

*Synthetic Methods*

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**Chemo- and Regioselective Preparation and Reaction of a Kinetic Zinc Enolate Formed from a Thiol Ester and Bis(iodozincio)methane\*\***

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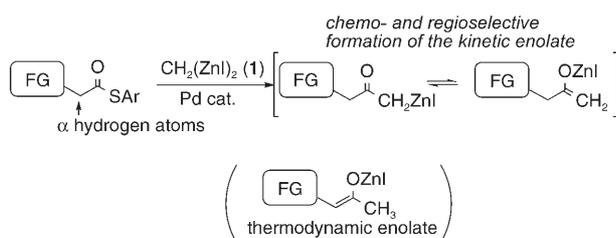
Bis(iodozincio)methane (**1**), which has a methylene carbon atom with two nucleophilic sites, has been used for a variety of molecular transformations in which C–C bond formation is repeated at the same carbon atom.<sup>[1,2]</sup> In other words, it functions as a zinciomethylation reagent. Such zinciomethy-

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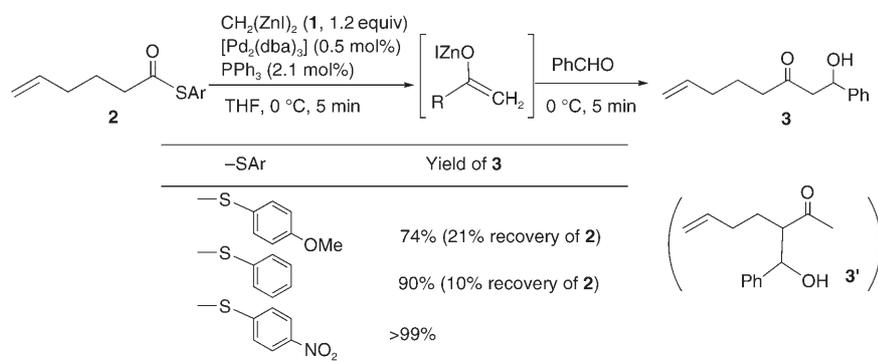
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lation of acylating reagents should afford the kinetic enolates of ketones. Many functional groups should be tolerated during the transformation because of the modest reactivity of organozinc compounds.<sup>[3]</sup> However, in previous studies some combinations of acylating reagents and **1**, regardless of their stoichiometric relationship, resulted in the formation of symmetrical 1,3-diketones through a double acylation of **1**. For example, the treatment of benzoyl chloride with **1** in any ratio in the presence of a palladium catalyst gave 1,3-diphenylpropane-1,3-dione.<sup>[4a]</sup> The treatment of an acyl cyanide with **1** gave a similar result.<sup>[4b]</sup> These highly reactive acylating reagents react preferentially with the  $\alpha$ -zincio-ketone intermediate over bis(iodozincio)methane (**1**). A mild and chemoselective transformation reported by Fukuyama and co-workers in which thiol esters are converted into ketones with alkyl zinc reagents in the presence of a palladium catalyst<sup>[5–7]</sup> suggested to us that a thiol ester may react with bis(iodozincio)methane (**1**)<sup>[2c]</sup> in the presence of a palladium catalyst to give an  $\alpha$ -zincio-ketone, that is, an enolate<sup>[8]</sup> that would not readily undergo palladium-catalyzed coupling with the thiol ester. The transformation should be chemoselective because of the modest reactivity of **1**. Furthermore, the terminal enolate formed initially would not isomerize to the corresponding thermodynamic enolate under these reaction conditions (Scheme 1).



**Scheme 1.** Preparation of a kinetic zinc enolate by zinciomethylation of a thiol ester. FG = functional group.

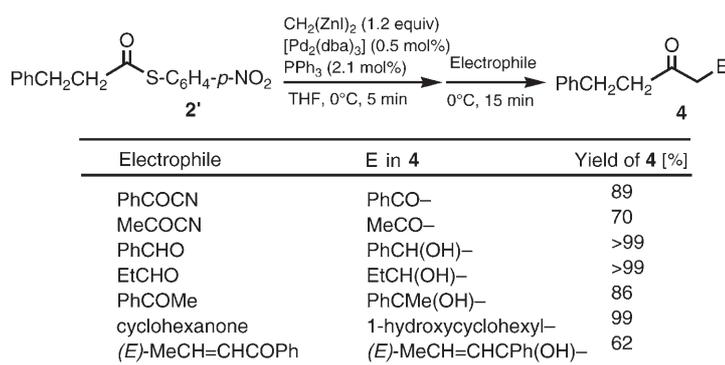
Arene thiol esters<sup>[9]</sup> of 5-hexenoic acid, **2**, were mixed with bis(iodozincio)methane (**1**) in the presence of a palladium(0) catalyst, which was prepared in situ from [Pd<sub>2</sub>(dba)<sub>3</sub>] (dba = *trans,trans*-dibenzylideneacetone) and triphenylphosphane, and treated subsequently with benzaldehyde (Scheme 2).



**Scheme 2.** Preparation of the kinetic zinc enolate from thiol esters **2** and reaction with benzaldehyde.

Tuning of the electron density of the aromatic ring of the thiol improved the yield. The aldol product **3** was obtained quantitatively when 4-nitrobenzenethiol was used to form the thiol ester. The only other possible aldol product **3'**, which may result if the enolate formed initially isomerizes to the thermodynamic enolate, was not observed. The use of ethanethiol ester as a substrate<sup>[5]</sup> resulted in the recovery of the starting material.

Various types of electrophiles can be added to the prepared kinetic enolate as reactants, as shown in Scheme 3. Treatment with acyl cyanides gave 1,3-diketones. Conjugate addition was not observed in the reaction of (*E*)-MeCH=CHCOPh with the kinetic enolate formed from **2'**.



**Scheme 3.** Reaction of the kinetic enolate prepared from thiol ester **2'** with various electrophiles.

Functional-group tolerance in the formation of the kinetic enolate was examined (Scheme 4). Terminal alkyne (in **5d**), primary bromide (in **5e**), silyl ether (in **5i**), and ester (in **5j**) functionalities remained intact during the reaction. Neither a bromophenyl (in **5f**) nor a sulfide (in **5g**) group interfered with the formation of the kinetic enolate, although these functional groups often interact with palladium(0) catalysts.

The chemo- and regioselective preparation of the kinetic enolate in the presence of a keto group was an attractive goal.<sup>[10]</sup> Unfortunately, the treatment of a thiol ester containing a keto group with bis(iodozincio)methane (**1**) in the presence of a palladium catalyst gave a polymeric compound

formed by an intermolecular reaction of the keto group with the enolate. The addition of the electrophile to the reaction mixture prior to the formation of the enolate, however, prevented this self-condensation. Mixtures of a thiol ester with a keto group, **7**, and benzoyl cyanide were treated with the dizinc reagent **1** in the presence of a palladium catalyst (Scheme 5). The desired triketones were formed in excellent yields. The initially formed kinetic enolate reacted with the electrophile without being transposed to the other methyl ketone in the same molecule, as shown by the reactions of **7d** and **7e**.



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