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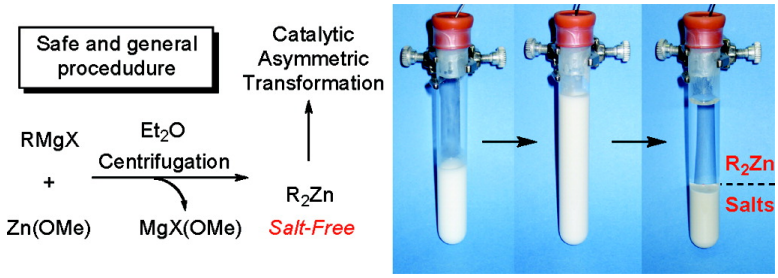
J. Am. Chem. Soc., **2008**, 130 (9), 2771-2773 • DOI: 10.1021/ja710864p



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General Method for the Expedient Synthesis of Salt-Free Diorganozinc Reagents Using Zinc Methoxide

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Finding the right balance between reactivity and selectivity is one of the greatest challenges in synthetic chemistry. In this context, diorganozinc reagents have proven effective, particularly in asymmetric catalysis.[1] The first diorganozinc reagents were prepared over a century ago.[2] However, only recently has progress been made in the synthesis of functionalized reagents, beginning with the seminal work of Knochel and co-workers.[3] Furthermore, a quick overview of the literature clearly indicates that functionalized diorganozinc reagents are underused in asymmetric catalysis, especially outside academic laboratories. One possible explanation for this is that current methods for preparing them are somewhat troublesome (eqs 1−3). One must deal with (1) the potential hazards caused by the handling of highly pyrophoric chemicals and/or (2) the presence of byproducts, which may be present in stoichiometric amounts and be incompatible with catalytic reactions.[4] Depending on the synthetic method used, the main byproducts are salts,[5] residual organometallic species such as boranes,[6] or simply an excess of reagent. Although some diorganozinc compounds can be purified by distillation or sublimation, the approach remains tedious and limited to volatile and relatively non-functionalized compounds. Herein we report an efficient, safe, and general method for preparing diorganozinc reagents while eliminating byproducts.

$$\mathrm{R{-}Metal} + \mathrm{ZnX_2} \rightarrow \mathrm{R_2Zn} + \mathrm{Metal{-}X} \qquad (1)$$

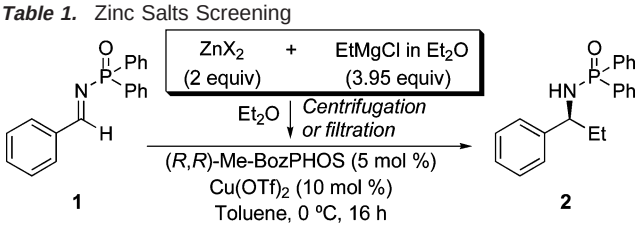
$$\mathrm{R^1{-}Metal} + \mathrm{R^2{}_2Zn} \rightarrow \mathrm{R^1{}_2Zn} + \mathrm{Metal{-}R^2} \qquad (2)$$

$$\mathrm{R^1{-}X} + \mathrm{R^2{}_2Zn} \rightarrow \mathrm{R^1{}_2Zn} + \mathrm{R^2{-}X} \qquad (3)$$

Advantages such as the high reactivity of organomagnesium reagents, their readily commercial availability, and their ease of preparation and handling all justified our choice to employ them as precursors for diorganozinc reagent synthesis.[7] As well, recent work from Knochel shows that Grignard reagents can tolerate many functionalities.[8] However, this approach inevitably leads to the formation of undesired magnesium salts (eq 1). To overcome this drawback, it is possible to add complexing agents, such as 1,4-dioxane[9] or 15-crown-5,[10] in order to initiate their precipitation as an insoluble complex, thereby eliminating the precipitate by filtration or centrifugation. Yet, even if this method is compatible with some catalytic systems,[11] both the [R_2Zn•dioxane] complex produced and/or the excess of 1,4-dioxane required for this step remain problematic in other cases.[12]

To avoid such excess of additive, we studied the effect of counterions on the reactivity of zinc salts, and we hoped to control the solubility of the magnesium salts so they could be removed by filtration/centrifugation without the need to add any additive. Since it is difficult to accurately quantify organometallic and inorganic impurities remaining in diorganozinc solutions,[13] we decided to identify the optimal conditions by using the prepared R_2Zn solution in the catalytic enantioselective addition to imines.[14] We chose a reaction developed in our laboratories employing Me-BozPHOS, which is known to be very sensitive to the presence of salts.

Table 1. Zinc Salts Screening



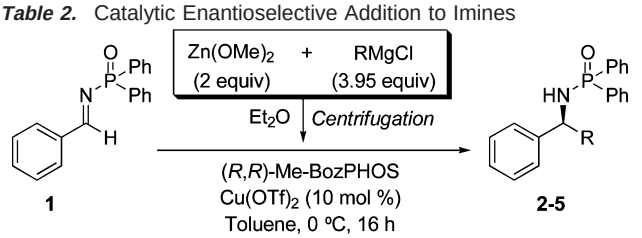
entry	X	yield[a] (%)	ee[b] (%)
1	none[c]	>95	0
2	Cl	51	27
3	F	>95	0
4	CN	>95	0
5	TfO	95	0
6	CO_3	93	0
7	MeO	95	97
8	CF_3CH_2O	46	10
9	*i*-PrO	83	0
10	$CH_3OCH_2CH_2O$	88	97
11	$CH_3OCH_2CH_2OCH_2CH_2O$	65	88
12	$(CH_3)_2NCH_2CH_2O$	78	2
13	*n*-$C_5H_{11}O$	45	41
14	Acac	44	55
15	AcO	94	97
16	BzO	57	27
17	$CH_2CH(CO)O$	45	89
18	OCH_2CH_2O	59	0
19[d]	MeO	21	35
20[e]	AcO	>95	97
21[e]	MeO	90	13

[a] NMR yields were determined using an internal standard. [b] Enantiomeric excesses were determined by SFC on chiral stationary phase. [c] No zinc salt was used. [d] EtMgBr (3.95 equiv) in Et_2O was used. [e] EtMgCl (4.5 equiv) was used.

The results in Table 1 indicate that, when Et_2Zn was prepared from EtMgCl and $ZnCl_2$ (entry 2), a decrease in reactivity and enantioselectivity was observed. Even if the exact nature of the interference is unknown, we established that species such as halogenated ions, MgX_2 and EtZnX, greatly altered the efficiency of the reaction.[4b,15] When zinc salts with counterions corresponding to F^-, CN^-, OTf^-, CO_3^{2-}, and $(OCH_2CH_2O)^{2-}$ ions were used (entries 3−6 and 18), the latter were too insoluble in Et_2O to react. Therefore, results clearly illustrated the uncatalyzed addition of Grignard reagents to imines.

Although zinc alkoxides appeared to be visually insoluble (with the exception of isopropoxide), they reacted with Grignard reagents in an exothermic fashion (entries 7−13). However, the solubility of the resulting magnesium salts greatly depended on the nature of the alkoxide, but outstanding yields and enantioselectivities were observed with zinc methoxide and methoxyethoxide.[16] Zinc acetate could also be used (entry 15), and it showed similar results as with

Table 2. Catalytic Enantioselective Addition to Imines



entry	R	yield[a] (%)	ee[b] (%)
1	Et	95 (**2**)	98
2	Et[c]	90 (**2**)	98
3	Et[d]	96 (**2**)	98
4	*i*-Pr	57 (**3**)	95
5	*n*-Bu	96 (**4**)	96
6[e]	*n*-$C_{10}H_{21}$	73 (**5**)	97

[a] Isolated yields. [b] Enantiomeric excesses were determined by SFC on chiral stationary phase. [c] $Zn(OMe)_2$ (2 equiv) was formed in situ from $ZnCl_2$ (2 equiv) and NaOMe (4.2 equiv). [d] Neat Et_2Zn was dissolved in Et_2O. [e] The reaction was run for 48 h.

zinc methoxide or neat Et_2Zn. Furthermore, zinc carboxylates were usually less soluble and less reactive than alkoxides. When an excess of Grignard reagent was used with $Zn(OAc)_2$ specifically, the reaction proceeded as well as with a stoichiometric quantity (entry 20). We believed that the carboxylate ions have the potential to act as a scavenger for Grignard reagents used in excess. A more detailed study led us to establish that there are reactivity issues between $Zn(OAc)_2$ and long alkyl chains. This prompted us to favor $Zn(OMe)_2$ for the rest of our investigation. The use of organomagnesium bromide was also tested, but it turned out to be problematic under these conditions (entry 19). Since the insolubility of the magnesium salts are strongly dependent on the solvent used, Grignard reagents have to be consistently dissolved in Et_2O, and not in THF. Chlorinated Grignard reagents and Et_2O were a crucial combination when it comes to controlling salt precipitation.

Overall, our developed protocol is technically simple, easy, and expedient. Filtration/centrifugation is a vital step in diorganozinc reagents synthesis. Although similar results can be obtained using either technique, each offers certain advantages. While centrifugation is quick and allows the simultaneous treatment of several samples, filtration allows a better recovery of the solution and works well on a large scale.

$Zn(OMe)_2$ is not commercially available and may be prepared from Et_2Zn and MeOH.[17] An alternate convenient protocol was developed to generate this salt in situ (eq 4) from $ZnCl_2$ and NaOMe.[18] The resulting mixture[19] can be used as a surrogate to pure $Zn(OMe)_2$ and is suitable for the diorganozinc reagent preparation. Excess NaOMe, required for complete conversion of $ZnCl_2$, was removed along with the other salts during centrifugation or filtration.[13b,20]

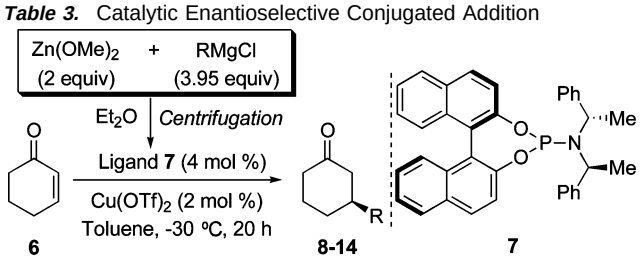
$$\underset{\text{(1 equiv)}}{ZnX_2} + \underset{\text{(2-2.5 equiv)}}{NaOMe} \xrightarrow{Et_2O} \underset{\text{(1 equiv)}}{Zn(OMe)_2} + \underset{\text{(2 equiv)}}{NaX} \quad (4)$$

X = Cl, Br

The use of $Zn(OMe)_2$, either preformed (from diethylzinc and methanol) or generated in situ, produced excellent yields and selectivities (Table 2, entries 1−3), comparable to those obtained with neat Et_2Zn. The addition of other alkyl chains also gave excellent enantioselectivities (entries 4−6).

The dialkylzinc solutions prepared by this method were then tested in other catalytic asymmetric reactions. The conjugated

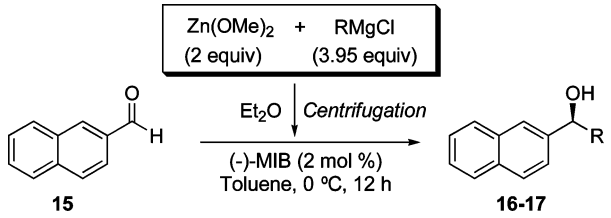
Table 3. Catalytic Enantioselective Conjugated Addition



entry	R	yield[a] (%)	ee[b] (%)
1	Et	89 (**8**)	>98
2	Et[c]	88 (**8**)	>98
3	Et[d]	86 (**8**)	>98
4[e]	*i*-Pr	93 (**9**)	94
5	*n*-Bu	94 (**10**)	>95
6	*i*-Bu	95 (**11**)	97
7[e]	*c*-Hex	94 (**12**)	94
8	*n*-$C_{10}H_{21}$	97 (**13**)	>98
9	$PhCH_2CH_2$	97 (**14**)	>98

[a] Isolated yield. [b] Enantiomeric excesses were determined by SFC on chiral stationary phase or by ^{13}C NMR spectroscopy after derivatization with 1,2-diphenylethylenediamine. [c] $Zn(OMe)_2$ (2 equiv) was formed in situ from $ZnCl_2$ (2 equiv) and NaOMe (4.2 equiv). [d] Neat R_2Zn was dissolved in Et_2O. [e] Styrene (1 equiv) was added according to ref 22.

Table 4. Catalytic Enantioselective Addition to Aldehydes



entry	R	yield[a] (%)	ee[b] (%)
1	Et (**16**)	93	98
2	Et[c] (**16**)	95	98
3	Et[d] (**16**)	96	97
4	*n*-$C_{10}H_{21}$ (**17**)	63[e]	97

[a] Isolated yields. [b] Enantiomeric excesses were determined by SFC on chiral stationary phase. [c] $Zn(OMe)_2$ (2 equiv) was formed in situ from $ZnCl_2$ (2 equiv) and NaOMe (4.2 equiv). [d] Neat Et_2Zn was dissolved in Et_2O. [e] The low yield is explained by the formation of the reduction product.

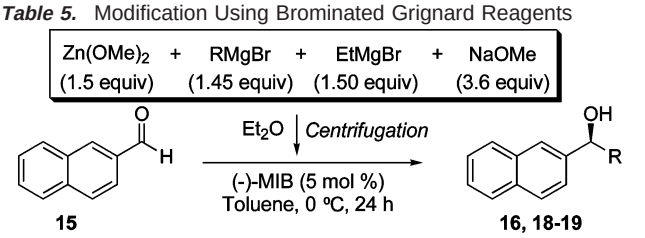
catalytic addition to cyclohexenone[21] also proceeded smoothly with excellent reactivity. As the data indicate in Table 3, the synthesis of dialkylzinc reagents from $Zn(OMe)_2$ tolerated primary, secondary, branched, linear, or long chains.

The addition to an aldehyde catalyzed with a chiral amino alcohol (Table 4)[23] also turned out to give high yields and enantiocontrol.

Due to the difficulty in forming aryl- or vinylmagnesium chlorides in Et_2O, we developed a modification to accommodate arylmagnesium bromides by adding NaOMe to the reaction. $Mg(OMe)_2$ and NaBr are then formed, which are insoluble in Et_2O.[24] This derived procedure gave comparable results to those obtained with the Walsh method[25] or with pure commercial reagents for the addition of a phenyl group to 2-naphthaldehyde (Table 5, entries 1−3). Notably, this reaction is a good example of why an excess of 1,4-dioxane can be detrimental to catalysis (entry 3). As well, the synthesis of mixed diorganozinc reagents is very simple: two different Grignard reagents must be added to $Zn(OMe)_2$ (entry 4).[26]

Since a slight excess of $Zn(OMe)_2$ is used in proportion to the Grignard reagent, traces of RZnOMe still remain in the solution. However, such species are known to generate a stable tetramer,[27] which has little or no interaction with catalytic systems, as illustrated

Table 5. Modification Using Brominated Grignard Reagents

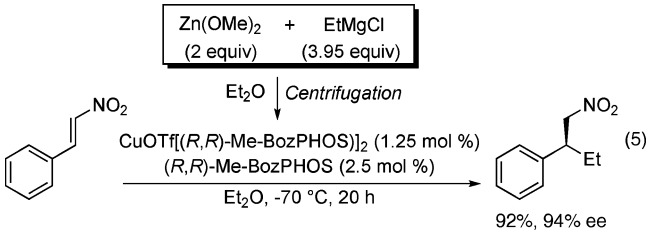


entry	R	yield[a] (%)	ee[b] (%)
1	Ph	90 (**18**)	98
2[c,d]	Ph	98 (**18**)	98
3[c,e]	Ph	63 (**18**)	93
4	Et	96 (**16**)	98
5[f]	Et	92 (**16**)	98
6	TBDMSO$(CH_2)_4$	70 (**19**)	98

[a] Isolated yield. [b] Enantiomeric excesses were determined by SFC on chiral stationary phase. [c] Mixed diorganozinc was used. [d] EtZnPh was generated from Et_2Zn (0.75 equiv) and Ph_2Zn (0.75 equiv). [e] EtZnPh was generated from EtMgBr (1.5 equiv), PhMgBr (1.45 equiv), $ZnCl_2$ (1.5 equiv), and 1,4-dioxane (10.5 equiv) (see ref 11). [f] EtMgBr (3.3 equiv) was used in combination with NaOMe (3.6 equiv) and NaOBz (0.6 equiv).

herein.[28] When necessary, the use of an excess of Grignard reagent in combination with an insoluble and slow-to-react scavenger, such as NaOBz,[29] will eliminate the presence of organozinc alkoxide (Table 5, entry 5).

Finally, these conditions were also applied to the addition to β-nitrostyrene[17] catalyzed with a copper•Me-BozPHOS complex (eq 5).[30]



In summary, we have exploited the weak solubility of magnesium methoxide in order to synthesize diorganozinc reagents dissolved in Et_2O without undesired reaction byproducts. It represents an attractive method to access both functionalized dialkylzinc and diarylzinc reagents.[31] Finally, the reagents produced show no change in the efficiency of all tested asymmetric catalytic reactions in comparison to purified reagents. The work presented herein is a good complement to other methods since it focuses on asymmetric catalysis and potentially improves the scope of already known enantioselective reactions.

Acknowledgment. This work was supported by NSERC (Canada), Merck Frosst Canada Ltd., Boehringer Ingelheim (Canada) Ltd., the Canada Research Chairs Program, the Canadian Foundation for Innovation and the Université de Montréal. A.C. is grateful to NSERC (ES D) for postgraduate fellowship, and to TD Bank Financial Group.

Supporting Information Available: Additional results, tables, experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Most methods to prepare highly functionalized Grignard reagents either generate partially soluble salts and/or need salts as additive and/or use complexing solvents. For any of these reasons, they are not compatible with our new protocol to generate salt-free diorganozinc reagents.

JA710864P