Organozinc Reagents

Preparation of Solid, Substituted Allylic Zinc Reagents and Their Reactions with Electrophiles

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Dedicated to Professor Ei-ichi Negishi on the occasion of his 80th birthday

Abstract: The treatment of various allylic chlorides or bromides with zinc dust in the presence of lithium chloride and magnesium pivalate $(Mg(OCOtBu)_2)$ in THF affords allylic zinc reagents which, after evaporation of the solvent, produce solid zinc reagents that display excellent thermal stability. These allylic reagents undergo Pd-catalyzed crosscoupling reactions with PEPPSI-IPent, as well as highly regioselective and diastereoselective additions to aryl ketones and aldehydes. Acylation with various acid chlorides regioselectively produces the corresponding homoallylic ketones, with the new C–C bond always being formed on the most hindered carbon of the allylic system.

Allylic organometallics are an important class of organometallic reagents owing to their enhanced reactivity compared to the corresponding alkyl, aryl, or even benzylic organometallics.^[1] For example, allylic magnesium halides are much more reactive than all other classes of Grignard reagents.^[2,3] This behavior can be explained by the higher ionic character of the allylic C-Mg bond. Although allylic derivatives of most maingroup elements have been reported,^[4] allylic zinc reagents are by far the most useful reagents in synthetic organic chemistry^[5] since they display high reactivity and are at the same time compatible with a range of functional groups, including ester^[6] or cyano functions.^[7] Furthermore, allylic zinc reagents are conveniently prepared through insertion of zinc (in the form of commercially available zinc powder) into the corresponding allylic bromide.^[8] Recently, we reported the preparation of solid aryl-, heteroaryl-, and benzylzinc reagents that are air stable but still display high reactivity for forming new carbon-carbon bonds.^[9] Herein, we report the synthesis of the first solid allylic zinc reagents of type 1, which were obtained through the insertion of zinc^[10] in the presence of LiCl^[11] and magnesium pivalate (Mg(OPiv)₂; OPiv = OCOtBu) into various allylic bromides or chlorides of type 2. After evaporation of the solvent, solid allylic zinc derivatives are obtained as white or yellow powders. Iodometric titration^[12] indicated that these zinc compounds were obtained in 51-90% yield (see Scheme 1). Important functional groups such as esters or nitriles are tolerated in these reagents (see 1e-h). Although these solids react rapidly with



Scheme 1. Preparation of functionalized solid allylic zinc pivalates of type **1** from the corresponding allylic halides of type **2** by using Zn, Mg(OPiv)₂, and LiCl. For determination of the half-lives $(t_{1/2})$ see the Supporting Information. Values given in brackets show the half-lives when the reagents were stored at -24 °C. [a] Complexed Mg(OPiv)X (X = Cl, Br) and LiCl are omitted for clarity.

air and moisture, they are stable for an extended period of time. The allylic zinc reagents **1a–d** are thermally very stable $(t_{1/2} > 2 \text{ years})$ at 25 °C as a solid under argon. The estersubstituted zinc reagents (**1e–f**) have somewhat lower room temperature stability $(t_{1/2} = 16-17 \text{ weeks})$. The stability of **1f** is increases to give a half-life of 40 weeks when stored at -24 °C. The nitrile-substituted allylic zinc species **1g–h** are more sensitive $(t_{1/2} = 33-59 \text{ d})$ but again, storage at -24 °C increases their stability significantly $(t_{1/2} = 50-152 \text{ d})$. The presence of LiCl and Mg(OPiv)₂ is essential for the success of the preparation of these allylic zinc reagents.^[13] The role of LiCl is to activate the zinc powder, whereas Mg(OPiv)₂ was found to be essential for the long-term stability of the solid allylic reagents.^[14]

We first examined the reactivity of the new allylic zinc pivalates in Pd-catalyzed cross-couplings. Buchwald and co-workers recently reported that prenylzinc bromide undergoes smooth cross-coupling with various unsaturated bromides in the presence of a Pd precatalyst and a sterically hindered phosphine ligand (CPhos).^[15] Consequently, we examined the cross-coupling of the allylic zinc reagents of type **1** with aryl bromides in the presence of various Pd catalysts. In our hands, PEPPSI-IPent, which was discovered by Organ and co-workers,^[16] gave by far the best results. Accordingly, prenyl-

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zinc pivalate (1b) undergoes cross-coupling with the bromouracil derivative 3a in the presence of 2 mol % of PEPPSI-IPent. Interestingly, the corresponding prenylzinc bromide (5b) as a 0.3 M solution in THF led only to traces of the crosscoupling product 4a. This behavior was general and the functionalized allylic zinc reagent 1 f reacts smoothly with 2bromotoluene (3b) in the presence of PEPPSI-IPent (2 mol %) to produce the cross-coupling product 4b in 79 % yield. Again, the use of the corresponding allylic zinc chloride 5f led only to traces of the desired product, thus showing the importance of Mg(OPiv)₂ for such cross-couplings (Scheme 2).



Scheme 2. PEPPSI-IPent-catalyzed cross-coupling of allylic organozinc reagents (1 b, f and 5 b, f) in THF within 4 h at 50 °C. [a] Complexed Mg(OPiv)X (X = Cl, Br) and LiCl are omitted for clarity.

The reaction scope of this Pd-catalyzed cross-coupling is quite broad and a range of unsaturated bromides provided the cross-coupling products (4c-g) in 69-79% yield (Table 1).^[17] The cross-coupling of zinc pivalate 1a with the electron-poor 1-bromo-3-(trifluoromethyl)benzene (3c) and 2 mol% of PEPPSI-IPent proceeds within 4 h at 50°C and provides the cross-coupling product 4c in 69% yield (entry 1). Remarkably, the electron-rich aryl bromides 3b and 3d also undergo the cross-coupling reaction to afford the expected products 4d-e (70-71% yield, entries 2-3). Similarly, the myrtenylzinc species 1c reacts with 1-bromo-3-fluorobenzene (3e) to provide only the linear regioisomer 4f in 77% yield (entry 4) after 4 h at 50 °C. The heteroaromatic bromide 3bromopyridine (3 f) was readily allylated with cinnamylzinc pivalate to give the functionalized heteroaromatic product 4g in 72% yield (entry 5). By following the same procedure, ester- and cyano-functionalized organozinc pivalates (1e-h) were converted into the corresponding polyfunctional crosscoupling products (4h-j) in 75-90% yield (entries 6-8).

Furthermore, as previously reported for allylic zinc halides,^[18] solid allylic zinc reagents of type **1** react with electrophiles such as carbonyl derivatives or acid chlorides with complete regioselectivity (formation of the new carbon-carbon bond from the most substituted end of the allylic system) and very high diastereoselectivity, as shown in Table 2 and Scheme 3. The cyclohex-2-en-1-ylzinc reagent **1a** (1.0 equiv) in THF adds to various methyl ketones^[7a]

Table 1: PEPPSI-IPent-catalyzed cross-coupling of allylic organozinc pivalates of type **1** in THF within 4 h at 50°C.



[a] Complexed Mg(OPiv)X (X = Cl, Br) and LiCl are omitted for clarity. [b] 0.80 equiv of electrophile were used. [c] Yields refer to analytically pure products.

(0.8 equiv) to give the corresponding homoallylic alcohols (**6a–b**) in 89–92 % yield with d.r. > 99:1 (Table 2, entries 1–2). The 2,3-disubstitured allylic zinc species **1c** reacts with furfural (**5c**) with complete regio- and diastereoselectivity to give the alcohol **6c** in 89 % yield (entry 3). Cinnamylzinc pivalate (**1d**) displays similar behavior and gives the *anti*-alcohol **6d** in 86 % yield with d.r. > 99:1. This zinc reagent enables stereocontrol of three contiguous centers and its addition to 2-trimethylsilyloxy cyclohexanone (**5e**) provides the alcohol **6e** in 80 % yield (d.r. = 95:5; entry 5). The structure of alcohol **6e** was confirmed by X-ray analysis.^[19] The functionalized solid zinc reagent **1e** reacts smoothly with 3-bromobenzaldehyde (**5f**) to furnish the secondary alcohol **6f** in 91 % (d.r. = 97:3; entry 6). Finally, the functionalized zinc reagents **1f–g**, which bear an ester or cyano function in



using functionalized solid allylic zinc pivalates of type I. ^{eg}			
Entry	Zinc Reagent ^[b]	Electrophile	Product ^[c]
	ZnOPiv	o II	HO Me
	\bigcup	F	F
1	1a	5 a	6 a : 89% d.r. > 99:1
	ZnOPiv	Me	HO Me
2	1 a	5 b	6 b : 92 % d.r. = 94:6
	Ме, Ме		QН
	ZnOPiv	СНО	Me
3	1c	5 c	6 c : 89 % d.r. > 99:1
	Ph ZnOPiv	Br CHO	OH Br
4	1 d	5 d	6 d : 86% d.r. > 99:1
	PhZnOPiv	OTMS	HO, Ph OTMS
5	1 d	5 e	6e : 80% d.r. = 95:5
	CO ₂ Et	Br CHO	EtO ₂ C OH
6	1e	5 f	6 f : 91 % d.r. = 97:3
	CO ₂ Et ZnOPiv	G Fe	Fe Me
7	1 f	5 g	6 g : 92 % d.r. > 99:1
	CN ZnOPiv	СНО	NC OH
8	1 g	5 c	6 h : 91 % d.r. > 99:1

Table 2: Diastereoselective preparation of homoallylic alcohols of type **6** using functionalized solid allylic zinc pivalates of type **1**.^[a]

[a] Reaction conditions: 0.80 equiv of electrophile, THF, -78 °C, 1 h. [b] Complexed Mg(OPiv)X (X=Cl, Br) and LiCl are omitted for clarity. [c] Yields refer to analytically pure products; The d.r. value was determined by NMR and/or GC analysis of the crude product.

position 2, react with the ferrocenyl methyl ketone (**5g**) and furfural (**5c**) to furnish the products **6g–h** in 91–92 % yield and d.r. > 99:1 (entries 7–8). In the case of the addition of the allylic zinc pivalate **1f** to **5g**, spontaneous lactonization leading to the bicyclic product **6g** was observed (entry 7).^[19]



Scheme 3. Reaction of the functionalized solid allylic zinc pivalates (1 a–h) with acid chlorides (7 a–f). [a] Complexed Mg(OPiv)X (X=Cl, Br) and LiCl are omitted for clarity. [b] 0.80 equiv of electrophile were used. [c] Yields refer to analytically pure products. [d] The reaction mixture was warmed to RT overnight.

The method was also applicable to the synthesis of various β , γ -unsaturated ketones of type 8 through addition of the functionalized solid allylic zinc pivalates of type 1 to acid chlorides in the absence of any transition metal catalyst (Scheme 3). Accordingly, the allylic reagents 1a and 1b react in THF under very mild conditions (1 h, -78°C) with 4chlorobenzoyl chloride (7a) and 4-methoxybenzoyl chloride (7b) to give the β , γ -unsaturated ketones 8a-c in 78-95% yield without any trace of the α,β -unsaturated isomers. Interestingly, the competitive formation of a mixed anhydride through reaction of the pivalate anion (PivO⁻) with the acyl chloride was not observed.^[9e] Starting from 3-bromobenzoyl chloride (7c) or 4-(tert-butyl)benzoyl chloride (7d), the corresponding β_{γ} -unsaturated ketones **8d–e** were obtained in 68-75% vield when using the functionalized organozinc pivalate 1e. Furthermore, the addition of the cyano-functionalized solid zinc reagent 1 f to thiophene-2-carbonyl chloride (7e) selectively furnished the corresponding ketone 8f in 77% yield.

In summary, we have prepared salt-stabilized solid allylic zinc pivalates from the corresponding allylic bromides or chlorides through a one-pot insertion under mild conditions with commercial zinc powder, LiCl, and Mg(OPiv)₂. After evaporation of the solvent, the resulting solid allylic zinc reagents can be stored under argon for an extended period of time ($t_{1/2}$ between ca. 5 weeks and > 2 years). These reagents show excellent reactivity in Pd-catalyzed cross-coupling reactions with aryl bromides when using PEPPSI-IPent and they undergo smooth additions to methyl ketones and aldehydes with high diastereoselectivity. In addition, the regioselective acylation of the reagents with acid chlorides produce β_{γ} -unsaturated ketones. Further applications are currently underway in our laboratories.



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