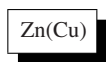


## Zinc/Copper Couple<sup>1</sup>



[12019-27-1]

Zn

(MW 65.39)

InChI = 1/Zn

InChIKey = HCHKCACWOHOZIP-UHFFFAOYAS

(an activated form of zinc metal that can be used for cyclopropanation;<sup>1</sup> conjugate addition of alkyl iodides to enones;<sup>2</sup> preparation of dichloroketene;<sup>3</sup> preparation of 2-oxallyl cations for cycloaddition reactions<sup>4</sup>)

**Physical Data:** see **Zinc**.

**Solubility:** insol organic solvents and H<sub>2</sub>O.

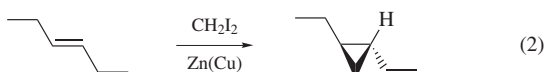
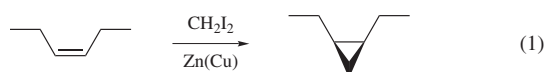
**Form Supplied in:** reddish-brown or dark gray powder; often prepared directly before use.

**Preparative Method:** although zinc–copper couple is commercially available, freshly prepared reagents are often more active. Of the many preparations described in the literature,<sup>1</sup> LeGoff's is both simple and results in a very active zinc–copper couple.<sup>5</sup> Zinc dust (35 g) was added to a rapidly stirred solution of 2.0 g Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (see **Copper(II) Acetate**) in 50 mL of hot acetic acid. After 30 s the couple was allowed to settle, decanted, and washed once with acetic acid and three times with ether. A less reactive couple can be prepared from granular zinc using the same procedure. Modified procedures for preparing zinc–copper couples are given in many of the references.

**Handling, Storage, and Precautions:** zinc–copper couple deteriorates in moist air and should be stored under nitrogen. Very active zinc–copper couple is oxygen sensitive. It evolves hydrogen on contact with strong aqueous acids.

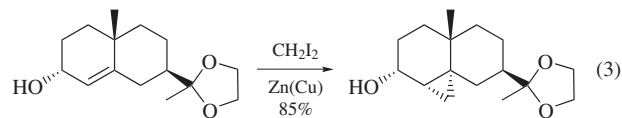
**Introduction.** Zinc–copper couple is an active form of zinc metal, and for many reactions the presence of copper does not appear to exert any special influence beyond activating the surface of the zinc. Many of the reactions of zinc–copper couple could probably be effected using zinc metal activated in situ with **Chlorotrimethylsilane** or **1,2-Dibromoethane**,<sup>6</sup> but the advantage of zinc–copper couple is that it is a storable form of activated zinc that is easily prepared and handled.

**Simmons–Smith Cyclopropanation.**<sup>1,7</sup> Zinc–copper couple reduces **Diiodomethane** to generate **Iodomethylzinc Iodide**, which is in equilibrium with bis(iodomethyl)zinc and zinc iodide.<sup>8</sup> This Simmons–Smith reagent is widely used to cyclopropanate alkenes. As shown in eqs 1 and 2, the cyclopropanation is stereospecific, with methylene adding cis to the starting alkene.<sup>7</sup>

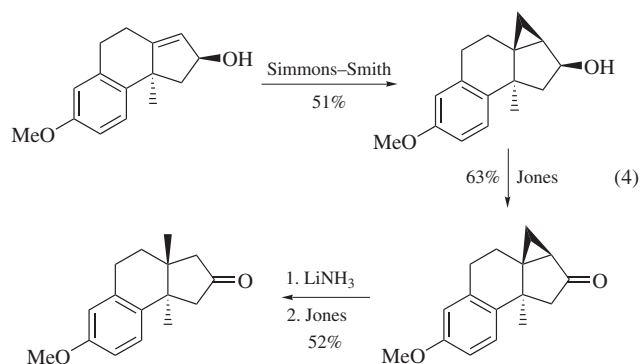


Hydroxyl groups or sterically accessible ethers will direct the Simmons–Smith reagent to the proximate face of an alkene,<sup>9</sup>

and this stereoselectivity has been used extensively in synthesis (eq 3).<sup>10</sup>

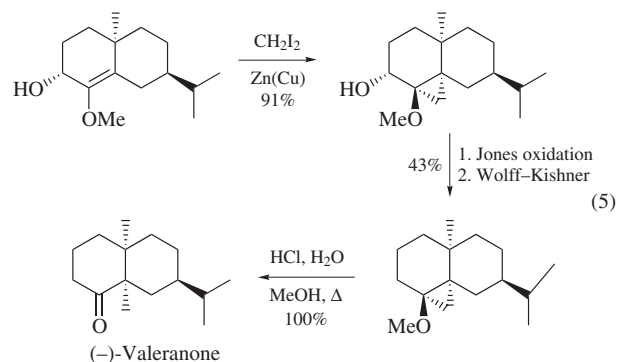


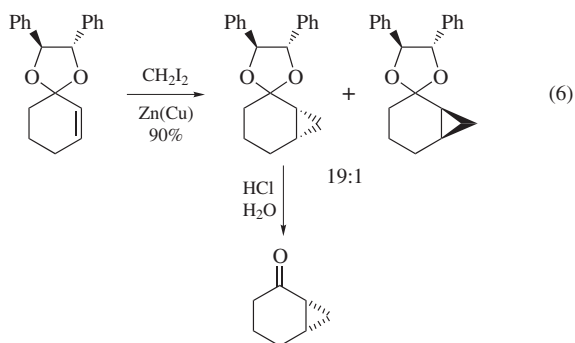
One important application of directed cyclopropanation is the stereoselective introduction of methyl groups in terpene synthesis. In eq 4 the allylic alcohol is again used to direct the cyclopropanation to the desired face of the ketone.<sup>11</sup> Oxidation to the ketone and lithium–ammonia reduction gave the  $\beta$ -methyl ketone. This stepwise approach to  $\beta$ -methyl substitution of an enone complements a **Lithium Dimethylcuprate** addition because it can be carried out on  $\beta$ -disubstituted enones and the stereochemistry is reliably predictable based on the alcohol stereochemistry.



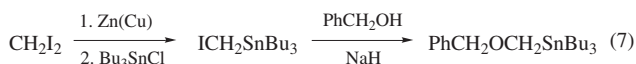
Wenkert developed an alternative to the classic alkylation of ketones by cyclopropanating the derived enol ether, followed by acid catalyzed hydrolysis of the cyclopropyl ether. This sequence was used to introduce the angular methyl group of (–)-valeranone with complete control of stereochemistry (eq 5).<sup>12</sup>

Mash has found that optically pure acetals prepared from chiral diols and cycloalkanones will cyclopropanate with good diastereoselectivity (eq 6), presumably through selective coordination of the Simmons–Smith reagent to the more accessible acetal oxygen. Hydrolysis of the acetals leads to bicyclo[*n*.1.0]alkanones in good to excellent optical purity.

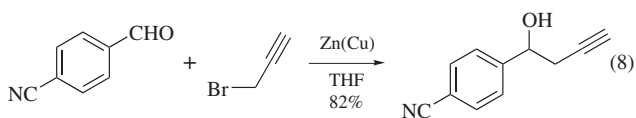




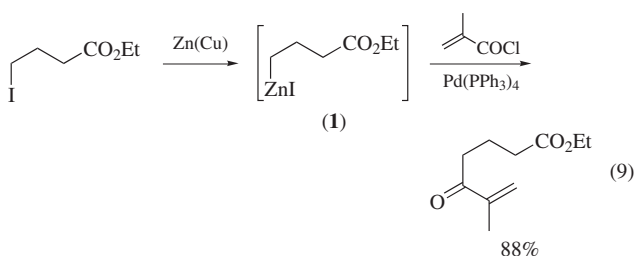
**Alkyl Zinc Preparations and Reactions.** Dialkylzinc compounds have been prepared from the corresponding alkyl iodides and zinc–copper couple,<sup>13</sup> but are more commonly prepared using activated zinc or from the appropriate Grignard reagent and **Zinc Chloride**. Zinc–copper couple is useful for preparing a variety of unusual alkyl zinc compounds such as (iodomethyl)zinc iodide. Apart from cyclopropanations, (iodomethyl)zinc iodide reacts with **Tributylchlorostannane** to give **(Iodomethyl)tributylstannane**, an important reagent in the preparation of  $\alpha$ -alkoxylithium reagents (eq 7).<sup>14</sup>



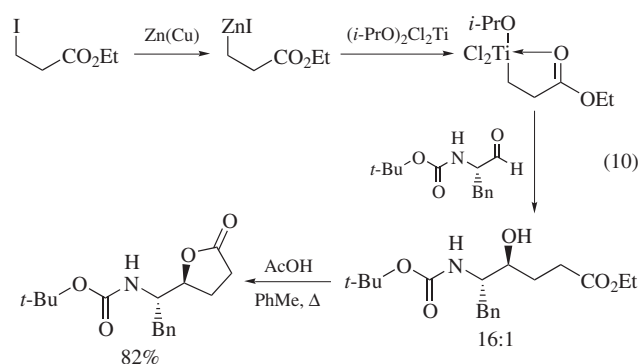
Propargyl bromide (see **Propargyl Chloride**) reacts with zinc–copper couple in the presence of an aromatic aldehyde to produce the alkyne adduct in good yield (eq 8). Presumably the allenylzinc bromide is formed in situ and reacts with 1,3-rearrangement; none of the allene adduct is reported.<sup>15</sup>



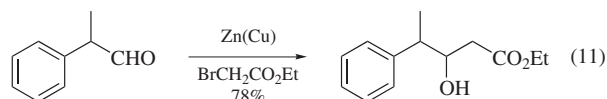
Yoshida's group found that zinc–copper couple was very effective in the preparation of zinc homoenolates and bishomoenolates. Reaction of ethyl 4-iodobutyrate with zinc–copper couple in benzene and DMA gave the homoenolate (**1**), which coupled with acyl chlorides, vinyl iodides, or vinyl triflates in the presence of **Tetrakis(triphenylphosphine)palladium(0)** (eq 9).<sup>16</sup>



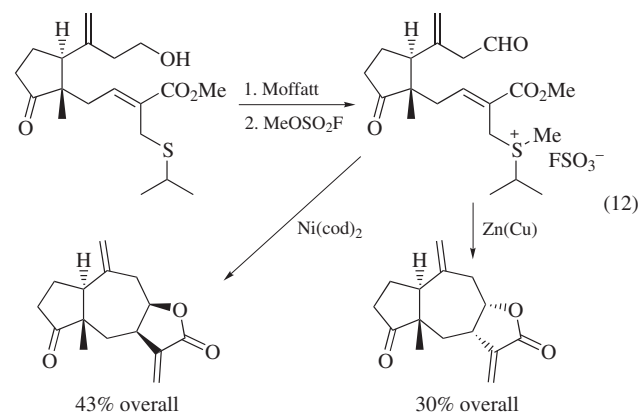
Zinc homoenolates prepared in this manner can be transmetalated to titanium homoenolates and coupled with aldehydes (eq 10),<sup>17</sup> or reacted with **tert-Butyldimethylchlorosilane** to give the cyclopropyl ethers.<sup>18</sup>



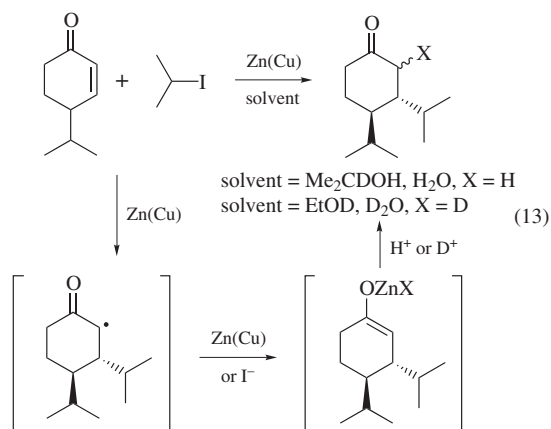
Zinc–copper couple leads to higher yield and faster reactions in the Reformatsky reaction than the more commonly used zinc metal (eq 11).<sup>19</sup>



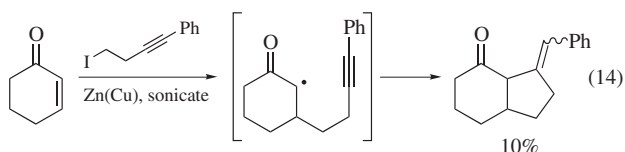
Semmelhack reported an unusual cyclization reaction that probably proceeds through an allylic zinc intermediate (eq 12).<sup>20</sup> Model cyclizations were carried out using allylic bromides, but the actual cyclization was performed on the allylic sulfonium salt. In contrast to the result with zinc–copper couple, cyclization of the sulfonium salt intermediate with **Bis(1,5-cyclooctadiene)-nickel(0)** gave the other *cis*-fused lactone in 43% overall yield.



**Conjugate Additions of Alkyl Iodides to Alkenes.** An intriguing new carbon–carbon bond forming reaction has been developed that promises to be very useful in synthesis. Luche's group found that alkyl iodides will add to alkenes bearing a strong electron-withdrawing group when sonicated with zinc–copper couple in an aqueous solvent.<sup>21</sup> This reaction is notable because the conditions are very mild, it is compatible with many reactive functional groups, and moderately hindered carbon–carbon bonds can be formed in good yield. Luche proposed that the reaction proceeds through a radical intermediate generated in the reduction of the alkyl iodide with zinc–copper couple, but the evidence is not completely clear. When the reaction is conducted in a solvent system with a good deuterium atom donor and a good proton source, the proton is incorporated into the product, whereas when the role of the hydrogen and deuterium are reversed, deuterium is incorporated into the product (eq 13).<sup>2</sup>

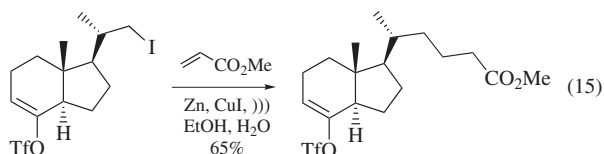


A radical intermediate should give the opposite incorporation pattern, but Luche invokes a rapid reduction of the  $\alpha$ -keto radical to give the enolate, which would give the observed incorporation. Thus the addition can still proceed through a radical even though the quenching is ionic. The best direct evidence of radical involvement is cyclization of the radical intermediate in eq 14, but the yield is quite low.

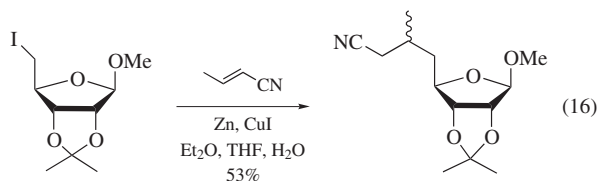


Several other features of this reaction are noteworthy: both water and copper are required, and (*S*)-octyl iodide couples well but leads to a racemic product.

The conjugate addition reactions of alkyl iodides work well in complex and highly functionalized molecules. The side chain of a vitamin D analog was prepared using the reaction shown in eq 15.<sup>22</sup> Unlike most transition metal-catalyzed reactions, this procedure did not affect the vinyl triflate.

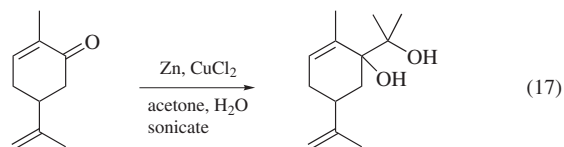


Surprisingly, the coupling reaction will also work in carbohydrate systems. The alkyl iodide derived from ribose was coupled in good yield with 2-butenitrile (eq 16), without undergoing reductive elimination to form an alkene.<sup>23</sup> This new coupling procedure promises to be very useful in synthesis.

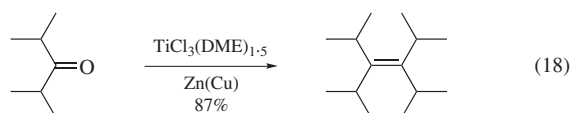


**Reductive Coupling of Carbonyl Compounds.** Carbonyl compounds can be reductively dimerized to diols or alkenes. A pinacol cross-coupling reaction between  $\alpha,\beta$ -unsaturated

ketones and acetone has been reported. When carvone is sonicated with zinc dust and **Copper(II) Chloride** in acetone/water, the cross-coupling product is isolated in 92% yield (eq 17).<sup>24</sup> Acetone itself does not dimerize under the reaction conditions, and  $\beta,\beta$ -disubstituted enones fail to react, presumably due to a higher reduction potential.

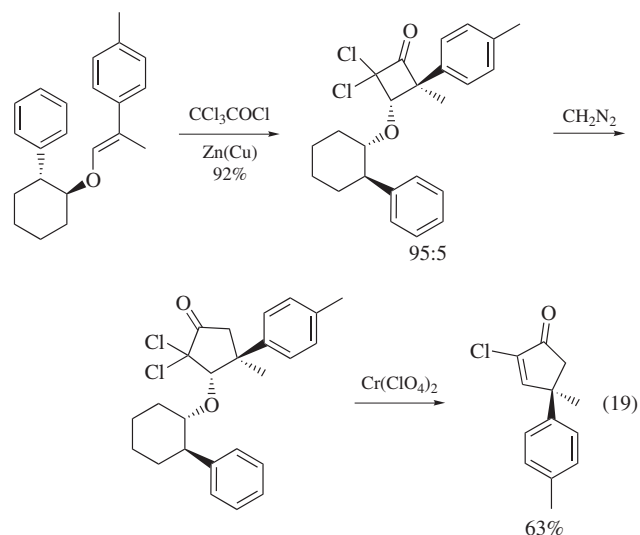


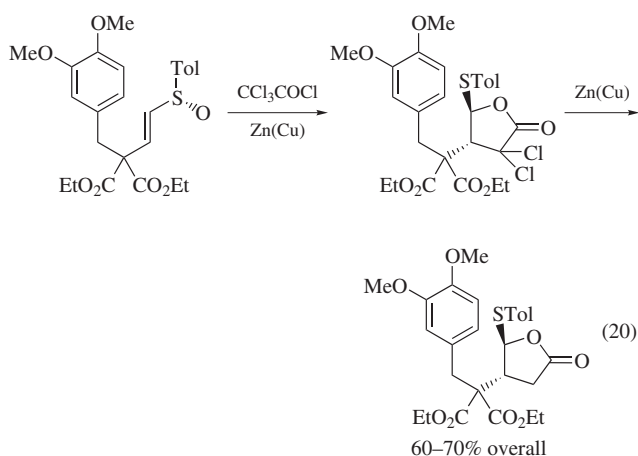
The McMurry coupling uses low valent titanium to reductively dimerize carbonyl compounds to alkenes.<sup>25</sup> The reagent is usually prepared from **Titanium(III) Chloride** and an added reducing agent like **Potassium**, **Lithium**, or **Lithium Aluminum Hydride**. One of the best reagents is prepared from  $\text{TiCl}_3(\text{DME})_{1.5}$  and zinc-copper couple (eq 18).<sup>26</sup> The same dimerization gives only 12% yield with  $\text{TiCl}_3/\text{LiAlH}_4$ .



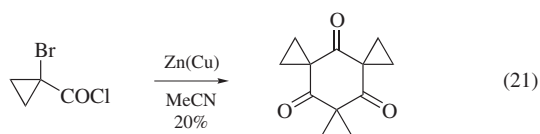
**Preparation of Dichloroketene.** *Dichloroketene* can be prepared by reducing **Trichloroacetyl Chloride** with zinc-copper couple.<sup>3</sup> Dichloroketene undergoes facile [2 + 2] cycloadditions with alkenes<sup>27</sup> and alkynes<sup>28</sup> to give cyclobutanones and cyclobutenones.<sup>29</sup> Recently the use of a chiral auxiliary has been reported to control the facial selectivity of dichloroketene additions (eq 19).<sup>30</sup> Ring expansion with **Diazomethane** gave the dichlorocyclopentanone, and subsequent reduction removed the chiral auxiliary and gave the optically enriched cyclopentanone.

Dichloroketene will react with vinyl sulfoxides to give  $\gamma$ -lactones with efficient stereochemical transfer from the sulfoxide stereogenic center (eq 20).<sup>31</sup> Optically pure vinyl sulfoxides give lactones with high enantiomeric excesses. The chlorine atoms can be removed by reduction with zinc-copper couple or **Aluminum Amalgam** to give the lactone.

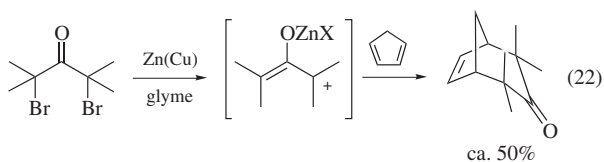




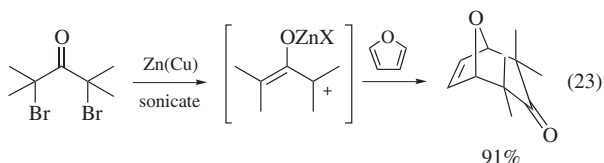
Reduction of  $\alpha$ -halo acyl chlorides normally gives ketenes, but Hoffmann has reported an unusual reductive trimerization of 1-bromocyclopropanecarbonyl chloride that does not proceed through the corresponding ketene.<sup>32</sup> Reduction with zinc–copper couple in MeCN gave the unusual trimer in 20% yield (eq 21), whereas the corresponding ketene is known to dimerize. Hoffmann suggests that a Reformatsky-type intermediate may react with a second molecule of acyl chloride rather than eliminating to generate the ketene.



**Preparation of 2-Oxyallyl Cations.** Zinc–copper couple reduces  $\alpha,\alpha'$ -dibromo ketones to zinc oxyallyl cations, and these allyl cations will undergo [3+4] cycloadditions with dienes (eq 22).<sup>33</sup>

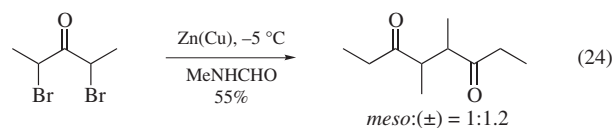


The original procedure used zinc–copper couple directly, but more recently sonicating the reactions has been reported to improve the yields significantly: the coupling in eq 23 gives 60% yield without sonication and 91% yield with sonication.<sup>4</sup>

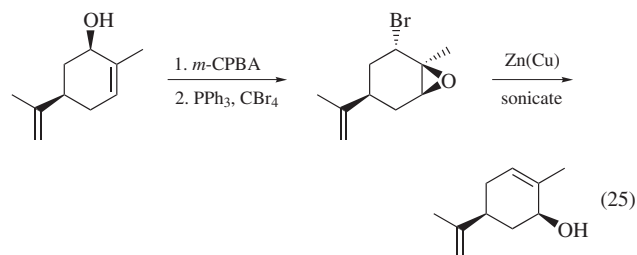


These reactions can be carried out using *Nonacarbonyldiiron* as the reducing agent in comparable yield, but the iron reagent is quite toxic and does not offer any advantage in simple cases.<sup>34</sup>

Reduction of  $\alpha,\alpha'$ -dibromo ketones under slightly different conditions, using *N*-methylformamide as the solvent without diene or sonication, leads to 1,4-diketones (eq 24).<sup>35</sup> Unsymmetrically substituted ketones give statistical mixtures of products.



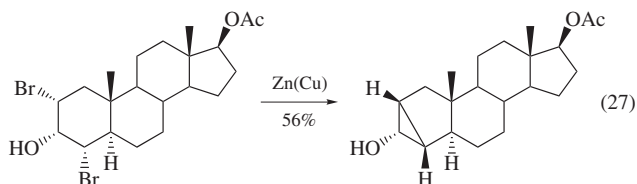
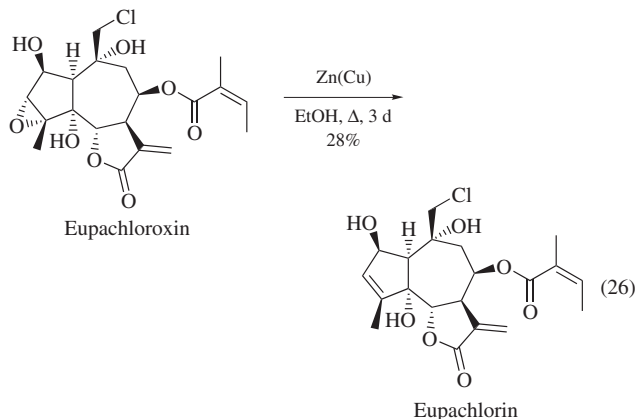
**Reduction of 1,2- and 1,3-Dihalides and Halo Ethers.** *Zinc–Acetic Acid* is commonly used to reduce 1,2-dihalides to alkenes. Several modifications of this procedure use zinc–copper couple as the reducing agent.<sup>36</sup> Bromooxiranes prepared from allyl alcohols are reduced with zinc–copper couple and sonication to give the 1,3-transposed allylic alcohol (eq 25).<sup>37</sup> The oxirane ring strain facilitates the alkene formation; notice that the tetrahydrofuran in eq 16 does not form an alkene.



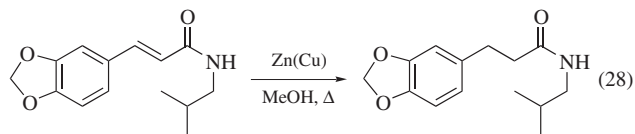
The 2,2,2-trichloroethyl group is used as a protecting group for many functional groups such as carboxylic acids and carbamic acids (amines), and is usually removed by reduction with zinc metal. In some cases it is advantageous to remove these protecting groups with zinc–copper couple.<sup>38</sup>

Under forcing conditions, oxiranes can be reduced to the corresponding alkene. Reaction of eupachloroxin with zinc–copper couple in refluxing ethanol for 3 d gave eupachlorin without reducing the many other functional groups in the molecule (eq 26).<sup>39</sup> The reduction is stereoselective: *cis*-oxiranes give *cis*-alkenes and *trans*-oxiranes give *trans*-alkenes.

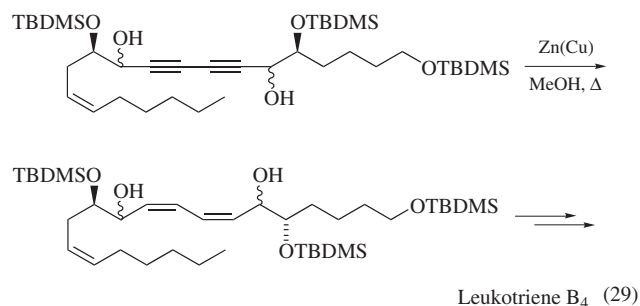
Reduction of 1,3-dibromides with zinc–copper couple gives cyclopropanes (eq 27).<sup>40</sup> Cyclopropanes are also formed when 2-bromoethyloxiranes are reduced using zinc–copper couple with sonication.<sup>41</sup>



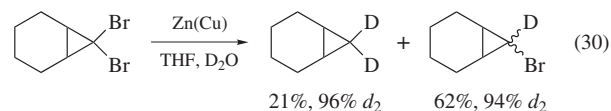
**Reduction of C–C Multiple Bonds.** Alkenes with powerful electron-withdrawing groups like esters, ketones, or nitriles are reduced with zinc–copper couple in refluxing methanol (eq 28).<sup>42</sup> Isolated alkenes are not reduced.



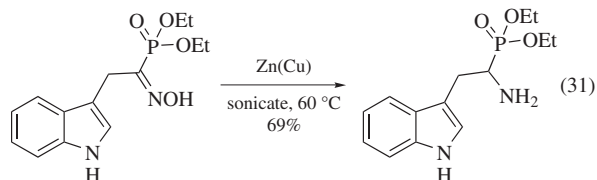
Unactivated alkynes are reduced to (*Z*)-alkenes under the same conditions.<sup>43</sup> Terminal alkynes are reduced to vinyl groups without the over-reduction that can sometimes accompany Birch-type reductions. This reduction was recently applied to the synthesis of leukotriene B<sub>4</sub> (eq 29).<sup>44</sup>



**Reduction of Other Functional Groups.** Zinc metal has been used to reduce many functional groups and zinc–copper couple would be effective in most of these reactions. Zinc–copper couple reduces alkyl halide to the corresponding hydrocarbon, and in the presence of D<sub>2</sub>O this leads to an expedient synthesis of specifically deuterated materials (eq 30).<sup>45</sup>



Aromatic nitro compounds are reduced to the protected hydroxylamines, *N*-acetoxy-*N*-acetylarylamines, with zinc–copper couple in the presence of acetic acid and acetic anhydride. In contrast, zinc metal reduces 4-nitrostilbene to azoxystilbene.<sup>46</sup> Oximes can be reduced to amines with zinc–copper couple, and this procedure is reported to be much more effective than an *Aluminum Amalgam* reduction (eq 31).<sup>47</sup>



**Related Reagents.** Chloriodomethane–Zinc/Copper Couple; Dibromomethane–Zinc/Copper Couple; Potassium Iodide–Zinc/Copper Couple; Titanium(III) Chloride–Zinc/Copper Couple.

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