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Rational Approach to Polymer-Supported Catalysts: Synergy between Catalytic Reaction Mechanism and Polymer Design

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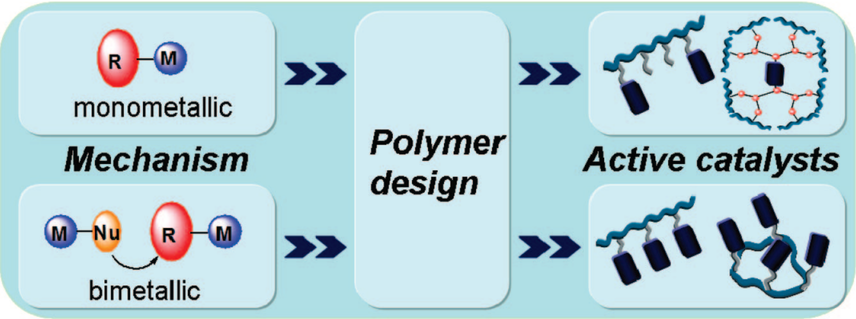

Supported catalysis is emerging as a cornerstone of transition metal catalysis, as environmental awareness necessitates "green" methodologies and transition metal resources become scarcer and more expensive. Although these supported systems are quite useful, especially in their capacity for transition metal catalyst recycling and recovery, higher activity and selectivity have been elusive compared with nonsupported catalysts. This Account describes recent developments in polymer-supported metal—salen complexes, which often surpass nonsupported analogues in catalytic activity and selectivity, demonstrating the effectiveness of a systematic, logical approach to designing supported catalysts from a detailed understanding of the catalytic reaction mechanism.

Over the past few decades, a large number of transition metal complex catalysts have been supported on a variety of materials ranging from polymers to mesoporous silica. In particular, soluble polymer supports are advantageous because of the development of controlled and living polymerization methods that are tolerant to a wide variety of functional groups, including controlled radical polymerizations and ring-opening metathesis polymerization. These methods allow for tuning the density and structure of the catalyst sites along the polymer chain, thereby enabling the development of structure—property relationships between a catalyst and its polymer support.

The fine-tuning of the catalyst—support interface, in combination with a detailed understanding of catalytic reaction mechanisms, not only permits the generation of reusable and recyclable polymer-supported catalysts but also facilitates the design and realization of supported catalysts that are significantly more active and selective than their nonsupported counterparts. These superior supported catalysts are accessible through the optimization of four basic variables in their design: (i) polymer backbone rigidity, (ii) the nature of the linker, (iii) catalyst site density, and (iv) the nature of the catalyst attachment.

Herein, we describe the design of polymer supports tuned to enhance the catalytic activity or decrease, or even eliminate, decomposition pathways of salen-based transition metal catalysts that follow either a monometallic or a bimetallic reaction mechanism. These findings result in the creation of some of the most active and selective salen catalysts in the literature.

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Introduction

The reuse and recycling of transition metal catalysts is currently an important focus area in organic and inorganic chemistry. The reasons are multifold and include a trend in society and industry toward "green" chemistry, that is, the removal of toxic metals from the waste stream, as well as the potential to control costs via catalyst recovery and recycle, as the transition metals and sophisticated ligands used are often expensive. The strategies for green catalysis are numerous and include tethering to inorganic and organic supports,[1−4] use of liquid/liquid biphasic extractions,[5] and solvent-free transformations,[6] with the immobilization of the catalysts on inorganic or organic supports being the bulk of the literature reports. While often successful in the recycling of metal catalysts as well as the removal of metal complexes from products, supported catalysts often suffer from lower activities (diffusion effects) and selectivities (site heterogeneity) when compared with their nonsupported analogues. It would be highly desirable if one could not only reuse and remove supported metal catalysts but also tune the desired catalytic activity and selectivity. Clearly, cooperativity between the support and the catalytic moiety or at least a detailed understanding of the support/catalyst interface and easy tunability of the support are key elements that could allow achievement of this goal.[4]

Catalyst supports based on organic polymers are arguably among the most versatile supports in the literature. Polymer supports range from insoluble resins to highly soluble oligomers. Soluble polymeric supports, in particular, allow for fine-tuning of polymer and ultimately support properties such as molecular weight, polydispersity, and support flexibility. The advent of highly functional group tolerant controlled and living polymerization methods such as controlled radical polymerization methods,[7−9] including atom-transfer radical polymerizations (ATRP),[10,11] nitroxide-mediated polymerizations (NMP),[12] and reversible addition−fragmentation transfer polymerizations (RAFT),[13] as well as ring-opening metathesis polymerization,[14−16] has allowed for the tuning of the structure and density of catalyst sites along polymers and the easy incorporation of catalysts into copolymer structures. Therefore, through careful considerations of the polymer structure and properties, the mechanism of the catalysis, and possible catalyst decomposition pathways, one can design supports that enhance the catalytic activity of the metal complexes. In this Account, we describe the recent progress in tuning polymeric supports to either enhance the activity of supported transition metal catalysts or limit the propensity of following known deactivation pathways of such catalysts. The basic design strategies that have allowed for this progress will be described using supported metallosalen catalysts as an example.

Metallosalen complexes have been instrumental in facilitating a wide variety of asymmetric synthetic transformations.[2,17,18] Polymer-supported salen catalysts can be broadly classified based on their synthetic design into three categories, as illustrated in Figure 1. Substantial breakthroughs in the design of easily recyclable salen catalysts have resulted in the publication of several review articles devoted to the development of reusable supported salens.[2,19,20] While the simple design of reusable salen catalysts is nontrivial, an equally if not more important aspect of catalyst design is the study of structure−activity relationships in supported metallosalen catalysis. In this Account, we focus on the importance of the catalytic reaction mechanism in dictating the design of improved polymeric salen catalyst supports that enhance catalytic activity and overcome limitations of their nonsupported analogues.

Salen Catalysis and Tunable Design Elements To Improve Catalysis

A wide variety of asymmetric reactions such as epoxidation, hetero-Diels−Alder reactions, epoxide kinetic resolutions, and

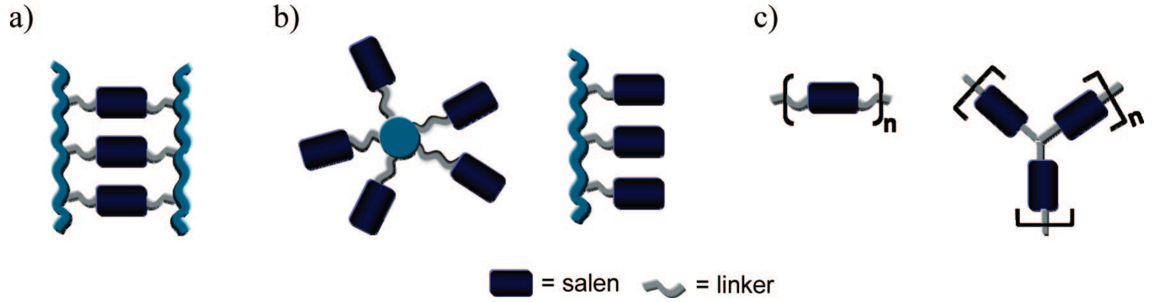


FIGURE 1. Polymer-supported salen complexes obtained from (a) salens symmetrically functionalized with monomeric units, (b) attachment of salens in a pendant fashion to resins, dendrimers, or linear polymers, and (c) incorporation of the salen ligand into the polymer main chain through condensation of diamine and aldehyde salen precursors.

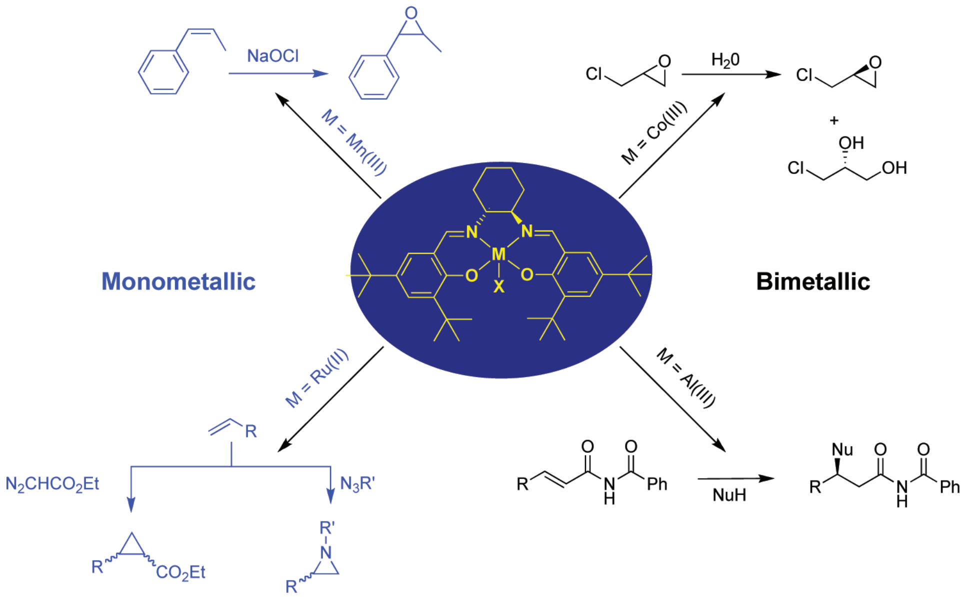


FIGURE 2. Representative reactions catalyzed by metallosalen catalysts classified based on the proposed reaction mechanisms.

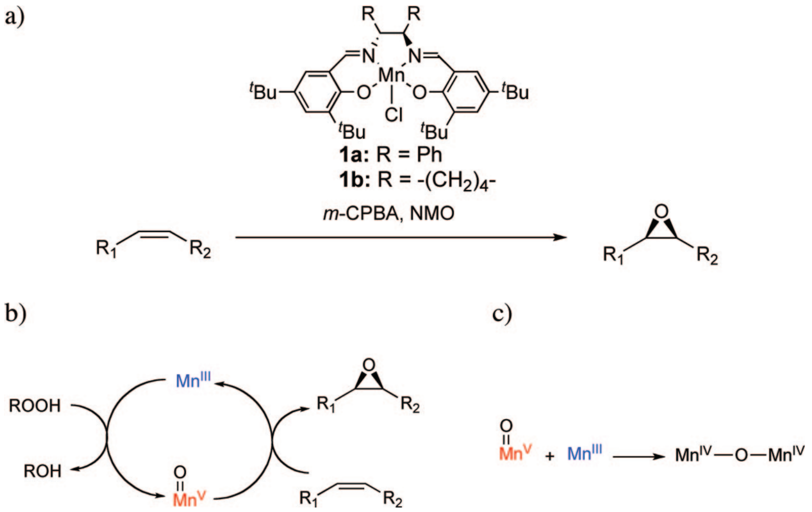


FIGURE 3. Mn−salen-catalyzed epoxidation: (a) representative reaction and general catalyst structure; (b) proposed mechanism; (c) proposed deactivation pathway of catalyst.

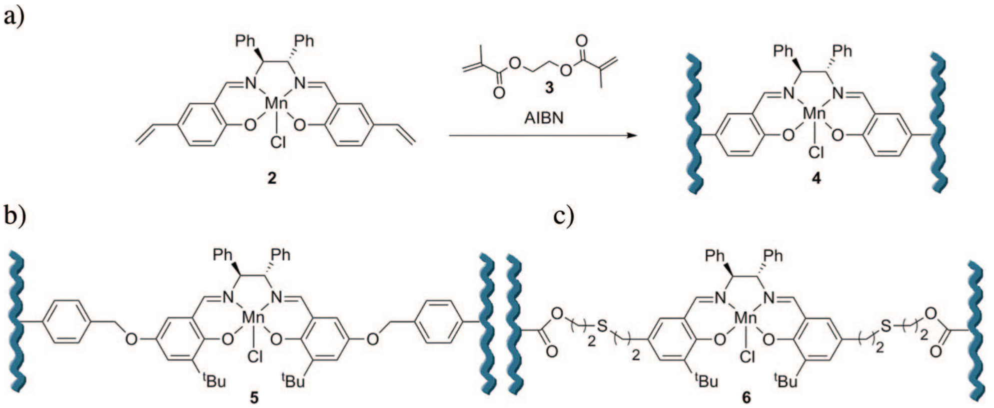


FIGURE 4. Catalysts developed by (a, b) the Dhal group and (c) the Salvadori group with different linkers to improve enantioselectivity.

conjugate additions have been catalyzed by metallosalens.[17,18,21,22] Figure 2 outlines a representative set from the myriad of salen-catalyzed reactions that can be classified based on their reaction mechanism as bimetallic or monometallic, depending on the number of metal centers hypothesized in the transition state of the slow step of the reaction.[17,23,24] The Mn−salen-catalyzed asymmetric epoxidation and Ru−salen-catalyzed cyclopropanation and aziridation presumably follow a monometallic reaction pathway.[17,25,26] In contrast, the hydrolytic kinetic resolution (HKR) and the cyanide addition reaction catalyzed by Co−salen and Al−salen, respectively, are hypothesized to follow a bimetallic reaction pathway.[27,28]

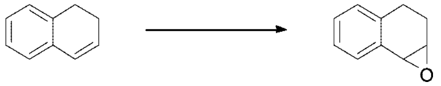
A logical approach to engineering highly active salen catalysts is to vary the design of the system depending on whether the target reaction is bimetallic or monometallic. The basic framework of polymer-supported salen catalysts comprises a polymeric backbone, a modified salen complex, and a linker connecting the two units. Four important design elements that should have a direct effect on the catalyst's activity are (i) the chemical nature of the polymer backbone, (ii) the catalyst site density along the backbone, (iii) the point of catalyst attachment, and (iv) the nature of the linker. For a monometallic reaction, one can envision enhanced activity with a polymeric system that not only ensures easy access to reagents but also facilitates isolation of catalytic sites. For bimetallic reactions, a flexible structure that allows catalytic sites to be in close proximity to each other is desirable.

Catalysts for Reactions That Follow a Monometallic Transition State

Mn−Salen Epoxidation. The asymmetric epoxidation of olefins catalyzed by Mn−salen complexes in the presence of an oxidant is among the earliest salen-catalyzed reactions discovered (Figure 3a).[26,29,30] The reaction mechanism initially involves the oxidation of a Mn(III) species to the active Mn(V)−oxo species as illustrated in Figure 3b. The Mn(V) species facilitates the epoxidation and gets reduced to the original Mn(III) complex in the process. One of the leading deactivation pathways for Mn−salen catalysts is the formation of an inactive oxo-bridged Mn(IV) dimer by the reaction of the active Mn(V) complex with Mn(III) (Figure 3c).[25]

One of the primary objectives in designing efficient supported Mn−salen catalysts involves enhancing the monometallic catalytic pathway over the detrimental bimetallic deactivation pathway. Polymeric supports can facilitate this by isolating the catalytic sites from each other. This is evidenced by the fact that several Mn-supported catalysts can be recycled up to 10 times without compromising the epoxide yields.[26] Among the earliest examples of polymer-supported Mn−salen catalysts was salen **4** developed by Dhal and coworkers, derived from symmetrically functionalized salen monomer **2** and ethylene glycol dimethacrylate **3** (Figure 4a).[31] The yields obtained for the epoxidation reaction using catalyst **4** were comparable to those obtained from the small molecule catalyst under similar conditions (Table 1).

TABLE 1. Effect of Linker Length on Catalysis



no.	catalyst (concn)	conditions	yield (ee)
1	**4** (3 mol %)	*a*	72 (8)
2	**5** (3 mol %)	*a*	70 (28)
3	**6** (10 mol %)	*b*	49 (37)
4	**8** (20 mol %)	*b*	90 (58)

[a] Iodosyl benzene, 25 °C. [b] *m*-Chloroperbenzoic acid (*m*-CPBA), 4-methylmorpholine-*N*-oxide (NMO), − 20 °C.

However, the enantioselectivities of the products obtained using the polymer were significantly lower than those made using the nonsupported catalyst **1** (78%). The loss in selectivity was attributed to the steric factors at the catalytic site due to rigidity of the polymer backbone and the absence of the *t*-butyl groups at the ortho positions of the salen. In order to improve the selectivities, catalysts **5** and **6** were developed by the Dhal and Salvadori groups, respectively, which incorporated *t*-butyl groups on the salen and used longer linkers.[32,33] Although marginal improvements in ee's were observed with both catalysts, the greater increase in catalyst **6** might be due to the presence of a longer linker indicating that the length of the linker does have an effect on the enantioselectivities. Catalyst site isolation seems to be maintained in these catalysts since no significant catalyst deactivation is observed. The effect of site isolation and linker on catalyst activity is also exemplified by Seebach's catalyst **8**, which was obtained from salen ligands incorporated with dendridic cross-linking units (Figure 5).[34] Since the salen catalyst formed the core of the dendrimer and was not attached to the dendrimer branches, the presence of the dendridic groups enabled isolation of the catalyst center and reduced steric congestion at the catalytic site, leading to significantly improved enantioselectivities for catalyst **8** (Table 1). The aforementioned examples illustrate that increased site isolation enhances the catalytic activity. An increase in linker length and flexibility also improves catalytic activity as long as the catalyst site isolation is not compromised.

One can envision further enhancement in catalytic activity by using more flexible systems with catalysts attached to the polymer backbone in a pendant fashion (Figure 2b).[35−39] In such cases, the site isolation can be maintained by lower-

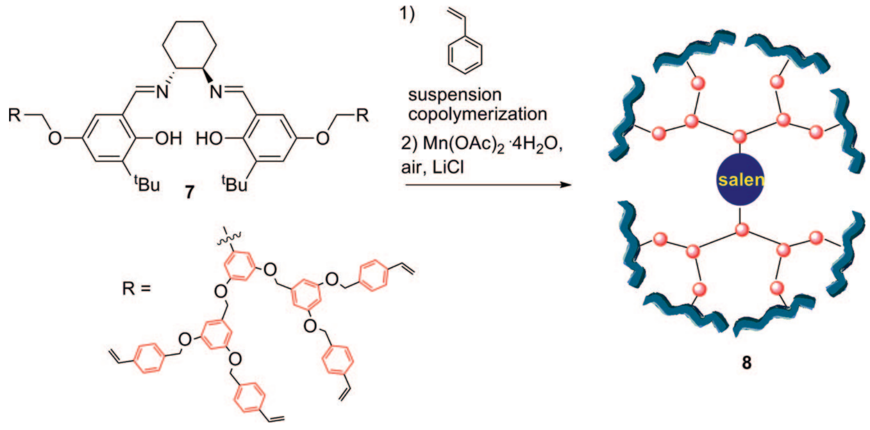
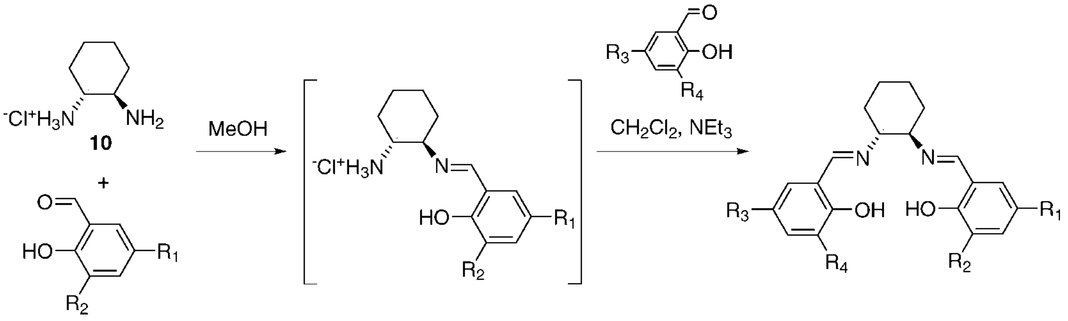
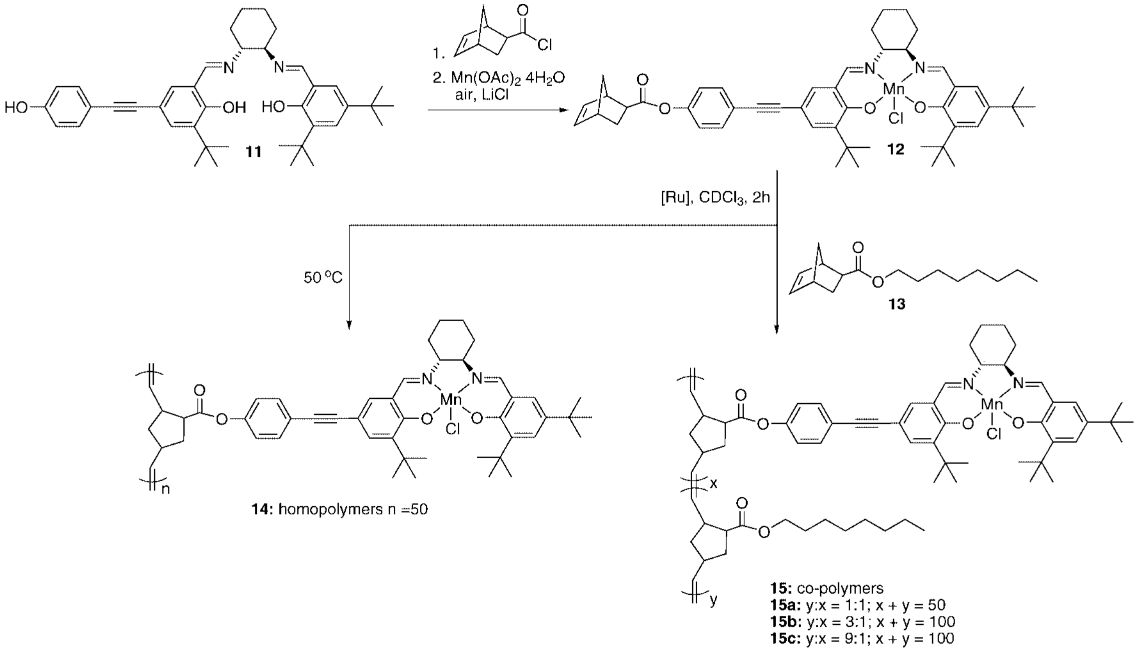


FIGURE 5. Dendritic cross-linking salen groups to improve enantioselectivity.

SCHEME 1. Optimized Procedure for the Synthesis of Unsymmetrically Functionalized Salen Ligands



SCHEME 2. Synthesis of Poly(norbornene)-Supported Mn(Salen) Complexes



ing catalyst loadings. The nature of the polymers that support the catalysts in a pendant fashion have a profound effect on the catalytic activity.[40,41] Sherrington demonstrated an increase in catalytic activity when highly porous polymers were used as supports for the Mn–salen.[40] Janda and co-workers studied the effect of polymer solubility on catalysis by using a variety of different supports ranging from soluble PEG and non-cross-linked poly(styrene)s to insoluble Merrifield and *JandaJel* resins (Figure 6).[41] The catalytic activities of the soluble catalysts **9a** and **9b** and *JandaJel* catalyst

9c were comparable to the highly active Jacobsen catalyst **1b** (Table 2). The high swelling capability and gel-like properties of the *JandaJel* resin explain the superior activity of salen **9c** to the resin-supported catalyst **9d**.

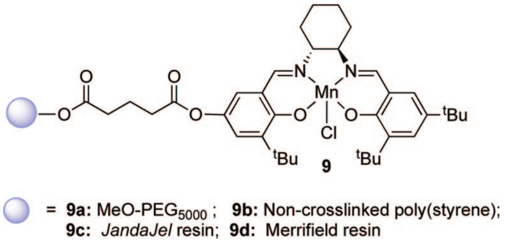
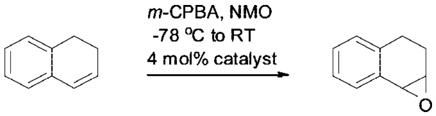


FIGURE 6. Catalysts functionalized with varied polymer matrices.

TABLE 2. Effect of Polymer Matrix on Catalysis



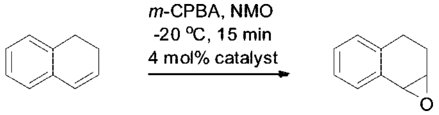
no.	catalyst	time (min)	yield (ee)
1	**1a**	15	80 (85)
2	**9a**	15	70 (76)
3	**9b**	15	69 (73)
4	**9c**	15	71 (79)
5	**9d**	60	69 (78)

One of the biggest challenges in accomplishing the single-point attachment of salens to polymers is the synthesis of unsymmetrical salen derivatives. The typical procedure for symmetrical salen synthesis involves the condensation of two equivalents of two different salicaldehydes with a diamine moiety, yielding statistical mixtures that are often tedious to separate.[42,43] A stepwise condensation approach via protection of one amine group of the diamine using tartaric acid derivatives has been employed but has not been useful in obtaining enantiopure salens in high yields.[44] Our group has developed a facile synthetic pathway for accessing enantiopure unsymmetrical salen ligands from monoprotected cyclohexyl diamine **10** by a two-step one-pot process (Scheme 1).[45]

Using this methodology, we have developed soluble poly(norbornene)-supported catalysts, where the catalyst site density can be varied readily by the incorporation of spacer units.[46] Poly(norbornene) was chosen as the backbone because the polymerization via ROMP of norbornene monomers is highly controlled and affords homo- as well as copolymers such as **14** and **15** (Scheme 2) with low polydispersities in a highly controlled manner.[14]

The catalyst activity of **14** and **15** were comparable to the Jacobsen catalyst **1b** with quantitative yields in all cases within 15 min (Table 3). We observed that copolymers **15b** and **15c** showed higher enantioselectivities than homopolymer **14** and copolymer **15a**, presumably due to the greater flexibility of the backbone and increased site isolation of the catalyst. Our Mn–salen poly(norbornene) catalysts exemplify that a modular approach for designing supported salen catalysts can lead to catalysts with activities on par with the Jacobsen Mn–salen catalyst.

TABLE 3. Enhancement of Catalytic Activity Using a Flexible and Soluble Polymer Backbone



no.	catalyst	yield (ee)
1	**1b**	100 (88)
2	**14**	100 (76)
3	**15a**	100 (76)
4	**15b**	100 (81)
5	**15c**	100 (82)

The results obtained for the epoxidation of olefins using Mn–salen complexes can be summarized as follows with reference to the four tunable design elements mentioned earlier.

(i) Nature of the polymer backbone: soluble polymers or resins with superior swelling properties and porosity are ideal for access of reagents provided catalyst site isolation is maintained.

(ii) Catalyst density: low catalyst density and site isolation favors the monometallic catalytic pathway over the bimetallic deactivation pathway.

(iii) Point of catalyst attachment: catalysts linked to the polymer backbone in a pendant fashion are more active.

(iv) Nature of the linker: longer and more flexible linkers facilitate access of reagents to the catalytic site so long as they do not increase salen–salen interactions.

Catalysts for Reactions with Bimetallic Transition States

Co–Salen-Catalyzed Hydrolytic Kinetic Resolution (HKR). HKR of racemic epoxides catalyzed by Co–salen is an extremely efficient method for obtaining enantiopure terminal epoxides (Figure 7a). The reaction typically requires low catalyst loadings and is highly functional group tolerant. Kinetic studies indicate a bimetallic mechanism for the HKR reaction, where one Co complex presumably activates the epoxide as a Lewis acid while the other complex binds to the nucleophile (Figure 7b).[27,47] In the rate-determining ring-opening step, the OH bound complex is hypothesized to react with the epoxide activated by the second Co complex. Electronic factors such as the nature of the counterion on Co and the

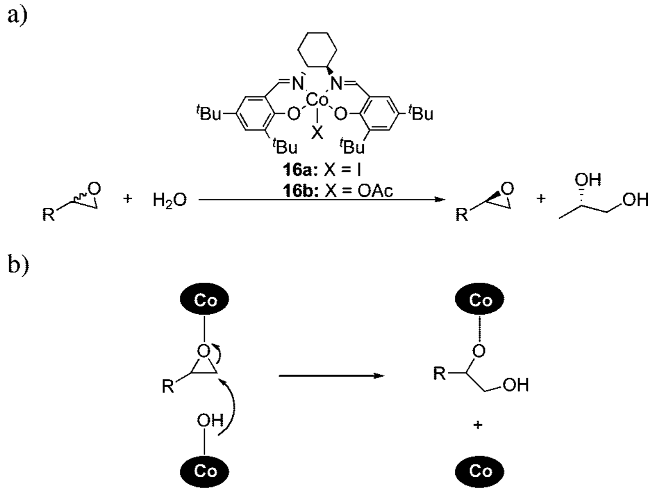
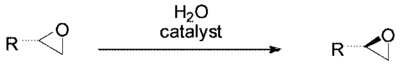
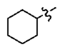


FIGURE 7. HKR of epoxides: (a) representative reaction; (b) proposed bimetallic reaction mechanism.

TABLE 4. HKR with Dendritic and Oligomeric Supported Catalysts



No.	R	Catalyst	Loading	Time (h)	Yield (*ee*)
1.		**16a**	0.025	40	<1 (n.d.)
2.	,,	**17**	0.027	20	50 (98)
3.	Me	**18a**	0.0004	24	45 (>99%)
4.	,,	**18b**	0.0003	24	40 (>99%)
5.	n-Bu	**20**	0.01	2	43 (>99%)

substituents on the aromatic ring have been shown to have a profound effect on the catalysis.[27,48] Following a cooperative bimetallic pathway, another important factor that affects the catalysis is the proximity of the catalysts to each other. Highly controllable and tunable supports should play an important role in adjusting this parameter.

The importance of catalyst proximity for HKR is exemplified by the improved reactivity of dimeric Co–salen catalysts developed by the Kureshy and Jacobsen groups.[43,49] In both cases, tethering two salen units led to enhancement of catalytic activity for the bimetallic HKR reaction. The Jacobsen group has also synthesized several catalysts by functionalizing various generations of PAMAM dendrimers with Co–salen units (Figure 8a).[50] The dendridic scaffolds had a significant effect in enhancing the catalytic activity as evidenced by the low catalyst loadings of 0.027 mol % and faster reaction rates observed with **17** compared with the monomeric catalyst **16a** (Table 4). Jacobsen also developed oligomeric catalyst **18** illustrated in Figure 8b to improve the HKR reaction.[51−53] In general, the oligomeric catalysts were found to be highly active and afforded the pure epoxide even with a low loading of 0.0003 mol % in some cases (Table 4).

The catalysis was also dependent on the nature of the linker and the cobalt counterion. Catalyst **18b** derived from the ether-substituted linker was found to be more soluble and hence more active than alkyl-substituted **18a**.[51] Also, more electron-deficient sulfonate counterions improved the activity of the oligomeric catalysts.[51]

Our research group has utilized ROMP with the third generation Grubbs initiator to synthesize cyclooctene-derived oligomeric catalysts with pendant Co–salen groups attached to the support (Figure 9a).[54] We observed that upon performing the ROMP under dilute conditions, oligomeric catalyst **20**

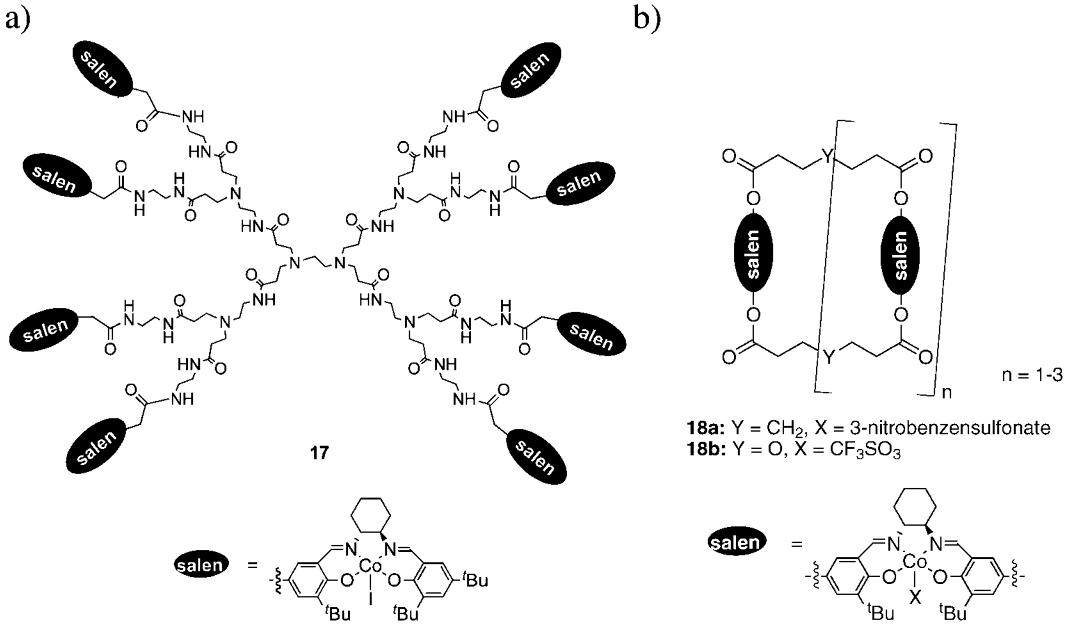


FIGURE 8. (a) Dendritic salen complexes and (b) cyclic oligomeric catalyst supports that enhance the cooperative bimetallic pathway of HKR.

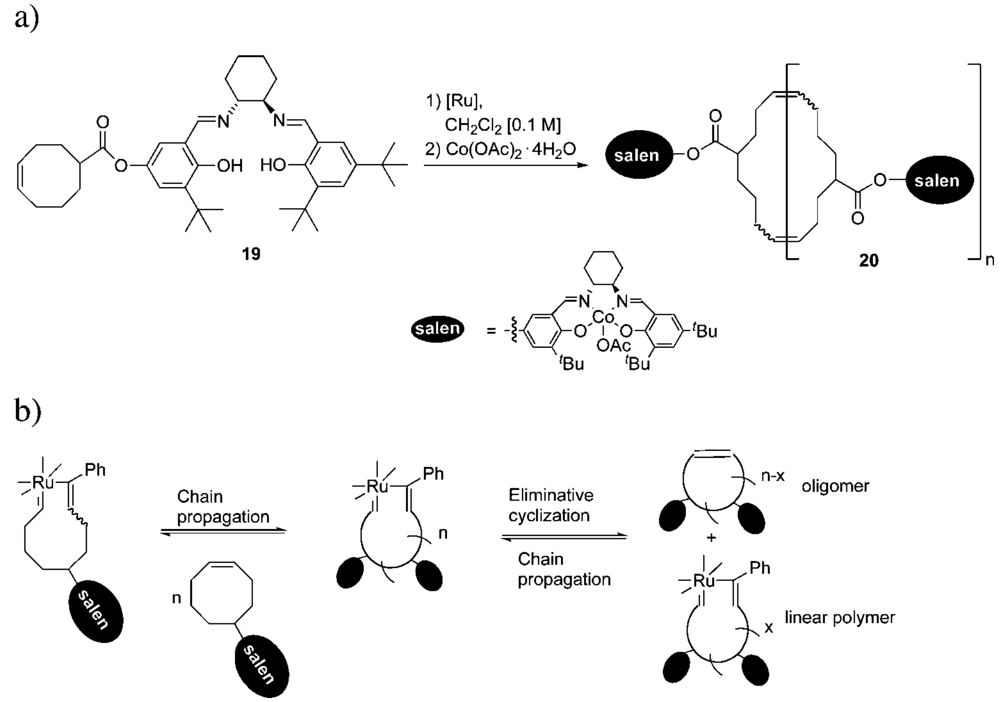


FIGURE 9. Synthesis (a) and proposed mechanism for the ROMP (b) of cyclooctene-based oligomeric Co−salen complexes.

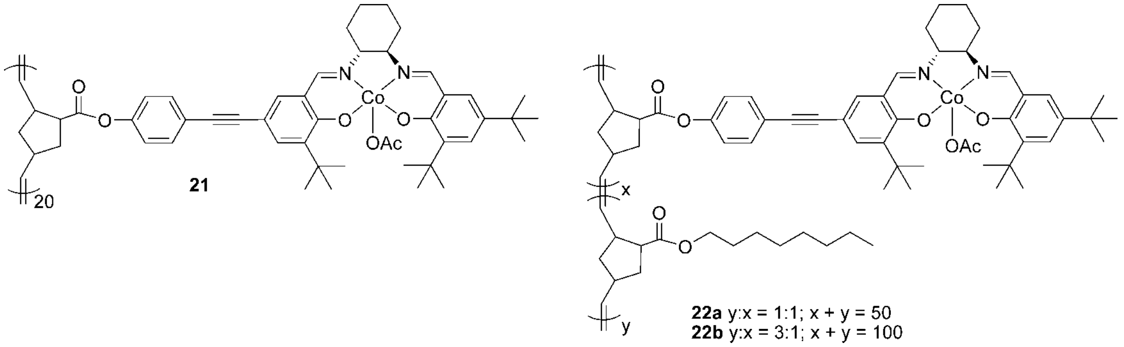
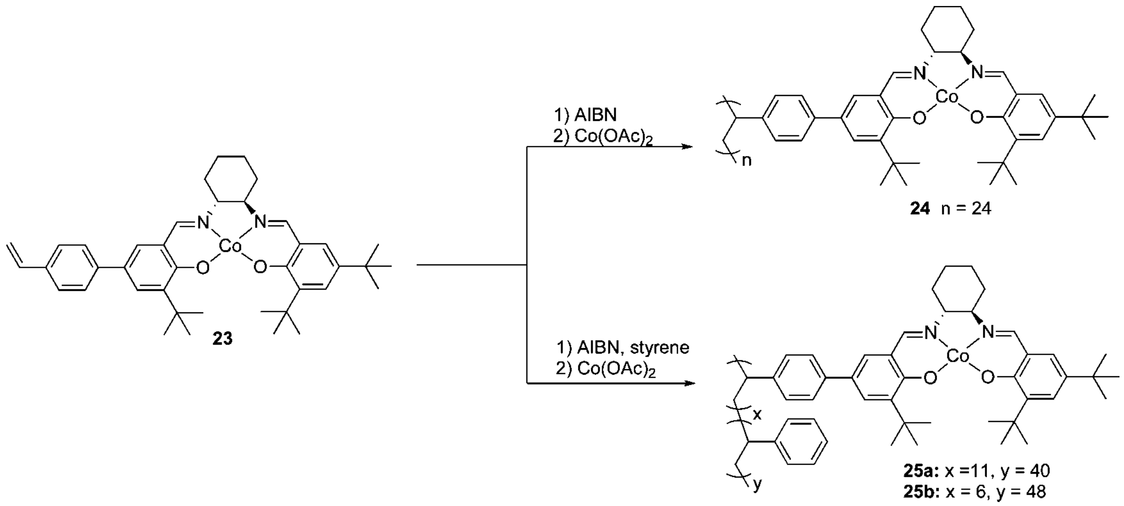


FIGURE 10. Poly(norbornene)-supported homo- and copolymers.

was obtained in good yields with a PDI of 1.3. The formation of oligomeric species can be explained by the simplified mechanism shown in Figure 9b. After initialization of the ROMP by the ruthenium catalyst, the active species can undergo chain propagation to afford polymer. A competing process with the chain propagation is the intramolecular eliminative cyclization, which leads to the formation of oligomers.[55,56] In the case of unstrained cyclooctene monomers, the ROMP is entropically driven leading to the formation of oligomers under dilute conditions via intramolecular cyclization.[57] The flexibility of the oligomer backbone enhanced the catalysis significantly, and extremely high conversions and ee's were observed for the HKR (Table 4). Catalyst **20** is among the most active unsymmetrically functionalized supported salen catalysts reported to date.

While oligomeric and dendritic catalysts have demonstrated enhanced catalytic activities, they lack the advantage of easy reusability that polymeric catalysts possess.[58] Our group has investigated the effect of polymer backbone and the nature of the linker on the HKR reaction using supported Co−salen catalysts. We employed poly(norbornene) and poly(styrene) as supports for the Co−salen catalysts.[46,59,60] The poly(norbornene)-supported salen−Co homopolymer **21** (Figure 10) and copolymer **22** were obtained by ROMP using a synthetic approach similar to that for the Mn−salen norbornene systems **14** and **15**.[46] The poly(styrene)-supported homopolymers **24** and copolymers **25** were obtained by free radical polymerization initiated by AIBN (Figure 11).[59] In general, the activities of our polymeric catalysts were comparable to the Jacobsen catalyst **16b** (Table 5). The poly(styrene)-supported catalysts **24** and **25** showed superior activity to the poly(norbornene)-supported catalysts **21** and **22,** which might be attributable to the more flexible polymer backbone of poly(styrene). Surprisingly, in both cases, the reaction rates using



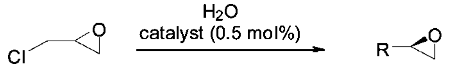
23

24 n = 24

25a: x =11, y = 40
25b: x = 6, y = 48

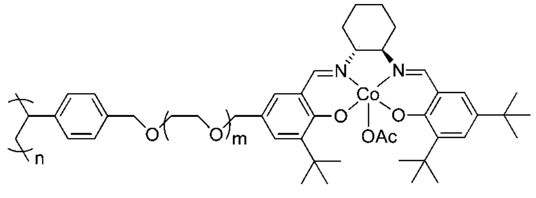
FIGURE 11. Co−salen-functionalized poly(styrene) homo- and copolymers.

TABLE 5. Results of the HKR Catalyzed by Poly(Norbornene) and Poly(styrene)-Supported Co−Salen Complexes



no.	catalyst	time (h)	conv (ee) [%]
1	**16b**	5	53 (>99)
2	**21**	5	55 (>99)
3	**22a**	5	55 (>99)
4	**22b**	5	55 (>99)
5	**16b**	1.5^{a}	52 (>99)
6	**24**	2^{a}	55 (>99)
7	**25a**	1^{a}	54 (>99)
8	**25b**	1^{a}	54 (>99)

[a] Reaction conducted neat.



26a: m = 0; **26b:** m = 1
26c: m = 2; **26d:** m = 3

FIGURE 12. Poly(styrene)-supported catalysts with varying linkers.

copolymers **22** and **25** were slightly higher than those with homopolymers **21** and **24** despite their lower catalyst density. The enhanced activity of the copolymers is presumably due to greater flexibility of their backbone compared with the sterically crowded homopolymers.

A systematic study investigating the effect of linker length on the HKR reaction was conducted by our group.[60] Poly(styrene)-supported catalysts **26a**−**d** derived from salens functionalized with varying lengths oligo(ethylene glycol) linkers were synthesized, and their catalytic reactivity was studied (Figure 12). The most efficient catalysis was observed with catalyst **26b** containing a six atom linker between the catalyst and the polymer. Further increase in the linker length resulted in slightly lower activities (**26c** and **26d**), while a decrease in linker length led to dramatically slower reaction rates for catalyst **26a**. For this catalyst system, a six atom linker length was optimal for the HKR reaction. However, we are not certain whether the rate enhancement can be merely correlated to the linker length or whether the increase in hydrophilicity plays a role as well, since one can envision an improvement in catalysis due to an appropriate balance in the hydrophilicity/hydrophobicity of the catalysts in this initially biphasic reaction.

Al−salen Catalyzed Conjugate Addition. Salen−Al complexes catalyze a variety of reactions such as conjugate additions, CO_2 addition to epoxides, and lactide polymerization. The conjugate addition of cyanides to α,β-unsaturated imides catalyzed by salen−AlCl affords highly enantiopure cyano adducts that are important precursors for the pharmaceutical and fine chemical industries (Figure 13a).[28,61] The reaction is hypothesized to follow a bimetallic pathway, wherein one Al−salen complex binds to the imide as a Lewis acid, while the other complex activates the cyanide nucleophile (Figure 13b).[28] This reaction has also been catalyzed by a combination of Er(pybox) and salen−Al via a cooperative dual metal bimetallic pathway.[62] In contrast to the salen−Co systems, the salen−AlCl catalysts are typically required in high catalyst loadings (10−15 mol %). Therefore, it is an ideal system to study the effect of polymeric supports in enhancing catalyst activities.

Recently, Jacobsen and co-workers developed several dinuclear salen−Al complexes (**28**) connected by diester linkers (Figure 14a).[63] Linking two salen complexes in such a fashion led to significant enhancement of catalysis as

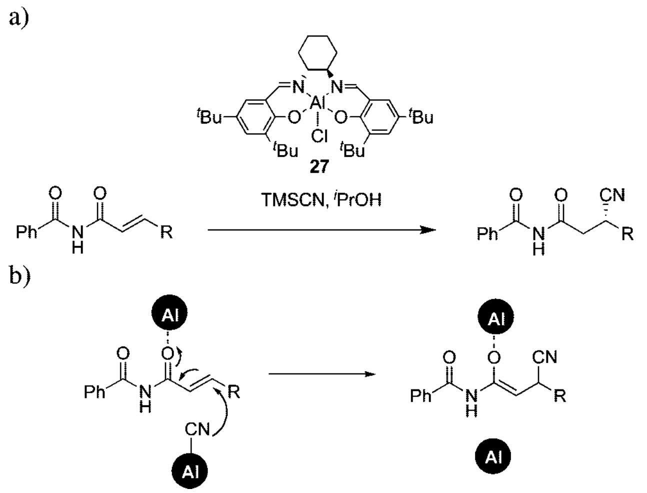
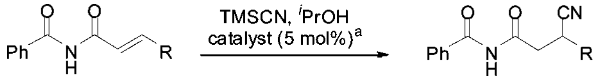


FIGURE 13. Al−salen-catalyzed 1,4-conjugate addition: (a) representative reaction; (b) proposed simplified mechanism.

illustrated in Table 6. Catalyst loadings could be lowered up to 50%, and reaction rates were significantly enhanced. Again, the enhancement in catalyst activity can be attributed to the increased proximity of the two catalytic centers in the dinuclear systems. The catalytic activity was found to increase when the linker length was varied from seven to nine atoms. However, further increase in linker length had no effect on the catalytic activity, suggesting again that an ideal linker length exists for this system as well. Our group has also investigated the effect of linker length and support structure by synthesizing cyclooctene-derived macrocyclic salen−Al catalysts **29** (Figure 14b).[64]

TABLE 6. Comparison of the Catalytic Activity of Tethered Al−Salen Catalysts[a]



no.	R	catalyst	time (h)	yield (ee) [%]
1	^{i}Bu	**27**	6^b	<10 (nd)
2	^{i}Bu	**28a**	20^b	47 (86)
3	^{i}Bu	**28c**	6^b	55 (>99)
4	^{i}Bu	**28e**	6^b	98 (95)
5	Me	**29a**	18^c	70 (93)
6	Me	**29b**	18^c	94 (82)
7	Me	**29c**	18^c	99 (98)
8	Me	**30**	6^c	96 (98)

[a] Based on Al content. [b] With 6.5 equiv of TMSCN and ^{i}PrOH. [c] With 4 equiv of TMSCN and ^{i}PrOH.

The flexibility of the macrocyclic backbone led to significantly improved activities of catalyst **29** in comparison with the monomeric catalyst **27**. In addition, the activity was dependent on the linker length, with maximum conversion observed with the longest seven carbon atom linker (Table 6). The enantioselectivity was also dependent on the nature of the linker. Catalyst **29c** with four tertiary carbon atoms flanking the catalytic site afforded the highest enantioselectivities.

We have also extended our accumulated knowledge with polymer-supported Mn−salen and Co−salen systems to Al−salen complexes by synthesizing a highly active polymer-supported catalyst. Hence, catalyst **30** was designed incorporating a flexible poly(norbornene) backbone and a long C-7

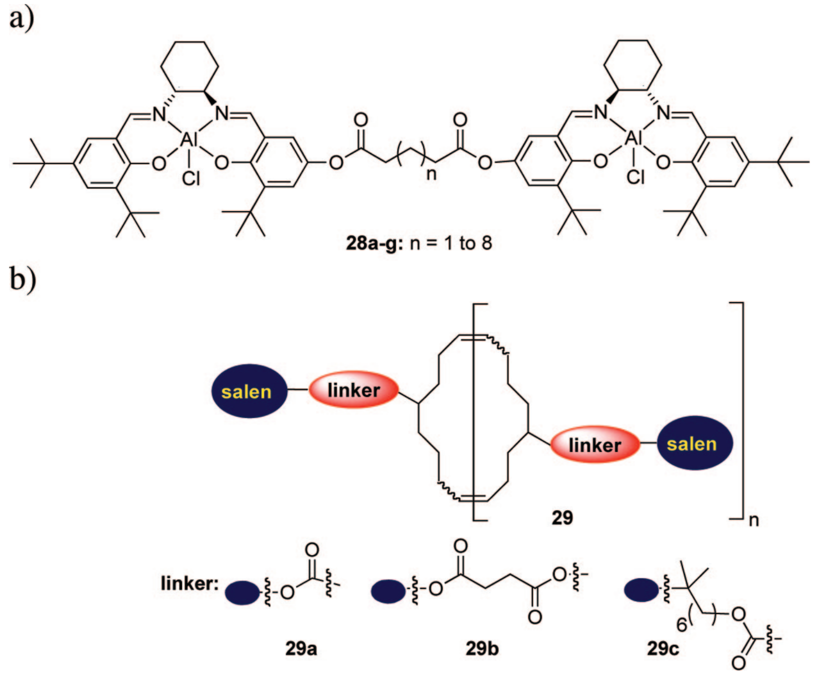


FIGURE 14. Supported salen−Al catalysts that incorporated close metal centers in their design: (a) dimeric salen−Al catalyst reported by Jacobsen and co-workers; (b) oligomeric salen−Al catalysts reported by us.

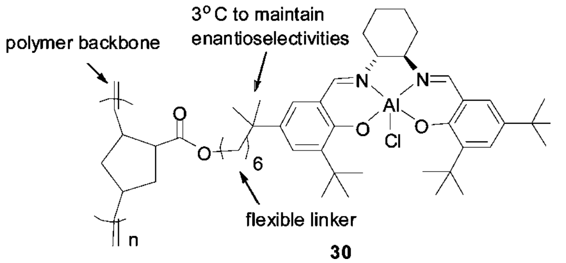


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FIGURE 15. Poly(norbornene)-based support system incorporating optimized components for a highly active and selective salen−Al catalyst.

linker to facilitate the bimetallic pathway and four tertiary carbon atoms at the linker−ligand connecting site to improve selectivity (Figure 15).[65] The poly(norbornene)-supported catalyst was highly active and efficiently performed the cyanation reaction within 6 h in high yields and enantioselectivities, with a low catalyst loading of 5 mol %. In addition, this polymer-supported catalyst could also be readily recycled up to five times increasing the turnover number from 7 to 34. The poly(norbornene) Al−salen catalyst **30** is an excellent example of how the optimal linker and support can significantly improve catalytic activity. We were able to successfully implement what we learned from the HKR bimetallic reaction using salen−Co catalysts in the salen−Al system through appropriate design and obtained a catalyst with high activity and selectivity.

The Co−salen and Al−salen examples indicate the importance of polymer design in improving cooperative catalysis. The results described provide solid guidelines for tuning the bimetallic pathway through the four earlier-mentioned design elements.

(i) Nature of the polymer backbone: soluble and highly flexible supports not only increase the access of reagents (similar to the monometallic reactions) but also increase catalyst proximity thereby facilitating site−site interactions.
(ii) Catalyst density: often high catalyst density or increased local concentration of catalysts improves salen−salen interactions for the bimetallic pathway.
(iii) Point of catalyst attachment: catalysts linked to the polymer backbone in a pendant fashion are desirable.
(iv) Nature of the linker: longer and more flexible linkers facilitate the bimetallic pathway. In addition, presence of dendrimeric branching units in the linker can also position catalysts in an orientation that favors their bimolecular interactions.

Conclusions and Outlook

In this Account, we describe recent advances in the area of polymer-supported salen catalysts as an example to illustrate how a logical approach to designing supported catalysts based on the reaction mechanism affords catalysts with optimized catalytic properties such as activity and selectivity that are unrivaled by their nonsupported analogues. Through manipulation of four variables, (i) the nature of the polymer support, (ii) the nature of the linker, (iii) catalyst density along the polymer support, and (iv) the nature of the connectivity of the catalyst to the support, one can design optimized supports for salen catalysts that follow either a monometallic or a bimetallic reaction pathway. While this Account focuses solely on supported metallated salen complexes, the conclusions and basic design principles described in it may not be limited to metal−salen catalysts but should be translatable to most transition metal systems; that is, carefully tuned polymeric supports could potentially be a key to substantially increasing catalytic activity for a wide variety of transition metal catalysts.

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BIOGRAPHICAL INFORMATION

Nandita Madhavan obtained her M.Sc. Degree in 2000 from the Indian Institute of Technology, Bombay. She joined the laboratory of Mary Gin at the University of Illinois at Urbana−Champaign in 2000 for her graduate studies. In 2006, she obtained her Ph.D. degree and subsequently joined the Weck group as a postdoctoral research associate. Her research interests are focused on the development of supported catalysts and design of three-dimensional cyclic peptide nanoassemblies.

Christopher W. Jones began his career in chemical engineering at the University of Michigan, Ann Arbor, where he obtained a B.S.E. degree in 1995. He subsequently obtained M.S. and Ph.D. degrees in chemical engineering at Caltech studying with Mark E. Davis. After a postdoctoral period at Caltech with Davis and John E. Bercaw, he joined the faculty at the Georgia Institute of Technology in 2000. Today he is a Professor of Chemical & Biomolecular Engineering and the J. Carl & Sheila Pirkle Faculty Fellow at Georgia Tech. His research interests are broadly focused on the synthesis of new materials, especially organic/inorganic hybrid materials, for applications in catalysis and separations.

Marcus Weck studied chemistry at the Universities of Mainz and California at Irvine. In 1994, he obtained his Diploma in Macromolecular Chemistry working with Helmut Ringsdorf and in 1998 his Ph.D. degree from the California Institute of Technology under the direction of Robert H. Grubbs. After a postdoctoral stay at Harvard University with George M. Whitesides, he joined the faculty at the Georgia Institute of Technology in 2000. In 2007, he moved to New York University, joining the newly established Molecular Design Institute as an Associate Professor. His research interests are in organic and polymer chemistry as well as materials science. The main foci of his group are on supported catalysis and the introduction of complexity through the use of multistep self-assembly to design and synthesize polymers, organized assemblies, and nanostructures.

FOOTNOTES

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REFERENCES

1 Takizawa, S.; Patil, M. L.; Marubayashi, K.; Sasai, H. Development of New Methods toward Efficient Immobilization of Chiral Catalysts. *Tetrahedron* **2007**, *63*, 6512–6528.

2 Baleizão, C.; Garcia, H. Chiral Salen Complexes: An Overview to Recoverable and Reusable Homogeneous and Heterogeneous Catalysts. *Chem. Rev.* **2006**, *106*, 3987–4043.

3 Barbaro, P. Recycling Asymmetric Hydrogenation Catalysts by Their Immobilization onto Ion-Exchange Resins. *Chem.—Eur. J.* **2006**, *12*, 5666–5675.

4 Notestein, J. M.; Katz, A. Enhancing Heterogeneous Catalysis through Cooperative Hybrid Organic-Inorganic Interfaces. *Chem.—Eur. J.* **2006**, *12*, 3954–3965.

5 Bergbreiter, D. E.; Sung, S. D. Liquid/Liquid Biphasic Recovery/Reuse of Soluble Polymer-Supported Catalysts. *Adv. Synth. Catal.* **2006**, *348*, 1352–1366.

6 Walsh, P. J.; Li, H.; de Parrodi, C. A. A Green Chemistry Approach to Asymmetric Catalysis: Solvent-Free and Highly Concentrated Reactions. *Chem. Rev.* **2007**, *107*, 2503–2545.

7 Kamigaito, M.; Ando, T.; Sawamoto, M. Metal-Catalyzed Living Radical Polymerization. *Chem. Rev.* **2001**, *101*, 3689–3746.

8 Hawker, C. J. "Living" Free Radical Polymerization: A Unique Technique for the Preparation of Controlled Macromolecular Architectures. *Acc. Chem. Res.* **1997**, *30*, 373–382.

9 Fischer, H. The Persistent Radical Effect: A Principle for Selective Radical Reactions and Living Radical Polymerizations. *Chem. Rev.* **2001**, *101*, 3581–3610.

10 Tsarevsky, N. V.; Matyjaszewski, K. "Green" Atom Transfer Radical Polymerization: From Process Design to Preparation of Well-Defined Environmentally Friendly Polymeric Materials. *Chem. Rev.* **2007**, *107*, 2270–2299.

11 Patten, T. E.; Matyjaszewski, K. Copper(I)-Catalyzed Atom Transfer Radical Polymerization. *Acc. Chem. Res.* **1999**, *32*, 895–903.

12 Sciannamea, V.; Jérôme, R.; Detrembleur, C. In-Situ Nitroxide-Mediate Radical Polymerization (NMP) Processes: Their Understanding and Optimization. *Chem. Rev.* **2008**, *108*, 1104–1126.

13 Barner-Kowollik, C.; Davis, T. P.; Heuts, J. P. A.; Stenzel, M. H.; Vana, P.; Whittaker, M. RAFTing Down Under: Tales of Missing Radicals, Fancy Architectures, and Mysterious Holes. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *41*, 365–375.

14 *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003; Vol. 3.

15 Buchmeiser, M. R. Homogenous Metathesis Polymerization by Well-Defined Group VI and Group VII Transition-Metal Alkylidines: Fundamentals and Applications in the Preparation of Advanced Materials. *Chem. Rev.* **2000**, *100*, 1565–1604.

16 Trnka, T. M.; Grubbs, R. H. The Development of $L_2X_2Ru{=}CHR$ Olefin Metathesis Catalysts: An Organometallic Success Story. *Acc. Chem. Res.* **2001**, *34*, 18–29.

17 Cozzi, P. G. Metal—Salen Schiff Base Complexes in Catalysis: Practical Aspects. *Chem. Soc. Rev.* **2004**, *33*, 410–421.

18 Katsuki, T. Unique Asymmetric Catalysis of Cis-beta Metal Complexes of Salen and its Related Schiff-base Ligands. *Chem. Soc. Rev.* **2004**, *33*, 437–444.

19 Canali, L.; Sherrington, D. C. Utilisation of Homogeneous and Supported Chiral Metal(salen) Complexes in Asymmetric Catalysis. *Chem. Soc. Rev.* **1999**, *28*, 85–93.

20 Leadbeater, N. E.; Marco, M. Preparation of Polymer-Supported Ligands and Metal Complexes for Use in Catalysis. *Chem. Rev.* **2002**, *102*, 3217–3274.

21 Kumar, P.; Naidu, V.; Gupta, P. Application of Hydrolytic Kinetic Resolution (HKR) in the Synthesis of Bioactive Compounds. *Tetrahedron* **2007**, *63*, 2745–2785.

22 Darensbourg, D. J. Making Plastics from Carbon Dioxide: Salen Metal Complexes as Catalysts for the Production of Polycarbonates from Epoxides and CO_2. *Chem. Rev.* **2007**, *107*, 2388–2410.

23 Katsuki, T. Some Recent Advances in Metallosalen Chemistry. *Synlett* **2003**, 281–297.

24 McGiarrigle, E. M.; Gilheany, D. G. Chromium—and Manganese—Salen Promoted Epoxidation of Alkenes. *Chem. Rev.* **2005**, *105*, 1563–1602.

25 Srinivasan, K.; Michaud, P.; Kochi, J. K. Epoxidation of Olefins with Cationic (Salen) Manganese(III) Complexes. The Modulation of Catalytic Activity by Substituents. *J. Am. Chem. Soc.* **1986**, *108*, 2309–2320.

26 Dhal, P. K.; De, B. B.; Sivaram, S. Polymeric Metal Complex Catalyzed Enantioselective Epoxidation of Olefins. *J. Mol. Catal. A: Chem.* **2001**, *177*, 71–87.

27 Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. Mechanistic Investigation Leads to a Synthetic Improvement in the Hydrolytic Kinetic Resolution of Terminal Epoxides. *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362.

28 Sammis, G. M.; Jacobsen, E. N. Highly Enantioselective, Catalytic Conjugate Addition of Cyanide to α,β-Unsaturated Imides. *J. Am. Chem. Soc.* **2003**, *125*, 4442–4443.

29 Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. Enantioselective Epoxidation of Unfunctionalized Olefins Catalyzed by Salen Manganese Complexes. *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803.

30 Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. Catalytic Asymmetric Epoxidation of Unfunctionalized Olefins. *Tetrahedron Lett.* **1990**, *31*, 7345–7348.

31 De, B. B.; Lohray, B. B.; Dhal, P. K. Polymer Supported Transition Metal Complexes for Catalytic Epoxidation of Olefins. *Tetrahedron Lett.* **1993**, *34*, 2371–2374.

32 De, B. B.; Lohray, B. B.; Sivaram, S.; Dhal, P. K. Polymeric Catalysts for Chemo- and Enantioselective Epoxidation of Olefins: New Crosslinked Chiral Transition Metal Complexing Polymers. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 1809–1818.

33 Minutolo, F.; Pini, D.; Petri, A.; Salvadori, P. Heterogeneous Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by Polymer-bound (salen) Manganese Complexes. *Tetrahedron: Asymmetry* **1996**, *7*, 2293–2302.

34 Sellner, H.; Karjalainen, J. K.; Seebach, D. Preparation of Dendritic and Non-Dendritic Styryl-Substituted Salens for Cross-Linking Suspension Copolymerization with Styrene and Multiple Use of the Corresponding Mn and Cr Complexes in Enantioselective Epoxidations and Hetero-Diels—Alder Reactions. *Chem.—Eur. J.* **2001**, *7*, 2873–2887.

35 Angelino, M. D.; Laibinis, P. E. Synthesis and Characterization of a Polymer-Supported Salen Ligand for Enantioselective Epoxidation. *Macromolecules* **1998**, *31*, 7581–7587.

36 Canali, L.; Cowan, E.; Deleuze, H.; Gibson, C. L.; Sherrington, D. C. Polystyrene and Polymethacrylate Resin-Supported Jacobsen's Alkene Epoxidation Catalyst. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2055–2066.

37 Zhang, H.; Zhang, Y.; Li, C. Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by Mn (Salen) Axially Immobilized onto Insoluble Polymers. *Tetrahedron: Asymmetry* **2005**, *16*, 2417–2423.

38 Song, C. E.; Roh, E. J.; Yu, B. M.; Chi, D. Y.; Kim, S. C.; Lee, K.-J. Heterogeneous Asymmetric Epoxidation of Alkenes Catalysed by a Polymer-bound (Pyrrolidine Salen) Manganese (III) Complex. *Chem. Commun.* **2000**, 615–616.

39 Kureshy, R. I.; Khan, N. H.; Abdi, S. H. R.; Iyer, P. Synthesis of Catalytically Active Polymer-Bound Mn (III) Salen Complexes for Enantioselective Epoxidation of Styrene Derivatives. *React. Funct. Polym.* **1997**, *34*, 153–160.

40 Canali, L.; Cowan, E.; Deleuze, H.; Gibson, C. L.; Sherrington, D. C. Remarkable Matrix Effect in Polymer-Supported Jacobsen's Alkene Epoxidation Catalysts. *Chem. Commun.* **1998**, 2561–2562.

41 Reger, T. S.; Janda, K. D. Polymer-Supported (Salen)Mn Catalysts for Asymmetric Epoxidation: A Comparison between Soluble and Insoluble Matrices. *J. Am. Chem. Soc.* **2000**, *122*, 6929–6934.

42 Annis, D. A.; Jacobsen, E. N. Polymer-Supported Chiral Co (Salen) Complexes: Synthetic Applications and Mechanistic Investigations in the Hydrolytic Kinetic Resolution of Terminal Epoxides. *J. Am. Chem. Soc.* **1999**, *121*, 4147–4154.

43 Konsler, R. G.; Karl, J.; Jacobsen, E. N. Cooperative Asymmetric Catalysis with Dimeric Salen Complexes. *J. Am. Chem. Soc.* **1998**, *120*, 10780–10781.

44 Renehan, M. F.; Schanz, H.-J.; McGarrigle, E. M.; Dalton, C. T.; Daly, A. M.; Gilheany, D. G. Unsymmetrical Chiral Salen Schiff Base Ligands Synthesis and Use in Metal-Based Asymmetric Epoxidation Reactions. *J. Mol. Catal. A: Chem.* **2005**, *231*, 205–220.

45 Holbach, M.; Zheng, X.; Burd, C.; Jones, C. W.; Weck, M. A Practical One-Pot Synthesis of Enantiopure Unsymmetrical Salen Ligands. *J. Org. Chem.* **2006**, *71*, 2903–2906.

46 Holbach, M.; Weck, M. Modular Approach for the Development of Supported, Monofunctionalized, Salen Catalysts. *J. Org. Chem.* **2006**, *71*, 1825–1836.

47 Jacobsen, E. N. Asymmetric Catalysis of Epoxide Ring Opening Reactions. *Acc. Chem. Res.* **2000**, *33*, 421–431.

48 Jain, S.; Zheng, X.; Jones, C. W.; Weck, M.; Davis, R. J. Importance of Counterion Reactivity on the Deactivation of Co—Salen Catalysts in the Hydrolytic Kinetic Resolution of Epichlorohydrin. *Inorg. Chem.* **2007**, *46*, 8887–8896.

49 Kureshy, R. I.; Singh, S.; Khan, N. H.; Abdi, S. H. R.; Ahmad, I.; Bhatt, A.; Jasra, R. V. Improved Catalytic Activity of Homochiral Dimeric Cobalt—Salen Complex in Hydrolytic Kinetic Resolution of Terminal Racemic Epoxides. *Chirality* **2005**, *17*, 590–594.

50 Breinbauer, R.; Jacobsen, E. N. Cooperative Asymmetric Catalysis with Dendrimeric[Co (salen)] Complexes. *Angew. Chem., Int. Ed.* **2000**, *39*, 3604–3607.

51 White, D. E.; Jacobsen, E. N. New Oligomeric Catalyst for the Hydrolytic Kinetic Resolution of Terminal Epoxides under Solvent-Free Conditions. *Tetrahedron: Asymmetry* **2003**, *14*, 3633–3638.

52 Ready, J. M.; Jacobsen, E. N. Highly Active Oligomeric (salen) Co Catalysts for Asymmetric Epoxide Ring-Opening Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 2687–2688.

53 Ready, J. M.; Jacobsen, E. N. A Practical Oligomeric[(salen) Co] Catalyst for Asymmetric Epoxide Ring-Opening Reactions. *Angew. Chem., Int. Ed.* **2002**, *41*, 1374–1377.

54 Zheng, X.; Jones, C. W.; Weck, M. Ring-Expanding Olefin Metathesis: A Route to Highly Active Unsymmetrical Macrocyclic Oligomeric Co—Salen Catalysts for the Hydrolytic Kinetic Resolution of Epoxides. *J. Am. Chem. Soc.* **2007**, *129*, 1105–1112.

55 Thorn-Csányi, E.; Ruhland, K. Quantitative Description of the Metathesis Polymerization/Depolymerization Equilibrium in the 1, 4-Polybutadiene System. *Macromol. Chem. Phys.* **1999**, *200*, 1662–1671.

56 Thorn-Csányi, E.; Ruhland, K. ROMP of COD under Equilibrium Conditions: The Turning Point Concept. *Macromol. Symp.* **2000**, *153*, 145–150.

57 Hodge, P.; Kamau, S. D. Entropically Driven Ring-Opening-Metathesis Polymerization of Macrocyclic Olefins with 21—84 Ring Atoms. *Angew. Chem., Int. Ed.* **2003**, *42*, 2412–2414.

58 Kwon, M.; Kim, G.-J. Synthesis of Polymeric Salen Complexes and Application in the Enantioselective Hydrolytic Kinetic Resolution of Epoxides as Catalysts. *Catal. Today* **2003**, *87*, 145–151.

59 Zheng, X.; Jones, C. W.; Weck, M. Poly(styrene)-Supported Co—salen Complexes as Efficient Recyclable Catalysts for the Hydrolytic Kinetic Resolution of Epichlorohydrin. *Chem.—Eur. J.* **2006**, *12*, 576–583.

60 Zheng, X.; Jones, C. W.; Weck, M. Engineering Polymer-Enhanced Bimetallic Cooperative Interactions in the Hydrolytic Kinetic Resolution of Epoxides. *Adv. Synth. Catal.* **2008**, *350*, 255–261.

61 Sigman, M. S.; Jacobsen, E. N. Enantioselective Addition of Hydrogen Cyanide to Imines Catalyzed by a Chiral (Salen) Al(III) Complex. *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316.

62 Sammis, G. M.; Danjo, H.; Jacobsen, E. N. Cooperative Dual Catalysis: Application to the Highly Enantioselective Conjugate Cyanation of Unsaturated Imides. *J. Am. Chem. Soc.* **2004**, *126*, 9928–9929.

63 Mazet, C.; Jacobsen, E. N. Dinuclear {(salen)Al} Complexes Display Expanded Scope in the Conjugate Cyanation of α,β-Unsaturated Imides. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762–1765.

64 Madhavan, N.; Takatani, T.; Sherrill, C. D.; Weck, M.,manuscript in preparation.

65 Madhavan, N.; Weck, M. Highly Active Polymer-Supported (Salen)Al Catalysts for the Enantioselective Addition of Cyanide to α,β-Unsaturated Imides. *Adv. Synth. Catal.* **2008**, *350*, 419–425.