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Generation of allyl Grignard reagents via titanocene-catalyzed activation of allyl halides

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ABSTRACT

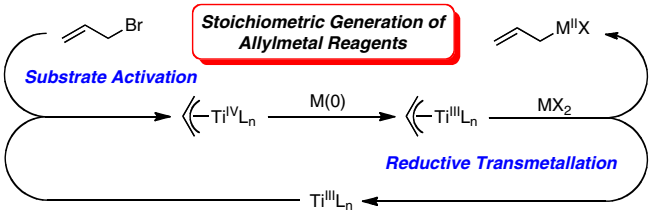
A protocol for the generation of allyl Grignard reagents via the catalytic activation of allyl halides is described herein. Subsequent nucleophilic addition to carbonyl derivatives provided the desired homo allylic alcohols in excellent yields (84–99%). Evidence suggests that titanocene dichloride catalyzes the formation of an allyl Grignard species which reacts solely with the carbonyl electrophile as evidenced by the complete absence of Würtz coupling. This methodology will have wide-ranging applicability in the generation of highly reactive organometallic reagents.

Given the ready availability of organohalides, metallation of carbon-halogen bonds with magnesium is still one of the most common methods of generating highly reactive organomagnesium reagents.[1] Quite possibly the most useful and well-known of the main group organometallics are Grignard reagents.[2–4] Although the synthetic utility of Grignard reagents is undeniable, their preparation can be rather tenuous.[5] Conventional methods rely on the initiation of magnesium turnings or powder with iodine or dibromoethane, or the use of highly reactive, pre-activated Rieke® magnesium.[6] All too often, these conditions are unsuitable for highly functionalized substrates, and even the generation of simple Grignard reagents can be complicated by homocoupling and degredation.[7] The generation of allyl Grignard reagents can be especially difficult due to their propensity to undergo Würtz coupling, resulting in a low yield of the desired organometallic species.[8] To circumvent these issues, we surmised that the allyl halide itself could be activated in a catalytic fashion by a titanocene complex in the presence of magnesium turnings for an efficient, high-yielding generation of allyl Grignard reagents, even in the presence of carbonyl electrophiles (Scheme 1).[9,10] We have recently reported the successful implementation of this reductive transmetallation protocol in the generation of organozinc reagents via the titanocene-catalyzed activation of alkyl halides.[10]

It is our contention that the titanocene-catalyzed method for the generation of organozinc reagents[11] could be expanded to include other organometallic reagents with broad reactivity profiles by simply exchanging the reducing metal to provide the desired organometallic reagent. We hypothesized that Grignard reagents could be generated in a mild and efficient manner utilizing our reductive transmetallation protocol by employing magnesium turnings as the reductant. Herein, we describe its successful implementation toward the facile generation of allyl Grignard reagents.

To test this hypothesis, we began by examining the allylation of simple ketones with allyl bromide in the presence of a titanocene catalyst and unactivated magnesium turnings. Thus, we were gratified to see that when a solution of enone **1a** and allyl bromide (**2a**) was treated with Cp_2TiCl_2 (1 mol %) and magnesium turnings (1.5 equiv) alcohol **3a** was obtained in 99% yield at room temperature after only 10 min (Eq. 1). Based on the reported slow rate at which allyltitanocene reagents undergo addition to ketones, this result would seem to indicate that the allyl bromide underwent a rapid metallation event to generate the corresponding allyl Grignard reagent, even in the presence of enone **1a**.[9g]

Although, allyl bromide underwent metallation rapidly at room temperature, we quickly discovered that the efficiency of the process was highly dependent on the nature of the halogen. Both allyl chloride and allyl iodide required gentle heating (50 °C) to reach completion, but still provided the desired adduct in 88% and 56% yield, respectively, (Eq. 1). The low yield of the allylation with allyl iodide is intriguing in that often this species is not a good metallation substrate due to the propensity for Würtz-coupling byproducts. However, considering that the 1,5-diene that would result from this unproductive side reaction was not observed, the lower



Scheme 1. Titanium-catalyzed allyl halide activation.

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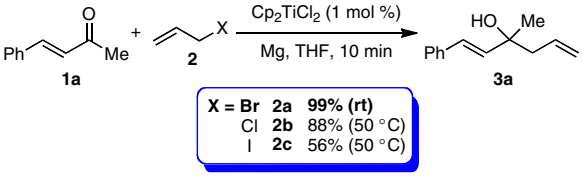
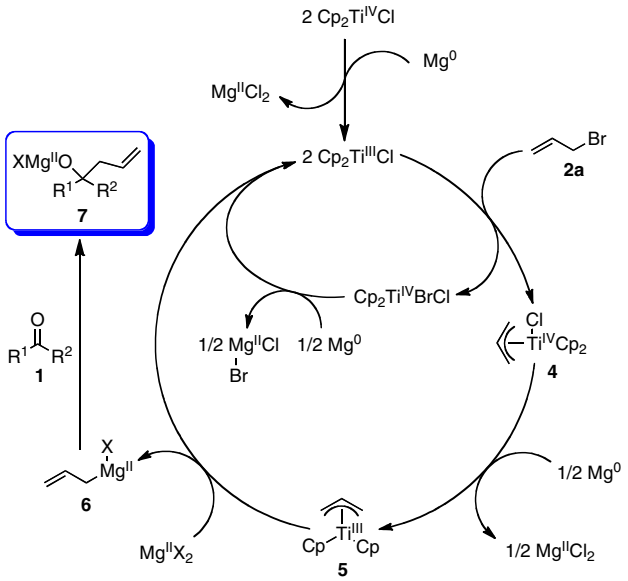
yield of allyl alcohol **3a** may be due to an inherent instability of the iodo allyltitanocene intermediates. Likewise, the lower yield when employing allyl chloride as the organometallic reagent precursor is likely the result of an inefficient initial metallation coupled with the thermal instability of low valent titanocene complexes. Based on this supposition, it did not come as a surprise that allyl acetate led to a quantitative recovery of the starting materials. Increasing the reaction concentration failed to provide an improvement.



(1)

Based on our empirical observations and previous mechanistic work with zinc as the reducing metal, a catalytic cycle for the titanocene-catalyzed activation/metallation procedure is proposed (Scheme 2).[10] Initial reduction of Cp_2TiCl_2 to Cp_2TiCl by Mg(0) precedes metallation of allyl bromide to yield the allyltitanium(IV) species **4**. A second reduction of (allyl)Ti(IV) **4** to (allyl)Ti(III) **5** enables the transmetallation to magnesium thereby generating a stoichiometric quantity of the allyl Grignard **6**. The titanocene(III) complex that is released can then re-enter the catalytic cycle and react with another equivalent of allyl bromide (**2a**). Finally, addition of the allyl Grignard reagent **6** to the carbonyl substrate **1** leads to the observed allylation product following protonation of magnesium alkoxide **7**.

The efficiency of the reductive transmetallation of allyl bromide with catalytic titanocene and magnesium turnings proved sensitive to the reaction temperature in a similar fashion to what we observed with the in situ generation of organozinc reagents (Table 1).[10] The titanocene-catalyzed activation/metallation/allylation sequence proceeded rapidly, and in near quantitative yield, when performed at room temperature or 0 °C (entries 1 and 2). If the reaction was cooled to −20 °C, allylic alcohol **3a** was obtained in a diminished 74% yield (entry 3). Interestingly, when the reaction was cooled further to −40 °C, the reductive transmetallation process appeared to completely shutdown, resulting in a near quantitative recovery of the starting enone **1a** (entry 4). However, the addition of 5 mol % 1,3-bis(diphenylphosphino)propane (dppp) restored the catalytic activity at −40 °C to provide alcohol **3a** in 98% yield after only 20 min. Similar results were obtained with various other phosphine additives.[12] This unusual effect which the addition of phosphines has on the metallation was also observed with zinc dust as the reducing metal when generating organozinc reagents. Although it is unclear what role phosphine is playing in the metallation event, the step in the catalytic cycle to benefit most from phosphine additives at low temperatures would be the reduction of allyltitanocene(IV) to allyltitanocene(III). However, any determination at this stage would be premature.



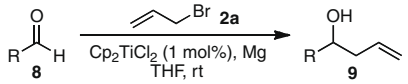
Scheme 2. Proposed catalytic cycle.

Table 1
Temperature and additive effect on metallation

Entry	Temp (°C)	Additive	Time (min)	Yield (%)
1	rt	—	5	>99
2	0	—	5	99
3	−20	—	10	74 (94)[a]
4	−40	—	300	NR
5	−40	5 mol % dppp	20	98

[a] Yield in parentheses based on recovered starting material.

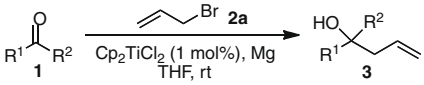
Table 2
Allylation of aldehydes[a]



Entry	Aldehyde	Yield (%)
1	Benzaldehyde (**8a**)	93
2	4-Tolualdehyde (**8b**)	94
3	4-Anisaldehyde (**8c**)	95
4	4-Dimethylaminobenzaldehyde (**8d**)	>99
5	4-Trifluoromethylbenzaldehyde (**8e**)	84
6	4-Chlorobenzaldehyde (**8f**)	96
7	4-Fluorobenzaldehyde (**8g**)	87
8	(*E*)-Cinnamaldehyde (**8h**)	>99
9	(*E*)-Crotonaldehyde (**8i**)	88
10	Cyclohexylcarboxaldehyde (**8j**)	87
11	Hexanal (**8k**)	91

[a] Allylation reactions were carried out using 0.8 mmol **8**, 0.96 mmol **2a**, 1 mol % Cp_2TiCl_2, and 1.2 mmol Mg turnings in THF (0.1 M) at room temperature for 10–30 min.

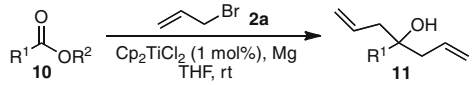
Table 3
Allylation of ketones[a]



Entry	Ketone	Yield (%)
1	Acetophenone (**1b**)	97
2	(*E*)-4-MeO–C_6H_4–CH=CH–C(O)CH_3 (**1c**)	97
3	(*E*)-2-HO–C_6H_4–CH=CH–C(O)CH_3 (**1d**)	99
4	(*E*)-4-CF_3–C_6H_4–CH=CH–C(O)CH_3 (**1e**)	97
5	(*E*)-4-Cl–C_6H_4–CH=CH–C(O)CH_3 (**1f**)	96
6	(*E*)-*c*-C_6H_{11}–CH=CH–C(O)CH_3 (**1g**)	94
7	(*E*)-*c*-C_3H_5–CH=CH–C(O)CH_3 (**1h**)	96
8	2-Cyclohexenone (**1i**)	98
9	Me_2C=CH–C(O)CH_3 (**1j**)	97
10	Me_2C=CH–C(O)C_6H_5 (**1k**)	94
11	4-*tert*-Butylcyclohexanone (**1l**)	94[b]

[a] Reaction conditions: 0.8 mmol **1**, 0.96 mmol **2a**, 1 mol % Cp_2TiCl_2, and 1.2 mmol Mg in THF (0.1 M) at room temperature for 10–30 min.
[b] *syn*/*anti* = 1.3:1.

Table 4
Diallylation of esters[a]



Entry	Ester	Yield (%)
1	(*E*)-PhCH=CHCO$_2$Me (**10a**)	96
2	2-Me-C$_6$H$_4$CO$_2$Me (**10b**)	93
3	(*E*)-4-MeO–C$_6$H$_4$CH=CHCO$_2$Me (**10c**)	92
4	(*E*)-4-Cl–C$_6$H$_4$CH=CHCO$_2$Me (**10c**)	97

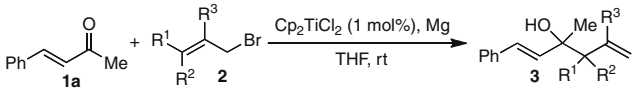
[a] Reaction conditions: 0.4 mmol **10**, 1.0 mmol **2a**, 1 mol % Cp_2TiCl_2, and 1.2 mmol Mg in THF (0.1 M) at room temperature for 30–90 min.

In an effort to establish the scope and versatility of the titanocene-catalyzed Grignard generation, a series of aldehydes were examined for their propensity to provide the corresponding homoallylic alcohols by treatment with allyl bromide (**2a**) (Table 2). Both electron-rich and electron-deficient benzaldehyde derivatives proved to be excellent substrates providing benzylic alcohols in high yield (entries 1–7). α,β-Unsaturated aldehydes underwent 1,2-allylation to yield the corresponding allylic alcohols (entries 8 and 9), and aliphatic aldehydes also proved to be viable substrates (entries 10 and 11).

The titanocene-catalyzed allyl halide activation protocol proved just as reliable for the allylation of ketones, providing exceptional yields of the desired homoallylic alcohols (Table 3).[13] Benzyl derivatives (electron rich and electron deficient) and α,β-unsaturated ketones underwent allylation in excellent yields (entries 1–10). The allylation of ketone **1d** is particularly noteworthy in that the presence of the free ortho-phenol moiety did not hinder the allylation event (entry 3). Aliphatic ketones were also viable substrates as is evidenced by the allylation of 4-*t*-butylcyclohexanone to provide alcohol **3l** in 94% yield and a *syn*/*anti* ratio of 1.3:1 (entry 11). This diastereomeric outcome is consistent with the addition of an allyl Grignard reagent and not an allyltitanocene(IV) species.[14,15]

We next examined the titanocene-catalyzed generation of allyl Grignard reagents in the presence of ester derivatives (Table 4). This class of substrates is particularly interesting due to their resistance to nucleophilic attack by allyltitanocene(IV) reagents. A series of α,β-unsaturated esters were examined, and in each case an excellent yield (⩾92%) of the diallylation product was observed. Regardless of the substrate or relative amount of allyl halide and magnesium used, the diallylation products were obtained exclusively. These results lend support to our hypothesis that the active allylmetal reagent is not an allyltitanocene(IV) derivative, but rather the more reactive allyl Grignard species.

Table 5
Effect of allyl substitution[a]



Entry	Allyl bromide	R^1	R^2	R^3	Yield (%)
1	**2b**	Me	Me	H	91
2	**2c**	Me	H	H	89[b]
3	**2d**	Ph	H	H	91[b]
4	**2e**	H	H	Me	95

[a] Allylation reactions were carried out using 0.8 mmol **1a**, 0.96 mmol **2a**, 1 mol % Cp_2TiCl_2, and 1.2 mmol Mg turnings in THF (0.1 M) at room temperature for 20 min.
[b] *syn*/*anti* = 1:1.

Next, we examined the effect that the substitution on the allyl moiety had on the regiochemical outcome of the allylation (Table 5). In particular, we were intrigued to see whether allylmetal reagents generated in situ would undergo addition to ketone **1a** in an S_E2 or S_E2' fashion. Treatment of prenyl bromide (**2b**) and ketone **1a** to our titanocene-catalyzed Grignard generation protocol resulted in clean S_E2' 1,2-addition, despite the sterically hindered gem-dimethyl motif, to provide the corresponding alcohol in 91% yield (entry 1). Crotyl (**2c**) and cinnamyl (**2d**) bromides also underwent S_E2' addition, resulting in homoallyl alcohols in 89% and 91% yield, respectively (entries 2 and 3). Substitution at the 2-position of the allyl motif, as demonstrated by methallyl bromide (**2e**), did not diminish the efficiency of the allylation event (entry 4).

In conclusion, we have demonstrated that Würtz-coupling byproducts in the stoichiometric generation of allyl Grignard reagents can be avoided under very mild conditions through the catalytic activation and subsequent reductive transmetallation of the corresponding allyl halide in the presence of 1 mol % Cp_2TiCl_2 and unactivated magnesium turnings. The conditions described herein allow for the in situ allylation of a wide variety of carbonyl derivatives, including aldehydes, ketones, and esters, in excellent yield within minutes at room temperature. This protocol effectively circumvents the traditional use of carcinogenic activators and often exothermic conditions required for Grignard reagent generation. Further, examination of the scope, mechanistic studies to elucidate the effect of phosphine additives on the metallation process, and the development of an enantioselective protocol are in progress, and will be reported in due course.

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Supplementary data

Supplementary data (detailed experimental procedures and spectral data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.144.

References and notes

1. (a) Ashby, E. C.; Laemmle, J. T.; Neumann, H. M. *Acc. Chem. Res.* **1974**, *7*, 272; (b) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521; (c) Shirley, D. A. *Org. React.* **1954**, *8*, 28; (d) Huryn, D. M. *Comp. Org. Syn.* **1991**, *1*, 49; (e) Gradén, H.; Kann, N. *Curr. Org. Chem.* **2005**, *9*, 733.
2. Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; (b)*Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcell Dekker: New York, 1996.
3. For recent reviews on allylations, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207; (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763; (c) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34; (d) Tietze, L. F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367.
4. For reviews on allyl metal carbonyl additions, see: (a) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732; (b) Roush, W. R. *Actual. Chim.* **2004**, 21; (c) Hall, D. G. *Synlett* **2007**, 1644.
5. (a) Ward, H. R.; Lawler, R. G.; Marzilli, T. A. *Tetrahedron Lett.* **1970**, *11*, 521; (b) Ashby, E. C.; Laemmle, J.; Neumann, H. M. *Acc. Chem. Res.* **1974**, *7*, 272; (c) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545; (d) Maeda, K.; Shinokuno, H.; Oshima, K. *J. Org. Chem.* **1996**, *61*, 6770; (e) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, 3955; (f) Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*, 1801; (g) Rottlander, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080; (h) Inoue, A.; Shinokubu, H.; Oshima, K. *Synlett* **1999**, 1582; (i) Inoue, A.; Shinokubu, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 651.
6. (a) Rieke, R. D.; Hudnall, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 7178; (b) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674; (c) Rieke, R. D.; Xiong, H. *J. Org. Chem.* **1991**, *56*, 3109.
7. Hoffmann, R. W.; Knopff, O.; Kusche, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1462.
8. (a) DeWolfe, R. H.; Young, W. G. *Chem. Rev.* **1956**, *56*, 753; (b) Hutchison, D. A.; Beck, K. R.; Benkeser, R. A.; Grutzner, J. B. *J. Am. Chem. Soc.* **1973**, *95*, 7075; (c)

Hill, E. A.; Boyd, W. A.; Desai, H.; Darki, A.; Bivens, L. *J. Organomet. Chem.* **1996**, *514*, 1.
9. (a) Ding, Y.; Zhao, G. *J. Chem. Soc., Chem. Commun.* **1992**, 941; (b) Ding, Y.; Zhao, G. *Tetrahedron Lett.* **1992**, *33*, 8117; (c) Ding, Y.; Zhao, Z.; Zhou, C. *Tetrahedron* **1997**, *53*, 2899; (d) Gänsauer, A. *Synlett* **1998**, 801; (e) Szymoniak, J.; Moise, C. *Titanium Zirconium Org. Synth.* **2002**, 451; (f) Rosales, A.; Oller-López Juan, L.; Justica, J.; Gänsauer, A.; Oltra, J. E.; Cuerva, J. M. *Chem. Commun.* **2004**, 2628; (g) Estévez, R. E.; Justica, J.; Bazdi, B.; Fuentes, N.; Paradas, M.; Choquesillo-Lazarte, D.; Garcia-Ruiz, J. M.; Robles, R.; Gänsauer, A.; Cuerva, J. M.; Oltra, J. E. *Chem. Eur. J.* **2009**, *15*, 2774; (h) Kosal, K.; Ashfeld, B. L. *Org. Lett.* **2010**, *12*, 44.
10. Fleury, L. M.; Ashfeld, B. L. *Org. Lett.* **2009**, *11*, 5670.
11. For the transition metal-catalyzed generation of Grignard reagents, see: (a) Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett.* **1996**, *37*, 7049; (b) Bogdanoviae, B.; Schwickardi, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610.
12. Other phosphines that restore catalytic activity at −40 °C: triphenylphosphine (95%), 1,2-bis(diphenylphosphino)ethane (94%), *rac*-BINAP (82%), tris(*o*-tolyl)phosphine (99%), tributylphosphine (95%).
13. Allylation of ketones can be problematic, see: (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349; (b) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Polyhedron* **2000**, *19*, 537; (c) McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Adv. Synth. Catal.* **2006**, *348*, 551; (d) Hargaden, G. C.; Müller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2007**, 4235.
14. (a) Gaudemar, M. *Tetrahedron* **1976**, *32*, 1689; (b) Ireland, R. E.; Armstrong, J. D.; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152.
15. The addition of an allyltitanium complex has been shown to proceed with in a diastereomeric ration of 2:1: Ireland, R. E.; Armstrong, J. D.; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152.