.¹² Furthermore, when polyconjugated aromatic compounds 1c are used, the formation of the over-reduced byproducts was cleanly controlled by using 3.0 equiv of Na/15-crown-5/iPrOH, giving reducible dihydro derivatives in nearly quantitative yield. By contrast, mixtures of products at different stages of the reduction are commonly obtained under the classic Birch conditions.^{1a} Alkenes and alkynes conjugated to aromatic rings (1d, 1f, 1g) were selectively reduced without any detectable reduction of aromatic rings. Tetrahydro derivatives can also be obtained in high yields by using 9.0 equiv Na/15-crown-5/ *i*PrOH (1e, 1o). Even aliphatic tertiary amides 1j–1o are stable under these conditions, which represents a rare example of benzene reduction in the presence of an unconjugated tertiary amide. The reduction of σ -bonded functional groups, such as the cleavage of halides 1k-1n and the removal of benzylic protecting groups from alcohol 1q and amine 1r, can also be achieved. Interestingly, the position of the electron-withdrawing fluoride substituents has no influence on the regioselectivity of this reaction (1k, 1l, 1m). Furthermore, scaling up the reaction from 0.5 to 5.0 mmol did not have a detrimental effect on the product yield (1b) (Table 1). However, the reduction reactions of 1-phenylbutan-1-one, methyl benzoate, and N,N-dimethylbenzamide resulted in lower yields and the formation of complicated byproducts.

Regarding heteroaromatic compounds, acridines 1s, quinolines 1t and 1v, isoquinolines 1u, and N-alkylated indoles 1w, were readily reduced (Table 2). Dimerization and over-reduced byproducts were not observed in our reactions.¹³ Reduction of benzofuran 1y afforded a significant amount of the C–O cleavage ring-opening product 2y', while furan is not reduced under these conditions, as is often the case in the traditional Birch reduction. Interestingly, free O–H phenol 1i and free N– H indole 1x were not reduced by Na/15-crown-5/*i*PrOH, indicating the high chemoselectivity of this protocol.

A series of competition studies were performed in order to assess the chemoselectivity of the reaction (Table 3). The results demonstrate that electron-deficient aromatic compounds like 1k (Table 3, entry 1), polynuclear aromatics such as 1c (Table 3, entry 2), conjugated alkenes such as 1d(Table 3, entry 4), and heteroaromatic compounds such as 1s crown-5/*i*PrOH^{*a*}

substrate product (yield)^b 1b 2b, [94% (92%^c)] M16 M16 2c (98%) 1c 2d (98%) 1d 1e 2e (65%) 1f 2f (90%) 2f (81%) -Ph 1g Ph ____ Ph 0 1h 2h (82%) OF 1i (>95% 1i recovered) **2j** (95%) 1j 2a C X = m-F (99%); X = o-F (62%) 1k, X = *m*-F; 1l, X = *o*-F X = p-F(89%); X = m-Cl(71%)1m, X = p-F; 1n, X = m-CI10 2a (79%) OMe OMe Ĥ 2p (87%) 1p Ĥ MeC 1q 2q (96%) 1r 2r (97%)

Table 1. Reduction of Aromatic Substrates Using Na/15-

^{*a*}Conditions: 1 (0.50 mmol, 1.0 equiv), Na/*i*PrOH/15-crown-5 (3.0–9.0 equiv), THF (3.0 mL), 0 °C. ^{*b*}Isolated yield. ^{*c*}1 (5.0 mmol).

(Table 3, entry 3) can be selectively reduced in the presence of unactivated benzenoids such as 1b. Furthermore, selective reduction of phenol ether 1h in the presence of the corresponding phenol 1i can also be readily achieved (Table 3, entry 5).

In summary, a practical and highly chemoselective ammoniafree Birch reduction mediated by Na/15-crown-5/*i*PrOH has been developed. The key to the success is the use of chelating 15-crown-5, which switches the electron transfer mediated by sodium from an inner to an outer sphere electron transfer. Critical from a practical standpoint, the reaction requires only inexpensive, air- and moisture-stable reagents. Excellent yields were obtained across a broad range of aromatic and heteroaromatic substrates. In general, the substrate scope and regioselectivity compare well with the classic Birch reduction; however, this new method is operationally trivial and gives much higher chemoselectivity. Rigorous purification of reagents, a strictly inert atmosphere, hazardous flammable

 Table 2. Reduction of Heteroaromatic Substrates Using Na/ 15-crown-5/*i*PrOH^a



^aConditions: 1 (0.50 mmol, 1.0 equiv), Na/iPrOH/15-crown- (3.0– 6.0 equiv), THF (3.0 mL), 0 °C. ^bIsolated yield.

Table 3. Competition Reactions

entry	substrate A	substrate B	Na/ <i>i</i> PrOH/ 15-crown-5	conversion A/B (%)
1	1b	1k	9.0 equiv	<5:60
2	1b	1c	3.0 equiv	<5:62
3	1b	1s	6.0 equiv	<5:84
4	1b	1d	3.0 equiv	<5:51
5	1i	1h	9.0 equiv	<5:>95

reagents, and impractical low reaction temperatures are not required. The high chemoselectivity of this method will potentially expand the application of the Birch reduction in the construction of complex molecules. Most importantly, this new practical method to prepare electride salts provides a general strategy for the application to other Na/NH_3 mediated reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b00891.

Experimental procedures and compound characterization data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: jie_an@cau.edu.cn. ORCID [©]

Peng Lei: 0000-0003-1685-9517 Jie An: 0000-0002-1521-009X

Author Contributions

[‡]P.L. and Y.D. contributed equally.

Notes

The authors declare no competing financial interest.

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