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Catalytic Asymmetric Addition of Alkylzinc and Functionalized Alkylzinc Reagents to Ketones

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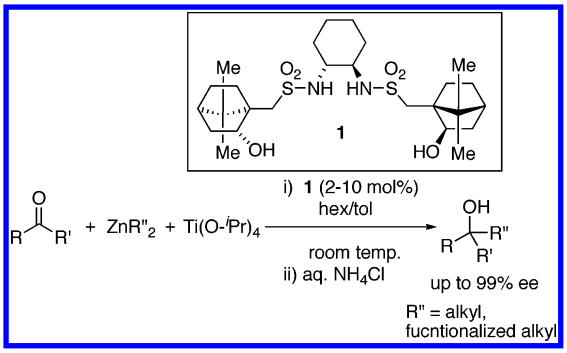

We describe our full report of the catalytic asymmetric addition of simple and functionalized dialkylzinc reagents to a broad range of saturated ketones and enones. The functionalized organozinc reagents contain esters, silyl ethers, alkyl chlorides, and alkyl bromides. In general, the resulting tertiary alcohol products are isolated with high ee's. With some substrates, yields are low as a result of the formation of aldol byproducts. Most substrates undergo additions with good yields reaching as high as 91%.

Introduction

The formation of C−C bonds lies at the very heart of organic synthesis. As such, the development of new reactions that result in the formation of C−C bonds is of fundamental importance. One of the most common methods to extend the carbon skeleton is through addition of organometallic reagents to carbonyl compounds.[1,2] Over the past 2 decades, the principal focus in this area has involved the asymmetric addition of alkyl groups to aldehydes. Beginning with the seminal works of Oguni[3,4] and subsequent mechanistic investigations by Noyori and co-workers,[5−7] well over 100 catalysts have been reported that promote the asymmetric addition of organozinc reagents to aldehydes with very high enantioselectivities.[2] Catalytic asymmetric additions of vinyl,[8−15] aryl,[16−22] and alkynyl[23−29] groups to aldehydes have received much

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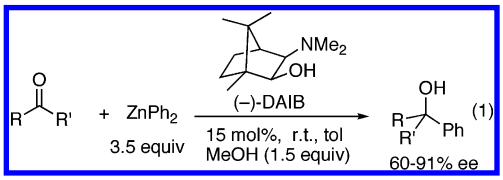
less attention. Recent studies, however, have resulted in the development of a variety of catalysts for these important processes.

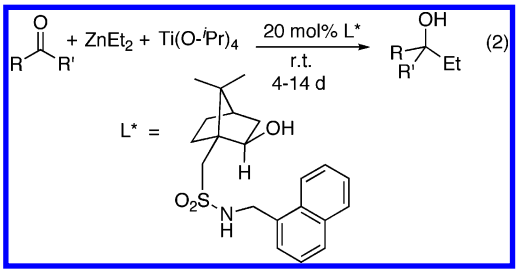
Despite significant activity in asymmetric carbonyl addition reactions, a long-standing problem in organic synthesis had been the absence of efficient and highly enantioselective methods to prepare tertiary alcohols. Although several examples involving organolithium and Grignard reagents have been reported,[6,30−34] these usually require greater than stoichiometric amounts of chiral ligands. In addition, the high reactivity of these reagents precludes the presence of many functional groups and, therefore, reduces the attractiveness of such strongly basic reagents. In contrast, organozinc reagents are mild and exhibit excellent functional group compatibility,[35] making them ideal for use in the synthesis of complex, highly functionalized targets. Organotitanium reagents and, to a lesser degree, organoaluminum complexes are also tolerant of functional groups and have been applied to the asymmetric addition to aldehydes.[36−42]

The first examples of the asymmetric addition of organozinc reagents to ketones[43,44] were reported from two groups in 1998. Dosa and Fu[45] employed Noyori's DAIB[5] ligand in the asymmetric addition of diphenylzinc to ketones (eq 1). Enantioselectivities as high as 91% were realized with up to 91% yield. Catalysts derived from amino alcohols such as DAIB will promote the addition of the more reactive diphenylzinc to ketones, but not dialkylzinc reagents, because of their reduced reactivity.

Also in 1998 Ramon and Yus,[46,47] reported the first example of asymmetric addition of alkyl groups to



ketones (eq 2). Although certain substrates underwent addition with enantioselectivities as high as 89%, most substrates gave only moderate to low enantioselectivities. The most significant drawback to this system, however, was not the low enantioselectivity but the poor catalyst turnover frequency. At 20 mol % catalyst loading, the reactions required between 4 and 14 days to reach completion.[46,47]



We have been actively investigating the mechanisms of titanium-catalyzed asymmetric additions of alkyl groups to aldehydes for several years.[48−53] The results of these works enabled us to develop the first practical and highly enantioselective catalyst for the asymmetric addition of alkyl,[44,54,55] phenyl,[56,57] and vinyl groups[58] to ketones. The enantioenriched tertiary alcohol products of this reaction are useful chiral building blocks and have been used in natural product synthesis.[59] A shortcoming associated with the use of dialkylzinc reagents, however, is that very few are commercially available. Furthermore, like most main-group organometallics, dialkylzinc reagents are sensitive to air and moisture. To circumvent the limited availability of organozinc reagents, Knochel and co-workers have developed several excellent methods to prepare dialkylzinc compounds bearing various functional groups.[39,60−62] These reagents can be synthesized

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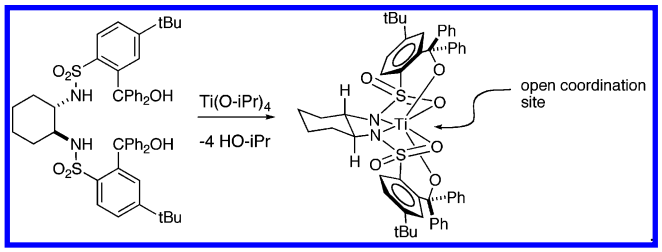
and used without isolation and have been successfully added to aldehydes with high enantioselectivity.

In this study we have successfully applied our catalyst to the asymmetric addition of dialkylzinc and functionalized organozinc reagents to a broad range of ketones. We have found, for the first time, that organozinc compounds bearing esters, chlorides, bromides, and silyl ethers can be added to ketones to provide functionalized tertiary alcohols with high levels of enantioselectivity. A portion of this research has been previously reported.[54,55]

Results and Discussion

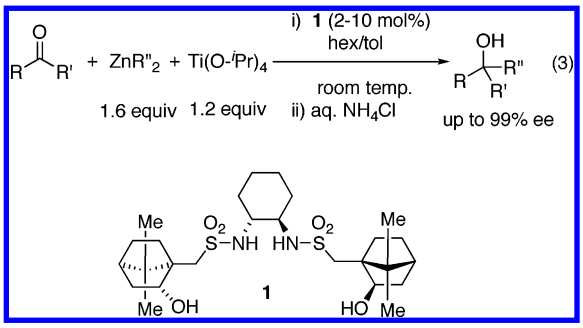
Asymmetric Addition of Diethyl- and Dimethylzinc to Simple Ketones. The development of our catalyst for the enantioselective addition of alkyl groups to ketones was based on mechanistic observations on related catalysts.[44] In these studies we have found that bis(sulfonamide) diol ligands react with titanium tetraisopropoxide to liberate 4 equiv of 2-propanol as illustrated in Scheme 1.[44] This compound and its ligand adduct have been characterized by X-ray crystallography. We believe that the bis(sulfonamide) diol ligand **1** binds to titanium in a multidentate similar fashion.

SCHEME 1. Reaction of a Bis(sulfonamide) Diol with Titanium Tetraisopropoxide; Reaction Can Be Driven to the Right by Removal of Liberated Isopropanol



In previous studies on the (BINOLate)Ti-based catalyzed asymmetric addition of alkylzinc reagents to aldehydes, we proved that the carbonyl addition step proceeds by delivery of an alkyl group from titanium to the carbonyl carbon rather than involving direct addition of an alkylzinc reagent to the carbonyl group.[66,67] It is entirely possible that an analogous reaction manifold is in operation in the addition of alkyl groups to ketones outlined in this report. In our studies we have found that the mechanism of titanium-catalyzed asymmetric addition reactions can be very complex.[53] Speculation on the reaction mechanism or mode of stereochemical induction is premature at this time.

We first explored the addition of simple, commercially available diethyl- and dimethylzinc reagents to a variety of substrates (eq 3). As shown in Table 1, catalyst loadings as low as 2 mol % could be employed, representing a reduction in the catalyst loading of up to a factor of 10 compared to the Yus system (eq 2).[46,47] Additionally, the reaction generally required 24−48 h to reach completion, a significant decrease in the reaction time from the previously reported best catalyst system. Furthermore, our method for the asymmetric addition of alkyl groups to ketones is operationally very simple and has been verified in other laboratories.[68,69]



Although electron-donating or electron-withdrawing substituents on acetophenone derivatives had little effect on the ee of the tertiary alcohol product from diethylzinc addition (Table 1, entries 1−6), the substituents did have a significant impact on the turnover frequencies of the catalyst (entries 2−5). Electron-deficient 3′-(trifluoromethyl)acetophenone reacted readily at 2 mol % catalyst loading, generating the product in 14 h at room temperature. At the other extreme, 4′-methoxyacetophenone underwent addition more slowly, requiring over 4 days for complete conversion, even at 10 mol % ligand loading. Although the electron-rich 4′-methoxyacetophenone was expected to react more slowly, we were surprised by the magnitude of this reactivity difference. Nonetheless, these acetophenone derivatives gave excellent enantioselectivities.

In the case of 2′-methylacetophenone, the increase in steric hindrance around the carbonyl group resulted in a dramatic drop in the isolated yield (entry 6). The shielding of the carbonyl group by the *o*-methyl substituent reduces the rate of the addition reaction and results in competitive and irreversible deprotonation of the ketone. Once formed, the resulting enolate then undergoes aldol condensation and dehydration, consuming another equivalent of substrate. Similar results were observed with α-tetralone, which gave the tertiary alcohol in only 35% isolated yield (entry 7). Nonetheless, the enantioselectivities of 2-methylacetophenone and α-tetralone were over 95%.

Acetophenone derivatives with longer alkyl chains, such as valerophenone and 1-chloropropiophenone, also exhibited enantioselectivities just under 90% in the asymmetric addition (entries 9, 10, and 12).

Enantioenriched allylic alcohols are among the most useful chiral building blocks in asymmetric synthesis, because the double bond can be selectively functionalized by employing hydroxyl-directed reactions. For this reason alkyl addition to simple enones was examined. As shown in Table 1 (entries 13 and 14), these substrates exhibited

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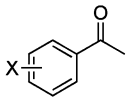
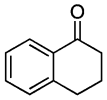
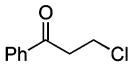
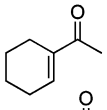
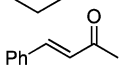
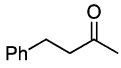
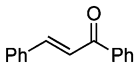
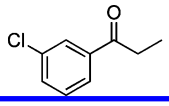
TABLE 1. Asymmetric Addition of Alkyl Groups to Ketones with Chiral Ligand in eq 3

entry	substrate	ZnR''_2	mol %	time (h)	yield (%)	ee (config)[a]
						
1	X = H	R" = Et	2	29	71	96 (*S*)
2	X = 3-Me	R" = Et	10	12	82	99
3	X = 3-Me	R" = Et	2	24	78	99
4	X = 4-OMe	R" = Et	10	111	85	94
5	X = 3-CF_3	R" = Et	2	14	56	98
6	X = 2-Me	R" = Et	10	48	24	96
7		R" = Et	10	22	35	>99
8		R" = Me	10	24	26	98
9		R" = Et	10	47	83	87 (*R*)
10		R" = Et	2	102	79	88 (*R*)
11		R" = Me	2	48	81	85
12		R" = Et	10	44	82	89
13		R" = Et	2	46	56	96
14		R" = Et	2	26	80	90
15		R" = Et	10	68	68	70
16		R" = Me	10	48	54	46
17		R" = Me	2	45	83	94 (*R*)
18		R" = Me	2	46	90	96

[a] ee's determined by HPLC or GC; see Supporting Information.

high levels of enantioselectivity in the asymmetric addition with diethylzinc. The dialkyl ketone 4-phenyl-2-butanone underwent addition with 70% enantioselectivity. Although the enantioselectivity with this substrate was not in the synthetically useful range, it is impressive that the catalyst is reasonably efficient at differentiating between the carbonyl lone pairs. In this case, the catalyst must bind syn to the methyl group or the alkyl chain, both of which have similar steric environments (Figure 1). Such dialkyl ketones will likely be a challenging class of substrates for asymmetric addition reactions.

It is interesting to compare *trans*-4-phenyl-3-butenone with the saturated analogue 4-phenyl-2-butanone (entries 14 and 15). The presence of the double bond allows a 5-fold reduction in the catalyst loading and a decrease in reaction time relative to that of the saturated ketone. Additionally, the yield and enantioselectivity with

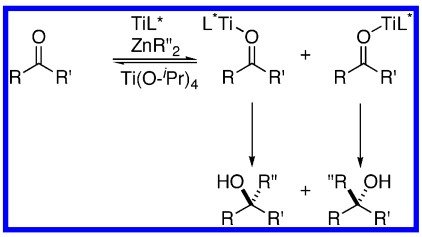
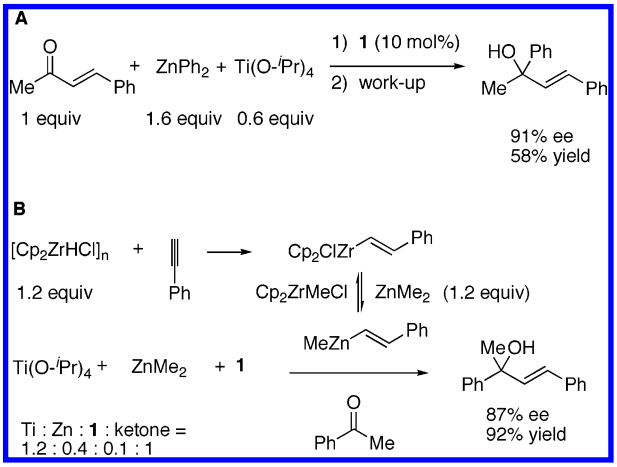


FIGURE 1. Isomeric catalyst−substrate adducts may lead to decreased enantioselectivity.

the enone substrate are also significantly higher. Although the enone is less sterically hindered, it is unlikely that steric effects alone can account for this significant reactivity and enantioselectivity difference. It is possible that there is an interaction between the double bond and either the zinc or titanium. This interaction must be

SCHEME 2. (A) Asymmetric Addition of Diphenylzinc to *trans*-4-Phenyl-3-buten-2-one; (B) Asymmetric Vinyl Addition to Acetophenone

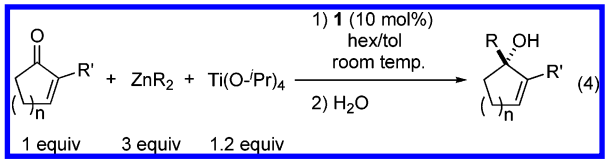


weak, however, because titanium(IV) and zinc(II) are unable to donate significant electron density into the C=C π^* orbital.

In the asymmetric addition of diethylzinc and dimethylzinc to aldehydes with catalysts derived from amino alcohol ligands, Noyori and co-workers have reported that dimethylzinc is less reactive than diethylzinc by a factor of 20. We have found that reaction of propiophenone with dimethylzinc and reaction of acetophenone with diethylzinc with our catalyst under the same conditions both yield 2-phenyl-2-butanol with similar rates and enantioselectivities between 94% and 96% (entries 1 and 17). The same configuration of the chiral catalyst provided 2-phenyl-2-butanol of opposite configuration in these additions, as expected. α-Tetralone again resulted in poor yield (26%) in the reaction with dimethylzinc. Nonetheless, the enantioselectivity was still high (98%, entry 8). Addition of dimethylzinc to valerophenone proceeded in 85% ee and in 81% yield with 2 mol % catalyst, and 3′-chloropropiophenone underwent reaction with 96% ee and 90% yield under the same conditions (entries 11 and 18).

Addition of dimethylzinc to chalcone proceeded slowly at 10 mol % over 2 d giving 54% yield of the tertiary alcohol with an enantioselectivity of 46% (entry 16). Alcohols of this type are better synthesized by either addition of diphenylzinc to *trans*-4-phenyl-3-buten-2-one[56] or vinyl addition to acetophenone derivatives,[58] as shown in Scheme 2.

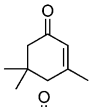
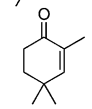
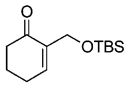
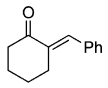
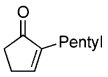
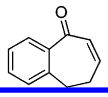
Asymmetric Additions to Cyclic Conjugated Enones. We next turned our attention to enantioselective 1,2-addition reactions of cyclic α,β-unsaturated ketones.[55] The resulting tertiary allylic alcohols are valuable synthetic intermediates that can be easily elaborated to achieve highly fuctionalized chiral building blocks.



Using the conditions described in eq 4, we found that conjugated cyclic enones underwent asymmetric alkylation with dimethyl- and diethylzinc to afford tertiary cyclic allylic alcohols in good to excellent enantioselectivities (Table 2). Reactions were conducted at room temperature with 10 mol % catalyst and were complete in less than 40 h in most cases. With the exception of entries 1−3 and the benzofuranone (entries 12 and 13), the enantioselectivities were ≥95%. In the case of entries 1−3, which have no substituent at the 2-position, the products were formed with reduced enantioselectivity (52−61%). This result was not unexpected, because the two lone pairs of the carbonyl oxygens are in very similar steric environments and the catalyst cannot easily differentiate between them. The substrate cyclohexenone exhibited reactivity higher than that of the 2-substituted enones in the asymmetric additions as a result of the decreased steric hindrance around the carbonyl group. We were, therefore, able to run the asymmetric addition of diethylzinc to cyclohexenone at 0 °C rather than at room temperature. Unfortunately, however, reducing the temperature did not significantly improve the enantioselectivity.

In contrast to substrates lacking a substituent at the 2-position, enones bearing substituents α to the carbonyl group exhibited excellent levels of enantioselectivity. As shown in Table 2, these include five-, six-, and seven-

TABLE 2. Asymmetric Addition of Alkyl Groups to Cyclic Enones[a]

entry	substrate	ZnR_2	time (h)	yield (%)	ee[b] (%)
1		R = Et	19	75	52
2		R = Et	46[c]	75	54
3		R = Et	80	50	61
4		R = Me	40	84	99
5		R = Et	40	76	98
6		R = Me	40	54	95
7		R = Et	40	40	95
8		R = Me	40	81	>99
9		R = Et	40	81	>99
10		R = Me	38	20	99
11		R = Et	38	32	99 (*R*)
12		R = Me	40	79	89
13		R = Et	40	88	89
14		R = Me	40	55	98 (*R*)
15		R = Et	37	65	96
16		R = Me	40	62	99
17		R = Et	40	50	99
18		R = Me	40	69	97
19		R = Et	40	70	96

[a] All reactions performed at 10 mol% catalyst loading. [b] ee's determined by GC or HPLC; see Supporting Information. [c] Reaction conducted at 0 °C.

membered cyclic enones. Methyl, phenyl, and TBS-protected hydroxy methyl substituents at the 2-position in the cyclohexenone series underwent addition with high levels of enantioselectivity. When the asymmetric addition to 2-hydroxymethyl-cyclohex-2-enone was conducted without protection of the hydroxyl, product of 5% ee was obtained. Gratifyingly, protection as the TBS ether allowed the asymmetric addition of dimethyl- and diethylzinc to proceed with 99% enantioselectivity in 81% yield in both cases (entries 8 and 9). Densely functionalized, highly enantioenriched products such as those formed in these addition reactions are expected to be useful chiral building blocks in enantioselective synthesis. Decreased yields were observed with an exocyclic enone, which gave 20% and 32% yield with 99% enantioselectivity in each case (entries 10 and 11). Presumably these low yields are due to formation of aldol products. The substrate 6,7-dihydro-5*H*-benzofuran-4-one participated in the asymmetric addition reaction with dimethyl- and diethylzinc with good yields (79% and 88%, entries 12 and 13, respectively). When compared to other ketones containing substituents α to the carbonyl, this furan derivative resulted in reduced enantioselectivities with all organozinc reagents employed in this study. At this stage, it is not clear what factors are responsible for the diminished enantioselectivities. The conjugation of the furanyl oxygen with the carbonyl gives the substrate vinylogous ester character. The resulting tertiary alcohol was expected to display an increased propensity for racemization. Consistent with this prediction, the addition products derived from this substrate racemize readily on standing. Cyclopentenone derivatives were found to give excellent enantioselectivities and moderate yields in the addition process (entries 14−17). Finally, the 8,9-dihydrobenzocyclohepten-5-one gave yields around 70% and enantioselectivities ≥96% (entries 18 and 19). This substrate, like the cyclohexenones in entries 1 and 2, does not possess a substituent on the double bond α to the carbonyl group. Nonetheless, the adjacent benzo group allows the catalyst to effectively differentiate between the prochiral faces of the ketone.

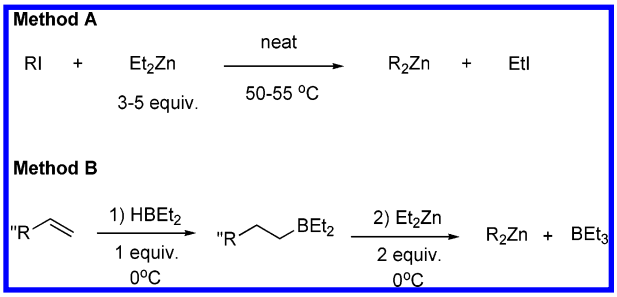
We have assigned the absolute stereochemistry of three products from Table 1 (entries 1,[70] 9,[46] and 17[70]) and two products from Table 2 (entries 11[71] and 14[72]). In each of these cases the catalyst based on the (*R,R*)-diamine added the alkyl group to the *si* face of the ketone substrate.

Overall, although the yields of the products in the asymmetric ketone alkylation reactions are variable, they are generally good and as high as 88%. In those cases that give low yields, we believe that the cause is irreversible deprotonation of the substrate under the basic reaction conditions followed by aldol condensation/dehydration. In some cases, the aldol products were isolated and characterized. It is interesting to note that the oxophilic titanium-based catalyst results in formation of the 1,2-addition products with no isolation of 1,4-addition products. In contrast, the softer copper(I) catalysts promote conjugate addition with dialkylzinc reagents.[73,74]

Asymmetric Additions of Functionalized Dialkylzinc Reagents to Ketones. The results in Tables 1 and 2 demonstrate that commercially available dimethyl- and diethylzinc readily add to a wide range of ketones with high enantioselectivities. Unfortunately, only a limited number of dialkylzinc reagents are commodity chemicals. To broaden the scope of our ketone addition chemistry, we desired to explore the use of functionalized dialkylzinc reagents. Dialkylzinc reagents have been prepared from zinc halides by a number of routes, the most popular being transmetalation with more electropositive organometallic compounds such as organolithium or Grignard reagents.[75,76] The metal halide products (LiX and MgX_2), however, are sufficiently Lewis acidic to catalyze some asymmetric addition reactions, resulting in erosion of the enantioselectivity. To circumvent this potential problem, Knochel and co-workers developed procedures for the generation of a variety of functionalized dialkylzinc reagents that do not produce salt byproducts.[39,60−62] These reagents have been successfully employed in asymmetric additions to aldehydes catalyzed by titanium bis(sulfonamide) complexes to provide functionalized secondary alcohols.[64,77]

Two of Knochel's methods for the synthesis of dialkylzinc reagents were employed in this study. The first, method A, involves reaction of functionalized primary alkyl iodides with diethylzinc, as outlined in Scheme 3.[60,63] This procedure was initiated by combining neat diethylzinc with the functionalized alkyl iodide and heating to 50 °C for 20 h. Under these conditions, alkyl exchange between the zinc and alkyl iodide ensues, establishing an equilibrium between diethylzinc, the functionalized alkyl iodide, ethyl iodide, and the functionalized organozinc reagents. Removal of the volatile materials (ethyl iodide and excess diethylzinc) drives the equilibrium toward the functionalized dialkylzinc reagents. We have generated the organozinc reagents from 1-iodooctane, 1-chloro-4-iodobutane, and 4-iodobutyl pivalate. It should be noted that the organozinc reagent derived from 1-chloro-4-iodobutane is light-sensitive and must be used shortly after generation. In our hands, storage of this reagent either neat or as a dilute solution resulted in formation of a precipitate that was unreactive in the asymmetric addition reactions.

SCHEME 3. Synthesis of Dialkylzinc Reagents by Method A and Method B



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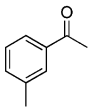
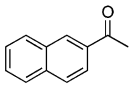
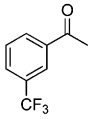
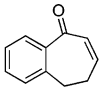
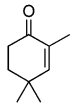
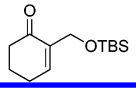
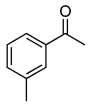
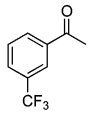
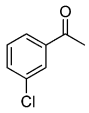
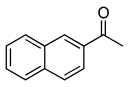
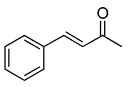
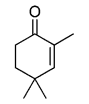
(72) Lee, S.-F.; Barth, G.; Djerassi, C. *J. Am. Chem. Soc.* **1981**, *103*, 295−301.
(73) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363.
(74) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141−5144.
(75) Seebach, D.; Behrendt, L.; Felix, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *20*, 1008−1009.
(76) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473−7484.
(77) Brieden, W.; Ostwald, R.; Knochel, P. *Angew. Chem., Int. Ed.* **1993**, *32*, 582−584.

TABLE 3. Functionalized Dialkylzinc Addition to Ketones using Method A[a]

entry	substrates	ZnR_2	time (h)	yield (%)	ee (%)[b]
1		$ZnOct_2$	40	91	98
2		$Zn((CH_2)_4Cl)_2$	40	95	99
3		$Zn((CH_2)_4OPiv)_2$	46	58	96
4		$ZnOct_2$	40	70	99
5		$Zn((CH_2)_4Cl)_2$	40	83	99
6		$Zn((CH_2)_4OPiv)_2$	46	53	99
7		$ZnOct_2$	40	85	97
8		$Zn((CH_2)_4Cl)_2$	40	62	96
9		$Zn((CH_2)_4OPiv)_2$	40	53	97
10		$ZnOct_2$	40	83	76
11		$Zn((CH_2)_4Cl)_2$	40	64	85
12		$Zn((CH_2)_4OPiv)_2$	40	83	83
13		$ZnOct_2$	40	85	>99
14		$Zn((CH_2)_4Cl)_2$	40	72	>99
15		$Zn((CH_2)_4OPiv)_2$	40	61	99
16		$ZnOct_2$	40	70	>99

[a] All reactions performed at 10 mol% catalyst loading. [b] ee's determined by HPLC or GC; see Supporting Information.

TABLE 4. Asymmetric Addition of Functionalized Alkyl Groups to Ketones using Method B[a]

entry	substrate	ZnR_2	time (d)	yield (%)	ee (%)[b]
1		$Zn((CH_2)_3CHMe_2)_2$	3	77	96
2		$Zn((CH_2)_3CHMe_2)_2$	3	61[c]	98
3		$Zn((CH_2)_4OTBS)_2$	3	89	98
4		$Zn((CH_2)_4OPiv)_2$	3	47	96
5		$Zn((CH_2)_5Br)_2$	3	89	96
6		$Zn((CH_2)_3CHMe_2)_2$	1	54	92
7		$Zn((CH_2)_4OPiv)_2$	3	40	99
8		$Zn((CH_2)_3CHMe_2)_2$	4	69	94
9		$Zn((CH_2)_4OTBS)_2$	5	51	93
10		$Zn((CH_2)_3CHMe_2)_2$	3	75	90
11		$Zn((CH_2)_4OTBS)_2$	5	52	98
12		$Zn((CH_2)_5Br)_2$	3	55	94
13		$Zn((CH_2)_3CHMe_2)_2$	3	86	93
14		$Zn((CH_2)_3CHMe_2)_2$	3	60[c]	92
15		$Zn((CH_2)_4OTBS)_2$	5	65	90
16		$Zn((CH_2)_5Br)_2$	2	48	90
17		$Zn((CH_2)_4OPiv)_2$	2	43	>99
18		$Zn((CH_2)_4OPiv)_2$	3	88	87

[a] All reactions performed at 10 mol% catalyst loading. [b] ee's determined by HPLC or GC; see Supporting Information. [c] ZnR_2 was made from $BH_3{\cdot}SMe_2$ instead of $HBEt_2$.

The in situ generated diorganozinc reagents were then employed in the asymmetric addition to a variety of ketones under the conditions outlined in eq 4. In the initial stages of our investigations, we found it easiest to generate organozinc reagents without functional groups. Once we had mastered the synthesis and asymmetric addition of the newly formed organozinc reagents, we focused on the use of functionalized derivatives. As outlined in the Experimental Section, care must be exercised in the preparation of the organozinc reagents using these methods. Examination of the results of these reactions (Table 3) indicates that the additions to acetophenone derivatives proceeded with enantioselectivities ≥96% (entries 1−6). In these cases, the yields were best with addition of octyl or 4-chlorobutyl groups (70−95%). Reactions of the dipivalyl derivative were slower and resulted in yields between 53% and 58% (entries 3 and 6). The reduced reactivity of the pivalyl derivative could be due to competitive binding of the ester carbonyl group to the catalyst or intra- or intermolecular coordination to zinc. The functionalized organozinc reagents were then examined in additions to cyclic enones (entries 7−16). Very high enantioselectivities were observed (≥96%) except for additions to the benzofuranone substrate, where enantioselectivities ranged from 76% to 85% (entries 10−12). The results in Table 3 indicate that the alkyl iodide/diethylzinc exchange method of Knochel can be readily employed in the asymmetric additions to ketones to provide access to functionalized tertiary alcohols with good to excellent levels of enantioselectivity and moderate to high yields.

The second procedure for the in situ preparation of dialkylzinc reagents, method B, is based on a boron−zinc exchange reaction (Scheme 3).[64,65] Initial hydroboration of the olefin employed either diethylborane or $BH_3{\cdot}SMe_2$ with olefin/borane ratios of 1:1 and 3:1, respectively at 0 °C. Combination of the resulting borane with diethylzinc at 0 °C initiated the alkyl group redistribution. Like method A, the resulting equilibrium must be driven toward the functionalized organozinc reagent by removal of the volatile material, including the remaining diethylzinc and triethylborane. Caution must again be exercised in quenching the excess diethylzinc and triethylborane (see the Experimental Section).

Results for the asymmetric ketone alkylation reactions using these reagents are shown in Table 4. Using the conditions outlined in eq 4, several classes of ketones were examined with dialkylzinc reagents containing a branched alkyl group, TBS ether, pivalyl ester, and bromide functional groups. Additions to acetophenone derivatives and acyclic and cyclic conjugated enones provided functionalized alcohols with high levels of enantioselectivity (90−99%). As observed in method A, however, the benzofuranone derivative resulted in slightly

lower enantioselectivity (entry 18). In our hands, yields were significantly better when the hydroboration was performed with diethylborane than with borane dimethyl sulfide (compare entries 1 and 2 as well as 13 and 14). There was essentially no impact of the choice of hydroborating reagent on the enantioselectivities. On the basis of these results, no further reactions were initiated with borane dimethyl sulfide.

In the addition of protected alcohols to 3′-methylacetophenone, the TBS ether and the pivalate both exhibited high enantioselectivities (entries 3 and 4). The yield of the tertiary alcohol with the TBS ether was much higher, however. The TBS ether additions showed variability in the yields ranging from 51% to 89% (entries 3, 9, 11, and 15), and yields with the pivalate derivative were, in general, lower than those with other zinc reagents (entries 4, 7, 17, and 18). We were also able to employ an alkylbromide in the addition reaction with 3′-methylacetophenone, 2-acetonaphthone, and *trans*-4-phenyl-3-buten-2-one (entries 5, 12, and 16). The enantioselectivities were ≥90% with yields between 48% and 89%.

Comparison of the zinc−alkyl iodide exchange (method A) with the hydroboration−transmetalation protocol (method B) indicates that, in general, the zinc−alkyl iodide method gives better yields with our catalyst in the asymmetric additions to ketones. Method B, however, allows addition of alkyl bromides, whereas such an addition with method A would be more difficult. The enantioselectivities with these methods are very similar. As observed in Tables 1−4, the levels of enantioselectivity are very high for a wide range of ketones and dialkylzinc reagents.

Conclusions

We report the first catalytic asymmetric addition of functionalized organozinc reagents to ketones. The organozinc reagents are generated from alkyl iodides or alkenes using the protocols of Knochel. These reactive dialkylzinc reagents are not isolated but can be used directly in the asymmetric addition reactions. The enantioselectivities generally exceed 90%, providing access to a broad range of tertiary alcohols and tertiary allylic alcohols. Also included are asymmetric additions of the commercially available dimethyl- and diethylzinc to a series of substituted ketones. Enantioselectivities in these reactions are excellent for the most part. In our hand, yields with the commercially available dialkylzinc reagents are higher and more consistent than with the in situ generated functionalized derivatives.

These investigations indicate that our catalyst for the asymmetric addition of organozinc reagents to ketones is tolerant of a variety of functionalized zinc reagents. The methods introduced here provide a solution to a long-standing problem in enantioselective synthesis: the preparation of highly enantioenriched, functionalized tertiary alcohols.

Experimental Section

Cautionary Note. Caution must be used in the synthesis of functionalized dialkylzinc reagents. The techniques employed herein require removal of volatile dialkylzincs and trialkylboranes under reduced pressure. These materials are collected in a cold trap cooled by liquid nitrogen. Quenching these reagents should be performed under a nitrogen atmosphere by dilution with hexanes followed by dropwise addition of a solution of 2-propanol in hexanes.

General Procedure for Asymmetric Addition Reaction. 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1-methyl-cyclohex-2-enol. The bis(sulfonamide) diol ligand **1** (11 mg, 0.02 mmol, 10 mol %) was weighed into a 10-mL flame-dried Schlenk flask and purged with dinitrogen. Dimethylzinc (0.6 mL of a 1 M toluene solution, 0.6 mmol, 3 equiv) was added followed by addition of the titanium(IV) isopropoxide (0.18 mL of a 1.4 M hexanes solution, 0.24 mmol, 1.2 equiv) at room temperature. After 5 min, 2-(*tert*-butyl-dimethyl-silanyloxymethyl)-cyclohex-2-enone (50 μL, 0.2 mmol) was added neat. The reaction mixture was stirred at room temperature. After 40 h the reaction was quenched with a few drops of water. Ethyl acetate (3−4 mL) was added, and the resulting solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 95/5) to give the product (41.5 mg, 81% yield, >99% ee) as an oil: $[\alpha]^{20}_D = +54.3$ (*c* 1.27, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.36 (s, 3H), 1.52−1.61 (m, 2H), 1.73−1.80 (m, 2H), 1.91−1.97 (m, 1H), 2.06−2.13 (m, 1H), 3.38 (br, 1H), 4.04 (d, J = 11.7 Hz, 1H), 4.50 (m, 1H), 5.67 (t, J = 3.6 Hz, 1H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ −5.14, −5.02, 18.6, 19.6, 26.0, 26.3, 28.4, 39.0, 66.6, 70.0, 127.0, 140.0 ppm; IR (NaCl) 3452, 2950, 2739, 1664, 1471, 1388, 1256, 1140 cm^{-1}; HRMS calcd for $C_{14}H_{27}OSi$ $(M-OH)^+$ 239.1831, found 239.1838.

General Procedure for the Generation of Functionalized Organozinc Reagents From Alkyl Iodides.[60,63] A 10-mL flame-dried Schlenk flask was equipped with a nitrogen inlet, a septum, and a stirring bar. It was then charged with the functionalized iodide $PivO(CH_2)_4I$ (2 g, 7.1 mmol) and diethylzinc (3.6 mL, 36 mmol). The reaction mixture was briefly evacuated, warmed to 50 °C, and stirred for 12 h. The flask was then cooled to room temperature and subjected to vacuum (0.4 mmHg). The volatile materials, including the ethyl iodide and the remaining diethylzinc, were removed under reduced pressure (ca. 3 h). The resulting organozinc reagent, $(PivO(CH_2)_4)_2Zn$, was dissolved in toluene to make 1 M solution and used in the asymmetric addition reaction as described in the General Procedure above.

General Procedure for the Generation of Functionalized Organozinc Reagents From Alkenes via Hydroboration.[64,65] The alkene $CH_2{=}CHCH_2CH_2OPiv$ (2.34 g, 15 mmol) was placed in a Schlenk flask and cooled to 0 °C, and Et_2BH (15 mL, 15 mmol, 1 equiv) was added via syringe (Et_2BH was prepared by combining $BH_3{\cdot}SMe_2$ (0.48 mL, 5 mmol), BEt_3 (1.41 mL, 10 mmol), and hexanes (13.1 mL)). After 3 h at 0 °C the volatile materials were removed under vacuum (0.5 mmHg), affording the diethyl(alkyl)borane, $(PivO(CH_2)_4)$-BEt_2. To this Schlenk flask was added Et_2Zn (20 mL of a 1 M hexanes solution, 20 mmol) slowly at 0 °C. After 0.5 h the volatile materials, including the excess of Et_2Zn and the Et_3B, were removed under reduced pressure at 0.5 mmHg for 3 h at room temperature. The resulting oil was dissolved in toluene to make a 1 M solution that was used in the General Procedure for the asymmetric addition outlined above.

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Supporting Information Available: General methods, synthesis of organozinc species, full characterization of new compounds, conditions for determination of ee, and determination of absolute stereochemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

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