

# Development of the First Practical Catalyst for the Asymmetric Addition of Alkyl- and Arylzinc Reagents to Ketones

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**Abstract:** A long-standing problem in organic synthesis is the catalytic asymmetric addition of alkyl groups to ketones to establish chiral quaternary centers. Such compounds are valuable chiral building blocks that can be further elaborated. In this account, we describe the previously unreported story of the development of the first effective catalyst for the enantioselective addition of dialkyl- and diphenylzinc reagents to ketones. The scope of this reaction is outlined, including a tandem enantioselective addition to cyclic enones/diastereoselective epoxidation protocol that establishes three contiguous stereocenters in a one-pot procedure.

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**Key words:** alcohols, alkylations, asymmetric catalysis, ketones, quaternary centers

## 1 Introduction

Carbon-carbon bond forming reactions lie at the heart of organic synthesis. As such, many methods have been developed to accomplish this key construction. One of the most common approaches to extension of the carbon framework involves carbonyl addition reactions, usually accomplished with Grignard and organolithium reagents. Demands for increased functional group tolerance, and enantioselective variants, however, have reduced the attractiveness of such strongly basic and reactive reagents. The search for milder organometallic reagents capable of addition to aldehydes and ketones was, therefore, reinitiated.

An early milestone in this quest came from the Oguni laboratories and entailed the use of dialkylzinc reagents.<sup>1,2</sup> Although dialkylzinc reagents react quite slowly with aldehydes, the presence of a mild Lewis acid catalyst great-

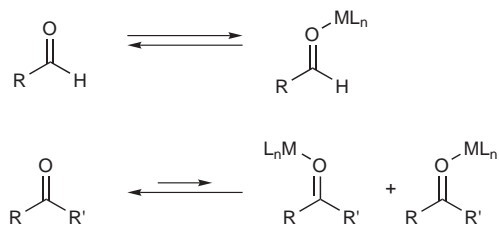
ly accelerates the addition. Oguni and co-workers employed catalysts generated from enantioenriched amino alcohols that afforded secondary alcohols with high enantioselectivity. The mechanism and nonlinear behavior of these catalysts were studied by Noyori and co-workers and form an integral part of our understanding of catalytic asymmetric reactions.<sup>3-5</sup>

Since these pioneering works, hundreds of catalysts have been developed that will promote addition of *alkylzinc reagents to aldehydes* with enantioselectivities over 90%.<sup>6</sup> This has led many researchers to believe that addition of organozinc reagents to carbonyl groups is a solved problem. In fact, this is far from the truth. For example, very few studies on the addition of *vinyl groups*<sup>7-14</sup> or *acetylides*<sup>14-17</sup> to aldehydes have been published; however, the products of these reactions, chiral allylic and propargylic alcohols, are valuable chiral building blocks. Furthermore, enantioselective additions to *ketones* have only been recently introduced.<sup>18-20</sup>

This account outlines our development of the first efficient and highly enantioselective catalyst for the asymmetric addition of alkyl and aryl groups to ketones. The products of these addition reactions, tertiary alcohols, contain chiral quaternary centers, which are difficult to generate with high enantioselectivity using other methodologies. The tertiary alcohol products can be transformed into a number of useful functionalized chiral building blocks.

### 1.1 Asymmetric Catalysis with Ketones

In asymmetric catalysis, there are many examples of efficient and highly enantioselective catalysts for reactions with aldehydes. These same catalysts, however, do not usually promote the analogous reactions with ketone substrates with similar levels of success. The origin of this discrepancy is rooted in both reactivity and enantioselectivity. The Lewis acid is coordinated *syn* to the aldehydic hydrogen (Scheme 1) because this is the sterically most accessible binding site. Binding *trans* to the aldehydic hydrogen results in unfavorable steric interactions between the alkyl substituent and the Lewis acid. In the case of ketones, however, the Lewis acid must bind *syn* to an alkyl substituent. It is not surprising, therefore, that aldehydes bind to Lewis acids with a higher binding constant than ketones.



**Scheme 1** Equilibrium binding of an aldehyde and a ketone to a Lewis acid.

A similar logic can explain the disparity in enantioselectivity between aldehydes and ketones. In order to achieve high enantioselectivities, catalysts must distinguish between the lone pairs of the carbonyl oxygen. This is straightforward with aldehyde substrates as outlined above. With ketones, however, discrimination of the lone pairs is challenging, because of the similarity of their environments. Isomeric ketone-Lewis acid adducts may give rise to addition products of low ee.

## 1.2 Prior Art

Introduction of catalysts for the asymmetric addition of alkyl and aryl groups to ketones lagged far behind analogous reactions with aldehydes. It was not until 1998 that Dosa and Fu reported the first example from this class (Scheme 2).<sup>18</sup> In this important study, these authors employed Noyori's DAIB ligand (**1**).<sup>21–23</sup> Although direct use of  $\text{Ph}_2\text{Zn}$  gave low yields, a mixed alkoxy phenyl zinc reagent, generated by reaction of  $\text{Ph}_2\text{Zn}$  with methanol, gave increased yields and enantioselectivities (Table 1). In contrast,  $\text{Ph}_2\text{Zn}$  and alkyl phenyl zinc reagents have been used successfully in the phenylation of aldehydes.<sup>24–30</sup>

As can be seen from the results in Table 1, in general the enantioselectivities are very high and the yields range from good to excellent.

About the same time as the report by Dosa and Fu, Ramón and Yus published the first catalytic asymmetric addition of alkyl groups to ketones.<sup>19,20</sup> This system was based on prior work by Takashi, Kobayashi, and Ohno<sup>31,32</sup> and

## Biographical Sketches



**Juan M. Betancort** received his B.Sc. in chemistry at the University of La Laguna, Tenerife, Spain in 1993 and stayed to study for his Ph.D. degree in Organic Chemistry (1998) with Professor Víctor S. Martín, working on the development of new methodologies for the synthesis of polysub-

stituted cyclic ethers and asymmetric variants of the Nicholas reaction. He then joined the laboratories of Professor Patrick J. Walsh at the University of Pennsylvania (1999–2000) as a postdoctoral fellow, where he worked on the use of bis(sulfonamide) and ferrocene-based ligands for

asymmetric catalysis. Next he joined the laboratory of Professor Carlos F. Barbas III at The Scripps Research Institute and worked in the area of organocatalysis. He is currently a Senior Scientist in the Department of Drug Discovery at Phenomix Corporation, La Jolla, CA.



**Celina García** received her B.Sc. in chemistry at the University of La Laguna, Tenerife, Spain in 1996 and stayed to study for her Ph.D. degree in Organic Chemistry (2001) with Professor

Víctor S. Martín, working on the enantioselective total synthesis of polyfunctionalized oxacyclic compounds isolated from marine sources. In 2001 she joined the laboratories of Professor

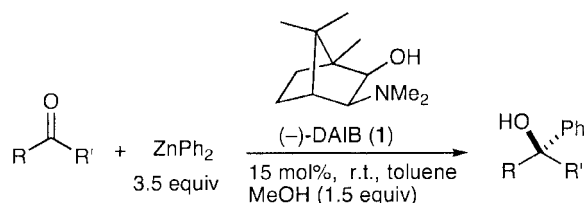
Patrick J. Walsh at the University of Pennsylvania as a postdoctoral researcher, where she worked on the catalytic asymmetric addition of alkyl and aryl groups to ketones.



**Patrick J. Walsh** hails from El Cajon, CA. He received his B.A. from UC San Diego (1986) where he worked in the laboratories of Prof. C. L. Perrin and his Ph.D. from UC Berkeley (1991) with Prof. R. G. Bergman.

He was a NSF postdoctoral fellow with Prof. K. B. Sharpless at the Scripps Research Institute. Moving across town in 1994, his first faculty position was at San Diego State University. In 1999 he moved to his

current position at the University of Pennsylvania. His interests are in stereochemistry, design of asymmetric catalysts, and elucidation of reaction mechanisms.

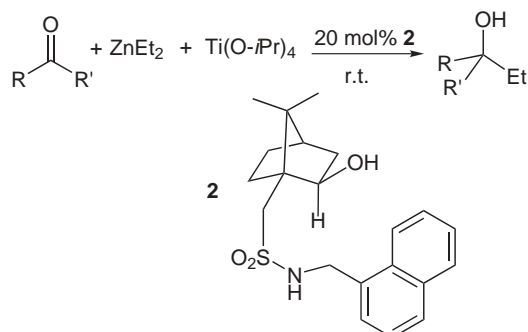


Scheme 2

Table 1 Results of Dosa and Fu from Scheme 2<sup>18</sup>

R	R'	Yield (%)	ee (%)
Me	4-C <sub>6</sub> H <sub>4</sub> -Br	53	80
Me	2-naphthyl	58	72
Et	3-C <sub>6</sub> H <sub>4</sub> -Br	91	91
Et	2-naphthyl	79	86
Et	4-C <sub>6</sub> H <sub>4</sub> -Br	83	90
Me	<i>i</i> -Pr	63	60
Me	C <sub>6</sub> H <sub>11</sub>	76	75

Seebach and co-workers<sup>33–35</sup> who found that titanium-based catalysts promote the asymmetric addition of alkyl groups to aldehydes. Ramón and Yus employed a series of hydroxy sulfonamide ligands derived from camphor in combination with Ti(O-*i*Pr)<sub>4</sub> to promote the addition of organozinc reagents to ketones (Scheme 3).



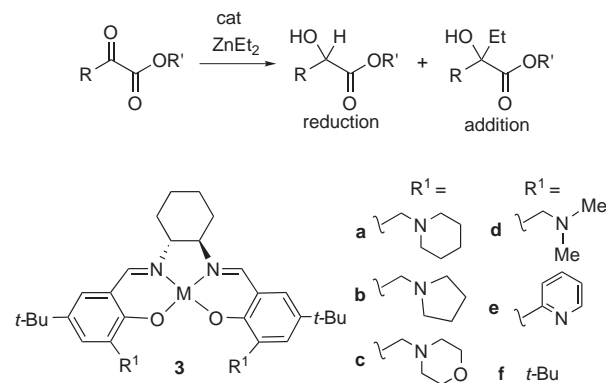
Scheme 3

Table 2 Results of Ramón and Yus from Scheme 3<sup>19,20</sup>

R	R'	Time (d)	Yield (%)	ee (%)
Me	Ph	4	85	82
<i>n</i> -Bu	Ph	6	78	86
Me	2-naphthyl	4	75	42
Me	<i>trans</i> -PhCH = CH	7	72	31
Me	cyclohexenyl	6	36	51
$\alpha$ -tetralone		14	25	89

The best results (Table 2) were obtained with the ligand **2** in Scheme 3. Although enantioselectivities approaching 90% were observed for some substrates, others resulted in low enantioselectivities. Furthermore, the catalysts exhibited low turnover frequency, requiring 4–14 days for completion of the reaction at 20 mol% catalyst loading.

At the same time that we were working on development of our catalyst for the addition of alkyl groups to ketones, the Kozlowski group was examining the use of novel bifunctional catalysts for the addition of organozinc reagents to  $\alpha$ -ketoesters.<sup>36,37</sup> The addition products are precursors to  $\alpha$ -hydroxy acids, which are valuable synthetic materials.<sup>38</sup>



Scheme 4  $\alpha$ -Ketoesters react with dialkylzinc reagents giving reduction and/or addition products. Kozlowski's catalysts give primarily addition products.

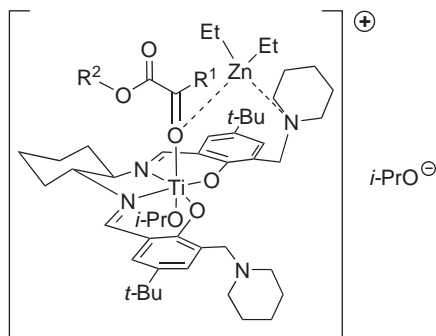
Alkyl additions to  $\alpha$ -ketoesters are more difficult than the additions of alkyl groups to aldehydes or ketones because 1) the background reaction, which is the uncatalyzed reaction of Et<sub>2</sub>Zn with  $\alpha$ -ketoesters, is rapid in contrast to aldehydes and 2) the catalyst must accelerate the addition pathway over ketone reduction (Scheme 4).

In the absence of catalyst, the major product was the reduced  $\alpha$ -hydroxy ester (Table 3). Use of the amino alcohol ligands such as MIB also gave predominantly reduced products with addition product formed in low enantioselectivity (5%). The bifunctional salen catalyst **3a** was employed in this challenging reaction (Scheme 4). The Lewis acidic and Lewis basic sites are sufficiently separated in bifunctional catalysts **3a–e** that internal coordination is not possible. Catalysts with M = Zn, Mg, and Ti generated the desired addition products with excellent chemoselectivity (Table 3).

Enantioselectivities up to 78% were obtained with salen **3a** and M = Ti(O-*i*Pr)<sub>2</sub>. When the salen **3f**, lacking the basic amino groups was employed, an increase in the reduction product was observed and the addition product was nearly racemic (4% ee). These results support a bifunctional cooperative interaction (Figure 1).

**Table 3** Reaction of  $\alpha$ -Ketoesters with  $\text{Et}_2\text{Zn}$  in the Presence of (-)-MIB and **3**

Catalyst	Temp. (°C)	Time (h)	Reduction (% Conv.)	Addition
None	-40	2	45	23
MIB·ZnEt	0	2	37	25
<b>3a</b> ·Zn	-40	24	6	93
<b>3a</b> ·Mg	-40	2	0	99
<b>3a</b> ·Ti(O- <i>i</i> Pr) <sub>2</sub>	-40	2	0	99

**Figure 1** Proposed addition of organozinc reagents to  $\alpha$ -ketoesters catalyzed by bifunctional salen catalysts.

The proposed mechanism involves alkoxide ionization to generate a 5-coordinate titanium cation that binds the keto group of the substrate (Figure 1). Support for this hypothesis is that the enantioselectivities are the same when  $\text{Ti}(\text{O-}i\text{Pr})_4$  and  $\text{Ti}(\text{O-}t\text{Bu})_4$  are used.

The bifunctional catalysts outlined here are not only highly efficient, but positively impact the product distribution such that the desired addition product is almost exclusively obtained.

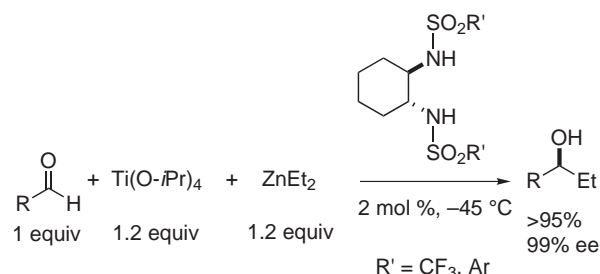
Just before the submission of this account, another catalyst for the asymmetric addition of  $\text{Me}_2\text{Zn}$  to  $\alpha$ -ketoesters employing bifunctional amino diol-based catalysts was reported by the Shibasaki group.<sup>39</sup> The final catalyst optimization was accomplished by addition of catalytic amounts of alcohols, which had a surprisingly large impact on the enantioselectivity of the catalyst. Enantioselectivities with a catalytic amount of 2-propanol as additive were excellent (59–96%) for a range of substrates.

It should also be noted that examples of the asymmetric addition of acetylides to  $\alpha$ -ketoesters<sup>40</sup> and ketones<sup>41</sup> have recently been reported, but are outside the scope of this account.

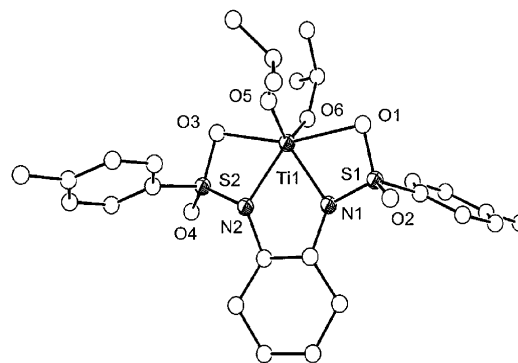
Although the results in Tables 1 and 2 represent a good starting point, there remained room for improvement. This review focuses on our efforts to develop better catalyst for the addition of alkyl and phenyl zinc reagents to ketones.

## 2 Our Approach to Catalyst Development

Much of our earlier work<sup>42–46</sup> was devoted to understanding catalyst structure and reaction mechanisms of the asymmetric addition of alkyl groups to aldehydes developed by Takashi, Kobayashi, and Ohno (Scheme 5).<sup>31,32</sup>

**Scheme 5** Asymmetric addition of alkyl groups to aldehydes developed by Takashi, Kobayashi, and Ohno.

The catalysts exhibit remarkable efficiency in the addition of alkyl groups to aldehydes with high enantioselectivities. In some cases, the reaction proceeds at  $-45\text{ °C}$  and is complete in 15 minutes with 99% enantioselectivity. Knochel has demonstrated that a variety of functionalized organozinc reagents can be employed to generate elaborate secondary alcohols with high enantioselectivities. The groups of Takashi<sup>31,32</sup> and Knochel<sup>47</sup> proposed that the active species in these reactions are the bis(sulfonamido)Ti(O-*i*Pr)<sub>2</sub> complexes. We synthesized, isolated, and crystallographically characterized these species (Figure 2) and demonstrated that they serve as precatalysts or catalysts for this reaction, providing products with the same enantioselectivities as catalysts generated under identical reaction conditions.<sup>48</sup>

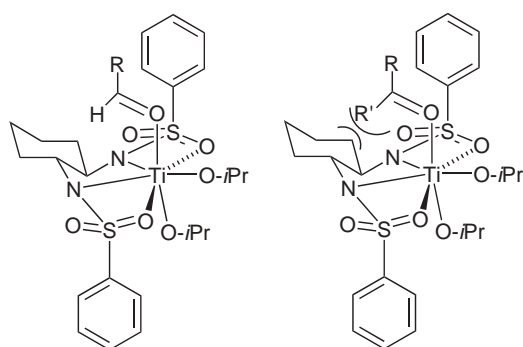
**Figure 2** Structure of bis(sulfonamido)Ti(O-*i*Pr)<sub>2</sub>.

### 2.1 Asymmetric Alkylation of Ketones

We employed the bis(sulfonamide)-based catalysts in the asymmetric addition of alkyl groups to ketones. Despite the high reactivity of these catalysts toward aldehydes, when ketone substrates were used, the reactions proceeded very slowly at room temperature, providing traces of the ketone addition product after several days. Adding further to our disappointment, the alcohol product produced was nearly racemic. This surprising result inspired

us to focus our efforts on the development of new catalysts for the addition of alkyl groups to ketones.

The disparity in alkylation rates of aldehydes and ketones with bis(sulfonamide)-based catalysts was attributed to the inability of the catalyst to activate the substrate. We envisioned that aldehydes should be preferentially bound to the catalyst *syn* to the hydrogen as shown in Figure 3. It is possible that the ketone substrate cannot bind, because the steric interactions incurred between the *syn* alkyl substituent and the ligand. It should be noted that this working model of substrate activation is based on crystal structures of the bis(sulfonamido)Ti(O-*i*Pr)<sub>2</sub> complexes<sup>48</sup> and conformational studies of the bis(sulfonamido)-based catalyst under the reaction conditions.<sup>43</sup> It is not known how the substrate binds to the catalyst in this system.



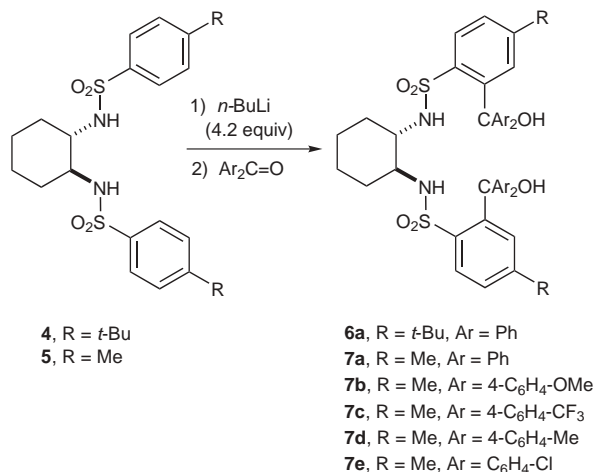
**Figure 3** Proposed activation modes for aldehydes and ketones by bis(sulfonamido)Ti(O-*i*Pr)<sub>2</sub> complexes.

## 2.2 Generation I Catalysts

The logic outlined above led us to propose the design of catalysts with larger binding sites that could accommodate the bulkier ketone. Because the bis(sulfonamide)-based catalysts exhibited high levels of efficiency and enantioselectivity in the alkylation of aldehydes, we thought it best to conserve the bis(sulfonamide) backbone in our design. We believed a larger binding pocket could be created by incorporating the isopropoxy groups on the proposed catalysts (Figure 3) into the bis(sulfonamide) backbone, thereby constraining the geometry of the catalyst.

The synthesis of our first generation ligands is shown in Scheme 6.<sup>49</sup> Treatment of the bis(sulfonamide) ligands **4** and **5** with just over 4 equivalents of *n*-BuLi proceeded by initial deprotonation of the sulfonamide hydrogens followed by metallation of the *ortho*-position of the aryl groups. Quenching the tetraanion with benzophenone derivatives gave the bis(sulfonamide) diol ligands **6** and **7**. The ease of this two step synthesis allowed us to prepare several derivatives by varying the substituents of the bis(sulfonamide) aryl groups as well as the benzophenone coupling partners.

The driving force behind our design of the constrained geometry bis(sulfonamide) diol ligands **6** and **7** was that they would have large binding pockets capable of activat-



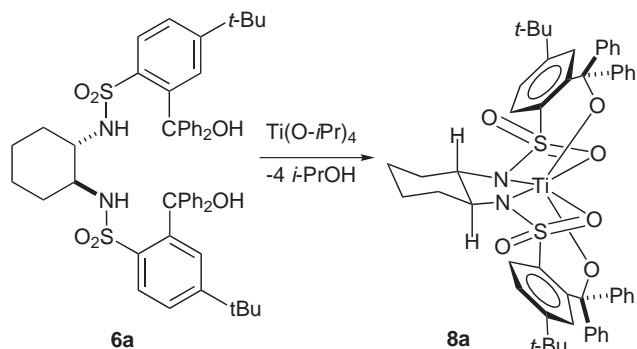
**Scheme 6** Synthesis of first generation ligands incorporating the constrained geometry design.

ing ketone substrates. To explore this possibility, we synthesized titanium complexes of these bis(sulfonamide) ligands by two routes, as illustrated in Schemes 7 and 8. Alkoxide exchange reactions with Ti(O-*i*Pr)<sub>4</sub> generally reach equilibrium rapidly. The equilibrium can be driven by removal of the liberated *i*-PrOH under reduced pressure. Addition of ligand **6a** to a toluene solution of Ti(O-*i*Pr)<sub>4</sub> followed by removal of the solvent and liberated *i*-PrOH (Scheme 7) and crystallization of the resulting solid gave X-ray quality crystals of the ligand adduct **8a**, as shown in Figure 4.

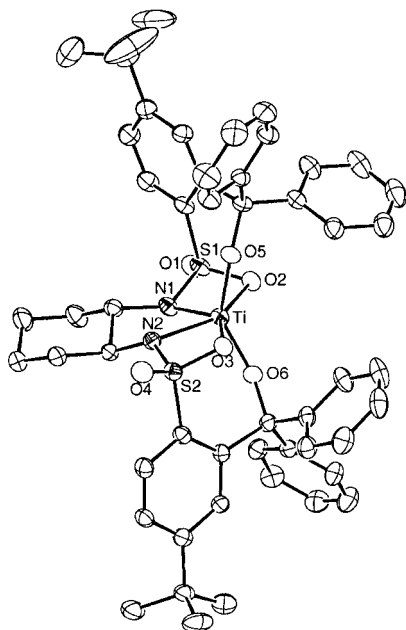
Examination of the structure of **8a** suggests that the substrate-binding site of this complex is between the aryl groups and that these groups define the chiral environment of the complex. To explore this possibility, we wanted to characterize a derivative with a bound substrate or substrate analog. We chose to explore binding of substrate analogs that exhibited tighter bind than ketones. The amido groups on Ti(NMe<sub>2</sub>)<sub>4</sub> are strongly basic and readily deprotonate sulfonamide NH's and alcohol OH's liberating Me<sub>2</sub>NH, a potential substrate analog. Reaction of ligand **7a** with Ti(NMe<sub>2</sub>)<sub>4</sub> formed the amine adduct **9a** (Scheme 8). The structure of **9a** is shown in Figure 5. The substrate-binding site of this complex is occupied by the coordinated *N,N*-dimethyl amine. Also evident is the large size of the binding pocket between the nearly parallel aromatic rings of the diphenyl carbonyl moiety.

The bis(sulfonamido)Ti(O-*i*Pr)<sub>2</sub> complexes (Figure 2) were synthesized by an analogous amine elimination reaction from Ti(O-*i*Pr)<sub>2</sub>(NMe<sub>2</sub>)<sub>2</sub>.<sup>48</sup> These complexes, however, show no propensity to coordinate the liberated Me<sub>2</sub>NH in contrast to those derived from ligands **6** and **7**. Thus, the constrained geometry complexes appear to be more Lewis acidic.

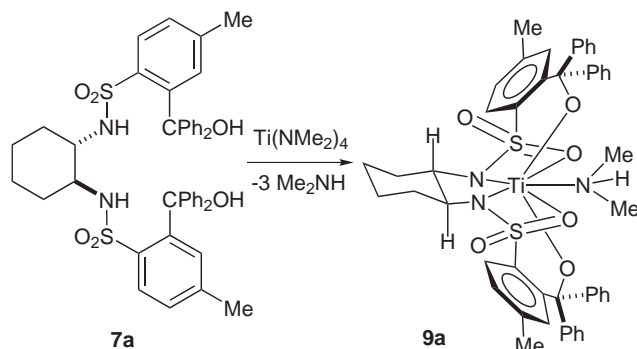
The bis(sulfonamide) diol ligands **6** and **7** were then used in the asymmetric addition of alkylzinc reagents to ketones, as illustrated in Scheme 9. Catalyst loadings of 10–20 mol% were employed with an excess of the dialkylzinc



**Scheme 7** Synthesis of titanium complex **8a** from  $\text{Ti}(\text{O-}i\text{Pr})_4$ .

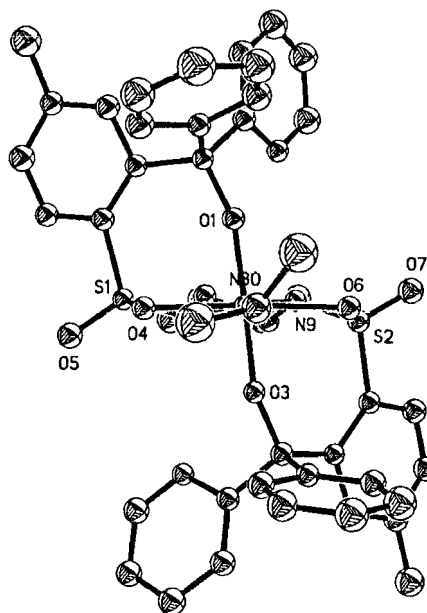


**Figure 4** ORTEP drawing of compound **8a**.



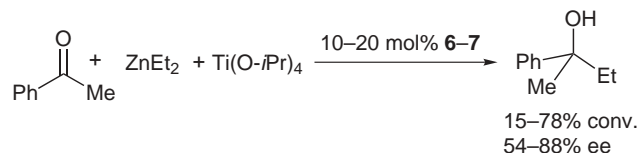
**Scheme 8** Synthesis of titanium complex **9a** from  $\text{Ti}(\text{NMe}_2)_4$

reagent and  $\text{Ti}(\text{O-}i\text{Pr})_4$ . We were excited to find that catalysts derived from these ligands did promote the asymmetric addition of alkylzinc reagents to ketones. The enantioselectivities for acetophenone ranged from 54–88% in most cases, which were approaching those of the best catalyst at the time. The reactions were painfully slow, however, and required several days to achieve high conversion. Nonetheless, the constrained geometry cata-



**Figure 5** ORTEP drawing of compound **9a**.

lysts represented our first breakthrough in the development process. Interestingly, despite the fact that the proposed catalysts for the asymmetric addition of alkyl groups to aldehydes, the bis(sulfonamido) $\text{Ti}(\text{O-}i\text{Pr})_2$  complexes, and the constrained geometry catalyst, derived from ligands **6** and **7**, appear to have identical atoms coordinated to titanium, only the constrained geometry catalysts generate the desired tertiary alcohol as the predominant product.



**Scheme 9**

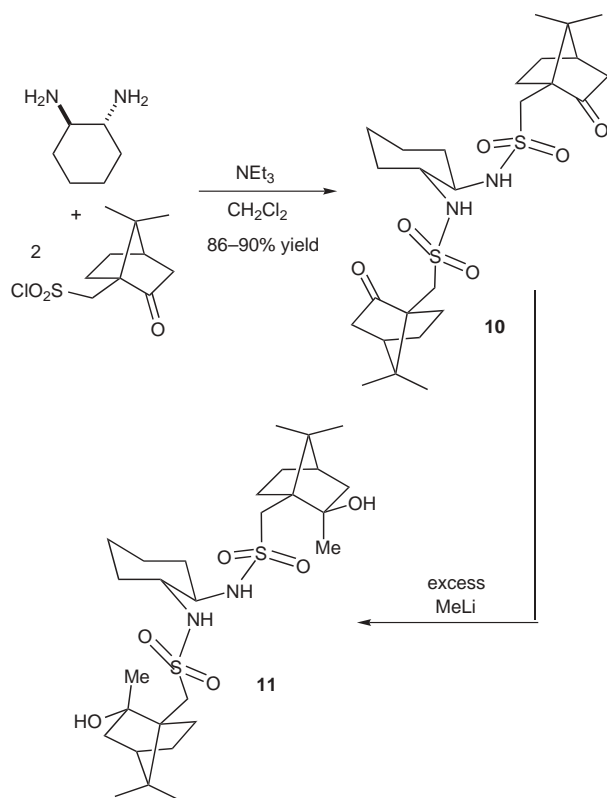
We spent several months attempting to optimize the ketone alkylation reaction by synthesizing ligands closely related to **6** and **7** with different substituents but to no avail. We changed solvents, temperature, and catalyst loading as well, but we were unable to make significant improvements in either enantioselectivity or efficiency. The sluggish nature of these catalysts was particularly troubling, because even if we were able to raise the enantioselectivities into the 90% range, a catalyst that required 20 mol% loading and several days to consume the starting material would be of little use. With this in mind, we opted to redesign the catalyst, retaining the bis(sulfonamide) backbone and the constrained geometry design feature.

### 2.3 Generation II Catalysts

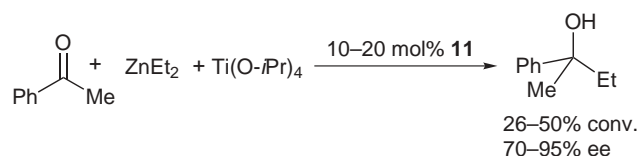
We initiated research to probe the relative rates of diastereomeric catalyst and catalyst inhibition by substrate analogs, and thus had synthesized the camphor derived

bis(sulfonamide) ligands **10** as shown in Scheme 10.<sup>50</sup> For this study, we also required the bis(sulfonamide) diol **11**, which was prepared as a single diastereomer by addition of an excess of MeLi to the diketone **10**. We then used ligand **11** in the asymmetric addition reaction, as shown in Scheme 11.

The catalyst generated from **11** was more enantioselective (70–95% ee, Scheme 11) than those formed from **6** and **7**. Like the first generation ligands, however, the catalyst turnover was problematic. Reactions were conducted at high catalyst loading (20 mol%) and frequently did not go to completion after several days. The diastereomer of **11** was also made, but exhibited lower enantioselectivity and efficiency, as did ligands derived from addition of PhLi to diketone **10**. Once again, we spent over a month attempting to optimize asymmetric additions with this family of catalysts, but to our disappointment, we failed to find conditions that led to meaningful increases in either enantioselectivities or activities.



Scheme 10



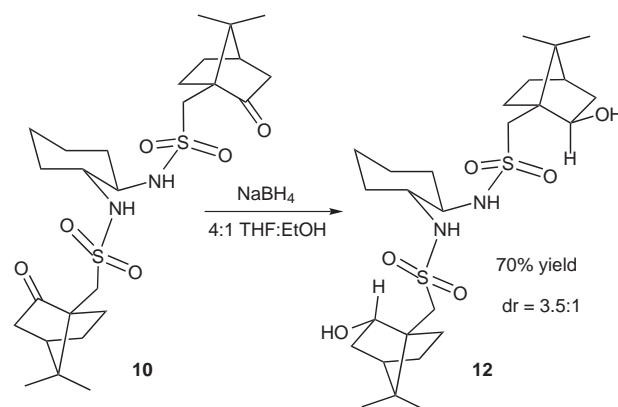
Scheme 11

## 2.4 Generation III Catalyst – Third Time's a Charm!

The first and foremost problem that we needed to address was the low turnover frequency of the catalyst. In thinking about the possible intermediates in the catalytic cycle we focused on two potential bottlenecks: the inability of the catalyst to activate the substrate (catalyst reactivity) and the removal of the alkoxide product from the catalyst. We focused on the latter because we had substantial experience studying alkoxide exchange processes with titanium-based asymmetric catalysts.<sup>42,51</sup>

We envisaged that ligand **11** would bind to titanium in a similar fashion to those we had previously characterized crystallographically (Figures 4 and 5). Coordination of the ketone substrate to this complex followed by delivery of the alkyl group generates the tertiary alkoxide product. In order to remove the alkoxide from the titanium center in this proposed intermediate, the alkoxide product must bind to a second metal (either zinc or titanium) forming a bridging alkoxide intermediate before the catalyst can be regenerated. We believed the oxygen of the alkoxide product to be nearly inaccessible because of steric shielding by the bulky chiral ligand (itself containing two tertiary alkoxides).

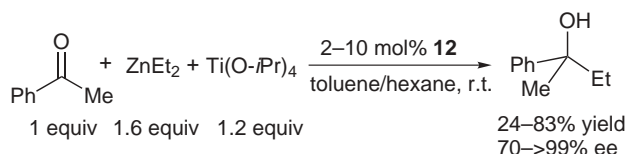
To reduce the severity of this problem we designed the third generation ligand with less bulk around the metal center in the hopes of facilitating product removal. At the same time, we wanted to keep the ligand scaffolding similar to that of the second-generation, because the enantioselectivities with ligand **11** were relatively high. Diketone **10** was, therefore, reduced to generate secondary hydroxyl groups. The reduction occurs with 3.5:1 diastereoselectivity with NaBH<sub>4</sub> affording the C<sub>2</sub>-symmetric product **12** in 70% isolated yield (Scheme 12).<sup>52</sup>



Scheme 12

We were excited that use of **12** in the asymmetric addition reaction with Et<sub>2</sub>Zn afforded the desired tertiary alcohol products with excellent enantioselectivities (Scheme 13).<sup>52</sup> Furthermore, the catalyst exhibited high activity with several substrates, having a turnover frequency over 40 times greater than the previous top catalyst for this reaction.<sup>19,20</sup> As shown in Table 4, catalyst

loadings as low as 2 mol% could be used for complete conversion in 24 hours at room temperature. The addition is exemplified by alkylation of 3-methylacetophenone with  $\text{Et}_2\text{Zn}$  on a 5g scale to give the product in 78% yield and 99% ee. The ligand **12** was recovered in 84% yield from this reaction and used in subsequent additions with no loss in enantioselectivity. The turnover frequencies of the catalyst is sensitive to the electronic nature of the acetophenone. Electron deficient 3-(trifluoromethyl) acetophenone reacted rapidly at 2 mol% catalyst loading while the 4-methoxy derivative reacted more slowly even at 10 mol% loading. Nonetheless, both substrates gave excellent enantioselectivities (entries 3 and 4).



Scheme 13

Increasing the steric hindrance around the carbonyl group or the acidity of the  $\alpha$ -hydrogens reduces the yield due to formation of products derived from aldol condensation/dehydration. Nonetheless, the enantioselectivities with 2-methylacetophenone and  $\alpha$ -tetralone remained very high. Aryl alkyl ketones gave high enantioselectivities, as did  $\alpha,\beta$ -unsaturated derivatives. The dialkyl ketone 4-phenyl-2-butanone underwent addition with 70% enantioselectivity (entry 11). Although not in the synthetically useful range, it is impressive that the catalyst can differentiate between the methyl and methylene groups of this substrate reasonably well.

We have also examined the addition of  $\text{Me}_2\text{Zn}$  to propiophenone. Interestingly, the addition to propiophenone using  $\text{Me}_2\text{Zn}$  gave the (*R*)-enantiomer of 2-phenyl-2-butanol (2 mol% ligand, 83% yield, 94% ee) while the addition of  $\text{Et}_2\text{Zn}$  to acetophenone gave the (*S*)-enantiomer of the same alcohol in 96% ee (Table 4, entry 1). It is interesting that both enantiomers of 2-phenyl-2-butanol can be obtained with excellent enantioselectivity using the same configuration of the ligand.

We were surprised to find that after our results in Table 4 were published, Yus and co-workers submitted a manuscript similar to ours using ligand **12** in the asymmetric addition of alkyl groups to ketones.<sup>53</sup> The manuscript added little new data, because no experimental support or procedure was given. Nonetheless, these authors did confirm the high enantioselectivity of the catalyst derived from **12**.

### 3 Asymmetric Additions to Cyclic Conjugated Enones – Tandem Asymmetric Alkylation/Epoxidation Reactions

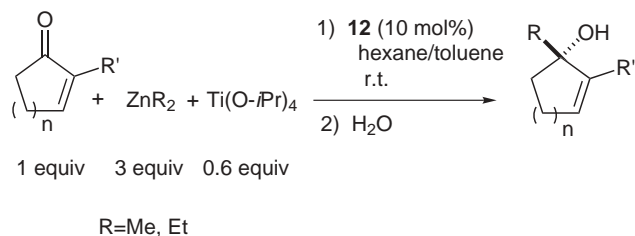
We next turned our attention to enantioselective 1,2-addition reactions of cyclic  $\alpha,\beta$ -unsaturated ketones.<sup>54</sup> The ter-

**Table 4** Asymmetric Addition of Ethyl Groups to Ketones with Ligand **12** in Scheme 13<sup>52</sup>

Entry		mol%	Time (h)	Yield (%)	ee (config.)
1		2	29	71	96 ( <i>S</i> )
2		10 2	12 24	82 78	99 99
3		10	111	85	94
4		2	14	56	98
5		10	48	24	96
6		10	22	35	>99
7		10 2	47 102	83 79	87 88
8		10	44	82	89
9		2	46	56	96
10		2	26	80	90
11		10	68	68	70

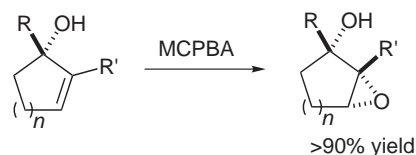
tiary allylic alcohols formed in this processes are valuable intermediates that can be further elaborated to provide rapid access to highly functionalized chiral building blocks.

Using the conditions outlined in Scheme 14, we found that conjugated cyclic enones underwent asymmetric alkylation with dimethyl- and diethylzinc affording the products in good to excellent enantioselectivities (Table 5).<sup>54</sup> Substrates with substituents  $\alpha$  to the carbonyl group gave outstanding enantioselectivities in the asymmetric addition reaction. The yields, however, were variable, ranging from 84% to 20%. In reactions that gave low yields, byproducts arising from aldol condensation/dehydration were again isolated. Conjugated enones lacking substituents in the  $\alpha$  position exhibited only moderate enantioselectivities in the asymmetric addition reaction. This result was expected, given the similarity of the lone pair environments.



**Scheme 14** Asymmetric addition of alkyl groups to cyclic enones.

The hydroxyl group is one of the most useful groups for directing subsequent transformations with high diastereoselectivity.<sup>55</sup> As shown in Scheme 15, epoxidation of the allylic alcohols with MCPBA cleanly afforded the *syn* epoxy alcohols in greater than 90% yield.

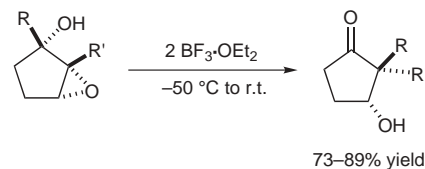


**Scheme 15** Epoxidation reactions gave very high diastereoselectivity.

**Table 5** Asymmetric Addition of Alkyl Groups to Cyclic Enones in the Presence of **12** (Scheme 14)<sup>54</sup>

Entry	Substrates	ZnR <sub>2</sub>	Yield (%)	ee (%)
1		R = Me	84	99
2		R = Et	76	98
3		R = Me	55	98
4		R = Et	65	96
5		R = Me	62	99
6		R = Et	50	99
7		R = Me	54	95
8		R = Et	40	95
9		R = Me	20	99
10		R = Et	32	99
11		R = Et	75	52
12		R = Et	50	61

The resulting epoxy alcohols undergo Lewis acid promoted semipinacol rearrangement (Scheme 16) to give  $\beta$ -hydroxy- $\alpha,\alpha$ -disubstituted ketones in good yields (Table 6). Depending on the substitution pattern, these compounds can contain chiral all-carbon quaternary centers. Densely functionalized chiral building blocks of this type would be challenging to prepare by other routes.



**Scheme 16**

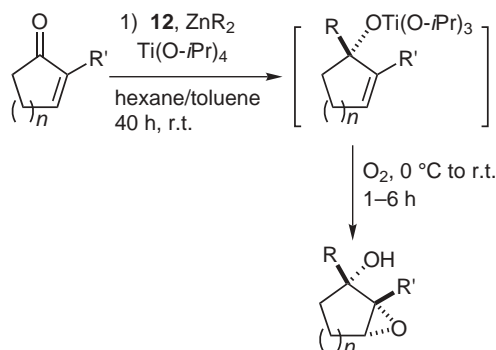
**Table 6** Lewis Acid Catalyzed Rearrangement of Epoxy Alcohols from Scheme 16<sup>54</sup>

Entry	Substrate	Product	Yield (%)	ee (%)
1			70	99
2			89	99
3			75	98
4			73	97

We have also developed a tandem, one-pot protocol for the enantioselective addition/diastereoselective epoxidation (Scheme 17). This procedure involves conducting the asymmetric addition reaction with an excess of Et<sub>2</sub>Zn. Once the starting material has been consumed, dioxygen is introduced into the reaction flask and a diastereoselective epoxidation of the alkene ensues. The yields of the two-step addition/epoxidation sequence are almost identical to those of the asymmetric addition reaction alone, suggesting that the epoxidation proceeds with high yield (Table 7).

The reaction of Et<sub>2</sub>Zn with dioxygen has been known for a long time.<sup>56</sup> The structure of the products of this reaction, however, are still the subject of ongoing research.<sup>57,58</sup> Nonetheless, the products of the reaction of oxygen with dialkylzinc reagents have been used in the epoxidation of electron deficient double bonds, such as  $\alpha,\beta$ -unsaturated enones<sup>59–62</sup> and nitro olefins.<sup>63</sup> We believe that our reaction is the first example of directed epoxidation of unactivated carbon-carbon double bonds with this oxidant. The

reaction likely proceeds through insertion of dioxygen into a Zn–C bond to give  $\text{EtZnOOEt}$ ,<sup>64</sup> which undergoes transmetalation to titanium and subsequent oxygen transfer to the allylic alkoxide.



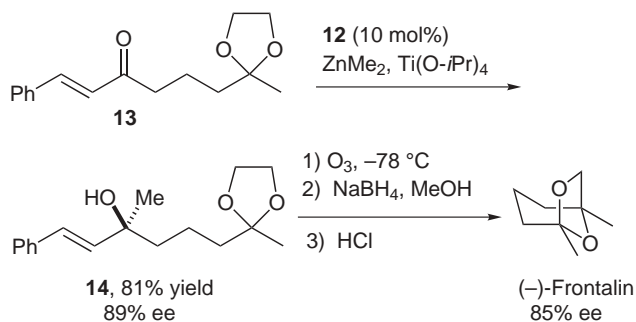
**Scheme 17** One-pot asymmetric addition/diastereoselective epoxidation sequence.

**Table 7** One-Pot Asymmetric Addition/Diastereoselective Epoxidation Sequence (Scheme 17)<sup>54</sup>

Entry	Substrates	ZnR <sub>2</sub> <sup>a</sup>	Yield (%)	ee (%)
1		R = Me	82	99
2		R = Et	80	99
3		R = Me	50	98
4		R = Et	60	97
5		R = Me	67	99
6		R = Et	60	99
7		R = Et	34	96

<sup>a</sup> For reactions with  $\text{Me}_2\text{Zn}$ , 1.5–2 equiv of  $\text{Et}_2\text{Zn}$  was added after complete ketone consumption.

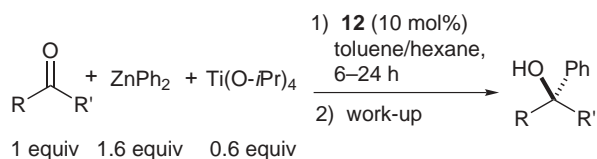
The enantioselective addition of alkyl groups to ketones has significant potential in asymmetric synthesis. A recent application of ligand **12** to the synthesis of (–)-frontalin has been reported.<sup>65</sup> As outlined in Scheme 18, the key step in the synthesis was the asymmetric addition of  $\text{Me}_2\text{Zn}$  to ketone **13**, which proceeded with 89% enantioselectivity, as expected based on the results in Table 4.



**Scheme 18** Synthesis of (–)-frontalin based on an asymmetric addition of  $\text{Me}_2\text{Zn}$  and catalyst generated from **12**.

#### 4 Asymmetric Phenylation of Ketones

As outlined in the introduction, the first catalyst to promote the asymmetric addition of  $\text{Ph}_2\text{Zn}$  to ketones was introduced by Dosa and Fu.<sup>18</sup> This (–)-DAIB-based catalyst exhibited yields ranging from 53–91% and enantioselectivities of 60–91% (Scheme 2, Table 1). In hopes of improving on these results, we employed ligand **12** in the asymmetric phenylation of ketones as illustrated in Scheme 19. Beginning with the conditions for the asymmetric addition of alkyl groups to ketones of Scheme 13, we examined various solvents, reagent stoichiometries, and temperatures. The optimal conditions involved a substoichiometric amount of  $\text{Ti}(\text{O}-i\text{Pr})_4$  (0.6 equivalents) in a mixture of toluene and hexanes at room temperature.<sup>66</sup>

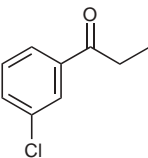
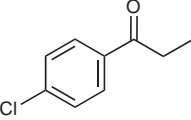
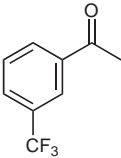
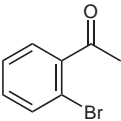
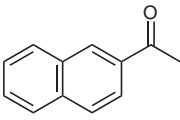
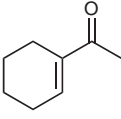
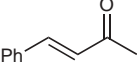
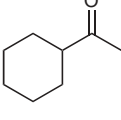



**Scheme 19** Asymmetric phenylation of ketones.

The results of our study are illustrated in Table 8. Propiophenone derivatives were good substrates, providing the ketone products in 99% yield and 88–92% enantioselectivity. Acetophenone derivatives were excellent substrates for this catalyst, exhibiting enantioselectivities between 95–96%. Conjugated enones underwent reaction with high levels of enantioselectivity (entries 6 and 7). Simple dialkyl ketones were good substrates for this catalyst. Cyclohexyl methyl ketone exhibited high enantioselectivity (87% ee) while 3-methyl-2-butanone provided the product in 75% ee.

During the preparation of our manuscript on phenyl additions to ketones, Yus and co-workers published a study involving phenyl addition to three 4-substituted acetophenone derivatives and 4-bromopropiophenone employing ligand **12** under different conditions.<sup>67</sup> Their enantioselectivities were similar to ours with the acetophenone derivatives (91–96%), but with 4-bromopropiophenone derivative the enantioselectivity was only

**Table 8** Results of the Asymmetric Phenylation of Ketones with  $\text{ZnPh}_2$ ,  $\text{Ti}(\text{O}-i\text{Pr})_4$ , and Ligand **12** (Scheme 19).

Entry	Substrate	Yield (%)	ee (%)
1		99	92
2		99	88
3		93	95
4		76	95
5		99	96
6		94	93
7		58	91
8		81	87
9		55	75

80%.<sup>67</sup> This substrate might give higher enantioselectivity under our conditions (Scheme 19).

The results in Table 8 on the phenylation of ketones compare favorably with those reported by Dosa and Fu. The catalyst derived from ligand **12** catalyzed the reaction with excellent enantioselectivities and yields in most cases.

## 5 Summary

This account describes the thought process and experimental observations behind our development of the first efficient and highly enantioselective catalyst for the addition of alkyl and phenyl groups to ketones. Some of the features that make this methodology attractive include: 1) the synthesis of either enantiomer of the ligand **12** is easily accomplished in two steps from commercially available materials, 2) the reactions are easy to perform and are carried out at room temperature, 3) many substrates give high enantioselectivities for the addition of alkyl and phenyl groups to ketones, 4) enantioenriched tertiary alcohols are difficult to prepare by other routes, 5) in several cases the chiral tertiary alcohol products can be easily elaborated, and 6) as many as three contiguous stereocenters can be generated with high enantio- and diastereoselectivity.

We are continuing our investigations of the scope of our catalyst based on ligand **12**. Studies to understand the mechanism of this catalyst are currently underway.

## Acknowledgment

We acknowledge our co-workers who participated in this chemistry and who's names appear in the reference section. We are grateful to the National Institutes of Health (National Institute of General Medical Sciences).

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