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Review

Metal-Catalyzed Asymmetric Aldol Reactions

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A reação aldólica é uma das ferramentas mais poderosas e versáteis para a construção de ligações C–C. Tradicionalmente, esta reação foi desenvolvida em sua versão estequiométrica, no entanto, grandes esforços no desenvolvimento de catalisadores quirais para reações aldólicas foram realizados nos últimos anos. Desta forma, neste artigo de revisão, é discutido o desenvolvimento de catalisadores metálicos em reação aldólica do tipo Mukaiyama, reação aldólica redutiva e reação aldólica direta. Além disto, a aplicação destes catalisadores na síntese total de moléculas complexas será abordada.

The aldol reaction is one of the most powerful and versatile methods for the construction of C–C bonds. Traditionally, this reaction was developed in a stoichiometric version; however, great efforts in the development of chiral catalysts for aldol reactions were performed in recent years. Thus, in this review article, the development of metal-mediated chiral catalysts in Mukaiyama-type aldol reaction, reductive aldol reaction and direct aldol reaction are discussed. Moreover, the application of these catalysts in the total synthesis of complex molecules is discussed.

Keywords: aldol reactions, asymmetric induction, chiral ligands, total synthesis

1. Introduction

The aldol reaction is one of the most powerful and versatile methods in the chemistry of carbonyl compounds for the construction of C–C bonds in a regio-, stereo- and enantioselective manner.[1] It is well known that the relative configuration of the aldol adduct (in those reactions that proceed by a cyclic six member transition state) is controlled by the geometry of the propionate-type enolate, in which *Z*-enolates lead to preferential formation of the 1,2-*syn* products and *E*-enolates to 1,2-*anti* products. These observations can be rationalized from the Zimmerman-Traxler model. In this proposal, the aldol reaction undergoes a chair-type six-membered cyclic transition state, being diastereoselectivity dependent on the steric demand of the enolate and the aldehyde substituents (Scheme 1).[2]

According to this model, the R^3 aldehyde substituent occupies, preferably, the pseudo-equatorial position, eliminating unfavorable 1,3-diaxial interactions between the R^3 group and the R^1 and L substituents, thus providing a transition state of lower energy. In the case of the *E*-enolates, 1,2-*anti* aldol adducts are preferably formed, since in the transition state **TS1** the 1,3-diaxial interactions are minimized with respect to transition state **TS2**, which leads to the formation of 1,2-*syn* aldol adduct.

In the case of the *Z*-enolates, the formation of 1,2-*anti* aldol adduct is disfavored due to 1,3-diaxial interactions present in the transition state **TS3**. Thus, the 1,2-*syn* aldol adduct is formed preferentially, since in the transition state **TS4** these repulsions are minimized. Thus, when preformed chiral enolates are employed together with aldehydes, it is possible to obtain aldol adducts with excellent levels of asymmetric induction.[3]

The aim of this review article is to discuss representative studies involving stereoselective aldol reactions using metal-mediated chiral catalysis with special attention to selectivity, substrate scope, current limitations and application in the total synthesis of natural products.[4,5] The literature is covered up to early 2012.

2. Crown Ethers and Related Ligands in Lanthanide-Catalyzed Mukaiyama Aldol Reactions

Reactions in aqueous media have several advantages over conventional dry synthetic procedures. In this context,

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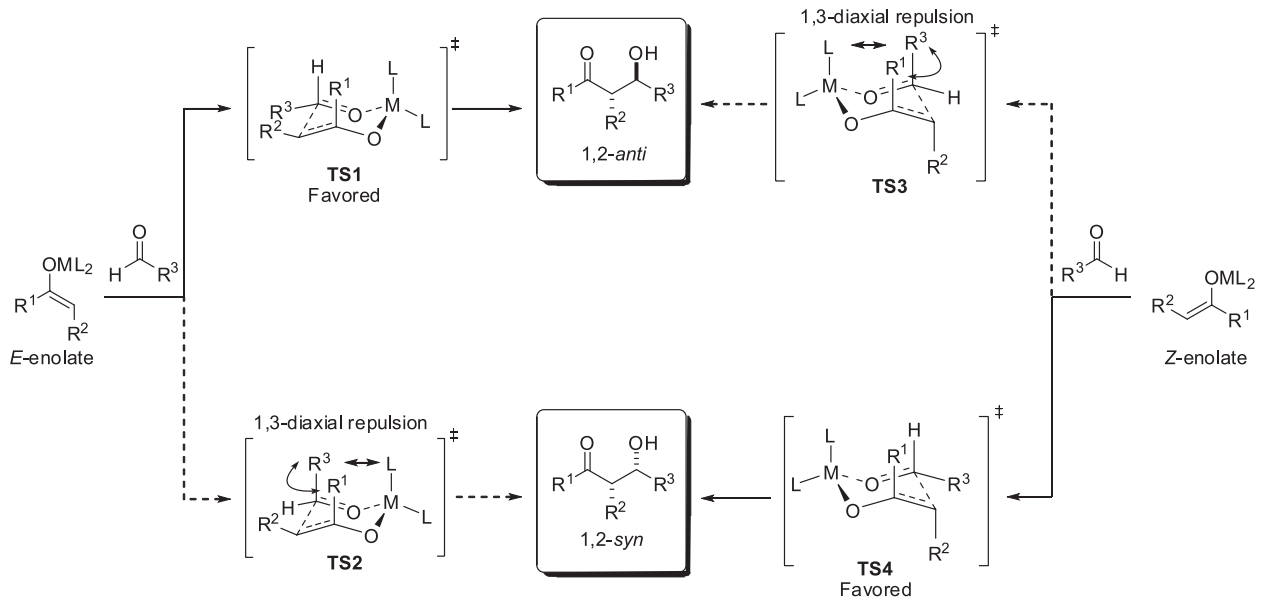


Scheme 1. Zimmerman-Traxler transition states.

rare earth metal triflates ($RE(OTf)_3$), which are water-tolerant Lewis acids, have been used in aldol reactions and can be effortlessly recovered and reused.[6]

Kobayashi and co-workers[7] showed that in the Mukaiyama aldol reactions involving chiral crown ether ligands that bind strongly with the larger rare earth metal cations (such as La, Ce, Pr and Nd), the ligands do not decrease the Lewis acid ability for the enantioselective transformations. The Mukaiyama aldol reactions in aqueous media between enolsilanes **1** and **2** and α,β-unsaturated aldehydes, mediated by $Pr(OTf)_3$ and *bis*-pyridino-18-crown-6 ether **15**, gave good to high yields and high diastereo- and enantioselectivities in favor of the corresponding *syn* aldol adducts (Table 1, entries 1-13). However, aliphatic aldehyde **12** was not a suitable substrate for this transformation (entry 14).

In 2010, Allen and co-workers[8] designed a new class of multidentate ligand **16** for aqueous europium-catalyzed Mukaiyama aldol reactions involving enolsilanes **2**. The complex Eu^{3+}·**16** yielded the corresponding aldol adducts in unprecedented enantioselectivities (90 to 96% *ee*) and diastereoselectivities (21:1 to 32:1) for aliphatic, aryl and α,β-unsaturated aldehydes (Table 1, entries 15-19).

For ligand **15**, the authors proposed transition state **TS5**, taking into account the coordination of the aldehyde to the Pr^{3+} cation and the shielding of the *Si* face of the aldehyde by the axially oriented methyl substituent of the Pr^{3+}·**15** complex, thus directing the attack of the enolate to the *Re* face of the aldehyde (Scheme 2).[7] For ligand **16**, in which the aldehyde is complexed with the Eu^{3+} cation, the authors proposed that the *Si* face of the aldehyde is blocked by the ester substituent, and the *Re* face of the aldehyde becomes proper for the enol attack.[8]

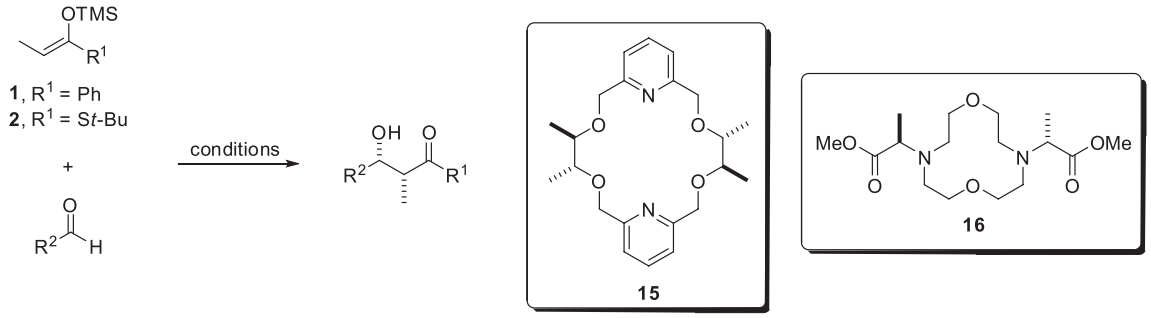
In 2012, Allen and co-workers[9] applied crown ether **16** as a ligand for neodymium-catalyzed Mukaiyama aldol reactions (Table 2).

As becomes evident from the results presented in Table 2, the Mukaiyama aldol reactions between enolsilane **1** and aromatic and α,β-unsaturated aldehydes, mediated by $Nd(OTf)_3$, gave good to high yields and high diastereo- and enantioselectivities in favor of the corresponding *syn* aldol adducts (Table 2, entries 1-6). The aldol reactions using aliphatic aldehyde **14** (Table 2, entry 7) led to the formation of aldol adduct with good diastereo- and enantioselectivities in favor of the *syn* isomer, but in low yield.

3. Diastereo- and Enantioselective Catalytic Reductive Aldol Reactions

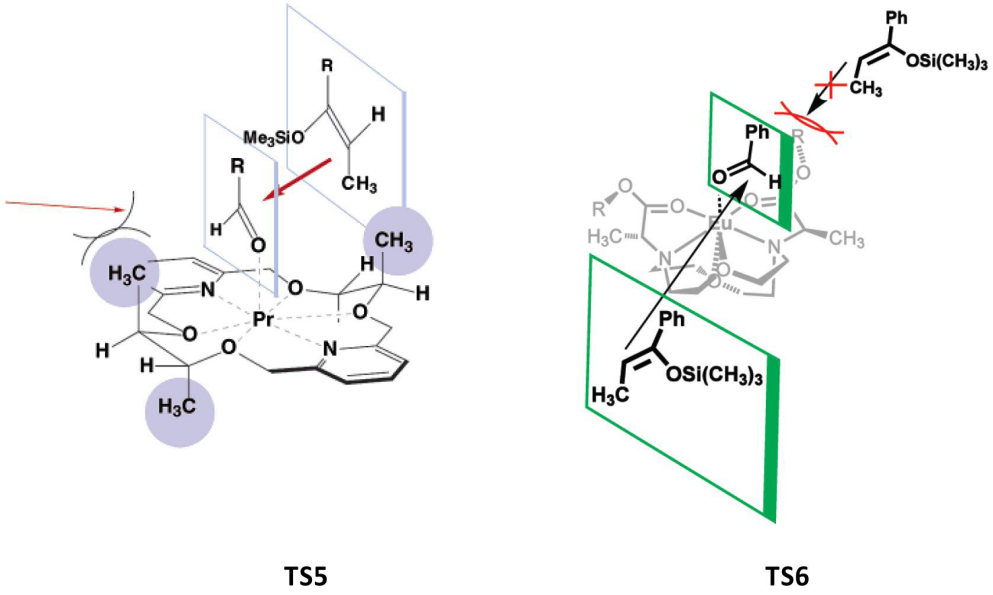
Catalytic reductive aldol reactions employing chiral ligands consist in a very exciting method to obtain aldol adducts in high diastereo- and enantioselective fashion.[10] The aldol coupling between α,β-unsaturated ester or ketone and aldehydes are promoted using catalytic amounts of a transition metal complex under hydrogenation conditions. The tremendous advantage of this method is that the regioselective reductive formation of a transition metal enolate, required to the aldol reaction, is generated *in situ* by conjugated addition of a metal hydride to an unsaturated carbonyl compound (Scheme 3).[11] The most common reductive agents are molecular hydrogen, silanes and stannanes in stoichiometric amounts. Among the reports involving Co-, Pt-, Pd-, Ni-, Cu-, Ir- and Rh-catalyzed reductive aldol reactions, so far Rh, Ir and Cu transition

Table 1. Lanthanide-catalyzed Mukaiyama aldol reactions



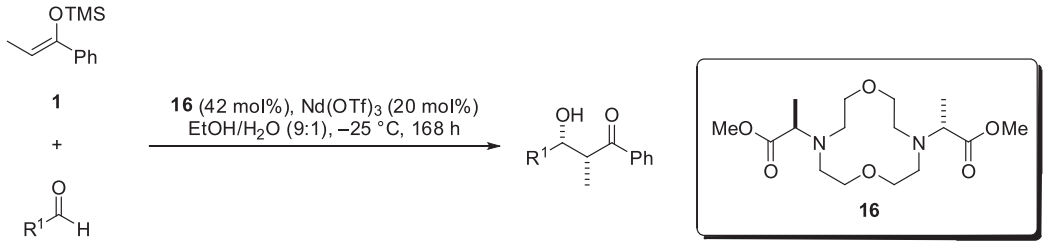
entry	Condition[a]	Aldehyde (R^2)	Enolate (R^1)	Yield / %	*dr* (*syn*:*anti*)	*ee* (*syn*) / %
1	A	*p*-$MeOC_6H_4$ (**3**)	**1**	91	92:08	75
2	B[b]	*p*-$MeOC_6H_4$ (**3**)	**2**	79	96:04	83
3	A	*o*-$MeOC_6H_4$ (**4**)	**1**	96	95:05	83
4	A	*p*-ClC_6H_4 (**5**)	**1**	87	90:10	83
5	A	1-naphthyl (**6**)	**1**	96	91:09	81
6	A	2-thiophenyl (**7**)	**1**	100	91:09	72
7	B	2-pyridyl (**8**)	**1**	99	85:15	85
8	B[b]	2-pyridyl (**8**)	**2**	62	88:12	83
9	A	(*E*)-CH(Ph)=CH (**9**)	**1**	77	78:22	76
10	B[b]	(*E*)-CH(Ph)=CH (**9**)	**2**	75	87:13	78
11	A	(*E*)-CH(Me)=CH (**10**)	**1**	70	81:19	68
12	B	Ph (**11**)	**1**	90	90:10	79
13	B[b]	Ph (**11**)	**2**	63	95:05	82
14	A	$BnCH_2$ (**12**)	**1**	53	67:33	47
15	C	Ph (**11**)	**1**	92	32:1	93
16	C	*p*-ClC_6H_4 (**5**)	**1**	75	21:1	91
17	C	*p*-MeC_6H_4 (**13**)	**1**	73	24:1	90
18	C	(*E*)-CH(Me)=CH (**10**)	**1**	65	21:1	93
19	C	hex (**14**)	**1**	22	23:1	96

[a]Condition A: $Pr(OTf)_3$ (10 mol%), **15** (12 mol%), H_2O/EtOH (1/9), 0 ºC. Condition B: $Pr(OTf)_3$ (20 mol%), **15** (24 mol%), H_2O/EtOH (1/9), 0 ºC. Condition C: **16** (48 mol%), $Eu(OTf)_3$ (20 mol%), EtOH/H_2O (9/1), –25 ºC; [b]2,6-di-*tert*-butylpyridine (1 equiv).

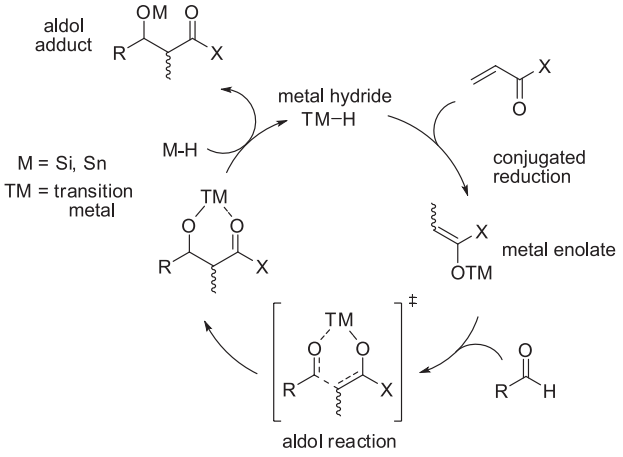


Scheme 2. Transition states for lanthanide-catalyzed Mukaiyama aldol reactions. TS5 reproduced from reference 7 with copyright permission 2003 from American Chemical Society. TS6 reproduced from reference 8 with copyright permission 2010 from American Chemical Society.

Table 2. Neodymium-catalyzed Mukaiyama aldol reactions



entry	Aldehyde (R^1)	Yield / %	*dr* (*syn*:*anti*)	*er* (*syn*)
1	Ph (**11**)	93	36:1	96:04
2	*p*-ClC_6H_4 (**5**)	90	12:1	95:05
3	*p*-MeC_6H_4 (**13**)	85	36:1	96:04
4	2-thiophenyl (**7**)	82	> 99:1	94:06
5	2-pyridyl (**8**)	55	> 99:1	89:11
6	(*E*)-CH(Me)=CH (**10**)	63	8:1	95:05
7	hex (**14**)	19	8:1	97:03



Scheme 3. Catalytic cycle of reductive aldol reaction.

metals and chiral ligand partners are the most prominent for this transformation. Efforts in order to get better diastereo- and enantioselective aldol adducts under milder conditions reaching high turnover and avoiding carbonyl reduction of the substrates are the driving forces of this field.

The first example of a catalytic asymmetric reductive aldol reaction was reported by Morken and co-workers[12] in 2000 employing acrylates and several aldehydes (Table 3). Using Rh catalyst and (*R*)-BINAP (**25**), *syn* aldol products **23** were obtained in good yields and good diastereo- and enantioselectivities (Table 3, entries 1-5). In the Morken's subsequent paper, the scope of the substrates showed synthetic flexibility, producing miscellaneous α,β-substituted β-hydroxyesters (Table 3, entries 6-13).[13] Subsequently, a new iridium catalyst was developed using $[(cod)IrCl]_2$ and In-pybox (**26**) as a chiral ligand partner, to selectively give *syn* aldol products **24** with benzaldehyde and alkoxy aldehydes (Table 3, entries 14-18).[14] The aldol adducts **37** and **38** were the precursors to establish the stereogenic centers at C3-C4 and C10-C11 respectively, for the enantioselective synthesis of borrelidin (**39**) (Scheme 4).[15]

In 2008, Krische and co-workers[16] introduced a new class of effective monodentate TADDOL-like phosphonite ligands with the ability to promote molecular hydrogen-mediated reductive aldol coupling of vinyl ketones with aldehydes (Scheme 5). High levels of *syn*-diastereoselectivity in the formation of aldol adducts **40a-e** were observed with miscellaneous aldehydes using the preformed complex $[Rh(cod)L_2]OTf$ (**41**) as precatalyst. A few examples are showed in Scheme 5.

Nishiyama and co-workers[17] showed the possibility to achieve aldol adducts in high *anti*-selectivity (Table 4).

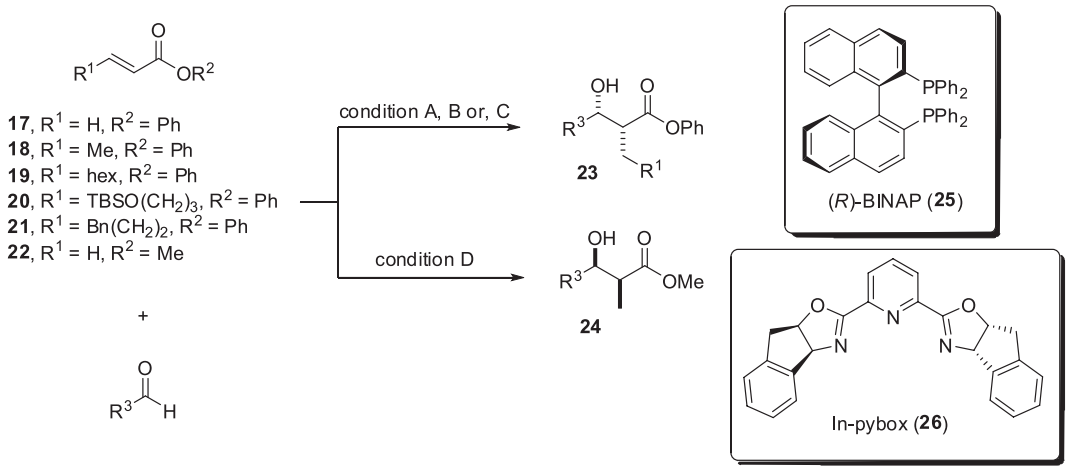
The reductive aldol reactions between acrylate **42** and a number of aldehydes were promoted by the chiral Rh-Phebox (**44**) catalyst and alkoxyhydrosilane providing *anti*-**43** in good to high levels of diastereo- and enantioselectivities.

The supposed stereochemical pathway for this transformation, supported by theoretical calculations, involves the Rh-(*E*)-enolate (identified by ^1H NMR) in a Zimmerman-Traxler-type transition state **TS7**, with attack to the complexed aldehyde from the less sterically hindered face of the enolate (Scheme 6).[18]

4. Chiral Lewis Base Catalysis in Enantioselective Aldol Reactions

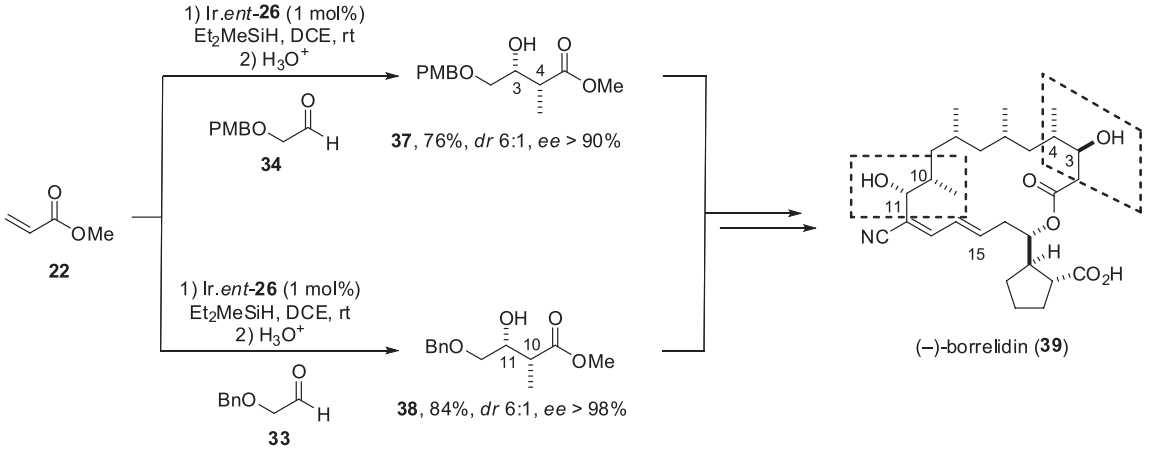
The concept of Lewis base catalysis in aldol reactions involving trichlorosilyl enolates with aldehydes has

Table 3. Metal-catalyzed reductive aldol reactions

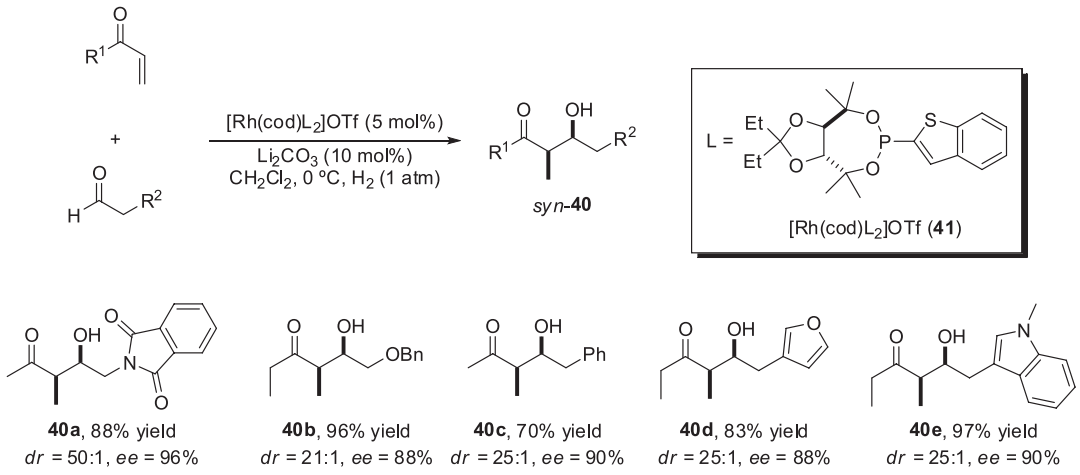


entry	Condition[a]	Enolate (R^1, R^2)	Aldehyde (R^3)	Yield / %	*dr* (*syn*:*anti*)	*ee* or *er* (*syn*)
1	A	R^1 = H, R^2 = Ph (**17**)	Ph (**11**)	72	3.4:1	87%
2	A	R^1 = H, R^2 = Ph (**17**)	Et (**27**)	59	5.1:1	88%
3	A	R^1 = H, R^2 = Ph (**17**)	*c*-Hex (**28**)	54	3.9:1	84%
4	A	R^1 = H, R^2 = Ph (**17**)	*t*-Bu (**29**)	48	1.8:1	45%
5	A	R^1 = H, R^2 = Ph (**17**)	1-naphthyl (**6**)	82	3.8:1	80%
6	B	R^1 = H, R^2 = Ph (**17**)	(*E*)-CH(Me)=CH (**10**)	54	6:1	71%
7	B	R^1 = H, R^2 = Ph (**17**)	Me_2C=CH (**30**)	86	6:1	83%
8	B	R^1 = H, R^2 = Ph (**17**)	(*E*)-CH(Me)=C(Me) (**31**)	90	3:1	75%
9	B	R^1 = H, R^2 = Ph (**17**)	1-(cyclohex-1-ene) (**32**)	73	7:1	81%
10	C	R^1 = Me, R^2 = Ph (**18**)	Et (**27**)	76	4.3:1	88%
11	C	R^1 = hex, R^2 = Ph (**19**)	Et (**27**)	54	4.2:1	88%
12	C	R^1 = $TBSO(CH_2)_3$, R^2 = Ph (**20**)	Et (**27**)	53	3.8:1	88%
13	C	R^1 = $Bn(CH_2)_2$, R^2 = Ph (**21**)	Et (**27**)	49	3.9:1	93%
14	D	R^1 = H, R^2 = Me (**22**)	Ph (**11**)	68	6.6:1	97:03
15	D	R^1 = H, R^2 = Me (**22**)	$BnOCH_2$ (**33**)	49	9.9:1	98:02
16	D[b]	R^1 = H, R^2 = Me (**22**)	$PMBOCH_2$ (**34**)	84	6:1	> 98%
17	D	R^1 = H, R^2 = Me (**22**)	$TBSOCH_2$ (**35**)	47	8.2:1	98:02
18	D	R^1 = H, R^2 = Me (**22**)	$BnO(CH_2)_2$ (**36**)	65	2.7:1	91:09

[a]Condition A: (*i*) $[(cod)RhCl]_2$ (2.5 mol%), (*R*)-BINAP (**25**) (6.5 mol%), Et_2MeSiH, 24 h, rt, DCE. (*ii*) H_3O^+. Condition B: (*i*) $[(cod)Rh(R)\text{-BINAP}]BF_4$ (5 mol%), Et_2MeSiH, 12 h, rt, DCE. (*ii*) H_3O^+. Condition C: (*i*) $[(cod)RhCl]_2$ (5 mol%), (*R*)-BINAP (**25**) (6.5 mol%), Et_2MeSiH, 48 h, rt, DCE. (*ii*) H_3O^+. Condition D: (*i*) $[(cod)IrCl]_2$ (2.5 mol%), **26** (7.5 mol%), Et_2MeSiH, 24 h, rt (*ii*) H_3O^+. [b]Ir-(**26**) (1 mol%) was used.

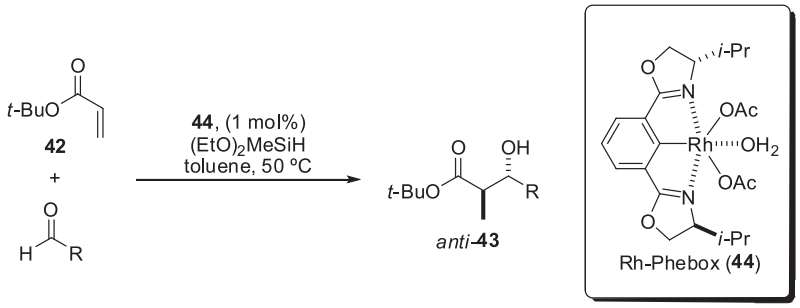


Scheme 4. Application of iridium-catalyzed reductive aldol reactions in the total synthesis of (–)-borrelidin (**39**).

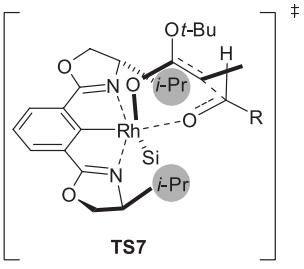


Scheme 5. TADDOL-like ligand in hydrogen-mediated reductive aldol reactions.

Table 4. Stereoselective *anti* asymmetric reductive aldol reaction with Rh-Phebox (**44**) catalyst



entry	Aldehyde (R)	Yield / %	*dr* (*anti*:*syn*)	*ee* (*anti*) / %
1	*p*-$MeOC_6H_4$ (**3**)	94	94:06	93
2	*m*-$MeOC_6H_4$ (**45**)	92	93:07	92
3	*p*-$CF_3C_6H_4$ (**46**)	93	92:08	89
4	1-naphtyl (**6**)	95	98:02	95
5	2-naphtyl (**47**)	92	93:07	93
6	*c*-Hex (**28**)	58	95:05	95
7	(*E*)-CH(Ph)=CH (**9**)	56	81:19	93
8	$BnOCH_2$ (**33**)	75	72:28	93

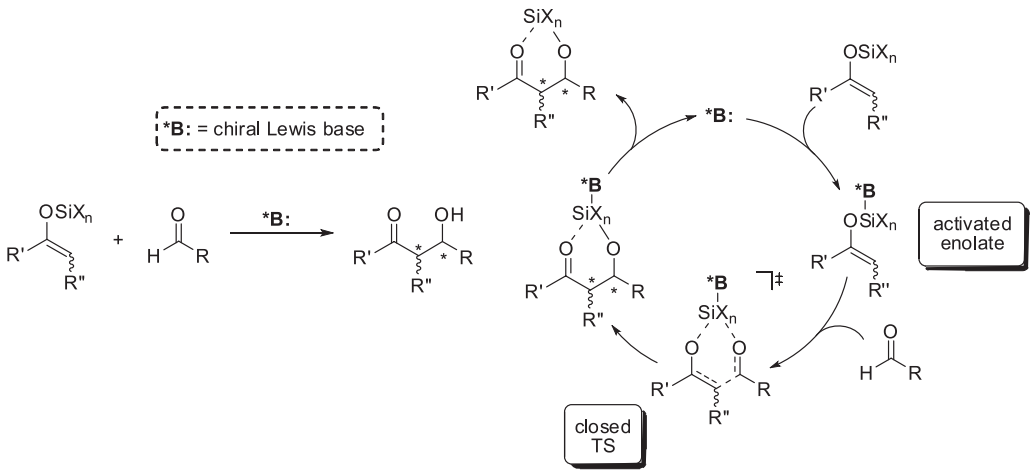


Scheme 6. Transition state for aldol reaction involving Rh-Phebox.

been extensively explored by Denmark *et al.*[19,20] since the first report in 1996 (Scheme 7).[21] In the context of stereoselective aldol transformations, the electron-pair of a chiral Lewis base catalyst interacts with an acceptor silicon atom of the enolate making it more reactive. In addition, the new chiral complex should interact with the carbonyl oxygen of aldehyde producing aldol adducts in a stereoselective manner.

The scope and generality of this transformation were extensively studied by Denmark *et al.*[19,20] using phosphoramide organocatalysts. Mukaiyama aldol reactions involving Lewis base catalysis were also reported involving trimethoxysilyl enol ethers activated by binaphtholate organocatalysts.[22]

An alternative strategy involving Lewis base catalysis in Mukaiyama aldol reactions involves the fluorine-



Scheme 7. General catalytic cycle for Lewis base catalyzed aldol reactions.

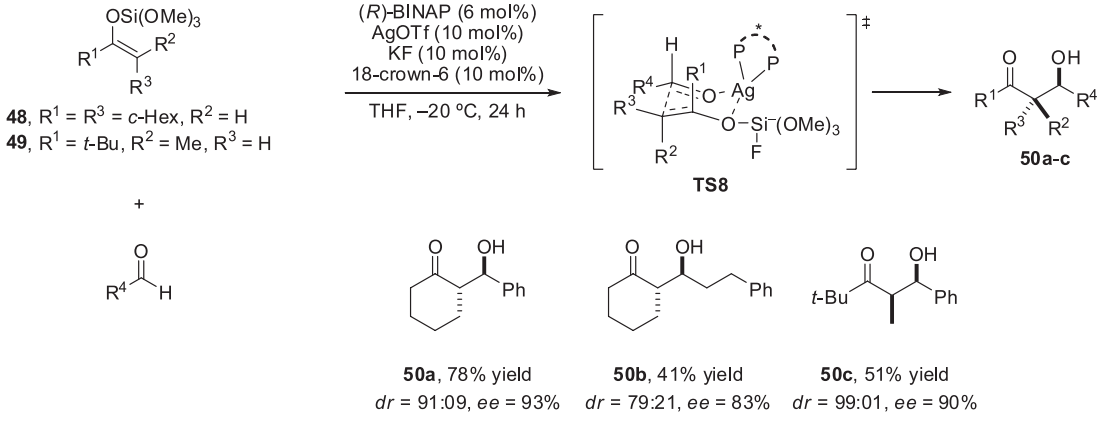
catalyzed bifunctional approach reaction with chiral Lewis acid catalysts, examined by Yamamoto and co-workers[23] using the catalyst system BINAP/AgOTf/KF/[18]crown-6 (Scheme 8). In this strategy, the fluoride ions act as an achiral Lewis base forming an anionic hypervalent silicate activating the trimethoxysilyl enol ether, as represented by the cyclic transition state **TS8**, explaining the diastereoselectivities of aldol adducts *syn*-**50c** or *anti*-**50a-b** from Z- or *E*-enolates, respectively.[23]

Another successful example involving catalytic enantioselective aldol reactions combines a weak achiral Lewis acid ($SiCl_4$) with a chiral phosphoramide (*R*,*R*)-**53** Lewis base catalyst generating a strong and activated chiral Lewis acid (Scheme 9). Denmark and Chung[24] developed Mukaiyama aldol reactions version using this concept. The sense of diastereoselectivity is modulated by the size of the protecting group of silyl ketene acetals and high levels of diastereo- and enantioselectivities were obtained (Scheme 9). Theoretical calculations support the cationic opening transition states **TS9** and **TS10** for aldol reactions involving enolates **51** and **54**, respectively.[25]

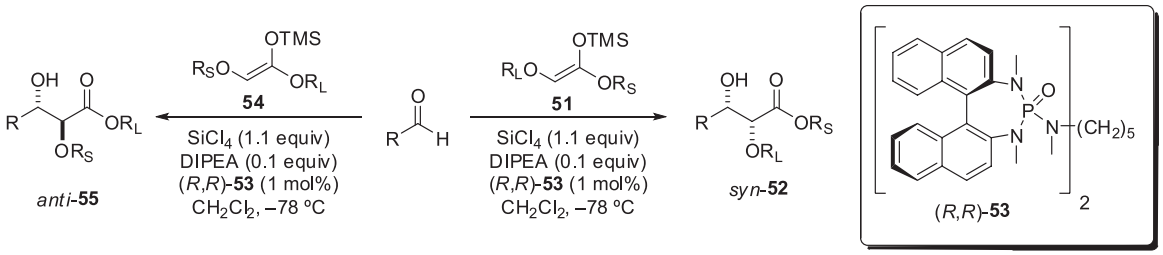
In 2012, Nakajima, Kotani and co-workers[26] presented an efficient method for the enantioselective reductive aldol reaction of α,β-unsaturated ketones with aldehydes (Table 5). The conjugated reduction was performed using a tertiary amine and trichlorosilyl triflate. Then, the aldol reaction was made in the presence of BINAP dioxide (BINAPO).

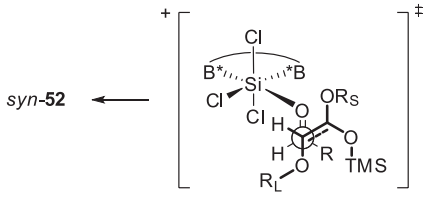
As evident from the results presented in Table 5, the reductive aldol reactions with the chalcone derivatives proceeded smoothly to give the corresponding products in good yields with high diastereo- and enantioselectivities (entries 2-7). Isopropyl ketone **63** provided the aldol product in high yield and selectivity (entry 8), whereas the stereoselectivity of the reaction with cyclopropyl ketone **64** was found to decrease (entry 9).

In addition, reductive aldol reactions between various aldehydes and chalcone (**56**) were conducted (entries 10-15). The aromatic aldehydes tended to give the aldol adducts with good yields and high stereoselectivities (entries 10-12). The conjugate aldehyde **9** furnished the product in high yield with high selectivity (entry 13).



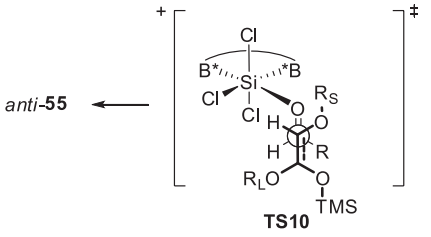
Scheme 8. Lewis base activation in aldol reactions.





R	Yield / %	*dr* (*syn*:*anti*)	*er* (*syn*)	51 R_S	51 R_L
Ph (**11**)	87	99:01	96.6:3.4	Me	Me_2PhC
p-$MeOC_6H_4$ (**3**)	98	99:01	97.7:2.3	Me	Me_2PhC
p-$CF_3C_6H_4$ (**46**)	99	99:01	98.0:2.0	Me	Me_2PhC
1-Naphtyl (**6**)	94	> 99:01	98.5:1.5	Me	Me_2PhC
$BnCH_2$ (**12**)	49	90:10	87.7:12.7	Me	TBS

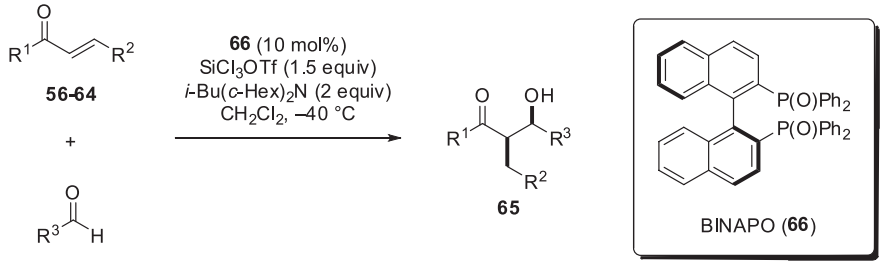
cationic silicon **TS**



R	Yield / %	*dr* (*anti*:*syn*)	*er* (*anti*)	54 R_S	54 R_L
Ph (**11**)	91	> 99:01	95.1:4.9	Me_2EtC	Me
p-$MeOC_6H_4$ (**3**)	93	> 99:01	98.3:1.7	Me_2EtC	Me
p-$CF_3C_6H_4$ (**46**)	96	> 99:01	98.3:1.7	Me_2EtC	Me
1-Naphtyl (**6**)	93	> 99:01	97.4:2.6	Me_2EtC	Me
$BnCH_2$ (**12**)	82	98:02	96.4:3.6	*i*-Pr_2CH	Bn

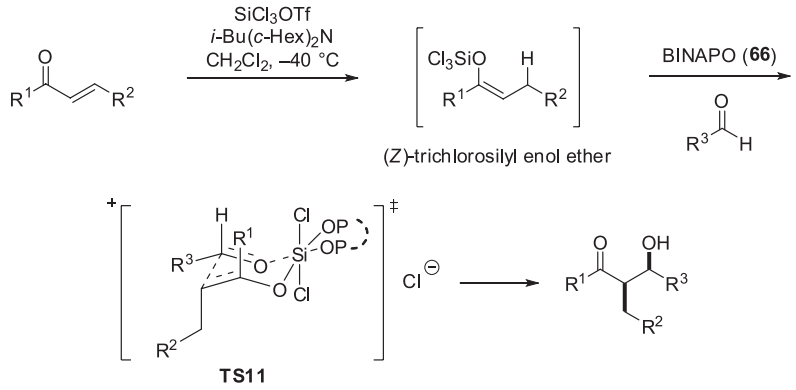
Scheme 9. Lewis base activation of Lewis acids in glycolate aldol reactions.

Table 5. Stereoselective *syn* asymmetric reductive aldol reaction[a]



entry	Ketone (R^1, R^2)	Aldehyde (R^3)	Yield[b] / %	*dr* (*syn*:*anti*)[c]	*ee* (*syn*)[d] / %
1	**56**, R^1 = Ph, R^2 = Ph	**11**, R^3 = Ph	83	95:05	95
2	**57**, R^1 = Ph, R^2 = *p*-$MeOC_6H_4$	**11**, R^3 = Ph	84	97:03	93
3	**58**, R^1 = Ph, R^2 = *p*-BrC_6H_4	**11**, R^3 = Ph	86	96:04	93
4	**59**, R^1 = Ph, R^2 = PhC≡C	**11**, R^3 = Ph	82	95:05	80
5	**60**, R^1 = *p*-$MeOC_6H_4$, R^2 = Ph	**11**, R^3 = Ph	69	74:26	81
6	**61**, R^1 = *p*-BrC_6H_4, R^2 = Ph	**11**, R^3 = Ph	83	97:03	88
7	**62**, R^1 = PhC≡C, R^2 = Ph	**11**, R^3 = Ph	56	89:11	84
8	**63**, R^1 = *i*-Pr, R^2 = Ph	**11**, R^3 = Ph	73	94:06	89
9	**64**, R^1 = *c*-Pr, R^2 = Ph	**11**, R^3 = Ph	79	70:30	32
10	**56**, R^1 = Ph, R^2 = Ph	**3**, R^3 = *p*-$MeOC_6H_4$	81	96:04	90
11	**56**, R^1 = Ph, R^2 = Ph	**67**, R^3 = *p*-BrC_6H_4	87	95:05	95
12	**56**, R^1 = Ph, R^2 = Ph	**68**, R^3 = 2-furyl	57	97:03	90
13	**56**, R^1 = Ph, R^2 = Ph	**9**, R^3 = (*E*)-CH(Ph)=CH	83	97:03	84
14[e]	**56**, R^1 = Ph, R^2 = Ph	**12**, R^3 = $BnCH_2$	50	96:04	89
15[e]	**56**, R^1 = Ph, R^2 = Ph	**28**, R^3 = *c*-Hex	68	99:01	70

[a]Unless otherwise noted, the reactions were conducted in the presence of aldehyde (0.5 mmol), ketone (1.2 equiv), *i*-Bu(c-Hex)$_2$N (2.0 equiv), $SiCl_3OTf$ (1.5 equiv) and BINAPO (10 mol %) in CH_2Cl_2 (5 mL). [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis. [e]The reaction was conducted with ketone (1.0 equiv), aldehyde (1.5 equiv) and $SiCl_3OTf$ (1.2 equiv).



Scheme 10. Mechanism proposed for the BINAPO-mediated aldol reaction.

Strikingly, the aliphatic aldehydes **12** and **28**, which were generally less reactive in Lewis base-catalyzed reactions, gave the corresponding aldol adducts in good yields with high diastereoselectivities (entries 14 and 15). The rationalization for the observed selectivity is shown in Scheme 10.

The conjugate reduction of ketone gave the (*Z*)-trichlorosilyl enol ether (Scheme 10). The aldol reaction of (*Z*)-trichlorosilyl enol ether with aldehyde proceeded via a six-membered transition state **TS11** involving hypervalent silicon species to afford the corresponding aldol adduct with high *syn*-diastereo- and enantioselectivities.

5. Metal-Catalyzed Direct Aldol Reactions

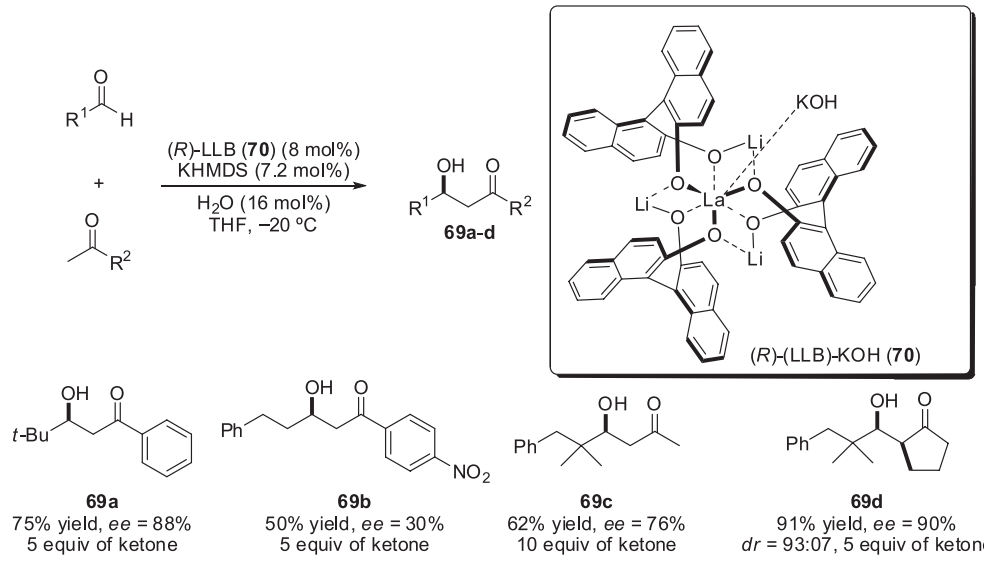
The so-called direct aldol reaction comprises an extraordinary category of aldol transformations developed aiming to atom economy through clean and economic reaction conditions.[27] The exciting challenges involving this transformation are to find new catalytic systems that allow the C–C bond coupling by the reaction of enolizable carbonyl compounds with itself or with another carbonyl compound, without the preactivation of the enolate nucleophile, in high chemo-, regio- and stereoselective fashion. Despite the remarkable success of organocatalytic direct aldol processes, heterobimetallic-catalyzed direct aldol reactions shows milder conditions than enamine-based organocatalysts employing nucleophilic amines. However, the requirement of long times under low temperature conditions for these reactions remains as the biggest drawback of this methodology. New organocatalytic approaches involving chiral phosphoric Brønsted acid in direct aldol processes have also emerged as a very attractive alternative.[28]

Numerous heterobimetallic complexes with chiral BINOL-based ligands have been emerged as very suitable catalysts for direct aldol reactions. A tremendous contribution was given by Shibasaki and co-workers[29] in this field. They reported the utilization of the heterobimetallic lanthanum-lithium-BINOL (LLB) complex catalyzing the aldol reaction between aromatic and aliphatic aldehydes with several equivalents of ketones in long reaction times. The heteropolymetallic catalyst LLB-KOH (**70**) was used in order to shorten the reaction times by enhancing the catalytic activity of LLB complex, giving aldol adducts **69a-d** in modest to good enantioselectivities (Scheme 11).[30]

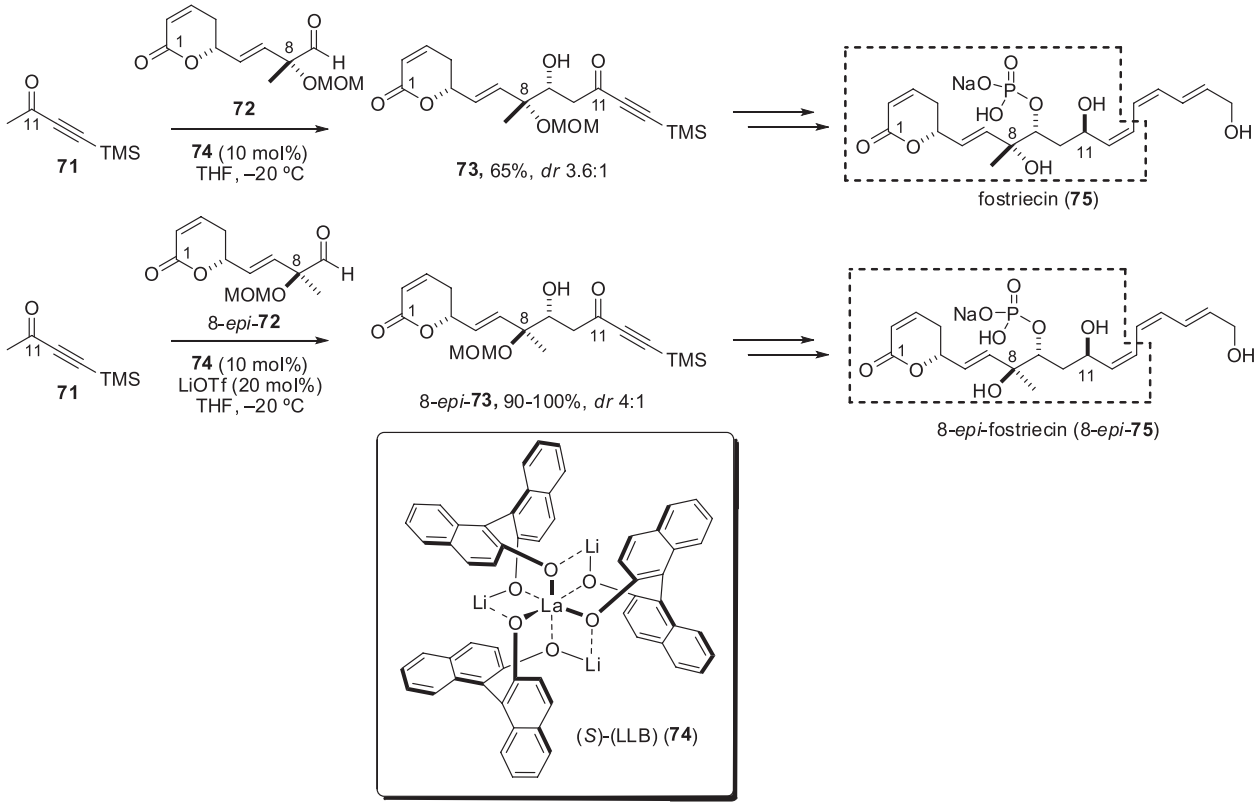
Shibasaki and co-workers[31] reported the use of (*S*)-LLB (**74**) catalyst in the formal total synthesis of fostriecin (**75**) and 8-*epi*-fostriecin (8-*epi*-**75**). The best reaction condition to the system of interest for fostriecin (**75**) afforded the aldol adduct **73** in good yield using ketone **71** and aldehyde **72** and the two-center Lewis acid-Brønsted base catalyst (*S*)-LLB (**74**) (Scheme 12). On the other hand, a new study was performed in order to improve the selectivity for the desired aldol adduct 8-*epi*-**73** used in the synthesis of 8-*epi*-fostriecin (8-*epi*-**75**), and the addictive LiOTf showed the best performance.

In early 2000, Trost and co-workers[32] reported a new chiral dinuclear zinc catalyst, prepared from Et_2Zn and chiral ligand **78** (Scheme 13).

In these works, the authors obtained aldol adducts with excellent levels of enantioselectivities using the version of direct aldol reaction between various ketones and aldehydes, mediated by a chiral dinuclear zinc catalyst. These results can be consistently explained by the proposed catalytic cycle (Scheme 14). The catalyst **83**, prepared *in situ* by treatment of ligand **78** with 2 equivalents of diethylzinc, involves initiation by liberation of 3 equivalents of ethane followed by a fourth by reaction with the active methylene partner (acetophenone in this case). The chiral space derives from the conformational preferences of the diphenylcarbinol moieties. Thus, the role of the two proximal zinc species is to provide both a zinc to form the requisite enolate (zinc functioning as a Brønsted base) and a second zinc to function as a Lewis acid to coordinate the aldehyde.



Scheme 11. Direct catalytic asymmetric aldol reaction catalyzed by La-Li-BINOL complex.

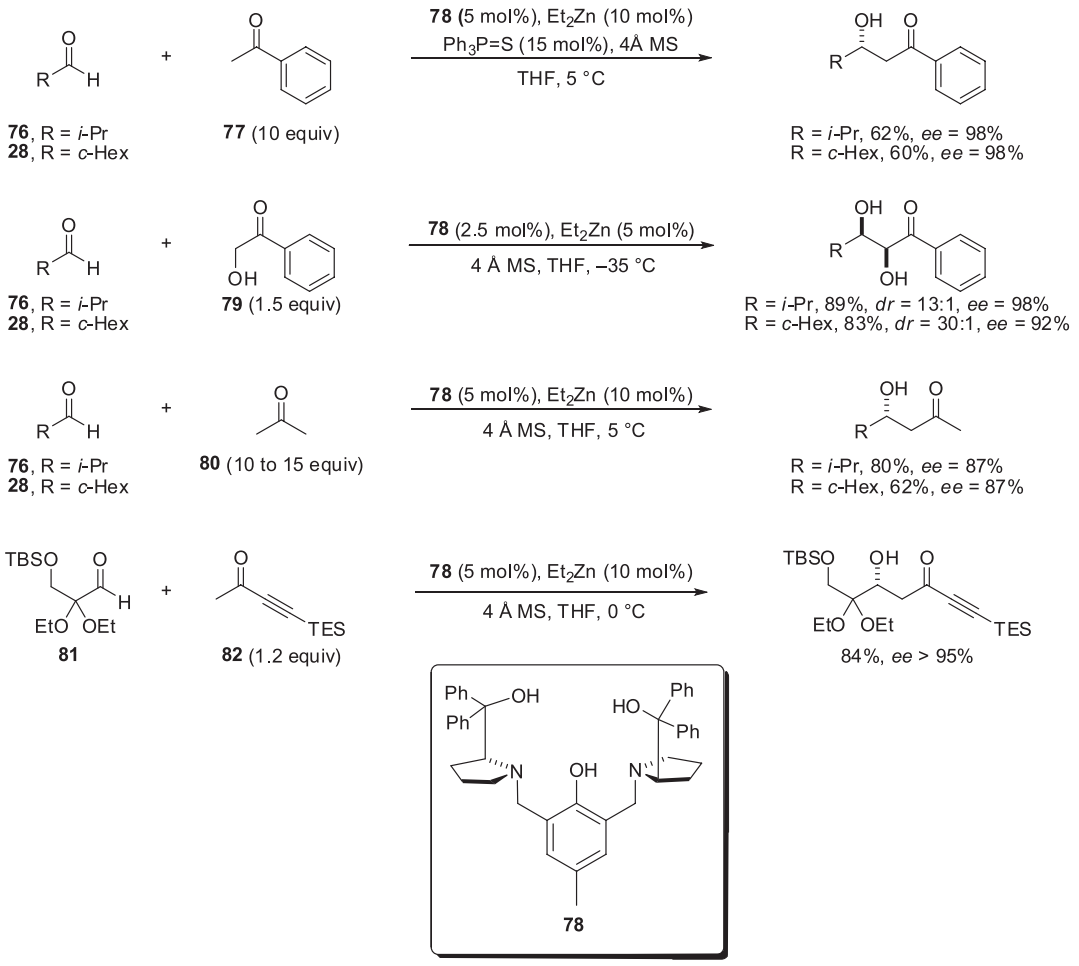


Scheme 12. Application of direct aldol reaction in the formal total synthesis of fostriecin (**75**) and total synthesis of 8-*epi*-fostriecin (8-*epi*-**75**).

In 2005, Trost and co-workers[33] described a formal synthesis of fostriecin (**75**) (Scheme 15). One of the steps of the synthesis consisted in the direct aldol reaction between ketone **85** and aldehyde **84**, mediated by chiral binuclear zinc catalyst **83**, which led to the formation of aldol adduct **86** with excellent level of enantioselectivity. Compound **86** corresponds to the C8-C13 fragment of fostriecin (**75**).

Recently, Kumagai, Shibasaki and co-workers[34] developed a direct catalytic asymmetric aldol reaction between thioamide **87** and aldehydes employing a soft Lewis acid/hard Brønsted base cooperative catalysis (Table 6).

As can be seen from Table 6, independently of the steric nature of the aldehyde, the aldol adducts were obtained with yields ranging from moderate to good and excellent level of enantiomeric excess.



Scheme 13. Enantioselective aldol reactions between ketones and aldehydes in the presence of **78** and Et_2Zn.

In 2012, Kumagai, Shibasaki and co-workers[35] reported the total synthesis of duloxetine (**92**), a dual serotonin and norepinephrine reuptake inhibitor in presynaptic cells. The key step of the synthesis was a direct catalytic aldol reaction between thioamide **90** and aldehyde **7**, mediated by chiral catalyst *ent*-**88**, which provided the aldol adduct **91** with high enantioselectivity (*ee* = 92%) (Scheme 16).

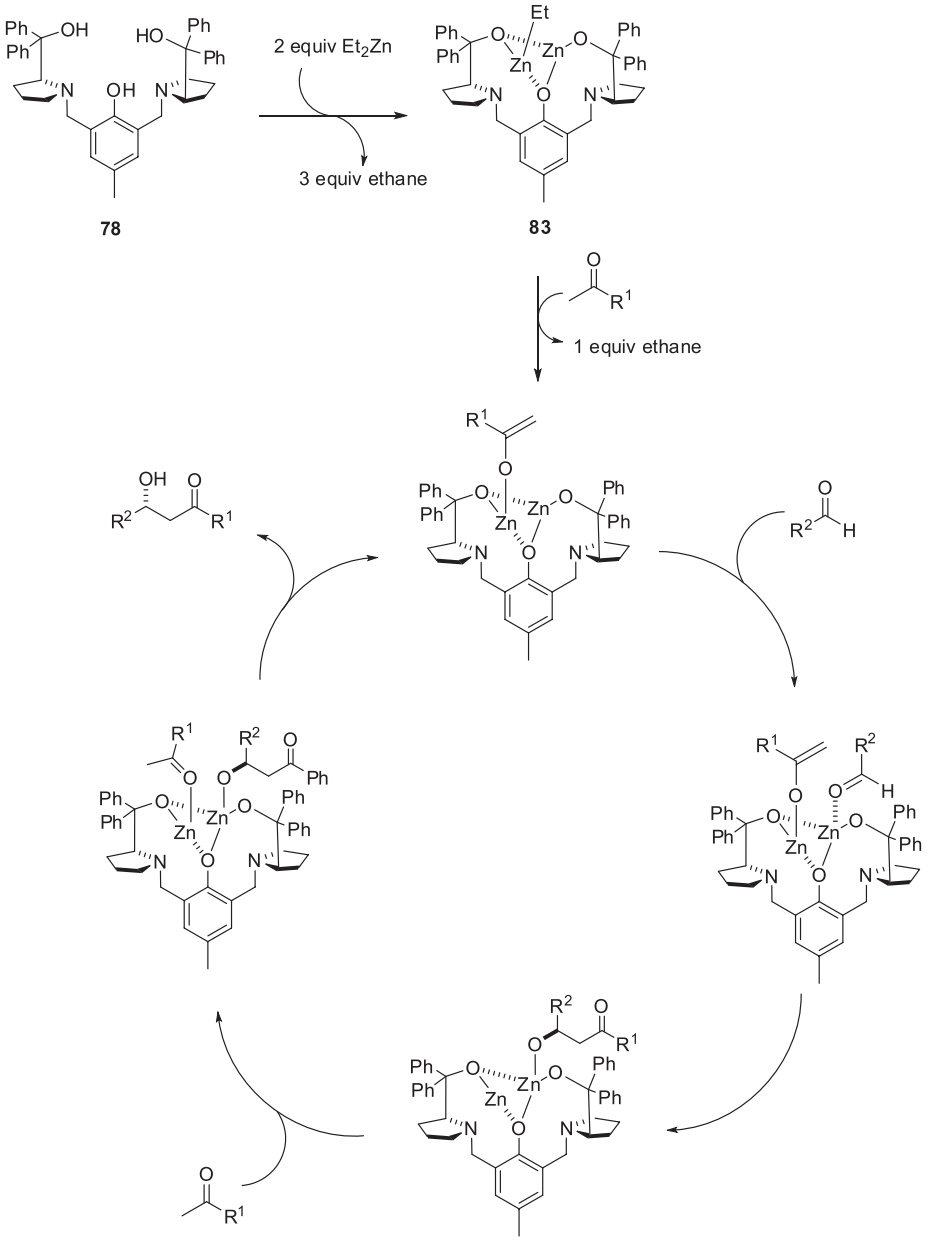
6. BINOL and Related Ligands in Catalytic Stereoselective Mukaiyama Aldol Reactions

The Lewis acid mediated aldol reactions involving silyl enol ethers with aldehydes are one of the most convenient methods to control the asymmetry in stereoselective catalytic aldol process. Catalytic asymmetric aldol reaction involving ligands possessing symmetry elements of pure rotation such as BINOL and derivatives have been extensively studied. Reetz *et al.*[36] firstly reported enantioselective Mukaiyama aldol reactions involving BINOL-Ti(IV) complex as Lewis acid.

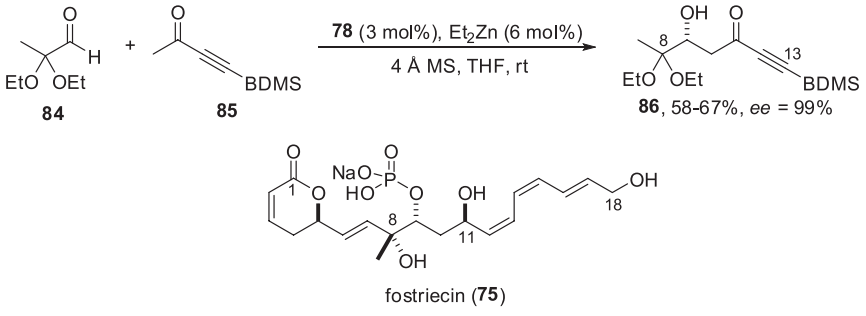
The research groups of Mikami[37] and Keck[38] gave important contributions to the development of the catalytic thioacetate Mukaiyama aldol reactions, involving, for example, BINOL-Ti(IV) complexes (*R*)-**98** and (*S*)-**95**, respectively (Scheme 17). In general, these reactions showed high enantioselectivities with several aldehydes.

In 1994, Carreira and co-workers[39] reported the design of a chiral tridentate Schiff base BINOL-derivative ligand **102** utilized for the preparation of the chiral complex **104** (Table 7). This complex presented a superior performance for Mukaiyama aldol reactions between silyl ketene acetals derived from O-alkyl acetates **105** and **106** and several aldehydes. As can be seen in Table 7, aromatic, unsaturated, and saturated aldehydes provided aldol adducts in high enatioselectivities in an *in situ* preparation of complex **104**.[40]

The Carreira's catalyst **104** was successfully applied in the total synthesis of the antitumor dipsipeptide romidepsin (**113**)[41] and the polyene macrolide roflamycoin (**116**)[42] (Scheme 18). In both synthetic studies, the asymmetric aldol reaction furnished the aldol adducts in high yields,

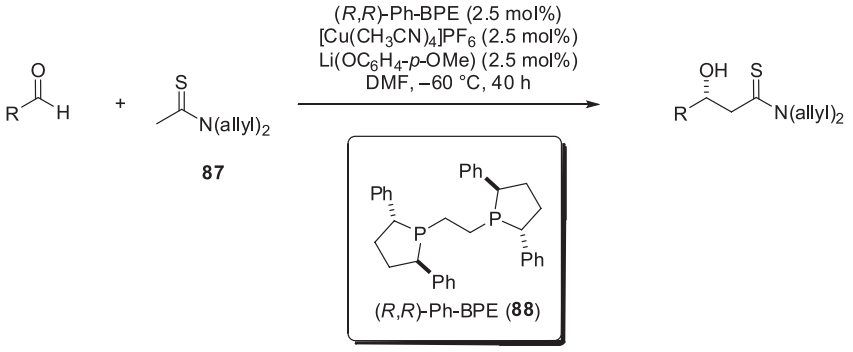


Scheme 14. Proposed catalytic cycle of the asymmetric aldol reaction.

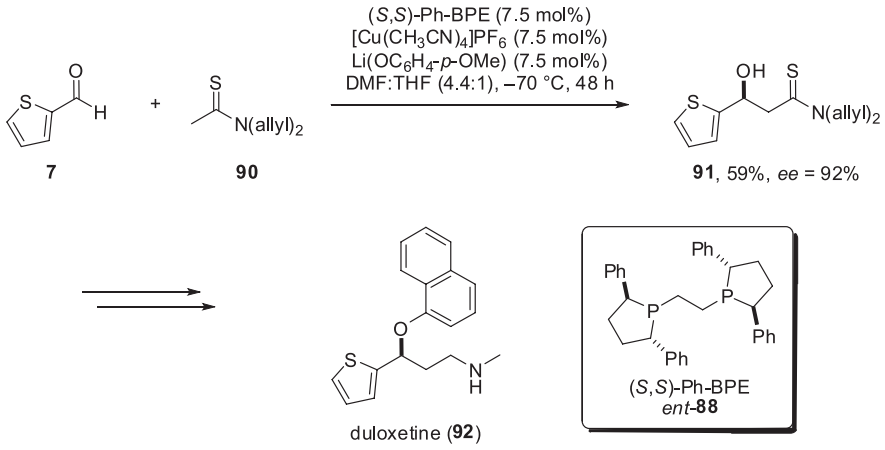


Scheme 15. Direct aldol reaction in the formal synthesis of fostriecin (**75**).

Table 6. Direct catalytic asymmetric aldol reaction between thioamide **87** and aldehydes



entry	Aldehyde (R)	Yield / %	*ee* / %
1	*i*-Pr (**76**)	87	91
2	*c*-Hex (**28**)	98	92
3	*t*-Bu (**29**)	90	92
4	$Ph(CH_2)_2$ (**12**)	63	88
5	$Me(CH_2)_6$ (**89**)	80	89



Scheme 16. Aldol reaction in the total synthesis of duloxetine (**92**).

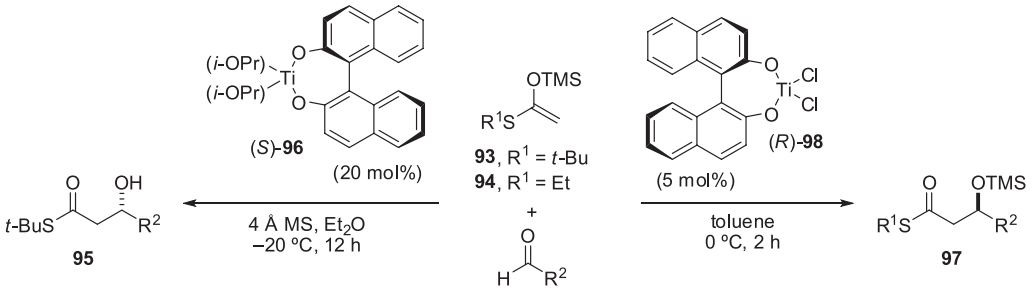
with high levels of enantioselectivities, which were utilized as precursors in the synthesis of the natural products.

In 2000, Kobayashi and co-workers[43] developed a Mukaiyama aldol reaction involving zirconium-Lewis acid complex **119** based on the chiral 3,3'-I_2-BINOL ligand. The Mukaiyama aldol reactions between several aldehydes and either silyl enol ether derived from *O*- or *S*-alkyl acetates preceded in high levels of diastereo- and enantioselectivities in good yields (Scheme 19). Notably, the best reaction condition involves the preparation of catalyst **119** with a small amount of water and in the presence of a primary alcohol.[44] The *Z*- and *E*-silylketene acetals (***Z*-120** and ***E*-120**) react in a stereoconvergent manner providing *anti*-**121** aldol adduct in high diastereo- and enantioselectivities. Further studies showed the development of an air-stable and storable Zr-BINOL catalyst, remaining unaltered the yield and stereoselectivities of aldol adducts.[45]

Chiral catalyst **119** was utilized by Inoue and co-workers[46] in the total synthesis of the potent toxin antillatoxin (**125**) (Scheme 20). The aldol reaction between aldehyde **123** and silyl enol ether **122** afforded the intermediate **124** in high diastereo- and enantioselectivity to set up the C4 and C5 stereocenters of antillatoxin (**125**).

7. Asymmetric Induction in Mukaiyama Aldol Reactions with Bis(oxazolinyl) (BOX) and Bis(oxazolinyl)pyridine (PYBOX) as Chiral Ligands

Early studies involving the C_2-symmetric chiral Lewis acid complexes in aldol reactions, such as bis(oxazolinyl)

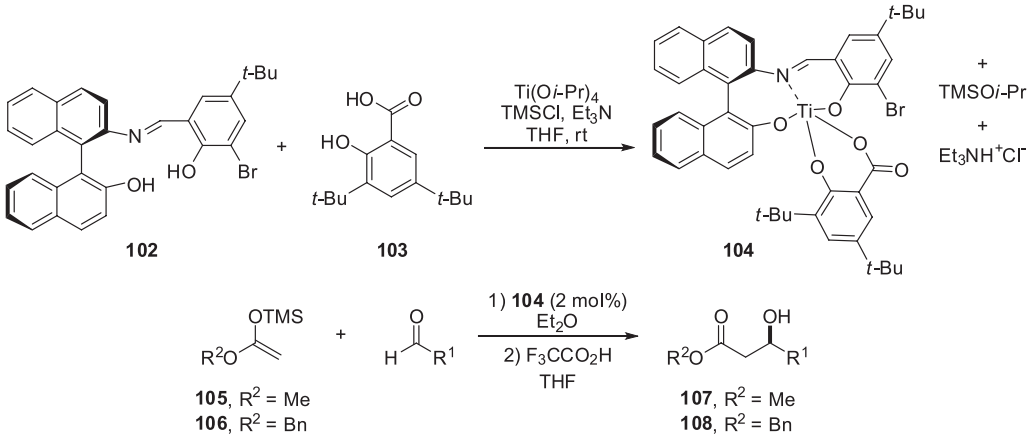


R^2	Yield / %	*ee* / %
Ph (**11**)	90	97
$BnCH_2$ (**12**)	80	97
n-C_8H_{17} (**99**)	74	98
furyl (**68**)	88	> 98
(*E*)-CH(Ph)=CH (**9**)	76	89
$BnOCH_2$ (**33**)	82	> 98

R^2	R^1	Yield / %	*ee* / %
Ph (**11**)	Et	81	94
$ClCH_2$ (**100**)	*t*-Bu	61	91
n-C_8H_{17} (**99**)	*t*-Bu	60	91
i-Pr (**76**)	Et	61	85
(*E*)-CH(Me)=CH (**10**)	Et	60	81
BnO_2C (**101**)	Et	84	95

Scheme 17. Catalytic asymmetric Mukaiyama aldol reactions involving BINOL-Ti(IV) complex.

Table 7. Mukaiyama aldol reaction with the *in situ* preparation of catalyst **104**



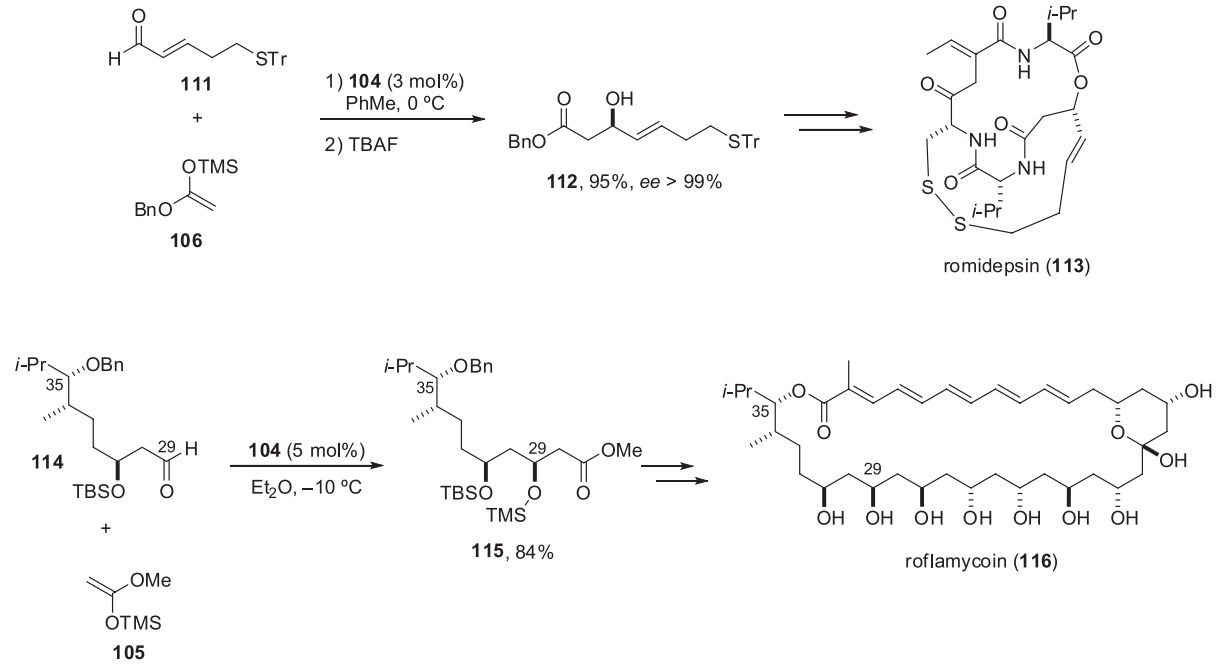
entry	Aldehyde (R^1)	**107**		**108**	
		Yield / %	*ee* / %	Yield / %	*ee* / %
1	(*E*)-CH(Ph)=CH (**9**)	95	98	98	96
2	$BnCH_2$ (**12**)	98	93	95	91
3	$TBSOCH_2C{\equiv}C$ (**109**)	91	99	99	99
4	(*E*)-CH(Ph)=C(Me) (**110**)	89	97	91	97
5	Ph (**11**)	94	96	94	96

(BOX) and bis(oxazolinyl)pyridine (PYBOX) ligands have been developed by Evans and co-workers.[47] In these works, the authors achieved excellent levels of regio-, diastereo- and enantioselectivities using electrophiles capable of chelation, for example, (benzyloxy)acetaldehyde (**33**) (Table 8).[47]

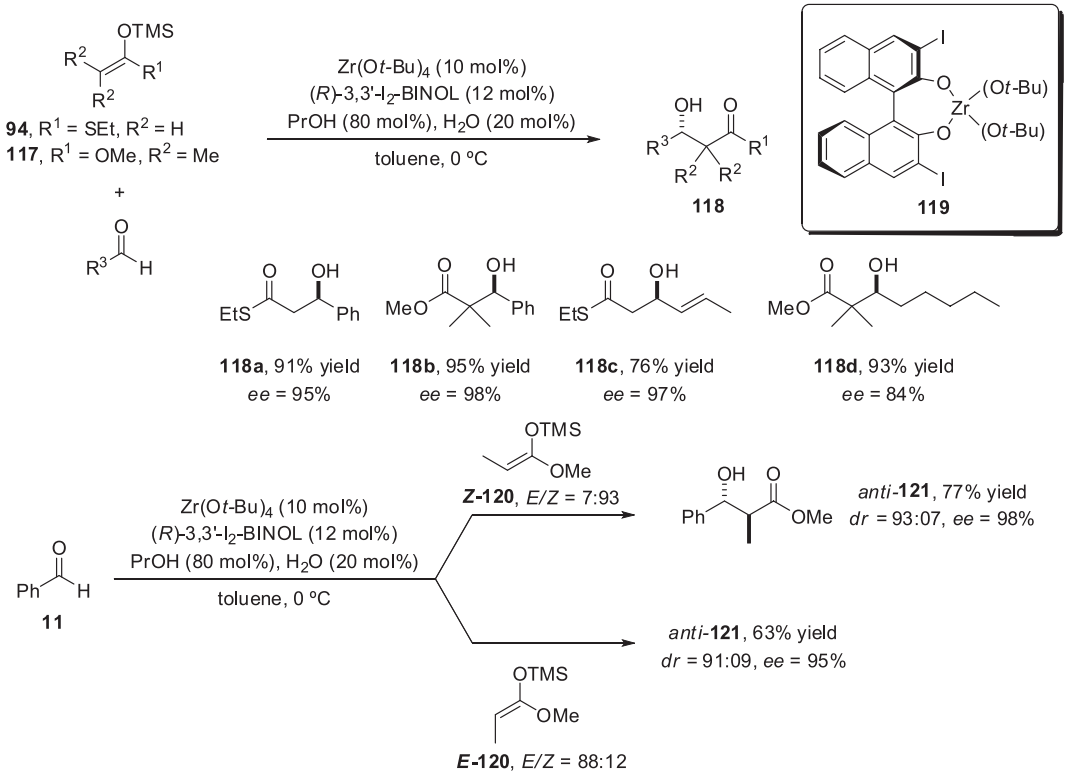
As can be seen, the reactions were found to be quite general with respect to the silylketene acetal structure. In all cases, excellent yields were obtained with enantiomeric excesses above 95%.

The requirement for a chelating substituent at the aldehyde partner is critical to catalyst selectivity, as (*tert*-butyldimethylsiloxy)-acetaldehyde gave low enantioselectivity (*ee* = 56%). Curiously, β-(benzyloxy) propionaldehyde provided racemic products, indicating a strict requirement for a five-membered catalyst-aldehyde chelate. The observed results can be rationalized based on a pyramidal square transition state **TS12** with a penta-coordination geometry (Scheme 21).

As can be seen from the proposed transition state **TS12**, the aldehyde is preferentially attacked from the *Si* face, justifying the absolute configuration of the observed aldol adducts.



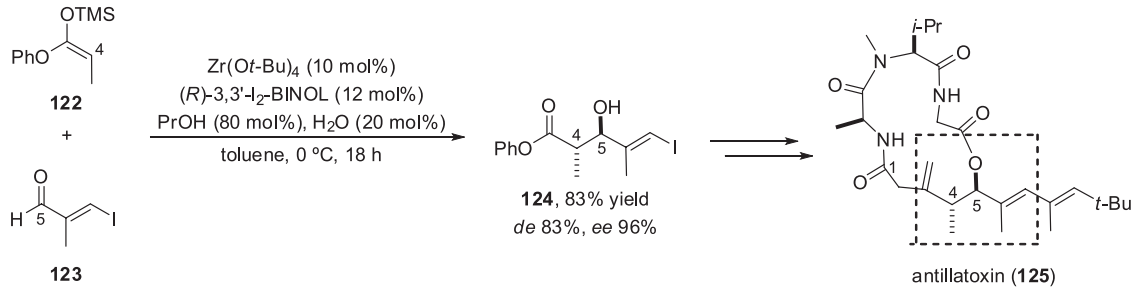
Scheme 18. Total synthesis of romidepsin (**113**) and roflamycoin (**116**).



Scheme 19. Zirconium-3,3'-I_2-BINOL complex in Mukaiyama aldol reactions.

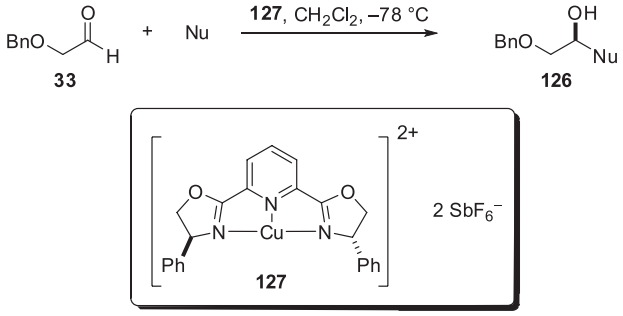
Evans and co-workers[47] have obtained excellent results from the Mukaiyama type aldol reaction between silyl enol ethers and methyl pyruvate (**128**) in the presence of box complex **130** (Table 9).

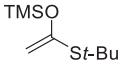
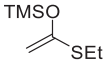
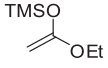
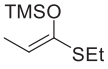
Structural variations of the silyl enol ether are possible without loss in enantioselectivity. Both silylketene acetals and ketone-derived enolsilanes afford highly enantioselective additions (Table 9, entries 1-3,

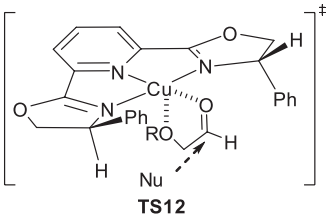


Scheme 20. Total synthesis of antillatoxin (**125**).

Table 8. Enantioselective catalyzed aldol reactions between (benzyloxy)acetaldehyde (**33**) and enolsilanes in the presence of PYBOX complex **127**



entry	Nucleophile (Nu)	**127** / mol%	*ee* / % (Yield / %)
1		0.5	99 (100)
2		0.5	98 (95)
3		0.5	98 (99)
4		10	97 (90) *dr* = 97:03 (1,2-*syn*:1,2-*anti*)
5		10	95 (95) *dr* = 96:04 (1,2-*syn*:1,2-*anti*)



Scheme 21. Transition state for aldol reaction involving Cu(II)-(PYBOX).

ee ≥ 93%). The catalyzed aldol addition of substituted silylketene acetals to pyruvate esters mediated by box complex **130** provides succinate derivatives with high *syn* diastereoselectivities. The *Z*- and *E*-isomers of the illustrated silylketene acetals (entries 4-7) react in a stereoconvergent manner, providing the *syn* aldol adducts in high diastereo- and enantioselectivity (*dr* ≥ 94:06 1,2-*syn*:1,2-*anti*, *ee* ≥ 93%).

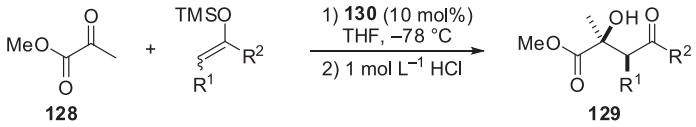
The observed results can be rationalized by invoking a square planar transition state **TS13** (Scheme 22).

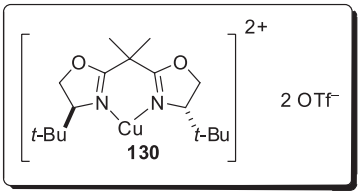
As can be observed from the proposed transition state **TS13**, the *Si* face is exposed to suffer an attack of the nucleophile, which is consistent with the results.

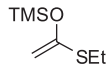
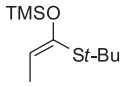
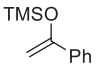
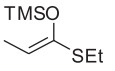
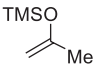
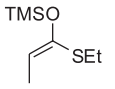
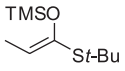
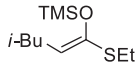
In addition, Evans and co-workers[47] showed that the use of tin C_2-symmetric complexes as chiral Lewis acid led to the formation of aldol adducts with 1,2-*anti* relationship in excellent levels of enantiomeric excess (Table 10).

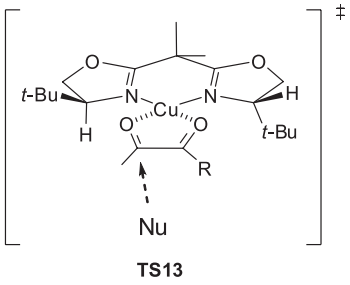
The catalyzed addition to pyruvates is general with respect to the silyl enol ether. Both *E*- and *Z*-isomers of the silyl enol ether (Table 10, entries 1 and 2) react in a stereoconvergent manner providing the substituted succinate derivative with excellent diastereo- and enantioselectivity (*dr* = 99:01 1,2-*anti*:1,2-*syn*, *ee* > 96%). Variation in the size of the alkyl substituent of the enolsilane is possible

Table 9. Catalyzed enantioselective aldol reactions between methyl pyruvate (**128**) and enolsilanes





entry	Enolsilane	*dr* (1,2-*syn*:1,2-*anti*)	*ee* / % (Yield / %)	entry	Enolsilane	*dr* (1,2-*syn*:1,2-*anti*)	*ee* / % (Yield / %)
1		–	97 (97)	5		95:05	98 (88)
2		–	99 (77)	6		94:06	93 (90)
3		–	93 (76)	7		98:02	98 (91)
4		94:06	96 (96)	8		90:10	93 (88)



Scheme 22. Transition state for aldol reaction involving Cu(II)-(BOX).

without significant loss in stereoselectivity (entries 2-4, *dr* > 98:2 1,2-*anti*:1,2-*syn*, *ee* > 96%).

In 2002, Evans *et al.*[48] reported the total synthesis of pectenotoxin-4 (**139**) and pectenotoxin-8 (**140**) (Scheme 23). The enantioselective Sn^{2+}-catalyzed aldol reaction between silyl enol ether **133** and glyoxylate **134** led to the formation of aldol adduct **135**, which corresponds to the C8-C11 fragment of pectenotoxins in excellent yields and enantiomeric excess (Scheme 23). Similarly, the aldol reaction between silyl enol ether **137** and glyoxylate **134**, mediated by chiral Lewis acid **132**, led to the formation of compound **138** (Scheme 23). This aldol adduct correspond to the C36-C39 fragment of pectenotoxins in excellent yields, diastereo- and enantiomeric excess.

In 2006, Jørgensen and co-workers[49] concluded the total synthesis of nonnatural indolizine alkaloid **145** (Scheme 24). For this purpose, the authors performed a Mukaiyama-type aldol reaction between silyl enol ether **142** and aldehyde **141**, mediated by a chiral (*S*,*S*)-*t*-Bu-BOX **144**, leading to the formation of the aldol adduct **143** in excellent levels of diastereo- and enantiomeric excess (Scheme 24).

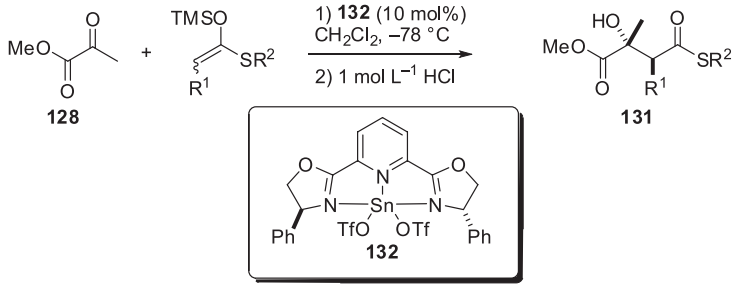
In 2006, Movassaghi and co-workers[50] concluded the total synthesis of acylfulvene (**148**) and irofulven (**149**) (Scheme 25). One of the steps consisted of the Mukaiyama-type aldol reaction between enolsilane **146** and methyl pyruvate **147** mediated by (*R*,*R*)-*t*-Bu-BOX *ent*-**130** leading to the formation of the aldol adduct **147** with excellent levels of enantioselectivities (Scheme 25). This aldol adduct corresponds to the C1-C4 fragment of acylfulvene (**148**) and irofulven (**149**).

8. Asymmetric Induction in Mukaiyama Aldol Reactions with Boron-Derivatives as Chiral Ligands

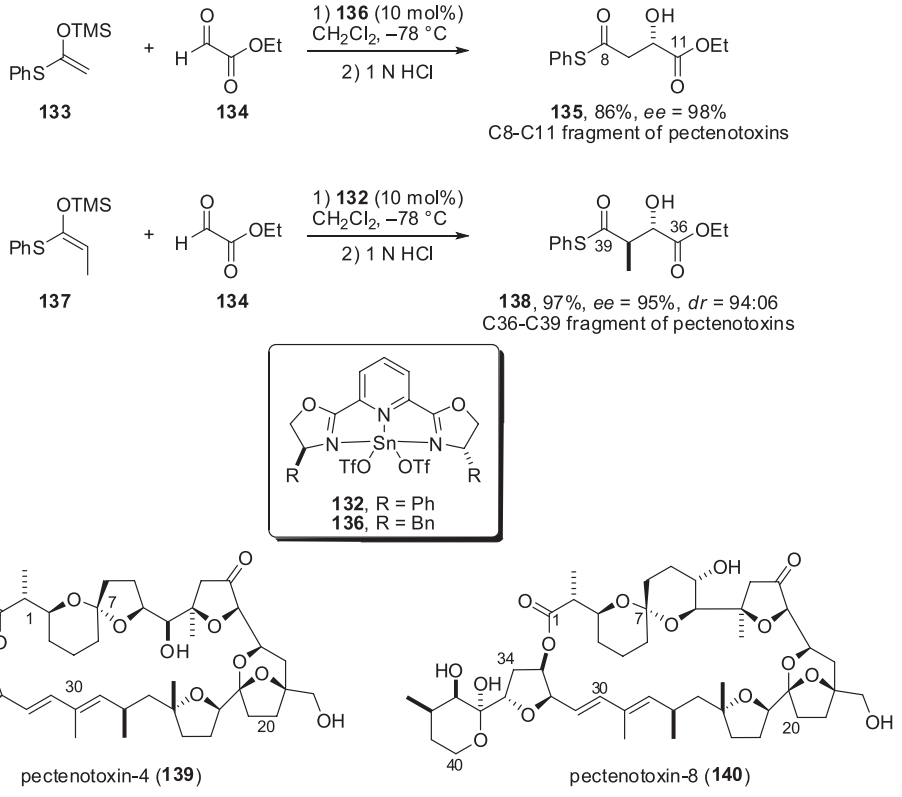
In the early 1990, Masamune and co-workers[51] and Corey *et al.*[52] developed, independently, an asymmetric aldol reaction catalyzed by amino acids derived oxazaborolidines (Scheme 26). In these works, the authors achieved good levels of enantioselectivities.

In 2010, Micoine and Fürstner[53] concluded the total synthesis of the potent cell migration inhibitor lactimidomycin (**159**) (Scheme 27). In this paper, the

Table 10. Catalyzed enantioselective aldol reactions between methyl pyruvate (**128**) and enolsilanes

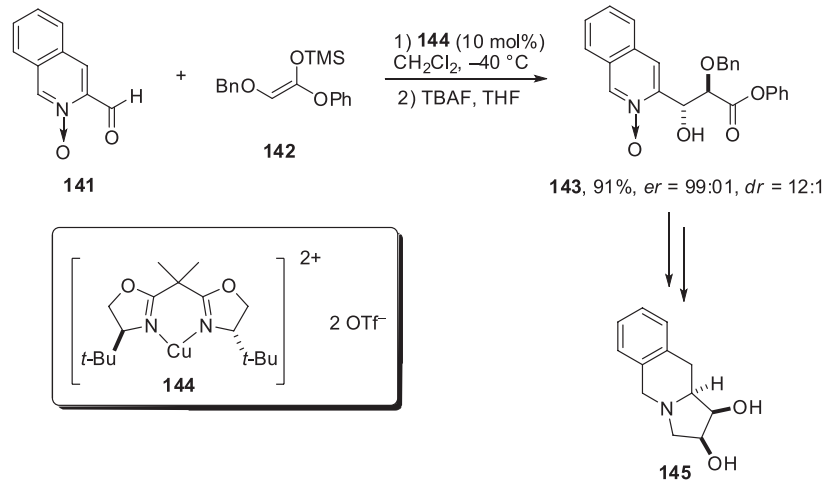


entry	Enolsilane	*dr* (1,2-*anti*:1,2-*syn*)	*ee* / % (Yield / %)	entry	Enolsilane	*dr* (1,2-*anti*:1,2-*syn*)	*ee* / % (Yield / %)
1	TMSO, St-Bu	99:01	99 (94)	5	TMSO, SEt	95:05	92 (91)
2	TMSO, St-Bu	99:01	96 (84)	6	TMSO, Et, SEt	99:01	97 (94)
3	TMSO, Et, St-Bu	98:02	97 (84)	7	TMSO, *i*-Bu, SEt	99:01	97 (76)
4	TMSO, *i*-Bu, St-Bu	99:01	99 (81)				

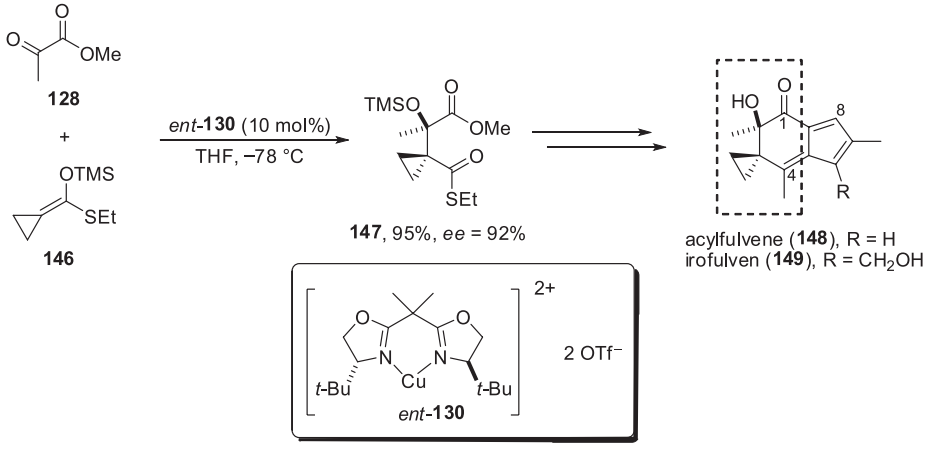


Scheme 23. Aldol reactions in the total synthesis of pectenotoxins **139** and **140**.

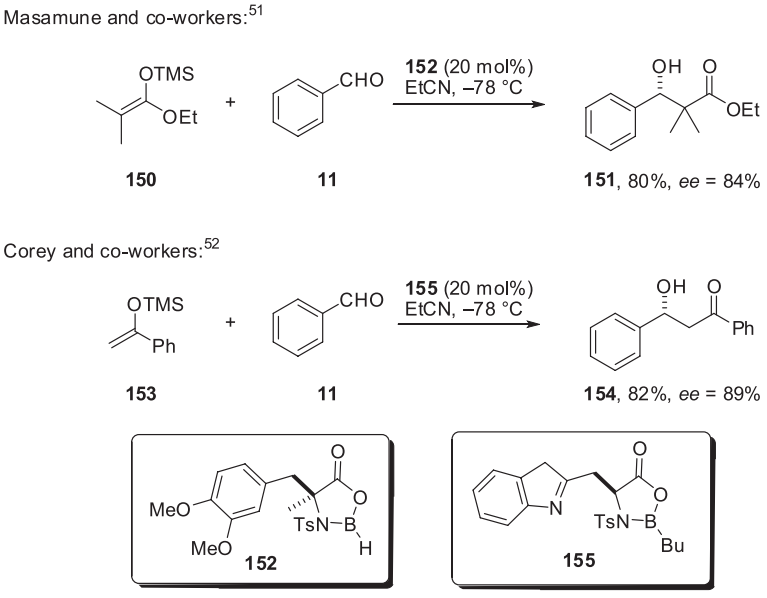
authors performed the late-stage Mukaiyama-type aldol reaction between the silyl enol ether prepared from ketone **156** and aldehyde **157** mediated by oxazaborolidine **158**, after work-up with HF-pyridine leading to the formation of lactimidomycin (**159**) in 60% yield and excellent selectivity.



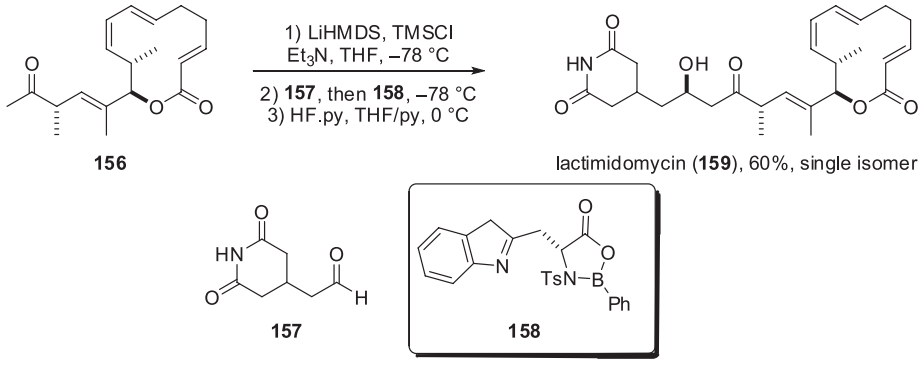
Scheme 24. Aldol reactions in the total synthesis of non-natural indolizine alkaloid **145**.



Scheme 25. Aldol reactions in the total synthesis of acylfulvene (**148**) and irofulven (**149**).



Scheme 26. Aldol reactions mediated by oxazaborolidines.



Scheme 27. Aldol reaction in the total synthesis of lactimidomycin (**159**).

9. Conclusions

In this review article, our group demonstrated representative examples of metal-mediated catalytic asymmetric aldol reactions. This type of aldol reactions using chiral catalysis are one of the most powerful methods to control the stereochemistry of aldol adducts. One of the major motivations for the development of new enantioselective catalysis is to reach higher catalytic efficiency under very mild reaction conditions. Thus, the design of new chiral catalyst systems continues to be an attractive field in organic synthesis.

Although, the applicability of the most asymmetric catalysis is limited in terms of substrate generality, we can predict a promising future for this field in the light of the search for synthetic ideality[54] and the green chemistry.[55]

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