Catalytic enantioselective synthesis of sterically demanding alcohols using di(2°-alkyl)zinc prepared by the refined Charette's method†

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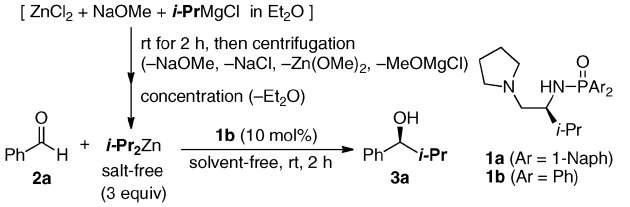
A highly practical, catalytic enantioselective 2°-alkyl addition to aldehydes and ketones was developed. Chiral phosphoramide ligand (1) with salt-free and solvent-free di(2°-alkyl)zinc reagents prepared from (2°-alkyl)MgCl was essential.

A catalytic enantioselective dialkylzinc addition to aldehydes has been recognized as an effective method for synthesizing optically active secondary alcohols.[1] In particular, the 2°-alkyl addition to aldehydes with di(2°-alkyl)zinc reagents has become increasingly important in pharmaceutical chemistry and in Soai's autocatalysis with pyrimidine-5-carbaldehyde and *i*-Pr_2Zn.[2] However, in sharp contrast to the di(1°-alkyl)-zinc addition to aldehydes, only a few limited examples of the di(2°-alkyl)zinc addition to aldehydes have been reported due to steric constraint.[3] Moreover, the lack of a commercially available source of di(2°-alkyl)zinc other than *i*-Pr_2Zn has discouraged work on the desired catalytic enantioselective 2°-alkyl addition to aldehydes. Although convenient methods have been reported for the preparation of dialkylzinc reagents *in situ*, they are accompanied by the generation of mono-alkylzinc complexes and/or inorganic salts, which sometimes disturb subsequent reactions.[4,5] To address this serious problem,[6] we report here a catalytic enantioselective 2°-alkyl addition to aldehydes and ketones with salt-free and solvent-free di-(2°-alkyl)zinc reagents that are prepared from Grignard reagents by using a refined Charette's method.[7]

Côté and Charette recently developed a highly useful method for the preparation of salt-free di(1°-alkyl)zinc reagents from $ZnCl_2$, NaOMe, and Grignard reagents.[7] However, methods for the preparation of salt-free di(2°-alkyl)zinc reagents have not yet been well-established. First, the isopropylation of benzaldehyde (**2a**) was investigated with chiral phosphoramide ligand **1b**[8] (10 mol%) (Table 1). By following a Charette's typical procedure for the preparation of di(1°-alkyl)zinc,[7,9] a 0.44 M solution of *i*-Pr_2Zn in Et_2O was prepared, but nearly racemic **3a** was obtained in 88–90% yield under Et_2O conditions (entries 1 and 2). We assumed that a small amount of remaining Grignard reagent might trigger the racemic pathway, since a highly active zinc(II) ate complex for alkylation, namely $[i\text{-}Pr_3Zn]^-[MgCl]^+$, would be generated *in situ*.[10] As expected, a conservative molar ratio of 1/2/1.6 of $ZnCl_2$/NaOMe/*i*-PrMgCl was effective, and **3a** was obtained in 73% yield with 91% ee (entry 3). However, an undesired reduction byproduct (*i.e.* BnOH) was also obtained in 26% yield (entry 3). Therefore, we examined the reaction under solvent-free conditions[11] by using salt-free liquid *i*-Pr_2Zn (bp. 134 °C),[12] which was prepared by the same method followed by the removal of Et_2O *in vacuo*. As a result, **3a** was obtained in an improved yield (93%) with 91% ee, along with a trace amount of BnOH (<2%) (entry 4). Moreover, with the use of 2.5 equiv. of NaOMe,[9] **3a** was obtained in 94% yield with 94% ee (entry 5). Both less bulky **1b** (10 mol%) and more bulky **1a** (3 or 10 mol%) were effective in this reaction (entries 5–7). It was noted that Côté and Charette used (2*S*)-(−)-3-*exo*-(*N*-morpholino)isoborneol [(−)-MIB], which has been known as a representative chiral ligand,[13] in their asymmetric 1°-alkylation to aldehydes.[7] However, (−)-MIB was less effective than chiral ligand **1** in the isopropylation of **2a** (See the ESI†).

Table 1 Optimization of the isopropylation of benzaldehyde[a]



Entry	Molar ratio of $ZnCl_2$: NaOMe : *i*-PrMgCl	Yield [%] of **3a**	ee [%] of **3a**
1[b]	1 : 2 : 1.9	90	3
2[b]	1 : 2.5 : 1.9	88	0
3[b,c]	1 : 2 : 1.6	73	91
4	1 : 2 : 1.6	93	91
5	1 : 2.5 : 1.6	94	94
6[d]	1 : 2.5 : 1.6	93	93
7[e]	1 : 2.5 : 1.6	84	92

[a] Unless otherwise noted, salt-free *i*-Pr_2Zn was used under solvent-free conditions. [b] *i*-Pr_2Zn (0.44 M, in Et_2O) was used. [c] BnOH was obtained in 26% yield. [d] 10 mol% of ligand **1a** in place of **1b** was used. [e] 3 mol% of ligand **1a** in place of **1b** was used. Reaction time was 4 h.

We next examined the catalytic enantioselective 2°-alkyl addition to various aldehydes under solvent-free conditions with salt-free di(2°-alkyl)zinc reagents derived from Grignard reagents (Table 2). The isopropylation of aromatic aldehydes (entry 1), heteroaromatic aldehydes (entries 2 and 3), and cycloaliphatic aldehydes (entries 4 and 5) proceeded, and the corresponding products were obtained in high yields with high enantioselectivities (90–>99% ee). The isopropylation of tiglic aldehyde as an α,β-unsaturated aldehyde provided only a 1,2-adduct (**3g**) with high enantioselectivity (97% ee) (entry 6). Catalytic enantioselective *sec*-butylation also proceeded for

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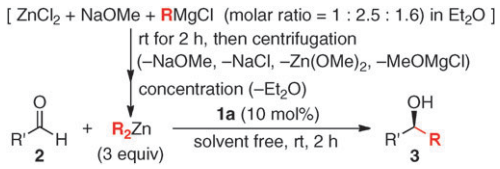
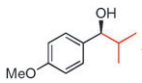
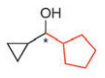
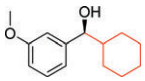
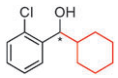
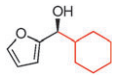
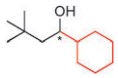
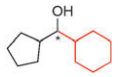
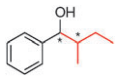
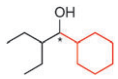
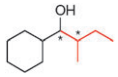
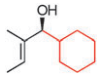
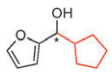
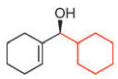
† Electronic supplementary information (ESI) available: Experimental details and product characterization. See DOI: 10.1039/c0cc01301c

Table 2 Enantioselective 2°-alkyl addition to aldehydes



Entry	Product (**3**)	Yield and ee	Entry	Product (**3**)	Yield and ee
1[a]		**3b** 95%, 96% ee	10[b]		**3k** 90%, 99% ee
2[a]		**3c** >99%, 95% ee	11[a,c]		**3l** 89%, 97% ee
3		**3d** 86%, 90% ee	12[a,c]		**3m** 96%, 90% ee
4		**3e** >99%, 96% ee	13[c]		**3n** 94%, 84% ee
5[a]		**3f** 98%, >99% ee	14[b,c]		**3o** 75%, 82% ee
6[b]		**3g** 97%, 97% ee	15[c]		**3p** 77% [36%][a], >99% ee
7		**3h** 76%, (dr 55/45) 94% ee/ 95% ee	16[b,c]		**3q** 80%, 99% ee
8		**3i** 45% [15%][a], (dr 59/41) 98% ee/ 96% ee	17[c]		**3r** 85% 99% ee
9		**3j** 56%, 96% ee	18[c]		**3s** 88% [42%][a], 98% ee

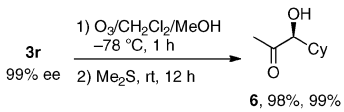
[a] 10 mol% of ligand **1b** was used in place of **1a**. [b] Temperature was 0 °C. [c] Toluene (2.5 M) was used as a solvent.

the first time, and the desired products were obtained with a low diastereomeric ratio (*ca.* 6 : 4) but with high enantioselectivities (94–98% ee) (entries 7 and 8). Next, as an unprecedented cyclic 2°-alkyl addition to aldehydes, the addition of $(c\text{-}C_5H_9)_2Zn$ and $(c\text{-}C_6H_{11})_2Zn$[14] was explored. Fortunately, the desired products were obtained with high enantioselectivities from aromatic aldehydes (entries 11 and 12), heteroaromatic aldehydes (entries 9 and 13), cycloaliphatic aldehydes (entries 10 and 15), a β-branched aliphatic aldehyde (entry 14), an α-branched aliphatic aldehyde (entry 16), and α,β-unsaturated aldehydes (entries 17 and 18). Less bulky **1b** was often less effective than more bulky **1a**[8] due to reduction byproducts, especially when less-reactive aliphatic aldehydes were used (entries 8, 15, and 18). Some of the secondary alcohols (**3**, R′RCHOH) which have two similar cyclic and/or acyclic fragments (R′ and R) can hardly be obtained *via* complementary methods such as asymmetric reduction of the corresponding ketones.[15] In this catalysis, optically active novel secondary alcohols with similar R′ and R were successfully obtained in high yields with high to excellent enantioselectivities (96–>99% ee).

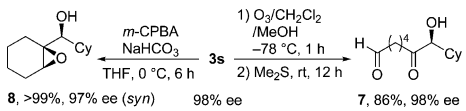
To demonstrate the synthetic utility of this approach, several transformations were examined. Compound **3n** was treated with *N*-bromosuccinimide in THF–H_2O,[16] and the desired cyclohexyl-substituted 6-hydroxy-2*H*-pyran-3-one **4**[17] was obtained *via* the oxidative Achmatowicz rearrangement in 89% yield with a diastereomeric ratio of 73 : 27 with 84% ee (eqn (1), left). Moreover, after the TBS-protection of the hydroxy group of **3n**, ozonolysis cleavage of the furan ring provided α-alkoxy carboxylic acid **5**[18,19] in 96% yield (eqn (1), right).

(1)

By ozonolysis and subsequent Me_2S treatment,[20] allyl alcohol **3r** was converted to α-hydroxy ketone **6**[21] in 98% yield with 99% ee (eqn (2)). This is synthetically important because compound **6** cannot be prepared directly from unstable methylglyoxal by alkylation. In the same way, α-hydroxy ketone **7** bearing a terminal formyl moiety was readily prepared from allyl alcohol **3s** in 86% yield with 98% ee (eqn (3), right). Moreover, the diastereoselective epoxidation of allyl alcohol **3s** with *m*-CPBA was examined (eqn (3), left).[22] Fortunately, *syn*-epoxide **8**, which is a key intermediate in the synthesis of optically active 1,3-diols with three consecutive chiral carbon centers,[23] was obtained with a diastereomeric ratio of 76 : 24 with 97% ee (*syn*).



(2)

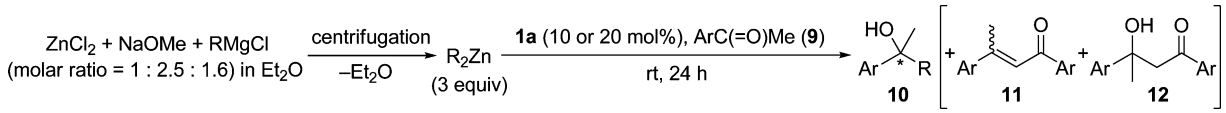


(3)

Finally, the 2°-alkylation of ketones in place of aldehydes was examined (Table 3).[24] Unfortunately, both isopropylation and cyclohexylation of acetophenone (**9a**) did not provide the desired products, and the mixture of undesired aldol product (**11**) and aldol condensation product (**12**) was obtained (entries 1 and 2). In sharp contrast, the isopropylation of 4′-(trifluoromethyl)acetophenone (**9b**) and 3′,5′-bis(trifluoromethyl)acetophenone (**9c**) proceeded without aldol formation at 0 °C for 24 h in the presence of 10 mol% of ligand **1a**, and the desired tertiary alcohols (**10c** and **10d**) were obtained in moderate yield with >99% ee (entries 3 and 4). Furthermore, the cyclohexylation of **9b** and **9c** in the presence of 20 mol% of ligand **1a** provided the desired products **10e** and **10f** in moderate to good yield with >99% ee (entries 5 and 6). To the best of our knowledge, this is the first example of catalytic asymmetric tertiary alcohol synthesis *via* di(2°-alkyl)zinc addition to ketones.[25]

In summary, we have developed a highly practical, catalytic enantioselective 2°-alkyl addition to aldehydes and ketones with salt-free di(2°-alkyl)zinc reagents. In this catalysis, refined Charette's reaction conditions using the molar ratio

Table 3 Enantioselective 2°-alkyl addition to ketones[a]



Entry	**1a** (mol %)	Product		Yield and ee of **10**	Yield of **11** and **12**	Recovery of **9**
1[a]	10	**10a**	(Ar = Ph, R = *i*-Pr)	0	84% (**11a**/**12a** = 2 : 3)	15%
2[b]	20	**10b**	(Ar = Ph, R = *c*-Hex)	0	85% (**11b**/**12b** = 1 : 1)	14%
3[a]	10	**10c**	(Ar = 4-$CF_3C_6H_4$, R = *i*-Pr)	38%, >99% ee	<3%	59%
4[a]	10	**10d**	(Ar = 3,5-$(CF_3)_2C_6H_3$, R = *i*-Pr)	40%, >99% ee	<3%	57%
5[b]	20	**10e**	(Ar = 4-$CF_3C_6H_4$, R = *c*-Hex)	40%, >99% ee	<3%	57%
6[b]	20	**10f**	(Ar = 3,5-$(CF_3)_2C_6H_3$, R = *c*-Hex)	56%, >99% ee	<3%	41%

[a] Reaction was examined under solvent-free conditions. [b] Reaction was examined under 2.5 M toluene conditions.

of 1/2.5/1.6 of $ZnCl_2$/NaOMe/RMgCl in the presence of chiral ligand **1** was essential. Moreover, solvent-free conditions were critical for minimizing undesired reduction byproducts. Optically active novel secondary alcohols could be transformed to synthetically useful γ-hydroxy-β-pyrone, α-alkoxy carboxylic acid, α-hydroxy ketone, and 2,3-epoxyalcohol.

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