

## Diiodomethane



[75-11-6]

CH<sub>2</sub>I<sub>2</sub>

(MW 267.84)

InChI = 1/CH2I2/c2-1-3/h1H2

InChIKey = NZZFYRREKKOMAT-UHFFFAOYAO

(precursor to methylene transfer reagents: in combination with various metals or alkyl metals, generates carbenoids which cyclopropanate alkenes<sup>1</sup> or methylenate carbonyls;<sup>2</sup> precursor to ICH<sub>2</sub>Met and I<sub>2</sub>CHMet nucleophiles;<sup>3</sup> participates in radical-mediated couplings<sup>4</sup>)

*Alternate Name:* methylene iodide.

*Physical Data:* mp 6 °C; bp 181 °C; *d* 3.325 g cm<sup>-3</sup>.

*Solubility:* slightly sol H<sub>2</sub>O; sol Et<sub>2</sub>O, CHCl<sub>3</sub>, EtOH, hexane, etc.

*Form Supplied in:* pale yellow liquid; crystallizes as pale yellow needles or plates; typically stabilized with copper powder.

*Purification:* fractional distillation from CaH<sub>2</sub> generally provides reagent of sufficient purity for typical uses.

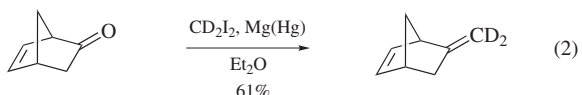
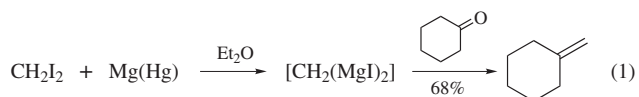
*Handling, Storage, and Precautions:* store over copper powder to inhibit radical-induced decomposition; protect from light; incompatible with many metals (Al, Mg, Na, etc.) and strong bases; mildly corrosive; toxicity presumed to be on par with CH<sub>2</sub>Cl<sub>2</sub>, i.e. moderately toxic, mutagenic; use in a fume hood.

## Original Commentary

James P. Edwards

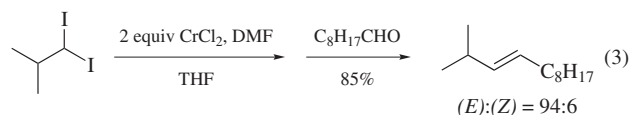
Ligand Pharmaceuticals, San Diego, CA, USA

**Methylenations.** A wide variety of carbonyl methylenating reagents utilize CH<sub>2</sub>I<sub>2</sub> as the carbon source. Several of these have proven to be useful alternatives to the Wittig reaction.<sup>5</sup> Cainelli and co-workers found that treatment of CH<sub>2</sub>I<sub>2</sub> with 2 equiv of **Magnesium Amalgam** in the presence of ketones affords alkenes in good yields (eq 1).<sup>6</sup> The intermediate in these reactions is presumed to be CH<sub>2</sub>(MgI)<sub>2</sub>, and the reaction works well with ketones and aldehydes of variable structure. This reagent is particularly useful for the formation of dideuterated terminal alkenes (using CD<sub>2</sub>I<sub>2</sub>, eq 2),<sup>7</sup> since methylenation using deuterated Wittig reagents is often accompanied by various degrees of scrambling of the deuterium label.<sup>8</sup>

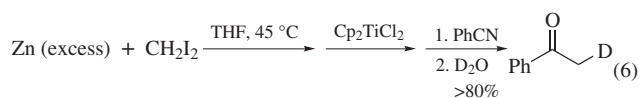
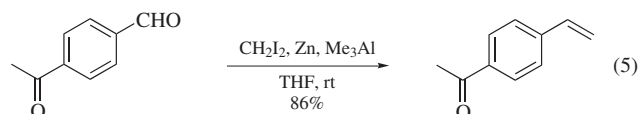
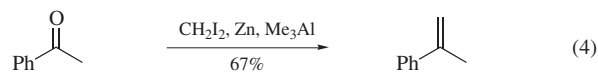


Chromium(II) also mediates the alkenation of aldehydes by geminal diiodides (eq 3).<sup>9</sup> This transformation presumably

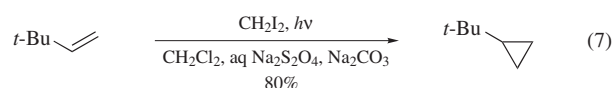
proceeds via a 1,1-bis[chromium(III)] species, and works best with substituted diiodides. Generally, high levels of (*E*) selectivity are obtained.

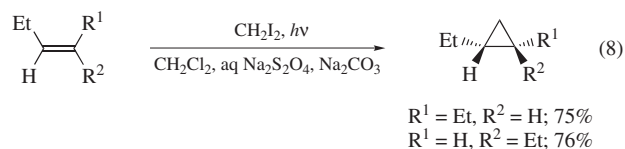


Certain methylenating reagents utilize CH<sub>2</sub>I<sub>2</sub> in combination with 2 equiv of **Zinc** and a Lewis acid.<sup>2,10,11</sup> A Lewis acid is not essential for this transformation,<sup>11</sup> but greatly accelerates the reaction and improves selectivity and yields. The most commonly used Lewis acids include **Trimethylaluminum**,<sup>2,10a</sup> **Titanium Tetraisopropoxide**,<sup>10a</sup> **Titanium(IV) Chloride**,<sup>10b,10c</sup> **Dichlorobis(cyclopentadienyl)zirconium**,<sup>10d</sup> and **Dichlorobis(cyclopentadienyl)titanium**.<sup>10e</sup> Of a variety of Lewis acids and dihalomethanes examined, Takai and co-workers found that CH<sub>2</sub>I<sub>2</sub>/Zn/Me<sub>3</sub>Al and CH<sub>2</sub>Br<sub>2</sub>/Zn/TiCl<sub>4</sub> afforded the best results.<sup>10f</sup> Substrates for these reactions can vary from simple ketones such as acetophenone (eq 4)<sup>2</sup> to complex steroidal ketones.<sup>10b</sup> Chemoselective methylenation of an aldehyde in the presence of a ketone can also be achieved (eq 5).<sup>10a</sup> Other unsaturated functionalities also react with these reagents. For example, the Eisch reagent<sup>10e</sup> [CH<sub>2</sub>(ZnI)<sub>2</sub>/Cp<sub>2</sub>TiCl<sub>2</sub>] has been shown to react with benzonitrile to afford, after hydrolysis, acetophenone (eq 6).

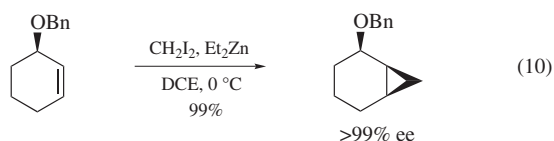
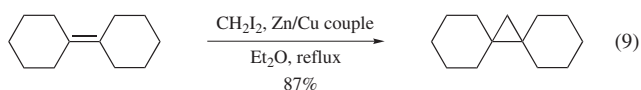


**Cyclopropanations.** A variety of metallic species mediate the cyclopropanation of alkenes in the presence of CH<sub>2</sub>I<sub>2</sub> (vide infra). A much simpler procedure is the photolysis of CH<sub>2</sub>I<sub>2</sub> in the presence of alkenes.<sup>12</sup> Although this method was initially reported to give a mixture of products in poor yields,<sup>12a</sup> the addition of iodine scavengers and acid scavengers to the reaction medium results in clean, high-yielding reactions.<sup>12b-d</sup> Sterically hindered alkenes are cyclopropanated much more readily than with metal-based reagents (eq 7), and double bond geometry is generally retained (eq 8). Remarkably, products arising from C–H bond insertion are not observed, ruling out the formation of free carbene in these reactions. The iodomethyl cation (ICH<sub>2</sub><sup>+</sup>) has been proposed as an intermediate in these reactions.<sup>12c,12d</sup>

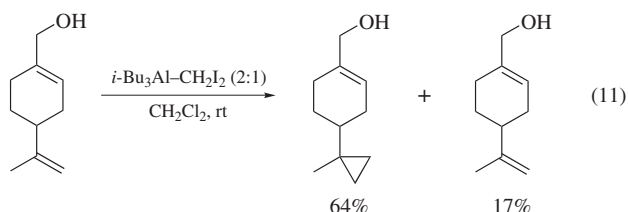




Perhaps the most common use of  $\text{CH}_2\text{I}_2$  in organic synthesis is in metal-mediated cyclopropanations. Foremost among these are zinc-mediated cyclopropanations (Simmons–Smith reaction).<sup>1,13</sup> This is a widely utilized and versatile transformation. Treatment of  $\text{CH}_2\text{I}_2$  and an alkene with **Zinc–Copper Couple** in refluxing  $\text{Et}_2\text{O}$  affords the corresponding cyclopropane, generally in good yield (eq 9).<sup>14</sup> The source of the zinc is crucial to the success of the reaction, and several reliable protocols exist.<sup>15</sup> The use of **Diethylzinc** in place of the Zn/Cu couple generates a similar reagent;<sup>16</sup> this modification has several advantages, including the option of using noncoordinating solvents. In many cases, the use of **Chloriodomethane**/ $\text{Et}_2\text{Zn}$  in place of  $\text{CH}_2\text{I}_2/\text{Et}_2\text{Zn}$  is desirable, as the former is more reactive.<sup>17</sup> Regardless of the method of reagent generation, the stereochemical course of the reaction is strongly influenced by proximal oxygen substituents (eq 10), and several effective chiral auxiliaries have been developed.<sup>18</sup>

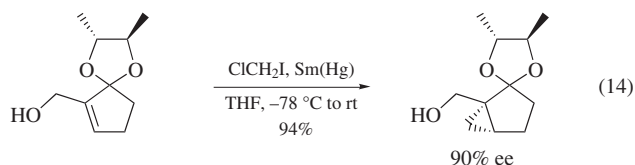
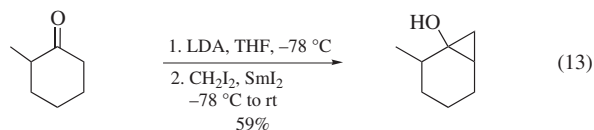
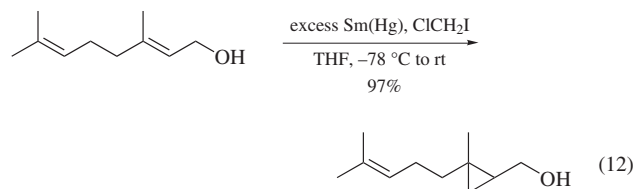


Similarly, treatment of  $\text{CH}_2\text{I}_2$  with a trialkylaluminum reagent (e.g. **Triisobutylaluminum**) in the presence of alkenes also affords cyclopropanes.<sup>19</sup> This reagent system exhibits a reactivity pattern complementary to the zinc- and samarium-based systems, reacting preferentially with isolated alkenes rather than with allylic alcohols (eq 11).<sup>19a</sup>

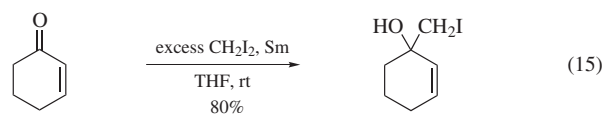


A very versatile reagent for the cyclopropanation of alkenes is derived from  $\text{CH}_2\text{I}_2$  and  $\text{Sm}(\text{Hg})$  or **Samarium(II) Iodide**.<sup>20</sup> These reagents react well with allylic alcohols (eq 12)<sup>20a,b</sup> and enolates (eq 13),<sup>20d</sup> and are subject to the same hydroxy-directing effects<sup>20a,b,f,g</sup> as the zinc-based reagents (vide supra). In fact, an oxygen substituent is required for cyclopropanation to occur.<sup>20b</sup> A diastereoselective cyclopropanation utilizing a chiral acetal as a chiral auxiliary has also recently been reported (eq 14).<sup>20g</sup> The substitution of  $\text{ClCH}_2\text{I}$  for  $\text{CH}_2\text{I}_2$  in these reactions often results in higher yields.<sup>20b</sup> Interestingly, a comparison of the response

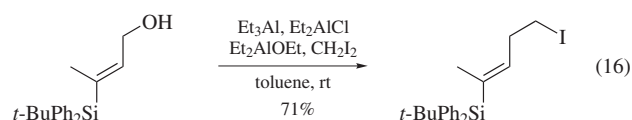
of the  $\text{CH}_2\text{I}_2/\text{Sm}(\text{Hg})$  and  $\text{CH}_2\text{I}_2/\text{SmI}_2$  reagents towards various allylic alcohols showed little or no difference in either reactivity, chemoselectivity, or stereoselectivity.<sup>20b</sup>



**Nucleophilic Additions of 'ICH<sub>2</sub>'.** Halomethyl lithium reagents are generally unstable except at very low temperatures (<−90 °C),<sup>21</sup> but the use of additives such as **Lithium Bromide** results in greater stability, particularly for **Chloromethyl lithium** and **Bromomethyl lithium**.<sup>21c,22</sup> The utility of  $\text{ICH}_2\text{Li}$  is still limited, however.<sup>23</sup> Fortunately, an alternative method for the generation of an iodomethyl nucleophile has been developed which utilizes **Samarium(0)** as the metal.<sup>3,20c</sup> Aldehydes, ketones, and enones all participate well in this reaction, and yields range from moderate to excellent (eq 15). In the illustrated example, the alkene is not cyclopropanated, consistent with the observation that tertiary allylic alcohols react sluggishly with samarium carbenoids.<sup>20b</sup>

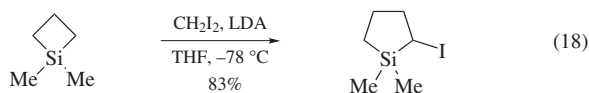
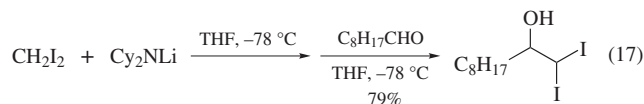


The replacement of an allylic alcohol oxygen by  $\text{CH}_2\text{I}$  has also been achieved by the use of aluminum reagents.<sup>24</sup> The combination of **Triethylaluminum**,  $\text{Et}_2\text{AlCl}$ , and  $\text{Et}_2\text{AlOEt}$  mediates this reaction (eq 16).

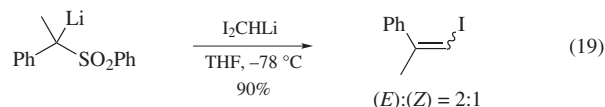


**Nucleophilic Additions of 'I<sub>2</sub>CH'.** Deprotonation of  $\text{CH}_2\text{I}_2$  by base affords  $\text{I}_2\text{CHMet}$  derivatives which are more stable than the corresponding  $\text{ICH}_2\text{Met}$  species and react well with a

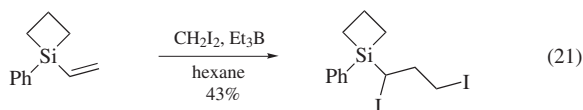
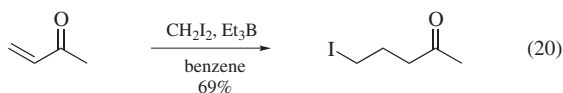
variety of electrophiles.<sup>25</sup> Among the bases used successfully are  $\text{Cy}_2\text{NLi}$ ,<sup>25a</sup> **Sodium Hexamethyldisilazide** ( $\text{NaHMDS}$ ),<sup>25b</sup> **Lithium Hexamethyldisilazide** ( $\text{LiHMDS}$ ),<sup>25b</sup> and **Lithium Diisopropylamide** ( $\text{LDA}$ ).<sup>25c</sup>  $\text{I}_2\text{CHLi}$  reacts well with aldehydes (eq 17),<sup>25a</sup> and also with silacyclobutanes, affording 2-iodosilacyclopentanes after ring enlargement of the intermediate five-coordinate silicate (eq 18).<sup>25c</sup>  $\text{I}_2\text{CHNa}$  has been shown to react with electrophiles such as **Chlorotrimethylsilane**, **Ethyl Iodide**, and **Allyl Iodide**.<sup>25b</sup>



A convenient synthesis of vinyl iodides using  $\text{I}_2\text{CHLi}$  has been reported by Julia and co-workers.<sup>25b</sup> Treatment of  $\text{CH}_2\text{I}_2$  with  $\text{LiHMDS}$  followed by the addition of a lithiated sulfone affords vinyl iodides after aqueous workup. The selectivity is generally low, however (eq 19).

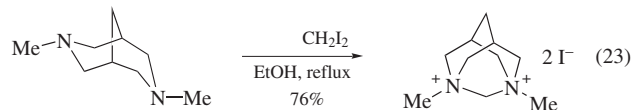
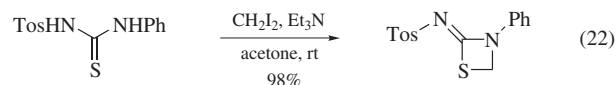


**Radical Additions Utilizing  $\text{CH}_2\text{I}_2$ .** The radical addition of the  $\text{ICH}_2$  fragment to  $\alpha,\beta$ -unsaturated ketones mediated by **Triethylborane** provides a route to  $\gamma$ -iodo ketones (eq 20).<sup>4</sup> The intermediate boron enolates can be either hydrolyzed or alkylated in some cases.<sup>4</sup> Vinylsilacyclobutanes are also alkylated by the putative  $\text{ICH}_2$  radical, affording highly functionalized silylcyclobutane derivatives (eq 21).<sup>26</sup>

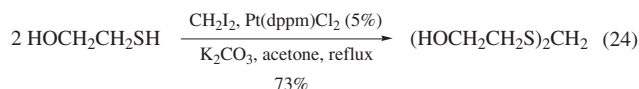


**Alkylation Reactions.**  $\text{CH}_2\text{I}_2$  has seen limited use as an alkylating reagent, since heterodihalomethanes such as  $\text{ClCH}_2\text{I}$  and  $\text{ClCH}_2\text{Br}$  are preferred for these reactions.<sup>27,28</sup>  $\text{CH}_2\text{I}_2$  has been used for alkylative cyclizations, however. A recent interesting application is the formation of 2-imino-1,3-dithiazetidines from thioureas (eq 22).<sup>29a</sup> Mixtures of isomers are obtained unless one of the urea nitrogen atoms is deactivated as a sulfonamide, amide, or carbamate. In addition, diamines are known to react with  $\text{CH}_2\text{I}_2$ :

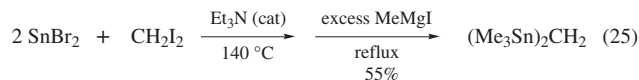
slow addition of the diamine to a solution of  $\text{CH}_2\text{I}_2$  is necessary to obtain good yields (eq 23).<sup>29b</sup>



In a mechanistically distinct but related example, dithianes are produced by the Pt-catalyzed coupling of  $\text{CH}_2\text{I}_2$  with thiols (eq 24).<sup>30</sup>



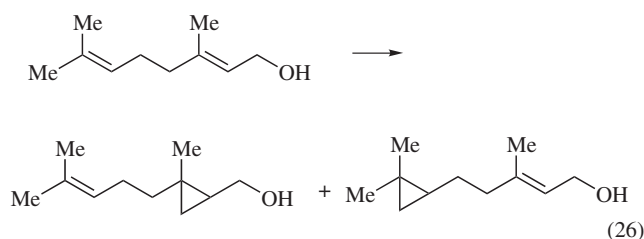
**Other Uses.** Several other transformations also utilize  $\text{CH}_2\text{I}_2$ . For example, heating  $\text{CH}_2\text{I}_2$  with 2 equiv of **Tin(II) Bromide** and a catalytic amount of **Triethylamine** affords a di-tin compound<sup>31a</sup> which can be exhaustively methylated to afford bis(trimethylstannyl)methane (eq 25).<sup>31b</sup> In addition, a convenient procedure for the in situ preparation of the valuable reagent  $\text{SmI}_2$  involves simply treating  $\text{Sm}$  powder with  $\text{CH}_2\text{I}_2$  in THF.<sup>32</sup>



## First Update

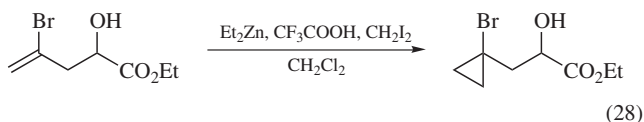
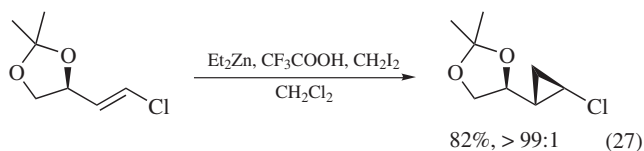
Andre B. Charette  
Université de Montreal, Montreal, Quebec, Canada

**Preparation of Iodomethylmetal Carbenoids.** Diiodomethane is the reagent of choice to prepare a variety of iodomethylmetal species. It is known to react with zinc/copper couple to generate iodomethylzinc iodide, with diethylzinc to afford either iodomethylethylzinc or bis(iodomethyl)zinc,<sup>33</sup> with trialkylaluminum to form iodomethyldialkylaluminum,<sup>34</sup> and with samarium (or samarium diiodide) to produce iodomethylsamarium.<sup>35</sup> The most important application of these reagents is in cyclopropanation reactions of alkenes.<sup>36</sup> As all these reagents are electrophilic species, the reaction typically proceeds more quickly with electron-rich alkenes. However, the chemoselectivity of the reaction depends upon both the reagent used and the nature of the substrate. An example of this is observed in the cyclopropanation of geraniol where the chemoselectivity of the reaction is highly dependent upon the nature of the iodomethylmetal reagent as well as on the reaction conditions (eq 26).<sup>37</sup>

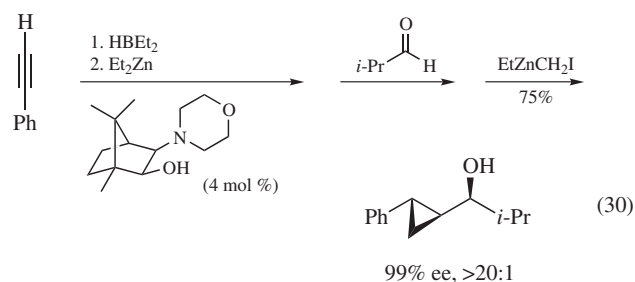
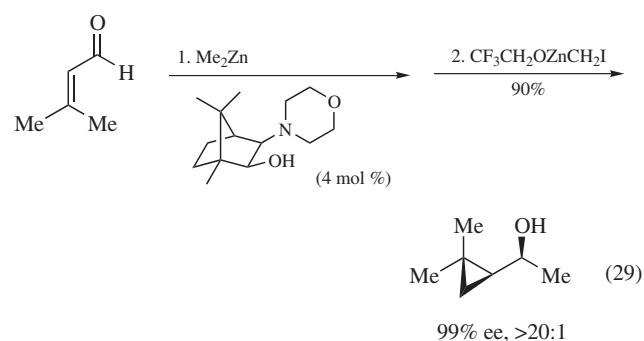


Et <sub>2</sub> Zn (2), CH <sub>2</sub> I <sub>2</sub> (1), CH <sub>2</sub> Cl <sub>2</sub>	74%	2%
Sm/Hg, CH <sub>2</sub> ICl, CH <sub>2</sub> Cl <sub>2</sub>	98%	0%
<i>i</i> -Bu <sub>3</sub> Al (2), CH <sub>2</sub> I <sub>2</sub> (1), CH <sub>2</sub> Cl <sub>2</sub>	1%	73%
<i>i</i> -Bu <sub>2</sub> AlCH <sub>2</sub> I (inverse addition)	67%	1%

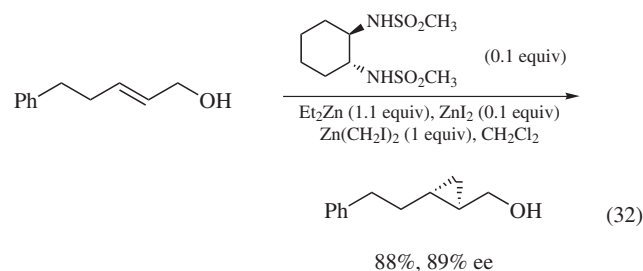
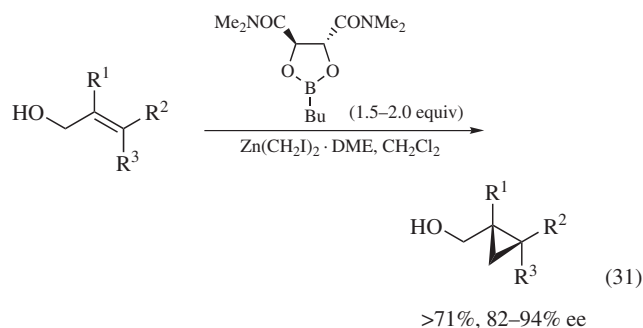
Modified iodomethylzinc reagents derived from trifluoroacetic acid,<sup>38</sup> phenols,<sup>39</sup> and phosphoric acids<sup>40</sup> have been reported as useful alternatives to bis(iodomethyl)zinc and iodomethylzinc iodide. Two notable examples are in the cyclopropanation of vinyl chlorides (eq 27)<sup>41</sup> and of vinyl bromides (eq 28)<sup>42</sup> using iodomethylzinc trifluoroacetate. Phenol and phosphoric acid-derived reagents are, however, less reactive and more stable than the corresponding iodomethylzinc trifluoroacetate.



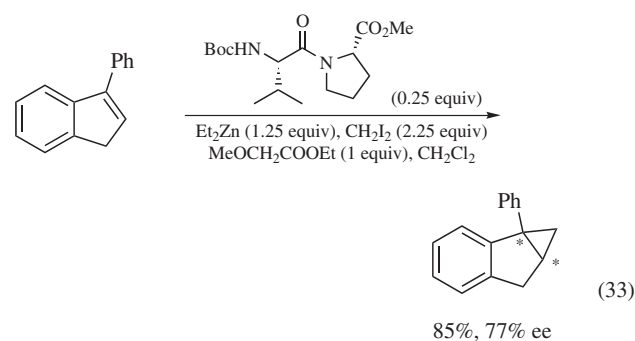
A trifluoroethanol-derived reagent has been applied in a methodology that affords chiral cyclopropylmethanol derivatives from achiral precursors. Chiral zinc allylic alkoxides generated in situ by the 3-*exo*-(morpholino)isborneol (MIB)-catalyzed addition of organozinc reagents to aldehydes are directly cyclopropanated following the addition of diiodomethane (eqs 29 and 30).<sup>43</sup>



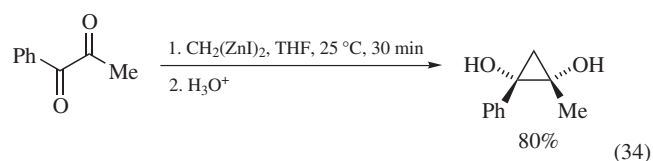
The zinc reagents have also been particularly useful in asymmetric cyclopropanation reactions of allylic alcohols using both stoichiometric (eq 31)<sup>44</sup> and catalytic chiral additives (eq 32).<sup>45</sup>



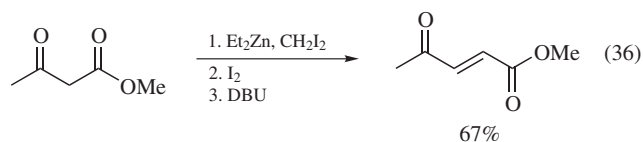
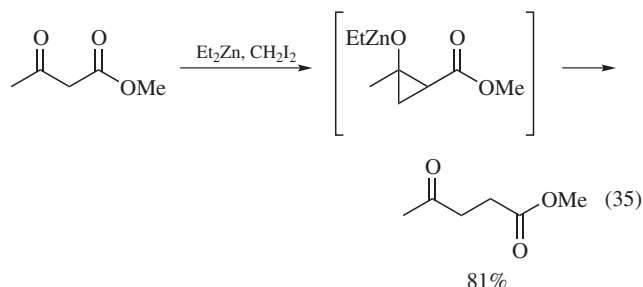
Unfunctionalized styrenes are successfully converted into the corresponding cyclopropane using either stoichiometric or catalytic amounts of a dipeptide (eq 33).<sup>46</sup> These reaction conditions have also been applied in the asymmetric cyclopropanation of silyl enol ethers.<sup>47</sup>



Finally, zinc reagents have been quite useful in various chain extension processes. For example, treatment of a 1,2-dicarbonyl derivative with CH<sub>2</sub>(ZnI)<sub>2</sub> (prepared from diiodomethane, Zn powder, and a catalytic amount of lead(II) chloride) led to the synthesis of a cyclopropane-1,2-diol (eq 34).<sup>48</sup>



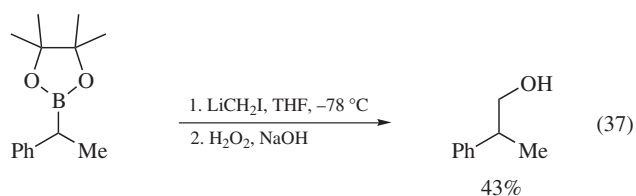
If a  $\beta$ -ketoester is treated with a mixture of diethylzinc and diiodomethane, a 1,4-dicarbonyl derivative can be generated (eq 35).<sup>49</sup> In addition, the intermediate zinc alkoxide obtained in this reaction can be further treated with iodine and then DBU to yield an  $\alpha,\beta$ -unsaturated- $\gamma$ -ketoester (eq 36).<sup>59</sup>



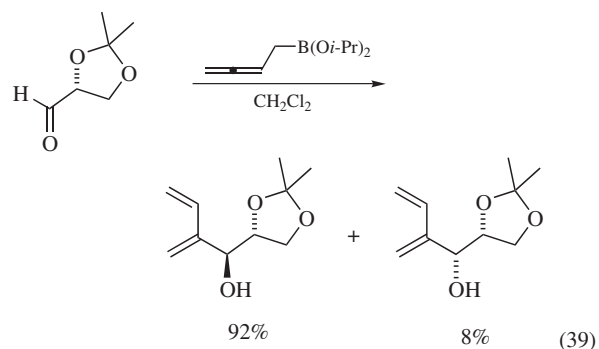
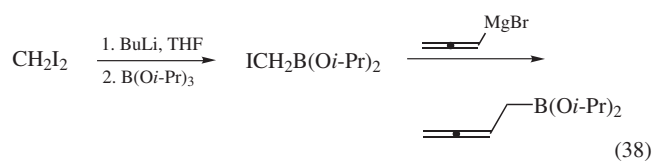
The chain extension reactions of  $\beta$ -ketophosphonates,<sup>51</sup>  $\beta$ -ketoamides,<sup>52</sup> and amino acid skeletons have also been reported.<sup>53</sup>

### One-carbon Homologation of Organometallic Reagents.

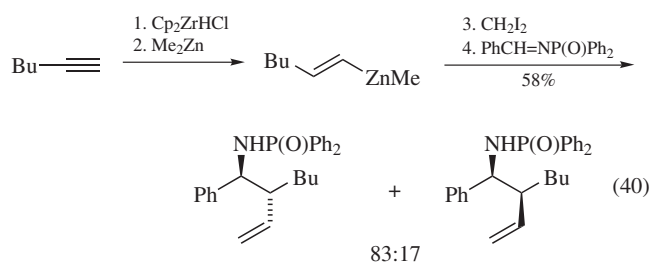
The homologation of boronate esters is observed upon treatment with iodomethyl lithium obtained by a lithium–iodine exchange of diiodomethane (eq 37).<sup>54</sup> The yields of the homologated product are higher if the lithium anion derived from bromochloromethane, iodochloromethane, or dibromomethane is used.



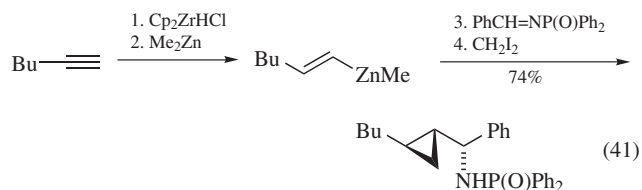
The preparation of homoallylboronates is effective by using a reagent obtained through the monoaddition of iodomethyl lithium to triisopropylboronate followed by the subsequent treatment with allenylmagnesium bromide (eq 38).<sup>55</sup> The resulting homoallylboronate reagent adds to carbonyl derivatives to generate substituted butadienylmethanol compounds (eq 39).



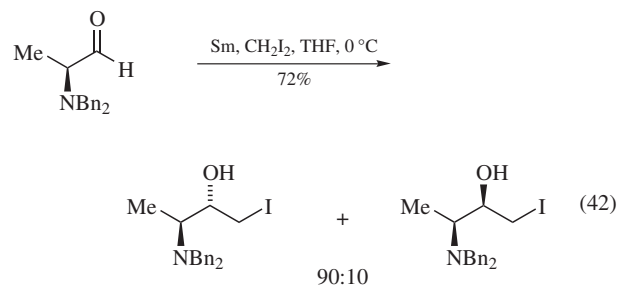
Alkenylalkylzinc reagents, obtained by the hydrozirconation/transmetalation of alkynes, react with diiodomethane to generate the corresponding allylzinc reagents, which can further react with imines to generate homoallylic amines (eq 40).<sup>56</sup>



Interestingly, the addition of the imine prior to that of diiodomethane generates the corresponding cyclopropylmethylamine (eq 41).<sup>57</sup>

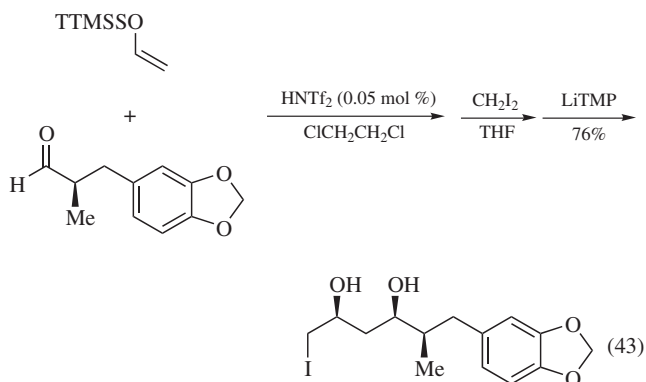


**Nucleophilic Iodomethylation.** The iodomethylation of carbonyl derivatives is known to be difficult to achieve under mild reaction conditions. However, treatment of diiodomethane with samarium iodide generates a reagent that reacts smoothly with carbonyl derivatives. This reaction has been further extended to the iodomethylation of chiral  $\alpha$ -amino aldehydes (eq 42).<sup>58</sup>

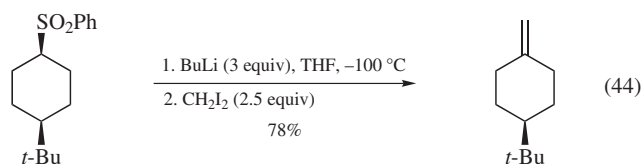


A sequential aldol–iodomethylation reaction has been developed (eq 43). An initial triflimide-catalyzed aldol reaction between an aldehyde and a tris(trimethylsilyl)silyl (TTMSS) enol ether leads to a  $\beta$ -hydroxyaldehyde. This aldehyde is directly treated with iodomethyl lithium (generated from diiodomethane

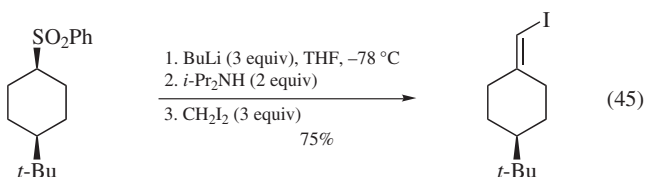
and lithium tetramethylpiperidide) to afford the corresponding diol.<sup>59</sup>



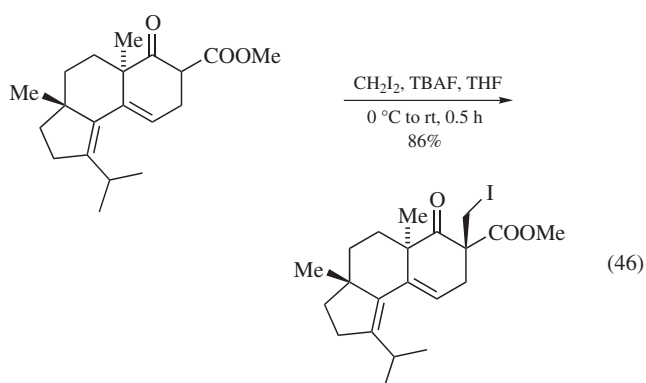
**Methylenation of Sulfones.** Treatment of a sulfone with 3 equiv of butyllithium followed by the addition of diiodomethane produces the *exo*-methylene derivative in good yield (eq 44).<sup>60</sup> Dibromomethane and bromochloromethane are also capable of achieving this transformation with high efficiency.



Alternatively, if lithium diisopropylamide is used in place of BuLi, the vinyl iodide is obtained (eq 45).

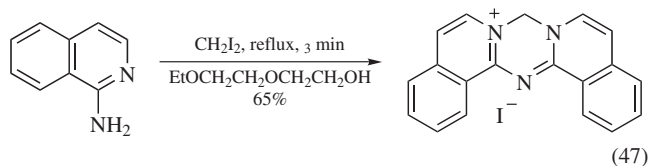


**Electrophilic Iodomethylation.** Diiodomethane can be used as a good iodomethylation reagent for soft enolates. Treatment of a  $\beta$ -ketoester with tetrabutylammonium fluoride and diiodomethane leads to the iodomethylated product (eq 46).<sup>61</sup>

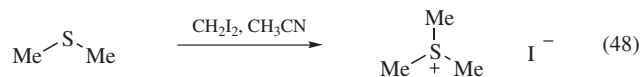


**Alkylation of Heteroatoms.** Lewis basic heteroatoms can be readily alkylated with diiodomethane. For example, azacyanines are generated when aminoisoquinolines are heated in the presence

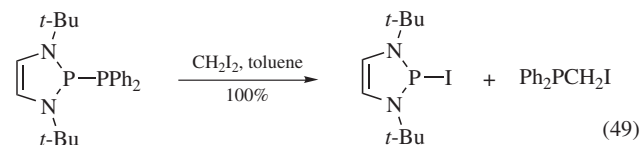
of diiodomethane in polar solvents such as acetonitrile or 2-(2-ethoxyethoxy)ethanol (eq 47).<sup>62</sup> In certain cases, diiodomethane has also been used as the reaction solvent.



Dimethylsulfide reacts with diiodomethane in acetonitrile at 50 °C to generate trimethylsulfonium iodide (eq 48).<sup>63</sup> The reaction proceeds through an unstable iodomethyldimethylsulfonium iodide, which decomposes via a single electron transfer reaction.



*P*-phosphinyl-diazaphospholenes are converted to *P*-iodo-diazaphospholenes upon treatment with diiodomethane (eq 49).



**Related Reagents.** Chloriodomethane; Dibromomethane; 1,1-Diiodoethane; Diiodomethane–Zinc–Titanium(IV) Chloride; Iodomethylzinc Iodide.

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