Synthetic Methods

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# Zirconocene-Mediated Carbonylative Coupling of Grignard Reagents

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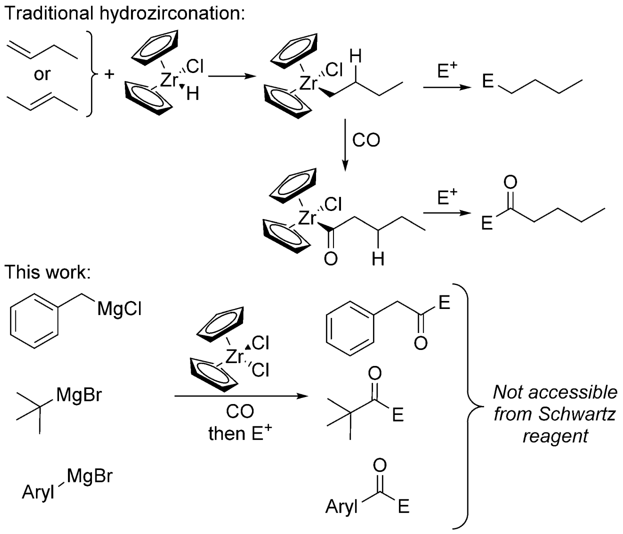
***Abstract:*** *Organozirconocenes are versatile synthetic intermediates that can undergo carbonylation to yield acyl anion equivalents. Zirconocene hydrochloride ([$Cp_2ZrHCl$]) is often the reagent of choice for accessing these intermediates but generates organozirconocenes only from alkenes and alkynes. This requirement eliminates a broad range of substrates. For example, organozirconocenes in which the zirconium center is bonded to an aromatic ring, a benzylic group, or an alkyl group that possesses a tertiary or quaternary carbon atom α to the carbon–zirconium bond can not be formed in this way. To provide more generalized access to acyl zirconium reagents, we explored the transmetalation of Grignard reagents with zirconocene dichloride under a CO atmosphere. This protocol generates acyl zirconium(IV) complexes that are inaccessible with the Schwartz reagent, including those derived from secondary and tertiary alkyl and aryl Grignard reagents.*

Hart and Schwartz first described the use of zirconocene hydrochloride for the functionalization of olefins in 1974,[1] and since then organozirconocenes have emerged as one of the most versatile classes of transition-metal derivatives in organic synthesis.[2] These organometallic reagents can participate in cross-coupling reactions, conjugate and nucleophilic addition reactions, and halogenation.[2–5] Among the most useful transformations of organozirconocenes is their carbonylation to yield acyl zirconium complexes.[6] These reagents serve as acyl anion equivalents and can undergo oxidation to yield carboxylic acid derivatives and react in C−C bond forming processes to yield unsymmetrical ketones. For example, acyl zirconium reagents add to ketones and enones to form α-hydroxyketones and 1,4-diketones, respectively.[7] Additionally, they couple with aryl and allyl electrophiles under metal-mediated conditions.[8–10] Enantioselective transformations of acyl zirconocenes have been developed to generate optically active ketone derivatives.[11]

Organozirconium reagents are generally prepared by the hydrozirconation of olefins or alkynes. These hydrometalation reactions are highly regioselective and generally provide the less-hindered alkyl or vinyl zirconium intermediate.[12] Indeed, the hydrozirconation of internal olefins usually forms the terminal alkyl complex through an isomerization sequence involving reversible hydrozirconation/β-hydride elimination (Scheme 1).[1] Additionally, hydrozirconation necessarily results in a zirconium complex with a β-C−H bond. This requirement excludes broad substrate classes, including aryl and benzyl zirconium complexes. We sought to expand the variety of available organozirconium reagents through transmetalation from readily available organometallic species. Although unprecedented, such a process could yield zirconium reagents that are currently inaccessible through hydrozirconation, including aryl, benzyl, and tertiary and secondary alkyl zirconocenes, and might reveal fundamental aspects of organozirconium chemistry.



***Scheme 1.*** Synthesis and reactivity of acyl zirconocenes. $E^+$ = electrophile.

We initiated our study by exploring the transmetalation of Grignard reagents with zirconocene dichloride, [$Cp_2ZrCl_2$]. This approach avoids the use of the Schwartz reagent, which, although synthetically useful, is expensive and has a short bench life and poor solubility.[13–15] Negishi and co-workers had previously demonstrated that *tert*-butyl and isobutyl Grignard reagents would react with zirconocene dichloride. However, the intermediate [(alkyl)$ZrClCp_2$] complex underwent rapid loss of isobutylene to form [$Cp_2Zr(H)Cl$] in situ.[16–18] From another relevant study, alkyl lithium and Grignard reagents are known to reduce [$Cp_2ZrCl_2$] to low-valent zirconium complexes.[19] By contrast, we were interested in accessing alkyl zirconium species and trapping them with suitable electrophiles. Furthermore, we wanted to exploit the ability of organozirconocenes to act as acyl anion equivalents. Accordingly, we focused our studies on accessing and functionalizing acyl zirconocenes from a diverse collection of Grignard reagents.

Taguchi and co-workers have developed an efficient copper-catalyzed cross-coupling of acyl zirconocenes with allylic or propargylic halides to give allylic or allenic

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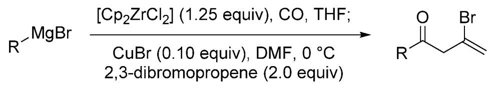
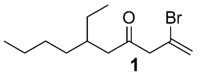
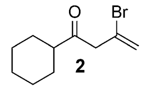
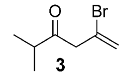
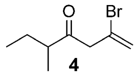
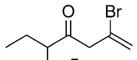
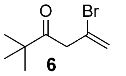
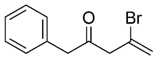
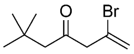
ketones.[7] Building on this work, we successfully developed a carbonylative coupling of Grignard reagents with allyl and propargyl bromides. First, alkyl Grignard reagents were treated with [$Cp_2ZrCl_2$] under a CO atmosphere for 4 h at room temperature (Table 1). The resultant acyl zirconocenes were stable up to 50 °C under a CO atmosphere as well as to filtration through Celite in air. Partial protonolysis was observed upon exposure to silica gel. However, the acyl zirconocenes were used without any purification. Thus, the addition of a representative allyl bromide and CuBr (10 mol %) led to the formation of unsymmetrical ketones **1**–**8** in good yield (Table 1).

***Table 1:*** Carbonylative coupling of alkyl Grignard reagents with [$Cp_2ZrCl_2$].[a]

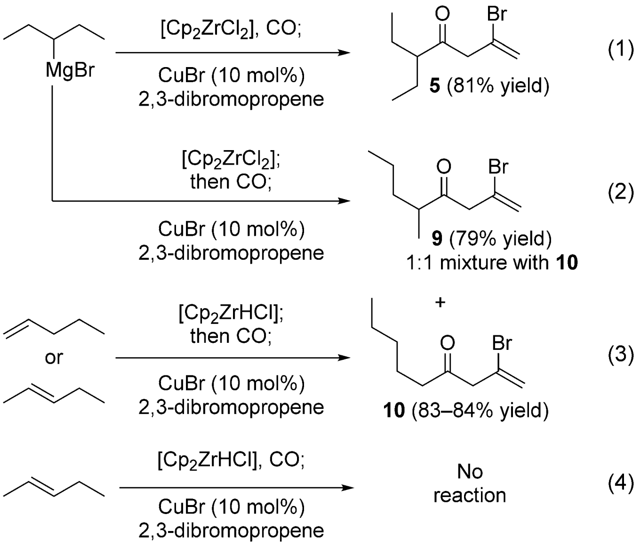


| Entry | Product | Yield [%][b] |
|---|---|---|
| 1 |  **1** | 88 |
| 2 |  **2** | 83 |
| 3 |  **3** | 75 |
| 4 |  **4** | 79 |
| 5 |  **5** | 81 |
| 6 |  **6** | 77 |
| 7 |  **7** | 88 |
| 8 |  **8** | trace |

[a] Reactions were carried out on a 1.0 mmol scale. See the Supporting Information for details. [b] Yield of the isolated product. DMF = dimethylformamide.

Primary, secondary, tertiary, cyclic, and benzylic organomagnesium reagents underwent the coupling reaction successfully. The ketones derived from benzylic and tertiary alkyl Grignard reagents (Table 1, entries 6 and 7) could not be synthesized by traditional hydrozirconation; the intermediate (benzyl)zirconocene lacks β-hydrogen atoms, thus rendering it inaccessible through hydrometalation. Likewise, hydrozirconation of isobutylene is slow and generates the isobutyl organometallic intermediate rather than the *tert*-butyl reagent.[17] Similarly, the ketones derived from branched Grignard reagents (Table 1, entries 1 and 3–5) could not be accessed through hydrozirconation with the Schwartz reagent because the linear isomers would dominate. Unfortunately, neopentyl Grignard reagents are not compatible with the current reaction conditions.

As previously described, secondary alkyl zirconocenes can rearrange through β-hydride elimination/hydrozirconation to generate primary zirconocenes. Attempts to reverse the normal regioselectivity of hydrozirconation have met with limited success. For example, the Wipf group formed substantial amounts of branched products by using directing groups or cationic zirconium reagents, although the linear products usually dominated.[20] In previous studies, we were able to reverse the normal regioselectivity of the hydrozirconation of alkynols, but the reaction was limited to terminal secondary propargylic alcohols or internal homopropargylic alcohols.[12,21] Why, then, do the secondary alkyl zirconocenes prepared through transmetalation as described herein not isomerize to the primary organozirconium species?

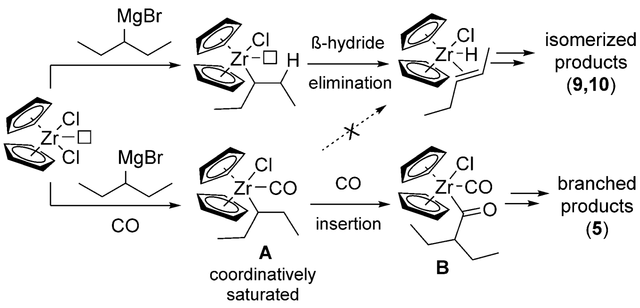


***Scheme 2.*** Product distribution observed for the carbonylative coupling through transmetalation versus hydrozirconation.

We hypothesized that the branched alkyl zirconocenes might be unable to isomerize under a CO atmosphere. To test this hypothesis, we compared the product distribution generated when transmetalation was performed under a CO versus an Ar atmosphere. Specifically, 3-pentylmagnesium bromide was treated with [$Cp_2ZrCl_2$] under a CO atmosphere according to our standard conditions. Copper-catalyzed allylation then generated the branched ketone **5** as described previously [Scheme 2, Eq. (1)]. In parallel experiments, transmetalation was performed under an Ar atmosphere. When the intermediate alkyl zirconium species was subsequently exposed to CO and then to the allylation conditions, complete isomerization was observed [Eq. (2)]. Ketone **5** was not formed, but instead the isomerized products **9** and **10** were obtained in good yield. As expected, hydrozirconation of either 1- or 2-pentene, followed by carbonylation and allylation, yielded the linear ketone **10** exclusively

[Scheme 2, Eq. (3)]. The ability of a CO atmosphere to maintain high branched selectivity is limited to the transmetalation protocol: hydrozirconation under a CO atmosphere failed to generate any of the desired product [Eq. (4)].

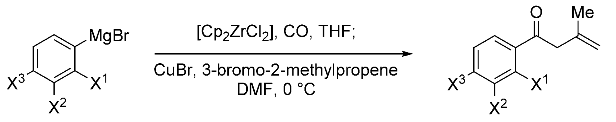
Carbon monoxide could prevent the isomerization of branched zirconocenes to the linear isomers through two potential mechanisms, which are not mutually exclusive. First, CO insertion could be irreversible and fast relative to isomerization. In this scenario, formation of the acyl zirconocene would outcompete isomerization.[22] Second, transmetalation under a CO atmosphere could form an 18 electron $[\mathrm{Cp_2Zr(CO)(alkyl)Cl}]$ complex. This intermediate lacks the open coordination site required for β-hydride elimination, which is the first step in the isomerization process. To study the mechanism of the transmetalation/CO insertion further, we performed an experiment designed to probe the reversibility of the CO insertion. Thus, 3-pentylmagnesium bromide was combined with $[\mathrm{Cp_2ZrCl_2}]$ under a CO atmosphere according to the standard reaction conditions. Next, the CO was purged with argon, and the presumed acyl zirconocene was stirred under argon for 2 h. Subsequent copper-catalyzed allylation provided only the branched ketone **5**. No evidence of decarbonylation or isomerization was noted. We interpret this result to suggest that CO insertion is effectively irreversible under the reaction conditions. Likewise, we note that CO inhibits hydrozirconation [see Eq. (4), Scheme 2]. The rate-limiting step in hydrozirconation is thought to be coordination of the olefin to $[\mathrm{Cp_2Zr(H)Cl}]$.[20a] Therefore, the inhibition by CO likely results from the formation of a coordinatively saturated $[\mathrm{Cp_2Zr(H)(CO)Cl}]$ complex. Similarly, CO may prevent the reverse of hydrozirconation—that is, β-hydride elimination—by forming a coordinatively saturated complex **A** (Scheme 3). Taken together, the results suggest that the CO atmosphere allows access to branched acyl zirconium intermediates, such as **B**, through rapid CO insertion and prevention of β-hydride elimination.



*Scheme 3.* Prevention by CO of the β-hydride elimination and isomerization of alkyl zirconocenes.

Hydrozirconation cannot generate aromatic acyl zirconocenes. For this reason, we wondered if aryl Grignard reagents could participate in the zirconium-mediated carbonylative coupling. Encouragingly, *ortho*-, *meta*-, and *para*-substituted aryl magnesium reagents performed equally well, and both electron-withdrawing and electron-donating groups were tolerated (Table 2).

*Table 2:* Carbonylative coupling of aryl Grignard reagents.[a]

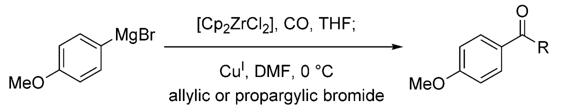


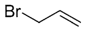
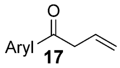
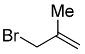
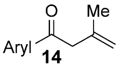
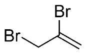
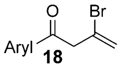
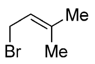
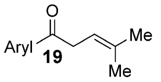
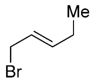
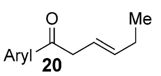
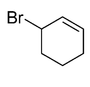
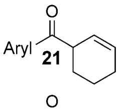
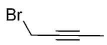
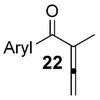
| Entry (product) | $X^1$ | $X^2$ | $X^3$ | Yield [%] |
|---|---|---|---|---|
| 1 (**11**) | H | H | H | 74 |
| 2 (**12**) | OMe | H | H | 72 |
| 3 (**13**) | H | OMe | H | 73 |
| 4 (**14**) | H | H | OMe | 77 |
| 5 (**15**) | H | H | *t*Bu | 70 |
| 6 (**16**) | H | H | F | 70 |

[a] Typical reaction conditions: R−MgBr (1 equiv, 1.0 mmol), $[\mathrm{Cp_2ZrCl_2}]$ (1.25 equiv, 1.25 mmol), THF (3 mL, including R−MgBr volume), followed by CuBr (0.10 equiv, 0.10 mmol), $\mathrm{H_2C{=}C(CH_3)CH_2Br}$ (2.0 equiv, 2.0 mmol), DMF (2 mL), 0 °C.

The generality of the carbonylative coupling was further defined by exploring various allylic and propargylic halides (Table 3).[23] Unsubstituted (product **17**), 2-substituted (products **14**, **18**), 3-substituted (product **20**), 3,3-disubstituted (product **19**), and 1,3-disubstituted allyl bromides (product **21**) were all viable coupling partners. For unsymmetrical allyl bromides, CuCl·2 LiCl provided higher ratios of the $\mathrm{S_N2}$ versus $\mathrm{S_N2'}$ product than CuBr (Table 3, entries 4 and 5). Exclusive selectivity was observed for the $\mathrm{S_N2'}$ product when

*Table 3:* Carbonylative coupling of (4-methoxyphenyl)magnesium bromide.[a]

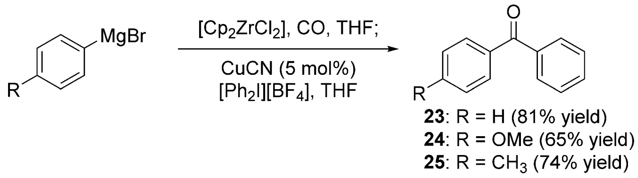


| Entry | Cu$^{\mathrm{I}}$[b] | R−Br | Product[c] | Yield [%] |
|---|---|---|---|---|
| 1 | CuBr |  |  | 71 |
| 2 | CuBr |  |  | 77 |
| 3 | CuBr |  |  | 74 |
| 4 | CuCl·2 LiCl |  |  | 74[d] |
| 5 | CuCl·2 LiCl |  |  | 77[e] |
| 6 | CuBr |  |  | 78 |
| 7 | CuBr |  |  | 70 |

[a] Reactions were carried out on a 1.0 mmol scale. See the Supporting Information for details. [b] CuBr was used in DMF; CuCl·2LiCl was used in THF. [c] Aryl = 4-methoxyphenyl. [d] Only the $\mathrm{S_N2}$ product was isolated. [e] An 88:12 mixture of $\mathrm{S_N2}$ and $\mathrm{S_N2'}$ products was obtained.

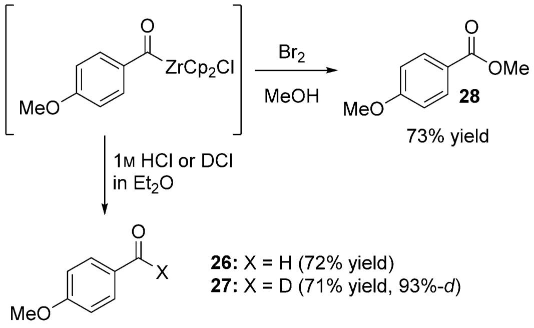
a propargyl bromide was used (product **22**). The coupling reaction itself was generally clean, but careful purification was required to avoid isomerization to the conjugated enone with the unsubstituted allyl group (product **17**) or elimination to form the allene with the vinyl bromide in the reaction in entry 3.[24]

To extend the carbonylative coupling to electrophiles beyond allyl and propargyl halides, we explored trapping the acyl zirconium species with iodonium salts.[9] Benzophenones are particularly important as photo-cross-linking moieties for target identification in drug discovery, so we evaluated the coupling of aryl Grignard reagents with phenyl iodonium tetrafluoroborate. Encouragingly, benzophenones **23**–**25** were formed in good yields in the presence of CuCN at ambient temperature (Scheme 4).



***Scheme 4.*** Carbonylative coupling of aryl Grignard reagents with iodonium salts.

Finally, the acyl zirconium intermediate could be converted into an aldehyde or ester. Surprisingly, protonation with water proved slow. However, quenching the reaction with HCl or DCl yielded the corresponding aldehydes **26** and **27** in good yield. Similarly, oxidation with bromine in methanol returned the methyl ester **28** (Scheme 5).[6]



***Scheme 5.*** Conversion of an acyl zirconocene into an aldehyde or ester.

Acyl zirconocenes are among the most synthetically useful acyl anion equivalents. They are partners in various C−C bond-forming reactions and precursors to diverse carbonyl compounds. Historically, acyl zirconocenes have been prepared exclusively through the hydrozirconation of alkenes and alkynes. Herein we have reported a significant expansion in the range of accessible acyl zirconocene complexes and demonstrated their synthetic utility. Transmetalation from branched, benzylic, and aryl Grignard reagents yielded previously inaccessible acyl zirconocenes that were shown to participate in carbonylative coupling. This discovery should find widespread applicability in the synthesis of complex molecules.

## Experimental Section

General procedure: A flame-dried vial was charged with [$Cp_2ZrCl_2$] (365 mg, 1.25 mmol), evacuated, and backfilled with CO. The zirconocene salt was dissolved in dry THF (3 mL) at room temperature, and the Grignard reagent (1 mmol) was added slowly to the suspension under a CO atmosphere. The reaction mixture was then stirred at room temperature for 4 h before anhydrous DMF (2 mL) was added. The reaction was then cooled to 0 °C, and the $Cu^I$ source (0.1 mmol) was added, followed by the allylic or propargylic bromide (2 mmol). The CO balloon was removed, and the reaction mixture was stirred at 4 °C overnight. After 12 h, the reaction was diluted with $H_2O$ and $Et_2O$. The aqueous layer was extracted with $Et_2O$, and the combined organic layers were washed with $H_2O$ and brine solution. The organic layer was dried with sodium sulfate, filtered, and concentrated. The residue was purified by silica-gel chromatography.

## Acknowledgements

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**Keywords:** carbonylation · carbonylative coupling · iodonium salts · isomerization · zirconium complexes

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[22] Bertelo and Schwartz describe the rate of CO insertion as "slow", but they were studying the CO insertion of preformed linear alkyl zirconocene complexes. Herein we are interested in the relative rate of CO insertion versus isomerization of a branched alkyl zirconocene to the linear form. CO insertion appears faster than isomerization. See Ref. [6].
[23] When 2 equivalents of (4-methoxyphenyl)magnesium bromide and 1 equivalent of [$Cp_2ZrCl_2$] were used under otherwise identical reaction conditions to those in Table 3, entry 3, the allylated product **18** was formed in a 1:0.2:0.05 ratio with the corresponding biphenyl and benzophenone, respectively (see the Supporting Information for details). When the reaction in entry 3 was carried out at room temperature, the yield decreased to 69%.
[24] See the Supporting Information for details.

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