

Preparation of Bicyclo[3.2.1]octan-6-ones from Substituted Cyclohexyl Diazo Ketones

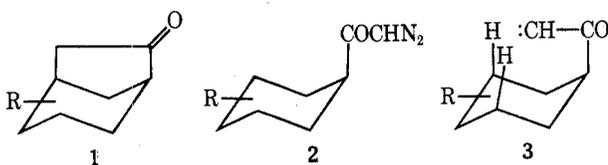
William C. Agosta* and Steven Wolff*

Laboratories of The Rockefeller University, New York, New York 10021

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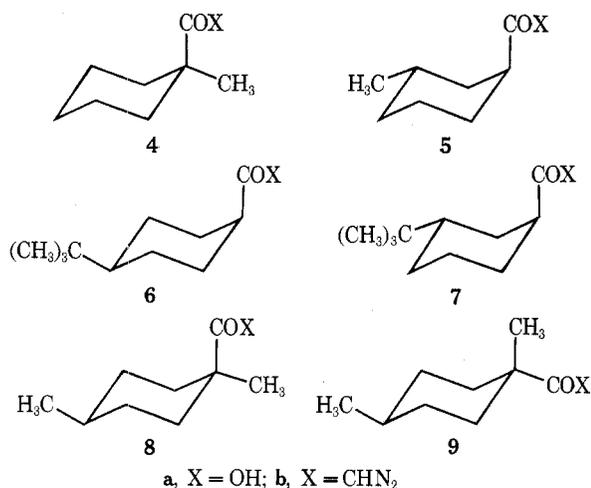
The copper or silver ion catalyzed decomposition of diazo ketones **4b–9b** has been examined with reference to formation of bicyclooctanones through carbon–hydrogen bond insertion at C(3). The course of the reaction is sensitive to the nature of alkyl substitution in the cyclohexane ring, and the results are analyzed in terms of both conformational effects and the degree of substitution at the site of insertion.

In the course of other investigations we required a number of bicyclo[3.2.1]octan-6-ones (**1**) bearing various substituents of known stereochemistry at different positions on the six-membered ring. An attractive route to several of the desired compounds involved metal ion catalyzed decomposition of the appropriately substituted cyclohexyl diazo ketones **2**. There are several known examples of this transformation in which bicyclooctanones are formed through insertion of the intermediate carbene or carbenoid species (formally **3**) into an axial carbon–hydrogen bond at

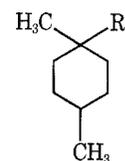


C(3).^{1–3} We describe here our experiments in preparing six new bicyclooctanones using this procedure. Points of general interest include the variable effectiveness of both silver and copper in catalyzing the reaction, and substituent effects which may be interpreted as involving both the degree of substitution at C(3) and also the preferred conformations of the side chain and the cyclohexane ring.

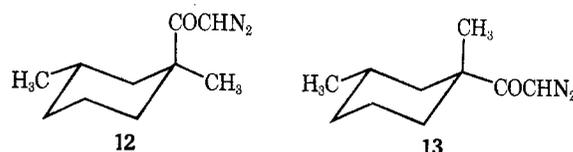
The carboxylic acids **4a–8a**, all of which have been previously described,^{4,5} were prepared as precursors of the desired diazo ketones. The configuration of **8a** and its epimer **9a** has been assigned^{5b} on the basis of retention times of



the methyl esters on vapor phase chromatography (VPC), NMR spectral data, and comparisons of refractive indices. Our present work provides corroboration for this stereochemical conclusion. We have prepared a mixture of these acids (**10**) by Koch carbonylation of 1,4-dimethylcyclohexanol (**11**) in sulfuric acid and formic acid.^{5a} VPC of the de-



10, R = COOH
11, R = OH

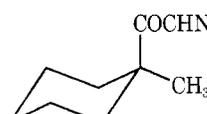
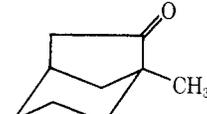
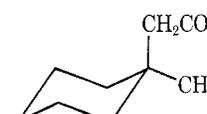
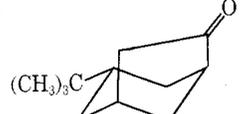
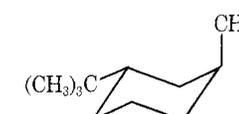
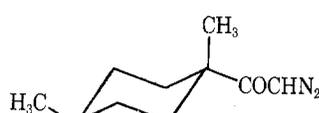
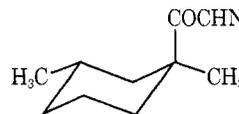
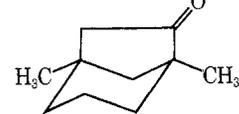
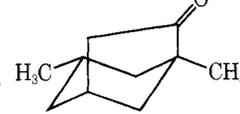


rived methyl esters indicated that the two isomers **8a** and **9a** were formed in the ratio 86:14. Since exposure of minor isomer **9a** to the reaction conditions did not lead to its epimerization, the carbonylation reaction is under kinetic control. Such Koch reactions are expected⁶ to proceed by preferential introduction of an axial carboxyl group, and this implies that the major isomer formed is **8a**, in line with the original assignment.^{5b} Furthermore, this stereochemistry is in keeping with subsequent transformations of **8a** and **9a** described below.⁷

Each of these carboxylic acids was converted through the acyl chloride to the diazo ketone in the usual manner,⁸ and these diazo ketones were then decomposed in one of two known ways. In the first procedure⁹ a methanolic solution of diazo ketone (~0.25 M) was treated with silver benzoate in triethylamine at room temperature with subsequent heating at reflux for 1 hr. The second method¹ involved very slow addition (~4 drops/min) of a dilute solution of diazo ketone in cyclohexane (~300 ml, ≤0.1 M) to a refluxing suspension of CuSO₄ in ~1.25 l. of the same solvent, followed by 5-hr reflux after addition was complete.

Products were isolated and purified by preparative VPC, and the results are gathered in Chart I. Yields are based on relative VPC areas and are referred to the carboxylic acid used. Those given for the reactions of **4b** include data from the original study by Wenkert and his coworkers, wherein other products also were isolated. Data for **12**, partly from work which we reported earlier,² are also included. The difference in behavior between **8b** and **9b**, with only **8b** undergoing the insertion reaction to yield a ketone, is parallel to earlier results² with **12** and its stereoisomer **13**. The present observation is in accord with the stereochemical assignment noted above for acids **8a** and **9a**. The structures of the products from **5b–9b** rest on ir and 220-MHz NMR spectroscopic properties recorded in the Experimental Section, as well as general previous experience^{1–3} with the transformation. In particular the two isomeric ketones **16** and **17** obtained from **5b**, as well as **21** and **22** from **7b**, could be

Chart I
Decomposition of Diazo Ketones

Diazo ketone	Metal ion	Products and yields		
 4b		 14	 15	
	Ag	8%		58%
	Ag ^a	6%		51%
	Cu	48%		
	Cu ^a	62%		
 5b		 16	 17	 18
	Ag	<1%	<1%	41%
	Cu	26%	2%	
 6b		 19		 20
	Ag ^b	16%		80% ^b
	Cu			
 7b		 21	 22	 23
	Ag	<1%	<1%	62%
	Cu	51%	7%	
 8b		 24		 25
	Ag	40%		36%
	Cu	67%		
 9b				 26
	Ag			53%
 12		 27	 28	 29
	Ag ^c	35%	15%	29%
	Cu	58%	22%	

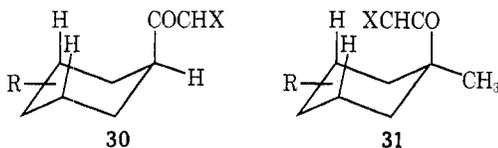
^a From ref 1; Ag reaction using silver oxide in methanol. ^b H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *J. Am. Chem. Soc.*, **92**, 2800 (1970); yield based on recrystallized **6b**. ^c From ref 2.

distinguished from each other by the multiplicity of the signals for the exo C(7) methylene protons (α to the carbonyl group). Vicinal coupling of this proton to the bridgehead was absent in **16** and **21**, but present in **17** and **22**. In this regard it was profitable to make comparisons with the NMR spectra of **27** and **28**, for which the structural distinction is firmly based on chemical degradation of **27**.^{2,10}

From Chart I it is clear that for preparation of these bicyclooctanones, copper catalysis is invariably superior to silver, and indeed it is well known^{1,11,12} that copper favors external reactions in decomposition of diazo ketones, while silver is particularly effective in promoting Wolff rearrangement. While the use of silver is then of no preparative value for the desired ketones, the results provide an in-

structive comparison with the copper-catalyzed process in evaluation of structural effects on the transformation.

These structural effects appear to be of three types from the product distributions observed, and we consider each of these individually. First, the degree of substitution of the carbon-hydrogen bond at C(3) into which insertion may occur plays a role. Thus in the copper decomposition of both **5b** and **7b** the intramolecular competition in each case strongly favors insertion into the tertiary bond (leading to **16** and **21**) rather than the secondary one (leading to **17** and **22**). Such regioselectivity in intermolecular insertion is well documented¹³ for a variety of other types of stabilized carbene species, including carboalkoxy and cyano carbenes. A second discernible effect is the conformational behavior of the cyclohexane ring. This is obvious in rather strongly biased systems such as **8b** and **9b**, in which essentially all reaction occurs from the stable conformations shown, but, more interestingly, the effect is also apparent when **8b** is compared with the conformationally more mobile **4b**. The latter system, lacking the anchoring effect of the 4-methyl substituent, presumably reacts from both chair conformers. Only the one shown can lead to ketone, however, and the result with silver catalysis is more ester and less ketone from **4b** than from **8b**. It is noteworthy that this effect is much less significant with copper catalysis, where Wolff rearrangement is inherently less favored. Finally, the success of these reactions depends importantly on the presence of substitution at C(1) in the diazo ketone. Without this substitution the silver reactions fail to give ketones at all, as seen with **5b** and **7b**, and the copper reactions are adversely affected. Thus, although there is little conformational difference between **4b** and **5b**, and despite the availability only in **5b** of a tertiary carbon-hydrogen bond for insertion, it is **4b** with a 1-methyl substituent that furnishes more ketone. Previous examples^{1,2} of the formation of bicyclooctanones by this process from diazo ketones all have involved only cyclohexanes bearing a methyl group at C(1), and the particular significance of this substitution, therefore, could not be appraised. We suggest that this behavior may be ascribed to a rotational conformation effect on the axial side chain when there is geminal substitution at C(1). In the absence of such C(1) substitution, the axial group will be preferentially rotated away from the ring (see **30**) to avoid nonbonded interactions with the C(3) and C(5) axial hydrogens. When a substituent is present at C(1), however, this orientation of the axial group is somewhat less favorable. The result is that the orientation toward the ring (see **31**), which is necessary for insertion at C(3) or



C(5), is then relatively more favorable. It is reasonable that this effect be more pronounced in the silver reactions, since, as noted with the ring conformational effect above, Wolff rearrangement provides better competition to insertion under these conditions.

Despite the sensitivity of yield to the specific substitution pattern involved, this cyclization clearly offers convenient access to a variety of alkylated bicyclo[3.2.1]octan-6-ones.

Experimental Section

Materials and Equipment. All VPC was carried out using a Varian Aerograph Model A-90-P3 gas chromatograph with one of the following columns: A, 25% DEGS, 20 ft \times 0.25 in.; B, 25%

DEGS, 25 ft \times 0.375 in.; C, 30% DEGS, 10 ft \times 0.375 in.; D, 25% PDEAS, 48 ft \times 0.25 in.; E, 30% Carbowax 20M, 10 ft \times 0.375 in.; F, 30% SE-30, 10 ft \times 0.375 in. All columns were prepared using 45/60 Chromosorb W in aluminum tubing. Ir and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian HR-220 (220 MHz) spectrometer. Mass spectra were obtained on a Du Pont 21-492 double-focusing mass spectrometer with a resolution of 10^4 , and results were processed with an AEI DS-30 data system. Boiling points are uncorrected; melting points are corrected. Solutions were dried over MgSO_4 . Unless otherwise noted, products were obtained as colorless oils.

Preparation of Diazo Ketones. The pure carboxylic acids were converted to acyl chlorides with thionyl chloride according to the procedure of Eliel;¹⁴ heating at the end of the reaction was omitted in the case of epimerizable acid chlorides. Excess thionyl chloride was removed in vacuo, and the residue was added immediately to an excess (>3 equiv) of distilled ethereal diazomethane cooled in an ice bath. The reaction mixture was allowed to warm to room temperature overnight. Excess diazomethane and solvent were removed by evaporation in a steam bath and then in vacuo. The diazo ketones thus prepared showed strong absorption at 2110 and 1640 cm^{-1} in their ir spectra (other carbonyl absorptions were absent) and were used in subsequent steps without further purification.

General Procedure for Silver(I)-Catalyzed Decomposition of Diazo Ketones. The method of Newman and Beal⁹—addition of a triethylamine solution of silver benzoate to the diazo ketone dissolved in alcoholic solvent—was employed without modification. The prescribed work-up yielded a residue which was distilled bulb-to-bulb to give a colorless distillate. Analysis of the reaction mixture and further purification were accomplished with VPC using the column indicated in each case. Products are described in order of their elution.

General Procedure for Copper(II)-Catalyzed Decomposition of Diazo Ketones. The crude diazo ketone (12–30 mmol) was taken up in cyclohexane (200–300 ml), filtered through Celite, and added at a very slow rate (<4 drops/min) through a constant addition funnel to a suspension of anhydrous CuSO_4 (2 equiv) in cyclohexane (800–1250 ml) heated to reflux; the reaction was mechanically stirred and protected from atmospheric moisture using a drying tube. Three to five days were usually necessary to complete the addition. To ensure complete decomposition of the diazo ketone, the reaction mixture was heated at reflux for at least another 5 hr after addition was complete. About $\frac{1}{3}$ of the solvent was removed by distillation through a 35-cm Vigreux column. After cooling, water (250 ml) was added and the organic phase was washed with 10% Na_2CO_3 (100 ml) and brine (100 ml), and then dried. The remainder of the cyclohexane was removed by careful distillation (Vigreux column) and the residue was distilled under reduced pressure. The yellow distillate obtained was further purified by VPC using the column indicated in each case. Products are described in order of their elution.

Silver(I)-Catalyzed Decomposition of **4b.** Products were analyzed on column A. 1-Methyl-1-cyclohexaneacetic acid methyl ester (**15**, 58%): ir 2945 (s), 2870 (m), 1738 (s), 1455 (m), 1225 (m), 1190 (m), 1165 (m), 1023 cm^{-1} (m); NMR δ 3.57 (s, 3 H), 2.16 (s, 2 H), 1.54–1.21 (br m, 10 H), 0.98 (s, 3 H).

Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_2$: C, 70.54; H, 10.66. Found: C, 70.49; H, 10.73.

5-Methylbicyclo[3.2.1]octan-6-one (**14**, 8%):¹ ir 2960 (s), 2890 (m), 1745 (s), 1450 (m), 1400 (w), 1038 cm^{-1} (w); NMR δ 2.50 (br, 1 H), 2.19 (dd, $J = 7, 18\text{ Hz}$, 1 H), 2.00 (dd, $J = 3.5, 18\text{ Hz}$, 1 H), 1.93–1.24 (br m, 8 H), 0.936 (s, 3 H).

Copper(II)-Catalyzed Decomposition of **4b.** Products were analyzed on column B. In addition to **14** (48%), there was obtained a small amount of a cyclobutanone (ir 1775 cm^{-1}).¹

Silver(I)-Catalyzed Decomposition of **5b.** Product analysis on column B indicated essentially one component. This was collected and identified as *trans*-3-methylcyclohexaneacetic acid methyl ester (**18**, 41%): ir 2920 (s), 1740 (s), 1455 (m), 1430 (m), 1165 (s), 1020 cm^{-1} (m); NMR δ 3.59 (s, 3 H), 2.21–2.03 (m, 2 H), 1.82–1.02 (br m, 10 H), 0.925 (d, $J = 7\text{ Hz}$, 3 H).

Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_2$: C, 70.54; H, 10.66. Found: C, 70.55; H, 10.69.

Copper(II)-Catalyzed Decomposition of **5b.** Product analysis on column B afforded two products. 1-Methylbicyclo[3.2.1]octan-6-one (**16**, 26%): ir 2945 (s), 2860 (m), 1745 (s), 1455 (m), 1377 (w), 1345 (w), 1255 (w), 1165 (m), 1122 (w), 1080 (m), 1023 cm^{-1} (w); NMR δ 2.33 (br, 1 H), 1.98 (dd, $J = 3, 18\text{ Hz}$, 1 H), 1.83 (dd, $J =$

0.5, 18 Hz, 1 H), 1.90–1.38 (br m, 8 H), 1.13 (s, 3 H); mass spectrum 138.1047 (M^+ , calcd for $C_9H_{14}O$, 138.1044).

exo-3-Methylbicyclo[3.2.1]octan-6-one (17, 2%): ir 2945 (s), 2860 (m), 2845 (m), 1745 (s), 1455 (m), 1407 (m), 1155 (m), 1052 cm^{-1} (m); NMR δ 2.54 (br, 1 H), 2.23 (br, 1 H), 2.12 (ddd, $J = 0.5, 7, 18$ Hz, 1 H), 1.95 (dd, $J = 3, 18$ Hz, 1 H), 2.04–1.05 (br m, 7 H), 0.90 (d, $J = 6$ Hz, 3 H); mass spectrum 138.1051 (M^+ , calcd for $C_9H_{14}O$, 138.1044).

Copper(II)-Catalyzed Decomposition of 6b. Product analysis on column C yielded *endo*-2-*tert*-butylbicyclo[3.2.1]octan-6-one (19, 16%): ir 2980 (s), 2900 (m), 1747 (s), 1445 (m), 1360 (m), 1162 cm^{-1} (m); NMR δ 2.63 (br, 1 H), 2.19 (br, 1 H), 2.16 (dd, $J = 3, 18$ Hz, 1 H), 2.02 (dd, $J = 6, 18$ Hz, 1 H), 1.86–1.23 (br m, 7 H), 0.89 (s, 9 H); mass spectrum 180.1512 (M^+ , calcd for $C_{12}H_{20}O$, 180.1513).

Silver(I)-Catalyzed Decomposition of 7b. Product analysis on column C indicated a single major component which was identified as *trans*-3-*tert*-butylcyclohexanecarboxylic acid methyl ester (23, 62%): ir 2965 (s), 2900 (m), 1742 (s), 1470 (m), 1448 (m), 1428 (m), 1360 (m), 1148 (m), 1022 cm^{-1} (w); NMR δ 3.56 (s, 3 H), 2.38–2.22 (m, 2 H), 1.78–1.04 (br m, 10 H), 0.81 (s, 9 H).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.44; H, 11.38.

Copper(II)-Catalyzed Decomposition of 7b. Products analysis on column C yielded *exo*-3-*tert*-butylbicyclo[3.2.1]octan-6-one (22, 7%): ir 2970 (s), 2895 (m), 1747 (s), 1460 (m), 1360 (m), 1140 cm^{-1} (w); NMR δ 2.58 (br, 1 H), 2.26 (br, 1 H), 2.11 (dd, $J = 6.5, 18$ Hz, 1 H), 1.94 (dd, $J = 3.5, 18$ Hz, 1 H), 1.95–1.20 (br m, 7 H), 0.84 (s, 9 H); mass spectrum 180.1510 (M^+ , calcd for $C_{12}H_{20}O$, 180.1513).

1-*tert*-Butylbicyclo[3.2.1]octan-6-one (21, 51%): ir 2980 (s), 2900 (m), 1747 (s), 1470 (br, m), 1365 (m), 1150 (m), 1088 cm^{-1} (m); NMR δ 2.34 (br, 1 H), 2.09 (dd, $J = 0.5, 18$ Hz, 1 H), 1.80 (dd, $J = 3, 18$ Hz, 1 H), 1.99–1.06 (br m, 8 H), 0.91 (s, 9 H); mass spectrum 180.1519 (M^+ , calcd for $C_{12}H_{20}O$, 180.1513).

Silver(I)-Catalyzed Decomposition of 8b. Product analysis on column D indicated two major components which were collected and identified as 1,*c*-4-dimethyl-*r*-1-cyclohexanecarboxylic acid methyl ester (25, 36%): ir 2950 (s), 2925 (s), 2870 (m), 2850 (m), 1740 (s), 1450 (m), 1430 (m), 1375 (m), 1195 (m), 1150 (m), 1095 cm^{-1} (m); NMR δ 3.55 (s, 3 H), 2.20 (s, 2 H), 1.92–1.02 (br m, 9 H), 0.96 (s, 3 H), 0.90 (d, $J = 6$ Hz, 3 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.72; H, 11.02.

endo-2,5-Dimethylbicyclo[3.2.1]octan-6-one (24, 40%): ir 2965 (s), 2940 (s), 2875 (m), 1745 (s), 1448 (m), 1400 (w), 1375 (w), 1130 (w), 1042 (w), 980 cm^{-1} (w); NMR δ 2.19 (br, 1 H), 2.09 (dd, $J = 4, 18$ Hz, 1 H), 1.98 (dd, $J = 7, 18$ Hz, 1 H), 1.98–1.00 (br m, 7 H), 0.93 (s, 3 H), 0.89 (d, $J = 6$ Hz, 3 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.66; H, 10.70.

Copper(II)-Catalyzed Decomposition of 8b. Distillation of the crude product (98–108°, 16 mm) yielded 24 (67%), identical with material described above.

Silver(I)-Catalyzed Decomposition of 9b. Product analysis on column C gave a single product identified as 1,*t*-4-dimethyl-*r*-1-cyclohexanecarboxylic acid methyl ester (26, 53%): ir 2950 (s), 2930 (s), 2860 (m), 2850 (m), 1740 (s), 1438 (m), 1250 (m), 1190 (m), 1140 (m), 1023 (w), 995 cm^{-1} (w); NMR δ 3.55 (s, 3 H), 2.07 (s, 2 H), 1.88–1.02 (br m, 9 H), 0.97 (s, 3 H), 0.89 (d, $J = 6$ Hz, 3 H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.75; H, 11.13.

Copper(II)-Catalyzed Decomposition of 12. Product analysis on column A gave ketones 27 (58%) and 28 (22%), identical with previously described material.²

1,*t*-3-Dimethyl-*r*-1-cyclohexanecarboxylic Acid. Addition of a solution of 3,5-dimethylcyclohexanol (32.1 g, 0.25 mol) in 97+% formic acid to 96% sulfuric acid¹⁵ gave 31.0 g (80%) of white, crystalline material, mp 76.5–81.5°. Two recrystallizations from aqueous methanol gave 1,*t*-3-dimethyl-*r*-1-cyclohexanecarboxylic acid, mp 88.5–89.5° (lit. mp 88.5–89.5°² and 92°^{5a}). Esterification of the crude acid with diazomethane and analysis by VPC on column E indicated two components in the ratio 19:1. The isomeric minor acid (also independently available²) was submitted to the reaction conditions; the recovery of material was quantitative, and VPC

analysis after diazomethane esterification indicated formation of $\leq 1\%$ of the major acid under these conditions.

1,*c*-4- and 1,*t*-4-Dimethyl-*r*-1-cyclohexanecarboxylic Acids (8a and 9a). Treatment of 1,4-dimethylcyclohexanol (9.45 g, 0.074 mol) with sulfuric and formic acid as described above gave 7.30 g (64%) of a colorless oil. After diazomethane esterification VPC analysis on column F showed the presence of two components in the ratio 86:14. Each of these compounds was collected and hydrolyzed with methanolic alkali to regenerate the acid. The major ester yielded an acid, mp 44.5–45.5° (lit.^{5b} mp 46.5–47°), and amide, mp 82–83° (lit.^{5a} mp 82°); the second ester yielded an acid, mp 41–42°, and amide, mp 129.5–130.5° (lit.^{5a} mp 134°). Submission of the minor acid (34.6 mg) to the reaction conditions described above again gave a quantitative recovery of material with essentially no isomerization.

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Registry No.—4b, 20609-36-3; 5b, 54277-24-6; 6b, 28125-14-6; 7b, 54277-25-7; 8a, 24097-70-9; 8b, 54277-26-8; 9a, 24097-71-0; 9b, 54277-27-9; 12, 38864-05-0; 14, 20608-68-8; 15, 20608-66-6; 16, 54277-28-0; 17, 54277-29-1; 18, 54277-30-4; 19, 54277-31-5; 21, 54277-32-6; 22, 54277-33-7; 23, 54277-34-8; 24, 54277-35-9; 25, 54277-36-0; 26, 54277-37-1; silver, 7440-22-4; copper, 7440-50-8; 1,*t*-3-dimethyl-*r*-1-cyclohexanecarboxylic acid, 38864-02-7; 3,5-dimethylcyclohexanol, 5441-52-1; 1,4-dimethylcyclohexanol, 5402-28-8; 1,*c*-4-dimethyl-*r*-1-cyclohexanecarboxamide, 54277-38-2; 1,*t*-4-dimethyl-*r*-1-cyclohexanecarboxamide, 54277-39-3.

References and Notes

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