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Organozinc Generation via the Titanium-Catalyzed Activation of Alkyl Halides

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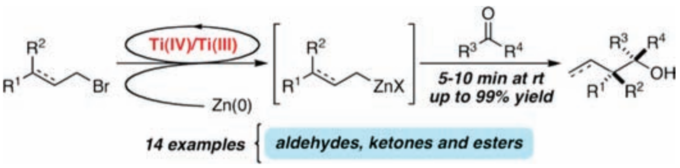
ABSTRACT



A protocol for the generation of organozinc reagents via catalytic activation of alkyl halides is described herein. Subsequent nucleophilic addition to carbonyl derivatives provided the desired products in good to excellent yields (76−99%). Evidence suggests that titanocene dichloride catalyzes the formation of an organozinc species. This discovery will have wide ranging applicability in the generation of highly reactive organometallic reagents.

The formation of reactive organometallic reagents often requires vigorous conditions or the preactivation of low valent metals, as in the Rieke metals of zinc[1] and magnesium.[2] In general, there are few mild, catalytic methods to generate stoichiometric quantities of highly reactive organometallics from alkyl halides.[3] Recently, Krische has introduced a powerful iridium-catalyzed hydrogenative carbonyl allylation employing 1,3-dienes,[4] allenes,[5] and allyl acetates[6] as allylmetal precursors. Alternatively, we considered the possibility of *catalytically* activating alkyl halides for the *stoichiometric* in situ generation of highly reactive organometallics. Rather than focus on activating the metal to facilitate the reduction of alkyl halides, our approach was to develop a protocol in which the *alkyl halide* is catalytically activated by an early transition metal complex. Transmetalation will then provide an organometallic reagent with a broader reactivity profile. We identified titanium as well suited for our purpose due to its excellent chemoselectivity, low electronegativity, inexpensiveness, and minimal toxicity.[7] Our procedural design involves formation of a $R{-}Ti^{IV}L_n$ from $R{-}X$ followed by zinc-mediated reduction of titanium to provide a transient $R{-}Ti^{III}L_n$ intermediate (Scheme 1).[8] Transmetalation to Zn(II) yields a stoichiometric amount of $RZn^{II}X$ and regenerates the catalytically active $Ti^{III}L_n$. This method can provide stoichiometric quantities of highly reactive organometallics under mild conditions without the need for an activated metal and can even be performed in the presence of the desired electrophile. The metalation occurs at or below room temperature to circumvent chemose-

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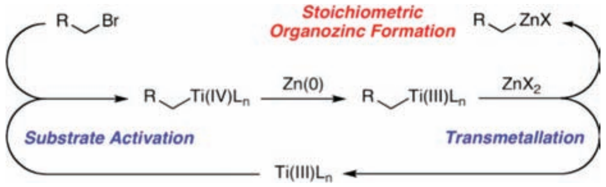
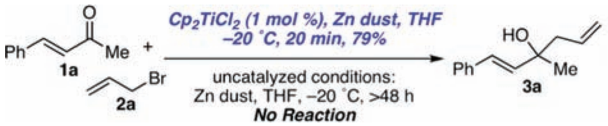
10.1021/ol902374v

Scheme 1. Titanium-Catalyzed Organozinc Formation



lectivity issues that may arise from conventional methods of alkylmetal formation. Inspired by the previous work of Ding,[9] and more recently Gansauer,[10] on titanocene-catalyzed carbon−carbon bond formations, we began by exploring in detail the reactivity observed by the combination of Cp_2TiCl_2 and zinc dust.

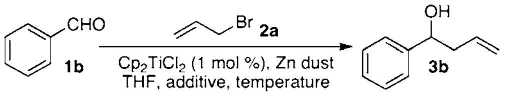
To evaluate our hypothesis, we chose to examine the formation of allylzinc intermediates and their use in carbonyl addition reactions.[11] The allylation of carbonyl derivatives is of fundamental importance to the field of organic synthesis, as it constitutes one of the principal methods for constructing polyketides.[12] Although remarkable advances in the stereo- and chemoselectivity of allylation protocols have occurred over the past four decades,[13] the pregeneration of stoichiometric organometallic species can be problematic.[14] Beginning with the seminal publications of Umani-Ronchi,[15] Keck,[16] and Denmark[17] on chiral Lewis acid-catalyzed allylations, whose methods require the stoichiometric pregeneration of organometallic reagents, and arriving at the work of Krische on the catalytic generation of allyliridium intermediates from 1,3-dienes,[2] the field of allylation has experienced a number of truly groundbreaking advances. However, a mild method by which an allyl halide can be activated catalytically for stoichiometric metalation in the presence of the carbonyl substrate has yet to be developed.[1,18] This method would ultimately allow for the formation of highly reactive allylmetal reagents in the presence of sensitive functionality often encountered complex total synthesis. Although allyltitanium(IV) complexes are known to undergo addition to aldehydes smoothly, ketones often require longer reaction times and elevated temperatures.[9,19] Therefore, this transformation would be an ideal testing ground for the metalation procedure illustrated in Scheme 1. Thus, addition of enone **1a** and allyl bromide (**2a**) to a mixture of zinc dust and 1 mol % of Cp_2TiCl_2 yielded alcohol **3a** in 79% yield at −20 °C and 99% in a mere 5 min at room temperature (eq 1). Titanium plays a clear role in the reaction, as is evidenced by the quantitative recovery of enone **1a** in the absence of Cp_2TiCl_2 at −20 °C. With this observation in hand, we sought to gain insight into the scope and mechanism of this titanium-catalyzed metalation protocol.



(1)

During our optimization studies with benzaldehyde (**1b**), we observed that the temperature of the reaction had a profound effect on the overall efficiency (Table 1). Excellent yields were obtained in 5−10 min at temperatures as low as −20 °C (entries 1 and 2), but at −40 °C the reaction failed completely, leading to recovered starting material (entry 3). However, we discovered that upon addition of 5 mol % PPh_3 catalytic activity was restored and alcohol **3b** was obtained in 96% yield (entry 4). A similar effect was witnessed with the trialkyl phosphine PCy_3 and bisphosphines dppp and (±)-

Table 1. Temperature and Additive Effects[20]



entry	additive (5 mol %)	temperature	yield (%)
1	-	0 °C	95
2	-	−20 °C	91
3	-	−40 °C	NR[a]
4	PPh_3	−40 °C	96
5	PCy_3	−40 °C	95
6	dppp	−40 °C	99
7	(±)-BINAP	−40 °C	98
8	PCy_3	−78 °C	NR[a]

[a] Reaction was run for ≥48 h.

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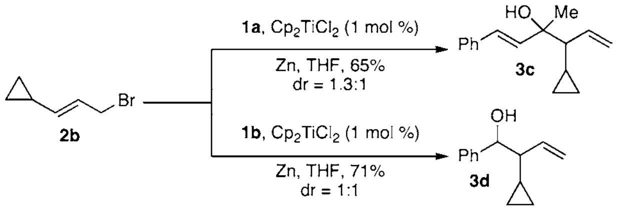
BINAP. Further cooling of the reaction to −78 °C resulted in no reaction. At this time, the role of the phosphine additive, and the effect it has on the metalation step, is unclear but appears to be quite general and a useful modification for performing the desired metalation at lower temperatures.

Given the extremely facile allylation depicted in eq 1, we initially set out to determine the role of titanium and zinc and the nature of the reactive organometallic reagent in the carbon−carbon bond-forming event. The pregeneration of $Cp_2Ti^{III}Cl$ from $Cp_2Ti^{IV}Cl_2$ and Zn(0) is required, as no reaction is observed without this initial reduction event. Allylation of enone **1a** with allyl bromide and zinc dust in the absence of $Cp_2Ti^{IV}Cl_2$ took substantially longer (>6 h) to reach full conversion, but the use of more reactive allyl iodide resulted in alcohol **3a** in 68% yield after 60 min.

Additionally, we observed no reaction with stoichiometric $Cp_2Ti^{III}Cl$ in the absence of zinc dust after prolonged reaction times (>24 h). These results indicate that *both* titanium and zinc participate in the allylation to achieve the levels of reactivity observed. We next considered the possibility that $ZnCl_2$, the byproduct of $Cp_2Ti^{IV}Cl_2$ reduction with Zn(0), could be acting as a Lewis acid in the addition of an allyltitanium(III) intermediate.[1] However, the addition of $ZnCl_2$ to allyl bromide, enone **1a**, and stoichiometric $Cp_2Ti^{III}Cl$ failed to provide alcohol **3a**.[21] These results support our hypothesis that although an allyltitanium(IV) reagent is formed a transmetalation event from an allyltitanium(III) species must occur.[22] The involvement of an allylzinc species is corroborated by the observation that the addition of allylzinc chloride[23] to enone **1a** yields alcohol **3a** in 98% yield, and allylation of 4-*t*-butylcyclohexanone provides the corresponding homoallyl alcohol in a syn/anti ratio of 6:1. These results are consistent with addition of an allylzinc reagent[24] and not an allyltitanium complex (dr = 2:1).[14b] Additionally, the use of manganese as the reducing metal gave quantitative recovery of enone **1a**, lending more weight to the intermediacy of an allylzinc species.

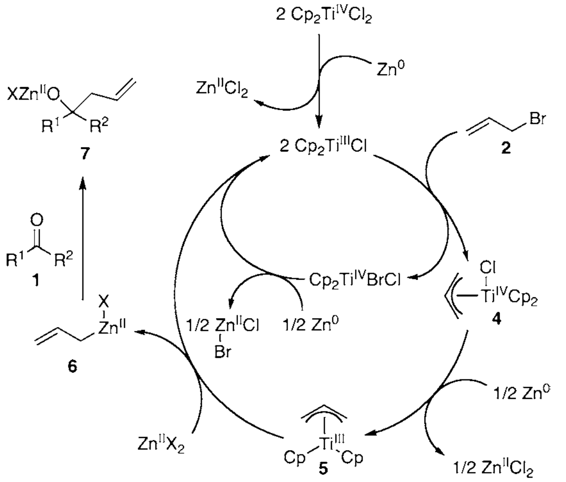
Although these results provide compelling support for the general mechanism depicted in Scheme 1, further evidence for two rapid single electron reductions of allyl bromide by $Cp_2Ti^{III}Cl$ was obtained by the examination of vinylcyclopropane **2b** as the allylmetal precursor (Scheme 2).[25] If the substrate were to demonstrate radical character en route to metalation, we would expect to see strain-driven ring expansion of the cyclopropane. However, if titanium induces an inner sphere reduction of the allyl bromide followed by rapid radical−radical annihilation, the cyclopropane ring should remain intact throughout the metalation process. Treatment of **2b** and either enone **1a** or benzaldehyde (**1b**) to Cp_2TiCl_2 (1 mol %) and Zn(0) cleanly provided alcohols **3c** and **3d**, respectively, absent any evidence of cyclopropane ring opening.

Scheme 2. Cyclopropyl Allyl Bromide Metalation



On the basis of our findings, it appears unlikely that the Lewis acidic properties of zinc or titanium alone are responsible for the overall efficiency of the allylation and that $Cp_2Ti^{III}Cl$ must be participating in the formation of a more reactive allylzinc species. Thus, a proposed mechanism is illustrated in Scheme 3.[26] Initial reduction of $Cp_2Ti^{IV}Cl_2$ is followed by metalation of bromide (**2**) to yield allyl-Ti^{IV} **4**.[27] Reduction to allyl-Ti^{III} **5**[6,28] facilitates transmetalation to zinc, thereby providing allylzinc **6**, which reacts rapidly with substrate **1** and regenerates titanocene(III). It should be noted that although titanium is not depicted as involved in the carbon−carbon bond-forming event, it may serve a secondary role as a Lewis acid.

Scheme 3. Proposed Catalytic Cycle



We next sought to explore the scope of this method by examining a series of carbonyl derivatives (Table 2). Electron-rich, electron-poor, and aliphatic aldehydes, even

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[20] A representative procedure can be found in the Supporting Information.

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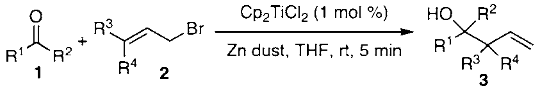
Table 2. Titanium-Catalyzed Allylation of Ketones and Esters[19]



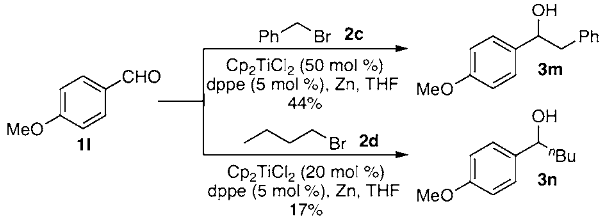
entry	R^1	R^2	**2**	R^3	R^4	**3**	yield (%)
1	p-$Me_2N{-}C_6H_4$ (**1d**)	H	**2a**	H	H	**3e**	91
2	p-$MeO_2C{-}C_6H_4$ (**1e**)	H	**2a**	H	H	**3f**	90
3	n-hexyl (**1f**)	H	**2b**	Me	Me	**3g**	82
4	o-HO-C_6H_4 (**1g**)	H	**2a**	H	H	**3h**	97
5	p-MeO-$C_6H_4CH{=}CH$ (**1h**)	Me	**2a**	H	H	**3i**	91
6	p-$CF_3{-}C_6H_4CH{=}CH$ (**1i**)	Me	**2a**	H	H	**3j**	92
7	c-$C_3H_5CH{=}CH$ (**1j**)	Me	**2b**	Me	Me	**3k**	97
8	p-MeO-$C_6H_4CH{=}CH$ (**1k**)	OEt	**2a**	H	H	**3l**	87[a]

[a] Reaction time = 3 h. $R^2 = CH_2CH{=}CH_2$ for product **3l**.

those containing free phenols, underwent allylation in <5 min (entries 1−4). Ketone allylation mediated by transition metal complexes, such as in chromium-catalyzed Nozaki−Hiyama−Kishi reactions, can be problematic.[29] However, in the presence of Cp_2TiCl_2 (1 mol %) and Zn(0), ketones and esters underwent rapid allylation in excellent yields (entries 5−8).

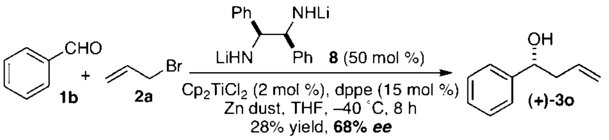
Not surprisingly, the metalation of benzyl and aliphatic bromides proved more difficult. Zincation of benzyl bromide (**2c**) in the presence of aldehyde **1l**, Cp_2TiCl_2, zinc dust, and 1,2-bis(diphenylphosphino)ethane (dppe) (5 mol %) provided alcohol **3m** in 44% yield (Scheme 4). To achieve an alkylzinc formation, it was necessary to increase the titanocene catalyst loading to 50 mol %. Addition of dppe appears to increase the rate of metalation in a similar fashion to that illustrated by Table 1. Substituting 1-bromobutane (**2d**) for benzyl bromide gave alcohol **3n** but in diminished yield. Increasing the amount of titanocene resulted in substantial pinacol coupling production.

Scheme 4. Benzyl and Aliphatic Organozinc Formation



Our observation that phosphine additives facilitate low-temperature metalation led us to hypothesize that an enantioselective allylation with a highly reactive allylmetal reagent could be performed with a catalytic amount of chiral ligand. We reasoned that this could be achieved by controlling the reaction temperature such that only the ligand-bound reagent would undergo carbonyl addition.

By controlling the reaction temperature, the unselective background reaction can be minimized. Thus, the addition of benzaldehyde and allyl bromide to a mixture of lithiated diamine **8** (50 mol %), Cp_2TiCl_2 (2 mol %), dppe (15 mol %), and Zn(0) at −40 °C for 8 h provided alcohol (+)-**3o** in 68% ee.[30] Interestingly, the direct use of a chiral phosphine or chiral titanocene proceeded with no selectivity. This result demonstrates that a substoichiometric amount of chiral ligand can be successfully used for the enantioselective addition of a highly reactive organometallic reagent, even when generated in the presence of a carbonyl substrate.



(2)

In conclusion, an efficient titanium-catalyzed metalation procedure is described. This method allows for the mild, stoichiometric production of highly reactive organometallic reagents utilizing a titanocene-catalyzed approach toward substrate activation. The procedure described herein represents a unique opportunity to confront the challenges of generating organometallic reagents with broad reactivity profiles in the company of sensitive functional groups. These studies, their applications in new carbon−carbon bond-forming transformations, expanding the scope to new organometallic reagents, and the development of an improved enantioselective protocol are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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