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Revelation of the Difference between Arylzinc Reagents Prepared from Aryl Grignard and Aryllithium Reagents Respectively: Kinetic and Structural Features

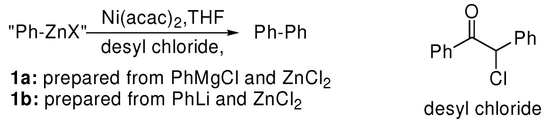
Liqun Jin,[†] Chao Liu,[†,§] Jing Liu,[†] Fang Hu,[†] Yu Lan,[†] Andrei S. Batsanov,[§] Judith A. K. Howard,[§]
Todd B. Marder,*[,§] and Aiwen Lei*[,†,‡]

College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072, P. R. China, State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai, 200032, P. R. China, and Department of Chemistry, Durham University, South Road, Durham DH1 3LE, U.K.

Received September 26, 2009; E-mail: aiwenlei@whu.edu.cn; todd.marder@durham.ac.uk

Organozinc reagents with the virtues of easy preparation, good reactivity, and broad functional group compatibility are increasingly commonly applied in bond construction reactions such as Negishi coupling,[1−4] Fukuyama coupling,[5] and oxidative cross-coupling, etc.[6,7] The reagents are easily prepared in situ from the exchange of Grignard reagents RMgX or organolithium reagents RLi with zinc halides ZnX_2, and it is usually considered that both methods generate the same organozinc halide RZnX product.[8,9] Side products, such as MgX_2 or LiX, are generally neglected in spite of their existence in the system. Walsh et al. showed that MgX_2 or LiX could significantly affect the enantioselectivities in the reaction of R_2Zn with ArCHO.[10] Knochel et al. recently reported that additives played specific roles in the preparation of organozinc reagents.[11,12] Furthermore, Fu et al. observed that sources of arylzinc reagents affected the yields of Ni-catalyzed Negishi type cross-coupling reactions.[13−16] These results indicate that the structures of organozinc reagents are possibly not as simple as RZnX. To date, however, detailed investigation of organozinc reagents regarding their structure and kinetic behavior in the transmetalation step is rather limited.[17,18] Herein, we communicate mechanistic studies employing arylzinc reagents generated from aryl-Grignard and aryllithium reagents, respectively, which revealed unprecedented differences in the nature of the two species.

Scheme 1. Oxidative Homocoupling of Phenylzinc Reagents



1a: prepared from PhMgCl and $ZnCl_2$
1b: prepared from PhLi and $ZnCl_2$

We have recently reported a Ni-catalyzed oxidative coupling of arylzinc reagents such as **1a** prepared from aryl Grignard reagents and $ZnCl_2$ (Scheme 1).[19] The reaction exhibited a zero-order kinetic plot and achieved 100% conversion within 4 min at −20 °C with 2 mol % of $Ni(acac)_2$ (Figure 1a). The transmetalation step of the reaction was established to be very fast, and reductive elimination was determined to be rate-limiting. However, when the same model reaction was employed to test the reactivity of phenylzinc reagent **1b** prepared from phenyllithium and $ZnCl_2$, the reaction was very slow and only proceeded to 13% conversion after 50 min under the same conditions; the reaction took over 50 min to achieve 87% conversion at 0 °C with 4 mol % of $Ni(acac)_2$ (Figure 1a). Moreover, the kinetic plot using **1b** was curved, indicating that the kinetic behavior was not zero-order.

Thus, the system with **1b** was investigated further. Variation of the initial concentration of desyl chloride displayed little influence upon the reaction as shown in Figure 1b, indicating that the reaction rate was zero-order in [desyl chloride].[20] However, a first-order kinetic plot was obtained in the initial concentration of phenylzinc reagent **1b** (Figure 2a). The results revealed that, in the **1b** system, the transmetalation step was rate-limiting, in complete contrast to the behavior of the **1a** system (*vide supra*).[21]

Consequently, it could be reasonably deduced that the transmetalation step in the **1b** system is much slower than that in the **1a** system as the species from which reductive elimination takes place is the same in both systems.[22] It is noteworthy that when $MgCl_2$ was added to the **1b** system, the reaction was much faster (Figure 2b).[23] Therefore, $MgCl_2$ may be involved in the structure of phenylzinc reagent **1a**, and its presence significantly accelerates the transmetalation step in some manner.

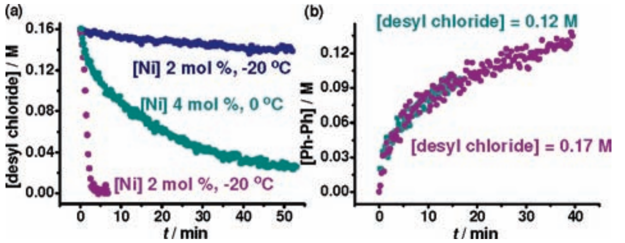


Figure 1. (a) Kinetic plots of Ni-catalyzed oxidative homocoupling of **1a** and **1b** with desyl chloride (0.16 M) as the oxidant. (b) Kinetic plots of Ni-catalyzed oxidative homocoupling of **1b** at 0 °C.

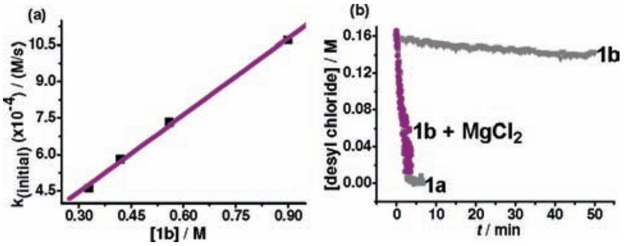
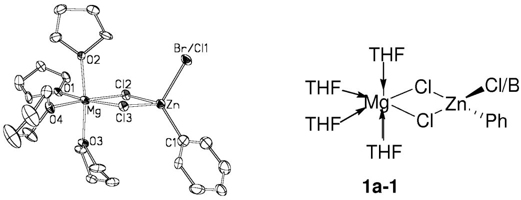


Figure 2. (a) Relationship between the initial rate constants and [**1b**] with [**1b**] = 0.33−0.9 M. (b) Kinetic plots of the Ni-catalyzed oxidative homocoupling of **1b** in the absence and presence of $MgCl_2$.



1a-1

Figure 3. X-ray molecular structure of $(THF)_4Mg(\mu\text{-}Cl)_2Zn(Ph)X$ **1a** (30% probability thermal ellipsoids, H atoms are omitted). Cl(1) and Br(1) share the same site in a 44:56 ratio, and the phenyl group site is partially occupied (ca. 10%) by Br.

The structures of arylzinc iodides generated from the corresponding aryllithium and zinc iodide were reported to be diiodo-bridged dimers

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[†] Wuhan University.
[§] Durham University.
[‡] Chinese Academy of Sciences.

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[ArZn(μ-I)$_2$ZnAr] by X-ray diffraction analysis,[24,25] and a dichloro-bridged dimer [Zn(μ-Cl)(C$_6$F$_5$)(η-C$_6$Me$_6$)]$_2$ with a similar structure was also reported.[26] A single crystal was obtained from **1a**, prepared from PhMgBr and ZnCl$_2$, which was shown by X-ray diffraction analysis to be the novel dichloro-bridged Zn/Mg complex **1a-1** (Figure 3). An analogous structure, in which Ph is replaced by ^{t}Bu, has recently been observed[27] from reaction of ^{t}BuMgCl and ZnCl$_2$, demonstrating that coordination of (THF)$_4$MgCl$_2$ to RZnX is likely to be a general phenomenon.

Attempts to obtain the crystal structure of **1b** failed, and only [(LiCl)(dioxane)]$_n$ crystallized (see Supporting Information). Surprisingly, the NMR spectra of **1a**, prepared from PhMgCl and ZnCl$_2$, were completely different from those of **1b** or PhMgCl (Figure 4). In THF, the *ipso*-Ph-carbon in PhMgCl gives rise to a sharp signal at 170.8 ppm, whereas the corresponding signals for **1b** (158.5 ppm) and **1a** (154.2 ppm) (Figure 4) are slightly broadened, although the remaining signals in the ^{13}C and all signals in the ^{1}H NMR spectra are sharp at room temperature.[28]

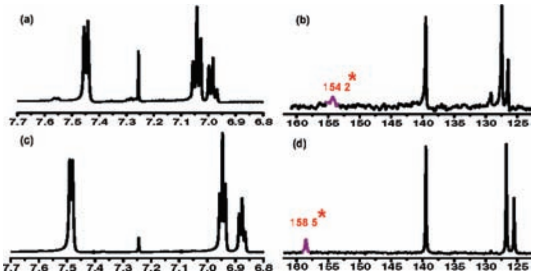
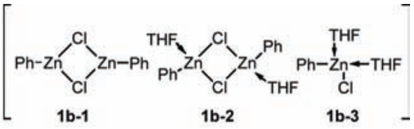


Figure 4. Solution NMR spectra: (a) ^{1}H NMR of **1a**; (b) ^{13}C NMR of **1a**; (c) ^{1}H NMR of **1b**; (d) ^{13}C NMR of **1b**.



	1a-1	1b-1	1b-2	1b-3
Gas Phase (kcal / mol)	155.0	228.1	183.6	182.2
THF (kcal / mol)	82.7	141.6	107.3	99.7

Figure 5. Heterolytic dissociation energy of phenyl anion from Zn.

To examine further the relevance between the reactivity differences and structures of **1a** and **1b**, we carried out DFT calculations on **1a-1** and three possible structures for **1b** (for a discussion of selected known ArZn structures, see the Supporting Information), shown in Figure 5 as **1b-1**, **1b-2**, and **1b-3**. The computed heterolytic dissociation energies of Ph$^-$ to Zn are also given in Figure 5. The dissociation energies of **1a-1** are much lower than those of **1b-1**, both in the gas phase and in THF (Figure 5). Other possible structures of **1b** with THF coordinated to the Zn center (e.g., **1b-2**, and **1b-3**) were considered, and their Ph−Zn heterolytic dissociation energies were all computed to be higher than those of **1a-1** under the same conditions. Thus, the Zn−Ph bond of **1a** is easier to break, suggesting a greater nucleophilicity of **1a**. The calculations are consistent with the kinetic results, which show increased transmetalation rates for **1a**, potentially indicative of increased nucleophilicity. In addition, DFT geometry optimizations gave C−Zn bond distances in **1a-1** and **1b-1** of 1.975 and 1.936 Å, respectively, consistent with a weaker bond in the former species.

In conclusion, a remarkable kinetic difference was observed in the Ni-catalyzed oxidative homocoupling of phenylzinc reagents **1a** and **1b** prepared from phenyl Grignard and phenyl lithium reagents, respectively. The **1a** system exhibited zero-order kinetic behavior, indicating a facile transmetalation process. In contrast, the **1b** system displayed first-order kinetics with respect to the concentration of **1b**, and the transmetalation step was determined to be rate-limiting and much slower than that in the **1a** system. NMR experiments revealed the differences in the nature of **1a** and **1b** in a THF solution. Addition of MgCl$_2$ to **1b** greatly accelerates the reaction rate, and MgCl$_2$ was shown to complex to the zinc reagent by single crystal X-ray diffraction.[29] Further investigations regarding the detailed structures and transmetalation processes of **1a** and **1b** are ongoing in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures and compound characterization and kinetic data, and discussion of structures of arylzinc complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) The detailed comparison is as follows: TM (**1a**) $\gg$ RE (**1a**), TM (**1b**) $\ll$ RE (**1b**), RE (**1a**) = RE (**1b**). Thus, TM(**1a**) $\gg$ TM(**1b**). TM: rate of transmetalation step. RE: rate of reductive elimination step.
(23) The mixture of phenylzinc chloride **1b** and MgCl$_2$ was stirred for 2 h before the addition of desyl chloride and Ni-catalyst.
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(28) There is clearly a dynamic process, but only the *ipso* C and *ortho* H resonances are significantly affected by temperature.
(29) Determination of how MgCl$_2$ facilitates the transmetalation and corresponding DFT calculations for this process are ongoing in this laboratory and will be reported in due course.

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