A Green Chemistry Approach to Asymmetric Catalysis: Solvent-Free and Highly Concentrated Reactions

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1. Introduction and Scope

In an age when organic chemists have shown that even the most complex natural and unnatural products can be synthesized,[1−3] the emphasis of synthetic chemistry is shifting to how they can be assembled in a truly practical fashion.[4−6] A pressing challenge facing organic chemists, therefore, is

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Patrick J. Walsh received his B.A. from UC San Diego (1986) where he was mentored by Prof. Charles Perrin. As a doctorial student, he studied organometallic chemistry with Prof. Robert G. Bergman at UC Berkeley (Ph.D., 1991). He was an NSF postdoctoral fellow with Prof. K. B. Sharpless at the Scripps Research Institute. Moving across town from 1994 to 1999, he became an assistant professor at San Diego State University and from 1996 to 1999 a professor at Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana (Mexico). In 1999, he moved to his current position at the University of Pennsylvania where he was promoted to associate professor in 2002 and professor in 2005. Walsh has received several awards, most recent of which was the 2006 Philadelphia Section Award of the ACS. Walsh's interests are in asymmetric reactions, development of new methods, reaction mechanisms, and inorganic chemistry.

Hongmei Li received her B.Sc. in chemistry at the Dalian University of Technology in 1999 and her M.Sc. degree in inorganic chemistry (2002) at the Peking University with Professor Jianhua Lin. She began her Ph.D. at the University of Pennsylvania under the direction of Professor Patrick J. Walsh in 2002, during which she worked on the catalytic asymmetric addition of organozinc reagents to ketones and application of bimetallic intermediates in organic synthesis. After graduation, she will work as a research scientist in the Department of Process Research at Merck & Co. Inc., Rahway, NJ.

to advance new processes that are not only efficient, selective, and high yielding but also environmentally friendly.[7,8] Historically, the metric of reaction success has been the yield. Although yields will remain imperative, alternative measures are the "greenness" of a reaction, or *E* factor,[9] and the volume productivity.[10] The *E* factor, introduced by Sheldon,[9] is defined as the ratio of weight of waste to weight of product, while the volume productivity is the grams of product per liter of reaction medium. The *E* factor for many pharmaceuticals has been estimated to exceed 100.[11,12] The largest contributors to the magnitude of *E* factor are organic solvents, many of which are ecologically harmful and require expensive remediation.

Cecilia Anaya de Parrodi received her B.Sc. in Chemistry at Universidad Iberoamericana in 1978. She has been working at Universidad de las Americas Puebla since 1980, where she was promoted to professor in 2002. She joined Henning Hopf's group at Technische Universität Braunschweig (Germany) as visiting scholar during 1986. She received her M.Sc. in Chemistry from Universidad Autonoma de Puebla with Professor L. Quintero in 1992 and her Ph.D. from CINVESTAV–IPN (Mexico City) with Professor E. Juaristi in 1997. Recently, she joined Patrick J. Walsh's group at University of Pennsylvania as visiting scholar during a sabbatical leave in 2003–2004 and as a Fulbright research scholar in 2005.

As global environmental legislation becomes stricter, consideration of environmental concerns must be addressed at early stages of product development. By doing so, project cost reductions of 50% or more have been realized.[13] Although steps toward sustainability can be made by reusing solvents, recycling is rarely accomplished with complete efficiency. An alternative strategy to reduce the *E* factor of reactions and their impact on the environment is to conduct them under solvent-free conditions.[11,14−16] Among the benefits of solvent-free processes are cost savings, decreased energy consumption, reduced reaction times, and a large reduction in reactor size and capital investment. As a result, introduction of solvent-free reactions, including solvent-free polymerizations,[14,17−20] radical additions,[14,21−24] ionic reactions,[25−31] solid-state reactions,[15,32−34] and photochemical reactions,[15,35−37] has increased steadily in recent years. Solvent-free catalytic enantioselective reactions, however, have received much less attention.

The paucity of catalytic asymmetric solvent-free reactions is not unexpected. Catalyst efficiency and enantioselectivity is frequently highly sensitive to the nature of the solvent.[38] Examples in which a catalyst can generate enantiomeric products with high levels of enantioselectivity in different solvents have been reported.[39] Moreover, enantioselectivities are often dependent on catalyst concentrations. Consequently, two of the most important variables for catalyst optimization, solvent properties and concentration, are eliminated under solvent-free conditions. Furthermore, under solvent-free conditions the reaction medium will change as reagents and substrates are converted to products. The impact of such changes is currently unpredictable, complicating reaction development. We believe that these limitations have dissuaded many investigators from considering solvent-free catalytic asymmetric reactions. The potential environmental benefits and the economic incentive, however, have created significant demand for such processes.

In response to these challenges, an increasing number of research groups are developing asymmetric catalysts for use under solvent-free or highly concentrated reaction conditions. The results of these studies have been mixed. In some cases,

catalysts that demonstrate excellent enantioselectivity and activity under standard solvent conditions exhibit lower selectivity in the absence of solvent. In contrast, other catalysts react with excellent levels of enantioselectivity and greatly increased activity, enabling significant reductions in catalyst loading under solvent-free conditions.

The potential advantages of asymmetric catalysis under solvent-free and highly concentrated reaction conditions have inspired this review. In turn, it is hoped that a comprehensive compilation of reports in this area will stimulate further investigations into solvent-free catalytic asymmetric reactions.

A significant body of research has been published concerning solvent-free organic synthesis, and the subject has been reviewed.[10,11,14,15,40] Solvent-free asymmetric catalysis, however, is a relatively new area, and we are not aware of reviews devoted to this topic. This review will cover small molecule catalyzed enantioselective reactions under solvent-free or highly concentrated reaction conditions up to the end of 2006. Additionally, we will include reactions of enantioenriched substrates with enantioselective catalysts in which the diastereoselectivity is catalyst controlled (not substrate controlled). We define solvent-free reactions as those employing less than 5 equiv of one reagent with respect to the substrate. The definition of highly concentrated reaction conditions used herein is those that utilize less than 5 equiv of solvent with respect to the substrate.

Despite amazing advances in chemistry database coverage, technology, and search engines, there are no straightforward ways to search the literature for "highly concentrated catalytic asymmetric reactions". Even reactions performed in the absence of solvent do not always contain the key words "solvent-free". The citations included herein come from extensive literature searches, scouring experimental sections and supporting information, and personal knowledge. Nonetheless, our apologies are extended to those who have made contributions in this area but whose work we missed.

2. Solvent-Free and Highly Concentrated Reactions in Asymmetric Catalysis

2.1. Epoxide-Opening Reactions

The catalytic asymmetric ring opening (ARO) of epoxides by nucleophiles can provide access to a variety of functionalized chiral building blocks that are of enormous utility in enantioselective organic synthesis.[41−45] In several cases, epoxide-opening reactions are also exemplary environmentally friendly processes in which all or nearly all of the atoms in the starting materials are present in the products; therefore, little or no waste is generated. Such processes have been classified as highly atom economical.[46,47]

The Jacobsen group has been actively investigating transition metal (salen)M(III)-based catalysts for the desymmetrization of *meso*-epoxides and the kinetic resolution of racemic epoxides via ARO reactions.[42] An important feature of (salen)M(III) catalysts is that a wide variety of complexes with diverse substitution patterns are easily synthesized, facilitating catalyst screening and reaction optimization.

The mechanisms of (salen)M-catalyzed epoxide-opening reactions have also been studied in detail and have provided significant insight into the operation of these highly efficient and enantioselective catalysts. The mechanistic understanding garnered by the Jacobsen group has allowed expedient optimization of both catalyst activity and enantioselectivity in epoxide-opening reactions. Most of the mechanistic studies have been conducted in common solvents, and it is assumed that the reaction mechanisms do not change significantly under solvent-free conditions.[42,48−53]

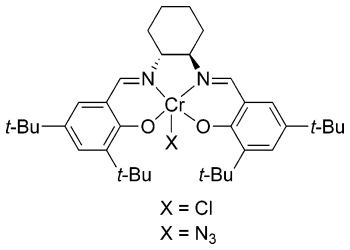
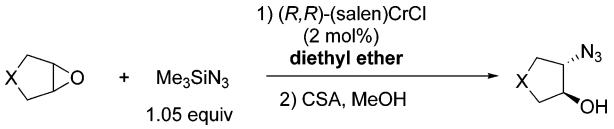


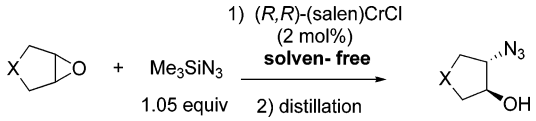
Figure 1. Jacobsen's (salen)CrCl precatalyst and (salen)CrN_3 catalyst for epoxide opening with trimethylsilyl azide. In this review, (salen)M will refer to a metal bound to this salen ligand unless otherwise stated.

Table 1. ARO of meso-Epoxides in Diethyl Ether with (*R,R*)-(salen)CrCl (Figure 1) as Precatalyst



entry	X	time (h)	isolated yield (%)	ee (%)
1	CH_2CH_2	18	80	88
2	CH_2	18	80	94
3	CH═CH	46	72	81

Table 2. ARO of *meso*-Epoxides under Solvent-free Conditions with (salen)CrCl (Figure 1) as Precatalyst Illustrating Catalyst Recyclability



cycle	X	time (h)	isolated yield (%)	ee (%)
1	CH_2CH_2	18	86	84
2	CH_2CH_2	21	88	87
3	CH_2CH_2	20	91	88
4	CH_2	4	81	94
5	CH═CH	18	75	83

2.1.1. Desymmetrization of meso-Epoxides

In pioneering studies, Jacobsen and co-workers reported the (salen)Cr(III)-catalyzed opening of *meso*-epoxides and the kinetic resolution of racemic terminal epoxides with trimethylsilyl azide.[49,51,54−67] The tetra-*t*-Bu-derived (salen)M complexes with the ligand illustrated in Figure 1 have proven so useful in solvent-free asymmetric catalysis[68] that (salen)M will refer to this ligand structure throughout this review unless otherwise mentioned.

Initial studies of ARO of *meso*-epoxides with (salen)CrCl precatalyst (Figure 1) were conducted in diethyl ether solvent.[54] A few representative examples are shown in Table 1 that demonstrate both the enantioselectivity and overall efficiency of this process. It was also reported that reactions could be conducted in the absence of solvent (Table 2).[54] Under solvent-free conditions, cyclic five- and six-membered epoxides underwent ring opening with 2 mol % (salen)CrCl and only a slight excess of Me_3SiN_3. After complete consumption of the epoxide, the reaction mixture was

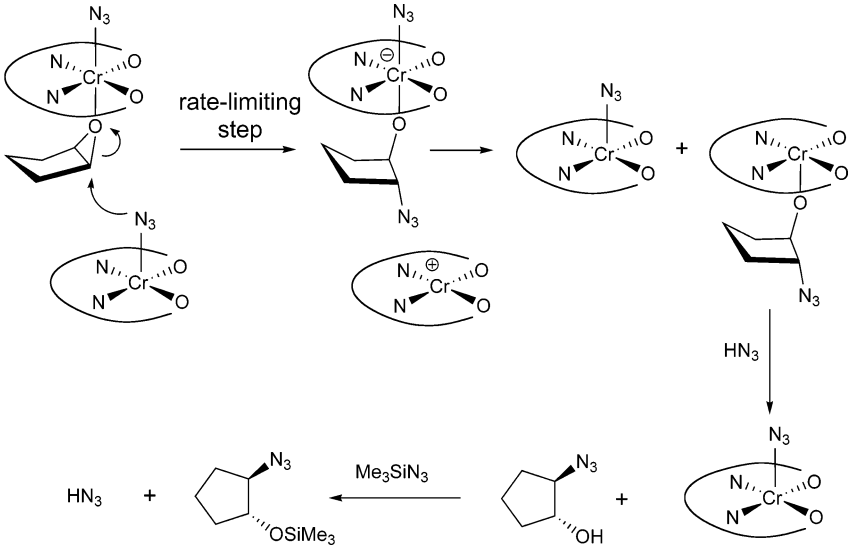
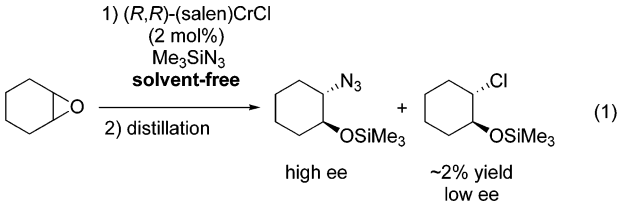


Figure 2. Key steps in the proposed mechanism of the ARO illustrating the bifunctional nature of the (salen)CrN_3 catalyst.

distilled under reduced pressure providing the ring-opened product in high purity. The catalyst can be easily recovered and reused for several cycles without loss of activity. For example, Table 2 illustrates the use of a single catalyst dose in three cycles with cyclohexene oxide (cycles one through three). In cycles four and five, cyclopentene oxide and 4,5-epoxycyclohexene were employed as substrates. In each case, isolated yields were ≥75% and enantioselectivities rivaled those outlined in reactions conducted with diethyl ether as solvent (Table 1).

2.1.2. Mechanistic Investigations and Implications for Solvent-Free Epoxide Opening

Insight into the mechanism of ARO with (salen)CrCl was first gained through product analysis,[54] where it was found that a chlorohydrin byproduct was generated in the initial stages of the reaction from epoxide opening by the chromium-bound chloride (eq 1). Elemental analysis of the recovered

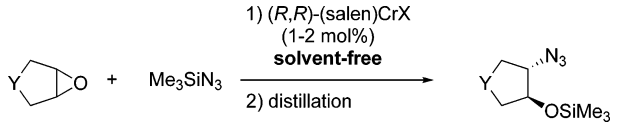


(1)

catalyst after completion of the reaction indicated the absence of chloride and a ratio of Cr/N of 1:5. The IR spectrum of the recovered catalyst contained a strong stretch at 2058 cm^{-1}, consistent with the formation of a chromium azide, $Cr-N_3$. In support of this proposal, (salen)$Cr(N_3)$(THF) has been isolated and characterized crystallographically.[51] Spectroscopic data support (salen)$Cr(N_3)$(epoxide) as the resting state of the active catalyst in the ARO, hinting that the catalyst activates the epoxide as well as the azide. Also of note, the reaction does not proceed in the absence of trace water, which is necessary to generate HN_3 from hydrolysis of Me_3SiN_3.

The dual role of the catalyst was confirmed by kinetic analysis, which indicated a second-order catalyst dependency, inverse order in epoxide, and zero order in azide. The key steps of the proposed mechanism are illustrated in Figure 2.

Table 3. Comparison of (salen)CrCl and (salen)CrN_3 in the Solvent-free Asymmetric Opening of *meso*-Epoxides



		% ee (% yield)[a]	
entry	Y	(salen)CrCl	(salen)CrN_3
1	CH_2	93 (97)	94 (99)
2	$(CH_2)_2$	85 (96)	88 (99)
3	O	97 (96)	97 (99)
4	$NCOCF_3$	95 (87)	95 (96)

[a] Scale: 25−50 mmol epoxide.

The second-order dependence on (salen)CrN_3 concentration has important practical implications. For example, decreasing the catalyst loading by 10-fold is predicted to result in *a 100-fold decrease in the rate of the reaction*. This drawback can be partially offset under solvent-free conditions, where the concentrations of the reagents and catalysts are maximized.

Guided by the results of the mechanistic studies, Jacobsen and co-workers proceeded to optimize the ARO reaction. To eliminate the chlorohydrin byproduct (eq 1) formed in conversion of the precatalyst (salen)CrCl to the catalyst (salen)CrN_3, (salen)CrN_3 was prepared synthetically.[55] A comparison of product ee from (salen)CrCl and (salen)CrN_3 was conducted under solvent-free conditions.[69] Direct application of (salen)CrN_3 resulted in slightly higher product ee's and yields than use of the precatalyst (salen)CrCl (Table 3). Also noteworthy is that these reactions were performed using 25−50 mmol of epoxide and generated important synthetic intermediates.

To overcome the second-order catalyst dependency of the ARO, tethered dimeric catalysts were used in diethyl ether to enforce the cooperative catalyst behavior (Table 4).[48] A kinetic study was performed and analysis of the rate data indicated that both intra- and intermolecular epoxide-opening pathways were in operation, and their ratio was dependent on the tether length. Dimers with $n = 2$ and 4 proceeded largely through intermolecular pathways, while catalyst with $n = 5$ exhibited the greatest intramolecular rate (Table 4).

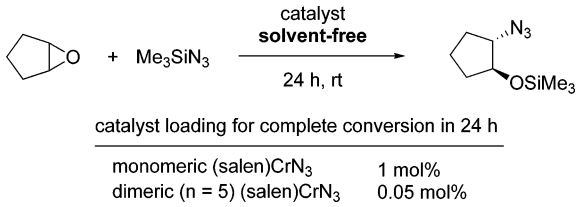
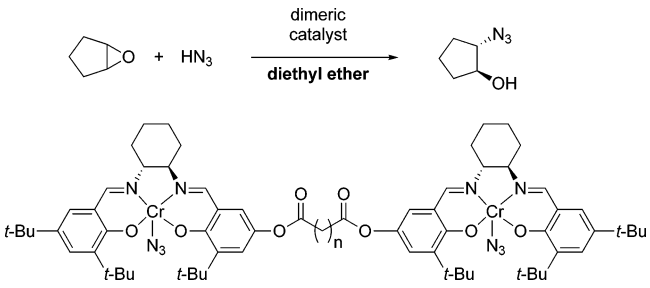


Figure 3. Comparison of catalyst loading with monomeric (salen)-CrN_3 and dimeric ($n = 5$) (salen)CrN_3 (from Table 4).

Table 4. Dimeric Catalysts with Tether Lengths between $n = 2$ and 10 Used in the ARO of Cyclopentene Oxide



n	ee (%)	k_{intra}[a] ($min^{-1} \times 10^{-2}$)	k_{inter} ($M^{-1}\ min^{-1}$)
2	90	4.4	15.7
4	90	5.4	15.1
5	93	42.9	27.4
6	93	31.7	15.8
7	93	20.9	7.9
8	94	14.7	10.5
10	92	3.8	4.4

[a] The rate constant k_{intra} is for the cooperative intramolecular pathway.

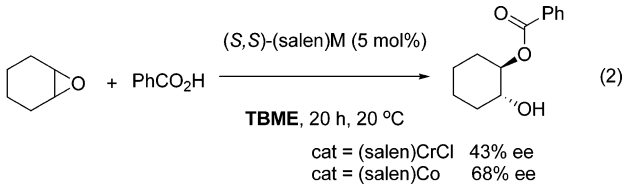
As the tether length is further increased, the ratio of intramolecular to intermolecular pathway decreases, presumably due to the increase in entropic cost with longer tethers.[48]

Based on these results, dimeric catalyst with $n = 5$ was compared with monomeric analogs in the solvent-free ARO (Figure 3). At 0.05 mol %, the dimeric catalyst promoted the ARO of cyclopentene oxide with Me_3SiN_3 in 24 h at room temperature, whereas the monomeric catalyst required a loading of 1 mol % to effect complete conversion under the same conditions.

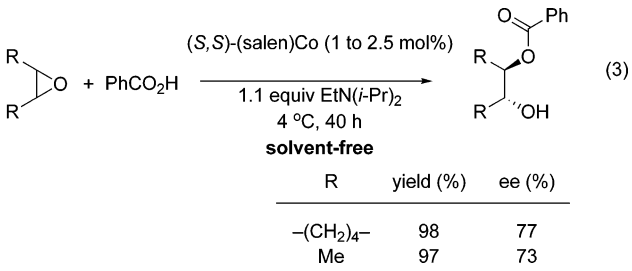
The ARO of *meso*-epoxides with trimethylsilyl azide is an important example of the design of environmentally friendly catalysts and reaction conditions. Not only can the reactions be conducted under solvent-free conditions, but the catalyst can be recycled and the products isolated by distillation. Furthermore, the highly enantioenriched products are very useful in the synthesis of biologically active molecules.[44,55,70−72]

2.1.3. ARO of meso-Epoxides with Benzoic Acid

In search of catalysts to promote the ARO of *meso*-epoxides with different nucleophiles, the Jacobsen group screened first row (salen)M complexes in the presence of benzoic acid.[58] It was found that the (salen)CrCl complex (5 mol %) promoted the ARO with 43% ee. In contrast, the cobalt analog, (salen)Co(II), promoted the ARO to give the ester product in 68% ee (eq 2). When the reaction was conducted in the presence of EtN(*i*-Pr)$_2$, the product ee increased, most likely due to the greater solubility of the benzoic acid in the *tert*-butyl methyl ether (TBME) in the presence of the amine.



The (salen)Co(II) complex was then employed in the solvent-free ARO with benzoic acid (eq 3). ARO with



R	yield (%)	ee (%)
$-(CH_2)_4-$	98	77
Me	97	73

cyclohexene oxide was conducted on multigram scale in the presence of 1 mol % catalyst, providing the product with 77% ee and 98% yield. While the product ee was moderate, a single recrystallization afforded the product with 98% ee in 75% isolated yield. Use of *cis*-2-butene oxide as substrate under solvent-free conditions furnished the product with 73% ee in 97% yield.

The products of the ARO of *meso*-epoxides with benzoic acid can be readily hydrolyzed to chiral diols, which are useful ligands in asymmetric catalysis and valuable building blocks in synthesis. The active catalyst in this reaction, as well as others introduced in the next sections, is generated by oxidation of the (salen)Co(II) to (salen)Co(III) by oxygen.

While the ARO of *meso*-epoxides represents elegant research that formed the basis of several other synthetically important reactions, it is limited to *meso*-epoxides. These substrates form a relatively small subset of epoxides. As will be outlined in the next sections, the kinetic resolution of epoxides enables the isolation of a broader range of chiral building blocks with high ee.

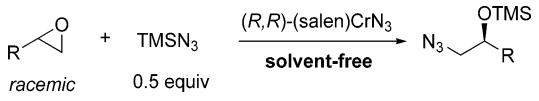
2.2. Reactions with Racemic Epoxides

2.2.1. Kinetic Resolution of Epoxides with Me_3SiN_3

The stereospecific nucleophilic ring opening of enantioenriched epoxides allows access to a wealth of chiral building blocks. As such, much effort has been invested in the direct enantioselective synthesis of epoxides and considerable progress has been made.[73−78] Nonetheless, certain classes of epoxides remain difficult to prepare enantioselectively. Highly enantioenriched terminal epoxides, which are probably the most synthetically challenging, are also among the most useful due to the high stereoselectivity with which they undergo nucleophilic ring opening.

Difficulties with direct enantioselective methods for the synthesis of epoxides have led researchers to examine methods for kinetic resolution of these substrates. The well-known drawback of resolution is that the maximum yield is 50%. This disadvantage, however, can be relatively minor when compared with the benefits of kinetic resolutions.[79−81] If the desired compound is the resolved starting material, it is relatively easy to control its ee simply by allowing reaction conversion to exceed 50%. Even in cases where the catalyst is only moderately enantioselective, starting material of high enantiopurity can be obtained. For example, if the relative

Table 5. Kinetic Resolution of Racemic Terminal Epoxides with Me_3SiN_3 Catalyzed by (*R,R*)-(salen)CrN_3 under Solvent-free Conditions



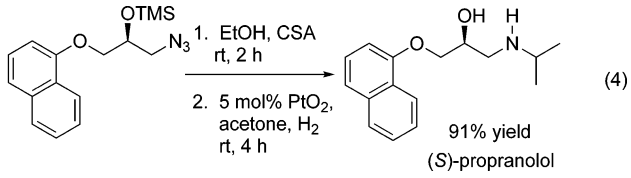
entry	R	cat. mol %	yield (%)[b]	ee (%)	k_{rel}
1	CH_3	1.0	98	97	230
2	CH_2CH_3	2.0	83	97	140
3	$(CH_2)_3CH_3$	2.0	89	97	160
4	$CH_2OTBDMS$	3.0	96	96	150
5	CH_2O(1-naphthyl)	5.0	74	93	48
6	$CH_2C_6H_5$	2.0	94	93	71
7	*c*-C_6H_{11}	2.0	84[c]	97	140
8	$(CH_2)_2CH{=}CH_2$	2.0	94	98	280
9	$CH(OEt)_2$	2.0	96	89	44
10	CH_2CN	2.0	80	92	45

[a] Reactions were run without solvent for 18−50 h at 0−2 °C. [b] Isolated yield of the azido silyl ether based on $TMSN_3$. [c] Isolated yield of the azido alcohol.

rate of the fast to slow reacting substrate ($k_{rel} = k_{fast}/k_{slow}$) is 10, the slower reacting starting material can be recovered in 95% ee and up to 34% yield. Of course, if k_{rel} is higher, the reaction can be quenched at lower conversion, providing greater yield of the recovered starting material.

Initial studies by the Jacobsen group in the kinetic resolution of terminal epoxides employed (salen)CrN_3.[54] Thus, reaction of racemic propylene oxide with 0.5 equiv of Me_3SiN_3 in the presence of 1 mol % (*R,R*)-(salen)CrN_3 at 0 °C in the absence of solvent gave a mixture of the azide product and propylene oxide. Removal of the volatile epoxide and distillation of the product furnished the azidoalcohol in near quantitative yield with 97% ee (Table 5, entry 1). The relative rate of the fast reacting enantiomer to the slow reacting enantiomer (k_{rel}) for the resolution of propylene oxide was determined to be >200. As outlined in Table 5, other substrates also exhibited very high k_{rel} values (44−280), and the ring opened products could be isolated with excellent ee's.[56]

The azidoalcohols synthesized in the KR reaction are very useful chiral building blocks for the synthesis of biologically important molecules, as exemplified by the synthesis of (*S*)-propranolol, a widely used anti-hypertensive agent (eq 4),



(4)

and the synthesis of an enantioenriched amino alcohol used in the synthesis of (*R*)-9-[2-(phosphonomethoxy)propyl]-adenine (PMPA), which displays prophylactic activity against simian immunodeficiency virus (SIV) infections (Figure 4).[56]

Terminal epoxides are excellent substrates for kinetic resolution reactions employing (salen)M-based catalysts. In contrast, chiral 2,2-disubstituted epoxides are less reactive and fail to undergo ARO with (salen)Co-based catalysts. These more sterically hindered epoxides do react with azide in the presence of (salen)CrN_3. Most of the substrates examined exhibited excellent relative rates and afforded product in ≥97% ee and ≥42% yield when TBME was

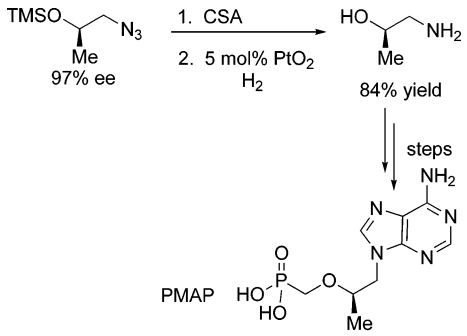
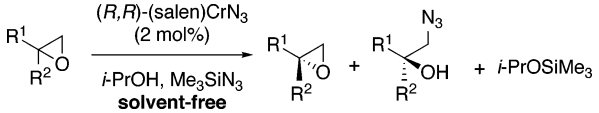
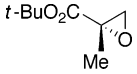
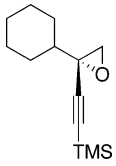


Figure 4. Application of enantioenriched azidoalcohol to the synthesis of (*R*)-9-[2-(phosphonomethoxy) propyl]adenine (PMPA).

Table 6. Kinetic Resolution of Racemic 2,2-Disubstituted Epoxides under Solvent-free Conditions

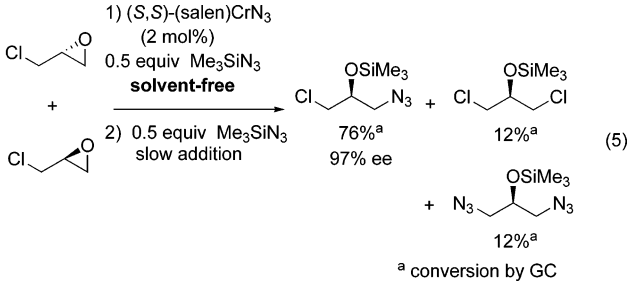


Me_3SiN_3 (equiv)	*i*-PrOH (equiv)	yield (%)	ee (%)	epoxide product
0.55	0.55	46	85	
0.70	0.70	48	80	

employed as solvent (not shown).[82] Certain substrates, however, gave better results when ARO was conducted under solvent-free conditions (Table 6).

2.2.2. Dynamic Kinetic Resolution of Epichlorohydrin

Kinetic resolutions, such as those outlined above, can be very effective for the preparation of organic compounds, particularly if the starting materials are readily available, k_{rel} is high, and the resolved starting material and product are easily separated.[79] Dynamic kinetic resolutions (DKR)[83,84] are more desirable, however, because it is possible to obtain highly enantioenriched product in significantly greater than the maximum yield in a kinetic resolution (50%). A rare example of a solvent-free DKR is the ARO of racemic epichlorohydrin, which provided the densely functionalized azidoalcohol in 76% yield and 97% ee after optimization (eq 5).[57] In the initial investigations of this reaction, full



(5)

conversion to the azidoalcohol was observed, but the ee was low (40%). It was hypothesized that ARO of the slow reacting epichlorohydrin enantiomer was competitive with

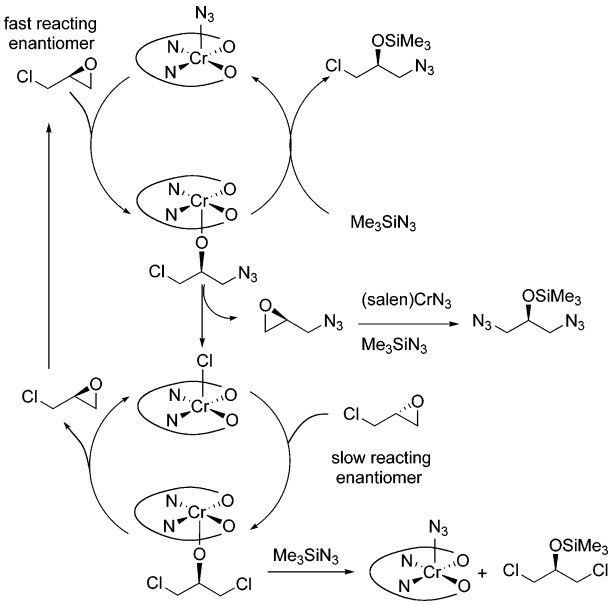


Figure 5. Proposed mechanism for the dynamic kinetic resolution of epichlorohydrin.

its racemization. To increase the rate of racemization relative to ARO, the Me_3SiN_3 was added in two portions. The first 0.5 equiv was combined with the epichlorohydrin to initiate the ARO. After the first 0.5 equiv of Me_3SiN_3 had reacted, most of the slow reacting epoxide remained. The second dose of Me_3SiN_3 was added slowly over 16 h to reduce the rate of the ARO with respect to the racemization.

Analysis of the reaction products provided insight into the DKR (eq 5). A mechanism that accounts for the formation of the 1,3-dichloro and 1,3-diazido byproducts is illustrated in Figure 5. It has been shown that the ARO with (salen)-CrN_3 results in the formation of an alkoxide intermediate (upper cycle).[48] This unsymmetrical alkoxide can react with Me_3SiN_3 to produce the desired azidoalcohol and regenerate the catalyst via the upper cycle. It can also undergo ring closure to generate the azidoepoxide and (salen)CrCl. Ring opening of the azidoepoxide by (salen)CrN_3 leads to the 1,3-diazide byproduct. The (salen)CrCl initiates the racemization of epichlorohydrin in the lower cycle. Ring opening of epichlorohydrin by (salen)CrCl generates a 1,3-dichloro alkoxide intermediate that can close to give either enantiomer of epichlorohydrin or undergo reaction with Me_3SiN_3 to regenerate (salen)CrN_3 and the 1,3-dichloro product. As outlined in the proposed mechanism, the formation of the byproducts is intimately tied to the DKR process and has been difficult to suppress while maintaining high ee.[57]

The densely functionalized product of the DKR is a useful chiral building block for the synthesis of enantioenriched biologically active compounds, such as U-100592, a promising antibacterial.[57]

2.2.3. Hydrolytic Kinetic Resolution of Epoxides

The kinetic resolution of terminal epoxides with (salen)-CrN_3 and Me_3SiN_3 is an excellent method to prepare useful enantioenriched 1-azido-2-alcohols; however, it has several drawbacks. One disadvantage is that it is difficult to prepare resolved epoxides with this method. Also, Me_3SiN_3 is too costly to make the epoxide resolution economically feasible for all but high value epoxides. Finally, there is some concern about the thermal stability of the azidoalcohol byproduct, especially on large-scale resolutions. For these reasons, the search for more practical methods for the solvent-free and highly concentrated kinetic resolution of epoxides was undertaken.

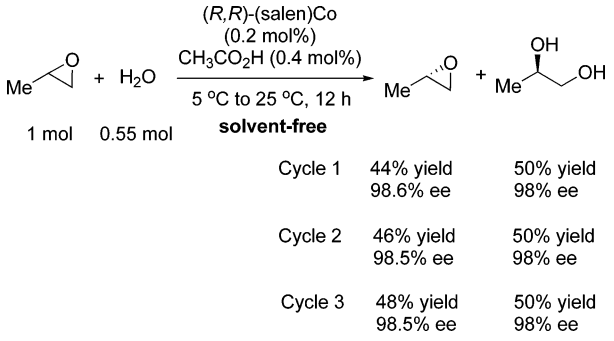


Figure 6. HKR of propylene oxide illustrating catalyst recycling.

In 1997, Jacobsen and co-workers reported a major breakthrough in the isolation of terminal epoxides with high enantioselectivity. It was found that water could serve as a nucleophile in the presence of catalytic (salen)Co(OAc) to open epoxides (Figure 6), giving rise to the hydrolytic kinetic resolution (HKR).[59]

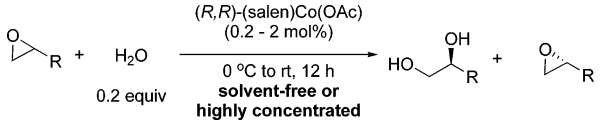
The HKR provides direct access to both unreacted epoxide and 1,2-diol products in high enantiomeric excess and yield. Many HKR processes are conducted under solvent-free conditions by combining the catalyst with slightly more than 0.5 equiv of water if the epoxide is the desired product. If the diol is desired, just under 0.5 equiv of water is needed. Due to the low water solubility of epoxides with hydrophobic substituents, many reactions are conducted by combining the epoxide with a suitable solvent (1:1 v/v) for the HKR. Under these conditions, a minimal amount of solvent is employed, and the reaction mixture is highly concentrated.

As an example of the HKR, the resolution of propylene oxide is outlined in Figure 6.[59] Preformed (salen)Co(OAc) (0.2 mol %) and propylene oxide were combined and cooled to 0 °C, and water was added. The reaction was stirred for 14 h at room temperature, and then the reaction mixture was distilled. The volatile epoxide was distilled at atmospheric pressure and the diol at 65 °C and 0.25 Torr, allowing facile separation of the mixture. The HKR of propylene oxide represents a special case, because both the epoxide and diol product are relatively volatile and can be distilled from the catalyst. The remaining catalyst residue is reactivated by addition of acetic acid and can be recycled without loss of activity or enantioselectivity for three cycles (Figure 6). It is also noteworthy that the HKR of propylene oxide has been performed on large scale (>200 kg).[42]

Many terminal epoxides have been tested in HKR, and the reaction has been found to be incredibly general and tolerant of functionality. The results of extensive studies will be succinctly summarized here. Table 7 contains k_{rel} values. Recovered resolved epoxide ee's and yields are given in the text. Aliphatic epoxides with small to sterically demanding substituents (Me to *t*-Bu) are excellent substrates for HKR (Table 7, enties 1−7). The resolved epoxides could be isolated in 82−92% of the theoretical yield (41−46% yield based on racemic epoxide) in ≥99% ee. While some substrates underwent HKR under solvent-free conditions, lipophilic epoxides with low solubility in water gave better results with a small amount of solvent (highly concentrated conditions).[66]

Halogenated epoxides (Table 7, entries 8−11), ether containing epoxides (Table 7, entries 12−16), and carbonyl

Table 7. Measured k_{rel} Values for a Series of Epoxides under Solvent-free and Highly Concentrated Reaction Conditions



entry	epoxide substituent	conv. (%)[c]	diol ee (%)	k_{rel}
	Aliphatic Epoxides			
1[a]	CH_3	19	99.5	500
2[a]	$(CH_2)_3CH_3$	19	99.2	310
3[b]	$(CH_2)_{11}CH_3$	18	99.5	490
4[b]	$(CH_2)_2CH{=}CH_2$	20	99.4	420
5[b]	CH_2Ph	20	97.4	96
6[b]	*c*-C_6H_{11}	19	99.6	630
7[b]	*t*-C_4H_9	16	97.0	79
	Halogenated Epoxides			
8[b]	CH_2Cl	20	98.7	190
9[b]	CH_2Br	20	96	49
10[a]	CH_2F	17	98	120
11[a]	CF_3	18	99.6	620
	Epoxides Bearing Ether and Carbonyl Functionality			
12[b]	CH_2OBn	20	97	83
13[b]	CH_2OTBS	18	99	250
14[b]	CH_2OPh	18	98	120
15[b]	CH_2O(1-naphthyl)	20	99	250
16[b]	CH_2CH_2OBn	19	97	82
17[b]	oxiranyl[d]	20	98	130
18[b]	CH_2OCO*n*-C_3H_7	54	99.4	68
19[b]	CH_2CO_2Et	20	98	130
20[b]	CH_2NHBoc	18	74	7.8
21[b]	CO_2CH_3	19	98	120
22[b]	$COCH_3$	18	97	81
23[b]	$COCH_2CH_3$	18	96	60
	Aryl, Vinyl, and Alkynyl Epoxides			
24[b]	C_6H_5	20	98	130
25[b]	4-ClC_6H_4	18	97	81
26[b]	3-ClC_6H_4	17	98	120
27[b]	3-$(CH_3O)C_6H_4$	19	98	120
28[b]	3-$(NO_2)C_6H_4$	19	99	280
29[b]	2-ClC_6H_4	18	98	120
30[b]	$CH{=}CH_2$	18	98	120
31[b]	CCTBS	19	99.4	420

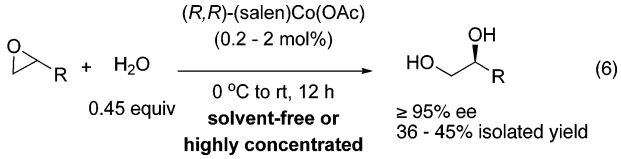
[a] Solvent-free. [b] Highly concentrated with epoxide/THF = 1:1 v/v ratio. [c] Isolated yield of 1,2-diol. [d] The substrate was *d,l*-butadiene diepoxide.

containing epoxides (bearing esters, ketones, and carbamates) (Table 7, entries 17−23) were all excellent substrates for HKR. Terminal epoxides bearing unsaturated C−C bonds, such as styryl, vinyl, and alkynyl derivatives (Table 7, entries 24−31) proved to be useful substrates in HKR, affording valuable epoxides with ≥99% ee in 36−44% yield (based on racemic epoxide).

Isolation of the product of a kinetic resolution, however, is more complicated because the product ee *decreases with increasing reaction conversion*. Nonetheless, with high k_{rel} values, products of very high ee can be isolated at yields approaching 50%. As outlined above, with k_{rel} of 10, starting material of 95% ee can be obtained in up to 34% yield. To obtain product with identical ee and yield, a k_{rel} value of 63 is necessary![66]

The k_{rel} values of a variety of epoxides were determined in the HKR as outlined in Table 7. In a kinetic resolution, the ee's of both the starting material and the product change with conversion. Thus, to describe a kinetic resolution with product ee's is not as informative as characterization by k_{rel} values. In the determination of k_{rel} values in Table 7, 0.2 equiv of water was employed.

The use of the HKR under solvent-free and highly concentrated conditions to isolate enantioenriched diols is illustrated in eq 6. In almost all cases, diol ee's exceeded



95% and isolated yields ranged from 36−45% (based on racemic epoxide).

Detailed investigations into the mechanism of the HKR by Nielsen, Stevenson, Blackmond, and Jacobsen[50] not only have provided insight into cooperative interactions between (salen)Co(III) complexes but have led to an improved catalyst for the solvent-free process. When (salen)CoCl is employed, it rapidly reacts with epoxide and water to generate (salen)Co(OH), which also serves as a Lewis acid to activate the epoxide. In contrast, with less nucleophilic counterions, such as acetate and tosylate, the reaction of the counterion with the epoxide is slower (Figure 7). The more Lewis acidic complexes (salen)Co(OAc) and (salen)Co(OTs) not only activate the epoxide more strongly, increasing its reactivity, but also exhibit greater binding constants for epoxide coordination. Thus, while the catalyst does play a dual role in the epoxide ring-opening reactions, the optimal characteristics of each (salen)Co(III) component are not identical. By way of comparison, when the precatalyst has been converted entirely to Co−OH, the HKR is up to *30 times slower* than when (salen)Co−OH and (salen)Co-OTs are both present. Under ideal conditions, the ratio of (salen)Co(OH) to (salen)Co(OTs) is 1:1. Comparison of the improved catalyst (salen)Co(OTs) to (salen)Co(OAc) in the HKR of several epoxides is illustrated in Table 8.

In summary, HKR with (salen)Co(III) displays an extraordinary scope, as a wide assortment of sterically and electronically varied epoxides can be resolved to 99% ee. The HKR has several appealing features from a practical standpoint, including the use of H_2O as a reagent, low loadings of a recyclable and commercially available catalyst, high yield and selectivity, low reagent cost, and low reagent toxicity. The ability to conduct reactions under solvent-free and highly concentrated reaction conditions results in high volumetric productivity and low waste generation. These characteristics make HKR attractive for large-scale applications.

2.2.4. Oligomeric (salen)Co(III) Catalysts for the HKR

Like the ARO of *meso*-epoxides by (salen)CrN_3 catalysts, the HKR with (salen)Co(III) catalysts proceeds by a cooperative bimetallic mechanism wherein one molecule of catalyst activates the epoxide and the second activates the water in the form of a (salen)Co(OH). As outlined previously, such second-order behavior in catalyst concentration results in dramatically increased reaction times as the catalyst loading is reduced. The catalyst loading of monomeric (salen)Co(III) used in the HKR of terminal epoxides, while relatively low (0.2−2 mol %), remains the primary cost determinant in the HKR. To circumvent this limitation, several cyclic oligomeric catalysts were prepared and

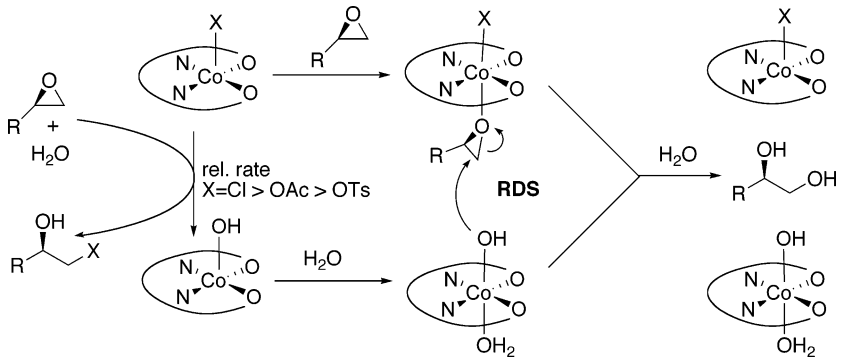
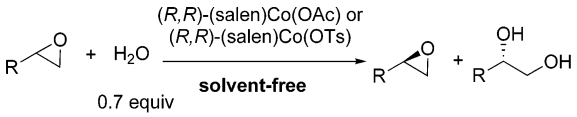


Figure 7. Mechanism of the HKR illustrating the dual roles of the (salen)Co(III) centers.

Table 8. Comparison of the HKR with (salen)Co(OAc) and (salen)Co(OTs) with Various Epoxides



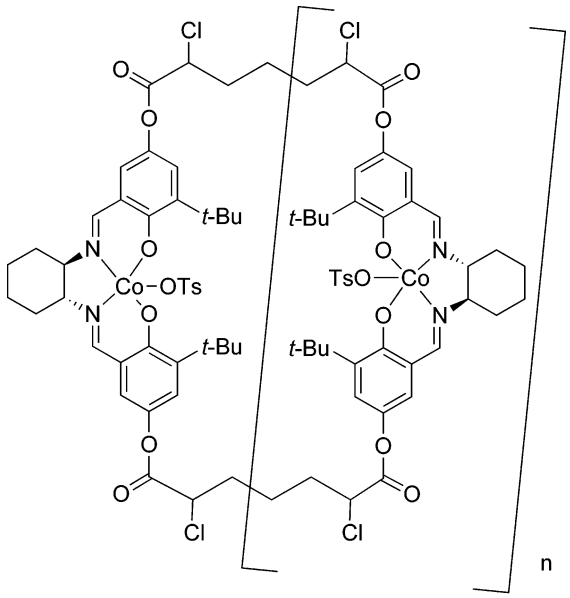
epoxide	catalyst	catalyst (mol%)[a]	time (h)	yield (%)[b]
n-Bu	(salen)Co(OAc)	0.5	16	43
	(salen)Co(OTs)	0.15	3	44
	(salen)Co(OTs)	0.05	16	45
t-Bu	(salen)Co(OAc)[c]	2.0	48	40
	(salen)Co(OTs)[c]	1.2	48	39
Cl	(salen)Co(OAc)	0.5	16	43
	(salen)Co(OTs)	0.2	16	42
MeO_2C	(salen)Co(OAc)	2.0	24	43
	(salen)Co(OTs)	0.5	16	42
BnO	(salen)Co(OAc)	0.5	16	47
	(salen)Co(OTs)	0.06	16	45

[a] Catalyst loading based on racemic epoxide. [b] Isolated yield of >99% ee epoxide based on racemate (theoretical maximum 50%). [c] Reaction at 0−4 °C.

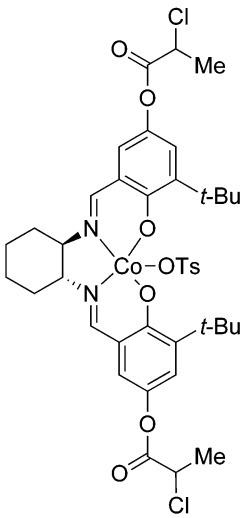
examined in the HKR of racemic epoxides under solvent-free and highly concentrated conditions.

Initial cyclic oligomeric catalyst structures are illustrated in Figure 8, along with a monomeric model system prepared for the purpose of comparison. The stereocenters on the tethers are random and give rise to diastereomeric catalyst mixtures. The reactivity of the oligomeric catalyst mixture was compared with the monomeric model system from Figure 8 in the challenging ARO of cyclohexene oxide under highly concentrated reaction conditions (Figure 9).[85] With 1.5 mol % loading of cobalt metal centers, the oligomeric catalyst reached completion in 11 h while the monomeric model system required 80 h. The enhanced reactivity of the oligomeric catalyst was attributed to the increase in effective molarity of the cobalt centers due to the tethering of the (salen)Co(III) units. Surprisingly, the oligomeric catalyst also exhibited much higher enantioselectivity (94%) than the monomeric model catalyst (49% ee). The remarkable increase in enantioselectivity of the oligomeric catalyst is likely due to the constrained orientation of the two reacting cobalt centers in the oligomeric catalyst system.

The positive effects of tethering on enantioselectivity and reactivity were encouraging with cyclohexene oxide, leading to examination of four racemic substrates in the HKR under solvent-free or highly concentrated conditions (Table 9).[85] The practicality of the oligomeric catalyst in Figure 8 is highlighted in entry 1. With 0.5 mol of epichlorohydrin and 0.3 mol of water, the HKR was performed at room temperature with only 50 mg of the oligomeric catalyst. After 11 h, the epoxide was vacuum transferred from the reaction

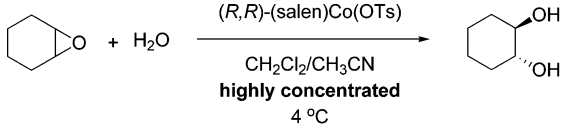


oligo-(*R,R*)-(salen)Co(OTs)
n = 1 - 5



model-(*R,R*)-(salen)Co(OTs)

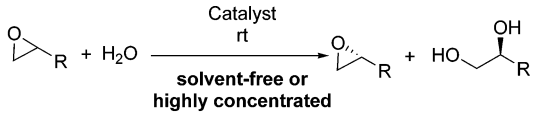
Figure 8. Structures of oligomeric Co(III) catalysts and a monomeric model system for the ARO of epoxides.

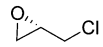
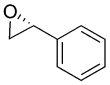
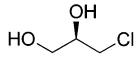
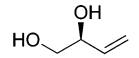
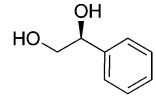
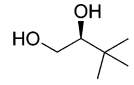


catalyst (1.5 mol% Co)	ee (%)	time (h)
oligo-(*R,R*)-(salen)Co(OTs)	94	11
model-(*R,R*)-(salen)Co(OTs)	49	80

Figure 9. Comparison of the ARO of cyclohexene oxide with oligomeric and monomeric model catalysts from Figure 8.

Table 9. Catalyst Comparison in the HKR of Terminal Epoxides with the Oligomeric Catalyst (Figure 8) and the Standard (*R,R*)-(salen)Co(OAc)



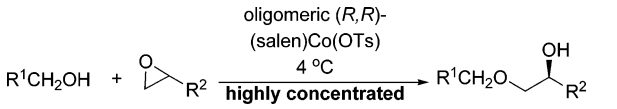
entry	isolated product	catalyst	Co (mol%)[a]	time (h)	% yield[f] (% ee)
epoxides[g]					
1[b]		monomer	0.5	18	42 (99)
		oligomer	0.01	11	45 (99)
2[c]		monomer	0.85	68	26 (99)
		oligomer	0.05	24	36 (99)
3[d]		monomer	0.8	72	44 (99)
		oligomer	0.08	24	37 (99)
4[e]		monomer	2.0	48	41 (99)
		oligomer	0.1	24	41 (99)
diols[g]					
5[d]		monomer	2.0	24	50 (96)
		oligomer	0.01	1.5	40 (97)
6[d]		monomer	0.64	20	49 (94)
		oligomer	0.03	4	46 (97)
7[d]		monomer	0.8	12	41 (98)
		oligomer	0.08	4	43 (96)
8[d]		monomer	2.0	20	40 (95)
		oligomer	0.05	18	49 (95)

[a] Loading on a Co basis relative to racemic epoxide. [b] Solvent-free. [c] Highly concentrated reaction using butyronitrile as solvent. [d] Highly concentrated reaction using 1:1 CH_2Cl_2/CH_3CN as solvent. [e] Highly concentrated reaction using 1,2-hexanediol as solvent. [f] Isolated yield based on racemic epoxide. [g] For reactions in which resolved epoxide was targeted, 0.55−0.60 equiv of H_2O was used for the resolution. For recovery of diol, 0.45 equiv of H_2O was employed.

mixture and filtered through a pad of $MgSO_4$ to remove the excess water, furnishing 23 g of epoxide (45% yield, >99% ee). As outlined in Table 9, use of the oligomeric catalyst allowed a 10- to 50-fold decrease in the cobalt loading with a simultaneous reduction of up to a factor of 16 in reaction time.

The oligomeric catalyst was also employed in the kinetic resolution of epoxides, using alcohols as the reacting partner (Table 10). Under highly concentrated conditions, a variety of primary alcohols participated in epoxide-opening reactions to afford monoprotected alcohols with high levels of regio- and enantioselectivity (94−99% ee). In most cases, yields were high, catalyst loading was low, and reaction times were 3−24 h. These results represented the first kinetic resolution of epoxides using alcohols as nucleophiles.[85]

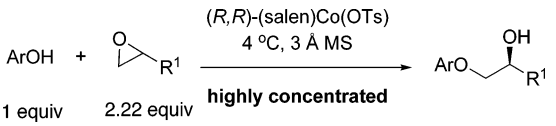
Table 10. Kinetic Resolution of Epoxides with Alcohols Using the Oligomeric Catalyst from Figure 8



entry[a]	R^1	R^2	Co (mol %)[b]	yield (%)[c,d]	ee (%)
1	Ph	$(CH_2)_3CH_3$	2.0	87	98
2	CH_2TMS	$(CH_2)_3CH_3$	0.2	97	99
3	H	$(CH_2)_3CH_3$	0.1	96	94
4	2-C_6H_4-Br	$(CH_2)_3CH_3$	0.1	99	99
5	4-C_6H_4-OMe	$(CH_2)_3CH_3$	2.0	62	94
6	2-C_6H_4-NO_2	$(CH_2)_3CH_3$	0.5	98	99
7	$CH{=}CH_2$	$(CH_2)_3CH_3$	0.5	87	97
8	Ph	CH_2Cl	2.0	91	98
9	Ph	CH_2O(allyl)	2.0	95	98

[a] Reactions were carried out with 5 M substrates in CH_3CN. [b] Catalyst loading on a per Co basis relative to alcohol. [c] Isolated yields based on RCH_2OH. [d] Reaction times 3−24 h.

Table 11. Comparison of the Oligomeric Catalyst from Figure 8 and the (salen)Co(OTs) in the Kinetic Resolution of Epoxides with Phenol Derivatives



entry	Ar	R^1	(*R,R*)-cat.	Co (mol %)[c]	yield (%)[d,e]	ee (%)
1	Ph	CH_2Cl	(salen)Co(OTs)[a]	4.0	96	99
			oligomer[b]	0.25	99	99
2	2-C_6H_4-(Oallyl)	CH_2Cl	(salen)Co(OTs)[a]	4.4	48	84
			oligomer[b]	0.25	99	98
3	Ph	Ph	(salen)Co(OTs)[a]	4.0	*f*	*h*
			oligomer[b]	1.0	60	97
4	Ph	*c*-hexyl	(salen)Co(OTs)[a]	8.0	89	94
			oligomer[b]	0.5	99	98
5	2-C_6H_4-Cl	*n*-Bu	(salen)Co(OTs)[a]	4.0	80[g]	68
			oligomer[b]	0.8	98	99

[a] Five molar substrates in TBME. [b] Five molar substrates in CH_3CN. [c] Catalyst loading on a per Co basis relative to ArOH. [d] Isolated yields based on ArOH. [e] Reaction times 4−24 h unless otherwise noted. [f] After 10 days, 63% conversion; 2:3 mixture favoring internal attack. [g] Seventy-two hour reaction time. [h] Not determined.

Kinetic resolution of terminal epoxides using phenol derivatives as nucleophiles provides α-aryloxy alcohols with high ee's. A comparison of the reactivity and enantioselectivity of the oligomeric (salen)Co(OTs) catalyst with the parent (salen)Co(OTs) was performed and is outlined in Table 11.[85] The oligomeric catalyst is significantly more reactive, as judged by entries 2 and 3, and in some cases is also more enantioselective.

Kinetic experiments with racemic 1,2-epoxyhexane, 2-chlorophenol, and the oligomeric catalyst indicated that the ring opening was first order in cobalt catalyst, consistent with an intramolecular ring opening. Such behavior can be contrasted with the second-order dependence observed for the monomeric (salen)Co(OTs). These results indicate that the epoxide opening with the oligomeric catalyst occurs in an intramolecular fashion via a cooperative mechanism involving at least two cobalt centers.

The primary drawback of the oligomeric catalyst system in Figure 8 is its hydrophobic character, which resulted in

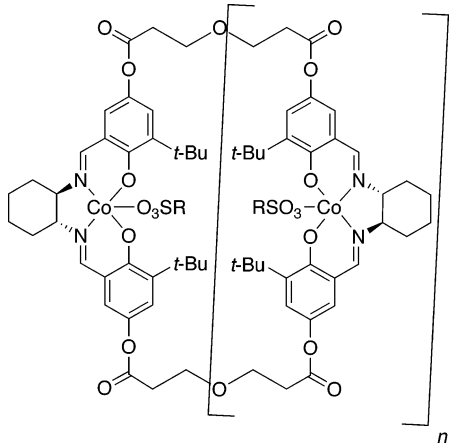
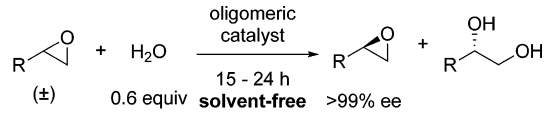
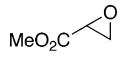
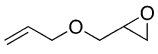


Figure 10. Next generation soluble oligomeric catalyst for the HKR of terminal epoxides (R = CF_3, 3-NO_2−C_6H_4).

Table 12. HKR of Terminal Epoxides Catalyzed by Oligomeric (salen)Co(O_3SR) from Figure 10



entry	epoxide	(salen)Co(O_3SR) R =	catalyst loading (mol%)	yield[a] (%)
1		CF_3	0.015	44
2		CF_3	0.0025	43
3		CF_3	0.001	44
4		CF_3	0.0003	40
5		3-NO_2-C_6H_4	0.04	40

[a] Isolated yields based on racemic epoxides (theoretical maximum = 50%).

limited solubility in the epoxide−water mixtures of the HKR. The solubility properties of the chlorinated oligomer required solvent to solubilize the catalyst, complicating the otherwise simple isolation of the volatile epoxide. This difficulty inspired continued investigation into oligomeric catalysts with greater solubility in the HKR reaction medium.

In designing the next generation of oligomeric catalysts, the Jacobsen group focused on the tether to modulate the solubility and the counterion to increase reactivity.[86,87] By use of tethers containing ether linkages and void of chloro groups, oligomeric catalysts with increased solubility in the epoxide/water mixture of the HKR were identified (Figure 10). To evaluate the reactivity of the new tethered catalyst, the HKR of methyl glycidate was studied (Table 12, entry 1). Under solvent-free conditions with 0.03 mol % catalyst, the reaction reached completion in 8 h. Resolved methyl glycidate with >99% ee was isolated. In contrast, under identical conditions with the monomeric (salen)Co(OAc), the epoxide ee was 8% after 8 h.

The HKR of propylene oxide, an important substrate, was also extremely efficient and easily scalable (Table 12, entry 4). Under solvent-free conditions, 1.5 mol of epoxide was resolved with 3.6 mg of catalyst (41 ppm by mass, 3 ppm on a molar basis) furnishing 35 g of isolated epoxide with >99% ee.[86]

The mixture of oligomers (Figure 10, n = 1−3) was separated to determine their individual reactivity. Surprisingly, a substantial difference in reactivity was observed with n = 3, which was significantly more reactive and enantioselective than the dimer or tetramer.[87]

The use of oligomeric catalysts has allowed circumvention of many of the pitfalls associated with systems that are second order in catalyst. By tethering (salen)Co(III) units, high effective concentrations of cobalt centers are achieved at low cobalt loading.

2.2.5. Supported (salen)Co(III) Catalyst for the HKR

The homogenization of (salen)Co(III) complexes has been examined to facilitate separation of the catalyst from the reaction mixture and as a method to maintain a high effective molar concentration of cobalt centers to promote the cooperative bimetallic mechanism.[49,88] The resulting supported catalysts have been employed under highly concentrated conditions and have exhibited high values of k_{rel}. While the catalysts have been recycled several times or even used in continuous flow systems,[49] their application has been limited to small scale kinetic resolutions, and they do not present advantages over the oligomeric systems outlined above. They are not covered further here.

2.2.6. Asymmetric Ring Opening of Epoxides Using Carbon Dioxide

In the nucleophilic ring opening of epoxides promoted by (salen)M complexes, there is ample evidence that the epoxide is activated by coordinating to the Lewis acidic (salen)M complex. In the systems that have been studied, the nucleophile is also activated by the (salen)M complex in the form of (salen)M−Nu. As illustrated below, however, this is not always the case.

An interesting partner for the asymmetric epoxide opening is carbon dioxide. This handy C1 building block does not readily react with epoxides in the presence of Lewis acids. It was discovered that, in the presence of certain nucleophiles, epoxide opening does occur, ultimately generating cyclic carbonates. The synthesis of five-membered cyclic carbonates via the coupling of CO_2 and epoxides is an environmentally benign process, and CO_2 is a safe and plentiful C1 building block.[89]

Based on the possible mechanisms of epoxide opening catalyzed by Lewis acids and nucleophilic cocatalysts (Figure 11), Lu et al. designed a system for generating optically active cyclic carbonates from racemic epoxides.[90] Using Jacobsen's chiral (salen)Co(III) catalysts[42] in combination with catalytic tetrabutylammonium halides (n-Bu_4NX), these researchers devised a convenient solvent-free kinetic resolution of propylene oxide to provide enantioenriched propylene carbonate (PC). Chiral (salen)Co−X complexes with a sterically bulky axial X-group, such as *p*-toluene sulfonate, were essential for maximizing enantioselectivity in the kinetic resolution. Additionally, the anion of the quaternary ammonium cocatalyst has a significant impact on propylene carbonate enantiomeric purity.

In the absence of the halide cocatalyst, no reaction was observed (Table 13, entry 1). Lu et al. found that reaction of neat *rac*-propylene oxide (0.5 mol) with 0.55−0.60 equiv of CO_2 in the presence of 0.1 mol % (salen)Co(OTs) complex

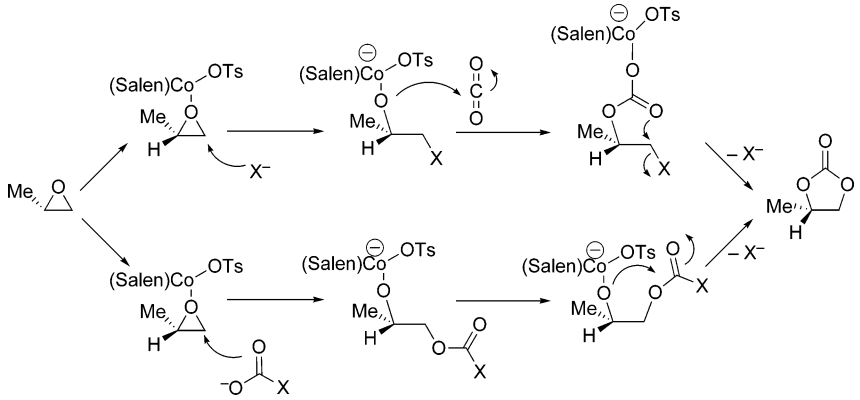
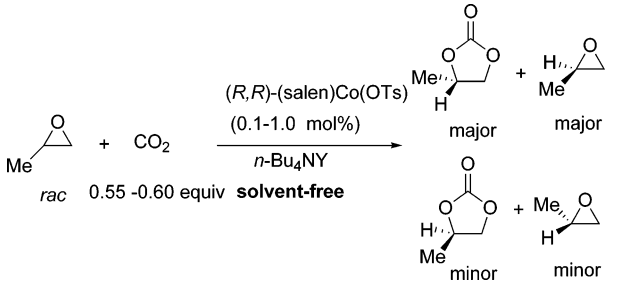


Figure 11. Two possible mechanisms for epoxide opening with carbon dioxide.

Table 13. Catalytic Kinetic Resolution of *rac*-Propylene Oxide by CO_2 Coupling



entry	cocatalyst *n*-Bu_4NY (equiv)	*T* (°C)	time (h)	conv (%)	k_{rel}	TOF (h^{-1})	PC ee (%)
1	none	25	10.0	0		0	
2	*n*-Bu_4NBr (1)	25	2.5	50.8	5.2	203	51.6
3	*n*-Bu_4NCl (1)	25	4.0	50.5	6.4	126	56.7
4	*n*-Bu_4NCl (2)	25	2.5	46.8	6.0	187	57.2
5	*n*-Bu_4NCl (10)	25	2.0	48.1	5.8	240	55.9
6	*n*-Bu_4NCl (2)	45	1.5	47.4	2.8	316	35.2
7	*n*-Bu_4NCl (2)	15	6.0	43.9	7.2	73	63.5
8	*n*-Bu_4NCl (2)	0	15.0	40.0	9.0	27	70.2

and 0.1 mol % *n*-Bu_4NBr as nucleophile produced optically active propylene carbonate (PC) of moderate ee in the kinetic resolution (Table 13, entry 2).[90] The relative rate of the fast vs slow reacting epoxide was just over 5. The best results were obtained with *n*-Bu_4NCl (Table 13, entries 3−8).

While the k_{rel} values measured in the epoxide resolution with carbon dioxide are below what is generally considered useful, these investigations are important because they address a long-standing challenge in organic chemistry: the feasibility of using CO_2 as a C1 source in asymmetric catalysis. The (salen)Co(OTs)/*n*-Bu_4NCl based catalyst system is highly efficient at catalyzing this reaction. The low relative rates of the fast and slow reacting enantiomers have inspired the search for better catalysts. Using the same (salen)CoX, Berkessel and Brandenburg[91] examined the use of different counterions, X, and cocatalysts under solvent-free conditions. They observed that the counterion X had a large impact on catalyst activity but not enantioselectivity and that the counterion of the cocatalyst influenced the activity and selectivity. After extensive screening, a catalyst system was found that operated under much lower pressure of carbon dioxide (Figure 12). Under optimal conditions, the selectivity factor was 18.7.

The results outlined in section 2.2 illustrate how a series of (salen)M-based catalysts have been applied to the ARO and kinetic resolution of epoxides. In general, these transformations work well under standard solvent conditions. Under solvent-free and highly concentrated reaction conditions, little or no loss in enantioselectivity is observed with respect to those reactions conducted in solvent. It is found that the (salen)M-based catalysts are more active under solvent-free and highly concentrated reaction conditions. Given the breadth of the reactions outlined above, one must wonder whether the (salen)M-based catalysts are unique in their ability to exhibit high levels of enantioselectivity under standard solvent conditions, highly concentrated conditions, and solvent-free conditions or whether these results are due primarily to the efforts of a few researchers interested in conducting reactions in a nontraditional fashion to develop more practical asymmetric processes. We believe that the latter rational is more likely and that many other catalysts may display similar levels of enantioselectivity and activity under highly concentrated and solvent-free conditions.

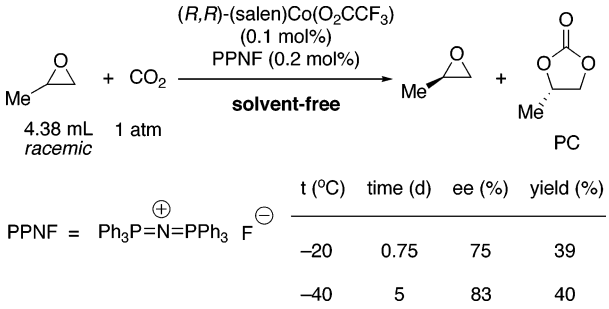
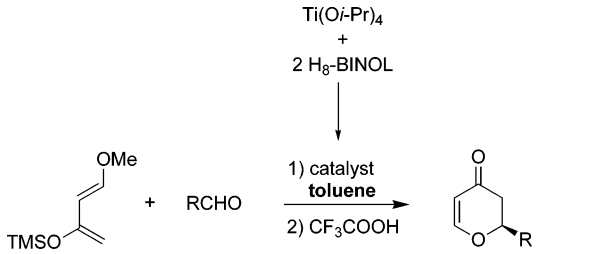


Figure 12. Kinetic resolution of propylene oxide with formation of enantioenriched propylene carbonate (PC).

2.3. Asymmetric Hetero-Diels−Alder Reaction

The catalytic asymmetric hetero-Diels−Alder (HDA) reaction is one of the most important asymmetric C−C bond-forming processes in heterocyclic chemistry.[92−94] It provides a highly effective method for preparing optically active six-membered ring compounds, such as dihydropyrans and dihydropyranones, and has been extensively utilized in the synthesis of natural products. Many main-group, transition metal, lanthanide, and even organocatalysts have been developed that promote the enantioselective HDA reaction.[95,96] The asymmetric HDA reaction has been frequently and successfully examined under solvent-free and highly concentrated reaction conditions. The successful adaptation of the HDA from solvent to solvent-free reaction conditions likely stems from the concerted nature of the cycloaddition

Table 14. Asymmetric HDA Reactions of Danishefsky's Diene and Aldehydes with Toluene Solvent



entry[a]	R	*T* (°C)	time (h)	yield (%)	ee (%)
1	Ph	0	24	92	97
2[b]	Ph	0	12	75	73
3	Ph	23−25	6	92	93
4	4-C_6H_4-OMe	0	24	52	>99
5	4-C_6H_4-Me	0	24	60	99
6	4-C_6H_4-F	0	24	54	99

[a] All reactions were carried out using 20 mol % of catalyst in toluene. [b] Ten mole percent of catalyst used.

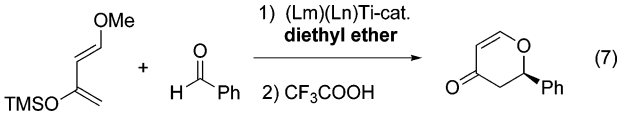
transition state, which exhibits only minimal dependency on the reaction medium.

2.3.1. Asymmetric Hetero-Diels–Alder Reaction of Danishefsky's Diene and Aldehydes

The formal HDA reaction between 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (Danishefsky's diene)[97] and aldehydes provides a powerful method to access dihydropyranones, a class of heterocycles with broad utility in organic synthesis. A number of chiral catalysts have been reported for HDA reactions under standard solvent conditions. For example, Keck and co-workers reported that a catalyst generated from (*R*)- or (*S*)-BINOL and Ti(O*i*-Pr)$_4$ in a 2:1 ratio in the presence of 4 Å molecular sieves and 3−4 equiv of CF_3COOH in Et_2O was able to promote the reaction of Danishefsky's diene with aldehydes to yield dihydropyranones with good to excellent ee's (55−97%).[98]

In 2000, Jiang and co-workers[99] also reported that asymmetric HDA reactions of Danishefsky's diene with aldehydes gave high enantioselectivity using chiral H_8-BINOL-Ti(O*i*-Pr)$_4$ complexes as catalysts and toluene as the solvent (Table 14). The yield and enantioselectivity were found to be dependent on the catalyst loading. When the amount of catalyst was reduced from 20 mol % to 10 mol %, the enantioselectivity and yield of the reaction decreased considerably (Table 14, entries 1 vs 2, 97% to 73% ee, yield 92% to 75%).

In related chemistry, Ding and co-workers discovered highly efficient catalysts for solvent-free enantioselective HDA reaction by high-throughput screening of a combinatorial library of chiral ligands attached to titanium (eq 7).[100,101]



(7)

Using titanium tetraisopropoxide and two ligands from the collection in Figure 13 in a Lm/Ln/Ti ratio of 1:1:1, a series of (Lm)(Ln)Ti-based catalysts were generated. By mixing of all possible combinations with L1−L13, a library of 104 catalysts can be generated. Most of the ligand combinations above will result in a mixture of titanium compounds under

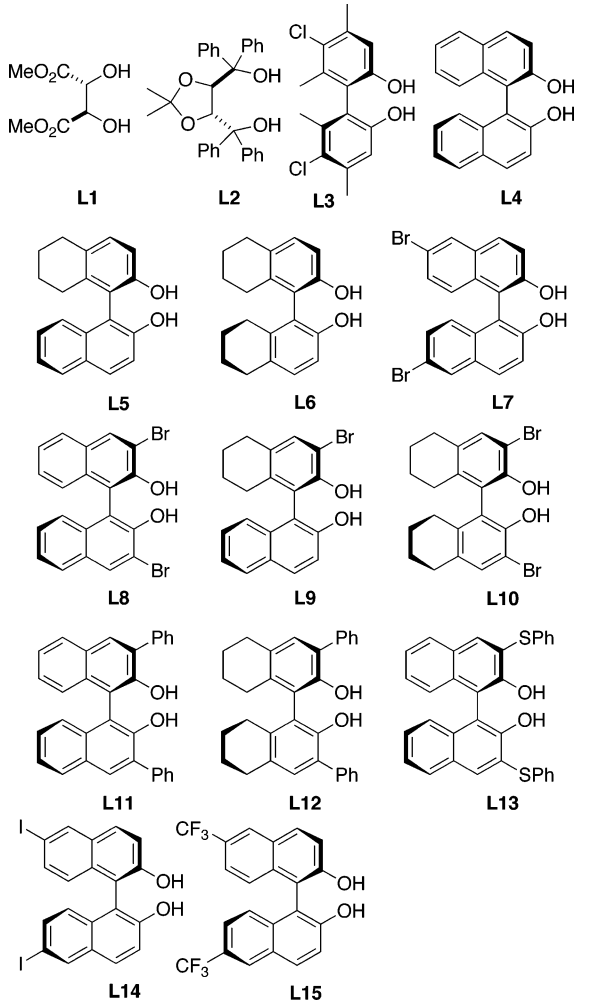
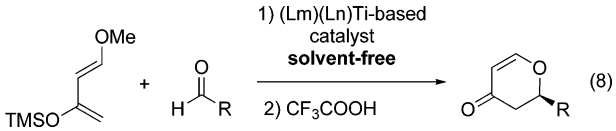


Figure 13. Ligands used to prepare (Lm)(Ln)Ti-based catalysts and (Lm)Zn-based catalysts for the solvent-free HDA.

thermodynamic control. It is anticipated that the titanium centers will bind identical ligands giving (Lm)$_2$Ti- and (Ln)$_2$Ti-based catalysts or two different ligands as in (Lm)(Ln)Ti-derivatives. Furthermore, the resulting complexes may exhibit monomer−dimer−oligomer equilibria, complicating analysis of the enantioselective reactions.

Initial screening of in situ prepared (Lm)(Ln)Ti-based complexes in the HDA reaction with Danishesky's diene and benzaldehyde (eq 7) in diethyl ether indicated ligands L4−L7 generated catalysts that exhibited >75% ee. The most promising ligand combinations were then examined under solvent-free conditions at lower catalyst loadings (eq 8). The



(8)

combinations (L5)$_2$Ti and (L5)(L6)Ti each exhibited 99% ee and then were both used with a series of aldehydes to define the scope of the catalysts, as outlined in Table 15.

Inspection of the results in Table 15 indicates that the reaction is particularly successful with aromatic aldehydes. It is noteworthy that in the cycloaddition with furfural, only 0.005 mol % of the (L5)(L6)Ti-based catalyst was needed to promote the reaction smoothly and furnish the product in 63% yield with 96.3% ee. This is one of the lowest catalyst

Table 15. Solvent-free Asymmetric HDA Reaction of Aldehyde with Danishefsky's Diene as Illustrated in Eq 8

	$(L5)_2Ti$				(L5)(L6)Ti			
aldehydes	loading (%)	time (h)	yield (%)	ee (%)	loading (%)	time (h)	yield (%)	ee (%)
benzaldehyde	0.05	24	>99	99.3	0.05	24	82	99.4
p-anisaldehyde	0.05	48	>99	90.8	0.05	48	>99	98.0
m-anisaldehyde	0.05	48	81	96.6	0.05	48	82.6	99.8
o-anisaldehyde	0.05	48	95	75.1	0.05	48	>99	95.1
3-phenylpropion-aldehyde	0.05	96	>99	97.9	0.05	96	>99	98.3
trans-cinnam-aldehyde	0.1	96	82	98.4	0.05	96	56.6	96.6
furfural	0.05	48	>99	99.2	0.05	48	>99	99.7
furfural	0.01	96	37	94.7	0.01	96	>99	97.7
furfural					0.005	144	63	96.2
m-tolualdehyde	0.1	48	95	98.5	0.05	48	92	99.5
1-naphth-aldehyde	0.05	48	55	85.6	0.05	48	65	98.5
p-cyanobenz-aldehyde	0.1	48	>99	92.9	0.05	48	98.4	97.9
m-bromobenz-aldehyde	0.1	48	>99	97.4	0.05	48	98.3	97.6
p-bromobenz-aldehyde	0.05	48	>99	98.0	0.05	48	>99	98.4
p-chlorobenz-aldehyde	0.05	48	>99	91.2	0.05	48	>99	99.1
p-nitrobenz-aldehyde	0.05	48	>99	97.3	0.05	24	>99	99.4

loadings reported in early transition metal Lewis acid catalyzed processes! Comparison of the results in Tables 14 and 15 obtained with two very similar catalysts, indicate the potential benefits of solvent-free and highly concentrated reaction conditions.

The dihydropyranones generated in this HDA reaction are very useful building blocks that have been employed in numerous syntheses. This study is particularly impressive given the unprecedented low catalyst loadings (0.1−0.005 mol %) and high enantioselectivities observed under solvent-free reaction conditions.

In a related study, the Ding group reported a highly enantioselective HDA reaction of Danishefsky's diene with aldehydes catalyzed by zinc-based chiral Lewis acids using toluene solvent.[102] Most of the chiral ligands examined in this chemistry are shown in Figure 13. The catalyst was generated in situ by combining 10 mol % of diethylzinc with an equal amount of one of the chiral ligands in Figure 13. The catalyst prepared from 3,3′-dibromo-1,1′-bi-2-naphthol (L8) exhibited the highest enantioselectivity (Figure 14). When the reactions were carried out under solvent-free conditions, however, the product ee dropped from 97% to 10%, even though the yield was 99%. This result illustrates the dramatic role played by the solvent in this example, especially when compared with the titanium system in eq 8 and Table 15.[100]

Many porphyrin complexes are unsaturated and can promote Lewis acid catalyzed processes such as the HDA reaction. Using Halterman's chiral porphyrin,[103,104] Berkessel and co-workers reported that chiral Cr(III) porphyrin complexes are efficient and highly enantioselective catalysts for HDA between aldehydes and Danishefsky's diene under highly concentrated conditions (Table 16).[105]

As illustrated, high enantioselectivities were observed with a variety of aldehydes. Interestingly, cinnamaldehyde underwent reaction at the carbonyl rather than the C−C double bond. Heteroaryl aldehydes proved to be excellent substrates for this system as shown with furfural and 2-pyridinecarboxaldehyde (Table 16, entries 5 and 7). It is surprising that the pyridyl group does not interfere with the activation of the carbonyl group in 2-pyridinecarboxaldehyde. It is hypothesized that sever steric hindrance about the metal center does not allow tight binding of the pyridine nitrogen.

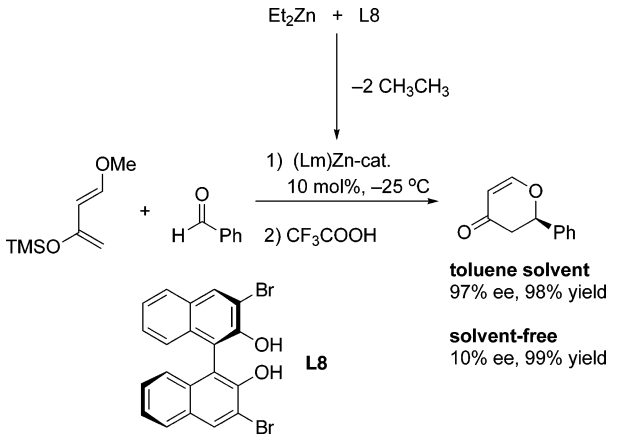
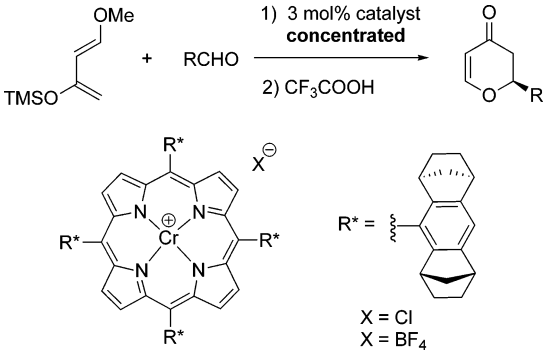


Figure 14. Comparison of toluene and the solvent-free HDA reaction with ligand L8 from Figure 13.

Table 16. Asymmetric HDA Catalyzed by Chiral Porphyrin Complexes



entry[a]	R	catalyst counterion (X^-)	T (°C)	yield (%)	ee (%)
1	Ph	Cl^-	−18	85	95
2	Ph	BF_4^-	−18	92	88
3	*c*-hexyl	Cl^-	−18	76	88
4	*n*-hexyl	Cl^-	−18	75	92
5	2-furyl	Cl^-	−18	70	97
6	(*E*)-CH=CHPh	Cl^-	0	55	74
7	2-pyridyl	Cl^-	−18	70	78

[a] The reactions were performed at 2.0 M substrate concentration in TBME.

The porphyrin-based catalysts will also promote the HDA reaction with monooxygenated dienes with moderate enantioselectivities.[105] The results of the HDA reaction above are impressive, given that porphyrin complexes have not been widely embraced by scientists working in asymmetric catalysis. This is because many consider the chirality to be overly distant from the Lewis acidic metal center.

2.3.2. Hetero-Diels–Alder Reaction Catalyzed by (salen)Cr(X) Complexes

Schaus, Brånalt, and Jacobsen optimized the asymmetric HDA reaction catalyzed by (salen)Cr-based catalysts under highly concentrated conditions and provided insight into the reaction mechanism.[106] Beginning with an initial substrate

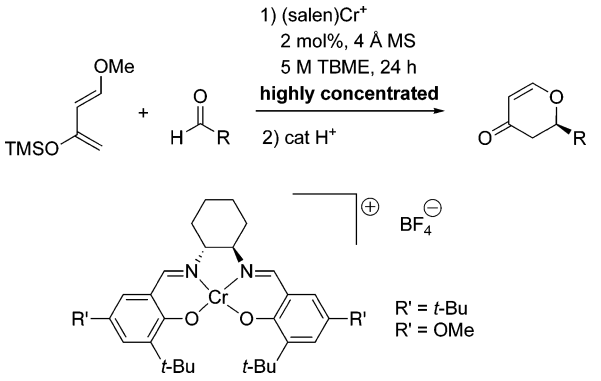


Figure 15. Enantioselective HDA reaction with cationic (salen)-Cr(III) catalysts under highly concentrated conditions.

Table 17. Results of the Asymmetric HDA Reaction Catalyzed by (salen)$Cr^{+}\cdot BF_4^{-}$ Complexes

			(salen)Cr^{+} R′ = *t*-Bu		(salen)Cr^{+} R′ = OMe	
entry	R	*T* (°C)	ee (%)	yield (%)	yield (%)	ee (%)
1	Ph	−30	87	85	98	65
2	*c*-C_6H_{11}	−20	93	71	76	85
3	*n*-C_5H_{11}	−40	83	86	85	62
4	2-furyl	−10	76	89	80	68
5	(*E*)-CH=CHPh	0	70	65	96	73
6	CH_2OCH_2(4-C_6H_4-Br)	−30	79	67	94[a]	84
7	CH_2O_2C(2-C_6H_4-Cl)	−20	83[a]	92	86	72

[a] Reactions were run on 10.0 mmol scale.

concentration of 1.0 M, the reaction achieved just over 90% conversion in 8 h with (salen)CrCl. Under highly concentrated conditions (5.0 M), complete conversion was attained after only 4 h with slightly higher ee (60%). The catalyst enantioselectivity was found to be highly dependent on the nature of the counterion, with the non-coordinating BF_4^{-} derivatives proving to be the most effective (Figure 15). Similar levels of enantioselectivity were observed with ligands R′ = *t*-Bu and OMe (Table 17). In two cases, reactions were successfully conducted on a 10 mmol scale under highly concentrated reaction conditions.

Lewis acid catalyzed HDA reactions typically proceed through either a Mukaiyama aldol mechanism (stepwise mechanism) or a [4 + 2] Diels−Alder cycloaddition (concerted mechanism). Examination of the ^{1}H NMR spectrum of the crude product indicated exclusive formation of cycloaddition product, a sign that the reaction likely proceeds through a concerted cycloaddition pathway. To test the possible intermediacy of a Mukaiyama aldol condensation adduct, the silyl ether product was independently synthesized and subjected to the conditions of the Cr(salen)-catalyzed HDA reaction (Figure 16). No detectable cyclization product was observed after 6 h at room temperature, suggesting that product formation proceeds via a concerted [4 + 2] mechanism.[106]

2.3.3. Organocatalytic Hetero-Diels–Alder Reaction Catalyzed by TADDOL Derivatives

In 2003, Rawal and co-workers reported a seminal work involving the asymmetric HDA reaction catalyzed by chiral Brønsted acids, such as the chiral diol TADDOL (TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol).[107] This

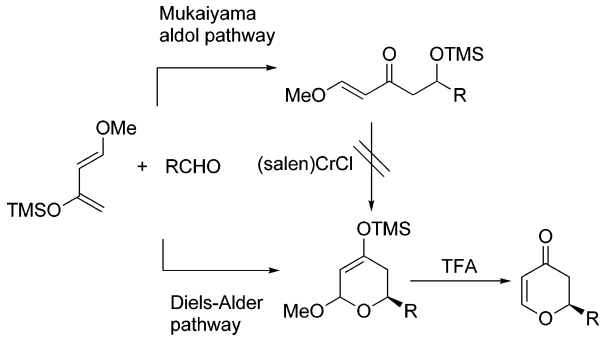
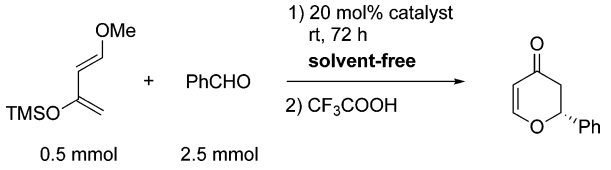
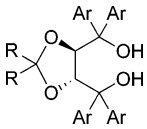


Figure 16. Addition of (salen)CrCl to the independently prepared Mukaiyama aldol product did not lead to cyclization, suggesting that the reaction proceeds through a concerted [4 + 2] cycloaddition pathway.

Table 18. HDA Reaction Catalyzed by Chiral TADDOL Derivatives



			yield (%)	ee (%)
	a: Ar = Ph	R = CH_3	18	12.1
	b: Ar = 1-naphthyl	R = CH_3	77	76.3
	c: Ar = 2-naphthyl	R = CH_3	36	18.7
	d: Ar = 1-naphthyl	R−R = $(CH_2)_4$	50	69.1
	e: Ar = 2-naphthyl	R−R = $(CH_2)_4$	60	4.0
	f: Ar = 1-naphthyl	R−R = $(CH_2)_5$	58	77.0
	g: Ar = 2-naphthyl	R−R = $(CH_2)_5$	58	21.2

work has served as the inspiration for numerous related asymmetric reactions promoted by chiral organocatalysts.[108−113] In one such example, Wu, Ding, and co-workers conducted experimental and theoretical studies on the asymmetric HDA promoted by TADDOL derivatives under solvent-free conditions.[114] As outlined in Table 18, reactions were typically conducted with 20 mol % TADDOL for 72 h at room temperature before treatment with TFA (trifluoroacetic acid). The ee and yield of the HDA product was found to be highly dependent on the structure of the TADDOL derivative employed.

To differentiate between the two common mechanisms for the HDA reaction (Figure 16), a ^{1}H NMR spectrum of the crude product was examined before treatment with acid. The absence of the Mukaiyama aldol product suggested that the reaction proceeded through the concerted [4 + 2] cycloaddition pathway.[114] To further investigate the mechanism of the asymmetric HDA reaction catalyzed by TADDOL derivatives, calculations were performed using the ONIOM (our own N-layered integrated molecular orbital and molecular mechanics) (B3LYP/6-31G* : PM3) method. These studies are consistent with an intramolecular hydrogen bond between the two hydroxyl groups of the TADDOL and activation of the benzaldehyde via a single hydrogen bond (Figure 17).

2.3.4. Diastereoselective Hetero-Diels–Alder Reaction

Typically, enantioselective syntheses of natural products begin with simple chiral building blocks that are elaborated

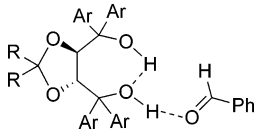


Figure 17. Proposed model for activation of benzaldehyde by TADDOL in the organocatalytic HDA reaction.

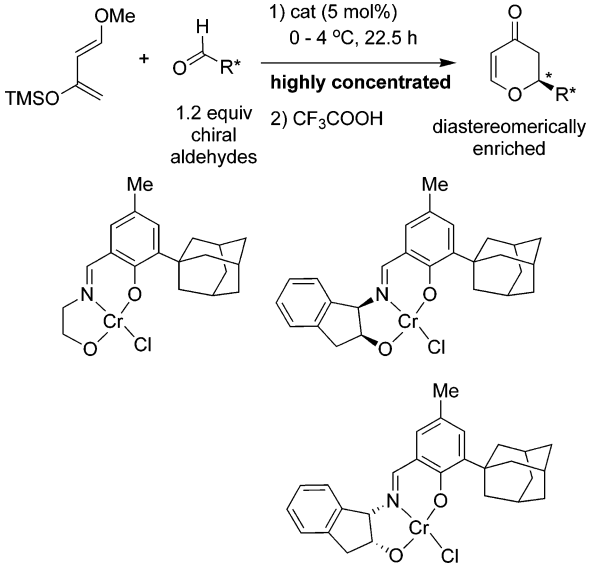


Figure 18. HDA of enantioenriched aldehydes with achiral and chiral Cr(III)−Schiff base complexes (see Table 19).

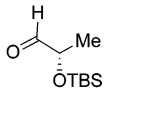
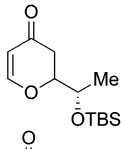
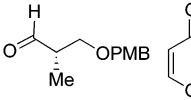
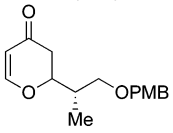
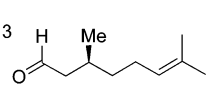
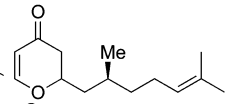
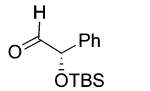
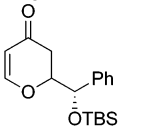
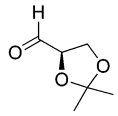
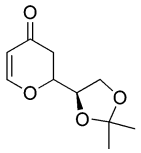
in a diastereoselective fashion to construct the molecular skeleton and to install additional stereogenic centers. Unfortunately, diastereoselective reactions under substrate control can be problematic if they lead to significant amounts of the undesired stereoisomer. An underappreciated approach to controlling formation of new stereocenters in chiral substrates is to employ enantioselective catalysts to enhance or even override the inherent diastereoselectivity of the substrate. Such an approach has been employed in the doubly diastereoselective HDA reaction under highly concentrated conditions (Figure 18).

Using achiral and enantiomeric Cr(III)−Schiff base catalysts under concentrated reaction conditions, Joly and Jacobsen examined the HDA between Danishefsky's diene and enantioenriched aldehydes (Figure 18).[115] While the achiral catalyst gave poor diastereoselectivity, the chiral catalysts exhibited high levels of stereocontrol with unhindered chiral aldehydes. For example, with the (*S*)-lactaldehyde derivative, the achiral catalyst promoted the cycloaddition reaction with modest diastereoselectivity (Table 19, entry 1, 1:2 dr). In contrast, use of the resolved catalysts provided the products with dr between 1:12 and 15:1. Similar results were obtained with other unhindered chiral aldehydes (entries 2 and 3). In general, bulkier substrates gave lower dr with the chiral catalysts (Table 19). Importantly, the ee of several of the products was determined to be ≥97%, indicating that no epimerization of the aldehyde occurred under the Lewis acid catalyzed HDA reaction conditions.

The challenging aldehydes in entries 4 and 5 of Table 19 underwent cycloaddition reactions with slightly higher diastereoselectivities with enantioenriched (salen)$Cr^{+}BF_4^{-}$ catalysts.[115]

These catalyst-controlled doubly diastereoselective HDA reactions selectively provide each of the four possible stereoisomers of the dihydropyranone products with good

Table 19. Results of HDA of Enantioenriched Aldehydes with Achiral and Chiral Cr(III)−Schiff Base Complexes from Figure 18

entry	aldehyde	product	cat.	yield (%)	dr
1			achiral	81	1 : 2.0
			(1*R*,2*S*)	96	1 : 12
			(1*S*,2*R*)	97	15 : 1
2			achiral	50	1 : 1.1
			(1*R*,2*S*)	90	1 :11
			(1*S*,2*R*)	86	9.3 : 1
3			achiral	85	1:1.3
			(1*R*,2*S*)	98	16 : 1
			(1*S*,2*R*)	99	1 : 11
4			achiral	58	1.7 : 1
			(1*R*,2*S*)	58	3.6 : 1
			(1*S*,2*R*)	54	1 : 2.6
5			achiral	68	1 : 4.5
			(1*R*,2*S*)	76	1 : 1.2
			(1*S*,2*R*)	84	1 : 33

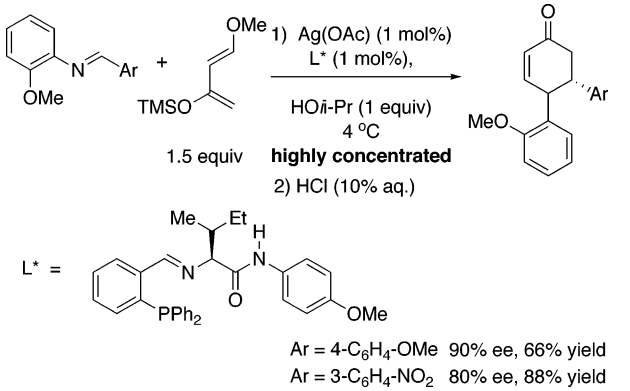


Figure 19. Asymmetric HDA reaction with a silver catalyst under highly concentrated conditions.

to excellent dr by judicious choice of aldehydes and catalyst enantiomers.[115]

2.3.5. Asymmetric Hetero-Diels–Alder Reaction of Danishefsky's Diene with N-Aryl Imines

The HDA of Danishefsky's diene with imines provides access to chiral nitrogen-containing heterocycles, which are useful intermediates in the synthesis of functionalized enantioenriched piperidones.[116−118] To develop catalysts prepared from readily available starting materials and used at low catalyst loading, Josephsohn, Snapper, and Hoveyda developed a highly enantioselective silver catalyst.[119] After screening a parallel library of amino acid-based ligands, metals, and additives, they discovered the system in Figure 19. Use of 1 mol % each of Ag(OAc) and L* in the presence of 1 equiv of 2-propanol under highly concentrated conditions resulted in formation of the HDA in 80−90% ee and 66−88% yield after workup with acid. For comparison, reactions under standard solvent conditions in THF gave

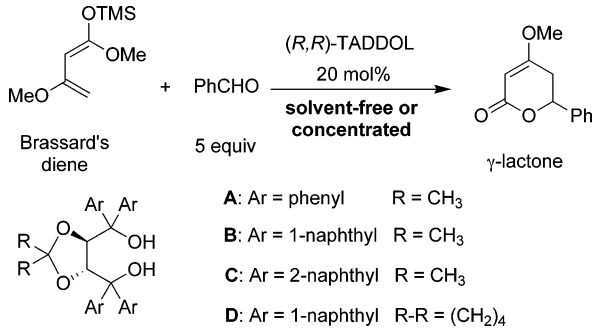


Figure 20. Enantioselective HDA reaction between Brassard's diene and benzaldehyde catalyzed by TADDOL derivatives.

Table 20. Results from the Enantioselective HDA Reaction between Brassard's Diene and Benzaldehyde (0.5 mmol) Catalyzed by TADDOL Derivatives A−D (Figure 20)

entry	catalyst	solvent (mL)[a]	T (°C)	time (h)	yield (%)	ee (%)
1	**A**	none	rt	12	30	7
2	**B**	none	rt	12	40	50
3	**B**	none	−30	24	70	71
4[b]	**B**	none	−30	24	50	72
5[b]	**C**	none	−30	24	40	0
6[b]	**D**	none	−30	24	37	74
7	**B**	toluene (0.05)	−30	24	70	75
8	**B**	toluene (0.1)	−30	24	68	76
9	**B**	toluene (0.2)	−60	48	67	83
10	**B**	toluene (0.4)	−60	48	50	86
11	**B**	toluene (0.2)	−78	48	26	89

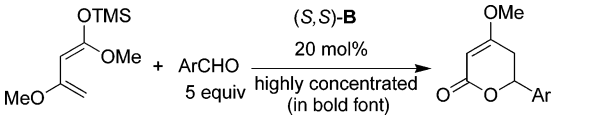
[a] All the reactions were carried out with 2.5 mmol of benzaldehyde and 0.5 mmol of diene. [b] Ten mole percent of catalyst was used.

higher yields (86−92%) with these substrates, and both were formed with 91% enantioselectivity. While the role of the 2-propanol is not understood, it is necessary for high TOF and enantioselectivity. Presumably a variety of other aryl imines would give similar results under the highly concentrated conditions in Figure 19.

2.3.6. Asymmetric Hetero-Diels–Alder Reaction of Brassard's Diene and Aldehydes

The asymmetric HDA reaction of electron-rich 1,3-dimethoxy-1-(trimethylsiloxy)butadiene (Brassard's diene)[120] with aldehydes provides a useful route to synthetically important enantioenriched γ-lactones. Based on Rawal's discovery that TADDOL derivatives catalyze the asymmetric HDA between aldehydes and Danishefsky's diene,[107] Ding and co-workers extended their earlier work to include asymmetric HDA with Brassard's diene.[121] As outlined in Figure 20, four TADDOL derivatives (**A**−**D**) were examined in the hydrogen-bond promoted HDA reaction. The results of screening these catalysts with benzaldehyde and Brassard's diene are illustrated in Table 20. Initially, the reaction was carried out at room temperature with 0.5 mmol of diene, 2.5 mmol of benzaldehyde, and 20 mol % of catalyst (*R*,*R*)-**A** (Figure 20) under solvent-free conditions (entry 1). The reaction proceeded enantioselectively forming the cycloaddition product in 30% yield and 7% ee. Employing TADDOL derivative **B** at −30 °C improved the ee to 71% with 70% yield. When the catalyst loading was reduced to 10 mol %, the product ee was unchanged although the yield decreased to 50% (entry 4). In contrast to the results with **A** and **B**, the use of TADDOL derivative **C** gave racemic product (entry 5), emphasizing the important role of the TADDOL aryl groups in the asymmetric induction. Changes in the ketal backbone were found to result in small differences in the product ee (compare entries 4 and 6).

Table 21. Reaction of Brassard's Diene with Various Aldehydes Catalyzed by TADDOL B (Figure 20)



entry	Ar	toluene (mL)[a]	T (°C)	yield (%)	ee (%)
1[b]	Ph	0.2	−60	67	83 (*S*)
2[b]	furyl	0.2	−60	80	87 (*S*)
3	2-C_6H_4-Me	0.2	−30	54	68 (*R*)
4	4-C_6H_4-Cl	0.2	−30	85	76 (*R*)
5	4-C_6H_4-Br	0.2	−30	72	78 (*R*)
6	3-C_6H_4-Br	0.2	−60	67	89 (*R*)
7	2-C_6H_4-Br	0.2	−60	75	82 (*R*)
8	3-C_6H_4-OMe	0.2	−60	45	91 (nd)

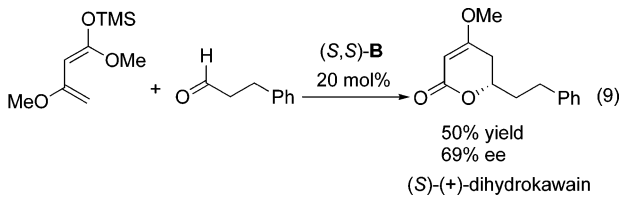
[a] All the reactions were carried out with 2.5 mmol of benzaldehyde and 0.5 mmol of diene. [b] The catalyst employed in this case was (*R*,*R*)-**B**.

In their work, Ding and co-workers experienced one of the limitations of solvent-free chemistry, the sharp increase in reaction medium viscosity with decreasing temperature. To circumvent this obstacle, small amounts of a low-melting solvent, toluene in this case, were added to the reaction vessel to reduce the solution viscosity. Under these concentrated conditions, the reaction temperature could be reduced to −60 °C, which afforded the product in 83−86% ee without a significant reduction in yield. At −78 °C, a slight increase in ee was observed, but the yield dropped sharply.

The TADDOL derivative **B** was effective for the reactions of a variety of aromatic aldehydes to give the corresponding 6-substituted 4-methoxy-5,6-dihydropyran-2-ones in 45−85% yield with 68−91% ee (Table 21). With solid aldehyde substrates, additional toluene was added to ensure that the reaction mixtures were homogeneous.

A comparison between the titanium- and zinc-based catalysts in eq 8 and Figure 14, respectively, which were successfully used in the HDA with Danishefsky's diene, and the TADDOL-derived organocatalyst **B** was made using Brassard's diene. In this case, the organocatalyst proved significantly more enantioselective and higher yielding than the metal-containing catalysts under the reaction conditions outlined above.[121]

The TADDOL derivative **B** was also employed in the synthesis of (*S*)-(+)-dihydrokawain. Thus, reaction of 3-phenylpropionaldehyde with Brassard's diene in the presence of the chiral diol led to formation of the natural product in one step in 50% yield with 69% ee (eq 9).



2.3.7. Asymmetric Hetero-Diels–Alder Reaction of Mono-oxygenated Dienes and Aldehydes

In contrast to the HDA reactions outlined above, which employ the electron-rich Danishefsky and Brassard dienes, asymmetric HDA reactions with less electron-rich dienes

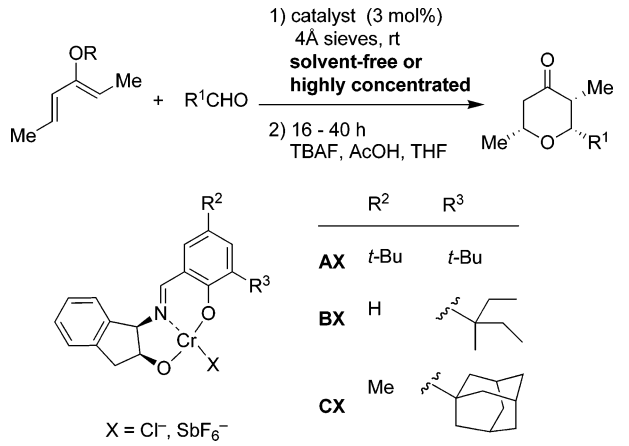


Figure 21. Asymmetric HDA with chiral tridentate Schiff base complexes of Cr(III) and monooxygenated dienes.

Table 22. Results from HDA Reaction in Figure 21

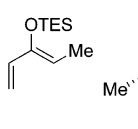
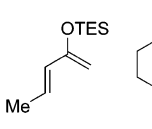
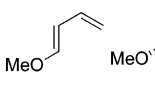
entry	diene OR	aldehyde R^1	solvent	catalyst	yield (%)	ee (%)
1	OTES	Ph	none	**A·SbF$_6$**	50	80
2	OTES	CH_2OTBS	none	**A·SbF$_6$**	*a*	57
3	OTES	CH_2OTBS	none	**B·SbF$_6$**	*a*	85
4	OTES	CH_2OTBS	none	**C·Cl**	88	98
5	OTES	CH_2OTBS	none	**C·SbF$_6$**	93	98
6	OTES	Ph	none	**C·Cl**	*a*	65
7	OTES	Ph	none	**C·SbF$_6$**	*a*	81
8	OTES	Ph	conc.	**C·SbF$_6$**	72 (80)[b]	90
9	OTES	CH_2OTBS	conc.	**C·Cl**	90	99
10	OTES	CH_2OTBS	conc.	**C·SbF$_6$**	97	>99
11	OTES	CH_2OBn	conc.	**C·SbF$_6$**	89	94
12	OTES	*n*-C_5H_{11}	none	**C·SbF$_6$**	85	98
13	OTES	$(CH_2)_4CH{=}CH_2$	none	**C·SbF$_6$**	78	98
14	OTES	CH_2CH_2Ph	conc.	**C·SbF$_6$**	78 (84)[b]	98
15	OTES	CH_2CH_2NHBoc	conc.	**C·SbF$_6$**	28 (31)[b]	96
16	OTES	2-furyl	conc.	**C·SbF$_6$**	77 (86)[b]	95
17	OTMS	*n*-C_5H_{11}	none	**C·SbF$_6$**	81	98
18	OTBS	*n*-C_5H_{11}	none	**C·SbF$_6$**	93	96
19	OTIPS	*n*-C_5H_{11}	none	**C·SbF$_6$**	77	94

[a] Not determined. [b] Reaction conversion after 40 h in parenthesis.

were not explored until 1999 when Dossetter, Jamison, and Jacobsen studied HDA reactions with monooxygenated dienes catalyzed by Cr(III) species.[122] Employing tridentate complexes **A·Cl** and **A·SbF$_6$** in the HDA with (2*Z*,4*E*)-triethylsilyloxy-2,4-hexadiene and two aldehydes (R^1 = Ph, CH_2OTBS) generated tetrahydropyranones after desilylation (Figure 21). While the ee's were moderate (80 and 57% ee, respectively), only the endo product was formed, leading to the all-*cis* stereochemistry of the tetrahydropyranone product (Table 22, entries 1 and 2). Increasing the size of the catalyst's R^3 substituent from *t*-Bu to 1-ethyl-1-methylpropyl and 1-adamantyl increased the product ee's to 98% (compare entries 2−5, Table 22). A similar increase in ee with benzaldehyde was not possible under solvent-free conditions (entries 6 and 7), inspiring the investigators to examine solvent additives.[122]

Screening various solvents under highly concentrated conditions led to the discovery that addition of acetone resulted in a significant increase in the product ee to 90% (entry 8). Addition of a small amount of acetone to the reactions was found to be general, as illustrated in Table 22; however, with some substrates (entries 12, 13, 17−19), the solvent-free conditions resulted in excellent enantioselectivities. It was also noted that the nature of the trialkylsilyl

Table 23. Catalytic Asymmetric HDA Reaction with Dienes and Aldehydes Catalyzed by 3 mol % C·Cl from Figure 21

entry	diene	product	conditions[a,b]	yield (%)	ee (%)	config.
1			200 μL acetone highly concentrated	78	98	(2*R*,6*R*)
2			sovent-free	50	91	(2*R*,3*R*)
3			sovent-free	91	>99	(2*S*,6*R*)

[a] Reactions were carried out with 1:1 diene/aldehyde on a 1.0 mmol scale with 3 mol % catalyst (*1R*,*2S*)-**C·Cl** and powdered 4 Å molecular sieves. [b] The products were isolated by treatment with either TFA in CH_2Cl_2 at 0 °C or TBAF, AcOH, and THF at 0 °C.

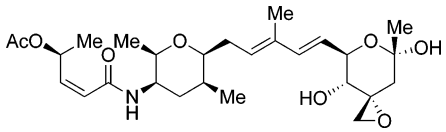


Figure 22. Structure of the natural product FR901464.

substituent had little impact on the ee or yield of the cycloaddition products (entries 12 and 17−19).

Given the successful HDA reactions between (2*Z*,4*E*)-triethylsilyloxy-2,4-hexadiene and various aldehydes catalyzed by **C·SbF$_6$** (Table 22), the authors examined the ability of **C·Cl** to promote HDA reactions with other dienes. As shown in Table 23, reaction of (2*E*)-2-triethylsilyloxy-1,3-pentadiene resulted in formation of the product in 78% yield with 98% ee (entry 1). Similar results were obtained with the isomeric pentadiene (entry 2). Use of 1-methoxybutadiene proceeded smoothly to furnish the product with >99% ee (91% yield, entry 3).

These new classes of solvent-free and highly concentrated HDA reactions provide straightforward methods to enantiomerically enriched dihydropyran derivatives. Furthermore, up to three stereocenters can be established in the cycloaddition reaction. The resultant products can be elaborated to provide tetrahydropyran derivatives with five defined stereocenters after functionalization of the double bond.

2.3.7.1. Application of the HDA Reaction to the Synthesis of FR901464. The natural product FR901464 (Figure 22) was isolated by Fujisawa Pharmaceutical Co. and discovered to possess interesting biological properties, including promising antitumor activity.[123−126] The synthesis of this complex target molecule was accomplished via two enantioselective HDA reactions under solvent-free and highly concentrated conditions employing the Cr(III) catalyst **C·SbF$_6$** (Figure 21) discussed above.[122,127]

The key step in the synthesis of the central fragment is a HDA reaction catalyzed by (1*R*,2*S*)-**C·SbF$_6$** under solvent-free conditions as illustrated in Figure 23. The HDA reaction proceeded in excellent yield and enantioselectivity, establishing three of the four stereocenters of the central ring in a single reaction. This intermediate was elaborated to the azide, a precursor to the coupling partner (Figure 23).[127]

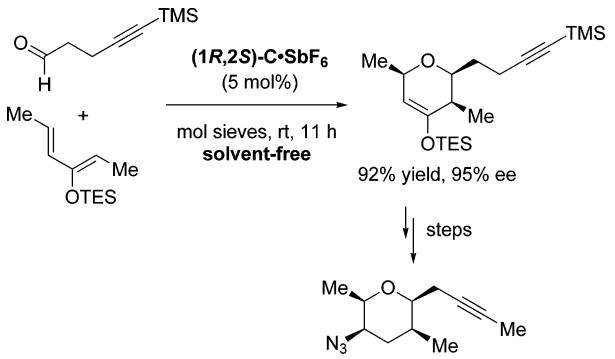


Figure 23. Synthesis of the central fragment of FR901464 via an enantioselective HDA reaction. The catalyst is from Figure 21.

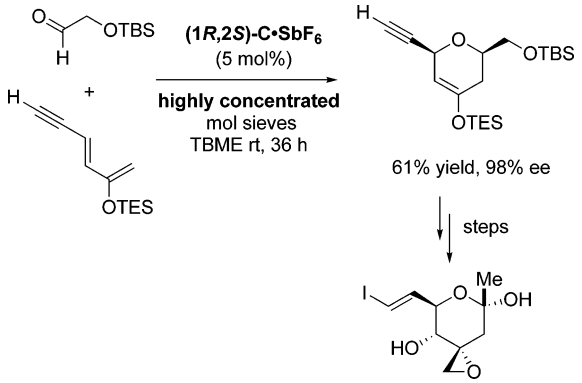


Figure 24. Synthesis of the right-hand fragment of FR901464 via an enantioselective HDA reaction. The catalyst is from Figure 21.

Likewise, the right-hand fragment was prepared under highly concentrated conditions via the HDA reaction using the same catalyst (Figure 24). Transformation of this intermediate to the epoxide was accomplished over several steps.

The efficient assembly of the fragments in Figures 23 and 24 allowed the rapid construction of FR901464. The flexibility of this synthesis enabled preparation and biological evaluation of FR901464 analogs.[127] The fact that this synthetic strategy employed solvent-free and highly concentrated catalytic asymmetric reactions in the generation of the key intermediates suggests that such approaches will also be applicable to other complex molecule syntheses.

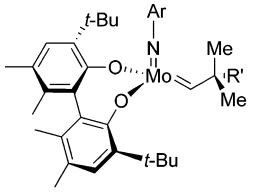
The level of interest in the catalytic asymmetric HDA reactions under solvent-free and highly concentrated reaction conditions can be judged by the large number of successful reports dedicated to catalyst development for this process. The practicality and utility of these methods is highlighted by the efficient synthesis of FR901464 and its analogs.

2.4. Asymmetric Metathesis Reactions

Metathesis reactions have rapidly become one of the most useful tools in synthetic organic chemistry. With the advent very active and enantioselective catalysts for these reactions, researchers are beginning to compare catalyst performance under solution and solvent-free conditions. The results of these studies, highlighted below, show that significantly better performance is often observed in the absence of solvent.[128,129]

2.4.1. Asymmetric Ring-Closing Metathesis Reactions

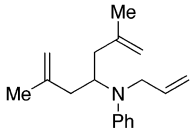
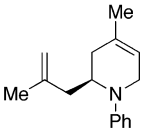
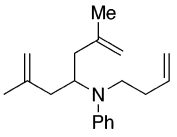
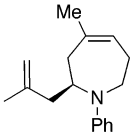
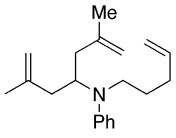
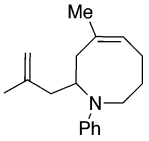
Ring-closing metathesis reactions are well established as powerful methods for the synthesis of natural and unnatural products.[130−133] Asymmetric ring-closing metathesis (ARCM) reactions are emerging as a useful method to prepare small carbocyclic and heterocyclic compounds. Of particular interest are nitrogen-containing heterocycles, which are commonly found in biologically active molecules and are relatively difficult to prepare enantioselectively.



A, Ar = 2,6-C_6H_3-(*i*-Pr)$_2$, R' = Ph
B, Ar = 2,6-C_6H_3-(Me)$_2$, R' = Ph

Figure 25. Catalysts for the ARCM.

Table 24. Desymmetrization of Acylic Amines Using ARCM under Solvent-free Conditions with Catalyst A (Figure 25)

entry	substrate	product	cat (mol%)	time (h)	yield (%)	ee (%)
1			2.5	0.2	76	>96
2			3.5	3.5	95	95
3			4	7	>98	97

In studies directed toward the synthesis of chiral *N*-heterocycles, Hoveyda, Schrock, and their co-workers examined the desymmetrization of acyclic amino trienes by ARCM under solvent-free conditions.[134] Using the chiral molybdenum catalyst **A** in Figure 25 (2.5−4 mol %), three amines were cyclized with excellent levels of enantioselectivity and high yields (Table 24). Importantly, this method delivers medium-ring unsaturated amines, including the challenging eight-membered derivative (entry 3). Interestingly, monitoring the reaction progress at 22 °C indicated that homodimers were the first-formed species from entries 2 and 3 (Table 24). On continued reaction, however, the oligomeric intermediates were almost entirely converted into cyclic products due to the reversibility of the olefin metathesis.[135−137] The enantioenriched cyclized amine products, with their hindered trisubstituted double bonds, do not readily undergo ring opening.

A related catalyst (**B**, Figure 25) has been used in the enantioselective desymmetrization of two allyl ethers. Under solvent-free conditions, **B** catalyzed the ARCM in 5 min affording highly enantioenriched dihydrofurans in high yields (Figure 26).[138]

The solvent-free desymmetrization of acyclic amines and ethers via ARCM is a unique and potentially useful entry into biologically important heterocycles. Given that there is little change in the solvent polarity in the ARCM reaction, it seems likely that other substrates that behave well under

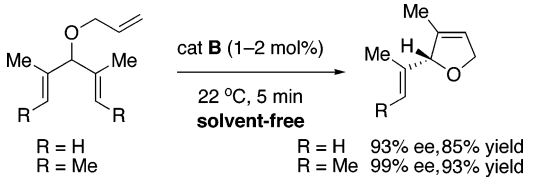


Figure 26. Enantioselective desymmetrization of allyl ethers with catalyst **B** (Figure 25).

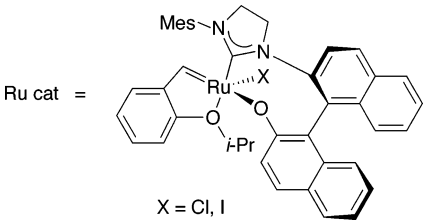


Figure 27. Catalysts for the AROM/CM reaction.

solvent conditions may also exhibit similar enantioselectivities under solvent-free and highly concentrated reaction conditions. Exceptions involve use of solid or semisolid substrates in which the catalysts have limited solubility. In such cases, addition of solvent is necessary for optimal catalyst performance.[139]

2.4.2. Asymmetric Ring-Opening Metathesis/ Cross-Metathesis Reactions

Enantioenriched 2,6-disubstituted pyrans are precursors to a variety of natural products of biological importance.[140−142] In an effort to synthesize these valuable building blocks, Hoveyda and co-workers[143] investigated the asymmetric ring-opening metathesis/cross-metathesis reaction (AROM/CM) of oxabicyclic olefins with the ruthenium catalysts in Figure 27.

A comparison of standard solvent vs solvent-free reactions was undertaken. When reactions in Figure 28 were conducted with 5 equiv of the cross-metathesis partner styrene in solution, less than 2% conversion was observed after 24 h. In contrast, in the absence of solvent, reactions of oxabicycles proceeded to high conversion allowing products to be isolated in good yields. Although the iodide-based catalyst was less reactive than the chloride derivative, it was more enantioselective, providing pyran with >90% ee.

This method was then applied to the preparation of a useful polypropionate precursors (Figure 29) using the iodide-based catalyst from Figure 27.[144,145]

Not only does the catalyst perform better in the absence of solvent in several instances, the catalysts can be isolated more easily and recycled in subsequent reactions.[143]

2.5. Asymmetric Carbonyl−Ene Reaction

The thermal pericyclic ene reaction represents a typical concerted pathway involving six electrons with a suprafacial orbital interaction. Like the HDA reaction, the carbonyl−ene reaction is concerted and less susceptible to solvent effects. This characteristic suggests that the asymmetric carbonyl−ene reaction might be a good candidate for adaptation to solvent-free reaction conditions, which has proven to be the case. Under standard solvent conditions, asymmetric versions have been achieved with various chiral Lewis acids including Al, Ti, Ni, Pt, Pd, Yb, and Cu complexes.[146−157] The catalyst loadings, however, are high, typically ranging from 1 to 10 mol %. Examination of this

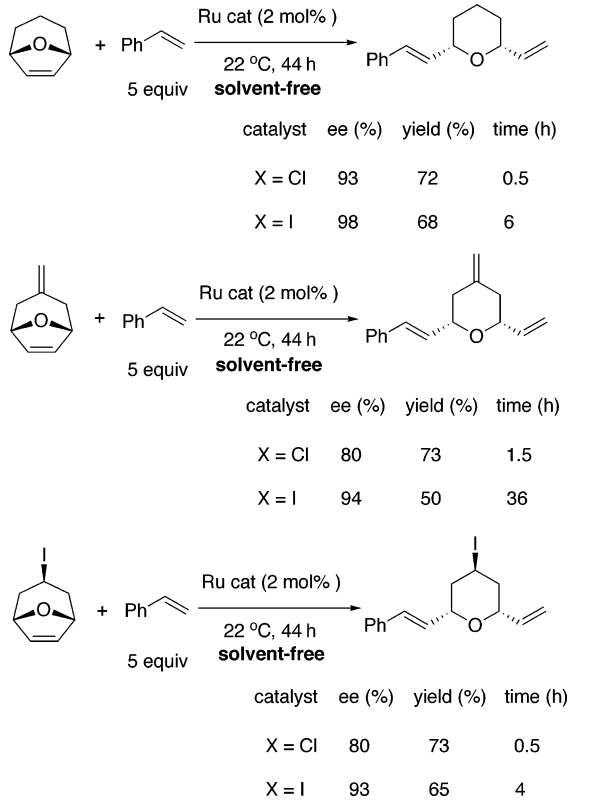


Figure 28. Catalyzed AROM/CM reactions with ruthenium catalysts in Figure 27.

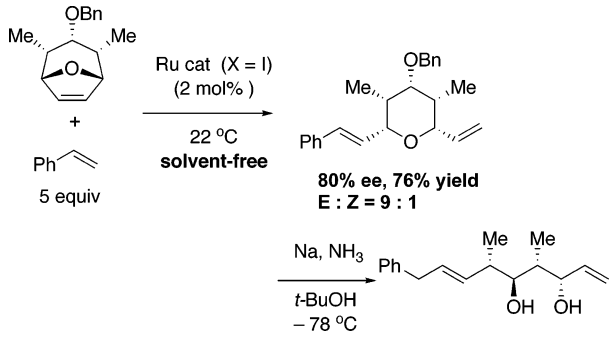
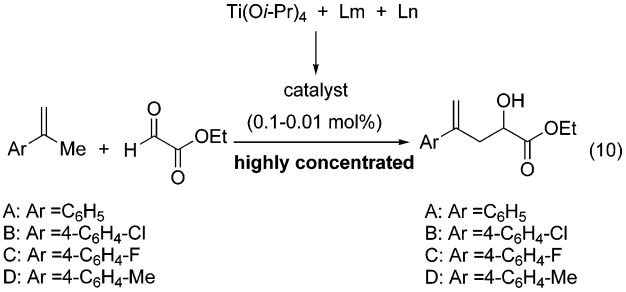


Figure 29. Application of the AROM/CM to a key intermediate in the total synthesis of natural polypropionates.

reaction under solvent-free conditions might allow for a reduction in the catalyst loading without sacrificing TOF.

With the idea of reducing the catalyst loading, Ding and co-workers developed a highly concentrated and solvent-free enantioselective carbonyl−ene reaction (eq 10).[158] Using



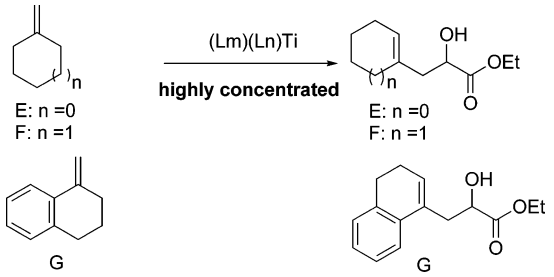
(10)

an approach similar to the one they developed for the titanium-catalyzed HDA reaction (eq 8), they employed a similar set of chiral BINOL and diol derivatives (Figure 13). Upon combination of 2 equiv of ligand with titanium

Table 25. Results of the Highly Concentrated Carbonyl−Ene Reaction (Eq 10) with L14 and L15 from Figure 13

entry	olefin	cat.	mol %	time (h)	yield (%)	ee (%)
1	**A**	$(L14)_2Ti$	0.1	48	98	98.2
2	**A**	(L14)(L15)Ti	0.1	48	85	97.6
3	**A**	$(L14)_2Ti$	0.01	72	76	97.2
4	**A**	(L14)(L15)Ti	0.01	72	49	97.9
5	**B**	$(L14)_2Ti$	0.1	48	89	99.4
6	**B**	(L14)(L15)Ti	0.1	36	96	98.2
7	**C**	$(L14)_2Ti$	0.1	48	83	98.4
8	**C**	(L14)(L15)Ti	0.1	48	96	98.4
9	**D**	$(L14)_2Ti$	0.1	36	92	97.1
10	**D**	(L14)(L15)Ti	0.1	36	>99	97.0

Table 26. Results of the Highly Concentrated Carbonyl−Ene Reaction (Eq 10) with L14 and L15 from Figure 13

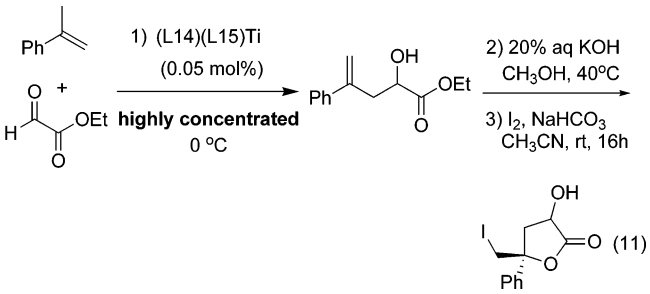


entry	olefin	cat.	mol %	time (h)	yield (%)	ee (%)
1	**E**	$(L14)_2Ti$	0.1	24	>99	91.6
2	**F**	(L14)(L15)Ti	0.01	42	42	91.8
3	**G**	$(L14)_2Ti$	0.1	48	97	92.2
4	**G**	(L14)(L15)Ti	0.1	48	94	96.3

tetraisopropoxide, a library of (Lm)(Ln)Ti-based catalysts was generated. The initial screening indicated that catalysts prepared from BINOL derivatives, substituted at the 3,3′-positions, resulted in reduced enantioselectivities relative to the parent BINOL ligand, as did partially hydrogenated BINOL ligands. Examination of electron-withdrawing bromo groups at the 6,6′-positions (L7, Figure 13) resulted in an increase in the enantioselectivity and inspired the synthesis of appropriately substituted BINOL ligands 6,6′-I_2-BINOL (L14) and 6,6′-$(CF_3)_2$-BINOL (L15) (Figure 13). Application of the homo- and heterocombinations of L14 and L15 was performed under highly concentrated reaction conditions (the solvent volume was about 13% of the reaction mixture) with very low catalyst loadings (0.1−0.01 mol %, eq 10). As illustrated in Table 25, α-hydroxy esters of very high ee were obtained from α-methyl styrene derivatives.

Three cyclic derivatives were also examined and shown to give excellent enantioselectivities under highly concentrated conditions, as shown in Table 26. It is noteworthy that several of the reactions in Tables 25 and 26 could be carried out on gram scale. This is particularly important in the case of olefin **E** (Table 26), because the product is a key intermediate in the synthesis of Trocade, a collagenase-selective inhibitor.[159]

The utility of this methodology was demonstrated by conducting the reaction of ethyl glyoxylate with α-methylstyrene on a 0.1 mol scale, employing 0.05 mol % (L14)-(L15)Ti at 0 °C (eq 11). The carbonyl−ene reaction product was obtained in >99% yield and 95% ee and was transformed into the functionalized γ-butyrolactone by iodolactonization in excellent yield.



This carbonyl−ene reaction introduced by the Ding group has several advantages: the catalyst is easily generated, the reaction is conducted under highly concentrated conditions, and the catalyst loading is extremely low. Furthermore, the products are furnished with very high enantioselectivities and yields, which make this protocol attractive for the preparation of enantiomerically enriched α-hydroxy esters.

2.5.1. Self-Supported (BINOLate)Ti-Based Catalysts for the Carbonyl–Ene Reaction

An emerging area of interest in asymmetric catalysis is the application of polymeric self-supported catalysts.[160−162] One method of preparation of self-supported catalysts involves condensation of a metal complex with a polyfunctional ligand that contains two independent binding sites.[163] This type of approach was taken by Ding and co-workers in the development of a chiral polymeric self-supported titanium complex for the asymmetric carbonyl−ene reaction. Using the linked bis(BINOL) ligands, they prepared the catalysts by condensation of ligands **A**−**A**, **B**−**B**, and **C**−**C** with Ti(O*i*-Pr)$_4$ (1:1 ratio) in $CHCl_3$ (Figure 30). The mixtures were stirred at rt for 4 h, and then the solvent was removed under reduced pressure.

The resulting solids **A**−**A**−**Ti**, **B**−**B**−**Ti**, and **C**−**C**−**Ti** (1 mol %) were subjected to the carbonyl−ene reaction of ethyl glyoxylate with α-methylstyrene under solvent-free or highly concentrated conditions with a small amount of toluene (Table 27). As showed in Table 27, the carbonyl−ene reaction proceeded readily at rt to generate corresponding α−hydroxy esters in high yield and ee. The nature of the linkers tethering the two BINOL units was found to have a significant impact on the catalyst enantioselectivity. Catalyst **B**−**B**−**Ti**, having a *meta*-phenylene linker, showed poor catalytic activity and enantioselectivity (entries 7 and 8). In contrast, catalyst **C**−**C**−**Ti** exhibited enhanced enantioselectivity and catalytic activity, affording product in >99% yield and 96.5% ee (entry 9). Under solvent-free conditions, the catalysts exhibited similar or slightly decreased yield and enantioselectivity (Table 27).

These investigations clearly indicate that solvent-free and highly concentrated asymmetric reactions can even be conducted under heterogeneous conditions and afford products with high levels of enantioselectivity and yields. Applications such as this hint that it may be possible to couple solvent-free chemistry with heterogeneous supported catalysts that can be recycled, providing systems that minimize the environmental impact on several fronts.

2.6. Asymmetric Addition of Organometallic Reagents to Aldehydes and Ketones

2.6.1. Enantioselective Alkylation of Aldehydes with Dialkylzinc Reagents

Enantioenriched secondary alcohols are very useful chiral building blocks in asymmetric synthesis that have been

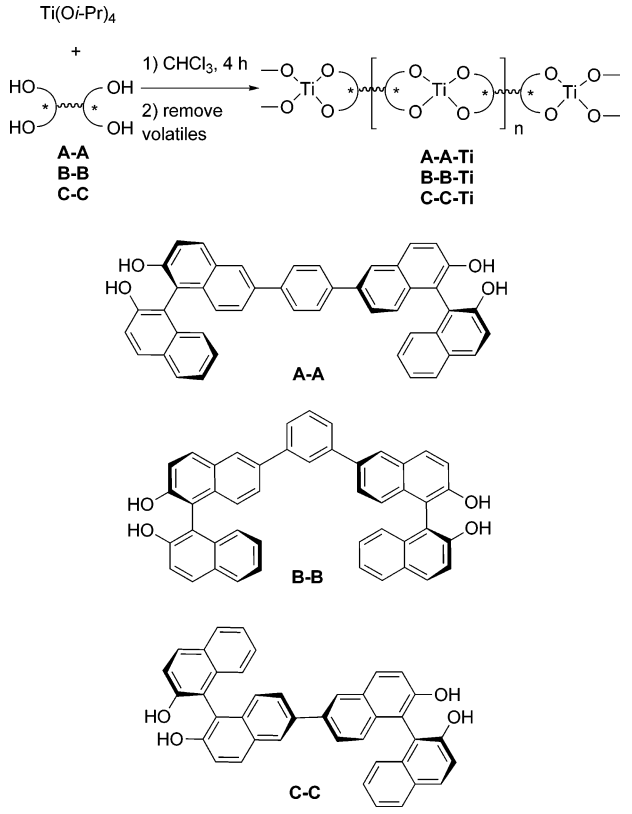
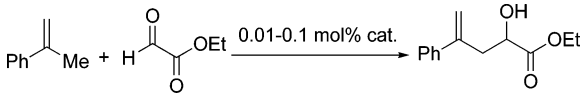


Figure 30. Condensation of bis(BINOL) ligands **A**−**A**, **B**−**B**, and **C**−**C** with Ti(O*i*-Pr)$_4$ (1:1). The titanium centers may contain coordinated isopropanol ligands.

Table 27. Enantioselective Carbonyl−Ene Reaction with Catalysts A−A−Ti, B−B−Ti, and C−C−Ti from Figure 30

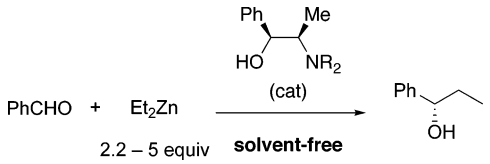


entry	catalyst	solvent additive	4 Å MS	stirring	*T* (°C)	time (h)	yield (%)	ee (%)
1	**A−A-Ti**	toluene	no	yes	rt	48	91	94.4
2	**A−A-Ti**	toluene	no	yes	0	120	85	95.4
3	**A−A-Ti**	toluene	no	no	0	120	96	95.6
4	**A−A-Ti**	toluene	yes	yes	rt	120	93	92.1
5	**A−A-Ti**	toluene	yes	yes	0	120	65	92.5
6	**A−A-Ti**	none	no	no	0	120	75	94.4
7	**B−B−Ti**	toluene	no	yes	rt	48	32	9.8
8	**B−B−Ti**	toluene	no	yes	0	120	9	24.2
9	**C−C−Ti**	toluene	no	yes	rt	30	>99	96.5
10	**C−C−Ti**	toluene	no	yes	0	96	95	91.5
11	**C−C−Ti**	toluene	yes	yes	rt	96	85	92.4
12	**C−C−Ti**	toluene	yes	yes	0	96	90	95.5
13	**C−C−Ti**	none	no	yes	0	96	90	92.7

prepared by asymmetric reduction of ketones[164] and asymmetric addition of alkyl groups to aldehydes.[165−167] Of these two methods, the latter results in simultaneous formation of a C−C bond and a stereocenter, making it more synthetically efficient. The asymmetric addition of alkyl groups to aldehydes has been one of the most studied reactions in asymmetric catalysis, with literally hundreds of catalysts that will promote this reaction with high enantioselectivity.[168−176] Despite the widespread attention that this reaction has received, it has seldom been examined under solvent-free or highly concentrated conditions.

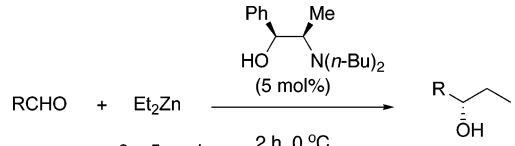
In an early report of solvent-free asymmetric catalysis, Soai and co-workers examined the asymmetric addition of alkylzinc reagents to aldehydes.[177] In the presence of *N*,*N*-dialkylnorephedrines as chiral ligands, the addition of diethylzinc to benzaldehyde was examined (Table 28). It was noted that the ligand loading could be decreased from 10 to 3.4 mol % with no loss in enantioselectivity. The reaction under solvent-free conditions reached completion in 6 h at −28 °C, whereas when toluene was used at this temperature, little conversion was observed. Thus, under solvent-free conditions, reactions times were dramatically reduced with no loss of enantioselectivity.

Table 28. Catalyst Evaluation in the Asymmetric Addition of Diethylzinc to Benzaldehyde under Solvent-free Conditions



entry	R	mol % cat.	*T* (°C)	time (h)	yield (%)	ee (%)
1	*n*-Bu	10	0	2	99	87
2	*n*-Bu	5	0	2	97	87
3	*n*-Bu	3.4	0	2	93	87
4	*n*-Pr	5	0	2	99	85
5	$-(CH_2)_4-$	5	0	2	97	86
6	*n*-Bu	5	−10	4	98	89
7	*n*-Bu	5	−28	6	99	87

Table 29. Asymmetric Addition of Diethylzinc to Aryl and Saturated Aldehydes under Solvent-free Conditions



entry	R	yield (%)	ee (%)
1	4-C_6H_4-Me	99	90
2	1-naphthyl	80	91
3	2-naphthyl	98	86
4	4-C_6H_4-Cl	99	85
5	4-C_6H_4-OMe	98	89
6	*c*-C_6H_{11}	96	88
7	CH_2CH_2Ph	92	84

A variety of aryl- and alkyl-substituted aldehydes were examined under solvent-free conditions with 3−5 equiv of Et_2Zn and 5 mol % of the enantioenriched amino alcohol (Table 29). The reactions were homogeneous and proceeded in 2 h at 0 °C in a highly enantioselective manner to afford secondary alcohols with 84−91% ee.

Soai and co-workers have also examined the asymmetric addition of diethylzinc to *N*-diphenylphosphinoylimines using chiral amino alcohol ligands. While enantioselectivities up to 97% were obtained under solvent-free conditions, the reactions were stoichiometric in chiral ligands and are not further discussed here.[178]

The results outlined above indicate that the asymmetric alkylation of aldehydes may be an ideal class of reactions for examination under solvent-free conditions. Given the efficiency of the addition, it might be possible to substantially reduce the catalyst loading without loss in enantioselectivity in this synthetically important transformation.

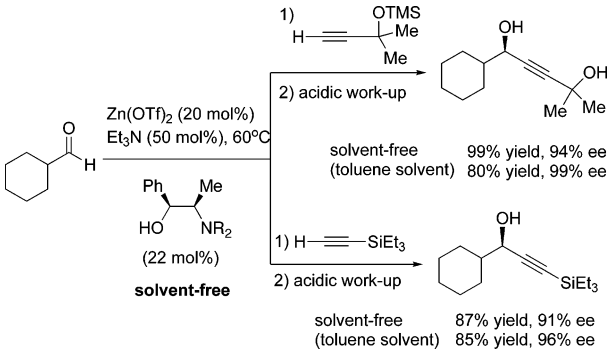


Figure 31. Catalytic asymmetric addition of alkynes to aldehydes under solvent-free conditions.

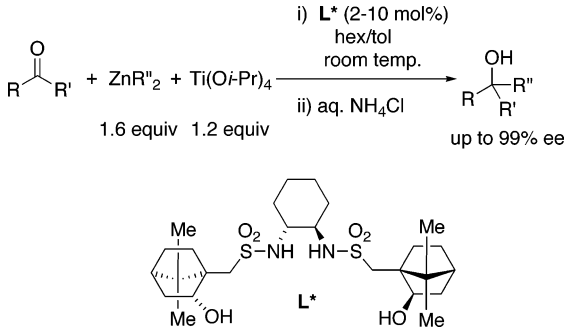


Figure 32. Asymmetric addition of alkyl groups to ketones.

2.6.2. Catalytic Asymmetric Acetylide Additions to Aldehydes

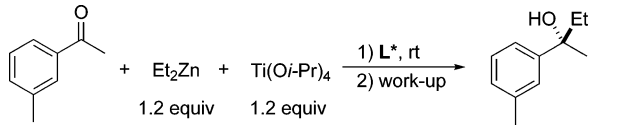
In 2001, Anand and Carreira reported the solvent-free catalytic asymmetric addition of acetylides to aldehydes to provide enantioenriched propargylic alcohols, which are valuable precursors to a wide range of chiral materials.[179] Under standard conditions with toluene as solvent, a variety of aliphatic aldehydes underwent addition providing propargylic alcohols with high levels of enantioselectivity (>90%) and good to excellent yields. Employing the solvent-free conditions, dry $Zn(OTf)_2$ was combined with the amino alcohol (22 mol %), alkyne (1.05 equiv), triethylamine (50 mol %), and the aldehyde (Figure 31). The reaction was stirred for 6 h at 60 °C before workup and isolation of the product. As outlined in Figure 31, enantioselectivities were excellent, although slightly diminished from reactions conducted with toluene as solvent. Isolated yields of the propargylic alcohols were higher using solvent-free conditions.

Although only two examples of solvent-free additions were outlined in this report, this chemistry represents a significant breakthrough in that it is not only catalytic in chiral ligand, but it is also catalytic in zinc. Presumably this novel methodology could be extended to other aldehydes and alkynes.

2.6.3. Asymmetric Addition of Alkyl Groups to Ketones

In contrast to the asymmetric addition of dialkylzinc reagents to aldehydes, which is promoted by a multitude of catalysts, the analogous addition to ketones has proven quite challenging.[180−191] The Walsh group has recently developed a catalyst for this process that exhibits high enantioselectivities with a broad range of ketone substrates in toluene and hexanes solvent (Figure 32). The resulting enantioenriched tertiary alcohols are useful chiral building blocks and have been used in natural product synthesis.[192]

Table 30. Diethylzinc Additions to 3′-Methylacetophenone under Solvent-free and Highly Concentrated Reaction Conditions



entry	solvent	L* (mol %)	time (h)	yield (%)	ee (%)
1	tol/hex	2	24	78	>99
2	none	1	4	79	99
3	2 equiv tol[a]	1	7	78	99
4	none	0.5	20	80	98
5	none	0.25	21	62	97
6	none	0.1	24	58	96

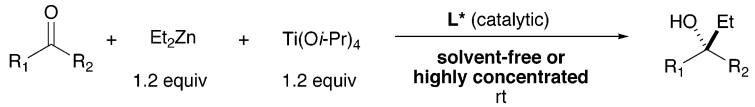
[a] Two equivalents of toluene relative to ketone substrate.

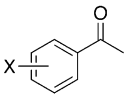
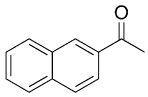
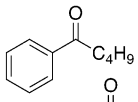
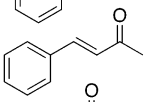
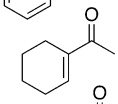
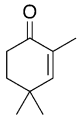
As outlined in Figure 32, the asymmetric addition of alkyl groups to ketones using a solvent mixture of toluene and hexanes required 2−10 mol % of the chiral bis(sulfonamide) diol ligand to achieve the highest levels of enantioselectivity. While 2 mol % ligand loading is low for early transition metal catalysts, many substrates required 10 mol % L* to maintain high enantioselectivities and reasonable reaction times. It was hypothesized that reducing the amount of solvent employed in the asymmetric addition would have several benefits. First, the corresponding increase in the concentration of the catalyst and reagents could result in greater catalyst turnover frequency, possibly allowing a reduction in catalyst loadings. Second, decreasing the quantity of solvent would make scale up more attractive by cutting waste generation and reducing costs.

In the initial examination of highly concentrated and solvent-free reactions, Jeon, Li, and Walsh[193] employed diethylzinc in the asymmetric addition to 3′-methylacetophenone (Table 30). Under standard conditions with toluene and hexanes solvents and 2 mol % catalyst, the reaction required 24 h providing 78% isolated yield of the tertiary alcohol with 99% ee (entry 1).[194] In the absence of solvent, the same addition reaction was complete in much less time (4 h) with half the catalyst loading (1 mol %) and essentially the same enantioselectivity and yield (Table 30, entry 2). Similar results were obtained under highly concentrated conditions, when 2 equiv of toluene (relative to ketone) was added to the reaction mixture (Table 30, entry 3). Given these observations, the possibility of further decreasing the catalyst loading to as low as 0.1 mol % was investigated. In these cases, the addition product was obtained in slightly lower yields and with a small decrease in enantioselectivity (up to 3%). As anticipated, the reactions also required longer times at the lower catalyst loadings (Table 30, entries 4−6). The results in Table 30 indicate that low catalyst loadings can be successfully employed, in part because the catalyst exhibits a high degree of ligand acceleration[195] over the uncatalyzed background reaction of diethylzinc with ketone substrates.

Table 31 shows the scope, limitations, and comparison of solvent-free, highly concentrated, and standard solvent conditions in diethylzinc additions to ketones. In several cases, the difference in these methods is quite large. For example, in toluene and hexanes, ethyl addition to 4′-methoxyacetophenone required 111 h at 10 mol % catalyst loading (Table 31, entry 3). Under the solvent-free conditions, the reaction was significantly faster, reaching comple-

Table 31. Diethylzinc Additions to Ketones under Solvent-free, Highly Concentrated, and Standard Conditions



		solvent-free or highly concentrated conditions				standard conditions			
entry	substrates	L* (mol%)	t (h)	y (%)	ee (%)	L* (mol%)	t (h)	y (%)	ee (%) (config.)
1	 X = H	1	4	75	97[a]	2	29	71	96 (*S*)
		0.5	21	78	96[a]				
2	X = 3-CF_3	0.5	17	77	96[a]	2	14	56	98
3	X = 4-OMe	1	12	50	81[a]	10	111	85	94
		1	15	72	89[b]				
4		0.5	12	74	98[a]	2	27	90	97
		0.5	24	76	98[b]				
5		1	24	78	80[a]	2	102	79	88 (*R*)
		1	24	85	80[b]				
6		1	15	71	90[b]	2	26	80	90
7		1	22	53	93[b]	2	46	56	96
8		1	22	36	96[b]	10	40	76	98

[a] Solvent-free conditions. [b] Two equivalents of toluene was added to the reaction.

tion in 12 h at 1 mol % catalyst loading. Unfortunately, both the yield and ee of the tertiary alcohol decreased to 50% and 81%, respectively. When the addition was conducted with 2 equiv of toluene relative to ketone, the enantioselectivity increased to 89%. Valerophenone exhibited a decrease in reaction time from over 4 days at 2 mol % ligand under standard conditions to 1 day at 1 mol % ligand under solvent-free and highly concentrated conditions. The enantioselectivity dropped, however, to 80% (Table 31, entry 5). These initial results highlight an important difference between standard, highly concentrated, and solvent-free conditions in this system: in the latter cases, the enantioselectivities are more sensitive to substrate structure.

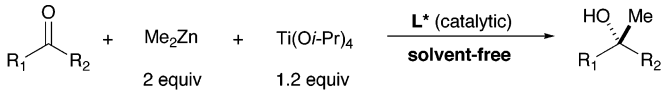
One important class of substrates for these asymmetric addition reactions is enones. The addition products are tertiary allylic alcohols that can be functionalized at the double bond through hydroxyl-directed reactions. As illustrated in Table 31, enantioselectivities >90% were observed with a variety of enones at 1 mol % catalyst loading with 2 equiv of toluene. Surprisingly, 2,4,4-trimethylcyclohexenone gave only 36% yield of the addition product, with the remainder of the material isolated as byproducts. This is in contrast to the standard conditions, where the product was isolated with 76% yield (Table 31, entry 8). The increased quantity of byproducts under the highly concentrated reaction conditions appears to be substrate dependent.

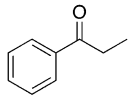
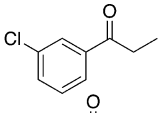
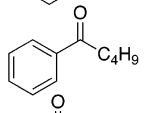
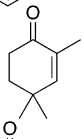
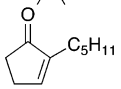
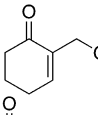
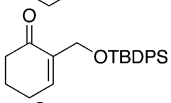
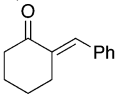
It is well-known that dimethylzinc adds to aldehydes around 20 times slower than diethylzinc with amino alcohol-based catalysts;[196] thus experiments to compare the reactivity of dimethyl- and diethylzinc under solvent-free conditions were performed. As shown in Table 32, excellent results were obtained in the solvent-free dimethylzinc addition reactions. In these reactions, 2 equiv of the dimethylzinc and 1.2 equiv of Ti(O*i*-Pr)$_4$ were generally employed. Propiophenone and 3′-chloropropiophenone gave excellent yields (83−95%) and enantioselectivities (92−94%) using 1.0 or 0.5 mol % L* (Table 32, entries 1 and 2). The enantioselectivity in the methyl addition to propiophenone decreased to 80% at 0.25 mol % catalyst loading, however. It was hypothesized that the background reaction promoted by Ti(O*i*-Pr)$_4$ could be playing a role in the erosion of enantioselectivity at 0.25 mol % catalyst. A substoichiometric amount of Ti(O*i*-Pr)$_4$ was, therefore, employed under otherwise identical conditions. When the Ti(O*i*-Pr)$_4$ was reduced from 1.2 to 0.4 equiv at 0.25 mol % catalyst loading, the enantioselectivity was restored to 92% (Table 32, entry 1).

Valerophenone provided an opportunity to directly compare the rates of addition of diethyl- and dimethylzinc with our catalyst in the absence of solvent. Under solvent-free conditions, diethylzinc was found to react about 2 times faster than dimethylzinc, as seen by comparison of entry 5 in Table 31 with entry 3 in Table 32.

Unlike diethylzinc addition to 2,4,4-trimethylcyclohexenone, which generated mostly byproducts, dimethylzinc addition proceeded smoothly in 75−83% yield with >95% enantioselectivity (entry 4). Other cyclic enones also proved

Table 32. Dimethylzinc Additions under Solvent-free and Standard Reaction Conditions



		solvent-free conditions				standard conditions				
entry	substrates	L* (mol %)	t (h)	y (%)	ee (%)	L* (mol %)	t (h)	y (%)	ee (%)	(config.)
1		1	15	85	92	2	45	83	94	(*R*)
		0.5	48	83	92					
		0.25	60	85	80					
		0.25	72	87	92[a]					
2		1	45	95	94	2	46	90	96	
		0.5	60	95	94					
3		1	43	95	83	2	48	81	85	
		0.5	45	93	77					
4		1	45	75	96	10	40	84	99	
		0.5	44	83	95					
5		1	22	77	96	10	40	62	99	
		0.5	44	78	97					
6		1	24	90	97	10	40	81	99	
		0.5	44	83	97					
		0.25	70	84	92					
7		1	60	90	96	10	60	84	98	
8		1	24	43	99	10	38	20	99	

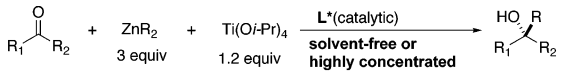
[a] $Ti(Oi\text{-}Pr)_4$ (0.4 equiv) was used.

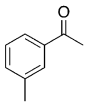
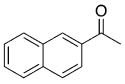
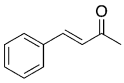
to be excellent substrates for the solvent-free dimethylzinc additions (Table 32, entries 5−7). Of particular note are the results of addition to 2-pentyl-2-cyclopenten-1-one (entry 5) and the TBS-protected enone (entry 6). For these substrates, the catalyst loading could be lowered 20-fold with similar or better enantioselectivity, yield, and reaction time as compared with the standard conditions. Furthermore, although the yield of addition to 2-benzylidene cyclohexanone remained low in the solvent-free reactions, it was double that of the standard solution-phase reaction (Table 32, entry 8).

Addition of functionalized organozinc reagents to ketones, under standard conditions with 10 mol % loading of ligand L*, resulted in high enantioselectivities but long reaction times (48−120 h).[185] With the goal to reduce the catalyst loading and reaction times, the addition of functionalized diorganozinc reagents to ketones was examined under solvent-free and highly concentrated reaction conditions.

By the methods of Knochel for the preparation of functionalized organozinc reagents,[197−203] a dialkylzinc reagent bearing a TBS-protected alcohol was employed in the solvent-free addition to 3′-methylacetophenone. When solvent-free conditions were employed with 1 mol % catalyst, the enantioselectivities were 80% or less, significantly below the 98% enantioselectivity recorded for the standard conditions at 10 mol % catalyst (Table 33, entry 1).[185] Addition of 2 equiv of toluene, however, restored the enantioselectivity to 97%. Similarly, addition of the bromoalkyl to this substrate exhibited higher yields and enantioselectivity under highly concentrated conditions than those under the solvent-free conditions (Table 33, entry 2). Higher enantioselectivities under the concentrated reaction conditions relative to the solvent-free conditions was found to be general for functionalized organozinc additions (Table 33, entries 1−3). Surprisingly, with 2-acetonaphthone, the enantioselectivities with the functionalized organozinc reagents were *higher* under the concentrated conditions than under the standard conditions. In Table 33, entry 3, reduction of the amount of titanium tetraisopropoxide from 1.2 to 0.6 equiv at 0.25 mol % catalyst resulted in an increase in the enantioselectivity from 76% to 90%. Additions to *trans*-4-phenyl-3-buten-2-one at 1 mol % catalyst loading under concentrated conditions exhibited similar enantioselectivities compared with the standard conditions with significantly reduced reaction times (Table 33, entries 5−7). In general, addition of 2 equiv of toluene allowed a 10-fold reduction in catalyst loading and reduced reaction times while maintaining high enantioselectivities. The origin of the beneficial effect of toluene is not understood. The results in Table 33 suggest that the highly concentrated nature of these reactions makes them particularly sensitive to the small changes in the composition of the reaction mixture.

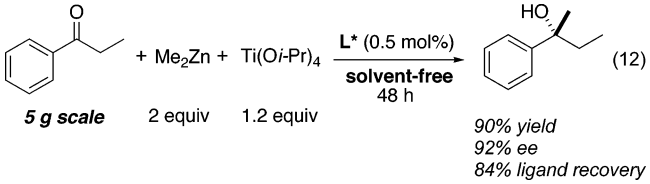
Table 33. Comparison of Solvent-free, Highly Concentrated, and Standard Reaction Conditions for the Asymmetric Addition of Functionalized Organozinc Reagents to Ketones



			solvent-free or highly concentrated conditions				standard conditions			
entry	substrates	ZnR_2	L* (mol%)	t (h)	y (%)	ee (%)	L* (mol%)	t (h)	y (%)	ee (%)
1		$Zn((CH_2)_4OTBS)_2$	1	48	68	79[a]	10	72	89	98
			0.5	70	53	80[a]				
			0.25	82	44	69[a]				
			1	40	68	97[b]				
2		$Zn((CH_2)_5Br)_2$	1	46	66	92[a]				
			0.5	50	41	92[a]	10	72	89	96
			1	46	71	97[b]				
3		$Zn((CH_2)_5Br)_2$	1	40	55	94[a]				
			0.5	76	47	94[a]				
			0.25	84	30	76[a]	10	72	55	94
			0.25	90	30	90[a,c]				
			1	38	72	97[b]				
4		$Zn((CH_2)_3CHMe_2)_2$	1	18	56	94[b]	10	72	75	90
5		$Zn((CH_2)_3CHMe_2)_2$	1	27	63	93[b]	10	72	86	93
6		$Zn((CH_2)_4OTBS)_2$	1	21	76	87[b]	10	120	65	90
7		$Zn((CH_2)_5Br)_2$	1	36	65	89[b]	10	48	48	90

[a] Solvent-free conditions. [b] Concentrated reaction conditions (2 equiv toluene was added to the reaction). [c] $Ti(Oi\text{-}Pr)_4$ (0.6 equiv) was used.

The scalability of the solvent-free procedure for the enantioselective addition of alkyl groups to ketones was examined (eq 12).[193] The reaction of 5 g of propiophenone



(12)

with dimethylzinc was conducted with 0.5 mol % L* under solvent-free conditions for 48 h to provide 5 g (90% yield) of the addition product with 92% ee. The ligand was recovered in 84% yield. These results highlight the potential scalability of this solvent-free process.

2.6.3.1. Tandem One-Pot Asymmetric Addition/Diastereoselective Epoxidation Sequence. Jeon and Walsh recently reported a one-pot procedure whereby the asymmetric addition to enones could be followed by a directed epoxidation to afford *syn* epoxy alcohols with three contiguous stereocenters.[191] In this chemistry, the asymmetric addition was conducted under standard conditions, and the resulting tertiary allylic alkoxide product was exposed to dioxygen to initiate the directed epoxidation. A proposed mechanism of this reaction (Figure 33) involves insertion of dioxygen into the Zn−C bond to generate a zinc peroxy species. Transmetalation of the peroxide to the titanium allylic alkoxide followed by oxygen atom transfer and work up affords the epoxy alcohol product. In support of this proposal, TBHP (*tert*-butyl hydroperoxide) can be substituted for dioxygen in the directed epoxidation step.[204] Presumably, the TBHP protonates the dialkylzinc to generate a similar zinc peroxide. An advantage of TBHP over dioxygen in the epoxidation is that it is easier to control the rate of addition of the TBHP.

A one-pot asymmetric addition/diastereoselective epoxidation protocol employing the solvent-free reaction conditions was developed on the basis of the addition of dimethylzinc to enones (Table 32). After the addition reaction was conducted under the solvent-free reaction conditions, the reaction mixture was cooled to 0 °C, and commercially available 5.5 M TBHP in decane was cautiously added (Table 34).[205] After 4 h, the reaction was complete, and the epoxy alcohols were isolated in high yields (87−95%, Table 34). It is noteworthy that these yields are significantly higher than those obtained under standard conditions.[191]

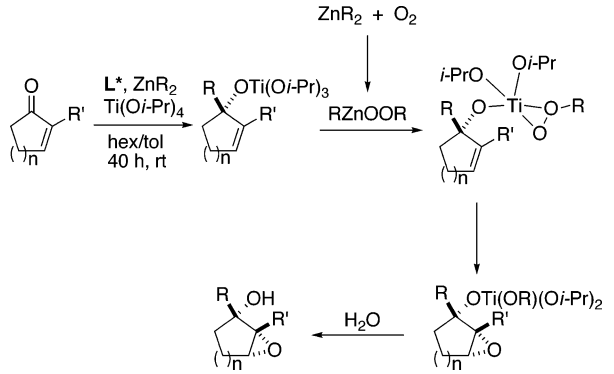
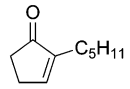
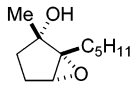
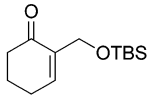
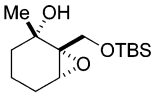
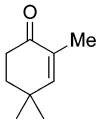
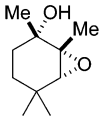
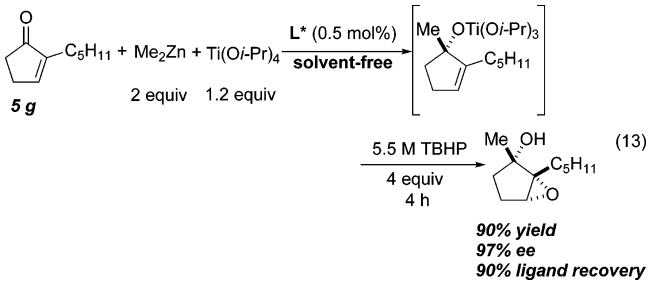


Figure 33. One-pot asymmetric addition/diastereoselective epoxidation reaction with dioxygen.

Table 34. One-Pot Asymmetric Addition/Diastereoselective Epoxidation of Cyclic Enones with TBHP

entry	substrates	time (h) addition	time (h) epoxidation	products	yield (%)
1		45	4		87
2		44	4		95
3		44	4		95

Inspired by these results in Table 34, the one-pot asymmetric addition/diastereoselective epoxidation was examined on a larger scale with dimethylzinc to 2-pentyl-2-cyclopenten-1-one using 5 g of the enone, 2 equiv of dimethylzinc, and 0.5 mol % ligand (eq 13). Upon completion of the



(13)

addition, the reaction was cooled to −10 °C, and 5.5 M TBHP (4 equiv) was carefully added. After 4 h, the reaction was quenched, and the epoxy alcohol was isolated in 90% yield (5.45 g) with 90% ligand recovery. The 90% yield of the *syn* epoxy alcohol obtained in this large-scale reaction represents a significant improvement over the 67% yield originally reported for the asymmetric addition/diastereoselective epoxidation under standard conditions.[194]

As outlined in this study of solvent-free and highly concentrated asymmetric additions to ketones, catalyst loading can be reduced 4- to 40-fold while maintaining similar yields and high levels of enantioselectivity compared with reactions conducted with solvents. This work represents the first examples of solvent-free asymmetric additions to ketones in tandem with a diastereoselective epoxidation reaction to provide *syn* epoxy alcohols with high levels of enantio- and diastereoselectivity. Furthermore, the results suggest that both the asymmetric alkylation of ketones and the asymmetric addition/diastereoselective epoxidation are amenable to scale up. The solvent-free and highly concentrated asymmetric additions outlined above represent the best methods to date to synthesize enantioenriched tertiary alcohols and tertiary epoxy alcohols.

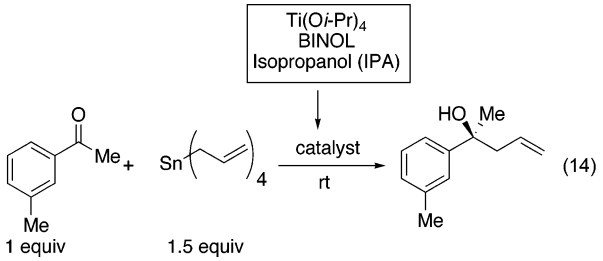
2.6.4. Asymmetric Allylation of Ketones

The catalytic asymmetric allylation of aldehydes and ketones has proven to be a very useful transformation in organic synthesis.[176,206] Although highly enantioselective catalysts for the allylation of aldehydes were reported in the early 1990s,[207,208] highly enantioselective catalysts for ketone allylation have proven more challenging. New catalysts for this reaction, however, are beginning to emerge.[176,206,209−218]

Table 35. Catalytic Asymmetric Allylation of 3′-Methylacetophenone from Eq 14

entry	solvent	Ti(O*i*-Pr)$_4$ (mol %)	BINOL (mol %)	IPA (equiv)	% ee (% yield)
1	CH_2Cl_2	20	20	20	96 (82)
2	CH_2Cl_2	20	20	3	94 (91)
3	CH_2Cl_2	10	10	20	88 (94)
4	CH_2Cl_2	10	10	3	81 (86)
5	no CH_2Cl_2	20	20	20	85 (91)
6	conc.	10	10	3	81 (88)
7		5	5	3	79 (84)

Waltz, Gavenonis, and Walsh introduced the first general and highly enantioselective catalyst for the asymmetric allylation of ketones (eq 14).[219,220] The catalyst, based on



(14)

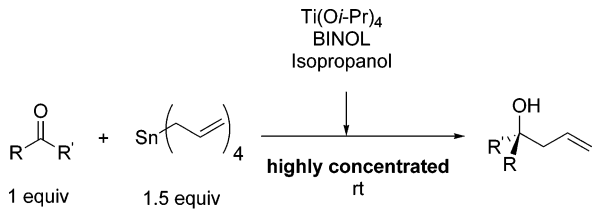
titanium tetraisopropoxide, BINOL, and isopropanol, required high loadings to achieve maximum enantioselectivity (Table 35, entry 1, 20 mol %). In an effort to reduce the amount of solvent employed, the allylation in entry 1 (96% ee) was conducted in the absence of dichloromethane solvent (eq 14). The enantioselectivity of the product dropped to 85% at 20 mol % catalyst (Table 35, entries 1 vs 5) and even further at lower loadings (entries 6 and 7). Under the highly concentrated conditions, the enantioselectivity fell below the useful level with this catalyst system.[221]

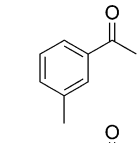
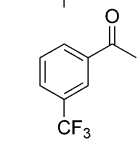
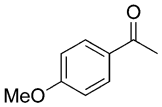
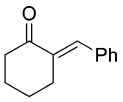
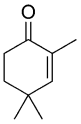
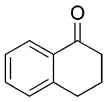
It is known that the ratio of titanium to BINOL can impact the enantioselectivity in the asymmetric allylation of aldehydes.[207,208,222] Wooten, Kim, and Walsh subsequently dem-

Table 36. Optimization of the Asymmetric Allylation of 3′-Methylacetophenone (Eq 14) by Variation of the Ti/BINOL and the mol % Catalyst Loading

entry	$Ti(O\textit{i}\text{-}Pr)_4$ (mol %)	BINOL (mol %)	IPA (equiv)	% ee (% yield)
1	10	10	3	88 (88)
2	10	20	3	95 (93)
3	5	10	3	90 (90)
4	2	4	3	55 (97)
5	1	2	3	28 (95)

Table 37. Substrate Scope in the Asymmetric Allylation of Ketones with 1:2 Ti/BINOL Ratio under Highly Concentrated Conditions

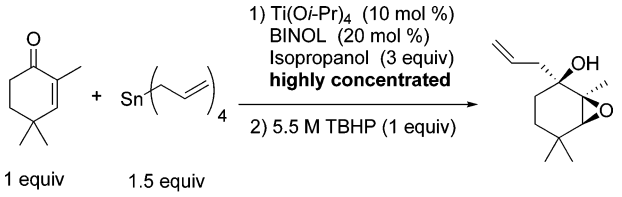


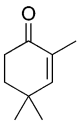
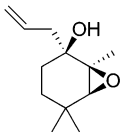
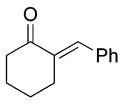
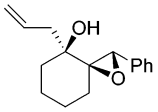
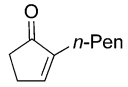
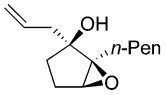
entry	substrate	Ti:BINOL (mol %)	IPA (equiv)	ee (%)	yield (%)
1		10 : 20	3	95	93
2		5 : 10	3	90	90
3		10 : 20	3	89	87
4		5 : 10	3	79	85
5		10 : 20	3	88	99
6		5 : 10	3	82	92
7		10 : 20	3	91	96
8		5 : 10	3	85	99
9		10 : 20	3	91	80
10		5 : 10	3	86	85
11		10 : 20	3	87	99
12		5 : 10	3	79	99

onstrated that under highly concentrated conditions (no dichloromethane), increasing the ratio of Ti/BINOL from 1:1 to 1:2 in eq 14 resulted in an increase in the enantioselectivity from 88% to 95% while maintaining high yield (compare entries 1 and 2, Table 36). On the basis of this observation, catalyst optimization was continued maintaining a 1:2 ratio of Ti/BINOL. Reduction of the titanium to 5, 2, and 1 mol % led to an erosion of enantioselectivity, which became large below 5 mol % (Table 36, entries 3−5).

The substrate scope was explored with a 1:2 ratio of Ti/BINOL and 3 equiv of IPA under highly concentrated conditions (Table 37). Substituted acetophenone derivatives, such as 3′-(trifluoromethyl) and 4′-methoxyacetophenone, underwent allylation at 10 mol % catalyst loading with

Table 38. Tandem Asymmetric Allylation under Concentrated Conditions Followed by a Chemo- and Diastereoselective Epoxidation



entry	substrate	product	ee (%)	yield (%)
1			91	84
2			91	87
3			90	85

similar enantioselectivities (89% and 88%, entries 3 and 5). For comparison, 3′-methylacetophenone underwent allylation under the same conditions generating the product in 95% ee (Table 37, entry 1). Catalyst reduction to 5 mol % in the allylation of acetophenone derivatives resulted in a decrease in enantioselectivities to 90%, 79%, and 82% (entries 2, 4, and 6, respectively). The enone in entries 7 and 8 proved to be an excellent substrate, affording enantioselectivities of 91% and 85% at 10 and 5 mol % catalyst, respectively.

Allylation of the endocyclic α,β-unsaturated enone provided the corresponding homoallylic alcohol in 91% and 86% enantioselectivity at 10 and 5 mol % catalyst (entries 9 and 10). The cyclic ketone α-tetralone reacted with slightly lower enantioselectivity (87% and 79%, entries 11 and 12). The results listed in Table 37 demonstrate the potential range of substrates that can be transformed into homoallylic alcohols with high levels of enantioselectivity using this new catalyst under highly concentrated conditions.

2.6.4.1. Tandem One-Pot Asymmetric Allylation/Diastereoselective Epoxidation Sequence. The synthetic efficiency of a transformation can be increased via tandem reactions, which enable rapid increases in molecular complexity with minimal isolation and purification.[223] Thus, Wooten, Kim, and Walsh conducted the asymmetric allylation of enones under highly concentrated conditions followed by a chemo- and diastereoselective directed epoxidation of the allylic double bond (Table 38).[221] In this reaction, the titanium allylation catalyst also catalyzes the diastereoselective directed epoxidation reaction. In this way, the ketone allylation under highly concentrated conditions was followed by addition of 1 equiv of anhydrous TBHP (5.5 M) (Table 38). The epoxidation proceeded smoothly at room temperature to provide *syn* epoxy alcohols as a single diastereomer in 84−87% yield (Table 38). No loss of ee was observed in the generation of the epoxy alcohols in Table 38 compared with the simple allylation products (Table 37). Starting from achiral precursors, this one-pot sequence results in the generation of three contiguous stereocenters with excellent enantio-, diastereo-, and chemoselectivity and with high yields.[221]

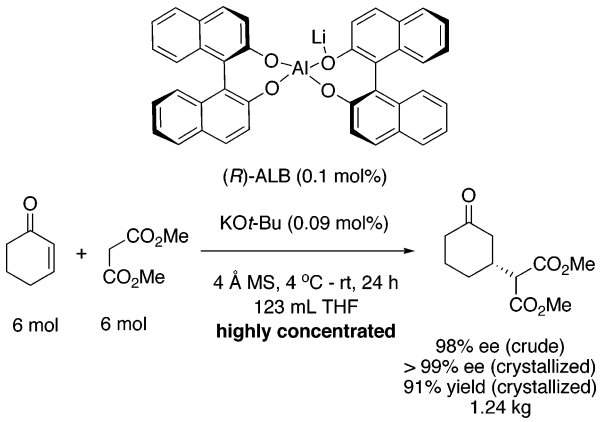


Figure 34. Highly efficient enantioselective Michael reaction catalyzed by (*R*)-ALB under highly concentrated conditions.

There are several noteworthy features about this system. Although the adaptation of the original highly enantioselective 1:1 titanium tetraisopropoxide/BINOL allylation catalyst to highly concentrated conditions resulted in significant loss in enantioselectivity (Table 35), a new catalyst was developed that exhibited high enantioselectivity under highly concentrated conditions. The new catalyst has a 1:2 ratio of titanium tetraisopropoxide/BINOL. Under highly concentrated conditions, the loading of titanium tetraisopropoxide and BINOL were reduced with respect to the original catalyst system in dichloromethane. Although elimination of the dichloromethane is significant, the use of tin reagents will need to be circumvented to increase the environmental friendliness of this process. Nonetheless, the enantioenriched products accessible with these methods are particularly useful intermediates in synthesis.

2.7. Lewis Acid Catalyzed Asymmetric Michael Reactions

A driving force in asymmetric catalysis is the development of catalysts that are efficient, highly enantioselective, scalable, and applicable to the synthesis of natural and unnatural products. One system that comes very close to meeting these requirements is Shibasaki's aluminum lithium BINOLate-based (ALB) catalyst (Figure 34).[224,225] At low catalyst loading (0.1 mol %), (*R*)-ALB promoted the asymmetric conjugate addition of dimethyl malonate to 2-cyclohexenone in the presence of catalytic KO*t*-Bu with 98% enantioselectivity as illustrated in Figure 34.[226] Crystallization furnished the product in 91% yield with an ee of >99%. The reaction was performed on *a 6 mol scale with only 123 mL of THF solvent*. The highly concentrated conditions allow the researchers to perform the asymmetric addition in a 2 L round-bottomed flask with very high volume productivity and atom efficiency.

The efficient and highly enantioselective generation of the Michael addition product allowed Shibasaki and co-workers[227] to synthesize (−)-strychnine, one of the most complex natural products for its weight. The Michael addition product is transformed into the *E*-ring of this alkaloid in an elegant synthesis (Figure 35).

The asymmetric Michael reaction catalyzed by the heterobimetallic ALB catalyst is exemplary in many respects and certainly attests to the potential utility of highly concentrated reaction conditions on large scales.

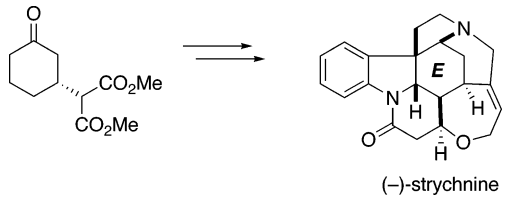


Figure 35. The asymmetric addition product was the starting material for the synthesis of (−)-strychnine.

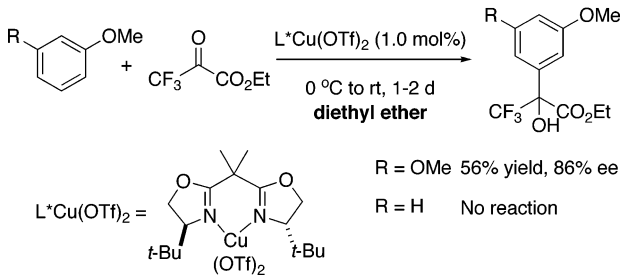


Figure 36. Asymmetric Friedel−Crafts reaction with diethyl ether solvent and a copper-based catalyst.

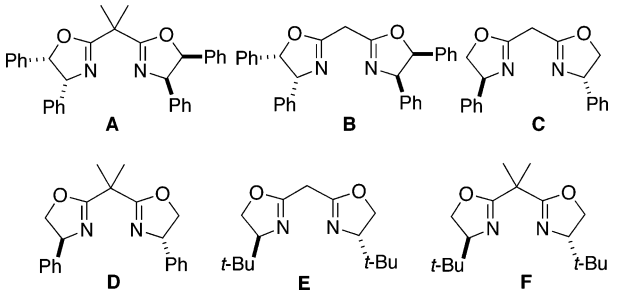


Figure 37. Bis(oxazoline) ligands **A**−**F** used in the solvent-free asymmetric Friedel−Crafts reaction (Tables 39 and 40).

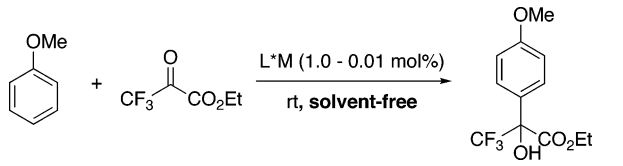
2.8. Asymmetric Friedel–Crafts with Aromatic Ethers

The catalytic asymmetric Friedel−Crafts reaction has received considerable attention in recent years, resulting in significant advances.[228] The products of these reactions contain benzylic carbon stereocenters, which are found in thousands of natural products and have achieved a privileged status in medicinal chemistry.[229]

Bis(oxazoline) ligands[230] have been shown to give high enantioselectivities under normal solvent conditions.[231,232] Jørgensen and co-workers had examined copper(II)-based bis(oxazoline) catalysts (10 mol %) in the asymmetric Friedel−Crafts reaction of 3′-methoxyanisole with ethyl 3,3,3-trifluoropyruvate in anhydrous diethyl ether. The pyruvate derivative is likely activated by chelation to the Lewis acidic copper catalyst through the two carbonyl oxygens before attack by the nucleophilic aryl ether. The electrophilic aromatic substitution product was isolated in 56% yield with 86% ee (Figure 36).[232] The less activated anisole, however, did not undergo reaction under these conditions.

To overcome the low reactivity of anisole, Liu, Wang, Chen, and their co-workers examined a series of bis(oxazoline) ligands (**A**−**F**, Figure 37) and metal salts in this reaction under solvent-free conditions.[233] The results of the initial screening are outlined in Table 39. In contrast to the reactions conducted in diethyl ether (Figure 36), by use of a slightly less bulky catalyst under solvent-free reaction conditions anisole reacted with 3,3,3-trifluoropyruvate to

Table 39. Catalyst Screening in the Asymmetric Friedel−Crafts Alkylation of Anisole with Ligands A−F of Figure 37



entry	ligand	metal salt	mol %	time (h)	yield (%)	ee (%)
1	**A**	$Cu(OTf)_2$	1.0	10	90	88
2	**A**	$Cu(ClO_4)_2$	1.0	18	95	81
3	**A**	$Cu(OAc)_2$	1.0	24	trace	
4	**A**	$CuCl_2$	1.0	24	trace	
5	**A**	Cu(OTf)	1.0	24	trace	
6	**A**	$Zn(OTf)_2$	1.0	24	45	81
7	**A**	$Mg(OTf)_2$	1.0	24	trace	
8	**A**	$Sc(OTf)_3$	1.0	24	trace	
9	**A**	$FeCl_3$	1.0	24	<5	
10	**B**	$Cu(OTf)_2$	1.0	15	80	80
11	**C**	$Cu(OTf)_2$	1.0	20	78	22
12	**D**	$Cu(OTf)_2$	1.0	17	85	79
13	**E**	$Cu(OTf)_2$	1.0	24	trace	
14	**F**	$Cu(OTf)_2$	1.0	24	trace	
15		$Cu(OTf)_2$	1.0	24	7	
16	**A**	$Cu(OTf)_2$	0.1	20	85	86
17	**A**	$Cu(OTf)_2$	0.01	20	70	85

furnish product in very high yield and enantioselectivity (up to 90% yield and 88% ee). As illustrated in Table 39, the highest yields at 1.0 mol % catalyst were obtained using copper salts, $Cu(OTf)_2$ and $Cu(ClO_4)_2$, in combination with ligand **A**. This represents a 10-fold reduction in catalyst loading from previous studies under solvent conditions (Figure 36).[232] Use of ligand **F** did not result in formation of product in diethyl ether (Figure 36) or under solvent-free conditions (entry 14), indicating the impact of subtle differences in the ligand structure on reactivity. These authors also found that lowering the catalyst loading to 0.1 and 0.01 mol % had little effect on the enantioselectivity or reactivity (compare entries 1, 16, and 17). The reaction of 1 g of anisole with catalyst derived from $Cu(OTf)_2$ and ligand **A** was conducted at 0 °C resulting in formation of the product with 90% ee and in 70% yield. It was noted that the reaction was very exothermic and that caution should be used with increasing scale. This warning, of course, applies to all reactions conducted under solvent-free and highly concentrated conditions.

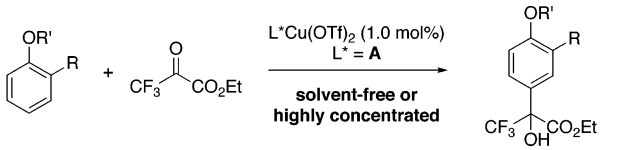
A series of aryl ethers were employed in the Friedel−Crafts asymmetric alkylation catalyzed by 1 mol % L*Cu-$(OTf)_2$ (L* = **A**, Figure 37). As illustrated in Table 40, yields ranged from 55% to 98% and enantioselectivities from 90% to 93%. In the case of solid substrates, reactions could be performed under highly concentrated conditions with CH_2Cl_2 solvent. The stereochemistry of the product in entry 7 was determined to have the (*S*)-configuration by X-ray crystallography.

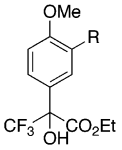
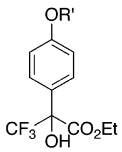
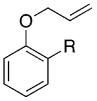
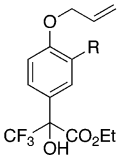
The solvent-free and highly concentrated Friedel−Crafts reaction outlined above enables access to densely functionalized and highly enantioenriched fluorinated products.

2.9. Asymmetric Pauson–Khand-Type Reaction

Carbonylative alkene−alkyne coupling (the Pauson−Khand reaction when a cobalt carbonyl complex is used) has been extensively investigated, because it provides access to various synthetically useful cyclopentenones. Recent

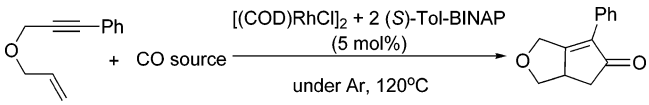
Table 40. Scope of the Asymmetric Friedel−Crafts Alkylation of Aryl Ethers with $Cu(OTf)_2$ and Ligand A of Figure 37 under Solvent-free and Highly Concentrated Reaction Conditions



entry	substrate		temp (°C)	time (h)	product	yield (%)	ee (%)
1		R = H	0	10		90	90
2		R = Me	−20	30		80	90
3		R = Ph	−20	28		55	90
4		R' = *n*-Bu	−20	40		88	92
5		R' = *Ph*	0	72		62	92
6[a]		R' = CH_2-2-C_6H_4-Br	15	18		96	92
7		R' = CH_2-4-C_6H_4-Br	25	36		85	91
8		R' = CH_2-Ph	0	16		98	90
9		R' = CH_2-3-C_6H_4-Cl	0	28		78	93
10		R = H	−20	30		62	93
11		R = Me	−20	30		75	90
12		R = Ph	−20	48		70	93

[a] Highly concentrated with CH_2Cl_2.

Table 41. Enantioselective Carbonylative Coupling of an Enyne under Solvent-free Conditions



entry	CO source (equiv)	solvent	time (h)	yield (%)	ee (%)
1	cinnamaldehyde (20)	none	4	89	82
2	CO gas	none	4	23	60
3	CO gas	xylene	36	51	10

advancements in Pauson−Khand-type reactions include catalytic and enantioselective versions.[234]

Shibata and co-workers reported an intramolecular catalytic carbonylative alkene−alkyne coupling using a rhodium(I) catalyst and aldehydes as a CO source.[235,236] In the absence of solvent, the authors found that the Pauson−Khand-type reaction using an achiral catalyst was faster when cinnamaldehyde was used as the CO source than when CO was employed. Based on these results, they prepared a chiral catalyst in situ from $[(COD)RhCl]_2$ (5 mol %) and Tol-BINAP (2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl, 10 mol %). In the presence of a large excess of cinnamaldehyde (20 equiv), the enyne coupling proceeded smoothly to give the cyclized product in good yield and 82% ee (Table 41, entry 1). When CO gas was used under solvent-free conditions, the reaction was accelerated with the sacrifice of both yield and enantioselectivity (Table 41, entry 2). For comparison, the asymmetric carbonylative coupling was also examined in xylene in the presence of CO gas, although the yield was

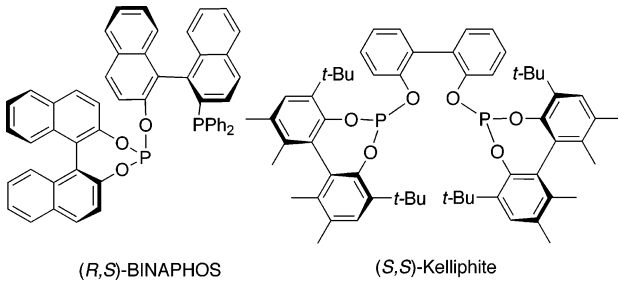


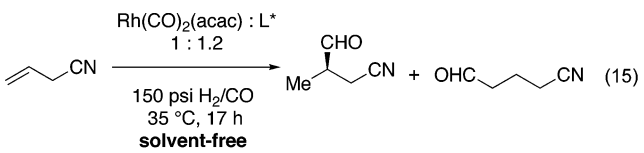
Figure 38. Useful ligands for rhodium-catalyzed hydroformylation, (*R*,*S*)-BINAPHOS and (*S*,*S*)-kelliphite.

moderate and ee dropped dramatically (Table 41, entry 3). Unfortunately, the enantioselective reaction was not examined with fewer equivalents of cinnamaldehyde in this study.

2.10. Asymmetric Hydroformylation

The asymmetric hydroformylation of olefins is a direct route to optically active aldehydes, which are valuable precursors for a variety of pharmaceuticals and agrochemicals. Although homogeneous hydroformylation is the largest volume transition metal-catalyzed process, catalytic enantioselective versions are still underdeveloped.[237] Much of the work in asymmetric hydroformylation has centered on vinyl arene substrates, which generate 2-aryl propionic acid derivatives, a class of nonsteroidal anti-inflammatory medications such as (*S*)-naproxen.[238] Among the catalysts successfully applied to the asymmetric hydroformylation reaction is the rhodium (*R*,*S*)-BINAPHOS-based catalyst (Figure 38), which promoted the hydroformylation of styrene in 96% ee.[239,240] On the basis of research performed at Union Carbide with bis(phosphite) ligands,[241,242] Colbey, Klosin, Whiteker, and their co-workers examined use of bis(phosphite) ligands with stereochemically dynamic biaryl backbones,[243] as represented by (*S*,*S*)-kelliphite (Figure 38).

These authors examined the catalytic asymmetric hydroformylation of allyl cyanide as a potential entry into important enantioenriched building blocks useful in the synthesis of biologically active compounds (Figure 39). Initially, a series of bis(phosphite) ligands were examined in the asymmetric hydroformylation in toluene. (*S*,*S*)-Kelliphite was identified as the most enantioselective over a series of related phosphite ligands with different backbones.[244] A comparison of rhodium-based (*R*,*S*)-BINAPHOS and (*S*,*S*)-kelliphos catalysts was undertaken at high substrate/catalyst ratios (2000−10000:1) under solvent-free conditions (eq 15). Reaction rates were found to be the highest in neat



allyl cyanide. Kelliphite was about 7 times more active than BINAPHOS at 10000:1 allyl cyanide/catalyst as shown in Table 42 (entries 3 vs 6). The kelliphite reaction was complete in 16 h with an average TOF of 635 per hour. Interestingly, the b/l ratio (b/l = branched/linear) increased at the highest substrate to catalyst ratio with kelliphite. The hydroformylation was scaled up to 75 mL of allyl cyanide in a 300 mL pressure vessel under conditions similar to those in eq 15 (1500:1 substrate/catalyst). Reaction completion was

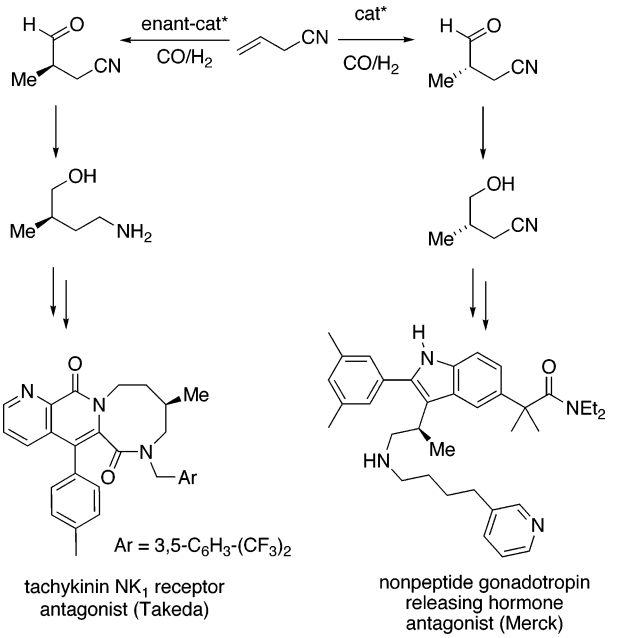


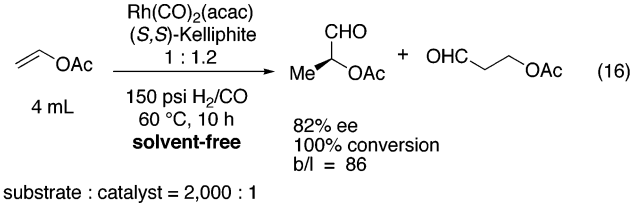
Figure 39. Catalytic asymmetric hydroformylation of allyl cyanide provides key enantioenriched building blocks for the synthesis of potent antagonists.

Table 42. Comparison of the Asymmetric Hydroformylation of Allyl Cyanide (Eq 15) with Rhodium Catalysts Based on (*R*,*S*)-BINAPHOS and (*S*,*S*)-Kelliphite under Solvent-free Conditions

entry	ligand	nitrile/Rh	conv (%)	regioselectivity (b/l)	ee (%)
1	(*R*,*S*)-BINAPhos	2000	64.0	2.8	74.7
2	(*R*,*S*)-BINAPhos	4000	37.1	2.9	75.1
3	(*R*,*S*)-BINAPhos	10000	14.8	2.7	77.2
4	(*S*,*S*)-kelliphite	2000	100	17.8	77.8
5	(*S*,*S*)-kelliphite	4000	100	17.3	78.8
6	(*S*,*S*)-kelliphite	10000	100	18.5	78.8

reached in 5 h with enantioselectivity of 80% and b/l of 20. It was found that the crude product could be readily used to prepare the enantioenriched precursors in Figure 39.

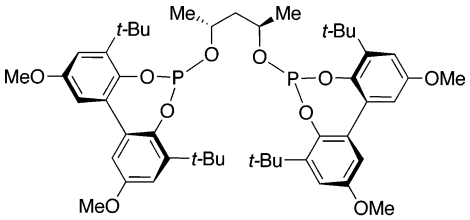
Similar results were obtained in the asymmetric hydroformylation reaction of vinyl acetate with kelliphite under similar conditions (eq 16). In this case, the enantioselectivity



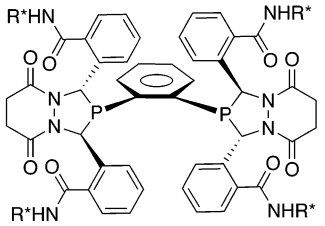
was 82%, the b/l ratio was 86, and the minimum average TOF was 200/h.[237]

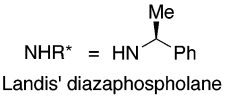
These studies clearly indicate the benefits of catalytic asymmetric solvent-free processes as reactions were conducted on large laboratory scale (up to 75 mL substrate) in a 300 mL reaction vessel with very high volume efficiency. Further, this reaction is very atom economical, as all the atoms of the substrates are incorporated into the product.

Although the results outlined above are impressive, industrial experts contend that the reaction does not meet the standard required by industry because (1) the reaction rates are too low at the temperatures needed to obtain good

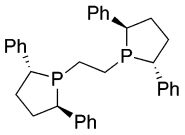


(2*R*,4*R*)-Chiraphite





Landis' diazaphospholane



(*R*,*R*)-Ph-BPE

Figure 40. Structures of ligands used in the asymmetric hydroformylation reaction: (2*R*,4*R*)-chiraphite, Landis' diazaphospholane, and (*R*,*R*)-Ph-BPE.

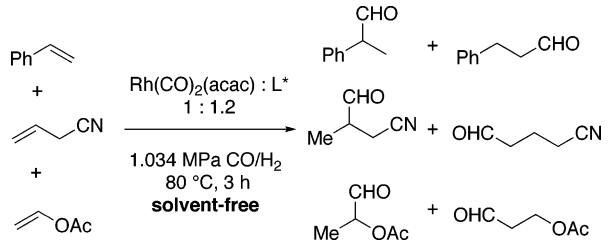


Figure 41. Simultaneous asymmetric hydroformylation of three olefins under solvent-free conditions. The total volume of olefins was 4.43 mL. The results are shown in Table 43.

selectivity, (2) there are difficulties simultaneously controlling both regio- and enantioselectivity, and (3) a ligand that exhibits broad substrate scope is lacking.[245] Thus, new generations of asymmetric hydroformylation catalysts are needed that can be used at higher temperature while maintaining selectivity.

In this study, Klosin and co-workers examined a series of ligands, including (*R*,*S*)-BINAPHOS,[240] (*S*,*S*)-kelliphite (Figure 38), (2*R*,4*R*)-chiraphite, Landis' diazaphospholane,[246] and a DuPHOS analog,[247,248] (*R*,*R*)-Ph-BPE (Figure 40).[249] Under solvent-free hydroformylation conditions, rhodium complexes of the ligands in Figures 38 and 40 were employed at 80 °C, 150 psi, and substrate/catalyst ratio of 30000:1 (Figure 41). The average TOF of catalyst derived from (*R*,*R*)-Ph-BPE was 4467/h, which was similar to (*R*,*S*)-BINAPHOS and (*S*,*S*)-kelliphite. Catalysts containing (2*R*,4*R*)-chiraphite and the diazaphospholane were even faster (although less selective). The results of these experiments are outlined in Table 43. It was found that rhodium complex of (*R*,*R*)-Ph-BPE gave the highest enantioselectivity with styrene (92%) and allyl cyanide (90%), while the diazaphospholane gave the best enantioselectivity with vinyl acetate (95%).

Table 43. Asymmetric Hydroformylation Reactions of Styrene, Allyl Cyanide, and Vinyl Acetate with Different Ligands under Solvent-free Conditions

entry	ligand	conv. (%)	b/l	ee (%)	config.
		Ph			
1	(2*R*,4*R*)-Chiraphite	32	10.8	51	*R*
2	(*R*,*S*)-BINAPHOS	35	4.6	81	*R*
3	(*S*,*S*)-Kelliphite	32	9.2	3	*S*
4	diazaphospholane	73	5.7	80	*R*
5	(*R*,*R*)-Ph-BPE	33	45	92	*R*
		CN			
6	(2*R*,4*R*)-Chiraphite	74	5.8	13	*R*
7	(*R*,*S*)-BINAPHOS	58	2.1	68	*R*
8	(*S*,*S*)-Kelliphite	99	10.1	66	*S*
9	diazaphospholane	100	3.9	80	*R*
10	(*R*,*R*)-Ph-BPE	67	7.6	90	*R*
		OAc			
11	(2*R*,4*R*)-Chiraphite	34	204	50	*R*
12	(*R*,*S*)-BINAPHOS	23	7.1	58	*S*
13	(*S*,*S*)-Kelliphite	32	100	75	*R*
14	diazaphospholane	92	47	95	*S*
15	(*R*,*R*)-Ph-BPE	34	263	82	*S*

On the basis of these results, the researchers concluded that (*R*,*R*)-Ph-BPE and diazaphospholane achieved sufficient TOF (>4000/h at 80 °C), yield, and enantioselectivity to be used in large-scale industrial processes.[245]

2.10.1. Heterogeneous Asymmetric Hydroformylation Reactions

Despite the many advantages of homogeneous asymmetric catalysts over their heterogeneous counterparts, there are two major drawbacks of soluble catalysts: separation of catalyst from products and use of organic solvents to suppress catalyst precipitation. Thus, the heterogenization of homogeneous catalysts on organic polymers has been investigated with great intensity.[250−255] Many examples employing supported catalysts suspended in organic solvents have been reported; however, use of supported catalysts under solvent-free conditions in flow reactors is relatively unexplored.

In this context, Shibahara, Nozaki, and Hiyama reported the solvent-free vapor-phase asymmetric hydroformylation of the volatile olefins *cis*-2-butene and 3,3,3-trifluoropropene using a batchwise reactor and a continuous vapor-flow column reactor. The catalyst used in these reactions was a highly cross-linked polystyrene-supported (*R*,*S*)-BINAPHOS−Rh(I) complex, which is illustrated with its homogeneous derivative in Figure 42.[256]

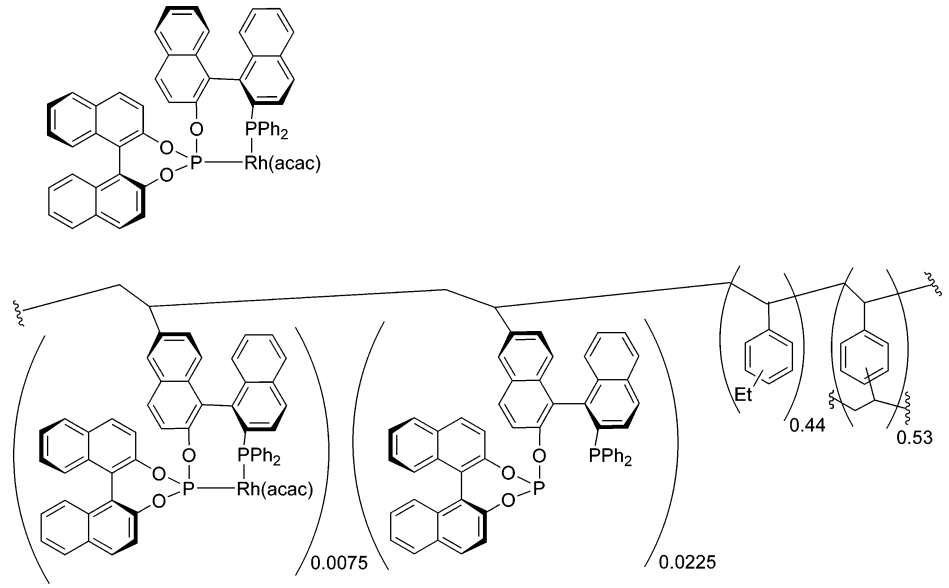
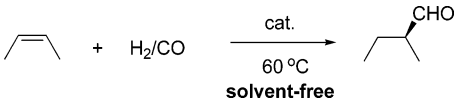


Figure 42. The homogeneous and highly cross-linked Rh(I) complexes of (*R*,*S*)-BINAPHOS.

Table 44. Asymmetric Hydroformylation of *cis*-2-Butene in a Batchwise Reactor with the Heterogeneous and Homogeneous Catalysts in Figure 42



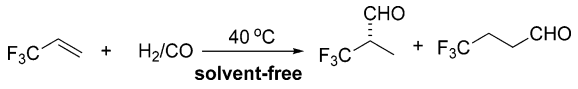
entry	*cis*-2-butene (atm)	solvent	syngas (atm)	time (h)	TON	TOF (h^{-1})	ee (%) (config)
1	3.0	none	24	2	20	10	82 (*S*)
2	3.5	none	21	6	52	9	18 (*S*)
3	2.6	none	32	6	28	5	75 (*S*)
4	liquefied	none	33	12	156	13	79 (*S*)
5	solution	benzene	32	8	184	23	82 (*S*)

They found that the initial pressure of hydrogen, carbon monoxide, and olefin greatly impacted the TON of the catalyst and the product ee. The results of vapor-phase asymmetric hydroformylation of *cis*-2-butene in a batchwise reactor are summarized in Table 44. When the reaction started with syngas (24 atm, H_2/CO 1/1), *cis*-2-butene (3 atm), and the supported catalyst (Figure 42), (*S*)-2-methylbutanal was generated in 82% ee after 2 h (Table 44, entry 1). The product ee decreased with increasing reaction time, however (entry 2). The ee erosion could be partially offset by increasing the pressure of *cis*-2-butene or using liquefied olefin (compare entries 2−4). The activity and selectivity of the supported catalyst were comparable to those of the homogeneous analog, although TON and TOF were lower (Table 44, entry 5).[257]

Asymmetric hydroformylation of 3,3,3-trifluoropropene was performed with the same catalyst in a continuous flow system with TOF of 9 h^{-1}, iso/n (iso/normal) ratio of 95/5, and 90% ee at 40 °C under H_2/CO pressure of 50 atm (Table 45, entries 1 and 2). High selectivities were achieved, but the TOF remained at a low level compared with the homogeneous reaction (Table 45, entry 3).[256]

The asymmetric hydroformylation reactions discussed here demonstrated the successful use of the polymer-supported catalyst under solvent-free conditions. Easy separation of the catalyst from the products has been achieved, increasing the attractiveness of this method.[258]

Table 45. Continuous Flow Asymmetric Hydroformylation of 3,3,3-Trifluoropropene with the Heterogeneous and Homogeneous Catalysts in Figure 42



entry	total pressure (atm)	solvent	time (h)	TON	TOF (h^{-1})	iso/n	ee (%) (config)
1	20	none	4	22	5.5	88/12	82 (*S*)
2	50	none	0.5	4.5	9	95/5	90 (*S*)
3	solution	benzene	18	1152	64	95/5	93 (*S*)

2.11. Asymmetric Hydrogenation Reaction

Transition metal-catalyzed enantioselective hydrogenation has been established as one of the most efficient strategies for the synthesis of enantioenriched molecules. While most effort has focused on the design of chiral ligands, which is a key issue for obtaining high activity and selectivity,[259−261] much less emphasis has been placed on the optimization of reactions under more environmentally friendly solvent-free conditions.

Great advances have been made in the asymmetric reduction of ketones via hydrogenations and transfer hydrogenation. The pioneering work of Noyori and co-workers has spawned numerous investigations into the application of bifunctional catalysts to ketone reduction as well as C−C bond-forming reactions.[262,263] To our knowledge, however, application of these catalysts under solvent-free or highly concentrated conditions has been limited.

Abdur-Rashid, Lough, and Morris examined several catalysts in the asymmetric reduction of ketones and imines under highly concentrated and solvent-free conditions.[264] Reactions were performed neat with liquid substrates, and a small amount of benzene was added to solid substrates. Precatalysts **A**, **B**, and **C** (Figure 43) were employed in the hydrogenation of ketones and imines. The results are shown in Table 46. Catalyst formed from **A** exhibited higher levels of enantioselectivity than that from **B**, although both gave only moderate enantioselectivity. With acetophenone, catalyst derived from **A** gave 88% enantioselectivity. Related catalysts gave lower enantioselectivities.[265] In the asymmetric

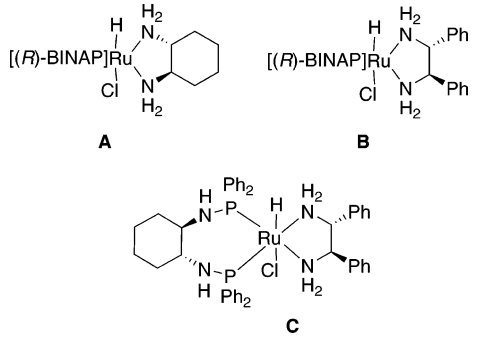
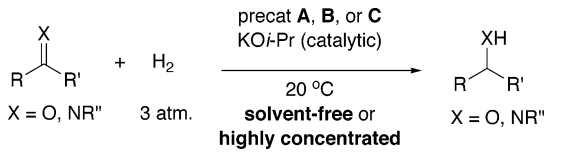
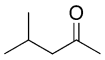
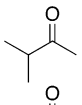
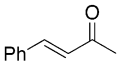
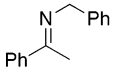


Figure 43. Precatalysts used in the asymmetric hydrogenation of ketones and imines (Table 46).

Table 46. Results from the Catalytic Asymmetric Hydrogenation of Imines under Solvent-free and Highly Concentrated Conditions with Precatalysts A−C (Figure 43)



substrate	precat.	S : C[a]	conv (%)	time (h)	ee (%)
	A	5,000	100	< 12	52
	A	3,600	100	< 12	46
	A	5,000	87	48	50
	A B	5,000 5,000	100 100	< 12 < 12	88 73
	A B	5,000 5,000	100 100	< 12 < 12	60 64
	A B	500 500	100 90	36 72	71 70
	A B	500 500	100 90	36 24	60 50
	A B C	500 500 1,500	12 17 91	60 60 60	60 60 92

[a] S:C = substrate/catalyst

hydrogenation of imines, catalyst derived from **C** gave up to 92% enantioselectivity with the *n*-Bu imine of acetophenone and was about an order of magnitude more active than the BINAP catalysts formed from **A** and **B**.

In a hydrogenation that goes by a more traditional mechanism involving metal hydride intermediates, Zhang et al. reported the synthesis and resolution of a bulky and electron-rich derivative of SEGPhos (SEGPhos′, Figure 44) and its application in Ru-catalyzed asymmetric hydrogenation reaction.[266]

The solvent-free catalytic enantioselective hydrogenation of ethyl acetoacetate with extremely low catalyst loading (20000:1, substrate/catalyst) was reported by Zhang et al. in

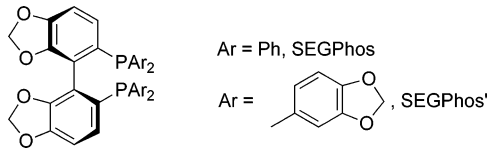
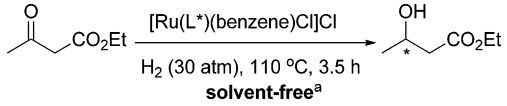


Figure 44. Structure of SEGPhos and a derivative, SEGPhos′.

Table 47. Comparison of the Asymmetric Hydrogenation of Ethyl Acetoacetate with SEGPhos and SEGPhos′ in Ethanol Solvent and under Solvent-free Conditions



entry	solvent	additive	L*	conv (%)	ee (%)
1	EtOH	none	SEGPhos′	35.9	96.0
2	EtOH	none	SEGPhos	35.7	96.6
3	none	none	SEGPhos′	56.8	91.6
4	none	none	SEGPhos	62.5	88.4
5[b]	none	H_2SO_4	SEGPhos′	100	96.8
6[b]	none	H_2SO_4	SEGPhos	100	97.5

[a] All reactions were carried out with a ratio of 20,000:1 (substrate/catalyst). [b]Additive: Ru = 1.5:1.

the presence of SEGPhos and SEGPhos′. The reaction was performed with 30 atm of H_2 at 110 °C for 3.5 h. Under the solvent-free conditions, the reaction was accelerated with only a small decrease in enantioselectivity (Table 47, entries 1 − 4). Interestingly, addition of catalytic sulfuric acid (H_2SO_4/[Ru] = 1.5:1) elevated both the reaction rate and the enantioselectivity, resulting in 100% conversion and 97.5% ee (Table 47, entries 5 and 6).

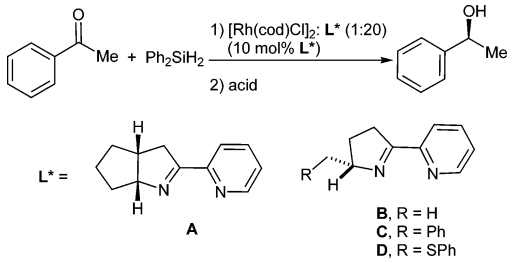
The application of SEGPhos and SEGPhos′ to the enantioselective solvent-free hydrogenation outlined above suggests that related hydrogenation catalysts may also exhibit high levels of enantioselectivity with very low catalyst loading under these conditions. Given the industrial importance of asymmetric reductions and the economic advantages of solvent-free reactions, it is anticipated that the examination of asymmetric hydrogenation catalysts under solvent-free conditions will become standard in the near future.

2.12. Asymmetric Hydrosilylation of Ketones

The enantioselective hydrosilylation of ketones is an excellent method for the synthesis of enantioenriched secondary alcohols. This approach to the preparation of chiral secondary alcohols has the advantage of very mild reaction conditions relative to other reduction methods. Further, the catalysts are often based on nitrogen-containing ligands, many of which can be prepared from naturally occurring enantiopure precursors.[267]

In research to design ligands for the asymmetric hydrosilylation of ketones, Martens et al. reported the synthesis of a series of optically active nitrogen-based chelating ligands **A**−**D** (Table 48).[268] These ligands (10 mol %) were employed in the rhodium-catalyzed enantioselective reduction of acetophenone with diphenylsilane and a $[(COD)RhCl]_2$/L* ratio of 1:20 under solvent-free conditions (Table 48, entries 1, 3, 5, and 7). The addition of a small amount of toluene reduced both yield and enantioselectivity (Table 48, entries 2, 4, and 6), except with the SPh derivative ligand **D**, which gave better results in the presence of toluene (Table 48, entry 8).

Table 48. Enantioselective Hydrosilylation of Acetophenone with Chelating Chiral Nitrogen-Based Ligands



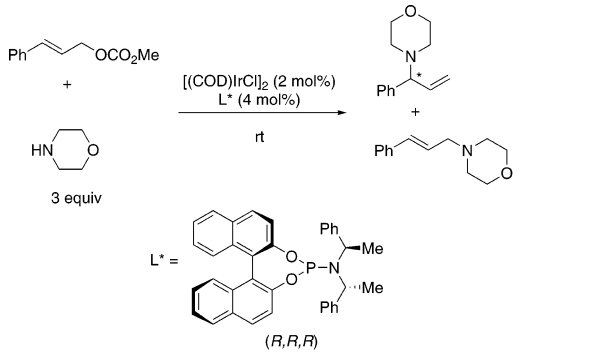
entry	ligand	solvent	yield (%)	ee (%)	config
1	**A**	none	53	28	*S*
2	**A**	toluene	38	40	*S*
3	**B**	none	86	54	*S*
4	**B**	toluene	32	25	*S*
5	**C**	none	60	39	*S*
6	**C**	toluene	40	38	*S*
7	**D**	none	36	31	*S*
8	**D**	toluene	44	41	*S*

Given the importance of asymmetric hydrosilylation reactions and in view of the modest enantioselectivities observed under solvent-free conditions in this study, it is anticipated that further investigations will be forthcoming in this area. Highly enantioselective catalysts that are compatible with a range of functional groups are in great demand and will find applications in complex molecule synthesis.

2.13. Asymmetric Allylic Amination

Enantioenriched amines are important precursors in synthetic and medicinal chemistry. One convergent strategy for the generation of chiral amines is by enantioselective C−N bond-forming reactions. Using ligands introduced by Feringa and co-workers,[269,270] Ohmura and Hartwig developed a regio- and enantioselective allylic amination reaction beginning with achiral allylic esters (Figure 45).[271] Most of the reactions in this report were conducted in THF solvent. One example is given using 3 equiv of morpholine and cinnamyl acetate. In ethanol, the iridium phosphoramidite-based catalyst promoted the reaction giving a ratio of chiral amine to achiral amine of 97:3. The enantioselectivity was 95%. Similar results were obtained under solvent-free conditions.

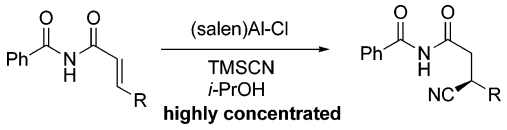
Allylic amines of this type can be easily functionalized to 1,3-amino alcohols and amino acids. It is likely that the



solvent	time	b/l	yield (%)	ee (%)
ethanol	16	97/3	95	95
none	72	96/4	87	96

Figure 45. Asymmetric allylic amination reactions.

Table 49. Conjugate Addition of TMSCN to α,β-Unsaturated Imides



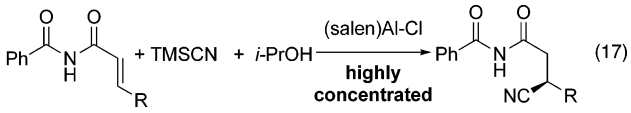
entry	R	method[a]	time (h)	yield (%)	ee (%)
1	Me	A	26	92	98
2	Et	A	26	95	97
3	*n*-Pr	A	26	90	97
4	*i*-Pr	A	26	91	94
5	*i*-Bu	A	26	93	96
6	$(CH_2)_3CH{=}CH_2$	A	48	96	95
7	*i*-Bu	B	48	90	97
8	CH_2OBn	B	48	70	87

[a] Reactions were carried out on a 0.5 mmol scale. Method A: 10 mol % (*S*,*S*)-(salen)AI-CI, 2.5 equiv of TMSCN, 2.5 equiv of 2-propanol, 0.2 mL of toluene, 24 °C. Method B: 15 mol % (*S*,*S*)-(salen)AI-CI, 4 equiv of TMSCN, 4 equiv of 2-propanol, 0.4 mL of toluene, 24 °C.

solvent-free conditions could be applied to related substrates with similar levels of success.

2.14. Asymmetric Conjugate Addition of Cyanide to α,β-Unsaturated Imides

Conjugate addition reactions to α,β-unsaturated carbonyl compounds are one of the most important and useful strategies in organic chemistry. These reactions provide access to difunctional intermediates that are readily converted to a variety of useful chiral building blocks, including β-substituted γ-aminobutyric acids and α-substituted β-amino acids.[272−276] Jacobsen and co-workers reported the application of (salen)Al(III) catalysts to the conjugate addition of hydrogen cyanide to α,β-unsaturated imides with high enantioselectivity (eq 17).[277] HCN was generated in situ from



TMSCN and 2-propanol. Employing (salen)Al−Cl complex as the catalyst under standard solvent conditions, these investigators found that the conjugate addition of HCN occurred with high enantioselectivity (90%), but the catalyst turned over only 1−2 times. Much better results were acquired when reactions were conducted in highly concentrated toluene solutions. Under these conditions, the product was generated with 90% isolated yield and 97% ee (method A). A significant substrate dependence on reactivity was observed, as shown in Table 49. In general, good results were obtained with imide substrates bearing aliphatic β-substituents. Slower-reacting imides required elevated temperature and catalyst loading (method B, entries 7 and 8). Imide derivatives bearing unsaturated β-substituents (R = aryl, vinyl, alkynyl) proved unreactive, even under forcing conditions.

Spectroscopic studies revealed that the chloride complex (salen)Al−Cl is converted to two distinct species, (salen)Al−CN and (salen)Al(imidate), under the reaction conditions. Initial rate studies reveal a second-order kinetic dependence on catalyst concentration. These preliminary data are consistent with a bimetallic, dual activation mechanism involving

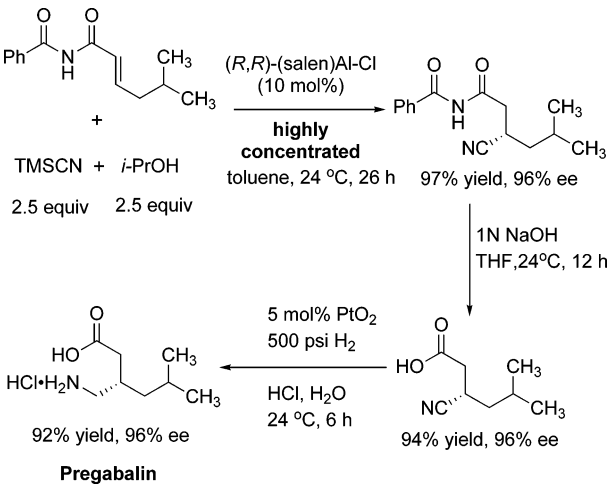


Figure 46. Synthesis of pregabalin using the catalytic asymmetric conjugate addition of cyanide.

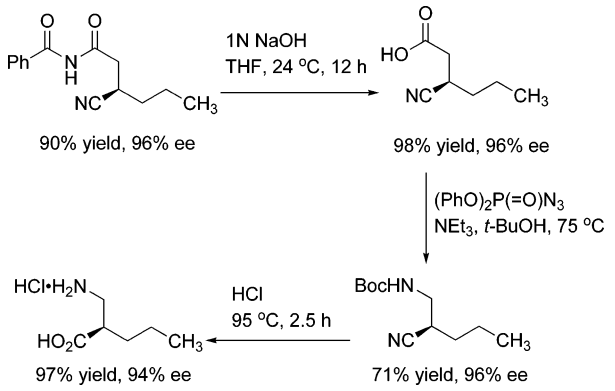


Figure 47. Synthesis of an enantioenriched α-substituted β-amino acid.

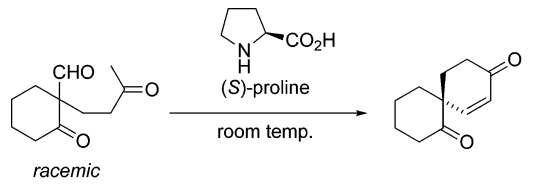
cyanide delivery from the complex (salen)Al−CN to the electrophile bound as the imidate complex, (salen)Al-(imidate).

The conjugate addition of cyanide outlined above can be applied to the synthesis of pregabalin [(*S*)-3-isobutyl-γ-aminobutyric acid], a promising anticonvulsant drug for the treatment for neuropathic pain (Figure 46). In general, enantioenriched β-substituted γ-amino acids are difficult to synthesize. For example, the manufacturing process for pregabalin entails a non-enantioselective 1,4-cyanation, followed by late-stage classical resolution. Using the chiral (salen)Al−Cl catalyst, the required cyanide adduct was prepared in 96% ee on a gram scale (Figure 46). The overall yield from commercially available materials was thus 62% over six steps.

Cyanide adducts prepared by this method can also be applied toward the synthesis of enantioenriched α-substituted β-amino acid derivatives (Figure 47).

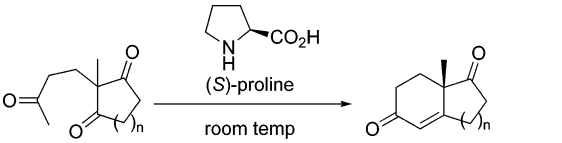
2.15. Asymmetric Organocatalytic Reactions

The discovery of the intramolecular aldol cyclizations of triketones was a milestone in asymmetric catalysis, the full impact of which would not be known for some 30 years.[111,278−280] Reported independently by the group of Hajos and Parrish[281] and the team of Eder, Sauer, and Weichert,[282,283] the reaction involved use of catalytic amounts of (*S*)-proline[284−286] to form enantioenriched enediones, which have been used in the synthesis of natural products.[287−292] These early works initiated the explosive growth in the area



conditions	yield (%)	ee (%)
(*S*)-proline **DMSO**	70	22
(*S*)-proline (0.05) **solvent-free**	49	43

Figure 48. (*S*)-Proline-catalyzed annulation employing racemic tricarbonyl substrate.



	yield (%)	ee (%)
n = 1	33	64.7
n = 2	63	68.4

Figure 49. Desymmetrization of the trione in the presence of catalytic (*S*)-proline under solvent-free conditions provides valuable diones with moderate ee's.

of organocatalysis. Although the application of enantioselective organocatalysts in synthesis is likely more environmently friendly than metal-based catalysts, few examples have been reported extending these catalysts to solvent-free reaction conditions. It is quite possible, however, that optimization of organocatalysts under solvent-free and highly concentrated reaction conditions will circumvent the high catalyst loadings frequently required for maximum enantioselectivity and short reaction times. Reported below are examples of organocatalytic reactions performed without solvent (also see sections 2.3.3 and 2.3.6).

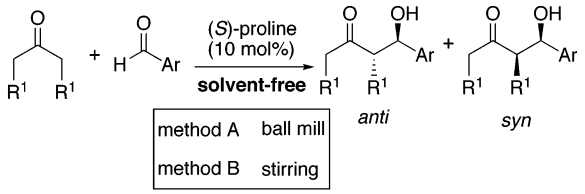
2.15.1. Asymmetric Hajos–Parrish Reaction

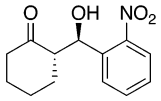
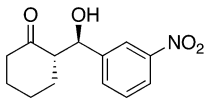
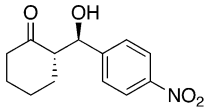
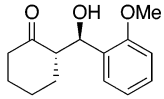
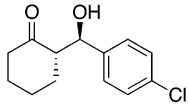
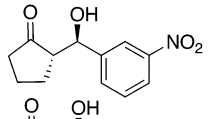
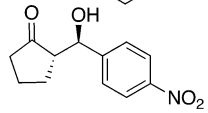
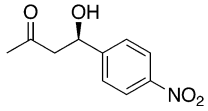
Swaminathan et al. carried out the proline-catalyzed reaction of carbonyl compounds to afford enantioenriched bicyclic diketones under solvent-free conditions.[293,294] The first type of reaction examined began with racemic diketo aldehyde (Figure 48). Reaction of this substrate with catalytic (*S*)-proline in DMSO solvent resulted in formation of the spirocycle in 70% yield with 22% ee. In contrast, when the reaction was conducted with catalytic proline in the absence of solvent, the product was formed in 49% yield with 43% ee. These numbers should be interpreted with care. First, the product ee's were determined by optical rotation, which is subject to a significantly larger experimental error than GC or HPLC with chiral columns. Second, this reaction appears to be a kinetic resolution, in which case the product ee is dependent on conversion. Increasing conversion in a kinetic resolution results in *decreased* product ee. Nonetheless, this is an interesting lead that is potentially useful in synthesis.

The second type of substrates examined was symmetric tricarbonyl compounds. In this case, a desymmetrization reaction was performed to generate the Hajos−Parrish ketone ($n = 1$) and the Wieland−Miescher ketone ($n = 2$) (Figure 49).[295,296]

Given the widespread interest in the development of organocatalytic reactions and catalysts, it is certain that

Table 50. Comparison of the Enantioselective Aldol Reaction Catalyzed by (*S*)-Proline under Solvent-free Conditions Using Ball Milling (Method A) and Stirring (Method B)



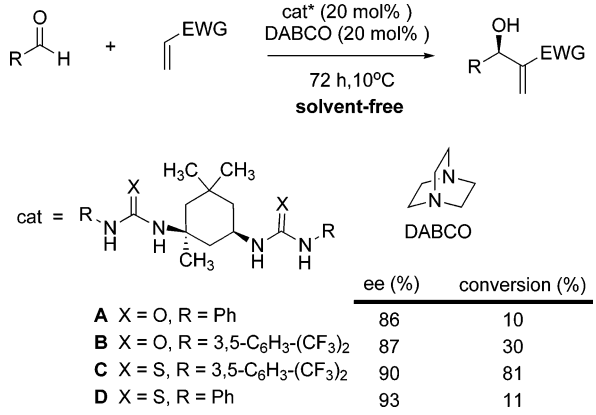
entry	product	method	time (h)	yield (%)	*anti* / *syn*	ee of *anti* (%)
1		A	7	97	93 : 7	97
2		B	36	89	91 : 9	97
3		A	7	94	88 : 12	>99
4		B	16	89	82 : 18	98
5		A	5.5	99	89 : 11	94
6		B	96	98	87 : 13	94
7		A	36	65	66 : 34	63
8		B	96	64	71 : 29	67
9		A	20	87	74 : 26	75
10		B	72	85	78 : 22	67
11		A	5	93	50 : 50	90
12		B	36	93	46 : 54	75
13		A	5	53	57 : 43	95
14		B	24	90	52 : 48	87
15		A	19	73	—	56
16		B	36	69	—	54

additional applications will continue to be introduced that employ solvent-free and highly concentrated reaction conditions.

2.15.2. Enantioselective Aldol Reaction

An interesting approach to asymmetric organocatalysis was taken by Rodríguez, Tantanen, and Bolm[297] in the intermolecular proline-catalyzed aldol reaction.[298−300] This important C−C bond forming reaction is typically conducted in polar solvents, most frequently dimethyl sulfoxide. Bolm and coworkers mixed ketones (1.1 equiv) and aldehydes (1.0 equiv) and 10 mol % (*S*)-proline in a ball mill. Ball milling is a mechanochemical method whereby chemically inert balls, in the present case composed of zirconium oxide, are placed inside a cylinder with the reagents. As the cylinder is rotated, the friction and impact of the tumbling balls grinds, mixes, and heats the contents. The results of this study are illustrated in Table 50 where method A is ball milling and method B is stirring.

As illustrated in Table 50, impressive results were obtained using ball milling (method A). Enantioselectivities above



	ee (%)	conversion (%)
A X = O, R = Ph	86	10
B X = O, R = 3,5-C_6H_3-$(CF_3)_2$	87	30
C X = S, R = 3,5-C_6H_3-$(CF_3)_2$	90	81
D X = S, R = Ph	93	11

Figure 50. MBR reaction catalyzed by bis(urea) and bis(thiourea) organocatalysts.

90% were measured for several substrates and poor to good control over the diastereoselectivity was observed. Comparison of ball milling with magnetic stirring under solvent-free conditions (method B) indicates that reactions times were considerably reduced with ball milling. Overall, the trends observed employing these two solvent-free methods were similar to those found in organic solvents[298−300] and in water.[301,302]

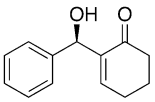
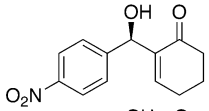
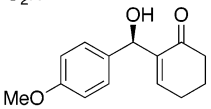
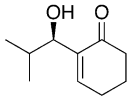
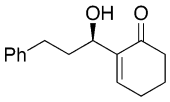
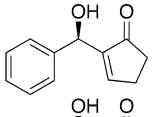
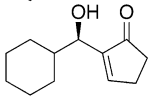
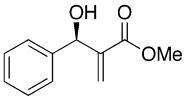
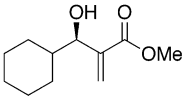
2.15.3. Enantioselective Morita–Baylis–Hillman Reaction

Another important C−C bond-forming reaction is the Morita−Baylis−Hillman (MBH) reaction. Recently, asymmetric versions of this reaction have been developed, including those catalyzed by organocatalysts.[303,304] The products of the MBH reaction are enantioenriched allylic alcohols, which are useful building blocks in enantioselective synthesis.

Berkessel, Roland, and Neudörf recently introduced bis(urea)- and bis(thiourea)-based catalysts derived from isophoronediamine, which is produced on a multiton scale and readily resolved (Figure 50).[305] These hydrogen bond donors activate the carbonyl group of the α,β-unsaturated carbonyl compound, and the cocatalyst DABCO undergoes conjugate addition to generate an intermediate enolate, which is then stabilized by hydrogen bonding to the catalyst.[306,307] Initial screening of several derivatives indicated that catalysts **A**−**D** (20 mol %) performed the best in this reaction in the presence of DABCO (20 mol %). These reactions were conducted under solvent-free conditions with 4 equiv of 2-cyclohexenone. Although the enantioselectivities were high, the conversions after 72 h were low except in the case of catalyst **C**. For the purpose of comparison, reactions were also conducted in the presence of solvent under similar conditions. Solvents with hydrogen bond accepting functionality, such as methanol, DMF, tetrahydrofuran, dioxane, and their mixtures with water deactivated the catalysts. The reaction in toluene with catalyst **C**, DABCO (20 mol % each), and 2 equiv of 2-cyclohexenone, however, resulted in 96% ee with only slightly reduced conversion (70%). The reaction with aldehydes other than cyclohexanecarboxaldehyde, however, exhibited significantly reduced conversions in the presence of solvent. The substrate scope was, therefore, determined under the solvent-free conditions of Figure 50.

As shown in Table 51, aliphatic aldehydes gave better enantioselectivities than their aromatic counterparts with each of the three α,β-unsaturated carbonyl substrates employed. The results of this study are promising, and it is likely that

Table 51. Solvent-free MBH Reaction Catalyzed by Organocatalysts A−C and DABCO (20 mol % Each) from Figure 50

entry[a]	product	cat.	yield (%)	ee (%)
1		**A**	65[b]	77
2		**C**	quant[c]	60
3		**A**	quant[c]	38
4		**C**	65[c]	34
5		**A**	35[c]	79
6		**C**	79[c]	50
7		**A**	62[c]	90
8		**A**	28[c]	79
9		**C**	52[b]	69
10		**C**	quant[b]	rac
11		**C**	22[b]	58
12		**C**	quant[b]	rac
13		**B**	47[c]	22

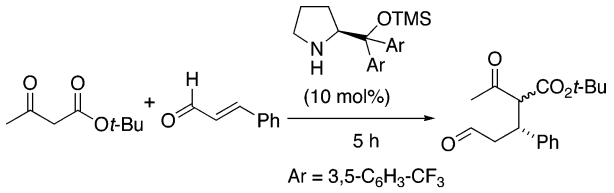
[a] The reaction was carried out with 1 equiv of aldehyde and 4 equiv of enone or acrylate in the presence of 20 mol % catalyst and DABCO at 10 °C for 72 h. [b] GC yield. [c] Isolated yield.

introduction of new catalysts will result in generation of synthetically valuable allylic alcohols in the MBH reaction with higher enantioselectivities.

2.15.4. Enantioselective Organocatalytic Conjugate Additions

As the chemical community gains experience in the development and applications of enantioselective organocatalysts, the use of these catalysts in tandem reactions will become more common. One example of such a process is the asymmetric conjugate addition of β-ketoesters to α,β-unsaturated aldehydes catalyzed by a pyrrolidine derivative (Figure 51).[308−311] Initial screening indicated that the catalyst enantioselectivity and reaction yield were insensitive to changes in the solvent, inspiring the researchers to conduct the reaction in the absence of solvent. Under the solvent-free conditions, the product was formed with 90% yield and 94% ee.[312]

To access enantioenriched 2-cyclohexenone derivatives, the solvent-free asymmetric conjugate addition of β-ketoesters to α,β-unsaturated aldehydes was incorporated into a one-pot procedure for the preparation of these synthetically valuable chiral building blocks. Thus, after the asymmetric Michael addition step, 20 mol % of a sulfonic acid was added



solvent	yield (%)	ee (%)
H_2O	97	94
5 M HOAc	89	95
none	**90**	**94**

Figure 51. Organocatalytic Michael addition with and without solvent.

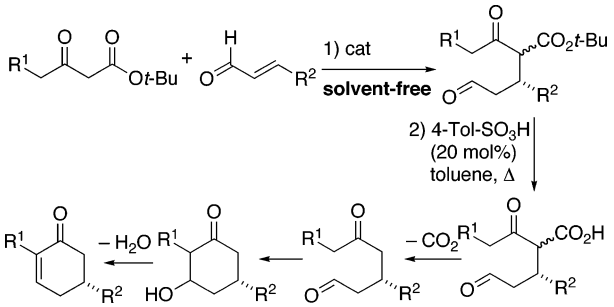
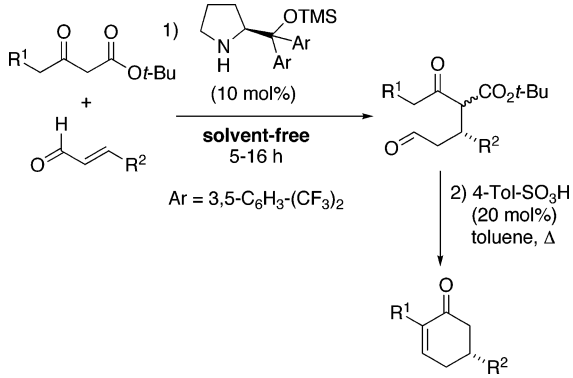


Figure 52. Reaction pathway for the one-pot organocatalytic synthesis of 2-cyclohexenone derivatives. The catalyst for the first step is shown in Figure 51.

Table 52. One-Pot Enantioselective Synthesis of 2-Cyclohexenone Derivatives



entry	R^1	R^2	yield (%)	ee (%)
1	H	Me	93	80
2	H	Et	98	94
3	H	*i*-Pr	56	96
4	H	*n*-Bu	69	92
5	H	Ph	63	94
6	H	4-C_6H_4-F	65	95
7	H	3-C_6H_4-Me	72	94
8	Me	Et	82	91

with toluene solvent, and the reaction was heated to reflux. As depicted in Figure 52, the next steps of the reaction are proposed to proceed by acid-catalyzed formation of the carboxylic acid, decarboxylation, and finally acid-catalyzed intramolecular aldol reaction and elimination of water.

The substrate scope of the one-pot procedure is outlined in Table 52. With the exception of 2-butenal, enantioselectivities were excellent (92−96%) and yields were good to very high (56−98%).

The asymmetric Michael reaction was also used in the synthesis of *cis*-2-methyl-4-phenylpiperidine derivative by

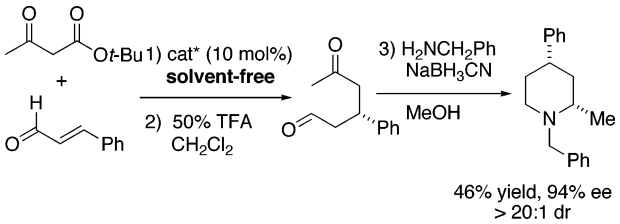


Figure 53. Synthesis of a piperidine derivative based on the catalytic asymmetric solvent-free Michael addition.

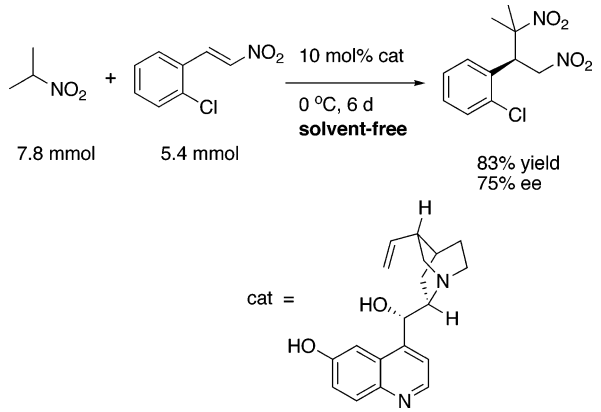


Figure 54. Michael addition of 2-nitropropane with a nitroalkene catalyzed by a modified *Cinchona* alkaloid under solvent-free conditions.

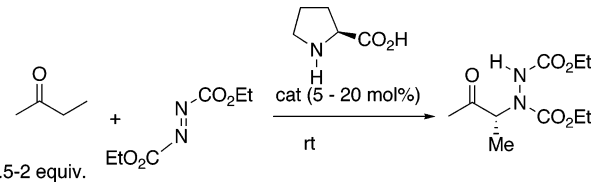
decarboxylation and double reductive amination with benzyl amine in 46% overall yield (Figure 53).[312]

Other related catalytic asymmetric Michael reactions have been explored and found to be quite useful for the construction of a variety of enantioenriched products.[110,313−316] One example is the organocatalytic conjugate addition of nitroalkanes to nitroolefins developed by Wang and co-workers using a modified *Cinchona* alkaloid catalyst (10 mol %).[317] Although no solvent was used in this study, all but one reaction was conducted with a large excess (>50 equiv) of nitroalkane. A single large-scale reaction, however, was performed with only a slight excess of 2-nitropropane and illustrates the potential of this approach (Figure 54). The addition took place over 6 d at 0 °C and afforded the product at 75% ee in 83% yield. In comparison, the reaction with a large excess of 2-nitropropane led to product with slightly higher ee (81%) but lower yield (83%) and longer reaction time (10 d). It was noted that both hydroxyl groups on the alkaloid catalysts were necessary to obtain high enantioselectivity. The 1,3-dinitro products could serve as a useful entry into enantioenriched 1,3-diamines after reduction. These initial results are promising and further investigations into this solvent-free process are warranted.

2.15.5. α-Amination of Ketones

The organocatalytic reactions above involve asymmetric C−C bond-forming reactions. Related C−N bond-forming reactions have also received attention. One example reported by Jørgensen and co-workers is the proline-catalyzed asymmetric α-amination of ketones with azodicarboxylates.[318] As illustrated in Table 53, reaction of butanone with diethyl azodicarboxylate (DEAD) in the presence of 20 mol % (*S*)-proline at room temperature proceeded in the absence of solvent with 92% enantioselectivity (entry 1). Under the solvent-free conditions, the catalyst loading could be lowered to 5 mol % with no significant increase in reaction time or drop in enantioselectivity. For the purpose of comparison, the best conditions with solvent resulted in 95% ee but with 20 mol % catalyst (entry 4).

Table 53. Catalytic Asymmetric α-amination of Butanone with (*S*)-Proline



entry	cat. (mol %)	solvent	time (h)	ee (%)
1	20	none	65	92
2	10	none	65	93
3	5	none	65	93
4	20	CH_3CN	52	96

3. Outlook

This review describes progress in the area of catalytic asymmetric reactions under solvent-free and highly concentrated conditions. Despite the enormous potential economic and environmental benefits, this area has been largely neglected by practitioners of asymmetric catalysis and synthetic chemistry. The research outlined herein, however, clearly indicates that a wide variety of structurally unrelated catalysts exhibit high enantioselectivities and yields in the absence of solvent. In several cases, the reactions under solvent-free and highly concentrated conditions constitute the best conditions reported.

Last, it is important to bear in mind that reactions conducted in the absence of solvent can rapidly generate heat. A greater degree of care must be exercised when reactions are performed at high concentrations to avoid run away reactions.

4. Abbreviations

ALB	aluminum lithium BINOLate-based catalyst
ARCM	asymmetric ring-closing metathesis
ARO	asymmetric ring opening
AROM/CM	asymmetric ring-opening metathesis/cross-metathesis
b/l	branched/linear
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINAPHOS	(*R*)-2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl (*S*)-1,1′-binaphthalene-2,2′-diyl phosphite
BINOL	1,1′-binaphthalenyl-2,2′-diol
chiraphite	6,6′-(((1*R*,3*R*)-1,3-dimethyl-1,3-propanediyl)bis-(oxy))bis-(4,8-bis(1,1-dimethylethyl)-2,10-dimethoxy-dibenzo(*d*,*f*)(1,3,2)-dioxaphosphepin
CSA	(*S*)-camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DMSO	dimethyl sulfoxide
DuPHOS	1-bis[(2*R*,5*R*)-2,5-dialkylphospholano]-benzene
H_8-BINOL	5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol
HDA reaction	hetero-Diels−Alder reaction
HKR	hydrolytic kinetic resolution
kelliphite	(*S*,*S*)-6,6′-((1,1′-biphenyl)-2,2′-diylbis-(oxy))bis-(4,8-bis(1,1-dimethylethyl)-1,2,10,11-tetramethyldibenzo(*d*,*f*)(1,3,2)dioxaphosphepin
MBH reaction	Morita−Baylis−Hillman reaction

ONIOM	our own N-layered integrated molecular orbital and molecular mechanics
PMPA	(*R*)-9-[2-(phosphonomethoxy)propyl]adenine
Ph-BPE	(*R*,*R*)-1,2-bis(2,5-dialkylphospholano)ethane
salen	bis(salicylidene)ethylenediamine
TADDOL	2,2-dimethyl-α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5 dimethanol
TBAF	tetra-*n*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBME	*tert*-butyl methyl ether
TFA	trifluoroacetic acid
Tol-BINAP	2,2′-bis[bis(*p*-tolyl)phosphino]-1,1′-binaphthyl
SEGPhos	(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diarylphosphine)

5. Acknowledgments

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