freshly prepared material in acidic solution. The cyclization product **7** was isolated as the hydrochloride, mp 187–190 °C dec. Anal. Calcd for $C_5H_8N_4{\cdot}HCl{\cdot}H_2O$: C, 33.62; H, 6.21; N, 31.37. Found: C, 34.09; H, 6.13; N, 31.64.

A preparative reaction yielding **4** was carried out by allowing a hydrochloric acid solution containing **2** and **3** plus a catalytic amount of **1** to stand for several days. Solvent evaporation and recrystallization of the residue gave **4** as the hydrochloride, mp 264–266 °C (from $H_2O-CH_3CH_2OH$). Anal. Calcd for $C_5H_{11}N_5{\cdot}2HCl$: C, 28.05; H, 6.72; N, 32.71. Found: C, 28.47; H, 6.12; N, 32.47. A stoichiometric adduct was preparatively obtained by allowing **1** to react with a slight excess of **8** and **9** in dilute hydrochloric acid for 14 days. Evaporation of solvent and recrystallization yielded the rotaxane as a hydrate, mp >300 °C (from $H_2O-CH_3CH_2OH$). Anal. Calcd for $C_{36}H_{36}N_{24}O_{12}{\cdot}C_{13}H_{17}N_5{\cdot}2HCl{\cdot}12.5H_2O$: C, 38.01; H, 5.86; N, 26.24. Found: C, 37.84; H, 6.19; N, 26.57.

NMR spectra consistent with the structures of all substrates and products were obtained.[1]

Kinetics. The standard reaction medium employed throughout this work consists of a 1:1 (v/v) mixture of 88% formic acid plus water at 40.0 (±1.0) °C.[6] Rate measurements were obtained by adding 1.0 mL of a freshly prepared 40 °C stock solution of substrate azide (0.015–0.09 M) to 2.0 mL of a stock solution of **1** (0.003–0.0075 M) and substrate alkyne (0.00375–0.12 M) in a spectrophotometer cell at 40.0 °C. The initial decrease in azide absorbance (281 nm) was recorded, and the tangent to the absorbance vs time curve was determined by a computer-assisted, iterative least-squares line-fitting procedure. The total absorbance change after the reaction had run to completion was subsequently obtained, for securing rates in concentration units.[28] Duplicate kinetic runs concordant within 10% were routinely observed. The same techniques were employed for the inhibition study involving **10**. Tolerances listed in this article are standard errors from least-squares analysis, for the most part.

Acknowledgment. This work was supported by the Dow Chemical Co. Foundation, the University of Illinois Research Board, and in part by the Office of Naval Research.

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[28] This procedure was essential for the catalytic reaction of **2** plus **3** and was found to be quicker and more reproducible than a full exponential fit of the absorbance vs time plot for the induced reaction of **8** plus **9** (probably because of the long-term instability of **9**). However, the latter procedure was employed for **6**, for measuring product release from **1·4**, and for the uncatalyzed control reaction of **2** plus **3** (second-order fit), with use of a quantitative NMR analysis.

Selective Reduction of Aryl Halides and α,β-Unsaturated Esters with Sodium Borohydride–Cuprous Chloride in Methanol and Its Application to Deuterium Labeling

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A reducing system, $NaBH_4-Cu_2Cl_2/MeOH$, was developed for dehalogenation of aryl halides, conjugate reduction of α,β-unsaturated esters, and deuterium labeling in a chemo- and regioselective manner. These reactions proceeded without reduction of isolated olefins. The Cu_2Cl_2 is assumed to function as the catalyst which generates a transient species of copper hydride as an active reducing agent, on contact with $NaBH_4$. Deuterium-labeling studies indicated that (i) the hydrogen which was transferred to the 4-position of methyl 4-iodobenzoate originates from MeOH and (ii) the hydrogens which were transferred to the α- and β-positions of the conjugated ester originate from MeOH and $NaBH_4$, respectively.

$NaBH_4$ is widely used as a common reagent for selective reduction of carbonyl compounds[1] and, in some cases, in combination with metal salts and various solvents provides a variety of reducing systems.[2] Expansion of the capability of these reducing systems would be useful, and it is also desirable to improve their chemo- and regioselectivity.

We needed a convenient method of preparing deuterated compound [4′-^{2}H]-**1** for synthetic studies, and one attractive route was the selective replacement of the iodine atom of aryl iodide **2** with a deuterium atom. Only two methods for such a reaction have been reported.[3,4] The reduction of *o*-iodonitrobenzene to *o*-deuterionitrobenzene was reported to be readily achieved by using $NaBH_4$ in a 4:1 mixture of DMSO–D_2O,[3] but **2** did not undergo reduction under similar conditions. Bosin and co-workers[4] have successfully used $NaBH_4$ in MeOH in the presence of $PdCl_2$ for selective reduction of *p*-chlorobenzoic acid to the corresponding para-deuterated derivative, but application of this method to **2** generated 21% of the undesired overreduction product **3** besides 34% of the desired product [4′-^{2}H]-**1**.

Thus we decided to find a method useful for this selective transformation. One possibility for improving reduction selectivity is the use of a transition-metal salt as the catalyst for the $NaBH_4$ reduction. Although a variety of reductions using combinations of $NaBH_4$ with many other transition-metal salts such as $NiCl_2$,[5] $CoCl_2$,[6] $CuCl_2$,[6a,7] $CeCl_3$,[8] $RhCl_3$,[9] and $AlCl_3$[10] have been cited in the

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[1] (a) Walker, E. R. H. *Chem. Soc. Rev.* **1976**, *5*, 23. (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.

[2] (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972. (b) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *J. Org. Chem.* **1982**, *47*, 4702.

[3] Bell, H. M.; Vanderslice, C. W.; Spehar, A. *J. Org. Chem.* **1969**, *34*, 3923.

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[5] (a) Truce, W. E.; Roberts, F. E. *J. Org. Chem.* **1963**, *28*, 961. (b) Takegami, Y.; Ueno, T.; Sakata, T. *Kogyo Kagaku Zasshi* **1965**, *68*, 2373. (c) Satoh, T.; Suzuki, Y.; Suzuki, S. *Yakugaku Zasshi* **1970**, *90*, 1553. (d) Back, T. G.; Birss, V. I.; Edwards, M.; Krishna, M. V. *J. Org. Chem.* **1988**, *53*, 3815.

[6] (a) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, 4555. (b) Atta-ur-Rahman; Ghazala, M.; Sultana, N.; Bashir, M. *Ibid.* **1980**, *21*, 1773. (c) Chung, S.-K.; Han, G. *Synth. Commun.* **1982**, *12*, 903. (d) Satoh, T.; Suzuki, S.; Kikuchi, T.; Okada, T. *Chem. Ind.* **1970**, 1626.

[7] Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817.

Table I. Reduction of 2 with $NaBH_4$–Transition Metal Salt (MX) in MeOH[a]

MX (mol)	$NaBH_4$ (mol)	solvent	time, min	yield of 1 or [4′-^{2}H]-1,[b] %
	$NaBD_4$ (13.5)	MeOH-d_4	300	3
$PdCl_2$[c] (1)	$NaBD_4$ (4)	MeOH-d_4	30	34
Cu_2Cl_2 (0.5)	$NaBD_4$ (6)	MeOH-d_4	30	97.5
$CuCl_2$[c] (1)	$NaBH_4$ (6)	MeOH	30	94
$FeCl_2$[c] (1)	$NaBH_4$ (10)	MeOH	80	67
$ZnCl_2$ (1)	$NaBH_4$ (6)	MeOH	60	0

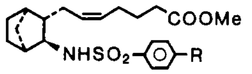
[a] All reactions were carried out at 0 °C; general procedure: see the Experimental Section. [b] The values are isolated yields of desired products. [c] Supplementary material.

literature, their uses for the dehalogenation of aryl halides were quite limited.[4,11]

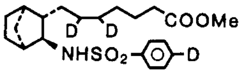
Herein we describe a reducing system of $NaBH_4$–Cu_2Cl_2/MeOH which performs dehalogenation of aryl halides, conjugate reduction of the α,β-unsaturated esters, and deuterium labeling in a chemo- and regioselective manner. The mechanism of the reaction is also discussed.

Results and Discussion

Reduction of Aryl Halides. First, the efficacy of several combinations of $NaBH_4$ (or $NaBD_4$) and various transition metals in MeOH (or MeOH-d_4) for the dehalogenation of 2 were investigated. $NaBH_4$ (or $NaBD_4$) was added in portions to an ice-cold MeOH (or MeOH-d_4) solution of 2 containing various metal salts. The reactions were generally exothermic with vigorous evolution of a gas. The results are summarized in Table I.



1, R=H
[4′-^{2}H]-1, R=D
2, R=I



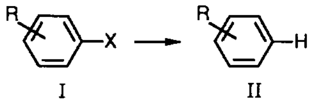
3

When 2 was treated with $NaBD_4$ in MeOH-d_4 in the presence of Cu_2Cl_2, [4′-^{2}H]-1 was obtained in good yield, and neither isomerization nor concurrent reduction of the olefin group was observed. Selective and relatively clean reduction was also observed when $CuCl_2$ was used instead of Cu_2Cl_2. With $FeCl_2$, the reduction proceeded inefficiently, resulting in 67% conversion, even though a large amount of $NaBH_4$ was used. With $ZnCl_2$, the reduction did not proceed. Thus, we concluded that Cu_2Cl_2 was the best salt for use with $NaBH_4$ to effect the dehalogenation of aryl halides.

We then proceeded to investigate the limitations of this reducing system. In order to know the reactivity of various aryl halides, simple halobenzenes and bromobenzenes, substituted with a methyl, methoxy, or methoxycarbonyl group, at suitable positions were reduced under standard conditions. The results are summarized in Table II.

All the iodo derivatives were reduced completely to the corresponding arenes, and the bromo derivatives were reduced at a moderate rate, while both chloro and fluoro derivatives were virtually inert to this reducing reagent.[12] An interesting substituent effect was observed for the bromobenzenes. With the methyl derivatives, the positions of substitution showed no significant effects on the reduction. The o-methoxy and o-carbomethoxy substitution accelerated the reaction significantly and the meta substitution moderately, while the para substitution decelerated it.[13]

Table II. Reduction of Halobenzenes with $NaBH_4$–Cu_2Cl_2 in MeOH[a]



I II

X	I, R (substitution)			yield of II,[b] %
	o-	*m*-	*p*-	
F				0
Cl				0
Br				20
Br	Me			22
Br		Me		19
Br			Me	15
Br	OMe			59
Br		OMe		31
Br			OMe	9
Br	COOMe			93
Br		COOMe		41
Br			COOMe	8
I				100
I			Me	100
I			OMe	100
I			COOMe	100

[a] All reactions were carried out on a 0.5-mmol scale at 0 °C; general procedure: see the Experimental Section. [b] Determined from the relative ratio of the area of the HPLC peak corresponding to II to that of I.

Conjugate Reduction of α,β-Unsaturated Esters. Although $NaBH_4$ has been known not to reduce olefins, the C═C double bond of α,β-unsaturated esters has been reported to be reduced with $NaBH_4$ under special conditions. In refluxing MeOH, methyl cinnamate was reduced partly by use of a large excess of $NaBH_4$ alone.[14] In C_6D_6 containing 1 equiv of water, benzyl crotonate was reduced with copper(I) hydride hexamer $[(Ph_3P)CuH]_6$, giving benzyl butyrate in a high yield.[15]

We therefore decided to apply the $NaBH_4$–Cu_2Cl_2/MeOH system to the conjugate reduction of ethyl cinnamate, and the reduction proceeded smoothly. The effects of molar ratios of Cu_2Cl_2 on the yield of ethyl hydrocinnamate are summarized in Table III.[16]

The features of the results are as follows: (i) Cu_2Cl_2 is essential for the reduction (entries 1–4), (ii) Cu_2Cl_2 functions as a catalyst (entry 10), and (iii) the combination of

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(8) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. (c) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (c) Rücker, G.; Hörster, H.; Gajewski, W. *Synth. Commun.* **1980**, *10*, 623.

(9) Nishiki, M.; Miyataka, H.; Niino, Y.; Mitsuo, N.; Satoh, T. *Tetrahedron Lett.* **1982**, *23*, 193.

(10) Ono, A.; Suzuki, N.; Kamimura, J. *Synthesis* **1987**, 736.

(11) $NaBH_4$ is reported to reduce aryl bromides to arenes in the presence of $Ni(Ph_3P)_3$. Lin, S.-T.; Roth, J. A. *J. Org. Chem.* **1979**, *44*, 309.

(12) According to the suggestion of one of the referees, we tried reduction of tosylate and mesylate of methyl salicylate by this system and found that, under the conditions described in Table II, both were reduced to methyl benzoate in 23 and 9% yields, respectively.

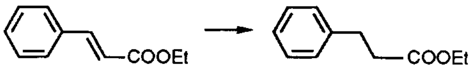
(13) For somewhat different observations with the $NaBH_4$–$PdCl_2$/MeOH system, see ref 4 above.

(14) Brown, M. S.; Rapoport, H. *J. Org. Chem.* **1963**, *28*, 3261.

(15) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

(16) According to ref 7, methyl cinnamate was reported to be quantitatively reduced with $NaBH_4$ to methyl hydrocinnamate in combination with $CuCl_2$ in place of Cu_2Cl_2 which was used in our case.

Table III. Conjugate Reduction of Ethyl Cinnamate with $NaBH_4$–Cu_2Cl_2 in MeOH[a]

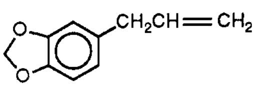


III IV

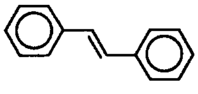
entry	temp, °C	time, min	Cu_2Cl_2, mol	$NaBH_4$, mol	yield,[b] % III	IV
1	0	30	0	5	>95	~5[c]
2	0	30	0.75	10	0	100
3	0	30	0.75	5	0	100
4	0	30	0.75	4	0	100
5	0	30	0.75	3	44	56
6	0	30	0.75	1.5	81	19
7	0	30	0.3	4	22	78
8	0	30	0.15	4	29	71
9	0	30	0.075	4	43	57
10	0	30	0.075	10	23	77
11	0	160	0.75	1.5	79	21
12[d]	-78	160	0.75	1.5	86	14
13[d]	-78	70	0.75	10	50	50

[a] All reactions were carried out on a 0.5-mmol scale at 0 °C; general procedure: see the Experimental Section. [b] Determined from the relative ratio of the ^1H NMR signal areas of IV to that of III obtained by repeated integrations. [c] Determined by HPLC. [d] $NaBH_4$ was added at once to a methanolic solution of III at the reaction temperature, and the resulting mixture was allowed to stand for the given time with stirring at the same temperature.

Table IV. Reduction of Olefins with $NaBH_4$–Cu_2Cl_2 and $NaBH_4$–$NiCl_2$ in MeOH[a]



4



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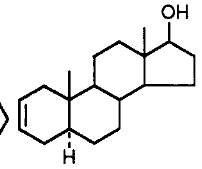


6

olefin	metal halide, mol	$NaBH_4$, mol	yield,[b] % redn prod.	recovd start. mat.
4	Cu_2Cl_2, 0.75	10	83	17
	$NiCl_2$,[c] 0.75	10	100	0
5	Cu_2Cl_2,[d] 0.75	10	8	92
	$NiCl_2$,[c,d] 0.75	10	100	0
6	Cu_2Cl_2,[d] 0.75	10	0	100[e]
	$NiCl_2$,[c,d] 0.75	10	100[e]	0

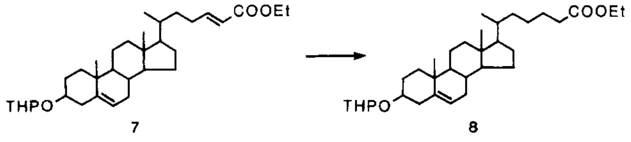
[a] All reactions were carried out on a 0.5-mmol scale at 0 °C; general procedure: see the Experimental Section. [b] Determined by integration of the appropriate ^1H NMR signals. [c] Reference 7. [d] Supplementary material. [e] Only a single peak was detected on GLC.

from 4 to 10 mol of $NaBH_4$ and 0.75 mol of Cu_2Cl_2 is required to complete the reduction (entries 2–4).

Reduction of Isolated Olefins. Since the active metal hydrides or metals, which were formed by treatment of many other metal salts with $NaBH_4$, can catalyze hydrogenation of olefins,[7,17] we determined if the system would reduce the typical isolated olefins such as safrole (**4**), *trans*-stilbene (**5**), and androst-2-en-17-ol (**6**) by using relatively large amounts of reagents. The results are summarized in Table IV together with those obtained for the corresponding system[7] for comparison.

The $NaBH_4$–Cu_2Cl_2 system reduced the monosubstituted olefin **4** at a significant rate and the disubstituted olefin **5** at a low rate, giving the reduction product in only 8% yield, while it reduced little of **6**, which is one of the most reactive olefin compounds among steroids. The $NiCl_2$ system,[7] on the other hand, completely reduced all the olefins examined.

In our synthetic studies, we needed to reduce the conjugated ester **7** to the corresponding saturated analogue **8**, with the olefin group being kept intact. When selective catalytic hydrogenation of **7** was attempted over 5% $Pd/BaSO_4$, it gave the desired **8**, accompanied by the formation of less than 5% of the perhydro derivative, which was rather difficult to separate. With the present system, **7** was reduced quantitatively, giving **8** without any over-reduction.



7 8

Deuterium-Labeling Experiments. To better understand the transient reducing species and the mechanistic aspects during the reduction of both halobenzenes and the double bond of ethyl cinnamate, deuterium-labeling experiments of methyl 4-iodobenzoate and ethyl cinnamate were conducted. When methyl 4-iodobenzoate was reduced with the $NaBD_4$–Cu_2Cl_2/MeOH system, the resulting methyl benzoate showed no deuterium incorporation, while the use of $NaBH_4$–Cu_2Cl_2/MeOH-d_4 gave the ester with 95% deuterium incorporation solely at the 4-position. This finding shows that the hydrogen transferred

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[17] (a) Brown, C. A.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 1003. (b) Brown, H. C.; Brown, C. A. *Ibid.* **1963**, *85*, 1005. (c) Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226.

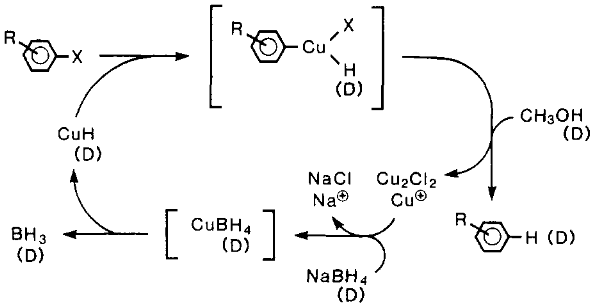

Figure 1. Reaction pathway for dehalogenation of aryl halides with $NaBH_4$–Cu_2Cl_2/MeOH.

to the arene arose from the proton of MeOH.

Reduction of ethyl cinnamate with the $NaBD_4$–Cu_2Cl_2/MeOH system gave ethyl hydrocinnamate with 39% deuterium (theory 50%) at the β-position, but no deuterium at the α-position, while reduction with $NaBH_4$–Cu_2Cl_2/MeOH-d_4 led to ethyl hydrocinnamate with 44% deuterium (theory 50%) at the α-position and 12% deuterium (theory 0%) at the β-position. These results indicate that the hydride species is added to the β-position, but the protic species to the α-position. The unexpected labeling observed might be interpreted by the scrambling caused by the exchange of hydrogen (or deuterium) atom of the active copper species with that of activated deuterium (or hydrogen) molecule.[18]

Mechanism. The reaction under study displayed vigorous gas evolution during addition of $NaBH_4$ to the methanolic solution of Cu_2Cl_2. Gasometric measurements showed that 1 molar equiv of $NaBH_4$ generates 2.5–2.6 molar equiv of hydrogen, suggesting that Cu_2Cl_2 catalyzes the formation of a transient species, followed by its simultaneous decomposition, giving BH_3, which reacts with MeOH, generating hydrogen gas. In a reducing system similar to this, the reduction of olefins was reported to proceed by hydrogenation catalyzed by the active transition metal generated in situ.[17]

In order to clarify which mechanism was operative in our case, ethyl cinnamate was introduced into the reaction mixture 10 min after completion of the addition of $NaBH_4$ under hydrogen atmosphere. Catalytic hydrogenation did not occur, and no detectable amount of ethyl hydrocinnamate was generated after prolonged reaction time. This excludes a mechanism involving catalytic hydrogenation.[19]

On the basis of this observation and the deuterium-labeling results, we concluded that the active reducing species in our system is transient copper hydride.[20,21] A reaction pathway, similar to that for the formation and decomposition of Grignard reagents,[22] might be depicted for the dehalogenation of aryl halides as Figure 1. Insertion of copper hydride to the carbon–halogen bond in aryl halide leads to formation of a Grignard reagent type organocopper compound, which is simultaneously solvolyzed by MeOH, giving the desired arenes. As a result, the proton replaces the halogen atom.

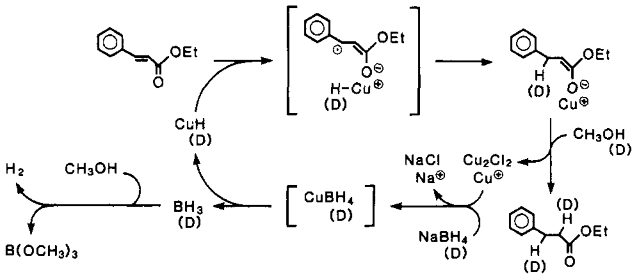

Figure 2. Reaction pathway for conjugate reduction of ethyl cinnamate with $NaBH_4$–Cu_2Cl_2/MeOH.

The lack of effect of a methyl group and the strong effects of the electron-withdrawing *o*-methoxy and *o*-methoxycarbonyl, located close to the halogen atom, on the rate of the reduction (vide supra) may be interpretable by assuming that the insertion reaction is dependent on the inductive effect of the substituents. Similar substituent effects have been reported for the formation of Grignard reagents of aryl halides.[23]

Although the reaction mechanism for conjugate reduction with a copper hydride complex has been reported by Semmelhack and co-workers,[21] we now propose the depicted reaction pathway together with the catalytic cycle of copper metal (Figure 2). They have also reported that 2-butanol may inhibit the characteristic dimerization of the radical anion intermediate and that MeOH may react too rapidly with the copper reagent to perform reduction. The effectiveness of the copper reagent in our methanol system appears to result from its relatively high reactivity toward the conjugated ester over MeOH. In addition, MeOH presumably serves not only to inhibit the dimerization but also to cause rapid decomposition of the unneccessary diborane generated in situ.

Conclusion

Our new system of $NaBH_4$–Cu_2Cl_2/MeOH efficiently achieves deiodination of various kinds of aryl iodides, and debromination of aryl bromides substituted with a methoxy or carbomethoxy group at the ortho position under mild conditions. The system did not harm most isolated olefins. Furthermore, it provides a convenient method for practically regioselective deuterium-labeling when used with an appropriate combination of reagents, i.e., $NaBH_4$–Cu_2Cl_2/MeOH-d_4 for α-deuterated esters and deuterated arenes, $NaBD_4$–Cu_2Cl_2/MeOH for β-deuterated esters,[15,24] and $NaBD_4$–Cu_2Cl_2/MeOH-d_4 for α,β-dideuterated esters.[25]

Experimental Section

Melting points were measured on a Yanagimoto micro hot-stage apparatus and are uncorrected. Unless otherwise stated, ^1H NMR spectra were taken in $CDCl_3$ with a Varian VXR-200 or EM-390 spectrometer using TMS as the internal reference. ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer operating at 50.057 MHz using $CDCl_3$ as solvent and TMS as the internal reference. HPLC analysis was carried out on a Shimadzu LC-6A chromatograph equipped with C-R5A integrator and SPD-6A

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[18] For heterolytic hydrogen activation by Cu(I) salts, see: Hahn, E. A.; Peters, E. *J. Phys. Chem.* **1965**, *69*, 547.

[19] The behavior of this system contrasts with the reported reaction in which nickel boride assumes an important role in the hydrogenation, see ref 17.

[20] (a) Whitesides, G. M.; San Filippo, J., Jr.; Stredronsky, E. R.; Casey, C. P. *J. Am. Chem. Soc.* **1969**, *91*, 6542. (b) Masamune, S.; Bates, G. S.; Georghiou, P. E. *Ibid.* **1974**, *96*, 3686. (c) Tsuda, T.; Fujii, T.; Kawasaki, K.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1013.

[21] (a) Semmelhack, M. F.; Stauffer, R. D. *J. Org. Chem.* **1975**, *40*, 3619. (b) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *Ibid.* **1977**, *42*, 3180.

[22] (a) Ashby, E. C. *Quart. Rev.* **1967**, *21*, 259. (b) Rogers, R. J.; Mitchell, H. L.; Fujiwara, Y.; Whitesides, G. M. *J. Org. Chem.* **1974**, *39*, 857. (c) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.

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variable-wavelength UV monitor. GLC analysis was performed on a Hewlett-Packard 5890A chromatograph fitted with a HP 3393A integrator and a flame-ionization detector.

Reduction of Aryl Halides: (a) Reduction of 2 to 1 with $NaBD_4$–Cu_2Cl_2/MeOH-d_4 (General Procedure for Table I). To a stirred solution of 2[26] (1.435 g, 2.77 mmol) and Cu_2Cl_2 (275 mg, 1.38 mmol) in MeOH-d_4 (20 mL) was added $NaBD_4$ (700 mg, 16.62 mmol) in small portions over a period of 30 min at 0 °C. After stirring for 10 min, the resulting black precipitate was removed by filtration, and the filtrate was acidified with 5% aqueous HCl and extracted with Et_2O. The extract was washed successively with saturated aqueous $NaHCO_3$ and water and dried (Na_2SO_4). The solvent was evaporated in vacuo, and the residue was flash chromatographed on silica gel [10 g, hexane–EtOAc (4:1)] to obtain methyl (5*Z*)-7-[3-*endo*-[[(4-deuteriophenyl)sulfonyl]-amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoate ([4′-^{2}H]-1) (1.06 g, 97.5%). Crystallization from cold hexane gave an analytical sample: mp 25–27 °C; ^{1}H NMR δ 3.70 (3 H, s), 5.20 (2 H, m), 7.51 (2 H, d, J = 9 Hz), 7.92 (2 H, d, J = 9 Hz). Anal. Calcd for $C_{21}H_{28}DNO_4S$: C, 64.25; H(D), 7.70; N, 3.57; S, 8.17. Found: C, 64.14; H(D), 7.47; N, 3.43; S, 8.01. HPLC analysis [column, Chemco Nucleosil $_5C_{18}$, 150 × 4.6 mm i.d.; solvent, CH_3CN–MeOH–H_2O–HOAc (300:200:300:1); flow rate, 1 mL/min] of the acid derived from the ester by hydrolysis showed only the presence of 1 and little 3 in the product by comparison of retention times of the peaks with those of standard references of acids corresponding to 1 and 3, respectively.

The following entries may be found in the supplementary material.

(b) Reduction of 2 with $NaBD_4$–$PdCl_2$/MeOH-d_4.

(c) Reduction of 2 with $NaBH_4$–$CuCl_2$/MeOH.

(d) Reduction of 2 with $NaBH_4$–$FeCl_2$/MeOH.

Reduction of Halobenzenes (General Procedure for Table II). All reductions of the substrates (0.5 mmol) were carried out using $NaBH_4$ (185 mg, 5 mmol) and Cu_2Cl_2 (74 mg, 0.375 mmol) in MeOH (10 mL) in a manner similar to that described in a, except that $NaBH_4$ and MeOH were used in place of $NaBD_4$ and MeOH-d_4, respectively. The products of each reaction were analyzed by calculating the ratio of the integration of the peaks corresponding to **I** and **II** on the HPLC [column, TOSOH ODS-120T, 150 × 3.9 mm i.d.; solvent, MeOH–H_2O (7:3 or 6:4); flow rate, 1 mL/min]. Commercial products were used as the standard references of each type of **II**. The structures of dehalogenation products were determined by comparison of the retention times in their HPLC with those of authentic samples of commercially available dehalogenated compounds.

Conjugate Reduction of α,β-Unsaturated Esters. (a) Reduction of Ethyl Cinnamate (General Procedure for Table III). Reduction of ethyl cinnamate (88 mg, 0.5 mmol) in MeOH (10 mL) was performed using various molar ratios of $NaBH_4$ and Cu_2Cl_2 as shown in Table III. The sole product of the reduction was identified as ethyl hydrocinnamate by comparison of the ^{1}H NMR spectrum and the retention time of HPLC with those of an authentic commercially available sample of ethyl hydrocinnamate. The ratio of signal areas for the latter to the recovered starting material was determined by ^{1}H NMR spectroscopy as shown in Table III. For the case of entry 1, HPLC analysis [column, TOSOH ODS-120T, 150 × 3.9 mm i.d.; solvent, MeOH–H_2O (7:3); flow rate, 1 mL/min] was applied because the signal for compound **IV** was too weak to integrate.

In a separate experiment, $NaBH_4$ (185 mg, 5 mmol) and Cu_2Cl_2 (74 mg, 0.375 mmol) were permitted to react as described in a for the reduction of aryl halides. Gasometric measurements showed evolution of 304 mL of gas corresponding to 12.67 mmol of hydrogen. After 10 min, ethyl cinnamate (88 mg, 0.5 mmol) was added under a hydrogen stream, and the mixture was stirred for 6 h under a hydrogen atmosphere at 0 °C. HPLC analysis of the reaction mixture showed only the presence of ethyl cinnamate and no detectable amount of ethyl hydrocinnamate.

(b) Reduction of α,β-Unsaturated Ester 7. Reduction of ester 7 (256 mg, 0.5 mmol) was performed with $NaBH_4$ (185 mg, 5 mmol) in MeOH (7 mL) and THF (3 mL) in the presence of Cu_2Cl_2 (73 mg, 0.37 mmol). The reaction mixture was filtered and extracted with Et_2O. The extract was washed with water, dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography of the residue on silica gel [4 g, toluene–EtOAc (9:1)] gave ethyl 3β-[(tetrahydropyranyl)oxy]-27-norcholest-5-en-26-oate (8) (255 mg, 99%). Crystallization gave an analytical sample: mp 102–103 °C; ^{1}H NMR δ 0.64 (3 H, s), 0.88 (3 H, d, J = 6 Hz), 0.99 (3 H, s), 1.22 (3 H, t, J = 7 Hz), 4.12 (2 H, q, J = 7 Hz), 4.71 (1 H, br s), 5.34 (1 H, br s). Anal. Calcd for $C_{33}H_{54}O_4$: C, 76.99; H, 10.57. Found: C, 76.91; H, 10.56. GLC analysis [column, Hewlett-Packard cross-linked methyl silicon, 25 m × 0.31 mm, at 280 °C, He 7.8 mL/min] of the alcohol derived from 8 by deprotection of THP ether showed only a single peak at 12.4 min and did not indicate any trace of the peak corresponding to the overreduction product.

Reduction of Isolated Olefins: (a) Reduction of Safrole (4) (General Procedure for Table IV). Reduction of 4 (0.5 mmol) was similarly carried out using 10 and 0.75 molar equiv of $NaBH_4$ and Cu_2Cl_2, respectively. The product was analyzed by ^{1}H NMR spectroscopy and shown to be a 17:83 mixture of the recovered 4 and 1,2-(methylenedioxy)-4-propylbenzene. The structure of the latter was confirmed by comparison of its ^{1}H NMR spectrum with that of an authentic sample of the product, independently prepared by catalytic hydrogenation of 4.

In a separate experiment on the reduction of 4, 1.5 molar equiv of $NiCl_2 \cdot 6H_2O$ was used in place of Cu_2Cl_2. The reduction proceeded completely, giving a single product, which was also identified as 1,2-(methylenedioxy)-4-propylbenzene by comparison of its ^{1}H NMR spectrum with that of the authentic sample described above.

The following entries may be found in the supplementary material.

(b) Reduction of *trans*-Stilbene (5).

(c) Reduction of Androst-2-en-17β-ol (6).

Reduction with Deuterated Reagents: (a) Reduction of Methyl 4-Iodobenzoate with $NaBD_4$–Cu_2Cl_2/MeOH. Methyl 4-iodobenzoate (131 mg, 0.5 mmol) was reduced using $NaBD_4$ (209 mg, 5 mmol) and Cu_2Cl_2 (74 mg, 0.375 mmol) in MeOH (10 mL). Ether extraction of the reaction mixture gave an oil (66 mg, 97%), which had no incorporated deuterium in its molecule according to examination of its ^{1}H and ^{13}C NMR spectra. The oil was identified as methyl benzoate by comparison of its ^{1}H NMR spectrum with that of an authentic sample of commercially available methyl benzoate.

(b) Reduction of Methyl 4-Iodobenzoate with $NaBH_4$–Cu_2Cl_2/MeOH-d_4. Reduction of methyl 4-iodobenzoate was carried out in a similar way to that described in a, using $NaBH_4$ and MeOH-d_4 in place of $NaBD_4$ and MeOH. Analysis of ^{1}H and ^{13}C NMR spectra of the product indicated that the obtained methyl benzoate was labeled with one atom of deuterium, and only a trace of unlabeled congener was formed. A characteristic triplet signal due to ^{13}C–D coupling at 132.61 ppm and a singlet signal at 132.90 ppm observed in its ^{13}C NMR spectum unambiguously confirmed the labeled carbon to be C-4. The percent deuterium incorporation was determined as 95% from the ratio of the signal area due to C-4 proton at δ 7.56 relative to the signal area due to C-3 proton at δ 7.45, both obtained by repeated integrations. Methyl 4-deuteriobenzoate: ^{1}H NMR δ 3.93 (3 H, s), 7.45 (2 H, br d, J = 8.5 Hz), 8.05 (2 H, br d, J = 8.5 Hz); ^{13}C NMR δ 52.07 (Me), 128.26 (C-3, C-5), 129.59 (C-2, C-6), 130.22 (C-1), 132.61 (t, J = 24 Hz, C-4), 167.10 (C=O).

(c) Reduction of Ethyl Cinnamate with $NaBD_4$–Cu_2Cl_2/MeOH. Reduction of ethyl cinnamate (88 mg, 0.5 mmol) was carried out in a similar way to that described in a. Ether extraction of the reaction mixture gave an oil (71 mg, 70%): ^{1}H NMR δ 1.20 (3 H, t, J = 7 Hz), 2.62 (br d, J = 7 Hz), 2.93 (br t, J = 7 Hz), 4.11 (2 H, q, J = 7 Hz), 7.07–7.43 (5 H, m). From the ratio of the signal areas due to the α-proton signal at δ 2.62 and the β-proton signal at δ 2.93 relative to the signal area due to the methylene protons at δ 4.11 of the ethyl group obtained by repeated integrations, deuterium incorporation was determined to be 39% (theoretical value 50%) at the β-position, but there was none at the α-position.

(d) Reduction of Ethyl Cinnamate with $NaBH_4$–Cu_2Cl_2/MeOH-d_4. Reduction of ethyl cinnamate (0.5 mmol) was carried out in a similar way to that described in b. Extraction

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of the reaction mixture with Et_2O gave an oil: ^1H NMR δ 1.20 (3 H, t, J = 7 Hz), 2.26 (m), 2.94 (d, J = 8 Hz), 4.12 (2 H, q, J = 7 Hz), 7.07–7.4 (5 H, m). The deuterium incorporations at the α- and β-positions, determined in a similar way to that described above, were 44% (theoretical value 50%) and 12% (0%), respectively.

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Supplementary Material Available: Experimental details for the nonrepresentative reactions (3 pages). Ordering information is given on any current masthead page.

Hydrogenation and Deuteration with the System $Zn–NiCl_2$ in Aqueous Medium: Stirring and Ultrasonic Improvement Procedures

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The system $Zn–NiCl_2–H_2O$ is used for conjugate reduction of methyl cinnamate under stirring and ultrasonic irradiation. It appears that in both cases the three steps metallic nickel formation on the zinc surface, hydrogen gas formation by nickel-assisted zinc reduction of water, and catalytic olefin reduction with molecular hydrogen on the nickel-activated zinc surface constitute the main reaction pathways. Deuteration of the substrate is achieved by substitution of deuterium oxide for water, and better results are observed in the stirred reaction. Scanning electron micrographs of the catalyst show that ultrasonic irradiation has cleaned the surface of the particles.

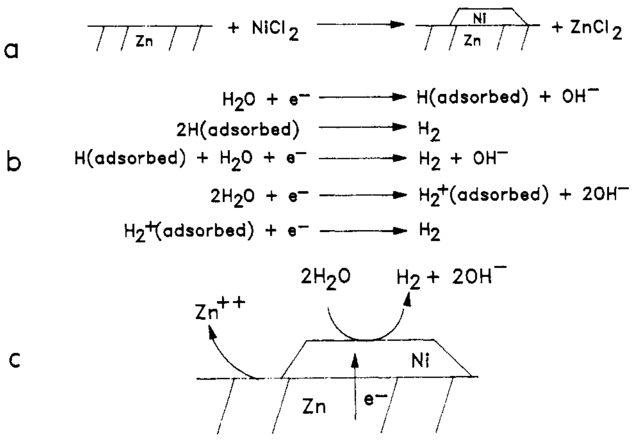
Introduction

Among the reactions improved by ultrasound,[1] hydrogenation has received some attention. Hydrogen transfer from formic acid or hydrazine with palladium on carbon has been successfully tested.[2,3] Reactions involving gaseous hydrogen in heterogeneous catalysis can also be promoted. It has been established that the catalyst surface is activated at 20 kHz by removal of the oxide shell.[4] Other results show optimum hydrogenation when the reaction is performed at higher frequencies, e.g., 500 kHz.[5]

Our investigations of ultrasonic reactions in aqueous media[6] have shown improvements of the reductive properties of the zinc–nickel chloride–water mixture, especially for the selective conjugate hydrogenation of α,β-unsaturated carbonyl compounds.[7] The method has several attractive features. It takes place in a neutral medium with simple reagents, and the reaction proceeds rapidly at a moderate temperature with excellent yields for the reduction of several functional groups.[8]

However the reduction mechanism has not been established. An interesting deuteration process would be expected if deuterium oxide replaces water, but a preliminary investigation gave inconsistent and erratic results when the reaction conditions were changed from sonication to stirring. A comparative study of hydrogenation and deuteration was carried out to provide some understanding of the reaction pathways and to study the modifications introduced in the catalytic process by sonication.

Scheme I[a]



[a] (a) Nickel chloride reduction on the zinc surface. (b) Electrochemical hydrogen formation.[17] (c) Proposed mechanism for the reduction of water on the nickel-coated zinc particle. Deuterium gas production follows the same pathways.

Results and Discussions

For reductions in protic media, zinc is generally activated and used under acidic or basic conditions.[9,10] Addition of a metallic salt to the suspension ($HgCl_2$, CuI, $NiCl_2$) is also known to provide a more reactive metal, but the effects of such treatments are not fully understood.[10,11] In

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