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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 including aromatic rings, benzylic groups, and alkyl groups that possess a tertiary or quaternary carbon alpha to the carbon-zirconium bond. To provide more generalized access to acyl zirconium reagents, we explored transmetalation of Grignard reagents with zirconocene dichloride under a CO atmosphere. This protocol generates acyl zirconium (IV) complexes that are inaccessible using the Schwartz reagent, including those derived from secondary and tertiary alkyl and aryl Grignard reagents.

Graphical Abstract

Acyl zirconocenes [$\text{Cp}_2\text{ZrCl}(\text{COR})$] are valuable acyl anion equivalents in synthetic chemistry. Traditionally, they have been prepared through hydrozirconation of olefins or alkynes, precluding generation of aryl, benzyl, tertiary alkyl or branched acyl zirconocenes. Here we describe a Zr-mediated carbonylative coupling of Grignard reagents that involves previously inaccessible zirconocene intermediates.

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Keywords

Zirconocene; carbonylative coupling; isomerization; iodonium salts

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 additions, and halogenation.^[2,3,4,5] 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 -hydroxy ketones and 1,4-diketones, respectively.^[7] Additionally, they couple with aryl and allyl electrophiles under metal-mediated conditions.^[8, 9, 10] Enantio-selective transformations of acyl zirconocenes have been developed to generate optically active ketone derivatives.^[11]

Organozirconium reagents are generally prepared by hydrozirconation of olefins or alkynes. These hydrometalations are highly regioselective, generally providing the less hindered alkyl or vinyl zirconium intermediate.^[12] Indeed, hydrozirconation of internal olefins usually forms the terminal alkyl complex product 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 scope of available organozirconium reagents through transmetalation from readily available organometallic species. While 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.

We initiated our study by exploring transmetalation of Grignard reagents with zirconocene dichloride, Cp_2ZrCl_2 . This approach avoids the use of Schwartz reagent, which, while synthetically useful, is expensive and has a short bench life and poor solubility.^[13,14,15] Negishi and coworkers had previously demonstrated that *tert*-butyl and *iso*-butyl Grignard would react with zirconocene dichloride. However, the intermediate (alkyl)ZrClCp₂ underwent rapid loss of isobutylene to form $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ in situ.^[16,17,18] In other relevant work, 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 coworkers have developed an efficient Cu-catalyzed cross-coupling of acyl zirconocenes with allylic or propargylic halides to give allylic or allenic ketones.^[7] Building on this work, we successfully developed a carbonylative coupling of Grignard reagents with allyl and propargyl bromides. As shown in Table 1, alkyl Grignard reagents were treated with Cp_2ZrCl_2 under a CO atmosphere for 4 h at room temperature. The resultant acyl zirconocenes were stable up to 50 °C under a CO atmosphere and to filtration through Celite under air. Partial protonolysis was observed upon exposure to silica gel. Nonetheless, the acyl zirconocenes were used without any purification. Thus, addition of a representative allyl bromide and 10 mol% CuBr led to the formation of unsymmetrical ketones **1–8** in good yield (Table 1).

Primary, secondary, tertiary, cyclic, and benzylic organomagnesium reagents coupled successfully in the reaction. The ketones derived from benzylic and tertiary alkyl Grignard reagents are particularly noteworthy (entries 6, 7). These products could not be synthesized using traditional hydrozirconation; the intermediate (benzyl)zirconocene lacks β -hydrogens, rendering it inaccessible through hydrometalation. Likewise, hydrozirconation of isobutylene is slow and generates the *iso*-butyl organometallic rather than the *tert*-butyl reagent.^[17] Entries 1, 3–5 highlight ketones derived from branched Grignard reagents. Again, these products could not be accessed through hydrozirconation with Schwartz reagent because the linear isomers would dominate. Unfortunately, neopentyl Grignards 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 using directing groups or cationic zirconium reagents, although the linear products usually dominated.^[20] We were able to reverse the normal regioselectivity in 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 here not isomerize to the primary organozirconium species?

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 under an Ar atmosphere. Specifically, 3-pentyl magnesium bromide was treated with Cp_2ZrCl_2 *under a CO atmosphere* according to our standard conditions. Copper-catalyzed allylation generated the branched ketone **5** as described previously (eq 1). However, 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). Specifically, no ketone **5** was formed while 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 (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 desired product (eq 4).

Carbon monoxide could prevent 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 out compete isomerization.^[22] Second, transmetalation under a CO atmosphere could form an 18 electron $\text{Cp}_2\text{Zr}(\text{CO})(\text{alkyl})\text{Cl}$ 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. In particular, 3-pentyl magnesium bromide was combined with Cp_2ZrCl_2 under a CO atmosphere using the standard reaction conditions. Next, the CO was purged with argon, and the presumptive acyl zirconocene was stirred under argon for 2h. Subsequent Cu-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). The rate-limiting step in hydrozirconation is thought to be coordination of the olefin to $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$.^[23] Therefore, the inhibition by CO likely results from the formation of a coordinatively saturated $\text{Cp}_2\text{Zr}(\text{H})(\text{CO})\text{Cl}$ complex. Similarly, CO may prevent the reverse of hydrozirconation – ie β -hydride elimination – by forming a coordinatively saturated complex (Scheme 3, **A**). Taken together, the results suggest that the CO atmosphere allows access to branched acyl zirconium intermediates (**B**) through rapid CO insertion and prevention of β -hydride elimination.

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 donating groups were tolerated (Table 3).

The generality of the carbonylative coupling was further defined by exploring various allylic and propargylic halides (Table 4).^[24] Unsubstituted (**17**) 2-substituted (**14**, **18**), 3-substituted (**20**), 3,3-disubstituted (**19**) and 1,3-disubstituted (**21**) allyl bromides were all viable

coupling partners. For unsymmetrical allyl bromides, $\text{CuCl} \cdot 2\text{LiCl}$ provided higher ratios of the $\text{SN}2'$ vs. $\text{SN}2$ product than CuBr (entries 4, 5). Exclusive selectivity was observed for the $\text{SN}2'$ product using a propargyl bromide (**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 (**17**) or elimination to form the allene with the vinyl bromide in entry 3.^[25]

To extend the carbonylative coupling to electrophiles beyond allyl and propargyl halides, we explored trapping the acyl zirconium species with iodonium salts.^[26] 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).

Finally, the acyl zirconium intermediate could be converted to aldehydes or esters. Surprisingly, protonation with water proved slow. However, quenching the reaction with HCl or DCI yielded the corresponding aldehydes **26** and **27** in good yield. Similarly, oxidation with bromine in methanol returned the methyl ester **28**.^[6]

Acylzirconocenes 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, acylzirconocenes have been prepared exclusively through hydrozirconation of alkenes and alkynes. Here we report a significant expansion in the range of accessible acyl zirconocene complexes and demonstrate their synthetic utility. Transmetalation from branched, benzylic, and aryl Grignard reagents yields previously inaccessible acyl zirconocenes that are shown to participate in carbonylative coupling. This discovery should find widespread applicability in the synthesis of complex molecules.

Experimental Section

General procedure for formation of acyl-zirconocene and copper-mediated coupling: 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 rt for 4 hours before anhydrous DMF (2 mL) was added. The reaction was then cooled to 0°C and the Cu(I) (0.1 mmol) source was then added followed by the allylic or propargylic bromide (2 mmol). The CO balloon was removed and the reaction 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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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22. Bertelo and Schwartz describe the rate of CO insertion as ‘slow’, but they were studying the CO insertion of pre-formed linear alkyl zirconocene complexes. Here we are interested in the relative rate of CO insertion vs. isomerization of a branched alkyl zirconocene to the linear form. CO insertion appears faster than isomerization. See ref 6.
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24. When 2 equiv (4-methoxyphenyl)MgBr and 1 equiv Cp₂ZrCl₂ were used under otherwise identical reaction conditions to those in Table 4 entry 3, allylated product 18 was formed in a 1:0.2:0.05 ratio with the corresponding biphenyl and benzophenone, respectively. See supporting information for details. When the reaction of entry 3 was carried out at room temperature, the yield decreased to 69%.
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Traditional hydrozirconation:

This work:

Scheme 1.

Synthesis and reactivity of acyl zirconocene. E⁺ = electrophile.

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Scheme 3.

CO prevents β -hydride elimination and isomerization of alkyl zirconocenes.

Scheme 4.

Carbonylative coupling of aryl Grignard reagents with iodonium salts.

Scheme 5.

Conversion of acyl zirconocene to aldehydes or esters.

Table 1Carbonylative 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

Entry	Product	Yield (%) ^[b]
8	8	trace

^[a] Reaction carried out on a 1.0 mmol scale. See Supporting Information for details.

^[b] isolated yield.

DMF = dimethylformamide, THF = tetrahydrofuran.

Table 3Carbonylative coupling of aryl Grignard reagents^[a]

Entry	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	<i>t</i> -Bu	70
6 (16)	H	H	F	70

^[a]Typical conditions: R-MgBr (1 equiv, 1.0 mmol), Cp₂ZrCl₂ (1.25 equiv, 1.25 mmol), THF (3 mL including R-MgBr volume) followed by CuBr (0.10 equiv, 0.10 mmol), H₂C=C(CH₃)CH₂Br (2.0 equiv, 2.0 mmol), DMF (2 mL), 0 °C.

Table 4Carbonylative coupling of 4-methoxyphenyl magnesium bromide^[a]

Entry	Cu(I) ^[b]	R-Br	Product ^[c]	Yield (%)
1	CuBr		 17	71
2	CuBr		 14	77
3	CuBr		 18	74
4	CuCl·2LiCl		 19	74 ^[d]
5	CuCl·2LiCl		 20	77 ^[e]
6	CuBr		 21	78
7	CuBr		 22	70

^[a]Reaction carried out on a 1.0 mmol scale. See Supporting Information for details^[b]CuBr used in DMF; CuCl·2LiCl used in THF

[c] Aryl = 4-methoxyphenyl [d] Solution in THF. See Supporting Information for details.

[d] Only SN2 product isolated

[e] 88:12 mixture SN2 vs. SN2' product.