Design, Reactivities, and Practical Application of Dialkylzinc Hydride Ate Complexes Generated *in Situ* from Dialkylzinc and Metal Hydride. A New Methodology for Activation of NaH and LiH under Mild Conditions

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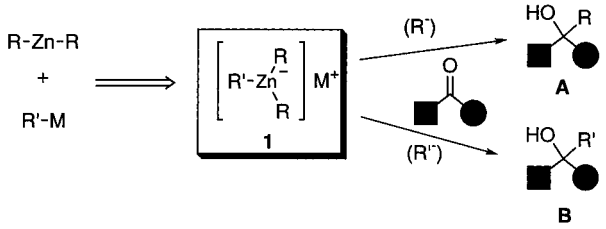
Abstract: We designed various dialkylzinc hydride "ate" complexes, prepared from dialkylzinc and metal hydride, and investigated the reactivities (and the transference aptitude of ligands) of these zincates toward benzophenone. The results clearly reveal that dimethylzinc hydrides are the most powerful and selective zincates for the reduction of the carbonyl group. This complex reagent turned out to be effective for the reduction of esters and amides as well as aldehydes and ketones to the corresponding alcohols and amines with good to excellent yields under mild conditions. Furthermore, the method was successfully used for the highly selective 1,2-reduction of α,β-unsaturated carbonyl compounds, the regioselective ring-opening reduction of epoxides, and the chemoselective reduction of aldehydes in the presence of ketones. We also discuss and clarify the active species and the mechanism of this reduction using the diastereoselective reductions of some carbonyl compounds with an adjacent chiral center. Also, this reducing system was found to constitute a powerful tool for the stereoselective synthesis of *syn*- and *anti*-1,2-diols. Moreover, we developed the catalytic version of this reducing system. The LiH−Me_2Zn−ultrasound system proved to be effective not only for the catalytic reduction of the carbonyl compounds and epoxides but also for the partial reduction (the conversion) of carboxylic acids to aldehydes. This system is a very attractive method for several reasons (good availability, low cost, and easy operation) and would be particularly useful for large-scale reductions.

Introduction

Organometallic reagents having Lewis acidity (vacant orbital) often form complexes with anion species, such as carboanions and alkoxy anions, to generate metallic anion complexes defined as ate complexes.[1] Ate complexes, being bimetallic compounds, are known to show unique reactivities that metallic reagents themselves do not possess. Such unique reactivities of ate complexes have also been reported in recent studies on organozinc reagents. For example, while organozinc halides (Reformatsky-type, symbolized as RZnX) and diorganozincs (R_2Zn) exhibit different reactivities, triorganozincs ($R_3Zn^-Metal^+$) are known to produce 1,4-conjugated additions toward α,β-unsaturated carbonyl compounds[2] and the metallation of aromatic halides[3] or vinyl halides.[4] Lithium trialkylzincates, one of the organozincates,[5] is a complex arising from dialkylzinc having Lewis acidity and alkyllithium having Lewis basicity.



Case	Zincate	Product	Reactivity (Yield of **A** and **B**)
R = R'	symmetric	**A** = **B**	equivalent
R ≠ R'	asymmetric	**A** ≠ **B**	nonequivalent

Figure 1. Classification of reactivities of triorganozincates.

Since all of alkyl ligands coordinated to Zn are usually the same, these reactivities, *i.e.*, the magnitude of the transference aptitude of alkyl groups, are essentially equivalent. However, the reactivities of the alkyl groups should be nonequivalent, if different alkyl groups do coordinate to Zn (Figure 1). Namely, when different alkyl groups coordinating triorganozincates react with electrophilic reagents, a problem is which alkyl group transfer occurs first. Such transference aptitude of alkyl groups on Zn has been discussed in 1,4-conjugated additions toward α,β-unsaturated carbonyl compounds[2b−d] and 1,2-additions to

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aldehydes.[3d] We are interested in the transference aptitude between alkyl and hydride groups above Zn, not between alkyl and alkyl groups as usually occurs, because the magnitude of the former is considered to be larger than that of the latter. If a hydride was selectively transferred compared with alkyl group from the dialkylzinc hydride ate complex, this complex would be a new reducing (hydrometallating) reagent.

Since the nature of the zinc−hydride bond is between that of saline hydrides, metallic hydrides, and molecular hydrides,[6] the structure and reactivities as a nucleophile or base[7] have been extensively studied in compounds of H_2Zn,[8] H_3ZnM (M = Li, Na, *etc*.),[9] H_4ZnM' (M′ = Li_2, Na_2, Mg, *etc*.),[9] and related compounds.[10] However, these hydride reagents have scarcely been used as a practical hydride donor for the reduction of carbonyl compounds in organic synthesis, because their difficulty of their preparations, low reactivity, and low selectivity. However, if the environment, *i.e*., ligands coordinated to Zn, is altered, the nature of the compound as a hydride source should be changed. We designed dialkylzinc hydride ate complexes made with dialkylzinc as the Lewis acid and metal hydrides as the Lewis base. In 1970, Kubas and Shriver reported that various kinds of dialkylzinc formed complexes with LiH or NaH in THF, Et_2O, or DMF.[11] However, the structure and reactivities of the complex have received little attention. On the other hand, although LiH and NaH have the advantages of good availability, low cost, and easy operation, they are known as essentially inert hydrides toward the reduction of carbonyl compounds. In this paper, we report the design and reactivities of dialkylzinc hydride ate complexes, prepared *in situ* from a metal hydride and dialkylzinc, toward carbonyl compounds and the practical applications of this system as a hydride source for chemoselective, stereoselective, and catalytic reductions. We also discuss the active species and the mechanism of this reduction using the diastereoselective reductions of some carbonyl compounds with an adjacent chiral center.[12]

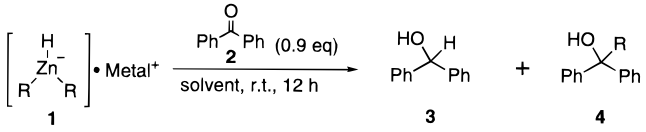
Results and Discussion

Reactivities of Dialkylzinc Hydride Ate Complexes. Initially, the reactivities and transference aptitude of ligands above Zn in various kinds of dialkylzinc hydride ate complexes (**1**) toward carbonyl compounds using benzophenone (**2**) as a model substrate were investigated. These results are summarized in Table 1. Very interestingly, use of the methyl group as a ligand on Zn produced benzhydrol (**3**) as the sole product; dimethylzinc hydrides selectively transferred the *hydride* compared with the methyl group from the zincate to **2** (entries 4 and 5, 8 and 9). Particularly, when sodium hydride was used as the metal hydride, a hydride adduct was obtained in high yield without the formation of any detectable amount of the methyl adduct **4** (entries 5 and 9). In diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2), these activations and selectivities were also observed without any problems (entries 10 and 11). A noteworthy fact is that no methylation product was obtained in all cases! However, when ethyl (primary alkyl) and *tert*-butyl (tertiary alkyl) groups, being more bulky and anionic alkyl groups, were used instead of the methyl group, a large amount of alkylated product (**4**) was obtained and accompanied by the hydride adduct (entries 6 and 7). Judging from the results that the reduction of **2** with LiH, NaH, and H_2Zn did not or scarcely proceeded (entries 1−3), we can assume that LiH or NaH was activated as a hydride source by ate complexation with Me_2Zn.

On the other hand, the low yield of **3** when the LiH−Me_2Zn system was used (entry 4) was attributed to the slower ate complexation reaction in comparison with the NaH−Me_2Zn system (entry 5),[11] not an effect of the countercation of the dimethylzinc hydride ate complexes, because reactivities, *i.e*., the yield of **3**, were found to be similar in both the NaH−Me_2-Zn system (entry 5) and NaH−$ZnCl_2$−2MeLi system (entry 9). Indeed, the reaction of **2** with the LiH−Me_2Zn system under sonication dramatically proceeded to give **3** in 96% yield (entry 12). This result indicates that LiH was activated by sonication and the ate complexation reaction was accelerated.[13] Since the methyl group was found to be excellent as an activating and nontransfer group, the wide applicability of this new reducing system is demonstrated by the reduction of other carbonyl compounds using the NaH−Me_2Zn system which exhibited the best reactivities and selectivities toward **2**.

Reduction of Other Carbonyl Compounds with NaH-Me_2-Zn System. The metal hydride reduction of carbonyl com-

Table 1 Reactivities of Dialkylzinc Hydride Ate Complexes



entry	preparations of **1**	R	metal$^+$	solvent	yield (%)[a] **3**	**4**
1	LiH			THF	0	
2	NaH			THF	0	
3	NaH + $ZnCl_2$			THF	16	
4	LiH + Me_2Zn	Me	Li^+	THF	32	<1
5	NaH + Me_2Zn	Me	Na^+	THF	99	<1
6	NaH + Et_2Zn	Et	Na^+	THF	56	43
7	NaH + $ZnCl_2$ + 2^{t}BuLi	^{t}Bu	Na^+ or Li^+	THF	4	18
8	LiH + $ZnCl_2$ + 2MeLi	Me	Li^+	THF	36	<1
9	NaH + $ZnCl_2$ + 2MeLi	Me	Na^+ or Li^+	THF	92	<1
10	NaH + Me_2Zn	Me	Na^+	Et_2O	88	<1
11	NaH + Me_2Zn	Me	Na^+	CH_2Cl_2	93	<1
12	LiH + Me_2Zn + sonication	Me	Li^+	THF	96	<1

[a] Isolated yield based on the amount of **2**.

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(11) Kubas, G. J.; Shriver, D. F. *J. Am. Chem. Soc.* **1970**, *92*, 1949−1954.

(12) Although there are some reports on using ZnX_2 (X = Cl or OSO_2-Me) or Zn(0) as activator of the *reductive silylation*, no papers of a method for direct activation of LiH or NaH as *a zinc ate complex* using dialkylzinc have been published. For examples using NaH−Cl$(CH_3)_3$Si−$ZnCl_2$ mixed system, see: (a) Caubére, P.; Vanderesse, R.; Fort, Y. *Acta Chem. Scand.* **1991**, *45*, 742−745. (b) Nordahl, Å.; Carson, R. *Ibid.* **1990**, *44*, 274−278. For examples using NaH−Cl$(CH_3)_3$Si−NaOCH_2C$(CH_3)_3$−$ZnCl_2$ (Zn-CRASi) mixed system, see: (c) Brunet, J.-J.; Besozzi, D.; Caubére, P. *Synthesis* **1982**, 721−723. (d) Caubére, P. *Pure Appl. Chem.* **1985**, *57*, 1875−1882. For examples using LiH−Cl$(CH_3)_3$Si−ZnX_2 (X = Cl or OSO_2Me) or Zn(0) mixed system, see: (e) Ohkuma, T.; Hashiguchi, S.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 217−221.

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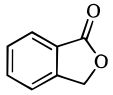
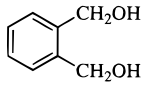
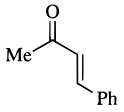
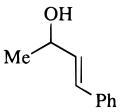
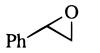
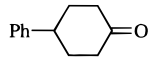
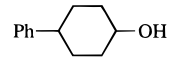
Table 2. Reduction of Carbonyl Compounds and Epoxide with NaH−Me_2Zn Reducing System[a]

Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	*p*-$MeOC_6H_4CHO$	*p*-$MeOC_6H_4CH_2OH$	96[c]	7	*p*-$MeOC_6H_4COOMe$	*p*-$MeOC_6H_4CH_2OH$	98[d]
2	$PhCH_2CH_2CHO$	$PhCH_2CH_2CH_2OH$	85[c]	8			100[d]
3	PhCH(Me)CHO	PhCH(Me)CH_2OH	91[c]	9			90[e] (73)[f]
4	PhCOMe	PhCH(OH)Me	91	10		PhCH(OH)Me	92 (0)
5			95	11	*p*-$ClC_6H_4NHCOMe$	*p*-$ClC_6H_4NHCH_2CH_3$	68[g, h]
6	PhCOOMe	$PhCH_2OH$	97[d]	12	$PhCONMe_2$	$PhCH_2OH$	88[g]

[a] Unless otherwise noted, the reaction was carried out using NaH (1.2 equiv), Me_2Zn (1.1 equiv), and substrate (1 equiv) in THF at room temperature for 12 h. [b] Isolated yield. Value in parentheses are yield of reduction using $NaBH_4$ under the same conditions. [c] The reaction was carried out at 0 °C for 1 h. [d] The reaction was carried out using NaH (2.2 equiv) and Me_2Zn (2.0 equiv) at 0 °C for 6 h. [e] No conjugate reduction product was obtained. [f] 4-Phenyl-2-butanone was also obtained in 25% yield. [g] The reaction was carried out using NaH (3.0 equiv) and Me_2Zn (3.0 equiv). [h] 4-Chloroacetanilide was recovered in 28% yield.

pounds such as aldehydes, ketones, esters, and enones to the corresponding alcohols is one of the most fundamental processes in organic synthesis.[14] Successful methods for accomplishing this transformation with metal hydrides or metal ate hydrides containing boron,[15] aluminum,[16] silicon,[17] and tin[18] have been reported. Unfortunately, however, many of these reagents also have some significant disadvantages: low reactivity, low chemoselectivity, the requirement of strict reaction conditions, and the cost of reagents especially on an industrial level. Thus, the development of a new, simple, and practical method for the highly selective reduction of various carbonyl compounds is still desirable.

The NaH−Me_2Zn "ate" complex proved effective for the reduction of other carbonyl compounds (Table 2). The reduction of an aromatic aldehyde gave alcohols in quantitative yield (entry 1). Interestingly, aliphatic aldehydes, particularly enolizable aldehydes, were also reducible in high yields and no aldol products were obtained (entries 2 and 3). This indicates that NaH completely eliminates the intrinsic basicity and dramatically increases the nucleophilicity by ate complexation with Me_2Zn. Furthermore, the reduction of esters and lactones, as well as aldehydes and ketones, also proceeded well to afford the corresponding alcohols in high yields (entries 4−8).

These remarkable reducing abilities of the NaH−Me_2Zn "ate" complex prompted us to further survey whether this reducing system could be used for chemoselective reduction. During the reduction of the α,β-unsaturated ketones by metal hydrides, two possible products can be obtained on the basis of the reaction direction of the hydrides, *i.e.*, addition to the carbonyl group (1,2-addition) to give the allylic alcohols or addition to the conjugated double bond (1,4-addition) to give the saturated ketones.[19] This complex reducing reagent proved effective for the highly selective 1,2-reduction of the enone (entry 9). No conjugate reduction products was isolated. Under the same conditions, the reduction using $NaBH_4$ gave 1,2-reduction and 1,4-reduction products in 73 and 25% yields, respectively. The ring opening reaction of the monosubstituted epoxide by metal hydrides can follow two pathways: the addition to the α-carbon (with respect to the substituent group) to give a primary alcohol or the addition to the β-carbon (less-hindered site) to give a secondary alcohol.[20] The NaH−Me_2Zn reducing reagent styrene oxide and 1-phenethyl alcohol was obtained in 92% yield with perfect regioselectivity (entry 10). On the other hand, the reduction of styrene oxide with $NaBH_4$ did not proceed at all under the same conditions.[21] Moreover, this reducing system proved effective in the reduction of the amide groups.[14] The reduction of the *N*-monoalkylamide proceeded normally to afford the corresponding dialkylamine, namely 4-chloroacetanilide, was converted to *N*-ethyl-4-chloroaniline in 68% yield, and 28% of the starting material was recovered (entry 11). However, the reduction of *N*,*N*-dimethylbenzamide, the *N*,*N*-dialkylamide, proceeded to give an abnormal product, benzyl

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(20) For the regioselective reduction of epoxides, see: Murai, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 4.4 and references cited therein.

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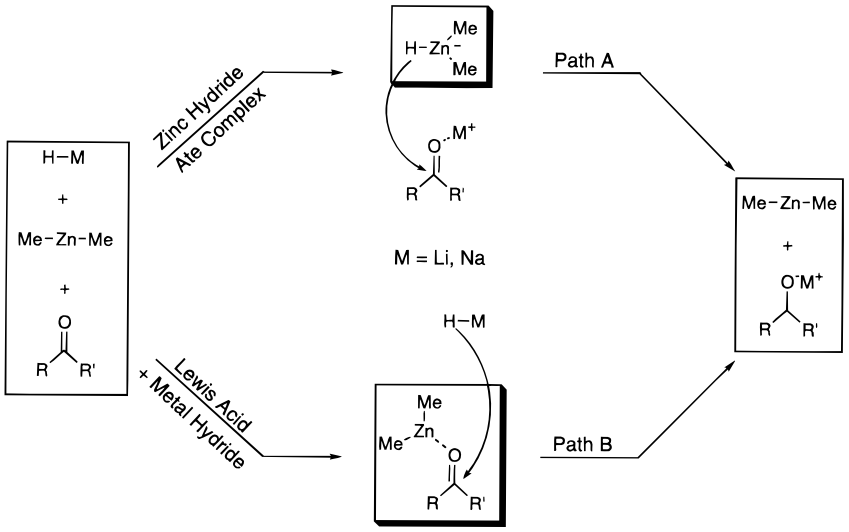


Figure 2. Possible mechanism for reduction of carbonyl compounds with metal hydride−Me_2Zn reducing system.

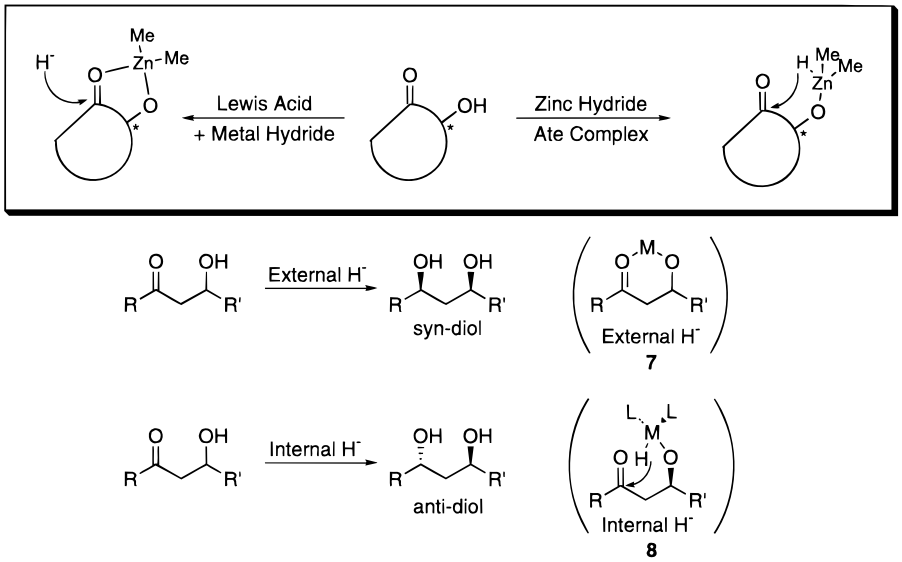


Figure 3. Diastereoselective reductions of carbonyl compounds with an adjacent chiral center.

alcohol, in 88% yield (entry 12). The scope and limitation of this amide reduction, in combination with the mechanism, are currently under investigation. Next, the wide applicability of this new reducing system is demonstrated by the selective reduction of more reactive aldehydes in the presence of ketone.[22] In the competitive reaction of 2-naphthaldehyde (**5**, 1 equiv) and benzophenone (**2**, 1 equiv) with NaH−Me_2Zn (1 equiv), the reduction of **5** was performed with more than 98% selectivity.

Finally, the complex reagent prepared *in situ* from NaH and Me_2Zn has proved to be a powerful (for reduction of esters, lactones, epoxides, and amides) and highly chemoselective (for reduction of α,β-unsaturated carbonyl compounds, monosubstituted epoxide, and amides) reducing reagent.

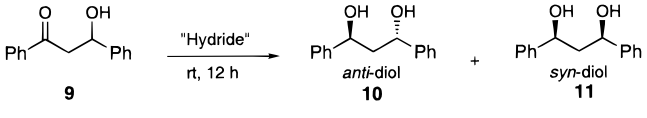
Active Species of This Complex Reducing System: Diastereoselective Reduction of β-Hydroxy Carbonyl Compounds. During the reduction of carbonyl compounds with this complex reducing system, the following two possible pathways can be considered, although we suppose the active species of this system is the *dimethylzinc hydride "ate" complex* (Figure 2): (1) In the initial step, dimethylzinc hydride *"ate complexes"* are generated from metal hydrides and Me_2Zn. Following the formation of the ate complexes, the carbonyl compounds are reduced to the corresponding metal alkoxides by the hydride ate complexes (path A). (2) Me_2Zn activates the carbonyl compounds as a Lewis acid, and the metal hydrides directly reduced them (path B).

Only a slight difference in reactivities due to the two possible mechanisms is observed in the reduction of the usual carbonyl compounds. However, in the reduction of carbonyl compounds with an adjacent chiral center, the reactivities or diastereoselectivities should differ based on the two possible mechanisms.[23] In particular, the reduction of β-hydroxy carbonyl compounds would give important information (Figure 3). For example, when a *syn*-diol was selectively obtained, the reduction was proved to proceed by attack of an external hydride on a six-membered chelate transition state such as **7**, the conformation of which was governed by the substituent at the alcohol center.[24] On the other hand, the *anti*-diol was produced by attack of an internal hydride above the metal complexes bound to the alcohol.[25] Therefore, it is helpful to distinguish between the

(22) For the selective reduction of more reactive aldehyde in the presence of ketone by metal hydrides, see: ref 14a.

(23) For the diastereoselective reductions using metal hydrides, see: (a) Davis, A. P. In *Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E 21d, Chapter 2.3.3.1 and references cited therein. (b) Mihály, N. In *Stereoselective Synthesis*, 2nd ed.; VCH: Weinheim, 1995. (c) Reference 14a.

Table 3. Diastereoselective Reduction of β-Hydroxy Ketones



9 **10** **11**

entry	"hydride"	yield (%) (*anti* + *syn*)	ratio (*anti*:*syn*)
1	$NaH + Me_2Zn$	65	83:17
2	$LiH + Me_2Zn$ + sonication	57	59:41
3	$NaBH_4$	91	50:50

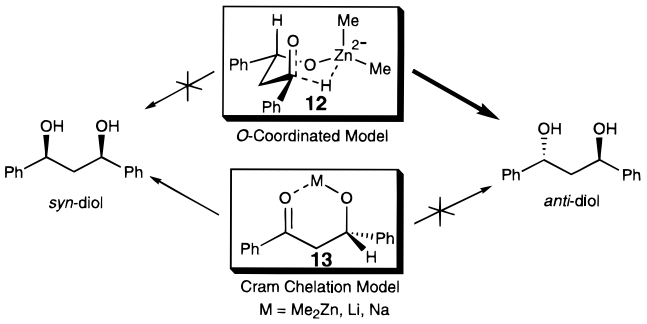
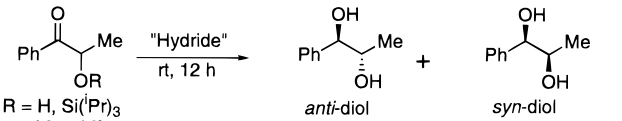


Figure 4. Possible mechanism for reduction of β-hydroxy ketones with metal hydride−Me_2Zn reducing system.

dialkylzinc hydride mechanism and the Lewis acid mechanism. Namely, when the active species of this reduction is dimethylzinc hydride, the *anti*-diols should be selectively obtained (Figure 2, path A). When Me_2Zn activates the carbonyl compounds as a Lewis acid and metal hydrides reduce them directly, the *syn*-diols should be selectively obtained (Figure 2, path B).

The reduction of 3-hydroxy-1,3-diphenyl-1-propanone (**9**) by various metal hydrides was investigated. The results are summarized in Table 3. In the reduction using this reducing system, the *anti*-diol was favored over the *syn*-diol. However, reduction with $NaBH_4$ exhibited no selectivity under the same conditions. Judging from the relation between diastereoselectivity and the reaction mechanism, the reduction using this reducing system was considered to proceed by attack of an internal hydride above the metal complexes bound to the alcohol *via* a chair transition state (**12**) to preferentially give the *anti*-diol (Figure 4, *O*-coordinated model). This result strongly supports the fact that the active species of this complex reducing system is *dimethylzinc hydride "ate" complex*. However, another path is also slightly possible. Residual Me_2Zn, Li^+, or Na^+ was chelated by β-hydroxy ketones to form a six-membered transition state (**13**), allowing attack of an external hydride to reduce the carbonyl group with *syn*-selectivity (Figure 4, Cram chelation model[26]). Therefore, the *anti*-selectivity was considered to be slightly lower (mismatched model[27]).

Table 4. Diastereoselective Reduction of α-Substituted Ketones



14a, **14b** **15** **16**

entry	R	"hydride"	yield (%) (*anti* + *syn*)	ratio (*anti:syn*)	
1	H	$NaH + Me_2Zn$	99	99:1	(99:1)
2	H	$LiH + Me_2Zn$ + sonication	72	89:11	(8:1)
3	H	$LiAlH_4$	92[a]	87:13	(7:1)[a]
4	H	$NaBH_4$	96	92:8	(12:1)
5	$Si(^iPr)_3$[b]	$NaH + Me_2Zn$	70	4:96	(1:24)
6	$Si(^iPr)_3$[b]	$LiH + Me_2Zn$ + sonication	85	22:78	(1:4)
7	$Si(^iPr)_3$[b]	$NaBH_4$	64	23:77	(1:4)

[a] In THF at −78 °C. Taken from ref 40. [b] Yields and ratios of products were determined after desilylation.

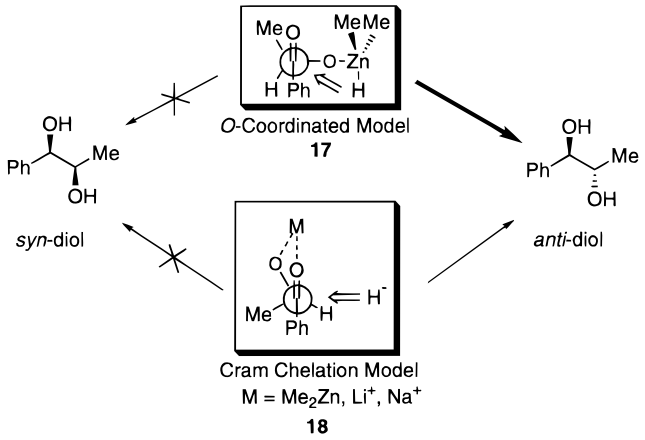


Figure 5. α-Hydroxy carbonyl compounds reduction model.

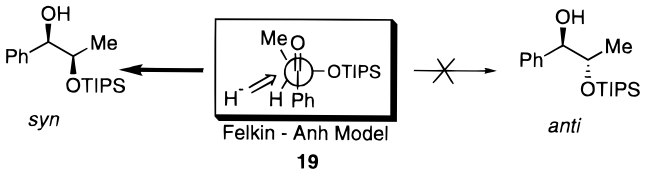


Figure 6. α-Substituted carbonyl compounds reduction model.

Diastereoselective Reduction of α-Hydroxy Carbonyl Compounds. The reduction of 2-hydroxy-1-phenyl-1-propane (**14a**) with various metal hydrides was investigated (Table 4, entries 1−4).[28] Although the yields and ratios of the products depend to some degree on the reducing reagent, the *anti*-diol is favored in all cases. The reduction of 2-hydroxypropiophenone with $NaH + Me_2Zn$ system was found to exhibit a remarkably high *anti*-selectivity (compared with $LiAlH_4$ or $NaBH_4$). Next, the reduction of α-triisopropylsilyloxy carbonyl compounds (**14b**) was also investigated (Table 4, entries 5−7).[29] Triiso-

(24) (a) Anwar, S.; Davis, A. P.; Fort, Y. *Tetrahedron*. **1988**, *44*, 3761−3770. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc*. **1988**, *112*, 3560−3578. (c) Evans, D. A.; Hoveyda, A. *Ibid*. **1990**, *112*, 6447−6449. (d) Sarco, C. R.; Collibee, S. E.; Knorr, A. L.; DiMare, M. *J. Org. Chem*. **1996**, *61*, 868−873.

(25) (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233−2238. (b) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G.-E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett*. **1987**, 1923−1926. (c) Chen, K.-M.; Hardtmann, G.-E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron. Lett*. **1987**, *28*, 155−158.

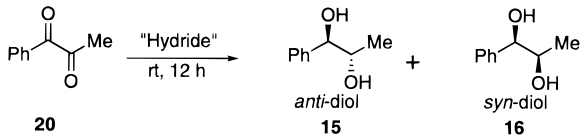
(26) (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc*. **1952**, *74*, 5828−5835. (b) Still, W. C.; McDonald, J. H., III *Tetrahedron. Lett*. **1980**, *21*, 1031−1034. (c) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc*. **1992**, *114*, 4536−4542.

(27) The term "mismatched model" is used to refer to the main two mechanisms (*O*-coordinated model and cram chelation model) exhibiting the same diastereoselectivities.

(28) (a) Cram, D. J.; Greene, F. D. *J. Am. Chem. Soc*. **1953**, *75*, 6005−6010. (b) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, *21*, 2199−2204. (c) Chérest, M.; Prudent, N. *Tetrahedron* **1980**, *21*, 1599−1606. (d) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim*. **1977**, *1*, 61. (e) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145.

(29) For the diastereoselective reduction of α-alkoxy carbonyl compounds, see: (a) Overmann, L. E.; McCready, R. J. *Tetrahedron. Lett*. **1982**, *23*, 2355−2358. (b) Takahashi, T.; Miyazawa, M.; Tsuji, I. *Ibid*. **1985**, *26*, 5139−5142. (c) Samuels, W. D.; Nelson, R. T.; Hallen, R. T. *Ibid*. **1986**, *27*, 3091−3094. (d) Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem*. **1989**, *54*, 2021−2024. (e) Ko, K.-Y.; Eliel, E. L. *Ibid*. **1986**, *51*, 5353−5362.

Table 5. Diastereoselective Reduction of 1,2-Diketones



20 15 16

entry	"hydride"	yield (%) (*anti* + *syn*)	ratio (*anti:syn*)	
1	$NaH + Me_2Zn$	61	98:2	(49:1)
2	$LiH + Me_2Zn$ + sonication	45	95:5	(19:1)
3	$LiAlH_4$	98[a]	72:28	(3:1)[a]
4	$NaBH_4$	98	67:33	(2:1)

[a] In THF at −78 °C. Taken from ref 40.

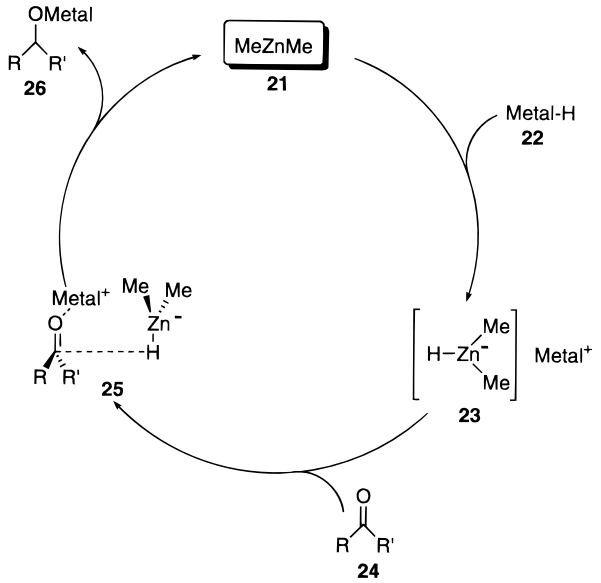
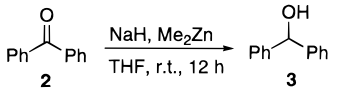


Figure 7. Possible mechanism for the catalytic reduction of carbonyl compounds.

propylsilyl moiety is known as the group which is deprived of the Lewis basicity of the oxygen atom. Yields and ratios of these reductions were determined after desilylation of the reduction products by treatment with *tetra-n*-butylammonium fluoride. In contrast to the case of **14a**, the *syn*-diol is favored over the *anti*-diol in these reductions. The NaH−Me_2Zn system was also found to exhibit high diastereoselectivity. These results indicate that this reducing system constitutes a powerful tool for the stereoselective synthesis of *syn*- and *anti*-1,2-diols.

The dimethylzinc hydride "*ate complex*" mechanism can successfully interpret these selectivities (Figure 5). Namely, for the reduction of α-hydroxy carbonyl compounds, the *anti*-diol was selectively produced by attack of an internal hydride above the dimethylzinc hydride ate complexes bound to the alcohol *via* an *O*-coordinated transition state such as **17** (Figure 5, *O*-coordinated model). Moreover, because the *anti*-diol was also supported by a chelation model in addition to this internal hydride path (matched model[27]), an extraordinarily high selectivity was obtained (Figure 5, Cram chelation model). On the other hand, for the reduction of α-triisopropylsilyloxy carbonyl compounds, the *syn*-diol supported by Felkin−Anh model was favored over the *anti*-diol (Figure 6, Felkin−Anh model). In the absence of a neighboring chelationable heteroatom, asymmetric induction from the remote center is generally ineffective during reductions of acyclic ketones.[30] Therefore, the dimethylzinc hydride ate complex turned out to be a highly selective reducing reagent.

Table 6. Dimethylzinc-Catalyzed Reduction of Benzophenone (**2**)[a]



2 3

entry	Me_2Zn (mol %)	yield (%)
1	50	99
2	20	98
3	10	89
4	5	56

[a] Unless otherwise noted, the reaction was carried out using NaH (1.2 equiv), Me_2Zn (cat.), and benzophenone (**2**) (1 equiv; 1 mmol) in THF at room temperature for 12 h. [b] Isolated yield based on the amount of **2**.

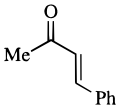
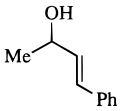
Diastereoselective Reduction of 1,2-Dicarbonyl Compounds. This reducing system was proved effective for the reduction of 1,2-diketones (Table 5).[14] Although the *anti*-diol is favored over the *syn*-diol in all cases, this dimethylzinc hydride complex exhibited higher *anti*-selectivities in comparison to the usual reducing reagents such as $LiAlH_4$ or $NaBH_4$. This reduction using dimethylzinc hydride complexes is attractive from a synthetic viewpoint, not only because high diastereoselectivity was obtained but also because two chiral centers are constructed at the same time.

Reaction Mechanism for the Reduction of Carbonyl Compounds with This Complex Reducing System and These Catalytic Reductions. On the basis of the result that no methylation product was obtained during the reduction of carbonyl compounds with this reducing system, we considered this reaction mechanism as follows (Figure 7). The proposed reaction mechanism involves an initial ate complexation reaction to generate the dimethylzinc hydride ate complexes **23**. Following the formation of **23**, the carbonyl compound **24** is reduced to the corresponding sodium alkoxide (**26**), and Me_2Zn (**21**) is regenerated at the same time. Therefore, this reduction possibly proceeds catalytically. Indeed, the reduction of benzophenone (**2**) with NaH in the presence of catalytic amounts of Me_2Zn proceeded smoothly to give benzhydrol (**3**) in high yields (Table 6). Although the reduction of **2** (1 mmol) using 5 mol % Me_2Zn gave **3** in 56% yield (entry 4), the reaction using 10 mol % Me_2Zn afforded the product in 89% yield (entry 3).

Reaction Condition-Dependent Catalytic Efficiency of This Reducing System. The catalytic efficiency of the reduction of benzophenone (**2**) with various metal hydrides was investigated (Figure 8). During the reduction of **2** with LiH, the yield of benzhydrol (**3**) was not much more than 100% even after 48 h, *i.e.*, the turnover number (TON, defined as moles of the product per mole of the catalyst) of the reduction was about 1 (Figure 8, solid line). However, when NaH in place of LiH was used, the reaction dramatically proceeded to give rise to **2** in 1000% yield after 6 h (TON = 10) and subsequently became saturated (Figure 8, dashed line). Furthermore, during the reduction with LiH under sonication, the yield of **3** reached 1700% after 2 h (TON = 17) and gradually rises thereafter (Figure 8, dotted line). Taking into account an amount (20 equiv) of metal hydride and **2** recently used, we can assume that the Me_2Zn-catalyzed LiH reduction system under sonication should intrinsically exhibit higher catalytic activities. Also, the initial complexation of Me_2Zn and metal hydride are considered to allow the existence of a certain amount of free (uncomplexed) metal

(30) (a) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159−7161. (b) Brown, H. C.; Hubbard, J. L.; Singaram, B. *Tetrahedron* **1981**, *37*, 2359−2362. (c) Suzuki, K.; Katayama, E.; Tsuchihashi, G.-i. *Tetrahedron. Lett.* **1984**, *25*, 2479−2482. (d) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338−344.

Table 7. Catalytic Reduction Using LiH−Me_2Zn−Sonication System[a]

Entry	Substrate	Product	Yield (%)[b]	Entry	Substrate	Product	Yield (%)[b]
1	*p*-$MeOC_6H_4CHO$	*p*-$MeOC_6H_4CH_2OH$	92	6	*p*-$ClC_6H_4NHCOMe$	*p*-$ClC_6H_4NHCH_2CH_3$	46[e]
2	$PhCH_2CH_2CHO$	$PhCH_2CH_2CH_2OH$	93[c]	7			88 (96 : 4)[f]
3	PhCH(Me)CHO	PhCH(Me)CH_2OH	94[c]	8		PhCH(OH)Me	94 (97 : 3)[g]
4	PhCOMe	PhCH(OH)Me	84	9	*p*-$MeOC_6H_4COOH$	*p*-$MeOC_6H_4CHO$	82[h]
5	*p*-$MeOC_6H_4COOMe$	*p*-$MeOC_6H_4CH_2OH$	95[d]	10	$PhCH_2CH_2COOH$	$PhCH_2CH_2CHO$	68[h]

[a] Unless otherwise noted, the reaction was carried out using LiH (1.2 equiv), Me_2Zn (20 mol %), and substrate (1 equiv) in THF at room temperature for 12 h. [b] Isolated yield. [c] The reaction was carried out at 0 °C for 1 h. [d] The reaction was carried out using LiH (3.0 equiv) and Me_2Zn (30 mmol %) at 0 °C for 6 h. [f] The reaction was carried out using LiH (3.0 equiv) and Me_2Zn (30 mol %) at room temperature for 48 h. *N*-Ethyl-4-chloroaniline was the sole product, and 4-chloroacetanilide was recovered in 32% yield. [e] Values in parentheses are ratio of 1,2-reduction and 1,4-reduction. [g] Values in parentheses are ratio of 1-phenethyl alcohol and 2-phenethyl alcohol. [h] The reaction was carried out using LiH (3.0 equiv) and Me_2Zn (100 mol %) at room temperature for 24 h.

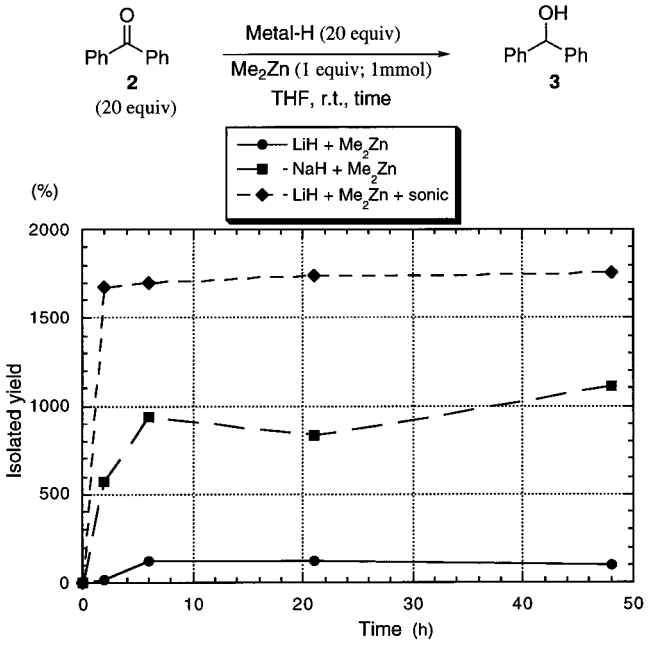


Figure 8. Reaction condition-depependent catalytic efficiency of reduction of benzophenone (**1**). The reaction was carried out using metal hydride (20 equiv), Me_2Zn (1 equiv; 1mmol), and benzophenone (**2**) (20 equiv) in THF at room temperature. Isolated yield is based on the amount of Me_2Zn.

hydride. Therefore, LiH is seemed to be superior to NaH in several respects such as (lower) basicity and (lower) reactivity.[31]

Finally, the LiH−Me_2Zn−ultrasound catalytic reduction system was found to be an effective method for the catalytic reduction of carbonyl compounds on the basis of the catalytic efficiency, cost, low basicity, and ease of operation.

Catalytic Reduction of Carbonyl Compounds with LiH−Me_2Zn−Ultrasound System. As we succeeded in optimizing the conditions for the catalytic reduction with the dimethylzinc hydride ate complex, we turned our interest to the catalytic reduction of other carbonyl compounds and epoxides with the LiH−Me_2Zn−ultrasound system (Table 7). Interestingly, aliphatic aldehydes, particularly enolizable aldehydes as well as an aromatic aldehyde were reducible in excellent yields without the formation of any detectable amount of aldol products, although there are free metal hydrides in plenty during the initial step of this reaction (entries 1−3). Ketones, esters, and amides are also reductively converted to the corresponding alcohols and amines in THF under mild conditions (entries 4−6). Furthermore, this method was successfully used for the highly selective 1,2-reduction of α,β-unsaturated carbonyl compounds and regioselective ring opening reduction of epoxides (entries 7 and 8).

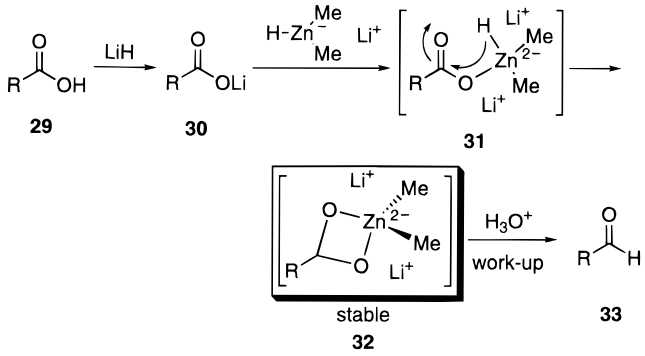


Figure 9. Possible mechanism for the partial reduction of carboxylic acids.

The reduction of carboxylic acids using a metal hydride is generally known to be difficult and proceeds to the corresponding alcohols.[32] However, this catalytic reduction turned out to be an effective method for the partial reduction of aromatic and aliphatic carboxylic acids to the corresponding aldehydes (entries 9 and 10). The best solvent for the reduction was THF; the rate of the reduction was slower in Et_2O and CH_2Cl_2. It seems difficult to explain this partial reduction using the ordinary accepted hydride reduction mechanisms.[33] A plausible mechanism for this partial reduction is shown in Figure 9, although

(31) Cotton, F. A.; Willkinson, G.; Langford, C. H. *Advanced Inorganic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1980; Part 2, Chapter 7.

(32) For the complete reduction of carboxylic acids to alcohols, see: Barrett, A. G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 1.10 and references cited therein.

(33) For the partial reduction of carboxylic acids to aldehydes, see: (a) Johnstone, R. A. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 1.11 and references cited therein. (b) Davis, A. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, Chapter 1.12 and references cited therein.

that is highly speculative. The reduction of the carbonyl group would proceed by attack of an internal hydride above the dimethylzinc hydride ate complexes bound to the hydroxy group *via* an *O*-coordinated transition state such as **31** which rapidly produces the Me_2Zn−acetal complex intermediate (**32**). Since **32** was very stable, this reduction was considered to stop at this stage. Although further investigation is needed to determine the mechanism, the present procedure provides a new convenient partial reduction of carboxylic acids to aldehydes.

Conclusion

We have shown the reactivities of various dialkylzinc hydride "ate" complexes prepared from a metal hydride and dialkylzinc; dimethylzinc hydride proved to be the most effective zincate for the reduction of the carbonyl groups based on reactivities and selectivities. We have also revealed that the active species of this complex reagent is the *dimethylzinc hydride "ate" complex* by using the diastereoselective reductions of some carbonyl compounds with an adjacent chiral center. This system was successfully used for chemoselective, diastereoselective, and catalytic reductions. These results suggest a possible way to develop catalytic asymmetric reduction using optically active diorganozincs as activating catalysts. The theoretical approach with the help of *ab initio* calculations for this new reduction, *i.e.*, reactivities, selectivities, nontransferability of alkyl group, mechanisms of unprecedented reductions, and the asymmetric version of this reducing system are currently under investigation. On the basis of simplicity, good availability, low cost, and ease of operation, the present work provides a new practical method for the reduction of carbonyl compounds.

Experimental Section

General Methods. Melting points were determined with a Yazawa micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 using tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) values, and coupling constants (J) are expressed in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and brs = broad singlet. Mass spectra were recorded on a JEOL JMS-O1SG-2 spectrometer. NaH (60% in oil) and LiH were obtained from Wako Chemicals Co., Ltd. MeLi in Et_2O, ^{t}BuLi in pentane, Me_2Zn (1.0 M solution in hexane), and Et_2Zn (1.0 M solution in hexane) were obtained from Kanto Chemical Co., Ltd. $ZnCl_2$ (0.5 M solution in THF) was obtained from Aldrich Chemical Co. The concentration of MeLi and ^{t}BuLi were determined by titration prior to use.[34]

Preparation of Dimethylzinc. Under Ar atmosphere, MeLi (1.02 M Et_2O solution, 2.0 mL, 2.0 mmol) was added to the mixture of dry THF (3 mL) and $ZnCl_2$ (1M THF solution; 1.0 mL, 1.0 mmol) at 0 °C, and the mixture was stirred for 30 min at this temperature.

Preparation of Di-*tert*-butylzinc. Under Ar atmosphere, ^{t}BuLi (1.46 M pentane solution, 1.4 mL, 2.0 mmol) was added to the mixture of dry THF (3 mL) and $ZnCl_2$ (1M THF solution; 1.0 mL, 1.0 mmol) at 0 °C, and the mixture was stirred for 30 min at this temperature.

General Procedure for Reduction of Benzophenone (2). Under Ar atmosphere, commercial dimethylzinc (1.1 mL, 1.1 mmol; 1.0 M hexane solution) was added to a mixture of dry THF (3 mL) and NaH (44.3 mg, 1.1 mmol; 60% in oil) at 0 °C, and the solution was stirred for 30 min at this temperature. To the mixture was successively added benzophenone (**2**) (183.5 mg, 1.0 mmol) in THF at 0 °C. After the solution was allowed to warm to room temperature, the mixture was stirred for 12 h. The solvent was removed under reduced pressure, and the residue was treated with aqueous NH_4Cl (30 mL) followed by extraction with $CHCl_3$ (30 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using AcOE/hexane (1:5) as eluent to give benzhydrol (**3**) (183.7 mg, 99%): mp 65−67 °C (recrystallized from *n*-hexane/ethyl acetate, colorless plates) (lit.[35] mp 68 °C).

Procedure for Chemoselective Reduction of 2-Naphthaldehyde (5) in the Presence of Benzophenone (2). Under Ar atmosphere, commercial dimethylzinc (1.1 mL, 1.1 mmol; 1.0 M hexane solution) was added to a mixture of dry THF (3 mL) and NaH (44.3 mg, 1.1 mmol; 60% in oil) at 0 °C, and the solution was stirred for 30 min at this temperature. To the mixture was successively added benzophenone (**2**) (183.5 mg, 1.0 mmol) and 2-naphthaldehyde (**5**) (156.2 mg, 1.0 mmol) in THF at −78 °C under Ar atmosphere. The mixture was stirred for 6 h at −20 °C. A saturated aqueous NH_4Cl solution (30 mL) was added to the mixture, and the aqueous layer was extracted with $CHCl_3$ (30 mL × 3). The combined $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using AcOEt/hexane (1:5) as eluent to give a mixture of 2-naphthalenemethanol (**6**) and benzhydrol (**2**). The ratio of the two products were determined through analysis of the ^{1}H NMR spectrum of the mixture in comparison to those of authentic samples.

Preparation of 3-Hydroxy-1,3-diphenyl-1-propanone (9).[36] To a cold (−78 °C) solution of $(^i\mathrm{Pr})_2$NLi [from 6.0 mmol of ^{n}BuLi (1.37 M hexane solution; 4.4 mL) and $(^i\mathrm{Pr})_2$NH (6.1 mmol)] in THF (8 mL) was added acetophenone (609 mg, 5.0 mmol) in THF (3 mL) under Ar atmosphere, and the mixture was stirred for 10 min at this temperature. To the resulting solution was added PhCHO (0.64 mL, 6.0 mmol). The solution was stirred for 30 min at this temperature. The solvent was removed under reduced pressure, and the residue was treated with aqueous NH_4Cl (10 mL) followed by extraction with $CHCl_3$ (10 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using AcOEt/hexane (1:5) as eluent to give 3-hydroxy-1,3-diphenyl-1-propanone (**9**) (667 mg, 59%): mp 51−52 °C (recrystallized from *n*-hexane, colorless needles); 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 7.96 (d, 2H, J = 7.1 Hz), 7.62−7.28 (8H, m), 5.35 (2H, dt, J = 3.0, 6.0 Hz), 3.57 (1H, d, J = 3.0 Hz), 3.38 (2H, d, J = 6.0 Hz).

Preparation of 2-Hydroxy-1-phenyl-1-propane (14a).[37] A solution of propiophenone (2.0 g, 15.0 mmol), $C_6H_5I(OAc)_2$ (5.0 g, 15.1 mmol), and NaOH (6.0 g, 150 mmol) in 30 mL of MeOH was stirred for 4 h at 0 °C under sonication. After neutralization by aqueous HCl, the solution was extracted with $CHCl_3$ (30 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using AcOEt/hexane (1:5) as eluent to give 2-hydroxy-1-phenyl-1-propane (**14a**) (1.46 g, 63%) as a colorless oil: 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 7.94 (2H, d, J = 7.1 Hz), 7.62 (1H, t, J = 7.6 Hz), 7.51 (2H, t, J = 7.6 Hz), 5.17 (1H, q, J = 7.1 Hz), 3.82 (1H, br), 1.46 (3H, d, J = 6.9 Hz).

Preparation of 2-((Triisopropylsilyl)oxy)-1-phenyl-1-propane (14b).[38] A solution of **14a** (260 mg, 1.69 mmol), imidazole (288 mg, 4.23 mmol), and triisopropylsilyl chloride (392 mg, 2.03 mmol) in DMF (5 mL) was stirred for 12 h at room temperature. The solution was treated with aqueous NH_4Cl (10 mL) followed by extraction with Et_2O (10 mL × 2). The Et_2O layer was dried over $MgSO_4$, and the Et_2O was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using AcOEt/hexane (1:25) as an eluent to give 2-((triisopropylsilyl)oxy)-1-phenyl-1-propane (**14b**) (449 mg, 87%) as a colorless oil: 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 8.11 (2H, d, J = 7.1 Hz), 7.55 (1H, t, J = 6.9 Hz), 7.44 (2H, t, J = 8.2 Hz), 4.98 (1H, q, J = 6.9 Hz), 1.56 (3H, d, J = 6.9 Hz), 1.16−0.74 (18H, m).

General Procedure for Diastereoselective Reduction of 3-Hydroxy-1,3-diphenyl-1-propanone (9) Using NaH−Me_2Zn System. Under Ar atmosphere, commercial dimethylzinc (1.1 mL, 1.1 mmol;

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1.0 M hexane solution) was added to the mixture of dry THF (3 mL) and NaH (88.7 mg, 2.2 mmol; 60% in oil) at 0 °C, and the solution was stirred for 30 min at this temperature. To the mixture was successively added **9** (220.0 mg, 0.97 mmol) in THF (3 mL) at 0 °C. After the solution was allowed to warm to room temperature, the mixture was stirred for 12 h. The solution was treated with aqueous NH_4Cl (30 mL) followed by extraction with $CHCl_3$ (10 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using AcOEt/hexane (1:2) as eluent to give a mixture of stereoisomers of the diol (145.1 mg, 65%). The ratios of the diastereomeric diols were determined by integration of the proton signals in the ^{1}H NMR spectra.[39] *rel*-(1*S*,3*S*)-1,3-Diphenyl-1,3-propanediol (*anti*-diol) (**10**): 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 4.99 (2H, dd, J = 9.9, 5.8 Hz), 2.78 (2H, d, J = 3.8 Hz), 2.19 (2H, t, J = 5.2 Hz). *rel*-(1*S*,3*R*)-1,3-Diphenyl-1,3-propanediol (*syn*-diol) (**11**): 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 5.05 (2H, d, J = 11 Hz), 3.21 (2H, s), 2.26−1.93 (2H, m).

General Procedure for Diastereoselective Reduction of 2-Hydroxy-1-phenyl-1-propane (14a). Under Ar atmosphere, commercial dimethylzinc (0.5 mL, 0.5 mmol; 1.0 M hexane solution) was added to the mixture of dry THF (3 mL) and NaH (40.3 mg, 1.0 mmol; 60% in oil) at 0 °C, and the solution was stirred for 30 min at the temperature. To the mixture was successively added **14a** (59.9 mg, 0.40 mmol) in THF (3 mL) at 0 °C. After the solution was allowed to warm to room temperature, the mixture was stirred for 12 h. The solution was treated with aqueous NH_4Cl (30 mL) followed by extraction with $CHCl_3$ (10 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using AcOEt/hexane (1:4) as eluent to give a mixture of stereoisomers of the diol (60.0 mg, 99%). The ratios of the diastereomeric diols were determined by integration of the proton signals in the ^{1}H NMR spectra.[40] *rel*-(1*S*,2*R*)-1-Phenyl-1,2-propanediol (*anti*-diol) (**15**): 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 7.37−7.28 (5H, m), 4.38 1 H, d, J = 7.7 Hz), 3.87 (1H, quint, J = 7.6 Hz), 2.88 (1H, br), 2.71 (1H, br), 1.00 (3H, d, J = 7.4 Hz). *rel*-(1*S*,2*S*)-1-Phenyl-1,2-propanediol (*anti*-diol) (**16**): 300 MHz ^{1}H NMR ($CDCl_3$/TMS) δ (ppm) 7.35−7.25 (5H, m), 4.66 (1H, d, J = 4.1 Hz), 3.99 (1H, dq, J = 4.1, 6.3 Hz), 3.17 (2H, br), 1.05 (3H, d, J = 6.3 Hz).

General Procedure for Diastereoselective Reduction of 2-((Triisopropylsilyl)oxy)-1-phenyl-1-propane (14b). Under Ar atmosphere, commercial dimethylzinc (0.5 mL, 0.5 mmol; 1.0 M hexane solution) was added to the mixture of dry THF (3 mL) and NaH (40.6 mg, 1.0 mmol; 60% in oil) at 0 °C, and the solution was stirred for 30 min at the temperature. To the mixture was successively added **14b** (118.5 mg, 0.38 mmol) in THF (3 mL) at 0 °C. After the solution was allowed to warm to room temperature, the mixture was stirred for 12 h. The solution was treated with aqueous NH_4Cl (30 mL) followed by extraction with $CHCl_3$ (10 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was hydrolyzed to the corresponding diols with $(^nBu)_4NF$ in the standard manner.[38] The solution was treated with NH_4Cl (30 mL) followed by extraction with $CHCl_3$ (10 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using AcOEt/hexane (1:4) as eluent to give a mixture of stereoisomers of the diol (42.5 mg, 70%). The ratios of the diastereomeric diols were determined by integration of the proton signals in the ^{1}H NMR spectra.[40]

General Procedure for Diastereoselective Reduction of 1-Phenyl-1,2-propanedione (20). Under Ar atmosphere, commercial dimethylzinc (2.2 mL, 2.2 mmol; 1.0 M hexane solution) was added to the mixture of dry THF (3 mL) and NaH (88.9 mg, 2.2 mmol; 60% in oil) at 0 °C, and the solution was stirred for 30 min at the temperature. To the mixture was successively added **20** (147.4 mg, 1.00 mmol) in THF (3 mL) at 0 °C. After the solution was allowed to warm to room temperature, the mixture was stirred for 12 h. The solution was treated with aqueous NH_4Cl (30 mL) followed by extraction with $CHCl_3$ (10 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography using AcOEt/hexane (1:4) as an eluent to give a mixture of stereoisomers of the diol (92.6 mg, 61%). The ratios of the diastereomeric diols were determined by integration of the proton signals in the ^{1}H NMR spectra.[40]

General Procedure for Catalytic Reduction. Under Ar atmosphere, commercial dimethylzinc (0,2 mL, 0.2 mmol; 1.0 M hexane solution) was added to the mixture of dry THF (3 mL) and LiH (10.0 mg, 1.2 mmol; 95%) at 0 °C, and the solution was stirred for 30 min at the temperature under sonication. To the mixture was successively added the carbonyl compound (1.0 mmol) in THF (3 mL) at 0 °C. After the solution was allowed to warm to room temperature, the mixture was stirred for 12 h under sonication. The solvent was removed under reduced pressure, and the residue was treated with aqueous NH_4Cl (30 mL) followed by extraction with $CHCl_3$ (30 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography to give product.

General Procedure for Partial Reduction of Carboxylic Acids to Aldehyde. Under Ar atmosphere, commercial dimethylzinc (1.0 mL, 1.0 mmol; 1.0 M hexane solution) was added to the mixture of dry THF (3 mL) and LiH (25.2 mg, 1.2 mmol; 95%) at room temperature, and the solution was stirred for 30 min at the temperature under sonication. To the mixture was successively added the carboxylic acid (1.0 mmol) in THF (3 mL) at 0 °C. After the solution was allowed to warm to room temperature, the mixture was stirred for 24 h under sonication. The solvent was removed under reduced pressure, and the residue was treated with NH_4Cl (30 mL) followed by extraction with $CHCl_3$ (30 mL × 3). The $CHCl_3$ layer was dried over $MgSO_4$, and the $CHCl_3$ was removed under reduced pressure. The residue was purified by SiO_2 column chromatography to give the corresponding aldehyde.

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