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Synthesis of Substituted Adamantylzinc Reagents Using a Mg-Insertion in the Presence of $ZnCl_2$ and Further Functionalizations

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Ⓢ *Supporting Information*

ABSTRACT: The LiCl-mediated Mg-insertion in the presence of $ZnCl_2$ allows an efficient synthesis of adamantylzinc reagents starting from the corresponding functionalized tertiary bromides. The highly reactive adamantylzinc species readily undergo a broad variety of functionalizations such as Negishi cross-couplings, Cu(I)-catalyzed acylations and allylations, and 1,4-addition reactions leading to the expected products in excellent yields. Furthermore, the adamantyl moiety could be introduced as α-substituent in terthiophene, increasing its solubility due to the higher lipophilicity and the prevention of π-stacking.

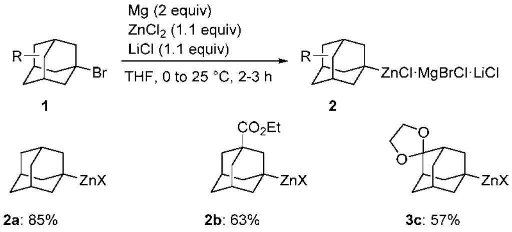
Adamantane derivatives have found numerous applications in medicinal chemistry and drug development.[1] Moreover, they have shown promising use in the fields of medicine, supramolecular chemistry, and nanotechnologies.[1c] Adamantane also is the parent of the so-called diamondoids,[2] which are readily available (from crude oil) nanometer-size diamond-like building blocks that resemble many of the unique properties of diamond (e.g., electron emission[3]). Until now, no general method has been reported for the preparation of adamantyl or diamondoid organometallic reagents. The synthesis of tertiary organometallics is not straightforward due to side reactions such as proton abstraction or β-hydride elimination. However, Dubois developed a so-called "static" method whereby the reaction of 1-bromo-adamantane (**1a**) with magnesium turnings was conducted without stirring of the reaction medium, leading to 1-adamantylmagnesium bromide in 58% yield.[4] Even the reaction of **1a** with highly reactive magnesium (Mg*) generated *in situ* by the standard method of Rieke[5] did not furnish traces of the organomagnesium compound. Instead, a 60% yield of hydrolyzed adamantane and a 30% yield of homocoupling product were isolated.[6] Noteworthy, by using highly active Rieke-zinc (Zn*) prepared via reduction of $ZnCl_2$ with lithium naphthalide; adamantylzinc bromide was obtained in 65% yield.[7]

Recently, we have developed a practical method for the synthesis of alkyl-,[8] aryl-,[9] benzyl-,[9,10] and alkenylzinc[11] halides via LiCl-mediated metal insertion into the corresponding chlorides and bromides. These preparations are based either on the use of commercially available zinc powder in combination with LiCl or magnesium turnings in the presence of $ZnCl_2$ and LiCl. Especially the second approach proceeds under exceedingly mild conditions, since magnesium acts as a stronger reducing agent than zinc (faster electron transfer in the insertion mechanism). Therefore, we anticipated that this method should be especially attractive for the preparation of tertiary organozincs. Hence, we now report a mild and convenient preparation of functionalized adamantylzinc reagents starting from readily available adamantyl bromides bearing for the first time sensitive functional groups. Moreover, this method has been used to attach an adamantyl moiety to terthiophene to increase its solubility.

Thus, **1a** undergoes a smooth magnesium insertion using commercially available magnesium turnings (2 equiv, 0 to 25 °C, 2 h) in the presence of LiCl (1.1 equiv) and $ZnCl_2$ (1.1 equiv), leading to the corresponding zinc reagent **2a** in 85% yield as determined via titration.[12] Remarkably, also the functionalized adamantylzinc reagents **2b** and **2c**[13] have been obtained for the first time in 57−63% yield, following this procedure (Scheme 1).

The resulting adamantylzinc reagents **2a−c** readily undergo a broad variety of functionalization reactions in the presence of an appropriate catalyst. Hence, zinc reagent **2a** smoothly reacts in a Pd-catalyzed Negishi cross-coupling[14] with aryl

Scheme 1. Mg-Insertion in the Presence of $ZnCl_2$ and LiCl into the Functionalized Adamantyl Bromides 1a−c



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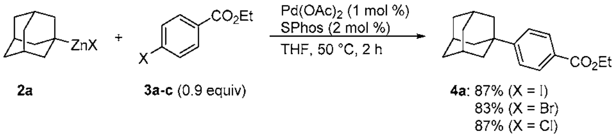
halides **3a**−**k**.[15] Using 1% $Pd(OAc)_2$ and 2% of the ligand SPhos introduced by Buchwald[16] as a catalytic system, zinc reagent **2a** reacts within 2 h at 50 °C with the ester-substituted aryl halides **3a**−**c** to provide the corresponding cross-coupling product **4a** in 83−87% yield (Scheme 2).

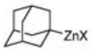
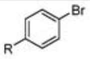
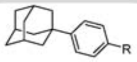
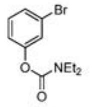
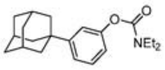
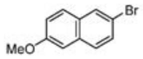
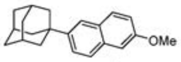
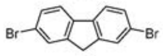
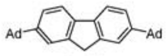
Scheme 2. Negishi Cross-Coupling of Adamantylzinc Reagent **2a** with Aryl Halides of Type 3



2a **3a-c** (0.9 equiv) **4a**: 87% (X = I)
83% (X = Br)
87% (X = Cl)

Various electron-rich and -poor electrophiles (0.9 equiv) were used in the cross-coupling performed at 50 °C, affording the corresponding arylated adamantyl derivatives **4b**−**h** in 62−95% yield, tolerating functional groups such as a nitrile, an aldehyde, a ketone, or a carbamate (Table 1, entries 1−7). Noteworthy, also a double cross-coupling has been achieved under these reaction conditions, furnishing the corresponding product **4i** in 82% yield (entry 8).

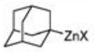
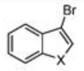
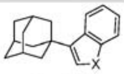
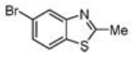
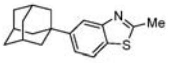
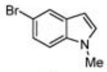
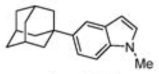
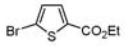
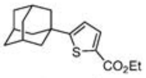
Table 1. Negishi Cross-Couplings of Adamantylzinc Reagent **2a** with Aryl Bromides

entry	adamantylzinc reagent	electrophile	product (yield [%])[a]
			
1	**2a**	**3d**, R = CN	**4b**: 88[b]
2	**2a**	**3e**, R = C(O)Me	**4c**: 84[b]
3	**2a**	**3f**, R = NMe_2	**4d**: 62[b]
4	**2a**	**3g**, R = TMS	**4e**: 80[b]
5	**2a**	**3h**, R = CHO	**4f**: 88[b]
6	**2a**	 **3i**	 **4g**: 70[b]
7	**2a**	 **3j**	 **4h**: 95[b]
8	**2a**	 **3k**	 **4i**: 82[c]

[a] Yield of analytically pure isolated product based on the amount of electrophile used. [b] Obtained after Negishi cross-coupling ($Pd(OAc)_2$ (1 mol %) and SPhos (2 mol %)) with ArBr (0.9 equiv). [c] Obtained after Negishi cross-coupling ($Pd(OAc)_2$ (1 mol %) and SPhos (2 mol %)) with 2,7-dibromo-fluorene (0.45 equiv) (Ad = 1-adamantyl).

A broad variety of heteroaryl bromides (**3l**−**p**) as electrophiles produce the desired products **4j**−**n** under standard conditions in excellent yields (Table 2). In particular, benzofuran, benzothiazole, protected indole, and an ester-substituted thiophene have successfully been employed in the cross-coupling reaction furnishing the corresponding hetero-arylated adamantanes **4j**−**n** in 53−91% yield (entries 1−5).

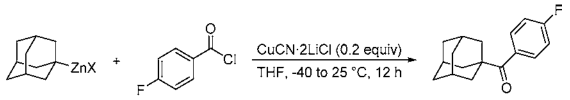
Table 2. Negishi Cross-Couplings of Adamantylzinc Reagent **2a** with Heteroaryl Bromides

entry	adamantylzinc reagent	electrophile	product (yield [%])[a]
			
1	**2a**	**3l**, X = S	**4j**: 84[b]
2	**2a**	**3m**, X = O	**4k**: 57[b]
3	**2a**	 **3n**	 **4l**: 91[b]
4	**2a**	 **3o**	 **4m**: 71[b]
5	**2a**	 **3p**	 **4n**: 53[b]

[a] Yield of analytically pure isolated product based on the amount of electrophile used. [b] Obtained after a Negishi cross-coupling ($Pd(OAc)_2$ (1 mol %) and SPhos (2 mol %)) with heteroaryl bromide (0.9 equiv).

Adamantylzinc reagent **2a** also undergoes Cu(I)-catalyzed acylations,[17] leading to the desired ketones **4o**−**r** in good to excellent yields (Scheme 3 and Table 3). Thus, **2a** reacts with 4-fluorobenzoyl chloride (**3q**, 0.9 equiv) and 20% CuCN·2LiCl to afford the corresponding ketone **4o** in 89% yield (Scheme 3).

Scheme 3. Cu(I)-Catalyzed Acylation of Adamantylzinc Reagent **2a** with 4-Fluorobenzoyl Chloride (**3q**)

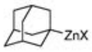
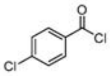
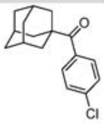
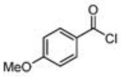
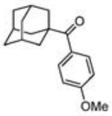
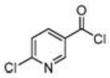
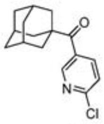
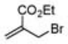
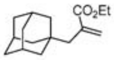
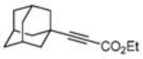
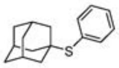
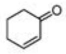
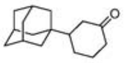


2a **3q** (0.9 equiv) **4o**: 89%

Under the same reaction conditions, also the acid chlorides **3r**−**t** were good substrates in the Cu(I)-catalyzed acylation. The substituted benzoyl chlorides **3r** and **3s** undergo the acylation with adamantylzinc species **2a** in 70−80% yield (Table 3, entries 1 and 2). Also the heteroaromatic 6-chloro-nicotinoyl chloride (**3t**) reacts with **2a** to afford the corresponding ketone **4r** in 44% yield (entry 3). Furthermore, the highly reactive adamantylzinc reagent **2a** furnishes in a Cu(I)-catalyzed allylation[17] with ethyl 2-(bromomethyl)-acrylate (**3u**, 0.9 equiv) the desired product **4s** in 91% yield (entry 4). Moreover, the copper-catalyzed alkynylation[18] of **2a** with bromoacetylene **3v**[18] (0.9 equiv) affords the functionalized acetylene **4t** in 66% yield (entry 5). Furthermore, the adamantylzinc reagent **2a** reacts smoothly with *S*-phenyl benzenesulfonothioate (**3w**, 0.9 equiv) to give thioether **4u** in 98% yield (entry 6). Additionally, the Cu(I)-mediated 1,4-addition[19] with cyclohex-2-enone (**3x**, 0.9 equiv) affords the desired 1,4-addition product **4v** in 91% yield (entry 7).

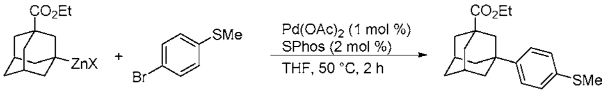
Analogous to the unfunctionalized adamantylzinc reagent **2a**, the ester-substituted adamantylzinc derivative **2b** readily reacts in a Pd-catalyzed Negishi cross-coupling with 4-bromothioanisole (**3y**, 0.9 equiv) at 50 °C within 2 h to

Table 3. Further Functionalizations of Adamantylzinc Reagent 2a with Various Electrophiles

entry	adamantylzinc reagent	electrophile	product (yield [%])[a]
1	 **2a**	 **3r**	 **4p**: 70[b]
2	**2a**	 **3s**	 **4q**: 80[b]
3	**2a**	 **3t**	 **4r**: 44[b]
4	**2a**	 **3u**	 **4s**: 91[c]
5	**2a**	$EtO_2C-\equiv-Br$ **3v**	 **4t**: 66[d]
6	**2a**	$PhSSO_2Ph$ **3w**	 **4u**: 98[e]
7	**2a**	 **3x**	 **4v**: 91[f]

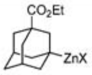
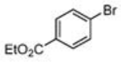
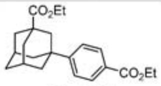
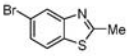
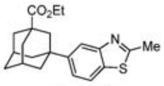
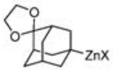
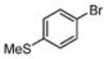
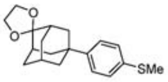
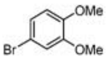
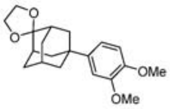
[a] Yield of analytically pure isolated product based on the amount of electrophile used. [b] Obtained after acylation (CuCN·2LiCl (0.2 equiv)) with an acid chloride (0.9 equiv). [c] Obtained after allylation (CuCN·2LiCl (0.2 equiv)) with ethyl 2-(bromomethyl)acrylate (0.9 equiv). [d] Obtained after alkynylation (CuCN·2LiCl (0.2 equiv)) with ethyl 3-bromopropiolate (0.9 equiv). [e] Obtained after addition to *S*-aryl benzenethiosulfonate (0.9 equiv). [f] Obtained after 1,4-addition (CuCN·2LiCl (1.1 equiv) and TMSCl (2.0 equiv)) with cyclohex-2-enone (0.9 equiv).

Scheme 4. Negishi Cross-Coupling of Adamantylzinc Reagent 2b with 4-Bromothioanisole (3y)



2b **3y** (0.9 equiv) **5a**: 87%

Table 4. Negishi Cross-Couplings of Adamantylzinc Reagents 2b–c with (Hetero)aryl Bromides

entry	adamantylzinc reagent	electrophile	product (yield [%])[a]
1	 **2b**	 **3b**	 **5b**: 84[b]
2	**2b**	 **3n**	 **5c**: 70[b]
3	 **2c**	 **3y**	 **5d**: 73[b]
4	**2c**	 **3z**	 **5e**: 71[b]

[a] Yield of analytically pure isolated product based on the amount of electrophile used. [b] Obtained after a Negishi cross-coupling (Pd(OAc)$_2$ (1 mol %)) and SPhos (2 mol %)) with (hetero)aryl bromide (0.9 equiv).

afford the highly functionalized adamantyl drivative **5a** in 87% yield (Scheme 4).

Under the same reaction conditions, also ethyl 4-bromobenzoate (**3b**, 0.9 equiv) and 5-bromo-2-methyl-benzothiazole (**3n**, 0.9 equiv) were used in the Pd-catalyzed Negishi reaction with the ester-substituted adamantylzinc species **2b**. The corresponding cross-coupling products **5b** and **5c** were obtained in 70–84% yield (Table 4, entries 1 and 2). Similarly, the adamantylzinc reagent **2c** was functionalized by Pd-catalyzed Negishi cross-coupling reactions with both electron-poor and -rich aryl bromides. Thus, the highly functionalized cross-coupling products **5d–e** have been obtained in 71–73% yield (entries 3 and 4).

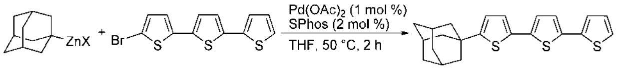
The synthesis and investigation of well-defined model oligomers is of high interest due to the structural and electronic properties of these molecules. Depending on their size and substitution pattern oligothiophenes are usually more soluble than polymers, allowing the precise characterization of the electronic and geometric structures both in solution and in the solid state.[20]

The solubility of oligothiophenes decreases dramatically with increasing chain length, which is due to the stiffness of the conjugated π-system and the strong interactions between the chains. The solubility issue can be solved with the synthesis of corresponding oligothiophenes bearing alkyl substituents.[21] Several α-alkyl-substituted oligothiophenes were prepared and characterized by various research groups. Especially monosubstituted derivatives are attractive candidates since they offer the possibility of dimerization leading to the corresponding α,α'-disubstituted oligothiophenes with a double conjugated chain length.[20]

Following this idea, adamantylzinc reagent **2a** was submitted to a Negishi cross-coupling with the 5-bromo-terthiophene **6**, furnishing the corresponding α-substituted oligothiophene **7** in 64% yield (Scheme 5).

Noteworthy, α-adamantyl-terthiophene **7** displays an excellent solubility in chloroform. Its solubility is $17.0\cdot10^{-2}$ M in $CHCl_3$ compared to $5.6\cdot10^{-2}$ M of the unsubstituted derivative (ca. 3 fold increase). The higher solubility arises most probably from two reasons; on one hand, the apolar adamantyl-moiety is known to strongly

Scheme 5. Synthesis of α-adamantyl-terthiophene 7



2a **6** (0.9 equiv) **7**: 64%

increase the lipophilicity of molecules, and on the other hand, its bulkiness prevents π-stacking of the oligothiophene molecules. Therefore **7** should be an ideal candidate for the synthesis of a highly soluble α,α'-substituted diadamantyl oligothiophene via literature known procedures.[20]

In summary, we have developed a mild and convenient procedure for the selective synthesis of adamantylzincs, tolerating for the first time functional groups on the adamantyl scaffold using a LiCl-mediated Mg insertion in the presence of $ZnCl_2$. The highly reactive adamantylzinc species **2a−c** readily undergo a broad variety of functionalization reactions in the presence of an appropriate catalyst. Furthermore, the adamantyl moiety was introduced as an α-substituent in an oligothiophene, increasing its solubility (ca. 3 fold). Further extensions of this work are currently underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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