Organozinc Reagents

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Functionalized Alkenylzinc Reagents Bearing Carbonyl Groups: Preparation by Direct Metal Insertion and Reaction with Electrophiles**

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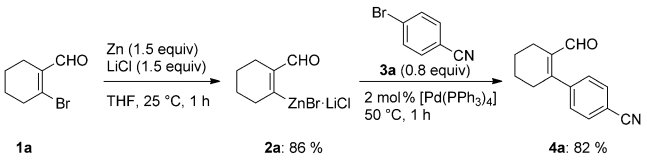
Dedicated to the Bayer company on the occasion of its 150th anniversary

Functionalized alkenes bearing aldehyde, keto, or ester functions are found in a plethora of natural products as well as in pharmaceutically active substances.[1] Consequently, functionalized alkenyl organometallic compounds bearing such sensitive carbonyl groups are important intermediates in organic synthesis. In particular, alkenylzinc halides would be useful targets due to their high functional-group tolerance and their excellent reactivity in the presence of an appropriate catalyst.[2] Functionalized alkenyl organometallic compounds are mostly prepared by halogen–metal exchange reactions of the corresponding iodoalkenes.[3] The major drawbacks of this method are the low reaction temperatures required and the use of expensive alkenyl iodides as the starting material. Furthermore, only a few direct insertion reactions for the synthesis of unfunctionalized alkenyl organometallics have been reported.[4] For instance, Rieke et al. described the use of highly active zinc (Zn*), which was prepared by reduction of $ZnCl_2$ with lithium naphthalide, for the synthesis of styrylzinc bromide.[5]

Recently, we have developed a practical and useful method for the synthesis of alkyl-,[6] aryl-,[6b,7] and benzylzinc halides[8] by the LiCl-mediated metal-insertion reaction of the corresponding chlorides and bromides. Herein, we now report the convenient, mild, and atom-economical[9] preparation of highly functionalized alkenylzinc reagents starting from readily available alkenyl bromides bearing, for the first time, sensitive functional moieties such as aldehyde, keto, and ester groups.

Thus, 2-bromocyclohex-1-enecarbaldehyde (**1a**) undergoes a smooth zinc insertion using commercially available zinc powder (1.5 equiv, 25 °C, 1 h) in the presence of LiCl (1.5 equiv), leading to the zinc reagent **2a** (86% yield, Scheme 1).[10] The presence of the electron-withdrawing formyl group on the double bond accelerates the electron transfer from the zinc to the organohalide through conjugation and enables therefore this exceptionally fast insertion reaction. A subsequent Pd-catalyzed Negishi cross-coupling reaction[11,12] with 4-bromobenzonitrile (**3a**) using 2 mol% $[Pd(PPh_3)_4]$[13] affords the highly functionalized benzonitrile **4a** in 82% yield. Moreover, the Cu^I-catalyzed allylation reaction[14] with ethyl 2-(bromomethyl)acrylate (**3b**) leads to the desired product **4b** in 94% yield (Table 1, entry 1). The copper-catalyzed reaction[14,15] of **2a** with bromoacetylene **3c**[16] affords the highly functionalized acetylene **4c** in 80% yield (Table 1, entry 2). Furthermore, the acylation reaction[13] using 2-bromobenzoyl chloride (**3d**) affords ketone **4d** in 51% yield (Table 1, entry 3). Additionally, the Pd-catalyzed cross-coupling reaction with 5-bromo-3-cyanopyridine (**3e**) furnishes the highly functionalized cyclohexenyl derivative **4e** in 65% yield (Table 1, entry 4). Finally, the reaction of **2a** with the Tietze immonium reagent **3f**[17] leads to the aminoaldehyde **4f** (68% yield; Table 1, entry 5). The heterocyclic dihydropyranylzinc derivative **2b** can also be prepared by direct zinc insertion using zinc powder (1.5 equiv) in the presence of LiCl (1.5 equiv, 25 °C, 1 h, 77% yield). After reaction with the immonium salt **3f**, the *N*,*N*-dimethylaminomethyl-substituted dihydropyran derivative **4g** was isolated in 88% yield (Table 1, entry 6).



1a 2a: 86 % 4a: 82 %

Scheme 1. LiCl-mediated zinc insertion in **1a** leading to **2a**.

Furthermore, alkenyl bromides bearing a keto function, such as 3-bromocyclohexenone (**1c**), react readily with zinc powder (2 equiv) and LiCl (2 equiv) at 25 °C within 30 min to give the corresponding zincated cyclohexenone **2c** (86%).[18] The subsequent Pd-catalyzed cross-coupling reaction with 4-bromobenzonitrile (**3a**) affords the 3-substituted cyclohexenone derivative **4h** in 88% yield (Table 1, entry 7). Cu^I-mediated reactions of **2c** with 3-bromocyclohexene (**3g**) and bromoacetylene **3c** furnish the unsaturated ketones **4i** and **4j**, respectively, in 71–76% yield (Table 1, entries 8 and 9). Analogously, 3-bromocyclopentenone (**1d**) was converted to the alkenylzinc reagent **2d** in 94% yield (25 °C, 5 h). The subsequent Pd-catalyzed cross-coupling with 4-(trifluoromethyl)bromobenzene (**3h**) leads to the substituted cyclo-

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Table 1: Reactions of alkenylzinc reagents of type **2** with electrophiles.

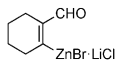
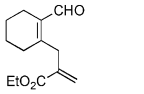
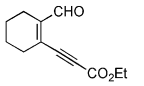
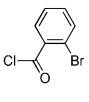
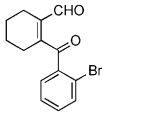
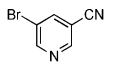
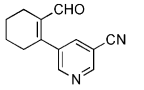
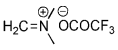
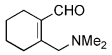
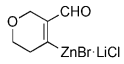
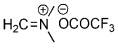
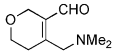
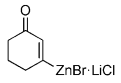
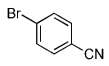
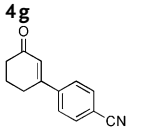
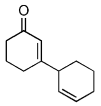
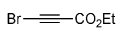
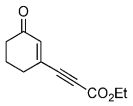
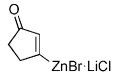
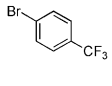
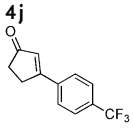
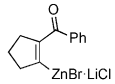
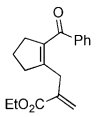
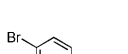
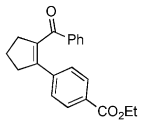
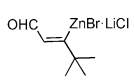
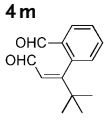
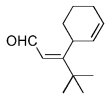
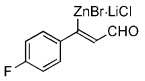
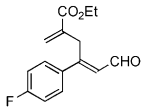
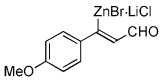
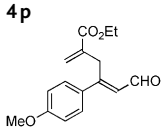
Entry	Organozinc reagent (yield [%])[a]	Electrophile	Product	Yield [%][b]
				
1	**2a** (86)	**3b**	**4b** 	94[c]
2	**2a**	**3c** 	**4c** 	80[d]
3	**2a**	**3d** 	**4d** 	51[d]
4	**2a**	**3e** 	**4e** 	65[e]
5	**2a** 	**3f** 	**4f** 	68
6	**2b** (77) 	**3f** 	**4g** 	88
7	**2c** (86)	**3a** 	**4h** 	88[e]
8	**2c**	**3g** 	**4i** 	76[c]
9	**2c** 	**3c** 	**4j** 	71[d]
10	**2d** (94) 	**3h** 	**4k** 	74[e]
11	**2e** (62)	**3b** 	**4l** 	79[d]
12	**2e** 	**3i** 	**4m** 	70[e]
13	**2f** (67)	**3j**	**4n**	92[e,f]

Table 1: (Continued)

Entry	Organozinc reagent (yield [%])[a]	Electrophile	Product	Yield [%][b]
				
14	**2f** 	**3g** 	**4o** 	96[c,f]
15	**2g** (35) 	**3b** 	**4p** 	95[d,f]
16	**2h** (41)	**3b**	**4q**	89[d,f]
17	**2i** (62)	**3b**	**4r**	79[d,f]
18	**2i**	**3k**	**4s**	85[d,f]

[a] Determined by titration with I_2. [b] Yield of isolated, analytically pure product. [c] 3 mol% CuCN·2 LiCl was used. [d] 1 equiv CuCN·2 LiCl was used. [e] 2 mol% $[Pd(PPh_3)_4]$ was used and the reaction was performed at 50 °C. [f] $Z/E > 99:1$.

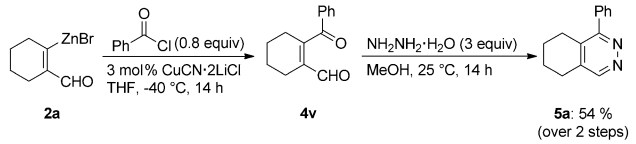
pentenone **4k** in 74% yield (Table 1, entry 10). Moreover, (2-bromocyclopent-1-en-1-yl)(phenyl)methanone (**1e**) readily undergoes metal insertion in the presence of zinc powder (1.5 equiv) and LiCl (1.5 equiv; 25 °C, 1 h) to give the corresponding zinc reagent **2e** in 62% yield. The Cu^I-catalyzed allylation reaction of **2e** with ethyl 2-(bromomethyl)acrylate (**3b**) furnishes the desired product **4l** in 79% yield (Table 1, entry 11). The Pd-catalyzed cross-coupling of **2e** with ethyl 4-bromobenzoate (**3i**) leads to **4m** in 70% yield (Table 1, entry 12).

Acyclic alkenylzinc reagents bearing a vicinal aldehyde were also prepared without losing the stereochemical information of the alkenyl precursors due to the chelation of the zinc center with the carbonyl group. In general, the formation of a five-membered-ring chelate stabilizes the corresponding organometallic compound by several kcal mol^{-1} [19] and reduces the nucleophilicity of the carbonyl group. Thus, (*Z*)-3-bromo-4,4-dimethylpent-2-enal (**1f**) reacts with zinc powder (1.5 equiv) in the presence of LiCl (1.5 equiv) to give the alkenylzinc reagent **2f** (67%, 25 °C, 1 h). Its Pd-catalyzed cross-coupling with 2-bromobenzaldehyde (**3j**) and Cu^I-catalyzed allylation using 3-bromocyclohexene (**3g**) furnish the unsaturated aldehydes **4n** and **4o**, respectively, in 92–96% yield (Table 1, entries 13 and 14). Moreover, the 4-fluoro- and the 4-methoxy-substituted derivatives **1g** and **1h** of (*Z*)-3-bromo-3-phenylprop-2-enal react to the corresponding zinc species **2g** and **2h** in 35–41% yield. The subsequent Cu^I-catalyzed allylation reaction with ethyl 2-(bromomethyl)-

acrylate (**3b**) furnishes the cinnamyl aldehydes **4p** and **4q** in 89–95% yield ($Z/E > 99:1$; Table 1, entries 15 and 16).

Furthermore, the acyclic alkenyl bromide (*Z*)-ethyl 3-bromo-3-phenylacrylate (**1i**) bearing an ester function was converted into the corresponding zinc reagent **2i** with zinc powder (1.5 equiv) and LiCl (1.5 equiv; 25°C, 1 h) in 62% yield. The copper-mediated reaction of **2i** with ethyl 2-(bromomethyl)acrylate (**3b**) and 4-chlorobenzoyl chloride (**3k**) affords the highly functionalized cinnamyl esters **4r** and **4s**, respectively, in 79–85% yield ($Z/E > 99:1$; Table 1, entries 17 and 18).

Unsaturated 1,4-dicarbonyl compounds are highly reactive and undergo condensation reactions with hydrazine providing tetrahydrophthalazines.[20] Thus, zinc reagent **2a** was acylated with benzoyl chloride using 3 mol% CuCN·2 LiCl as the catalyst to afford the 1,4-dicarbonyl derivative **4v**. After aqueous workup, the crude unsaturated 1,4-dicarbonyl compound undergoes a smooth condensation reaction with hydrazine hydrate ($NH_2NH_2{\cdot}H_2O$) in methanol to afford the 1-substituted tetrahydrophthalazine **5a** in 54% yield (Scheme 2).[21]

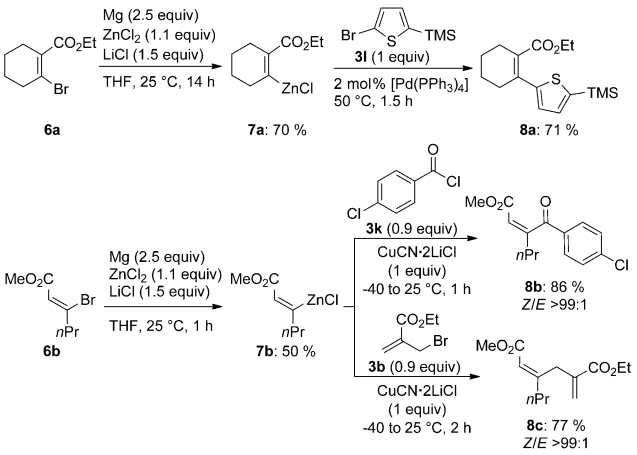


2a **4v** **5a**: 54% (over 2 steps)

Scheme 2. Synthesis of substituted tetrahydrophthalazines of type **5**.

The direct insertion of zinc into alkenyl bromides requires the presence of adjacent electron-withdrawing groups. Alkenyl bromides without such electronic activation either do not undergo an insertion reaction or react only at elevated temperatures and require long reaction times. To avoid these drawbacks, we have used a more strongly reducing metal, magnesium. Thus, a LiCl-mediated Mg insertion in the presence of $ZnCl_2$ allows an efficient synthesis of alkenylzinc halides starting from weakly activated alkenyl bromides.[22] Whereas a vicinal ethyl ester does not sufficiently activate the alkenyl bromide **6a** for a LiCl-mediated zinc insertion, it undergoes selective magnesium insertion in the presence of $ZnCl_2$ and LiCl furnishing the alkenylzinc reagent **7a** in 70% yield (Scheme 3). The subsequent Pd-catalyzed cross-coupling with (5-bromothiophen-2-yl)trimethylsilane (**3l**) leads to the substituted thiophene **8a** in 71% yield. Remarkably, the zinc insertion also proceeds well with the acyclic unsaturated bromoester **6b**. The LiCl-mediated Mg insertion in the presence of $ZnCl_2$ furnished the corresponding zinc reagent **7b** in 50% yield without any loss of stereochemical information due to the chelation of the zinc center with the carbonyl group. The subsequent copper-catalyzed reaction of **7b** with 4-chlorobenzoyl chloride (**3k**) and ethyl 2-(bromomethyl)acrylate (**3b**) affords the functionalized acyclic compounds **8b** and **8c**, respectively, in 77–86% yield ($Z/E > 99:1$, Scheme 3).

This method turned out to be general and the preparation of several new functionalized alkenylzinc reagents are described in Table 2. In analogy to **6a**, the ester-substituted



Scheme 3. Selective insertion of Mg in the presence of $ZnCl_2$ and LiCl in the ester-substituted alkenyl bromides **6a** and **b** (additional complexed salts are not shown for the sake of clarity).

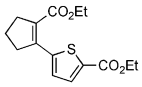
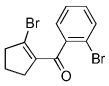
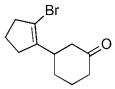
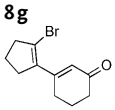
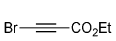
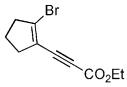
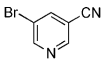
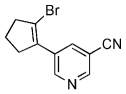
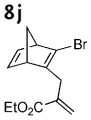
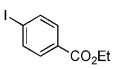
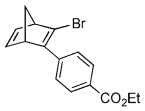
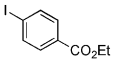
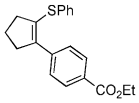
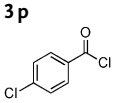
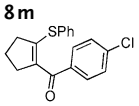
cyclopentene derivative **6c** was converted to its corresponding zinc reagent **7c** and submitted to Cu^I-mediated allylation with **3b** affording the unsaturated product **8d** in 86% yield (Table 2, entry 1). Its Pd-catalyzed cross-coupling with the bromothiophene **3m** leads to the substituted thiophene **8e** in 79% yield (Table 2, entry 2).

Although 1,2-dibromocyclopentene (**6d**) can be converted to the corresponding magnesium reagent by Br/Mg exchange with *i*PrMgCl·LiCl,[23] a more atom-economical approach using Mg/$ZnCl_2$/LiCl is possible. Thus, the treatment of **6d** with magnesium in the presence of $ZnCl_2$ and LiCl leads to the desired alkenylzinc reagent **7d** in quantitative yield. Its Cu^I-catalyzed acylation reaction using 2-bromobenzoyl chloride (**3d**) affords the unsaturated ketone **8f** in 64% yield (Table 2, entry 3). Additional Cu^I-mediated reactions with cyclohexenone (**3n**), 3-iodocyclohexenone (**3o**), and bromoacetylene **3c** lead to the expected products **8g–8i**, respectively, in 65–78% yield (Table 2, entries 4–6). Finally, the Pd-catalyzed cross-coupling reaction of **7d** with 3-bromo-5-cyanopyridine (**3e**) furnishes the substituted pyridine **8j** in 54% yield (Table 2, entry 7).

Functionalization of the related 1,2-dibromocyclohexene by using this method was not possible. As the six-membered ring has lower ring strain, the initially formed organometallic reagent presumably eliminates $MgBr_2$ leading to cyclohexyne which undergoes side reactions. However, the increased ring strain in the dibromonorbornadiene **6e** prevents this elimination reaction and the corresponding zinc reagent **7e** was obtained within 1 h in 70% yield using Mg (2.5 equiv) in the presence of LiCl (1.5 equiv) and $ZnCl_2$ (1.1 equiv). The Cu^I-catalyzed allylation reaction of **7e** with ethyl 2-(bromomethyl)acrylate (**3b**) leads to the desired product **8k** in 61% yield (Table 2, entry 8). The Pd-catalyzed cross-coupling of **7e** with ethyl 4-iodobenzoate (**3p**) furnishes the arylated norbornadiene **8l** in 60% yield (Table 2, entry 9).

Also (2-bromocyclopent-1-en-1-yl)(phenyl)sulfane (**6f**) does not undergo a direct zinc insertion. However, the use of Mg (2.5 equiv) in the presence of LiCl (1.5 equiv) and $ZnCl_2$ (1.1 equiv) furnishes **7f** within 1 h in 68% yield. The

Table 2: Reactions of alkenylzinc reagents of type **7** with electrophiles.

Entry	Organozinc reagent[a] (Yield [%])[b]	Electrophile	Product	Yield [%][c]
				
1	**7c** (84)	**3b**	**8d** 	86[d]
2	**7c** 	**3m** 	**8e** 	79[e]
3	**7d** (98)	**3d** 	**8f** 	64[f]
4	**7d**	**3n** 	**8g** 	70[f]
5	**7d**	**3o** 	**8h** 	65[f]
6	**7d**	**3c** 	**8i** 	78[d]
7	**7d** 	**3e** 	**8j** 	54[e]
8	**7e** (70)	**3b** 	**8k** 	61[f]
9	**7e** 	**3p** 	**8l** 	60[e]
10	**7f** (68)	**3p** 	**8m** 	81[e]
11	**7f**	**3k**	**8n**	86[f]

[a] Additional complexed salts are not shown for the sake of clarity. [b] Determined by titration with I_2. [c] Yield of isolated, analytically pure product. [d] 2 mol% CuCN·2 LiCl was used. [e] 2 mol% $[Pd(PPh_3)_4]$ was used and the reaction was performed at 50 °C. [f] 1 equiv of CuCN·2 LiCl was used.

subsequent Pd-catalyzed cross-coupling reaction with ethyl 4-iodobenzoate (**3p**) leads to the arylated cyclopentene **8m** in 81% yield (Table 2, entry 10). The Cu^I-mediated acylation of **7f** with 4-chlorobenzoyl chloride (**3k**) furnishes the unsaturated ketone **8n** in 86% yield (Table 2, entry 11).

In summary, we have demonstrated that alkenylzinc reagents bearing sensitive carbonyl groups can readily be generated by direct metal insertion. In the case of activated substrates a direct zinc insertion in the presence of LiCl proceeds well,[6b,8a] whereas for less activated alkenyl bromides the use of magnesium in the presence of LiCl and $ZnCl_2$ is required for the insertion.[6a,8c] Functional groups, such as aldehydes, ketones, and esters are well tolerated. Furthermore, acyclic alkenylzinc reagents could be prepared from the corresponding acyclic bromides without losing their stereochemistry due to the chelating effect of the vicinal carbonyl group; in this way trisubstituted olefins could be synthesized with excellent Z selectivity ($Z/E > 99{:}1$). Subsequent functionalization reactions like Negishi cross-couplings, acylations, and allylations have been performed, readily furnishing polyfunctional compounds in excellent yields. Further extensions of this work are currently underway in our laboratories.

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