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Kneading Chemistry: Solvent-Regulated Semi-Solid NaBH_4 Reduction by Robotic Kneading

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Abstract

Physical-AI robotic systems are being developed as platforms for autonomous organic synthesis. However, solvent handling remains a practical challenge in robotic operations, as the use of organic solvents imposes requirements on equipment materials, fluid delivery, and product recovery. Here, we introduce Kneading Chemistry,

a semi-solid reaction method with controlled solvent content designed for robotic organic synthesis. We investigated the reduction of ketones with NaBH_4 under semi-solid conditions using a robotic kneading system equipped with force monitoring and programmable motion control. The amounts of solvent and silica gel were adjusted according to the substrate. Silica gel serves as both a reaction medium and a reservoir for protic solvents, helping maintain the semi-solid reaction environment during kneading. A structurally diverse range of ketones was reduced in moderate to good yields with reduced solvent use. Products were recovered directly from the silica gel reaction mixture by elution, without conventional aqueous work-up.

Keywords

Kneading Chemistry; Semi-solid reaction; Mechanochemistry; Robotic organic synthesis; Sodium borohydride reduction

Introduction

Recent advances in data-driven molecular design make it possible to propose numerous candidate molecular structures.[1] Testing these proposals through synthesis and experimental evaluation is necessary to drive the research cycle. This creates a need for efficient organic synthesis systems. Various laboratory automation platforms have therefore been developed to increase experimental throughput and reproducibility, such as Chemputer,[2,3] ChemSpeed,[4] and automated flow synthesis systems based on ASKCOS.[5,6] Integration of artificial intelligence with robotic experimentation is leading to Physical-AI robotic systems for autonomous molecular research.[7] Organic synthesis, however, involves diverse experimental procedures that must frequently be adapted to the properties of individual substrates, reagents, intermediates, and products. Reaction methodologies for autonomous organic synthesis must therefore be compatible with robotic operation. The use of large volumes of organic solvents is a practical challenge in robotic organic synthesis. Handling these solvents requires chemically resistant equipment and reliable systems for liquid delivery, sealing, cleaning, and solvent recovery. These requirements complicate robotic operation and can limit the robustness of the experimental platform.

Reducing solvent use is therefore an important consideration in developing reaction methods for robotic synthesis.

Among reaction methodologies that minimize solvent use, mechanochemistry has attracted considerable attention as an alternative to conventional solution-phase synthesis.[8] Ball milling, the most extensively investigated mechanochemical technique, has demonstrated that externally applied mechanical force can promote a broad range of organic transformations.[8–11] Many ball-milling reactions can proceed under solvent-free or solvent-minimized conditions.[8,12–14] Such approaches may offer advantages for robotic synthesis by reducing solvent handling. In ball-milling reactions, however, product recovery from sealed milling vessels may require additional solvent-assisted work-up. Product recovery and subsequent handling are important considerations in robotic synthesis because they form part of the overall automated process. This led us to consider whether a semi-solid reaction environment could be combined with direct robotic manipulation, allowing reaction and product handling to be performed without relying on large volumes of solvent.

Kneading offers a simple means of continuously mixing semi-solid reaction mixtures through shear and compression.[15] Although kneading has long been used as a practical laboratory operation, its use as a reaction methodology has been limited, in part because manual manipulation is difficult to standardize and semi-solid reaction states are difficult to control reproducibly. Our previously developed force-controlled robotic mechanochemical system, equipped with programmable motion control and force monitoring,[16] provides a means of performing such operations reproducibly and systematically examining semi-solid reaction conditions. In semi-solid reaction mixtures, small amounts of solvent can significantly affect conversion. Previous mechanochemical studies have shown that changes in liquid content can markedly affect reaction efficiency.[17] In the NaBH_4 reduction examined here, a protic solvent may also facilitate protonation of boron alkoxide intermediates. Thus, the amount of solvent is not simply a matter of solvent minimization but also a means of controlling the conditions under which the reaction proceeds. We refer to this semi-solid reaction strategy as Kneading Chemistry.

Herein, we demonstrate Kneading Chemistry through the NaBH_4 -mediated reduction of ketones using a robotic kneading system. Silica gel is employed as a solid medium in combination with controlled amounts of protic solvent to provide semi-solid conditions suitable for robotic kneading. The silica gel also facilitates product recovery

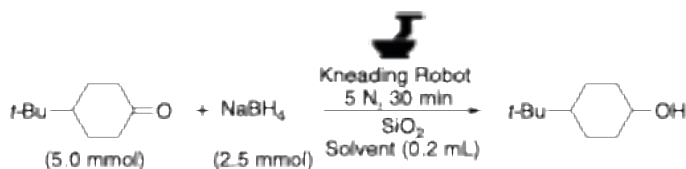
by direct elution without conventional aqueous work-up. This study explores robotic kneading as an approach to solvent-regulated semi-solid organic synthesis and its potential application to Physical-AI robotic systems.

Results and Discussion

Design of a Solvent-Regulated Semi-Solid Reaction Environment

We began our investigation of Kneading Chemistry with the NaBH_4 -mediated reduction of ketones using our previously developed force-controlled robotic mechanochemical synthesis system.[16] Silica gel was selected as a solid medium for constructing a semi-solid reaction environment for robotic kneading. Notably, the use of wet silica gel to promote the NaBH_4 reduction of carbonyl compounds under solvent-free conditions has previously been reported.[18] We therefore examined the effects of silica loading and protic solvent on the NaBH_4 reduction of 4-*tert*-butylcyclohexanone under robotic kneading conditions (Table 1, see also a movie file in supporting information). As summarized in Table 1, silica loading strongly affected the reaction. In the absence of silica gel, the desired alcohol was obtained in only 28% isolated yield despite the presence of 2-propanol. Higher silica loadings gave the desired alcohol in 88–94% isolated yield. In contrast, only trace conversion was observed in the absence of added solvent, indicating that a small amount of protic solvent was required for efficient reduction. These results show that both silica gel and a protic solvent are important for the NaBH_4 reduction under kneading conditions. The lower product yields observed at reduced silica loadings may reflect less efficient hydrolysis of boron alkoxide intermediates, although the precise role of silica gel remains to be clarified.

Table 1: Effect of silica gel loading on robotic kneading NaBH_4 reduction of 4-tert-butylcyclohexanone under solvent-minimized conditions.^a



Entry	SiO_2	Solvent	yield ^b	cis/trans
1	5 g	No solvent	6%	15/85
2	5	2-propanol	88	8/92
3	2	2-propanol	94	7/93
4	1	2-propanol	49	8/92
5	0	2-propanol	28	11/89
6	2	<i>t</i> -BuOH	66	6/94
7	2	1-propanol	48	11/89

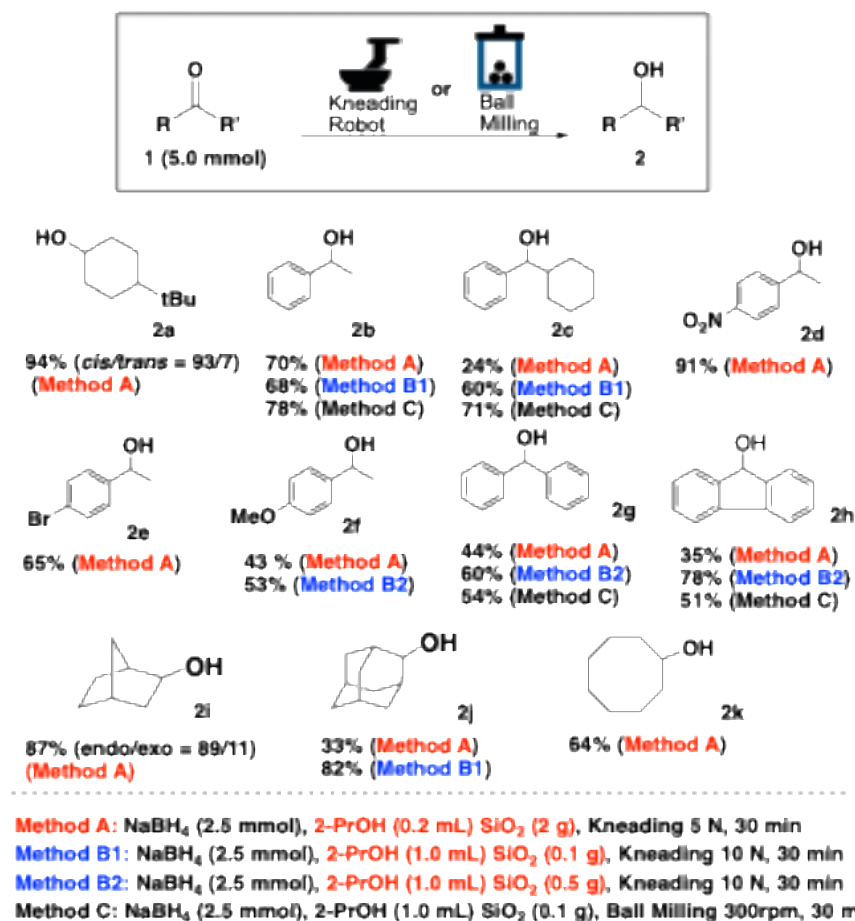
^a 4-tert-butylcyclohexanone (5.0 mmol), NaBH_4 (2.5 mmol), 2-PrOH (0.20 mL). ^b Isolated yield.

Substrate-Dependent Selection of Semi-Solid Reaction Conditions

For the substrate scope, three kneading conditions with different amounts of 2-PrOH and silica gel were used. **Method A** employed 0.2 mL of 2-PrOH and 2.0 g of silica gel under solvent-minimized semi-solid conditions. **Method B1** employed 1.0 mL of 2-PrOH and 0.1 g of silica gel, giving a slurry-like mixture. **Method B2** used the same amount of 2-PrOH (1.0 mL) with a higher silica loading (0.5 g). The effects of liquid loading on mixing and reaction efficiency in mechanochemical reactions have been reported previously.[19–21] For comparison, ball milling was also performed under **Method C** using 1.0 mL of 2-PrOH and 0.1 g of silica gel.

As shown in Scheme 1, the effective kneading conditions varied with the substrate. Aryl alkyl ketones, including electron-deficient derivatives, were generally reduced efficiently under the solvent-minimized conditions of **Method A**. Several other substrates gave higher yields under the more highly solvated conditions of **Methods B1** or **B2**. For example, the yield of **2j** increased from 33% with **Method A** to 82% with **Method B1**, while that of **2h** increased from 35% with **Method A** to 78% with **Method B2**. Ball milling (**Method C**) was effective for several substrates, with yields

comparable to those obtained by kneading in some cases. Overall, these results show that a single kneading condition is not optimal for all ketones and that the solvent and silica loadings need to be adjusted according to the substrate.

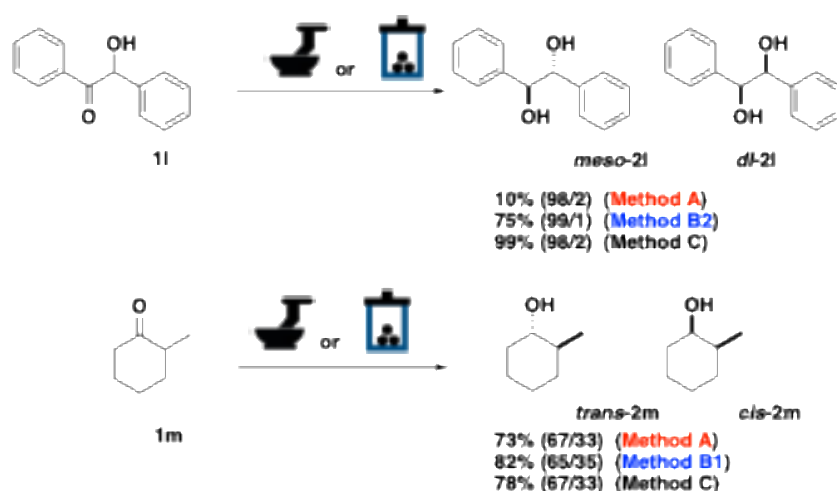


Scheme 1: Substrate scope of NaBH₄-mediated reduction under kneading and ball milling conditions.

Stereoselectivity under Solvent-Minimized Kneading Conditions

The reductions of benzoin **1l** and 2-methylcyclohexanone **1m** were compared under **Methods A–C** (Scheme 2). For benzoin, the yield varied markedly with the reaction conditions, from 10% under **Method A** to 75% under **Method B2** and 99% under ball-milling conditions (**Method C**). In contrast, the diastereomeric ratio remained essentially unchanged (98/2–99/1). The high diastereoselectivity of NaBH₄ reduction of benzoin has previously been rationalized in terms of substrate conformation and hydrogen-bond-directed hydride approach.[22] A similar tendency was observed for 2-methylcyclohexanone. The yields ranged from 73 to 82% under the different

conditions, whereas the trans/cis ratio remained nearly constant (65/35–67/33). This selectivity is consistent with that previously reported for NaBH₄ reduction of 2-methylcyclohexanone.[23] Notably, despite the greatly reduced amount of solvent used under the kneading conditions, the diastereoselectivities were similar to those reported for conventional NaBH₄ reductions in solution.[22,23] Thus, the use of solvent-minimized semi-solid conditions affected the reaction efficiency but did not substantially alter the stereochemical outcome of these reductions.



Scheme 2: Influence of semi-solid reaction conditions on the reduction of benzoin (**1I**) and 2-methylcyclohexanone (**1m**).

Discussion

Kneading Chemistry provides a means of carrying out organic reactions under solvent-minimized semi-solid conditions. In the NaBH₄ reduction examined here, both the amount of 2-PrOH and the silica loading affected reaction efficiency, and the effective conditions varied with the substrate. **Method A**, using a small amount of 2-PrOH and a higher silica loading, was effective for many ketones, whereas some substrates gave higher yields under the more highly solvated conditions of **Methods B1** or **B2**. These results demonstrate that the semi-solid reaction environment can be adjusted according to the substrate without relying on conventional solution-phase conditions. The stereochemical results provide an additional feature of these reactions. Although the yield of benzoin varied markedly among **Methods A–C**, its diastereoselectivity remained essentially unchanged. Similarly, the trans/cis ratio obtained from 2-methylcyclohexanone showed little dependence on the reaction conditions. Despite

the greatly reduced amount of solvent used in the kneading experiments, these stereochemical preferences were similar to those reported for conventional NaBH_4 reductions in solution.[22,23] These results suggest that changes in the semi-solid reaction conditions can affect reaction efficiency without substantially altering stereochemical preference.

Ball milling also gave effective reduction for several substrates, with yields comparable to those obtained by kneading in some cases. This comparison suggests that the principal feature of robotic kneading is not the reaction itself, but the manner in which the semi-solid reaction mixture is handled. The force-controlled robotic system enables continuous mixing through controlled mechanical motion, while the use of silica gel allows the products to be recovered directly by elution without conventional aqueous work-up. These features integrate reaction and product recovery within a simple robotic operation.

These features are relevant to robotic organic synthesis, where reducing solvent handling and simplifying product recovery can reduce the operational requirements of the experimental platform. Kneading Chemistry therefore provides a practical approach to solvent-minimized organic synthesis that can be implemented using programmable robotic operation.

Conclusion

We have introduced Kneading Chemistry as an approach to solvent-minimized organic synthesis using robotic kneading and demonstrated its application to the NaBH_4 -mediated reduction of structurally diverse ketones. The reactions were performed under semi-solid conditions using silica gel and controlled amounts of 2-PrOH. The amounts of 2-PrOH and silica gel could be adjusted according to the substrate, affording a range of ketones in moderate to good yields. Changes in the semi-solid reaction conditions affected reaction efficiency without substantially altering the stereochemical preferences observed for the substrates examined. Products could also be recovered directly from the silica gel by elution without conventional aqueous work-up.

These results show that robotic kneading provides a means of performing organic reactions under solvent-minimized semi-solid conditions while allowing the reaction environment to be adjusted through solvent and silica loading. Although demonstrated

here for NaBH_4 reduction, Kneading Chemistry offers an approach to the development of semi-solid reaction methods compatible with robotic organic synthesis.

Experimental

Robot kneading system

The robotic kneading experiments were performed with the system shown in Figure 3, which is derived from the force-controlled robotic powder-grinding platform reported by Nakajima et al. [16]. In that platform, reproducible mechanical input is achieved by controlling the contact between a pestle held by a robot arm and a mortar. The same basic operating principle was adopted here for the kneading of semi-solid reaction mixtures, with the hardware and software modifications described below.



Figure 3. Overview of the automated kneading robot system.

Hardware and force setting

A six-axis collaborative robot arm (UF850, UFactory) was used: A commercial deep-type agate mortar and pestle (AS ONE, 80 mm inner diameter, 32 mm depth) were rigidly mounted, together with the arm, on an aluminum frame.

A six-axis force/torque sensor (PFS055YA251U6, Leptrino) was installed between the tool flange and the pestle holder so that the force applied to the pestle could be measured directly at the end effector. The rated capacities of this sensor are ± 250 N for F_x , F_y and F_z , and ± 6.0 N m for M_x , M_y and M_z , with a resolution of $\pm 1/2000$ of the rated capacity (approximately 0.13 N for F_z). The sensor was connected to the control

PC through a USB serial interface (460800 bps, no parity, 8 data bits). The sensor was operated in continuous transmission mode, and the force and torque values were acquired and recorded at 1200 Hz. Before each measurement, the sensor output was zeroed with the pestle held out of contact to remove the offsets arising from the weight of the tool and from its mounting.

The vertical load during kneading was applied by precise position control of the pestle by the robot arm. Prior to the experiments, the pestle tip was brought into contact with the inner surface of the mortar and its vertical position was varied stepwise while F_z was measured with the force sensor, giving the relationship between the vertical position of the pestle and the resulting vertical load. The pestle position corresponding to the target load was determined from this relationship and was held constant during kneading. The target vertical load was defined as the value at the start of kneading and was set to 5 N for **Method A** and to 10 N for **Methods B1** and **B2**.

Software

Robot control was implemented based on the open-source package `powder_grinding` (https://github.com/quantumbeam/powder_grinding) released with the above report. As this package was originally written for Universal Robots manipulators, it was modified for the UF850 as follows: the robot driver and MoveIt[24] configuration were replaced by those for the UF850, the URDF of the end effector was extended to include the Leptrino force/torque sensor and the pestle holder, and a node publishing the Leptrino measurements as ROS wrench messages was added. For the force/torque sensor, an existing BSD-licensed ROS driver [25] was modified for use in the present system. The modified version is publicly available on GitHub [26]. The control software was run under ROS Noetic in a Docker container on Ubuntu 22.04 (host PC: Intel Core i7-6567U, 16GB memory). Containerization was adopted so that the ROS Noetic environment could be reproduced independently of the host distribution and identical settings could be deployed for every experiment.

Motion

Kneading was performed with a circular motion of 16 mm diameter, matching the size of the pestle tip, and the depth of the trajectory was defined based on an ellipsoidal model of the inner surface of the mortar. The target end-effector poses were converted into joint trajectories using TrackIK[27] and executed by a joint trajectory controller in ROS. The kneading speed was set by the joint velocity between waypoints and

corresponded to one revolution of the circular motion per second, that is, 60 rpm. Each experiment was continued for 30 min under these conditions.

Reduction

Method A: Silica gel 60 (2.0 g, spherical 60 μm for flash chromatography, TCI), sodium borohydride (2.5 mmol, 95 mg, TCI), and ketone (5.0 mmol) were placed in a mortar. 2-Propanol (0.2 mL) was then added, and the resulting mixture was kneaded for 30 min with an initial vertical load of approximately 5 N. The resulting silica gel was transferred to a glass column, and washed with 30 mL of ethyl acetate. The filtrate was concentrated *in vacuo*.

Method B1: Silica gel 60 (0.1 g, spherical 60 μm for flash chromatography, TCI), sodium borohydride (2.5 mmol, 95 mg, TCI), and ketone (5.0 mmol) were placed in a mortar. 2-Propanol (1.0 mL) was then added, and the resulting mixture was kneaded for 30 min with an initial vertical load of approximately 10 N. Silica gel 60 (2.0 g) was then added and the resulting mixture was kneaded for an additional 5 min. The resulting silica gel was transferred to a glass column, and washed with 30 mL of ethyl acetate. The filtrate was concentrated *in vacuo*.

Method B2: Silica gel 60 (0.5 g, spherical 60 μm for Flash Chromatography, TCI), sodium borohydride (2.5 mmol, 95 mg, TCI), and ketone (5.0 mmol) were placed in a mortar. 2-Propanol (1.0 mL) was then added, and the resulting mixture was kneaded under a controlled force of approximately 10 N for 30 min. Silica gel 60 (2.0 g) was added and the resulting mixture was kneaded for 5 min. The resulting silica gel was transferred to a glass column, and washed with 30 mL of ethyl acetate. The filtrate was concentrated *in vacuo*.

Method C: Silica gel 60 (0.1 g, spherical 60 μm for flash chromatography, TCI), sodium borohydride (2.5 mmol, 95 mg, TCI), 2-propanol (1.0 mL), and ketone (5.0 mmol) were placed in a 12 mL stainless-steel milling vessel (containing 3 stainless balls). The sealed vessel was subjected to ball milling at 120 Hz for 30 min using a planetary ball mill (FRITSCH P-7 classic line). After 30 min, the mixture was washed with 1 M HCl(aq) (20 mL) and extracted with ethyl acetate (60 mL). The separated organic layer via a separating funnel was washed with brine (20 mL). The organic layers were dried over Na_2SO_4 , and concentrated *in vacuo*.

Characterization Data

4-(*tert*-butyl)cyclohexan-1-ol (2a) (Method A)

Isolated as a white solid (0.72 g, 94% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 4.07-4.11 (*cis*, m, 0.09H), 3.41-3.58 (*trans*, m, 0.91H), 1.90-2.10 (m, 2H), 1.50-1.85 (m, 4H), 1.10-1.40 (m, 2H), 0.90-1.10 (m, 2H), 0.82 (s, 1H, $J = 6.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 71.2(*trans*), (60.5 *cis*), 47.2, 36.1, 32.4, 27.7, 25.7 ppm; HRMS (EI) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{10}\text{H}_{20}\text{O}$ 156.1514; Found 156.1433; IR (film): 3253.9, 2941.4, 2360.9, 1467.8, 1448.5, 1052 cm^{-1}

1-Phenyl-1-ethanol (2b) (Method A)

Isolated as a colorless oil (0.42 g, 70% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 7.20-7.40 (m, 5H), 4.77 (q, $J = 7.5$ Hz, 1H), 2.75 (bs, 1H), 1.40 (d, $J = 7.5$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 145.7, 128.2, 127.1, 125.5, 69.9, 24.9 ppm; IR (film): 3360, 2920, 1460, 700 cm^{-1} CAS 98-85-1[28]

Cyclohexyl(phenyl)methanol (2c) (Method B1)

Isolated as a white solid (0.58 g, 60% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 7.20-7.40 (m, 5H), 4.35 (d, $J = 4.4$ Hz, 1H), 1.82 (d, $J = 7.6$ Hz, 1H), 1.5-2.0 (m, 5 H), 1.36 (d, $J = 12$ Hz, 1H), 0.8-1.4 (m, 5 H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 143.7, 128.3, 127.5, 126.7, 79.5, 45.0, 29.4, 28.9, 26.5, 26.2, 26.1 ppm; IR (film): 3370, 2920, 1460, 700 cm^{-1} CAS 945-49-3[29]

1-(4-Nitrophenyl)ethan-1-ol (2d) (Method A)

Isolated as a colorless oil (0.76 g, 91% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 8.20 (d, $J = 10.0$ Hz, 2H), 7.54 (d, $J = 10$ Hz, 2H), 5.01 (q, $J = 8.0$ Hz, 1H), 1.93 (bs, 1H), 1.51 (d, $J = 8.0$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 153.1, 147.3, 126.2, 123.9, 69.6, 25.6 ppm; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_8\text{H}_{10}\text{NO}_3$ 168.0660; Found 168.0654; IR (film): 3380, 2976, 1605, 1516, 1350, 854 cm^{-1}

1-(4-Bromophenyl)ethan-1-ol (2e) (Method A)

Isolated as a white solid (0.66 g, 65% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 7.46 (d, $J = 5.5$ Hz, 2H), 7.25 (d, $J = 5.5$ Hz, 2H), 4.88 (q, $J = 6.0$ Hz, 1H), 1.65 (bs, 1H), 1.48 (d, $J = 6.0$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 144.7, 131.5, 127.1, 121.1, 69.7, 25.2 ppm; IR (film): 3380, 2976, 1605, 1516, cm^{-1} CAS 5391-88-8[30]

1-(4-Methoxyphenyl)ethane-1-ol (2f) (Method B2)

Isolated as a colorless oil (0.40 g, 53% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 7.27 (d, $J = 6.0$ Hz, 2H), 6.85 (d, $J = 6.0$ Hz, 2H), 4.85-4.90 (m, 1H), 2.01-2.30 (m, 1H), 1.40-1.50 (m, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 159.0, 138.1, 126.8, 113.9, 70.0, 55.3, 25.1 ppm; IR (film): 3380, 2970, 2380, 1610, 1510, 1033, 829 cm^{-1} CAS 3319-15-1[31]

Diphenylmethanol (2g) (Method B2)

Isolated as a white solid (0.56 g, 60% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 7.15-7.55 (m, 10H), 5.83 (d, $J = 1.2$ Hz, 1H), 2.89 (d, $J = 1.2$ Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): 143.8, 128.6, 127.7, 126.6, 76.3 ppm; HRMS (EI) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{13}\text{H}_{12}\text{O}$ 184.0888; Found 184.0884; IR (film): 3280, 3026, 2360, 1492, 1446, 1016, 699 cm^{-1}

9H-Fluoren-9-ol (2h) (Method B2)

Isolated as a pale yellow solid (0.70 g, 78% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 7.55-7.70 (m, 4H), 7.25-7.41 (m, 4H), 5.56 (d, $J = 10$ Hz, 1H), 1.90 (d, $J = 10$ Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 145.7, 140.1, 129.2, 127.9, 125.2, 120.1, 75.3 ppm; HRMS (EI) m/z : $[\text{M}-\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_9\text{O}$ 181.0653; Found 181.0651; IR (film): 3200, 2440, 1210, 720 cm^{-1}

Bicyclo[2.2.1]heptan-2-ol (2i) (Method A)

Isolated as a white solid (0.48 g, 87% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 4.10-4.20 (m, 0.9H, *endo*), 3.70-3.80 (m, 0.1H, *exo*), 2.10-2.30 (m, 2H), 0.90-2.0 (m, 8H), 0.70-0.90 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): For *endo* δ 73.1, 42.6, 39.6, 37.7, 37.2, 29.9, 20.0; for *exo* δ 75.0, 44.3, 42.4, 35.5, 34.5, 28.2, 24.5 ppm; HRMS (EI) m/z : $[\text{M}]^+$ Calcd for $\text{C}_7\text{H}_{12}\text{O}$ 112.0888; Found 112.0888; IR (film): 3400, 2920, 1452, 1034, 731 cm^{-1}

Adamantan-2-ol (2j) (Method B1)

Isolated as a white solid (0.62 g, 82% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 3.85 (bs, 1H), 2.05 (d, $J = 12.8$ Hz, 2H), 1.40-1.90 (m, 11H), 1.51 (d, $J = 12.8$ Hz, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 74.7, 37.7, 36.6, 34.6, 31.1, 27.6, 27.1 ppm; HRMS (EI) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{10}\text{H}_{16}\text{O}$ 152.1201; Found 152.1198; IR (film): 3200, 2900, 1724, 1056, 1022 cm^{-1}

Cyclooctanol (2k) (Method A)

Isolated as a colorless oil (0.40 g, 64% yield). ^1H NMR (CDCl_3 , 400 MHz): δ 3.77-3.85 (m, 1H), 1.20-1.90 (m, 15H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 72.3, 34.8, 27.5, 27.2, 25.3, 25.1, 22.7 ppm; IR (film): 3350, 2360, 1446, 1053, 906 cm^{-1} CAS 696-71-9[32]

1,2-Diphenylethane-1,2-diol (2l) (Method B2)

Isolated as a white solid (0.80 g, 75% yield, *meso/dl* = 99/1). ^1H NMR (CDCl_3 , 400 MHz): δ 7.05-7.4 (m, 10H), 4.83 (*meso*, s, 1.98 H), 4.71 (*dl*, d, 0.02H), 1.58 (bs 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 139.8, 128.3, 128.2, 127.1, 78.1 ppm; HRMS (ESI) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{14}\text{H}_{14}\text{O}_2\text{Na}$ 237.0891; Found 237.0887; IR (film): 3350, 2920, 1471, 1053, 906 cm^{-1} CAS 579-43-1[33]

2-Methylcyclohexanol (2m) (Method B1)

Isolated as a colorless oil (0.46 g, 82% yield, *trans/cis* = 65/35). ^1H NMR (CDCl_3 , 400 MHz): δ 3.77-3.85 (*cis*, m, 0.35H), 3.10 (*trans*, dq, J = 4.0, 7.0 Hz, 0.65H), 1.10-2.00 (m, 10H) 0.98 (*trans*, d, J = 6.4 Hz, 1.95H), 0.91 (*cis*, d, J = 6.4 Hz, 1.05H), ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 76.0 (*trans*), 71.2 (*cis*), 40.3 (*trans*), 35.9 (*cis*), 35.6 (*trans*), 33.7 (*trans*), 32.6 (*cis*), 28.8 (*cis*), 25.8 (*trans*), 25.3 (*trans*), 24.6 (*cis*), 20.7 (*cis*), 18.6 (*trans*), 17.0 (*cis*) ppm; IR (film): 3350, 2360, 1446, 1053, 906 cm^{-1} CAS 696-71-9[34]

Supporting Information

Supporting Information File 1:

File 1: Kneading(Reaction Table 1 entry2).mp4

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