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Catalyzed enantioselective aldol additions of latent enolate equivalents

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Contents

1. Introduction

Aldol addition reactions are among those transformations that have greatly simplified the construction of asymmetric C–C bonds and, thus, satisfy the most stringent of requirements for salient asymmetric organic synthesis methodology. Numerous examples attesting to the strategic nature of asymmetric aldol reactions exist in the context of both complex molecule synthesis and the preparation of optically active small molecule building blocks.[1] Demand within the pharmaceutical and fine chemical industries for efficient and economical methodologies for the asymmetric synthesis of both simple and complex target molecules has resulted in new developments in aldol-based reaction technology being increasingly

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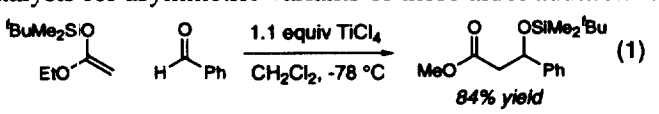
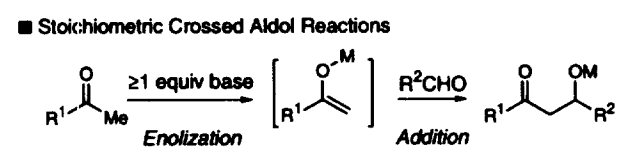
shaped by concerns for potential industrial applicability. As a consequence, an increasing emphasis has been placed on developing catalyzed asymmetric aldol bond constructions as a means of addressing the issues of cost and operational simplicity inherent in industrial-scale chemistry. Catalytic variants of the aldol addition reaction have evolved primarily from reaction design strategies that employ preformed, latent enolates that require some activating agent, often substoichiometric quantities of a Lewis acid, to undergo addition to the electrophilic reaction component. Investigations that have successfully implemented this reaction design strategy to the execution of asymmetric catalytic cross aldol reactions are the subject of the present account.

Many of the fundamental issues that confronted initial development of chemoselective cross aldol reactions are inherent to the design of catalyzed variants of this important bond construction. Establishing procedures for achieving chemo- and regioselective enolization, an essential prerequisite to chemoselective aldol addition reactions, was among the seminal achievements that ultimately led to aldol bond constructions reaching their current level of sophistication.[2] Reaction designs for catalyzed aldol reactions must similarly incorporate mechanisms for selective enolate formation and the controlled reaction of the resulting nucleophile with aldehyde electrophiles. It is not surprising, therefore, that the most widely explored strategy for executing catalyzed and, ultimately, asymmetric aldol additions exploits preexisting stoichiometric methodologies for generating the desired enolate structures. This design strategy shares with stoichiometric protocols the procedural requirement for making enolate formation (enolization) and C–C bond construction (addition) separate and distinct chemical operations (Scheme 1). However, the catalyzed reaction schemes necessarily require a reaction catalyst to initiate and mediate the reaction of the resulting enolate, thus presenting the catalyst as a vehicle for influencing reaction stereoselection. Implementing this reaction design, therefore, required the identification of suitable latent enolate equivalents that would add to aldehyde electrophiles only upon the intervention of a suitable activating agent (catalyst). (Silyloxy)alkenes were first recognized as the requisite latent enolate equivalents, undergoing addition to aldehydes in the presence of Lewis acid activators, a process ultimately to become known as the Mukaiyama aldol reaction (Eq. 1).[3] The reaction parameters enumerated by Mukaiyama's initial investigations provided a reaction platform and a mechanistic guideline for the subsequent design and development of chiral catalysts for asymmetric variants of these aldol addition reactions.





Scheme 1.

The primary objective of this review is to present a comprehensive survey of catalyzed enantioselective aldol reactions in which asymmetric induction is derived solely from the catalyst complex. Catalyzed aldol reactions that translate preexisting chirality in one of the reaction partners to the bond

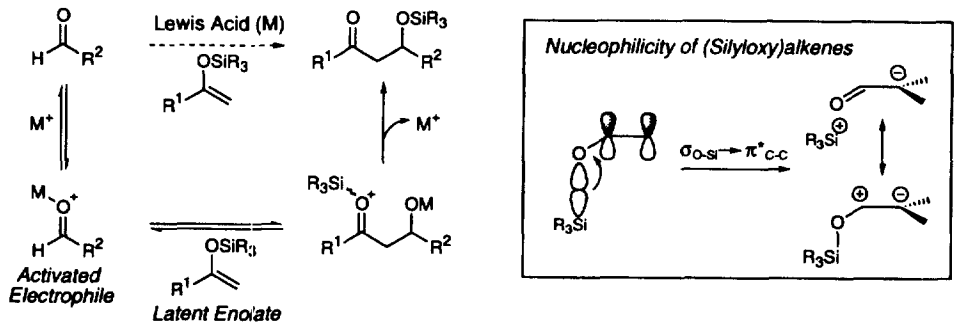


Fig. 1. Lewis acid-catalyzed additions of (silyloxy)alkenes

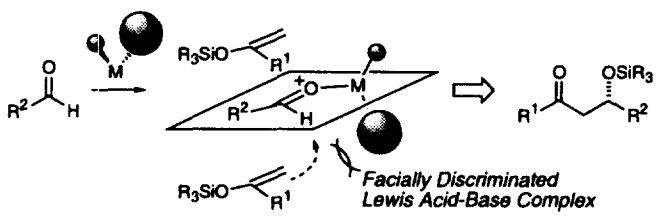
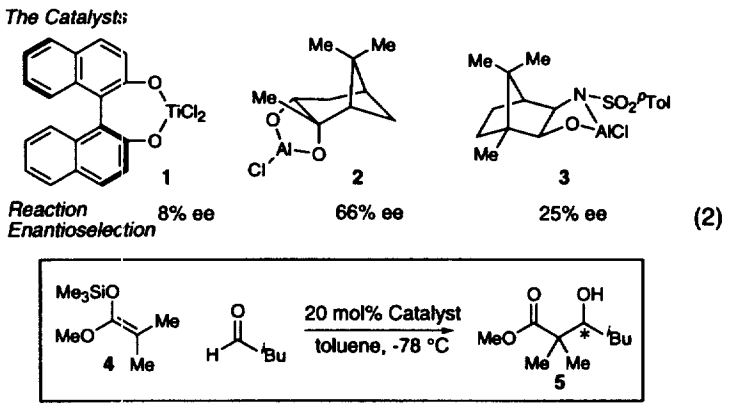


Fig. 2. Asymmetric aldol reactions catalyzed by chiral Lewis acids

construction event (diastereoselective reactions) are, therefore, not included. Furthermore, reactions requiring stoichiometric quantities of a chiral reaction promoter are discussed only as they pertain to the subsequent development of catalytic reaction variants. Many of the studies pertinent to this review appeared nearly concurrently from a number of research groups. Therefore, rather than attempt to present these investigations in rigorous chronological order, the present account organizes these studies according to the structure and function of the various catalyst systems.

Analysis of the C–C bond construction resulting from the Lewis acid-mediated reaction of (silyloxy)alkenes with aldehydes suggests addition of the latent enolate to a Lewis acid activated aldehyde complex to be a viable mechanistic hypothesis for Mukaiyama aldol reactions (Fig. 1). Silylated enolates possess significant nucleophilic character owing to electron donation to the alkene π-system derived from resonance interaction with the oxygen lone pairs and the β-silicon effect.[4] Thus, Lewis acid activation of the aldehyde elicits enolate addition with subsequent transfer of the silicon residue to the aldolate oxygen or direct hydrolysis of the metal alkoxide intermediate providing the silylated or unsilylated aldol adducts, respectively. While succeeding investigations would reveal the mechanistic profile of Mukaiyama aldol reactions to be considerably more complex, this mechanistic paradigm implicated reaction designs employing optically active Lewis acid complexes to create facially discriminated aldehyde electrophiles as a strategy for effecting asymmetric catalyzed aldol reactions (Fig. 2).[5]

In 1986, Reetz provided the first indication that asymmetry in catalyzed Mukaiyama aldol reactions could be induced by substoichiometric quantities of chiral Lewis acid complexes. The Ti(IV)–BINOL complex **1** and the Al(III)-based Lewis acids **2** and **3** were evaluated as chiral catalysts for the addition of 1-methoxy-1-trimethylsilyloxy-3-methylpropene (MTMP; **4**) to aliphatic aldehydes.[6] Especially encouraging levels of enantioselection were obtained in reactions employing the Al(III)-pinanediol catalyst system **2** (~20 mol% catalyst loading), providing the aldol adduct **5** with 66% ee (Eq. 2).

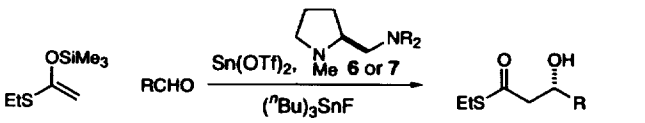


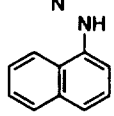
The poor enantioselection realized in reactions catalyzed by the Ti(IV)–BINOL complex **1** contrasts sharply with the high levels of asymmetric induction that would ultimately be derived from catalyst systems that are nearly identical in composition. Furthermore, despite the promising levels of asymmetric induction achieved in this study using Al(III)-derived Lewis acid catalysts, no aluminum-based catalyst systems that elicit highly enantioselective aldol reactions have been reported subsequently. Collectively, these preliminary investigations foreshadow the considerable sensitivity of enantioselection in Lewis acid-catalyzed aldol reactions to subtle variations in the preparative details of catalyst generation, the solution-state structure of the catalytically active species, and minor variations in reaction conditions that would be encountered repeatedly in subsequent studies.

2. Sn(II) catalyst systems

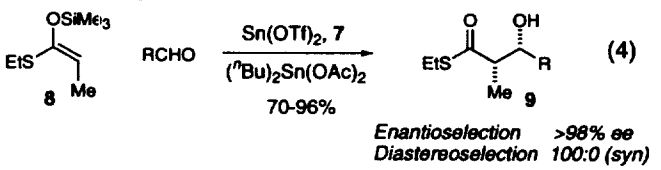
2.1. Sn(II)–diamine reaction promoters

Divalent tin complexes modified with chiral, chelating diamine ligands provided some of the earliest indications that absolute stereochemical control could be established in Mukaiyama aldol reactions using non-covalently bound chiral controllers integrated into the metal-based reaction promoter.[7] The development of these catalyst systems was predicted on the preliminary finding that substoichiometric quantities of $SnCl_2$ in combination with trityl chloride function as a catalyst for the aldol addition reaction of silyl thioketene acetals and aldehydes; substoichiometric quantities of either constituent of this catalyst system do not promote the addition reaction.[8] This observation implicated a cationic Sn(II) species, generated by cocatalyst-induced halide abstraction, as the active reaction promoter and resulted in divalent tin complexes emerging as templates for developing chiral aldol catalysts. Stoichiometric quantities of Sn(II) triflate and specific combinations of optically active chelating diamines and Lewis acidic cocatalysts, typically Sn(IV) salts, provided excellent yields and enantioselectivities in the addition of ketene acetals to various aldehyde electrophiles (Eq. 3).



diamine	NR_2	% yield	% ee
6		70-90	78->98
7		50-52	81-92

Reaction enantioselectivity proved to be especially sensitive to the structure of both the Lewis acid cocatalyst and the diamine ligand, with the most effective promoters being derived from either *n*-Bu_3SnF or *n*-Bu_2SnOAc_2 as cocatalysts and the proline-derived diamine ligands **6** and **7**. Near-perfect levels of relative and absolute stereochemical control were achieved in the aldol reactions of the (*Z*)-*O*-propionate enolate equivalent **8** and both unsaturated and aliphatic aldehydes using this chiral promoter system; *syn* propionate aldol adducts **9** emerged from these reactions with high optical purity (≥98% ee), generally in excess of 85% chemical yield (Eq. 4).[9]



2.2. *Sn(OTf)$_2$-based catalysts*

2.2.1. *Reaction design*

Subsequent attempts to elucidate the mechanism of the Sn(II)/Sn(IV)-promoted aldol reactions revealed that a catalytic cycle for the addition of silyl thioketene acetals to benzaldehyde could be established using substoichiometric quantities of Sn(II) triflate.[10] The sensitivity of enantioselection in the Sn(II)[diamine]-promoted aldol reactions to the identity of the Sn(IV) cocatalyst was ultimately ascribed to the Sn(IV) cocatalyst functioning as a scavenger of TMSOTf generated during the course of the addition reaction (Fig. 3).[7] Trialkylsilyl triflates are sufficiently Lewis acidic to promote the aldol addition reaction and, therefore, offer a reaction manifold that is independent of the diamine chiral controller, resulting in attenuated reaction enantioselection.[11] It was reasoned that substoichiometric quantities of the Sn(II) triflate–diamine complex might provide useful levels of enantioselection provided a reaction protocol that precluded the intervention of the 'silicon-catalyzed' pathway could be established. Indeed, the $Sn(OTf)_2$–diamine complex **10** (20 mol%) catalyzes the addition of silyl thioketene acetals to aldehydes with enantioselectivities approaching those obtained for the stoichiometric Sn(II)-promoter system. Realizing optimum enantioselection in the Sn(II)-catalyzed propionate aldol reactions require the slow addition of the enolate equivalent to a propionitrile solution of aldehyde and catalyst. The initial events in the catalytic reaction cycle are proposed to parallel those of the Sn(II)-promoted reaction with the tin aldolate adduct **11** emerging from ketene acetal addition to a Lewis acid activated aldehyde (Fig. 4).[12] Silyl group transfer to the aldolate oxygen regenerates the chiral tin catalyst **12** in providing the silylated aldol product **13**. Alternatively, ligand exchange in **11** can occur to liberate TMSOTf, a mechanistic

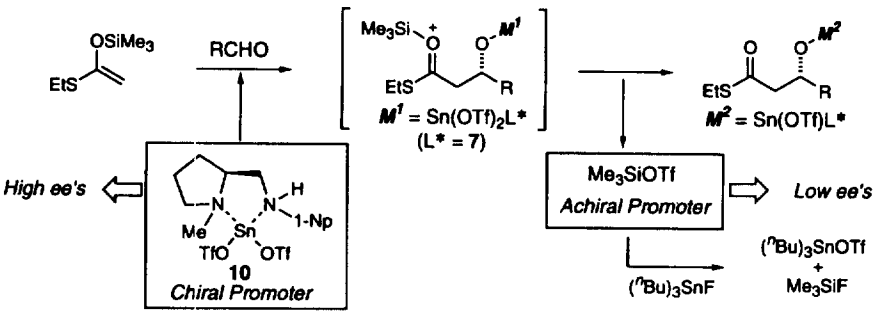


Fig. 3. Mechanism of Sn(II)/Sn(IV)-promoted aldol reactions

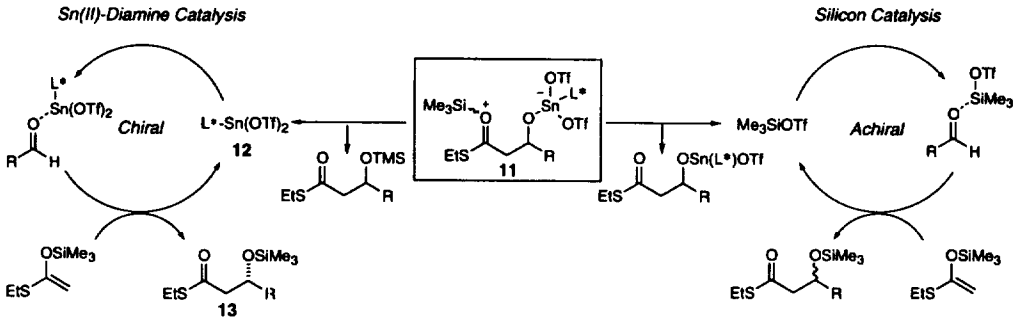


Fig. 4. Competing Sn(II) versus TMSOTf-catalyzed reaction pathways

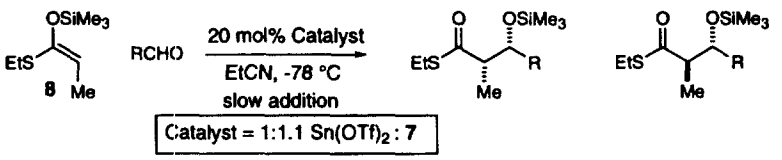
scenario that rationalizes the procedural requirement for slow substrate addition in order to obtain high enantioselectivities. Specifically, a build-up of TMSOTf resulting from direct addition of the silylketene acetal to the aldehyde–catalyst complex results in partioning of the reaction mechanism between the chiral Sn-mediated process and an achiral TMSOTf-catalyzed reaction manifold. Slow substrate addition allows transmetallation of the initial tin aldolate **11** to remove free TMSOTf from the reaction mixture, thus shunting the achiral reaction pathway. Accelerated rates of aldolate silylation precipitated by Lewis base coordination to the metal ion, and the resulting amplified alkoxide nucleophilicity, have been suggested as an explanation for improved reaction enantioselection and turnover frequencies in propionitrile relative to dichloromethane reaction solvents.[13]

2.2.2. *Acetate and propionate aldol reactions*

The optimized Sn(II) triflate–diamine catalyst system has been successfully applied to the aldol addition of the silyl thioketene acetals, representing propionate and acetate enolate equivalents, with a wide variety of aldehyde electrophiles.[13] The complex derived from a 1:1.1 mixture of $Sn(OTf)_2$ and diamine **7** (20 mol%, EtCN, −78°C) catalyzes the addition reaction of the (*E*)-*O*-ketene acetal **8** to aryl, α,β-unsaturated, and aliphatic aldehydes with excellent relative and absolute stereochemical control: *syn*:*anti*=89:11–100:0, ee=89–>98% (Table 1).[14] The reactions of the corresponding (*Z*)-*O*-ketene acetals are not reported, presumably due to the poor diastereo- and enantioselectivity afforded by these nucleophiles in the Sn(II)–diamine promoted reactions. The catalyst derived from $Sn(OTf)_2$ and diamine **15** affords the acetate aldol adducts **16** with high optical purity via the addition of the unsubstituted ketene acetal **14** to several aliphatic aldehydes (90–93% ee); however, conjugated aldehydes afford considerable variability in enantioselection (68–88% ee) (Table 2).[15]

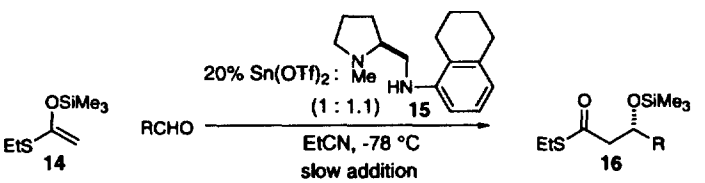
The sense of asymmetric induction in the preceding reactions can be rationalized by assuming that the reaction proceeds via the intermediacy of the square pyramidal aldehyde–Sn(II) complex **17** (Fig. 5).[10]

Table 1
Sn(II)–diamine catalyzed additions of thioketene acetals



entry	aldehyde	% yield	*syn*:*anti*	% ee (*syn*)
a	C_6H_5CHO	77	93:7	90
b	$CH_3(CH_2)_6CHO$	80	100:0	>98
c	$^cC_6H_{11}CHO$	71	100:0	>98
d	4-$CH_3C_6H_4CHO$	75	89:11	91
e	(*E*)-CH_3CH=$CHCHO$	76	96:4	93
f	(*E*)-^{n}BuCH=CHCHO	73	97:3	93

Table 2
Sn(II)–diamine catalyzed additions of acetate enolate equivalents



entry	aldehyde	% yield	% ee
a	$CH_3(CH_2)_3CHO$	79	93
b	$^cC_6H_{11}CHO$	81	92
c	Me_2CHCHO	48	90
d	^{n}BuCCCHO	68	88
e	$Me_3SiCCCHO$	75	77

Orientation of the amine and triflate ligands arrayed about the Sn ion to minimize mutual non-bonded interactions result in adjacent ligands shielding opposite faces of the square planar $Sn(OTf)_2$–diamine complex **10**. Lewis acid–base association occurs preferentially at the more accessible apical coordination site on tin, opposite the pyrrolidine and triflate ligands. The resulting Lewis acid–base complex orients the 1-naphthyl substituent to efficiently shield the (*re*) aldehyde diastereoface, thus affording aldol adducts having the (*S*) configuration (R^1=Ph) at the hydroxyl-bearing stereocenter. Addition of β-substituted ketene acetals to the activated Sn–aldehyde complex **17** via an open transition state that minimizes developing gauche interactions rationalizes the fidelity of these reactions for the production of the *syn* aldol diastereomer.

3. Boron heterocycle catalysts

3.1. (Acyloxy)borane complexes

Chiral boron heterocycles have proven to be among the most successful platforms for developing chiral Lewis acids with applications to organic synthesis. Mukaiyama aldol addition reactions are among the

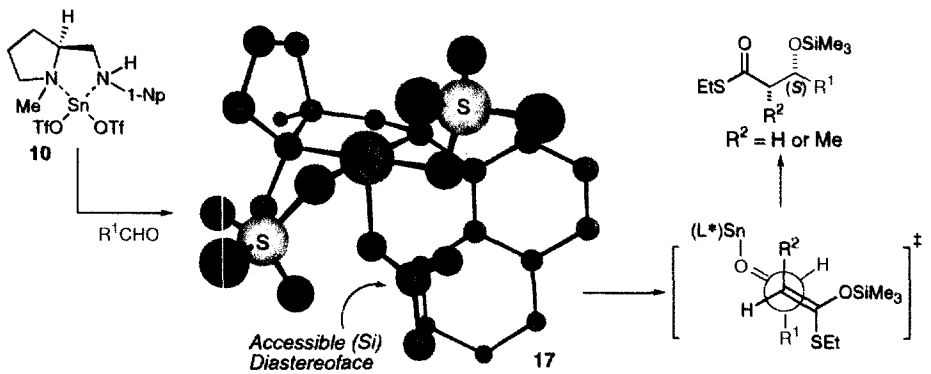


Fig. 5. Chiral Sn(II)[diamine]–aldehyde complex

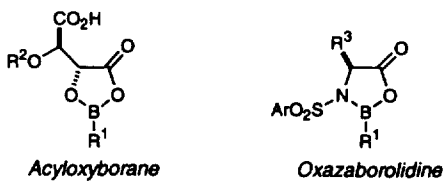
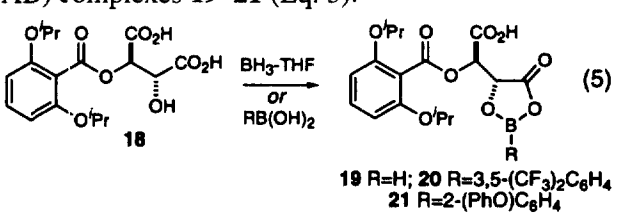


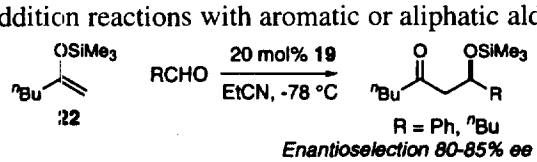
Fig. 6. Chiral boron heterocycle Lewis acids

numerous asymmetric bond constructions catalyzed by acyloxyborane and oxazaborolidine complexes, prototypical examples of boron heterocycles that are readily obtained in optically active form (Fig. 6). Reaction of the mono-arylester of tartaric acid **18** with borane or a suitable boronic acid provides the chiral (acyloxy)borane (CAB) complexes **19–21** (Eq. 5).



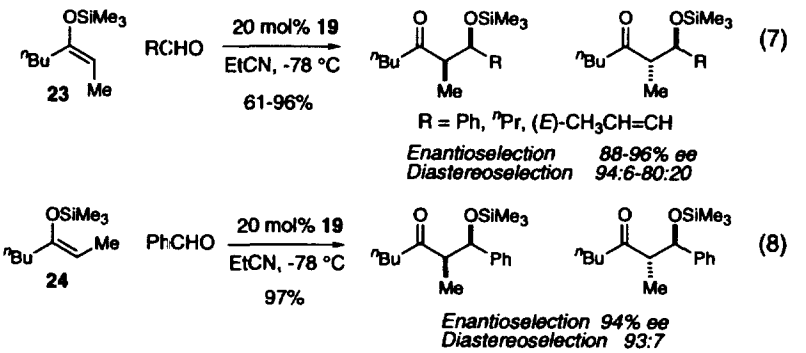
(5)

The parent CAB complex **19** affords good levels of relative and absolute stereoselection in the catalyzed addition of various enol silane and silyl ketene acetal nucleophiles with a limited number of aldehyde electrophiles.[16,17] Terminal enol silane **22** affords enantioselectivities ranging from 80–85% ee in the CAB-catalyzed addition reactions with aromatic or aliphatic aldehydes (70–98% yield) (Eq. 6).



(6)

Internal enol silanes **23** and **24** afford similarly high levels of enantioselection and commensurately high relative stereocontrol in CAB-catalyzed additions to benzaldehyde (Eqs. 7 and 8).



Lower catalyst loadings (10 mol%) may be used and modest increases in enantioselection are achieved when the arylboronic acids **20** and **21**, respectively, are employed as catalysts.[16b] Analogous aldol additions employing aliphatic aldehyde electrophiles suffer from attenuated levels of diastereo- and enantioselectivity relative to those values obtained using benzaldehyde. Reaction diastereoselection is insensitive to the stereochemistry of the substituted enolate equivalents; both (*E*) and (*Z*) enol ethers selectively provide the *syn* aldol diastereomer (Fig. 7). This result is suggested to provide evidence that these reactions are proceeding via open, extended transition states; minimization of close contact between the enolate substituent R_1 and the aldehyde alkyl residue R_2 in the transition state lead, preferentially, to the *syn* aldol adducts regardless of the initial enolate geometry.[18]

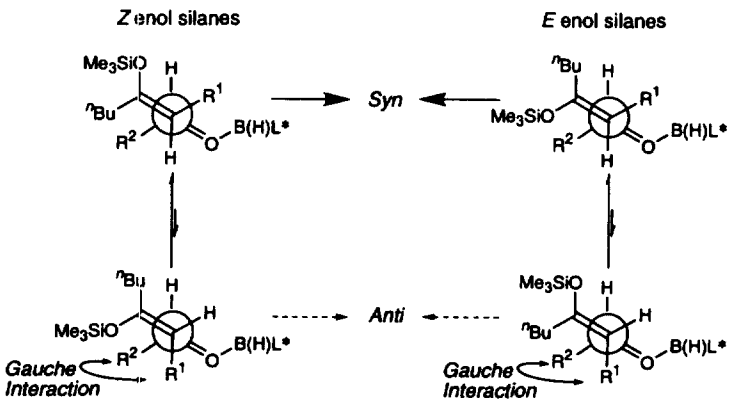
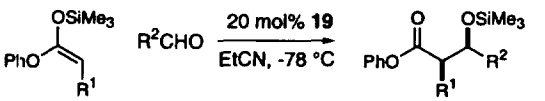
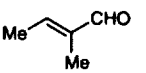


Fig. 7. Transition states for CAB-catalyzed additions of β-substituted enol silanes

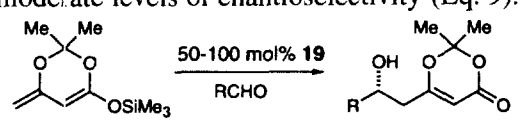
An investigation into the effectiveness of silyl ketene acetals as nucleophiles in CAB-catalyzed Mukaiyama aldol reactions revealed an interesting relationship between reaction stereoselectivity and the identity of the ketene acetal *O*-alkyl substituent. Under the reaction conditions optimized for catalyzed enol silane additions (20 mol% CAB catalyst, EtCN, −78°C), aldol reactions employing *O*-ethyl silyl ketene acetals provided stereorandom mixtures of diastereomeric aldol adducts.[19] In contrast, the phenyl acetate-derived enolate equivalent **25** provided good to moderate asymmetric induction in CAB-catalyzed aldol reactions (Table 3). Analogous levels of enantioselection were achieved using the β-substituted silyl ketene acetal **26**, with α,β-unsaturated aldehydes providing optimum chemical yields and stereoselectivity, delivering aldol adducts with both diastereo- and enantioselection in excess of 90% (entries f and g). The role that *O*-phenyl substitution within the enolate plays in influencing the stereochemical course of these reactions (the 'phenyl ester effect') is currently undefined; however, this effect subsequently proved to be operative in other Lewis acid catalyzed aldol reactions. Silyl ketene acetal **27a**, derived from the commercially available 1,3-dioxin-4-ones, has been investigated as another

Table 3
CAB-catalyzed aldol additions of silyl ketene acetals



entry	ketene acetal	aldehyde	% yield	*syn:anti*	% ee (*syn*)
a		PhCHO	63	NA	84
b	**25**	^{n}PrCHO	49	NA	76
c		PhCHO	83	79:21	92
d	**26**	^{n}PrCHO	57	65:35	88
e	**26**	^{i}PrCHO	45	64:36	79
f	**26**		97	96:4	97
g	**26**		86	>95:5	94

class of nucleophile in CAB-catalyzed aldol reactions with limited success; reactions require high catalyst loadings and deliver only moderate levels of enantioselectivity (Eq. 9).[20,21]



(9)

27a

Enantioselection 38-73% ee

Acyloxyborane catalyst systems share several of the procedural requirements for achieving highly stereoselective aldol additions associated with the $Sn(OTf)_2$-diamine catalysts. Lewis basic solvents such as propionitrile or nitromethane were found to elicit optimum catalyst efficiency, suggesting that Lewis base accelerated silicon-transfer to the putative aldolate intermediate is required to facilitate catalyst turnover in both the CAB and Sn(II) catalyst systems. Furthermore, relatively high catalyst loadings ($\geq$20 mol%) are required to achieve the indicated levels of stereoinduction. Whether these catalyst loadings reflect an attempt to ensure the chiral catalyzed reaction kinetically dominates competitive catalysis by adventitious Lewis acidic species (silicon catalysis), or are indicative of an inherent lack of catalytic competency of the CAB complexes, with higher loadings being required to drive the reaction to completion, is unclear.

A transition state model that rationalizes the observed sense of asymmetric induction in acyloxyborane-catalyzed aldol reactions has been developed in the context of related CAB-catalyzed Diels–Alder cycloadditions (Fig. 8). Solution and solid state conformational analysis of CAB complexes of various α,β-unsaturated aldehydes by NOE measurements and X-ray crystal structure determination, respectively, reveal that the Lewis acid–base complexes adopt a folded conformation that aligns the aldehyde and aromatic π-systems to engage in face-to-face π-stacking interactions.[22] Similar conformational preferences in the activated (*R,R*)-CAB catalyst–aldehyde complex **28** would expose the aldehyde (*re*) diastereoface to nucleophilic attack, delivering the observed aldol adduct **29**.

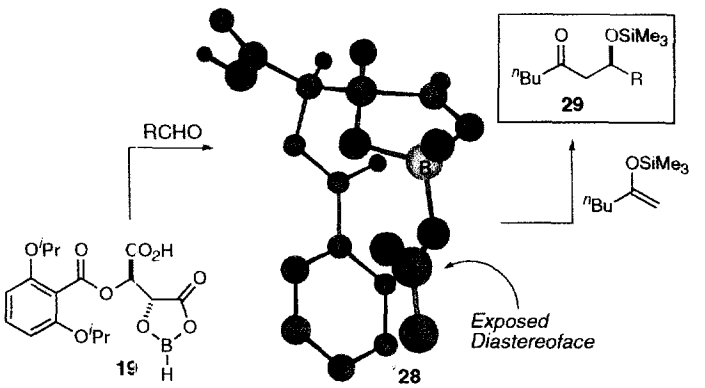
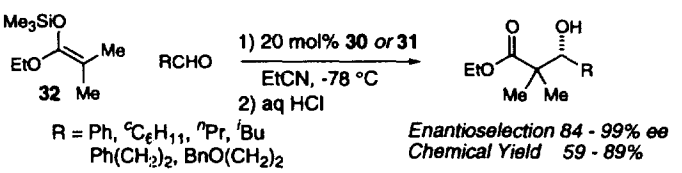


Fig. 8. Chiral (acyloxy)borane–aldehyde complex

3.2. *Oxazaborolidine catalysts*

3.2.1. *Catalysts incorporating α,α-disubstituted amino acids*

Oxazaborolidine complexes share considerable structural homology with (acyloxy)borane Lewis acids and, accordingly, have been investigated as catalysts for effecting asymmetric Mukaiyama aldol addition reactions. Structurally similar oxazaborolidine complexes have been investigated by several research groups as potential aldol catalysts. In one of these studies, optically active α,α-disubstituted amino acids were identified as essential components of catalytically competent oxazaborolidine aldol catalysts based upon speculation regarding the mechanism by which oxazaborolidine complexes would mediate Mukaiyama-type bond constructions.[23] Either of the catalyst complexes **30** and **31**, derived from relatively easily obtained α,α-disubstituted α-amino acids, provide near-perfect enantioselection (≥97% ee) in addition reactions of the disubstituted silyl ketene acetal **32** with unbranched aliphatic aldehydes (Eq. 10).



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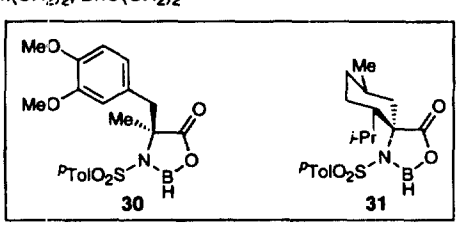


In contrast to the Sn(II)-based aldol catalysts, oxazaborolidine complexes are proposed to offer an active mechanism for scavenging electrophilic silicon species generated during the reaction cycle, an event previously determined to be imperative for achieving efficient chirality transfer and catalyst turnover (Fig. 9). Specifically, the silyl oxocarbenium ion **33** that emerges from initial nucleophilic addition situates the boron carboxylate to effect intramolecular silicon transfer in providing the boron aldolate **34**, thereby precluding the potential for silicon (achiral) catalysis that might be initiated by such electrophilic silicon species. Regeneration of the five-membered boron heterocycle provides an enthalpic impetus for ensuing silicon transfer to the aldolate oxygen, thereby liberating the silylated

aldol adduct with concomitant turnover of the oxazaborolidine catalyst. Catalyst liberation from the aldolate intermediate was postulated to be the rate-limiting step and, thus, disubstitution of the catalyst's amino acid backbone was considered a mechanism for facilitating catalyst turnover by accelerating oxazaborolidine ring closure, and the attendant silicon transfer event, by virtue of the Thorpe–Ingold effect. The efficiency of the essential intramolecular silicon transfer event is questionable, however, as slow addition of the nucleophile to the reaction mixture is still required to achieve high enantiomeric excesses.

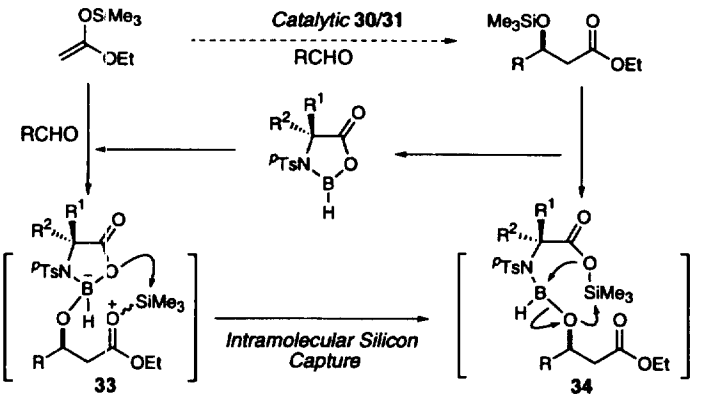
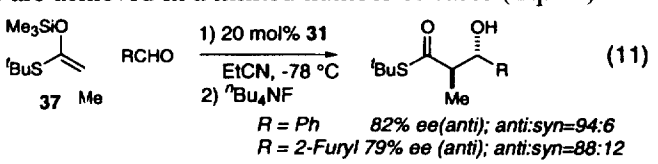


Fig. 9. Silicon-shuttle mechanism for oxazaborolidine-catalysis

Enantioselection in the oxazaborolidine catalyzed aldol reactions exhibits a pronounced dependence on nucleophile structure, with some attenuation of asymmetric induction being derived from ketene acetals other than **32**.[24] The *O*-phenyl or *S*-*t*-butyl silyl ketene acetals **25** and **35** provide the derived acetate aldol adducts **36** (R^1=OPh or S*t*-Bu) with enantiomer ratios ≥91:9; the menthone-derived catalyst **31** provided optimum enantioselection in addition reactions employing these ketene acetal nucleophiles (Table 4). Furthermore, the 'phenyl ester effect' enumerated by Yamamoto proved to be operative in these oxazaborolidine-catalyzed reactions as other *O*-alkyl-substituted ketene acetals afforded little to no stereoinduction. Propionate aldol products can also be obtained from the catalyzed aldol reactions employing (*E*) propionate enolate equivalents **37**; however, useful levels of relative and absolute stereoinduction are achieved in a limited number of cases (Eq. 11).



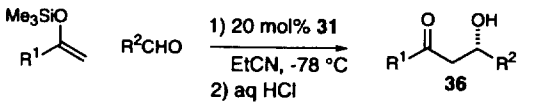
(11)

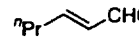
Diastereo- and enantioselectivity in the propionate aldol reactions are highly variable, exhibiting a marked dependence on the identity of both the nucleophilic and electrophilic reaction components. In fact, the highest levels of asymmetric induction are achieved in the minor diastereomeric aldol adduct. The predominance of the *anti* aldol diastereomer derived from the catalyzed propionate aldol reactions is in contrast to the diastereoselection observed in CAB and Sn(II)[diamine]-catalyzed reactions of β-substituted enolate equivalents that uniformly provide the *syn* aldol adduct as the major reaction product.

3.2.2. Valine-derived complexes

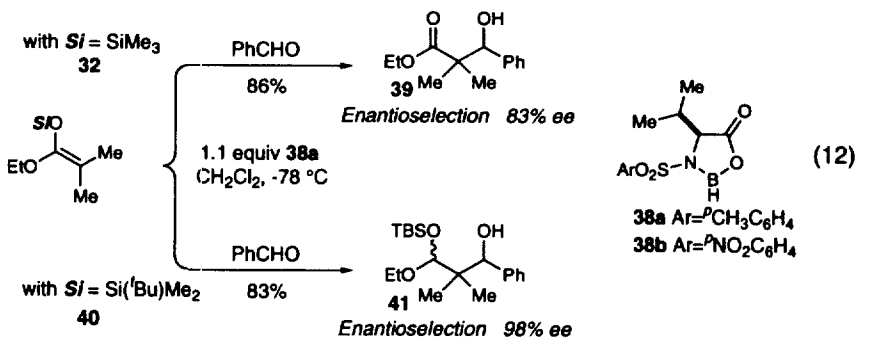
Kiyooka[25] and Corey[26] have independently developed oxazaborolidine complexes derived from simple, naturally occurring α-amino acids as effective catalysts for the addition of ketene acetals and enol

Table 4
Oxazaborolidine **31**-catalyzed acetate aldol reactions



entry	R^1	aldehyde	% yield	% ee
a	S^{t}Bu (**35**)	PhCHO	86	87
b	OPh (**25**)	PhCHO	77	93
c	S^{t}Bu	$Ph(CH_2)_2CHO$	77	91
d	OPh	$Ph(CH_2)_2CHO$	78	85
e	S^{t}Bu	$^cC_6H_{11}CHO$	75	81
f	OPh	$^cC_6H_{11}CHO$	87	84
g	S^{t}Bu		91	82
h	S^{t}Bu	(2-furyl)CHO	98	95

silanes, respectively, to various aldehyde electrophiles. In an initial disclosure, stoichiometric quantities of oxazaborolidine **38a** were reported to mediate the addition of **32** to hydrocinnamaldehyde with relatively high optical and chemical yields (87% yield, 93% ee).[27] More significantly, the product distribution derived from the oxazaborolidine-mediated aldol reactions was found to be sensitive to the structure of the ketene acetal silyl group. Trimethylsilyl ketene acetal **32** provided the anticipated aldol adducts **39** exclusively (83–93% ee), while the *t*-butyldimethylsilyl ketene acetal **40** afforded the silyl acetal **41** as the predominant reaction product (92–98% ee) (Eq. 12)



Acetal formation results from a partitioning of the reaction pathway that typically leads to aldol adducts (c.f., Fig. 9) elicited by slow transmetallation of the boron–aldolate intermediate **42** (Fig. 10). Reaction variables that function to slow silyl transfer to the aldolate oxygen, such as the poor migratory aptitude of *t*-butyldimethylsilyl groups, allow hydride migration to the carbonyl carbon to compete effectively with the silicon transfer event that affords the typical aldol adducts. Hydrolysis of the resulting azaborate **43** upon work-up provides the observed β-hydroxy acetal **41**.

These observations have led to the direct preparation of optically active *syn* 1,3-diols by the tandem asymmetric aldol addition–diastereoselective carbonyl reduction promoted by optically active oxazaborolidine complexes.[28] Oxazaborolidine-mediated (1.0 equiv **38a**, EtCN, −78°C) addition of terminal enol silanes **44** to a limited number of aldehydes afford the derived *syn* diols **45** as the major reaction products (53–70%), regardless of silyl group structure, with the corresponding aldol adduct **46** com-

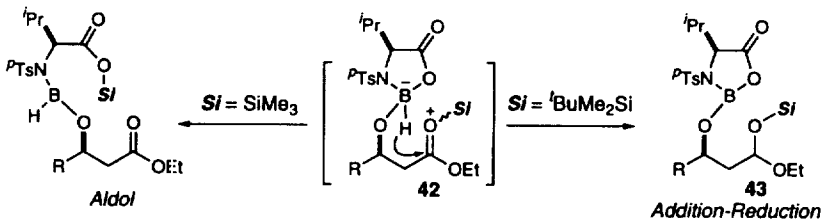
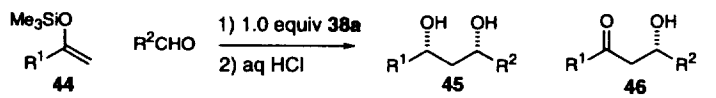


Fig. 10. Mechanism for competing addition–reduction reactions

Table 5
Oxazaborolidine-mediated tandem asymmetric aldol–reduction reaction



			45		46	
entry	R^1	R^2	% yield (*syn*:*anti*)	% ee (*syn*)	% yield	% ee
a	Ph	$^iC_3H_7$	65 (97:3)	99	17	60
b	BnO(CH$_2$)$_2$	$^iC_3H_7$	55 (89:11)	86	15	67
c	$^nC_6H_{13}$	$^iC_3H_7$	70 (90:10)	99	23	60
d	$^nC_6H_{13}$	$^nC_3H_7$	66 (90:10)	98	25	49
e	$^nC_6H_{13}$	Ph	53 (97:3)	85	18	72

prising the remainder of the product mixture (6–25%) (Table 5). Selectivity for the formation of the *syn* diol diastereomer is high (*syn*:*anti*=89:11–97:3) with enantioselection generally exceeding 94% ee. The enantiomeric purity of the 1,3-diols is substantially higher than that of the accompanying aldol products suggesting that reduction of the intervening diastereomeric β-keto azaborate complexes (c.f., **47**) is subject to double stereodifferentiation (Fig. 11). While several transition state models rationalizing diastereoselectivity for the carbonyl reduction are advanced, reaction via a non-chelated transition state **48** in which hydride is delivered to the silicon-activated carbonyl residue finds considerable precedence in closely related (triacetoxy)borohydride-mediated reductions of similar β-hydroxy carbonyls.[29] In addition to being a more reactive electrophile, the silyl oxocarbenium ion may also serve to create a conformational preference for orienting the silyloxy function in the pseudo-equatorial position in transition state assembly **48**. In the absence of such conformational perturbations, the related substrate-directed reductions of β-hydroxy ketones exhibit a strong proclivity for providing the 1,3-*anti* diol adducts via the transition state assembly **49** in which the carbonyl oxygen occupies the pseudo-axial orientation.

Solvent also plays an important role in defining the mechanistic course of these oxazaborolidine-mediated ketene acetal–aldehyde addition reactions.[25] Aldol addition of MTMP (**4**) that requires stoichiometric quantities of **38a** in CH_2Cl_2 could be executed in high yield with 20 mol% of **38b** if nitroethane was substituted as the reaction solvent. While the mechanistic details of the reaction were not investigated, nucleophilic assistance provided by the Lewis basic solvent was postulated to sufficiently accelerate silyl transfer to the intervening boron aldolate such that catalyst turnover was realized. This hypothesis is consistent with the notion that Lewis acid–base association of nitroethane and boron in the aldolate intermediate would amplify the nucleophilicity of the alkoxide oxygen. Under these reaction conditions, **38b** catalyzes the addition of MTMP (**4**) to a limited set of aldehyde electrophiles with enantioselection exceeding 90% ee. However, the unsubstituted ketene acetal **25** and/or α,β-unsaturated

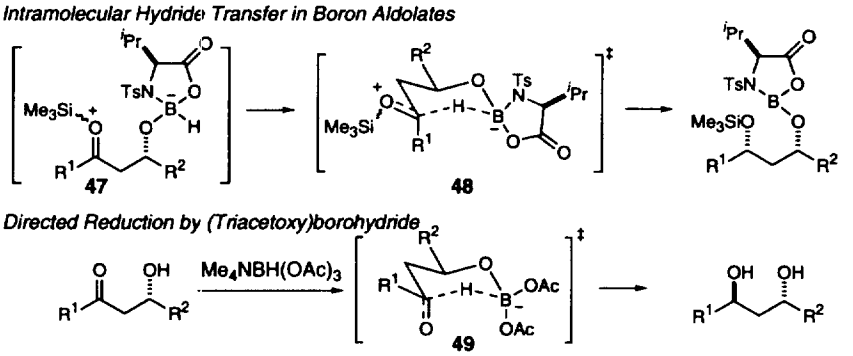
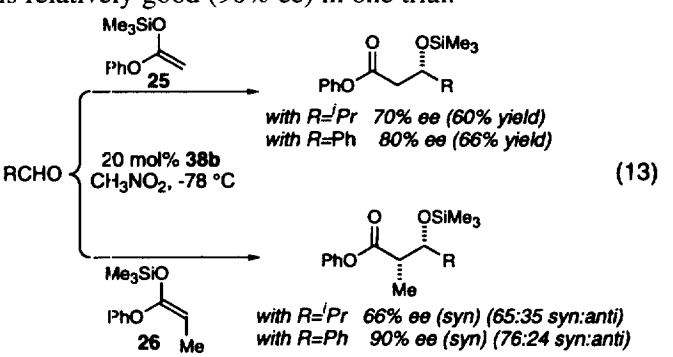


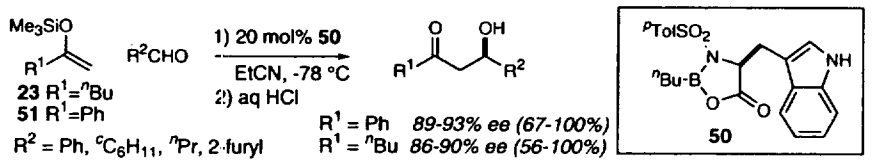
Fig. 11. Diastereoselective reduction of boron aldolates

or α-branched aldehydes afford significantly eroded levels of asymmetric induction (Eq. 13). Moreover, the (*E*) enolate equivalent **26** provides low levels of diastereoselection, although asymmetric induction in the major diastereomer is relatively good (90% ee) in one trial.



3.2.3. *Tryptophan-derived complexes*

Tryptophan-derived oxazaborolidine **50** has also undergone development as a catalyst for the asymmetric addition of trimethylsilyl enol ethers to various aldehydes.[26] Enantioselectivity in the catalyzed aldol reactions utilizing terminal enol silanes **23** and **51** is superior to that obtained in analogous CAB-catalyzed additions, with enantioselection generally exceeding 89% ee (Eq. 14). However, the oxazaborolidine **50** shares the relative lack of catalyst efficiency common to other boron-derived aldol catalysts, a fact alluded to by the high catalyst loadings required for these reactions and the high percentages of unreacted aldehyde that are recovered in several instances. Nonetheless, the oxazaborolidine catalyst **50** provides an expedient entry to optically active dihydropyrone derivatives via aldol addition reactions of dienyl enol silanes. Nucleophilicity of the silyloxy diene **52** is expressed exclusively by the enol silane terminus, providing the vinylogous ester **53** upon catalyzed aldol addition; acid-promoted cyclization then affords the dihydropyrone **54** with good to moderate levels of optical purity (Eq. 15).



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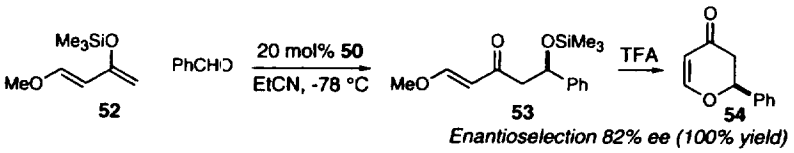


(15)

Despite the structural homology existing among the various oxazaborolidine Lewis acids, an analysis of aldol stereoselection derived from each of these catalysts reveals some divergence in the operative stereochemical control elements. Enantioselectivity in aldol reactions catalyzed by the disubstituted oxazaborolidines **30** and **31** or the valine-derived complex **38b** is consistent with steric shielding provided by the amino carboxylate alkyl substituent forcing aldehyde association to occur from the opposite face of the oxazaborolidine ring (Fig. 12). Pyramidalization of the sulfonamide nitrogen due to 'gearing' interactions with the backbone alkyl substituent in the resulting Lewis acid–base complex **55** then orients the sulfonamide residue to effectively shield the (*re*) aldehyde diastereoface.[30] In contrast, Lewis base coordination to boron in the tryptophan-derived catalyst **50** occurs *syn* to the indole substituent, suggestive of an attractive π–π interaction between the carbonyl and indole moieties in the activated aldehyde complex **56**.[31] The resulting preorganization of the coordinated aldehyde leaves the aldehyde (*re*) face exposed to nucleophilic attack.

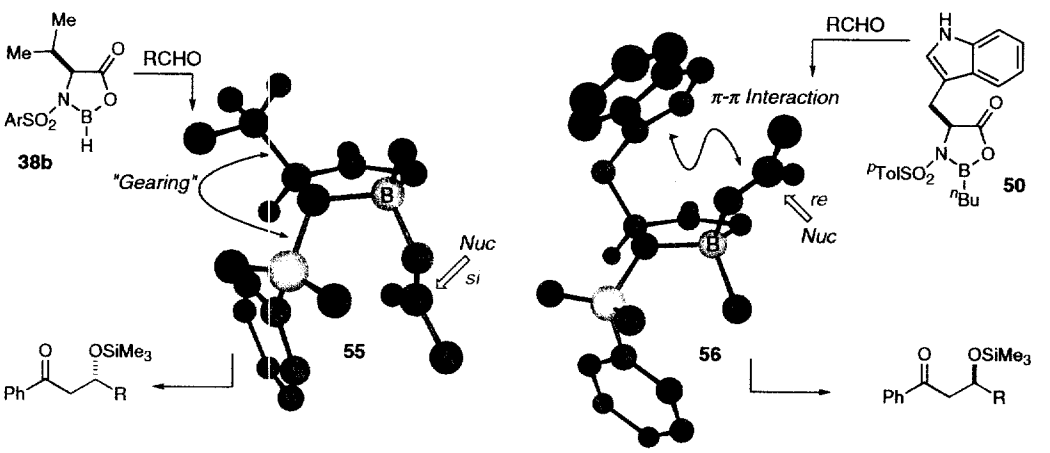


Fig. 12. Origin of enantioselectivity in oxazaborolidine-catalyzed aldol reactions

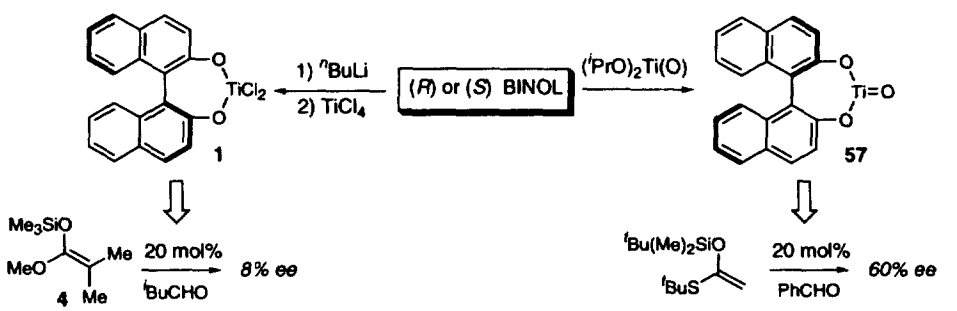
4. Early transition metal catalysts: Ti(IV)

4.1. Introduction

Titanium-based complexes are among the most widely utilized Lewis acids in organic chemistry and, as such, have undergone considerable development as vehicles for effecting asymmetric catalytic

Mukaiyama aldol reactions.[32] Indeed, the Ti(IV)-promoted addition of silyl ketene acetals to carbonyl compounds was among Mukaiyama's initial observations during preliminary investigations of these C–C bond constructions.[3c] Subsequent studies revealed that even relatively weak Lewis acids efficiently promoted these reactions, implicating modified Ti(IV) complexes possessing substantially attenuated Lewis acidities relative to $TiCl_4$ as potential catalysts for aldol addition reactions.[8b] As a result, tetra(alkoxy)titanium complexes were identified as effective catalysts for addition reactions employing a variety of silylated enolate equivalents. Furthermore, tetra(alkoxy)titanium complexes provided for the expedient synthesis of chiral catalyst structures by exploiting the facile substitution of monodentate alkoxide ligands for chelating optically active diols.

Among the numerous chiral Ti(IV) complexes that are available from optically active chelating diols, Lewis acids derived from binaphthol have undergone the largest degree of development as catalysts for the Mukaiyama aldol reaction.[33] Reetz was the first to report enantioselective Mukaiyama aldol reactions catalyzed by Ti(IV) complexes modified with chiral ligands.[6] The Ti–BINOL complex **1**, obtained by the substitution reaction of $TiCl_4$ with the bis-lithium alkoxide of (*S*)-binaphthol, catalyzed (20 mol%) the addition of MTMP (**4**) to isobutyraldehyde with minimal enantioselection (8% ee) (Scheme 2). A close structural analog to the putative Ti–BINOL catalyst investigated by Reetz, the chiral (BINOL)Ti–oxo complex **57**, catalyzes the addition of *t*-butyldimethylsilyl thioketene acetals to a limited number of aromatic and α,β-unsaturated aldehydes with good to modest levels of enantioselection.[34] These two early studies portend an observation that would pervade subsequent development of Ti-based Lewis acids as catalysts for asymmetric aldol reactions: reaction enantioselection is highly sensitive to minor variations in catalyst preparation and, presumably, the solution-state structure that is derived therefrom, resulting in nearly identical catalyst systems providing dramatically different results, ranging from negligible to nearly perfect asymmetric induction.



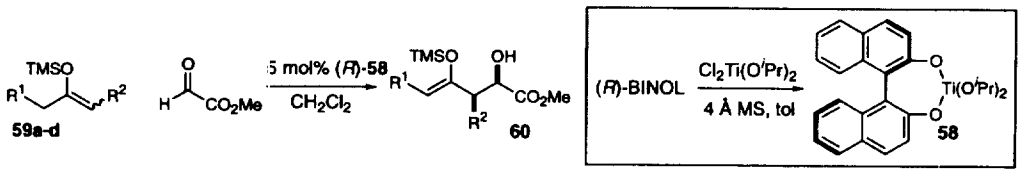
Scheme 2.

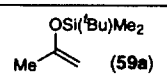
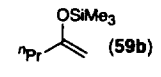
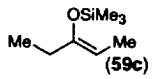
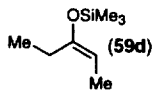
4.2. *Ti(IV)[BINOL]-catalyzed aldehyde ene reactions*

4.2.1. *Ene addition reactions of enolsilanes*

The Ti(IV)-BINOL complex **58** provides an exceptionally efficient catalyst for the asymmetric addition of silyl enol ethers to glyoxylate esters and silyl ketene acetals to aldehydes.[35,36] The Ti(IV) complex **58**, prepared by the exchange reaction of (*R*)-BINOL with $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ in the presence of 4 Å molecular sieves, catalyzes (5 mol%) the addition of the enol silanes **59a–d** to alkyl glyoxylate esters to afford the homoallylic alcohols **60** with ≥99% ee (54–75% yield) (Table 6).[37] Isolation of the enol silanes **60** as the sole products from these reactions was inconsistent with the mechanistic paradigm previously associated with Mukaiyama aldols, indicating Mukaiyama-type addition reactions to be mechanistically more complex than originally believed. A Lewis acid catalyzed ene reaction pathway was offered as

Table 6
Ti[BINOL]-catalyzed ene addition reactions



entry	enol silane	% yield	*syn*:*anti*	(Z):(E)	% ee
a	 (59a)	75	NA	NA	>99
b	 (59b)	67	NA	95:5	>99
c	 (59c)	58	98:2	94:6	99
d	 (59d)	54	98:2	94:6	99

a mechanistic alternative that accommodated the salient characteristics of these reactions including product structure, the olefin geometry of the derived enol silane adducts, and the insensitivity of reaction diastereoselection to enolate geometry (Fig. 13).[38] Thus, terminal enol silanes **59a** and **59b** provide the corresponding ene products with near perfect asymmetric induction and, in the latter case, high selectivity for the formation of the *Z* olefin isomer (*Z*:*E*=95:5). Substituted silyl enol ethers **59c** and **59d** afford analogously high enantiomeric excesses and excellent fidelity for the formation of the *syn* aldol diastereomer.

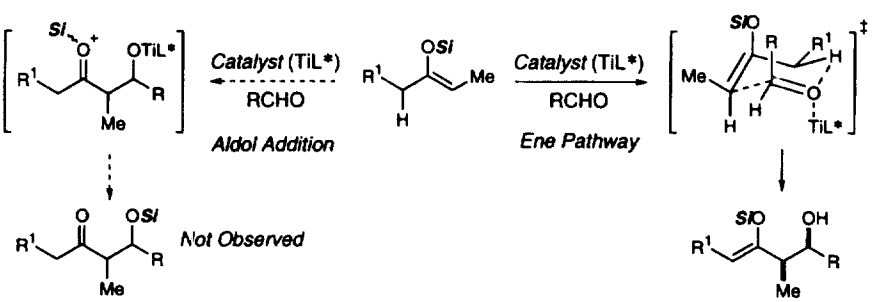


Fig. 13. Ene reaction pathway for enol silane addition reactions

The stereoselection exhibited by these reactions has been proposed to derive from the intrinsic conformational preferences associated with the competing ene reaction transition states (Fig. 14).[35] Reaction of *E* enol silanes provide *Z*, *syn* addition products **61** via the closed transition state assembly **62** that alleviates the developing *syn*-pentane interaction incurred between the pseudoaxial alkyl substituent (R_2) and titanium ion in the alternate assembly **63**. In the absence of incipient transannular interactions, the developing gauche interaction incurred between the ester residue and the enol silane substituent (R_2) in **64** appears to be the dominant influence in the reaction of *Z* enolate equivalents; the closed transition state **65** that eliminates this non-bonded interaction predicts the observed sense of stereoselection. There must exist a relatively subtle interplay of interactions that operate to differentiate the various transition

structures as reactions of *E* enol silanes appear to proceed via a chelated Lewis acid–glyoxylate complex (**62**) while a non-chelated Ti(IV)–aldehyde complex (**65**) seems involved in the reaction of *Z* enol silanes.[39] For example, the transannular interaction incurred in **63** is apparently sufficient to destabilize the transition state involving the monodentate Ti(IV)–glyoxylate complex, but is insufficient to disrupt organization of the alternative transition state **62** that incorporates the chelated glyoxylate complex. Furthermore, transition structure **65** neglects consideration of the transannular interaction that would exist between the pseudoaxial silyloxy and ester groups, raising as a possible reaction manifold addition of *Z* enol silanes via an open transition state that mitigates such steric interactions.[40]

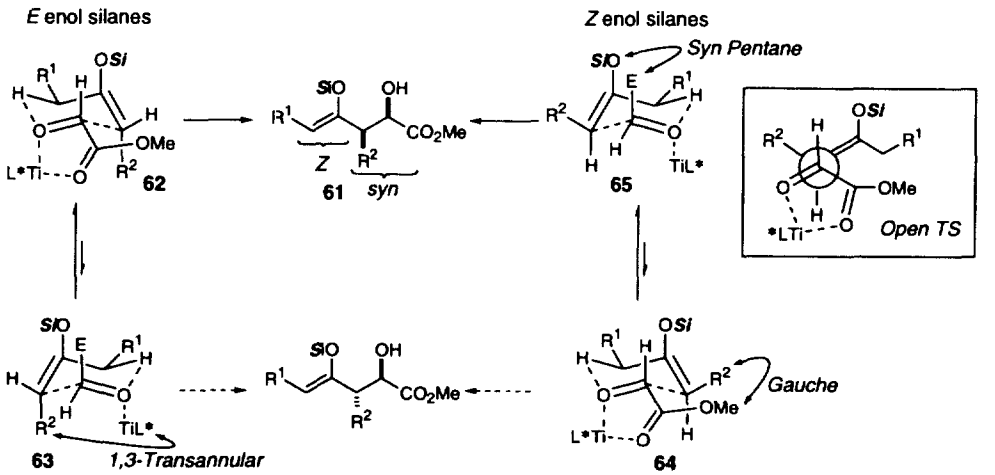
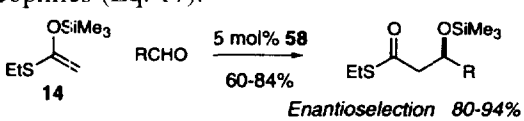
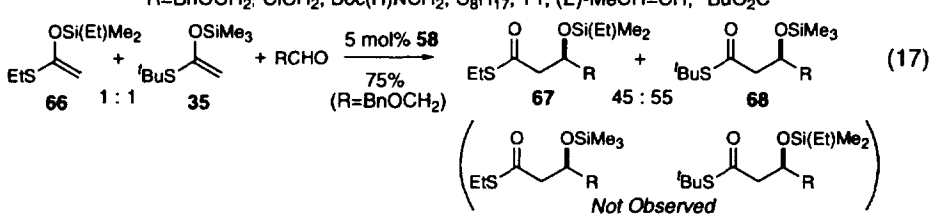


Fig. 14. Competing transition states for Ti[BINOL]-catalyzed ene reactions

4.2.2. *Silatropic ene reactions of silyl ketene acetals*

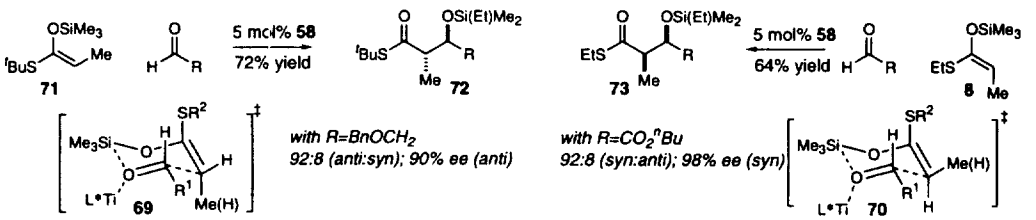
Mikami has also found a related ene reaction pathway to be operative in the Ti[BINOL]-catalyzed addition of silyl ketene acetals to aldehydes.[41] Low catalyst loadings of the titanium complex **58** (5 mol%) mediate the addition of thioacetate-derived enolate **14** to a number of functionalized aldehydes with uniformly high levels of enantioselectivity (Eq. 16).[42] A silatropic ene reaction pathway was hypothesized to be operative in these reactions based on a series of crossover experiments involving 'labeled' ketene acetal nucleophiles (Eq. 17).





The catalyzed addition of an equimolar mixture of silyl ketene acetals **35** and **66** to α-benzyloxy acetaldehyde affords a ~1:1 mixture of the two aldol products **67** and **68**, while none of the crossover products were detected. This result provides persuasive evidence for a reaction mechanism that proceeds

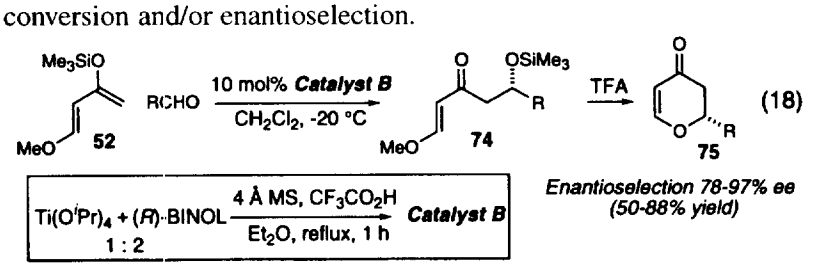
with concerted silyl group transfer to the incipient aldolate oxygen; a silatropic ene reaction (Scheme 3). Thus, C–C bond construction proceeds via the Zimmerman–Traxler transition state assemblies **69** and **70** involving concerted silicon transfer from the enolate to the electrophile oxygen. Relative stereocontrol in these reactions, (*Z*)-*O*-enolate equivalent **71** affords *anti* aldol adducts **72** while (*E*)-*O*-ketene acetal **8** provides the *syn* diastereomers **73**, is consistent with the documented relationship existing between metalloenolate geometry and aldol reaction diastereoselectivity derived from Zimmerman–Traxler transition states.[2] In order for the proposed closed transition structures to be operative, the coordination geometry typically associated with Lewis acid–aldehyde complexes must be relaxed to accommodate titanium coordiantion *syn* to the aldehyde alkyl residue or, at least, significantly out of the carbonyl π-plane.[43]



Scheme 3.

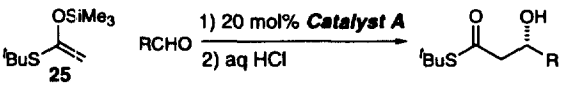
4.3. *Ti(Oi-Pr)4[BINOL] catalyst systems*

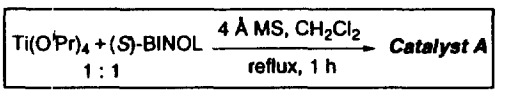
The striking contrast in results obtained in the Reetz and Mikami investigations of closely related reactions employing catalyst systems that are proposed to be nearly identical in constitution, highlights the pronounced sensitivity to reaction variables that characterize asymmetric Ti(IV)-catalyzed aldol reactions. This aspect of Ti-based Mukaiyama aldol catalysts was further emphasized during Keck's development of Ti(IV) complexes derived from Ti(O*i*-Pr)$_4$ and BINOL [1:1 Ti(O*i*-Pr)$_4$:BINOL=Catalyst A] as catalysts for the enantioselective addition of acetate enolate equivalent **25** to aldehydes (Table 7).[44,45] Ultimately, the derived catalysts were found to provide excellent levels of enantioselectivity for aldol additions employing an array of structurally diverse aldehydes. Some generality in nucleophile structure is also offered by these catalyst systems as silyloxy(dienes) **52** also add to aldehydes with good to excellent asymmetric induction using a similar Ti(O*i*-Pr)$_4$[BINOL]-derived catalyst system [2:1 Ti(O*i*-Pr)$_4$:BINOL=Catalyst B] (Eq. 18).[46] The resulting β-hydroxy vinylogous esters **74** are converted to the corresponding optically active dihydropyrone derivatives **75** upon treatment with acid. However, optimum chemical and optical yields in the Ti(O*i*-Pr)$_4$[BINOL]-catalyzed aldol reactions are achieved only within a narrow reaction parameter window; conversion and enantioselection are extremely sensitive to the method of catalyst preparation, reaction solvent, and catalyst loadings. Relatively minor deviations from this optimized reaction protocol (e.g., use of 10 mol% catalyst rather than the 20 mol% specified) result in reduced conversion and/or enantioselection.



Keck emphasizes, and these sentiments are reinforced here, that little to no conclusive evidence exists concerning the solution state structures of the Ti(IV)[BINOL] complexes utilized in this study or the

Table 7
Ti(O*i*-Pr)$_4$[BINOL]-catalyzed Mukaiyama aldol reactions



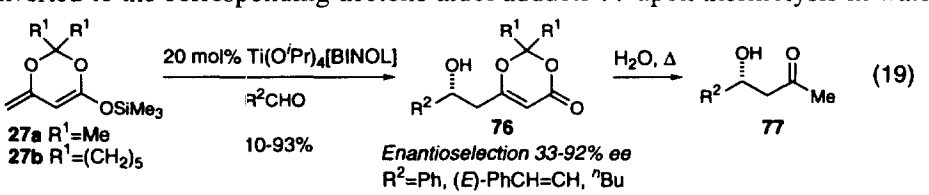


entry	aldehyde	% yield	% ee[a]
a	PhCHO	90	97
b	PhCHO	71	97[b]
c	PhCHO	45	92[c]
d	$Ph(CH_2)_2CHO$	80	97
e	$^nC_8H_{17}CHO$	74	98
f	(2-furyl)CHO	88	>98
g	$^cC_6H_{11}CHO$	70	89
h	(*E*)-PhCH=CHCHO	76	89
i	$BnOCH_2CHO$	82	>98

[a]Reported values are for reactions employing 20 mol% catalyst and 0.25M in aldehyde, except entries b and c. [b]Reaction using 10 mol% catalyst. [c]Reaction 0.50M in PhCHO.

other investigations involving Ti-based catalyst systems. The structural representations of the presumed Ti-based catalysts presented herein are intended to represent only the metal:ligand stoichiometry used in the published preparation of these catalysts and are not intended to depict solution-state structures of the catalytically active species. Indeed, the nonlinear relationship that exists between catalyst optical purity and reaction enantioselection documented by Keck[47] and Mikami[48] in related Ti–BINOL-catalyzed reactions is indicative of catalyst aggregation in solution.

Dienyl ketene acetal **27a** and **b**, prepared from the corresponding dioxinone derivative, provide limited degrees of success in Ti(O*i*-Pr)$_4$[BINOL]-catalyzed addition reactions (Eq. 19).[49] Chemical and optical yields of the β-hydroxy dioxinone aldol adducts **76** vary considerably with chemical yields generally below 60% and enantioselection exceeding 90% ee in only two instances. The dioxinone aldol products **76** can be converted to the corresponding acetone aldol adducts **77** upon thermolysis in water.



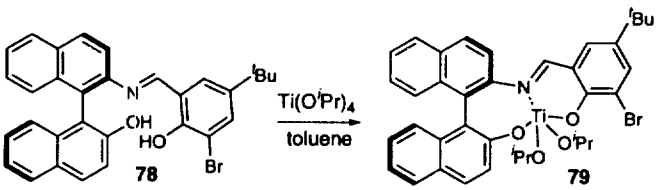
(19)

4.4. *Ti(IV)–Schiff base catalysts*

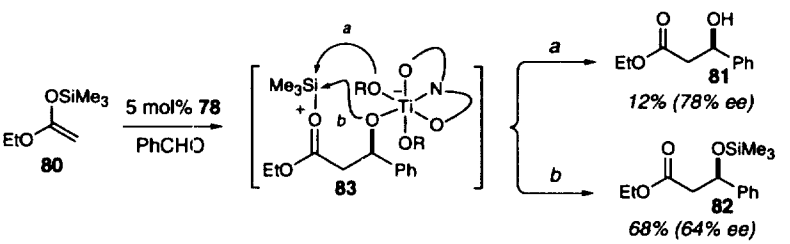
4.4.1. *Salicylate-modified complexes for silyl ketene acetal additions*

Analysis of the preceding investigations reveals a conspicuous lack of catalyst systems that effectively mediate the aldol addition of simple *O*-alkyl ketene acetals with uniformly high enantioselection. The amplified reactivity and sensitivity of *O*-alkyl silyl ketene acetals relative to their thioketene and silyl enol ether analogs is considered a contributory factor in the generally inferior results obtained in catalyzed Mukaiyama aldol reactions employing this class of nucleophile.[50] Mechanistic investigations suggest that the intervention of a silicon-catalyzed reaction manifold that is independent of the initial

chiral metal catalyst is responsible for the observed lack of asymmetric induction derived from *O*-alkyl ketene acetal addition reactions.[12] These mechanistic considerations proved instrumental in the design and development of chiral Ti–Schiff base complexes that are remarkably efficient catalysts for the enantioselective addition of simple *O*-alkyl ketene acetals to a wide array of functionalized aldehyde electrophiles.[51] The parent Ti(IV) catalyst is prepared by the reaction of the axially chiral Schiff base **78** with Ti(O*i*-Pr)$_4$ to provide the putative catalyst structure **79** (Eq. 20). In a preliminary investigation, **79** was found to catalyze the aldol addition of the ethyl acetate derived ketene acetal **80**, affording a mixture of unsilylated and silylated aldol adducts, **81** (78% ee) and **82** (64% ee), respectively (Eq. 21).



(20)



(21)

Isolation of the carbinol **81** was consistent with a reaction mechanism proceeding through Ti–aldolate **83** in which indiscriminate silicon transfer to either an isopropoxide ligand or the aldolate would account for the observed product distribution. Efficient transfer of the silicon residue to the aldolate oxygen had previously been identified as a prerequisite for limiting silicon-catalyzed reaction pathways that might be initiated by silyl oxocarbenium ion intermediates similar to **83**. As a means of engineering catalyst structures that would provide a mechanism for facilitating the requisite silicon-to-aldolate oxygen transfer, modified catalyst complexes incorporating salicylic acid-derived ligands were investigated (Fig. 15). Indeed, the Schiff base complex **84** incorporating the 3,5-di-*t*-butylsalicylic acid ligand afforded dramatically enhanced yields, enantioselectivity, and catalyst efficiency relative to the parent Schiff base complex **79**. The salicylic acid ligand is postulated to function as a silyl group shuttle, scavenging electrophilic silicon species at the stage of the silyl oxenium ion intermediate **85**. The resulting silyl carboxylate **86** is then suitably disposed to provide for eventual silylation of the aldolate oxygen, the most nucleophilic of the oxygen ligands arrayed about the Ti ion. Thus, aldolate silylation liberates the protected aldol adduct and reestablishes the salicylic acid chelate in regenerating the catalyst complex **84**. This mechanistic construct finds a close analogy to the silicon shuttle mechanism proposed to be operative in oxazaborolidine-catalyzed aldol reactions.[23]

The Ti(IV)–Schiff base catalyst system **79** developed by Carreira is unique among the aldol catalysts reported to date in terms of operational simplicity, catalyst efficiency, chirality transfer, and substrate generality. Enolate equivalents derived from inexpensive, readily available methyl or ethyl acetate (**87**) react with alkenyl, alkynyl, aromatic, and functionalized aliphatic aldehydes using the Ti–salicylate catalyst **84** to afford the corresponding β-hydroxy esters **88** with near perfect enantioselection (≥94% ee) (Table 8). Furthermore, high yields of the enantiomerically enriched aldol adducts are obtained using catalyst loadings as low as 2 mol% and do not require slow addition protocols. The Ti(IV)–Schiff base catalyst exhibits similarly high activity and enantioselectivity in addition reactions employing the dienyl

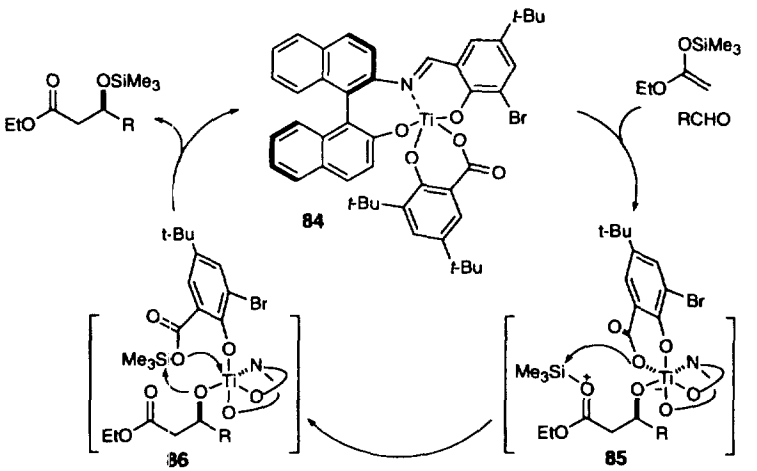
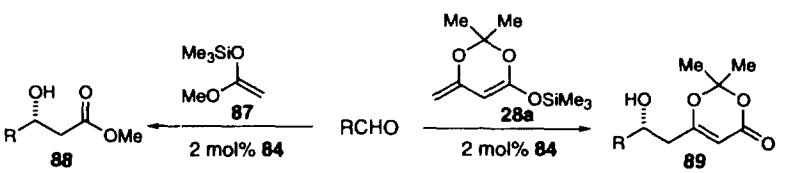


Fig. 15. Silicon shuttle mechanism for Ti(IV)–salicylate catalyzed aldol

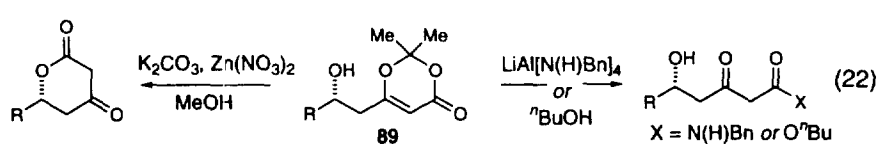
Table 8
Ti[salicylate]-catalyzed addition of silyl ketene acetals



entry	aldehyde	ketene acetal 87 % ee[a]	ketene acetal 28a % ee[a]
a	$^{i}Pr_3Si$—≡—CHO	97	91
b	$TBSOCH_2$—≡—CHO	96	—
c	TBSO— /\ —CHO	—	94
d	Ph— /\ —CHO	94	80
e	PhCHO	96	84
f	$^{c}C_6H_{11}CHO$	95	—
g	Me— /\/\ —CHO	98	92

[a]Yields for two steps (addition and desilylation) range from 72 to 98%.

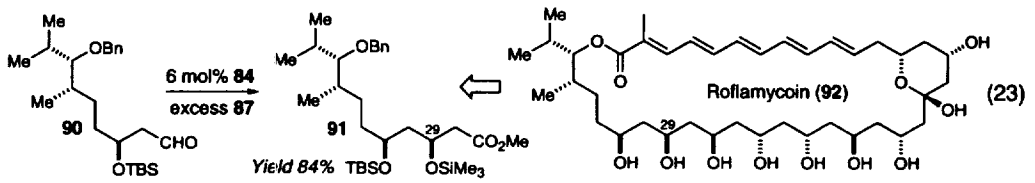
ketene acetal **28a**; the derived optically active β-hydroxy dioxinones **89** represent masked acetoacetate aldol adducts and provide versatile precursors to δ-hydroxy-β-keto esters, amides and β-keto-δ-lactones (Eq. 22).[52]



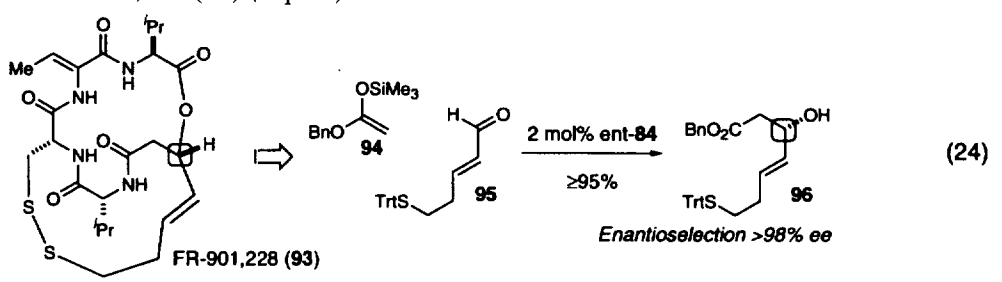
(22)

The enantioselective acetate aldol bond constructions accessed by Ti–salicyclate **84**-catalyzed Mukaiyama aldol additions have been exploited in the context of several total syntheses. Catalyzed addition of the acetate enolate equivalent **87** to the highly functionalized aldehyde **90** provides the

all *syn* triol **91**, thereby installing the C_{29} stereocenter in a major segment of the macrolide antibiotic roflamycoin (**92**) (Eq. 23).[53]



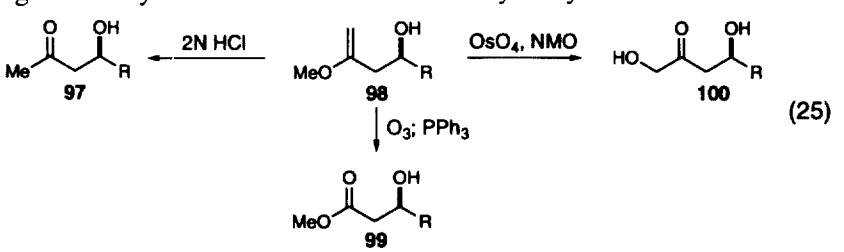
Significantly, reaction stereoselection is consistent with the catalyst complex operating as the sole stereochemical control element and does not appear to be complicated by resident chirality within the aldehyde reaction component.[54] The Carriera catalyst also serves as the chiral source for introduction of the only stereogenic center derived from non-natural sources in the total synthesis of the antitumor depsipeptide FR-901,228 (**93**) (Eq. 24).[55]



Thus, addition of the *O*-benzyl silyl ketene acetal **94** to the α,β-unsaturated aldehyde **95** proceeds to afford the optically active heptenoic acid derivative **96** with near-perfect enantioselection (>98% ee, ≥95% yield).

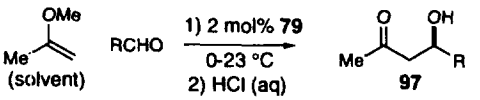
4.4.2. *Catalyzed additions of O-alkyl enol ethers*

Aldol reaction protocols that would eliminate the procedural requirement for generating the enolate equivalent in a separate operation, either by incorporating enolate formation into the catalytic cycle or by using commercially available enolate surrogates, would impart considerable operational simplification to Mukaiyama aldol reactions. The latter strategy has been successfully implemented in the context of Ti–Schiff base catalyzed aldol additions employing commercially available 2-methoxypropene as the requisite latent enolates (Table 9).[56] The acetone aldol adducts **97**, derived from the hydrolysis of the initial enol ether adduct, are produced with very high enantioselectivity in reactions employing a variety of functionalized aldehydes. In addition to the acetone aldols **97**, the initial enol ether reaction products **98** provide a conduit to a number of aldol adducts upon differential functionalization of the enol ether function, including the methyl acetate aldol **99** and the α-hydroxyacetone aldol adduct **100** (Eq. 25).



The catalyst complex **79** required for executing these reactions further distinguishes them from their Mukaiyama aldol counterparts; reactions employing the 2-methoxypropene nucleophile do not offer

Table 9
Catalyzed additions of 2-methoxypropene



entry	aldehyde	% yield	% ee
a	$Ph(CH_2)_3$—≡—CHO	99	98
b	$TBSOCH_2$—≡—CHO	85	93
c	Ph—≡—CHO	99	91
d	Ph, CHO	98	90
e	PhCHO	83	66
f	$^cC_6H_{11}CHO$	79	75

the potential for establishing a competitive silicon-catalyzed reaction pathway thus obviating the need for catalyst structures incorporating the salicylic acid ligand. The modest attenuation in electrophile generality (Table 9, entries e and f) associated with the 2-methoxypropene additions relative to the Mukaiyama reactions suggest that the salicylic acid ligand may play a small role in defining the stereochemical outcome of the catalyzed silyl ketene acetal aldol reactions.

5. Late transition metal catalysts: Cu(II)

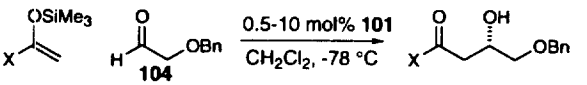
5.1. Cu(II)[pyridine(bisoxazoline)]-catalyzed additions to α-benzyloxyacetaldehyde

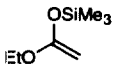
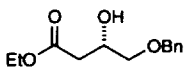
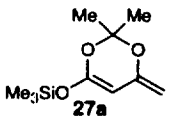
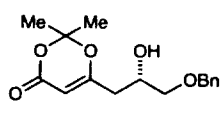
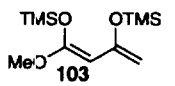
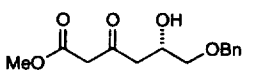
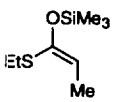
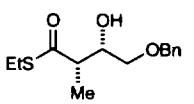
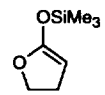
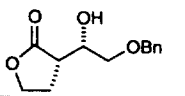
Cationic Cu(II) complexes are among the rare examples of late transition metal Lewis acid catalysts that have been successfully applied to organic reaction methodology. Cationic Cu(II)-complexes incorporating chiral pyridine–bisoxazoline (pybox) and bidentate bisoxazoline ligands, **101** and **102** respectively, provide exceptional levels of asymmetric induction in Mukaiyama aldol reactions employing a variety of structurally diverse enolate equivalents (Table 10).[57] Low catalyst loadings (5 mol%) of the cationic Cu(II) complex **101** mediate the addition of *S*-alkyl and *O*-alkyl silyl ketene acetals, and the acetoacetate enolate equivalents **27a** and **103** to α-benzyloxyacetaldehyde (**104**) with enantioselectivities exceeding 92% ee (≥90% yield). Substituted enolate equivalents are also functional nucleophiles providing the derived propionate aldol adducts with excellent relative and absolute stereochemical control (entries d and e). Electrophilic reaction components capable of engaging in five-membered chelates with the catalyst appear to be a prerequisite for attaining high levels of asymmetric induction as non-chelating electrophiles, or those providing expanded chelate sizes, afford significantly reduced enantioselection (≤56% ee).

5.2. Cu(II)[bisoxazoline]-catalyzed additions to pyruvate esters

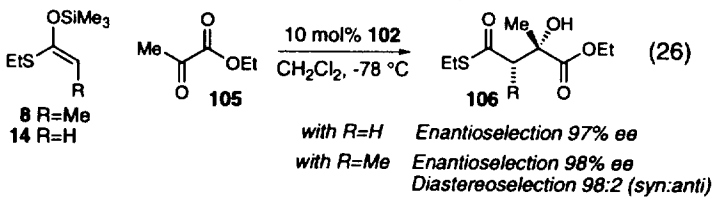
Mukaiyama aldol reactions employing carbonyl electrophiles other than aldehydes are relatively rare and, as a result, reactions utilizing ketone electrophiles as a means of preparing optically active tertiary alcohol derivatives have received little attention.[58] Copper(II)[bisoxazoline]-catalyzed aldol additions to pyruvate esters successfully address this issue and provide an efficient synthesis of optically active tertiary alcohols.[59] Acetate and propionate enolate equivalents, **8** and **14** respectively, undergo catalyzed

Table 10
Cu(II)[pybox]-catalyzed aldol reactions

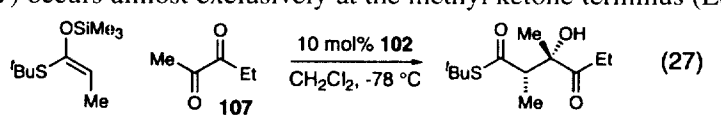


entry	ketene acetal	product	% yield	% ee
a			99	98
b			94	92
c			99	97
d			90	97
e			95	95

addition to various pyruvate ester electrophiles (**105**) to afford the derived optically active succinate ester derivatives **106** with excellent absolute and, in the latter case, relative stereochemical control (Eq. 26).



Reaction enantioselection is insensitive to structural variations in the pyruvate ester, tolerating a number of *O*-alkyl and ketone substituents; only branching at the ketone terminus results in significant erosion of enantioselection. However, these reactions exhibited an especially pronounced sensitivity to subtle steric perturbations about the reacting centers within the electrophile; catalyzed ketene acetal addition to 2,3-pentanedione (**107**) occurs almost exclusively at the methyl ketone terminus (Eq. 27).



The mechanistic details of these Cu(II)-catalyzed Mukaiyama aldol reactions are especially intriguing in considering that preceding investigations unanimously agreed upon the deleterious effect of adventitious silicon catalysis has on asymmetric induction. Crossover experiments reveal that intermolecular silyl group transfer is a general phenomenon in Cu(II)-catalyzed aldol reactions, indicating that electrophilic silicon species are available for intermolecular reaction processes, including silicon-catalyzed reaction pathways. The fact that high levels of asymmetric induction are attained despite

this phenomenon suggests that electrophilic silicon species are not competitive catalysts relative to the chiral Cu(II) complexes. Indeed, addition of TMSOTf to the Cu(II)[bisoxazoline]-catalyzed addition of hindered nucleophiles to pyruvate esters accelerated aldol reaction rates with no loss in enantioselectivity; silylation of the intervening copper aldolate and the resulting catalyst turnover has been suggested as the origin of the observed rate acceleration.

Catalyst–electrophile structures have been proposed as predictive models for the Cu(II)-catalyzed α-benzyloxyacetaldehyde and pyruvate ester aldol reactions (Fig. 16). The regular square pyramid geometry of the Cu(II)[pybox]–aldehyde complex **108**, alluded to by ESR spectroscopy, results in effective shielding of the *re* aldehyde face by the pybox phenyl substituent, affording the observed (*S*)-β-hydroxy ester aldol adducts. Asymmetric induction derived from Cu(II) complexes incorporating bidentate bisoxazoline ligands is consistent with the reaction proceeding via the intermediacy of a square planar Cu(II)-α-diketone complex **109**. Projection of the proximate alkyl substituent over the π-system of the reacting carbonyl function effectively differentiates the prochiral faces of the pyruvate electrophiles.

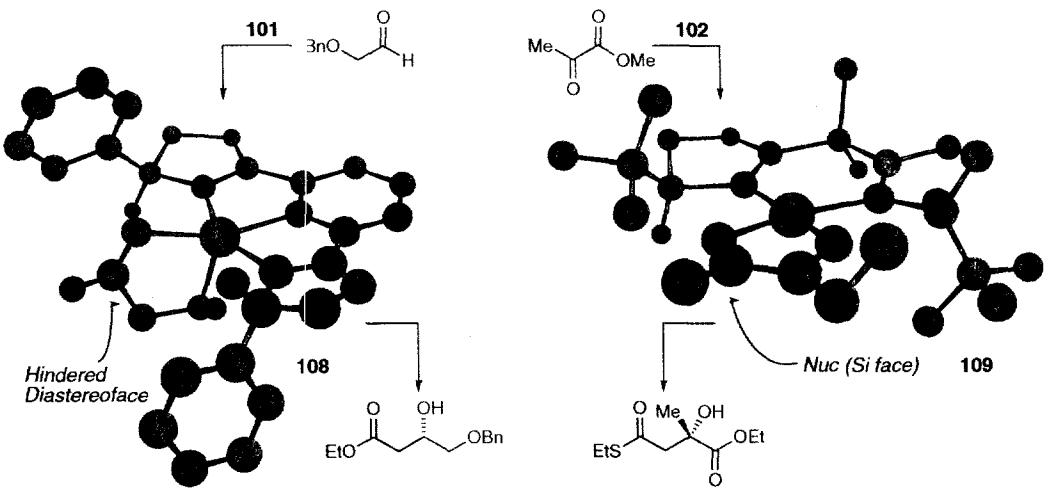
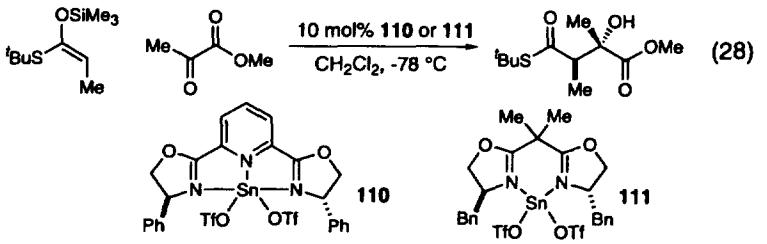
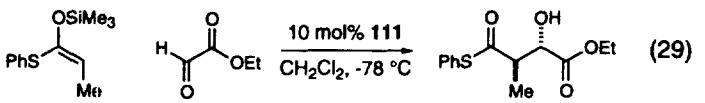


Fig. 16. Cu(II)[bisoxazoline]-electrophile complexes

Divalent tin complexes have also been developed as effective catalysts for aldol additions involving α-dicarbonyl electrophiles.[60,61] The Sn(II)–pyridyl bisoxazoline complex **110** catalyzes the highly enantioselective *S*-alkyl ketene acetal–pyruvate aldol addition with a complete reversal in diastereoselection (99:1 *anti:syn*) relative to the analogous *syn*-selective Cu(II)–bisoxazoline catalyzed reaction (Eq. 28). The Sn(II)–bisoxazoline complex **111** is an equally efficient catalyst for the pyruvate aldol additions as well as ketene acetal additions to glyoxylate esters, each providing the 2,3-*anti* aldol adducts characteristic of these Sn(II)-catalyzed reactions (Eq. 29).



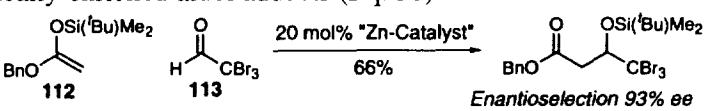
catalyst	*anti:syn*	% ee	% yield
110	99:1	99	94
111	92:8	94	—



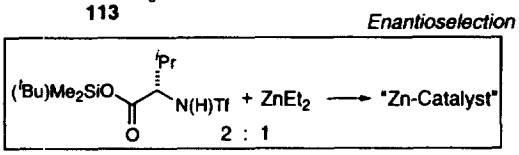
Enantioselection 95% ee
Diastereoselection 90:10 (anti:syn)

6. Group 2B, lanthanide and other late transition metal catalysts

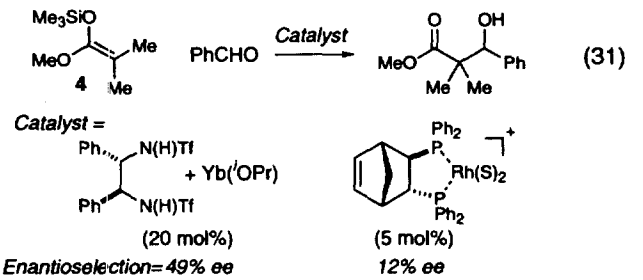
Limited degrees of success have been achieved in developing optically active Rh(I)-,[62] Zn(II)-,[63] and lanthanide-based[64] complexes as catalysts for enantioselective Mukaiyama aldol reactions. Divalent zinc complexes modified with α-amino acid derived triflamide ligands mediate the addition of *O*-alkyl silyl ketene acetal **112** to a variety of aldehydes. However, the Zn(II)-catalyzed aldol reactions impose especially rigid constraints on aldehyde structure as only α,α,α-tribromoacetaldehyde (**113**) provides highly enantiomerically enriched aldol adducts (Eq. 30).



Enantioselection 93% ee



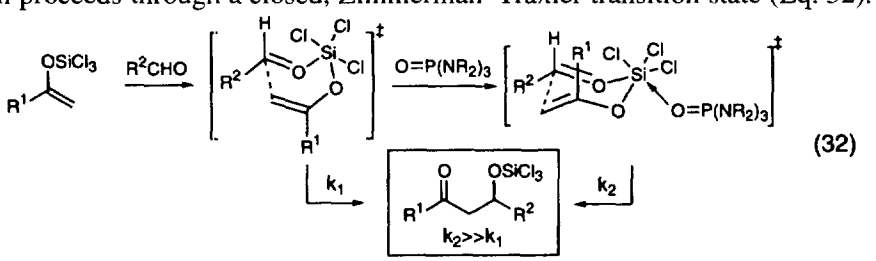
Chiral lanthanide-based catalysts derived from the corresponding lanthanide triflates and optically active bis(triflamide) ligands provide only moderate optical and chemical yields in the standard test reaction involving MTMP (**4**)/aryl aldehyde aldols (Eq. 31). The complex coordination chemistry associated with the lanthanide metals makes meaningful predictions concerning catalyst or transition state structure exceedingly difficult for this catalyst system. Cationic Rh(I) complexes incorporating chiral chelating bisphosphine ligands exhibit modest catalytic activity in the identical MTMP (**4**)/benzaldehyde addition reaction, but afford negligible enantioselection (≤12% ee) (Eq. 31).[65]



7. Nucleophilic (Lewis basic) catalysts

7.1. Additions of (trichlorosilyloxy)alkenes

Catalytic asymmetric aldol reaction design has been predicated almost exclusively on generating activated, facially discriminated electrophiles by virtue of complexation with a chiral Lewis acid catalyst. A less explored strategy for catalyzing Mukaiyama-type bond constructions involves the transient activation of the latent enolate equivalent via Lewis base coordination to the enolate silicon residue (Fig. 17).[66] Latent enolate equivalents incorporating trichlorosilyl groups are subject to this type of Lewis base activation, an observation that has resulted in the realization of Lewis base catalyzed aldol additions.[67] The addition of (trichlorosilyloxy)alkenes (enol ethers and ketene acetals) to aldehyde electrophiles is initiated by Lewis acid–base preassociation of the nucleophile and electrophile, dictating that the reaction proceeds through a closed, Zimmerman–Traxler transition state (Eq. 32).



While reaction of the resulting nucleophile–electrophile aggregate is often spontaneous, aldol reaction rates are substantially accelerated by substoichiometric quantities of Lewis base addends. Based on these observations, a series of optically active Lewis basic catalysts have been developed for asymmetric aldol addition reactions involving (trichlorosilyloxy)alkenes; the optically active phosphoramide **114** catalyzes the highly stereoselective addition of the trichlorosilyl enolate **115** to aryl and α,β-unsaturated aldehydes (84–96% ee) (Eq. 33). Enantioselection in reactions employing the trichlorosilyl ketene acetal nucleophile **116** is eroded considerably relative to the enol silane aldols, presumably due to the intervention of the uncatalyzed reaction pathway (Eq. 34). Computational investigations of Lewis base promoted aldehyde additions of allyl trichlorosilanes suggest that amplified alkene nucleophilicity engendered upon silicon–phosphoramide association and/or the spatial compression of the reacting centers elicited by the accompanying change in silicon geometry from trigonal bipyramidal to octahedral is responsible for the observed Lewis base acceleration.[68]

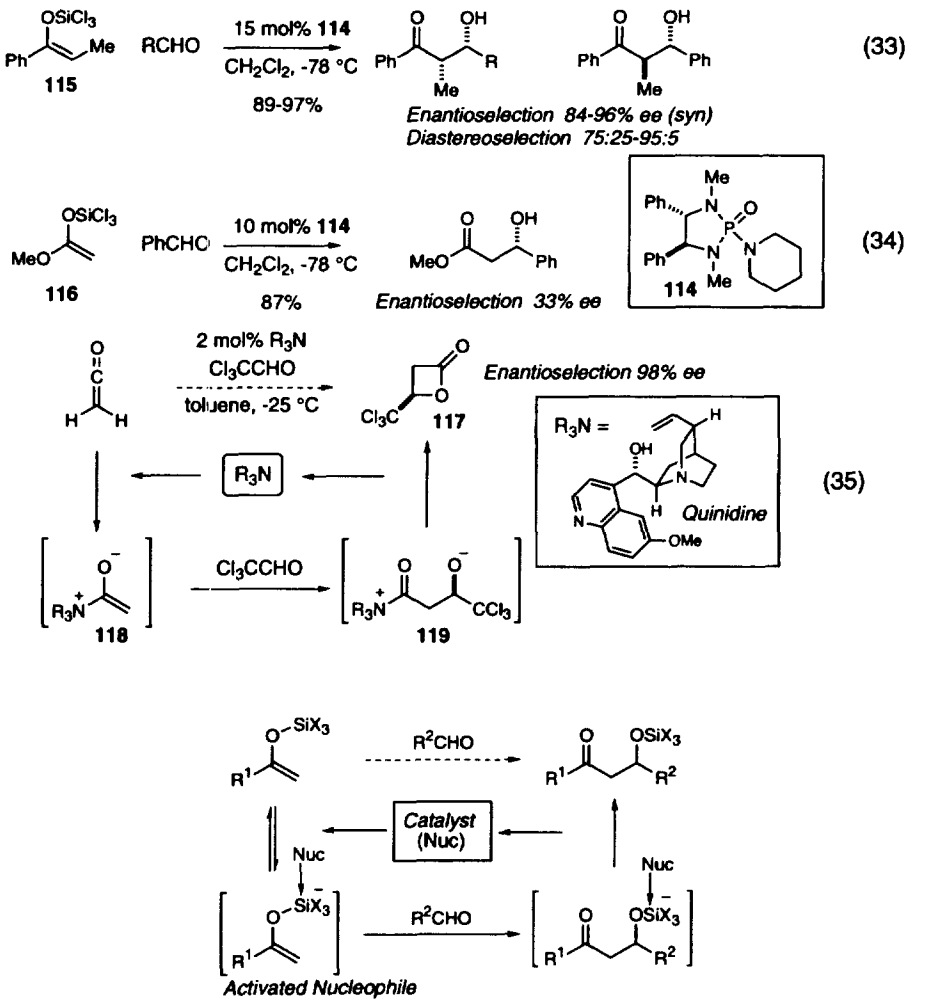


Fig. 17. Lewis base-catalyzed aldol additions of (silyloxy)alkenes

7.2. *Additions of latent enolate equivalents derived from ketene*

Optically active tertiary amine bases (quinine and quinidine) catalyze the addition of ketene to electron-deficient aldehydes and ketones, providing the derived 2-oxetanones **117** with high optical purity (Eq. 35).[69] The chiral ammonium enolate **118** resulting from nucleophilic addition of the amine catalyst to ketene is postulated to be the reactive species in these processes. Subsequent to enolate addition, lactonization ensues upon addition of the aldolate oxygen to the acyl ammonium ion **119** with concomitant regeneration of the amine catalyst. These cyclocondensation reactions represent an interesting example in which the latent nucleophilic reaction component is not derived from an enol ether functionality.[70]

8. Conclusion

Substantial progress has been realized in rendering asymmetric catalytic aldol reactions as reliable, easily executed organic reaction methodology. While efficiency and selectivity provide the benchmarks by which the various catalysts systems are evaluated, the extent to which each of these investigations built upon and benefited from the data and observations accumulated in preceding studies cannot be underappreciated. Similarly, the investigations detailed in this account will undoubtedly serve to accelerate research directed toward addressing the issues that confront further development of these important C–C bond constructions. The fact that little if any information exists regarding the structure of the catalytically active species or the mechanism by which these catalysts translate chirality to the incipient C–C bond is among the most prominent of these issues. Insights in these areas will greatly facilitate further developments of catalyst systems that will provide high levels of stereoselection in aldol reactions involving a broad range of enolate and electrophile structures. Future developments toward the reliable and efficient production of propionate aldol adducts with well-defined relative and absolute stereochemistry, and the preparation of optically active materials derived from latent enolate additions to eletrophiles other than aldehydes (e.g., ketones, acetals, imines) will serve to further expand the already considerable impact of these reactions on asymmetric organic synthesis.

Acknowledgements

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