Enantioselective Radical Processes†

Mukund P. Sibi,* Shankar Manyem, and Jake Zimmerman

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105

Received February 3, 2003

Contents

1. Introduction

The title "Enantioselective Radical Processes" should raise a rather interesting thought to the curious reader: Why do I not normally see a similar review on enantioselective ionic reactions? So, what is unique to radical chemistry that sets it apart? Upon reflection, one realizes that the initial misconception about radicals as highly reactive short-lived species that are difficult to tame hindered their use in stereoselective reactions. This misconception has long since been negated, and the synthetic utility of radicals has been properly recognized. Radical reactions have been shown to be compatible with many functional groups, and tedious protection/deprotection steps can quite often be avoided. The naïve debutant might have many questions regarding the potential of radical chemistry and the appropriate methods for its application in organic synthesis. There are many good sources of literature disseminating information in this regard.[1]

Radical methodologies typically involve the generation of radicals from non-radical species, followed by their reaction with other radicals or with neutral molecules. The diffusion-controlled rates of radical/radical recombination need to be minimized to effect efficient stereoselective radical/molecule reactions. In cases where the transformation involves radical/radical coupling, the high rates dictate that the stereocontrolling factor be strong enough to prevent nonselective processes. Enantioselective radical processes have been approached in various ways.[2] Researchers have certainly taken advantage of lessons learned from ionic and cycloaddition chemistry.

In a very simple line of thought, it is helpful to visualize the radical process in its various elementary steps (Scheme 1) and question which steps provide a handle for enantiotopic discrimination. If a chiral initiator is used, the chiral source needs to be bound to the substrate during radical generation and remain bound to it until the propagation event is complete. In the propagation steps, one can think of several ways to control enantioselectivity:

(a) A chiral Lewis acid[3] can be used to bind to substrate or radical species and determine the approach of the other reacting component while accelerating the chiral pathway relative to the background reaction.

(b) A chiral catalyst can be coordinated temporarily to the substrate and/or the reacting radical and bring about the reaction in an intramolecular sense.

(c) A chiral chain-transfer agent can be used: this will determine the approach in an atom-transfer step.

(d) A chiral environment can be provided, as in the photolysis of chiral crystals.

(e) A chiral inductor along with the substrate can be trapped in an organized medium.

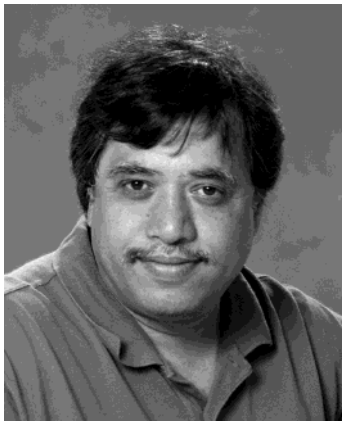
(f) The chirality inherent in the molecule can be converted to molecular chirality (memory of chirality).

Among all of the above-mentioned approaches, the most popular has been the use of a chiral Lewis acid. This method is powerful when the Lewis acid activates the substrate/radical species and the reaction in the absence of the Lewis acid (background reaction) is negligible. This situation leads to the catalytic use of the chiral source (in view of chiral economy). Although stated explicitly for case (a), this difference

† This paper is dedicated to Prof. Robert Lichter on his birthday and for his support and mentorship.

* To whom correspondence should be addressed. E-mail: Mukund.Sibi@ndsu.nodak.edu. Phone: (701) 231-8251. Fax: (701) 231-1057.

10.1021/cr020044l CCC: $44.00
Published on Web 07/15/2003



Mukund Sibi hails from Bangalore, India. After undergraduate studies in Bangalore, he joined Hunter College, CUNY, and received his Ph.D. degree under the guidance of Prof. Robert Lichter. He carried out postdoctoral studies with Profs. Gordon Gribble (Dartmouth College), Victor Snieckus (University of Waterloo), and Robert Holton (Florida State University). He joined North Dakota State University in 1987, where he is currently Professor of Chemistry. His research interests include development of new asymmetric processes, free radical chemistry, and total synthesis of natural products.

Shankar Manyem obtained his B.Sc. in 1993 from the University of Madras, India. He went on to the Indian Institute of Technology, Madras, for his M.Sc. (chemistry). His M.Sc. thesis, under Dr. D. Loganathan and Dr. T. S. Chandra, involved screening of microbial sources for β-D-xylosidases. He was the recipient of a Rajiv Gandhi science talent research fellowship (1993) from Jawaharlal Nehru Center for Advanced Scientific Research (JNCASR, Bangalore) and worked with Prof. G. Mehta during the summer of 1993. He is currently pursuing his doctoral degree at North Dakota State University with Prof. Mukund Sibi. He is interested in free radical chemistry and asymmetric synthesis, especially catalysis.

in rates needs to be borne in mind for designing all the enantioselective radical reactions to be performed catalytically.

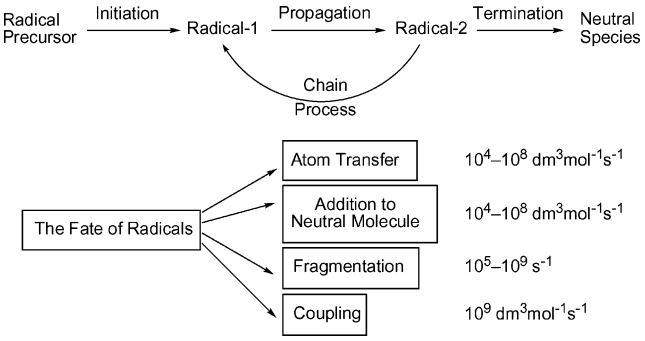
This review has been organized in terms of the different types of radical reactions so that the reader can be updated quickly depending on his/her interest. The focus is on enantioselective radical reactions of simple systems as well as diradicals generated by chemical, photolytic, and electron-transfer methods. A bit of lenience has been taken in including reactions that are not completely proven to be proceeding through a radical mechanism. We have used literature available through January 2003.

2. Atom/Group-Transfer Reactions

Atom/group-transfer reactions can be broadly defined as those that involve the transfer of an atom

Jake Zimmerman was born in Wolf Point, MT, in 1978, and received his B.S. degree (2001) from Montana State University–Billings, where he majored in chemistry. In the fall of 2001, he began his Ph.D. studies at North Dakota State University under the direction of Professor M. P. Sibi. His present research area involves exploring enantioselective free radical reactions.

Scheme 1. Elementary Steps in Radical Reactions and Fate of Radicals



(or a group) from a chain-transfer agent to a radical species to generate another radical in a potentially chain-propagating step. The two major classes of atom-transfer reactions involve the transfer of either a hydrogen or a halogen atom. Although many examples of group-transfer reactions are known, enantioselective examples are missing at present.

2.1. Hydrogen Atom Transfer

Enantioselective H-atom-transfer reactions can be performed in two distinct ways: (1) by H-atom transfer from an achiral reductant to a radical complexed to a chiral source, or alternatively (2) by H-atom transfer from a chiral reductant to a radical.

2.1.1. Chiral Lewis Acid

Chiral Lewis acid-mediated reductions at a carbon atom α to a carbonyl group can be carried out either by generation of the radical from α-halo carbonyl compounds or from conjugate addition to a β-carbon atom. Figure 1 shows both a C-centered and an enol form of a radical generated in the presence of a chiral Lewis acid. The hydrogen atom can be delivered selectively to one face of either **2** or **3**. Murakata et al. described the reduction of α-alkyl-α-iododihydrocoumarins using stoichiometric amounts of MgI_2 and a C_2-symmetric diamine (synthesized from proline)

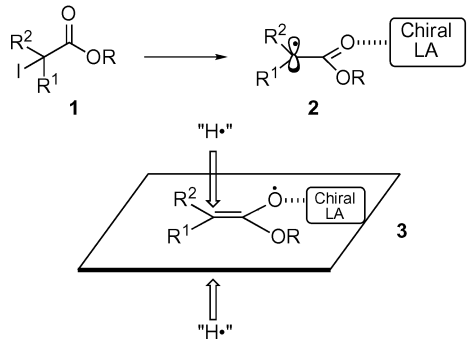


Figure 1. Chiral Lewis acid-controlled H-atom transfer.

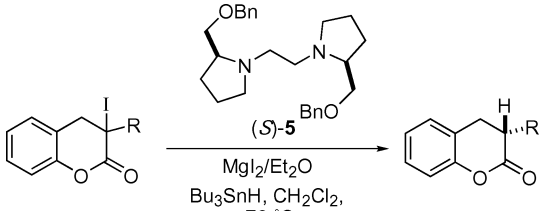
as a chiral Lewis acid in the presence of Bu_3SnH as a hydrogen atom source.[4]

The results from reduction of the α-alkyl-α-iododihydrocoumarins **4a**−**d** are shown in Table 1. It was found that the substrate concentration greatly affected the observed enantioselectivities (compare entries 1 and 2). This may suggest that under dilute conditions there is a higher amount of uncomplexed enol, leading to product with low enantioselectivity. Under higher concentrations (e.g., 36 mM **4a**), however, excellent chemical yields and good to moderate selectivities were achieved. The reaction efficiency depends on the rate of H-atom transfer: reactions using Ph_3SnH were much slower than those with Bu_3SnH (5 h vs 40 min), but their chemical yields and selectivities were similar. Tris(trimethylsilyl)silane (TTMSS), a weaker H-atom donor, proved ineffective, and no reaction was observed. The nature of the binding of substrate to the chiral Lewis acid is not apparent. Substrates **4a**−**c** give higher selectivities than **4d**, and this leads us to conclude that bidentate binding of the substrates is essential for higher ee's in this system. Marukata and co-workers[4] prepared the MgI_2 in ether and used this solution for their reactions. As is generally known in chiral Lewis acid catalysis, the presence of donor solvents can lead to competition with the chiral ligand for coordination to the metals. This situation would, in principle, lead to less than optimal results. The tertiary iodides undergo C−I bond homolysis readily, and hence there was no need to use a separate initiator in this reaction.

In one of the earliest reports on enantioselective radical reactions, chiral Lewis acid-mediated conjugate addition, followed by enantioselective H-atom transfer α to a carbonyl, was reported by Sato and co-workers (Scheme 2).[5] The single-point-binding chiral aluminum complex presumably coordinates to the carbonyl oxygen of the α-methylene-γ-butyrolactone as shown in **10**. The strong Lewis acidity of the aluminum complex activates the substrate **7** to nucleophilic conjugate addition, which is followed by an enantioselective H-atom transfer from Bu_3SnH in a chiral environment provided by BINOL ligand in **8**. Only 28% ee was observed for product **9**.

Sibi et al. recently demonstrated chiral Lewis acid-mediated conjugate additions to dehydroalanines followed by enantioselective H-atom transfer to provide a variety of α-amino acid derivatives (Scheme 3).[6] The chiral Lewis acid system derived from Mg-

Table 1. Reduction of α-Iodo Lactones

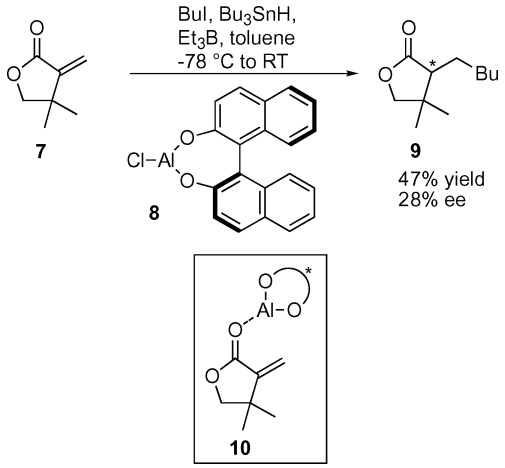


4a: R = CH_2OMe
4b: R = CH_2OEt
4c: R = CH_2OBn
4d: R = Me

6

Entry	Substrate	Conc. of **4** (mM)	Yield (%)	ee (%)
1	**4a**	11	75	12 (*R*)
2	**4a**	36	88	62 (*R*)
3	**4b**	37	84	65 (*R*)
4	**4c**	38	89	58 (*R*)
5	**4d**	35	78	30 (*S*)

Scheme 2. Reductions Mediated by Chiral Aluminum Lewis Acid



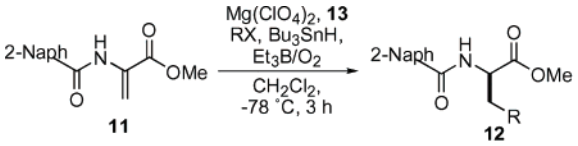
7 **8** **9**

10

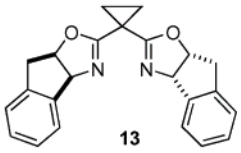
$(ClO_4)_2$ and ligand **13** gave the best ee's. The intermediate obtained by the addition of a variety of nucleophilic radicals to **11** underwent H-atom transfer with good selectivity. It was shown that acetyl, α-alkoxyalkyl, primary alkyl, secondary alkyl, and cycloalkyl radical additions all give good selectivity in H-atom transfer (see entries 1−6). An exception to this trend was the reaction with the bulky *tert*-butyl radical, which gave low selectivity. This decrease in selectivity was attributed to the bulky *tert*-butyl group and the chiral Lewis acid shielding opposite faces, resulting in reactions occurring from a mono-coordinated or noncomplexed substrate. The Lewis acid coordination is essential to activate the substrate toward conjugate addition of the nucleophilic radical. The enantioselective H-atom transfer, however, follows the conjugate addition, and it is assumed that the structure of the intermediate radical resembles the that of starting complex. On the basis of these results, a conjugate addition to a seven-membered chelate in the ternary complex (**14**, starting material + ligand + Lewis acid) followed by a H-atom transfer was proposed which is consistent with the observed stereochemistry.

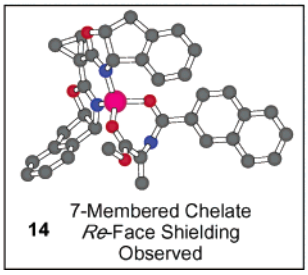
It was recently reported that Lewis acid-mediated nucleophilic conjugate radical additions to α-methacrylates, followed by enantioselective H-atom trans-

Scheme 3. α-Amino Acids from Dehydroalanines via Enantioselective H-Atom Transfer



Entry	RX	Yield (%)	ee (%)
1	AcBr	76	80
2	$MeOCH_2Br$	71	65
3	EtI	72	85 (*R*)
4	*i*-BuI	76	79
5	*i*-PrI	62	83 (*R*)
6	*c*-HexI	62	55 (*R*)
7	*t*-BuI	54	27 (R)

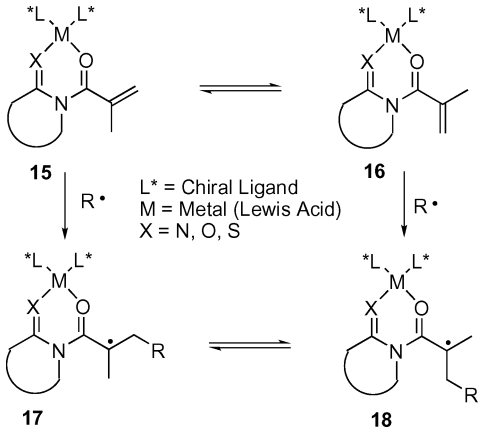




fer using a novel naphthosultam template, can occur with a high degree of selectivity.[7] In conjugate radical additions, the high selectivity may be attributed to control of various rotamers of the substrate with reaction occurring from one reactive conformation. On the other hand, preferential conformations in α-alkyl-substituted systems such as **15** (Scheme 4) are not as easily predicted. It may be possible for an s-cis (**15**), s-trans (**16**), or an alternate twisted conformer to predominate. Previous results show that twisting does readily occur, and thus any additional stabilization from π conjugation is secondary to relief of steric strain. In the chiral Lewis acid-complexed system, after conjugate addition, H-atom transfer to the intermediate radical should occur selectively from one reactive conformation. If hydrogen atom transfer can occur much faster than conformational interconversion (**17** to **18**), then maximum face shielding from a substrate−chiral Lewis acid complex (ground-state conformer) should provide high selectivity.

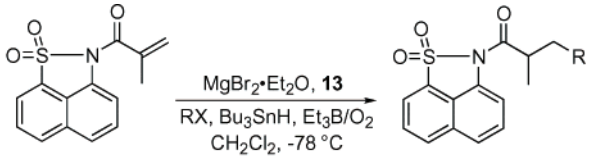
It was found that a commercially available achiral template, 1,8-naphthosultam, in conjunction with a chiral Lewis acid, efficiently controlled the rotamer of the acyl side chain of α-methacrylates. Scheme 5 shows the results of nucleophilic radical additions followed by enantioselective H-atom transfer to α-methacrylates containing the naphthosultam template. In the absence of a Lewis acid, isopropyl radical addition did not occur (<5% product was observed by NMR of the crude reaction product, entry 1). In the presence of $MgBr_2 \cdot Et_2O$ (1 equiv) and ligand **13**, however, both high yield and high selectivity were observed (entry 2). Substoichiometric amounts of chiral Lewis acid (30 mol %) proved to be just as efficient as stoichiometric catalyst loading, giving high yield and 80% ee (entry 3). Raising the temperature of the reaction to −40 °C (entry 4) or 0 °C (entry 5) led to decreased yields and selectivities. Use of an

Scheme 4. Rotamer Issues in Control of Selectivity



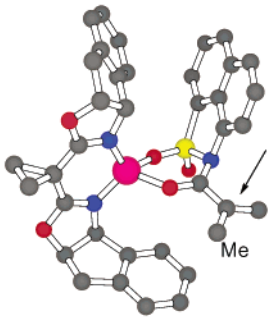
alternate H-atom donor, triphenyltin hydride, resulted in a slight decrease in chemical yield but proved to be as efficient as tributyltin hydride for selectivity (compare entries 3 and 6). Other nucleophilic radicals could be added successfully using catalytic amounts of chiral Lewis acid in excellent yields and selectivities (entries 7−9). The enantioselectivities of these alternate radical additions were quite good, ranging between 82 and 90%.

Scheme 5. Sultam Templates in Enantioselective H-Atom Transfer



Entry	R	Temp (°C)	Lewis Acid (equiv.)	Yield (%)	ee (%)
1	*i*-Pr	-78	none	<5	0
2	*i*-Pr	-78	$MgBr_2 \cdot Et_2O$ (1.0)	90	78
3	*i*-Pr	-78	$MgBr_2 \cdot Et_2O$ (0.3)	80	80
4	*i*-Pr	-40	$MgBr_2 \cdot Et_2O$ (0.3)	71	59
5	*i*-Pr	0	$MgBr_2 \cdot Et_2O$ (0.3)	52	5
6[a]	*i*-Pr	-78	$MgBr_2 \cdot Et_2O$ (0.3)	55	80
7	*t*-Bu	-78	$MgBr_2 \cdot Et_2O$ (0.3)	84	89
8	c-Hex	-78	$MgBr_2 \cdot Et_2O$ (0.3)	71	82
9	$MeOCH_2$	-78	$MgBr_2 \cdot Et_2O$ (0.3)	89	90

[a] Ph_3SnH was used



s-trans rotamer **21**
Mg+**19**+**13**
Arrow shows direction
of H-atom transfer (Chem 3D)

A model describing the stereochemical outcome for the naphthosultam template in Lewis acid-mediated

enantioselective H-atom transfer is depicted in **21**. It is known that radical reactions progress via an early transition state, and thus the transition state's structure closely resembles that of the starting material (complex). In this analysis (vide supra), it is assumed that H-atom transfer occurs rapidly in relation to any rotamer interconversion, and thus the precursor geometry impacts on the product stereochemistry. Additional evidence for this conclusion was provided by the poor selectivity and reactivity found for reactions with the corresponding lactam template (data not shown). Product stereochemistry analysis suggests that the reaction should occur from the conformer shown in **21** with H-atom transfer taking place from the *re*-face of the radical intermediate. The reasons for the preference for this rotamer are not apparent. Models suggest that higher selectivities may be possible with the s-cis rotamer.

The example described above requires that the intermediate radical **17** or **18** be trapped with a hydrogen atom source faster than their interconversion. Interestingly, Rychnovsky et al. considered the formation of achiral conformers from chiral molecules and trapping of the prochiral radical with a hydrogen atom donor based on memory of chirality (Scheme 6).[8] The photo-decarboxylation of optically active tetrahydropyran **22** leads to an intermediate **23**, which can racemize through ring inversion. If the intermediate **23** can be trapped by some hydrogen atom source before ring inversion takes place, then an optically active product **25** will be formed. This is an example of conformational memory effect in a radical reaction. It was reported that the radical inversion barrier is low (≤0.5 kcal/mol), while the energy for chair flip **23** ⇔ **24** is higher (5−10 kcal/mol).

Scheme 6. Memory of Chirality in H-Atom Transfer

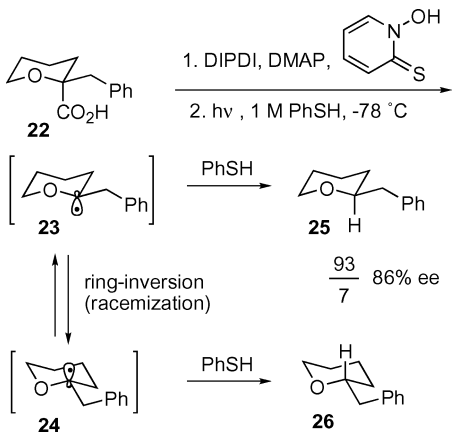
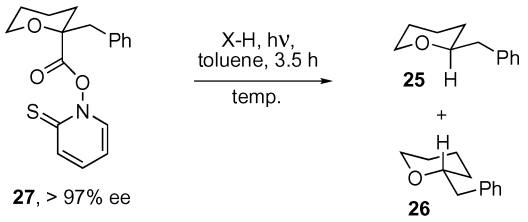


Table 2 shows that photolysis of the optically active ester **27** at −78 °C in the presence of 1 M PhSH as a hydrogen atom donor led to a reduced product with 86% ee. This suggests that, in the presence of PhSH, an efficient hydrogen atom source, the radical trapping is competitive with the ring/radical inversion, producing an enantiomerically enriched product. Since a more efficient hydrogen atom donor will produce higher selectivities, several hydrogen atom sources were studied. Bu_3SnH proved to be a poor H-atom donor for this reaction. Phenylselenol, although an efficient trap, gave low yields. It was found that PhSH in stoichiometric amounts was the most effective hydrogen atom donor.

Table 2. Reduction of Barton Esters

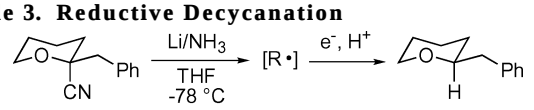


27, > 97% ee

Entry	Donor	[X-H] (M)	Temp (°C)	Yield (%)	ee (%)
1	Bu_3SnH	1.0	-78	70	3
2	*t*-BuSH	1.0	-78	83	26
3	PhSH	1.0	-78	92	86
4	PhSH	0.5	-78	75	70
5	PhSH	0.5	-40	50	40
6	PhSH	0.5	0	77	15
7	PhSH	0.5	22	72	8
8	PhSeH	0.05	-78	28	35

The reductive decyanation of **28** in metal−ammonia solutions proceeds via a stepwise mechanism, producing a radical intermediate similar to **23/24** (Table 3). Reduction using sodium resulted in lower selectivities, which may be attributed to the lower reducing ability of sodium allowing for a longer lifetime of the intermediate radical and thus more racemization (entry 1). The concentration of lithium showed a strong correlation with enantioselectivity of the reduced product **25**. Interestingly, it was found that above a 4 M concentration of Li in NH_3, the ee was drastically increased (see entries 4 and 5). At high Li concentration, the intermediate radical is reduced much faster than the ring inversion, leading to high levels of retention of configuration. It could also be plausible for the reduction mechanism to switch to a two-electron process under high Li concentrations. This would also result in the reduction of the nitrile proceeding with retention of configuration. This two-electron theory was tested using a single diastereomer of a tetrahydrofuran nitrile. It is well known that the inversion of a five-membered-ring radical intermediate is much faster than that of a six-membered-ring radical such as **23/24**. The tetrahydrofuran nitrile gave low selectivities (1.15:1) at both low (0.8 M) and high (6.0 M) Li concentrations. This suggests that the two-electron process is not taking place, presuming that both substrates react via the same mechanism.

Table 3. Reductive Decycanation



28, > 97% ee **23/24** **25**

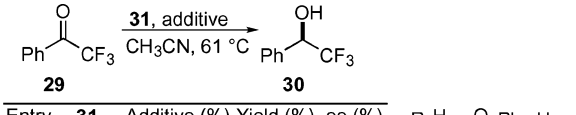
Entry	Conditions	% ee (**25**)
1	Na (1.8 M)/NH_3	16
2	Li (0.8 M)/NH_3	30
3	Li (3.5 M)/NH_3	30
4	Li (5.4 M)/NH_3	54
5	Li (6.4 M)/NH_3	90

2.1.2. Chiral Reagent

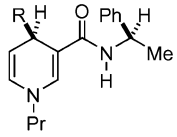
The use of a chiral chain-transfer agent is a straightforward strategy for discrimination of the prochiral faces of the radical. The geometry of the approach in an atom-transfer step is linear, and hence a primary requirement of a successful chiral reagent is that it should possess steric-differentiating elements adjacent to the hydrogen atom being transferred. At the same time, this should not hinder the approach of the reagent to the prochiral radical. For reaction efficiency, stoichiometric amounts of the chiral transfer reagent are generally required. However, an important advancement would be the use of chiral transfer reagent in catalytic amounts, which has been addressed below in one example.

An early example of a chiral atom-transfer reagent, later recognized to proceed through a radical mechanism, is the chiral nicotinamides **31a**,**b**. The reduction of ketones with chiral 1,4-dihydropyridines was reported by Ohno et al. to proceed with ~70% ee.[9] Tanner and Kharrat studied this reaction (Scheme 7) and found that the reaction of ketone **29** was inhibited in the presence of *m*-dinitrobenzene (DNB, an efficient electron acceptor) and was initiated with AIBN.[10] The ee's obtained were comparable under all these conditions, alluding to the fact that these reactions were proceeding through a radical pathway. The enantioselective transfer of hydrogen atom to the ketyl radical **32** is shown in the scheme; the dihydropyridyl radical **33** then propagates the chain.

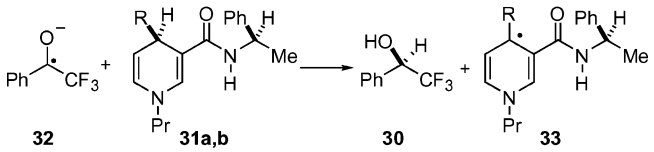
Scheme 7. Reduction of Ketones: Chiral Nicotinamides



Entry	31	Additive (%)	Yield (%)	ee (%)
1	**31a**	-	28	22
2	**31a**	DNB (4)	11	21
3	**31a**	AIBN (3)	69	22
4	**31b**	-	43	66
5	**31b**	DNB (4)	13	66
6	**31b**	AIBN (3)	82	68



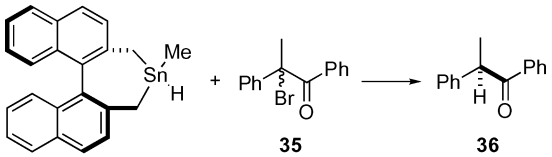
31a, R = H
31b, R = Me



32 **31a,b** **30** **33**

Syntheses and evaluations of chiral organotin hydrides provided the first examples of chiral reducing agents to be reported in the literature. Early investigations into chiral tin hydride reagents examined the transfer of chirality via a chiral tin center.[11] These tin hydrides, however, were prone to racemization, and as a result, chiral carbon-based ligands were studied. The first chiral tin hydride **34**, containing a C_2-symmetric binaphthyl substituent, was reported by Nanni and Curran in 1996 (Table 4).[12] They showed that, in the presence of excess triethylborane at −78 °C, moderate ee's (up to 41%) could be achieved in the reduction of α-bromoketone **35** using chiral tin reagent **34**. AIBN-initiated reactions were more efficient but low ee's were obtained, even at −78 °C.

Table 4. Reduction of α-Bromoketone: Chiral Tin Hydride

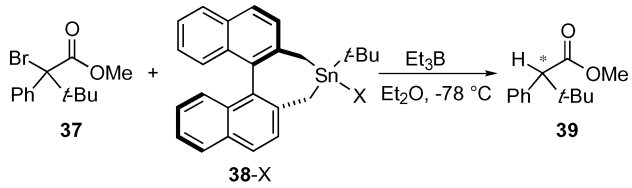


34 **35** **36**

Entry	Conditions	Yield (%)	ee (%)
1	AIBN, 80 °C	70	11
2	AIBN, -78 °C	54	20
3	Et_3B, -78 °C, air	30	41

Metzger et al. independently reported the synthesis of chiral tin hydride **38**-H (Table 5).[13] This chiral tin reagent is similar to Curran's chiral binaphthyl organotin hydride, where the methyl group on the tin atom has been replaced with a bulky *tert*-butyl group. In the presence of triethylborane and chiral tin hydride **38**-H at −78 °C, bromoester **37** can be reduced with slightly increased enantioselectivities up to 52%. Surprisingly, these authors used substoichiometric amounts of chiral tin hydride in entries 1 and 2. The chiral tin bromide, **38**-Br, could be used in catalytic amounts with in situ generation of tin hydride **38**-H, and comparable ee's were obtained. Other chiral tin hydride sources utilizing optically active 2-[(1-dimethylaminoalkyl)phenyl] ligands (DAAP) have been examined, but these showed low to moderate ee's (26%) in the reduction of α-bromo esters.[14]

Table 5. Reduction of α-Bromoesters: Chiral Tin Hydride



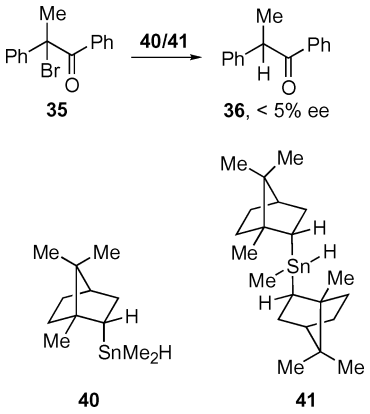
37 **38**-X **39**

Entry	**38**-X	Temp. (°C)	ee (%)
1	**38**-H (0.5 eq.)	-78	52
2	**38**-H (0.5 eq.)	24	28
3	**38**-Br (0.1 eq.) + $Na(CN)BH_3$ (3 eq.)	24	26

Enantiomerically enriched bicyclo[2.2.1]hept-2-yltin hydrides **40** and **41** were synthesized from camphor by Thomas et al. (Scheme 8).[15] Preliminary studies, however, showed very low enantioselectivities (<5% ee) for the reduction of bromoketone **35** in the presence of chiral organotin hydrides **40** and **41**.

The above examples focused only on chiral tin hydrides. Schiesser et al. showed that the efficacy of this reduction could be enhanced with achiral and chiral Lewis acids.[16] Table 6 shows that Lewis acid additives greatly enhance enantioselectivity (entries 1−5) in free radical reductions of halo esters and ketones **42a**−**e** in the presence of menthol or cholic acid-derived chiral stannanes. One equivalent of Lewis acid was essential for the selectivity enhance-

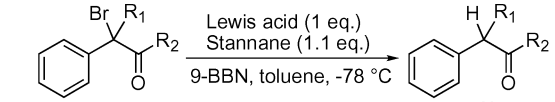
Scheme 8. Chiral Stannanes from Camphor



ment. Among the Lewis acids used, BF_3 and Cp_2ZrCl_2 gave moderate ee's, whereas in the presence of Jacobsen's catalyst **45**, excellent ee's were observed (entry 5). The enantiomeric catalysts **45** and **46** gave comparable ee's, pointing to the fact that the Lewis acid acts only to provide an increase in bulk at the coordinating carbonyl and does not have much of a role in controlling the face selection in the hydrogen atom-transfer process. Although the Lewis acid additive greatly enhances the enantioselectivity, the chirality transfer is derived primarily from the chiral ligand on the organotin reagent. This is supported by the fact that, when stannane **48** is used, the ee of **43** increases from 2% in the absence of Lewis acid to 36% in the presence of the achiral Lewis acid **44**. It was also demonstrated that Bu_3SnH reduces **42d** in the presence of **44** to give a racemic product, showing the importance of chiral tin reagent. Another line of evidence is presented in entry 14, where the enantiomer of **48** was used as the reductant and the product was obtained with *R* configuration. Among the stannanes derived from cholic acid, the stannane **50c**, with the tin located in the cavity of the molecule, produced better selectivity compared to **50b**, which has tin in the terminal cyclohexane ring (entries 15 and 16). The dependence of ee's on the substituents on the substrates is less understandable: ketone **42e** always gave lower ee's, and among the esters a regular trend is not apparent.

A new class of chiral dithiogermanium hydrides prepared from C_2-symmetric dithiols has shown promising selectivities in asymmetric hydrometalation reactions. Curran and Gualtieri prepared chiral stannanes/germanes **51**−**53** because the corresponding dithiostannanes are either labile or unstable under the reaction conditions.[17] Scheme 9 shows the results from hydrometalation of methyl methacrylate using (*S*)-**51**, (*R*)-**52**, and (*R*)-**53**. Hydrogermylation using (*R*)-**52** yielded **56/59** in a 3/1 ratio, while (*R*)-**53** displayed much higher selectivities (compare entries 1 and 3). In this asymmetric hydrometalation, two germanium species are involved: **54** and a second molecule of chiral germane doing the hydrogen atom transfer. This reaction requires the use of enantiopure germanes. If racemic germanes are used, the selectivity drops significantly because the two germanium species involved in the hydrogen atom-transfer step need to be matched. If mismatched species are involved, the selectivity decreases (entry 5). This study demonstrates the efficacy of naphthalene C3 and C3′ substituents in effecting the enantioselective reductions with higher ee's.

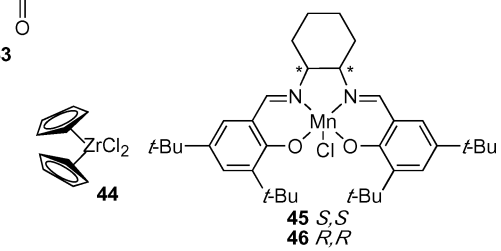
Table 6. Lewis Acids as Additives in Reductions

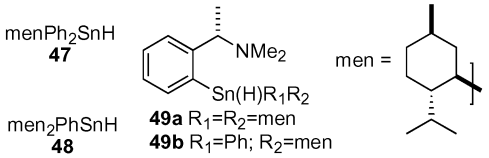


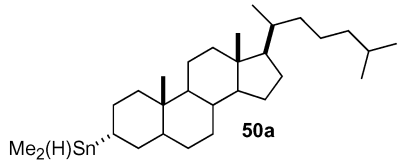
42a R_1 = Me R_2 = OEt
42b R_1 = Et R_2 = OEt
42c R_1 = cyclopentyl R_2 = OEt
42d R_1 = Bu^t R_2 = OEt
42e R_1 = Me R_2 = Ph

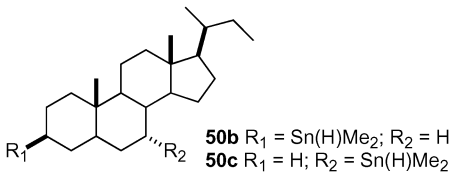
Entry	Substrate	Lewis Acid	Stannane	ee (%)	Yield[a] (%)
1	**42b**	None	**48**	4 (*S*)	81
2	**42b**	BF_3	**48**	20 (*S*)	68
3	**42b**	**44**	**48**	46 (*S*)	52
4	**42b**	**45**	**48**	86 (*S*)	75 (71)
5	**42b**	**46**	**48**	84 (*S*)	69
6	**42b**	**45**	**47**	70 (*S*)	78
7	**42b**	**45**	**49a**	72 (*S*)	68
8	**42b**	**45**	**49a**	>99 (*S*)	N/A
9	**42b**	**45**	**50a**	62 (*S*)	67
10	**42a**	**45**	**49a**	90 (*R*)	73 (68)
11	**42c**	**45**	**49a**	>96 (*S*)	75 (67)
12	**42d**	**45**	**49a**	80 (*S*)	76
13	**42e**	**45**	**49a**	62 (*S*)	74
14	**42b**	**46**	*ent*-**48**	86 (*R*)	72
15	**42c**	**45**	**50b**	62 (*S*)	>90
16	**42c**	**45**	**50c**	90 (*S*)	>90

[a] GC conversion; numbers in parentheses are isolated yields.

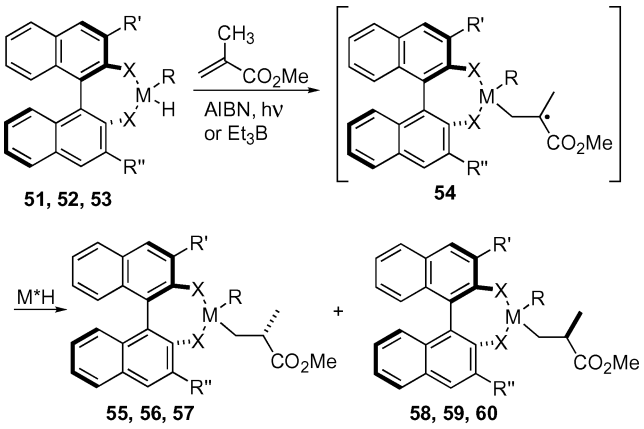








Scheme 9. Hydrometalations with Chiral Stannane and Germanes



		X	M	R	R'	R"	
51	→ **55**	CH_2	Sn	Me	H	H	**58**
52	→ **56**	S	Ge	*t*-Bu	H	H	**59**
53	→ **57**	S	Ge	*t*-Bu	TMS	TMS	**60**

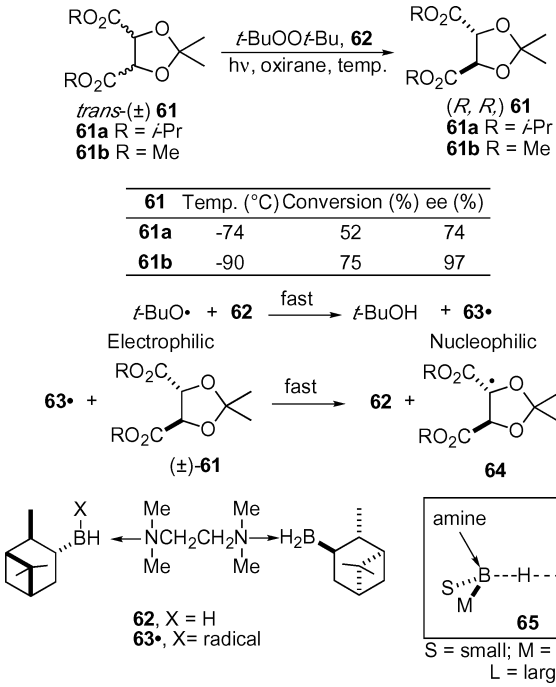
Entry	Hydride	Temp (°C)	Products	Yield (%)	Ratio
1	(*S*)-**51**	25	(*S*)-**55/58**	60	1.3/1
2	(*R*)-**52**	-78	(*R*)-**56/59**	61	3/1
3	(*R*)-**53**	25	(*R*)-**57/60**	56	15/1
4	(*R*)-**53**	-20	(*R*)-**57/60**	55	25/1
5	*rac*-**53**	-20	(*rac*)-**57/60**	63	14/1

All the examples presented until now have involved the generation of the radical species either from a halide or by the addition of a radical to olefins. Are we limited to halides/xanthates as precursors for radicals? No! Polarity reversal catalysis (PRC, explained below), among other applications, allows for the production of radicals from C−H and Si−H bond homolysis. There are several examples of reagent-based enantioselective radical reactions using polarity reversal catalysis.

The kinetic resolution of racemic ester **61a** using catalytic amounts of chiral amine−borane **62** (derived from menthol and TMEDA) and di-*tert*-butyl peroxide as initiator under photolytic conditions at −74 °C gave 74% ee of the residual enantiomer (*R*,*R*)-**61a** after 52% consumption of racemate (Scheme 10).[18] For the ester **61b** at −90 °C, after 75% consumption of racemate, 97% ee of (*R*,*R*)-**61b** was recovered. The *tert*-butoxyl radical, being electrophilic, cannot selectively abstract the α-hydrogen atom from **61** to generate another electrophilic radical in the absence of **62**. The reaction of *t*-BuO• with **62** generates a highly nucleophilic radical, **63•**, which is then poised to abstract the α-hydrogen atom from **61**. The amine−borane catalyst is a *hydridic* polarity reversal catalyst. Enantioselective hydrogen atom abstraction by chiral amine−boryl radicals from **61** leads to the radical **64**, which then decomposes, thereby enhancing the ee of residual ester. The enantioselection for this reaction is explained by the transition state **65** for the H-atom abstraction step.

Roberts and co-workers also examined the enantioselective radical chain hydrosilylation of electron-rich prochiral alkenes using various sugar-derived chiral thiols.[19] Scheme 11 illustrates the uncatalyzed reaction (A) along with the catalytic cycle for the

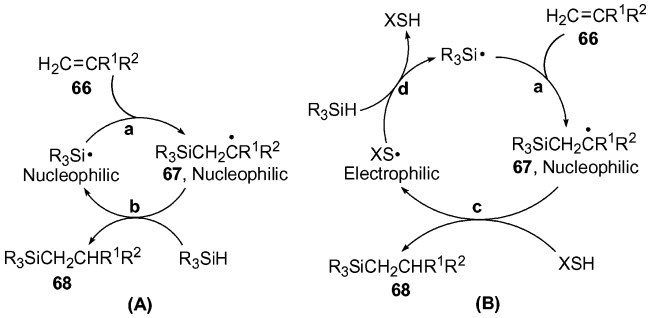
Scheme 10. Chiral Amine−Borane-Catalyzed Kinetic Resolution



61	Temp. (°C)	Conversion (%)	ee (%)
61a	-74	52	74
61b	-90	75	97

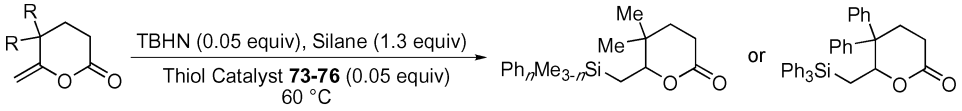
thiol-catalyzed reaction (B). The normally slow H-atom transfer from a silane to a carbon radical, step **b**, hinders this reaction, whereas in catalysis with thiols, step **b** is replaced by the faster propagation reactions **c** and **d**. Here, the thiols act as *protic* polarity reversal catalysts. If **67** is a prochiral radical and the thiol is optically active, then step c could proceed enantioselectively.

Scheme 11. Hydrosilylation: Thiols as *Protic* Polarity Reversal Catalysts



Several optically active organosilanes, **71** and **72**, were synthesized from methylene-δ-lactones **69** and **70** (Table 7). The sugar-derived thiols (5 mol %), in the presence of a slight excess of silane, and di-*tert*-butyl hyponitrite (TBHN, 5 mol %) as the initiator were used. The stronger S−H bonds and the high electrophilicity of the thiyl radicals, due to the many electron-withdrawing groups in **73**−**76**, are the keys to their success. It was found that a mixture of hexane/dioxane (H/D, 5:1 or 4:1) and thiol catalysts **73**−**76** gave the highest yields and selectivities when starting from substrate **69** or **70**. Other systems studied using chiral thiol catalysts include kinetic resolution of silanethiyl radicals[20] and reductive carboxyalkylation of electron-rich alkenes.[21]

Table 7. Hydrosilylation of Lactones



69 R = CH_3
70 R = Ph

71a, n = 1
71b, n = 2
71c, n = 3

72

Entry	Alkene	Silane	Thiol	Solvent	Product	Yield (%)	ee (%)
1	**69**	$PhMe_2SiH$	**73**	Dioxane	**71a**	74	16
2	**69**	$PhMe_2SiH$	**73**	Hexane	**71a**	52	23
3	**69**	Ph_2MeSiH	**73**	Dioxane	**71b**	78	26
4	**69**	Ph_2MeSiH	**73**	Hexane	**71b**	65	32
5	**69**	Ph_3SiH	**73**	Dioxane	**71c**	63	40
6	**69**	Ph_3SiH	**73**	Hexane	**71c**	72	50
7	**70**	Ph_3SiH	**73**	Dioxane	**72**	88	80
8	**70**	Ph_3SiH	**73**	Benzene	**72**	92	86
9	**70**	Ph_3SiH	**73**	H + D (5:1)	**72**	93	87
10	**70**	Ph_3SiH	**74**	H + D (5:1)	**72**	90	95
11	**70**	Ph_3SiH	**75**	H + D (4:1)	**72**	73	85
12	**70**	Ph_3SiH	**76**	H + D (4:1)	**72**	87	94

73

74

R' = 2-$BrC_6H_4C(O)$-
75

76

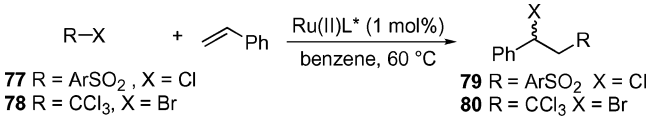
2.2. Halogen Atom Transfer

Halogen atom-transfer reactions involve homolysis of a C−X or an X−X bond in a neutral molecule, followed by the transfer of both radical components to unsaturated functional groups. There is atom economy in such processes, and these processes provide functionality for further transformations.[22] Ruthenium complexes are capable of catalyzing halogen atom-transfer reactions of olefins. This has been illustrated in the enantioselective atom-transfer reactions of alkane- and arenesulfonyl chlorides and bromotrichloromethanes with olefins using chiral ruthenium complexes (Scheme 12). Moderate ee's up to 40% can be achieved for β-chlorosulfones **79** starting from substrates **77**.[23] Reactions with a slightly different substrate, bromotrichloromethane **78**, provided **80** in 32% ee.[24] These specific reactions are believed to follow a radical redox-transfer chain process. The Ru(II) catalyst **82** abstracts a halogen (either chlorine or bromine) from the reagent to yield an arenesulfonyl radical and a Ru(III) species, **83**. Next is a π-complexation between the Ru(III) and alkene substrate **84**, followed by radical addition (**85**) and halogen atom transfer to produce the product **79** or **80**.

A chiral Lewis acid-promoted atom-transfer reaction (Kharasch reaction) of α-halo oxazolidinone imide **86** and 1-octene **87** was reported by Mero and Porter (Scheme 13).[25] In this example, $Zn(OTf)_2$ and phenyl bisoxazoline ligand **88** were combined to form the chiral Lewis acid. The yields of the products, however, were quite low, ranging from 5 to 15%, and only moderate enantioselectivities were achieved (up to 40%).

Arylation of activated double bonds with diazonium salts in the presence of copper catalysts is known as the Meerwein reaction. The reaction is postulated to

Scheme 12. Chiral Ruthenium-Catalyzed Halogen Atom-Transfer Reaction

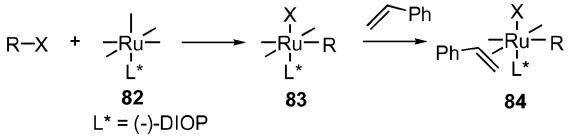


77 R = $ArSO_2$, X = Cl
78 R = CCl_3, X = Br

79 R = $ArSO_2$ X = Cl
80 R = CCl_3 X = Br

Entry	**77**, Ar	DIOP	ee (%)
1	p-$CH_3C_6H_4$	(-)	29 (*R*)
2	p-$CH_3C_6H_4$	(+)	24 (*S*)
3	C_6H_5	(-)	26 (*R*)
4	p-ClC_6H_4	(-)	25 (*R*)
5	p-$CH_3OC_6H_4$	(-)	40 (*R*)

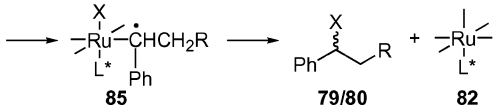
81
(+)-DIOP



82
L* = (-)-DIOP

83

84

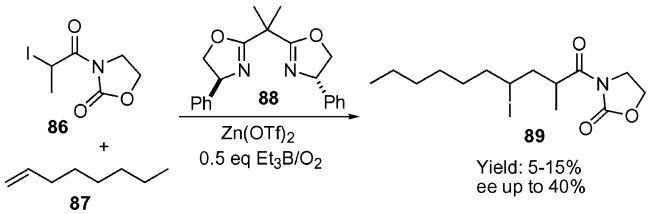


85

79/80

82

Scheme 13. Atom-Transfer Addition of α-Iodoimide 86



86

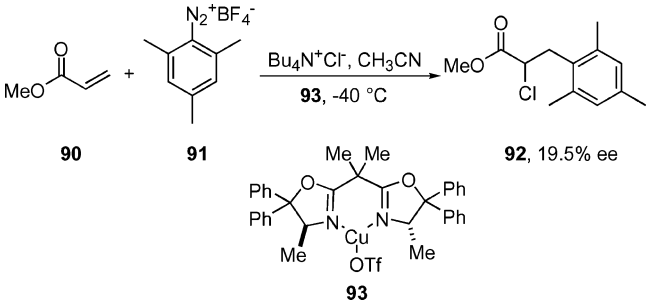
87

88

89

of mesityldiazonium tetrafluoroborate **91** with methyl acrylate using catalytic amounts of Cu(I)−bisoxazoline **93** and were able to obtain 19.5% ee for the product **92** (Scheme 14).[26] The use of *p*-tolyl diazonium salts gave lower ee's. Since the mechanism of the Meerwein reaction is unclear, it is difficult to rationalize the low ee's obtained and to plan for further modifications.

Scheme 14. Enantioselective Meerwein Arylation



2.3. Cyclization

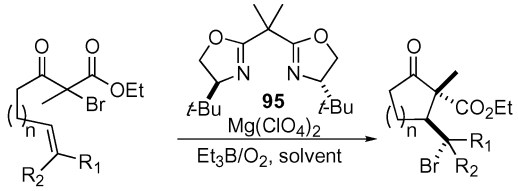
Recently, highly enantioselective atom-transfer radical cyclization reactions catalyzed by chiral Lewis acids were reported by Yang et al.[27] Two main advantages of these enantioselective cyclizations include installing multiple chiral centers and retaining a halogen atom in the product, which allows for further functionalization.

Table 8 shows the atom-transfer radical cyclizations of unsaturated *β*-keto esters **94a**−**d** using $Mg(ClO_4)_2$ and chiral ligand **95**. It was found that toluene as a solvent generally gave higher enantioselectivities than CH_2Cl_2 (see entries 1 and 2). Both 5-exo and 6-exo cyclization proceeded equally well. One notable observation was the addition of activated 4Å molecular sieves, which proved to enhance ee's and allow for the use of substoichiometric amounts of chiral Lewis acid (see entries 3, 6, 7, and 9). The molecular sieves are thought to act as a drying agent: the addition of 1.0 equiv of water drastically reduces the selectivity and cyclization rate of **94a** (see entries 2 and 4). Catalytic loading of the chiral Lewis acid showed efficiency nearly identical to that obtained with stoichiometric amounts of chiral Lewis acid with respect to both chemical yields and enantioselectivities (compare entries 2 and 3).

The high selectivity can be explained by the model shown in Scheme 15, in which magnesium is tetrahedral. Due to the steric bulk of the *tert*-butyl groups of bisoxazoline ligand **95**, *re*-face cyclization (**98**) should be favored over *si*-face cyclization (**97**). Transition state **98** results in the lowest overall steric interaction and leads to product **96a** with (2*R*,3*S*) configuration, where the ester group on C2 and the alkyl group on C3 are trans to one another.

Enantioselective tandem (cascade) radical cyclization reactions are synthetically useful since in one step they provide highly functionalized polycyclic compounds with multiple stereocenters. Yang et al.[28] recently reported the first Lewis acid-catalyzed enantioselective atom-transfer tandem cyclization reaction (Table 9). It was found that the enantioselective tandem cyclization of **99** using $Mg(ClO_4)_2$ and chiral

Table 8. Atom-Transfer Cyclization



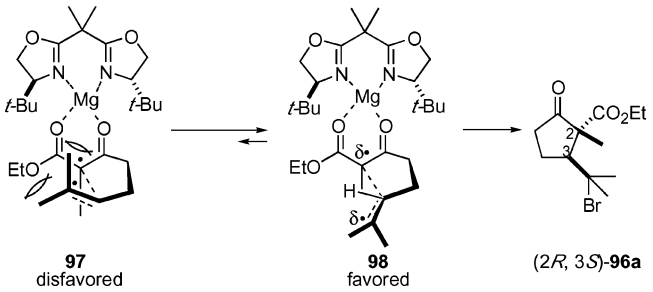
94a n =1, $R_1 = R_2$ = Me
94b n =2, R_1 = Et, R_2 = H
94c n =2, R_1 = H, R_2 = Et
94d n =2, $R_1 = R_2$ = Me

96a-d

Entry	Substrate	Catalyst (equiv.)	Solvent	Time (h)	Yield (%)	ee (%)
1	**94a**	1.1	CH_2Cl_2	7.5	68	71
2	**94a**	1.1	toluene	5	67	94
3[a]	**94a**	0.5	toluene	7	65	93
4[b]	**94a**	1.1	toluene	9	53	21
5	**94b**	1.0	toluene	9.5	57 (1/1.2)[c]	68/78[d]
6[a]	**94b**	0.3	toluene	12	58 (1/1)[c]	74/87[d]
7[a]	**94c**	0.3	toluene	9.5	81 (1/1.4)[c]	74/95[d]
8	**94d**	1.1	toluene	7.5	62	93
9[a]	**94d**	0.5	toluene	7.5	53	94

[a] MS 4Å (500mg/mmol substrate); [b] 1.0 equiv. of water was added [c] ratio of **96b:96c**; [d] ee's for **96b** and **96c**

Scheme 15. Model for Selectivity in 5-Exo Cyclization

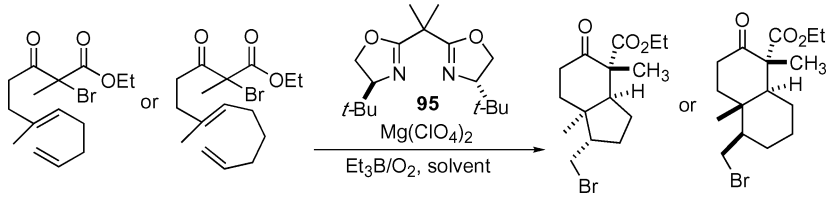


ligand **95** in CH_2Cl_2 gave poor ee's (entry 1). The use of molecular sieves slightly increased the ee but reduced the chemical yield by half (entry 2). Substrate **100** in toluene at higher temperatures gave good enantioselectivities, but still poor yields were obtained (entries 3 and 4).

Cyclizations of substrate **99** could also be performed with $Yb(OTf)_3$ as the Lewis acid in the presence of several chiral ligands (Table 10).[28] The best results were obtained using the **105**/Yb complex in CH_2Cl_2, which gave a 60% yield of **101** with 66% ee (entry 2). It is interesting to note that the addition of 4Å molecular sieves gave a nearly complete reversal of enantiofacial selectivity in the tandem radical cyclization, along with an increase in the reduced product (compare entries 2 and 3). The use of toluene as solvent gave a low yield of **101** and an ee comparable to that obtained in methylene chloride.

Scheme 16 explains the stereochemical outcome from the tandem radical cyclization in the presence of the [Yb(Ph-pybox)$(OTf)_3$] (pybox = 2,6-bis(2-oxazolin-2-yl)pyridine). The ytterbium complex **107** is shown in an octahedral geometry (with one triflate still bound to the metal), where *re*-face cyclization is favored due to the steric interactions of the substrate and the phenyl groups of the ligand. The 6-endo cyclization takes place via a chairlike transition state,

Table 9. Tandem Cyclizations Using Atom-Transfer Additions

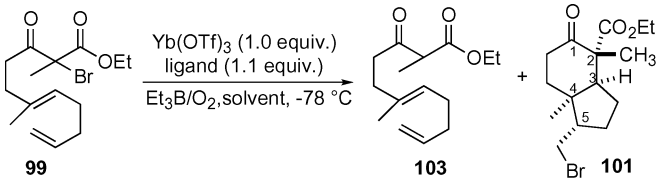


99 100 101 102

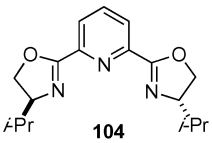
Entry	Substrate	T (°C)	Solvent	Product	Yield (%)	ee (%)
1	**99**	-78	CH_2Cl_2	**101**	41	13
2[a]	**99**	-78	CH_2Cl_2	**101**	24	33
3	**100**	-40	toluene	**102**	23	82
4	**100**	-20	toluene	**102**	16	84

[a] MS 4Å was added

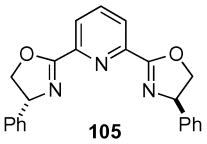
Table 10. Ytterbium-Mediated Tandem Cyclization



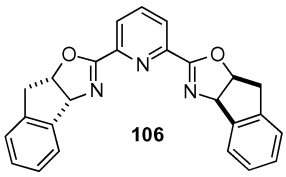
99 103 101



104



105



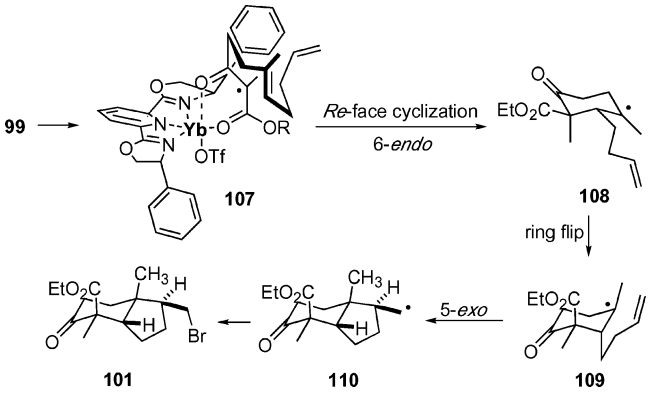
106

Entry	Ligand	Solvent	t (h)	Yield (%) [**103**]	Yield (%) [**101**]	ee (%)
1	**104**	CH_2Cl_2	13	11	28	-37
2	**105**	CH_2Cl_2	15	23	60	66
3[a]	**105**	CH_2Cl_2	13	68	11	-56
4	**105**	toluene	12	30	37	50
5	**106**	toluene	10	64	17	-43

[a] MS 4Å was used

to yield a tertiary radical, **108**, followed by a ring flip and a 5-exo cyclization (**108** to **109** to **110**). The primary radical in **110** then abstracts a bromine atom from **99** to yield (2*R*,3*S*,4*S*,5*S*)-**101**.

Scheme 16. Model/Mechanism for $Yb(OTf)_3$-Mediated Cyclization



107 108 109 110 101

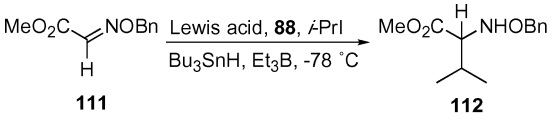
3. Reductive Alkylations

Addition of radicals to carbon−carbon or carbon−heteroatom multiple bonds, followed by trapping of the resulting radicals with a hydrogen atom source, leads to reduced products. A very favorable situation for catalytic processes exists here if the chiral Lewis acid modulates the reactivity of the substrate suitably.

3.1. Additions to Imines

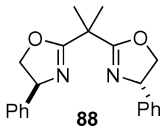
Glyoxylate imines have proven to be good substrates for the enantioselective ene and hetero-Diels−Alder reactions.[29] Radical addition to glyoxylate imines has been carried out with chiral Lewis acids. These reactions can provide optically active aliphatic α-amino acids. The radical methodology is advantageous since anionic nucleophiles do not distinguish the imine and the carboxylic esters and regioselectivity is not attained.[30] The only other case where such selectivity is obtained is in the addition of allylmetal reagents. Naito et al. utilized catalysts derived from **88** with various metal salts in the addition of isopropyl radical to **111** with limited success (Scheme 17).[31] Among the Lewis acids evaluated, only magnesium bromide gave reasonable ee's. A tetrahedral model, **113**, has been proposed for the observed selectivity. Similar studies were carried out by Halland and Jørgensen using a chiral Lewis acid derived from Cu(I) and Tol-BINAP, **116**, with less success (Scheme 18).[32] The use of Et_3B as the initiator at room temperature in the absence of TBTH seems novel in this study. At low temperature, where the concentration of *i*-Pr radicals is low, higher amounts of ethyl addition products ($Et^{\bullet}$ obtained from Et_3B)

Scheme 17. Addition to Glyoxylate Imines

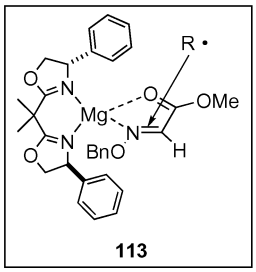


111 112

Entry	Lewis acid	Solvent	Yield (%)	ee (%)
1	$Zn(OTf)_2$	CH_2Cl_2	73	10 (*R*)
2	$Yb(OTf)_3$	CH_2Cl_2	92	24 (*R*)
3	$Mg(OTf)_2$	CH_2Cl_2	85	2 (*R*)
4	$MgBr_2$	CH_2Cl_2	97	52 (*R*)
5	$MgBr_2$	Et_2O	98	13 (*R*)
6	$MgBr_2$	toluene	98	10 (*R*)



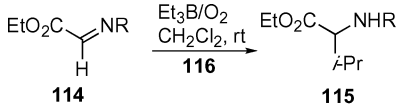
88



113

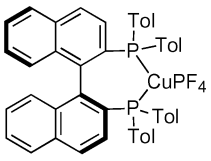
were observed. At room temperature, the atom-transfer step (Et• + *i*-PrI → *i*-Pr• + EtI) to produce the *i*-Pr radical is more efficient, and the use of tributyltin hydride can be avoided. This also restricts this particular process to alkyl iodides; other haloalkanes have much smaller halogen-transfer rates.

Scheme 18. Addition to Glyoxylate Imine Using Cu−BINAP



114 115

R	Yield (%)	ee (%)
OBn	56	15
p-OMePh	40	33



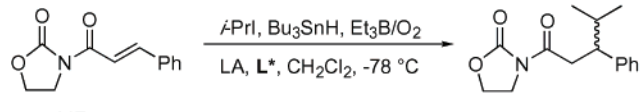
116

3.2. Conjugate Addition

Intermolecular conjugate addition[33] of nucleophilic radicals to α,β-unsaturated compounds has been carried out enantioselectively using chiral Lewis acids. Sibi, Porter, and co-workers showed that magnesium and zinc Lewis acids, along with bis-oxazoline ligands, can catalyze the reaction of oxazolidinone cinnamate **117** with *i*-PrI to give the addition product **118** (Scheme 19).[34] The success of this process depends on the activation provided by the Lewis acids, which make the reaction possible at −78 °C. The non-Lewis acid-mediated process is negligible at this temperature. Bidentate chelation of the substrate and chiral ligand to the Lewis acid generates the reactive complex. The substrate adopts an s-cis orientation at the C(O)−C(sp^2) bond when bound to the Lewis acid. The use of Et_3B, an efficient initiator at low temperatures, in the presence of oxygen generates radicals from haloalkanes. These radicals then add to the substrates bound to the chiral Lewis acid in an enantioselective manner. Interestingly, face selection depends on whether the C-4 substituent on the bisoxazoline ligand has an alkyl (**119**) or an aryl (**120**) group.[35] Moreover, zinc Lewis acids gave good selectivities with **120**, whereas magnesium salts gave good selectivities with **119**. The process was shown to be catalytic in the chiral Lewis acid. Sibi and Ji then evaluated various bisoxazoline ligands with MgI_2 and found that ligands derived from *cis*-aminoindanol were more effective in these reactions.[36] Further optimization based on the ring size at the bridging carbon showed ligand **121** to be the best ligand. This combination of MgI_2 and **121** catalyzed the reaction, even at 10 mol % loading (entry 3) and also at room temperature (entry 5), without significant loss in enantioselectivity. The observed stereochemical outcome of the reactions was explained using octahedral models, as shown in **122** and **123**. A cis-octahedral model **122** is proposed with **121**, whereas a trans-octahedral model **123** accounts for the selectivity with **120**.

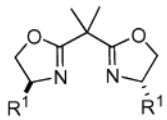
Iserloh, Curran, and Kanemasa explored the use of DBFOX/Ph ligand **124** in this reaction.[37] This ligand had previously proven to be effective in Diels−Alder reactions. Evaluation of various main-group and transition-metal Lewis acids revealed that only

Scheme 19. Conjugate Addition to Oxazolidinone Cinnamate

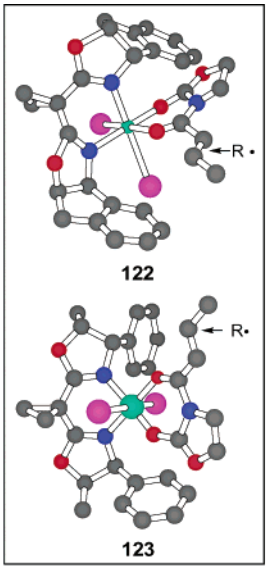


117 118

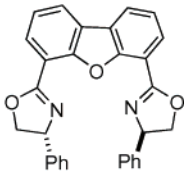
Entry	LA	L* (eq)	Yield (%)	ee (%)
1	MgI_2	**119** (1.0)	88	82 (*R*)
2	MgI_2	**119** (0.5)	86	79 (*R*)
3	MgI_2	**120** (1.0)	88	47 (*S*)
4	$Zn(OTf)_2$	**120** (1.0)	88	61 (*S*)



119 R^1 = *i*-Bu
120 R^1 = Ph

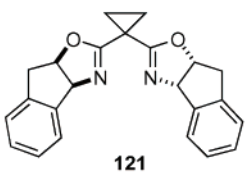


122 123



124
(*R, R*)-DBFOX/Ph

Entry	LA	L* (eq)	Temp (°C)	Yield (%)	ee (%)
1	MgI_2	**121** (1.0)	-78	88	93 (*R*)
2	MgI_2	**121** (0.3)	-78	91	97 (*R*)
3	MgI_2	**121** (0.1)	-78	88	95 (*R*)
4	MgI_2	**121** (0.3)	-20	93	95 (*R*)
5	MgI_2	**121** (0.3)	25	87	93 (*R*)
6	$Zn(OTf)_2$	**121** (1.0)	-78	-	53 (*R*)

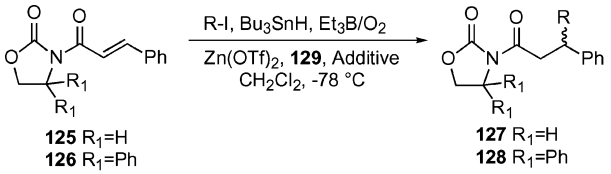


121

$Mg(ClO_4)_2$ gave good reactivity (100% yield) and enantioselectivity (75% ee). DBFOX, a tridentate ligand, increases the electron density on Mg and makes it a weaker Lewis acid. This leads to the nonselective background reaction (non-Lewis acid-catalyzed) and hence to the lowering of the enantioselectivity.

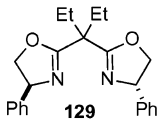
Murakata et al. also examined enantioselective conjugate addition, as shown in Table 11.[38] In an effort to evaluate the role of additives in chiral Lewis acid-mediated reactions, they chose $Zn(OTf)_2$ as the Lewis acid. Ligand **129**, with diethyl substitution at the bridging carbon of bisoxazoline, was utilized throughout their study. Under stoichiometric chiral Lewis acid, very low enantioselectivity of the product was observed. When additives **130** and **131** were added, there was a marked increase in ee's (entries 2 and 3). This increase was more dramatic when 4,4-diphenyl-substituted oxazolidinone **126** was used as the template, along with **131** as the additive (entries 4 and 5). In an effort to understand the origin of this additive effect, the *N*-methylated compound **132** was prepared and tested. The fact that there was no change in selectivity compared to that found in the experiment without any additive suggested that the additives **130** and **131** were coordinating to zinc through the NH group. Further support for this hypothesis was obtained through low-temperature NMR experiments, which showed that the substrate could displace the additive **132** but not **131**. It was also possible for the reaction to be carried out at substoichiometric loading of chiral Lewis acid, without substantial loss in selectivity (entries 9 and 10).

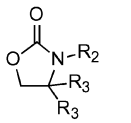
Table 11. Oxazolidinone Additives in $Zn(OTf)_2$-Catalyzed Conjugate Additions



125 R_1=H
126 R_1=Ph
127 R_1=H
128 R_1=Ph

Entry	R_1	**CLA** (eq.)	Additive	R	Yield (%)	ee (%)
1	H	1.0	-	*t*-Bu	88	9 (*S*)
2	H	1.0	**130**	*t*-Bu	86	41 (*S*)
3	H	1.0	**131**	*t*-Bu	78	52 (*S*)
4	Ph	1.0	-	*t*-Bu	80	3 (*S*)
5	Ph	1.0	**131**	*t*-Bu	96	88 (*R*)
6	Ph	1.0	-	*i*-Pr	72	32 (*S*)
7	Ph	1.0	**131**	*i*-Pr	86	82 (*R*)
8	Ph	1.0	**132**	*i*-Pr	98	29 (*S*)
9	Ph	0.25	**131**	*i*-Pr	92	80 (*R*)
10	Ph	0.25	**131**	*t*-Bu	72	83 (*R*)

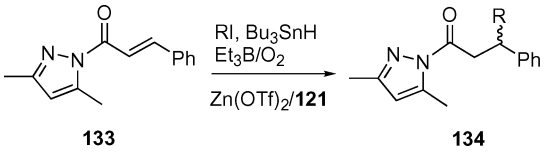




130 R_2=R_3=H
131 R_2=H; R_3=Ph
132 R_2=Me; R_3=Ph

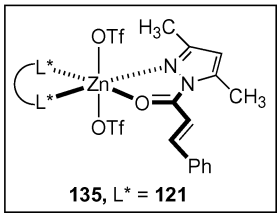
The templates used in these reactions have a significant impact on the outcome, modulating reactivity and determining selectivity. Sibi et al. also showed that changing the oxazolidinone template in **117** to a 3,5-dimethylpyrazole, as in **133**, resulted in a reversal of stereochemistry when using the same chiral Lewis acid (Scheme 20).[39] Additions in the presence of stoichiometric amounts of zinc triflate and ligand **121** gave good yields and moderate selectivities of **134**. These acylated pyrazoles **133** form five-membered chelates, unlike the six-membered chelate formed with oxazolidinones **117** (vide supra). This change in chelate ring size, accompanied by a trans-octahedral geometry with **133** and **121**, has been proposed to account for the reversal of enantioselectivity (see **135**).

Scheme 20. Pyrazole Templates: Five-Membered Chelation for Reversal of Enantioselectivity



133 **134**

R	Yield (%)	ee (%)
i-Pr	76	51 (*S*)
Et	80	39 (*R*)
c-C_6H_{11}	81	81



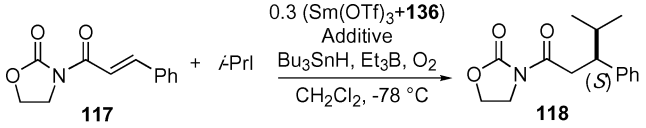
135, L* = **121**

All the examples of conjugate additions outlined above utilized either main-group or transition-metal Lewis acids. To expand the scope of these reactions, Sibi and Manyem developed a lanthanide Lewis acid−ligand system (Table 12).[40] Lanthanide Lewis acids are unique in that they are less sensitive to air and moisture (ease of handling), and they also make it possible for reactions to be carried out in aqueous media.[41] The reaction under study was similar to that shown in Scheme 19. After a brief survey of lanthanide triflates, the authors found the best combination to be samarium triflate in the presence of ligand **136**, with 30 mol % of the chiral Lewis acid being optimal. Examination of various substitutions in the ligand allowed determination of the importance of different groups. The aryl groups in the tertiary alcohol were necessary for good selectivity. After it was determined that the product was binding to the chiral Lewis acid and lowering the ee's (see entry 2), the importance of additives in improving selectivity was investigated. Among various additives, acyloxazolidinones **137**−**140** were the best, and two equivalents relative to the chiral Lewis acid were required. A size dependence of the substitution on the exo carbonyl of the additive was also investigated (entries 3−6). Two equivalents of benzoyl oxazolidinone **137**, along with 4-Å molecular sieves in addition to chiral Lewis acid, gave the highest selectivity (entry 7). Sibi and Manyem proposed that the additives aid in blocking the vacant coordination sites in the lanthanide complex,[40] hence making a more robust complex, as first demonstrated in enantioselective Diels−Alder cycloadditions by Kobayashi.[41]

3.3. Cyclizations

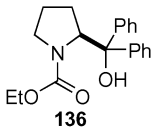
Enantioselective cyclizations by radical additions to olefins have been reported, and a few of them have already been discussed in section 2.3. Cyclizations were performed by Nishida et al. using chiral aluminum Lewis acid derived from Me_3Al and BINOLs (Scheme 21).[42] Formation of a vinyl radical, followed by a 5-exo or 6-exo (for n = 1 or 2) cyclization

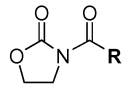
Table 12. Lanthanide-Mediated Conjugate Addition



Entry	Conditions	Yield (%)	ee (%)
1	-	84	79
2	(±) product	83	49[a]
3	**137** (2eq)	67	89
4	**138** (2 eq)	95	84
5	**139** (2eq)	75	73
6	**140** (2eq)	77	80
7	**137** (2 eq)+MS 4Å	63	92

[a] corrected for added (±) **118**

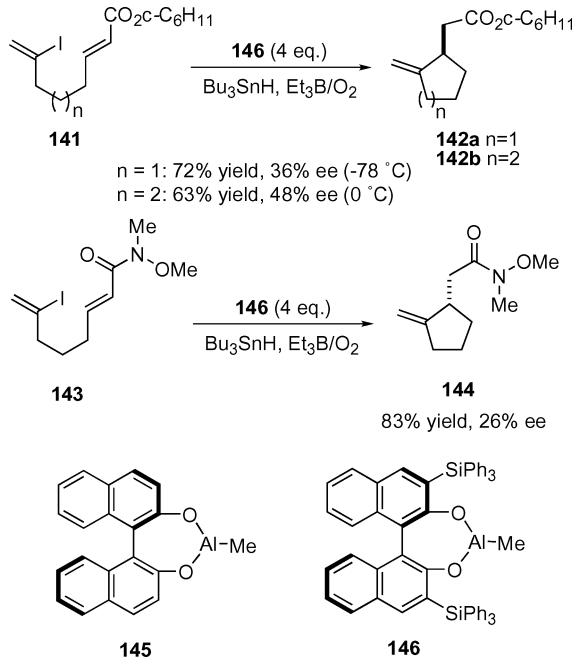




R	
Ph	137
Me	138
1-Np	139
2-Np	140

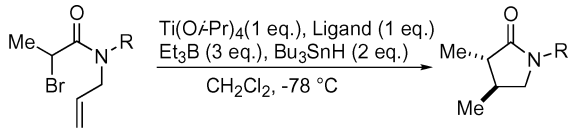
controlled by the chiral Lewis acid, provides enantiofacial selection. For the carboxylic esters **141**, the cyclizations were carried out at −78 °C for the cyclopentane formation and at 0 °C for the cyclohexane formation. Lower yields of the six-membered-ring products are due to difficulty in 6-exo cyclizations. The use of 1 equiv of either **145** or **146** provided cyclized products in low ee's, with **146** performing slightly better. With use of 4 equiv of **146**, cyclized products (*R*)-**142a** and (*R*)-**142b** were obtained in 36 and 48% ee, respectively. When the ester was replaced with the Weinreb amide, the cyclization proceeded smoothly to provide the enantiomeric product (*S*)-**144** in 26% ee. The low ee's are due to the background reaction of the amide in the absence of complexed **146**. The importance of the carboxylic substituents is evidenced in this example. The esters, upon complexation, are oriented in an s-trans fashion, whereas the Weinreb amides adopt an s-cis conformation.

Scheme 21. Cyclization via Conjugate Addition



Hiroi and Ishii performed cyclizations of α-bromo-*N*-allyl amides and sulfonamides **147a**−**c** with radical generation by using triethylborane and trapping the cyclized radical with tin hydride (Table 13).[43] The use of various Lewis acids was explored, and titanium tetraisopropoxide emerged as superior to either triethylaluminum or magnesium triflate. Among the substrates, less bulky substituents on nitrogen resulted in better reaction efficiency, with larger substituents such as 2,4,6-triisopropylphenyl and 1-naphthalenesulfonyl leading to reduced products along with recovered starting materials. The substrate **147c** with *p*-tolyl sulfonyl (tosyl) substituent was ideal in terms of both reaction efficiency and enantioselectivity. The products obtained possessed trans geometry at the newly formed C−C bond. The best selectivity (77%) was obtained with ligand **150** for the trans product **148c**.

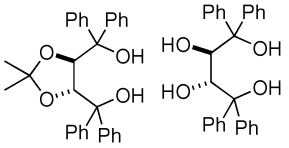
Table 13. Cyclization of α-Bromo-*N*-allylamides and Sulfonamides



147a R = Ph
147b R = SO_2Me
147c R = Tosyl

148a
148b
148c

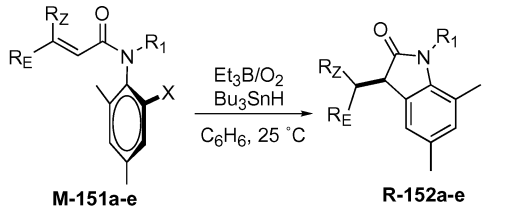
Entry	Substrate	Ligand	ee (%)
1	**147a**	**149**	5
2	**147b**	**149**	4
3	**147c**	**149**	47
4	**147c**	**150**	77



149 **150**

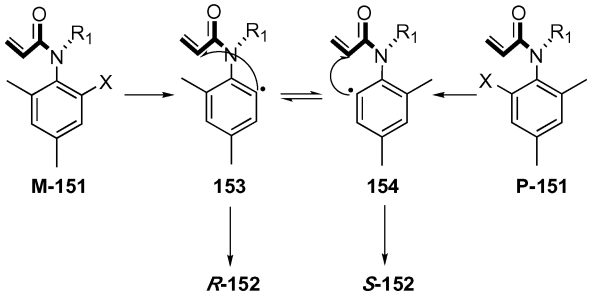
A unique cyclization procedure was conducted by Curran et al., in which they showed that axial chirality can be transferred into a new stereocenter with retention of chirality (Scheme 22).[44] Substrates *M*- and *P*-**151a**−**e** were prepared either from the chiral pool or by racemic synthesis, followed by preparative chiral HPLC separation. When these substrates were subjected to the conditions shown in Scheme 22, the products (*R*)- and (*S*)-**152** were obtained in good yields and high ee's. The radical can be derived from both aryl bromides and aryl iodides, and the ee's are very similar (entries 1 and 3). The high ee's are due to the almost complete absence of racemization of radical intermediates **153** and **154**. This is, in turn, related to the efficiency of the aryl radical addition to the olefin. A point of note is that the olefin bond has to move out of conjugation from the carbonyl bond during cyclization. The intermediate **153** obtained from *M*-**151** has to rotate around the aryl−nitrogen bond in order for the proper overlap required for cyclization to occur. If the cyclization is not efficient, there is a possibility of the bond rotation going further, leading to **154** and hence to racemization. These factors are borne out in the examples presented. In entries 5 and 6, higher ee's are obtained when R_E is phenyl: the delocalization (and hence stabilization) provided by the carbonyl group becomes less important due to the delocalization provided by conjugation with the phenyl ring. This allows for *M*-**151c** to react faster, furnishing higher ee's.

Scheme 22. Memory of Chirality in Cyclization



M-151a-e R-152a-e

Entry	Precursor	R_1	R_E	R_Z	X	Yield (%)	ee (%)
1	**M-151a**	Me	Me	H	I	73	89 (*R*)
2	**P-151a**	Me	Me	H	I	70	85 (*S*)
3	**M-151b**	Me	Me	H	Br	60	92 (*R*)
4	**P-151b**	Me	Me	H	Br	60	87 (*S*)
5	**M-151c**	Me	Ph	H	I	75	94 (*R*)
6	**P-151c**	Me	Ph	H	I	73	92 (*S*)
7	**M-151d**	Me	Me	Me	I	91	49 (*R*)
8	**P-151d**	Me	Me	Me	I	88	50 (*S*)
9	**M-151e**	Et	Me	H	I	93	90 (*R*)
10	**P-151e**	Et	Me	H	I	86	90 (*S*)



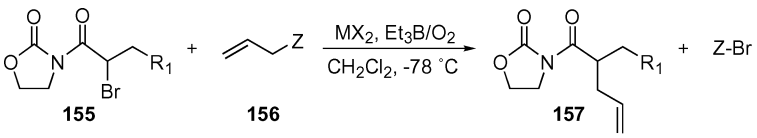
4. Fragmentations

Fragmentation reactions involve the addition of radicals to a neutral molecule, followed by β-elimination of the resultant radical, generating a terminal olefin.[45] The most common trap for a radical is allyltributylstannane, which was used initially by Keck and Yates.[46] Porter et al. performed the trapping of acyl radicals obtained from α-bromo oxazolidinones **155** with allylstannanes and allylsilanes (Table 14).[47] Magnesium and zinc Lewis acids were used with bisoxazolines to induce enantioselectivity. Although the allylstannanes are good trapping agents, this reaction produces stannyl halides that are Lewis acidic and can compete with the chiral Lewis acid in catalyzing the reaction. This results in racemic products, which then reduces the overall enantioselectivity of the products (entry 1). Replacement of allylstannanes with allylsilanes overcomes this problem, and higher selectivities are obtained (compare entries 1−4). With the same bisoxazoline ligand, magnesium and zinc Lewis acids gave enantiomeric products (entries 5 and 6), as was observed in the conjugate addition reactions (vide supra). However, magnesium Lewis acids provided higher levels of selectivity with alkyl substituents at R_3 than with aryl substituents (entries 6 and 7). In addition, a spirocyclic ligand gave better ee's compared to the dimethyl ligand (entries 7 and 8). The authors also showed that addition of Me_3SnBr decreases the enantioselectivity, depending on the amount, supporting the hypothesis that this is the most probable cause for the decreased ee's in allylstannane reactions.

A similar study was published independently by Renaud and Fhal, in which they reported the use of aluminum Lewis acids (Table 15).[48] This study utilized the α-iodo acyloxazolidinones **159** as substrates, and the corresponding radical was generated either by photolysis (−10 °C) or by using triethylborane (−78 °C). The Et_3B method always gave better selectivities than photolysis. In the case of **159a**, (*S*)-BINOL **161**, bistriflamide **162**, and the TADDOL **163** were ineffective, giving <20% ee's. Substituents at C-4 can influence the s-cis versus s-trans conformers in the reactive radical species, but in this instance, the increase in ee's for **159b** was less than expected (entries 4−6). Similar ee's were obtained with both allylstannane and methallylstannane (entries 5 and 6).

In a related study, Porter et al. showed that α-bromo γ-lactams **164a**−**d**, containing a pyridyl moiety, can react with allyltrimethylsilane enantioselectively in the presence of chiral Lewis acids derived from zinc and **167** (Table 16).[49] In contrast to the above study, the ligand of choice for substrates **164** was found to be the bisoxazoline ligand **167**. Excellent ee's were obtained in the presence of 2 equiv of the chiral Lewis acid. When substoichiometric amounts of the catalyst were used, turnover was demonstrated, albeit with lower selectivity. Different substituents on the pyridyl moiety of **164** were also examined, although no predictable trend was observed. A trans-octahedral model similar to that in

Table 14. Allylations of α-Bromo Oxazolidinones



155 156 157

		158						
Entry	R_1	R_2	R_3	config.	MX_2	Z	Yield (%)	ee (%)
1	Me	Me	Ph	(*R*, *R*)	$Zn(OTf)_2$	$SnBu_3$	84	42 (*S*)
2	Me	Me	Ph	(*R*, *R*)	$Zn(OTf)_2$	$Si(OEt)_3$	65	60 (*S*)
3	*t*-Bu	Me	Ph	(*R*, *R*)	$Zn(OTf)_2$	$SnBu_3$	63	74 (*R*)
4	*t*-Bu	Me	Ph	(*R*, *R*)	$Zn(OTf)_2$	$SiMe_3$	88	90 (*R*)
5	*t*-Bu	Me	Ph	(*R*, *R*)	MgI_2	$SiMe_3$	86	68 (*S*)
6	*t*-Bu	Me	*t*-Bu	(*S*, *S*)	MgI_2	$SiMe_3$	61	78 (*R*)
7	*t*-Bu	$-(CH_2)_2-$	*t*-Bu	(*S*, *S*)	MgI_2	$SiMe_3$	65	88 (*R*)
8	*t*-Bu	Me	*t*-Bu	(*S*, *S*)	MgI_2	$SiMe_3$	83	82 (*R*)

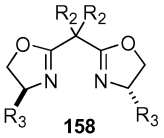
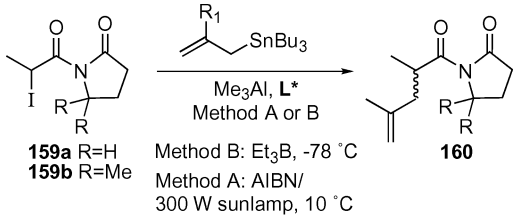
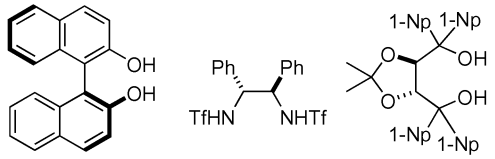

158

Table 15. Allylations Using Trimethylaluminum





161 162 163

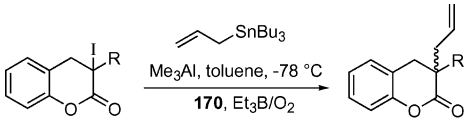
Entry	R	R_1	L*	Method	Yield (%)	ee(%)
1	H	H	**161**	A	90	0
2	H	H	**162**	A	89	20 (*S*)
3	H	H	**163**	A	88	15 (*S*)
4	Me	Me	**163**	A	95	24 (*R*)
5	Me	Me	**163**	B	93	34 (*R*)
6	Me	H	**163**	B	90	32 (*R*)

123 was proposed to explain the stereochemical outcome of the reaction.

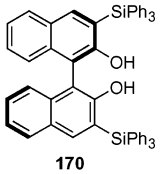
Hoshino and co-workers demonstrated the creation of chiral quaternary centers by using allyltributylstannane.[50] In this study, a monodentate substrate, **4a**−**c**, was used (Table 17; cf. Table 1). An initial evaluation of Lewis acids showed that, among MgI_2, $MgBr_2$, $Zn(OTf)_2$, Et_2AlCl, and Me_3Al, only Me_3Al activated the substrate to provide the desired product. Use of this Lewis acid with ligand **170** provided the allylated product **169** in low (27%) ee. Addition of diethyl ether (1 equiv to Lewis acid and ligand) produced a dramatic increase in selectivity to 81% ee. Other additives, such as diisopropyl ether, THF, or *N*-methylpyrrolidine (NMP) were not as effective as diethyl ether. Substrates containing either a simple methyl group **4a**, or those with an alkoxyalkyl group **4b**,**c**, benefited from added ether. The reaction was also shown to be catalytic in chiral Lewis acid (entries 10 and 11). A five-coordinate aluminum complex, **171**, has been proposed to account for the selectivity. Sulfonamido ligands derived from (*R*)-1,2-diphenylethylenediamine were also studied by Hoshino et al., with both trimethylaluminum and triisobutylaluminum, with much less success: a maximum of 54% ee was achieved (Table 18).[51] The chiral Lewis acids were prepared by refluxing **172a**−**c** with aluminum salts and then cooled to −78 °C before the reaction. The heterogeneity of the catalyst in toluene was an issue. This was overcome by using larger amounts of the aluminum salts relative to the ligand or by using substoichiometric amounts of the catalyst. Similar levels of ee's (54%) were achieved in the lower loading of catalyst (entry 9).

In fragmentation reactions involving sulfonamides **173**, Hiroi and Ishii examined various Lewis acids with chiral diamines, diols, and sulfoxides (Scheme 23).[43] Among these ligands, the sulfoxide ligand **178** gave good selectivity with magnesium triflate. The tosyl group in the substrate was important, as the smaller methane sulfonamide gave much lower ee's (data not shown). The origin of selectivity with magnesium Lewis acid was explained using the model **180**. It is important to note that the sulfonyl

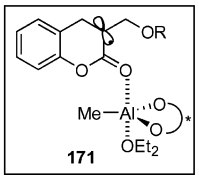
Table 17. Allylation of α-Iodo Lactones: Al-BINOL as Single-Point-Binding Chiral Lewis Acid



Entry	R	CLA (eq.)	Additive	Yield (%)	ee (%)
1	Me	1.0	-	72	27 (*R*)
2	Me	1.0	Et_2O	84	81 (*R*)
3	CH_2OMe	1.0	-	75	10 (*S*)
4	CH_2OMe	1.0	Et_2O	85	82 (*R*)
5	CH_2OMe	1.0	*i*-Pr_2O	83	43 (*R*)
6	CH_2OMe	1.0	THF	71	33 (*R*)
7	CH_2OMe	1.0	NMP	59	3 (*R*)
8	CH_2OBn	1.0	-	72	3 (*S*)
9	CH_2OBn	1.0	Et_2O	76	91 (*R*)
10	CH_2OBn	0.2	Et_2O	73	82 (*R*)
11	CH_2OBn	0.1	Et_2O	78	71 (*R*)

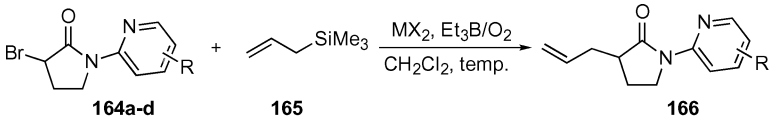


170



171

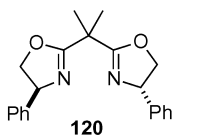
Table 16. Allylation of γ-Lactams: Pyridine as Template



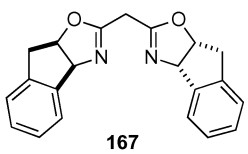
164a-d 165 166

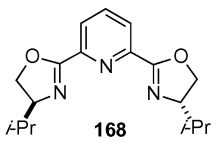
a H
b 4-Me
c 5-Cl
d 5-CO_2Me

Entry	Substrate	Ligand	MX_2(eq.)	T (°C)	Yield (%)	ee (%)
1	**164a**	**120**	$Zn(OTf)_2$ (1.0)	-78	70	59 (*S*)
2	**164a**	**167**	$Zn(OTf)_2$ (1.0)	-78	75	96 (*S*)
3	**164a**	**168**	$Zn(OTf)_2$ (1.0)	-78	42	75 (*R*)
4	**164a**	**167**	$MgBr_2$ (1.0)	-78	54	84 (*R*)
5	**164a**	**167**	$Zn(OTf)_2$ (2.0)	-78	83	>99 (*S*)
6	**164a**	**167**	$Zn(OTf)_2$ (2.0)	-20	94	95 (*R*)
7	**164a**	**167**	$Zn(OTf)_2$ (1.0)	-20	93	91 (*R*)
8	**164b**	**167**	$Zn(OTf)_2$ (1.0)	-20	85	70 (*R*)
9	**164c**	**167**	$Zn(OTf)_2$ (1.0)	-20	88	67 (*S*)
10	**164d**	**167**	$Zn(OTf)_2$ (1.0)	-20	91	80 (*S*)
11	**164a**	**167**	$Zn(OTf)_2$ (0.2)	-20	69	81 (*S*)



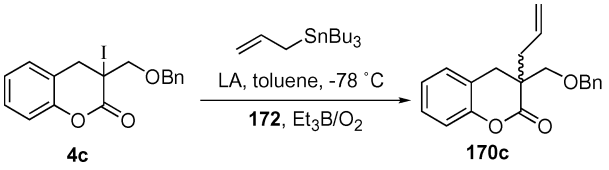
120


167



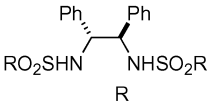
168

Table 18. Allylation with Sulfonamide Ligands



4c 170c

Entry	172 (eq)	LA (eq.)	Yield (%)	ee (%)
1	**172a** (1)	Et_2AlCl (1)	19	0
2	**172a** (1)	Me_3Al (1)	75	25 (*R*)
3	**172a** (1)	*i*-Bu_3Al (1)	62	16 (*R*)
4	**172b** (1)	Me_3Al (1.5)	73	54 (*R*)
5	**172b** (1)	Me_3Al (2)	76	51 (*R*)
6	**172b** (1)	*i*-Bu_3Al (2)	75	43 (*R*)
7	**172c** (1)	Me_3Al (1)	76	13 (*S*)
8	**172c** (1)	*i*-Bu_3Al (1)	68	42 (*S*)
9	**172b** (0.5)	Me_3Al (1)	72	54 (*R*)
10	**172b** (0.5)	Me_3Al (1.5)	75	10 (*R*)



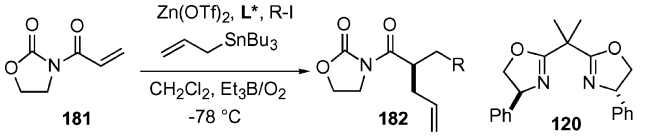
172a CF_3
172b C_6H_5
172c CH_2CF_3

oxygens are enantiotopic, and hence one can form four different complexes, depending on the orientation of the substrate and the sulfonyl oxygen that binds to the metal. The orientation shown in **180** is the lowest energy conformation, and the radical is trapped by the allylstannane from the face opposite to the *p*-tolyl group. In this case, although not mentioned by the authors, one cannot rule out the assisted addition of the radical to allylstannane: tin can coordinate to the uncoordinated sulfonyl oxygen and hence assist the addition. Tin salts are known to coordinate to oxygen atoms, as has been shown by Porter et al.[47] (vide supra).

5. Tandem Reactions: Addition–Trapping

The previous section detailed the possibility of generating radicals followed by fragmentation reactions with allylstannanes. Such α-acyl radicals are intermediates in the conjugate addition of nucleophilic radicals to α,β-unsaturated compounds and can further react with allylstannanes. In doing so, a stereocenter is created at the carbon atom α to the carbonyl. In principle, one can create two stereocenters in this tandem reaction. A first example, though, involved creation of a single chiral center: addition of radicals to oxazolidinone acrylate **181**, followed by trapping with stannane (Scheme 24).[52]

Scheme 24. Installation of α-Stereocenter through Addition–Trapping

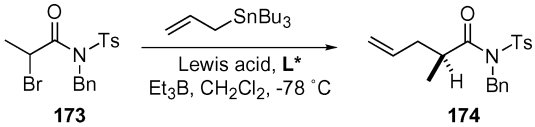


181 182 120

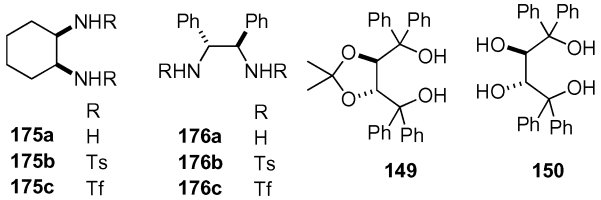
Entry	RI (eq.)	L*	181:M:L*	Solvent	Yield (%)	ee (%)
1	c-HexI (10)	(*S*, *S*)-**120**	1:1:1	CH_2Cl_2	62	50 (*S*)
2	c-HexI (10)	(*S*, *S*)-**120**	1:1:1	ether	90	64 (*S*)
3	c-HexI (10)	(*S*, *S*)-**120**	1:2:2	ether	61	80 (*S*)
4	c-HexI (1.5)	(*R*, *R*)-**120**	1:1:1.2	CH_2Cl_2:pent 4:6	62	68 (*R*)
5	c-HexI (1.5)	(*R*, *R*)-**120**	1:2:2.4	CH_2Cl_2:pent 4:6	92	72 (*R*)
6	*t*-BuI (5)	(*S*, *S*)-**120**	1:1:1.2	CH_2Cl_2:pent 4:6	78	88 (*S*)
7	*t*-BuI (5)	(*R*, *R*)-**120**	1:1:1.2	CH_2Cl_2:pent 4:6	92	90 (*R*)
8	*t*-BuI (5)	(*R*, *R*)-**120**	1:2:2.1	ether	55	88 (*R*)

Zinc triflate was found to be the ideal Lewis acid; zinc chloride, magnesium triflate, and scandium triflate were ineffective. Ether as solvent proved to be better than methylene chloride (entries 1 and 2), an anomalous behavior that possibly hints at a superior chiral catalyst with ether coordinated to zinc or stannane. Further experiments were carried out with CH_2Cl_2–pentane (40:60) mixtures, and *tert*-butyl radical additions gave up to 90% ee (entry 7). High selectivity could be obtained with ether, although 2 equiv of the chiral Lewis acid was required (entry 8). Unlike tributyltin bromide, tributyltin iodide, being a weaker

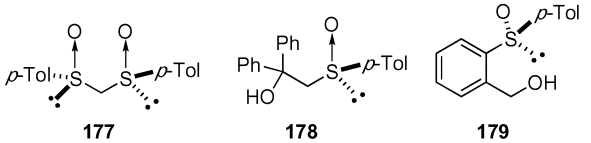
Scheme 23. Allylations Using Acyclic Template: Sulfonamide



173 174

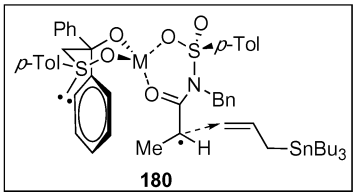


149 150



177 178 179

Entry	Ligand	Lewis acid	Yield (%)	ee (%)
1	**175a**	Et_3Al	72	53
2	**175b**	Et_3Al	68	60
3	**175c**	Et_3Al	83	58
4	**176a**	Et_3Al	88	53
5	**176b**	Et_3Al	80	64
6	**176c**	Et_3Al	83	63
7	**149**	$Ti(O$*i*-$Pr)_4$	44	50
8	**150**	$Ti(O$*i*-$Pr)_4$	52	52
9	**177**	$Mg(OTf)_2$	65	52
10	**178**	$Mg(OTf)_2$	41	83
11	**179**	$Mg(OTf)_2$	64	50



180

Lewis acid, did not have a detrimental impact on selectivity. A tetrahedral zinc complex with bidentate chelation to substrate and ligand was proposed to account for the observed stereochemistry (Figure 2).

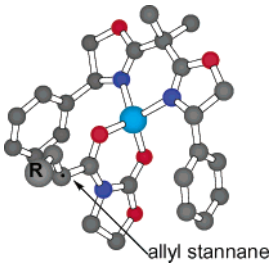
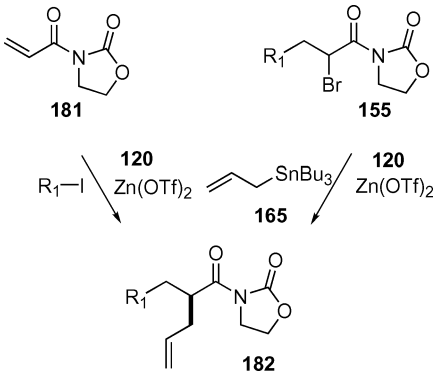


Figure 2. Model for allylation.

Porter et al. made a direct comparison of the stereochemical efficiency of the fragmentation reaction versus the tandem reaction as a function of the steric effect based on the Taft parameters for different substituents.[53] Their results are shown in Figure 3 for the reactions shown in Scheme 25. In general, the tandem reactions perform better and provide higher levels of ee's than the fragmentation reactions. This effect could be due to the tin bromide byproduct catalyzing a non-stereoselective process, as has been uncovered by the same authors (vide supra) and by Sibi and Ji in their diastereoselective studies.[47,54]

Scheme 25. Addition−Trapping vs Fragmentation: Influence of Sterics on Selectivity



Sulfones are an appealing class of substrates and have been used in tandem reactions with generation of a chiral center α to the sulfonyl group (Scheme 26).[55] To achieve bidentate chelation with metal, pyridyl or benzimidazolyl moieties were also introduced in the substrates **183a**−**c**. The results indicate that the benzimidazolyl substrates **183c** perform better than pyridyl substrate **183a**. The effect of an N-substituent is not apparent: with allyltributyltin, the ee's increase from **183a**−**c** (entries 3−5), whereas with allyltriphenyltin, the ee's follow the reverse order (entries 6−8). The reaction efficiency is dependent on the amount and nature of the trapping agent employed. Diallyldibutylstannane performed better than all other stannanes. In addition, 10 equiv of the stannane gave the best results in terms of yield and selectivity (entries 10, 12, and 13). The model proposed for the observed selectivity is shown in Figure 4. In attempting to understand the structures of the chiral complex, one has to remember that the

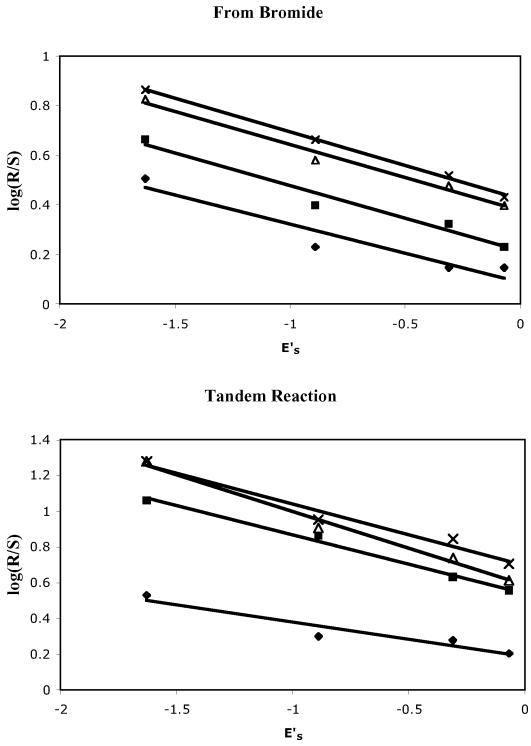
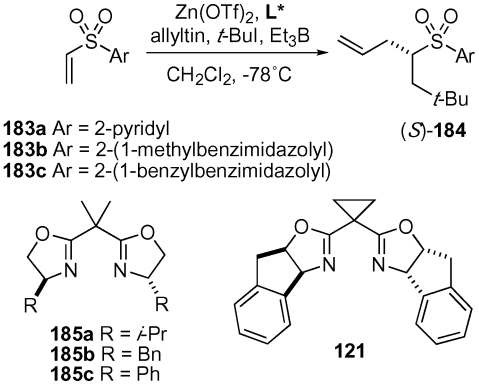


Figure 3. Comparison of fragmentation and tandem reactions. Legend: ◆, 0.2 equiv; ■, 0.6 equiv; △, 1.0 equiv; ×, 2.0 equiv.

sulfonyl oxygens are enantiotopic and can form diastereotopic complexes with the chiral Lewis acid. Selection at this level is then translated in combination with discrimination from the ligand into the final ee's observed in the products.

Scheme 26. Addition−Trapping to Sulfones



Entry	Substrate	Ligand	Allylstannane	Time (min)	Yield (%)	ee (%)
1	**183a**	**185a**	$AllylBu_3Sn$	30	60	10
2	**183a**	**185b**	$AllylBu_3Sn$	120	47	4
3	**183a**	**185c**	$AllylBu_3Sn$	120	36	46
4	**183b**	**185c**	$AllylBu_3Sn$	120	35	62
5	**183c**	**185c**	$AllylBu_3Sn$	120	35	80
6	**183a**	**185c**	$AllylPh_3Sn$	90	82	50
7	**183b**	**185c**	$AllylPh_3Sn$	90	88	24
8	**183c**	**185c**	$AllylPh_3Sn$	180	49	16
9	**183c**	**185c**	$Allyl_4Sn$	120	87	51
10	**183c**	**185c**	$Allyl_2Bu_2Sn$	120	74	50
11	**183c**	**185c**	$AllylBu_2SnCl$	180	85	17
12	**183c**	**185c**	$Allyl_2Bu_2Sn$	50	86	78
13	**183c**	**185c**	$Allyl_2Bu_2Sn$	20	80	84
14	**183c**	**121**	$Allyl_2Bu_2Sn$	15	18	4

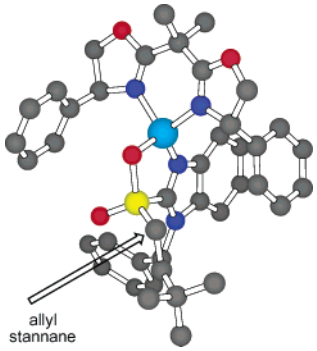
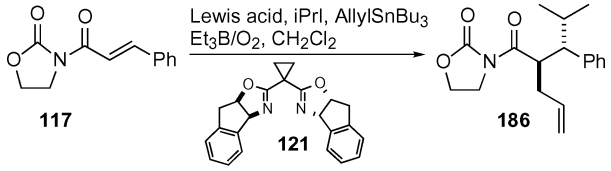


Figure 4. Allylation of sulfones.

Sibi and Chen demonstrated for the first time that relative and absolute stereocenters of both α and *β* carbons can be controlled in the intermolecular addition−trapping experiments (Table 19).[56] Magnesium and copper Lewis acids performed better than zinc. The use of 30 mol % of chiral Lewis acid gave higher selectivities than the stoichiometric amounts for both magnesium and copper. Interestingly, copper triflate gave better selectivities with allyltriphenyl stannane, whereas no such difference was found with magnesium Lewis acids. Among the magnesium salts, iodide counterion was found to be more effective than bromide or perchlorate. The products obtained predominantly had anti stereochemistry. Another point of note was that copper triflate and magnesium iodide gave enantiomeric products. The selectivity was noted to be dependent on both the size of the radical being added and the size of the *β*-substituent (Table 20). The best selectivities were obtained when *tert*-butyl radical was added and for the *β*-phenyl substituent. In the case of crotonate substrates, changing the template from oxazolidinone **187** to pyrrolidinone **188** led to higher selectivities. The anti selectivity was shown to depend mainly on the *β*-stereocenter.

Table 19. Vicinal Stereocenters in Addition−Trapping



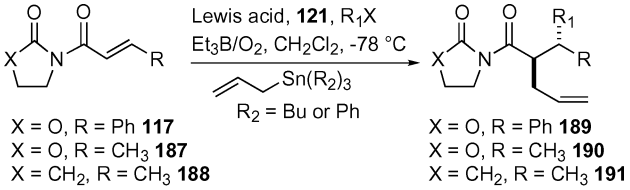
Entry	Lewis acid (eq.)	Yield (%)	dr	ee (%)
1	MgI_2 (1)	82	19	86
2	MgI_2 (0.3)	93	37	93
3	$MgBr_2$ (0.3)	90	30	90
4	$Mg(ClO_4)_2$ (0.3)	91	40	87
5	$Zn(OTf)_2$ (0.3)	69	33	-43
6[a]	$Cu(OTf)_2$ (1)	84	30	-76
7[a]	$Cu(OTf)_2$ (0.3)	93	30	-79

[a] Allyltriphenyltin was used.

6. Electron-Transfer Reactions

Reactions involving metals to generate radicals from oxygenated substrates such as aldehydes, ketones, and epoxides comprise a unique class in enantioselective radical reactions. Here, the radical-generating reagent is bound to the radical precursor and remains bound to the reacting radical species, allowing for stereocontrol in subsequent reactions in the presence of a chiral ligand suitable for the metal. Some popular reagents in this class are titanocenes and samarium diiodide. Two recent reviews detail the development of transition-metal reagents for catalysis in radical reactions.[57] This section will summarize the developments in this field.

Table 20. Scope of Addition−Trapping Reactions



Entry	Substrate	LA (0.3 eq.)	R_1X	Yield (%)	dr	ee (%)
1	**117**	MgI_2	$MeOCH_2Br$	80	20	72
2	**117**	MgI_2	EtI	79	32	77
3	**117**	MgI_2	*c*-HexI	80	60	92
4	**117**	MgI_2	*t*-BuI	84	99	97
5[a]	**117**	$Cu(OTf)_2$	*t*-BuI	90	99	-96
6	**187**	$Mg(ClO_4)_2$	EtI	83	4	61
7	**187**	$Mg(ClO_4)_2$	*c*-HexI	83	4	62
8	**188**	$Mg(ClO_4)_2$	EtI	83	7	66
9	**188**	$Mg(ClO_4)_2$	*c*-HexI	84	7	69
10	**188**	$Mg(ClO_4)_2$	$MeOCH_2Br$	83	2.4	53
11	**188**	$Mg(ClO_4)_2$	*i*-PrI	84	7	76
12[a]	**188**	$Cu(OTf)_2$	*i*-PrI	95	10	-76
13	**188**	$Mg(ClO_4)_2$	*t*-BuI	85	19	92
14	**188**	$Cu(OTf)_2$	*t*-BuI	66	50	-83

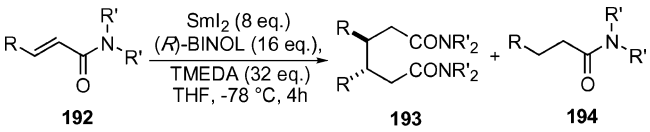
[a] Allyltriphenyltin was used.

6.1. Ketyl Radical Reactions

The ability of HMPA to facilitate SmI_2 (Kagan reagent)-mediated reactions has been well recognized, and chiral ligands that have similar electron-donating capabilities have been tested in these reactions. Inanaga et al. applied chiral Sm(II) complexes toward the hydrodimerization of acrylic acid amides **192** (Scheme 27).[58] Dimerization of conjugated ketyl radicals in a ligand-controlled environment leads to the enantioselective formation of 3,4-trans-disubstituted adipamides **193**. Among the various bases that were evaluated, TMEDA proved to be the best. The reactions could be carried out with 2 equiv of SmI_2, but as shown in the scheme, 4 equiv was preferred due to the gradual decomposition of the chiral samarium complex, even at −78 °C. The requirement of such an excess of (*R*)-BINOL is discouraging, but the ligand could be recovered in pure form following a simple workup. The yield of **193** obtained in this reaction is rather low and is accompanied by the reduced product **194**. No meso products were observed in the majority of cases. Good selectivities but moderate yields were obtained when *β*-substitution involved a linear alkyl group (entries 1−3). The efficiency of the reaction was lowered when bulky substituents were placed in the *β*-position, and no homo-coupling was observed when isopropyl or *tert*-butyl groups were present (entries 5 and 6). Interestingly, when the amide substitution was

changed from benzyl to phenyl, the dl:meso ratio decreased and the opposite enantiomer was formed (entry 7). The higher reactivity of this substrate was postulated as the reason for this change in stereochemistry.

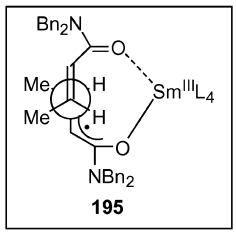
Scheme 27. Hydrodimerization through Ketyl Radicals



192 193 194

Entry	R	R'	Yield (%)	ee (%)
1	Me	Bn	70	71 (+)
2	Et	Bn	45	82 (+)
3	*n*-Pr	Bn	35	82 (+)
4	$BnCH_2$	Bn	20	85 (+)
5	*i*-Pr	Bn	-	-
6	*t*-Bu	Bn	-	-
7[a]	Me	Ph	55	44 (-)

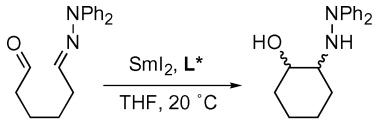
[a] *dl:meso =63:37*



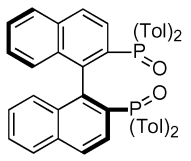
195

In cyclization reactions of ketyl radicals with hydrazone, Skrydstrup and co-workers used different ligands to control the face selectivity in these coupling reactions (Scheme 28).[59] Reaction of carbonyl hydrazone **196** in THF with SmI_2, precomplexed with stoichiometric amounts of ligands **198**−**200**, led to cyclization products in varying yields and low ee's, depending on the ligand. The (*S*)-BINAPO ligand **198**, which was moderately successful in Mikami's experiments (vide infra), decreased the reactivity, providing only 15% yield of the cyclized product with 10% ee. Only ligand **200** gave a reasonable yield (62%) but with low (5%) enantioselectivity of the trans product.

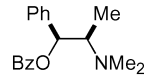
Scheme 28. Cyclization: Ketyl Radical Addition to Hydrazone



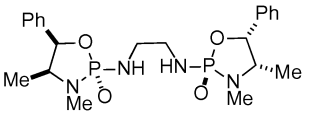
196 197



(*S*)-198
15% yield (*trans*)
10% ee



199
9% yield (*trans*)
0% ee



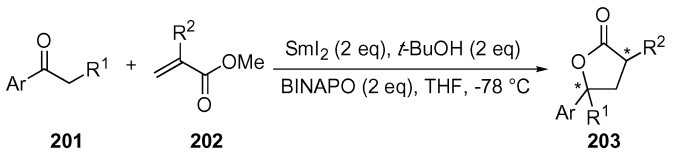
200
62% yield (*trans*)
5% ee

Mikami and Yamaoka demonstrated enantioselective addition of ketyl radicals, generated using SmI_2, to olefins.[60] As shown in Scheme 29, the reductive coupling of acetophenone with methyl acrylate **202** in the presence of chiral 2,2′-bis(diphenylphosphinyl)-1,1′-binaphthyl (*R*-BINAPO, (*R*)-**198**) gives somewhat low yields (mostly under 50%) but moderate to good levels of enantioselectivity (60−70% ee) for the γ-butyrolactone products **203**. The mechanism is shown for this reaction. Samarium diiodide is a one-electron donor, and hence 2 equiv of the metal is required in order for the reaction to proceed. The first electron donated from the samarium produces a chiral ketyl radical **204** that undergoes enantioselective addition to the acrylate according to the chelated transition state **205**. The second electron donation then provides a samarium enolate intermediate **206** that can potentially undergo stereoselective proton transfer in the formation of a second chiral center.

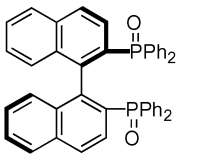
6.2. Pinacol Coupling

Reductive coupling of aldehydes using organometallic reagents to make pinacols is a powerful method. Most common metals for this process are titanium, vanadium, samarium, and niobium, and of these, titanium reagents are popular. The reaction involves generation of the ketyl radicals, which upon coupling provide 1,2-diols. Various issues need to be considered regarding this reaction: control of both relative and absolute stereochemistry is required; in catalytic conditions, the product inhibition due to diol should be addressed; the reductant used for catalytic turnover further complicates the structure of the heterobimetallic reactive complex involved. Catalytic turnover can be achieved by cleaving the Ti−O bond using either TMSCl or proton. While TMSCl activates the aldehydes toward electron transfer, a general concern is the catalysis due to chlorosilane, especially for less reactive substrates. Low-valent titanium species can be either used directly (stoichiometric) or generated in situ (catalytic) using a reducing agent. Both methods have been investigated in the enantioselective reactions (Table 21). Commercially available $TiCl_3$ has been used in stoichiometric amounts with (+)-dimethyltartarate **211**, resulting in a drastic reduction in diastereoselectivity (compared to the reaction without any chiral ligand) and very poor enantioselectivity (entry 2).[61] $TiCl_2$ has been used along with diamine **212**, providing diols with moderate ee's (entries 3 and 4). The added amines accelerate the reaction by making a homogeneous catalyst.[62] Although the solution was visibly homogeneous, the authors performed small-angle X-ray scattering (SAXS) and atomic force microscopy (AFM) to analyze the nature of the titanium reagent in solution. They found that there were two sets of particles with different sizes. This, combined with the X-ray structure of the titanium−amine complex available in the literature, led them to conclude that two species were present: one of them being a cluster of the $TiCl_2$−**212** and the other being a monomeric species with coordinated THF. It seems that the cluster leads to lower ee's: addition of tetrahydrothiophene resulted in higher selectivity (58% ee).[63] Enders used SMP, **213**, under similar conditions with low yields and moderate ee's (entry 5).[64] Brintzinger's *ansa*-metallocene **214** is the most successful chiral catalyst to date in pinacol coupling (entry 6).[65] Other

Scheme 29. Ketyl Radical Addition and Cyclization



201 202 203



(*R*)- BINAPO, (*R*)-**198**

Ar	R^1	R^2	Yield (%)	*cis* : *trans*	ee (%) *cis/trans*
Ph	H	H	46		67
Ph	H	Me	42	66:34	89/55
Ph	Me	H	18		63

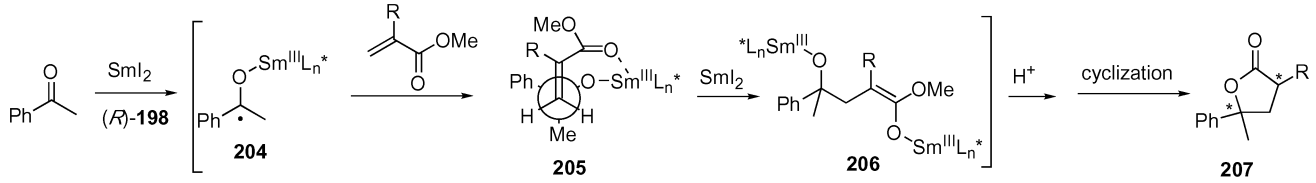
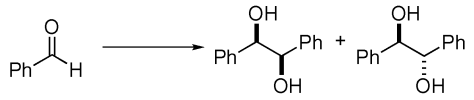
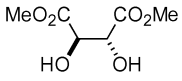


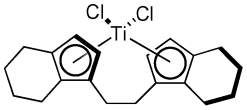
Table 21. Pinacol Coupling Using Titanium Catalysts



208 (*S,S*)-**209** **210**



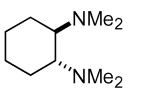
(+)-**211**



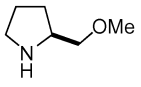
214

Entry	Catalyst (eq.)	Conditions	Yield (%)	*dl:meso*	ee (%)	Ref.
1	$TiCl_3$ (1.0)	CH_2Cl_2/THF, rt, 30 min.	65	200:1	-	61
2	$TiCl_3$ (1.0) + **211** (0.5)	CH_2Cl_2/THF, rt, 30 min.	64	6.5:1	4	61
3	$TiCl_2$ (1.0) + **212** (2.0)	THF, rt, 8 h	37	11:1	41 (*S,S*)	62
4	$TiCl_2$ (2.0) + **212** (4.0)	THF, rt, 8 h	88	14:1	40 (*S,S*)	62
5	$TiCl_2$ (2.0) + **213** (4.0)	THF, rt, 15 min.	31	4:1	65	64
6	**214** (0.1), Mn/TMSCl $TiCl_4(THF)_2$ (0.03)	THF, MS 4Å, rt, 24 h	-	7:1	60	65
7	**215** (0.06), Mn/TMSCl	CH_3CN, rt, 48 h	40	9:1	10	66
8	**216** (1.0), Mn (3.0)	CH_3CN, -10 °C	>95	49:1	77	67
9[a]	**216** (1.0), Mn (3.0)	CH_3CN, -10 °C	>95	49:1	91	67
10[a]	**216** (0.1), Mn (1.5) TMSCl(1.5)	CH_3CN, rt	84	19:1	58	67

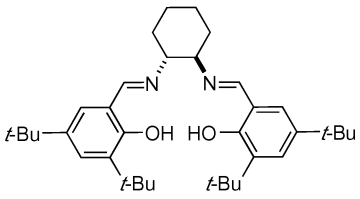
[a] p-Methoxybenzaldehyde was used.



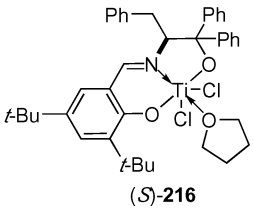
212



213



(*R, R*)-**215**



(*S*)-**216**

ligands, such as the salen ligand **215**, have been screened (entry 7).[66] A general observation is that the use of chelating ligands decreases the dl:meso selectivity in most cases. It appears that the structural/mechanistic concepts in this process are rather uncertain in the literature, but enough is known that a synthetically useful process is imminent. Recently, air-stable catalysts **216,** derived from tridentate salen ligands and $TiCl_4$, were prepared and used in enantioselective pinacol coupling in both stoichiometric and catalytic amounts.[67] A survey of various reductants (Mn, Ce, SmI_2, and Zn) indicated manganese to be the ideal choice at −10 °C. Good ee's were obtained with benzaldehyde and *p*-methoxybenzaldehyde (entries 8 and 9). The lowering of ee's under catalytic conditions was a result of increasing the temperature rather than due to the poor turnover. Electron-deficient benzaldehydes, on the other hand, resulted in poor ee's for the pinacols.

6.3. Epoxide Ring Opening

Titanium catalysts have long been used in electron-transfer reactions involving epoxides, mostly as stoichiometric reagents. Gansäuer et al. developed a catalytic version of these reactions using titanocenes along with zinc metal to generate the active catalyst (Scheme 30).[68] In situ reduction of Ti(IV) with zinc metal provides Ti(III) species **217**, which coordinates to the epoxide **218** and does the electron transfer. The α-titanoxy radical **219** can be reduced with 1,4-cyclohexadiene, generating **221**, which is then protonated with collidine hydrochloride to provide the product, and the Ti(IV) species **223**, which proceeds to the next catalytic cycle. On the other hand, **219** can add to an electron-deficient olefin to give **224**. Using chiral titanocenes allows for stereocontrol in the ring opening as well as further reactions of the generated radical. Table 22 shows the results from the reductive opening of epoxides **225** to alcohols

Scheme 30. Mechanism for Titanocene-Catalyzed Epoxide Ring Opening and Tandem Reaction

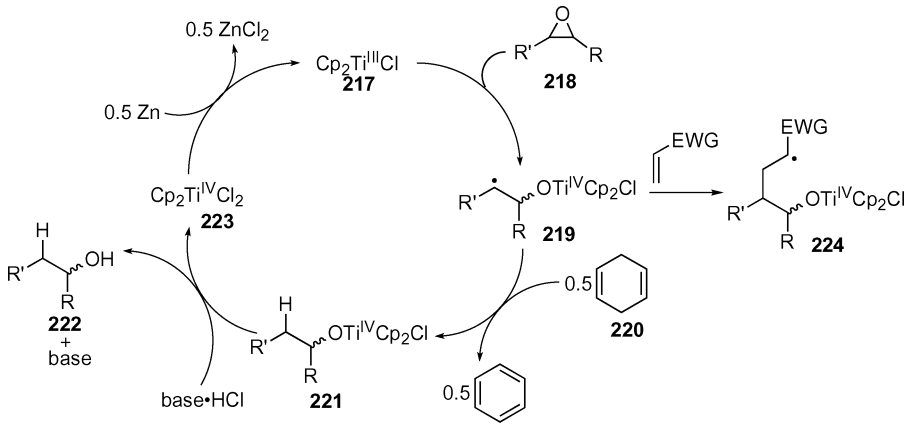
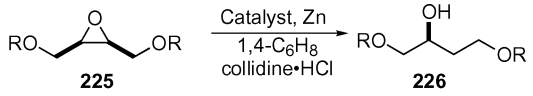
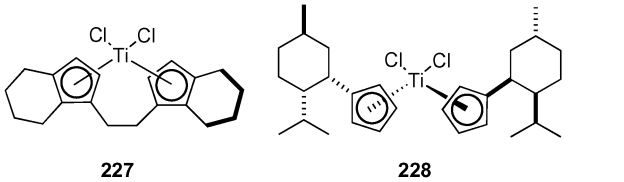


Table 22. Epoxide Ring Opening Using Titanocene Catalysts



Entry	R	Catalyst	Yield (%)	ee (%)
1	Et	**227**	55	56
2	Et	**228**	45-51	20-52
3	Et	**229**	76	93
4	Et	**230**	72	94
5	*n*-Pr	**230**	60	92
6	*n*-Pr	**229**	70	91
7	*t*-Bu	**230**	68	74
8	*t*-Bu	**229**	66	86



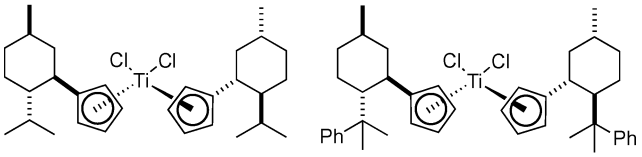
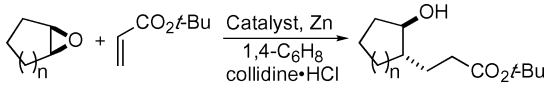


Table 23. Tandem Reactions with Titanocene Catalysts



Entry	n	Catalyst	Yield (%)	ee (%)
1	1	**230**	69	74
2	1	**229**	72	81
3	2	**230**	61	82
4	3	**230**	65	82
5	3	**229**	78	80

226.[68] Among the catalysts derived from menthol **228**, neomenthol **229** and phenylmenthol **230** performed excellently, providing products in >93% ee (entries 3 and 4). Linear alkyl chains as substituents in the terminal ether of **225** are tolerated, whereas bulkier *tert*-butyl groups decrease selectivity due to the steric disorientation of the discriminating groups (entries 7 and 8). The same catalysts were also utilized in the ring opening of cyclic epoxides **231**, followed by addition to *tert*-butyl acrylate **232** (Table 23). The trans:cis selectivities were greater than 4:1, and good enantioselectivities for the trans isomers **233** were obtained. The selectivity was only slightly dependent on the ring size. Enantioselective cyclizations using this methodology would certainly lead to complex systems and will undoubtedly be useful in total synthesis.

7. Oxidations

The previous section described reactions in which the electron transfer takes place from the metal to the organic substrate. The reverse scenario can also be used in radical reactions via oxidative generation of cationic radical species, which can undergo coupling reactions. The other, more common situation is the use of air or other terminal oxidant.

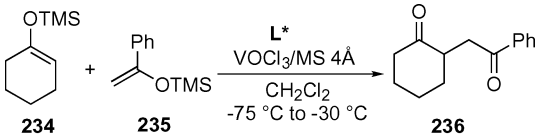
7.1. Oxidative Coupling

Kurihara et al. used chiral oxovanadium species as a one-electron-transfer oxidant to silylenol ethers in a hetero-coupling process.[69] Treatment of **234** with a catalyst prepared in situ from $VOCl_3$/chiral alcohol/4Å molecular sieves, followed by addition of **235**, provided the coupling product **236** (Table 24). 8-Phenylmenthol **239** was found to be the best ligand for this process. The use of 4Å molecular sieves is essential to the success in generating the active catalyst. Although the results are good, a catalytic variant is not available at this time.

Oxidative homo-coupling of enolates generated from acyl oxazolidinones to give the corresponding dimers can be achieved in the presence of oxidants. Titanium and ytterbium enolates of **240** were coupled in the presence of a chiral diol or chiral bisoxazoline in the presence of ferrocenium cation **242** (Table 25).[70] The amount of the meso dimer varied with the chiral ligand, with a maximum of 3:1. TADDOL **149** performed best, providing a 76% ee for the product **241**. Ytterbium enolate gave a low ee of 34% with the same ligand.

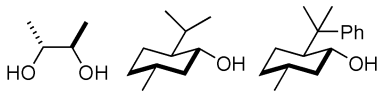
Cyclizations of dihydroxystilbene **245** using 4 mol % of chiral ruthenium complexes under photolytic conditions was investigated by Katsuki et al. (Table

Table 24. Oxidative Coupling of Enol Silanes



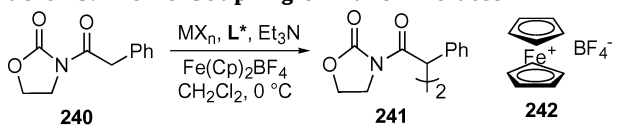
234 235 236

Entry	Ligand	Yield (%)	ee (%)
1	**237**	11	0
2	**238**	55	31
3	**239**	58	85



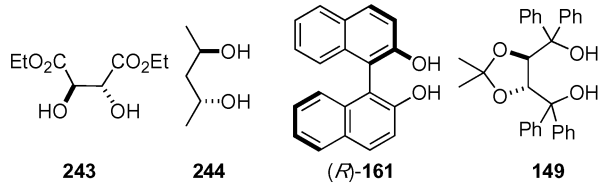
237 238 239

Table 25. Homo-Coupling of Ti/Yb Enolates

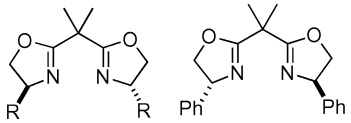


240 241 242

Entry	MX_n	L*	Yield (%)	*dl*:*meso*	ee (%)
1	$TiCl_4$	**243**	67	54:46	39 (*R*, *R*)
2	$TiCl_4$	**244**	63	31:69	5 (*R*, *R*)
3	$TiCl_4$	**161**	52	24:76	16 (*R*, *R*)
4	$TiCl_4$	**149**	91	25:75	76 (*R*, *R*)
5	$TiCl_4$	**185a**	59	35:65	6 (*S*, *S*)
6	$TiCl_4$	**95**	81	45:55	24 (*S*, *S*)
7	$TiCl_4$	**120**	58	48:52	46 (*S*, *S*)
8	$Yb(OTf)_3$	**149**	53	54:46	34 (*R*, *R*)



243 244 (*R*)-161 149



R = *i*-Pr **185a**
R = *t*-Bu **95**

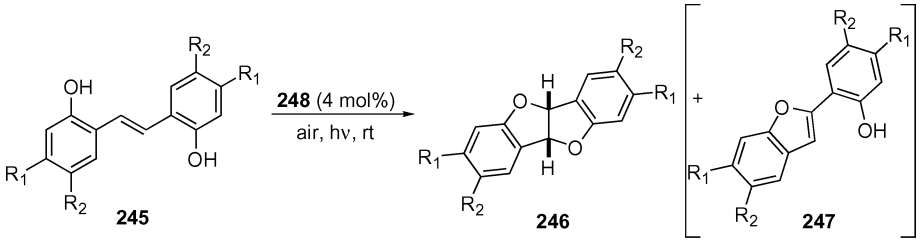
120

26).[71] Coordination of alcohols/phenols to Ru(IV) species generates a cation radical with concomitant reduction of metal to Ru(III). Cyclization of this oxygen radical, followed by another cyclization, provides the product **246**. Catalyst **248** provided 81% ee of the product in chlorobenzene solvent. Optimization of the solvent polarity led to a mixture of toluene and *tert*-butyl alcohol in a 2:3 ratio as the ideal solvent. Substituents on the phenyl rings led to a decrease in selectivity. Low yields were due to the byproduct **247**.

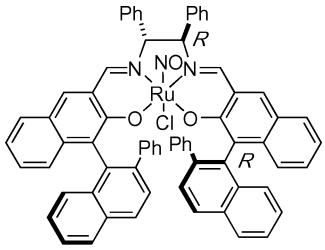
Chiral binaphthol (BINOL) derivatives are popular ligands in asymmetric catalysis. Chiral BINOLs, both symmetrical and unsymmetrical, can be prepared by the enantioselective oxidative coupling of naphthols using copper, vanadium, and ruthenium catalysts.[72] The goal of chiral BINOL synthesis was achieved almost a decade ago, albeit with stoichiometric amounts of copper−chiral amine reagents. These results were possible due to either a second-order asymmetric transformation (the selective precipitation of the less solvated diastereomer in the presence of a kinetically favorable epimerization equilibrium) or diastereoselective crystallization. Examples in which enantioselectivity arises in the coupling step are described here. Smrcina et al. reported enantioselective cross-coupling of **249** and **250** using both stoichiometric and catalytic amounts of a Cu(II)−(−)-sparteine combination (Scheme 31).[73] Enantiomeric excess of 41% was obtained in the stoichiometric reaction, which could be increased to 71% due to selective precipitation. The catalytic version was developed with a stoichiometric amount of silver chloride to reoxidize Cu(I) to Cu(II) and hence aid catalytic turnover. However, lower yield and ee were obtained for **251**.

Copper(I) salts along with chiral amines have also been exploited in homo-coupling of naphthols. Nakajima and co-workers evaluated chiral diamines derived from L-proline in the presence of CuCl (Table 27).[74] Under these conditions, Cu(I) is oxidized to Cu(II) in situ due to the presence of air/O_2 and enters the catalytic cycle. (−) Sparteine **252** proved to be inefficient in terms of both reactivity and selectivity. Hence, ligands **254** were considered. For the oxidative coupling of methyl 2-hydroxynaphthoate **250**, ligands **254** with different substitution patterns were studied. Entries 2−4 show that a secondary amine is required in the ring nitrogen and the side chain should possess a tertiary nitrogen for good selectivities to be achieved. Ligand **254C** was found to be the ideal ligand. Furthermore, reaction efficiency increased when preformed Cu(OH)Cl was used as catalyst: 85% yield of product with 78% ee. These conditions could not be extended for the coupling of the parent naphthol **249** nor to other non-ester substitution at C3: the presence of an ester group at C3 was essential. Kozlowski et al. investigated this reaction in greater detail.[75] Starting from ligands **255** that were identified through a computer-aided procedure and using Cu(I) halides under homogeneous conditions, they obtained good yields and selectivities. Many Cu(I) salts could be used: although the reaction efficiency was dependent on the counterion, the ee's were similar. Entries 6−8 show that introducing substituents on either one or both of the nitrogen atoms decreases selectivity. Solvents do not greatly affect the selectivity, but acetonitrile was used in some cases to ensure homogeneous reaction conditions and partly due to the stabilization provided by acetonitrile to Cu(I) species. Molecular sieves proved beneficial in increasing the catalyst turnover. The selectivity obtained with **255A** (93% ee) is the best reported for this copper-catalyzed reaction. Here too, the parent naphthol (entry 11) provided low enantioselectivity. The authors obtained several crystal structures of various copper−diamine complexes utilized in their studies. A slightly positive nonlinear effect was also observed, indicating the initial formation of a 2:1 complex of the diamine and copper, which coexists with other μ-hydroxo species. The coordination of the substrate to the precatalyst leads to a Cu−ligand−substrate complex. Radical generation, followed by stereoselective reaction with a second substrate, provides the product **253A** or **253B**.

Table 26. Cyclizations under PET Conditions

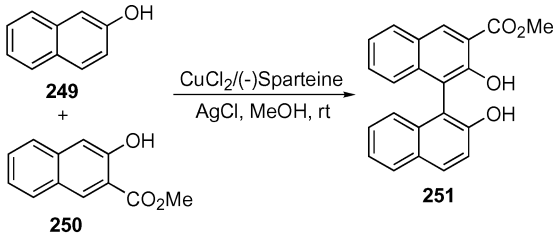


Entry	R_1	R_2	Solvent	Yield (%)	ee (%)
1	H	H	chlorobenzene	79	81
2	H	H	*t*-BuOH	23	89
3	H	H	*i*-Pr_2O	12	85
4	H	H	toluene	78	82
5	H	H	tol:*t*-BuOH(2:3)	87	86
6	Me	H	tol:*t*-BuOH(2:3)	72	66
7	Me	H	*i*-Pr_2O	38	69
8	H	Me	tol:*t*-BuOH(2:3)	86	10
9	H	Me	*i*-Pr_2O	24	71

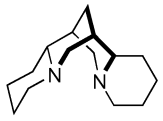


248

Scheme 31. Copper-Mediated Oxidative Coupling



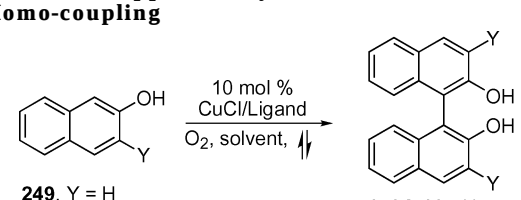
$CuCl_2$ (equiv.)	(-)Sparteine (equiv.)	AgCl	Yield (%)	ee (%)
1.0	2.4	-	99	41
0.1	0.2	1.1	41	32



(-) Sparteine, **252**

Biaryl coupling can also be achieved with vanadium complexes. The groups of Uang[76] and Chen[77] independently reported the use of chiral tridentate Schiff base ligands **256** and **257** derived from 2-hydroxynaphthaldehyde and α-amino acids in the enantioselective coupling (Table 28). Moderate selectivities were obtained in both cases, but the reaction was faster in the presence of TMSCl as a promoter (entry 1). Barhate and Chen improved the catalyst by using (+)-ketopinic acid in place of 2-hydroxynaphthaldehyde to form **258** and obtained 84% ee for the BINOL adduct.[78] A crystal structure of the catalyst was obtained. It showed vanadium in a 5+ oxidation state, which might be the active catalyst. Vanadium(IV) is rapidly oxidized to vanadium(V) under the reaction conditions. Gong et al. utilized a catalyst derived from 3,3′-diformyl-BINOL to form catalyst **259A** and **259B**, both of which gave the desired product in good yield and selectivity.[79] The reaction times are too long, and the most common solvent seems to be carbon tetrachloride. Both of these requirements need to be improved for practical applications. The catalyst **260**, which also has a binaphthyl skeleton with a free hydroxyl group, was developed by Chu and Uang.[80] The reaction with

Table 27. Copper-Catalyzed Oxidative Homo-coupling

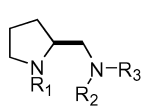


249, Y = H
250, Y = CO_2Me

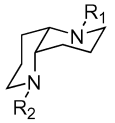
253A, Y = H
253B, Y = CO_2Me

Entry	Substrate	Ligand	Solvent	Yield (%)	ee (%)	Ref.
1	**250**	**252**	CH_2Cl_2	38	47 (*S*)	74
2	**250**	**254A**	CH_2Cl_2	77	4 (*S*)	74
3	**250**	**254B**	CH_2Cl_2	11	0	74
4[a]	**250**	**254C**	CH_2Cl_2	85	78 (*S*)	74
5[a]	**249**	**254C**	CH_2Cl_2	89	17 (*S*)	74
6	**250**	**255A**	$Cl(CH_2)_2Cl$	41	86 (*R*)	75
7	**250**	**255B**	$Cl(CH_2)_2Cl$	53	79 (*R*)	75
8	**250**	**255C**	$Cl(CH_2)_2Cl$	43	3 (*R*)	75
9	**250**	**255A**	CH_2Cl_2	56	91 (*R*)	75
10[b]	**250**	**255A**	$Cl(CH_2)_2Cl$/ MeCN 2/1	81	93 (*R*)	75
11	**249**	**255A**	CH_2Cl_2	80	13 (*R*)	75

[a] Preformed Cu(OH)Cl was used. [b] CuI was used.



254A: R_1 = Me, R_2 = Ph, R_3 = H
254B: R_1 = H, R_2 = H, R_3 = H
254C: R_1 = H, R_2 = Ph, R_3 = Et

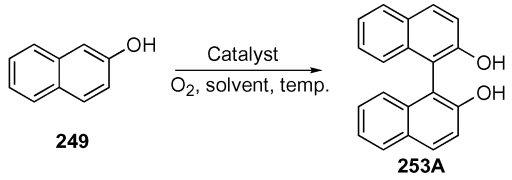


255A: R_1 = R_2 = H
255B: R_1 = H, R_2 = Me
255C: R_1 = R_2 = Me

catalyst **260** was much faster and could be performed in chloroform with only 2 mol % catalyst loading. The ee obtained with this catalyst is low (54%). In the catalysts containing a binaphthyl skeleton, the stereochemistry of the amino acid component determines the stereoselectivity in the final product. However, there is a match−mismatch among the stereochemistry of the binaphthyl unit and the amino acid unit (data not shown).

Katsuki et al. used catalyst **263** in the synthesis of BINOLs **262** in what is thought to be a single-

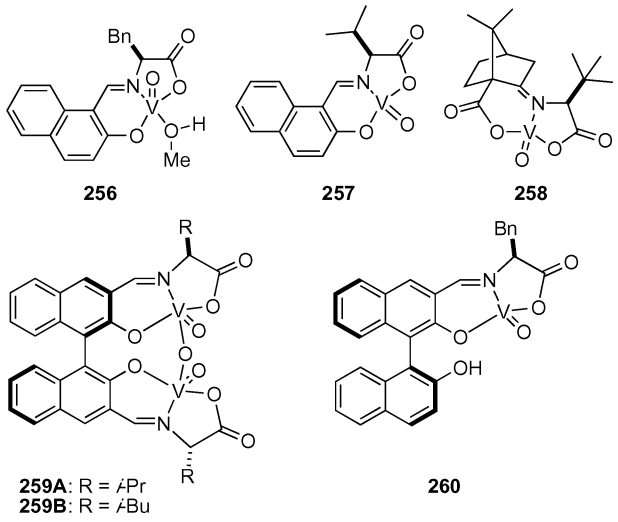
Table 28. Vanadium-Catalyzed Oxidative Homo-coupling



249 **253A**

Entry	Cat. (mol %)	Solvent	Temp.	Time	Yield (%)	ee (%)	Ref.
1[a]	**256** (2)	$CHCl_3$	rt	24 h	82	51 (*R*)	76
2	**257**(10)	CCl_4	rt	6 d	94	62 (*R*)	77
3	**258**(3)	CCl_4	45 °C	7 d	99	84 (*R*)	78
4	**259A** (10)	CCl_4	0 °C	8 d	70	81 (*R*)	79
5	**259B** (10)	CCl_4	0 °C	6 d	93	83 (*R*)	79
6	**260** (5)	$CHCl_3$	rt	16 h	93	54 (*R*)	80

[a] 2 mol% TMSCl was used.



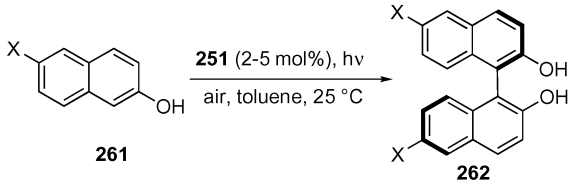
256 **257** **258**

259A: R = *i*-Pr
259B: R = *i*-Bu

260

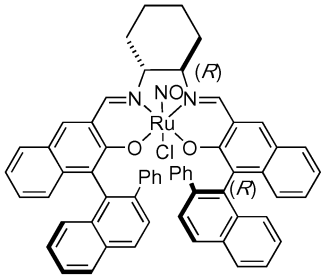
electron-transfer (SET) mechanism.[81] Naphthols **261** were converted to BINOLs with moderate enantioselectivities using only 2−5 mol % of **263** in the presence of air and light at ambient temperatures (Table 29). The less reactive (electron-deficient) substrates needed 5 mol % of the catalyst and usually gave higher ee's compared to the faster reacting (electron-rich) substrates.

Table 29. BINOL Synthesis



261 **262**

Entry	X	Yield (%)	ee (%)
1	H	72	65 (*R*)
2	Br	77	69 (*R*)
3	PhC	93	68 (*R*)
4	OMe	73	33 (*R*)
5	CO_2Me	trace	-

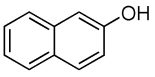
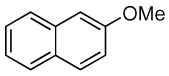
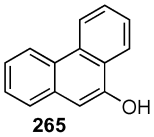


(*R,R*) - **263**

Another case of the use of a ruthenium complex in biaryl coupling involves $M(C_3)$-Δ-$[Ru(menbpy)_3]^{2+}$ (menbpy = 4,4′-di(1*R*,2*S*,5*R*)-(−)-menthoxycarbonyl-2,2′-bipyridine) as a photosensitizer and $Co(acac)_3$ as the oxidant. Ohkubo showed that 2-naphthol can be oxidized to BINOL in acetonitrile by irradiation at 400 nm, albeit in low enantioselectivity (16% ee).[82]

Electrocatalytic oxidation of naphthol **249**, 2-methoxynaphthalene **264**, and phenanthrol **265** with high ee's was reported by Bobbitt et al. (Table 30).[83] The electrolysis was carried out on a poly(acrylic acid)-coated graphite electrode in acetonitrile. In the presence of 1 equiv of (−)-sparteine **252**, the authors were able to make the corresponding binaphthyls in >90% yields and very high ee's.

Table 30. Electrolytic Oxidative Coupling

Substrate	Current Efficiency (%)	Yield (%)	ee (%)
 **249**	89	99	99
 **264**	91	92	94
 **265**	90	98	98

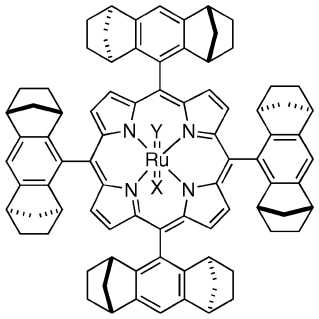
7.2. Oxidation of Activated C–H Bonds

Oxidation of benzylic carbon has been attempted with porphyrin-based metal complexes mimicking the cytochrome P-450 enzyme.[84] A chiral ruthenium−porphyrin complex **280** was utilized by Che et al.[85] Oxidations were carried out with either stoichiometric amounts of **280A** or catalytic amounts of **280B** in the presence of 2,6-dichloropyridine *N*-oxide (Cl_2-PyNO) as a terminal oxidant. Table 31 shows the results. Overoxidation of the hydrocarbons to ketone was unavoidable. Stoichiometric catalyst loading of **280A** led to lower ee's than the catalytic reactions with the Ru(II) catalyst **280B**. Moderate to good enantioselectivities were obtained at low conversions for the catalytic reactions. Benzene- and naphthalene-derived substrates **266**−**270** gave much better ee's than the cyclic substrates **271** and **272**. Kinetic isotope studies revealed that the hydrogen abstraction step was rate determining. It is possible that chiral ion-pairs **281A** and **281B** are generated and the face selection in the radical collapse step leads to the observed selectivity, as shown in Scheme 32.

Benzylic oxidation was investigated by Katsuki and co-workers using chiral (salen)manganese(III) complexes (Table 32).[86] The reaction proceeds through a radical mechanism, with the prochiral hydrogen atom abstraction from the benzylic position being the rate-determining step. To preserve the enantioselective hydrogen atom abstraction obtained in this step, it is necessary to use a highly viscous solvent. This leads to the increased lifetime of the diastereomeric species in the solvent cage. As shown in the table, good enantioselectivities were obtained, but the yields were low. Other substrates such as ethyl benzene and

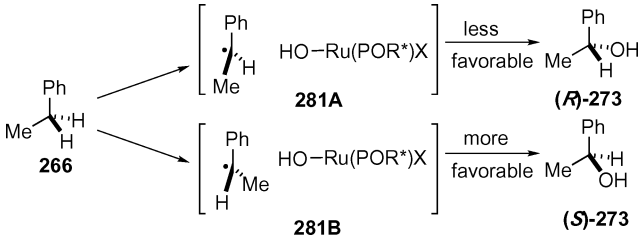
Table 31. Benzylic Oxidations Using Ruthenium Catalysts

		280A (stoichiometric)			**280B** (catalytic) + Cl_2PyNO				
Substrate	Product	Alcohol Yield (%)	ee (%)	Ketone Yield (%)	t (h)	Conv. (%)	Alcohol Yield (%)	ee (%)	Ketone Yield (%)
266	**273**	32	45 (*S*)	33	12	13	62	72 (*S*)	37
267	**274**	31	51 (*S*)	32	30	20	72	76 (*S*)	24
268	**275**	35	55 (*S*)	31	18	23	28	74 (*S*)	70
269	**276**	44	55 (*S*)	26	8	15	65	62 (*S*)	32
270	**277**	32	58 (*S*)	31	20	15	62	75 (*S*)	38
271	**278**	48	9 (*S*)	25	6	54	65	12 (*S*)	34
272	**279**	47	18 (*S*)	24	2	42	60	12 (*S*)	40



280A: X = Y = O
280B: X = CO, Y = EtOH

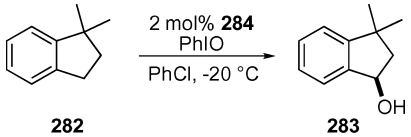
Scheme 32. Chiral Atom Transfer in Benzylic Oxidation



tetralin were also tested, and moderate to good ee's were obtained.

The same authors applied this methodology to desymmetrization of *meso*-pyrrolidine and *meso*-tetrahydrofuran derivatives. These oxidations were carried out with Mn-salen catalysts **295**−**296** with iodosyl benzene as the oxidant (Table 33). Low yields and ee's were obtained for the tetrahydropyran **286**.[87] This was attributed to the presence of two conformers that underwent oxidation at different rates. This situation was avoided when bicyclic ethers **287A**,**B** were used as substrates: higher yields and ee's were realized. The nitrogen variant **289** was also oxidized in 70% yield and 88% ee with the catalyst **296** derived from phenylene diamine.[88] In all of these examples, second-generation Mn-salen catalysts, with chirality residing on both the amine moiety and the binaphthyl moiety, were used. In contrast to the benzylic oxidation described above, the (*R*,*R*) catalysts were more effective in the oxidations shown in Table 33. The authors attempted to explain this difference in terms of the different structures of the diastereomeric complexes and the distance of approach required for the oxidation processes.[89] Murahashi et al. utilized similar catalysts in desymmetrization of **291** under similar conditions with added 4-phenylpyridine *N*-oxide as a donor ligand.[90] Low ee's were obtained. Higher selectivity was obtained for the indan derivative **294**.

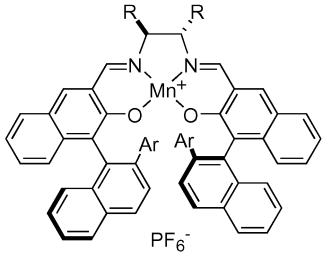
Table 32. Benzylic Hydroxylation



282 **283**

284	Time	Yield (%)	ee (%)
284A	10 min	4.8	84 (*R*)
284A	20 h	25 (10)[a]	90 (*R*)
284B	10 min	4 (0.15)	70 (*R*)
284B	20 h	17 (12)	81 (*R*)

[a] yields in parenthesis are for the ketone

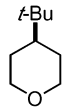
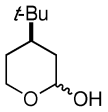
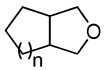
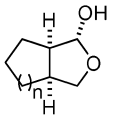
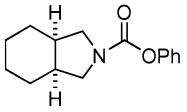
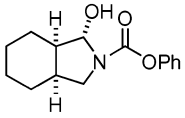
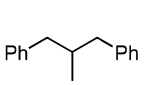
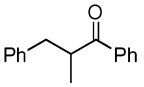
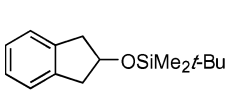
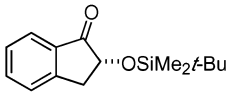


284A: Ar = 4-[*t*-Bu(C_6H_5)$_2$]SiC_6H_4
R = 3,5-$(CH_3)_2C_6H_3$
284B: Ar = 4-[*t*-Bu(C_6H_5)$_2$]SiC_6H_4
R = $(CH_2)_4$

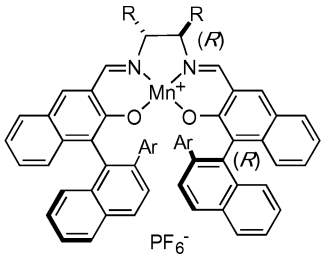
Kinetic resolution of 2-phenylbutane **299** was attempted by Schulz et al. using CuOTf and PyBOX ligand **104** (Scheme 33).[91] At 57% conversion of the *tert*-butyl hydroperoxide, the peroxide **300** was obtained in 4% ee. No further optimization has been reported.

The oxidation of olefins to allylic alcohols using copper salts and peresters, the Kharasch−Sosnovsky reaction, has been investigated, and many reports of the catalytic enantioselective reaction are known. This topic was recently reviewed independently by Andrus and also by Eames.[92] No significant developments have been reported since then. Hence, the

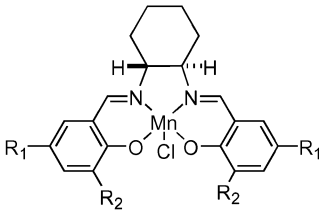
Table 33. Oxidation at Activated C−H Bonds

Substrate	Product	Catalyst[a]	Temp (°C)	Solvent	Yield (%)	ee (%)	Ref.
 **285**	 **286**	**295**	-40	PhCl	13	48	87
 **287A** n=1 **287B** n=2	 **288A** n=1 **288B** n=2	**295**	-30	PhCl	59	82	87
		295	-30	PhCl	61	61	87
 **289**	 **290**	**296**	-25	CH_3CN	70	88[b]	88
 **291**	 **292**	**297**[c]	23	PhCl	24	22	90
 **293**	 **294**	**298**[c]	40	PhCl	13	70	90

[a] PhIO was used as the oxidant. [b] ee was determined after oxidizing hydroxyl group to ketone [c] 4-phenylpyridine-*N*-oxide was used as additive.

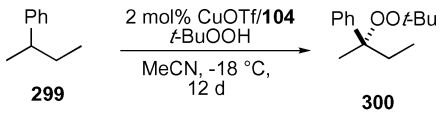


295: Ar = Ph; R = -$(CH_2)_4$-
296: Ar = R = Ph



297: R_1 = Me; R_2 = *t*-Bu
298: R_1 = *t*-Bu; R_2 = *t*-Bu

Scheme 33. Benzylic Peroxidation



299 → (2 mol% CuOTf/**104**, *t*-BuOOH, MeCN, -18 °C, 12 d) → **300**, 70% yield, 4% ee

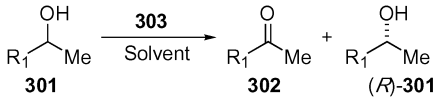
reader is directed to those references for a comprehensive treatment of this topic.

7.3. Oxidation of Alcohols/Amines

Oxidations of alcohols **301** under photolytic conditions, catalyzed using a nitroso-ruthenium complex **303**, led to kinetic resolution with high ee's and with good k_{rel} values (Table 34).[93] The same ruthenium complex has been used previously in the presence of *N*-oxides for epoxidation, but in this case no epoxidations were observed when substrates containing olefins were used. The *N*-oxide decomposes slowly under these conditions. Different secondary alcohols were utilized, and high ee's were obtained for the recovered alcohols.

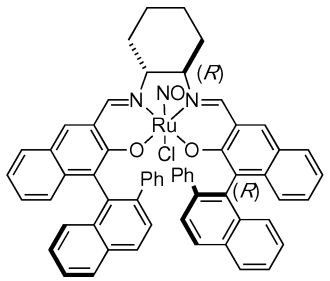
Electrocatalytic oxidation of alcohols and amines **304** can be carried out with nitroxyl radicals. The use of chiral nitroxyl radicals in enantioselective oxidation has been explored. Kashiwagi et al. carried out a kinetic resolution of secondary alcohols and amines under electrocatalytic conditions using **305** as the catalyst in a "H"-type divided cell separated by a cation-exchange membrane.[94] Two equivalents of 2,6-lutidine and 0.5 equiv of $NaClO_4$, along with a chromatographic standard and 5 mol % of the catalyst **305** in acetonitrile, were used as the catholyte. The anolyte was a solution of $NaClO_4$ in acetonitrile.

Table 34. Kinetic Resolution under Photolytic Conditions



301 → (**303**, Solvent) → **302** + (*R*)-**301**

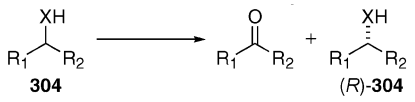
R_1	Solvent	ee (%)	Conversion (%)	k_{rel}
Ph-CH=CH-	C_6H_6	97 (*R*)	76	8
Ph	C_6H_5Cl	95 (*R*)	65	11
Ph-≡	C_6H_5Cl	>99 (*R*)	65	20
Ph-CH_2	$C_6H_5CH_3$	82 (*R*)	58	11



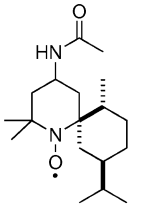
303

In the case of amines, a 4:1 mixture of CH_3CN and water was used. The (*R*) and (*S*) enantiomers of 1-phenylethanol were oxidized at different rates, and after 10 h of electrolysis the (*R*) alcohol was recovered in 70% ee. Other alcohols were also resolved but with lower ee's (Table 35). Amines in general gave higher selectivities and turnover numbers (TONs). It was also shown that the chiral center α to the amine was essential: the last entry shows that the *β*-chiral center has no effect in this oxidation procedure. It was subsequently demonstrated that this process could be carried out on a gold electrode containing a self-assembled monolayer of chiral nitroxyls with thiol groups appended to them.[95] The authors alluded

Table 35. Electrocatalytic Oxidation Using Chiral Nitroxyl Radical



XH	R_1	R_2	Charge passed C	Current efficiency %	ee (%)	Conversion %	S	Turnover number
OH	Ph	Me	144.1	85.6	70 (*R*)	63.9	4.6	25.6
OH	Ph	Et	116.7	87.3	52 (*R*)	52.8	4.1	21.1
OH	1-Np	Me	112.8	87.9	50 (*R*)	51.4	4.5	20.6
OH	2-Np	Me	135.1	86.1	60 (*R*)	60.3	4.1	24.1
NH_2	Ph	Me	137.9	91.5	78 (*R*)	65.4	5.3	26.2
NH_2	*p*-Tol	Me	134.6	94.8	75 (*R*)	66.1	4.7	26.5
NH_2	1-Np	Me	115.5	90.7	62 (*R*)	54.3	5.8	21.7
NH_2	2-Np	Me	124.8	92.3	66 (*R*)	59.7	4.0	23.9
NH_2	Ph(Me)CHCH$_2$	H	192.4	96.1	0	95.8	0	38.3



(6*S*, 7*R*, 10*R*)-**305**

to application of such chiral differentiation in determination of optical purity of amines.

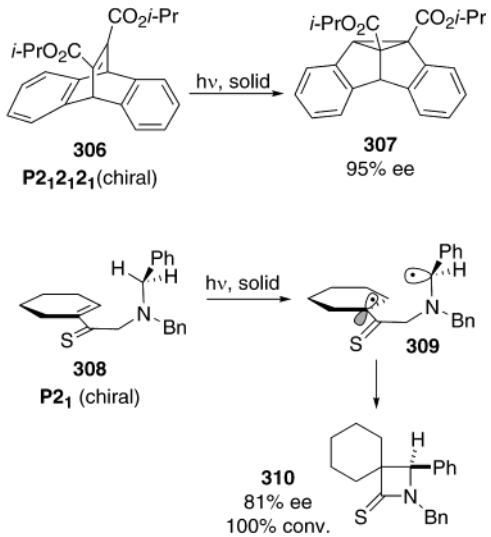
8. Photochemical Processes

Photochemical processes involving the generation of biradicals followed by recombination are discussed in this section. Two reactions that involve such a process are the Norrish−Yang photocyclization and the di-π-methane rearrangement. These reactions have been done both in the solid state[96] and in the solution phase. In the solid state, enantioselective reactions can be carried out using (a) crystals that grow in a chiral space group,[97] (b) crystals grown with ionic chiral auxiliaries,[98] (c) host−guest complexes, or (d) zeolites in which a chiral inductor is present along with the substrate in the cavity.[99] The advantage of doing chemistry in the solid state is that once a chiral environment is established in the crystal, it is transferred to the product due to the restricted rotations in the crystal.

There are several issues at hand: (a) the number of achiral molecules that crystallize in a chiral space group is limited; (b) in the case of using chiral ionic auxiliaries, it is necessary to have an acidic/basic group in the substrate to form suitable chiral crystals; (c) although there is restricted rotation in the crystals, the crystals should have high melting points so that they do not melt during the photoreaction; and (d) the ee's of the reactions decrease with increasing conversions for most reactions. It is encouraging that there are numerous examples of enantioselective photoprocesses despite the above-mentioned hurdles. We have included selected examples from the literature to illustrate the different methods available to perform enantioselective photochemical reactions. For a deeper discussion and greater breadth of examples, the reader should plunge into comprehensive/insightful reviews available in asymmetric synthesis using photochemistry.[96−99]

Chiral crystals can be grown from organic molecules, but no concrete correlation or guidelines are available in terms of which molecules will crystallize in one of the 64 chiral space groups. Nevertheless, when chiral crystalline compounds are obtained, photochemical reactions can most often faithfully transform this environmental chirality into molecular chirality (Scheme 34). A first example was the di-π-methane rearrangement of **306** in the solid state to **307** in 95% ee.[100] Sakamoto et al. performed a crystal-to-crystal photocyclization of olefin **308** to obtain a spirocyclic thiolactam **310** in 81% ee, even at 100% conversion.[101]

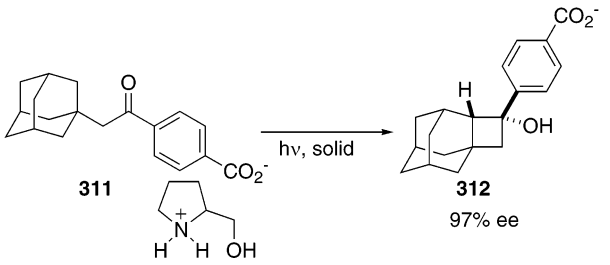
Scheme 34. Photochemistry in Chiral Crystals



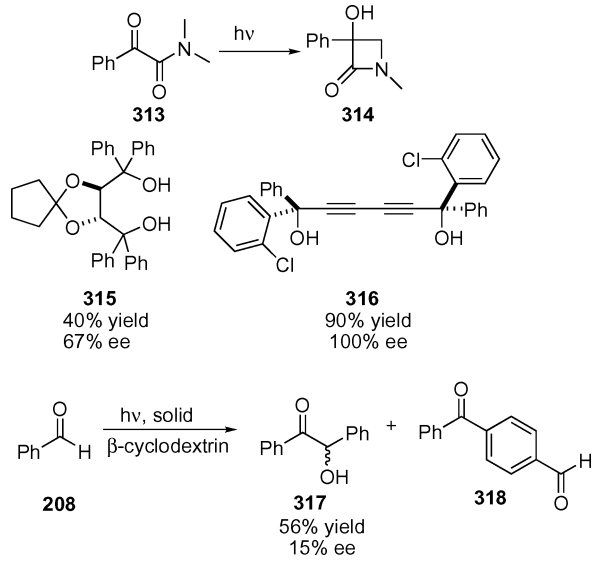
The use of ionic chiral auxiliaries provides a temporary alternative to the need to grow chiral crystals. This method necessitates the presence of an acidic/basic group to form a corresponding chiral salt, which can be crystallized. The advantages of this method are that one need not have isomorphous crystals and that the salt formation usually results in crystals with higher melting points. Norrish−Yang photocyclization of **311**, a prolinol salt of the adamantyl keto acid, resulted in the cyclobutanol product **312** in good yield and 97% ee (Scheme 35).[102]

Host−guest complexations (inclusion compounds) have been applied in solid-state photochemical processes. It is possible to prepare such complexes just by mixing the components and crystallizing them in a suitable solvent. Optically active hosts need to interact with the substrate in a well-defined manner. Examples presented here include β-lactam formation[103] from **313** with chiral diols **315** and **316** as hosts and benzoin condensation in a β-cyclodextrin cavity (Scheme 36).[104]

Scheme 35. Ionic Chiral Auxiliaries

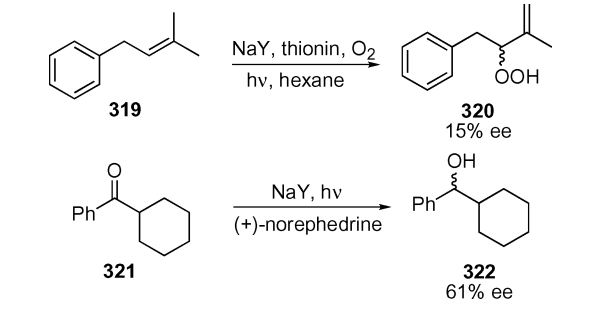


Scheme 36. Host−Guest Complexes



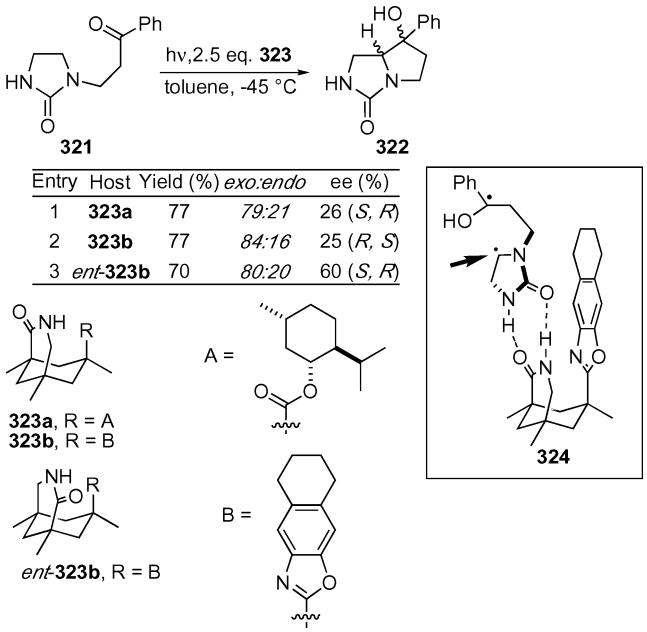
Zeolites, crystalline aluminosilicates, have been used to effect asymmetric photochemical reactions in their cavities. Ramamurthy et al. showed that, by using chiral inductors that can coexist with substrates in the cavities, enantioselective transformations can be performed.[105] Two examples are presented here (Scheme 37). The Schenk ene reaction, involving hydroperoxidation of olefins using singlet oxygen, was performed on olefin **319**, and it was observed that reaction in zeolite NaY produced **320** in a highly regioselective manner. The presence of (+)-pseudoephedrine hydrochloride led to the product in a low 15% ee. They also reported the photoreduction of arylalkyl ketones **321** to chiral alcohol **322** in 61% ee in the presence of (+)-norephedrine.[106]

Scheme 37. Photochemistry in Zeolites



Solution-phase asymmetric photochemical processes have not been successful in the past due to the stronger and more rigid interaction needed in solution to achieve high ee's. Very recently, Bach and co-workers solved this problem in one case of Norrish−Yang photocyclization (Scheme 38).[107] The imidazolidinone **321** was irradiated in the presence of 2.5 equiv of a chiral host in toluene to obtain the cyclized product **322** in good yields and moderate ee's. The host *ent*-**323b** proved to be the best, providing good face shielding due to a more rigid planar structure. Decreasing the amounts of the chiral host lowered the ee's. A model for explaining the observed selectivity was proposed, as shown in **324**. The authors also carried out reactions in the solid state and obtained 78% ee at 1% conversion and 28% ee at 36% conversion. Hence, the solution-phase chemistry was better than the solid-state reaction in this case.

Scheme 38. Solution Photochemistry



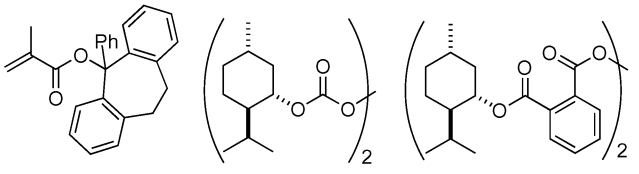
Entry	Host	Yield (%)	*exo:endo*	ee (%)
1	**323a**	77	*79:21*	26 (*S, R*)
2	**323b**	77	*84:16*	25 (*R, S*)
3	*ent*-**323b**	70	*80:20*	60 (*S, R*)

9. Polymerizations

Enantioselective radical polymerization is an interesting area of study but is rather limited at present. Polymerizations proceeding through a radical mechanism have been investigated using chiral initiators, additives, or chain-transfer agents. Helical polymers can be formed from a variety of monomers. Polymers preferring either right- or left-handed helix formation can be obtained through anionic polymerizations. One example of such helix-sense-selective polymerization has been reported, achieved using the radical method (Table 36). The challenge is in understanding the key chirality-determining step: the chain growth process. Nakano et al. performed polymerization using 1-phenyldibenzosuberyl methacrylate (PDBSMA) **325**.[108] This monomer gives a highly isotactic helical polymer. When chiral initiators (−)-dimenthyl peroxydicarbonate **326** and (−)-*o*-carbomethoxybenzoyl peroxide **327** were used in the polymerization with a monomer:initiator of 1:1, optically active polymers were obtained but in low optical yields. These results indicate that enantioselection is minimally governed by the initiator. Chiral additives had a positive impact: chiral alco-

hols resulted in a better selection than the chiral initiators (entries 4−6). In one experiment (entry 6), both (−)-menthol and thiophenol were added, and the product polymer was racemic. Thiophenol is a faster chain-transfer agent than menthol. Hence, the authors concluded that the predominance of one helix sense over the other was determined in the chain-transfer step. This was further confirmed and optimized using a chiral chain-transfer agent, (−)-neomenthylthiol **329** (entries 7−9). Interestingly, the optical yields were lower than those obtained in the presence of chiral alcohols. The most efficient chain-transfer agent was eventually found to be the chiral cobalt(II) complex **330** in chloroform/pyridine as solvent (entry 13). Finally, copolymerization was done with small amounts of chiral monomer **328** (entries 10−12). Higher optical yields were obtained, but the magnitude was dependent on the amount of **328** added. The added chiral monomer presumably acts as a template for the polymer formation.

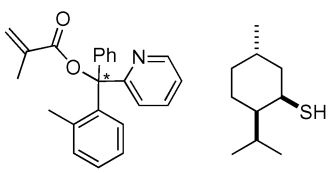
Table 36. Helix-Sense-Selective Polymerizations



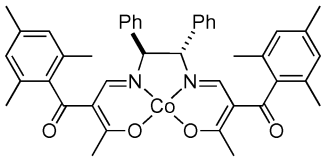
325 **326** **327**

Entry	Chiral agent (amount)	$[\alpha]^{25}_{365}$
1	**326** (50)[a]	~ 0
2	**326** (1)[a]	+ 40
3	**327** (1)[a]	+ 20
4	(+)-menthol[b]	– 200
5	(–)-menthol[b]	+ 180
6[e]	(–)-menthol[b]	~ 0
7	(+)-**329** (0.05)[c]	– 80
8	(+)-**329** (0.1)[c]	– 130
9	(+)-**329** (0.2)[c]	– 140
10	(–)-**328** (20)[d]	– 352
11	(–)-**328** (10)[d]	+ 53
12	(–)-**328** (5)[d]	+ 183
13	**330** (0.039M)	+ 550

[a] [Monomer]/[Initiator], % [b] 4.6M in toluene [c] [thiol]/[monomer] [d]mol% [e]thiophenol was added



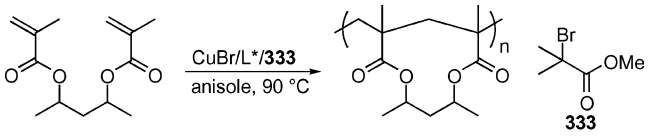
328 **329**



330

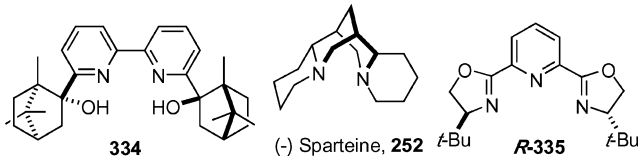
When a racemic monomer is used along with a chiral polymerization catalyst, it is possible that one of the antipodes adds to the growing polymer, whereas the opposite antipode is enriched in the unconsumed monomer. Kakuchi and co-workers demonstrated such a process by using racemic 2,4-pentanediyl dimethacrylate (*rac*-**331**) under Kharasch atom-transfer conditions (Table 37).[109] In the presence of CuBr/L*/**333** in anisole at 90 °C, the free radical cyclopolymerization took place with relatively narrow molecular weight distributions. Among the ligands evaluated, (−)-sparteine **252** and **335** showed higher optical rotation for the polymer **332**. The selectivity obtained was dependent on the nature of ligand. The authors also showed that the selectivity indeed originated from the ligand by using enantiomeric ligand (*S*)-**335**, which resulted in the (*S,S*) monomer being left behind (entries 3 and 4).

Table 37. Enantiomer-Selective Polymerization



trans-(±)-**331** polymer-**332** **333**

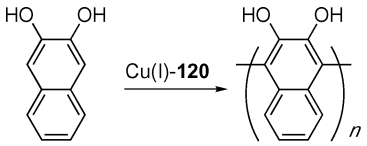
Entry	Ligand	Conv. (%)	Monomer ee (%)	Polymer M_n (M_w/M_n)	Polymer $[\alpha]_{435}$ (deg.)
1	**334**	26.9	6.8 (*R,R*)	13,500 (1.23)	-18.9
2	**252**	18.5	9.4 (*R,R*)	11,000 (1.30)	-35.5
3	*S*-**335**	24.6	15.3 (*R,R*)	12,300 (1.25)	-36.5
4	*R*-**335**	22.8	13.4 (*S,S*)	11,200 (1.23)	+38.6



334 (-) Sparteine, **252** *R*-**335**

The oxidative biaryl coupling discussed in section 7.1 was applied in the polymerization of 2,3-dihydroxynaphthalene **336** by Okamoto et al., using various Cu(I)-bisoxazoline catalysts (Scheme 39).[110] Polymers of molecular weight of 41 000 were obtained and showed different properties, depending on the catalyst used for the synthesis. The actual enantioselectivities obtained were not measured and were presumed to be low.

Scheme 39. Polymerization Using Oxidative Coupling

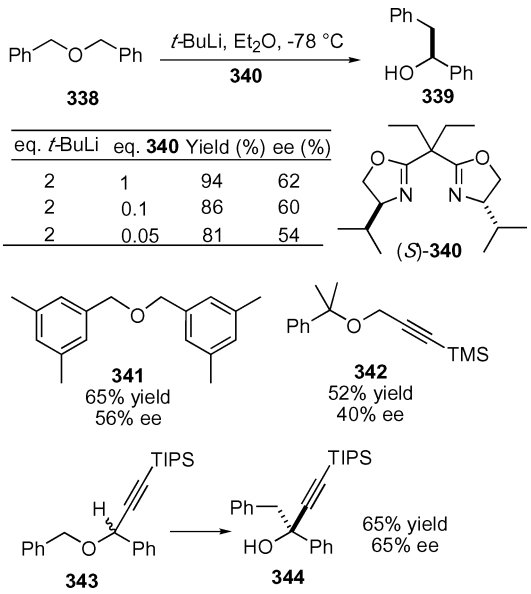


336 **337** low ee's

10. Miscellaneous Reactions

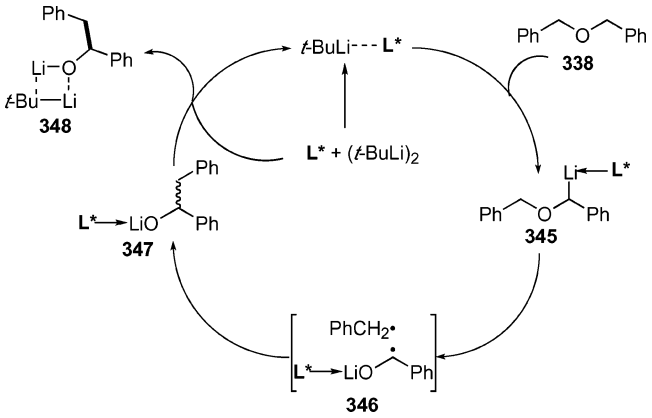
The [1,2] Wittig rearrangement of α-lithiated ethers proceeds through a homolytic cleavage of the C−O bond, followed by radical transposition and recombination. Chiral ligands along with *t*-BuLi were used by Nakai et al. for this asymmetric transformation (Scheme 40).[111] Chiral bisoxazoline ligand **340**, with ethyl substituents on the bridging carbon, was used; sparteine gave much lower (24%) ee's. Two equivalents of *t*-BuLi were needed in order to regenerate the chiral lithium species responsible for α-lithiation. It was found that the uncomplexed *t*-BuLi, which exists as a dimer, is not capable of deprotonation: a clear example of ligand acceleration. On the basis of this difference in reactivity, the authors considered using substoichiometric amounts of the ligand and indeed succeeded in obtaining ee's (60%) comparable to those obtained in the the stoichiometric reaction (62%). Other substrates gave similar levels of selectivity, as shown in the scheme. On the basis of deuterated substrates in this reaction, the authors

Scheme 40. Wittig Rearrangement



clearly showed that the radical recombination step, and not the deprotonation step, was stereo-determining. The mechanism outlining the concepts mentioned above is shown in Scheme 41.

Scheme 41. Mechanism of Wittig Rearrangement



11. Summary and Future Outlook

The development of enantioselective radical reactions outlined in this review is remarkable. Barring a few examples, most of the processes described in this review involve formation of either C−C or C−H bonds (except for halogen atom transfer and one example of a C−O bond, the Schenk-ene reaction). All the examples in section 2 involved atom-transfer reactions, but no examples of enantioselective group transfer were found in the literature. Furthermore, enantioselective cyclizations have been sparsely investigated. Establishing multiple stereocenters in a single reaction is intriguing, and until now, the record stands at four stereocenters for two-bond construction.

Although these are important achievements, there is a need to further the applications by introducing more functional groups during the radical process: in the complexity of substrates used or the radicals that are being added. Radical reactions in alternate media, for example, aqueous media, polymer-supported chiral reagents, or even enantioselective radical reactions on solid support, are awaiting exploration. Interestingly, enantioselective radical chemistry is young enough that it has not yet been utilized in any total synthesis. We hope and believe that the next major review in this field will have many more interesting transformations as we build our understanding and solve existing and yet unimagined problems in radical chemistry.

12. Acknowledgments

We thank the National Institutes of Health, General Medical Sciences (NIH-GM-54656), for support of our research programs. We also thank all of the co-workers who have participated in our research program on radical chemistry: Prof. Craig Jasperse, Dr. Jianguo Ji, Dr. Tara Rheault, Dr. John Shay, Dr. Yasutomi Asano, Dr. Jianxie Chen, Dr. S. Chandramouli, Dr. Hideto Miyabe, Dr. Saumen Hajra, Mr. Justin Sausker, and Ms. Pingrong Liu. Thanks are also due to Prof. Ned Porter for initial collaborative work and Prof. Philippe Renaud for helpful discussions and support.

13. References

(1) Renaud, P., Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: New York, 2001; Vols. 1 and 2. Parsons, A. F. *An Introduction to Free Radical Chemistry*; Blackwell Science: Oxford, 2000. Alfassi, Z. B. *General Aspects of the Chemistry of Radicals*; Wiley: New York, 1999. Fossey, J.; Lefort, D.; Sorba, J. *Free Radical in Organic Chemistry*; Wiley: New York, 1995. Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelheck, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, p 715. Giese, B. *Radicals in Organic Synthesis. Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, 1986.
(2) Sibi, M. P.; Rheault, T. R. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 461. Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. Curran, D. P., Porter, N. A., Giese, B., Eds. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, 1996. Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296. Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*; Pergamon: Oxford, 1996; Vol. 14.
(3) Renaud, P.; Gèrster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2563.
(4) Murakata, M.; Tsutsui, H.; Takeuchi, N.; Hoshino, O. *Tetrahedron* **1999**, *55*, 10295.
(5) Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem.* **1995**, *60*, 3576.
(6) Sibi, M. P.; Asano, Y.; Sausker, J. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 1293.
(7) Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984.
(8) Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386.
(9) Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc.* **1979**, *101*, 7036.
(10) Tanner, D. D.; Kharrat, A. *J. Am. Chem. Soc.* **1988**, *110*, 2968.
(11) Mokhtar-Jamai, H.; Gielen, M. *Bull. Chem. Soc. Belg.* **1975**, *84*, 197. Vigeron, J.; Jacquet, J. *Tetrahedron Lett.* **1976**, *32*, 939. Gielen, M.; Tondeur, Y. *J. Organomet. Chem.* **1979**, *169*, 265.
(12) Nanni, D.; Curran, D. P. *Tetrahedron: Asymmetry* **1996**, *7*, 2417.
(13) Blumenstein, M.; Schwarzkopf, K.; Metzger, J. O. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 235.
(14) Schwarzkopf, K.; Blumenstein, M.; Hayen, A.; Metzger, J. O. *Eur. J. Org. Chem.* **1998**, 177.
(15) Helliwell, M.; Thomas, E. J.; Townsend, L. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1286.
(16) Schiesser, C. H. *Arkivoc* **2001**, *2*, U34. Dakternieks, D.; Schiesser, C. H. *Aust. J. Chem.* **2001**, *54*, 89. Dakternieks, D.; Dunn, K.; Perchyonok, V. T.; Schiesser, C. H. *Chem. Commun.* **1999**, 1665. Dakternieks, D.; Dunn, K.; Schiesser, C. H.; Tiekink, E. R. T. *J. Organomet. Chem.* **2000**, *605*, 209. Perchyonok, V. T.; Schiesser, C. H. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1999**, *151*, 193. Skidmore, M. A.; Schiesser, C. H. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1999**, *151*, 177. Schiesser, C. H.; Skidmore, M. A.; White, J. M. *Aust. J. Chem.* **2001**, *54*, 199.
(17) Curran, D. P.; Gualtieri, G. *Synlett* **2001**, 1038.

(18) Mok, P. L. H.; Roberts, B. P. *Tetrahedron Lett.* **1992**, *33*, 7249. Mok, P. L. H.; Roberts, B. P.; McKetty, P. T. *J. Chem. Soc., Perkin Trans. 2* **1993**, 665. Dang, H. S.; Diart, V.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2511. Dang, H. S.; Diart, V.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1039.
(19) Haque, M. B.; Roberts, B. P. *Tetrahedron Lett.* **1996**, *37*, 9123. Haque, M. B.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2881. Cai, Y. D.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1376.
(20) Dang, H. S.; Roberts, B. P. *Tetrahedron Lett.* **1995**, *36*, 3731.
(21) Dang, H.-S.; Kim, K.-M.; Roberts, B. P. *J. Chem. Soc., Chem. Commun.* **1998**, 1413.
(22) Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 72.
(23) Kameyama, M.; Kamigata, N. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 648.
(24) Murai, S.; Sugise, R.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 475.
(25) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155.
(26) Brunner, H.; Bluchel, C.; Doyle, M. P. *J. Organomet. Chem.* **1997**, *541*, 89.
(27) Yang, D.; Gu, S.; Yan, Y. L.; Zhu, N. Y.; Cheung, K. K. *J. Am. Chem. Soc.* **2001**, *123*, 8612.
(28) Yang, D.; Gu, S.; Yan, Y. L.; Zhao, H. W.; Zhu, N. Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3014.
(29) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10. Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. Yao, S.; Saaby, S.; Hazell, R.; Jørgensen, K. A. *Chem.-Eur. J.* **2000**, *6*, 2435. Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. Mikami, K.; Yajima, T.; Kaneko, M. *Amino Acids* **1998**, *14*, 311.
(30) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415.
(31) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176.
(32) Halland, N.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290.
(33) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.
(34) Sibi, M. P.; Ji, J.; Wu, J. H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200.
(35) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879.
(36) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800.
(37) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417.
(38) Murakata, M.; Tsutsui, H.; Hoshino, O. *Org. Lett.* **2001**, *3*, 299.
(39) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955.
(40) Sibi, M. P.; Manyem, S. *Org. Lett.* **2002**, *4*, 2929.
(41) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. L. *Chem. Rev.* **2002**, *102*, 2227.
(42) Nishida, M.; Hayashi, H.; Nishida, A.; Kawahara, N. *Chem. Commun.* **1996**, 579.
(43) Hiroi, K.; Ishii, M. *Tetrahedron Lett.* **2000**, *41*, 7071.
(44) Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012.
(45) Rosenstein, I. J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, p 50.
(46) Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590.
(47) Porter, N. A.; Wu, J. H. L.; Zhang, G. R.; Reed, A. D. *J. Org. Chem.* **1997**, *62*, 6702.
(48) Fhal, A. R.; Renaud, P. *Tetrahedron Lett.* **1997**, *38*, 2661.
(49) Porter, N. A.; Feng, H.; Kavrakova, I. K. *Tetrahedron Lett.* **1999**, *40*, 6713.
(50) Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997**, *119*, 11713.
(51) Murakata, M.; Jono, T.; Hoshino, O. *Tetrahedron: Asymmetry* **1998**, *9*, 2087.
(52) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029.
(53) Wu, J. H.; Zhang, G. R.; Porter, N. A. *Tetrahedron Lett.* **1997**, *38*, 2067.
(54) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063.
(55) Watanabe, Y.; Mase, N.; Furue, R.; Toru, T. *Tetrahedron Lett.* **2001**, *42*, 2981.
(56) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472.
(57) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344*, 465.
(58) Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1999**, *40*, 7497.
(59) Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 5382.
(60) Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501.
(61) Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1996**, *37*, 3035.
(62) Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, 1411.
(63) Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem. Soc.* **2001**, *123*, 1503.
(64) Enders, D.; Ullrich, E. C. *Tetrahedron: Asymmetry* **2000**, *11*, 3861.
(65) Dunlap, M. S.; Nicholas, K. M. *Synth. Commun.* **1999**, *27*, 1097.
(66) Bandini, M.; Cozzi, P. G.; Morganti, S.; Umani-Ronchi, A. *Tetrahedron Lett.* **1999**, *40*, 1997.
(67) Bensari, A.; Renaud, J. L.; Riant, O. *Org. Lett.* **2001**, *3*, 3863.
(68) Gansäuer, A.; Bluhm, H.; Lauterbach, T. *Adv. Synth. Catal.* **2001**, *343*, 785. Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltemeyer, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2909.
(69) Kurihara, M.; Hayashi, T.; Miyata, N. *Chem. Lett.* **2001**, 1324.
(70) Nguyen, P. Q.; Schafer, H. J. *Org. Lett.* **2001**, *3*, 2993.
(71) Masutani, K.; Irie, R.; Katsuki, T. *Chem. Lett.* **2002**, 36.
(72) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503.
(73) Smrcina, M.; Poláková, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem.* **1993**, *58*, 4534.
(74) Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S.-i. *Tetrahedron Lett.* **1995**, *36*, 9519. Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-i.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264.
(75) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137. Kozlowski, M. C.; Li, X.; Carroll, P. J.; Xu, Z. *Organometallics* **2002**, *21*, 4513.
(76) Chu, C.-Y.; Hwang, D.-R.; Wang, S.-K.; Uang, B.-J. *Chem. Commun.* **2001**, 980.
(77) Hon, S.-W.; Li, C.-H.; Kuo, J.-H.; Barhate, N. B.; Liu, Y.-H.; Wang, Y.; Chen, C.-T. *Org. Lett.* **2001**, *3*, 869.
(78) Barhate, N. B.; Chen, C.-T. *Org. Lett.* **2002**, *4*, 2529.
(79) Luo, Z.; Liu, Q.; Gong, L.; Cui, X.; Mi, A.; Jiang, Y. *Chem. Commun.* **2002**, 914.
(80) Chu, C.-Y.; Uang, B.-J. *Tetrahedron: Asymmetry* **2003**, *14*, 53.
(81) Irie, R.; Masutani, K.; Katsuki, T. *Synlett* **2000**, 1433.
(82) Hamada, T.; Ishida, H.; Usui, S.; Watanabe, Y.; Tsumura, K.; Ohkubo, K. *J. Chem. Soc., Chem. Commun.* **1993**, 909.
(83) Osa, T.; Kashiwagi, Y.; Yanagisawa, Y.; Bobbitt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2535.
(84) Katsuki, T. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 113.
(85) Zhang, R.; Yu, W. Y.; Lai, T. S.; Che, C. M. *Chem. Commun.* **1999**, 1791.
(86) Hamachi, K.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4979. Hamada, T.; Irie, R.; Mihara, J.; Hamachi, K.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10017.
(87) Miyafuji, A.; Katsuki, T. *Tetrahedron* **1998**, *54*, 10339. Miyafuji, A.; Katsuki, T. *Synlett* **1997**, 836.
(88) Punniyamurthy, T.; Katsuki, T. *Tetrahedron* **1999**, *55*, 9439. Punniyamurthy, T.; Miyafuji, A.; Katsuki, T. *Tetrahedron Lett.* **1998**, *39*, 8295.
(89) Hashihayata, T.; Punniyamurthy, T.; Irie, R.; Katsuki, T.; Akita, M.; Moro-oka, Y. *Tetrahedron* **1999**, *55*, 14599. Nishida, T.; Miyafuji, A.; Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 7053.
(90) Komiya, N.; Noji, S.; Murahashi, S.-I. *Tetrahedron Lett.* **1998**, *39*, 7921.
(91) Schulz, M.; Kluge, R.; Gelalcha, F. G. *Tetrahedron: Asymmetry* **1998**, *9*, 4341.
(92) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845. Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567.
(93) Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 5119.
(94) Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J.; Osa, T.; Bobbitt, J. M. *Tetrahedron Lett.* **1999**, *40*, 6469. Kashiwagi, Y.; Kurashima, F.; Kikuchi, C.; Anzai, J.; Osa, T.; Bobbitt, J. M. *Chem. Commun.* **1999**, 1983.
(95) Kashiwagi, Y.; Uchiyama, K.; Kurashima, F.; Anzai, J.; Osa, T. *Anal. Sci.* **1999**, *15*, 907.
(96) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
(97) Sakamoto, M. *Chem.-Eur. J.* **1997**, *3*, 684.
(98) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203. Scheffer, J. R. *Can. J. Chem.* **2001**, *79*, 349.
(99) Joy, A.; Ramamurthy, V. *Chem.-Eur. J.* **2000**, *6*, 1287.
(100) Evans, S. V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J. R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* **1986**, *108*, 5648.
(101) Sakamoto, M.; Takahashi, M.; Kamiya, K.; Yamaguchi, K.; Fujita, T.; Watanabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 10664.
(102) Jones, R.; Scheffer, J. R.; Trotter, J.; Yang, J. *Tetrahedron Lett.* **1992**, *33*, 5481.
(103) Kaftory, M.; Yagi, M.; Tanaka, K.; Toda, F. *J. Org. Chem.* **1988**, *53*, 4391.
(104) Rao, V. P.; Turro, N. J. *Tetrahedron Lett.* **1989**, *30*, 4641.
(105) Joy, A.; Robbins, R. J.; Pitchumani, K.; Ramamurthy, V. *Tetrahedron Lett.* **1997**, *38*, 8825.
(106) Shailaja, J.; Ponchot, J.; Ramamurthy, V. *Org. Lett.* **2000**, *2*, 937.
(107) Bach, T.; Aechtner, T.; Neumüller, B. *Chem.-Eur. J.* **2002**, *8*, 2464.
(108) Nakano, T.; Okamoto, Y. *Chem. Rev.* **2001**, *101*, 4013. Nakano, T.; Shikisai, Y.; Okamoto, Y. *Polym. J.* **1996**, *28*, 51. Nakano, T.; Shikisai, Y.; Okamoto, Y. *Proc. Jpn. Acad. Ser. B—Phys. Biol. Sci.* **1995**, *71*, 251.

(109) Tsuji, M.; Sakai, R.; Satoh, T.; Kaga, H.; Kakuchi, T. *Macromolecules* **2002**, *35*, 8255.
(110) Habaue, S.; Seko, T.; Okamoto, Y. *Macromolecules* **2003**, *36*, 2604.
(111) Tomooka, K.; Yamamoto, K.; Nakai, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 3741.

CR020044L