A Concise Synthesis of (*S*)-(+)-Ginnol Based on Catalytic Enantioselective Addition of Commercially Unavailable Di(*n*-alkyl)zinc to Aldehydes and Ketones

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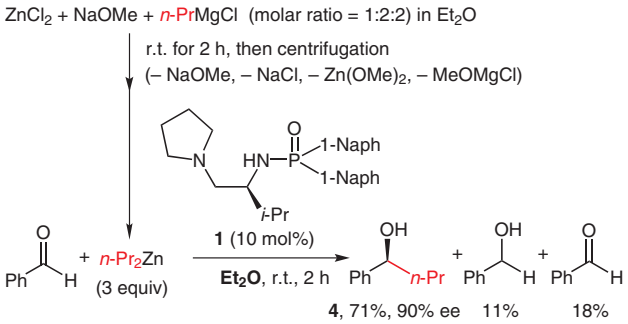
Abstract: Catalytic, enantioselective *n*-alkyl addition of commercially unavailable di(*n*-alkyl)zinc reagents, which were prepared by a refined version of Charette's procedure with Grignard reagents, to aldehydes and ketones was developed. To minimize the side reactions in the catalysis by chiral phosphoramide ligand (**1**) or 3,3′-diphosphoryl-BINOL ligand (**2**), a preparation of di(*n*-alkyl)zinc reagents with a 1:2.5:1.6 molar ratio of $ZnCl_2$/NaOMe/RMgCl under solvent-free conditions was essential. Optically pure (*S*)-(+)-ginnol (**17**) was readily synthesized in one step for the first time by the catalytic enantioselective *n*-nonylation of icosanal.

Key words: alcohol, asymmetric catalysis, ginnol, Grignard reagent, zinc

Traditional Grignard reagents are some of the most useful and safe reagents for alkylating carbonyl compounds in academic and industrial research and process chemistry.[1] Today, more than 200 inexpensive Grignard reagents can be purchased. In particular, the transmetallation of alkyl groups in Grignard reagents to other less-reactive metal complexes such as Zn^{II} and Ti^{IV} should be attractive for the catalytic enantioselective alkylation of carbonyl compounds because the reaction would proceed only when the catalysts are present.[2,3] In this regard, Harada et al. recently reported a catalytic enantioselective Zn^{II}-free secondary alcohol synthesis from aldehydes and Grignard reagents/Ti(O*i*-Pr)$_4$.[4] Moreover, Côté and Charette reported the preparation of salt-free di(*n*-alkyl)zinc reagents from $ZnCl_2$, NaOMe, and Grignard reagents.[5] Except for Me_2Zn, Et_2Zn, *i*-Pr_2Zn, *n*-Bu_2Zn, and Ph_2Zn, dialkylzinc reagents are not commercially available. Therefore, Charette's method for preparing di(*n*-alkyl)zinc reagents under salt-free conditions is valuable. In that report, they presented a few examples of the catalytic enantioselective addition of di(*n*-alkyl)zinc reagents {i.e., Et_2Zn, $[TBSO(CH_2)_4]_2Zn$, and $(n\text{-}C_{10}H_{21})_2Zn$} to 2-naphthaldehyde. However, addition of long *n*-alkyl chains to aldehydes might still be an unresolved problem since, in their report, the representative (–)-MIB [(2*S*)-(–)-3-*exo*-(*N*-morpholino)isoborneol][6]-catalyzed *n*-decylation of 2-naphthaldehyde gave the desired product in 63% yield with 97% ee in addition to the undesired reduction byproduct.[5] In this regard, we found that even much shorter *n*-propylation of benzaldehyde did not work well due to a recovery of the starting material (18%) and a reduction side product (11% yield) under Charrete's original conditions (1:2:2 molar ratio of $ZnCl_2$/NaOMe/RMgCl) in Et_2O with the use of our chiral phosphoramide ligand **1**[7] (Scheme 1).



Scheme 1 *n*-Propylation under Charette's original conditions with the use of chiral phosphoramide ligand **1**

To overcome this problematic low reactivity and/or side reaction, we report here a catalytic enantioselective addition of various di(*n*-alkyl)zinc reagents to aldehydes and ketones using chiral phosphoramide ligand (**1**) or chiral 3,3′-diphosphoryl-BINOL ligand (**2**)[8].

By taking advantage of Charette's report,[5] we found that solvent-free di(*n*-alkyl)zinc reagents were effective both to increase the reactivity and to minimize formation of the reduction side product in the catalytic enantioselective addition to aldehydes with the use of **1**. Moreover, the refined 1:2.5:1.6 molar ratio of $ZnCl_2$/NaOMe/RMgCl was critical to suppress the adventitious racemic pathway triggered by a small amount of remaining Grignard reagent.[9] To expand the scope of *n*-alkyl groups, we prepared di(*n*-alkyl)zinc reagents and performed the subsequent addition reaction to benzaldehyde under the optimized conditions with the use of chiral ligand **1** (Table 1). Ethylation (see **3**), *n*-propylation (see **4**), *n*-butylation (see **5**), *n*-pentylation (see **6**), *n*-heptylation (see **7**), and *n*-octylation (see **8**) proceeded smoothly, and the corresponding secondary alcohols were obtained in almost quantitative yields with 92–97% ee. To our delight, as a representative long *n*-alkyl chain, *n*-decylation also proceeded, and the desired product **9** was obtained in >99% yield with 95%

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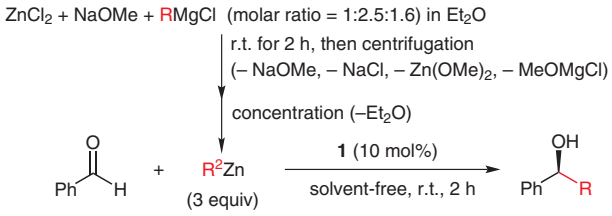
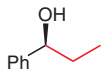
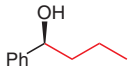
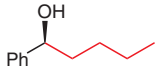
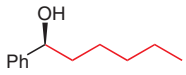
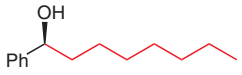
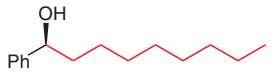
Table 1 *n*-Alkylation of Benzaldehyde



Product	Yield (%)	Enantioselectivity (% ee)	Alkyl source
 **3**	92	94	(EtMgCl)
 **4**	99	97	(*n*-PrMgCl)
 **5**	98	96	(*n*-BuCl·LiCl + Mg)
 **6**	>99	96	(*n*-C_5H_{11}Cl·LiCl + Mg)
 **7**	98	92	(*n*-C_7H_{15}Cl·LiCl + Mg)
 **8**	98	96	(*n*-C_8H_{17}Cl·LiCl + Mg)
 **9**	>99	95	(*n*-$C_{10}H_{21}$Cl·LiCl + Mg)

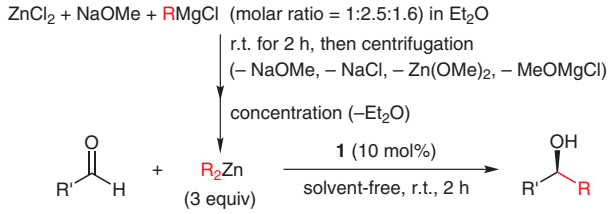
ee. When the reaction was performed in a solvent (e.g., in hexane or toluene)[7] a comparatively prolonged reaction time (2–6 h) was required, whereas under solvent-free conditions, the reaction was completed within two hours without side reactions. Remarkably, the use of Grignard reagents prepared in situ (RCl + Mg + LiCl[10]) appeared to have no negative effects (see **5**–**9**).

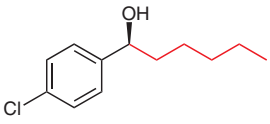
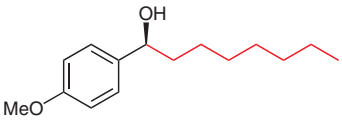
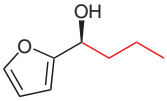
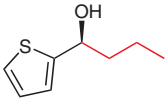
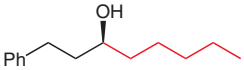
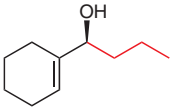
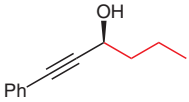
The addition of other commercially unavailable di(*n*-alkyl)zinc reagents to a variety of aldehydes was examined (Table 2). Aromatic aldehydes with electron-donating and electron-withdrawing groups and heteroaromatic aldehydes were acceptable for highly enantioselective *n*-propylation (see **12** and **13**), *n*-pentylation (see **10**), and *n*-heptylation (see **11**). *n*-Pentylation of aliphatic aldehyde gave the corresponding product **14** with moderate enantioselectivity. The addition of di(*n*-alkyl)zinc to α,β-unsaturated aldehydes was also examined. Although the *n*-propylation of 1-cyclohexene-1-carbaldehyde showed high enantioselectivity (**15**; 91% ee), phenylpropargyl aldehyde gave the corresponding *n*-propyl-adduct **16** in 90% yield but with 6% ee with the use of chiral ligand **1**. In sharp contrast, our previous chiral BINOL-derived ligand **2** in toluene–THF (2:1)[8] was found to be effective, and the adduct **16** was obtained with high enantioselectivity (82% ee).[11]

We next examined the synthesis of a chiral long-chain aliphatic alcohol, (*S*)-(+)-ginnol (**17**),[12] which is an optically active natural product that has been noted in chiral bilayers of the wax tubes of higher plants. The reaction of icosanal (*n*-$C_{19}H_{39}CHO$) with di(*n*-nonyl)zinc [(*n*-$C_9H_{19})_2Zn$] in the presence of chiral ligand **2** (20 mol%) proceeded in toluene–THF (2:1) at room temperature for 12 hours, and enantioenriched (*S*)-(+)-ginnol was obtained in one step in 81% yield with 97% ee (Scheme 2). To the best of our knowledge, this is the first one-step example, and is thus the simplest asymmetric synthesis of (*S*)-(+)-ginnol. Fortunately, a single recrystallization in *n*-hexane provided optically pure (*S*)-(+)-ginnol (>99% ee).

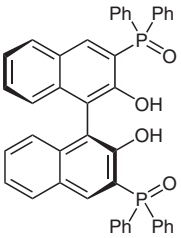
Finally, *n*-alkyl addition to much less reactive ketones, in place of aldehydes, was examined (Scheme 3). Unfortunately, *n*-propylation of acetophenone (**18a**) provided the desired product **19a** in low yield (31%), and the undesired aldol condensation product **20a** was instead obtained. In sharp contrast, *n*-propylation of CF_3-activated 3′,5′-bis(trifluoromethyl)acetophenone (**18b**) proceeded without aldol formation at room temperature in 24 hours, in

Table 2 *n*-Alkylation of Aldehydes



Product	Yield (%)	Enantioselectivity (% ee)	Alkyl source
 **10**	>99	88	(*n*-C_5H_{11}Cl·LiCl + Mg)
 **11**	>99	94	(*n*-C_7H_{15}Cl·LiCl + Mg)
 **12**	98	87	(*n*-PrMgCl)
 **13**	98	98	(*n*-PrMgCl)
 **14**	85	76	(*n*-C_5H_{11}Cl·LiCl + Mg)
 **15**	97	91	(*n*-PrMgCl)
 **16**	90 90[a]	6 82[a]	(*n*-PrMgCl)

[a] In place of **1**, chiral ligand **2** (10 mol%) was used in toluene–THF (2:1).



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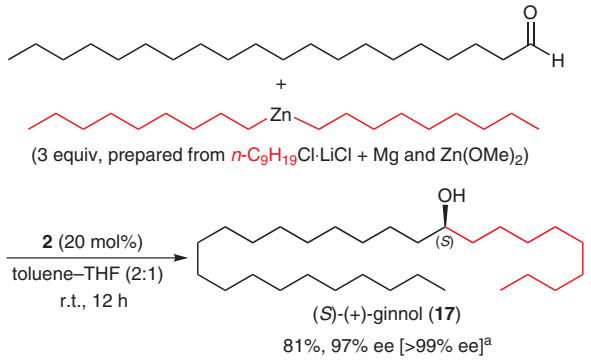
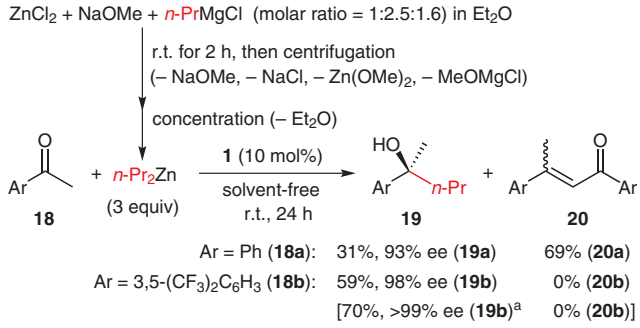
the presence of 10 mol% chiral ligand **1**, and the desired tertiary alcohol **19b** was obtained in 59% yield with 98% ee. Moreover, the presence of 20 mol% chiral ligand **1** further improved the yield (70%) and enantioselectivity (>99% ee) of **19b**; in this case, **18b** was recovered (30%) without any side products.



Scheme 2 Synthesis of (*S*)-(+)-ginnol (**17**) ([a] Enantioselectivity after recrystallization from *n*-hexane.)



Scheme 3 Catalytic enantioselective addition of di(*n*-propyl)zinc reagents to ketones ([a] Yield and enantioselectivity when 20 mol% chiral ligand **1** was used.)

In summary, we have developed a catalytic, enantioselective *n*-alkyl addition to aromatic and aliphatic aldehydes and to activated aromatic ketones, with Grignard reagent-derived di(*n*-alkyl)zinc reagents.[13] Optically active alcohols with either short- or long-chain *n*-alkyl groups could be successfully synthesized in high yields with high enantioselectivities. To minimize the side reactions in the catalysis by chiral phosphoramide ligand **1** or 3,3′-diphosphoryl-BINOL ligand **2**, a preparation of di(*n*-alkyl)zinc reagents in a refinement of Charette's molar ratio ($ZnCl_2$/NaOMe/RMgCl, 1:2.5:1.6) under solvent-free conditions was essential. Remarkably, optically pure (*S*)-(+)-ginnol was readily synthesized by the catalytic enantioselective *n*-nonylation of icosanal in one step. Since inexpensive Grignard reagents are now widely available, whereas di(*n*-alkyl)zinc reagents are commercially less common, this simple method for the synthesis of optically active alcohols may be effective, particularly for process chemistry based on green technology.

Acknowledgment

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References and Notes

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(9) Significantly low enantioselectivities (<20% ee) of the products in the *n*-alkylation of aldehydes were sometimes observed using a 1:2:2 molar ratio of $ZnCl_2$/NaOMe/RMgCl. Probably, from a small amount of remaining RMgCl, a highly active zinc(II)-ate complex $[R_3Zn]^-[MgCl]^+$ would be generated. See: (a) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998. (b) Hatano, M.; Suzuki, S.; Ishihara, K. *Synlett* **2010**, 321.

(10) It has been reported that LiCl generally improves the activity of Grignard reagents, see: (a) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. (b) Armstrong, D. R.; García-Álvarez, P.; Kennedy, A. R.; Mulvey, R. E.; Parkinson, J. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 3185.

(11) During the preliminary investigation, we found that chiral ligand **1** was less suitable for the *n*-alkylation of non-aromatic aldehydes. This is probably due to the flexibility of non-aromatic aldehydes, which can avoid significant

repulsion in the transition states using chiral ligand **1** (Figure 1). Also see refs. 7 and 8.

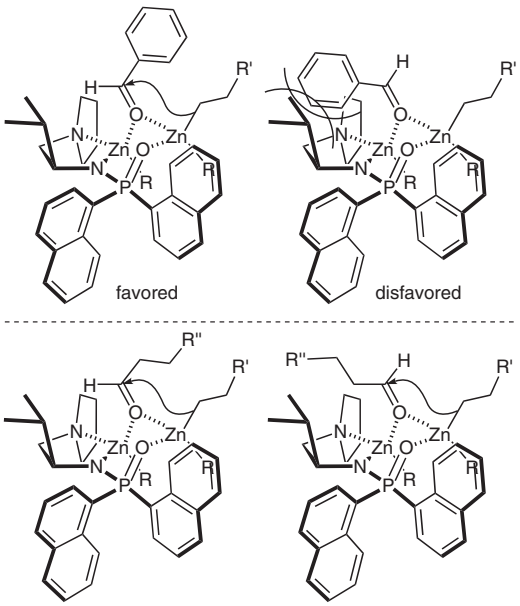

Figure 1

(12) (a) Beckmann, S.; Schühle, H. *Z. Naturforsch., B* **1968**, *23*, 471. (b) Fuhrhop, J.-H.; Bedurke, T.; Hahn, A.; Grund, S.; Gatzmann, J.; Riederer, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 350. (c) Kusumi, T.; Takahashi, H.; Hashimoto, T.; Kan, Y.; Asakawa, Y. *Chem. Lett.* **1994**, *23*, 1093. (d) Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 9007. (e) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229. (f) Berkenbusch, T.; Brückner, R. *Tetrahedron* **1998**, *54*, 11471. (g) Dommisse, A.; Wirtz, J.; Koch, K.; Barthlott, W.; Kolter, T. *Eur. J. Org. Chem.* **2007**, 3508.

(13) **General Procedure for the Preparation of Salt-free Di(*n*-alkyl)zinc Reagents**: To a test tube equipped with a magnetic stirrer and charged with $ZnCl_2$ (682 mg, 5 mmol) and NaOMe (676 mg, 12.5 mmol), was added Et_2O (5 mL) at r.t. under a nitrogen atmosphere. The suspension was stirred for 20 min and cooled to 0 °C for another 10 min. RMgCl in Et_2O (8 mmol, titrated before use) was added dropwise with vigorous stirring over 10 min at 0 °C [If RMgCl in Et_2O solution was not commercially available, RMgCl was prepared from RCl (1 equiv), LiCl (1.1 equiv), and magnesium turnings (1.5 equiv) in Et_2O, and the suspension was allowed to stir at 35 °C for 12 h before titration]. The mixture was centrifuged for 10 min (4,000 rpm) and the Et_2O solution of R_2Zn reagent was gently transferred via cannula into a well-dried pyrex Schlenk tube to be stored prior to use.

General Procedure for the Catalytic Enantioselective Addition of Di(*n*-alkyl)zinc Reagents to Aldehydes: A well-dried pyrex Schlenk tube was charged with **1** (22.8 mg, 0.05 mmol) and the salt-free R_2Zn reagent (0.4–0.6 M in Et_2O, 1.5 mmol) at r.t. under a nitrogen atmosphere. Et_2O was removed under reduced pressure to generate the solvent-free R_2Zn reagent containing **1** in situ. Aldehyde (0.5 mmol) was added to the mixture at r.t. and the resulting mixture was stirred at r.t. for 2 h. After hydrolysis with saturated NH_4Cl (10 mL), the product was extracted with Et_2O (3 × 10 mL) and washed with brine (10 mL). The combined extracts were dried over $MgSO_4$, the organic phase was concentrated under reduced pressure and the crude product was purified by neutral silica gel column chromatography (*n*-hexane–Et_2O) to give the desired products.

Catalytic, Enantioselective Synthesis of (*S*)-(+)-Ginnol (17): A well-dried pyrex Schlenk tube was charged with **2** (68.7 mg, 0.10 mmol) and the salt-free $(n\text{-}C_9H_{19})_2Zn$ reagent (0.44 M in Et_2O, 3.4 mL, 1.5 mmol) at r.t. under a nitrogen atmosphere. Et_2O was removed under reduced pressure to generate the solvent-free $(n\text{-}C_9H_{19})_2Zn$ reagent containing **2** in situ. Toluene (1.5 mL) and THF (0.7 mL) were then added and the mixture was stirred at r.t. for 1 h. Icosanal (148.3 mg, 0.5 mmol) was added to the mixture, which was stirred at r.t. for 12 h. After hydrolysis with saturated aqueous NH_4Cl (10 mL), the product was extracted with EtOAc (3 × 10 mL) and washed with brine (10 mL). The combined extracts were dried over $MgSO_4$, and the organic phase was concentrated under reduced pressure. The crude product was purified by neutral silica gel column chromatography (*n*-hexane–Et_2O) to give ginnol (172.5 mg, 81% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 6 H), 1.20–135 (m, 48 H), 1.42 (m, 4 H), 1.56 (s, 1 H), 3.58 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.7, 25.7, 29.3, 29.4, 29.8, 32.0, 37.6, 72.1. IR (KBr): 3449, 2917, 2850, 1467, 1561, 1101 cm^{-1}. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{29}H_{60}O$: 406.4538; found: 406.4535. $[\alpha]_D^{20}$ +1.8 (>99% ee, *c* 2.0, $CHCl_3$) {Lit.[12a] $[\alpha]_D^{20}$ +2.18 (*c* 1.1, $CHCl_3$) for (*S*)-ginnol}. Enantioselectivity was confirmed by HPLC analysis of the diastereotopic (*R*)-MTPA-esters of the resulting ginnol. Chiral HPLC, Daicel chiralpack AD-3 × 2 at 4 °C; *n*-hexane–*i*-PrOH, 2000:1; flow rate = 0.1 mL/min; t_R = 100.3 min [major, (*S*)-derivative], 103.5 min [minor, (*R*)-derivative].