## NOVEL METHOD FOR GENERATION OF SECONDARY ORGANOZINC REAGENT: APPLICATION TO TANDEM CARBON-CARBON BOND FORMATION REACTION OF 1,1-DIBROMOALKANE

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Summary: Reaction of 1,1-dibromoalkane  $(R^1CHBr_2)$  with trialkylzincate  $((R^2)_3ZnLi)$  followed by a palladium catalyzed coupling reaction of the resulting secondary organozinc reagent  $(R^1CH(R^2)ZnL)$  with various electrophiles (El-X) afforded  $R^1CH(R^2)El$ .

Organozinc compounds which can lead to an efficient and highly selective carbon-carbon bond formation are of increasing importance as intermediates in synthetic organic chemistry.<sup>1-4</sup> Due to their versatility, considerable effort has been devoted, especially in recent years, to the preparation of organozinc compounds.<sup>5</sup> Development of the improved procedure for direct metallation of organic iodide with Zn/Cu allowed the preparation of a variety of functionalized organozinc reagents.<sup>2,5a</sup> Halogen/metal exchange reactions frequently employed for the preparation of organometallics are less common but promising route to organozinc compounds.<sup>6</sup> In this respect, we recently reported facile generation of alkenylzinc (1a) and 1-alkylcyclopropylzinc (2a) by the Br/Zn exchange reaction of the corresponding *gem*-dibromo compounds with lithium trialkylzincate (( $\mathbb{R}^3$ )<sub>3</sub>ZnLi) followed by an intramolecular alkylation of the resulting zincate carbenoid 1b and 2b, respectively.<sup>7,8</sup> Here we report a novel method for generation of secondary organozinc reagents from 1,1-dibromoalkanes by utilizing the Br/Zn exchange reaction with trialkylzincate and their application to a tandem carbon-carbon bond formation reaction of 1,1-dibromoalkanes.<sup>9</sup>

$$\begin{array}{ccc} R^{1} & X & R^{1} & X \\ R^{2} & Y & R^{2} & Y \\ 1a,b & & 2a,b \end{array} \qquad a; X = R^{3}, Y = ZnL \\ b; X = Zn(R^{3})_{2}Li, Y = Bn \\ \end{array}$$

We found that secondary organozinc reagent 5 can be generated by the reaction of 1,1-dibromoalkane  $3^{10}$  with  $(R^2)_3$ ZnLi<sup>11</sup> (5 equiv) in THF at temperatures from  $-85^{12}$  to 20 °C (Scheme 1). Hydrolysis of the resulting mixture gave the corresponding alkylation product 6 in considerable yields. As shown in the results summarized in Table 1 (entries 1-5), a primary, secondary, and tertiary alkyl group as well as a methyl group can be introduced by using the corresponding trialkylzincate.<sup>13</sup>

Scheme 1



## Scheme 2



1,1-Dibromoalkane 3 exhibited lower reactivity in the Br/Zn exchange reaction in comparison with 1,1dibromoalkene and 1,1-dibromocyclopropane which undergo a rapid exchange reaction at -85 °C<sup>7</sup> to afford stable zincate carbenoid 1b and 2b at this temperature. In contrast, the reaction of 3a with (Bu)3ZnLi did not go to completion even at -40 °C for 1 h and gave alkylation product 6 in 27% yield with the recovery of 3a (58%). Absence of 1-bromononane in this reaction strongly suggests that the rate of the Br/Zn exchange reaction of 3 is slower than that of the subsequent alkylation reaction.

While it is well established that various organozinc compounds undergo a palladium catalyzed crosscoupling reaction with organic halides,<sup>1</sup> few examples of the reaction of secondary organozinc compounds were reported.<sup>1c</sup> This may be not only due to the less accessibility of the secondary organozinc compounds possessing wide-range of structures but also due to their susceptibility to isomerization under the cross-coupling reaction conditions.<sup>1c</sup> We found that secondary organozinc reagents generated by the reaction of 1.1dibromoalkanes with trialkylzincate lead to an efficient carbon-carbon bond formation reaction with various electrophiles in the presence of a proper palladium catalyst (Scheme 2).

Reactions of the secondary organozinc species 5 with acyl chlorides in the presence of  $Pd(PPh_3)_2$  (5 mol%) prepared in situ from  $PdCl_2(PPh_3)_2$  and DIBALH gave ketones 7 in considerable yields (entries 6-10). Addition of  $ZnCl_2$  and employment of  $PdCl_2(P(o-Tol)_3)_2$  (5 mol%) as a catalyst are necessary for the reaction of 5 with aryl (entries 11-13) and alkenyl halides (entries 14-17).<sup>14</sup> Results summarized in Table 1 demonstrate broad applicability of the present reaction as a tandem carbon-carbon bond formation reaction of 1,1-dibromoalkanes.<sup>15</sup> It should be noted that the formation of isomeric products which would be derived from the possible isomerization of organozinc intermediates were not detected by the capillary GC and/or 200 MHz <sup>1</sup>H-NMR analysis of crude products in these reactions.

In summary, we have shown that (1) the reaction of 1,1-dibromoalkane with trialkylzincate provides a novel method for the generation of secondary organozinc species which accompanies carbon-carbon bond formation, and (2) organozinc species thus generated further undergoes the palladium catalyzed coupling reaction with various electrophiles. Present reaction allows the utilization of readily available 1,1-dibromoalkane<sup>10</sup> as  $a^{1}/d^{1}$  synthon<sup>16</sup> affording wide range of carbon structures by the successive introduction of carbon nucleophiles and electrophiles.

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Entry	Dibromoalkane	Nucleophile	Electrophile	Procedurea	Productb	Yield(%) <sup>C</sup>
1	3a	Bu3ZnLi	H <sub>2</sub> O	Α	tridecane	77d
2	3a	<sup>s</sup> BuzZnLi	H <sub>2</sub> O	Α	3-methyldodecane	62 <sup>d</sup>
3	3a	<sup>t</sup> Bu3ZnLi	H <sub>2</sub> O	Α	2,2-dimethylundecane	71d
4	3a	MezZnLi	H <sub>2</sub> O	Α	decane	61 <sup>d</sup>
5	3b	BuzZnLi	H <sub>2</sub> O	Α	1-phenylheptane	83
6	3a	Bu3ZnLi	AcCl	В	Octyl H Bu Bu	62
7	3a	BuzZnLi	PhCOCl	В	Octvl APh	75
8	3a	Bu3ZnLi	<sup>t</sup> BuCOCl	В		57
9	3b	<sup>t</sup> Bu3ZnLi	AcCl	В		72
10	3c	Bu3ZnLi	AcCl	В		64
11	3b	BuzZnLi	PhBr	с	Ph Ph	62
12	3b	Bu3ZnLi	p-AcC6H4Br	с	Ph C <sub>6</sub> H <sub>4</sub> (p-Ac)	57
13	3b	<sup>s</sup> Bu3ZnLi	PhBr	С	Ph Ph	62
14	3b	Bu3ZnLi	(Me) <sub>2</sub> C=CHB	r D	Ph	72
15	3b	BuzZnLi	CH <sub>2</sub> =C(Me)B	r D	Ph	61
16	3b	<sup>s</sup> Bu3ZnLi	CH <sub>2</sub> =C(Me)B	r D	Ph Charles Bu	62
17	3c	Bu3ZnLi	CH <sub>2</sub> =C(Me)B	r D	тнро	57

Table 1 Tandem Carbon-Carbon Bond Formation of 1,1-Dibromoalkane 3 via Zincate Carbenoid

<sup>a</sup>For the reaction procedures A-D, see captions in Schemes 1 and 2. <sup>b</sup>All new compounds showed satisfactory <sup>1</sup>H- NMR, IR, and high resolution MS data. <sup>c</sup>Isolated yield, unless otherwise noted. <sup>d</sup>Determined by GC analysis.

## **References and Notes**

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- (11) Zincate (R3ZnLi) was prepared by the reaction of anhydrous ZnCl<sub>2</sub> with 3 equiv of RLi in THF at 0 °C.
- (12) The temperature -85 °C is not critical in the present reaction. Authors usually use a Neslab Cryocool CC-80 immersion cooler in performing low temperature reactions.
- (13) When an excess amount of trialkylzincate was not used, considerable amount of bromide R<sup>1</sup>CH(Br)R<sup>2</sup>
  (i), a product of a formal displacement reaction of 3 with trialkylzincate, was obtained as by-product. Since its formation was completely suppressed in the presence of an excess amount of the reagent, i was most probably produced by the competitive Br/Zn exchange reaction of 3 with zincate R<sup>1</sup>CH(Zn(R<sup>2</sup>)<sub>2</sub>Li)R<sup>2</sup> which is formed by a ligand exchange reaction of 5 with (R<sup>2</sup>)<sub>3</sub>ZnLi.
- (14) Without the addition of ZnCl<sub>2</sub>, no cross-coupling product was obtained in the reaction with bromobenzene or 2-bromopropene in the presence of the following Pd catalysts; (PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>(dppf) (dppf; 1,1'-bis(diphenylphosphino)ferocene), and PdCl<sub>2</sub>(P(o-Tol)<sub>3</sub>)<sub>2</sub>).
- (15) Typical reaction procedures are as follows (entry 11 in Table 1). To a solution of (Bu)3ZnLi (2.5 mmol) in THF (8 mL) was added 0.5 mmol of dibromoalkane 4b in THF (1.5 mL) at -85 °C under nitrogen atmosphere, and the resulting mixture was slowly warmed up to a room temperature during 3 h. To this were added successively 5.0 mmol of ZnCl<sub>2</sub> in THF (15 mL), 7.5 mmol of bromobenzene, and 0.025 mmol of PdCl<sub>2</sub>(P(o-Tol)<sub>3</sub>)<sub>2</sub> in THF (1 mL) and the mixture was stirred overnight at the room temperature. After the addition of 1N HCl followed by extraction with hexane and the subsequent washing with aq NaHCO<sub>3</sub>, the dried organic layers were concentrated in vacuo and the resulting crude mixture was purified with silica gel column chromatography (hexane) to give 1,3-diphenylheptane in 62% yield.
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