Adamantylzinc Bromides: Direct Preparation and Application to Cross-Coupling Reaction

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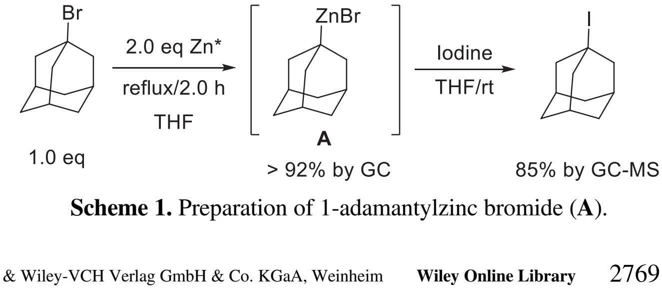
The cross-coupling reaction of zinc-based organometallic reagent has been regarded as a valid protocol for the generation of new carbon–carbon bonds mainly due to the excellent tolerance of the organic functional groups.[1] In addition, organic fragments of organozinc reagents easily transfer to the catalyst metal in the course of metal-catalyzed coupling reactions. Owing to the reliable nature of organozinc chemistry, this protocol has become prominent in a wide range of organic synthesis. For the preparation of organozinc reagents, both transmetallation of Grignard or organolithium with zinc halide and direct insertion of zinc metal have been the most utilized methodologies.[2] Tremendous work on the synthesis and application of organozincs have been accomplished.

Very recently, we have provided several works on the applications of highly active zinc prepared by the reduction of zinc halides in the presence of lithium naphthalide in tetrahydrofuran (THF).[3] Considering the promising results from our research, we supposed that the direct preparation of an adamantylzinc reagent would be possible. Since the adamantane moiety has been frequently found in various fields, such as medicinal, drug, supramolecular, and nanochemistry,[4] developing a facile pathway to introduce an adamantane scaffold is a frequently encountered subject in the synthesis of functional organic molecules, and, until now, this goal has been mostly achieved by utilizing a limited number of adamantylmetallic reagents including as adamantylmagnesium[5] and adamantylzinc.[6]

Among the previous work, a very recent publication presented by Knochel *et al.* has immediately attracted our attention.[7] In this work, the preparation of adamantylzinc reagents via LiCl-mediated Mg-insertion in the presence of $ZnCl_2$ and their applications to the coupling reactions were presented. And, interestingly, an inefficient work on the formation of 1-adamantylzinc bromide from using the Rieke zinc and 1-bromoadamantane was highly emphasized (65% conversion). However, on the basis of the several established results from both Rieke's[6] and our laboratories,[8] this citation could be a potentially controversial subject. Therefore, we decided to readdress the direct preparation of adamantylzinc reagents and their applications to cross-coupling reactions in anticipation of more positive results.

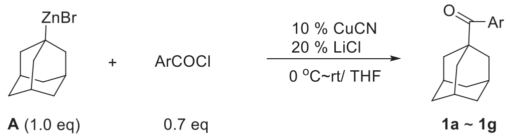
To accomplish the intended goal, an initial investigation was made, starting with readily available 1-bromoadamantane and highly active zinc (Zn*) prepared by the literature procedure.[6] To our delight, treatment of 1.0 equiv of 1-bromoadamantane with 2.0 equiv of active zinc at refluxing temperature for 2 h showed the total consumption of 1-bromoadamantane, leading to a peak corresponding to organozinc (**A**) with over 92% conversion as described in Scheme 1. Prior to the general application of **A** to cross-coupling reactions, the reactivity of the organozinc reagent was examined by iodine quenching. An aliquot of the organozinc solution in THF was treated with iodine and the resultant solution was analyzed by both gas chromatography (GC) and gas chromatography–mass spectrometry (GC–MS). Both analysis data conclusively showed the formation of 1-adamantyl iodide with over 85% yield. To confirm this result, isolation by flash column chromatography was used and showed 79% isolated yield of 1-adamantyl iodide. Consequently, it can be concluded that the expected organozinc bromide, 1-adamantylzinc bromide, was successfully obtained under the conditions used in this study.

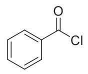
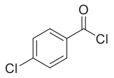
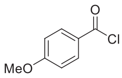
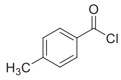
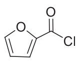
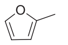
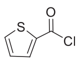
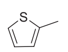
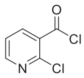
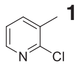
With the verified reactivity of the organozinc reagent (**A**) in hand, we next turned our attention to expanding the scope of **A**, which was accomplished by the cross-coupling reactions with several electrophiles. Our first attempt for the coupling reactions with a wide range of acid chlorides was to prepare ketones (results are summarized in Table 1). The coupling reactions were carried out under typical copper-catalyzed reaction conditions: 10 mol % CuCN and 20 mol % LiCl at 0 °C in THF. The coupling reaction of 1-adamantylzinc bromide with benzoyl chloride proceeded smoothly to produce



Scheme 1. Preparation of 1-adamantylzinc bromide (**A**).

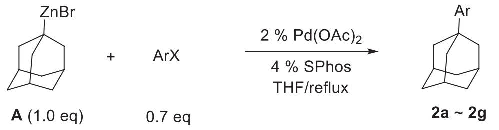
Table 1. Coupling reaction of **A** with acid chlorides.

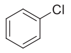
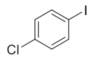
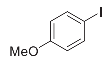
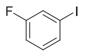
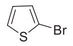
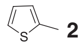
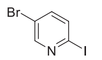
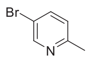
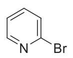
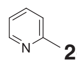


Entry	ArCoCl	Time (h)	Product (Ar)	Yield (%)[a]
1		5	C_6H_5 **1a**	40
2		3	4-ClC_6H_4 **1b**	62
3		3	4-$MeOC_6H_4$ **1c**	42
4		2	4-$CH_3C_6H_4$ **1d**	55
5		24	 **1e**	39
6		24	 **1f**	20
7		3	 **1g**	54

[a] Isolated yield (based on acid chloride).

Table 2. Coupling reaction of **A** with aryl halides.



Entry	ArX	Time (h)	Product (Ar)	Yield (%)[a]
1		24	C_6H_5 **2a**	51
2		2	4-ClC_6H_4 **2b**	32
3		1	4-$MeOC_6H_4$ **2c**	55
4		12	3-FC_6H_4 **2d**	26
5		24	 **2e**	41
6		24	 **2f**	53
7		24	 **2g**	44

[a] Isolated yield (based on aryl halide).

adamantan-1-yl(phenyl)methanone (**1a**) in a moderate isolated yield (entry 1, Table 1).

This catalyst system worked well for the other acid chlorides containing an electron-donating group (OCH_3 and CH_3) and a halogen (Cl), producing the ketones (**1b–1d**) in moderate yields (entries 2–4, Table 1). Heteroaromatic acid chlorides were also shown to be suitable coupling partners for the preparation of aryl adamantyl ketones (**1e–1g**) under the same conditions. Relatively lower results were obtained from the coupling reactions with 2-furancarbonyl chloride (entry 5, Table 1) and 2-thiophenecarbonyl chloride (entry 6, -Table 1). It is of much interest that the reaction conditions used for the aforementioned coupling reactions also worked well for the coupling reaction with 2-chloronicotinyl chloride. As shown in Table 1, the coupling product (**1g**) was successfully produced through the reaction with 2-chloronicotinyl chloride with a 54% yield (entry 7, Table 1).

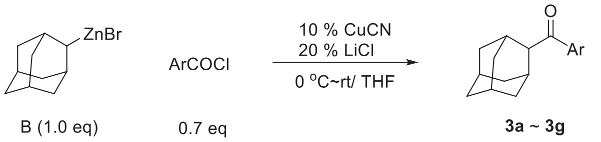
The application of **A** to the coupling reactions was not only limited to the preparation of ketones. In our next effort to expand the scope of 1-adamantylzinc bromide, a palladium-catalyzed carbon–carbon bond was also used. In this application, a $Pd(OAc)_2$ and SPhos-catalyst system was selected after a catalyst-screening test. It worked well to provide 1-aryl-substituted adamantane derivatives and the results are summarized in Table 2.

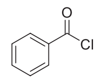
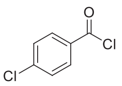
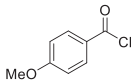
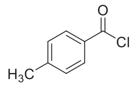
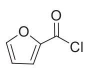
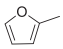
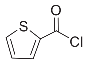
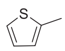
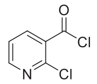
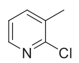
The promising observation from the applications of 1-adamantylzinc bromide (**A**) allowed us to explore other adamantylzinc reagent, such as 2-adamantylzinc bromide (**B**) which has less steric demand. The preparation of **B** was carried out under the same conditions used for **A**. As expected, treatment of 2-bromoadamantane with active zinc easily converted to the corresponding organozinc (**B**). Then, the resulting organozinc (**B**) was examined with a variety of electrophiles in the same manner employed with **A**. The results are summarized in Table 3. Again, the coupling reactions with acid chlorides proceeded smoothly under the mild conditions, affording the desired ketones (**3a–3g**) in slightly higher yields than those obtained from using organozinc reagent **A**. This result could be easily understood considering the less steric demand of the reaction site of the organozinc reagent **B**, *i.e.*, tertiary (**A**) vs. secondary (**B**).

Palladium-catalyzed coupling reactions of **B** with halogenated benzenes (entries 1–4, Table 4) proceeded smoothly, resulting in the formation of the corresponding aryl-substituted adamantanes (**4a**, **4b**, **4c**, and **4d**) in good yields. Reaction with heteroaryl halides also proceeded smoothly to yield heteroaryl-substituted adamantanes in good yields. 2-Bromothiophene reacted with **B** to afford **4e** with 70% yield (entry 5, Table 4). A good result was obtained from the coupling reaction using 2-iodo-5-bromopyridine (entry 6, Table 4). The coupling reaction with 2-bromopyridine also proceeded well to generate **4g** in moderate yield (entry 7, Table 4).

We then attempted the coupling reaction of the organozincs (**A** and **B**) with haloaromatic compounds containing an amine functional group, and this reaction was more challenging. Even though there are very limited examples of coupling reactions of organozinc compounds with haloaromatic amines,[9] to

Table 3. Coupling reaction of **B** with acid chlorides.



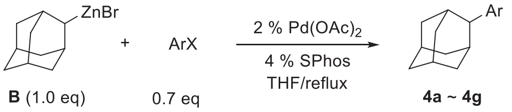
Entry	ArCoCl	Time (h)	Product (Ar)	Yield (%)^a
1		5	C_6H_5 **3a**	58
2		5	4-ClC_6H_4 **3b**	65
3		5	4-$MeOC_6H_4$ **3c**	62
4		5	4-$CH_3C_6H_4$ **3d**	59
5		24	 **3e**	43
6		24	 **3f**	28
7		3	 **3g**	54

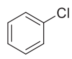
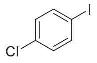
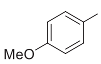
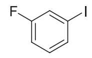
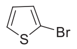
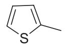
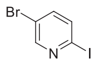
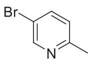
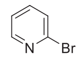
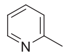
^{a} Isolated yield (based on acid chloride).

the best of our knowledge, no report revealed the coupling reaction with adamantylzinc halides. As illustrated in Figure 1, the reaction of **A** with 4-iodoaniline in the presence of 2 mol % $Pd(OAc)_2$ and 4 mol % SPhos gave rise to the cross-coupling product, 4-(adamantan-1-yl)aniline (**5a**), with 53% isolated yield. 3-Iodoaniline was also coupled with **A** under the same conditions, affording **5b** in a similar manner. More successful coupling reactions were achieved using **B** under the same conditions, yielding **5c** and **5d** in 73% and 84% isolated yields, respectively.

In conclusion, we have demonstrated an efficient synthetic route for the direct preparation of adamantylzinc bromides (**A** and **B**) from active zinc and adamantyl bromides, as well as their applications to the cross-coupling reactions with a variety of electrophiles. The direct oxidative addition of active zinc into 1- and 2-bromoadamantanes and the subsequent coupling reactions were completed under mild reaction conditions. From these observations, it can be concluded that the synthetic strategy of using highly active zinc and bromoadamantanes for the preparation of the corresponding adamantylzinc reagents can be effective.

Table 4. Coupling reaction of **B** with arylhalides.



Entry	ArX	Time (h)	Product (Ar)	Yield (%)^a
1		24	C_6H_5 **4a**	67
2		2	4-ClC_6H_4 **4b**	85
3		4	4-$MeOC_6H_4$ **4c**	83
4		4	3-FC_6H_4 **4d**	82
5		24	 **4e**	70
6		24	 **4f**	81
7		24	 **4g**	57

^{a} Isolated yield (based on ArX).

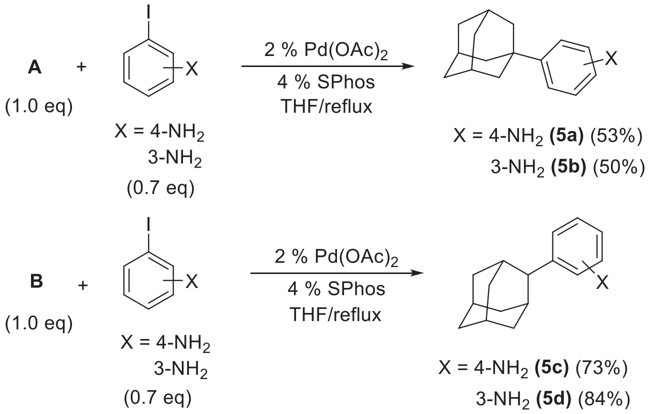


Figure 1. Coupling reaction with iodoanilines.

Experimental

Representative Procedures. Preparation of 1-adamantylzinc bromide (**A**): In an oven-dried 250 mL round-bottomed flask equipped with a stir bar was added 6.54 g of active zinc (Zn*, 100.0 mmol) in 100 mL of THF. Next, 1-bromoadamantane (10.5 g, 50.0 mmol) was cannulated into the flask at room temperature. The resulting mixture was then allowed to reflux for 2 h. The solution was cooled to room temperature and settled down. Then the supernatant was used for the subsequent coupling reactions.

Preparation of adamantan-1-yl-(4-methoxyphenyl)methanone (**1c**): Into a 25 mL round-bottomed flask were placed CuCN (0.02 g, 10 mol %) and LiCl (0.02 g, 20 mol %). The flask was pumped down and recharged with argon gas. Then, 2.0 mL of THF was added to dissolve. The flask was cooled to 0 °C using an ice-bath. 4-Methoxybenzoyl chloride (0.24 g, 1.4 mmol) dissolved in 2.0 mL of THF was added into the flask. Next, 4.0 mL of 1-adamantylzinc bromide (0.5 M in

THF, 2.0 mmol) was cannulated into the flask under argon atmosphere at 0 °C, then the whole mixture was allowed to warm up gradually to room temperature over 3 h while being stirred. Quenched with saturated 3 M HCl solution, then extracted with ethyl ether (10 mL × 3). Washed with saturated $NaHCO_3$, 8% NH_4OH solutions, and brine, then dried over anhydrous $MgSO_4$. Purification by flash column chromatography (hexanes/ethyl acetate) afforded 0.16 g of **1c** in 42% isolated yield as a pale yellow solid (mp 91–94 °C); ^1H NMR ($CDCl_3$, 500 MHz) $\delta = 7.77$ (d, $J = 9.0$ Hz, 2H), 6.88 (d, $J = 9.0$ Hz, 2H), 3.85 (s, 3H), 2.09–2.05 (m, 9H), 1.76 (br s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) $\delta = 207.2$, 161.6, 131.6, 131.0, 55.3, 46.8, 39.5, 36.6, 28.3.

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