Highly Efficient and Air-tolerant Calcium-based Birch Reduction Using Mechanochemistry

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In this study, we report a mechanochemical protocol for highly efficient and air-tolerant calcium-based Birch reduction. The developed mechanochemical approach allows the use of readily available calcium metal as a safer-to-handle reductant for Birch reduction of various aromatic compounds. The reaction was rapid, and the desired dearomatization products were obtained in good yields within 15 min at ambient temperature. Notably, all synthetic operations can be performed under ambient conditions without a complicated reaction setup involving inert gases. The feasibility of the gram-scale synthesis was demonstrated, further highlighting the practical utility of this protocol.

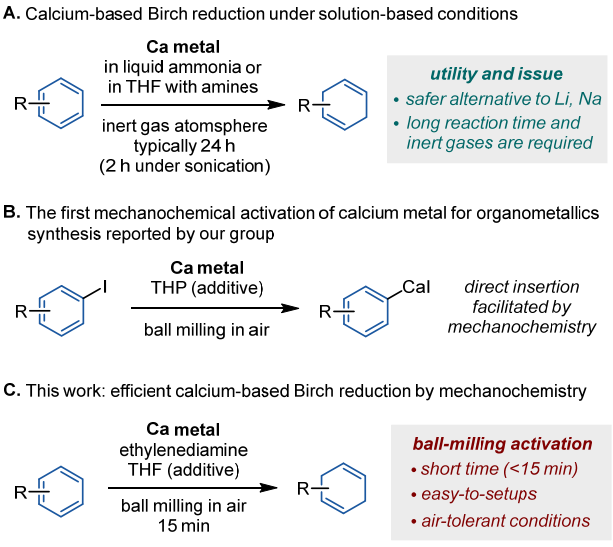
Keywords: Ball milling, Mechanochemistry, Calcium, Birch reduction

The Birch reduction, discovered nearly eight decades ago, is a powerful method for dearomatizing aromatic rings to produce 1,4-cyclohexadiene derivatives.[1-3] Owing to its versatile synthetic utility, Birch reduction has been widely used in synthesizing complex natural products, pharmaceuticals, and fine chemicals from readily available aromatic compounds. The traditional approach involves the use of alkali metals (Li, Na, and K) dissolved in liquid ammonia.[1-3] To avoid the use of toxic ammonia in complicated reaction setups, several ammonia-free systems using organic solvents have been developed.[2,3] However, the highly reactive and potentially hazardous alkali metals often require special precautions or delicate operating conditions. This safety concern is a major drawback of traditional Birch reduction protocols, particularly in large-scale settings.

In this context, Birch reduction using less reactive alkaline earth metals, such as calcium has attracted attention as a safer alternative to classic methods using alkali metals (Scheme 1A).[4] Although several calcium-based protocols have been developed, long reaction time and large excess of the metal are often required owing to the lower reducing power of calcium metal in comparison to that of the alkali metals.[4] Suslick reported that sonication could accelerate the calcium-based Birch reduction and the reactions were completed in 2 h.[4e] However, the use of significant amounts of dry and degassed organic solvents and the need to operate under an atmosphere of inert gases are still important limiting factors.

Recently, mechanochemical synthesis using ball milling has emerged as a new tool to perform organic transformations.[5-7] This mechanochemical approach is not only considered a simple and sustainable solvent-less alternative to conventional solution-based methods but has also allowed for unique achievements in synthetic chemistry, including uncovering novel reactivity and selectivity that are not available in solution. Among these applications, the mechanical activation of zero-valent bulk metals by ball milling has attracted significant attention as a powerful protocol for performing organometallic reactions.[8] As a recent example, we developed a mechanochemical protocol for extremely fast lithium-based Birch reduction.[9] By utilizing the mechanical activation of lithium metal, most of the reactions are completed within one minute. At almost the same time, Lu et al. reported a solvent-free mechanochemical Birch reduction using K+(LiHMDS)e− (HMDS: 1,1,1,3,3,3-hexamethyldisilazide) as a metal reductant.[10] More recently, we also demonstrated a highly efficient Birch reduction using sodium metal enabled by mechanochemistry.[11] Related to this strategy, our group first reported that the mechanical activation of calcium metal in a ball mill facilitates direct metalation of organic halides to generate calcium-based heavy Grignard reagents (Scheme 1B).[12] Notably, this protocol does not require activated calcium metal, such as Rieke calcium because the ball-milling process allows the surface activation of relatively unreactive calcium metal owing to the high atomization energy.[12]

Scheme 1. Mechanochemical Birch reduction using safer-to-handle calcium metal.



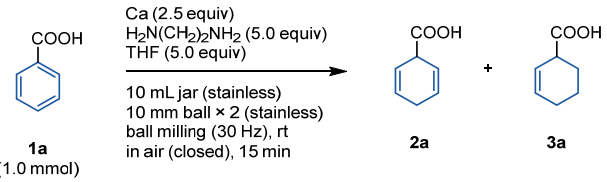
Inspired by these previous studies regarding the mechanochemistry for both calcium activation and efficient Birch reduction with alkali metals, we envisioned that the

mechanical activation of less reactive calcium metal could considerably accelerate calcium-based Birch reduction under ball-milling conditions. Herein, we report the development of a highly efficient and air-tolerant calcium-based Birch-reduction process using mechanochemistry (Scheme 1C). Notably, this method does not require liquid ammonia or bulk solvents and all synthetic operations can be performed under ambient conditions. Various aromatic compounds were reduced within 15 min to afford the desired products in good yields. The practical utility of this protocol was further demonstrated by an efficient gram-scale synthesis.

Initially, we conducted a study to optimize the conditions for Birch reduction using commercially available calcium metals (Table 1). Using benzoic acid (**1a**) as the model substrate, all reactions were performed in a Retsch MM400 mixer mill (stainless-steel milling jar: 10 mL; stainless-steel ball: 10 mm diameter). Based on the optimized conditions for the mechanochemical lithium-based Birch reduction developed by our group[10], the mechanochemical reaction was initially conducted with calcium (2.5 equiv), ethylenediamine (5.0 equiv), and tetrahydrofuran (THF) as a liquid-assisted grinding[13] additive at room temperature. Note that all reactions were conducted under atmospheric conditions and that all reagents and liquid chemicals were purchased from common commercial suppliers and used as received without drying and degassing. The desired Birch reduction product (**2a**) was obtained in a good yield under the initial conditions (85%, entry 1). In addition, a small amount of the over-reduction product (**3a**) was generated as a side product (3%, entry 1). No reaction occurred in the absence of calcium metal, ruling out the possibility that the jar materials promoted reduction (entry 2). The reaction did not proceed in the absence of ethylenediamine (entry 3). Although **2a** was obtained in the absence of THF, its yield was slightly lower than that in the reaction with THF (80%, entry 4). We found that lowering the vibration frequency (25 Hz) resulted in a better yield of **2a** (89%, entry 5). However, the reaction performed at 20 Hz resulted in a lower yield of **2a** (82%, entry 6). A prolonged reaction time (30 min) did not improve the yield (79%, entry 7), and a reaction time of 10 min resulted in almost no generation of **2a** (2%, entry 8), suggesting that 15 min was the optimal reaction time for the present protocol. Using a stainless-steel ball (10 mm in diameter) produced a slightly lower yield of **2a** than using two stainless-steel balls (81%, entry 9).

We conducted control experiments to validate our working hypothesis that ball milling could activate calcium metal to facilitate efficient Birch reduction (Table 2). Under the developed mechanochemical conditions (entry 1), the calcium metal was fully consumed after the reaction (Figure 1). In contrast, when the reaction was performed in a test tube with a magnetic stirring bar in the air, the calcium metal remained intact, and almost no conversion of **1a** was observed, even after a long reaction time (2 h) (entry 2 and Figure 1). The reaction under a nitrogen atmosphere provided a similar result (entry 3, Figure 1). These results suggest that the mechanical activation of calcium metal by the ball milling process considerably accelerated the Birch reduction, which is in good agreement with our working hypothesis.

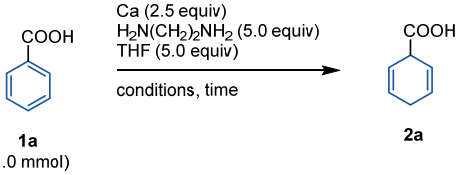
Table 1. Optimization study on calcium-based Birch reduction of benzoic acid (**1a**) under mechanochemical conditions.[a]



entry	variation from standard conditions	recovery of **1a** (%)[b]	yield of **2a** (%)[b]	yield of **3a** (%)[b]
1	none	2	85	3
2	without Ca metal	>99	–	–
3	without $H_2N(CH_2)_2NH_2$	>99	–	–
4	without THF	3	80	5
5	ball milling at 25 Hz	3	89	5
6	ball milling at 20 Hz	2	82	4
7	ball milling at 25 Hz for 30 min	2	79	4
8	ball milling at 25 Hz for 10 min	88	2	1
9	ball milling at 25 Hz with a ball (diameter: 10 mm)	4	81	6

[a]Conditions: **1a** (1.0 mmol), Ca (2.5 mmol), $H_2N(CH_2)_2NH_2$ (5.0 mmol), THF (5.0 mmol) were added to a stainless-steel ball mill jar (10 ml) with two stainless steel balls (diameter: 10 mm). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture using an internal standard.

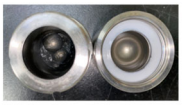
Table 2. Control experiments.[a]



entry	conditions	recovery of **1a** (%)[b]	yield of **2a** (%)[b]
1	our ball milling conditions for 15 min	3	89
2	neat conditions using test tube in air for 2 h	>99	1
3	neat conditions using test tube in N_2 gas for 2 h	91	4

[a]Conditions: **1a** (1.0 mmol), Ca (2.5 mmol), $H_2N(CH_2)_2NH_2$ (5.0 mmol), THF (5.0 mmol) were used. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture using an internal standard.

Figure 1. Reaction mixtures after Birch reduction under different conditions.



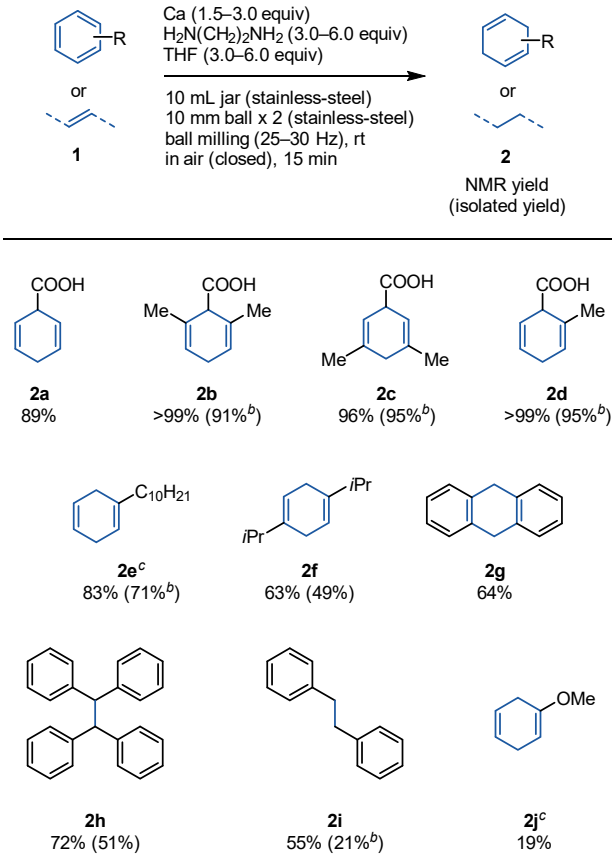
15 min
in ball mill
(entry 1)

2 h, air
in test tube
(entry 2)

2 h, N_2
in test tube
(entry 3)

With the optimized mechanochemical conditions, we explored the substrate scope of the mechanochemical Birch reduction using calcium metal (Table 3). Overall, this method is comparable to solution protocols for calcium-based Birch reduction. The reduction of benzoic acid derivatives (**1a**–**1d**) afforded the corresponding products (**2a**–**2d**) in excellent yields (89–99%). Substrates bearing alkyl groups (**1e** and **1f**) efficiently underwent Birch reduction under the mechanochemical conditions (83% and 63%, respectively). For the reaction of **1e**, the addition of *t*BuOH (2.5 equiv) was crucial for achieving high selectivity toward the Birch-type product **2e** over the over-reduction side product **3e** (refer to the Supporting Information for details). The reaction of anthracene **1g** afforded desired product **2g** in good yield (64%). This calcium-based system is also applicable to the reduction of alkenes. Tetraphenylethylene (**1h**) and stilbene (**1i**) were reduced under mechanochemical conditions to afford the corresponding products (**2h** and **2i**) in moderate-to-good yields (72% and 55% yields, respectively). Unfortunately, the reaction of anisole (**1j**) was sluggish, and the desired reduction product **2j** was obtained in low yield (19%). At this stage, the present system is not effective for electron-rich alkoxyarenes.

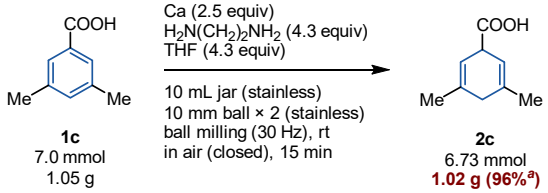
Table 3. Substrate scope of mechanochemical calcium-based Birch reduction.[a]



[a]Conditions: **1** (1.0 mmol), Ca (2.5 mmol), $H_2N(CH_2)_2NH_2$ (5.0 mmol), THF (5.0 mmol) were added to a stainless-steel ball mill jar (10 ml) with two stainless steel balls (diameter: 10 mm). The NMR yields were determined by ^1H NMR analysis of the crude reaction mixture using an internal standard. [b]A small amount of unreacted substrate was contained. See the Supporting Information for details. [c]*t*BuOH (2.5 equiv) was used.

To demonstrate the synthetic utility of this reaction, we investigated a gram-scale synthesis of **2c** (Scheme 2). A 7 mmol-scale reaction was conducted in a 10 mL stainless-steel jar with two 10 mm stainless-steel balls. After ball milling, the reaction was quenched with water and the mixture was subjected to extraction. After removing the solvent, pure **2c** was obtained in 96% yield (1.02 g), which was comparable to the yield obtained in the small-scale reaction. This result emphasizes the practical utility of the calcium-based Birch-reduction protocol.

Scheme 2. Mechanochemical calcium-based Birch reduction on a gram scale.



[a]A small amount of unreacted substrate was contained. See the Supporting Information for details.

In conclusion, we demonstrated a mechanochemical protocol that enables highly efficient calcium-based Birch reduction without the use of bulk solvents or a complicated reaction setup involving inert gases.[14] Most aromatic substrates were reduced within 15 min to produce the desired products in good-to-high yields. A gram-scale reaction under mechanochemical conditions was also demonstrated. These results suggest that mechanochemical Birch reduction using calcium metal could serve as a safer and more sustainable alternative to established solution-based protocols that use potentially hazardous alkali metals.

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Supporting Information is available at http://dx.doi.org/10.1246/cl.******.

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