Exploring stable, sub-ambient temperatures in mechanochemistry via a diverse set of enantioselective reactions

Joel Andersen, James Brunemann, and James Mack

Department of Chemistry, University of Cincinnati, 301 Clifton Court, Cincinnati, Ohio 45221-0172, United States

Supporting Information

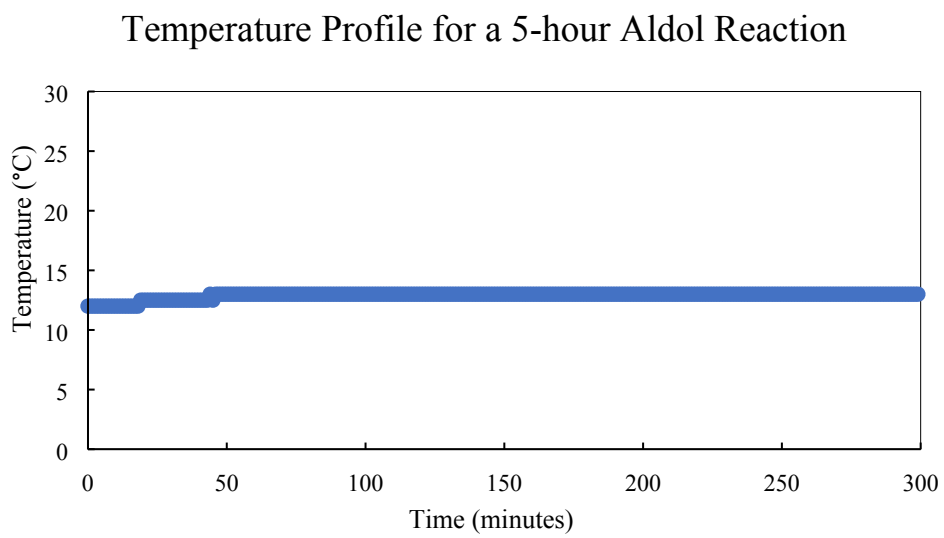
Manufacturer data

All chemical were purchased from Acros Organics with the following exceptions. HPLC Solvents (acetonitrile, heptane, water, and IPA) were purchased from Tedia. From TCI Chemicals was purchased 9,10-dimethylanthracene. The ligand for the A^3 coupling reaction was synthesized in the same manner as that study (ref. 42). Copper (II) triflate was purchased from Alfa Aesar.

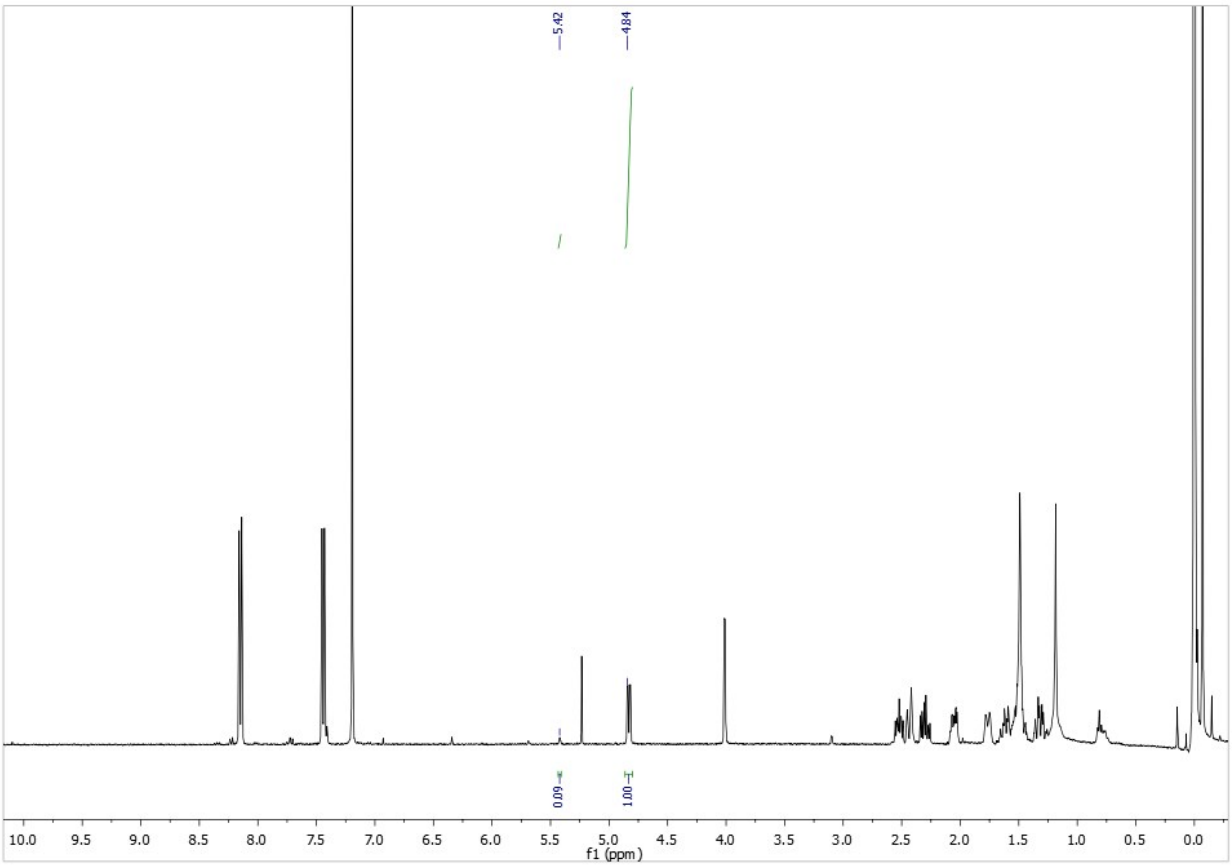
Aldol reaction general procedure

The setup is similar to that of the original study (ref. 39). The following modifications were made for the present study: First, the chilling system was set to the targeted temperature and the cooling jacket (ref. 26) was allowed to equilibrate with it. Next, cyclohexanone (0.5 mmol), (S)-Proline (0.05 mmol, 0.10 equiv), and (when included) the prescribed loading of grinding auxiliary were added to the 15 mL SmartSnap grinding jar (FormTechScientific, https://www.formtechscientific.com/). After this, the 4-nitrobenzaldehyde (0.5 mmol, 1.0 equiv) was added as well as a ¼" stainless steel ball and the jar was sealed. This was inserted into the cooled jacket in the mill and the jar was allowed to equilibrate with the rest of the system prior to starting the mill. Temperature was tracked using an iButton (Maxim Integrated, https://www.maximintegrated.com/en/products/digital/ibutton.html) in a manner described also in Ref. 26. Supporting Figure 1 outlines a typical temperature profile, using the 13 °C reaction as an example. After five hours reaction time, the reaction was worked up in the same manner as the original paper. NMR spectra were compared to the literature for confirmation of chemical identities. Diastereomeric excess was determined by crude H^1 NMR by comparing the ratios of peaks for HOC<u>H</u>: δ 5.4 (*syn*) and 4.6 (*anti*), vide infra for an example. Although the diastereomers separate poorly from each other by column chromatography, a racemic sample containing predominately an H^1 NMR spectrum of the *anti* diastereomer is presented in Supporting Figure 2. HPLC separations were run on an AD-H (250 x 4.6 mm) chiral column manufactured by DIACEL using the following parameters: flowrate 0.700 ml/min, 10% IPA in hexane, wavelength = 254 nm, 10 µL injection volume. Since the diastereomers separate well by HPLC, no subsequent attempts were made to separate them from one another during flash chromatography.

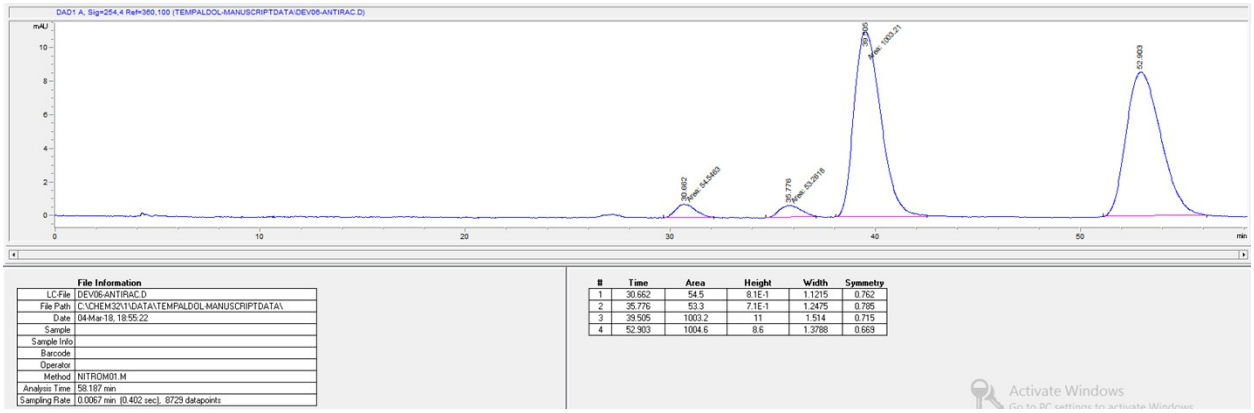
The sample from Supporting Figure run through the HPLC produced by the trace contained in Supporting Figure 3.



Supporting Figure 1.



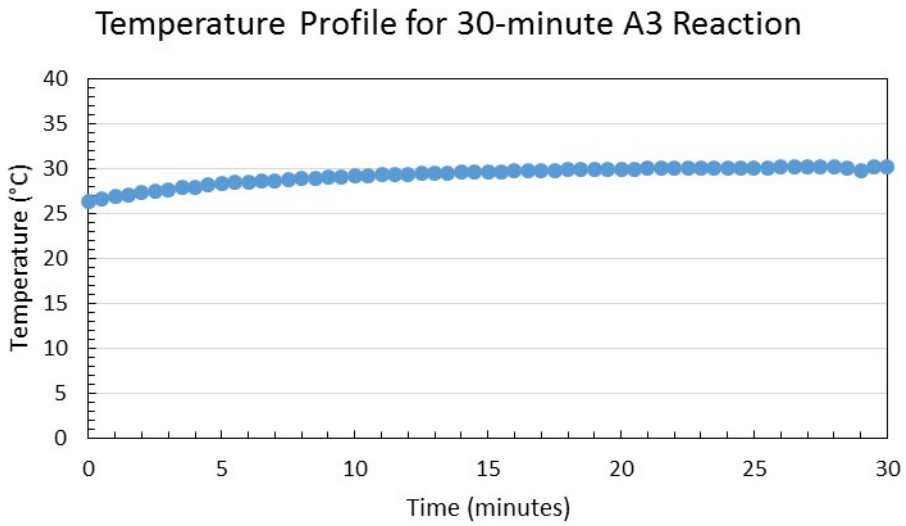
Supporting Figure 2. H NMR spectrum of predominately the *anti* isomer based on comparison to literature values.



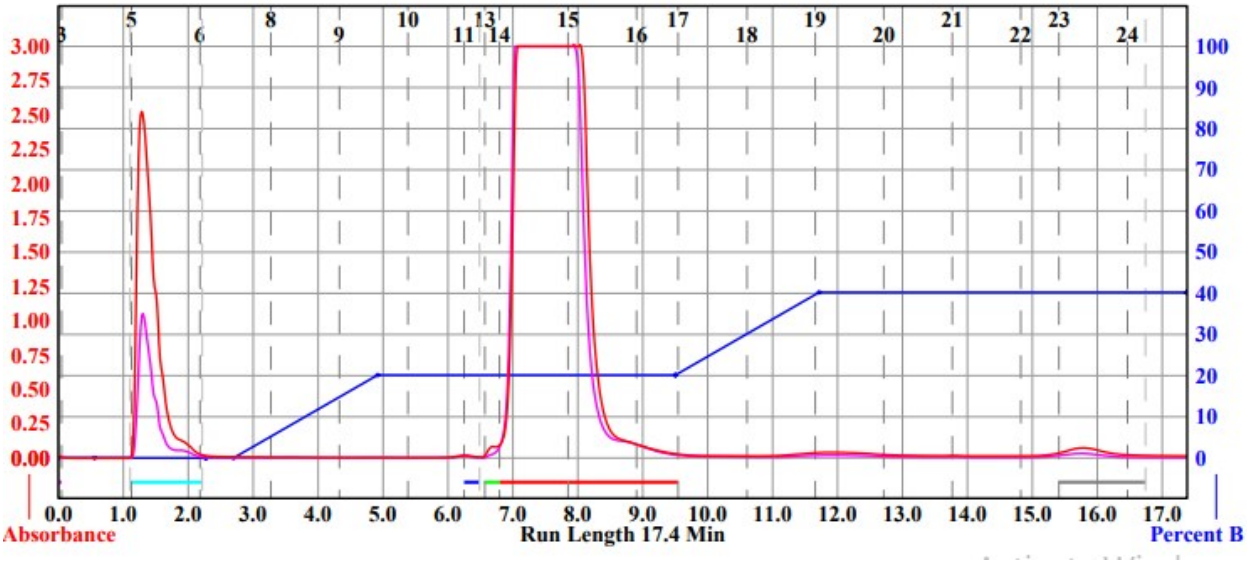
Supporting Figure 3. Racemic sample of *anti* diastereomer. For t=39.5 the integral is 1003.2 and for t=52.9 the area is 1004.6. Small amounts of the *sys* diastereomer are visible at t=30.7 and t=35.8, with areas of 54.5 and 53.3, respectively.

A^3 multicomponent coupling reaction general procedure:

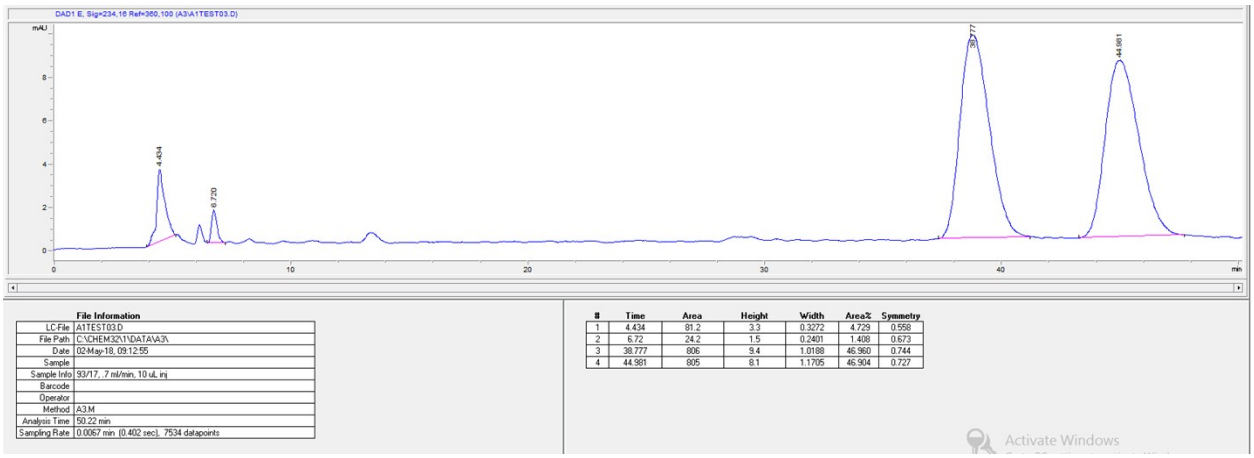
The setup is similar to that of the original study (ref. 42). The following modifications were made for the present study: The solid aldehyde was added last (after the silica) to ensure minimal contact during the non-mixing temperature equilibration period. Reactor, jar, and temperature-measurement details are available in the earlier **"Aldol Reaction"** portion of this SI. After 30 minutes of reaction time, the reaction was ended and the powder scraped out of the vial and transferred to a cartridge for automated flash chromatography separation. Supporting Figure 4 contains an example temperature profile from one of the experiments. Supporting Figure 5 outlines an example separation. We compared the H^1 NMR spectrum of the target material to ref. 42 for confirmation of the identity. Enantiomeric excess was determined by separation on a CHIRALPAK AD-H (250 x 4.6 mm) using the following parameters: flowrate 0.7 ml/min, wavelength 234 nm, 7% hexane:IPA, injection volume 10 µL. An example racemic HPLC separation is provided in Supporting Figure 6. As the flash column separations were not always pure, a calibration curve was incorporated during the HPLC analysis to obtain more reliable yields. Samples were prepared as follows, the relevant fractions from flash chromatography had their solvent removed under reduced pressure and dissolved in 100 mL of ethanol. Of this, 0.25 mL was added to 5.0 mL of the HPLC solvent system. This sample was then run and the calibration curve in Supporting Figure 7 allowed back calculation of the mass of the product.



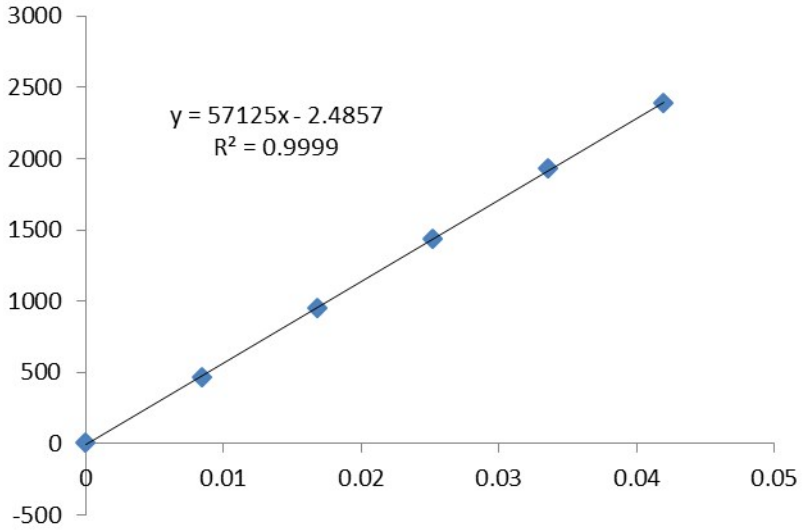
Supporting Figure 4.



Supporting Figure 5. Chromatogram of automated flash chromatography. The target material is contained in fractions 14-16.



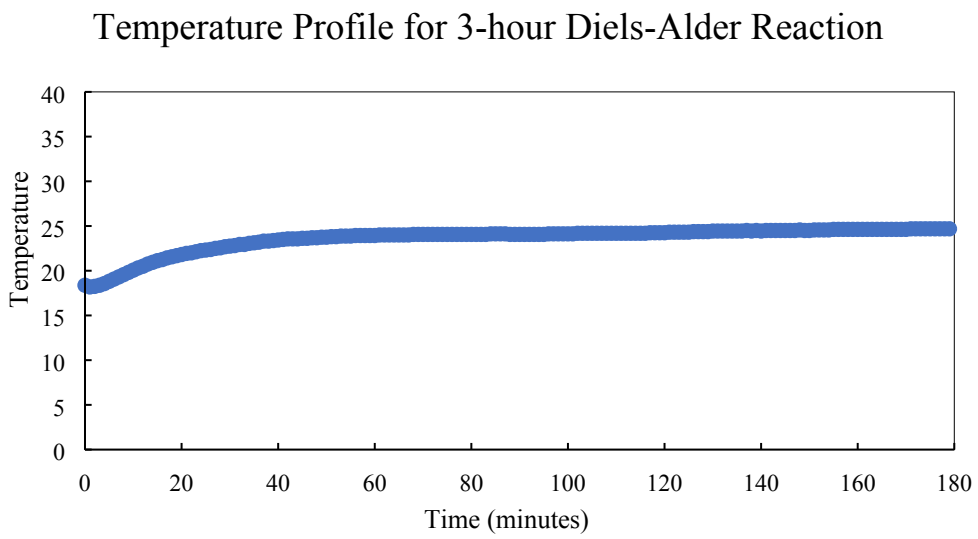
Supporting Figure 6. A racemic sample of the propargyl amine. Retention times are 38.8 minutes and 45.0 minutes, with areas of 806 and 805, respectively.



Supporting Figure 7. Calibration curve for determining concentration and yield of the propargyl amine. The highest concentration extends beyond that which would be obtained by quantitative yield.

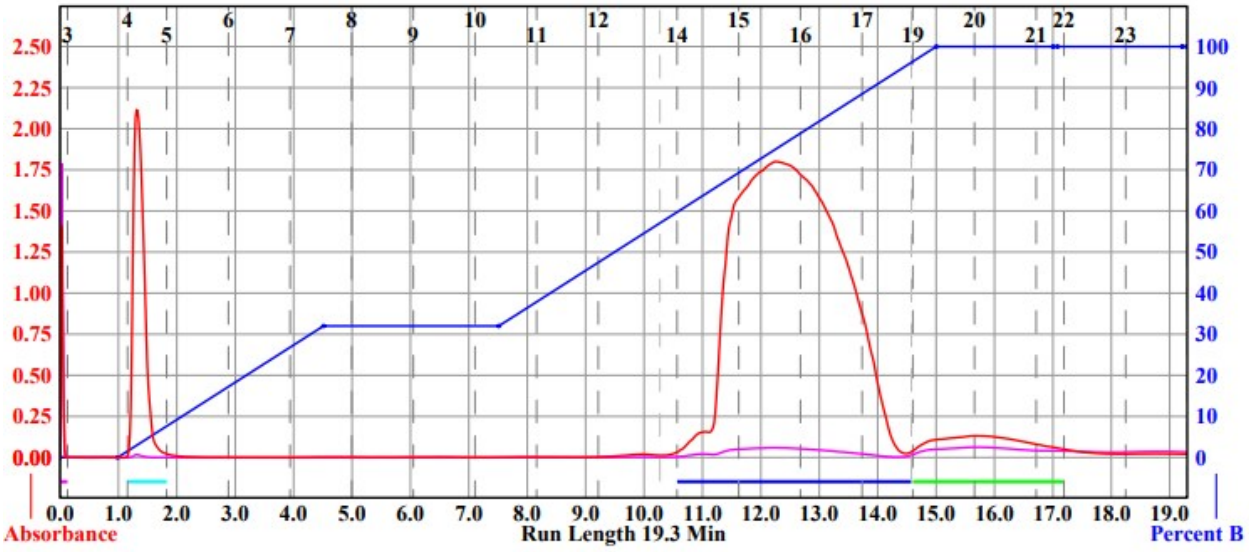
Diels Alder reaction procedures:

Benzoquinone + 9,10-dimethylanthracene with no catalyst: The setup and workup was identical to the original study (ref. 23), except temperature control was included. Spectra were in agreement with our previous literature data. No new compounds were identified. Supporting Figure 8 contains an example temperature profile from one of the experiments.



Supporting Figure 8.

Benzoquinone + 9-methylanthracene (9-MA) with catalyst: The setup is similar to above. In the case with the Co-(III) catalyst, the catalyst (synthesized according to ref. 23) was added first (3 mol%). After this, the appropriate diene (0.5 mmol was added as well as the prescribed dienophile (0.5 mmol, 1.0 equiv). Prior to starting the mill, an equilibration period was allowed for the temperature of the reactor was described in the **"Aldol Reaction"** portion of this SI. Reactor, jar, and temperature-measurement details are available in that section as well. The reaction was run for three hours. The crude reaction mixture was quenched by extracting the crude mixture from the vial with using a mixture of cyclohexane and DCM (80:20) and quickly run through a plug of silica until eluent spots on TLC plates no longer show fluorescence (indicative of 9-MA). The plug (which still retains the catalyst, benzoquinone, and the product) is transferred to a round-bottom flask and suspended in DCM and swirled. The DCM is then removed under reduced pressured to prepare a dry-load sample for automated column chromatography analysis (See Supporting Figure 9 below for method).



Supporting Figure 9. The target compound has very low absorbance, and is found in fractions 19-21. Fraction 4 contains the remaining traces of 9-methlyanthracene (only a few milligrams upon removing solvent). Fractions 14-18 account for the remaining benzoquinone. The identity of the product was determined by comparison of NMR spectra with literature.

Several obstacles presented themselves in our attempts to determine enantiomeric excess via HPLC. Most significantly, the solubility of the BQ + 9-MA adduct is exceedingly low in the solvents available to use on our non-immobilized columns while at the same time the molar absorptivity is also very low. These two issues combine to make obtaining reproducible data difficult. However, as mentioned in the paper, we decided there was sufficient usefulness in the results even in the absence of the selectivity data.