ORGANIC CHEMISTRY

Scalable Birch reduction with lithium and ethylenediamine in tetrahydrofuran

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The Birch reduction dearomatizes arenes into 1,4-cyclohexadienes. Despite substantial efforts devoted to avoiding ammonia and cryogenic conditions, the traditional, cumbersome, and dangerous procedure remains the standard. The Benkeser reduction with lithium in ethylenediamine converts arenes to a mixture of cyclohexenes and cyclohexanes; this is operationally easier than the Birch reduction but does not afford 1,4-cyclohexadienes. Here, we report a Birch reduction promoted by lithium and ethylenediamine (or analogs) in tetrahydrofuran at ambient temperature. Our method is easy to set up, inexpensive, scalable, rapid, accessible to any chemical laboratory, and capable of reducing both electron-rich and electron-deficient substrates. Our protocol is also compatible with organocuprate chemistry for further functionalization.

Dearomatization is widely used in chemical synthesis (*1*). The Birch reduction dearomatizes arenes into 1,4-cyclohexadienes with lithium, sodium, or potassium in liquid ammonia at ≤−33°C (Fig. 1A) (*2*, *3*) and has been employed throughout the pharmaceutical industry (*4*, *5*), perfumery industry (*6*, *7*), and academia (*8*–*11*).

Liquid ammonia must be prepared with specialized equipment and carefully dissipated after the reaction is complete. Both steps are time consuming; for example, removal of 1 L of liquid ammonia (850 L as gas) can take up to 12 hours (*12*), and as much as 7.5 L of liquid ammonia per mole of substrate may be needed (*5*, *13*). Even on a 3.5-mmol scale, the Birch process requires 7 hours from setting up equipment to the completion of biphasic extraction (*14*). These logistical challenges make it difficult to perform multiple Birch reductions in parallel. Also, the liquid ammonia solvent has long been deemed necessary to solubilize alkali metals to form the solvated electron.

To overcome these challenges, researchers have developed ammonia-free conditions. For example, the Benkeser group used lithium and neat ethylamine, ethylenediamine, or a mixture of primary and secondary amines, providing a mixture of over-reduced products, and did not use any other solvents (Fig. 1B) (*15*–*17*). Arenes could be reduced to the Birch-type products with lithium in a mixture of methylamine and isopropanol, but overreduction appeared inevitable (*18*). Benzoic acid was reduced to benzaldehyde in 25% yield in the presence of lithium, methylamine, and ammonium nitrate (*19*). The benefit of ethylenediamine as a solvent for dissolving metal reductions was also demonstrated by others (*20*). The Dolby group reduced three substates to the corresponding Birch-type products in 45% to quantitative yield using lithium, ethylenediamine, *n*-propylamine, and *t*-butanol (*4*). This method was moderately successful in one instance (*21*) and was not effective in the *N*-detosylation of a challenging substrate (*22*). Donohoe and House reported the reduction of electron-deficient arenes and heterocycles using di-*tert*-butylbiphenyl ($1000/mol; Sigma-Aldrich) and lithium at −78°C (Fig. 1C) (*23*). Their method was highly oxygen sensitive and as lengthy as the standard Birch procedure (*14*). An's method (Fig. 1D) requires sodium and 3 to 9 equivalents of 15-crown-5 ($1579/mol; Sigma-Aldrich) and is limited to electron-rich or neutral substrates (*24*). The Baran group described an electrochemical reduction of electron-rich arenes (Fig. 1E) with 3.5 to 10 equivalents of tri(pyrrolidin-1-yl)phosphine oxide ($5040/mol; Sigma-Aldrich) and 3 equivalents of 1,3-dimethylurea ($5/mol; Sigma-Aldrich), both of which must be removed from the product by column chromatography (*13*). Their 0.45-mol scale reaction took 3 days in a flow reactor without tri(pyrrolidin-1-yl)phosphine oxide (*13*). The Sugai group treated arenes with lithium and ethylenediamine in tetrahydrofuran (THF) or Et_2O but did not isolate 1,4-cyclohexadiene products (*25*, *26*) and indicated that THF might be a ligand for a lithium ion (*25*).

Despite these efforts, the original, cumbersome, and dangerous Birch protocol remains the current standard (*14*, *27*). Because of the

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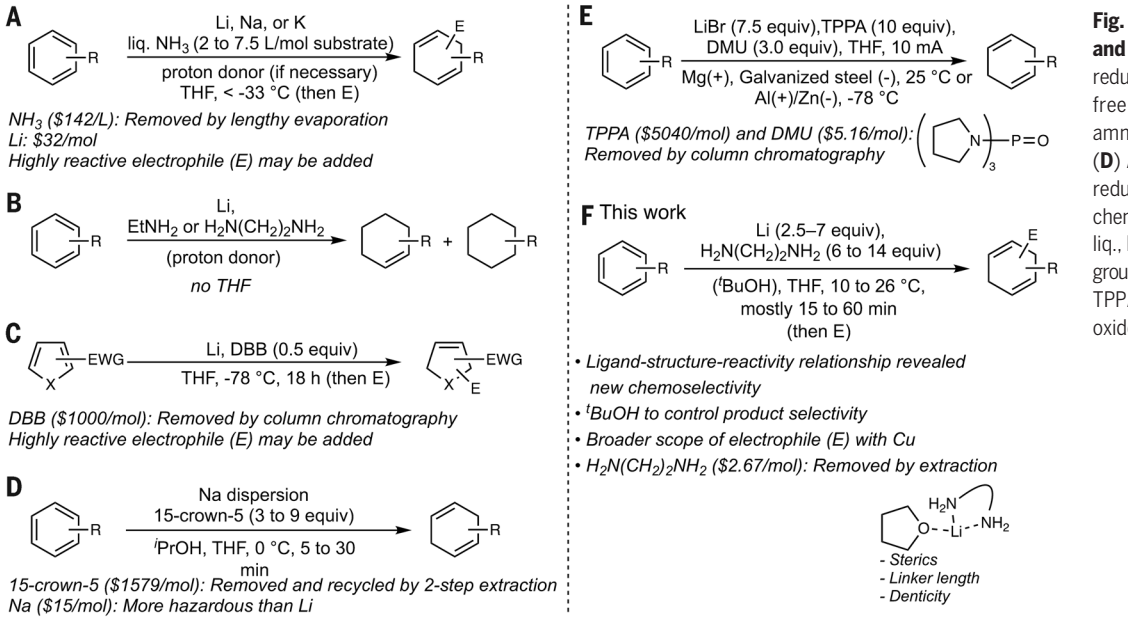

Fig. 1. Previous Birch reductions and this work. (**A**) General Birch reduction. (**B**) Benkeser's ammonia-free reduction. (**C**) Donohoe's ammonia-free Birch reduction. (**D**) An's ammonia-free Birch reduction. (**E**) Baran's electrochemical reduction. (**F**) This work. liq., liquid; EWG, electron-withdrawing group; DBB, 4,4′-di-*tert*-butylbiphenyl; TPPA, tri(pyrrolidin-1-yl)phosphine oxide; DMU, 1,3-dimethylurea.

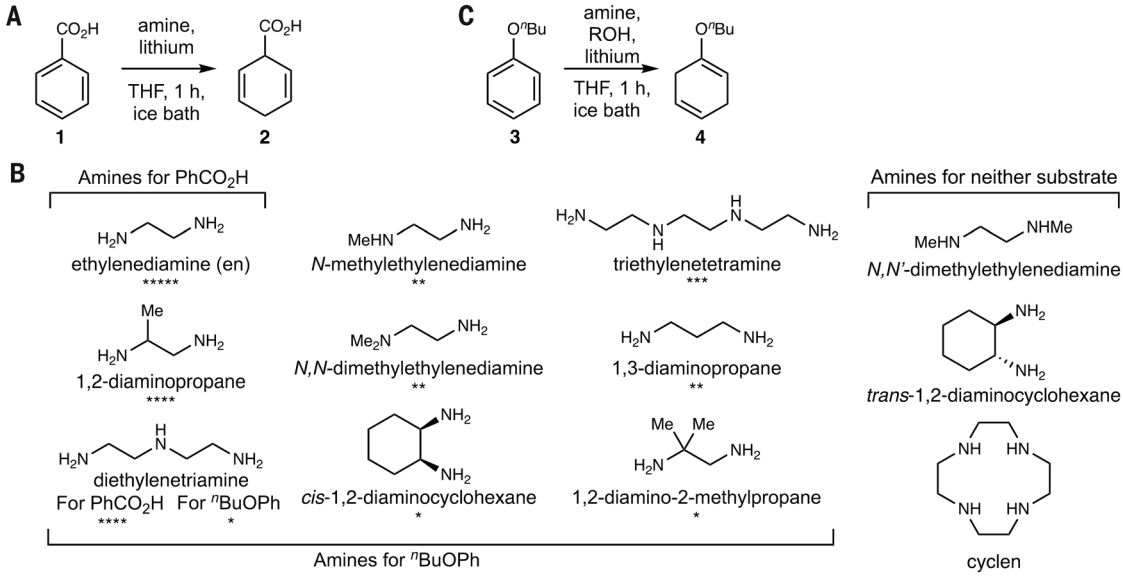

Fig. 2. Summary for the optimization study. (**A**) Reduction of $PhCO_2H$ (**1**). (**B**) Amine structures and efficiency. (**C**) Reduction of *n*-butoxybenzene (**3**).

inconvenient procedure, Birch reductions are often avoided in favor of safer and often lengthier synthetic schemes (*28*, *29*). Therefore, there remains a need for a Birch reduction protocol that is fast and effective for both electron-rich and -deficient arenes without ammonia, specialized equipment, or expensive additives. Here, we report such a Birch reduction with ethylenediamine as a ligand ($2.67/mol; Sigma-Aldrich) and lithium in THF (Fig. 1F). We also report influence of the amine structure on the selectivity, including inverse electron-demand chemoselectivity. Finally, we propose more active roles for amines, alcohols, and solvents than previously considered, providing a platform for controlling the chemoselectivity.

Benzoic acid ($PhCO_2H$, **1**; Fig. 2A) was chosen as our starting model substrate because of the deficiency of currently reported conditions for the reduction of electron-deficient arenes. First, we evaluated a protocol in which a balloon was filled with ammonia gas and attached to a flask containing lithium and the substrate in THF (*30*) to find that diene **2** was obtained in 83% yield (table S1, entry 1). However, this method was not effective for electron-rich substrates, typically resulting in incomplete reactions. Consequently, we began to investigate alternative amine-based ligands (Fig. 2B) that could be broadly applicable, inexpensive, and easy to handle while also affording the desired Birch reduction products. With 5.0 equivalents of lithium and 1.0 or 2.5 equivalent(s) of ethylenediamine, diene **2** was produced in 4 or 83% yield, respectively, after 6 hours (entries 2 and 3). Using 5.0 equivalents of ethylenediamine could lower the necessary amount of lithium to 2.5 equivalents and the time to 1 hour (90% yield; entry 4).

The reaction did not proceed without ethylenediamine (entry 5). Also, the combination of ethylenediamine and lithium was essential as there was no reduction when sodium metal was employed (entry 6). We then began to investigate whether the reaction could be improved further by fine-tuning the linker length and denticity of the ligand. 1,3-Diaminopropane gave no product (entry 7). Diethylenetriamine was as effective as ethylenediamine, providing **2** in 86% yield (entry 8), but triethylenetetramine was ineffective (entry 9). Other 1,2-diamines (*N*-methylethylenediamine, *N*,*N*′-dimethylethylenediamine, *trans*-1,2-diaminocyclohexane, and *cis*-1,2-diaminocyclohexane) failed to promote the reduction (entries 10 to 13). Although 1,2-diaminopropane had similar reactivity as ethylenediamine, affording diene **2** in 85% yield (entry 14), the reaction did not progress with 1,2-diamino-2-methylpropane (entry 15). Also, no reduction occurred with cyclen (entry 16). Although diethylenetriamine was as effective as ethylenediamine, we continued to use ethylenediamine (ethylenediamine, $2.67/mol, versus diethylenetriamine, $7.59/mol). The reaction could be scaled up to 10 g (82 mmol), resulting in 95% isolated yield (entry 17).

We proceeded to optimize the reaction conditions for an electron-rich system using *n*-butoxybenzene (^{n}BuOPh, **3**; Fig. 2C) as a model substrate, lithium (2.5 equivalents), and amine (5 equivalents) in THF on ice. This substrate was not reduced without alcohol present (table S2, entry 1). This is consistent with the known mechanism in which electron-rich arenes cannot accept the second electron unless the radical anion intermediate is protonated to form the corresponding radical species (*31*). Also, we did not observe any of the dealkylated phenol by-product that was reported in the method developed by Sugai (*25*). With methanol, ethanol, isopropanol, *t*-butanol, (*2*, *32*) and *t*-amyl alcohol, diene **4** was produced in 33, 58, 62, 75, and 68% yields, respectively, with the over-reduced product **5** in 4 to 11% yields (entries 2 to 6). To study the importance of the acidity of the alcohol, we tested 2,2,2-trifluoroethanol and 1,1,1,3,3,3-hexafluoroisopropanol, which afforded yields of 52 and 26%, respectively (entries 7 and 8). Use of 1,3-diaminopropane and diethylenetriamine diminished yields to 33 and 9%, respectively (entries 9 and 10). The yield was increased to 51% with triethylenetetramine (entry 11; as compared with entry 9 in table S1). The effects of the *t*-butanol/ethylenediamine ratio are described in fig. S1. The reaction did not proceed when sodium was used in lieu of lithium (entry 12). With *N*-methylethylenediamine, *N*,*N*′-dimethylethylenediamine, and *N*,*N*-dimethylethylenediamine, diene **4** was produced in 33, 3, and 27% yields, respectively (entries 13 to 15). When employing cyclen, no reduction occurred (entry 16). *Trans*-1,2-diaminocyclohexane was ineffective even after 3 hours (entry 17), and *cis*-1,2-diaminocyclohexane promoted the reduction, albeit more slowly than ethylenediamine (entries 18 and 19). Use of 1,2-diaminopropane and 1,2-diamino-2-methylpropane produced diene **4** in 65 and 11% yields (entries 20 and 21). To fully consume the starting material, the equivalents of lithium and ethylenediamine were increased to 3 and 6, respectively, to form diene **4** in 85% yield (entry 22).

After obtaining the optimal reaction conditions for $PhCO_2H$ and ^{n}BuOPh, we investigated the substrate scope. All of the experiments were performed on 2.5- to 10-mmol scales and took only 0.25 to 3 hours, including preparation and workup. $PhCO_2H$ and its analogs were reduced

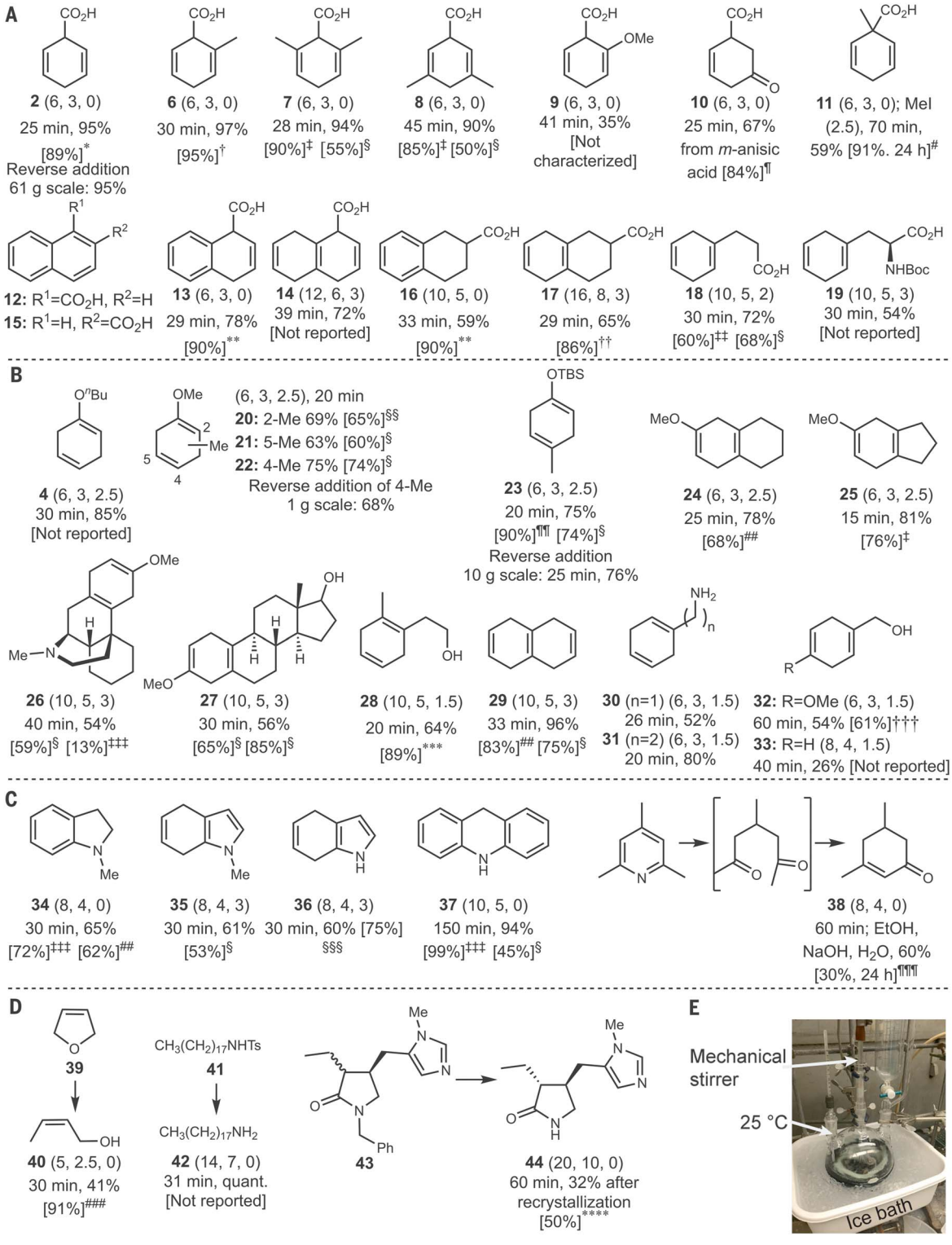

Fig. 3. Scope of the current method. The numbers in the parentheses are the equivalents of ethylenediamine, lithium, and t-butanol, in this order. All reactions were performed in THF on ice bath. Previous yields with other methods are shown in brackets. (**A**) Products of the Birch reduction of carboxylic acids. (**B**) Products of the Birch reduction of aryl ethers and phenyl derivatives. (**C**) Products of the Birch reduction of assorted N-heterocycles. (**D**) Assorted dissolving-metal reduction reaction products. (**E**) Photograph of setup for 0.5-mol reduction of $PhCO_2H$. Symbols indicate the following references: *, (*58*); †, (*59*); ‡, (*60*); §, (*13*); ¶, (*61*); #, (*62*); **, (*33*); ††, (*34*); ‡‡, (*63*); §§, (*64*); ¶¶, (*65*); ##, (*66*); ***, (*35*); †††, (*37*); ‡‡‡, (*24*); §§§, (*67*); ¶¶¶, (*40*); ###, (*6*); ****, (*4*).

to the corresponding products **2**, **6**, **7**, **8**, **9**, and **10** in mostly high yields (Fig. 3A). We also found that quenching the reduction of $PhCO_2H$ with methyl iodide gave the corresponding alkylated product **11** in 59% yield. The streamlined process allowed us to expeditiously modify stoichiometries and probe scarcely investigated reactivities; for example, carboxylic acid **12** was reduced to the typical Birch reduction product **13** in 78% yield without *t*-butanol. With *t*-butanol, triene **14** was produced in 72% yield. Carboxylic acid **15** was reduced to acid **16** or diene **17** without or with *t*-butanol in 59 or 65% yield, respectively (*33*, *34*). Hydrocinnamic acid was converted to the corresponding diene **18** in 72% yield. *N*-Boc-L-phenylalanine was reduced to diene **19** in 54% yield.

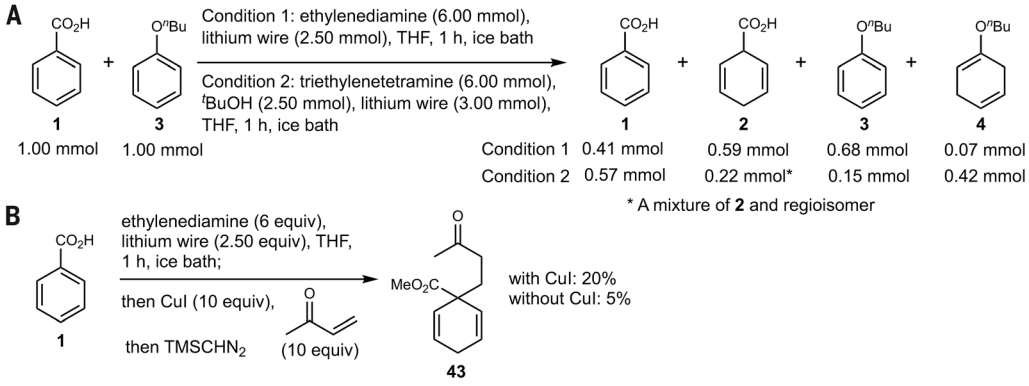

Fig. 4. Tuning selectivity and downstream reactivity. (**A**) Normal chemoselectivity with ethylenediamine and reversed chemoselectivity with triethylenetetramine. (**B**) The Birch reduction–cuprate addition reaction.

Next, we subjected ^{n}BuOPh and 2-, 3-, and 4-methylanisole to the reaction conditions to form 1-alkoxy-1,4-cyclohexadienes **4**, **20**, **21**, and **22** in 85, 69, 63, and 75% yields, respectively (Fig. 3B). The Baran group demonstrated the industrial application of the reduction of 4-TBSO-toluene to form the silyl enol ether **23** in 74% yield after 16 hours in batch (*13*). The current method produced the same product on a similar scale in 75% yield after 20 min. 6-Methoxy-1,2,3,4-tetrahydronaphthalene was reduced to methyl ether **24** in 78% yield. A similar transformation was equally efficient (81% yield) to afford methyl ether **25**, which was previously used in synthetic studies for (–)-daphlongamine H (*11*). Dextromethorphan (cough suppressant) and estrone-3-methyl ether were reduced to **26** and **27** in 54 and 56% yields, respectively. The demethylated phenol products were also not observed with dienes **20** to **22** and **24** to **27**. The Birch reduction of 2-(*o*-tolyl)ethanol to form **28** was the first step in the total synthesis of atractyligenin (*35*). Here, our method produced **28** in 64% yield. Naphthalene was reduced to triene **29** in 94% yield. Our method reduced benzylamine and phenethylamine to dienes **30** and **31** in 52 and 80% yields, respectively. The benzylic hydroxy group is generally lost in the Birch reduction (*36*), but *p*-methoxybenzylic alcohols may be converted to the corresponding reduced alcohols (*37*, *38*). Our method reduced *p*-methoxybenzyl alcohol to diene **32** in 54% yield. Benzyl alcohol was reduced to diene **33** in 26% yield under our conditions without losing the benzylic hydroxy group. This diene was previously prepared in two steps (*39*).

N-Methylindole was converted to **34** or **35** without or with *t*-butanol in 65 or 56% yield (Fig. 3C), whereas other methods afforded only one of the two products (*13*, *24*). Indole and acridine were reduced to pyrrole **36** and dihydroacridine **37** in 60 and 94% yields, respectively. The transformation of pyridines to cyclohexenones is useful but underutilized (*40*, *41*). Although our standard reaction conditions with 2,4,6-collidine produced cyclohexenone **38** in 27% yield, the simple procedure enabled rapid screenings to discover that *t*-butanol was unnecessary, improving the yield to 60%.

Previously, reductive ring openings of cyclic allylic ethers were performed at –78°C (*6*) or at ambient temperature for 48 hours (*7*). Here, our method reductively opened 2,5-dihydrofuran (**39**; Fig. 3D) to produce Z-allylic alcohol **40** in 41% yield after 30 min on ice (lower yield is because of the volatility of the alcohol) (*6*). Tosyl amide **41** was deprotected under our reaction conditions to form amine **42** in quantitative yield. The *N*-debenzylation of **43** (a mixture of diastereomers) to form amide **44** was of industrial interest (*4*) and was accomplished in 32% yield after recrystallization. Failed substrates are shown in fig. S2.

We found that the reaction proceeded faster with a greater stir rate (fig. S3A). Also, the current method is compatible with trace water and air, as the use of distilled and degassed THF only mildly improved the yield (78 versus 75%) (fig. S3A). For the development of scalable procedures, it was desirable to perform the reaction at higher concentrations. We found (fig. S3, B and C) that the $PhCO_2H$ and ^{n}BuOPh concentrations could be increased up to 0.8 M, which also accelerated the reduction. Although the yield of diene **2** was unaffected, the increased reaction rate led to monoolefin **5** and the 1,3-cyclohexadiene with ^{n}BuOPh (fig. S3B). To further improve the scalability, we suspended lithium in THF then cooled the flask on ice, after which a solution of ethylenediamine and $PhCO_2H$ in THF was added. This procedure was equally effective when we scaled up this reaction to 61 g (0.50 mol) (Fig. 3E). Monitoring the internal temperature revealed that the reaction proceeded at ~10°C; therefore, we decided to keep the internal temperature in the 10° to 26°C range. The 0.50-mol scale reaction took 1 hour including preparation and workup to obtain diene **2** in 95% yield. A similar reverse-addition protocol was applied to 4-methylanisole and 4-OTBS toluene. It was necessary to add *t*-butanol to the suspension last to suppress both the overreduction and isomerization of the desired product to the 1,3-cyclohexadiene. 4-Methylanisole was reduced to diene **22** in 68% yield, and 4-OTBS toluene (10-g scale) was reduced to diene **23** in 76% yield. Both of these experiments (setup plus reaction plus isolation of the products) also took 1 hour, which is substantially shorter than literature precedent (1 to 2 days) (*13*).

Generally, electron-withdrawing groups increase reduction rates, whereas electron-donating groups decrease them (*42*–*44*). Specifically, the Birch reduction of benzoate is more than 61 times as fast as that of anisole under traditional conditions (*45*). In Fig. 2A, we summarize the relative reactivity with asterisks, which suggested that it might be possible to reduce an electron-rich arene in preference to an electron-deficient arene. We performed a reduction with an equimolar mixture of $PhCO_2H$ and ^{n}BuOPh, ethylenediamine, and lithium without *t*-butanol to obtain acid **2** and ether **4** in 59 and 7% yields, respectively (Fig. 4A), which is consistent with the literature (*45*). The same conditions with *t*-butanol gave a mixture of acid **2** along with other intractable products. We then exploited our earlier results by replacing ethylenediamine with triethylenetetramine to discover that the electron-rich arene ^{n}BuOPh was more reactive than the electron-deficient arene $PhCO_2H$ (43% consumption of $PhCO_2H$ versus 85% consumption of ^{n}BuOPh), affording **2** and **4** in a 1:2 ratio.

The liquid ammonia solvent in the Birch reduction has hampered productive interception of the carbanion intermediate. For example, a Birch alkylation with methyl vinyl ketone failed because ammonia caused the polymerization of the ketone (*46*). The large excess of amine solvent can also interfere with added metals for cross-coupling reactions. This would not be circumvented under Dolby's conditions with ethylenediamine and *n*-propylamine (*4*). Given the use of only 6 equivalents of ethylenediamine under our conditions, we hypothesized that the Birch reduction could be coupled with cuprate chemistry. After the reduction of $PhCO_2H$ under our reaction conditions, CuI

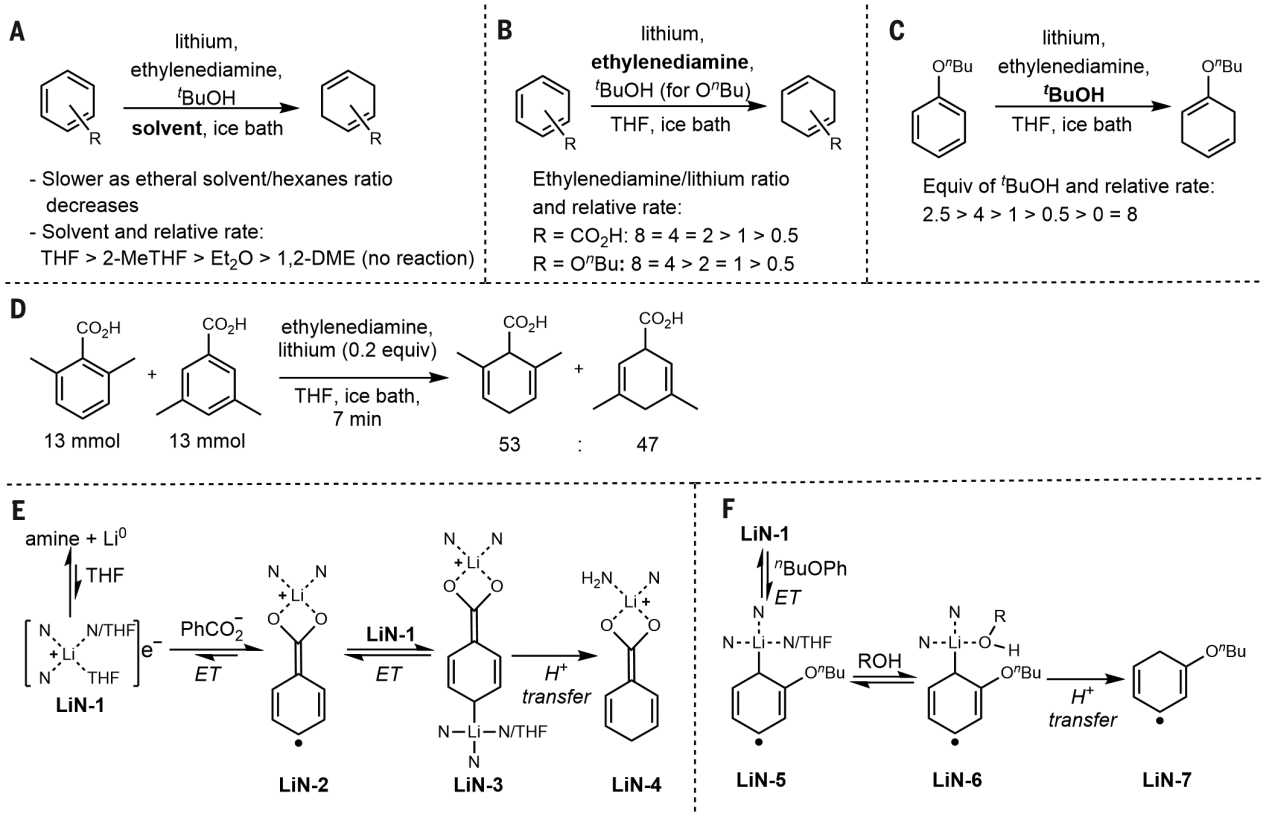

Fig. 5. Summary of kinetic studies and proposed mechanisms. (**A**) Rate dependence on solvent for the reduction of $PhCO_2H$ or ^{n}BuOPh. (**B**) Dependence on ethylenediamine/lithium ratio for the reduction of $PhCO_2H$ or ^{n}BuOPh. (**C**) Dependence on *t*-butanol for the reduction of ^{n}BuOPh. For all data, the yields were determined by proton nuclear magnetic resonance (^{1}H NMR) spectroscopic analysis using 1-methoxyadamantane as an internal standard. (**D**) Competition experiment. (**E**) Proposed mechanism for $PhCO_2H$. (**F**) Proposed mechanism for ^{n}BuOPh. Hydrogen atoms, linkers, and methyl groups on ligands are omitted for clarity. ET, electron transfer.

and methyl vinyl ketone were added (Fig. 4B). Under these unoptimized conditions, ketone **45** was generated in 20% yield while forming a quaternary carbon.

We then investigated the kinetics for both ^{n}BuOPh and $PhCO_2H$ reduction under various conditions (fig. S3, D to K). First, we found that the reduction rates depended upon THF concentrations as well as the choice of ethereal solvent (Fig. 5A and fig. S3, D to G). The decreasing polarity of the reaction medium most likely affects the stability and solubility of the radical anion that is usually stabilized by ammonia (*47*). Next, as the ethylenediamine/lithium ratio increased (Fig. 5B and fig. S3, H and I), so did the reaction rate (fig. S3, J and K). However, the reduction of ^{n}BuOPh produced increasing amounts of 1-butoxy-1,3-cyclohexadiene as well as monoolefin **5**. This outcome is similar to the results observed when we only increased the initial concentration of the reaction mixture. Finally, the reduction rate steadily increased when changing from 0 equivalents to 2.5 equivalents of *t*-butanol (Fig. 5C). However, when increasing the equivalents of *t*-butanol past 2.5, the reduction rate decreased (fig. S4A).

From the data presented here, we propose that the reduction of $PhCO_2H$ proceeds according to Fig. 5E; first, lithium(0) is dissolved through the coordination of the amine ligand and THF to create LiN-1. Second, an electron transfer occurs to give radical anion LiN-2. Subsequently, another electron transfer occurs to afford trianion LiN-3, which may be in equilibrium with higher-order aggregates (*48*). Finally, this species is protonated to form LiN-4. Figure 5F shows our hypothesized mechanism for the reduction of ^{n}BuOPh. An electron is transferred from LiN-1 to the substrate to form radical anion LiN-5. Next, *t*-butanol binds the lithium to give LiN-6, which triggers the rate-determining intramolecular protonation to form the radical species LiN-7. In Fig. 5, E and F, the lithium dissolution and electron transfer are in equilibrium (*45*).

To understand the ligand's effect on reactivity, we first considered the dissolution of lithium(0). If the dissolution step accounts for the structure-reactivity relationship, the effective amines should dissolve lithium faster than ineffective amines (Fig. 2A). Our qualitative experiments with lithium and ethylenediamine, *cis*-, or *trans*-1,2-diaminocyclohexane in THF without arenes showed that although ethylenediamine partially dissolved lithium, the other two amines did not. This is distinct from the fast dissolution of lithium in the presence of arene substrates. Therefore, dissolution alone cannot account for the structure-reactivity relationship.

Second, how do the ligand structures affect the electron transfer processes? We reason that as the denticity of the ligand increases from ethylenediamine to diethylenetriamine then to triethylenetetramine, the amino groups displace the benzoate of LiN-2 with nitrogens, disrupting the electron transfer step, particularly if this is an inner-sphere electron transfer. Currently, it is unclear how many nitrogen atoms are bound to lithium in each intermediate, but the failure with cyclen suggests that when four amino groups are bound, such a complex appears unreactive. Steric effects of amines warrant further studies.

Third, how do the amines influence the rate-determining protonation step (*49*, *50*) for the reduction of ^{n}BuOPh? Organolithum's carbon is protonated faster with 1,2-diamines than with 1,3-diamines (*48*). Therefore, we suggest that the protonations of LiN-3 and LiN-6 are faster with ethylenediamine than with 1,3-diaminopropane.

Fourth, we considered how the alcohol affects the protonation and product distribution in our reduction. Figure S4 indicates that the alcohol may play a more substantial role than only a proton donor. For example, if *t*-butanol intermolecularly protonates radical anion LiN-5,

the rate should be linearly proportional to the alcohol concentration. Instead, we observed a bell-shaped trend (fig. S4B), which indicates that protonation may occur intramolecularly through LiN-6. The slight preference between related substrates with different steric environments (Fig. 4D) bodes well with this hypothesis. Notably, the reaction mixture containing ^{n}BuOPh turned light blue with 8 equivalents of *t*-butanol, although the desired reduction did not occur. This suggests that excess alcohol may outcompete amino groups on the lithium at an earlier stage of the reaction, forming less-reductive solvated electrons, similar to work with SmI_2 (*51*). A mass effect may have obscured the additional role of *t*-butanol in the past; traditionally, the amine has been used in greater excess than the alcohol, outcompeting the alcohol for coordination to the lithium.

When <1 equivalents of *t*-butanol were present in the reduction of ^{n}BuOPh, the monoolefin was formed in ~20% yield. This is similar to the Benkeser reduction without alcohol (Fig. 1B) (*15*–*17*, *52*–*54*). Although the addition of an alcohol under the Benkeser-type conditions gave Birch-type products (*4*, *18*, *55*), these findings have not garnered widespread use. The alcohol is necessary to synthesize Birch products by protonating both the organolithiated species (LiN-5 or LiN-6) and the lithium amide in the reaction mixture (*18*). The protonation of the lithium amide then hinders the isomerization of the 1,4-diene to the 1,3-diene, which slows the formation of the monoolefin. Potential effects of *t*-butoxide would warrant further investigation.

Literature has shown that more acidic alcohols (e.g., methanol and ethanol) give faster reductions but lower yields than bulkier alcohols (e.g., isopropanol and *t*-butanol) because of an off-reaction with lithium to create H_2 (*45*, *50*). Although our data mostly support such a notion, we wish to consider other factors based on the data with trifluoroethanol (52%), methanol (33%), and ethanol (58%) (table S2) combined with the structural requirements of the amine (Fig. 2A), including optimal bite angle (*56*) (ethylenediamine versus 1,2-diamino-2-methypropane). For example, fig. S5 describes how the equilibrium between a monomer and higher-order aggregates of various ligated lithium intermediates can be affected by the amine ligand among other factors.

The switch of the solvent from an amine to an ethereal solvent (THF) was essential for this work. Altundas's conditions (ammonia gas in a balloon, lithium, and THF) (*30*) suggested that the amine might not be needed as a solvent. 1,2-Dimethoxyethane was ineffective as the solvent, which indicates that only one molecule of THF binds to a lithium ion to form reactive species. The role of THF as a ligand for the alkali metal ion most likely had not been considered before because the ethereal solvent was previously used in smaller amounts than the amine solvent.

The method discussed in this paper could reverse the chemoselectivity for the reduction of $PhCO_2H$ and ^{n}BuOPh by two orders of magnitude with triethylenetetramine (61-fold difference under the standard Birch reduction conditions in favor of $PhCO_2H$ and twofold difference under our conditions in favor of ^{n}BuOPh). More broadly, the structure-reactivity relationship indicates the potential for (reverse) chemoselective reduction in synthesis. To control the selectivity, inner- and outer-sphere electron transfer processes may be considered (*22*, *24*). Our work also suggests a broader role for the alcohol than previously considered, including the product selectivity with naphthalene and indole systems. Also, this study gives a platform to investigate solvated electrons at room temperature.

In addition to the theoretical advancements, the practicality of the technology should render the lithium-mediated reduction and deprotection more accessible to a broader scientific community and more amenable to the time-economic synthesis of complex molecules (*57*). Finally, the scope of the Birch reduction may be expanded by combining the chemistry of organolithium with other organometallic chemistry.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S6
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Scalable Birch reduction with lithium and ethylenediamine in tetrahydrofuran

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Easy aryl reductions

The Birch reduction has been widely used for more than half a century to achieve partial reduction of aryl rings by alkali metals at just two diametrically opposed carbon sites. However, the conditions require condensation of caustic gaseous ammonia. A variation developed soon afterward by Benkeser used safer liquid ethylene diamine but was prone to overreduction. By diluting ethylene diamine in tetrahydrofuran solvent, Burrows *et al*. now obtain selectivities comparable to Birch conditions but without the need for condensed ammonia. —JSY