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Spectroscopic Characterization of Diiodomethylzinc Iodide: Application to the Stereoselective Synthesis and Functionalization of Iodocyclopropanes.

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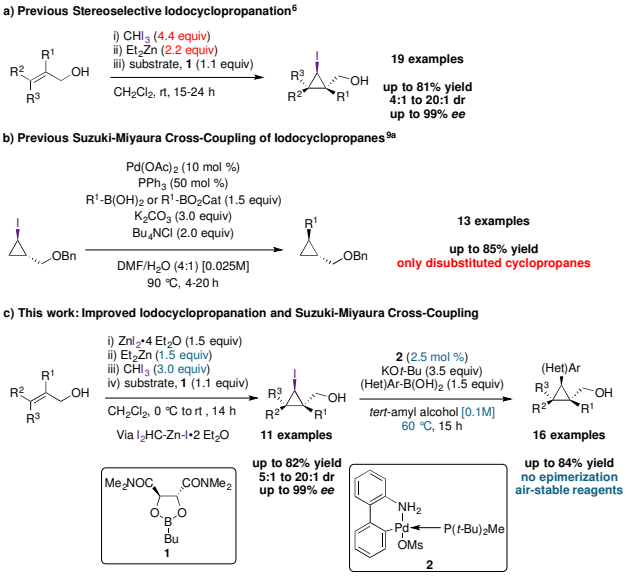
Herein is described an improved synthetic route to enantio- and diastereoenriched iodocyclopropylmethanols using (diiodomethyl)zinc iodide etherate as the active species. The products obtained by this methodology were successfully functionalized by Suzuki-Miyaura cross-coupling reactions. A Buchwald-type palladium precatalyst allowed access to highly substituted and stereo-enriched cyclopropanes without requiring a protecting group.

The cyclopropane moiety is present in a large number of bioactive molecules,[1] having recently being ranked as the 10th most commonly used cyclic scaffold for the elaboration of new drugs.[2] The introduction of such crucial motifs in various structures is, therefore, of interest. One way to achieve this goal would be the palladium-catalyzed Suzuki-Miyaura cross-coupling of iodocyclopropanes with various boronic acids, as this reaction is one of the most used reactions in the pharmaceutical industry for the formation of carbon-carbon bonds.[3,4,5] Recently, our group reported the first enantioselective synthesis of such iodocyclopropanes starting from allylic alcohols using diethylzinc and iodoform as reagents.[6,7] Although this methodology delivers the desired iodocyclopropanes in good yields and moderate to excellent stereoselectivities, it suffers from the large amount of iodoform needed (Scheme 1a). Following our work on the bromocyclopropanation reaction,[8] in which only 1.3 equivalents of diethylzinc and 2.6 equivalents of bromoform were needed for the reaction, we investigated whether we could develop a more atom-economical iodocyclopropanation to minimize the amount of reagents needed for the optimal preparation of the (diiodomethyl)zinc carbenoid (Scheme 1a).



Scheme 1 a) and b) Previously developed methodologies and c) This work.

In this communication, we report the first spectroscopic characterization of (diiodomethyl)zinc iodide and its application to the iodocyclopropanation reaction as well as the first set of conditions allowing the Suzuki-Miyaura cross-coupling of 1,2,3-substituted iodocyclopropanes that do not required an initial protection of the primary alcohol (Scheme 1b).[9,10,11,12]

We began our investigations by monitoring the preparation of the active carbenoid by ^{1}H NMR to insure that it was formed under optimal conditions. Ethylzinc iodide etherate was formed by mixing zinc iodide, diethylzinc and diethyl ether in a 1:1:2 molar ratio in CD_2Cl_2.Upon cannulation of this mixture over a suspension of CHI_3 in CD_2Cl_2 at 0 °C and stirring for 20 minutes, we were delighted to observe a new signal at 4.21 ppm, attributed to the carbenoid (Figure 1a). This intermediate was formed in 75% yield and was fully characterized by ^{1}H, ^{13}C and HSQC experiments.[13] Although this carbenoid is stable at 0 °C, it rapidly degrades even at room temperature.

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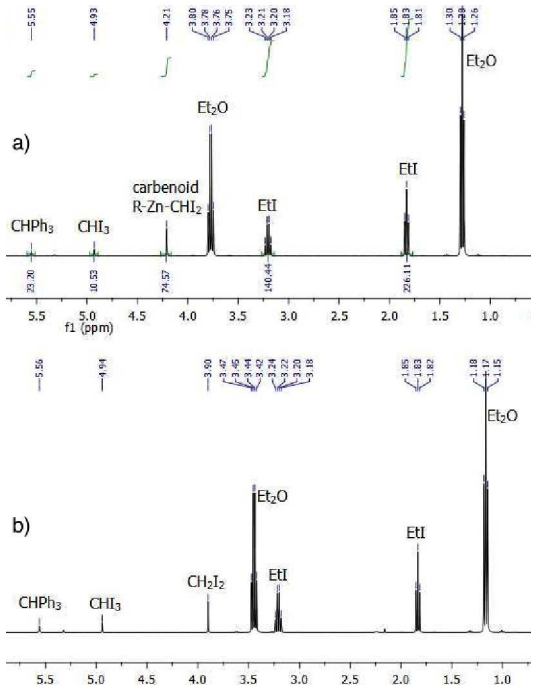
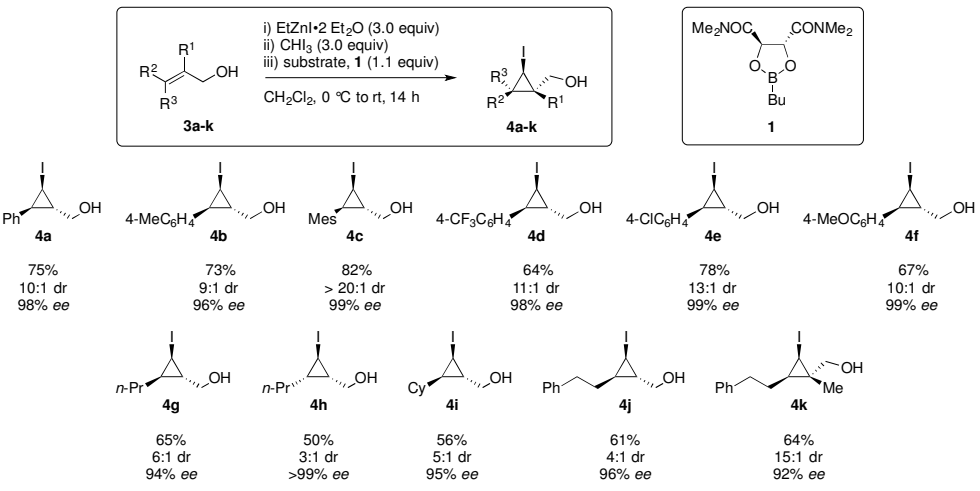


Figure 1 a) ^{1}H NMR spectra of a mixture 1:1:2:2 $ZnI_2/Et_2Zn/CHI_3/Et_2O$ in CD_2Cl_2. Triphenylmethane used as internal standard. b) ^{1}H NMR spectra of the previous mixture quenched with aqueous 1N HCl.

Quenching the reaction mixture with 1N HCl triggered the disappearance of this signal and the appearance of diiodomethane at 3.90 ppm (Figure 1b). This protocol led to an effective monoiodocyclopropanation of cinnamyl alcohol to generate iodocyclopropane **4a**. After optimization,[13] **4a** was obtained in 75% yield and with 10:1 dr and 98% ee using only 1.5 equivalents of diethylzinc and 3.0 equivalents of iodoform. These conditions were effective to cyclopropanate a wide range of allylic alcohols producing various iodocyclopropanes in good to excellent yields and high enantiomeric excesses (Scheme 2). As illustrated by compound **4b**, the presence of a weakly donating methyl group on the phenyl ring of the substrate has a negligible effect both on the yield and the stereoselectivities of the reaction. Steric bulk around the alkene drastically improved the diastereochemical outcome (**4c**). Electron-poor alkenes, such as **3d**, afford the desired product in a lower yield. This lack of reactivity can be attributed to the substrate's poor nucleophilicity. Alkyl and halogen substituents on the phenyl group are well tolerated, as depicted by compounds **4b** and **4e**. The electron-rich product **4f** was obtained in a slightly lower yield but good conversion. In this case, the degradation of **4f**, possibly by a ring-opening pathway, is the cause of the diminished product recovery. Non-aromatic alkenes, lacking the stabilizing effect of conjugation, generally gave slightly diminished yields and disatereoselectivities (**4g**, **4i**, **4j**). *cis*-Disubstituted alkene **3h** gave the lowest yield, likely due to a steric clash with the dioxaborolane auxiliary. Finally, the addition of a third aliphatic substituent *gem* to the hydroxymethyl increased the diastereoselectivity, which was also compatible under these conditions (**4k**). It is noteworthy that, in almost all examples, the desired products were obtained in a similar or improved yield compared to the previously described methodology.[6]

Our group previously described the first Suzuki cross-coupling of iodocyclopropanes using palladium(II) acetate, triphenylphosphine, potassium carbonate and tetrabutylammonium chloride in a mixture of DMF and water (Scheme 1b).[9a]

Under those conditions, only one example involving a *trans*-2-iodocyclopropylmethanol was described. When they were applied to a 1,2,3-substituted iodocyclopropane, the starting material was completely consumed, but none of the Suzuki products could be isolated (Scheme 3a). It appears that the initial oxidative addition process took place, yet the cyclopropylpalladium readily decomposed prior to undergoing transmetalation.



Scheme 2 Scope of the improved stereoselective iodocyclopropanation. 0.5 mmol scale. Yields of the isolated major diastereomer. Diastereomeric ratios determined by ^{1}H NMR on the crude mixture. Enantiomeric excess verified by chiral SFC.

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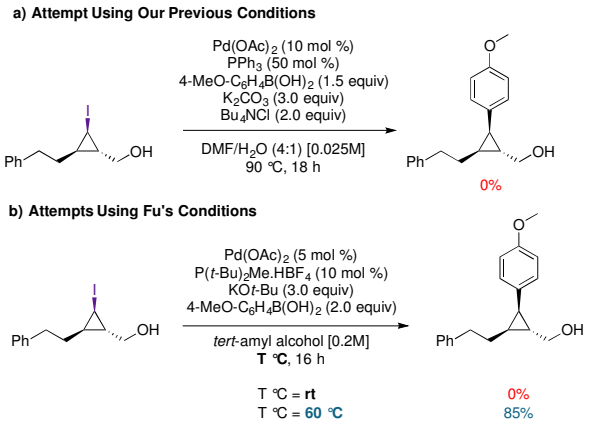
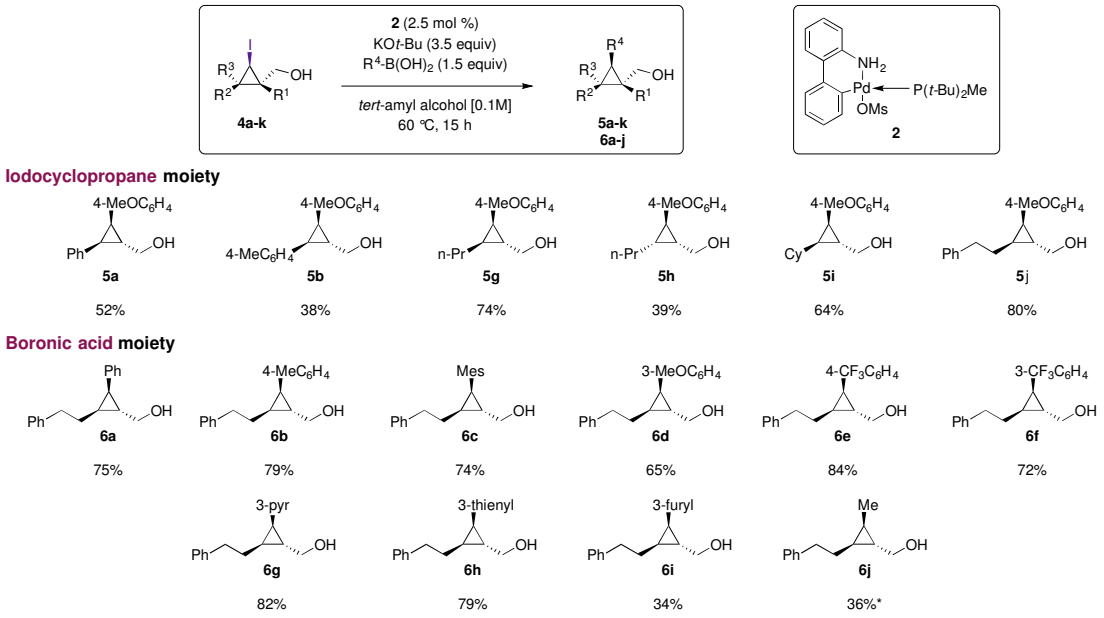
With our more efficient synthesis of enantioenriched and highly substituted iodocyclopropanes in hand, we decided to develop conditions for the Suzuki cross-coupling reaction that would not only be applicable to a broader range of substituted iodocyclopropanes, but also would allow the coupling of unprotected cyclopropylmethanol derivatives.

Over the past decades, a lot of efforts have been invested to promote the development of more efficient, user-friendlier and milder reaction conditions for the cross-coupling of both sp^2 and sp^3 centers.[11] Notably, Fu described a protocol for the effective Suzuki coupling of primary alkyl bromides in *tert*-amyl alcohol.[14] Applying Fu's conditions at 60 °C instead of room temperature, we observed the formation of the desired product in 85% yield by ^{1}H NMR with no trace of epimerization (Scheme 3b). Despite an extensive screening of ligands, bases and solvents, those conditions proved to be the most effective.[13] Although suitable, the source of the Pd(II) catalyst could affect the reproducibility of the results, as studied by Colacot.[15] On the other hand, Buchwald's precatalysts are known to be air- and moisture-stable and very powerful sources of palladium(0).[16] Therefore, the Buchwald's third generation precatalyst using the di-*tert*-butylmethylphosphine ligand was synthesized.[17] After optimization,[13] 80% of the desired product **5j** was isolated when iodocyclopropane **4j** was treated with 1.5 equivalents of 4-methoxyphenylboronic acid, 2.5 mol % of precatalyst **2** and 3.5 equivalents of potassium *tert*-butoxide in *tert*-amyl alcohol at 60 °C for 15 hours. The scope of the reaction was then investigated using various iodocyclopropanes and boronic acids (Scheme 4). It can be noted that an aromatic substitution on the iodocyclopropane moiety is well tolerated under those conditions, although the corresponding products are obtained in modest yields (**5a**, **5b**).



Scheme 3 Initial trials of Suzuki Cross-Coupling using a) our previous conditions and b) adapted conditions from the Fu group.

This lower efficiency may be the result of one of the cyclopropylpalladium(II) intermediates undergoing ring-opening due to the propensity of aromatic rings to stabilize electronic charges at the benzylic position. Iodocyclopropanes bearing strongly electron-donating or -withdrawing groups on the aryl substituent (i.e. **4d** to **4f**) were not compatible with the coupling conditions. Alkyl substituted iodocyclopropanes could be smoothly converted into the coupling products (**5g** to **5j**). The attempted coupling of more sterically hindered iodocyclopropanes (**4c** and **4k**) led to the degradation of the starting materials, and only traces of the desired products were observed.



Scheme 4 Scope of the newly developed Suzuki-Miyaura cross-coupling of iodocyclopropanes. 0.3-0.4 mmol scale. *^{1}H NMR yield on the crude mixture, triphenylmethane used as internal standard.

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The nature of the boronic acid component was then surveyed. Phenylboronic and *p*-tolyl boronic acids gave the desired compounds **6a** and **6b** in good yields. Mesitylboronic acid was also successfully coupled (**6c**), showing high tolerance to steric hindrance on the boronic acid partner. The reaction seems unaffected by electronic effects, as both electron-rich and electron-poor arylboronic acids were viable coupling partners (**5j**, **6d**, **6e** and **6f**). Interestingly, heteroaryl boronic acids, such as 3-pyridyl and 3-thienylboronic acids, provided access to compounds **6g** and **6h** in good yields. Unfortunately, 3-furanylboronic acid gave a lower yield (**6i**). Finally, using an alkylboronic acid as methylboronic acid (**6j**) gave an observed low yield by ^{1}H NMR and was not separable from the dehalogenated cyclopropyl by-product. It is noteworthy that no epimerization was observed by ^{1}H NMR on the cyclopropane in any of the described examples.

In conclusion, two synthetic methodologies were developed in this study. First, we devised an improved and more economical stereoselective iodocyclopropanation reaction for allylic alcohols, of which the active species has been characterized and its formation optimized. The highly substituted products obtained by this methodology were then successfully engaged in stereospecific Suzuki-Miyaura cross-coupling reactions thanks to the development of new conditions using bench-stable and easy-to-handle reagents.

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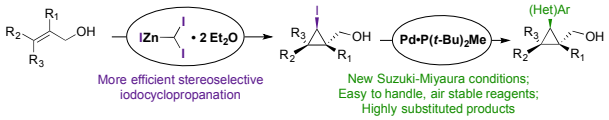

Herein are described more efficient methodologies for the synthesis of highly substituted cyclopropanes as well as the first characterization of a diiodomethylzinc carbenoid.