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Efficient Ruthenium-Catalyzed Transfer Hydrogenation/Hydrogenation of 1,3-Cycloalkanediones to 1,3-Cycloalkanediols Using Microwave Heating

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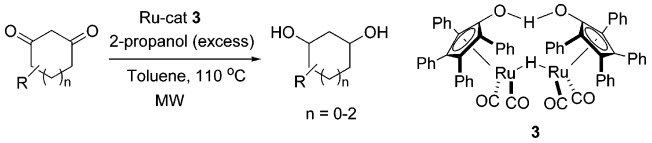
Received June 19, 2006

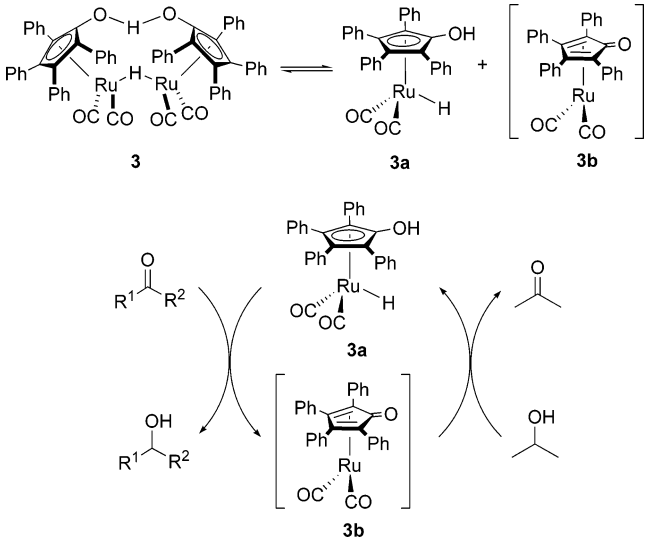


A number of 1,3-cycloalkanediones were efficiently reduced to the corresponding diols in good yield by the use of a ruthenium catalyst, 2-propanol, and hydrogen gas under microwave heating.

1,3-Cycloalkanediols are useful building blocks in pharmaceuticals. They can be obtained from reduction of the corresponding diones. In our ongoing project on dynamic kinetic asymmetric transformations of diols, we were in need of a general method for the reduction of different 1,3-cycloalkanediones to the corresponding diols.[1] However, all existing methods require either long reaction times and high pressure of hydrogen gas and elevated temperatures, or they cannot be applied to more than a few substrates.[2−4]

β-Diketones have a keto−enol equilibrium, and the extent of enolization depends on the substituents, the ability of conjugation, the temperature, and the ability of the solvent to stabilize the enol form.[5−8] For cyclic 1,3-diones, the equilibrium is shifted far to the enol form, and this is an obstacle in their reduction to diols. For example, it is known that reduction of cyclohexane-1,3-dione with lithium aluminum hydride results in unsaturated alcohols obtained from dehydration of the enol form,[9] although there have been successful reports on such reductions of seven-membered rings.[10] Reduction with DIBAL-H gave similar results. Attempted reduction of cyclohexane-1,3-dione with $NaBH_4$ was unsuccessful, and most of the starting material was recovered.[11]

SCHEME 1



We have previously studied the transfer hydrogenation of ketones by 2-propanol using the Shvo complex **3**[12] as catalyst,[13,14] and recently, our group reported a successful transfer hydrogenation of imines by 2-propanol with this catalyst.[15] By the use of microwave heating, the reaction time and catalyst loading could be significantly reduced in the latter case.[16] Catalyst **3** has also been used as a racemization/epimerization catalyst for secondary alcohols in dynamic kinetic resolution.[17−19]

Catalyst **3** is a dimer, which upon heating is in equilibrium with monomers **3a** and **3b** (Scheme 1). Both monomers are active in the transfer hydrogenation. While **3a** can hydrogenate a hydrogen acceptor (e.g., a ketone), monomer **3b** can dehydrogenate a hydrogen donor such as 2-propanol. These processes interconvert **3a** and **3b**. The advantage of using 2-propanol as a hydrogen donor is that the only side product will be acetone, which can be easily removed during workup. To ensure a complete conversion, hydrogen gas can be added to push the equilibrium toward the hydrogenated species.

In this paper, we report an efficient transfer hydrogenation/hydrogenation of cyclic 1,3-diones using catalyst **3**, 2-propanol, and microwave heating.

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10.1021/jo0612527 CCC: $33.50
Published on Web 10/05/2006

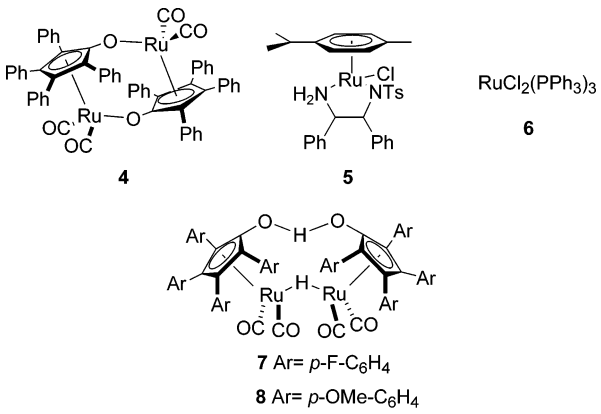


FIGURE 1.

TABLE 1. Transfer Hydrogenation of 1a to 2a by 2-Propanol Employing Various Catalysts[a]

entry	catalyst (mol %)	base (mol %)	conversion (%) after 60 min
1	**3** (1)		>95
2	**4** (1)		>95
3	**5** (2)[b]	KOH (10)	5
4	**6** (2)[b]	KOH (10)	5
5	**7** (1)		90
6	**8** (1)		>95

[a] Unless otherwise noted, all reactions were run on a 1 mmol scale with the given amounts of catalyst and base and 24 equiv of 2-propanol in 2.5 mL of toluene at 110 °C in a microwave oven. [b] The reaction was run in 4 mL of 2-propanol without toluene.

In our first attempt, we tried the transfer hydrogenation/hydrogenation of 1,3-dione **1a**, using 2 mol % of catalyst **3** and 10 equiv of 2-propanol under ambient pressure of hydrogen with toluene as a solvent. After 2 h of heating at 110 °C, all dione had been converted into diol **2a**. By increasing the amount of 2-propanol to 24 equiv, the catalyst loading could be decreased to 1 mol %, and the reaction was complete within 60 min (Scheme 2). The reaction was clean, and no products from dehydration could be detected.[20] With the increased amount of hydrogen donor, the hydrogen atmosphere was not necessary since the reaction went to completion within the same time with or without H_2.

To evaluate the efficiency of catalyst **3** in the transfer hydrogenation of dione **1a**, we compared it to some other ruthenium catalysts (Figure 1). Catalyst **4** gave a very similar result as catalyst **3**, and full conversion was obtained after 1 h (Table 1, entries 1 and 2). Noyori's catalyst **5** has recently been used in microwave-mediated asymmetric transfer hydrogenation of ketones.[21] Although diol **2a** was obtained with catalyst **5**, the activity was much lower (Table 1, entry 3) with only 5% conversion after 1 h. Also, catalyst **6** gave a slow reaction with 5% conversion after 1 h.

The Shvo analogues **7** and **8** (Figure 1) were recently studied in our group for the racemization of primary amines.[22] These catalysts possess different electronic properties, and therefore, they have different abilities to hydrogenate a ketone. When catalysts **7** and **8** were tested in the transfer hydrogenation of **1a**, both reactions gave high conversions within 1 h (Table 1, entries 5 and 6). To compare their efficiency with catalysts **3** and **4**, samples were taken every 5 min and analyzed by ^{1}H NMR. The results in Figure 2 show that **8** is the most efficient

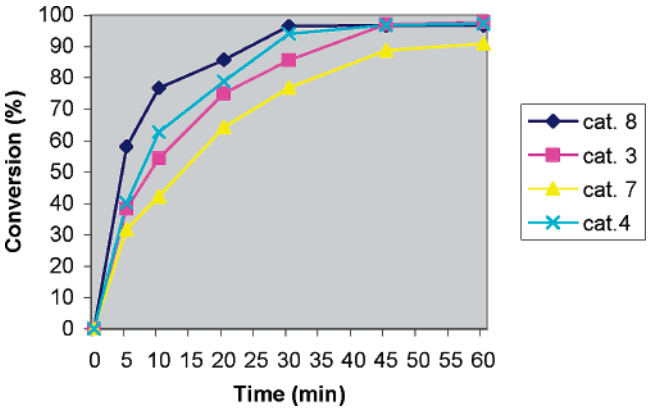


FIGURE 2. Transfer hydrogenation of **1a** to **2a** by 2-propanol using catalysts **3**, **4**, **7**, and **8**. All reactions were run on a 1 mmol scale with 1 mol % of catalyst and 24 equiv of 2-propanol in 2.5 mL of toluene at 110 °C in a microwave.

catalyst with almost 80% conversion after 10 min and full conversion after 30 min. The least active catalyst (complex **7**) gave only about 40% conversion after 10 min.

Catalysts **3** and **4** are also efficient, **4** being somewhat faster than **3**, and both gave full conversion after 45 min. We chose to use catalyst **3** since it is readily synthesized from commercially available tetraphenylcyclopentadienone, and the differences between **3**, **4**, and **8** are small. These optimized reaction conditions were tested on several cyclic 1,3-diones, and the reactions were run to completion within 30−120 min. The unsubstituted six-membered ring was the fastest substrate, and full conversion was obtained within 30 min (Table 2, entry 2). Surprisingly enough, dione **1d** required heating for 120 min at 120 °C for full conversion (Table 2, entry 4), while the more sterically demanding diones **1a** and **1c** were reduced to the corresponding diols in 60 min at 110 °C (Table 2, entries 1 and 3).

In the case of 1,3-indanedione **1g**, the reaction never went to completion under transfer hydrogenation conditions (Table 2, entry 7), and a 1:1 mixture of diol **2g** and hydroxy ketone **2h** was obtained. When starting from **2h**, the reaction stopped after 20 min, and only 50% had been converted to diol **2g** (Figure 3). The low conversion was considered to be due to catalyst decomposition, catalyst inhibition, or an equilibrium disfavoring diol **2g**.

To investigate this further, the reaction with dione **1g** was run for 2 h after which a second aliquot of catalyst was added.

SCHEME 2. Transfer Hydrogenation of 1a by 2-Propanol Catalyzed by 3 with or without H_2

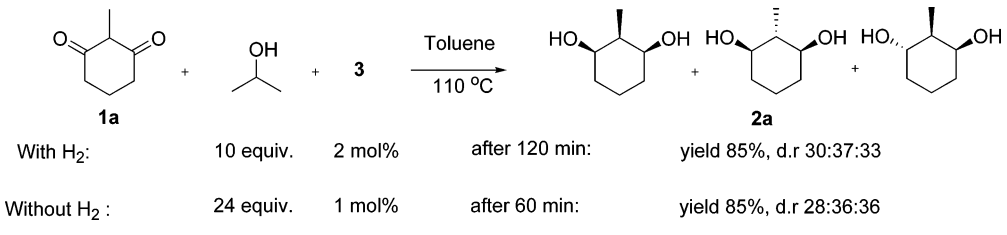


TABLE 2. Transfer Hydrogenation of Diones 1 to Diols 2 by 2-Propanol Using Catalyst 3[a]

Entry	Substrate	Product	Time (h)	Conversion[b,c] (%)	Diastereomeric Ratio[c]	Isolated yields (%)
1	**1a**	**2a**	1	100	28:36:36	85
2	**1b**	**2b**	0.5	100	58:42	88
3	**1c**	**2c**	1	100	56:44	83
4	**1d**[d]	**2d**	2	100	35:19:46	73
5	**1e**[e]	**2e**	24	100	48:52	73
6	**1f**[e]	**2f**	48	80	69:31	69
7	**1g**[f]	**2g**	2	100[g]	67:33	49[b]
8	**1g**[e]	**2g**	30	100	91:9[h]	93

[a] Unless otherwise noted, all reactions were run on a 1 mmol scale with 1 mol % of **3** and 24 equiv of 2-propanol in 2.5 mL of toluene at 110 °C in a microwave oven. [b] This refers to conversion of 1,3-dione. [c] Determined by ^{1}H NMR. [d] Heated at 120 °C. [e] 2 mol % of **3** was used, and the reaction was heated at 80 °C in an oil bath under H_2(g). [f] 2 mol % of **3** was used, and the mixture was heated at 120 °C. [g] Although conversion of dione was completete, a ~1:1 mixture of keto alcohol and diol was formed. [h] After workup.

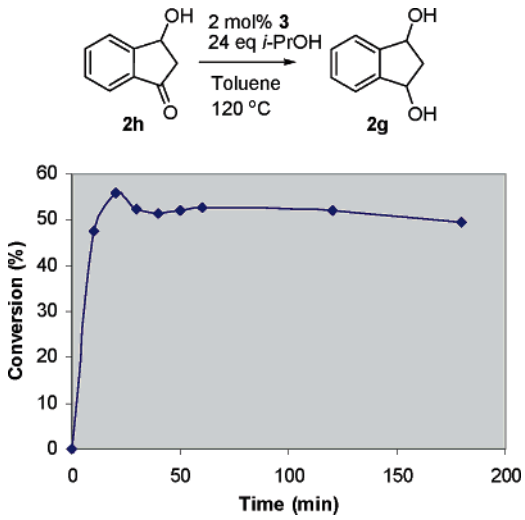
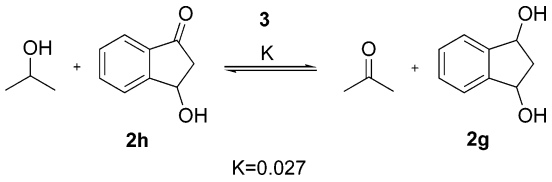


FIGURE 3. Study of the transfer hydrogenation of hydroxyketone **2h** by 2-propanol using catalyst **3**.

After another 2 h of heating, analysis of the reaction by ^{1}H NMR showed that the ratio of hydroxyketone **2h** to diol **2g** was still 1:1. This seems to rule out that the catalyst is decomposed or inhibited by the product during the reaction, and a more likely explanation is that the equilibrium between

SCHEME 3. Equilibrium between Hydroxyketone 2h and Diol 2g



2g and **2h** strongly favors **2h**. This was demonstrated by an experiment starting from diol **2g** in the presence of 1 equiv of acetone and a large excess of 2-propanol (23 equiv). After 2 h, the ratio of **2g** and **2h** was 53:47, and this confirms that the equilibrium between **2g** and **2h** was strongly shifted toward hydroxyketone **2h** (K = 0.027, Scheme 3).

To push the equilibrium toward diol **2g**, the transfer hydrogenation of dione **1g** was combined with hydrogenation at 80 °C using ambient pressure of hydrogen gas.[23] This removes the small amount of acetone formed in the reaction. Both catalysts **3** and **8** were tested, and in both cases, about 90% conversion was obtained within 24 h (Figure 4). By extending the reaction time, **2g** could be isolated in 93% yield (Table 2, entry 8).

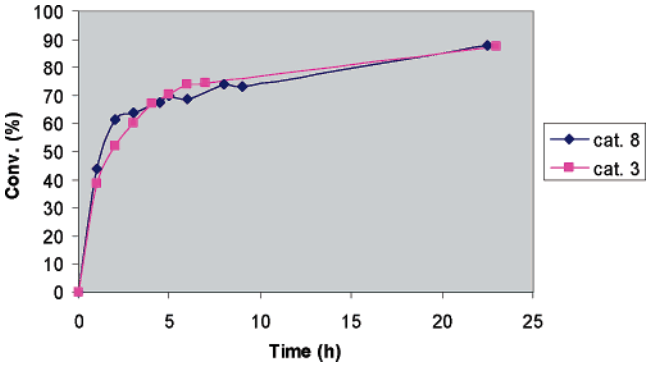


FIGURE 4. Comparison of catalysts **3** and **8** in the combined transfer hydrogenation/hydrogenation of dione **2g.** The reactions were run on a 1 mmol scale with 2 mol % of catalyst and 24 equiv of 2-propanol in 2.5 mL of toluene at 80 °C under an atmosphere of H_2(g).

1,3-Cycloheptanedione **1e** showed a similar behavior as **1g** and was therefore reduced under the same reaction conditions (Table 2, entry 5), although some monoreduced dione still remained after 24 h.

In the transfer hydrogenation of five-membered cyclic 1,3-diones, only very low conversions were obtained in the absence of hydrogen gas, but at lower temperature and with hydrogen gas present, 1,3-cyclopentanediol could be isolated in 69% yield after 48 h (Table 2, entry 6). Somehow, the system could not reduce 2-methyl-1,3-cylopentanedione. Only low conversions were obtained after 3 days at 80 °C under hydrogen gas, and practically all starting material could be recovered.

In conclusion, we have found that six-membered cyclic 1,3-diones can be reduced to the corresponding 1,3-diols via transfer hydrogenation using ruthenium catalyst **3** and 2-propanol as a hydrogen donor under microwave heating. The diols were obtained in up to 93% yield. Five- and seven-membered cyclic 1,3-diones could also be reduced to the corresponding diols in good yield, but hydrogen gas and longer reaction times were required. The diol products are useful starting materials in dynamic kinetic asymmetric transformations, in which the meso/

D,L mixture of a diol can be converted into one stereoisomer of the diol diacetate.[1]

Experimental Section

General Procedure for the Preparation of 1,3-Cycloalkanediols: 1,3-Cyclohexanediol (2b). A Pyrex tube (5 mL) was charged with 1,3-cyclohexanedione **1b** (112 mg, 1 mmol), ruthenium catalyst **3** (11 mg, 0.01 mmol), 2-propanol (1.83 mL, 24 mmol), and toluene (2.5 mL) and fitted with a silicone/Teflon septum. The septum was closed, and the reaction vessel was inserted to a microwave oven and heated at 110 °C for 30 min. The solvents were evaporated, and the crude product was purified by chromatography (CH_2Cl_2 to remove the yellow band, then EtOAc) to afford **2b** (103 mg, 88%) as a colorless oil in a cis/trans ratio of 58:42. Analytical data were in accordance with those reported in the literature.[1]

2-Methyl-1,3-cyclohexanediol (2a). Following the general procedure, the reaction mixture was heated for 60 min in a microwave oven. Chromatography (CH_2Cl_2 to remove the yellow band, then *n*-pentane/EtOAc 3:2 to 1:2) afforded **2a** (111 mg, 85%) as a pale brown oil in a disatereomeric ratio of 28:36:36. Analytical data were in accordance with those reported in the literature.[3]

2,2-Dimethyl-1,3-cyclohexanediol (2c).[24] Following the general procedure, the reaction mixture was heated for 60 min in a microwave oven. Chromatography (CH_2Cl_2 to remove the yellow band, then *n*-pentane/EtOAc 2:1 to 1:1) afforded **2c** (120 mg, 83%) as a white solid in a cis/trans ratio of 56:44. *cis*- **2c** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (dd, J = 3.5, 7.9 Hz, 2H), 1.79 (m, 3H), 1.55 (m, 2H), 1.34 (m, 1H), 1.03 (s, 3H), 1.00 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 76.2, 39.7, 29.3, 24.6, 17.1; *trans*-**2c** ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (dd, J = 3.3, 7.1 Hz, 2H), 1.72 (m, 2H), 1.64 (m,2H), 1.50 (m, 2H), 0.99 (s, 6H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 74.9, 39.8, 29.4, 21.1, 19.1

5-Methyl-1,3-cyclohexanediol (2d).[2] Following the general procedure, the reaction mixture was heated at 120 °C for 2 h in a microwave oven. Purification by distillation (230 °C, 0.6 mbar) afforded **2d** (95.5 mg, 73%) as a white solid in a diasteromeric ratio of D,L-**2d** (*trans*-**2d**)/*meso-anti*-**2d**/*meso-syn*-**2d** (*all-cis*-**2d**) of 35:19:46.[25] D,L-**2d** ^{1}H NMR (400 MHz, pyridine-d_5): δ 4.67 (tt, J = 15.4, 4.2 Hz, 1H), 4.51 (m, 1H), 2.63 (dm, J = 12.8 Hz, 1H), 2.33 (dm, J = 11.3 Hz, 2H), 1.98 (dm, J = 13.4 Hz, 1H), 1.71 (td, J = 11.3, 2.7 Hz, 1H), 1.30 (app. q, J = 12.8 Hz, 1H), 1.18 (td, J = 13.9, 2.7 Hz, 1H), 0.97 (d, J = 6.6 Hz, 3H) ^{13}C NMR (100 MHz, pyridine-d_5): δ 67.3, 66.2, 46.3, 43.8, 42.3, 26.4, 23.0.

meso-anti-**2d**:^{1}H NMR (300 MHz, pyridine-d_5): δ 4.30 (m, 2H), 2.50 (m, 1H), 2.15 (dm, J = 13.5 Hz, 1H), 1.99 (dm, J = 13.2 Hz, 2H), 1.85 (dt, J = 13.5, 3.0 Hz, 1H), 1.37 (td, J = 10.2, 2.8 Hz, 2H), 0.94 (d, J = 6.9 Hz, 3H) ^{13}C NMR (100 MHz, pyridine-d_5): δ 67.4, 42.4, 40.3, 22.7, 22.2

meso-syn-**2d**: ^{1}H NMR (300 MHz, pyridine-d_5): δ 3.86 (tt, J = 11.0, 4.1 Hz, 2H), 2.83 (dm, J = 11.6 Hz, 1H), 2.17 (dm, J = 11.6 Hz, 2H), 1.79 (app. q, J = 11.2 Hz, 1H), 1.49 (m, 1H), 1.22 (app. q, J = 11.6 Hz, 2H), 0.95 (d, J = 6.6 Hz, 3H) ^{13}C NMR (100 MHz, pyridine-d_5): δ 68.6, 46.9, 45.3, 28.7, 22.6

1,3-Cycloheptanediol (2e) via Combined Transfer Hydrogenation and Hydrogenation. A Pyrex tube (5 mL) was charged with 1,3-cycloheptanedione **1e** (126 mg, 1 mmol), ruthenium catalyst **3** (21.7 mg, 0.02 mmol), 2-propanol (1.83 mL, 24 mmol), and toluene (2.5 mL) and fitted with a silicone/Teflon septum. The septum was closed, and the atmosphere was exchanged to hydrogen gas. A balloon filled with hydrogen gas was fitted to the flask, and the mixture was heated at 80 °C in an oil bath for 24 h. The solvents were evaporated, and the crude product was purified by chromatography (CH_2Cl_2 to remove the yellow band, then pentane/EtOAc 1:1) to afford **2h** (95 mg, 73%) as a brown oil in a cis/trans ratio of 48:52. Analytical data for *trans*-**2e** were in accordance with those reported in the literature.[26]

cis-**2e.**[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (app. sep, J = 3.6 Hz, 2H), 2.10 (dt, J = 13.7, 3.3 Hz, 1H), (2.00−1.81, m, 5H), (1.76−1.61, m, 4H), (1.55−1.39, m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.4, 45.4, 37.5, 23.1

1,3-Cyclopentanediol (2f). Following the same procedure as for **2e**, the reaction mixture was heated at 80 °C in an oil bath for 48 h. Purification by chromatography (CH_2Cl_2 to remove the yellow band, then CH_2Cl_2/MeOH 9:1) afforded **2f** (70 mg, 69%) as a brown oil in a cis/trans ratio of 69:31. Analytical data were in accordance with those reported in the literature.[28,29]

1,3-Indanediol (2g). Following the same procedure as stated previously, the reaction mixture was heated at 80 °C in an oil bath for 30 h. Purification by distillation (300 °C, 0.6 mbar) afforded **2g** (140 mg, 93%) as a white solid in a cis/trans ratio of 91:9. Analytical data were in accordance with those reported in the literature.[30]

Acknowledgment. Financial support from the Swedish Foundation for Strategic Research and the Swedish Research Council is gratefully acknowledged.

Supporting Information Available: General experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **2c**, **2d**, and **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) The corresponding hydrogenation using Pd/C gave 2-methyl-2-cyclohexen-1-ol as the major product.

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(23) There seemed to be a loss of H_2 (g) from the catalyst over time, so a constant atmosphere of hydrogen was needed. Since 2-propanol has a boiling point of 82 °C, the temperature had to be decreased. For H_2 elimination from **3a**, see Casey, C. P.; Johnson, J. B.; Singer, S. W.; Cui, Q. *J. Am. Chem. Soc*. **2005**, *127*, 3100−3109.

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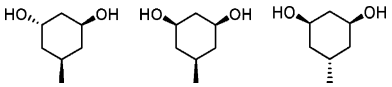

here called D,L-**2d**, *meso-syn*-**2d** (*all-cis*-**2d**), and *meso-anti*-**2d**, respectively.

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