

CATALYTIC, ASYMMETRIC SYNTHESIS OF TERTIARY ALCOHOLS

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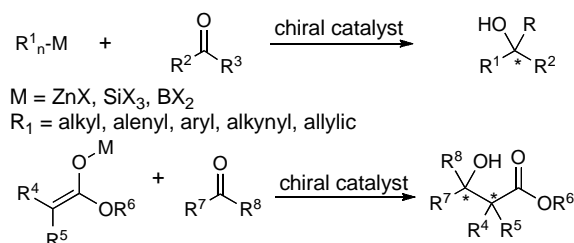
INTRODUCTION

Chiral, non-racemic tertiary alcohols are important structural subunits in chemical building blocks and biologically active compounds.¹ One of the most direct routes to enantiomerically enriched, tertiary alcohols is through the enantioselective addition of organometallic reagents to ketones. A majority of these reactions, however, employ highly nucleophilic and basic Grignard or organolithium reagents with stoichiometric amounts of chiral ligands.¹ Thus, the development of milder reagents that require a lesser amount of chiral ligands is needed.

Although many catalytic, enantioselective addition reactions with aldehydes have been successfully developed, the analogous reactions with ketones are generally less efficient. Two major challenges are apparent. First, ketones are less reactive, and the attenuated reactivity means that strong nucleophiles and/or activators are necessary for reasonable reaction rates. Second, enantiofacial discrimination is difficult when the two substituents on the carbonyl groups are sterically and electronically similar.

Following the first report of a catalytic, enantioselective addition to ketones in 1998,² numerous methods have been described.¹ This review will highlight the development of catalytic, enantioselective additions to unactivated ketones by organozinc reagents, allylsilanes, allylboranes, and metalloenolates (Scheme 1). The application of these methods to organic synthesis will also be reported.

Scheme 1. Addition Reactions to Unactivated Ketones

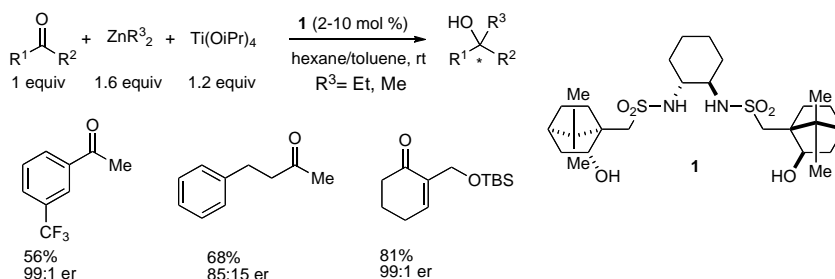


ADDITION OF ORGANOZINC REAGENTS TO KETONES

Alkylation

In 1992, Ohno and coworkers showed that the combination of 1,2-bis(sulfonamides) and titanium tetraisopropoxide successfully effected the addition of alkylzinc reagents to aldehydes.³ Following this work, Walsh et al. employed a modified bis(sulfonamide) ligand **1** in the addition of dialkylzinc reagents to ketones to afford chiral tertiary alcohols in good yields and good enantiomeric ratios (Scheme 2).⁴

Scheme 2. Catalytic, Enantioselective Alkylation of Ketones



Aromatic and α,β -unsaturated ketones often give higher enantiomeric ratios than aliphatic ketones. In addition, good yields and excellent enantioselectivities (14-199:1 er) are observed with the addition of functionalized dialkylzinc reagents, such as $\text{Zn}[(\text{CH}_2)_n\text{X}]_2$, $\text{Zn}[(\text{CH}_2)_n\text{OPiv}]_2$, $\text{Zn}[(\text{CH}_2)_n\text{OTBS}]_2$, where $n = 3-5$ and $\text{X} = \text{Br}, \text{Cl}$. These reagents are prepared by combining either the corresponding alkyl iodide or alkylborane with diethylzinc. This method is superior to the traditional addition of alkylmagnesium halides or alkyllithiums to zinc halides because the byproducts LiX and MgX_2 can catalyze the background addition of alkylzinc reagents to ketones, leading to an erosion of the enantioselectivity. Despite these advances, the mode of stereochemical induction, the transition-state structure, and the nature of the active catalyst are still ambiguous. Moreover, the need for excess amounts of $\text{Ti}(\text{O}i\text{-Pr})_4$ is a significant drawback.

Arylation

On the basis of the Noyori addition of diethylzinc reagents to aldehydes using amino alcohol ligand **2**,⁵ Fu and coworkers reported the first catalytic, enantioselective addition of a phenyl group to ketones, employing **2** and diphenylzinc (Table 1).³ Good yields (60-91%) and moderate enantioselectivities (3-21:1 er) were observed with aromatic ketones, while aliphatic ketones gave less satisfactory results. Walsh and coworkers have employed ligand **1** and $\text{Ti}(\text{O}i\text{-Pr})_4$ to achieve similar results.⁶

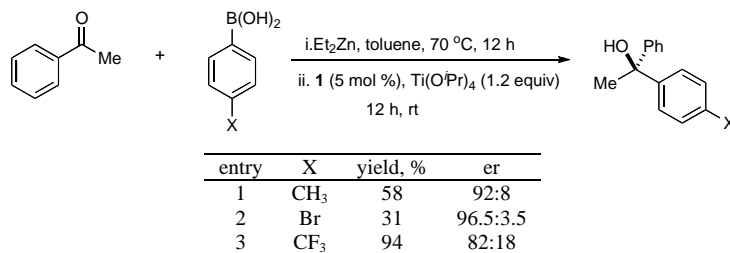
Table 1. Catalytic, Enantioselective Phenylation of Ketones using Amino Alcohol Ligand

Reaction		Ligand		Product	
R^1	R^2	yield, %	er	R^1	R^2
2-naphthyl	CH_3	58	86:14	2-naphthyl	CH_3
cyclohexyl	CH_3	76	87:13	4- BrC_6H_4	C_2H_5
4- BrC_6H_4	C_2H_5	83	95:5	isopropyl	CH_3
isopropyl	CH_3	63	80:20		

The range of transferable aryl groups is expanded by the use of arylboronic acids in combination with diethylzinc in the presence of ligand **1** and $\text{Ti}(\text{O}i\text{-Pr})_4$, albeit with modest yields and

enantioselectivities (Table 2).⁷ Currently, only a few arylboronic acids have been employed. On the other hand, the scope of ketone substrates is broad, ranging from aromatic, olefinic to aliphatic ketones.

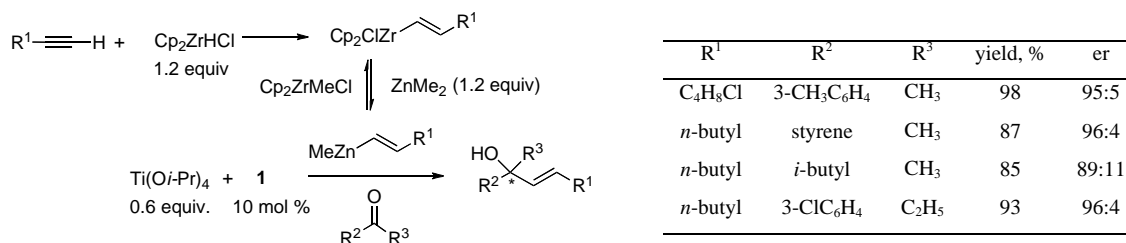
Table 2. Arylation of Ketones Using Boronic Acids and Dimethylzinc



Alkenylation

Most of the methods developed for alkenylation of ketones are derived from those for alkenylation of aldehydes. Alkenylzinc reagents are generated in situ by two methods. First, the hydroboration of terminal alkynes followed by transmetalation to zinc generates the alkenylzinc species, which then undergoes addition to ketones, affords low yields of allylic tertiary alcohols. On the other hand, hydrozirconation of terminal alkynes using Schwartz's reagent followed by transmetalation to zinc, affords the active alkenylzinc species that adds to ketones in good yields (84-98%) and enantioselectivities (8.5-66:1 er).⁸ This method selectively produces *Z*-allylic tertiary alcohols. The scope of ketone substrates is broad, ranging from aromatic, aliphatic to acyclic and cyclic α,β -conjugated ketones (Table 3).

Table 3. Alkenylation of Ketones from Alkenylzirconium Reagents



Trisubstituted and vicinally disubstituted alkenylzinc reagents cannot be generated from hydrozirconation of alkynes. However, Walsh and coworkers have shown that bis(2-methyl-1-propenyl)zinc and bis(2-propenyl)zinc are generated from 1-bromo-2-methylpropene and 2-bromopropene, respectively, by combining these alkenyl bromides with zinc bromide and lithium.⁹ Of these two alkenylzinc reagents, only bis(2-methyl-1-propenyl)zinc has been successfully used in the alkenylation of various ketones. The authors have postulated that steric hindrance from the methyl

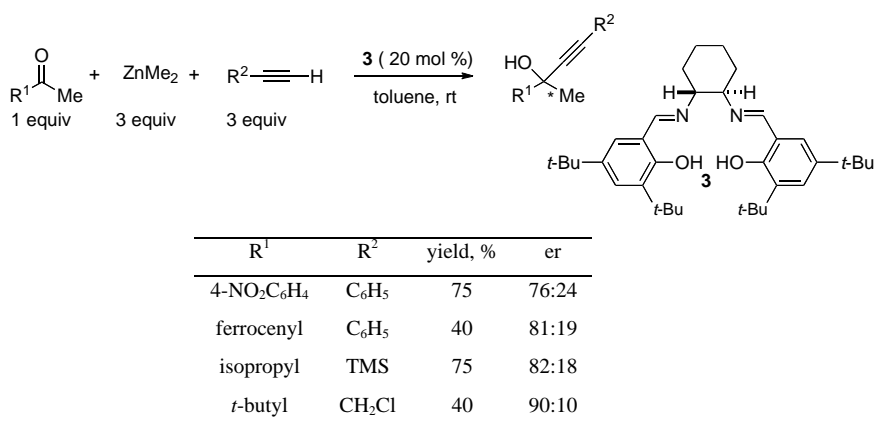
group in bis(1-methylvinyl)zinc is the cause for low reactivity of this reagent. In general, this alkenylation method performs well with a broad range of ketones, but the scope of alkenylzinc reagents is still limited.

Alkynylation

Chiral, propargylic tertiary alcohols are useful synthetic intermediates for a variety of applications.¹⁰ The synthesis of these alcohols is usually accomplished by addition of an alkynylzinc species, which is generated in situ by combining dimethylzinc with a terminal alkyne, to activated ketones such as α -ketoesters.¹¹ However, the same transformation with unactivated ketones is less common. Chan and coworkers have shown that a relatively strong Lewis acid, $\text{Cu}(\text{OTf})_2$, can be used to enhance the reactivity of unactivated ketones, effecting the addition of alkynylzinc species.¹² Aromatic ketones give moderate to good yields (39-94%) and enantioselectivities (6-66:1 er). However, alkynylation of aliphatic ketones has not been reported.

The reactivity of ketones in alkynyl additions can also be enhanced by using bifunctional catalysts.¹³ Thus, zinc-salen complex **3** have been employed in the addition of alkynyl groups to ketones, affording moderate yields with a wide range of ketones and alkynes (Table 4).¹⁴

Table 4. Alkynylation of Ketones Catalyzed by Zn-Salen Complex



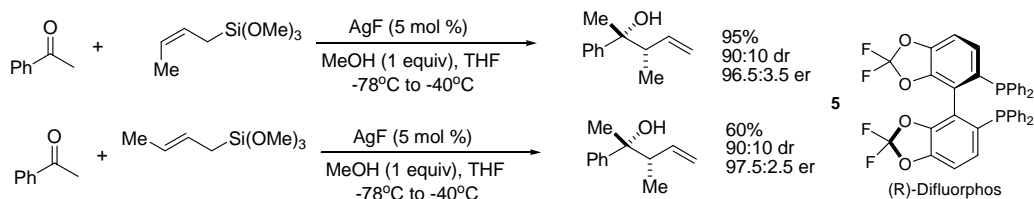
ALLYLATION

Whereas addition of alkyl, aryl, alkynyl and alkenyl groups to ketones is mediated by zinc reagents, the addition of allyl groups has been effected by allylstannanes, allylsilanes, allylboranes and allylboronates.⁴ Of the three reagents, allylsilanes and allylboranes are the most attractive because of their availability and ease of use. Extensive studies have led to numerous reports on the use of a

stoichiometric amount of chiral allylsilanes, boranes and boronates.¹⁵ However, catalytic enantioselective versions of these reactions with ketones have just been developed recently.

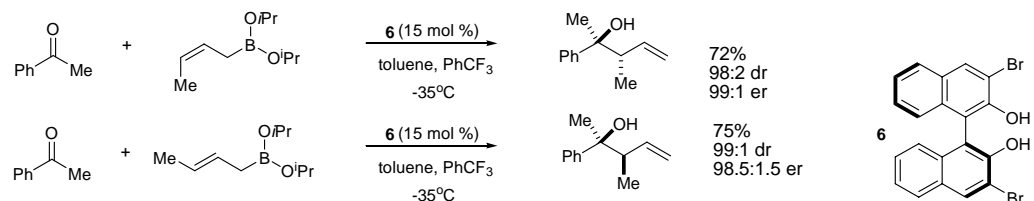
Allyltrimethoxysilanes add to ketones in the presence of a fluoride source. For example, Yamamoto and coworkers have employed AgF as a catalyst in the Sakurai-Hosomi allylation of ketones. The desired homoallylic tertiary alcohols are obtained in high enantiomeric purity, diastereoselectivities and yields regardless of the configuration of the allylsilanes, indicative of a Type II reaction²¹(Scheme 4).¹⁶

Scheme 4. Enantioselective and Diastereoselective Sakurai-Hosomi Allylation of Ketones



Catalytic, enantioselective allylation using allylboronates has also been achieved.^{17,18} For example, Schaus and workers recently reported the catalyzed addition of allylisopropoxyborane to ketones with diol **6** (Scheme 5).¹⁹ Good yields, high diastereo- and enantioselectivities were observed. The syn/anti diastereoselectivity reflected the *E/Z* ratio of the allylborane (Type I reaction).¹⁹

Scheme 5. Catalytic, Enantioselective Addition of Allyltrimethoxyborane

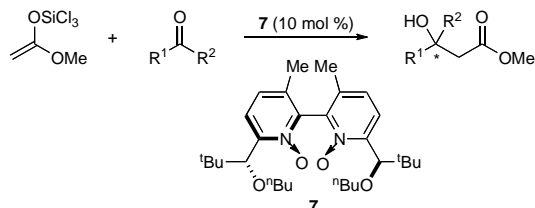


CATALYTIC AND ENANTIOSELECTIVE ALDOL ADDITIONS TO KETONES

The traditional aldol reaction with ketones as the electrophile is another attractive method that has only recently received attention. Whereas the catalytic, enantioselective aldol reaction with aldehydes has been extensively developed, the analogous reaction with ketones has been a daunting challenge.²⁰ In 1997, Evans and coworkers reported the first catalytic, enantioselective aldol addition to activated ketones (α -ketoesters and α -diketones).²¹ The first catalytic, enantioselective aldol addition to unactivated ketones was reported by Denmark and Fan in 2002 (Table 5).²² In this unique method, the reactive trichlorosilyl ketene acetal is used as the enolate source. A Lewis base is employed to doubly activate the enolate and the ketone in a closed transition state.²³ Thus, the reactivity of ketone is

enhanced. With N-oxide **7**, which possesses both central and axial chirality, as the chiral Lewis-base catalyst, the addition of trichlorosilyl ketene acetal to ketones affords β -hydroxy esters in high yields and highly variable enantiomeric ratios. Generally, the best enantiomeric ratios are observed with aromatic ketones.

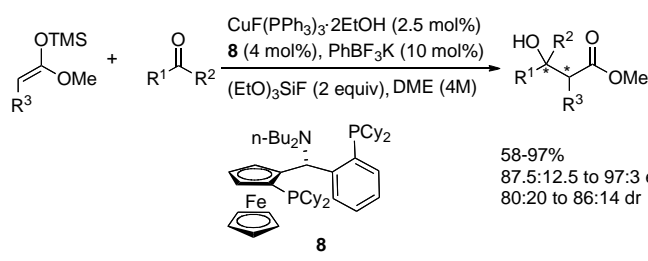
Table 5. Lewis-Base Catalyzed, Enantioselective Aldol Addition to Ketones



R ¹	R ²	yield, %	er
4-CF ₃ C ₆ H ₄	CH ₃	91	88:12
4-MeOC ₆ H ₄	CH ₃	94	83.9:16.1
cyclopropyl	CH ₃	84	60.1:39.9
<i>t</i> -butyl	CH ₃	87	71.5:28.5

Recently, Shibasaki and coworkers described the addition to ketones by employing a copper-based Lewis acid and trimethylsilyl ketene acetal as the nucleophile.²⁴ In the presence of bidentate phosphine ligand **8**, copper catalyst and a fluoride source, high yields and high enantiomeric and diastereomeric ratios were observed with aromatic ketones (Table 6). In general, the disadvantages of these aldol additions to ketones are the need for preformed silyl enol ethers and the sensitive trichlorosilyl ketene acetal.

Table 6. Enantioselective and Diastereoselective Lewis-Acid Catalyzed Aldol Addition to Ketones

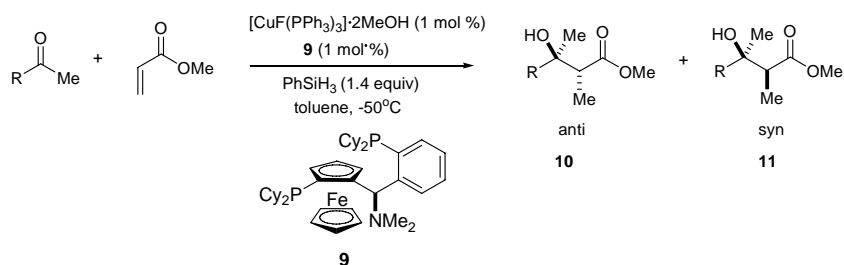


R ¹	R ²	R ³	yield, % (dr)	er
4-MeOC ₆ H ₄	CH ₃	H	95	95.5:4.5
2-naphthyl	CH ₃	H	92	95:5
C ₆ H ₅	CH ₃	CH ₃	58 (86/14)	97:3*
C ₆ H ₅	CH ₃	<i>n</i> -butyl	97 (81/19)	95.5:4.5*

58-97%
87.5:12.5 to 97:3 er
80:20 to 86:14 dr

* Enantiomeric ratios of the major diastereomer

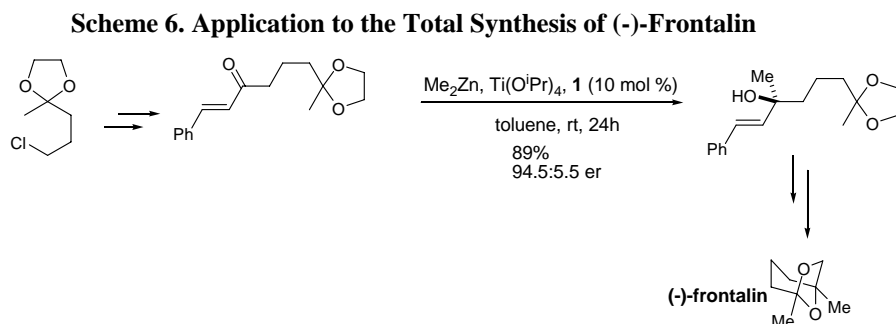
By combining the Shibasaki's Cu(I)-catalyzed aldol reaction, shown in Table 6, with Buchwald's and Lipshutz's Cu(I)-catalyzed enantioselective reduction of C-C double bonds in α,β -unsaturated carbonyl compounds,²⁵ Shibasaki et al.²⁶ and Riant et al.²⁷ have independently developed the reductive aldol addition of methyl acrylate to acetophenone. High enantioselectivities and diastereoselectivities are observed (Table 7). Although still in its infancy, this method allows the in-situ formation of the metalloenolate species, obviating the need for preformed silyl enol ethers.

Table 7. Diastereoselective, Enantioselective Reductive Aldol Addition to Ketone


R	yield, %	10/11	er
4-ClC ₆ H ₄	95	86:14	95:5
4-MeOC ₆ H ₄	31	92:8	95:5
2-thiophenyl	94	96:4	95:5

APPLICATIONS

Despite the limitations in scope of the aforementioned methods, many examples of practical application to natural product syntheses have been reported such as: (-)-frontalin,²⁸ fostriecin,²⁹ and taurospongins A.³⁰ For example, the key step in the synthesis of (-)-frontalin, is the addition of dimethyl zinc to an α,β -unsaturated ketone with ligand **1**, setting one of the two stereogenic centers of the final target molecule with high enantioselectivity (Scheme 6).



CONCLUSIONS

Despite the challenges of low reactivity and stereochemical ambiguity posed by ketones, catalytic and enantioselective addition reactions with ketones have been developed in recent years. The additions of alkyl, alkenyl, aryl, and alkynyl groups are achieved via organozinc reagents. The major drawbacks of this method are limited scope of zinc reagents, low enantioselectivities observed with dialkyl ketones, and the use of an excess amount of titanium alkoxides. Mechanistic understanding of these processes is still limited. On the other hand, the addition of allyl groups from allylsilane and allylboronate reagents has been more successful. The substrate scope is broad. Furthermore, recent success in the aldol reactions with ketones has increased the number of synthetic routes to chiral, non-racemic tertiary alcohols. Future developments will no doubt increase the utility of these reactions in organic synthesis.

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