Carbozincation of Dipolar Trimethylenemethane. A New Route to Functionalized Organozinc Reagents

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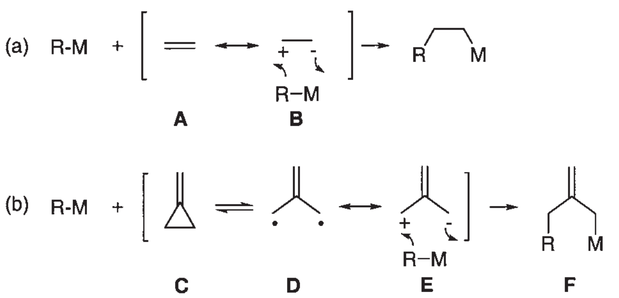
Dipolar trimethylenemethane species, thermally generated from 2,2-dialkoxy-1-methylenecyclopropane, reacts with a dialkylzinc reagent to generate an allylic zinc reagent, which then reacts in situ with a carbonyl compound to give a hydroxy acetal product as the result of coupling of the three reactants.

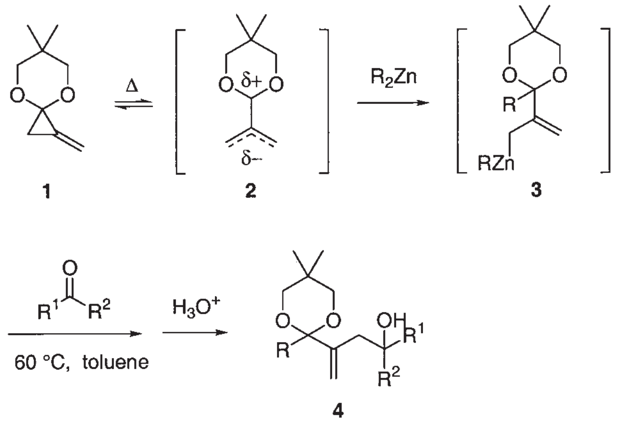
Addition of an organozinc reagent across an olefin **A** is a well-established method for the synthesis of functionalized organozinc reagents[1] as we have described in our previous reports.[2,3] One can rationalize this reaction in terms of a polarized resonance form **B** of the olefin (Scheme 1a, M = Zn). In a similar way, one would expect that an organometallic reagent undergoes addition also to a trimethylenemethane (TMM) intermediate, that is, to its 1,3-dipole resonance form **E** (Scheme 1b). Ideally, one may hope that methylenecyclopropane **C** undergoes ring opening to generate a TMM, dipole **E**, that reacts with an organozinc reagent to generate an allylic zinc reagent **F**. This straightforward scheme so far never produced any fruitful experimental outcome, since, first, methylenecyclopropane does not produce any TMM species under mild thermal conditions, and, second, the TMM intermediates generally exist as biradical species **D**, and seldom exhibit dipole character.[4]



Scheme 1.

In this Letter, we report the first demonstration of the feasibility of this synthetic scheme for a combination of dialkoxymethylenecyclopropane (DMCP) **1** and a dialkylzinc reagent R_2Zn (Scheme 2). The addition of R_2Zn to dialkoxy TMM intermediate **2**,[5,6] a biradical species possessing dipolar character,[4] generates a functionalized allylic zinc reagent **3**. This new carbometalation reaction provides a unique method for in-situ three-component coupling of a dialkylzinc reagent, DMCP and a carbonyl compound that produces a richly functionalized hydroxy acetal product **4**.

The synthetic protocol to achieve the three-component coupling developed after considerable experimentation is very simple: Heating of a 1 : 2 : 1.1 mixture of **1**, R_2Zn, and a carbonyl compound in toluene at 60 °C results in complete consumption of DMCP **1** after 2.5–4 h.[7,8] For instance, the coupling of **1**, Et_2Zn and cyclohexanone afforded the product **4** in 80% isolated yield. There also formed a small amount of the acetal of an α-methylene-γ-lactone (6%), the product of direct [3 + 2] cycloaddition between TMM **2** and the ketone–an inevitable side reaction.[6c–h] The same experiment using a 1 : 1 : 1 stoichiometry afforded the desired product only in 43% yield together with the lactone acetal (5%).



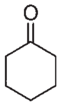
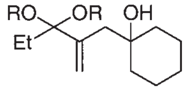
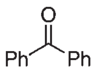
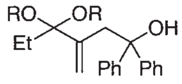
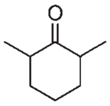
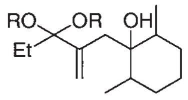
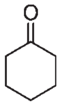
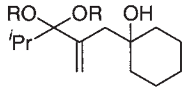
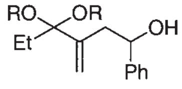
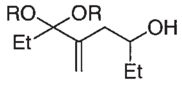
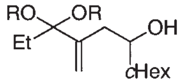
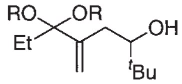
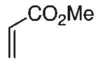
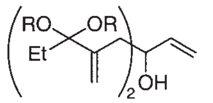
Scheme 2.

The results of the three-component coupling are summarized in Table 1. There was found an interesting trend in the correlation of the product yield and the steric hindrance of the carbonyl group. Thus, the yield was the highest for the hindered ketones, benzophenone (90%, entry 2) and 2,6-dimethylcyclohexanone (88%, entry 3), and decreased in an order of cyclohexanone (80%, entry 1) to aldehydes (71–79%, entries 5–8). The major side product was the lactone acetal mentioned above. For 2,6-dimethylcyclohexanone, no lactone acetal side product was detected in the mixture, while it was formed in 10–20% in the aldehyde reactions. In addition to the primary alkyl zinc reagent (Et_2Zn), a secondary alkyl zinc reagent could also be employed for the reaction (entry 4). A relatively unreactive ester took part in the allylation reaction. The reaction with methyl acrylate, thus, afforded a tertiary alcohol as a multi-component coupling product in 61% yield through double allylation of the methoxy carbonyl group (entry 9).

We could not detect any product due to direct addition of the dialkylzinc reagent to the carbonyl compound including reactive aldehydes (entries 5–7). This is particularly interesting since the dialkylzinc reagent reacts preferentially with the TMM intermediate **2**, which however is generated in an undetectably small amount in the equilibrium with the DMCP **1**.[4] Thus, the reaction of R_2Zn with **2** must be an extremely fast reaction, and the resulting allylic zinc reagent must selectively react with the carbonyl compound rather than with the TMM **2**.

In summary, we have demonstrated that the dialkoxy TMM

Table 1. Three-component coupling reaction among dialkylzinc, DMCP and carbonyl compound[a]

Entry	Organozinc reagent	Carbonyl compounds	Coupling product	Yield/%[b, c]
1	Et_2Zn			80 (6)
2	Et_2Zn			90 (9)
3	Et_2Zn			88 [d](n.d.)[e]
4	$^{i}Pr_2Zn$			67 (5)
5	Et_2Zn	PhCHO		79 (21)
6	Et_2Zn	EtCHO		71 (<11)
7	Et_2Zn	*c*HexCHO		74 (13)
8	Et_2Zn	^{t}BuCHO		75 (13)
9	Et_2Zn			61[f]

[a] All reactions were carried out in toluene at 60 °C for 2.5-4 h except entry 4 (8 h). [b] Isolated yield. [c] Yields in parentheses refer to the yield of the lactone acetal side product due to direct [3 + 2] cycloaddition between **1** and the carbonyl compound. [d] An 85:15 mixture of 2,6-dimethylcyclohexanone was used and the product was a 75:25 mixture of diastereomers. [e] Not detected. [f] Isolated yield based on **1**.

intermediate **2** generated in a minute quantity in equilibrium with DMCP **1** can be utilized as a carbozincation acceptor, and that the resulting functionalized allylic zinc reagent **3** can be exploited for further C–C bond formation reaction. We believe that the present study has paved a way for development of reactions of biradical reactive intermediate with nucleophilic organometallic reagents, and are currently investigating further possibilities of such reactions.

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

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7 Representative procedure: Typical experimental procedure is as follows: To a solution of DMCP **1** (308 mg, 2.0 mmol) and cyclohexanone (218 mg, 2.2 mmol) in 6.0 mL of toluene was added diethylzinc (2.0-M toluene solution, 2.0 mL, 4.0 mmol). The reaction mixture was stirred at 60 °C for 2.5 h, then quenched by the addition of H_2O (0.3 mL). The resulting mixture was passed through a pad of florisil® (eluent: ether) to remove zinc salt, and concentrated *in vacuo* to afford crude oily product (718 mg). The crude product was purified by silica gel chromatography (eluent: EtOAc/hexane 2–5%) to give alcohol **4** (R^1,R^2 = -$(CH_2)_5$-) in 80% yield (455 mg). Physical data of **4** (R^1,R^2 = -$(CH_2)_5$-): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 7.3 Hz, 3H, $C\mathit{H}_3CH_2$), 0.91 (s, 3H, $C(CH_3)(C\mathit{H}_3)$), 1.00 (s, 3H, $C(C\mathit{H}_3)(CH_3)$), 1.35–1.63 (m, 10H), 1.81 (q, J = 7.3 Hz, 2H, $CH_3C\mathit{H}_2$), 2.28 (s, 2H, $C\mathit{H}_2CR = CH_2$), 3.33 (brs, 1H, $O\mathit{H}$), 3.47 (s, 4H, $OC\mathit{H}_2$), 5.33 (s, 1H, $CH_2CR = C\mathit{H}H$), 5.42 (s, 1H, $CH_2CR = CH\mathit{H}$); ^{13}C NMR (100 MHz, CDCl3) δ 7.53 ($\mathit{C}H_3CH_2$), 22.40 ($\mathit{C}H_2CH_2C(OH)$), 22.70 ($(\mathit{C}H_3)_2C$), 22.86 ($(\mathit{C}H_3)_2C$), 25.91 ($\mathit{C}H_2CH_2CH_2C(OH)$), 27.24 ($CH_3\mathit{C}H_2$), 30.18 ($(CH_3)_2\mathit{C}$), 38.38 ($\mathit{C}H_2C(OH)$), 43.81 ($\mathit{C}H_2CR = CH_2$), 65.82 ($\mathit{C}(OH)$), 70.58 ($O\mathit{C}H_2$), 70.77 ($O\mathit{C}H_2$, 101.98 ($\mathit{C}(OR)_2$), 118.37 ($R = \mathit{C}H_2$), 142.19 ($\mathit{C}R = CH_2$). Anal. Calcd for $C_{17}H_{30}O_3$: C: 72.30, H: 10.71%. Found: C: 72.00, H: 10.59%.

8 Organozinc halide (BuZnI) and organozinc alkoxide (BuZnO*t*-Bu) and some other organozinc reagent did not afford any three-components coupling product.