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Catalytic Asymmetric Formation of β-Lactones

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Conatact Ion Pair Directed *Lewis* Acid Catalysis: Asymmetric Synthesis of *trans*-Configured β-Lactones

Angew. Chem. Int. Ed. **2008**, *47,* 5461-5464; *Angew. Chem.* **2008**, *120,* 5541-5544.

Peters, R.; Fischer, D. F.; Jautze, S.; Koch, F. M.; Kull, T.; Tiseni, P. S.; Xin, Z.; Zajac, M.

Catalytic Methods for Direct Access to Chiral High-Added-Value Products

Chimia **2008**, *62,* 497-505.

Table of Contents

List of Abbreviations

Abbreviations which are frequently used in this thesis are listed below. Abbreviations which are used only once or only in one paragraph are explained in the text.

Ac	acetyl	GC	gas chromatography
aq.	aqueous	h	hour(s)
Binol	2,2‘-dihydroxy-1,1‘-di-naphthyl	Hi-Res	high resolution
Bn	benzyl	HPLC	high-performance liquid chromatography
Bu	butyl	*i*Bu	isobutyl
Cat.	catalyst	*i*Pr	isopropyl
*c*Hex	cyclohexyl	IR	infrared spectroscopy
d	day(s)	*i.v.*	*in vacuo*
Dibal	diisobutylaluminum hydride	KHMDS	potassium hexamethyldisilazide
DIEA	*N,N*-diisopropylethylamine (*Hünig*’s base)	LDA	lithium diisopropyl amide
DMAP	4-*N,N*-dimethylaminopyridine	L.A.	*Lewis* acid
DMF	*N,N*-dimethylformamide	M	molar
DMS	dimethylsulfide	*m*	*meta*
DMSO	dimethylsulfoxide	Me	methyl
de	diastereomeric excess	min	minute(s)
dr	diastereomeric ratio	mp	melting point
ee	enantiomeric excess	Ms	methylsulfonyl
EI	electron impact ionization	MS	mass spectrometry
equiv.	equivalent	MTBE	methyl *tert*-butyl ether
ESI	electron spray ionization	n.d.	not determined
Et	ethyl	NMR	nuclear magnetic resonance
FC	flash chromatography	*o*	*ortho*

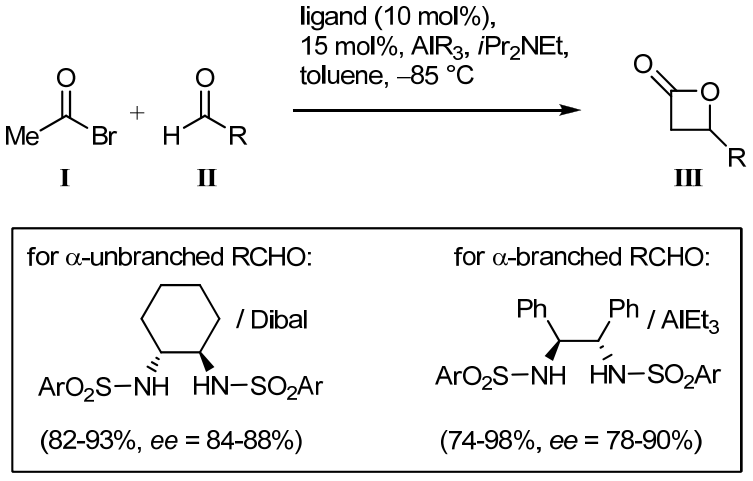
p	*para*	Tf	trifluoromethanesulfonyl
Ph	phenyl	THF	tetrahydrofuran
py	pyridine	TLC	thin layer chromatography
rf	reflux	TMS	trimethylsilyl
sat.	saturated	Ts	*p*-toluenesulfonyl
TBS	*tert*-butyldimethylsilyl	TsOH	*p*-toluenesulfonic acid
*t*Bu	*tert*-butyl	triflate	trifluoromethanesulfonate
TEA	triethylamine	UV	ultraviolet light

1 Abstract

Part A: *Lewis* Acid Catalysis

The demand for the development of practical catalytic routes to optically active β-lactones is still high due to the advanced utility of the title compounds in organic synthesis. β-Lactones undergo, e.g., readily nucleophilic ring-opening reactions as a result of their intrinsic ring strain and thus behave as activated aldol equivalents.

In Part A of this work the development of an efficient and practical aluminum-bissulfonamide catalyzed enantioselective formation of monosubstituted β-lactones **III** by [2+2] cycloaddition of ketene (generated *in situ* from acetylbromide **I** by dehydrobromination) with various α-unbranched and -branched aliphatic aldehydes **II** is described (Scheme 1). Compared to alternative *Lewis* acid catalyzed methods this system offers the advantage of operational simplicity. The ligand synthesis requires just a single sulfonylation step from commercially available enantiomerically pure diamines. The products are formed in high to excellent yield with *ee* values typically ranging from 78 to 90% using 10 mol% of the bissulfonamide ligand. The key finding of this work is a remarkable rate acceleration by using an Al / ligand ratio of 1.5:1, which can be explained by *Lewis* acid activation of the *Lewis* acid catalyst, e.g., by coordination of the sulfonyl groups in the Al-sulfonamide complex to an achiral Al-source.

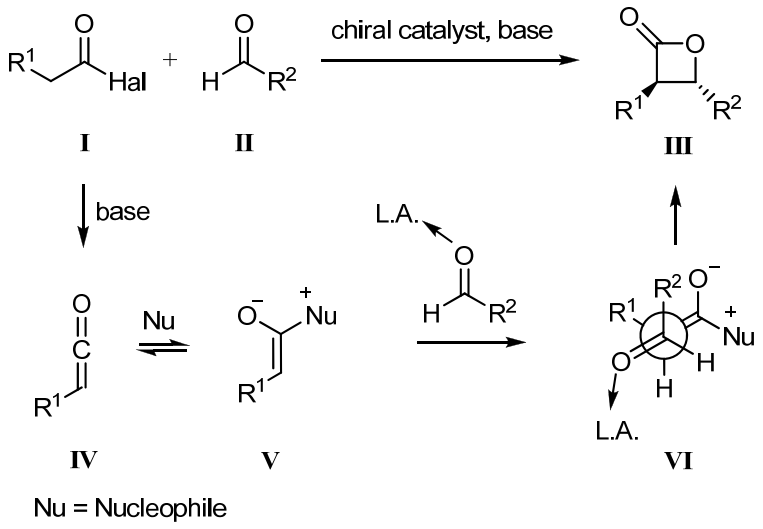


Scheme 1

Part B: Dual Activation Catalysis

β-Lactones are not only very useful building blocks, but also represent a structural motif in a number of important natural and synthetic bioactive products such as the *anti*-obesity drug tetrahydrolipstatin (Xenical®, *F. Hoffmann La-Roche*). The majority of these bioactive compounds have a *trans*-configuration about the heterocyclic system. Unfortunately, almost all of the known catalytic asymmetric [2+2] cycloadditions provide preferentially the *cis* isomers.

The aim of Part B of this work was to develop the first *trans*-selective catalytic asymmetric [2+2] cyclocondensation of acyl halides **I** and aliphatic aldehydes **II**. As no such system has been presented before using classical strategies, a novel concept within the context of dual-activation catalysis is introduced, the contact ion pair directed *Lewis* acid catalysis, and applied to the formation of *trans*-configured β-lactones. The development of this concept was based upon the idea to make use of enolate **V** rather than ketene **IV** as reactive intermediate (Scheme 2).



Scheme 2. Concept for the formation of *trans*-configured β-lactones.

The enolate nucleophilically attacks the aldehyde activated by a chiral *Lewis* acid possessing only one available coordination site *via* an open transition state which adopts a staggered conformation around the generated C-C-bond, thus explaining the observed *trans* selectivity. The unstable anionic nucleophile is presumably generated by the catalyst's pyridinium bromide counterion, and stabilized and directed by the formation of a contact ion pair (CIP) (Figure 1).

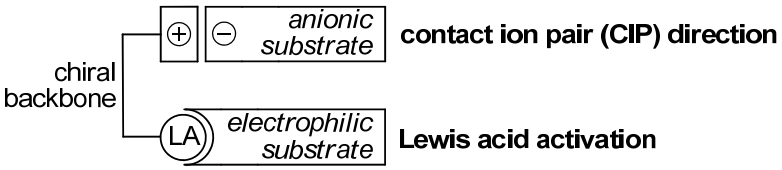
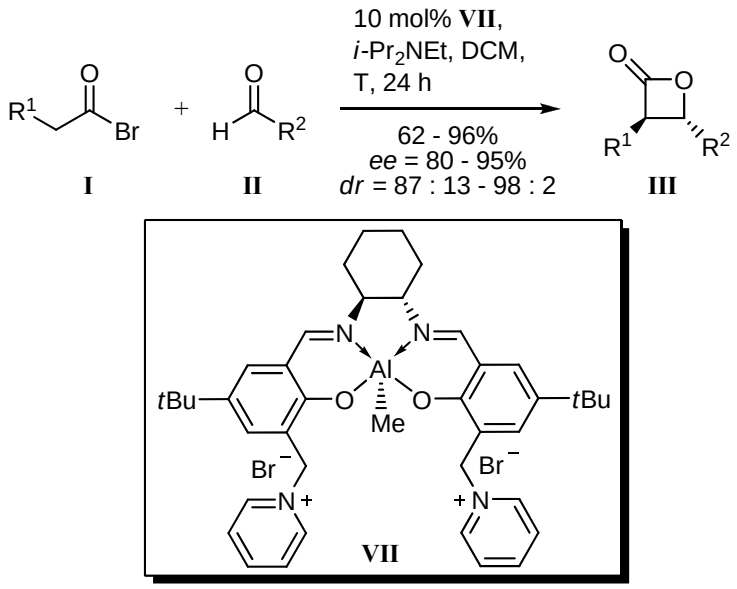


Figure 1. The concept of CIP directed *Lewis* acid catalysis.

The reaction generally provided high *trans* selectivities with aliphatic aldehydes (Scheme 3). The enantioselectivity did not significantly depend on the aldehyde, and almost identical results were obtained with sterically demanding and undemanding aldehydes **II**. High enantioselectivities have previously never been reported for small aliphatic aldehydes such as propanal using alternative catalytic asymmetric cycloadditions with acyl halides or ketenes.



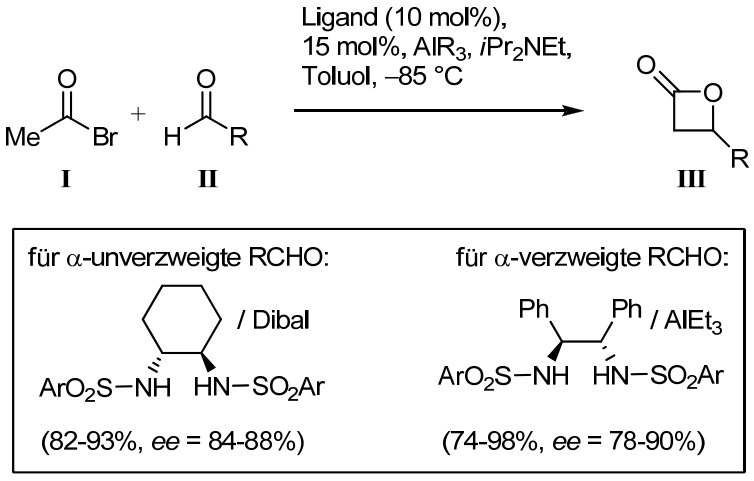
Scheme 3

2 Zusammenfassung

Teil A: *Lewis*-Säure Katalyse

Auf Grund der vielseitigen Anwendungsmöglichkeiten von β-Lactonen ist die Nachfrage nach effizienten, katalytischen Routen für die Herstellung von optisch aktiven β-Lactonen sehr hoch. Wegen ihrer hohen Ringspannung können β-Lactone leicht mit Nukleophilen geöffnet werden und verhalten sich somit wie aktivierte Aldol-Äquivalente.

In Teil A dieser Arbeit wird die Entwicklung eines effizienten und praktischen Aluminium-Bissulfonamid-Katalysators für die katalytische, enantioselektive Bildung monosubstituierter β-Lactone **III** über eine [2+2]-Cycloaddition von Keten (mittels Dehydrobrominierung aus Acetylbromid **I** *in situ* gebildet) und verschiedenen α-unverzweigten und -verzweigten Aldehyden **II** beschrieben (Schema 4). Dieses System ist im Vergleich zu alternativen *Lewis*säure katalysierten Methoden operationell sehr einfach. Die Liganden-Synthese erfolgt ausgehend von kommerziell erhältlichem Diamin in einem einzigen Sulfonylierungsschritt und die Produkte können mit guten bis sehr guten Ausbeuten und *ee*-Werten in einem Bereich von 78 bis 90% mit 10 mol% des Bissulfonamid-Liganden hergestellt werden. Die wichtigste Entdeckung in dieser Arbeit ist eine erstaunliche Beschleunigung der Reaktion durch Verwendung eines Verhältnisses von Al / Ligand von 1.5:1. Dies kann durch eine *Lewis*säure-Aktivierung des *Lewis*säure-Katalysators erklärt werden, wobei zum Beispiel die Sulfonylgruppen des Al-Sulfonamid-Komplexes an eine achirale *Lewis*säure koordinieren.

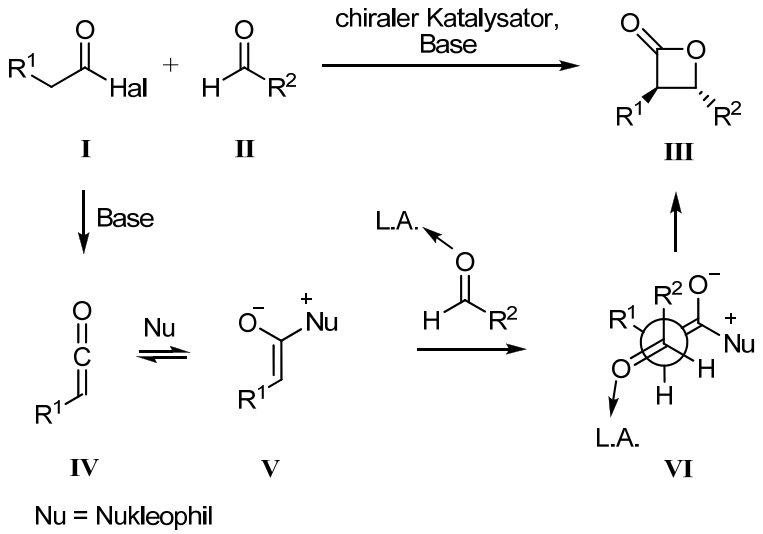


Schema 4

Teil B: Bifunktionelle Katalyse

β-Lactone sind nicht nur sehr nützliche Ausgansmaterialien, sondern repräsentieren auch ein strukturelles Motiv in einer Vielzahl wichtiger natürlicher und synthetischer, bioaktiver Produkte wie etwa Tetrahydrolipstatin, welches von *F. Hoffmann La-Roche* als Mittel gegen Übergewicht unter dem Namen Xenical® vertrieben wird. Die meisten dieser bioaktiven Verbindungen weisen eine *trans*-Konfiguration für den heterocyclischen Ring auf. Leider führen fast alle katalytischen, asymmetrischen [2+2]-Cyloadditionen zu den *cis*-konfigurierten Isomeren.

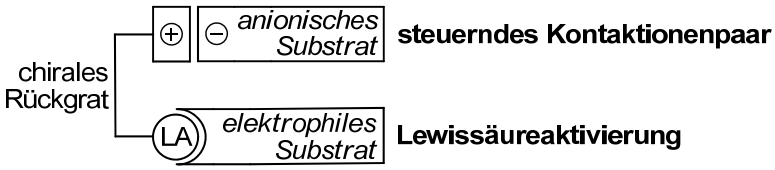
Das Ziel des zweiten Teils dieser Arbeit war die Entwicklung der ersten *trans*-selektiven, katalytischen, asymmetrischen [2+2]-Cyclocondensation eines Acylhalogenides **I** und aliphatischen Aldehyden **II**. Da ein solches System noch nie zuvor präsentiert wurde, wird hier ein neues bifunktionelles Katalyse-Konzept eingeführt, welches eine Kontaktionenpaar dirigierte *Lewis*säurekatalyse beinhaltet. Die Entwicklung dieses Konzepts basierte auf der Idee, dass in der Reaktion Enolat **V** und nicht Keten **IV** als reaktives Intermediat fungiert. (Schema 5).



Schema 5. Konzept für die Bildung von *trans*-konfigurierten β-Lactonen.

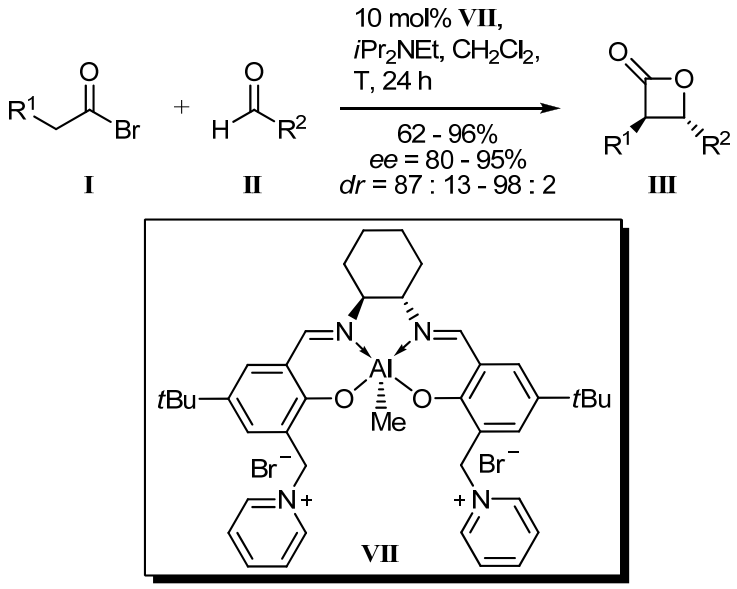
Das Enolat greift dabei den durch die chirale *Lewis*säure, welche nur eine verfügbare Koordinationsstelle besitzt, aktivierten Aldehyd an. Die Reaktion verläuft über einen offenen Übergangszustand bei welchem eine gestaffelte Konformation um die neu gebildete C-C-Bindung vorliegt, was die *trans*-Selektivitäten erklärt.

Das instabile, anionische Nukleophil wird vermutlich direkt in der Katalysatorsphäre durch den Angriff des Bromid-Gegenions auf das Keten gebildet und sowohl stabilisiert als auch dirigiert durch Ausbildung eines Kontaktionenpaares (Figur 2).



Figur 2. Das Konzept von Kontaktionepaar dirigierter Lewissäurekatalyse.

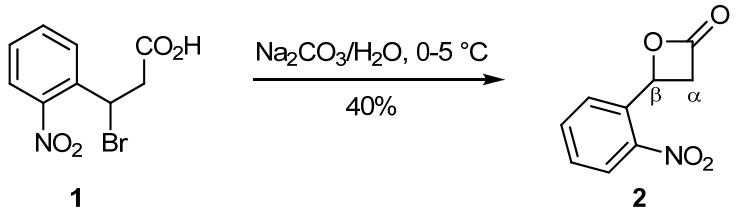
Reaktionen mit aliphatischen Aldehyden ergaben generell hohe *trans*-Selektivitäten (Schema 6). Die Enantioselektivität variiert nur leicht bei Verwendung unterschiedlicher Aldehyde und fast identische Resultate wurden für sterisch anspruchsvolle und weniger anspruchsvolle Aldehyde **II** erzielt. Hohe Enantioselektivitäten wurden noch nie zuvor für sehr kleine aliphatische Aldehyde wie Propanal, Butanal oder Pentanal bei Verwendung alternativer katalytischer, asymmetrischer Cycloadditionen mit Acylhalogeniden oder Ketenen erzielt.



Schema 6

3 Introduction

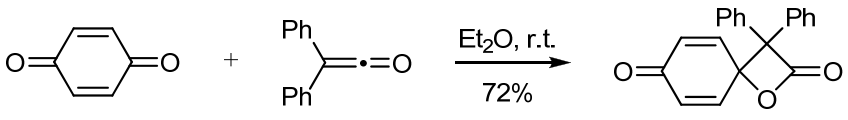
Although β-lactones possess a strained and therefore very reactive four-membered heterocyclic ring, they are known for a very long time. 2-Oxetanone, the parent β-lactone, was first prepared in 1916 by *Johanson* by treatment of an aqueous solution of sodium β-iodopropionate with silver nitrate,[1] but more stable substituted β-lactones have been known ever since the end of the century before last when *Einhorn* was, in 1883, the first to isolate and purify crystalline lactone **2** which was obtained on treatment of 3-bromo-3-(2-nitrophenyl)propionic acid (**1**) with sodium carbonate, and purified by crystallization (Scheme 7).[2]



1 **2**

Scheme 7

Amazingly, the [2+2] cycloaddition between a ketene and a carbonyl group, one of today's most important reactions to form β-lactones, was already introduced in 1911 by *Staudinger* and *Bereza*. They observed a reaction between benzoquinone (**3**) and diphenyl ketene (**4**) which led to β-lactone **5** (Scheme 8).[3]

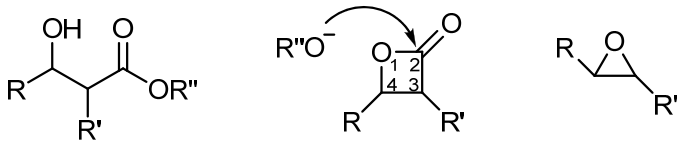


3 **4** **5**

Scheme 8

Despite the fact that the first β-lactone was synthesized 125 years ago, it is only lately that these heterocycles have received significant attention as synthetic intermediates. One reason for this disparity is a lack of asymmetric methods for their synthesis.[4] In recent years, several significant advances in this area have begun to reveal the rich potential of β-lactones as valuable synthetic intermediates for natural and unnatural product synthesis.

Most important, β-lactones can be viewed as masked aldol products since they combine the constitution of aldol products with an inherent reactivity similar to epoxides due to considerable ring strain (β-lactones: 23 kcal/mole; epoxides: 27 kcal/mole)[5].



Aldol products β-lactone epoxide

In addition, various bioactive natural and synthetic products possessing a β-lactone structural motif have been identified as specific enzyme inhibitors.[6] For example, Omuralide and the salinosproamides are highly potent and specific inhibitors of the proteasome function.[7] Some natural products or β-lactone precursors to natural products are compiled in Figure 3. Among the natural products, tetrahydrolipstatin is identified as an antiobesity agent, being the first over-the-counter weight-loss medication and approved by the FDA under the trade name Xenical®.

Of late, especially *trans*-β-lactones have generated renewed interest among synthetic chemists due to the recent findings that they are specific inhibitors of fatty acid synthase (FAS-TE), an approved drug target for anticancer acitivity.[8] The postulated mechanism for this potent inhibitory activity is due to irreversible covalent binding to an active site serine of pancreatic lipase. Owing to the significant activity of these molecules, a number of approaches have been reported for their synthesis.[9]

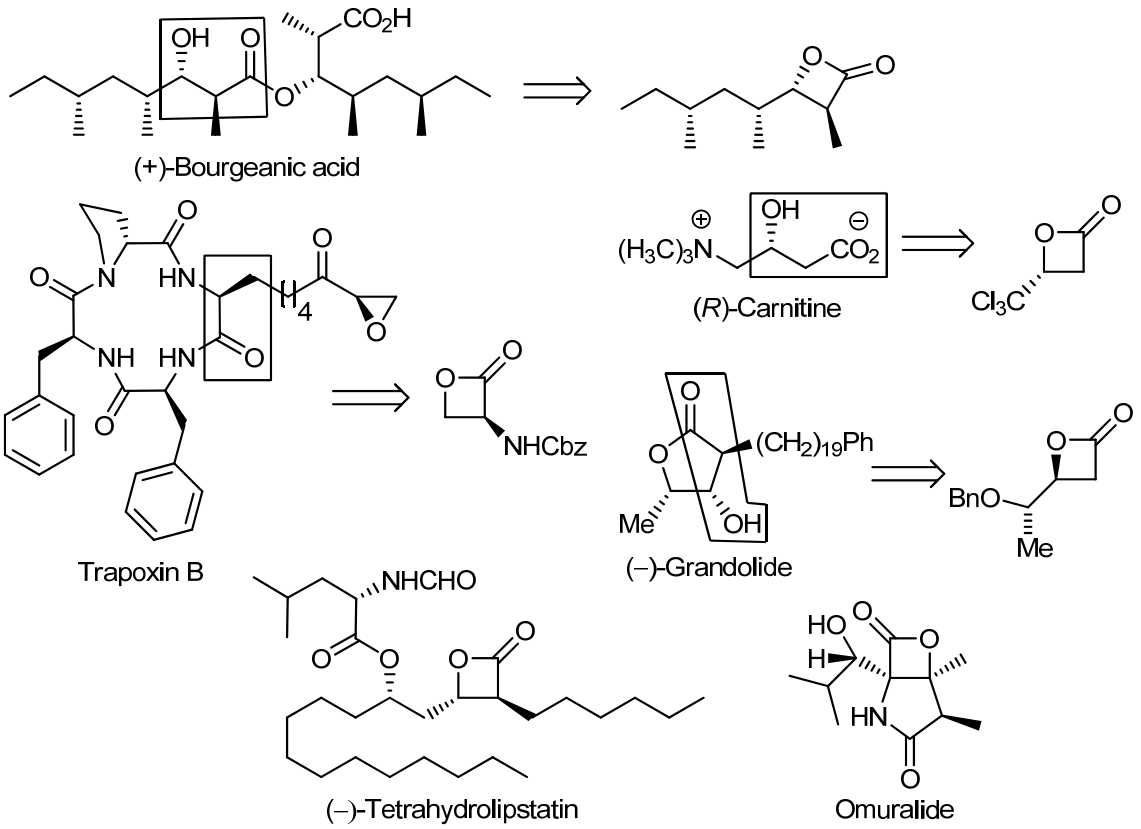
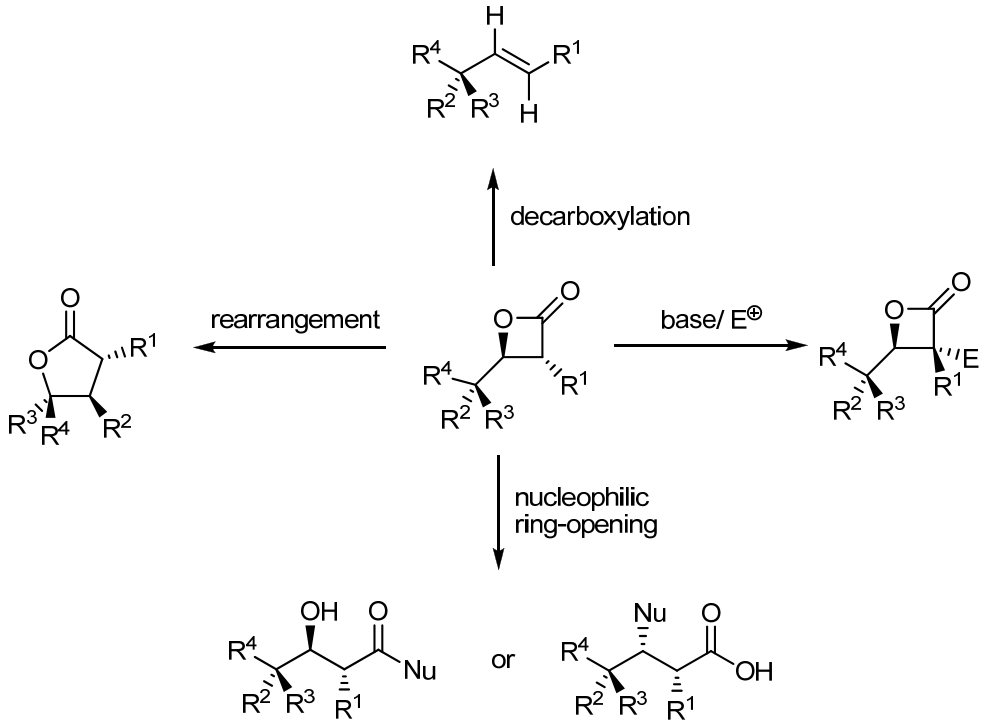


Figure 3. Bioactive natural and synthetic products and/or β-lactone precursors (atoms derived from the β-lactone nucleus are framed).

3.1 Reactivity of β-Lactones

The high strain of the β-lactone ring is reflected in a reactivity, which is unusual in comparison with "normal" esters and lactones. Among the reactions which β-lactones may undergo, four are of particular importance (Scheme 9).

- Nucleophilic ring-opening reactions
- Decarboxylations
- *Lewis* acid promoted rearrangements
- Enolate formation and subsequent trapping reactions with electrophiles

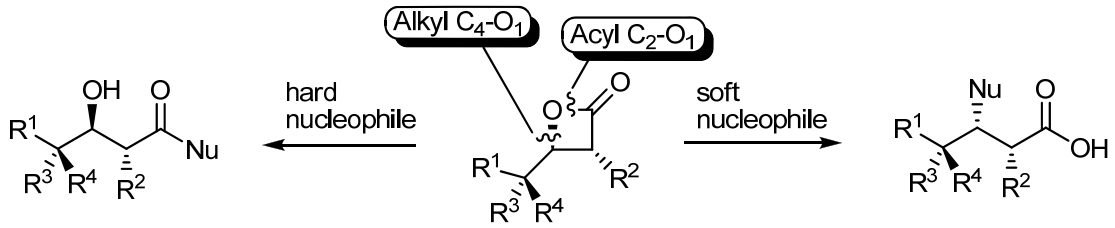


Scheme 9. General reactivity of β-lactones.

3.1.1 Nucleophilic Ring-Opening Reactions

Just as β-lactones can be formed by oxygen-alkyl or oxygen-acyl bond formation (see Chapter 3.2.1 and 3.2.2), they can also undergo an oxygen-alkyl or oxygen-acyl bond cleavage in the presence of nucleophiles. Hence, they can be regarded as ambident electrophiles.

In general, hard nucleophiles such as alkoxides, alkyllithiums, and *Grignard* reagents react with β-lactones by cleaving the oxygen-acyl bond, while oxygen-alkyl bond cleavage occurs with soft nucleophiles including organocuprates, azides, halides, and thiolates (Scheme 10).[10]



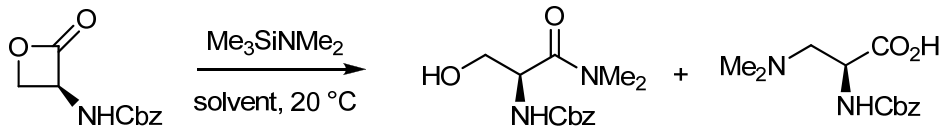
Scheme 10. Nucleophilic ring-opening of β-lactones.

3.1.1.1 Cleavage with N-Nucleophiles

Vederas and co-workers showed that α-amino-β-lactones, especially those derived from *N*-protected serine and threonine, are excellent precursors to unnatural α-amino acids by nucleophilic attack at the β-carbon.[11] On the other hand, various nitrogen nucleophiles may cleave optically active β-lactones *via* alkyl-oxygen bond cleavage thus delivering β-amino acids.

The same group also demonstrated that trimethylsilylamines are useful nucleophiles to form β-amino-L-alanine derivatives in good yields from Cbz-serine-β-lactone (**6**) (Table 1).[12] The product distribution between oxygen-alkyl and oxygen-acyl cleavage showed a high solvent dependency.

Table 1. Solvent effects on addition of trimethylsilylamine to serine-β-lactone (**6**).



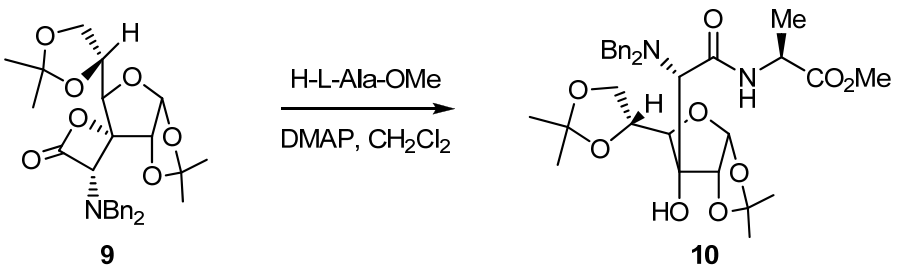
6 **7** **8**

		Product ratio		
Entry	**Solvent**	**Amide 7**	**Amino acid 8**	**Yield[a] [%]**
1	$CHCl_3$	80	20	88
2	CH_2Cl_2	65	35	85
3	$Cl(CH_2)_2Cl$	35	65	90
4	THF	20	80	92
5	CH_3CN	5	95	95

[a]Refers to combined yield of amide **7** and acid **8**.

The use of less polar solvents gave predominantly the amide **7** (entries 1 and 2), whereas the use of dipolar aprotic solvents gave the amino acid **8** as the major product (entries 4 and 5).

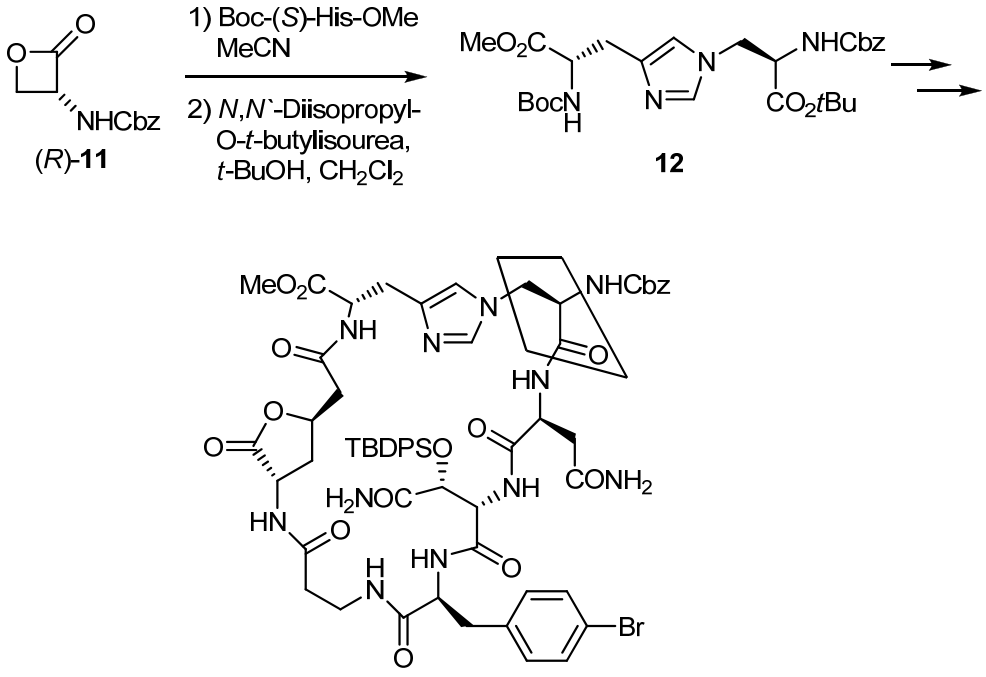
Lavergne and co-workers coupled spirocyclic 2-oxetanones with various amino esters to form glycopeptides with retentive transfer of the configuration.[13] The acylation of spirolactone (**9**) with alanine methyl ester employing DMAP as catalyst delivered glycopeptide **10** in 90% yield (Scheme 11).



9 **10**

Scheme 11

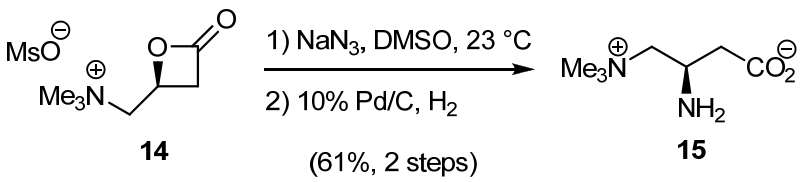
In an application of the *Vederas* β-lactone approach to α-amino acids, *Shiori* and co-workers reported the synthesis of the southern hemisphere of theonellamide F starting from serine β-lactone (*R*)-**11** (Scheme 12)[14] which was treated with Boc-(*S*)-His-OMe leading to oxygen-alkyl cleavage by the imidazole ring nitrogen. *t*-Butylester formation with *N,N'*-diisopropyl-O-*t*-butylisourea delivered protected α-amino acid **12** in 40% yield for the two steps. This was further elaborated into the southern hemisphere **13** of theonellamide F.



Theonellamide F (**13**) (southern hemisphere)

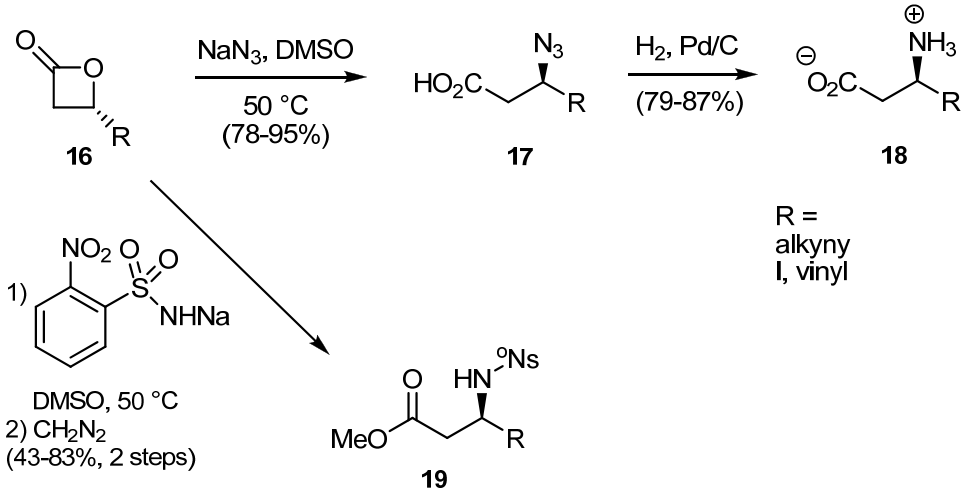
Scheme 12

Giannessi and co-workers showed that β-lactone intermediates are useful for the synthesis of carnitine derivatives.[15] Oxygen-alkyl bond cleavage of β-lactone (**14**) by sodium azide followed by azide reduction gave aminocarnitine (**15**) in >99% *ee* (Scheme 13).



Scheme 13

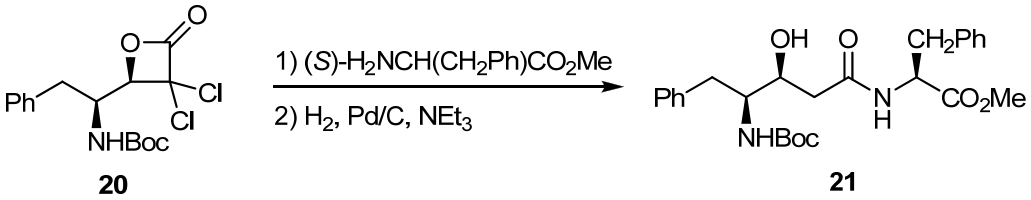
Similarly, *Nelson* and co-workers used sodium azide to form β-azido acids **17** with complete inversion of the absolute configuration. These intermediates can be further reduced to β-amino acids **18** (Scheme 14).[16]



Scheme 14

The same group also developed a new method for the addition of a protected amino moiety to β-lactone substrates. The sodium salt of *o*-nitrobenzenesulfonamide was employed as nucleophile to cleave the oxygen-alkyl bond of β-lactone **16** delivering *N*-nosyl-β-amino acid methyl esters **19** (Scheme 14).

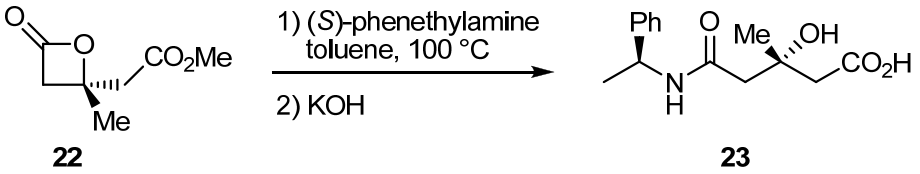
Palomo and co-workers used α,α-dichlorinated β-lactones, obtained by [2+2] cycloaddition of dichloroketenes and optically pure α-amino aldehydes, for the synthesis of peptide mimics.[17] (*S*)-Phenylalanine was used as amino nucleophile to attack the oxygen-acyl bond in **20** providing an intermediate chlorinated amide in excellent yield (Scheme 15). Subsequent dehalogenation produced peptide mimic **21** in 87% overall yield from β-lactone **20**.



20 **21**

Scheme 15

Shirama and co-workers employed a β-lactone intermediate to synthesize chiral HMGA (3-hydroxy-3-methylglutaric acid) esters and amides.[18] HMGA is an important intermediate in the biosynthesis of terpenoids, steroids, and carotenoids. β-Lactone **22** underwent oxygen-acyl cleavage with (*S*)-phenylethylamine to yield acid **23** after hydrolysis (Scheme 16). Several natural products possess related HMGA fragments, for instance fasciculol D and dicrotaline.



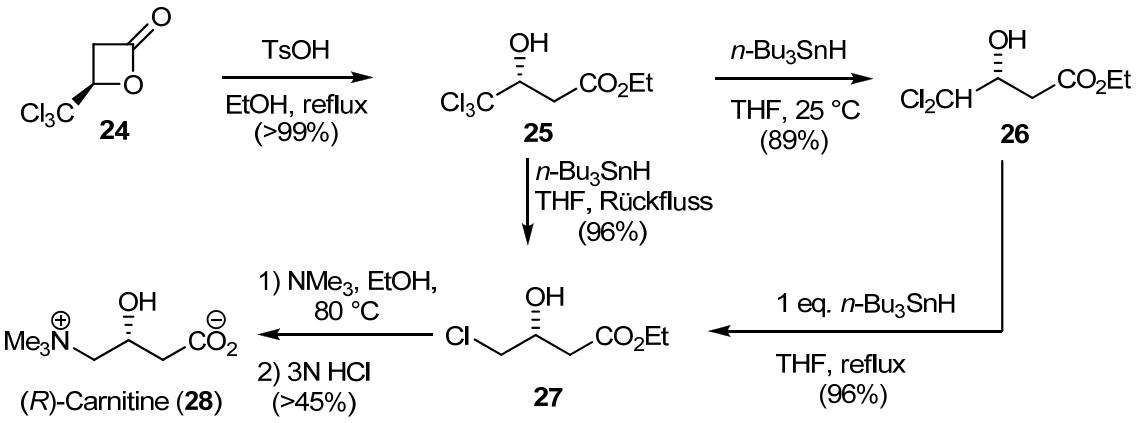
22 **23**

Scheme 16

3.1.1.2 Cleavage with O-Nucleophiles

Song and co-workers developed an efficient process for the preparation of (*R*)-carnitine (**28**) *via* a β-lactone intermediate.[19] (*R*)-Carnitine (vitamin B_T) regulates the transport of long-chain fatty acids through mitochondrial membranes and plays an important role in human metabolism.[20] The process involved oxygen-acyl cleavage of commercially available β-lactone **24** with acidic ethanol to produce β-hydroxy ester (**25**) in quantitative yield (Scheme 17).

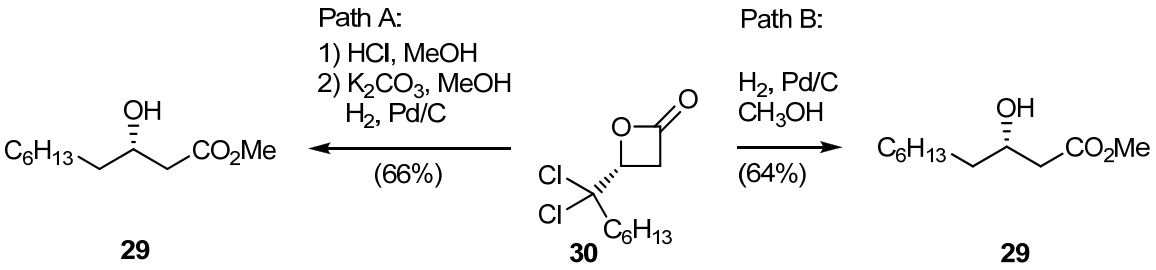
Controlled dechlorination with tributyltin hydride gave either the monochlorinated product **27** or the mono-dechlorinated product **26**, depending on the reaction temperature.



Scheme 17

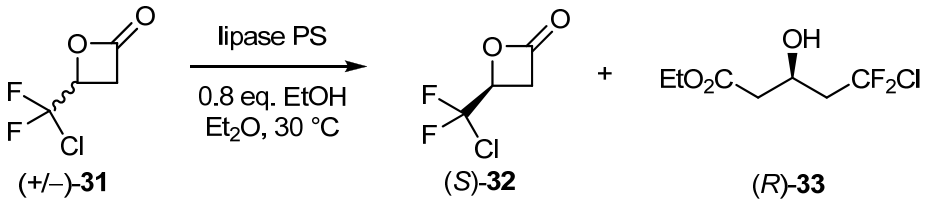
In a subsequent report, *Song* and *Choi* found that β-lactone **24** could be directly converted to ester **27** by a selective hydrogenation using Pd-C/KOAc in EtOH.[21]

In a related process, *Wynberg* and *Staring* developed a two-step method to convert β-lactone **30** to β-hydroxy ester **29** (Scheme 18, Path A).[22] More recently, *Romo* and *Tennyson* demonstrated that this process could also be performed in a single pot (Scheme 18, Path B).[23]



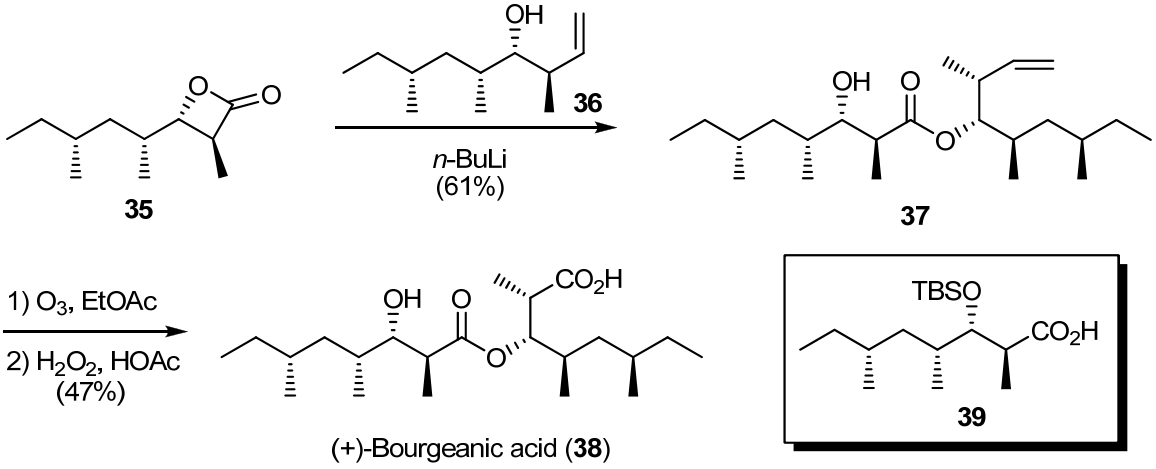
Scheme 18

Fujisawa and co-workers employed a lipase to achieve an enzymatic kinetic resolution of racemic fluorinated β-lactones by conversion to the corresponding ethyl ester (Scheme 19).[24] Treatment of racemic β-lactone **31** with lipase PS and ethanol in ether gave the (*S*)-β-lactone **32** in 97% *ee* (43% yield), and the (*R*)-β-hydroxy ester **33** in 81% *ee* (40% yield).



Scheme 19

White and *Johnson's* synthesis of (+)-bourgeanic acid (**38**) involved acylation of a highly hindered secondary homoallylic alcohol by a β-lactone intermediate. β-Lactone **35** was utilized as an acylating agent for the lithioalkoxide derived from alcohol **36** to give ester **37** in 61% yield (Scheme 20) while typical methods for acid coupling failed.[25]

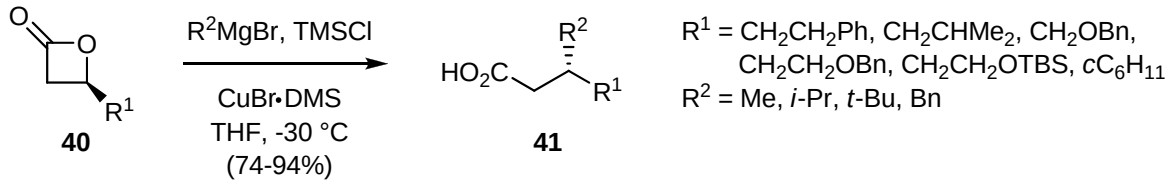


Scheme 20

3.1.1.3 Cleavage with C-Nucleophiles

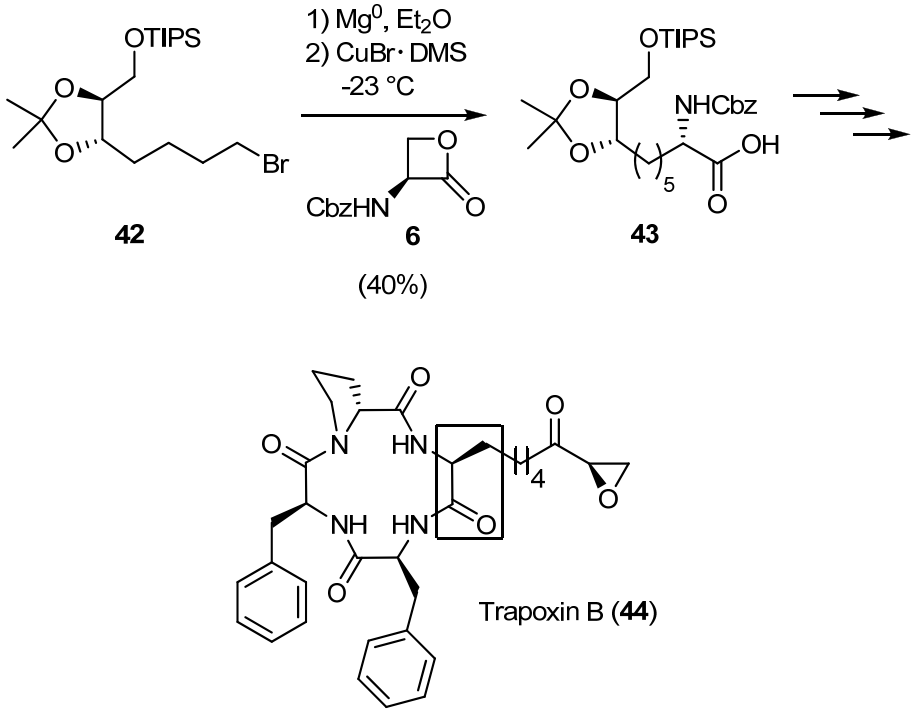
Organomagnesium and -lithium reagents attack β-lactones in the absence of Cu(I) salts at the carbonyl group leading to oxygen-acyl bond cleavage. E.g., *Canonne* and co-workers reported a convenient method for the preparation of diols from propiolactone and organodimagnesium compounds.[26] In contrast, *Fujisawa*[27] and co-workers as well as *Normant*[28] and co-workers independently showed that organocuprates react with β-lactones *via* oxygen-alkyl cleavage leading to a useful 3-carbon homologation.[11b,29]

Based on the work of *Fujisawa*, *Nelson* and co-workers optimized the *Grignard*-mediated oxygen-alkyl cleavage of optically active β-lactones **40** as a generally useful asymmetric synthesis of β-disubstituted carboxylic acids **41** and as an alternative to conjugate addition.[30] Stoichiometric amounts of CuBr and TMSCl are important for achieving consistently high yields (Scheme 21).



Scheme 21

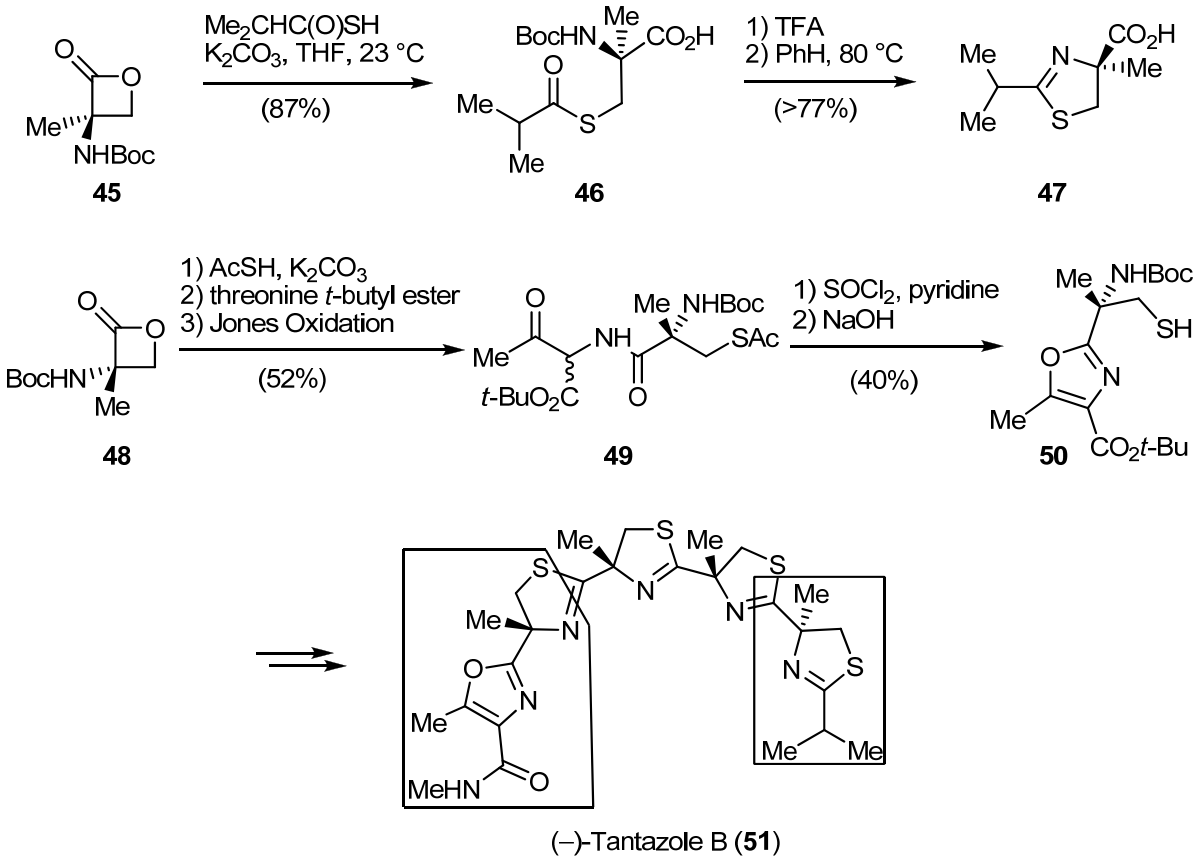
For the total synthesis of trapoxin B (**44**) *Schreiber* and co-workers utilized an organocuprate addition to Cbz-serine β-lactone **6** (Scheme 22).[31] The reaction of the organocuprate derived from bromide **42** with β-lactone **6** gave acid **43** in 40% yield, employing the conditions of *Vederas*.[11b]



Scheme 22

3.1.1.4 Cleavage with S-Nucleophiles

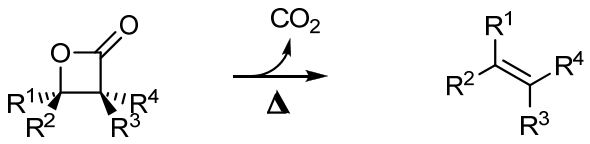
Fukuyama and *Xu* elegantly utilized 2-methylpropanethioic *S*-acid additions to α-methylserine-derived β-lactones **45** and **48** (oxygen-alkyl cleavage despite neopentyl position) in the first total synthesis of (–)-tantazole B (**51**) (Scheme 23).[32] Further transformations of β-lactones **45** and **48** led to both thiazoline **47** and oxazole **50** which were then incorporated into the final target molecule (as shown in boxes). Tantazole B and other members of the family exhibit selective cytotoxicity against murine solid tumors.



Scheme 23

3.1.2 Decarboxylations

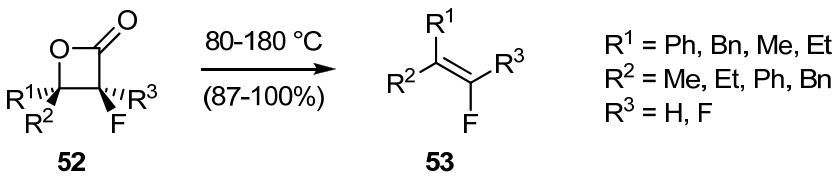
Decarboxylation of β-lactones can proceed *via* thermal decomposition, photolytic or radical cleavage. These CO_2-extrusion reactions are in general stereospecific with complete retentive transfer of the configuration of the β-lactone to the olefin, *i.e*. *E*-olefins are obtained from *trans*-β-lactones and *Z*-olefins from *cis*-β-lactones (Scheme 24).[33]



Scheme 24. Decarboxylation of β-lactones.

3.1.2.1 Thermal Decarboxylations

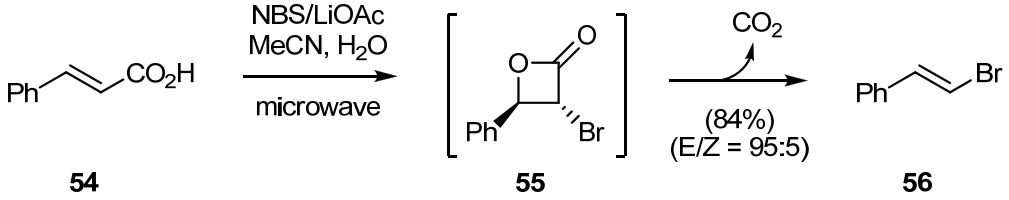
Dolbier and co-workers prepared 1,1-difluoro- and 1-fluoroalkenes *via* stereospecific decarboxylation of the corresponding β-lactones in excellent yield. Fluoroalkenes **53** were obtained by heating β-lactones **52** between 80-180 °C (Scheme 25).



Scheme 25

3.1.2.2 Photolytic Cleavage

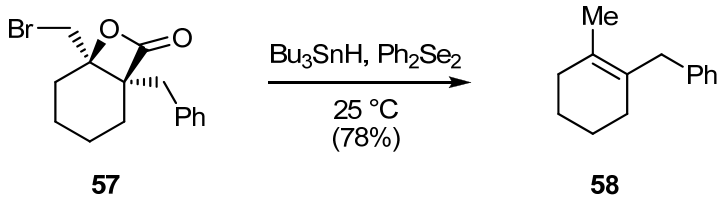
Tokuda and co-workers synthesized (*E*)-β-arylvinyl halides via 2-oxetanones in good yields and with excellent stereoselectivity.[34] Under microwave irradiation, halolactonization of cinnamic acid **54** with *N*-bromosuccinimide produced β-lactone **55** (Scheme 26). Under the reaction conditions, the β-lactone intermediate fragments with loss of CO_2 to deliver vinyl bromide **56** in 84% yield with high *E*/*Z* selectivity.



Scheme 26

3.1.2.3 Radical Cleavage

Crich and *Mo* showed that free-radical reactions of γ-bromo-β-lactones mediated by catalytic benzeneselenol (generated *in situ* from Bu_3SnH and Ph_2Se_2) gave decarboxylated products in good yield (Scheme 27).[35] The authors noted that treatment of lactone **57** with tributyltin hydride and AIBN alone was not effective.



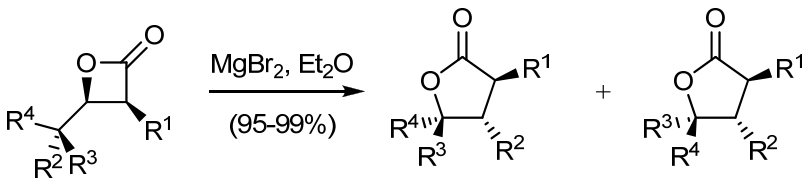
57 **58**

Scheme 27

3.1.3 Rearrangements

Mulzer and co-workers reported the dyotropic ring expansion of β-lactones to form γ-lactones in excellent yield (Table 2).[36] This procedure involves treatment of β-lactones **59** with $MgBr_2$ in Et_2O at 25-30 °C for 12-60 hours.

Table 2. Dyotropic ring expansion of substituted β-lactones.



59 **60** **61**

Entry	R^1	R^2	R^3	R^4	60:61	Yield [%]
1	Ph	Ph	Me	OMe	78:22	96
2	Ph	Ph	OMe	Me	22:78	97
3	Ph	Ph	Me	H	97:3	96
4	Ph	Ph	H	Me	85:15	95
5	Ph	OBn	*t*-Bu	Me	>99:1	86
6	Ph	OBn	Me	Et	>99:1	99
7	Ph	OBn	Et	Me	>99:1	99

The reaction can, in principal, proceed *via* a concerted or stepwise mechanism, as shown in Figure 4. In a concerted mechanism, only γ-lactone **60** should arise where the oxygen-alkyl bond is cleaved simultaneously with migration of R^2. The stepwise process can also deliver γ-lactone **60**, but it can also undergo bond rotation prior to formation of lactone **61**. The observed formation of lactone **61** provided evidence for a stepwise mechanism. The migratory aptitude of substituents was also established to be in the order of π-donor > *n*-donor > σ-donor.

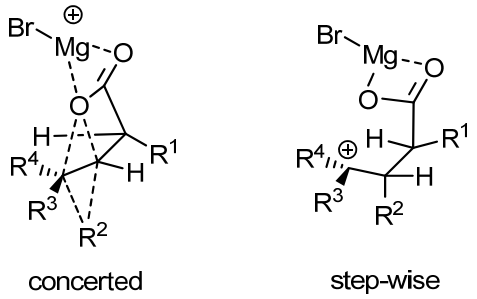
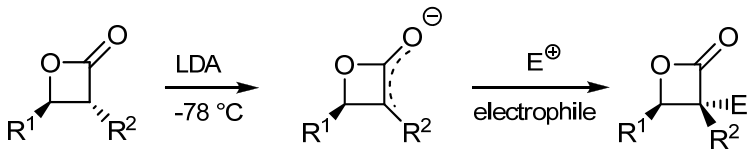


Figure 4

3.1.4 Reactions with Electrophiles

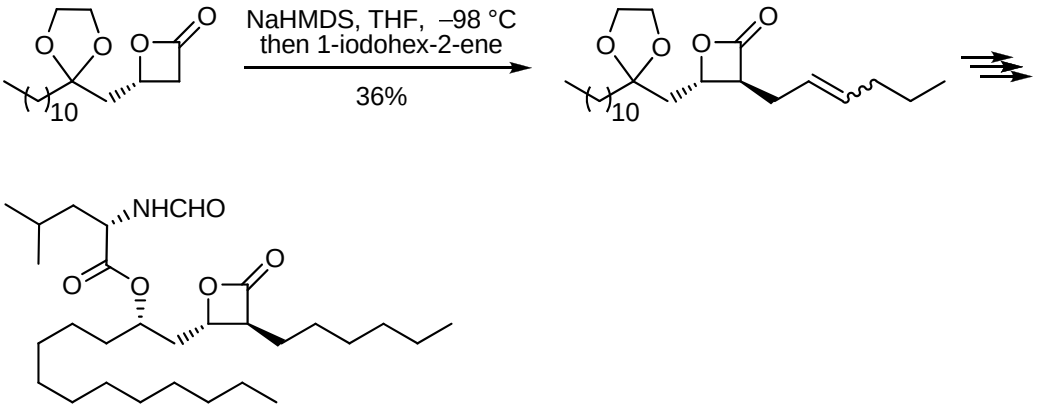
Enolates of β-lactones can be formed at low temperature (−78 or −100 °C) and react with a variety of electrophiles in a highly diastereoselective fashion. For steric reasons, the attack usually takes place opposite to the β-substituent (Scheme 28).[37]



Scheme 28

While enolates of α-substituted β-lactones are surprisingly stable and react with electrophiles quite efficiently, alkylation of β-lactone enolates without α-substitution is difficult and often thwarted by side reactions such as self-acylation.[38]

Some success was achieved recently in a total synthesis of (+/–)-tetrahydrolipstatin (**62**) using low temperature, inverse addition, and an allyl iodide as electrophile (Scheme 29).[39]



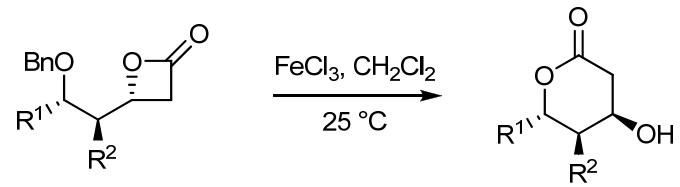
(–)-Tetrahydrolipstatin (**62**)

Scheme 29

3.1.5 Miscellaneous

3.1.5.1 Tandem Transacylation/Deprotection of β-Lactones with Pendant Ethers

Romo and *Zemribo* demonstrated that γ- and δ-lactones can be prepared from β-lactones bearing pendant benzyl ethers via a tandem transacylation/debenzylation pathway.[40] On the basis of prior work by *Ganem* who developed a method for conversion of benzyl ethers to the corresponding acetates,[41] $FeCl_3$ was employed and the reaction afforded δ-lactones **64** in good yields (Scheme 30).

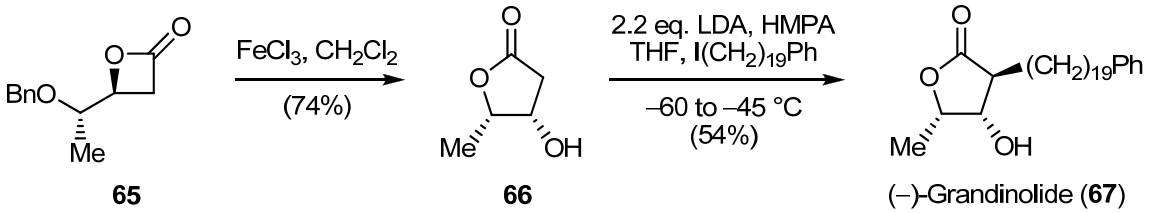


63a R^1 = H, R^2 = Me
63b R^1 = Me, R^2 = H

64a R^1 = H, R^2 = Me (68%)
64b R^1 = Me, R^2 = H (64%)

Scheme 30

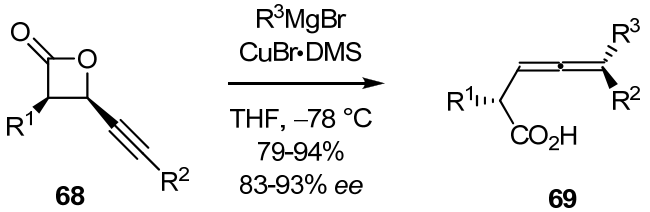
The tandem acylation/debenzylation was employed by the same group to prepare (–)-grandinolide,[40] a bark extract from the South American tree *Iryanthera grandis*. Treatment of β-lactone **65** with $FeCl_3$ in CH_2Cl_2 gave γ-lactone **66** in 74% yield (Scheme 31). A subsequent *anti*-selective α-alkylation with 1-iodo-19-phenylnonadecane delivered (–)-grandinolide **67** in 54% yield.



Scheme 31

3.1.5.2 Allene Formation

Based on initial studies of *Fujisawa* on racemic substrates,[42] *Nelson* and *Wan* recently explored S_N2' additions of cuprates to optically active β-alkynyl-β-lactones to give allenes **69** with excellent enantiopurity (Scheme 32).[43] The stereochemical outcome is consistent with *anti*-1,3-substitution as expected.[44]

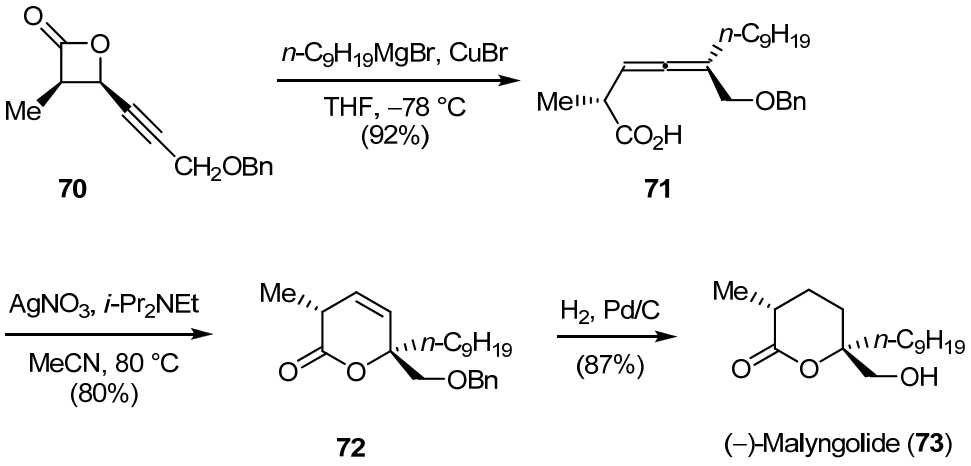


R^1 = H, Me, Bn
R^2 = CH_2Bn, $SiMe_3$, $(CH_2)_2OPMB$
R^3 = Me, Ph, *t*-Bu, CH_2CN, CH_2CO_2t-Bu
$CHMe_2$, $CH_2CH_2CHCH_2$

Scheme 32

This latter chiral allene synthesis was then applied to a concise and stereocontrolled synthesis of (–)-malyngolide (**73**). Optically active β-lactone **70** was treated with *n*-$C_9H_{19}MgBr$ in the presence of catalytic CuBr to form allene **71** in 92% yield (Scheme 33). This was followed by silver(I)-promoted cyclization to δ-lactone **72**.

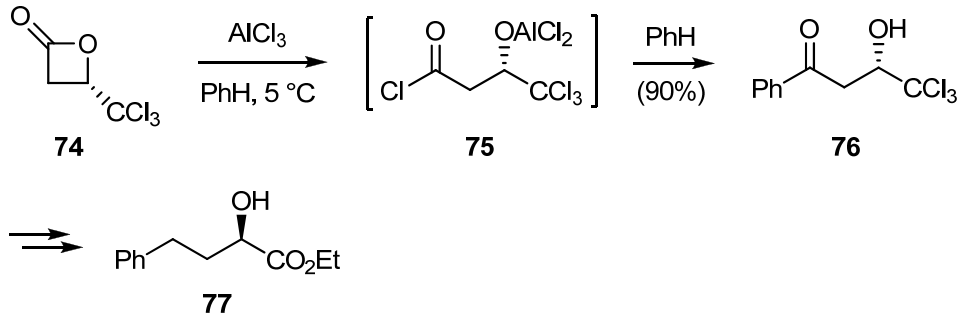
Hydrogenolysis of the benzyl ether was accompanied by saturation of the alkene delivering the antibiotic natural product **73** in 87% yield.



Scheme 33

3.1.5.3 Friedel-Crafts Acylation

Fujisawa and *Wynberg* reported a facile synthesis of (*S*)-β-hydroxy-β-trichloromethylated aromatic ketones *via Friedel-Crafts* acylation involving cleavage of the oxygen-acyl bond.[45] For example, reaction of β-trichloromethyl-β-propiolactone (**74**) with $AlCl_3$ (3.75 equiv.) in benzene gave the butanone **76** in 90% yield (Scheme 34).

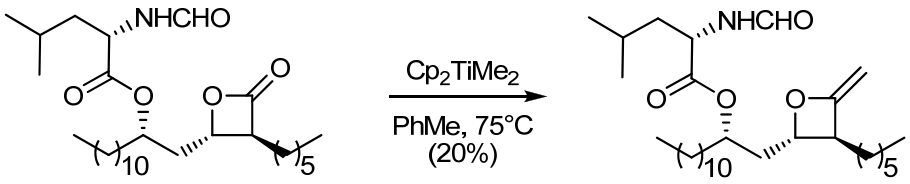


Scheme 34

This reaction was proposed to involve *Lewis* acid induced formation of the intermediate acid chloride **75**, which then undergoes *Friedel-Crafts* acylation with benzene to deliver the aryl ketone **76**. However, direct generation of a β-alkoxyacylium ion would also appear to be possible. Other β-hydroxy aromatic ketones were also obtained in good yields (68-74%) with anisole, *m*-xylene, mesitylene, and *N*-methylpyrrole as nucleophiles.

3.1.5.4 Methylenation

Howell and co-workers employed the *Petasis* reagent to convert a variety of β-lactones to 2-methyleneoxetanes, a relatively unexplored class of strained heterocycles.[46] The *Petasis* reaction also proceeded with unprotected (–)-tetrahydrolipstatin (**62**) in an unoptimized 20% yield affording the corresponding 2-methyleneoxetane analog **78** (Scheme 35).[47]



(–)-Tetrahydrolipstatin (**62**) **78**

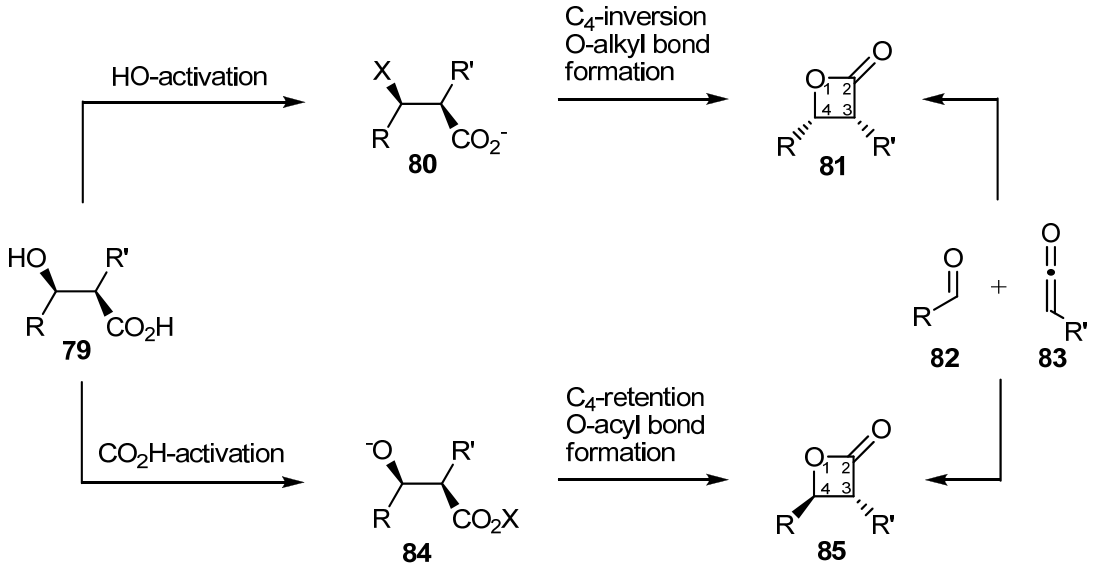
Scheme 35

One noteworthy feature of the *Petasis* methylenation is the observed chemoselectivity. It was found that the β-lactone carbonyl was preferred over alkenes, esters, carbamates, and most remarkably ketones.[48]

3.2 Preparation of Optically Active β-Lactones

The large number of different methods for the enantioselective and/or diastereoselective formation of β-lactones, can be classified in the following way:

- Lactonization *via* oxygen-alkyl bond formation
- Lactonization *via* oxygen-acyl bond formation
- [2+2] Cycloaddition
- Miscellaneous



Scheme 36

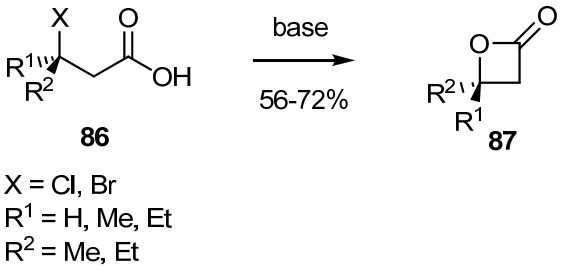
The focus of this chapter will be on [2+2] cycloaddition strategies as in this thesis only this concept was investigated. Due to the huge number of different publications on the formation of β-lactones by other methodologies, only some outstanding examples will be discussed. The reviews by *Pommier* and *Pons* as well as *Yang* and *Romo* among other publications provide a more detailed insight.[49]

3.2.1 Lactonization *via* Oxygen-Alkyl Bond Formation

Carboxylic acids carrying a suitable leaving group in the β-position undergo intramolecular nucleophilic displacement reactions leading to lactonization (Scheme 36). A number of common substrates have been employed. The lactonization generally results in an *inversion* of configuration at the β-carbon atom.

3.2.1.1 Lactonization of β-Halocarboxylic Acids

The intramolecular lactonization of β-halocarboxylic acid salts under basic conditions is the oldest preparative method for β-1actone synthesis. *Einhorn* reported the first example of this reaction in 1883 as a route to 4-(2-nitrophenyl)oxetan-2-one (**2**) from the corresponding β-bromocarboxylic acids **86** precursor.[50] Several optically active β-lactones have been prepared from chiral β-halocarboxylic acids **86** in this manner (Scheme 37).

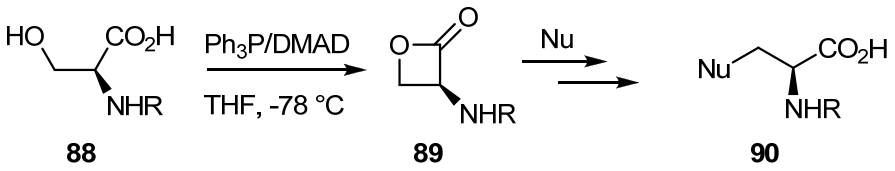


Scheme 37

Later *Guérin* and co-workers used the lactonization of β-halocarboxylic acid salts for the formation of chiral β-substituted β-1actones, which are considered useful monomers for the synthesis of biodegradable polymers *via* ring opening polymerization or copolymerization.[51]

3.2.1.2 Lactonization of β-Hydroxy Carboxylic Acids

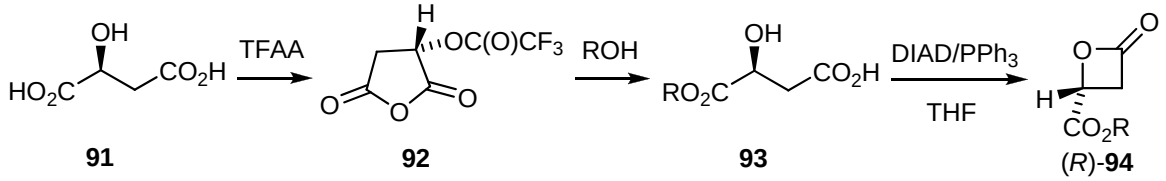
Vederas and co-workers developed *N*-protected-α-amino β-lactones **89** as versatile intermediates for the synthesis of β-substituted-α-amino acids **90** via ring opening reactions by various nucleophiles.[52] They achieved efficient formation of β-lactones **89** without racemization using modified *Mitsunobu* conditions (Scheme 38).



Scheme 38

Optically pure *N*-benzyloxycarbonyl or *N*-*tert*-butyloxycarbonyl substituted serines **88** underwent facile cyclization with the preformed adduct of triphenylphosphine and dimethyl azodicarboxylate (DMAD) at –78 °C in good yields.[52a] Mechanistic studies by *Vederas* using ^{2}H and ^{18}O labeled β-hydroxy acids have indicated that these reactions proceed *via* hydroxyl group activation.[52b] The utility of the derived *N*-protected-β-lactones has been demonstrated in the synthesis of many unnatural amino acids,[53] of β-lactone containing natural products,[54] and of several natural product syntheses including theonellamide and trapoxin B.[32,55]

One route to β-lactones used as monomers for the synthesis of biodegradable polymers starts from (*S*)-malic acid (**91**). *Guérin* and co-workers reported a novel synthesis of optically active 4-benzyloxy- and 4-alkyloxycarbonyl β-lactones **94** with very high optical purity (>98% *ee*) *via Mitsunobu* cyclization of malate monoesters **93** (Scheme 39).[56]



Scheme 39

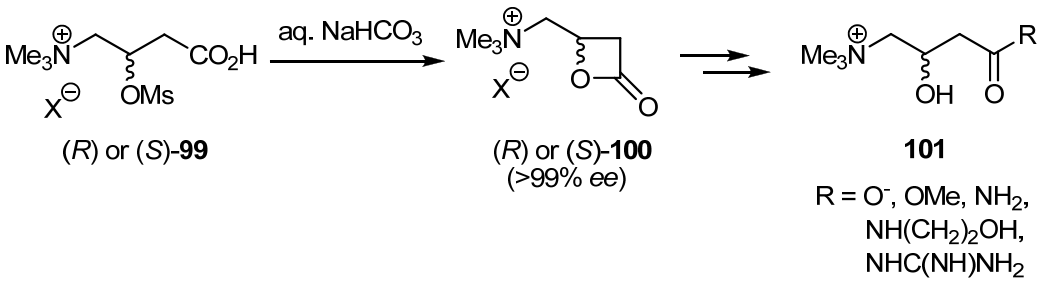
Their synthesis began with (*S*)-malic acid (**91**) from the chiral pool. In the presence of trifluoroacetic anhydride (TFAA), the optically pure starting material was converted to the corresponding malic acid anhydride **92**. Treatment of this intermediate with anhydrous alcohols provided the optically pure monoesters **93** with high regioselectivity. Finally, the monoesters **93** were lactonized using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine to afford (*R*)-alkyl malolactonates **94** in good yield and in high optical purity (98% *ee*).

The observed (4*R*)-configuration in the product β-lactones **94** was attributed to inversion of the β-stereocenter in monoesters **93** *via* hydroxyl group activation. This method generally provided excellent optical purity (>98% *ee*) for all cases reported.

Lenz and co-workers prepared (*S*)-β-butyrolactone (**98**) in >97% *ee* from (*R*)-β-O-mesylbutyric acid (**97**) under basic aqueous conditions (Scheme 40).[57] In their synthesis, the starting material, methyl (*R*)-β-hydroxybutyrate (**96**) was prepared by methanolysis of poly[(*R*)-β-hydroxybutyrate] (**95**), a bacterial product.[58]

Scheme 40

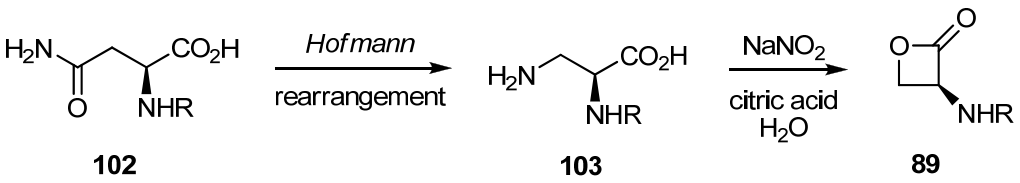
In their studies of a β-1actone route to carnitine derivatives, *Giannessi* and co-workers utilized (*S*)- and (*R*)-carnitine mesylates **99** for the formation of the corresponding β-1actones **100** by lactonization through an inversion process.[59] These β-1actones **100** were subsequently converted to a variety of carnitine derivatives **101** via *O*-acyl fission (Scheme 41).



Scheme 41

3.2.1.3 Lactonization of β-Diazonium Carboxylic Acids

One useful route to α-amino protected β-1actones was reported by *Miyoshi* and co-workers. This method involved the synthesis of *l*-α-*N*-tosylamino-□-propiolactones **89** from *l*-*N*-tosylamino-asparagines **103** (Scheme 42).[60a]



Scheme 42

The transformation consists of a *Hofmann* rearrangement and a diazotation followed by an *in situ* cyclization. The methodology was utilized for the synthesis of β-1actones (Table 3) which were subsequently employed as starting materials for the synthesis of (*S*)-seryl peptides by ring opening with various amino or peptide esters.[60b]

Table 3. Optically active β-lactones **89** prepared from asparagine.

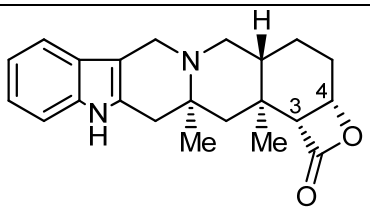
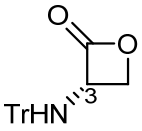
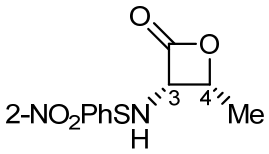
Entry	R	Yield [%]	Config. (C3)[a]	Ref.
1	*p*-TolSO_2	56	*S*	60a
2	*p*-Me$OC_6H_4SO_2$	62	*S*	60b
3	PhSO_2	28	*S*	60b
4	*p*-Cl$C_6H_4SO_2$	52	*S*	60b

[a]Optical purities were not reported.

3.2.2 Lactonization *via* Oxygen-Acyl Bond Formation

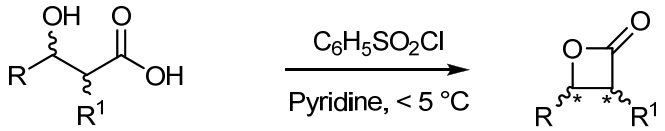
The lactonization of β-hydroxy acids via carboxyl group activation has been known since the late 1950's. Early application of this strategy for the preparation of β-1actones through a carboxylic anhydride intermediate[61] or by use of *N*,*N*-diisopropylcarbodiimide[62a] generally provided low yields. However, the subsequent discovery of new peptide coupling reagents made this route more popular for the preparation of β-1actones. In general, these reactions lead to net retention of the configuration since no bonds to stereocenters are formed or broken. Optically active β-lactones prepared by this method are shown in Table 4. Employing the coupling reagent, bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl), this strategy has been applied to the total synthesis of a proteasome inhibitor, lactacystin, and analogs.[63]

Table 4. Optically active β-lactones prepared by carboxyl group activation.

Entry	β-lactone	Reagents[a]	Yield [%]	Config. (C3, C4)	Ref.
1		$ClCO_2Et$	35	3*R*,4*S*	61
2		DIC	15	3*S*	62a
3		DIC, DMAP	26	3*S*	62b
4		DCC	10	3*S*	62c
5		BOPCl, Et_3N	95	3*S*	62d
6		MsCl, Py, K_2CO_3[b]	23	3*S*,4*R*	64

[a]DIC = *N,N*-diisopropylcarbodiimide. DMAP = *N,N*-dimethylaminopyridine. DCC = *N,N*-dicyclohexylcarbodiimide. BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride. [b] The cyclization precursor was a benzylhydroxamate, rather than the carboxylic acid, derived from *N*-(*o*-nitrophenylsulfenyl)-*l*-threonine.

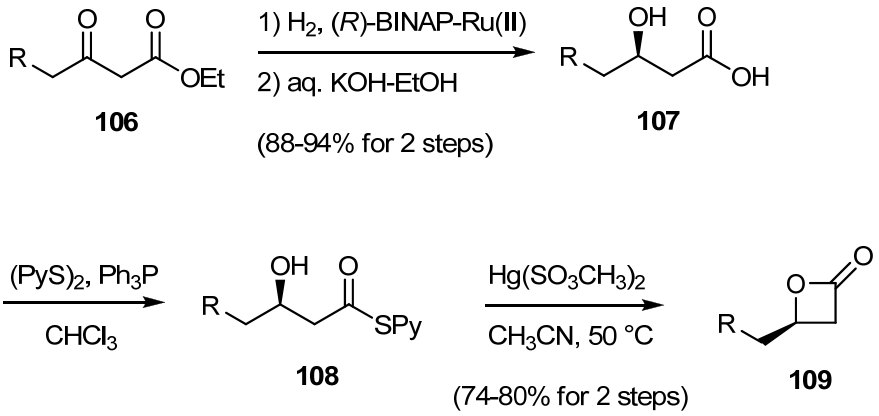
A versatile method for carboxyl group activation of β-hydroxy acids **104** for the synthesis of β-1actones **105** was developed by *Adam* and co-workers (Scheme 43). They reported the formation of β-lactones *via* intramolecular cyclization of β-hydroxy acids **104** using benzenesulfonyl chloride in pyridine at low temperature (< 5 °C).[65] In this method, at least one C3-substituent ($R^1 \neq H$) is necessary for efficient cyclization, suggestive of the requirement of the *Thorpe-Ingold* (gem-dialkyl) effect for efficient lactonizations. The configuration of the β-carbon center was retained as expected for carboxyl group activation. *Adam's* procedure has become one of the most widely used preparative methods for optically active β-1actones and racemic β-1actones (Table 5). Many total syntheses of naturally occurring β-1actones have been accomplished employing this method for construction of the β-1actone ring.[54,66]



104 **105**

Scheme 43

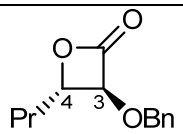
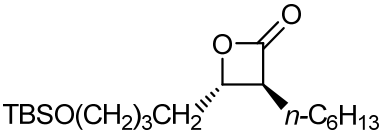
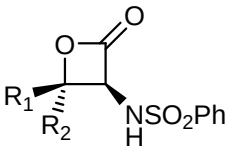
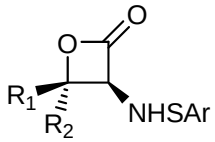
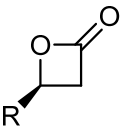
Roelens and co-workers developed a general method for the synthesis of optically pure β-1actones employing modified *Masamune*[67] conditions *via* thioesters (Scheme 44).[68] Optically pure hydroxy acids **107** were obtained by asymmetric hydrogenation of β-ketoesters **106**, available in two steps from acid chlorides, using *Noyori's* BINAP-Ru(II) catalyst. After conversion to the corresponding thiopyridyl esters **108**, application of modified *Masamune* conditions provided enantiomerically pure β-1actones **109** (Table 5). While this method affords access to a number of 4-substituted β-lactones, the number of steps involved and the use of Hg(II) salts detract from the practicality of this methodology.



106 **107** **108** **109**

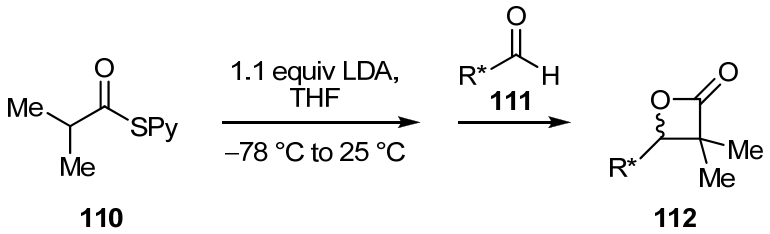
Scheme 44

Table 5. Optically pure β-lactones prepared by Adam's or Roelens' procedures.

Entry	β-lactone			Yield[a] [%]	Config. (C3, C4)	Method[b]	Ref.
1				72	3*S*,4*S*	A	69
2				70	3*S*,4*S*	A	70
		R^1	R^2				
3		Me	H	54	3*S*,4*R*	A	71
4		H	Me	55	3*S*,4*S*	A	71
5		Et	H	39	3*S*,4*R*	A	71
		R^1	R^2				
6		Me	H	56	3*S*,4*R*	A	71
7	Ar = 2-NO_2Ph	H	Me	45	3*S*,4*S*	A	71
		R					
8		$PhCH_2$		78	4*R*	B	68
9		4-MeO-$PhCH_2$		80	4*R*	B	68
10		3,4-$(MeO)_2$-$PhCH_2$		74	4*R*	B	68

[a] 2 Steps from hydroxy acids **107**. [b]Method A: *Adam's* procedure (Ref. 65). Method B: *Roelens'* procedure (Ref. 68).

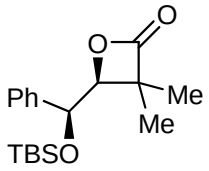
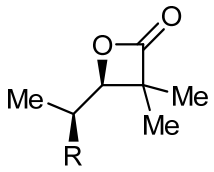
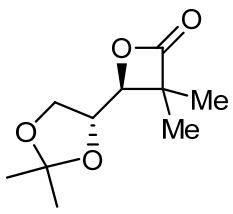
Cossio and co-workers applied *Danheiser's* aldol-lactonization methodology for β-1actone synthesis[72] to optically pure aldehydes **111** bearing α-stereogenic centers using the lithium enolate of thiopyridyl isobutyrate **110** (Scheme 45).[73]



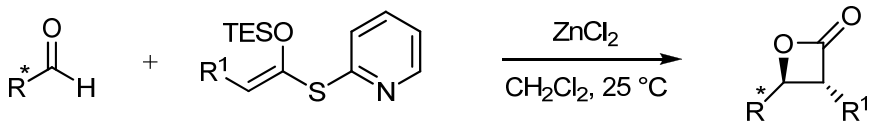
Scheme 45

In most cases, they obtained β-lactones resulting from non-chelation controlled addition as major products (>98:2) except in the case of a *t*-butyldimethylsilyl protected mandelic acid derived aldehyde (Table 6, entry 1). They also found that the use of enolates derived from thiopyridyl isobutyrate **110** afforded the best results in terms of stereoselectivities and yields. The latter result possibly reflecting the requirements of a gem-dialkyl effect for efficient lactonization as described above and previously noted in related reactions.[74] Only α,α-dimethyl-substituted β-lactones have been synthesized to date using this methodology (Table 6). Another aldol-lactonization process involving a chiral oxazaphophorinane was reported by *Evans* and *Gordon*. However, the only β-lactone reported, (*S*)-3-methyl-4-phenyl-2-oxetanone, was not isolated but rather directly hydrolyzed.[72b]

Table 6. Optically active β-lactones prepared by the tandem aldol-lactonization.

Entry	β-lactone	*anti*/*syn*	Yield [%]	Config. (C4)
1		12:88	41	*S*
2	 R = OBn, NBn_2	>98:2	39-61	*R*
4		>98:2	38-55	*S*

Romo and *Yang* used the tandem *Mukaiyama* aldol-lactonization (TMAL) reaction[75] for a variety of optically active aldehydes (Scheme 46).[76] High internal (*trans/cis*) and relative (*syn/anti*) stereoselectivity for the propionate ketene acetal **116** (R^1 = Me) was obtained (Table x). In most cases, less than 2% racemization of α-epimerizable aldehydes was observed despite the fact that these reactions were conducted at 25 °C in the presence of a potential base (thiopyridyl group) and a *Lewis* acid. This methodology was exploited in a concise synthesis of the potent pancreatic lipase inhibitor, (–)-panclicin D[75b,c] and in the total synthesis of (–)-belactosin C[75d] as well as orlistat[75e].

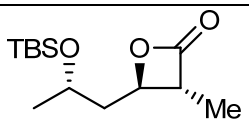
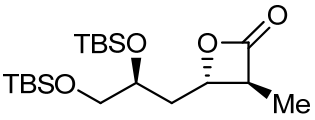
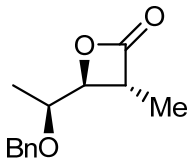
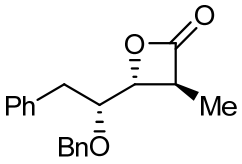
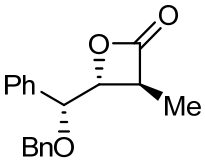
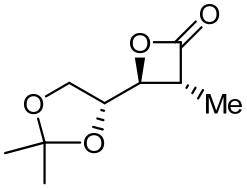
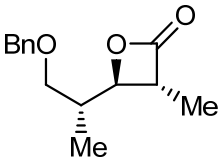


115 **116** **117**

Scheme 46

Interestingly, in contrast to *Cossio'*s results, the configuration of the major diastereomer obtained with α-benzyloxy aldehydes (Table 7, entries 3-5) is consistent with a chelation-controlled aldol reaction.

Table 7. Optically active β-lactones prepared by the tandem *Mukaiyama* aldol-lactonization.

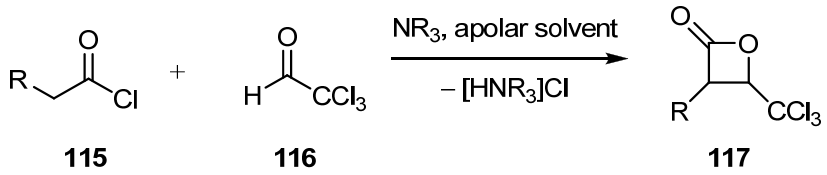
Entry	β-lactone	*ee* [%]	*trans/cis*	*syn/anti*	Yield [%]	Config. (C3,C4)
1		85	>19:1	1:9.1	62	3*R*,4*R*
2		98	>19:1	1:4.8	46	3*S*,4*S*
3		96	>19:1	20:1	69	3*R*,4*S*
4		98	>19:1	22:1	63	3*S*,4*R*
5		69	>19:1	>19:1	50	3*S*,4*R*
6		99	3.6:1	<1:19	82	3*R*,4*S*
7		99	>19:1	1:1.9	29	3*R*,4*R*

3.2.3 [2+2] Cycloadditions of Ketenes and Carbonyl Compounds

The [2+2] cycloadditions of ketenes with carbonyl compounds reported to date can be divided into three categories according to the types of catalysts employed: (1) nucleophile-promoted net [2+2] cycloadditions, (2) *Lewis* acid catalyzed [2+2] cycloadditions and (3), a combination of both catalyst types, namely a bifunctional *Lewis* acid/*Lewis* base catalyzed [2+2] cycloaddition.

3.2.3.1 Catalysis by Chiral Nucleophiles

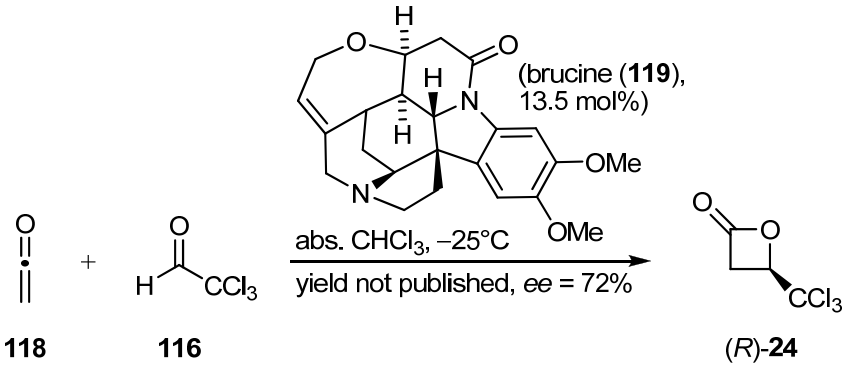
In 1966, *Borrmann* and *Wegler* (Bayer Wuppertal) reported the tertiary amine promoted reaction of strongly polarized carbonyl compounds like chloral (**116**) with carboxylic acid chlorides **115**.[77] They assumed that *in situ* generated ketenes underwent [2+2] cycloadditions with the aldehyde functionality thus forming β-lactones **117** (Scheme 47).



115 **116** **117**

Scheme 47

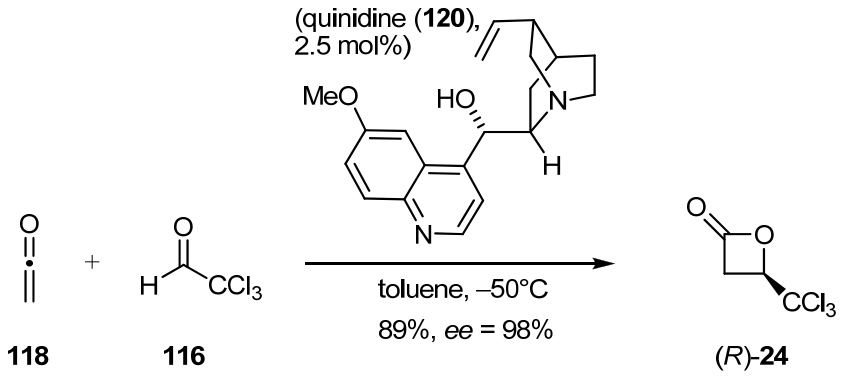
Borrmann and *Wegler* also discovered that enantiomerically enriched β-lactone **24** can be obtained by assistance of chiral tertiary amines like brucine (**119**).[78] An enantiomeric excess of ca. 72% (calculated from the specific optical rotation) was obtained for the synthesis of (*R*)-**24** (Scheme 48). This is one of the first examples for a catalytic asymmetric C-C bound formation with significant enantioselectivity.



118 **116** (*R*)-**24**

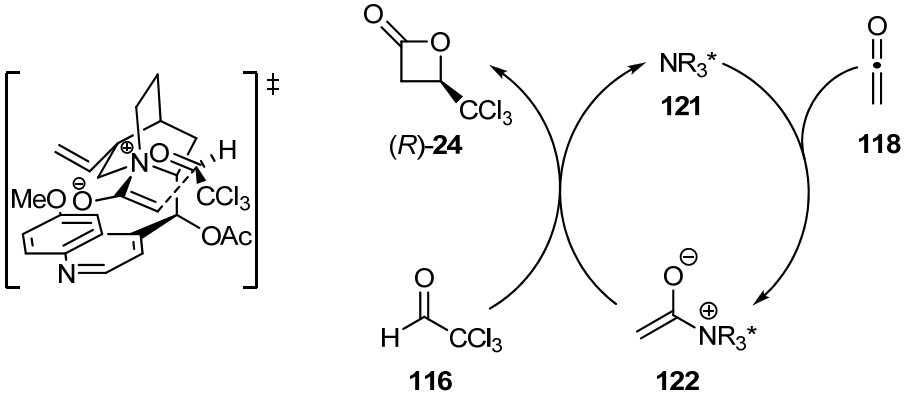
Scheme 48

Almost fifteen years later, *Wynberg* and *Staring* improved the enantioselectivity significantly by using quinidine (**120**) as chiral nucleophile.[79] They found an *ee* of 98% favoring (*R*)-**24** (Scheme 49), while the (*S*)-isomer was prepared with quinine as pseudoenantiomeric nucleophilic catalyst precursor (*ee* = 76%).[80] The ketene was prepared by pyrolysis of acetone vapors in an apparatus described by *Williams* and *Hurd*.[81]



Scheme 49

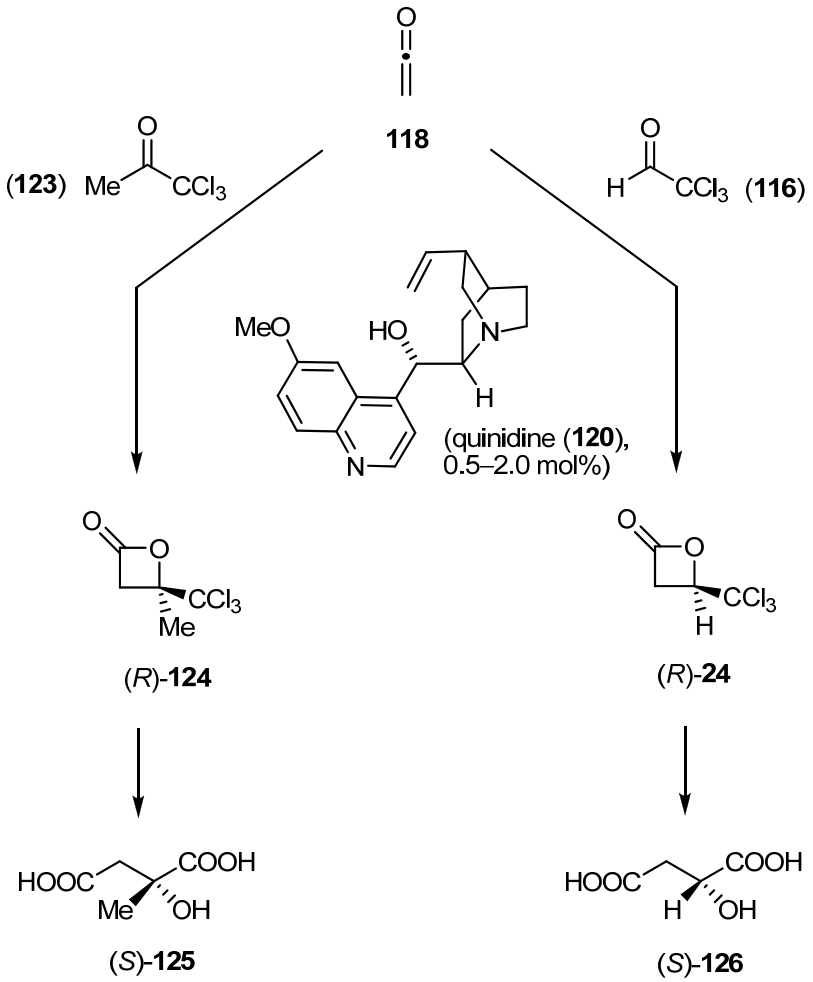
The proposed simplified mechanism is based on the chiral nucleophile's addition to achiral ketene **118** (Scheme 50).



Scheme 50

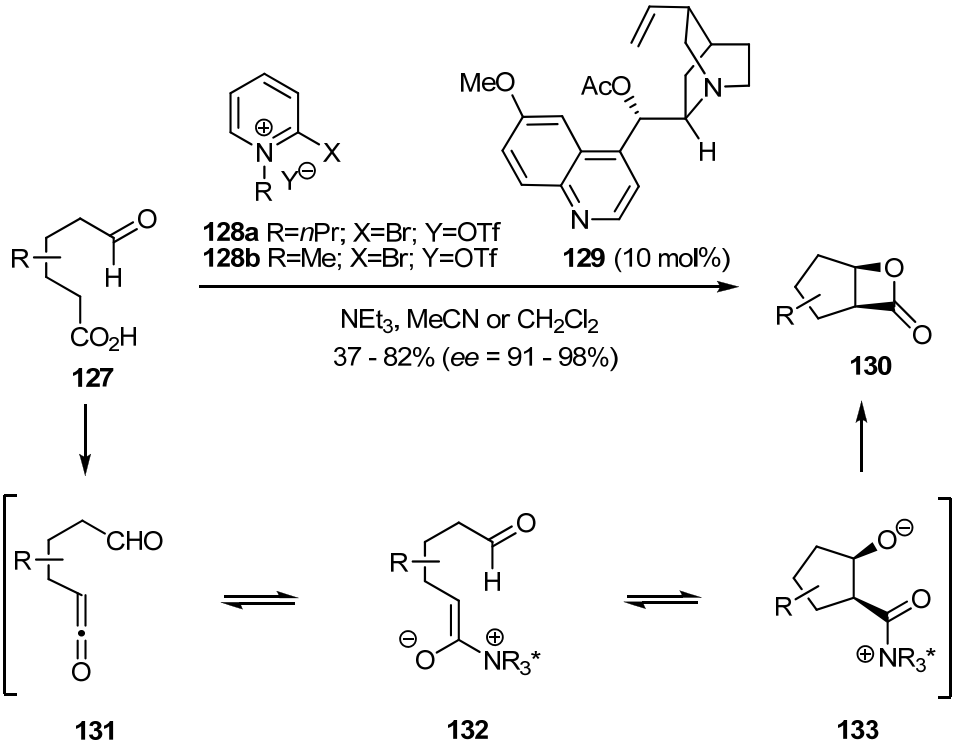
A chiral zwitterionic enolate **122** is thus formed, which is believed to attack aldehyde **116**. It is assumed that the product formation proceeds *via* a stepwise aldol/lactonization mechanism.[82] *Wynberg* and *Staring* observed that only very strongly polarized, at least doubly α-halogenated carbonyl compounds could be employed.[83] However, the reactions' utility was demonstrated by the fact that Lonza Ltd used this process for the ton scale production of optically active malic and citramalic acids (Scheme 51).[84] Nearly quantitative chemical yields of the β-lactone products have been obtained routinely by this procedure, the enantiomeric excess being at least 96% for each of the examples in Scheme 51. This optical purity can be improved further by subsequent recrystillisation of the β-lactones from methylcyclohexane.

Later *Romo* and *Tennyson* simplified *Wynberg* and *Staring* procedure by the *in situ* formation of ketene with acetyl chloride and *Hünig*'s base.[85]



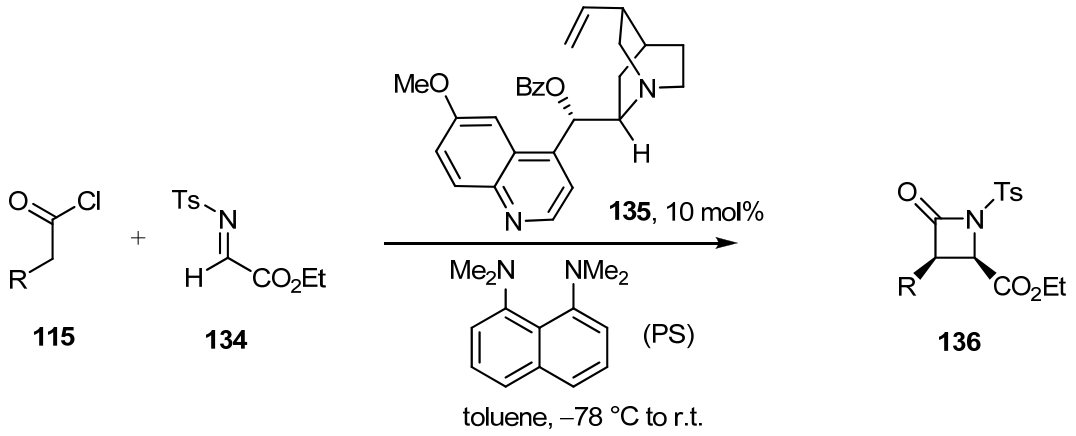
Scheme 51. Synthesis of (*S*)-malic acid (**125**) and citramalic acid (**126**).

Romo and co-workers recently synthesized some optically active bicyclic lactones **130** in moderate to good yields and with good to excellent enantioselctivities taking advantage of an acetylquinidine (**129**) catalyzed aldol-lactonization reaction (Scheme 52).[86] ω-Oxocarbocylic acids **127** were treated with modified *Mukaiyama* reagent **128** and NEt_3 furnishing ω-oxoketenes **131** *in situ*. Owing to ring strain considerations, only *syn*-fused bicyclic rings were formed.



Scheme 52

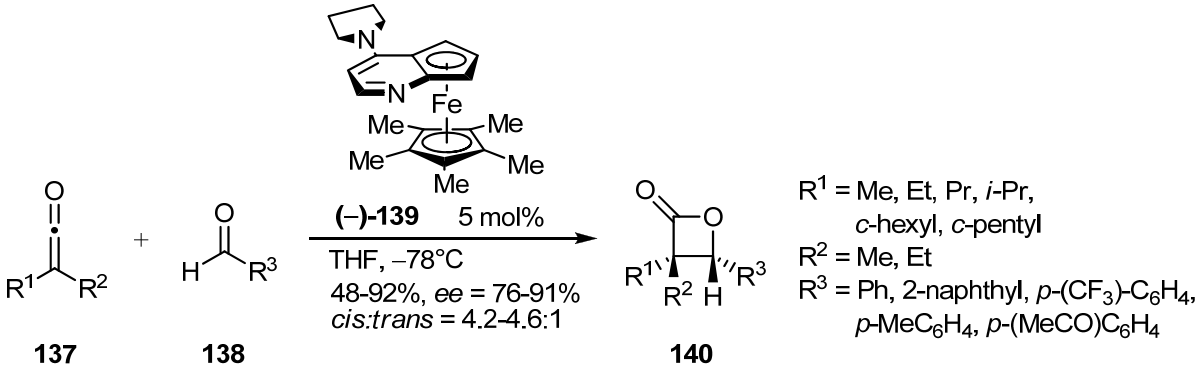
Based on *Wynberg's* work, *Lectka* and co-workers accomplished a benzoylquinidine (**135**)-catalyzed cycloaddition of non-nucleophilic imino esters **134** and ketenes in order to synthesize optically active β-lactams **136** with high enantio- and *syn* diastereoselectivities[87] (Scheme 53).[88] The yields could be later improved by addition of *Lewis* acids like $In(OTf)_3$, $Zn(OTf)_2$ or $Sc(OTf)_3$.[89]



without Lewis acid: 36 - 65%, *ee* = 95 - 99%, *dr* > 99/1
addition of 10 mol% $In(OTf)_3$: 92 - 98%, *ee* = 96 - 98%, *dr* = 9/1 - 60/1

Scheme 53

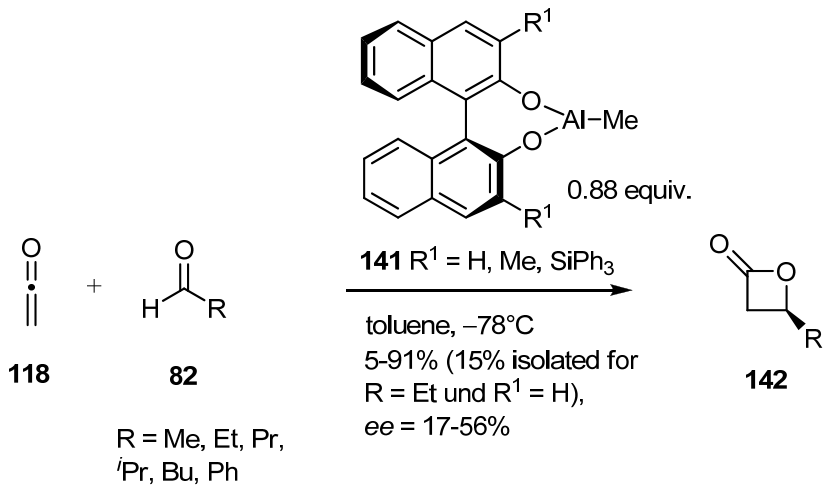
Fu and co-workers were the first to describe the formation of β-lactones with disubstituted ketenes utilizing planar chiral DMAP-derivative **139** (Scheme 54).[90] The synthesis of β-lactones with a quaternary stereocenter in α-position was accomplished with moderate to very good yields and with good enantioselectivities, though diastereoselectivities were only moderate. The method is limited to aromatic aldehydes and disubstituted ketenes which have to be preformed presumably to avoid protonation of the basic catalyst which might not be regenerated by tertiary amine auxiliary bases as a result of extended catalyst basicity.



Scheme 54

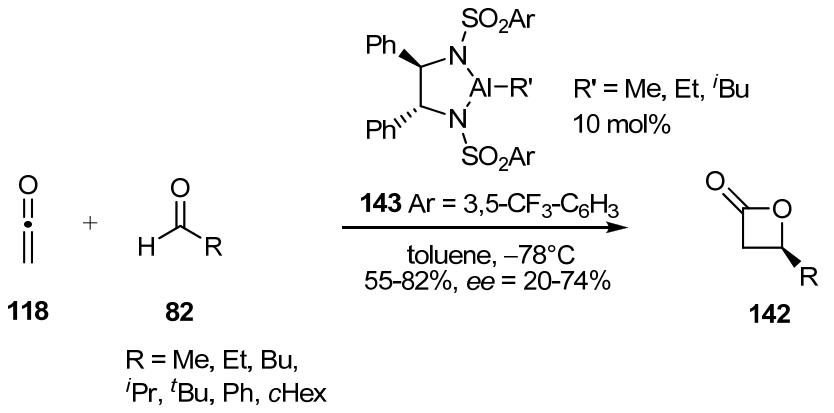
3.2.3.2 Catalysis by Lewis Acids

Miyano and co-workers utilized the C_2 symmetrical Al-binaphthol complex **141** for the formation of monosubstituted β-lactones **142** in moderate to good yields from simple aliphatic aldehydes (Scheme 55). The yields were determined by GC analysis though and the only isolated yield for propanal was poor (15%). In general, the reactions yielded β-lactones with low enantioselectivities. Due to O-acylation of the catalyst an almost stoichiometric amount of binaphthyl complex **141** had to be employed.[91] The ketene was prepared by pyrolysis of acetone vapors at 550 °C.



Scheme 55

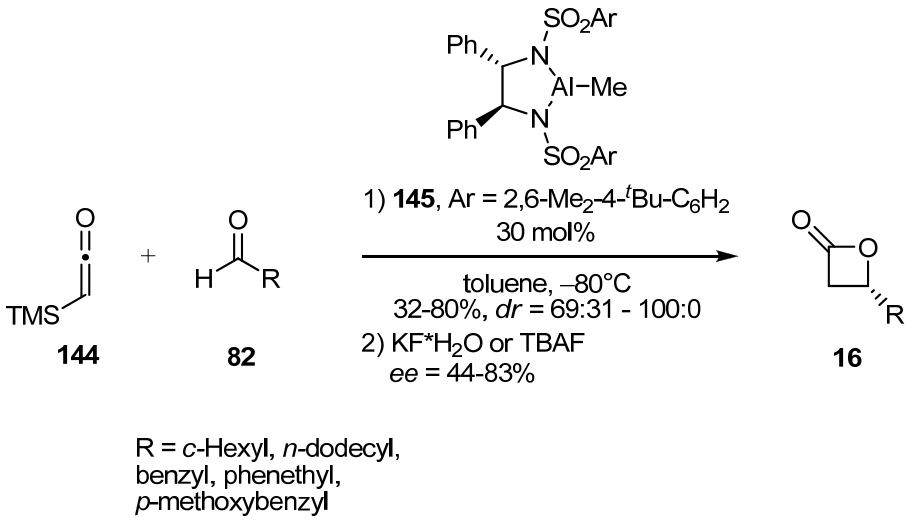
Subsequent to the studies with binaphthol complex **141**, *Miyano* and co-workers investigated the reaction with bissulfonamide complex **143** (Scheme 56).[92] The use of aliphatic aldehydes provided moderate to good yields. Starting from benzaldehyde, the corresponding lactone was formed with a poor yield of 11% and an *ee* of 14%. Yields were determined again by GC anaylsis. In most other cases the targeted products were obtained with moderate selectivities. Only with cyclohexylcarbaldehyde a synthetically useful enantioselectivity (*ee* = 74%) was attained.



Scheme 56

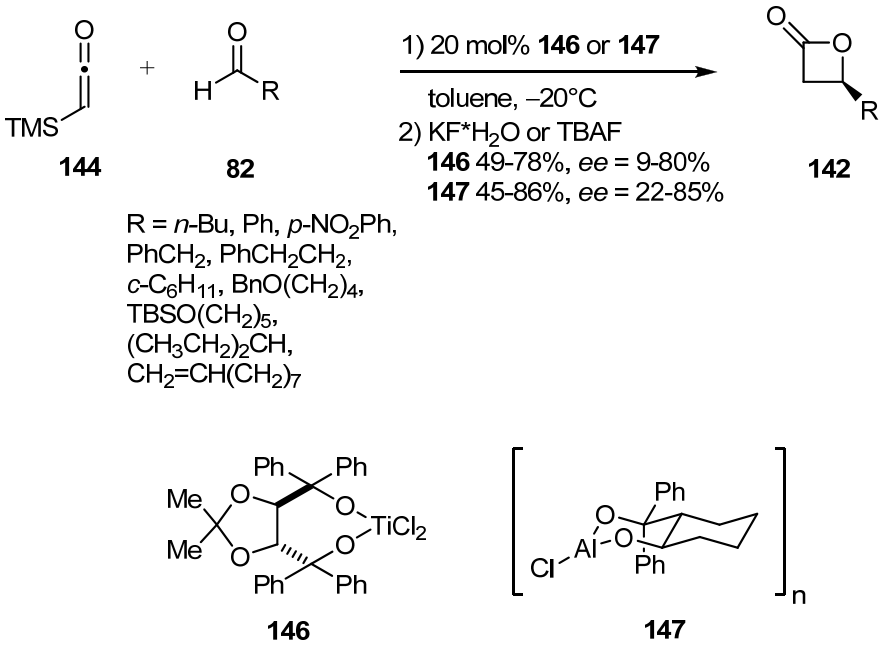
Kocienski and co-workers developed the closely related bissulfonamide-aluminum complex **145**, differing only in the arylsulfonyl residues from *Miyano's* system.[93] For the formation of β-lactones **16** with trimethylsilyl ketene **144**, the catalyst was used in substoichiometric amounts and poor to good yields (32-80%) were obtained (Scheme 57).

Enantiomeric excesses range from poor 30% to good 83%, the most favorable substrates being α-unbranched aryl acetaldehydes (both 83%). For the arylsulfonyl groups *ortho*-substituents are essential for high enantio-induction. The steric limits of the system are exceeded with bis-2,4,6-tri-*iso*-propylbenzenesulfonamide which is completely unreactive even with 100 mol% catalyst.



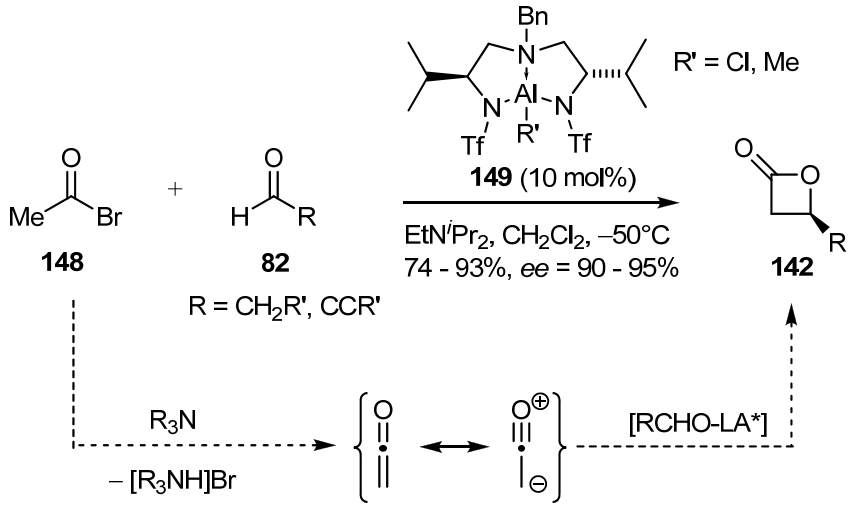
Scheme 57

Romo and co-workers studied the formation of β-lactones **142** employing silyl ketene **144** in combination with *Seebach's* dichlorotitanium-TADDOL catalyst[94] **146** respectively catalyst **147** which both exhibited moderate to good yields but except for cyclohexylcarboxaldehyde (*ee* = 80-85%) only moderate selectivities (Scheme 58).[95]



Scheme 58

More recently, significant progress toward the development of a more broadly applicable catalytic, enantioselective β-lactone synthesis has been reported. *Nelson* and co-workers developed aluminum complex **149**, which was shown to be capable of catalyzing the [2+2] cycloaddition of ketene and aldehydes under mild conditions and in high yields with good selectivities.[96] The ketene component was generated *in situ* from acetyl bromide by treatment with *Hünig*'s base and treated directly with the aldehyde complexed by the chiral *Lewis* acid (10 mol%). The catalyst is limited to the use of α-unbranched aliphatic aldehydes (α-branched aldehydes result in low *ee*'s and moderate yields) and acetylenic aldehydes (Scheme 59). The use of aromatic aldehydes and ketones was not reported.



Scheme 59

On the basis of accepted criteria for *Lewis* acidity, the neutral tetracoordinate, electron-rich Al(III)-alkyl complex **149** (R = Me) would seem to be a poor candidate for a *Lewis* acidic catalyst.[97] To understand the potent catalytic activity expressed by **149**, an X-ray diffraction structure analysis of the Al(III)-based cyclocondensation catalyst was conducted.[98] The X-ray structure indicates **149** to be a four-coordinate complex adopting a trigonal monopyramidal (tmp) geometry with the methyl and trifluoromethylsulfonamide ligands defining the equatorial plane of the bipyramidal structure (Figure 5). This crystal structure data suggested that the distorted trigonal monopyramidal coordination geometry defined in **149** by the tridentate ligand was responsible for the observed *Lewis* acidity by providing a vacant d_z^2p orbital disposed ideally to accept a fifth ligand.

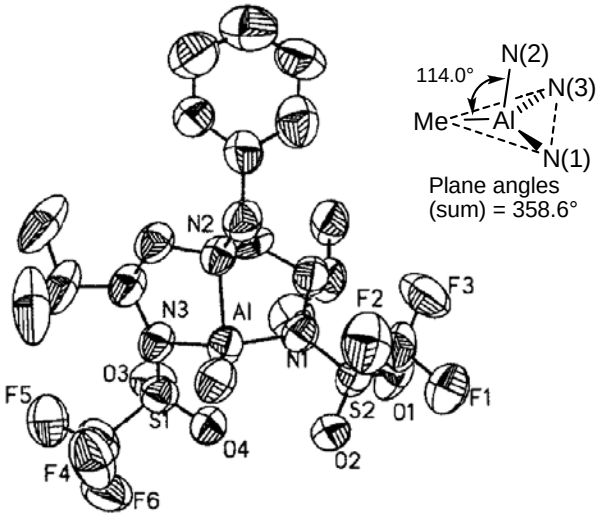


Figure 5. X-ray structure of Al(III)-triamine complex **149**.

X-Ray crystal structure analysis in conjunction with $^{1}H/^{13}C$ NMR investigations of *Lewis* acid/base association expressed by **149** provided further evidence for a neutral, five-coordinate *Lewis* acid/base complex acting as the catalytically active species in the cycloaddition reaction. A toluene solution of **149** containing dimethylformamide (DMF) as a representative carbonyl *Lewis* base deposited colorless crystals of the **149**·DMF complex (Figure 6). *Lewis* base coordination occurs at the vacant "apical" coordination site on the trigonal monopyramidal Al ion to deliver the five-coordinate *Lewis* acid/base complex, with DMF coordination imparting minimal perturbation to the Al ion's trigonal plane relative to the free catalyst [$\sum_{angles}$(**149**) = 358.6°; $\sum_{angles}$(**149**·DMF) = 357.8°].

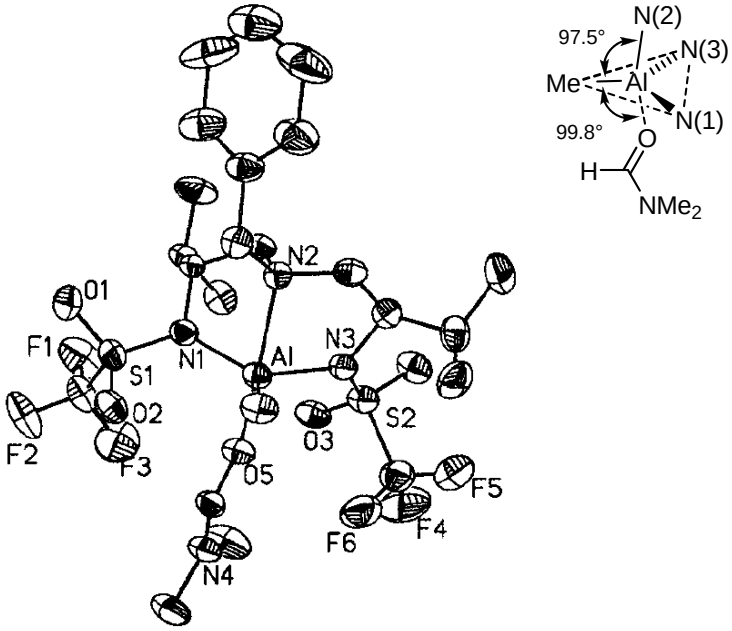


Figure 6. X-ray structure of Al(III)-triamine complex **149**·DMF.

To probe the dynamics of *Lewis* acid/base association promoted by the Al-triamine catalyst, *Nelson* and co-workers examined the binding of DMF to **149** by ^{1}H-NMR. The spectra obtained from titrating **149** with progressive amounts of DMF [0.10 equiv. (0.012M) to 2.0 equiv. (0.24M)] in CD_2Cl_2 are presented in Figure 7. Only the *Lewis* acid/base complex and the parent catalyst complex are observed during the titration experiment; no time-averaging of resonances that would accompany dynamic *Lewis* acid/base association is observed. Only in the presence of excess DMF was the unbound *Lewis* base observed.

Therefore, despite the electron-rich nature of the highly coordinated Al-alkyl complex **149**, carbonyl binding seems strongly favored even at ambient temperatures and dissociation of the *Lewis* acid/base complex is slow on the NMR time scale.

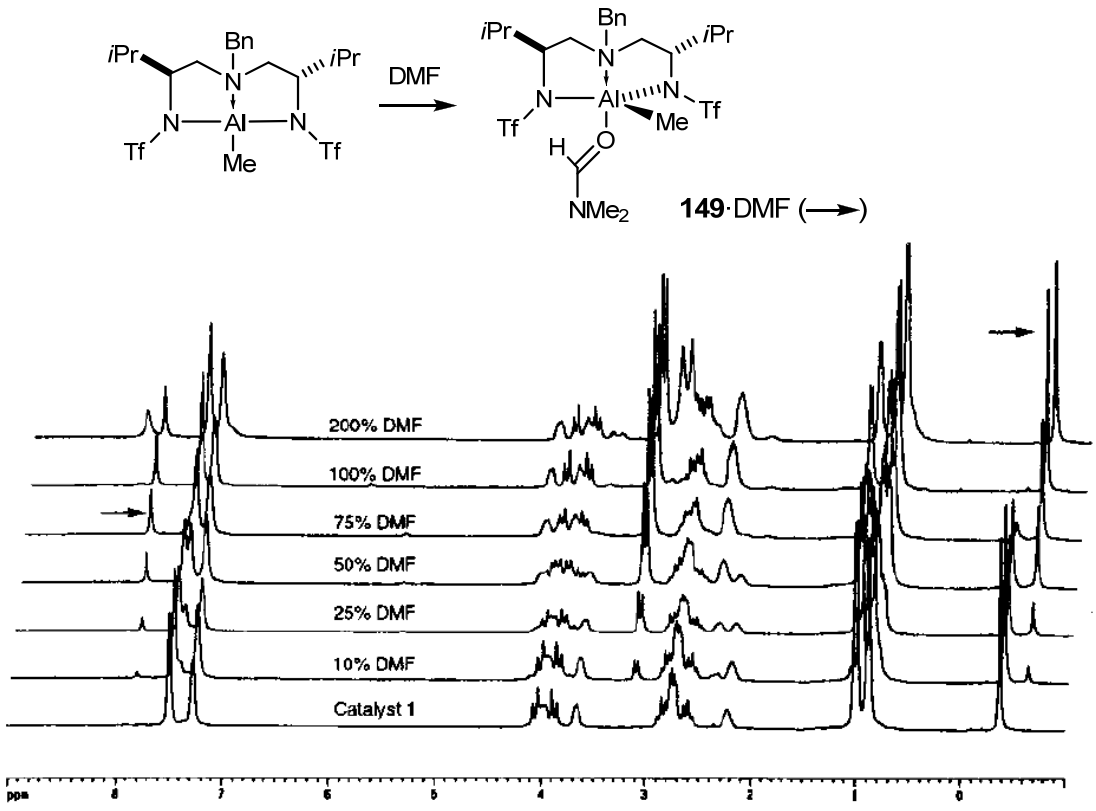
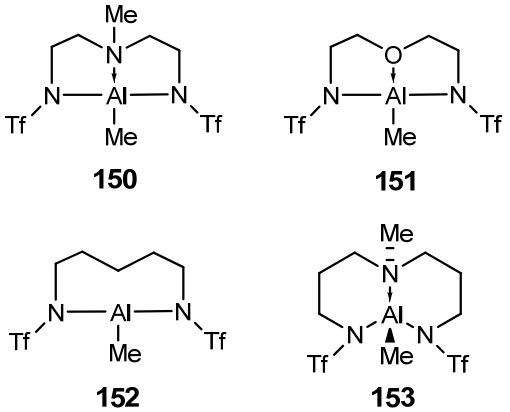


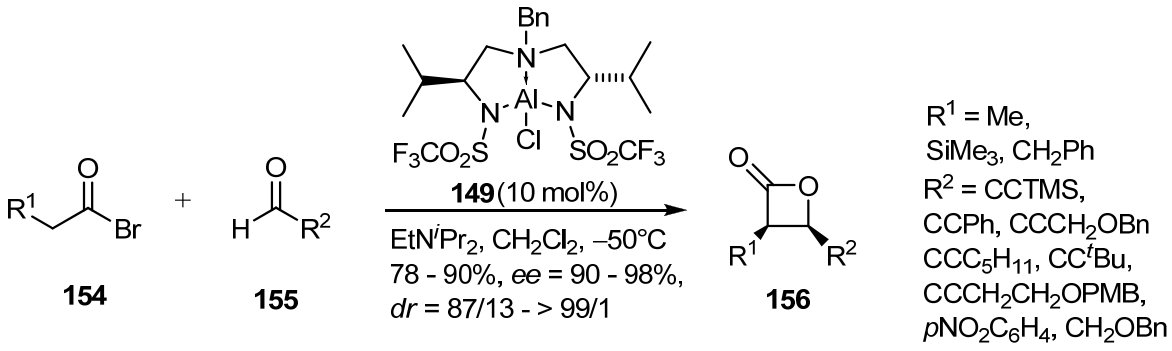
Figure 7. Titration of **149** with DMF (^{1}H NMR).

Nelson and co-workers prepared Al(III) complexes **150-153** to probe the structural requirements for *Lewis* acidic behavior in structurally and electronically related Al(III) complexes.



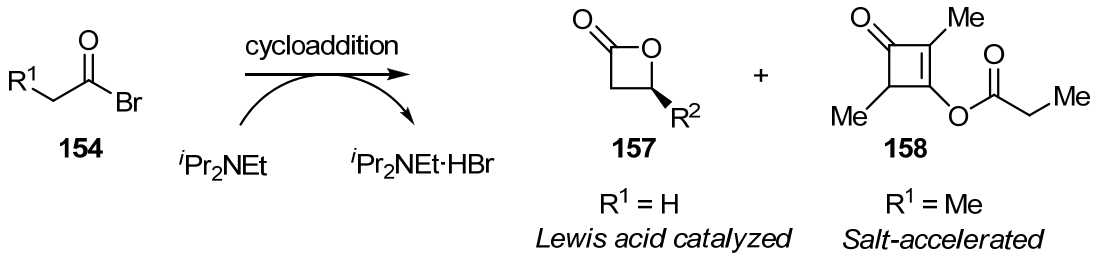
The tetracoordinate complexes **150** and **151**, direct structural analogues of **149**, are effective reaction catalysts (10 mol%), providing ≥95% conversion in 1.8-7.5 h. Complex **152** lacking a *Lewis* basic residue in the ligand backbone and, thus, the coordinative distortion present in **149-151** is inactive as a reaction catalyst despite being coordinatively unsaturated. This observation suggests that despite the more highly coordinated nature of **149-151**, ligand-defined geometric distortion enhances *Lewis* acidity relative to the coordinatively unsaturated analogue. The *Lewis* acidity of complex **153**, identical in coordination number and ligand electronics to **149** and differing only in chelate size, provided further evidence of the relationship between metal coordination geometry and catalyst activity. Geometry optimization of complex **153** indicated that the expanded chelate size of the propylene triamine-derived ligand conferred sufficient conformational mobility to allow the Al(III) ion to adopt a low-energy, tetrahedral coordination geometry. The Al(III) complex **153** did not form a *Lewis* acid/base adduct with DMF even in the presence of excess *Lewis* base and is completely inactive as a cycloaddition catalyst.

Nelson and co-workers also used complex **149** for the formation of 3,4-disubstituted-2-oxetanones (Scheme 60).[99] The cyclocondensation of propionyl bromide (**154**) and several aldehydes afforded β-lactone adducts **156** with uniformly high enantioselection, diastereoselection and yields. Nevertheless, the scope of this reaction is rather limited. Besides acetylenic aldehydes only the activated benzyloxyacetaldehyde and the electron-deficient 4-nitrobenzaldehyde were useful substrates. Aliphatic aldehydes or conjugated enals afforded low yields and variable *ee* levels.



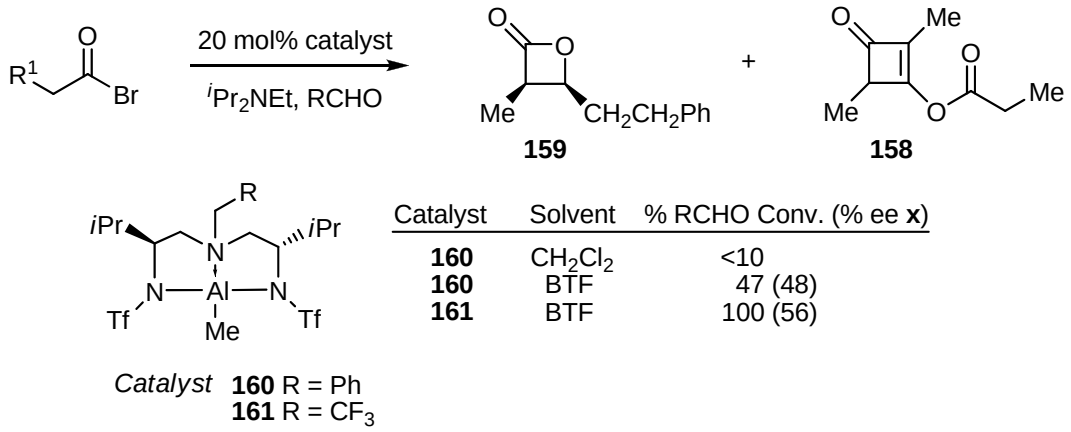
Scheme 60

While cycloaddition reactions employing catalyst **149** and acetyl bromide-derived ketene reliably generated the β-lactone cycloadducts, substituted ketenes exhibited substantially suppressed reactivity toward aldehydes, allowing competing reaction manifolds to interfere with the desired [2+2] pathway. For example, reacting propionyl bromide (methylketene precursor) with various aliphatic aldehydes afforded methylketene trimer **158** as the major reaction product, while the analogous acetyl bromide cycloaddition reactions delivered exclusively lactone **157** (Scheme 61).



Scheme 61

Attempted cycloaddition reactions of substituted ketenes with aliphatic aldehydes employing first-generation reaction conditions (10-20 mo% **160**, CH_2Cl_2) afforded primarily ketene trimer **158** and less than 10% of the desired β-lactone. Kinetic evidence indicated that while ketene trimerization was *Lewis* acid independent, this reaction manifold was accelerated substantially by the ammonium bromide byproduct of *Hünig*'s base mediated ketene generation. *Nelson* discovered that pseudo-salt-free conditions could be achieved by substituting benzotrifluoride (BTF) for CH_2Cl_2 as solvent. In BTF, the ammonium bromide salts are insoluble and reaction conversion improved considerably in the standard propionyl bromide-hydrocinnamaldehyde test reaction (<10% to 47%) due to extended ketene lifetimes (Scheme 62).

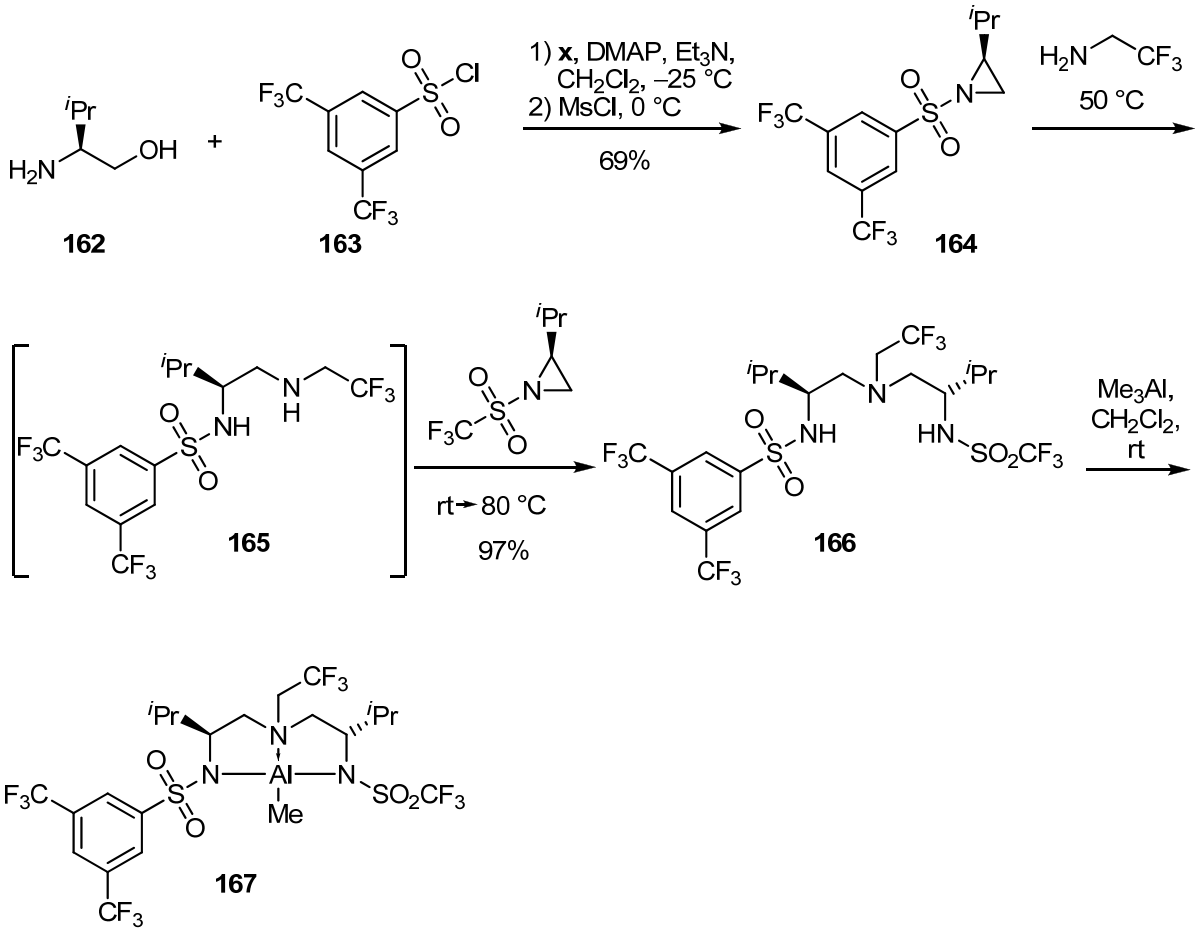


Catalyst	Solvent	% RCHO Conv. (% ee **x**)
160	CH_2Cl_2	<10
160	BTF	47 (48)
161	BTF	100 (56)

Scheme 62

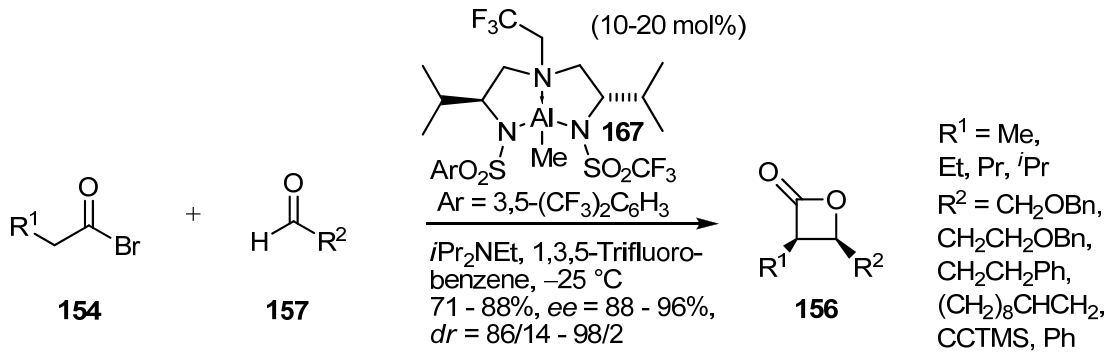
To achieve useful enantioselectivities the catalyst design had to be altered. The trigonal monopyramidal (tmp) coordination geometry and the central Al-N *Lewis* acid-base contact that defines the tmp geometry were demonstrated to be crucial to catalyst activity. Thus, new catalyst designs evolved from Al-triamine based structures that retain the essential metal coordination geometry while delivering enhanced metal electrophilicity. For example, the *N*-2,2,2-trifluoroethyl-substituted catalyst **161** showed significantly enhanced reactivity relative to the analogous *N*-benzyl catalyst **160** (Scheme 62). *Nelson* speculated that inductive electron withdrawal from nitrogen decreased electron density at aluminum, thereby enhancing *Lewis* acidity, while retaining sufficient central nitrogen *Lewis* basicity to maintain the integrity of the catalytically active tmp coordination geometry. Reactions employing propionyl bromide, catalyst **161** and BTF as solvent afforded β-lactone **159** as the single product (Scheme 62).

The next phase of their investigations focused on identifying modified Al-triamine catalysts that would provide the requisite levels of enantioselectivity at reaction temperatures above the freezing point of BTF (–29 °C). The catalyst derived from unsymmetrical triamine **166** provided an Al(III)-catalyst **167** exhibiting substantially improved competency in the substituted ketene cycloaddition reaction. The synthesis of catalyst **167** is outlined in Scheme 63.



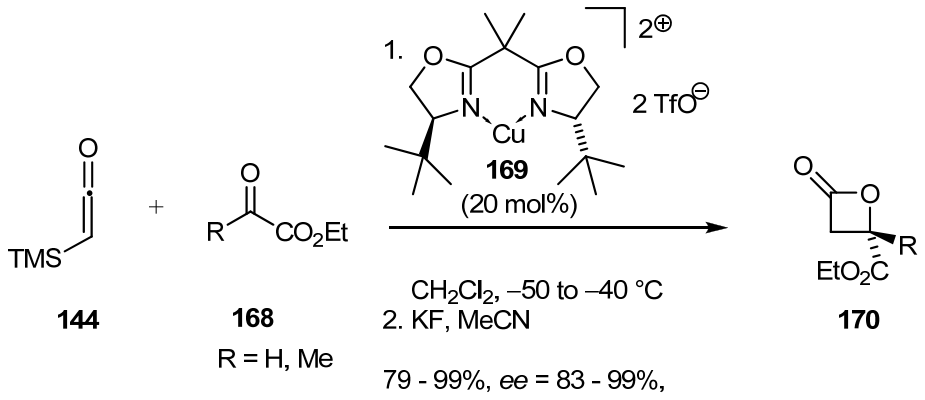
Scheme 63

This second-generation Al-catalyst **167** in conjunction with pseudo-salt-free reaction conditions (BTF, –25 °C) combined to deliver substituted ketene cycloaddition reactions exhibiting high levels of enantio- and *syn*-diastereoselection (Scheme 64). Slow-reacting aliphatic aldehydes require 20 mol% catalyst to ensure that ketene-aldehyde cycloaddition competes effectively with trimerization of methylketene (R^2 = CH_2CH_2Ph, $(CH_2)_8CHCH_2$, CH_2CH_2OBn). Conjugated enals, α-branched aliphatic aldehydes and ketones were not reported.[100]



Scheme 64

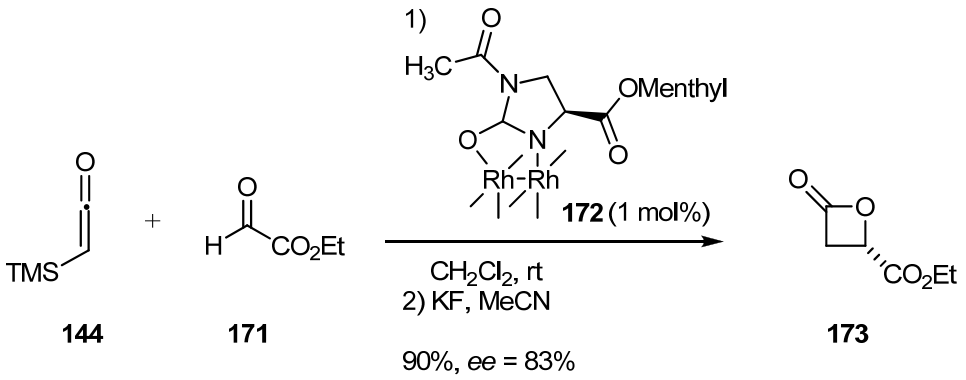
While almost all previously described *Lewis* acid catalysts were based on Al(III) central metal ions, *Evans* and *Janey* utilized the C_2-symmetric copper(II)bisoxazoline complex **169** as a chiral catalyst for [2+2] cycloadditions of the more stable, commercially available, but expensive trimethylsilyl ketene **144** with ethylglyoxylate **168** (R = H) affording optically active β-lactones **170** in excellent yield and with high enantioselectivity (Scheme 65).[101]



Scheme 65

Other α-oxygenated carbonyl compounds, such as ethyl pyruvate **168** (R = Me) and α-diketones, are also good substrates for the cycloaddition and yield the corresponding β-lactones **170** in high yields and with good *ee*'s. Simple aldehydes like dihydrocinnamaldehyde resulted in poor yield (28%) and low selectivity (*ee* = 35%).

More recently *Doyle* and co-workers developed the dirhodium(II) carboxamidate catalyst **172** for the [2+2] cycloaddition reaction between ethyl glyoxylate **171** and trimethylsilylketene **144** and obtained a good selectivity (83% *ee*) and a very good yield (90%) (Scheme 66).[102] However, the reaction is very slow (72 h) and with aromatic aldehydes and cinnamaldehyde no cycloaddition was observed.

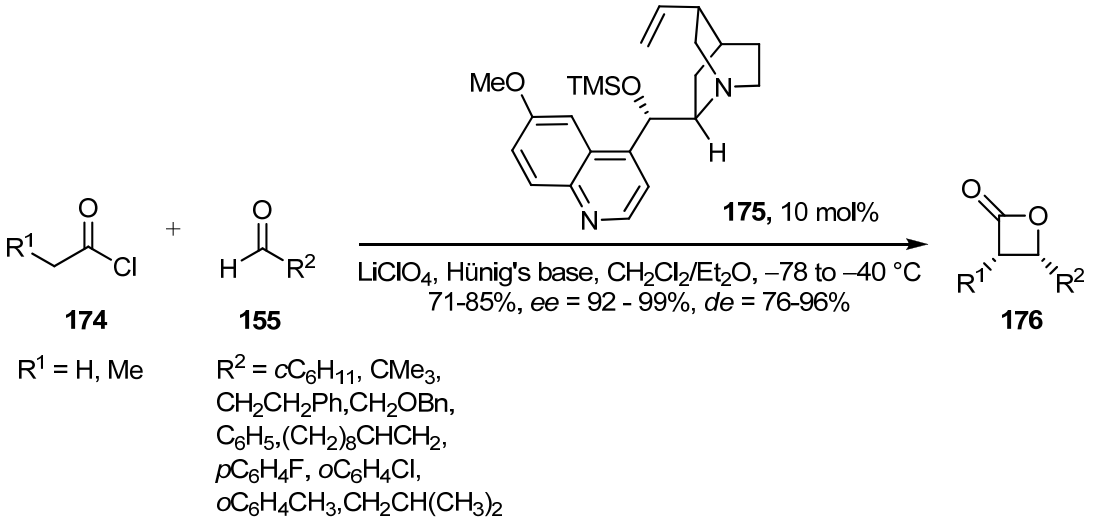


Scheme 66

3.2.3.3 Bifunctional Catalyst Systems for the Formation of β-Lactones

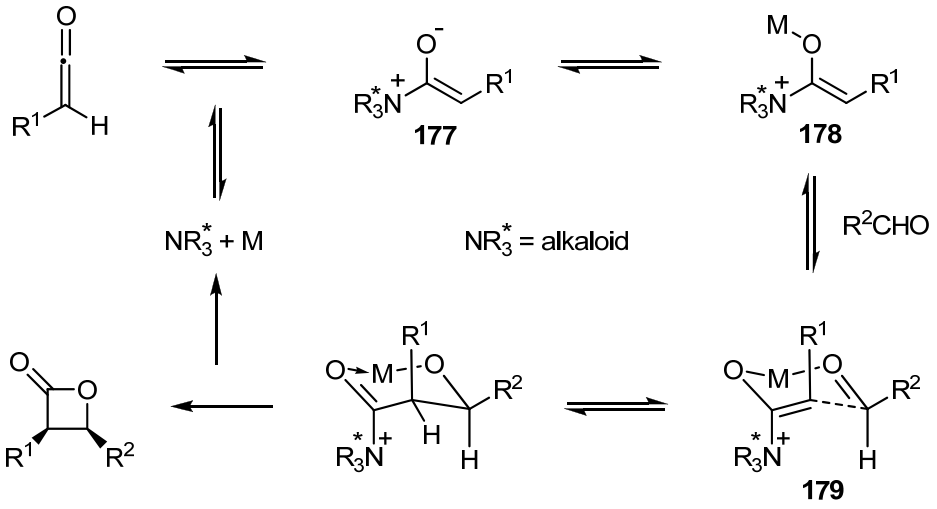
The summary of the existing methods for *Lewis* acid or *Lewis* base catalyzed ketene-aldehyde cycloadditions reveals that impressive stereoselectivities are obtained for certain substrates. However, there is still a lack of a general method that tolerates a broad spectrum of aldehydes and especially ketones can only be used in certain cases, if they are electronically strongly activated. A possible solution to this problem could be the combination of both reaction principles – cooperative nucleophilic and *Lewis* acid catalysis.[103] In the past few years, considerable progress has been made in the development of bifunctional catalyst systems for organic synthesis wherein a *Lewis* base is used to work in concert with a *Lewis* acid. For a more detailed discussion about *Lewis* acid / *Lewis* base catalysis, see Chapter 8.

Utilizing cooperative catalysis, *Nelson* and co-workers successfully extended *Wynberg*'s[79] cinchona alkaloid-catalyzed ketene-aldehyde cycloaddition, which is limited to highly activated aldehydes and ketones as substrates, to structurally diverse aldehyde types. With TMSQd (**175**) as chiral nucleophile in the presence of $LiClO_4$ as *Lewis* acid co-catalyst lactones **176** were produced in high yields and with excellent enantioselectivities from both α-branched and -unbranched aliphatic aldehydes (Scheme 67).[104] Very good selectivities were also obtained for aromatic aldehydes. However, this process has substantial drawbacks for potential large scale applications, since solutions of $LiClO_4$ in Et_2O are explosive. Later, in the total synthesis of (–)-pironetin[105] and (–)-rhazinilam[106] *Nelson* and co-workers utilized LiI or $MgCl_2$ as *Lewis* acid co-catalyst.



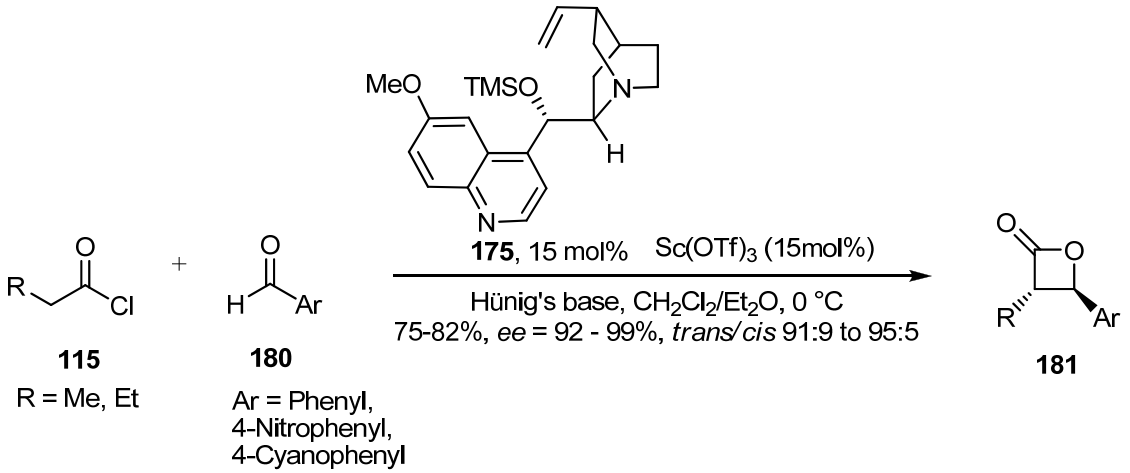
Scheme 67

Alkaloid additives catalyze ketene–aldehyde additions through nucleophilic addition to ketene, generating the acylammonium enolate **177** responsible for mediating C–C bond construction (Scheme 68).[107] The specifity of *Wynberg*'s original cycloaddition for highly electrophilic aldehydes (e.g., chloral) suggested that these enolates possess relatively limited nucleophilicity. In considering strategies for generalizing the alkaloid-catalyzed ketene–aldehyde additions, *Lewis* acid activation of the aldehyde electrophiles emerges as an alternative for eliciting the nucleophilicity from the ammonium enolates.[108] Furthermore, alkaloid-mediated enolate formation in the presence of metallic *Lewis* acid cocatalysts (M) is considered a plausible conduit to metal-stabilized ammonium enolates **178**. Such enolates could be expected to mediate aldehyde addition through a metal-templated, closed transition state **179**, providing both enthalpic and entropic activation to the ensuing enolate–aldehyde addition.



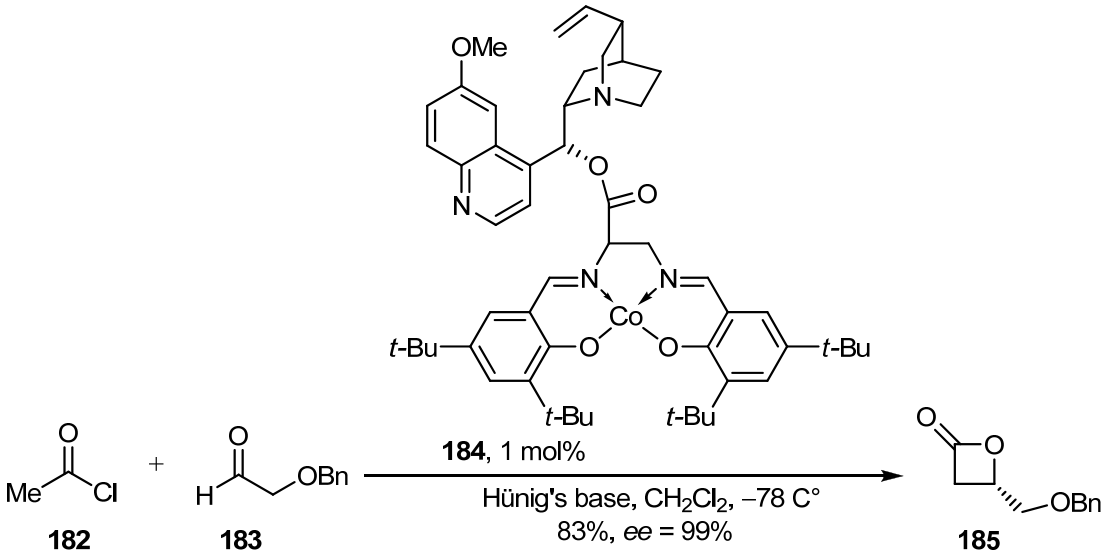
Scheme 68

Calter and co-workers were the first to report the catalytic asymmetric formation of *trans*-configured β-lactones.[109] This transformation is limited though to the use of benzaldehyde or electron-poor aromatic aldehydes **180**. Different metal triflates were screened and the best results were obtained with $Sc(OTf)_3$ in combination with TMSQd (**175**) as chiral nucleophile (Scheme 69).



Scheme 69

By combination of metal-salen complexes with cinchona alkaloid *Lewis* bases, *Lin* and co-workers developed the catalytic system **184** that promotes the [2+2] cycloaddition between ketene and benzyloxyacetaldehyde **183** as the only reported substrates to produce the corresponding β-lactone **185** in high yield and *ee* (Scheme 70).[110]



Scheme 70

The configuration of the diaminopropanoic acid linker proved to be inconsequential; the chiral induction is controlled only by the *Lewis* base. This is notable because the quinuclidine-bound enolate is assumed to attack the metal-activated aldehyde intramolecularly (Figure 8). A bifunctional mode of action was proposed based on several control experiments, including one test where no product was formed in a catalytic system composed of a discrete Co(II)-salen complex and a quinine derivative.

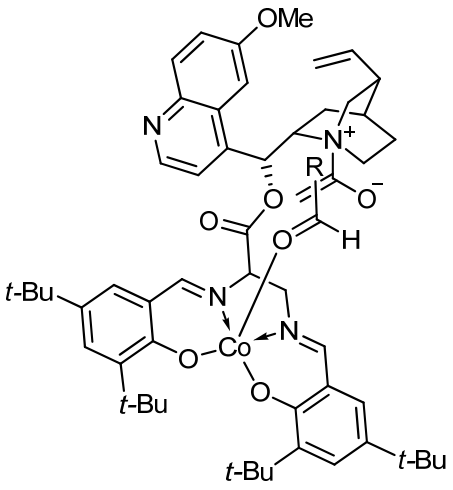
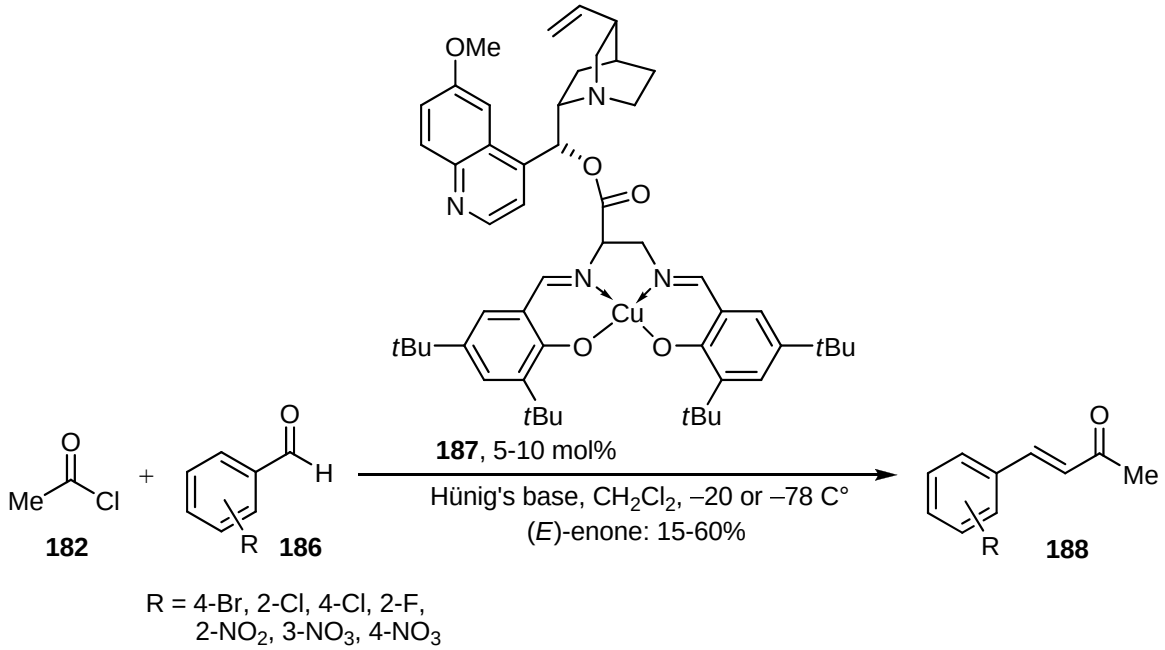


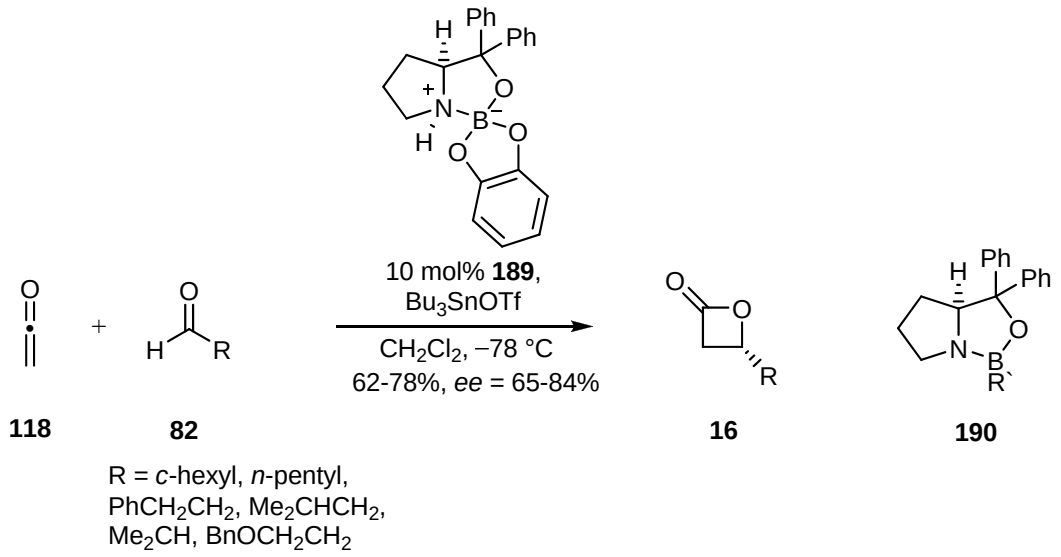
Figure 8. Proposed activated complex.

Shortly afterwards *Lin* and co-workers reported the discovery of a catalytic, diastereoselective aldehyde olefination reaction catalyzed by the Cu(II) complex **187** (Scheme 71).[111] By employing activated aromatic aldehydes the (*E*)-enones **188** were selectively formed but in poor to moderate yields (15-60%). This alternative reaction pathway might be the reason for the limited substrate scope of the [2+2] cycloaddition.



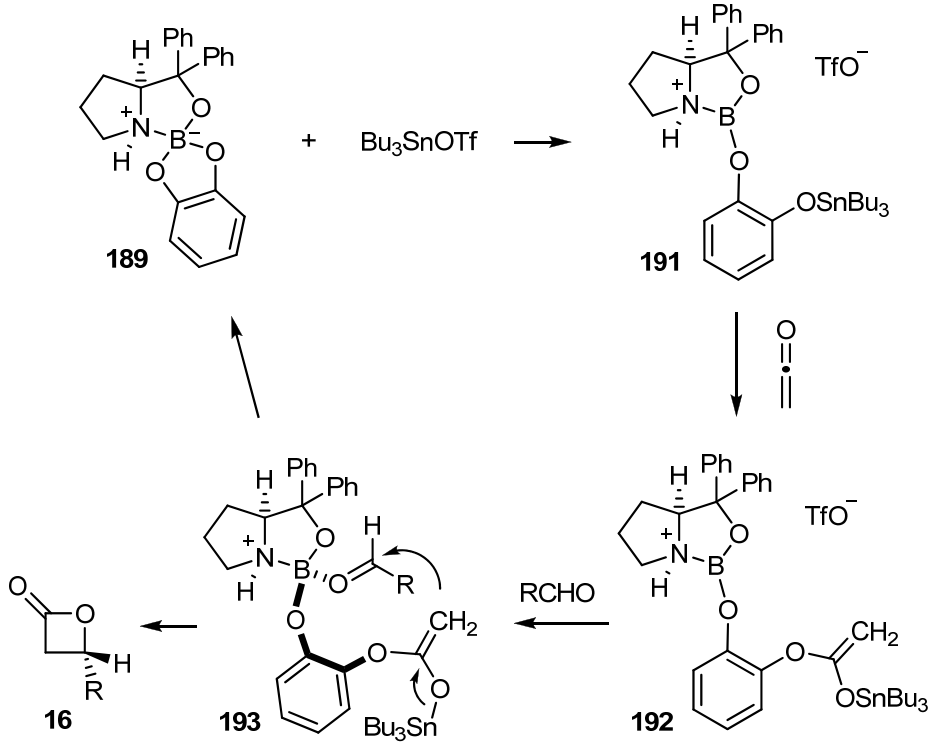
Scheme 71

By modification of the CBS oxazaborolidine catalyst **189** often used for the catalytic asymmetric reduction of ketones with borane, *Corey* and co-workers could catalyze the [2+2] cycloaddition of ketene **118** to α-branched and -unbranched aldehydes **82** with moderate to good yields and enantioselectivities (Scheme 72).[112] Ketene **118** was used in a large excess (10 equiv.) and was prepared by thermolysis of diketene at 550 °C.



Scheme 72

Corey postulated a bifunctional mode of action for catalyst **191** but no experimental support was provided. The mechanistic hypothesis is outlined in Scheme 73. Activation of precatalyst **189** by Bu_3SnOTf is expected to produce the ion pair **191**, which by reaction with ketene might form the intermediate **192**. This intermediate acts as *Lewis* acid for the activation of the aldehyde. The formation of the new C-C bond is followed by ring closure and extrusion of the β-lactone.

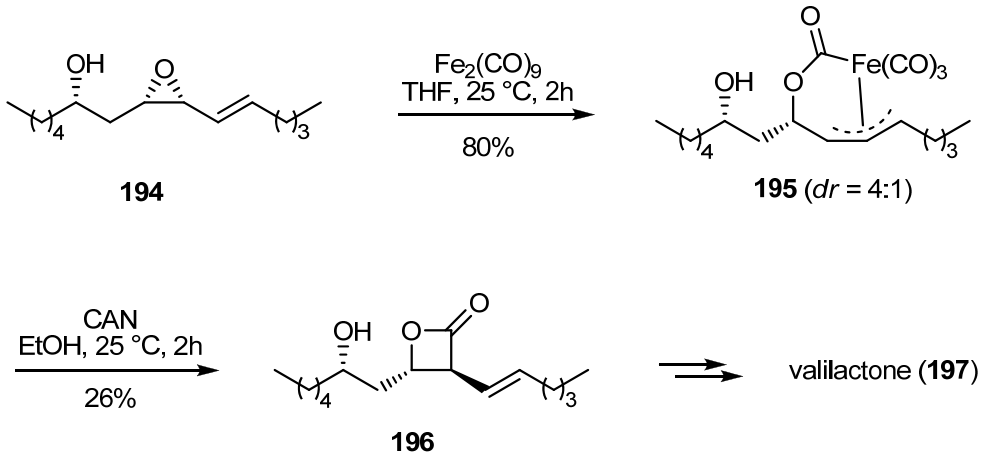


Scheme 73. Proposed pathway for the formation of β-lactones.

3.2.4 Miscellaneous

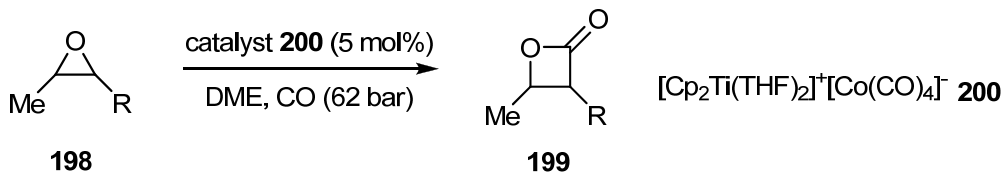
3.2.4.1 Transition-Metal Promoted Reactions

Various methods involving the use of transition-metal complexes have been proposed to prepare β-lactones. *Ley* and co-workers obtained β-lactones via π-allyltricarbonyliron complexes prepared from vinyl oxiranes and ironpentacarbonyl.[113] The method, using diironnonacarbonyl [$Fe_2(CO)_9$] was applied to a synthesis of the β-lactone esterase inhibitor (–)-valilactone (**197**). Epoxide **194** is complexed with $Fe_2(CO)_9$ leading to π-allyl complex **195** which on oxidation with ceric ammonium nitrate (CAN) affords in a poor yield *trans*-β-lactone **196**, a suitable intermediate for the synthesis of (–)-valilactone (**197**) (Scheme 74).[114]



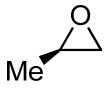
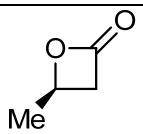
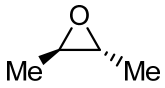
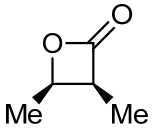
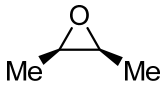
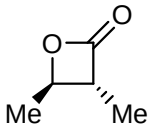
Scheme 74

Recently, *Coates* and co-workers used catalyst **200** for the selective carbonylation of methyl epoxides to form β-lactones in high yields (Scheme 75).[115] The synthetic problem is then reduced to the enantioselective preparation of epoxides. In Table 8 only examples starting from chiral enantiopure epoxides are listed. Drawbacks are the necessity of high pressure and the toxicity of CO.



Scheme 75

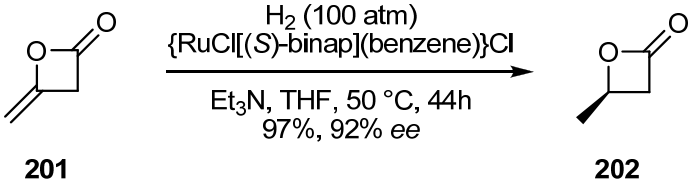
Table 8. Carbonylation of epoxides to β-lactones.

Entry	Epoxide	Time [h]	β-lactone	Yield [%]
1		4		62
2		10		46
3		10		69

Coates and co-workers also developed metal salen complexes for the carbonylation of epoxides.[116]

3.2.4.2 Asymmetric Hydrogenation

Both enantiomers of 4-methyloxetan-2-one (**202**) have been synthesized with up to 92% *ee* by asymmetric hydrogenation of diketene **201** employing a catalytic amount (0.1-0.2 mol%) of binap-Ru(II) complexes in the presence of triethylamine (Scheme 76).[117] β-Lactone **202** has been utilized as a starting material for the important biodegradable polymer poly[(*R*)-3-hydroxybutyrate, *via* ring opening polymerization.[118]



Scheme 76

Triethylamine was found to be a critical additive (0.5 to 0.9 equiv., relative to Ru(ll)) in this reaction to prevent polymerization of diketene and to control competitive hydrogenolysis leading to butyric acid.[118]

The procedure of *Roelens*[68] described above (Chapter 3.2.2; see Scheme 44 and Table 5) which employs an asymmetric *Noyori* hydrogenation of β-ketoesters as the stereochemical setting step also falls into the category of asymmetric hydrogenation. This is one of the most general routes reported to date and is thus mentioned here again.

Part A: Development of a *Lewis* Acid Catalyst

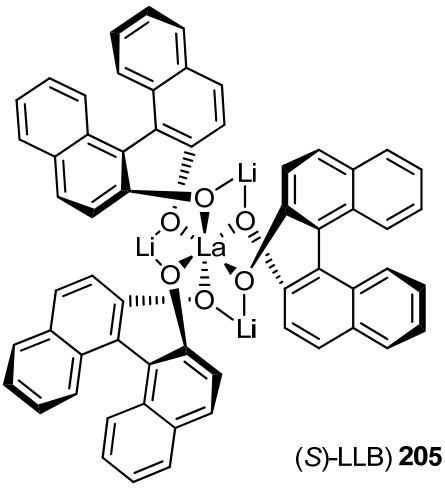
4 Background

4.1 *Lewis* Acid Assisted *Lewis* Acid Catalysis

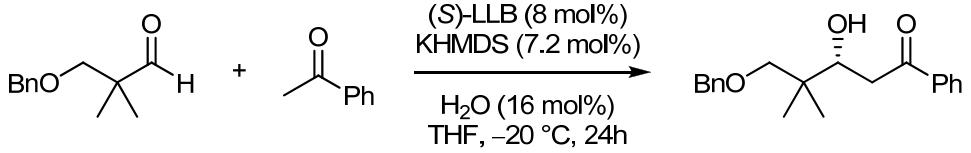
Chiral *Lewis* acid catalysts further activated by a second *Lewis* acid have recently emerged as a novel intriguing concept for catalyst design. Electron-deficient metal complexes can be further activated as electrophiles through hetero- and homodimeric associative interaction. In several instances, naked metal cations are generated. This has been widely encountered in many acid-catalyzed reactions including the *Friedel-Crafts* reaction and the *Ziegler-Natta* polymerization. However, its full recognition as a synthetically useful tool for asymmetric catalysis does not appear to be widespread yet.

The associative interactions can be crucial not only for higher reactivity but also for the construction of a well-organized chiral environment. Two representative examples of *Lewis* acid assisted *Lewis* acid catalysts which have higher reactivity and/or allow for highly organized transition states by the aid of associative interactions will be discussed in this introduction. More examples or a more detailed discussion can be found in reviews by *Yamamoto* and *Futatsugi* or by *Shibasaki* and *Yoshikawa*.[119]

Shibasaki and co-workers developed the chiral heterobimetallic complex system, $LaLi_3$-bis(binaphthoxide) (LLB), which is an efficient asymmetric catalyst for direct aldol reactions of aldehydes and unmodified ketones (Scheme 77).[120] The LLB catalyst functions not only as a base to remove an α-proton from the ketone, but also as a *Lewis* acid, giving the aldol product in high yield and with high enantioselectivity.



(*S*)-LLB **205**

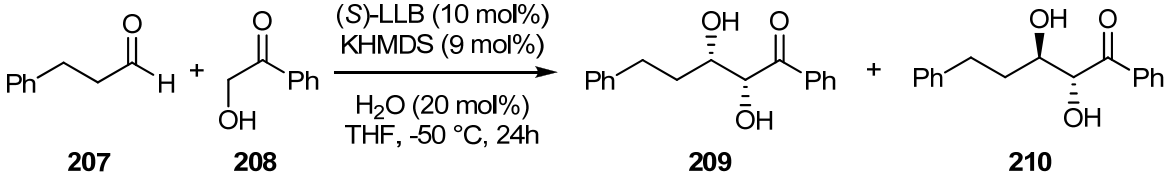


203 **204** **206**

70%, 93% *ee*

Scheme 77

The LLB catalyst also works well for the direct aldol reaction of aldehydes with α-hydroxy ketones to provide 1,2-dihydroxketones with high enantiomeric excess (Scheme 78).[121]

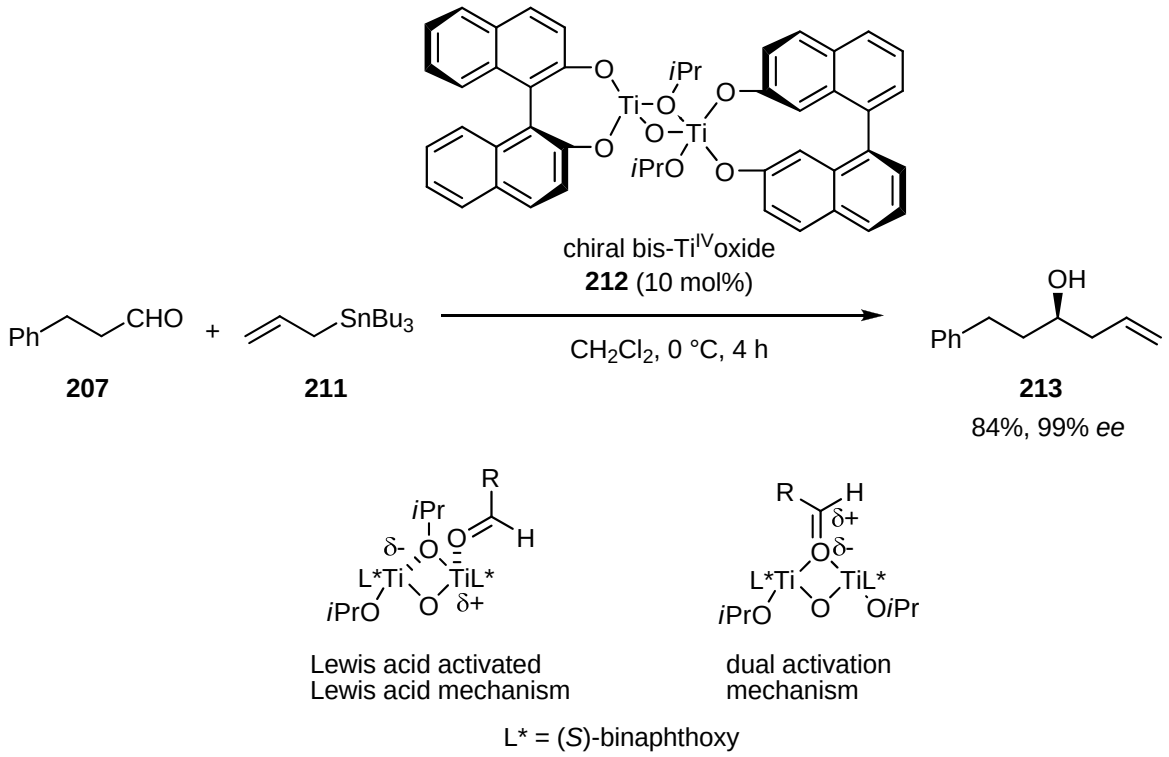


207 **208** **209** **210**

89% (*syn*/*anti* = 2:1), 95% *ee* (*syn*), 87% *ee* (*anti*)

Scheme 78

A new chiral bis-Ti^{IV} oxide was designed by *Maruoka* and co-workers and can be utilized for strong activation of aldehydes, thereby enabling the enantioselective allylation of aldehydes with allyltributyltin (Scheme 79).[122] The chiral bis-Ti^{IV} catalyst can be readily prepared either by treatment of bis(triisopropoxy)titanium oxide [(*i*-PrO)$_3$Ti–O–Ti(*i*-OPr)$_3$] with (*S*)-binol or by reaction of ((*S*)-binaphthoxy)isopropoxytitanium chloride with silver(I) oxide. The reaction of 3-phenylpropanal with allyltributyltin (1.1 equiv) under the influence of chiral bis-Ti^{IV} oxide (10 mol%) generated *in situ* in CH_2Cl_2 at 0 °C for 4 h afforded 1-phenyl-5-hexen-3-ol in 84% yield with 99% *ee*.



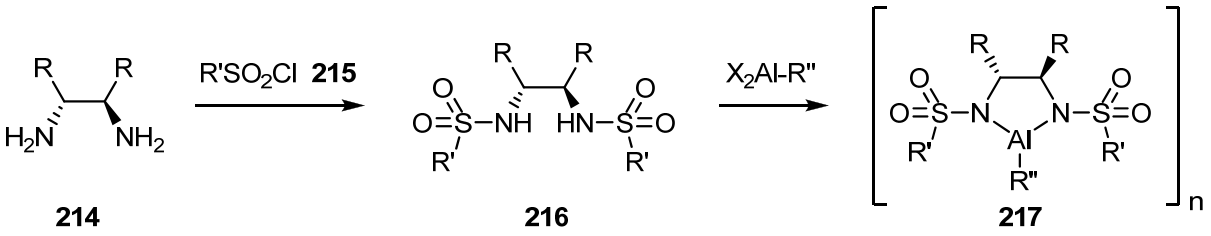
Scheme 79

This asymmetric approach provides a very useful way for obtaining high reactivity and selectivity by the simple introduction of the M-O-M unit in the design of chiral *Lewis* acid catalysts. The authors proposed that the high reactivity of this chiral bis-Ti^{IV} oxide might be ascribed to the intramolecular coordination of one isopropoxy oxygen atom to the other titanium center, thereby enhancing the otherwise weak *Lewis* acidity of the original Ti^{IV} center for carbonyl activation. This mode of activation is a typical example of the *Lewis* acid assisted *Lewis* acid mechanism. Alternatively, a dual activation of the carbonyl group by the simultaneous coordination of two Ti centers was also proposed as the origin of the high reactivity.

5 Development of a *Lewis* Acid Catalyst

The potential of the existing methods for ketene-aldehyde cycloadditions reveals that impressive stereoselectivities can be obtained for certain substrates. However, there is still a lack of a general method that tolerates a broad spectrum of aldehydes and, in particular; the use of non-activated ketones is an unsolved problem. Previous work by other groups had shown that the asymmetric formation of β-lactones can be catalyzed either nucleophilically, by *Lewis* acid catalysts or by a combined cooperative strategy. The most promising results for the *Lewis* acid strategy were obtained by aluminum-based systems. In the pioneering work by *Miyano*[92] and later *Kocienski*[93] bissulfonamide ligands derived from chiral *C2* symmetric 1,2-diamino-1,2-diphenylethane (DiPh) were utilized employing either the preformed gaseous parent ketene[92] or the commercially available, yet expensive trimethylsilyl-ketene[93].

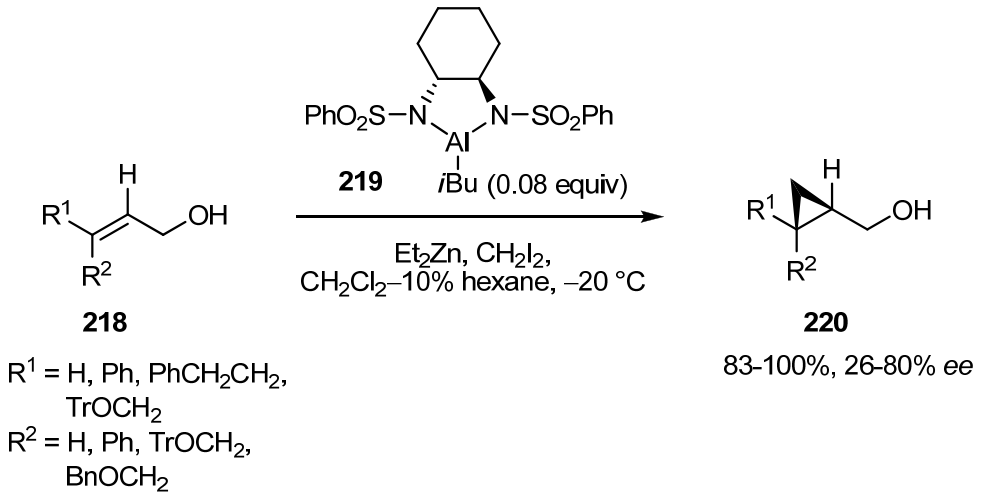
Moreover, as later demonstrated by *Nelson* using a different Al-based catalyst system (see Scheme 59), the ketene substrates could be generated in situ by dehydrobromination from acyl bromides by treatment with *Hünig*'s base. Based on these precedents the overall goal was to develop a system with enhanced practicality which should be as simple as possible, but still should provide high enantioselectivities and yields. For that reason bissulfonamide-derived Al complexes **217** (Scheme 80) were reinvestigated. The corresponding ligands can be prepared in a single step from the commercially available diamines **214** and sulfonyl chlorides **215**. They allow, although simple to prepare, a high structural diversity: along these lines the influence of different Al substituents R'', sulfonamide residues R' and C_2 symmetric diamino backbones can be investigated.



Scheme 80. Formation of bissulfonamide Al complexes **217**.

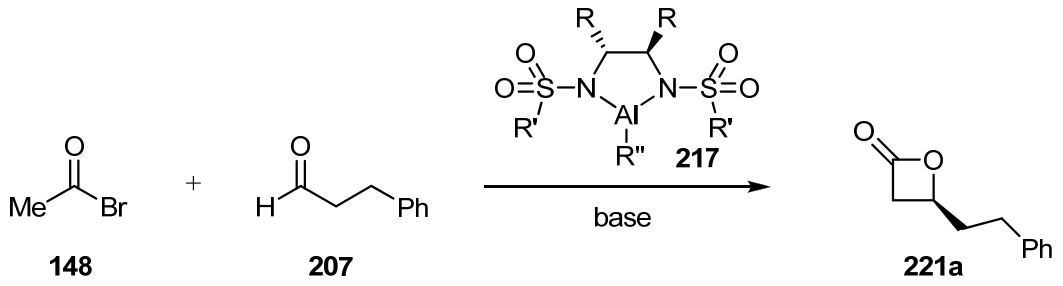
Surprisingly, only a single application of this type of Al catalyst possessing a bissulfonylated cyclohexane-1,2-diamino (Cy) ligand backbone has been reported in literature, namely the investigation of Al-catalyzed cyclopropanations (Scheme 81),[123] whereas the corresponding 1,2-diphenylaminoethane-derived aluminum catalysts have been frequently applied in

catalysis after the pioneering studies by *Corey* and co-workers on catalytic enantioselective *Diels-Alder* reactions.[124]



Scheme 81

The cyclocondensation of acetyl bromide **148** and dihydrocinnamaldehyde (**207**) was selected as model reaction for these studies (Scheme 82).



Scheme 82. Model reaction.

5.1 Initial Studies with 20 mol% Catalyst

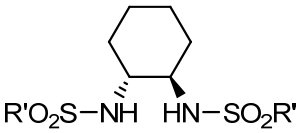
5.1.1 Ligand Screening

5.1.1.1 C_2 Symmetric Ligand 222 and the Effect of Different Sulfonyl Residues

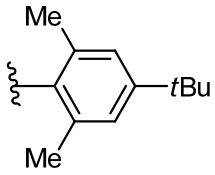
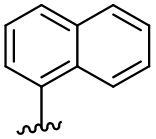
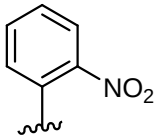
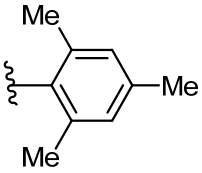
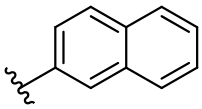
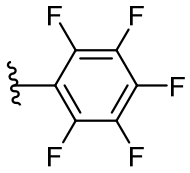
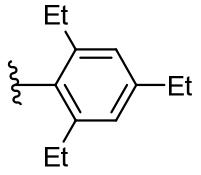
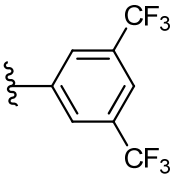
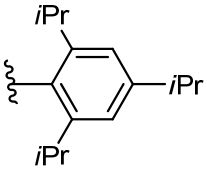
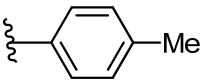
To gain a rapid insight into the optimal catalyst design and reaction conditions a substoichiometric amount of catalyst **217** (20 mol%) was utilized for an initial screening.

The screening started with the investigation of the influence of the substitution pattern on aromatic sulfonyl residues **222 a-k** (Table 9). In addition to the aromatic sulfonyl residues also a trifluoromethanesulfonyl residue **222k** was utilized. The catalysts were generally prepared *in situ* by stirring a 1:1 mixture of the ligands **222** and Dibal at room temperature for 1 h followed by heating the mixture to 80 °C for 4 h and were used without further isolation.

Table 9. Bissulfonamide ligands **222** for the initial screening.



ligands 222 a-k

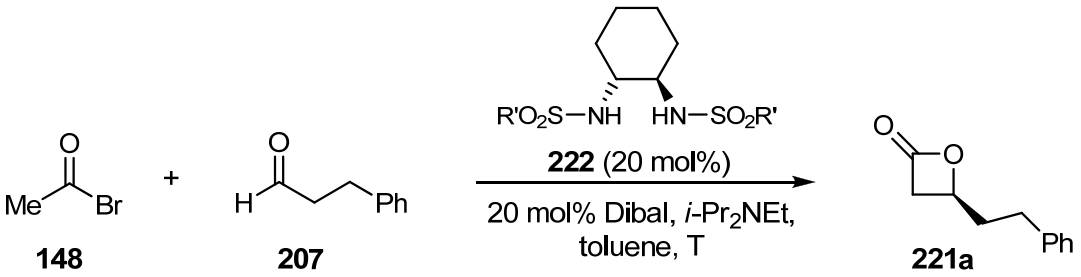
	R'		R'		R'
a Cy-Dmtb		**e** Cy-1-Naph		**i** Cy-2-NO_2	
b Cy-Trim		**f** Cy-2-Naph		**j** Cy-PFP	
c Cy-Trie		**g** Cy-BTFM		**k** Cy-Tf	
d Cy-Trip		**h** Cy-Ts			

Cy = (*R*,*R*)-cyclohexane-1,2-diamino; Dmtb = 4-*tert*-butyl-2,6-dimethyl-benzenesulfonyl; Trim = 2,4,6-trimethylbenzenesulfonyl; Trie = 2,4,6-triethylbenzenesulfonyl; Trip = 2,4,6-triisopropylbenzenesulfonyl; 1-Naph = 1-naphthylsulfonyl; 2-Naph = 2-naphthylsulfonyl; BTFM = 3,5-trifluoromethylbenzenesulfonyl; Ts = *p*-toluolsulfonyl; 2-NO_2 = 2-nitrobenzenesulfonyl; PFP = pentafluorobenzenesulfonyl; Tf = Trifluoromethylsulfonyl.

Initial experiments revealed that two *ortho*-substituents on an aromatic sulfonyl residue R' are essential to achieve acceptable enantioselectivities with 20 mol% catalyst, but that the *ortho*-substituents also slow down the reaction to a large degree (Table 10).

Al-complexes lacking the *ortho*-substituents on R' generally catalyzed the model reaction smoothly at −78 °C (half conversion after 0.1 to 0.7 h with the exception of entry 9 as determined by ^{1}H NMR monitoring), but the enantioselectivities were far from being preparatively useful (entries 5 to 8, 10). With methyl or ethyl *ortho*-substituents, the reaction temperature had to be increased to −60 °C to obtain reasonable reaction rates (entries 1 to 3), while in the case of isopropyl residues, the conversion was very slow even at –50 °C (entry 4). The bis-*ortho*-substituted aromatic residues R' allowed the formation of lactone **221a** with *ee* values >70%, the best results being realized with Cy-Dmtb ligand **222a** (*ee* = 80%, half conversion after 2.5 h, entry 1). Entries 1 and 2 also revealed, that the *para*-substituents have a substantial influence upon the reaction rate.

Table 10. Initial screening of bissulfonamide ligands **222** derived from (*R*,*R*)-cyclohexyl-1,2-diamine.[a]

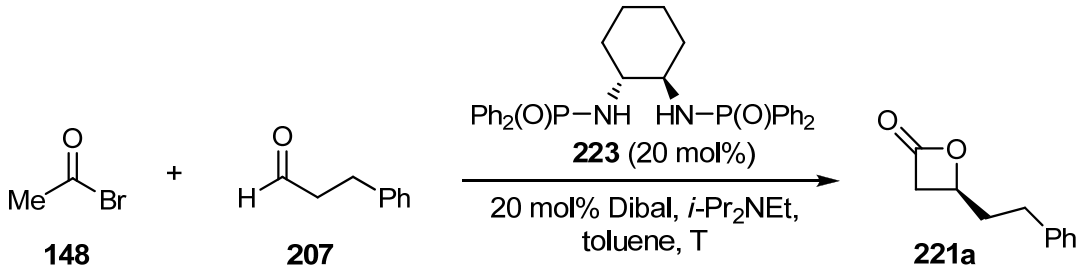


Entry	Ligand	Temp. [°C]	$\tau_{1/2}$[b] [h]	*ee*[c] [%]
1	Cy-Dmtb **222a**	–60	2.5	80
2	Cy-Trim **b**	–60	8	80
3	Cy-Trie **c**	–60	3.3	73
4	Cy-Trip **d**	–50	21	71
5	Cy-1-Naph **e**	–78	0.2	43
6	Cy-2-Naph **f**	–78	0.25	37
7	Cy-BTFM **g**	–78	0.2	35
8	Cy-Ts **h**	–78	0.1	30
9	Cy-2-NO_2 **i**	–78	35	19
10	Cy-PFP **j**	–78	0.7	17
11	Cy-Tf **k**	–78	<0.5	2

[a] All reactions were performed at a concentration c = 0.13 M. The ketene was preformed in a separate flask by treatment of acetyl bromide (3 equiv.) with *Hünig*'s base (2.5 equiv.) in toluene at –78°C for 4 h. The ketene solution was subsequently transferred *via* canula into the reaction flask. [b] Determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

5.1.1.2 C_2 Symmetric Ligand 223

The structurally related phosphinic amide ligand **223** was investigated in combination with Dibal and Me_3Al as Al-sources (Scheme 83). The reaction was followed *via* ^1H NMR but with both aluminum sources no conversion of the aldehyde **207** was observed at –78 °C. Even after raising the temperature to +10 °C no product was formed after 5 h.



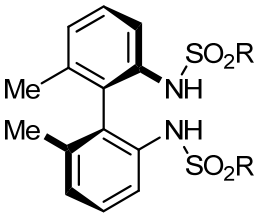
Scheme 83. Screening with phosphinic amide ligand **223**.

This might be attributed to the steric demand of the two phenyl moieties on the pentavalent phosphorous atom thus preventing a coordination of the aldehyde to the metal center. Another reason could be a self-quenching process of the *Lewis* acidic aluminum center by the *Lewis* basic oxygen of the P(O)-groups since this oxygen displays an increased basicity as compared to the oxygen of sulfonyl groups.

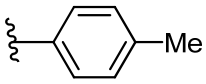
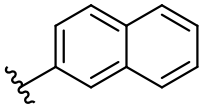
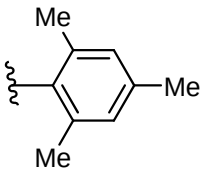
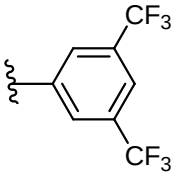
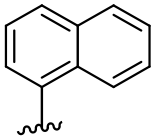
5.1.1.3 Axially Chiral Biphenyl Ligand 224

The [2+2] cycloaddition reaction of dihydrocinnamaldehyde (**207**) and ketene **118** was also investigated with ligands **224 a-e** (Table 11).

Table 11. Bissulfonamide ligands **224** for the initial screening.



ligand **224**

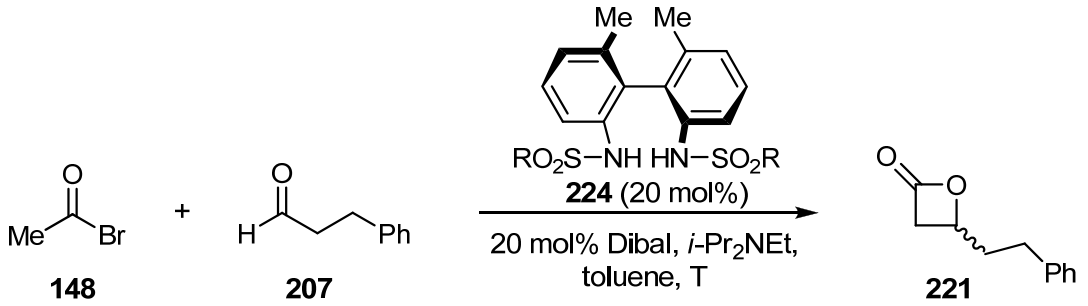
	R		R
a Biph-Ts		**d** Biph-2-Naph	
b Biph-Trim		**e** Biph-BTFM	
c Biph-1-Naph			

Biph = (*R*)-6,6'-dimethylbiphenyl-2,2'-diamine; Ts = p-toluolsulfonyl; Trim = 2,4,6-trimethylbenzenesulfonyl;; 1-Naph = 1-naphthylsulfonyl; 2-Naph = 2-naphthylsulfonyl; BTFM = 3,5-trifluoromethylbenzenesulfonyl; Dmtb = 4-*tert*-butyl-2,6-dimethyl-benzenesulfonyl.

In a typical experiment to a mixture of the biphenyl ligand **224** (0.1 mmol, 0.2 equiv.) in toluene (2 mL) was slowly added at ambient temperature a solution of Dibal (0.1 mmol, 0.2 equiv., 1.0 M in toluene). The mixture was heated to 80 °C and stirred for 2 h. Subsequently, the solution was stirred for 1 h at ambient temperature. The catalyst solution was then cooled to the indicated temperature and addition of aldehyde (0.5 mmol, 1 equiv.) was followed by acetyl bromide (1.5 mmol, 3 equiv.) and *Hünig*'s base (1.25 mmol, 2.5 equiv.).

With all residues R a significant loss of enantioselectivity was observed as compared to sulfonamide ligands **222** derived from cyclohexane-1,2-diamine (Table 12). As shown for ligand **222**, *ortho* substituents on the aromatic sulfonyl residues R again allow for the best selectivities (entry 2). However, the maximum *ee* of 39% was far from being preparatively useful (entry 2). Due to these results further studies with ligand **224** were abondoned.

Table 12. Screening of bissulfonamide ligands **224** derived from (*R*)-6,6'-dimethylbiphenyl-2,2'-diamine.[a]



Entry	Ligand	Temp. [°C]	Time [h]	Yield[b] [%]	*ee*[c] [%]	Config. [d]
1	Biph-Ts **224a**	–60	26	66	3	(*S*)
2	Biph -Trim **b**	–78	44	52	39	(*S*)
3	Biph -1-Naph **c**	–78	72	37	4	(*S*)
4	Biph -2-Naph **d**	–78	22	47	15	(*R*)
5	Biph -BTFM **e**	–60	69	29	31	(*R*)

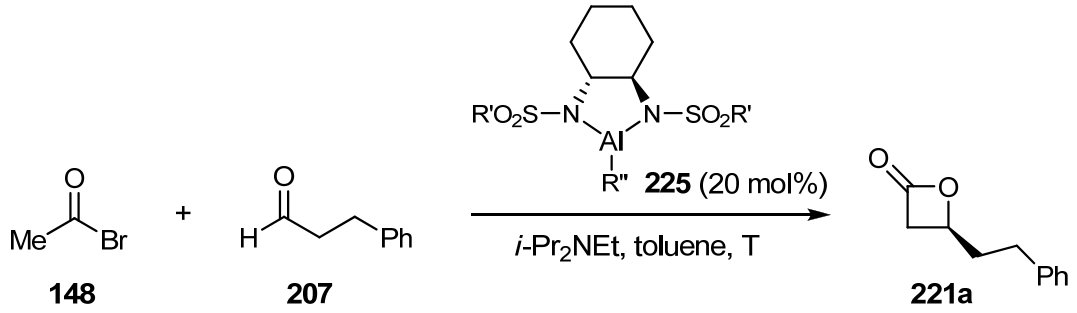
[a] All reactions were performed at a concentration c = 0.25 M. The ketene was formed *in situ*. [b] Determined by ^{1}H NMR with pyridine as an internal standard. [c] *ee* determined by HPLC on a chiral support. [d] The configuration was determined by comparison of the $[\alpha]_D$ value of compound **221** with literature data.

5.1.2 Further Studies with C_2 Symmetric Ligand 222

5.1.2.1 Effect of the Al Substituent R''

The investigation of the influence of the Al substituent R'' showed that the bulky isobutyl moiety permitted a significantly higher enantioselectivity (*ee* = 80%, Table 13, entry 1) than ethyl (*ee* = 72%, entry 2) or methyl (*ee* = 53%, entry 3) residues, but again the higher selectivity was at the expense of a reduction in the reaction rate.

Table 13. Investigation of the effect of different Al substituents R".[a]



Entry	Ligand	R"	Temp. [°C]	*ee*[b] [%]
1	Cy-Trim **222b**	*i*-Bu	–60	80
2	Cy-Trim	Et	–60	72
3	Cy-Trim	Me	–78	53

[a] All reactions were performed at a concentration c = 0.13 M. The ketene was preformed in a separate flask by treatment of acetyl bromide (3 equiv.) with *Hünig*'s base (2.5 equiv.) in toluene at –78°C for 4 h. The ketene solution was subsequently transferred *via* canula into the reaction flask. [b] *ee* determined by HPLC on a chiral column.

Reactions with R" = Cl (*ee* = 50%, Table 14, entry 1) or F (*ee* = 14%, entry 2) were less enantioselective and although the *Lewis* acidity is supposed to increase compared to an alkyl substituted aluminium center a slower reaction was observed.

Table 14. Investigation of *i*-Bu_2AlF and Et_2AlCl as Al sources.[a]

Entry	Ligand	R"	Temp. [°C]	*ee*[b] [%]
1	Cy-Trip **222d**	Cl	–78	50
2	Cy-Trip	F	–78	28

[a] All reactions were performed at a concentration c = 0.25 M. The ketene was formed *in situ*. [b] *ee* determined by HPLC on a chiral column.

5.1.2.2 Temperature Dependence

The [2+2] cycloaddition reaction showed a linear temperature dependence, meaning that with decreasing temperature the enantioselectivity increased. However, temperatures below –60 °C led to a drastically reduced rate of conversion (Table 15).

Table 15. Temperature dependence of the [2+2] cycloaddition reaction.[a]

Entry	Temp. [°C]	Time [h]	Conversion [%]	*ee*[b] [%]
1	−50	21	99	74
2	−60	15	100	80
3	−70	17	50	82

[a] All reactions were performed at a concentration *c* = 0.13 M with 20 mol% of ligand **222a** and 20 mol% Dibal. The ketene was formed *in situ*. [b] *ee* determined by HPLC on a chiral support.

5.1.2.3 Catalyst Formation

To generate a catalyst species allowing for the highest enantioselectivities, heating to 80 °C for several hours proofed to be essential. Investigation of the heating time period revealed an optimum time of 4 h (Table 16, entry 2) whereas prolonged heating for 6 h (entry 1) or a shorter heating period of just 2 h (entry 3) exhibited diminished enantioselectivities.

Table 16. Influence of the duration of the heating period on catalyst formation.[a]

Entry	Heating period [h]	Time [h]	Conversion [%]	*ee*[b] [%]
1	6	43	66	62
2	4	44	77	71
3	2	43	52	64

[a] All reactions were performed at a concentration *c* = 0.13 M with 20 mol% of ligand **222d** and 20 mol% Dibal at –50 °C. The ketene was preformed in a separate flask by treatment of acetyl bromide (3 equiv.) with *Hünig*'s base (2.5 equiv.) in toluene at –78°C for 4 h. The ketene solution was subsequently transferred *via* canula into the reaction flask. [b] *ee* determined by HPLC on a chiral support.

Further studies of the catalyst formation disclosed an additional temperature dependency: after heating the catalyst solution for 4 h to 80 °C the time frame between removal of the heating bath and the active cooling to the corresponding low reaction temperature clearly influenced the rate of conversion (Table 17). The experiments revealed that a direct cooling to –50 °C (entry 1) resulted in a slower reaction as compared to prestirring for additional 1.5 h at ambient temperature (entry 2). This effect was observed despite a lower reaction temperature (ΔT = 10 °C).

Table 17. Influence of the cooling period on catalyst formation.[a]

Entry	Cooling period [h]	Temp. [°C]	Time [h]	Conversion [%]	*ee*[b] [%]
1	0	−50	21	99	74
2	1.5	−60	15	99	80

[a] All reactions were performed at a concentration c = 0.13 M with 20 mol% of ligand **222a** and 20 mol% Dibal. The ketene was preformed in a separate flask by treatment of acetyl bromide (3 equiv.) with *Hünig*'s base (2.5 equiv.) in toluene at −78°C for 4 h. The ketene solution was subsequently transferred *via* canula into the reaction flask. [b] *ee* determined by HPLC on a chiral support.

5.1.2.4 Ratio Dibal / Ligand

With a 1:1 respectively 2:3 ratio of ligand to Dibal the obtained enantioselectivities are in a comparable range (Table 18, entries 1 and 2). In contrast, by rising the Dibal amount to 2 equiv. per equiv. of ligand, the selectivity dropped drastically (entry 3). This observation led to the conclusion that Dibal or an achiral species formed from Dibal is able to catalyze the reaction leading to racemic product.

Table 18. Ratio Dibal / ligand.[a]

Entry	Ligand / Dibal [mol%]	*ee*[b] [%]
1	20 : 20	80
2	20 : 30	77
3	20 : 40	33

[a] All reactions were performed at a concentration c = 0.13 M with 20 mol% of ligand **222a** and 20 mol% Dibal at –60 °C. The ketene was preformed in a separate flask by treatment of acetyl bromide (3 equiv.) with *Hünig*'s base (2.5 equiv.) in toluene at –78°C for 4 h. The ketene solution was subsequently transferred *via* canula into the reaction flask. [b] *ee* determined by HPLC on a chiral support.

5.1.2.5 Effect of Additives

Shibasaki and co-workers recently described a new catalytic system affording improved enantioselectivities with the addition of phosphine oxide additives.[125] This was rationalized by a change in the geometry of the catalyst from tetrahedral to trigonal pyramidal caused by the additive (for a more detailed discussion see Chapter 8.2.1.2).

The effect of triphenylphosphine oxide in combination with ligand **222d** was also tested for the model reaction at –78 °C (Table 19). With the additive the [2+2] cycloaddition came to an almost complete halt (entry 1).

Assuming that ligand **222d** might be sterically too demanding to achieve a similar effect as previously observed, the sterically less demanding ligand **222k** was investigated next, but again a decreased reaction rate was observed and the product was formed in almost racemic form (entry 2). These results show that the additive does not effect the complex geometry in the present case. Instead, the additive blocks the only free coordination site of the tetrahedral complex **225** and therefore hampers the product formation.

Table 19. Study of Ph_3PO as additive.[a]

Entry	Ligand	Additive	Time [h]	Conversion [%]	*ee*[b] [%]
1	Cy-Trip **222d**	Ph_3PO	88	5	-
2	Cy-Tf **222k**	Ph_3PO	126	56	2

[a] All reactions were performed at a concentration c = 0.13 M with 20 mol% bissulfonamide and 20 mol% Et_2AlCl at –78 °C. The ketene was formed *in situ*. [b] *ee* determined by HPLC on a chiral support.

Yamamoto and *Futatsugi* stress in their review article that with the use of a second *Lewis* acid associative interactions can occur.[119b] These interactions can not only lead to a higher reactivity (*Lewis* acid activation of another *Lewis* acid) but also to the formation of a well-organized chiral environment.

Assuming that with the use of a second *Lewis* acid similar associative interactions could also be used to accelerate a β-lactone formation, studies with Me_2Zn as co-catalyst were conducted. Me_2Zn is not *Lewis* acidic enough to catalyze the [2+2]-cycloaddition but could still coordinate to the sulfonyl-moieties thereby increasing the acidity of the catalytically active centre.

However, initial studies with 0.2 equiv. (Table 20, entry 2) and 0.4 equiv. of Me_2Zn (entry 3) led to depleted reaction rates as well as enantioselectivities as a result of unidentified side reactions.

Table 20. Effect of Me_2Zn as *Lewis* acid cocatalyst.[a]

Entry	Additive / equiv.	Time [h]	Conversion [%]	*ee*[b] [%]
1	-	15	99	80
2	Me_2Zn / 0.2	22	75	67
3	Me_2Zn / 0.4	50	38	50

[a] All reactions were performed at a concentration c = 0.13 M with 20 mol% of ligand **222b** and 20 mol% Dibal at –60 °C. The ketene was preformed in a separate flask by treatment of acetyl bromide (3 equiv.) with *Hünig*'s base (2.5 equiv.) in toluene at –78°C for 4 h. The ketene solution was subsequently transferred *via* canula into the flask. [b] *ee* determined by HPLC on a chiral support.

Nelson and co-workers utilized TMSQd as chiral nucleophile in the presence of $LiClO_4$ as *Lewis* acid co-catalyst in their dual activation approach for the formation of β-lactones.[104] With TMSQd the corresponding ketene formed a zwitterionic enolate, while the aldehyde could be activated with $LiClO_4$. Also in the present work, the formation of a zwitterionic enolate, chiral or achiral, might in principle accelerate the cycloaddition reaction. The respective enolate, might also result in increased enantioselectivity.

In order to study the influence of nucleophilic additives, Et_3N (Table 21, entry 1) and tetrabutylammonium iodide (entries 2 and 3) were chosen. With both additives lower conversions and enantioselectivities were obtained, but with Et_3N the diminished enantioselectivity was more accentuated. A reaction employing 1 equiv. of tetrabutylammonium iodide (entry 3) proceeded faster and was more selective than the reaction with 0.1 equiv. (entry 2), but compared to the system without additives, basically no improvement was observed.

Table 21. Reactions with nucleophilic additives.[a]

Entry	Additive / equiv.	Time [h]	Conversion [%]	*ee*[b] [%]
1	Et_3N / 0.1	72	80	70
2	TBAI / 0.1	22	47	74
3	TBAI / 1.0	22	60	77

[a] All reactions were performed at a concentration c = 0.13 M with 20 mol% of ligand **222a** and 20 mol% Dibal at –60 °C. The ketene was preformed in a separate flask by treatment of acetyl bromide (3 equiv.) with *Hünig*'s base (2.5 equiv.) in toluene at –78°C for 4 h. The ketene solution was subsequently transferred *via* canula into the reaction flask. [b] *ee* determined by HPLC on a chiral support.

5.1.2.6 Acetyl Chloride as Ketene Precursor

With acetyl chloride as ketene precursor no or only very little conversion of the aldehyde was observed. A reason for that could be that chloride, which is according to the HSAB[126] principle (HSAB = hard and soft acids and bases) harder than bromide, blocked the catalyst by a strong coordination to the hard Al center. However, removal of the ammoniumchloride salt, generated during the dehydrochlorination of acetyl chloride, led only to a minute change in the reaction rate.

In general, the best results were obtained by use of 3 equiv. of acetyl bromide and 2.5 equiv. of *Hünig*'s base. An excess of base was used to prevent side reactions like self aldol additions of the aldehyde.

However, the excess of base also slightly decelerated the reaction. To simplifiy the reaction setup the ketene was formed *in situ*, rather than preformed.

5.3 Studies with 10 mol% Catalyst

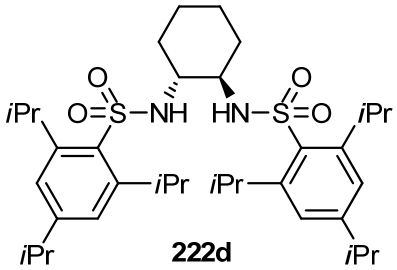
Having established an operationally simple, asymmetric reaction for the conversion of dihydrocinnamaldehyde (**207**) as model aldehyde to β-lactone **221a** using substoichiometric amounts of the chiral *Lewis* acid complex, the next goal was to reduce the amount of catalyst. Based on the preliminary findings with 20 mol% catalyst the following reactions were conducted with *ortho*-disubstituted bissulfonamide ligands **222a** , **b** or **d**.

5.3.1 Effect of the Al Source / Ligand Ratio

*5.3.1.1 Ligand **222d***

With a lower catalyst loading of 10 mol% the reaction was not only further decelerated, but proceeded also less enantioselectively (Cy-Trip **222d**, T = –70 °C, *ee* = 65%). The catalysts with *ortho*-disubstituted aromatic residues R" selected for further investigations were generally prepared *in situ* by stirring a 1:1 mixture of the bulky ligands **222a**, **b** or **d** and Dibal at room temperature for 1 h followed by heating the mixture to 80 °C for 4 h. The complex ^{1}H NMR spectra of these mixtures showed that about one third of the ligand was not consumed under these conditions. Rising the Dibal amount to 1.5 equiv. per equiv. of bissulfonamide ligand, the signals of the free ligand completely disappeared. Utilizing 10 mol% of ligand and 15 mol% of Dibal the reaction was not only dramatically accelerated by the excess of Dibal, but was also more selective than with a 1:1 stoichiometry of ligand and Al source (Table 22, entry 3). As demonstrated for **222d**, the reaction which was very sluggish at –50 °C with 20 mol% of catalyst (half conversion of the aldehyde after 21 h), proceeded to completion within 15 h at –70 °C employing 10 mol% of the chiral ligand and 15 mol% of Dibal. A further increase of the amount of Dibal is detrimental to both yield and enantioselectivity (entries 4 and 5).

Table 22. Investigation of the effect of the ligand **222d** / Al-source ratio.[a]



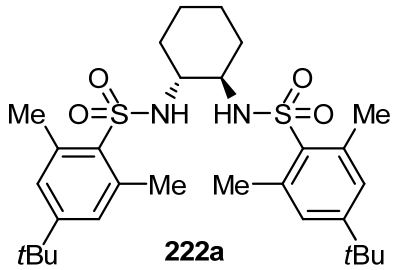
Entry	222d:Dibal [mol%]	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
1	10:10	18	37	32	65
2	10:12.5	18	57	55	70
3	10:15	15	100	87	78
4	10:17.5	15	100	62	77
5	10:20	15	98	66	72

[a] All reactions were performed at a concentration c = 0.25 M at –70 °C. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

*5.3.1.2 Ligand **222a***

Similar results as with ligand **222d** were obtained with ligand Cy-Dmtb **222a**. Again, a 3:2 ratio of Al source and ligand provided the best yield and selectivity (Table 23, entry 2).

Table 23. Investigation of the effect of the ligand **222a** / Al-source ratio.[a]



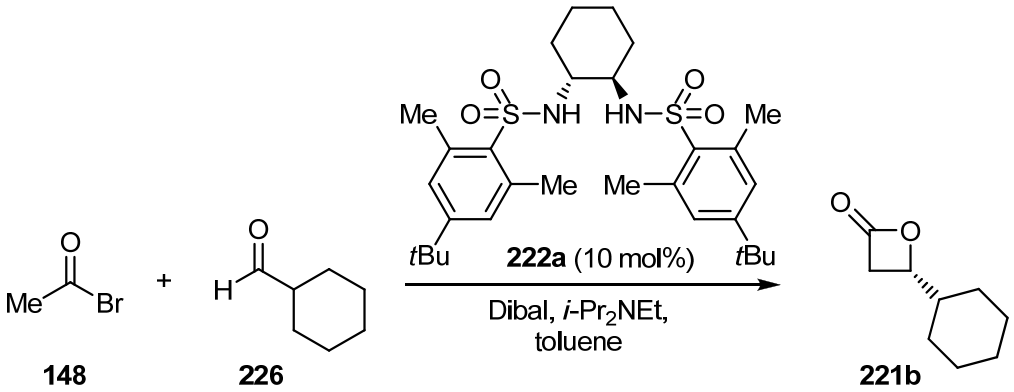
Entry	222a/Dibal [mol%]	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
1	10:12	66	72	76	74
2	10:15	65	92	85	78
3	10:20	16	96	73	67

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –60 °C. The ketene was preformed in a separate flask by treatment of acetyl bromide (3 equiv.) with *Hünig*'s base (2.5 equiv.) in toluene at –78 °C for 4 h. The ketene solution was subsequently transferred *via* canula into the reaction flask. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

When the same conditions were applied to cyclohexylcarbaldehyde (**226**), chosen as a model substrate for α-branched aldehydes, the variation of the stoichiometry of ligand and Al source did not influence the enantioselectivity (Table 24).

Moreover, with ligand **222d** in combination with cyclohexylcarbaldehyde the product was obtained in a disappointing yield of 17% after 40 h at –85 °C (20% conversion) and with moderate enantioselectivity (72% *ee*). However, with ligand Cy-Dmtb **222a**, which performed inferiorly for dihydrocinnamaldehyde (**207**), product **221b** could be obtained with good yield and selectivity.

Table 24. Investigation of the effect of the ligand **222a** / Al-source ratio.[a]



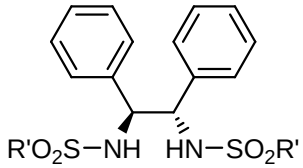
Entry	222a:Dibal [mol%]	Time [h]	Conversion[b] [%]	Yield[c] [%]	*ee*[d] [%]
1	10:12.5	40 (23)	(84)	94	86
2	10:15	40 (23)	(99)	87	86
3	10:17.5	40 (23)	(99)	96	86
4	10:20	40 (23)	(98)	92	86

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –85 °C. The ketene was formed *in situ*. [b] Refers to the reaction time in parentheses. [c] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [d] *ee* determined by HPLC on a chiral support.

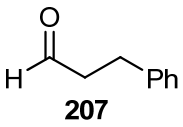
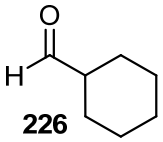
*5.3.1.3 Ligand **227***

Experiments with 1,2-diphenyl-1,2-diaminoethane based ligand **227** and an excess of Dibal also led to enhanced reactivity and enantioselectivity (Table 25). This was not only found for α-unbranched aldehyde **207** (entries 1 to 4) but also for the α-branched substrate **226** (entries 5 to 8), albeit the influence for dihydrocinnamaldehyde (**207**) is less pronounced in that case. Additionally, with ligand **222b** (entries 1-2 and 5-6) superior enantioselectivities were obtained as compared to ligand **222a** (entries 2-3 and 6-7).

Table 25. Investigation of the effect of the ligand **227** / Al-source ratio.[a]



227a (10 mol%), R' = 2,6-$(CH_3)_2$-4-(*t*-Bu)C_6H_2
227b (10 mol%), R' = 2,4,6-(*i*-Pr)$_3C_6H_2$

Aldehyde	Entry	Ligand	227:Dibal [mol%]	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
 **207**	1	Diph-Dmtb **227a**	10:15	44	68	45	82
	2	Diph-Dmtb	10:10	44	45	33	80
	3	Diph-Trip **227b**	10:15	44	100	79	78
	4	Diph-Trip	10:10	44	57	42	74
 **226**	5	Diph-Dmtb **227a**	10:15	45	64	61	90
	6	Diph-Dmtb	10:10	45	45	46	87
	7	Diph-Trip **227b**	10:15	45	79	77	75
	8	Diph-Trip	10:10	45	49	47	70

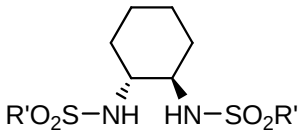
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –85 °C. The ketene was formed *in situ*. [b] Refers to the reaction time in parentheses. [c] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [d] *ee* determined by HPLC on a chiral support.

5.3.2 Effect of Different Sulfonyl Residues

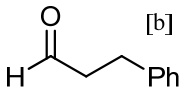
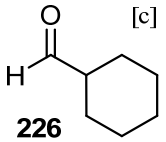
Table 26 summarizes representive results for ligand **222** which is based on the (*R*,*R*)-cyclohexane-1,2-diamino (Cy) backbone. In the initial screening of different sulfonyl residues at –60 °C the best selectivities were obtained with ligand **222d** (entry 2) and it was therefore most often selected for subsequent studies.

For cyclohexylcarbaldehyde (**226**) the sterically less demanding ligand **222a** was found to be superior (entry 5).

Table 26. Representive Results for Cy-Dmtb **222a**, Cy-Trim **222b** and Cy-Trip **222d**.[a]



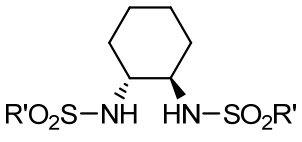
222a (10 mol%), R' = 2,6-$(CH_3)_2$-4-(*t*-Bu)C_6H_2
222b (10 mol%), R' = 2,4,6-$(Me)_3C_6H_2$
222d (10 mol%), R' = 2,4,6-(*i*-Pr)$_3C_6H_2$

Aldehyde	Entry	Ligand	Temp. [°C]	Time [h]	Conversion [%]	Yield[d] [%]	*ee*[e] [%]
 [b] **207**	1	**Cy-Trip 222d**	**−85**	**48**	**98**	**93**	**88**
	2	Cy-Trip **222d**	−60	16	100	99	75
	3	Cy-Dmtb **222a**	−60	19	100	72	73
 [c] **226**	4	Cy-Trim **222b**	−60	17	100	62	70
	5	**Cy-Dmtb 222a**	**−85**	**23**	**99**	**87**	**86**
	6	Cy-Trip **222d**	−85	39	20	17	72

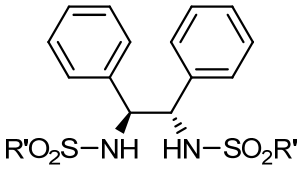
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with a 3:2 ratio of Al source and 10 mol% ligand. The ketene was formed *in situ*. [b] Dibal as Al source. [c] Et_3Al as Al source. [d] Yield after aqueous workup determined by ^1H NMR using acetophenone as an internal standard. [e] *ee* determined by HPLC on a chiral support.

For α-branched aldehydes the combination of ligand **227a** and Et_3Al generally afforded improved enantioselectivities (Table 27, entries 1, 3 and 5). The same tendency was found for β-branched isovaleraldehyde (**230**, entry 7), although the difference here is less accentuated. For the α-unbranched dihydrocinnamaldehyde ligand **222d** was superior (entry 10).

Table 27. Results for α-branched and -unbranched aldehydes.[a]

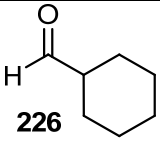
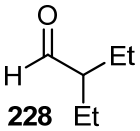
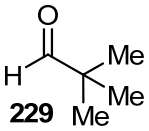
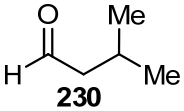
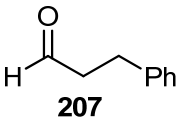


222



227

222a (10 mol%), R' = 2,6-$(CH_3)_2$-4-(*t*-Bu)C_6H_2 **227a** (10 mol%), R' = 2,6-$(CH_3)_2$-4-(*t*-Bu)C_6H_2
222d (10 mol%), R' = 2,4,6-(*i*-Pr)$_3C_6H_2$ **227b** (10 mol%), R' = 2,4,6-(*i*-Pr)$_3C_6H_2$

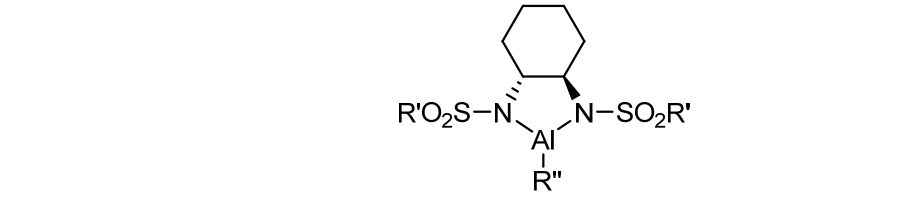
Aldehyde	Entry	Ligand	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]	Al source
 **226**	1	Diph-Dmtb **227a**	25	100	88	90	Et_3Al
	2	Cy-Dmtb **222a**	23	99	87	86	Et_3Al
 **228**	3	Diph-Dmtb **227a**	136	95	94	80	Et_3Al
	4	Cy-Dmtb **222a**	113	98	87	68	Et_3Al
 **229**	5	Diph-Dmtb **227a**	135	100	83	78	Et_3Al
	6	Cy-Dmtb **222a**	135	100	89	75	Et_3Al
 **230**	7	Diph-Trip **227b**	26	100	98	85	Dibal
	8	Cy-Trip **222d**	49	100	84	84	Dibal
 **207**	9	Diph-Dmtb **227a**	48	78	66	82	Dibal
	10	Cy-Trip **222d**	48	98	93	88	Dibal

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with a 3:2 ratio of Al source and ligand. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

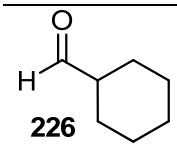
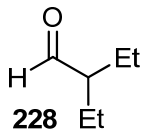
5.3.3 Effect of the Al Substituent R''

While Dibal as Al source was superior for dihydrocinnamaldehyde (**207**) as substrate, $AlEt_3$ was more efficient for the α-branched cyclohexylcarbaldehyde (**226**, Table 28, entries 1 and 2) and 2-ethylbutyraldehyde (**228**, entries 3 and 4).

Table 28. Effect of the Al Substituent R''.[a]



148 **82** **231**

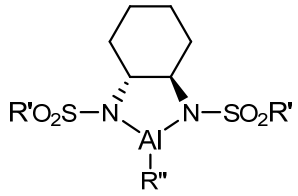
Aldehyde	Entry	R''	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
 **226**	1	*i*-Bu	47	84	71	82
	2	Et	48	98	87	86
 **228**	3	*i*-Bu	139	52	38	55
	4	Et	139	100	87	68

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –85 °C with a 3:2 ratio of Al source and ligand (10 mol%). The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

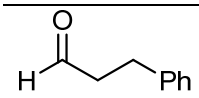
Assuming that an increased cationic character of the aluminum center could further accelerate the reaction, the ethyl substituent R'' on Al was substituted for triflate (Table 29). Initially, the catalyst prepared from ligand **222d** and Et_3Al was formed by the standard procedure: to a mixture of ligand **222d** (0.15 mmol) in absolute toluene (6.0 mL) was slowly added at ambient temperature a solution of Et_3Al (1.0 M in hexane, 0.225 mmol). The mixture was heated to 80 °C and stirred for 4 h. Subsequently, the solution was stirred for 1 h at ambient temperature. Than trifluoromethylsulfonic acid (0.15 mmol) was added and the mixture was cooled to the indicated reaction temperature.[127]

However, with the triflate counteranion the reaction was accelerated but proceeded less enantioselectively (entry 1).

Table 29. Exchange of the ethyl substituent R'' for triflate.[a]



225d, R' = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$

Aldehyde	Entry	R''	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
 **207**	1	Et → TfO	87 (71)	(72)	44	62
	2	Et	87 (71)	(48)	42	76

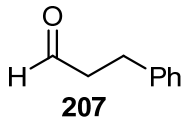
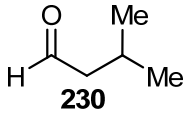
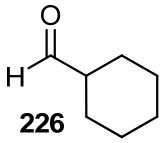
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –85 °C with a 3:2 ratio of Al source and ligand. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

5.3.4 Temperature Dependence

Working with a lower catalyst loading of 10 mol% (1:1 ratio of Al source and ligand) the reaction was strongly decelerated at –60 °C as already mentioned above. But as a result of the markedly enhanced activity with the 3:2 ratio of Al source and ligand the reaction temperature could be further reduced to –85 °C with 10 mol% catalyst. Even at such low temperatures an almost complete conversion could be achieved.

In general, at lower temperatures higher enantioselectivities were attained (Table 30). Employing ligand Cy-Trip **222d** at –85 °C the best *ee*-values were 88% for dihydrocinnamaldehyde (**207**) (entry 4) and 84% for isovaleraldehyde (**230**) (entry 8). For cyclohexylcarbaldehyde (**226**) in combination with ligand Cy-Dmtb **222a** an *ee*-value of 82% was obtained (entry 10). Interestingly, ligand Cy-Trip **222d** resulted in an *ee*-improvement of 19-22% when the temperature was lowered from –60 °C to –85 °C (entries 3-6, 11 and 12), whereas with ligand Cy-Dmtb **222a** the differences were much less pronounced (2-9% *ee*, entries 1,2 and 7-10). A reasonable explanation that may account for this observation is the occurrence of two or more catalytically active species displaying different temperature profiles.

Table 30. Temperature dependance.[a]

Aldehyde	Entry	Ligand	Temp. [°C]	Time [h]	Conversion [%]	Yield[c] [%]	*ee*[b] [%]
 **207**	1	Cy-Dmtb **222a**	−60	18	100	73	74
	2	Cy-Dmtb	−85	48	40	nd	76
	3	Cy-Trip **222d**	−60	18	88	62	69
	4	Cy-Trip	−85	48	92	nd	88
 **230**	5	Cy-Trip **222d**	−60	18	100	68	62
	6	Cy-Trip	−85	49	100	85	84
	7	Cy-Dmtb **222a**	−60	18	100	85	69
	8	Cy-Dmtb	−85	49	65	53	76
 **226**	9	Cy-Dmtb **222a**	−60	18	100	69	73
	10	Cy-Dmtb	−85	18	97	63	82
	11	Cy-Trip **222d**	−60	18	97	63	55
	12	Cy-Trip	−85	72	50	25	74

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with a 3:2 ratio of Al source and ligand (10 mol%). The ketene was formed *in situ*. [b] *ee* determined by HPLC on a chiral support. [c] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard.

5.3.5 Effect of the Temperature on Catalyst Formation

To clarify the influence of the temperature for the catalyst formation with the 3:2 ratio of Al source and ligand a series of reactions was conducted with dihydrocinnamaldehyde (**207**). The experiments revealed an optimum at 90 °C (Table 31, entry 3) but the *ee* obtained with a catalyst generated at 80 °C was only marginally lower and in most experiments no difference between 80 and 90 °C could be observed. Therefore, formation of the catalyst at 80 °C was kept for the typical formation procedure.

Table 31. Effect of the temperature for the catalyst formation.[a]

Entry	Temp. [°C]	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
1	70	14	78	82	71
2	80	14	100	90	74
3	90	14	100	100	75

[a] All reactions were performed at a concentration *c* = 0.25 mol/L of the aldehyde X at –70 °C with a 3:2 ratio of Dibal and ligand Cy-Trip **222d** (10 mol%). The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

5.3.6 Effect of the Aldehyde Concentration

At an dihydrocinnamaldehyde concentration *c* = 0.13 mol/L the model reaction in combination with ligand Cy-Dmtb **222a** became very slow (Table 32, entry 1). At higher concentrations *c* = 0.17 or 0.25 mol/L the reaction was drastically accelerated yet with decreased enantioselectivity (entries 2 and 3).

Table 32. Effect of the aldehyde concentration.[a]

Entry	Conc. [mol/L]	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
1	0.13	65	92	85	78
2	0.17	25	95	75	77
3	0.25	16	100	75	71

[a] All reactions were performed at –60 °C with a 3:2 ratio of Dibal and ligand Cy-Dmtb **222a**. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

Utilization of ligand Cy-Trip **222d** at different aldehyde concentrations led to less accentuated differences for the enantioselectivity (Table 33, entries 1-4). However, yields vary in a wide range with the best result obtained at *c* = 0.17 mol/L (entry 3).

Table 33. Effect of the aldehyde concentration.[a]

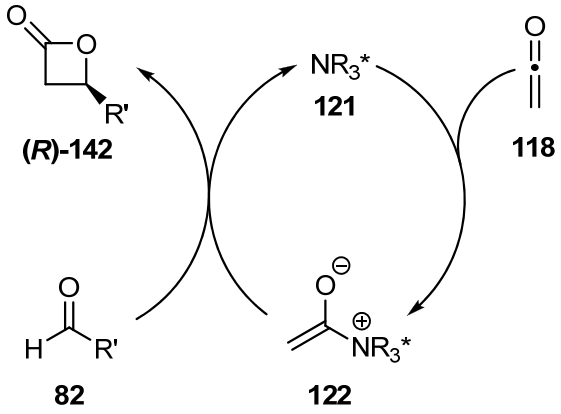
Entry	Conc. [mol/L]	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
1	0.5	13	99	73	80
2	0.25	13	94	62	80
3	0.17	13	96	95	77
4	0.13	13	52	31	77

[a] All reactions were performed at –70 °C with a 3:2 ratio of Dibal and 10 mol% ligand Cy-Trip **222d**. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

5.3.7 Effect of Additives

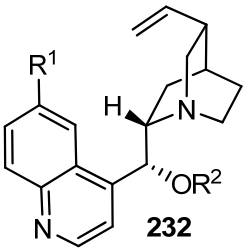
5.3.7.1 Attempts to make use of zwitterionic enolate intermediates

Assuming that by formation of a more electron rich zwitterionic enolate the [2+2] cycloaddition reactions might be further accelerated, studies with different nucleophilic cocatalysts were conducted. The mechanism of the targeted formation of a zwitterionic enolate with a chiral tertiary amine and the following cycloadditon is depicted in Scheme 84.



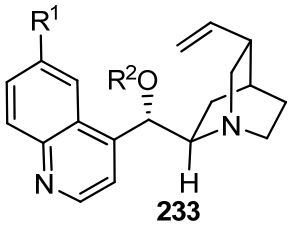
Scheme 84

Various nucleophilic cocatalysts like tertiary amines and tetrabutylammonium iodide (TBAI) were tested (Figure 9).



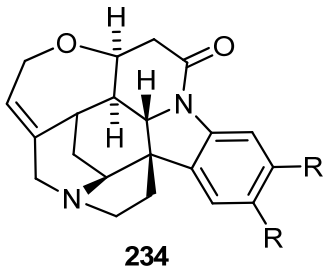
232

R^1 = H, R^2 = $SiMe_3$: TMS-cinchonidine
R^1 = H, R^2 = $SiMe_2tBu$: TBS-cinchonidine
R^1 = H, R^2 = Bz: Bz-cinchonidine
R^1 = OMe, R^2 = Me: methyl-quinine



233

R^1 = H, R^2 = Bz: Bz-cinchonine



234

R = H: Strychnine
R = OMe: Brucine

Figure 9

Alkaloids generally resulted in lower selectivities and diminished reaction rates (Table 34, entries 2-6, 8, 9) compared to the reactions without any additives (entries 1 and 7). TBAI had just a slight influence on the selectivity (entries 11 and 12). Due to the limited solubilily of TBAI in toluene all experiments were carried out at an aldehyde concentration c = 0.125 mol/L. However, with 0.5 equiv. TBAI per equiv. of aldehyde the additive was not soluble anymore. 0.2 equiv. of TBAI could be initially dissolved but after addition of acetylbromide a precipitation occured.

Based on the outcome of these experiments a reaction path *via* the ketene rather than a zwitterionic enolate is most probably preferred. A zwitterionic enolate might be sterically too demanding to pass the bulky sulfonamide catalyst residues to reach the reaction center.

Table 34. Effect of nucleophilic additives.[a]

Entry	Additive	Ligand	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
1[d]	no additive	Cy-Dmtb **222a**	16	100	75	71
2[d]	TMS-Cinchonidine	Cy-Dmtb	16	86	62	65
3[d]	TBS-Cinchonidine	Cy-Dmtb	15	40	34	61
4[d]	Bz-Cinchonidine	Cy-Dmtb	15	55	41	66
5[d]	Bz-Cinchonine	Cy-Dmtb	19	68	53	63
6[d]	Me-Quinine	Cy-Dmtb	16	67	50	66
7[d]	no additive	Cy-Trip **222d**	16	86	69	68
8[d]	Brucine	Cy-Trip	16	60	ND	62
9[d]	Strychnine	Cy-Trip	21	68	61	67
10[e]	no additive	Diph-Dmtb **227a**	88 (23)	100 (66)	88	90
11[e]	TBAI (0.5 equiv.)	Diph-Dmtb	88 (23)	100 (44)	90	90
12[e]	TBAI (0.2 equiv.)	Diph-Dmtb	88	16	ND	92

[a] All reactions were performed with a 3:2 ratio of the Al source and 10 mol% ligand. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support. [d] All reactions were performed at a dihydrocinnamaldehyde (**207**) concentration c = 0.25 mol/L at –60 °C with Dibal as Al source and 5 mol% additive except for entries 1 and 7 where no additives were used. [e] All reactions were performed at a cyclohexylcarbaldehyde (**226**) concentration c = 0.125 mol/L at –85 °C with Et_3Al as Al source and an additive except for entry 10 where no additive was used.

5.3.7.2 Effect of Additives on the Complex Geometry

As mentioned in Chapter 5.1.2.5 the complex geometry might be influenced by the addition of additives which could coordinate to the aluminum center.

Besides the initial studies with Ph_3PO (Chapter 5.1.2.5, Table 19) experiments with *n*-Bu_3PO, Ph_3P und THF were performed (Table 35). For an estimation of the Al-additive dissociation enthalpies typical values are listed in Table 36.

Table 36. Dissociation enthalpies of simple adducts of alanes with *Lewis* bases.[128]

Donor	Acceptor	$\Delta H°$ [kcal/mol]
Ph_3P	Me_3Al	17.6
Et_2O	Me_3Al	20.2
Et_3P	Me_3Al	22.1
THF	Me_3Al	22.9
Et_3N	Me_3Al	26.5
Ph_3PO	Me_3Al	28.7
Me_3PO	Me_3Al	32.0

The additives were added at ambient temperature, after the catalyst had been preformed for 4 h at 80 °C, followed by the remaining reagents at the indicated reaction temperature.

Table 35. Effect of additives.[a]

Entry	**Additive**	**Ligand**	**Time [h]**	**Conversion [%]**	**Yield[b] [%]**	***ee*[c] [%]**
1[d]	no additive	Diph-Dmtb **227a**	88 (23)	100 (66)	88	90
2[d]	Ph_3P (1 equiv.)	Diph-Dmtb	88 (23)	100 (50)	89	90
3[e]	no additive	Cy-Dmtb **222a**	48	98	87	86
4[e]	THF	Cy-Dmtb	48	91	78	86
5[e]	*n*-Bu_3PO (0.15 equiv.)	Cy-Dmtb	48	< 10 %	-	52
6[e]	*n*-Bu_3PO (0.30 equiv.)	Cy-Dmtb	48	< 10 %	-	10

[a] All reactions were performed with cyclohexylcarbaldehyde and with a 3:2 ratio of Et_3Al and 10 mol% ligand at –85 °C. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^1H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support. [d] All reactions were performed at an aldehyde concentration c = 0.125 mol/L. [e] All reactions were performed at an aldehyde concentration c = 0.25 mol/L.

According to Table 36, Ph_3P and THF form labile adducts with alanes. Experiments indicate that this is also true for the bissulfonamide catalysts (entries 2 and 4) where only a slightly diminished reaction rate and no change for the selectivities were observed. This shows that Ph_3P and THF are readily exchanged for the aldehyde. Morerover, these results are lending further support that a change of the complex geometry from tetrahedral to trigonal bipyramidal does not occur in the present case in contrast to findings by *Shibasaki*[125] and co-workers, who used phosphine oxide additives.

For a more detailed discussion about their work see Chapter 8.2.1.2.
In a standard procedure tributylphosphine oxide was added after the formation of the catalyst and had the effect that the reaction was drastically decelerated (entries 5 and 6) probably due to the blocking of the only available coordination site on the aluminum.

5.3.8 Effect of the Reaction Setup

In a typical experiment to a mixture of the bissulfonamide ligand **222d** in toluene was slowly added at ambient temperature a solution of Dibal (1.0 M in toluene). The mixture was heated to 80 °C and stirred for 4 h. Subsequently, the solution was stirred for 1-1.5 h at ambient temperature (step A). The catalyst solution was then cooled to the indicated temperature and after addition of aldehyde the mixture was stirred for 1 h (step B) before adding acetyl bromide and *Hünig*'s base.
The reaction setup became more and more complex and time consuming during the optimization process. Therefore, in order to simplify the setup, each operational step was reconsidered (Table 37).
According to these experiments it is not necessary to stir for 1 h after adding the aldehyde (step B). Furthermore, after heating the catalyst solution for 4 h at 80 °C the subsequent stirring at ambient temperature was shortend to 1 h (step A).

Table 37. Effect of the reaction setup.[a]

Entry	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]	Remarks
1	19 (24)[d]	51	56	89	typical procedure
2	20 (25)[d]	83	ND	**90**	without step B[e]
3	65	53	45	88	typical procedure
4	67	48	52	88	without A[f] and B[e]
5	41	67	65	87	without step B[e]

[a] All reactions were perfumed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% Cy-Trip **222d** and 15 mol% Dibal at –85 °C. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Total reaction time in parenthesis. [e] A: Stirred for 1 h at –85 °C after addition of the aldehyde. [f] B: Oil bath removed and reaction mixture stirred for 1-1.5 h at rt.

5.3.9 Reproducibility Problems

A major concern during the development of the described process was its limited reproducibility. Possible reasons were excluded step by step and finally the purity of the aldehyde turned out to be the major reason. Therefore, for all subsequent reactions the aldehyde was freshly distilled over CaH_2 before use.

5.3.10 Effect of the Solvent Source

So far, all solvents were acquired from a solvent purification system (SPS), in which the solvents are pressed with nitrogen through a column filled with molecular sieves pellets. To ensure that the observed stoichiometry effect, which accelerates the process and allows for enhanced selectivities utilizing an excess of the corresponding Al source, was not caused by quenching parts of the active Al with water or oxygen, alternative solvent sources were tested. Thus, toluene was distilled over sodium/benzophenone to remove water and oxygen. Almost identical results with both solvent sources indicate that the SPS solvent had a high and reliable quality (Table 38, entries 1-5).

Table 38. Effect of the solvent source.[a]

Entry	Solvent source SPS / Dist.	Ratio Dibal / Ligand	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
1	SPS	3:2	15	100	99	75
2	Dist.	3:2	15	100	99	75
3	Dist.	3:2	15	100	99	75
4	Dist.	1:1	19	41	24	60
5	SPS	1:1	19	45	37	61

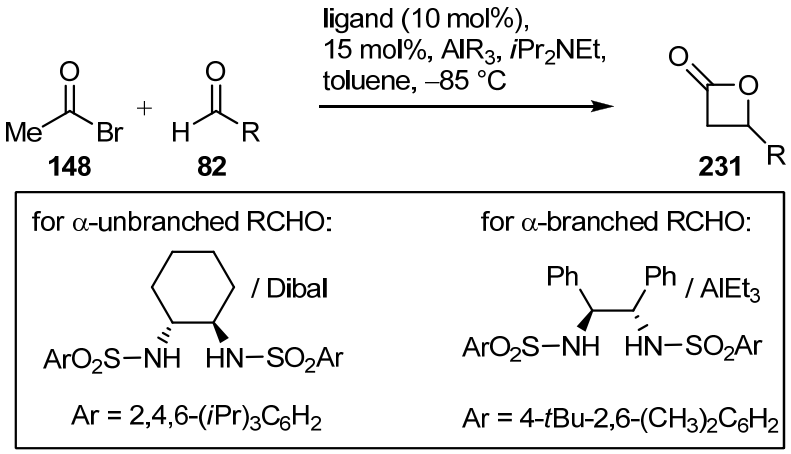
[a] All reactions were performed at an aldehyde concentration c = 0.25 mol/L at –60 °C with a 3:2 ratio of Dibal and 10 mol% ligand Cy-Trip **222d**. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

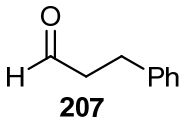
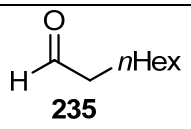
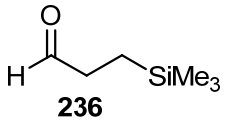
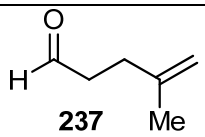
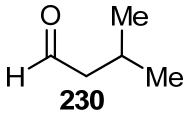
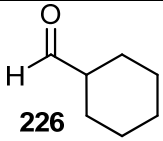
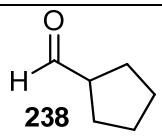
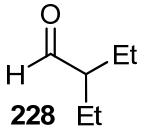
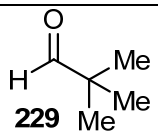
5.3.11 Reaction Scope

While the cyclohexane-1,2-diamino (Cy) backbone was in general superior for α-unbranched aldehydes (Table 39, entries 1, 3, 5, 7 and 9) ligands derived from 1,2-diphenyl-1,2-diamine (DiPh) were more efficient for α-branched aldehydes (entries 11, 13, 15 and 17). In the latter case Et_3Al was superior as Al source. Under these conditions the product for the cycloaddition with cyclohexylcarbaldehyde (**226**) was obtained in 88% yield after 25 h and with 90% *ee* (entry 11).

The products are generally formed in high to excellent yields with *ee* values typically ranging from 78 to 90%.

Table 39. Scope of the Al-bissulfonamide-catalyzed enantioselective formation of β-lactones **231**.[a]

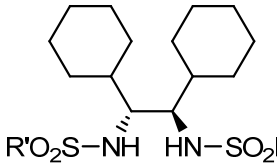


Entry		Ligand	Time [h]	Conversion[b] [%]	Al source	Yield[c] [%]	*ee* [%]	Config.[g]
1	 **207**	**Cy-Trip 222d**	**48**	**98**	**Dibal**	**93**	**88[d]**	**(*S*)**
2		DiPh-Dmtb **227a**	48	78	Dibal	66	82[d]	**(*R*)**
3	 **235**	**Cy-Trip 222d**	**63**	**100**	**Dibal**	**86**	**84[e]**	**(*S*)**
4		DiPh-Trip **227b**	144	75	Dibal	44	73[e]	**(*R*)**
5	 **236**	**Cy-Trip 222d**	**62**	**100**	**Dibal**	**82**	**84[f]**	**(*R*)**
6		DiPh-Dmtb **227a**	88	85	Dibal	71	79[f]	**(*S*)**
7	 **237**	**Cy-Trip 222d**	**140**	**100**	**Dibal**	**92**	**88[f]**	**(*S*)**
8		DiPh-Dmtb **227a**	140	40	Dibal	34	74[f]	**(*R*)**
9	 **230**	**DiPh-Trip 227b**	**26**	**100**	**Dibal**	**98**	**85[f]**	**(*R*)**
10		Cy-Trip **222d**	49	100	Dibal	84	84[f]	**(*S*)**
11	 **226**	**DiPh-Dmtb 227a**	**25**	**100**	**Et_3Al**	**88**	**90[f]**	**(*S*)**
12		Cy-Dmtb **222a**	23	99	Et_3Al	87	86[f]	**(*R*)**
13	 **238**	**DiPh-Dmtb 227a**	**84**	**100**	**Et_3Al**	**90**	**80[f]**	**(*S*)**
14		Cy-Dmtb **222a**	84	100	Et_3Al	81	80[f]	**(*R*)**
15	 **228**	**DiPh-Dmtb 227a**	**136**	**95**	**Et_3Al**	**94**	**80[f]**	**(*S*)**
16		Cy-Dmtb **222a**	113	98	Et_3Al	87	68[f]	**(*R*)**
17	 **229**	**DiPh-Dmtb 227a**	**135**	**100**	**Et_3Al**	**83**	**78[e]**	**(*S*)**
18		Cy-Dmtb **222a**	135	100	Et_3Al	89	75[e]	**(*R*)**

[a] All reactions were performed at an aldehyde concentration c = 0.25 mol/L at –85 °C with a 3:2 ratio of the Al source and ligand. The ketene was formed *in situ*. [b] Determined by ^{1}H NMR. [c] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [d] *ee* determined by HPLC on a chiral support. [e] *ee* determined by HPLC on a chiral support after nucleophilic ring opening of the product with (*S*)-1-methylbenzyl amine (see Chapter 11.1.1.4). [f] *ee* determined by GC on a chiral support. [g] The configuration was determined by comparison of the $[\alpha]_D$ values of compounds with literature data . Since a uniform reaction pathway can be assumed, the absolute configuration has been assigned to all cycloaddition products **231**. [h] The isolated yield on a larger scale was 90% (see Experimental Part).

5.4 Studies with 1,2-Dicyclohexyl Bissulfonamide Ligand 239

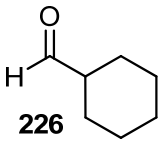
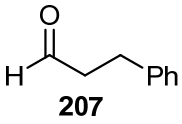
Reactions with ligand **239** were performed with an α-unbranched and -branched aldehyde (Table 40, entries 1-4).



239, R' = 2,6-$(CH_3)_2$-4-*t*-BuC_6H_2

Compared to ligands **222** and **227**, with ligand **239** a significant drop in reactivity and selectivity was observed. Interestingly, the best results for both aldehydes were obtained with Et_3Al, whereas for ligands **222a** and **222d** Dibal proofed to be superior.

Table 40. Representative results for ligand 239.[a]

Aldehyde	Entry	Time [h]	Conversion [%]	Yield [%]	ee [%]	Al source
 **226**	1	40	22	21	75	Et_3Al
	2	40	< 5	5	44	Dibal
 **207**	3	61	27	17	62	Et_3Al
	4	61	14	14	42	Dibal

[a] All reactions were performed at an aldehyde concentration *c* = 0.25 mol/L at –85 °C with a 3:2 ratio of the Al source and ligand. The ketene was formed *in situ*. [b] Yield after aqueous workup determined by ^1H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support.

5.5 Studies on Formation and Structure of the Catalyst

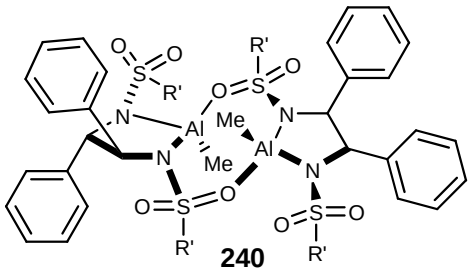
5.5.1 NMR Studies

At an early stage of this work NMR studies were conducted to monitor the formation of the catalyst. Initial studies with Me_3Al and ligand **227a** showed an almost complete conversion of the ligand after already 30 min at 80 °C.

Similar studies with ligands **222a**, **222b**, **222d** and Dibal never led to a complete conversion with a 1:1 stoichiometry of the ligand and Al source. Experiments with ligand **227a** and Et_3Al provided the same results with a 1:1 ratio (see spectrum 1; 5.94 ppm N-*H*; 4.63 ppm Ar-C*H*). Changing the stoichiometry to 3:2 (Dibal:ligand) the N-*H* signal of the ligand disappeared almost completely (see spectrum 2). Interestingly, at the same time new signals with a weak intensity appeared (5.28, 4.97, 4.80, 4.71 ppm). These signals might belong to new reactive catalyst species, in which the excess of Al source coordinates to the sulfonyl groups of the sulfonamide complex for which the *Lewis* acidity might hence be increased.

However, from these spectra it is difficult to unambiguously conclude the structure of the active catalyst species. Most likely the main part of the Al complexes adopt the form of a C_1-symmetrical dimer as previously described by *Corey*[129] and co-workers (Figure 10). By adding the aldehyde substrate this dimer might dissociate to form a monomer. The dimeric form would also explain the appearance of four different NC*H* frequencies of the main species.

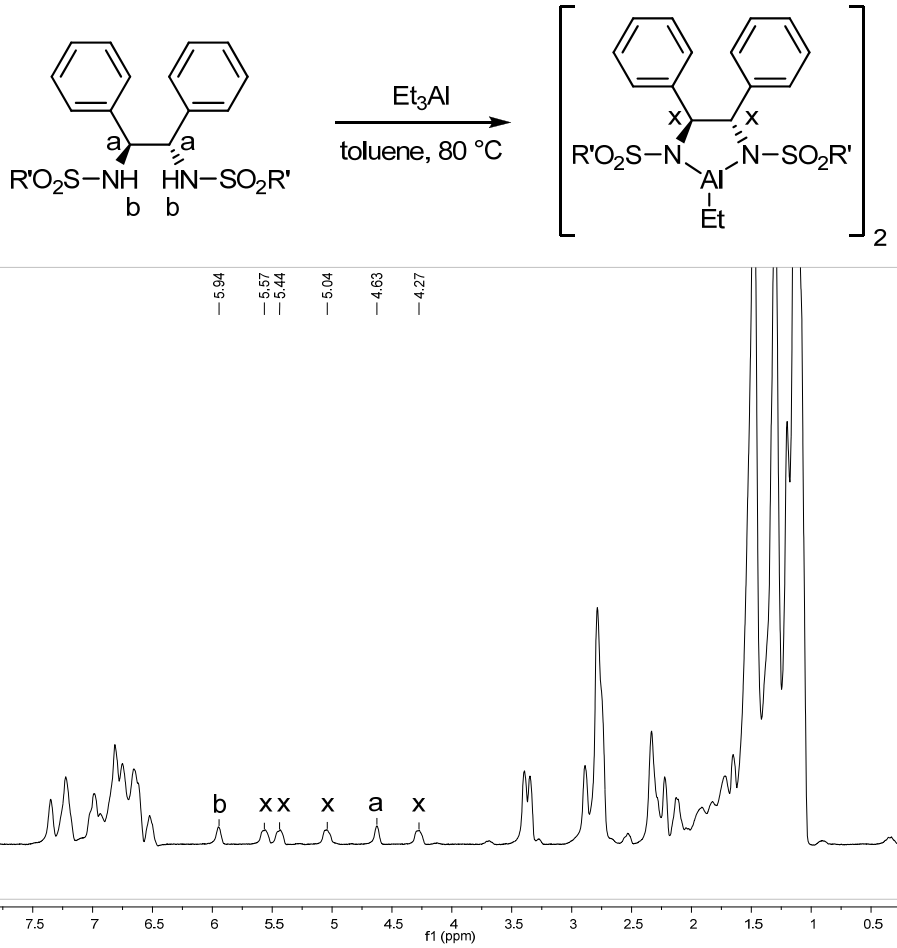
All spectra were recorded on a Varian 300 MHz instrument. Toluene-*d8* was dried and distilled over sodium and stored together with the ligand in a glove box.



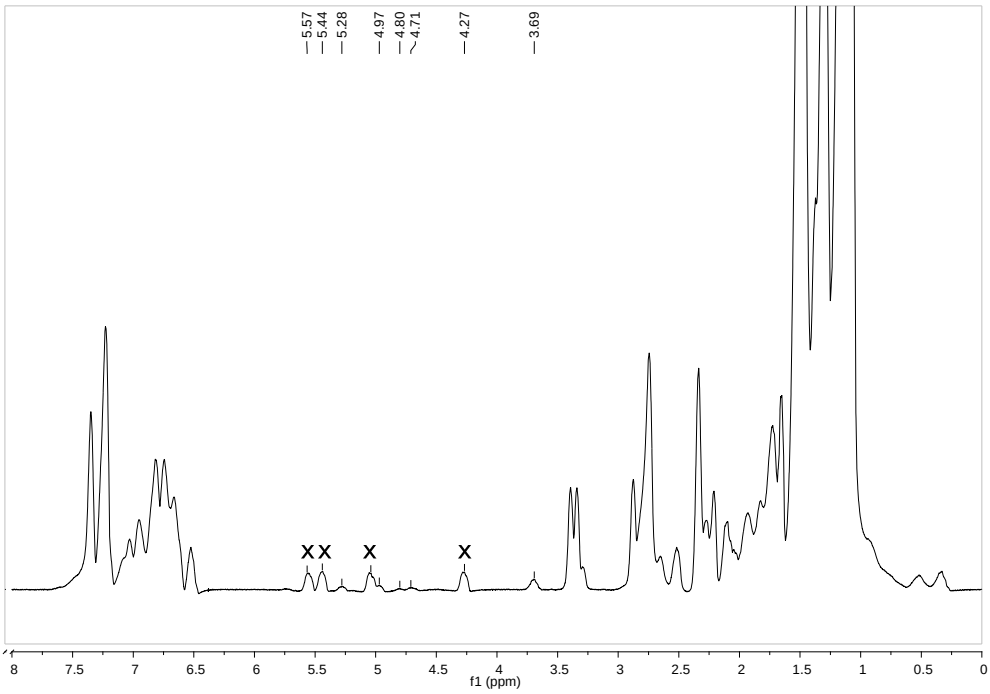
240

Figure 10. Dimeric form of the catalyst.

Spectrum 1. Catalyst formation with a 1:1 ratio of ligand **227a** and Et_3Al.

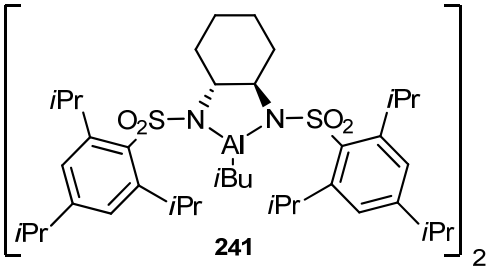


Spectrum 2. Catalyst formation with a 2:3 stoichiometry of ligand **227a** and Et_3Al.



5.5.2 Pulsed Gradient Spin-Echo (PGSE) NMR Diffusion Methods

The determination of the relative molecular size in solution remains a subject of considerable interest to the chemistry community. This is especially true with respect to the formation of aggregated materials. Apart from mass spectroscopic methods, diffusion methods have found increasing application. Pulsed gradient spin-echo (PGSE) NMR diffusion methods represent a possible supplement to mass spectroscopy.[130] In this work PGSE NMR experiments for catalyst **241** were conducted by Dr. H. Rüegger at the Laboratory of Inorganic Chemistry at the ETH Zürich.



241

These studies support the hypothesis that the catalyst is mainly present as a dimer as outlined in Figure 10.

5.5.3 Attempts to Grow Crystals of the Catalyst

Attempts to crystallize complex **225d** in the presence of the non-enolizable *trans*-cinnamonaldehyde failed due to decomposition at ambient temperature. The colorless catalyst solution turned brown shortly after addition of the aldehyde and precipitation occurred.

Further attempts to grow crystals were carried out without the addition of an aldehyde and in a glove box to avoid hydrolysis of catalyst **225d**. The catalyst was prepared according to the standard procedure in toluene and two techniques were used for crystallization: (1) slow evaporation of the solvent and (2) vapor diffusion with a second more volatile solvent. Unfortunately, even under dry glove box conditions with both techniques hydrolysis could not be avoided and only crystals of ligand **222d** were obtained.

5.5.4 Attempts to Determine the Catalyst Structure by Mass Spectroscopy

Initial attempts to determine the mass of the catalyst were carried out by the MS service of the ETH Zürich. Measurements with Electron Spray Ionisation (ESI) and Matrix Assisted Laserdesorption Ionisation (MALDI) spectroscopy mainly showed the free ligand **222d**. Samples were prepared as follows: the catalyst was prepared according to the standard procedure in toluene under an atmosphere of argon. An aliquot of this stock-solution was transferred to another Schlenk tube, diluted with dry CH_2Cl_2 to a concentration $c = 10^{-3}$ mol/L and directly used for the measurements. At such a low concentration the moisture sensitive catalyst might have been hydrolyzed by traces of water while the sample was prepared for injection into the MS apparatus.

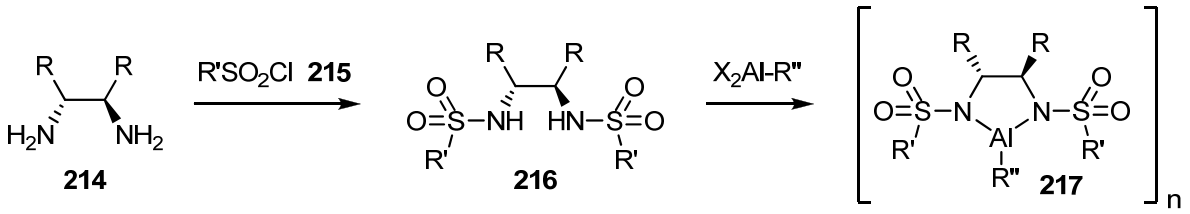
Further ESI measurements were conducted by E. Zocher in the group of Prof. Dr. P. Chen on an LCQ Finnigan™ with an ion trap, in which the ionized catalyst species are collected and therefore also small amounts should be traceable. However, since the catalyst cannot be easily ionized it was only possible to detect the monomeric catalyst species whereas no signal could be found that accounts for the dimeric complex or the species consisting of a 3:2 ratio of Al source and ligand.

6 Conclusion and Outlook

β-Lactones are versatile building blocks. The development of catalytic asymmetric [2+2] cycloadditions of ketenes and aldehydes offers, for example, the possibility to replace catalytic asymmetric ester aldol reactions which in most cases require the preformation, isolation and purification of moisture sensitive silyl ketene acetals. From both a technical and economical point of view, the use of silyl protecting groups is an issue on production scale, not only because SiO_2 being formed during waste combustion processes has the tendency to block the combusters' chimneys, but also due to low cost-efficiency.

The present work successfully contributes to this research field by the development of a new simple *Lewis* acid catalyst for the [2+2] cycloaddition of ketenes (generated *in situ* from acetyl bromide by dehydrobromination) and various α-unbranched and -branched aliphatic aldehydes.

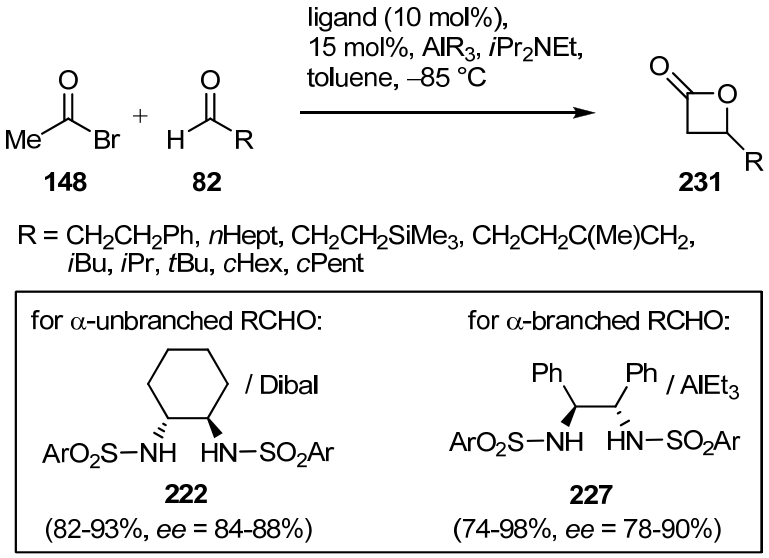
The methodology offers the advantage of operational simplicity and the ligand synthesis requires just a single sulfonylation step from commercially available enantiomerically pure diamines (Scheme 85).



Scheme 85. Formation of bissulfonamide aluminum complexes **217**.

Initial optimization was conducted with 20 mol% of catalyst **217**. When the catalyst loading was reduced to 10 mol%, product formation was significantly decelerated, and the reaction proceeded less enantioselectively. The key finding of this work was the observation that with 10 mol% of the ligand and 15 mol% of the Al source the reaction was not only dramatically accelerated by the excess of Al source, but surprisingly also more selective than with a 1:1 stoichiometry of ligand and Al source. Due to the markedly enhanced activity the reaction temperature could be further reduced.

The products are generally formed in high to excellent yields with *ee* values typically ranging from 78 to 90% (Scheme 86).



Scheme 86

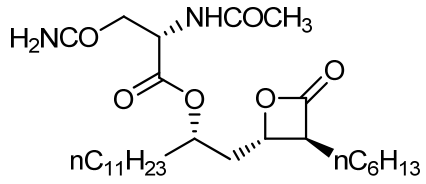
At present there is no direct experimental evidence about the origin of the ligand/Al stoichiometry effect. The ^{1}H NMR spectra of complexes which were formed from various combinations of 1.0 equiv. of the bissulfonamide ligands **222** or **227** and 1.5 equiv. of the Al sources show, like in the case of a 1:1 stoichiometry, C_1-symmetric dimeric complexes **217** (n = 2 in Scheme 85) as the main species. However, in addition to these dimers, the formation of small amounts of unidentified complexes has been detected which might differ from the 1:1 stoichiometry and which might possess a significantly higher reactivity. The higher activity could finally result from a *Lewis* acid-assisted *Lewis* acid activation (LLA concept).[119b]

Part B: Dual Activation Catalysis

7 Background

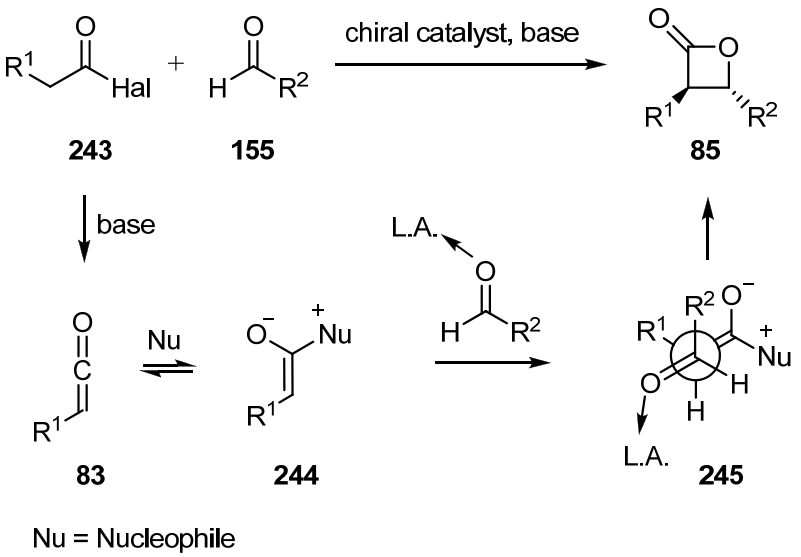
7.1 Motivation and Concept

The summary of the existing methods for *Lewis* acid or *Lewis* base catalyzed ketene-aldehyde cycloadditions (see Chapter 3.2.3) reveals that impressive stereoselectivities can be obtained for certain substrates. However, there is still a lack of highly enantioselective methods which tolerate a broad spectrum of aldehydes including sterically undemanding aldehydes, α-branched aliphatic aldehydes, conjugated enals, aromatic aldehydes or non-activated ketones. The reasons for that dilemma are known: in the case of chiral nucleophile catalyzed cycloadditions, the *in situ* generated zwitterionic enolates are not reactive enough to attack regularly polarized aldehydes or ketones. Similarly, the nucleophilicity of the corresponding ketene itself is not sufficient to enable a reaction with challenging substrates activated by chiral *Lewis* acid complexes and usually necessitates aldehyde substrates with certain steric requirements to afford high enantioselectivities. Furthermore, using substituted ketene substrates, almost all of the known catalytic asymmetric [2+2] cycloadditions provide preferentially β-lactones with a *cis*-configuration about the heterocyclic system, whereas the large majority of natural and synthetic bioactive products have a *trans*-configuration.[131] So far, there is only one [2+2] cycloaddition available, developed during the course of these Ph.D. studies, for the catalytic enantioselective formation of *trans*-configured β-lactones, which is limited though to the use of aromatic aldehydes, whereas most bioactive systems such as tetrahydrolipstatin (**242**), a potent inhibitor of pancreatic lipase, thus making this compound an ideal candidate for the reduction of fat absorption through diet in man, contain an aliphatic chain at the 4-position of the 3,4-disubstituted oxetanone.



Tetrahydrolipstatin (**242**)

The aim of the present work was not only to develop a widely applicable and practical highly enantioselective catalyst, but also a catalyst for the *trans*-selective catalytic asymmetric [2+2] cyclocondensation of acyl halides and aliphatic aldehydes, thus representing a surrogate for the rare type of catalytic asymmetric *anti*-aldol additions. It was hypothesized that a possible way to achieve this goal could be the use of a novel bifunctional catalyst system, a catalyst which includes a mono-coordinating *Lewis* acid moiety for aldehyde activation and a nucleophilic moiety which generates and directs the enolate to attack the aldehyde *via* an open transition state adopting a staggered conformation around the generated C-C bond with minimized steric repulsion thus resulting in the desired relative configuration (Scheme 87). The choice of a *Lewis* acid with only one available catalytic coordination site is considered to be essential in this regard to avoid a cyclic transition state, traditionally leading to the *cis*-configured products. The initial aldol adduct would then cyclize to form the heterocyclic product.



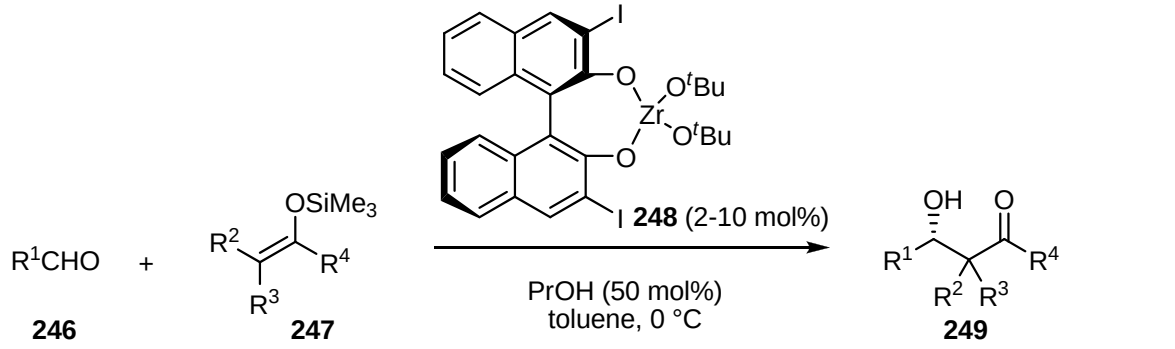
Scheme 87. Concept for the asymmetric formation of *trans*-configured β-lactones.

One key aspect would be that the enolate **244**, which should be present at least in small quantities in equilibrium with ketene **83**, would have to react faster than the ketene intermediate **83** itself. Since this preference is usually not observed, the enolate would have to be further activated and/or generated by the catalyst.

7.2 Catalytic Asymmetric *anti*-Aldol Reactions

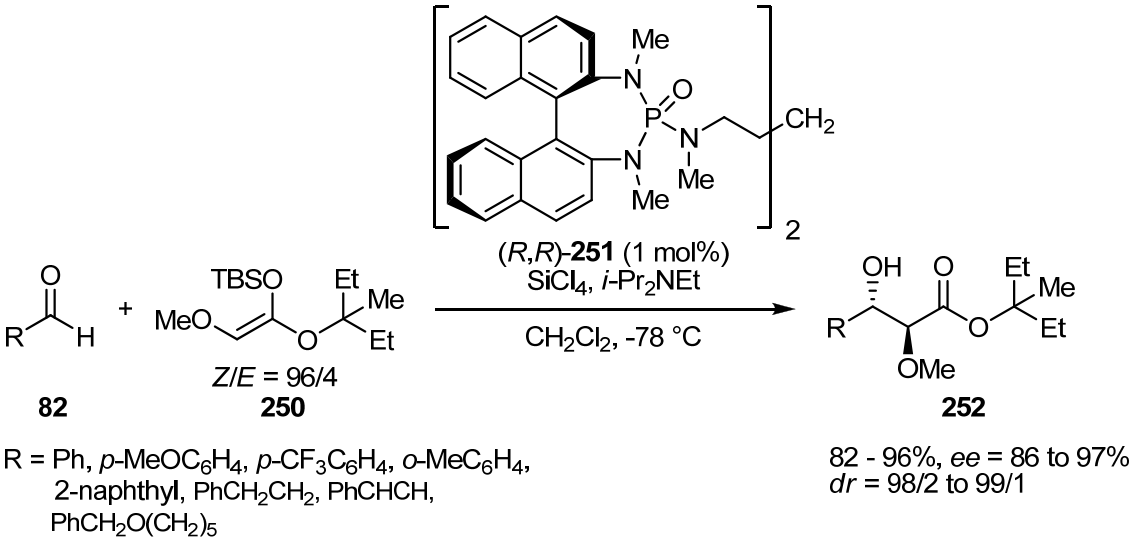
The development of an exceptionally large number of asymmetric aldol catalysts has proven to be a valuable contribution to asymmetric synthesis.[132] However, there are only few examples of catalytic asymmetric *anti*-aldol reactions. Preformation of a reactive donor species such as an enol silyl ether or a ketene silyl acetal is usually an unavoidable necessity utilizing carboxylic acid derived nucleophiles.[133] Following two examples for *anti*-selective catalytic asymmetric aldol reactions are given.

Kobayashi and co-workers used the chiral zirconium complex **248** for the reaction of aldehydes **246** with silyl enolates **247** (Scheme 88). High yields and *ee*'s were obtained with aromatic aldehydes as well as α,β-unsaturated and aliphatic aldehydes.[134]



Scheme 88

The latest contribution to this topic was reported by *Denmark* and *Chung*.[135] They developed a *Lewis* base catalyzed, stereoselective glycolate aldol reaction with a variety of aldehydes (Scheme 89). Interestingly, both *syn*- and *anti*-1,2-diols can be obtained under the same catalytic system by modulating the size of the substituents on the silyl ketene acetal. Nonetheless, a preformation, isolation and purification of the moisture sensitive silyl ketene acetals is necessary.



Scheme 89

8 Development of a *Lewis* Acid/*Lewis* Base Catalyst

8.1 Concept

For the activation of both substrates, a bifunctional system wherein a *Lewis* acid is used to work in concert with a *Lewis* base could be imagined. This combination could also be suitable for the development of a *trans*-selective catalytic asymmetric [2+2] cyclocondensation of acyl halides and aliphatic aldehydes. The aldehyde would be activated by a *Lewis* acid (L.A.) moiety and the enolate could be generated by a *Lewis* base (L.B.) functionality acting as a catalytic nucleophile as outlined in Chapter 7 (Background, Scheme 87). The enolate would be directly formed in the catalyst sphere and therefore was assumed to react faster than the less nucleophilic ketene intermediate, which would provide the *syn*-isomer.

8.2 General Aspects of *Lewis* Acid/*Lewis* Base Catalysis

The design and development of new high-performance catalysts for applications in asymmetric reactions is of ongoing interest in organic chemistry. The cooperative combination of a *Lewis* acid and a *Lewis* base is now considered state of the art in stereoselective synthesis (Figure 11).

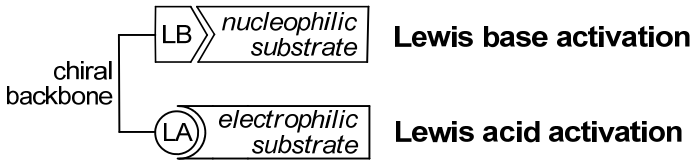


Figure 11. The concept of *Lewis* acid / *Lewis* base catalysis.

The synergistic activation by two or more reactive centers often allows for high reaction rates and excellent transfer of stereochemical information due to the formation of highly organized transition states. Despite possible self-quenching reactions between *Lewis* acids and *Lewis* bases which might lead to an inactive catalyst, considerable effort has been directed towards the development of the dual-activation concept. The ultimate goal is to mimic the efficiency of nature by the discovery of catalytic systems operating in an analogous way to enzymatic processes that involve metal-ion cocatalysts (Figure 12).

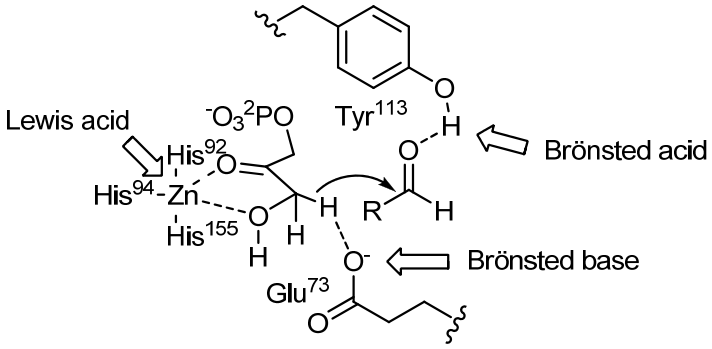


Figure 12. Mode of action of class-II-aldolases.

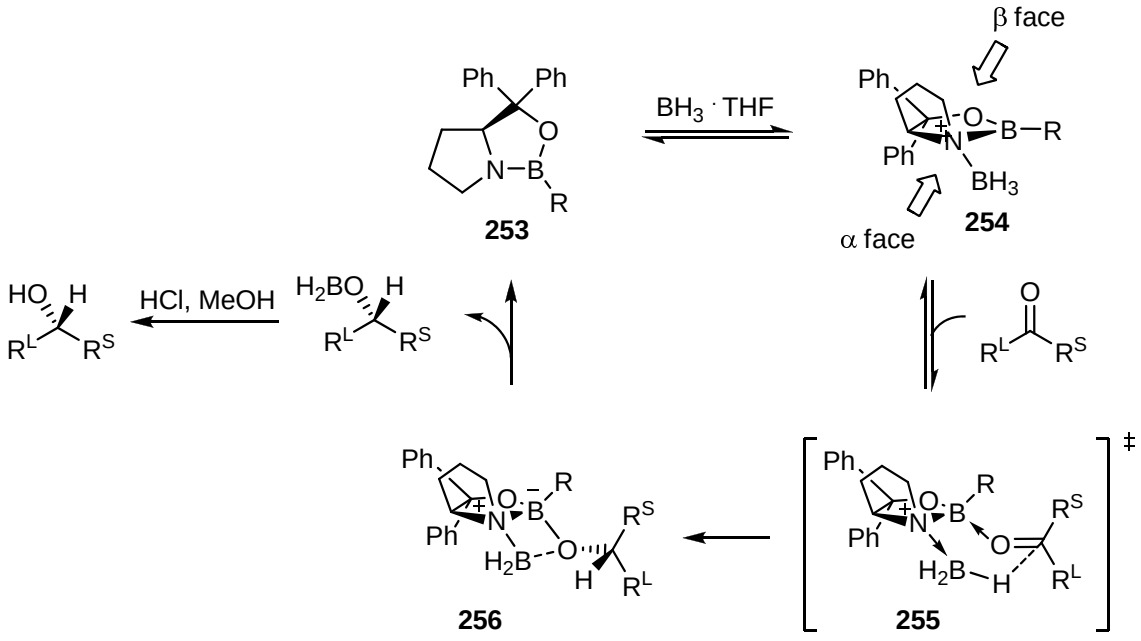
The dual activation concept might greatly broaden the range of artificial catalysts. In the following some of the pioneering and/or most efficient bifunctional catalytic systems are reviewed, and their mechanisms of action will be briefly discussed. The focus of this introduction is centered on metal catalysts due to the relevance for this Ph.D. thesis.

Further information about dual activation catalysis can be found in a recent review by *Ma* and *Cahard*.[136]

8.2.1 Literature

8.2.1.1 Borane-Mediated Asymmetric Reduction of Carbonyl Compounds

The development of the borane-mediated enantioselective reduction of ketones was initiated by *Itsuno* and co-workers in the 1980s.[137] Later, in 1987, a breakthrough was reported with modified chiral oxazaborolidine catalysts by *Corey's* group (CBS reduction).[138] The CBS reduction is an excellent example of dual activation catalysis: The mechanism proceeds through the rapid coordination of BH_3 to the *Lewis* basic nitrogen atom from the α-face of **253** to give **254**, resulting in the activation of the borane as hydride source with simultaneous enhancement of the *Lewis* acidity of the endocyclic boron atom for activation of the ketone (Scheme 90).



Scheme 90. Proposed mechanism for the CBS reduction of ketones.

The increased electrophilicity of the endocyclic boron atom facilitates the coordination of the ketone substrate with the less sterically demanding lone pair of electrons.

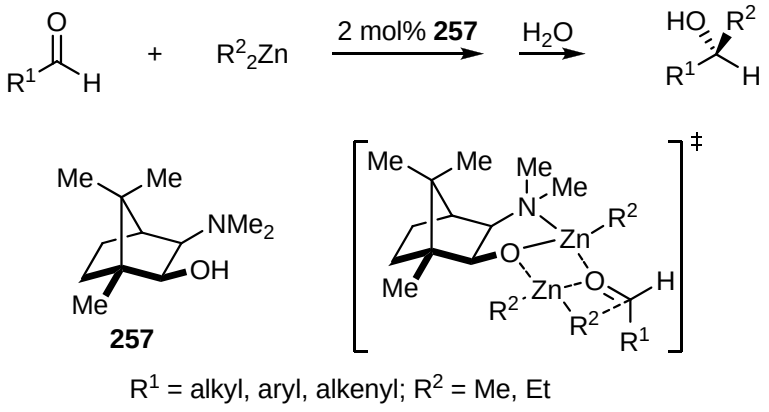
The resultant spatial arrangement minimizes the steric interactions between the oxazaborolidine and the ketone and aligns the electron-deficient carbonyl group with the electronically activated boron-hydrogen bond to allow hydride transfer via a six-membered transition state **255**, leading to the formation of the reduction product **256** (Scheme 90). Since the ground-breaking research of *Corey*, a number of chiral ligands for the borane-mediated reduction of ketones have been developed.[139]

8.2.1.2 Catalytic Asymmetric 1,2-Additions to Carbonyl Compounds

Nucleophilic 1,2-addition of organometallic reagents (such as alkyl, allyl, and aryl metal reagents) to carbonyl substrates is one of the most fundamental reaction types in organic synthesis. The catalytic asymmetric version offers a convenient approach to create optically active compounds, and the dual-activation approach appears both efficient and elegant.

Catalytic Asymmetric Alkylation of Carbonyl Compounds

In 1986, *Noyori's* group reported the first example of a highly enantioselective nucleophilic alkylation of aldehydes with diethylzinc, catalyzed by (–)-DAIB (**257**; (–)-3-exo-(dimethylamino)isoborneol) with up to 99% *ee* (Scheme 91).[140]

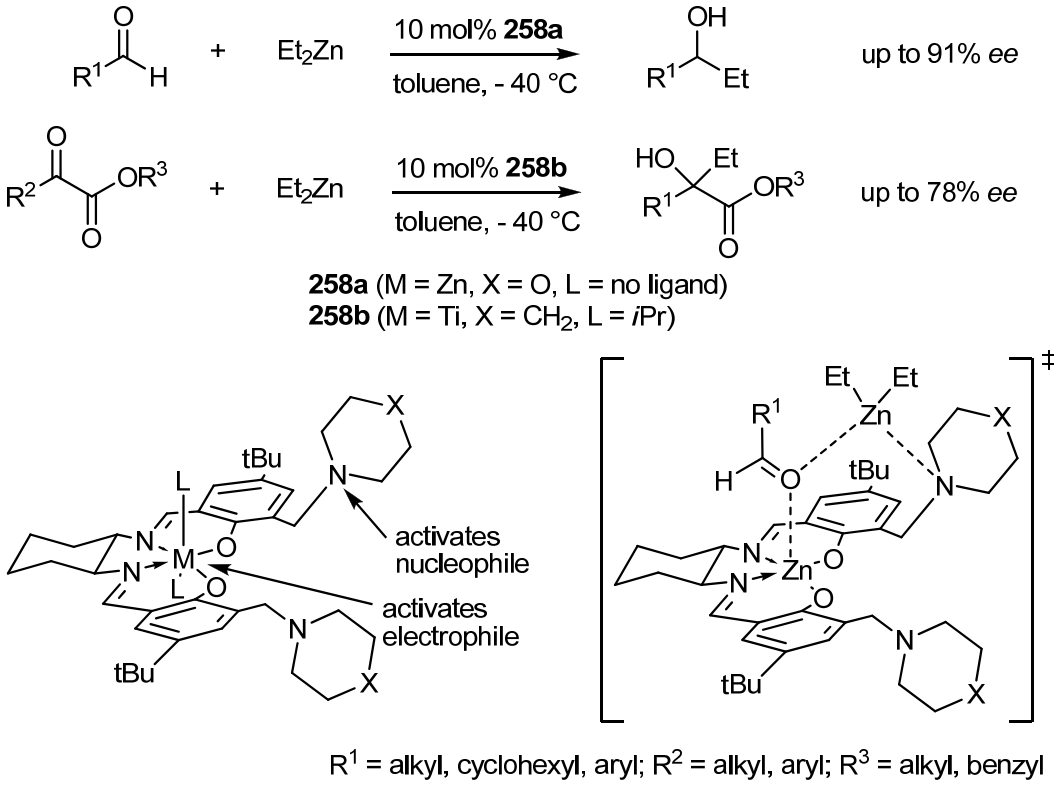


Scheme 91. Chiral aminoalcohol-catalyzed addition of dialkyl zinc reagents to aldehydes.

A bimetallic transition-state model can account for the high catalytic activity and excellent enantioselectivity of this reaction: one zinc atom forms an amino alcoholate complex with the ligand and acts as a *Lewis* acid; the second zinc atom coordinates to the *Lewis* basic oxygen atom of the generated complex, and is thus activated for a directed nucleophilic addition of

the alkyl residue. The successful application of (–)-DAIB resulted in a significant enhancement in ligand design for asymmetric alkylation of carbonyl compounds, and many novel ligands have been developed since.[141] Most are believed to proceed by a similar mechanism to that suggested by *Noyori* and other groups.[142]

Recently, *Kozlowski* and co-workers developed a set of modular bifunctional salen (*N,N'*-bis(salicylidenethylenediamine) catalysts **258** which contain both *Lewis* acid and *Lewis* base functionalities; these can be altered independently to control nucleophilic and electrophilic activation of the substrates (Scheme 92).[143]



Scheme 92. Salen-derived catalysts for catalytic asymmetric addition of Et_2Zn to aldehydes and α-ketoesters.

The apical coordination site on the salen metal center acts as a *Lewis* acid site to activate aldehydes, while the tethered base is assumed to independently activate the Et_2Zn nucleophile.[144] The reaction proceeded in the presence of 10 mol% **258a** (M = Zn, X = O, L = no ligand) to obtain secondary alcohols in good to high yields (78-99%) and with moderate to high enantioselectivities (69-91% *ee*).

While these results are not particularly special as compared to simple amino alcohol-Zn catalyst systems, the authors also reported the first asymmetric addition of dialkyl zinc to α-ketoesters by using the bifunctional salen catalyst **258b** (M = Ti, X = CH_2, L = *i*PrO). α-Hydroxyesters with new quaternary stereogenic centers were obtained in high yield (up to 99%) and moderate enantioselectivity (up to 78% *ee*).

Shibasaki and co-workers reported the use of ligand **259** for the enantioselective addition of Me_2Zn to α-ketoesters in which three Zn(II) metal ions are involved (Figure 13).[145] They used a zinc alkoxide as additional *Lewis* base, because anionic *Lewis* bases have a larger electron-donating ability than neutral *Lewis* bases such as amines or phosphane oxides hence resulting in a higher reactivity of the alkyl transferring Zn center. The reaction proceeded to give the corresponding products in up to 95% yield and 96% *ee* from aromatic and acetylenic α-ketoesters. Slow addition of Me_2Zn and an alcohol as a protic additive were required for high catalyst activity and enantioselectivity.

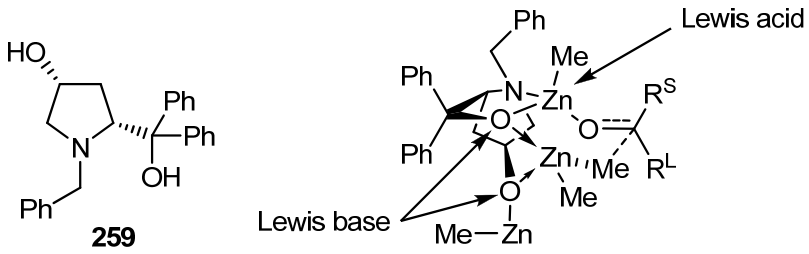


Figure 13. Ligand **259** in the nucleophilic alkylation of α-ketoesters.

Catalytic Asymmetric Cyanation

It is well known that the addition of trimethylsilyl cyanide (TMSCN) to carbonyl compounds is catalyzed by both *Lewis* acids or *Lewis* bases to afford silylated cyanohydrins, which can easily be converted into various important building blocks such as α-hydroxy (or amino) carbonyl derivatives, and β-aminoalcohols.[146] Chiral titanium complexes, e.g., catalyze the asymmetric addition of TMSCN to a wide range of carbonyl compounds. *Belokon'*, *North* and co-workers studied the titanium complexes of salen ligands **260** (Figure 14; R^1 = H, *t*Bu, Cl; R^2 = H, Me, *t*Bu, OMe, Cl) as catalysts for the asymmetric cyanosylation of aldehydes and ketones.[147] It was found that a bimetallic complex is the actual catalyst, which simultaneously activates both the carbonyl compound and the TMSCN (Figure 14).

The key step is the intramolecular transfer of cyanide to the coordinated aldehydes from the *Re* face, thus leading predominantly to the formation of one enantiomer.

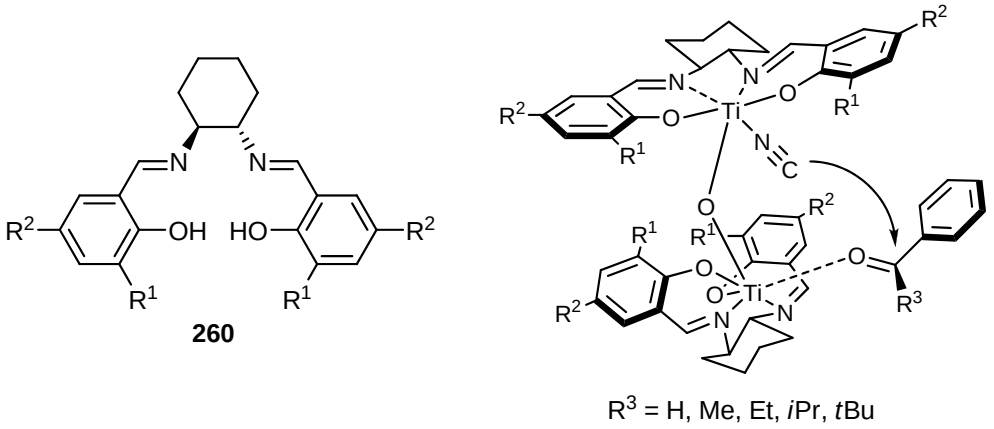


Figure 14. Ligand **260** and transition-state model.

Shibasaki and co-workers described a new bifunctional catalyst **261** containing a *Lewis* acid and a *Lewis* base for the asymmetric cyanosilylation of aldehydes (Figure 15).[148] In the presence of phosphine oxide additives ($Bu_3P=O$) for aliphatic and α,β-unsaturated aldehydes or $H_3CP(O)Ph_2$ for aromatic aldehydes, cyanohydrins were obtained with 83-98% *ee*. This improvement can be rationalized by the proposed transition state (Figure 15), where the additive is believed to change the geometry of the aluminum center from tetrahedral to trigonal bipyramidal, allowing the phoshpine oxide moiety of the bifunctional ligand system to be arranged in a more favorable position relative to the aldehyde. An operational limitation of this catalyst system is the need for slow addition of TMSCN for optimal enantioselectivity.

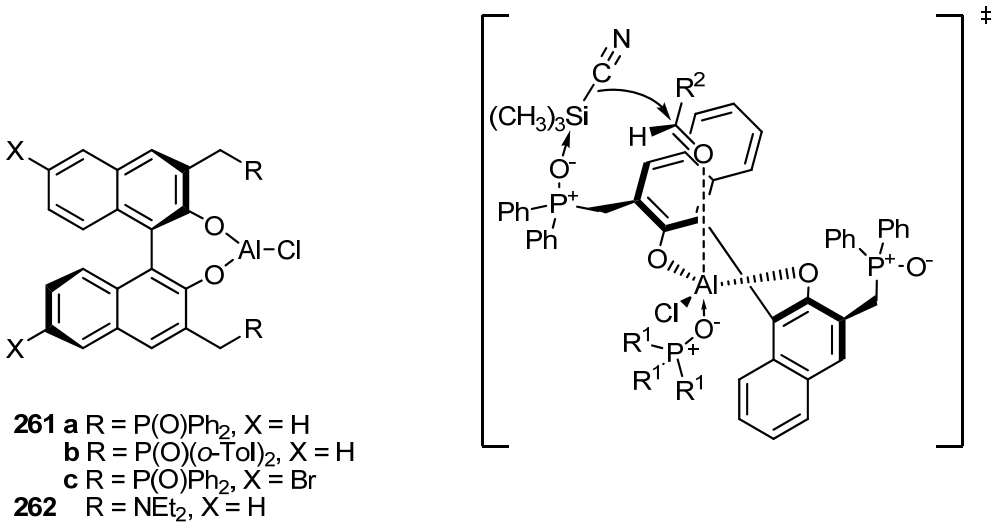
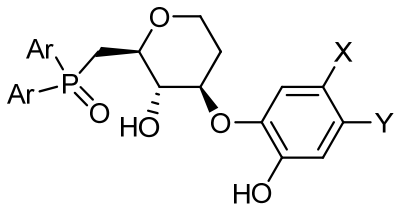


Figure 15. *Lewis* acid / *Lewis* base catalysts **261**/**262** and transition-state model.

Najéra and co-workers prepared catalyst **262** in which the phosphine oxide groups of **261a** were replaced by diethylamino groups performing as a *Lewis* base to activate the nucleophile (Figure 15).[149] Complex **262** was found to catalyze the asymmetric addition of TMSCN to aldehydes to give cyanohydrins with modest to excellent enantioselectivities. In contrast to the related system of *Shibasaki*, all the reagents could be added at the beginning of the reaction, and the binol ligand could be recovered and reused by a simple acid/base workup. Both the *Shibasaki* and *Najéra* groups also employed cyanoformates as alternative reagents for the cyanation.[149b,150] In addition, *Najéra* and co-workers reported the first cyanophosphorylation by means of diethyl cyanophosphonate for the enantioselective synthesis of cyanohydrins and derivatives.[149c]

Shibasaki and co-workers extended the concept of cooperative *Lewis* acid / *Lewis* base catalysts to non-binol systems: carbohydrate-derived ligands **263** were synthesized and complexed to different metals.[151]



263 a X = Y = H, Ar = Ph
b X = COPh, Y = H, Ar =Ph
c X = Y= F, Ar = *p*-MeC_6H_4

The corresponding titanium complexes were found to be efficient catalysts. For example, 10 mol% of the titanium complex **263a** was sufficient to convert several aromatic and aliphatic ketones into (*R*)-cyanohydrins with 69-95% *ee*. Mechanistic studies suggested that the key features of transition state structure **A** (Figure 16) are the simultaneous activation of both reaction components through the combined *Lewis* acid / *Lewis* base activity of the catalyst and the transfer of cyanide directly from activated TMSCN. Interestingly, the corresponding gadolinium complex of ligand **263a** (the same enantiomer) could be used to synthesize the enantiomeric (*S*)-cyanohydrins with 62-97% *ee*. *Shibasaki* and co-workers proposed the bimetallic transition state **B** (Figure 16) to explain this reactivity and selectivity. In this structure, two of the ligands behave as tridentate donors while the bridging ligand is pentacoordinate. The cyanide ion is activated by coordination to one of the metal ions rather than by the *Lewis* basic phosphane oxides.

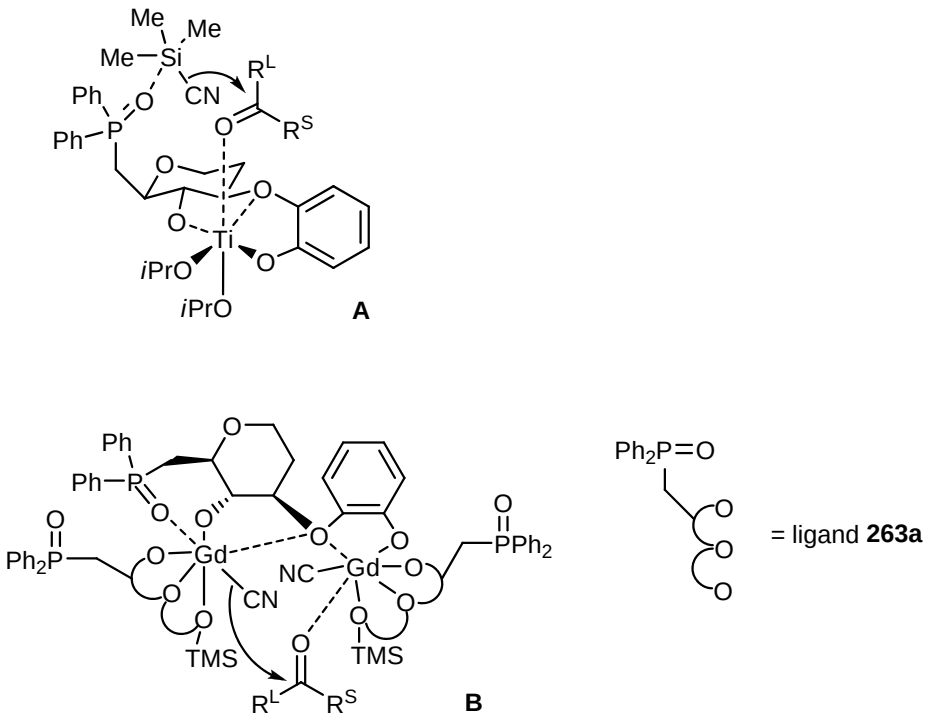


Figure 16. Postulated transition states for Ti-**263a** and Gd-**263a** systems.

Further information about cyanohydrin syntheses can be found in a review by *Brunel* and *Holmes*.[146b]

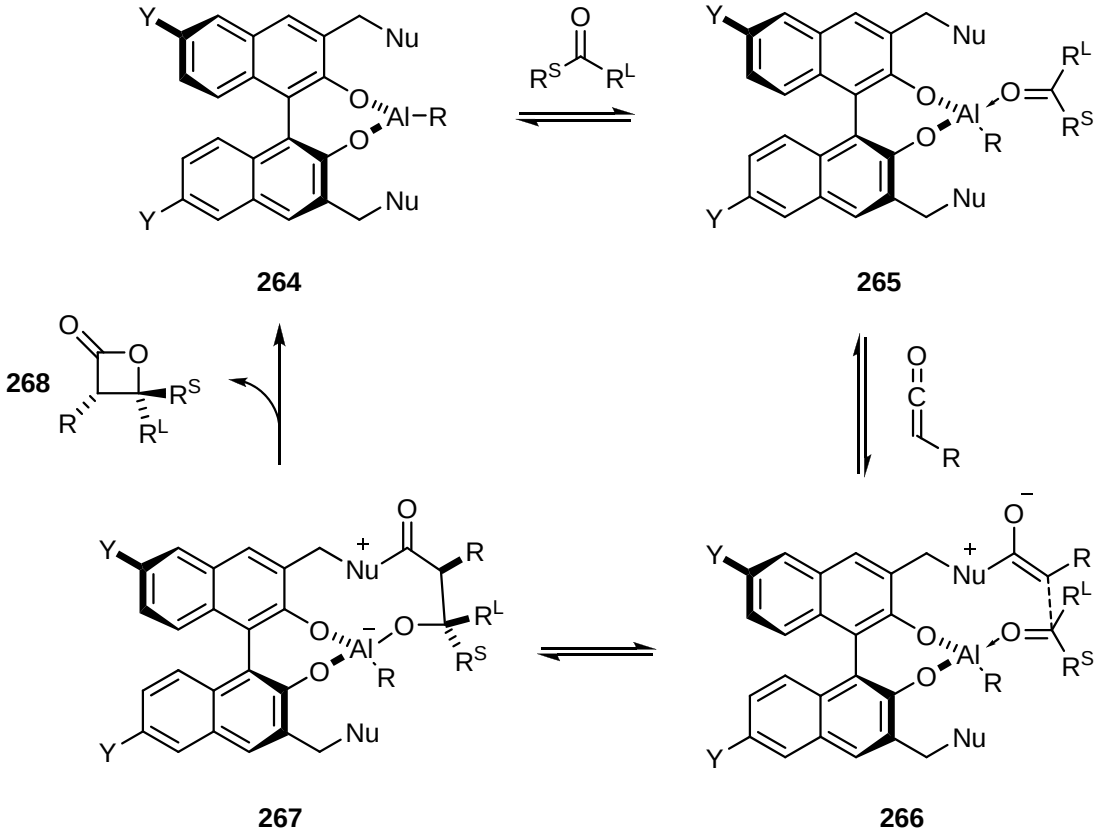
8.3 Results and Discussion

8.3.1 Development of Bifunctional Binol Catalyst 269

Binol acts as the axially chiral backbone for *Shibasaki* type catalysts **264** (Scheme 93). The *Lewis* acid metal is connected to two naphthoxides and the nucleophilic groups are connected to the 3,3'-positions of Binol. The design of these catalysts is very flexible for optimization by altering the metal (e.g. Al, Ga, Ti, Zr, etc.), the *Lewis* basic moiety Nu and the linker length connecting *Lewis* base and BINOL. In addition, the substituents Y can be modified thus changing the naphthoxide electron density.

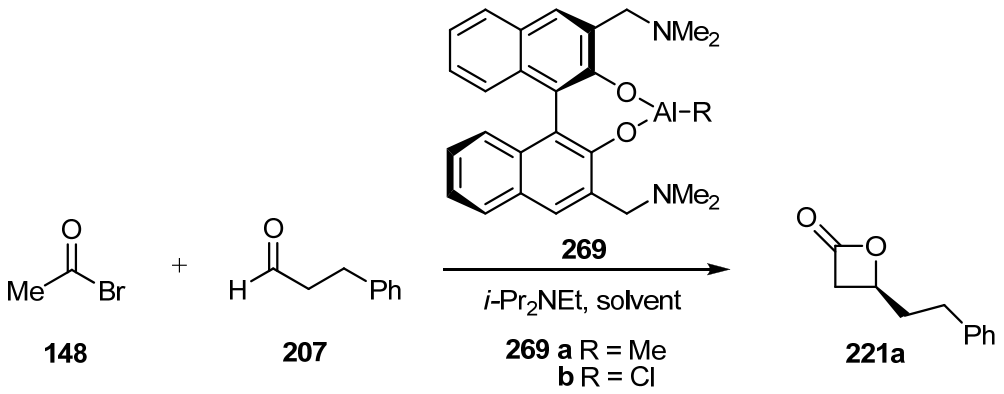
Screening different combinations in the investigated title reaction to form β-lactones might lead to catalysts, which activate both the ketene and the carbonyl compound and avoid a self-quenching process by internal coordination.

The activation abilities of the *Lewis* acid and base moieties would have to be balanced in order to promote the reaction *via* a dual activation pathway. Like mentioned above, these kind of systems have already been applied to the cyanosilylation of aldehydes (Al central metal ion, Nu = $Ph_2P{=}O$, Y = H).[149] In the proposed mode of operation the aldehyde is assumed to bind with its sterically more accessible lone pair to the aluminum to form a tetrahedral complex. The nucleophilic moiety, most like a tertiary amino group, attacks the ketene and the thereby formed zwitterion reacts further with the aldehyde.



Scheme 93. Shibasaki type catalysts.

To establish proof of principle, the readily available enantiopure Al-Binol[149] complex **269** (Al central metal ion, Nu = NMe_2, Y = H) was selected. The transformation of acetyl bromide with dihydrocinnamaldehyde was initially investigated as model reaction (Scheme 94).

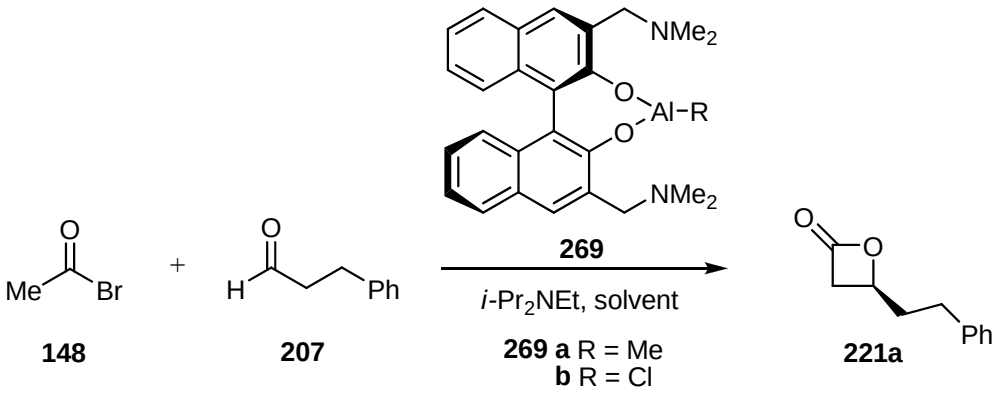


Scheme 94. Model reaction.

At −60 °C aldehyde **207** did not react to form β-lactone **221a** (Table 41). Therefore, the temperature was raised to −30 °C. In toluene, which proved to be optimal for reactions with bissulfonamide ligands **222** and **227** (see Chapter 5.1), the formation of β-lactone **221a** could not be observed (entry 1) and the corresponding diketene was formed as major product. When CH_2Cl_2 was substituted for toluene an aldehyde conversion of 62% could be achieved (entry 2) but with almost no enantioselectivity (*ee* = 12%). It is well known that sterically undemanding nucleophilic tertiary amines can catalyze the formation of diketene **201**.[152] Therefore, it was no surprise that diketene was produced in toluene and to some extent in CH_2Cl_2.

To overcome the problem of low enantioselectivities, Me_3Al was replaced with Et_2AlCl (entry 3) and Me_2AlCl (entry 4). The rationale for this change of the Al source is based on the work of *Najéra* and co-workers in the synthesis of *O*-methoxycarbonyl cyanohydrins employing the same ligand system (see Chapter 8.2.1.2).[153] *Najéra* describes in her work that only with Me_2AlCl (76% *ee*), rather than Et_2AlCl (12% *ee*) or Me_3Al (0% *ee*), useful enantioselectivities could be attained. For the formation of β-lactones, though, neither the use of Et_2AlCl (0% *ee*) nor of Me_2AlCl (2% *ee*) resulted in better selectivities.

Table 41. Summary of initial results obtained with ligand **269**.[a]



148 **207** **269 a** R = Me **b** R = Cl **221a**

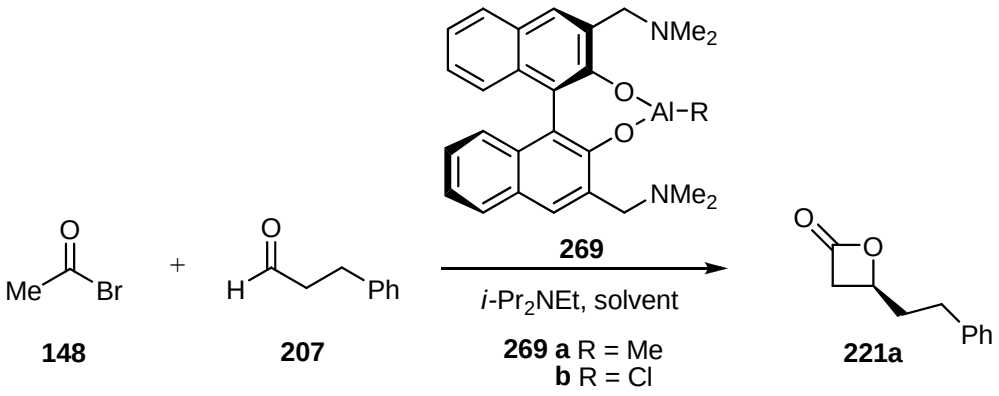
Entry	Al source	Solvent	Temp. [°C]	Time [h]	Conversion[b] [%]	*ee*[c] [%]
1	Me_3Al	toluene	−60 to −30	24	0	-
2	Me_3Al	CH_2Cl_2	−60 to −30	50	62	12
3	Et_2AlCl	CH_2Cl_2	−30	26	75	0
4	Me_2AlCl	CH_2Cl_2	−20	25	66	2

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% catalyst. The catalyst was preformed for 1 h at ambient temperature. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

8.3.1 Variation of the Ratio of Base and Acetyl Bromide

In order to test if protonation of the amino functionalities could influence the stereochemical outcome of the reaction, studies with different ratios of *Hünig*'s base and acetyl bromide were conducted. Use of 2.8 equiv. of *Hünig*'s base and 3 equiv. of acetyl bromide results in an excess of 0.2 equiv. of acetyl bromide. These conditions could therefore lead to protonation of both amino functionalities (Table 42, entry 2 and 4). In contrast, in reactions with ≥ 3 equiv. of *Hünig*'s base and 3 equiv. acetyl bromide (entry 1 and 3) the amino functionalities should remain unprotonated. The experiments revealed that protonation of the amino functionalities has no influence on the enantioselectivity and only little on the conversion though.

Table 42. Variation of the ratio of base and acetyl bromide.[a]



148 **207** **269 a** R = Me **b** R = Cl **221a**

Entry	AcBr [equiv.]	Base [equiv.]	Al source	Time [h]	Conversion[b] [%]	*ee*[c] [%]
1	3	3	Me_3Al	25	38	8
2	3	2.8	Me_3Al	25	46	8
3	3	3	Me_2AlCl	25	74	2
4	3	2.8	Me_2AlCl	25	66	2

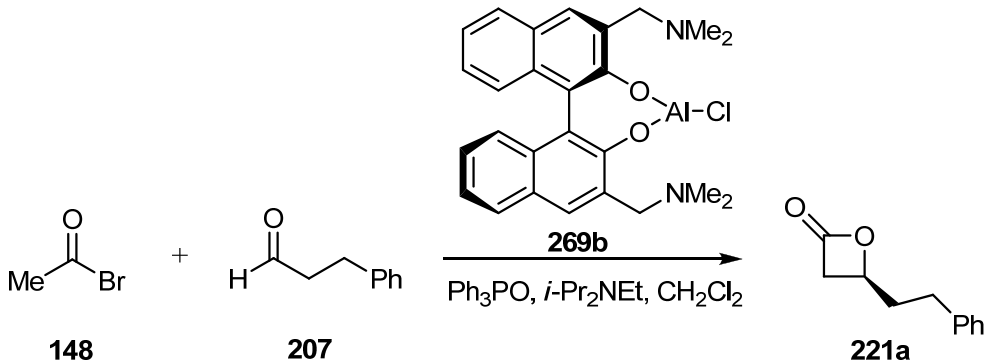
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –20 °C with 10 mol% catalyst. The catalyst was preformed for 1 h at ambient temperature. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

8.3.2 Influence of Additives

Both *Najéra*[149a] and *Shibasaki*[148a] had to utilize additives like R_3PO (R = alkyl or phenyl) to increase the selectivity. *Shibasaki* claims that the additive could change the aluminum geometry from tetrahedral to trigonal bipyramidal, allowing the phosphine oxide to be arranged in a more favorable position relative to the aldehyde.

Ph_3PO was also investigated as additive for the β-lactone formation. Reactions conducted with 40 mol% Ph_3PO provided β-lactone **221a** with low conversions in almost racemic form (Table 43, entry 2 and 3). When the amount of Ph_3PO was increased to 80 mol% the conversion dropped to 7% (entry 4). In the latter case impurities impeded the *ee* determination of β-lactone **221a**.

Table 43. Reactions with Ph_3PO as additive.[a]



148 **207** **221a**

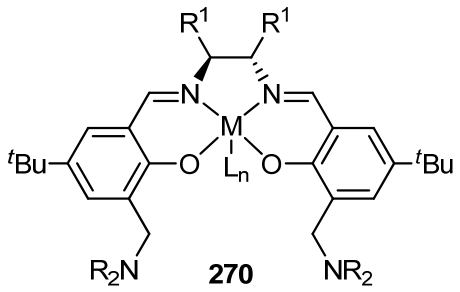
Entry	Additive (mol%)	Al source	Temp. [°C]	Time [h]	Conversion[b] [%]	*ee*[c] [%]
1	-	Et_2AlCl	−30	26	75	0
2	Ph_3PO (40)	Et_2AlCl	−30	26	20	8
3	Ph_3PO (40)	Me_2AlCl	−30	49	19	4
4	Ph_3PO (80)	Me_2AlCl	−30	49	7	-

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% catalyst. The catalyst was preformed for 1 h at ambient temperature. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

In conclusion, all experiments conducted with catalyst **269** and different Al sources resulted in poor enantioselectivity. Addition of Ph_3PO slowed down the reaction and did not increase the selectivities. For this reason, a different class of ligands was studied.

8.3.2 Development of a Bifunctional Catalyst Based on Salen Ligand 270

Salen ligands **270** were subsequently chosen due to their highly modular nature. The salen motif is one of several so-called privileged ligand systems[154] for asymmetric catalysis that impart high levels of enantioselectivity in many diverse transformations.[155] Salen ligands are readily available from inexpensive salicylaldehyde or alternative phenol precursors and are typically air-stable crystalline solids.



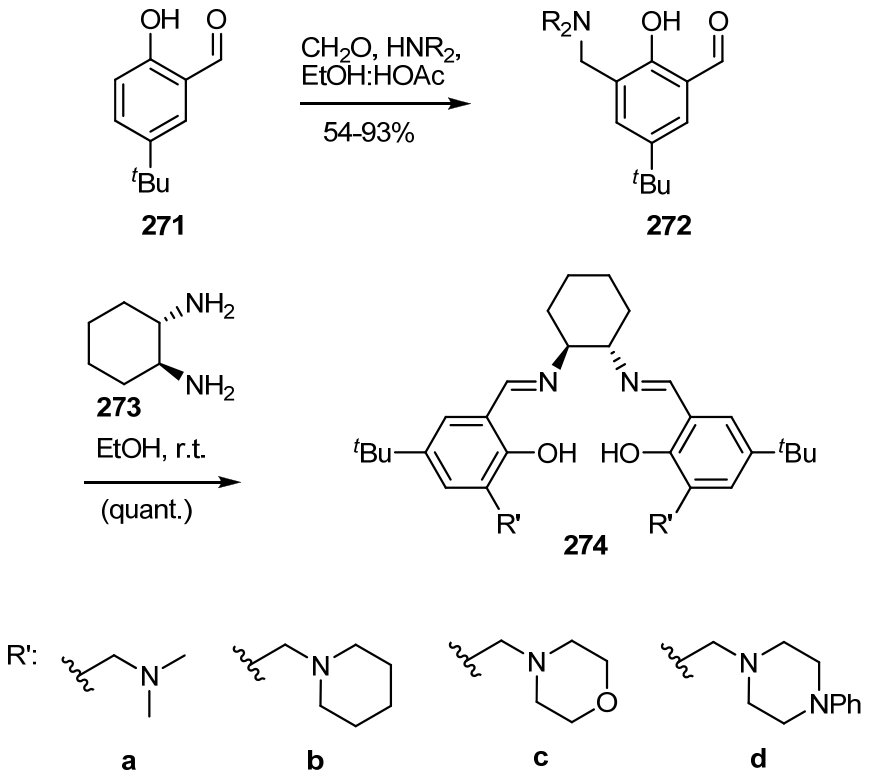
270

Kozlowski and co-workers first described catalyst systems of the general structure **270**, which incorporate a basic amino moiety into a structurally well-defined and rigid salen complex.[143] Bifunctional salen complexes **270** provide an accessible *Lewis* acid center for electrophile activation while the basic functional group activates a suitable nucleophile (see Chapter 8.2.1.2).

Based on *Kozlowski'*s work, formation of β-lactones with ligand **270** was investigated.

8.3.2.1 Ligand Synthesis

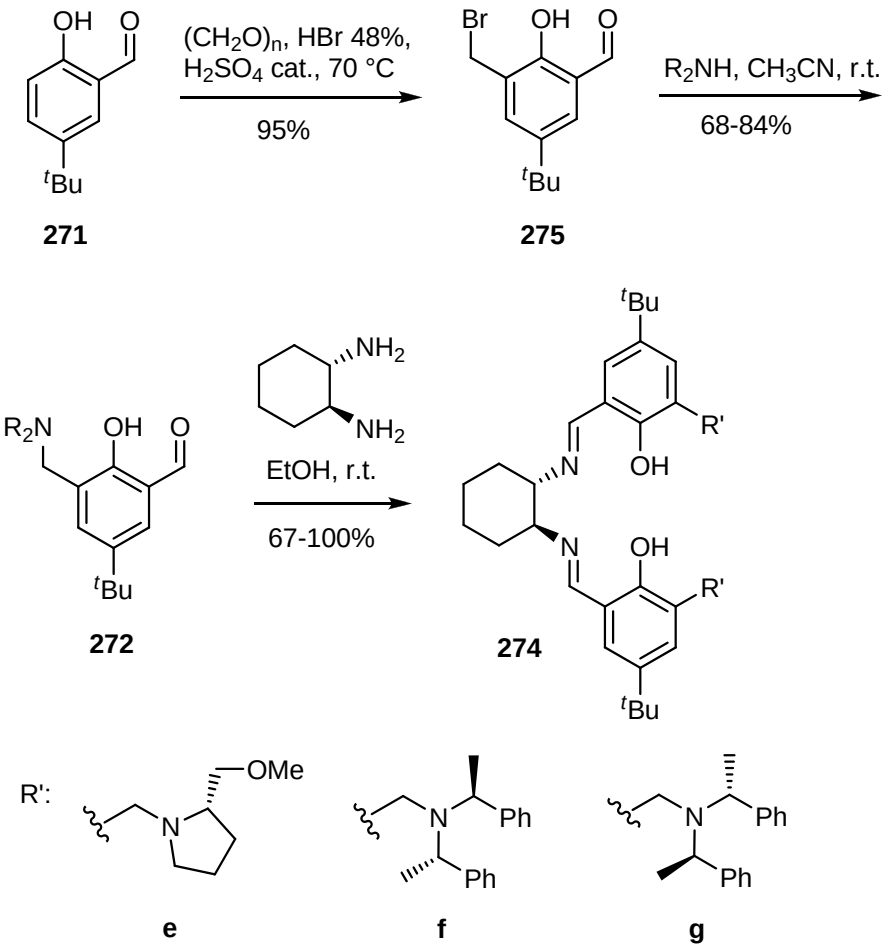
Two expedient routes to chiral methylene-amine functionalized salens were used.[143] Method A, outlined in Scheme 95, permits the rapid construction of amino salens in two steps from aldehyde **271**. Mannich reaction of **271** with a secondary amine provides aldehyde **272**, which is then condensed with (*S,S*)-cyclohexanediamine to give salen **274**. Although this route provides access to a number of amino salicylaldehydes, it is not without limitations. It was therefore necessary to employ an alternative synthetic route for α-branched amines (Scheme 96).



Salen **274**	Yield [%]
a	93
b	63
c	54
d	61

Scheme 95. Synthesis of salen ligands **274** (Method A).

This alternative route proceeds *via* bromide **275** which is prepared in one step from commercially available 5-*tert*-butyl-2-hydroxybenzaldehyde **271** (Scheme 97). Direct addition of secondary amines with α-branched alkyl chains affords amino salicylaldehydes **272**.



Salen **274**	Yield[a] [%]
e	68
f	55
g	57

[a] Two steps from bromide **275**.

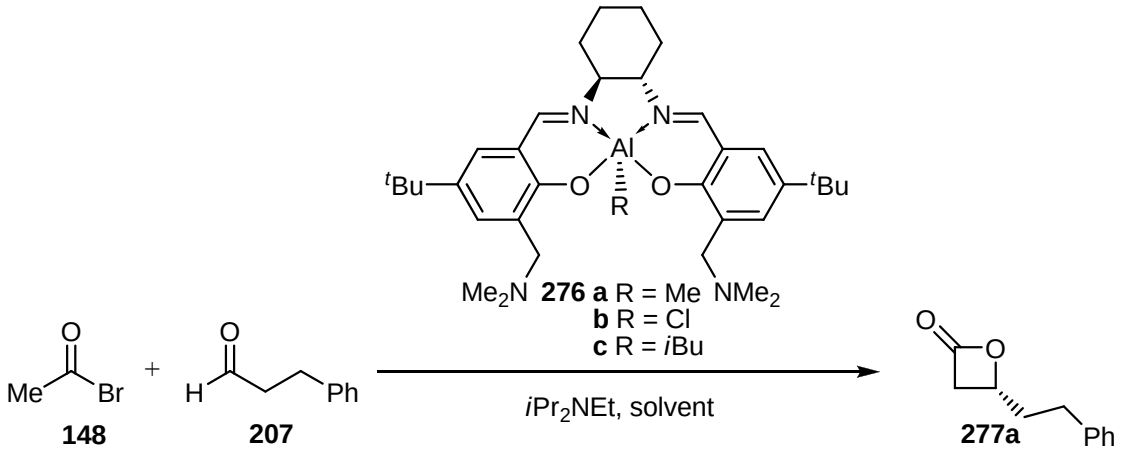
Scheme 97. Synthesis of salens **274** (Method B).

8.3.2.2 Influence of the Solvent

The solvent is a vital part of the process and as such the optimal choice is of great importance. For aluminum salen complexes **276** the solvent scope is quite limited though for the title reaction. Only non-protic, non-coordinating solvents are tolerated for the obvious reason that they otherwise block the free coordination site thereby hampering or totally inhibiting the reaction.

Initial studies with different aluminum sources were conducted in toluene and CH_2Cl_2 and revealed that with toluene no β-lactone formation was accomplished (Table 44). When Et_2AlCl was used as Al source a precipitation of complex **276b** occurred shortly after the addition of the Et_2AlCl solution (1M in hexanes). The solvent had to be removed *in vacuo* and exchanged by CH_2Cl_2 to obtain a homogenous solution (entry 2). As it was the case for reactions with binol ligand **269**, in both solvents the formation of diketene **201** was observed. As toluene proved to be unsuitable and most other solvents would have most likely led to inhibition of the catalyst, further experiments were performed in CH_2Cl_2.

Table 44. Initial studies in toluene and CH_2Cl_2.[a]



Entry	Solvent	Al source	Temp. [°C]	Time [h]	Conversion[b] [%]	*ee*[c] [%]
1	toluene	Me_3Al	−85 to −40	70	-	-
2	toluene → CH_2Cl_2	Et_2AlCl	−85 to −40	70	55	54
3	toluene	Dibal	−85 to −40	70	-	-

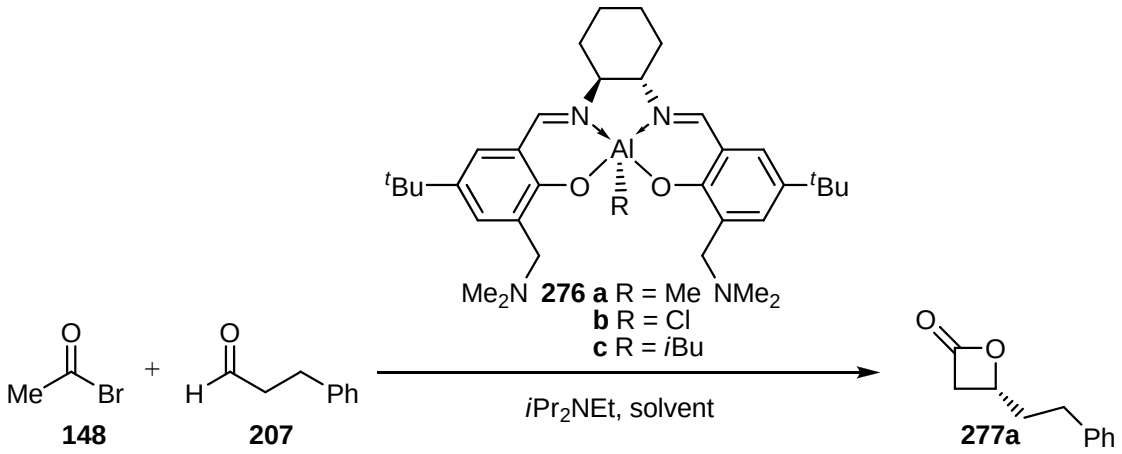
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% catalyst. The catalyst was preformed for 24 h at ambient temperature. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] Conversion of aldehyde determined by ^{1}H NMR. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

8.2.3 Influence of the Aluminum Source

For initial studies the complex was preformed with different aluminum sources for 24 h at ambient temperatures (Table 45, entries 1 to 3). The best result for the model reaction with dihydrocinnamaldehyde (**207**) was obtained with Me_3Al (54% *ee*, entry 1). Et_2AlCl (42% *ee*, entry 2) and Dibal (38% *ee*, entry 3) led to somewhat inferior enantioselectivities. With the use of Me_3Al and Et_2AlCl conversions were almost identical (77% and 78%, entries 1 and 2), whereas with Dibal as aluminum source not only the enantioselectivity but also conversion (54%, entry 3) was moderate.

Even though the selectivities were not yet in a synthetically useful range, these first results already showed the higher potential of salen system **276** (38-54% *ee*) as compared to binol system **269** (0-12% *ee*).

Table 45. Studies with different aluminum sources.[a]



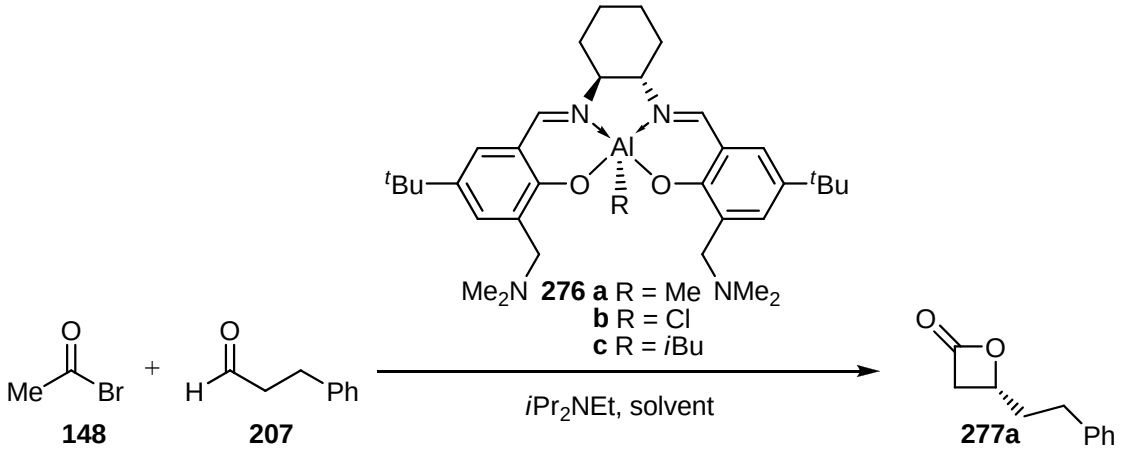
Entry	Al source	Complex formation Time / Temp.	Reaction Time [h]	Temp. [°C]	Conversion[b] [%]	*ee*[c] [%]
1	Me_3Al	24 h / r.t.	45	−50 to −20	78	54
2	Et_2AlCl	24 h / r.t.	45	−50 to −20	77	42
3	Dibal	24 h / r.t.	45	−50 to −20	54	38

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% catalyst. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

8.2.4 Influence of the Catalyst Formation

Elevated temperatures were investigated next for the complexation. After addition of the aluminum source the mixture was heated up to 40 °C and stirred for 1-4 h (Table 46, entries 3 to 6). Although both selectivities (26-46% *ee*, entries 3 to 6) and conversions (51-61%, entries 3 to 6) increased with prolonged time of catalyst formation at this temperature, the values were never as high as for the experiment in which the catalyst was preformed for 24 h at ambient temperatures. Additionally, Me_3Al (46% *ee*, entry 7) still proofed to be superior to Et_2AlCl (38% *ee*, entry 8), although the difference is less accentuated.

Table 46. Initial studies on the formation of complex **276**.[a]



Entry	Al source	Complex formation Time / Temp.	Reaction Time [h]	Temp. [°C]	Conversion[b] [%]	*ee*[c] [%]
1	Me_3Al	24 h / RT	45	−50 to −20	78	54
2	Et_2AlCl	24 h / RT	45	−50 to −20	77	42
3	Me_3Al	1 h / 40 °C	48	−50 to −20	51	26
4	Me_3Al	2 h / 40 °C	48	−50 to −20	47	34
5	Me_3Al	3 h / 40 °C	48	−50 to −20	59	42
6	Me_3Al	4 h / 40 °C	48	−50 to −20	61	46
7	Me_3Al	4 h / 40 °C	23	−20	67	46
8	Et_2AlCl	4 h / 40 °C	23	−20	68	38

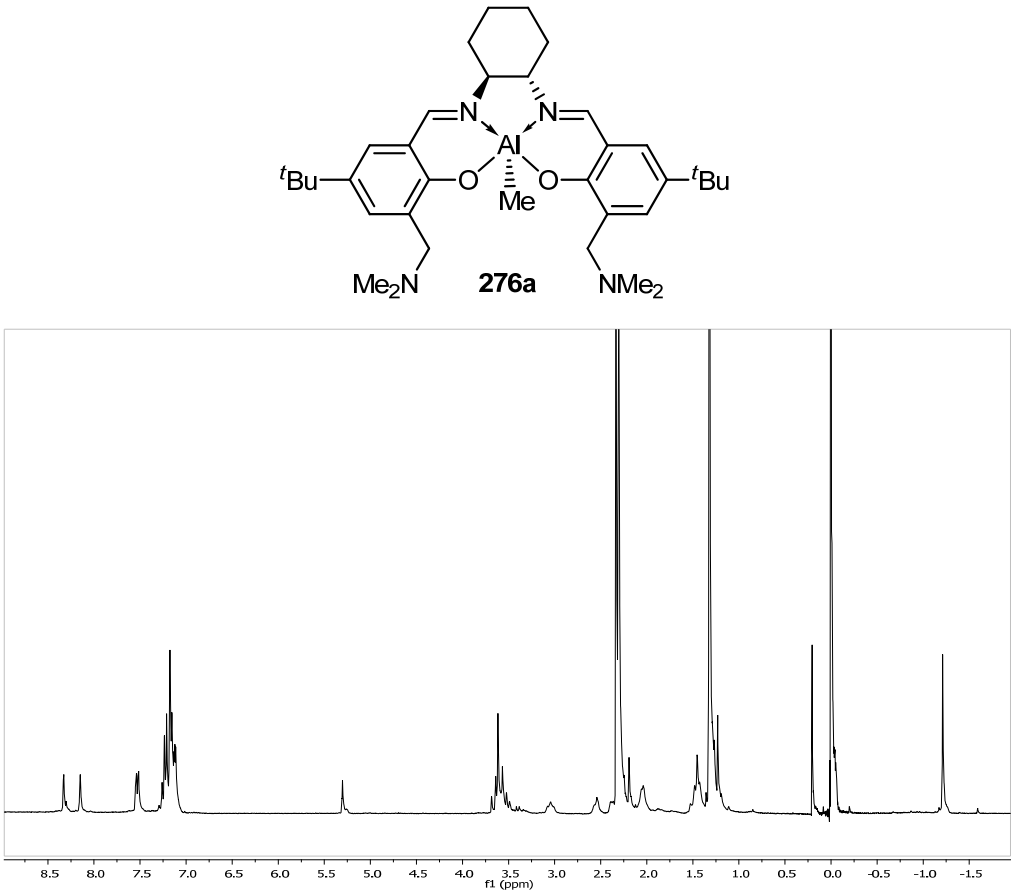
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% catalyst. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

8.2.5 NMR Studies on Catalyst Formation

In order to obtain more detailed information about the complexation, ^{1}H-NMR experiments were conducted. In a typical procedure the NMR tube was charged with ligand **274a** under nitrogen and CD_2Cl_2 was added. The solution was then treated with Me_3Al (2M in toluene) and the sample was analyzed in distinct intervals.

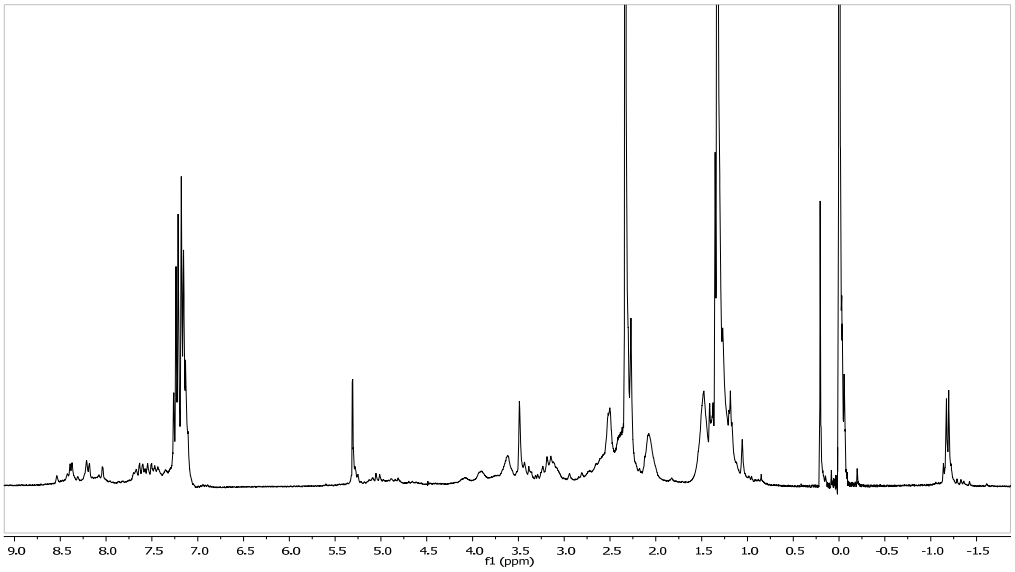
Spectrum 3 shows complex **276a** 20 min after the addition of Me_3Al. Upon incorporation of the pentacoordinate aluminum the C_2 symmetry is lost and therefore two signals for the imino C-*H* atoms are exhibited at 8.33 and 8.15 ppm each integrating for 1 proton. The spectrum reveals that a uniform species is already formed after 20 min.

Spectrum 3. ^{1}H NMR spectrum (300 MHz, CD_2Cl_2) of complex **276a** 20 min after addition of Me_3Al.



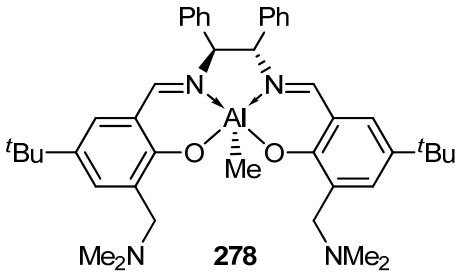
When the same sample was analyzed after 24 h, a complex mixture was found (Spectrum 4).

Spectrum 4. ^{1}H NMR spectrum (300 MHz, CD_2Cl_2) of complex **276a** 24 h after addition of Me_3Al.

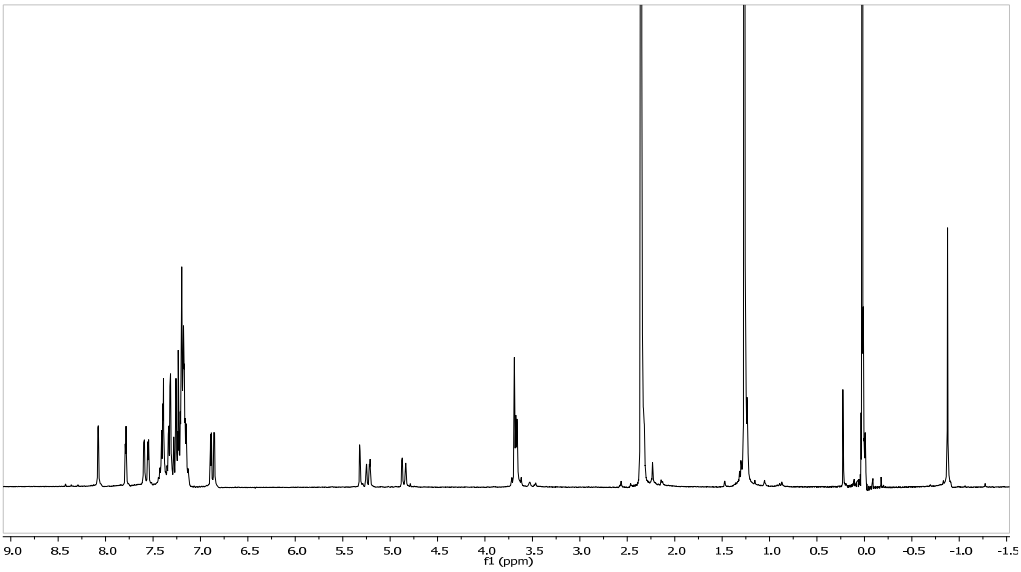


Similar experiments were performed with catalyst **278** carrying a 1,2-diphenylethylene backbone. A sample was prepared as before but after addition of Me_3Al the mixture was warmed to 40 °C. Just as for catalyst **276a** already after 20 min a uniform complex was formed (Spectrum 5).

Spectrum 5. ^{1}H NMR spectrum (300 MHz, CD_2Cl_2) of complex **278** 20 min after addition of Me_3Al at 40 °C.

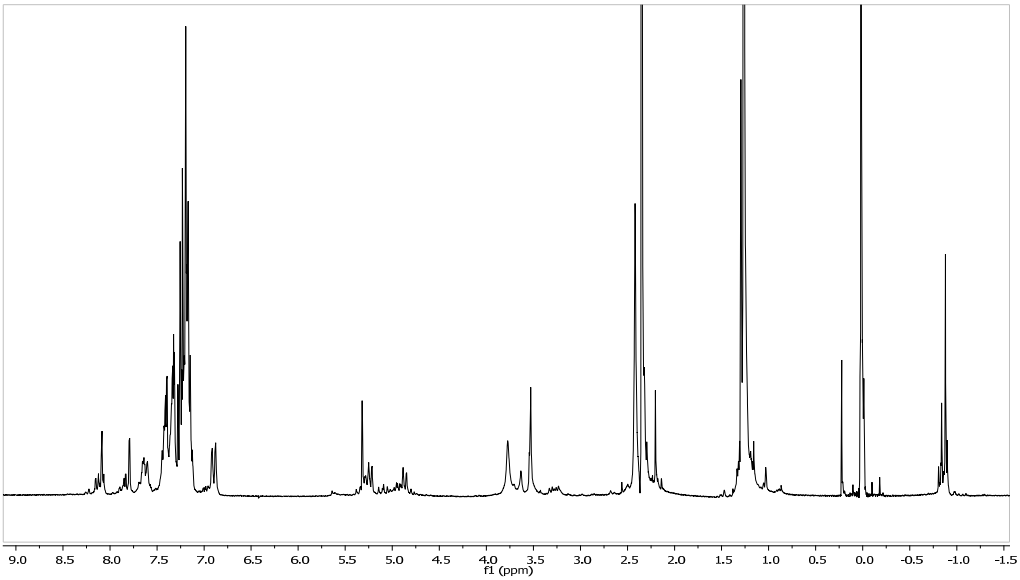


278

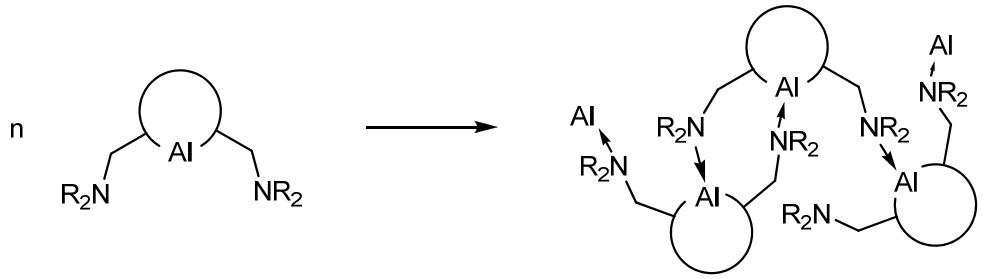


When the same sample was analyzed after 1 h, a complex mixture was detected (Spectrum 6).

Spectrum 6. ^{1}H NMR spectrum (300 MHz, CD_2Cl_2) of complex **278** 1 h after addition of Me_3Al at 40 °C.



The ^{1}H NMR studies showed a fast and uniform formation of Al-complex **276a** at ambient temperature and of complex **278** at 40 °C. With extended precomplexation time the spectra displayed a mixture of various different species, probably as a result of the formation of oligomers (Scheme 98). Nevertheless, the highest enantioselectivities were surprisingly obtained when the catalyst was preformed for 24 h at ambient temperature. Therefore, oligomers seem to play a crucial role in the reaction.



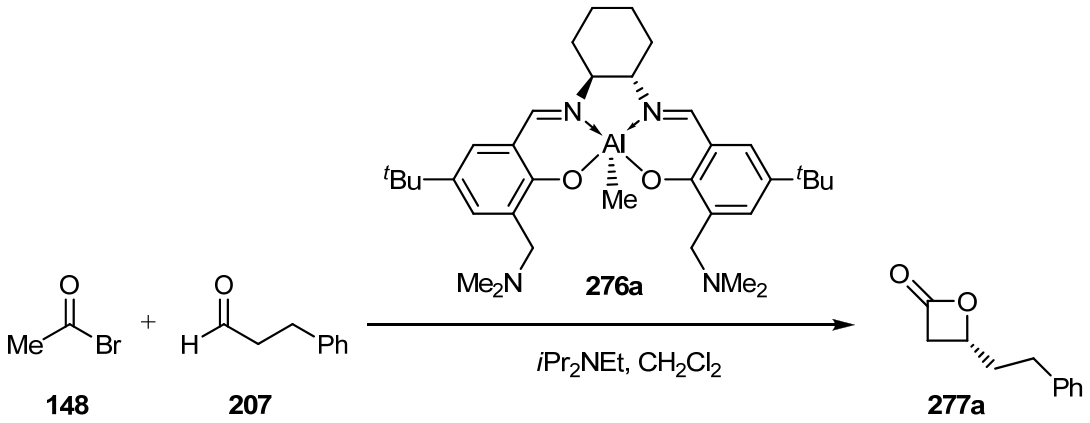
279 **280**

Scheme 98. Proposed formation of oligomers.

8.2.6 Influence of the Aldehyde Concentration

To investigate the influence of the concentration on conversion rate and selectivity reactions were carried out at c = 0.5, 0.25 and 0.17 mol/L. At the highest concentration the catalyst was not completely soluble (Table 47, entry 1). When the concentration was lowered to c = 0.17 mol/L (entry 3) the reaction rate was decreased but the selectivity was almost unchanged as compared to a concentration of 0.25 mol/L (entry 2).

Table 47. Influence of the aldehyde concentration.[a]

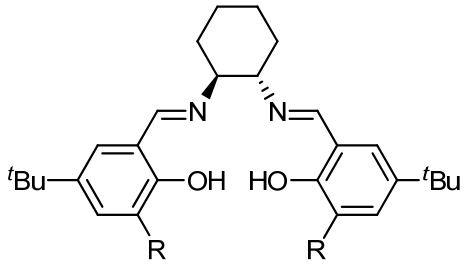


Entry	Concentration [mol/L]	Temp. [°C]	Time [h]	Conversion[b] [%]	*ee*[c] [%]
1	0.5	−80 to −20	48	62	42
2	0.25	−80 to −20	48	84	50
3	0.17	−80 to −20	48	78	51

[a] All reactions were performed with 10 mol% catalyst. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. The catalyst was preformed for 24 h at ambient temperature. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

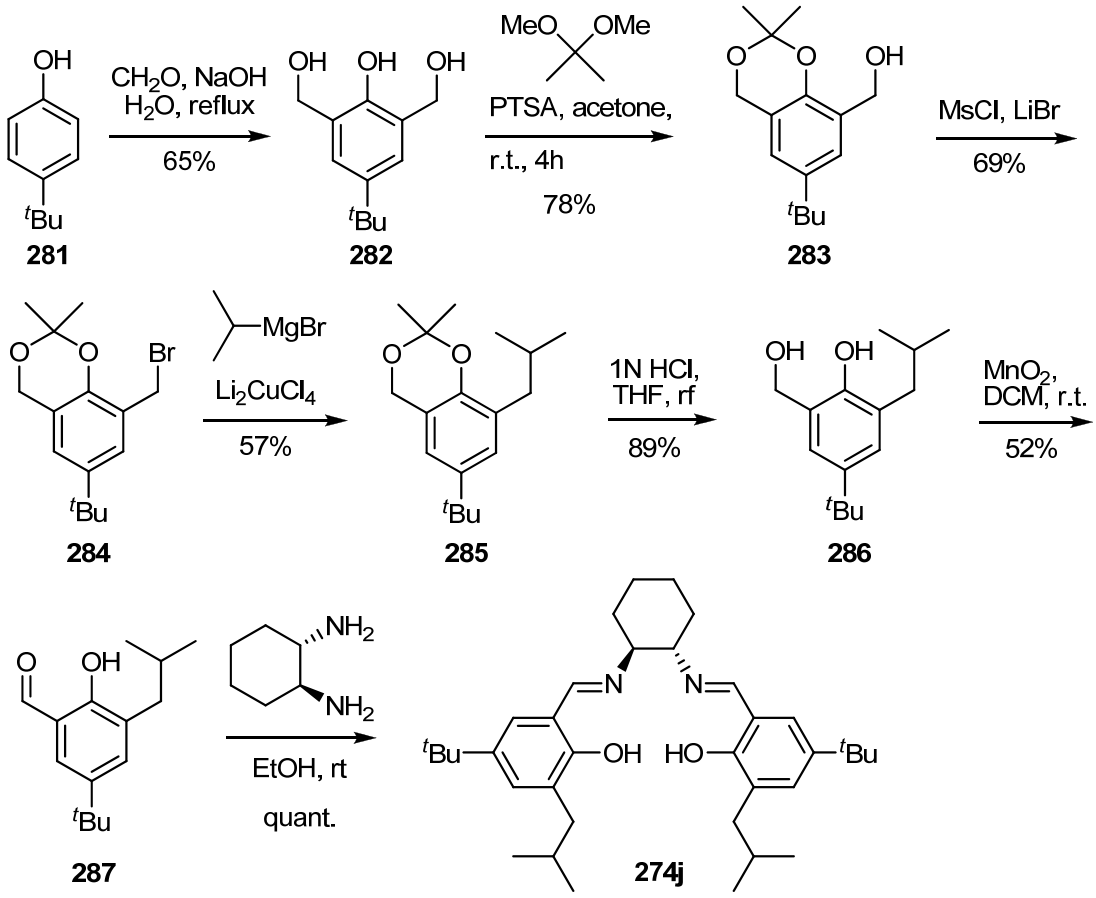
8.2.7 Control Experiments with Monofunctional Ligands

To evaluate the role of the amino functionalities different ligands lacking these nucleophilic / basic groups were synthesized and studied. Ligand **274i** was prepared in a single condensation step starting from 5-*tert*-butyl-2-hydroxybenzaldehyde and (*S,S*)-1,2-diaminocyclohexane. Ligand **274h**, known as (*S,S*)-*Jacobsen* ligand, is commercially available.



274 h R = ^{t}Bu
i R = H
j R = ^{i}Bu

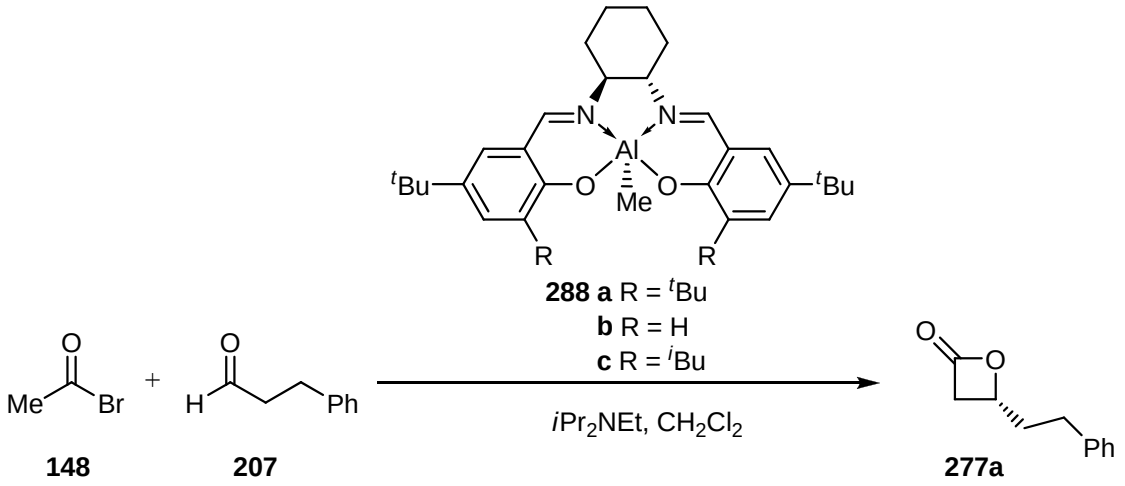
In contrast the synthesis of isobutyl substituted ligand **274j** was quite tedious (Scheme 99). In particular, the oxidation of the benzylic alcohol **286** with manganese dioxide furnished the aldehyde in moderate yield due to the formation of side products. Furthermore, separation of aldehyde **287** from these side products proofed to be difficult and several chromatography steps were needed. The synthesis of ligand **274j** was necessary, because the *iso*-butyl groups in the 6-position of the phenol ring are of comparable size as the amino functionalities in ligand **274a**.



Scheme 99. Formation of ligand **274j**.

With *Jacobsen*'s ligand **288a** neither in CH_2Cl_2 nor in toluene any product was formed. This can probably be attributed to sterical hindrance by the two additional *tert*-butyl groups (Table 48, entries 1 and 2). In contrast, without any substituents in the 6-position of the phenol rings, as it is the case for ligand **288b**, the cycloaddition provides the product with good conversion yet in almost racemic form (entry 3). Use of *iso*-butyl substituted ligand **288c** (entry 4) also led to rapid formation of the desired product, but the enantioselectivity obtained was again inferior to the one obtained with the sterically comparable ligand **276a** carrying dimethylamino methylene donors.

Table 48. Studies with monofunctional catalysts.[a]



148 **207** **277a**

Entry	R	Solvent	Temp. [°C]	Time [h]	Conversion[b] [%]	*ee*[c] [%]
1[d]	*t*Bu	CH_2Cl_2	−20	29	0	-
2[d]	*t*Bu	toluene	−20	29	0	-
3[d]	H	CH_2Cl_2	−20	45	73	2
4[e]	*i*Bu	CH_2Cl_2	−50 bis −20	48	95	6

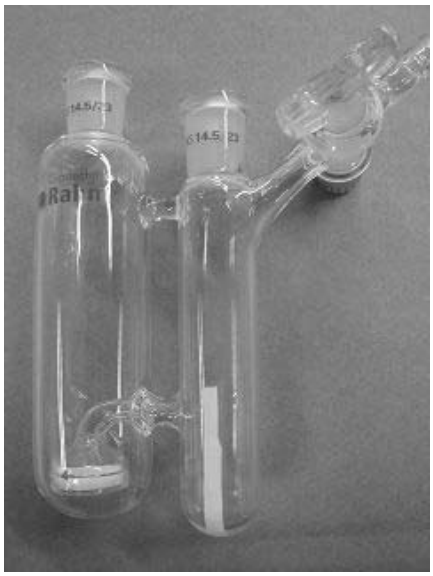
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% catalyst. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. The catalyst was preformed for 24 h at ambient temperature. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support. [d] The catalyst was preformed for 1 h at ambient temperature. [e] The catalyst was preformed for 24 h at ambient temperature.

These results clearly show that the amino functionalities are playing a decisive role in the enantioselectivity outcome of the reaction, whereas the reaction rates are seemingly less sensitive to a change of substituents.

For the cycloaddition with catalyst **276a** bearing amino functionalities two general modes of action are presumably competing explaining the moderate values of enantioselectivity: a *Lewis*-acid catalyzed process either with or without assistance of the amino functionalities.

8.2.8 Influence of the Ammonium Salt

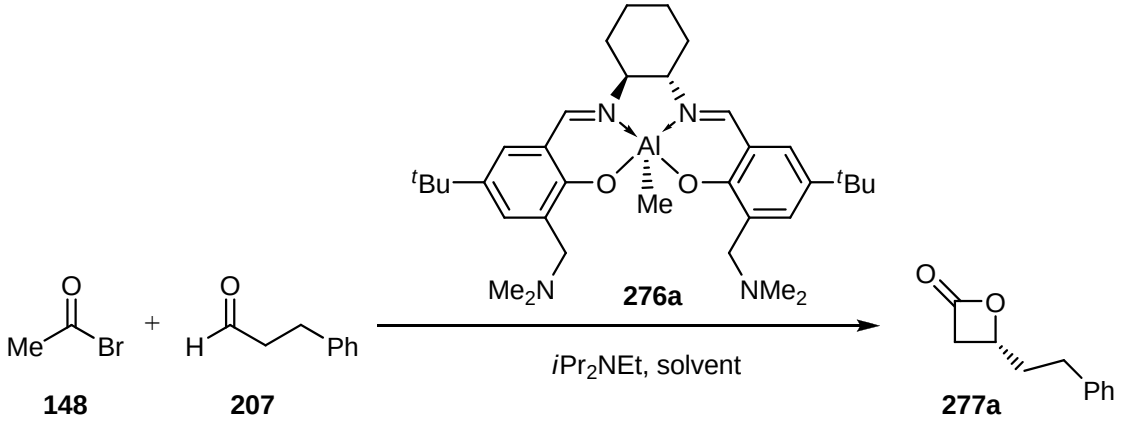
In order to assess if the released bromide shows a predisposition to coordinate to the catalyst and could thus slow down the cycloaddition reaction, attempts were undertaken to remove bromide from the reaction mixture. Specially for this purpose a double *Schlenk* apparatus equipped with a filtration unit was manufactured (Picture 1). In a typical experiment, in one compartment of the *Schlenk* apparatus (reaction flask) Me_3Al and ligand **274a** were stirred in either dichloromethane or toluene for 1 h at ambient temperature. Subsequently, the *Schlenk* apparatus was transferred into a cooling bath, at the indicated temperature. To the second compartment of the *Schlenk* apparatus (ketene flask) toluene, acetyl bromide and *Hünig*'s base were added. Precipitated ammonium salt generated from the reaction of acetyl bromide and *Hünig*'s base clearly indicated the formation of ketene. After stirring the reaction mixture for 1 h the ketene/toluene solution was transferred by means of an overpressure of argon through the filtration unit. Studies with a 3 : 2.5 and 3 : 3 ratio of acetyl bromide and base were conducted.



Picture 1. Double *Schlenk* apparatus with filtration unit.

Only the first experiment (Table 49, entry 1) yielded product **277a** with a reasonable conversion and a selectivity comparable to the standard reaction procedure thus indicating that the bromide has no influence on the reaction rate. For entries 2 and 3 a suspension was formed after addition of the ketene solution, probably due to the poor solubility of the protonated catalyst in toluene. In entry 3 an additional amount of CH_2Cl_2 was added to dissolve the catalyst again. This dilution led to a decrease in turnover rate. Reactions with equimolar amounts of acetyl bromide and base furnished no product at all (entry 4).

Table 49. Influence of the ammonium salt.[a]



Entry	Solvent	Ratio AcBr/base	Temp. [°C]	Conc. [mol/L][b]	Time [h]	Conversion[b] [%]	*ee*[c] [%]
1	CH_2Cl_2/toluene	3 : 2.5	−30 to −20	0.17	66	66	44
2	toluene	3 : 2.5	−20	0.17	52	0	-
3	CH_2Cl_2/ toluene	3 : 2.5	−20	0.08	42	20	n.d.
4	CH_2Cl_2/ toluene	3 : 3	−20	0.17	21	0	-

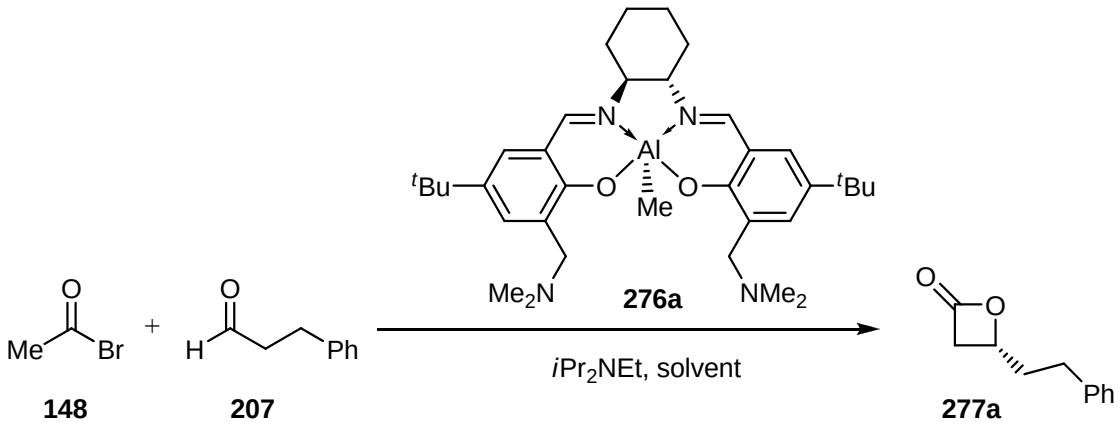
[a] All reactions were performed with 10 mol% catalyst. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. The catalyst was preformed for 24 h at ambient temperature [b] Approximate values for the aldehyde concentration. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

8.2.9 Influence of the Ligand / Al Source Ratio

Given the fact that with simple *Lewis* acids like Me_3Al in the absence of an additional ligand (Table 50, entry 1) the cycloaddition proceeds at temperatures ≥ −60 °C leading to racemic products, the influence of the ratio of aluminum source to ligand **274a** had to be investigated. Ligand **274a** itself did not catalyze the [2+2] cycloaddition, neither with a 3:2.5 ratio of acetyl bromide to base nor with a 3:3 ratio (entries 3 and 5).

When ligand **274a** and the aluminum source were used in a 15 mol%:10 mol% ratio, neither with a 3:2.5 ratio of acetyl bromide to base nor with equimolar amounts, product formation could be detected (entries 2 and 4). This can be attributed to the action of the ligand excess, which might block the free coordination site of the aluminum central metal ion.

Table 50. Variation of the ratio of ligand **276a** to aluminum source.[a]



Entry	Ligand (mol%)	Al source (mol%)	Ratio AcBr/*Hünig*'s base	Time [h]	Conversion[b] [%]	*ee*[c] [%]
1	-	10	3:2.5	20	38	rac
2	15	10	3:2.5	45	0	-
3	10	-	3:2.5	20	0	-
4	15	10	3:3	68	0	-
5	10	-	3:3	68	0	-

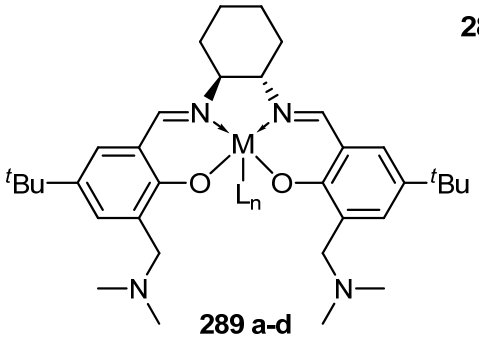
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –20 °C. The catalyst was preformed for 24 h at ambient temperature. The ketene was formed *in situ.* [b] Conversion of aldehyde determined by ^{1}H NMR. [c] *ee* determined by HPLC on a chiral support.

8.2.10 Studies with Different Metal Centers

Following *Kozlowski*'s[143] protocol for the catalyst formation, studies with catalysts **289 a-d** possessing a Zn(II), Ti(IV) or Co(II) central metal ion were carried out. In a typical experiment a *Schlenk* tube was charged with CH_2Cl_2 (2 mL), followed by ligand **274** (27.4 mg, 0.05 mmol) and the metal source as a solution in toluene (0.05 mmol). For complex **289a**, shortly after addition of the metal source, the formation of a suspension was observed. Acetyl bromide was subsequently added followed by *Hünig*'s base resulting in the formation of a homogeneous solution. After approximately 3 h the catalyst started to precipitate again.

These solubility problems eventually might have prevented the formation of the targeted product (Table 51, Entries 1 and 2). With the use of complex **289c** ($TiCl_4$ as metal source) the same problem occurred (Entries 4 and 5). Although for complexes **289b** and **d** the solubility was not an issue, still no lactone formation was observed (entries 3, 6 and 7).

Table 51. Studies with different metal centers.[a]



289 a-d

289 a M = Zn
b M = Ti; L_n = 2 O*i*Pr
c M = Ti; L_n = 2 Cl
d M = Co

Entry	M-L_n	Ratio AcBr/*Hünig*'s base	Temp. [°C]	Time [h]	Conversion [%]
1[b]	Zn	3 : 2.8	−30 to 0	68	0
2[c]	Zn	3 : 3	−20	92	0
3[d]	Ti-(O*i*Pr)$_2$	3 : 2.5	−20	48	0
4[e]	Ti-Cl_2	3 :2.5	−20	48	0
5[e]	Ti-Cl_2	3 : 3	−20	48	0
6[f]	Co	3 :2.5	−20	24	0
7[f]	Co	3 : 3	−20	24	0

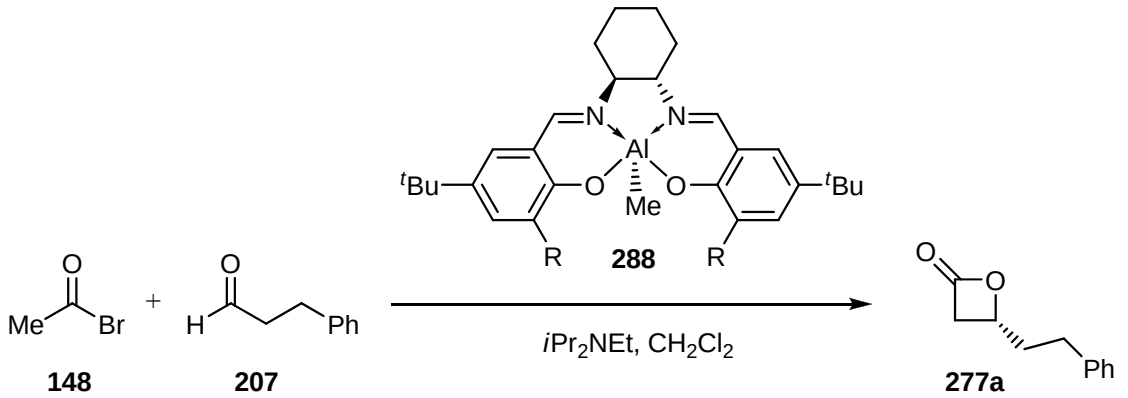
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde in CH_2Cl_2 with 10 mol% of catalyst. The ketene was formed *in situ.* [b] The catalyst was preformed for 6 h at ambient temperature after addition of a 1.1 M solution of Et_2Zn in toluene. [c] The catalyst was preformed for 1 h at ambient temperature after addition of a 1.1 M solution of Et_2Zn in toluene,. [d] The catalyst was preformed for 1 h at ambient temperature after addition of a 2.0 M solution of Ti(O*i*Pr)$_4$ in toluene. [e] The catalyst was preformed for 1 h at ambient temperature after addition of a 1.0 M solution of $TiCl_4$ in toluene. [f] $Co(ClO_4)_2$*$6H_2O$ was added to a solution of ligand **274** in toluene and the mixture was heated to reflux for 3 h. The solvent was removed *i.v.* and the catalyst dissolved in CH_2Cl_2.

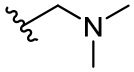
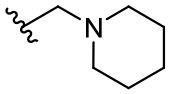
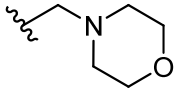
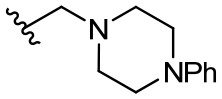
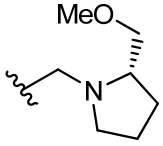
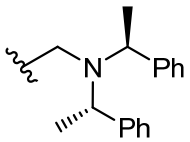
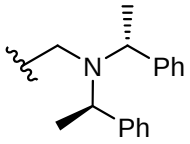
8.2.11 Studies with Different Amino Functionalities

After the investigation of different reaction parameters (see prior Chapters) the observed selectivities were still not satisfactory. Therefore, to survey the role of the *Lewis* base component, aluminum complexes of selected amino salens were examined (Table 52).

Reactions were conducted at −20 °C and quenched after 48 h for a direct comparison of catalyst reactivity. While identical enantioselectivities were observed with piperidyl salen **288e** (44% *ee*, entry 2) and morpholine salen **288f** (44% *ee*, entry 3), the sterically more demanding *N*-phenyl piperazine salen **288g** turned out to be slightly less selective (40% *ee*, entry 4). Catalysts derived from salens **274 e-g**, containing α-branched amines, were less selective (entries 5 to 7). These results indicate that interaction of the *Lewis* base with ketene decreases with increasing steric hindrance.

Table 52. Studies with different amino functionalities.[a]



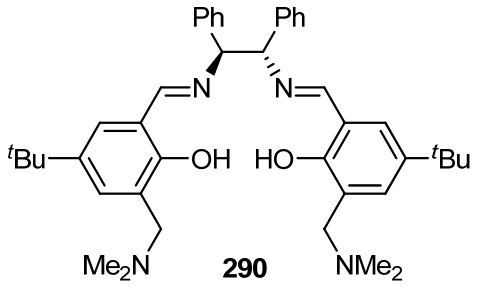
Entry	Ligand	R	Conversion[b] [%]	Yield[c] [%]	*ee*[d] [%] (Config.)
1	Cy-Salen-NMe_2 **288d**		80	65	50 (*R*)
2	Cy-Salen-Pip **288e**		65	49	44 (*R*)
3	Cy-Salen-Morph **288f**		74	54	44 (*R*)
4	Cy-Salen-*N*-Ph-piperazin **288g**		67	51	40 (*R*)
5	Cy-Salen-SMP **288h**		61	47	32 (*R*)
6	Cy-Salen-*N*-(*S*)-(αMBA)$_2$ **288i**		85	69	10 (*R*)
7	Cy-Salen-*N*-(*R*)-(αMBA)$_2$ **288j**		81	62	10 (*R*)

[a] In a typical procedure a solution of Me_3Al (2M in toluene, 0.05 mmol, 0.1 equiv.) was added to a solution of ligand **274** (0.05 mmol, 0.1 equiv.) in CH_2Cl_2 (2 mL) and the mixture was stirred for 24 h at ambient temperature. Aldehyde **207** (0.50 mmol, 1 equiv.), acetyl bromide (1.50 mmol, 3 equiv.) and *Hünig*'s base (1.25 mmol, 2.5 equiv.) were subsequently added at −50 °C. The mixture was stirred for 5 h at −50 °C before raising the temperature to −20 °C. All reactions were quenched after 48 h. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [d] *ee* determined by HPLC on a chiral support.

8.2.12 Studies with Ligand 290

Compared to cyclohexane-1,2-diamine derived ligand **274**, reactions with ligand **290** posessing a 1,2-diphenyl ethylene-1,2-diamine backbone resulted in inferior enantioselectivities and therefore no further studies were conducted with this system (Table 53).

Table 53. Experiments with ligand **290**.[a]



290

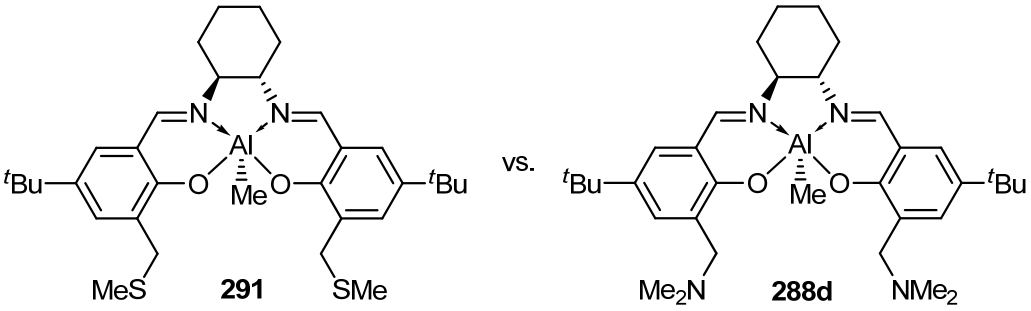
Entry	Al source	Solvent	Temp. [°C]	Time [h]	Conversion[b] [%]	Yield[c] [%]	*ee*[d] [%]
1	Me_3Al	CH_2Cl_2	−60 to −30	50	60	43	26
2	Et_2AlCl	CH_2Cl_2	−60 to −30	50	54	36	14

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% catalyst. The ketene was formed *in situ* from 3 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] Conversion of aldehyde determined by ^{1}H NMR. [c] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [d] *ee* determined by HPLC on a chiral support.

8.2.13 Studies with Catalyst 291 Equipped with Thioether Donor Groups

After discovering that sterically more hindered amines lead to decreased selectivities, the decision was made to synthesize and employ complex **291**, where the tertiary amino groups have been replaced thioether moieties (Table 54). The new catalyst (entry 1) was found to be much more reactive but, unfortunately, less enantioselective than catalyst **288d** (entry 2) at –50 °C.

Table 54. Comparison of catalysts **291** and **288d**.[a]



Entry	Catalyst	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
1[d]	**291**	3	100	79	46
2[e]	**288d**	23	94	49	60

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde in CH_2Cl_2 with 10 mol% ligand and aluminum source at –50 °C. The ketene was formed *in situ.* [b] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Catalyst preformed for 19 h at ambient temperature. Reaction time: 3 h. [e] Catalyst preformed for 24 h at ambient temperature. Reaction time: 23 h.

8.2.14 Influence of the AcBr / *Hünig*'s Base Ratio

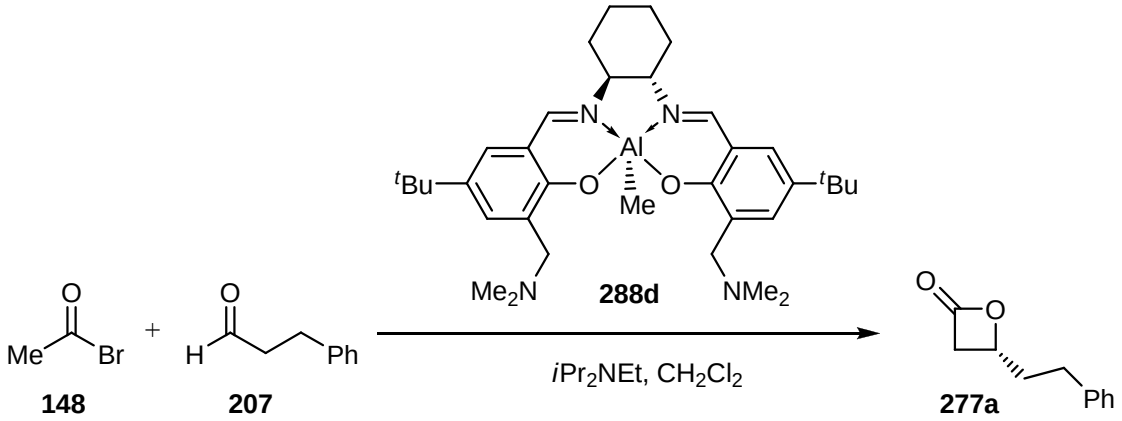
Bearing in mind that an excess of 0.5 equiv. of acetyl bromide is used relative to the achiral auxiliary base, one reasonable explanation for the observed formation of β-lactones with low enantioselectivity could be that the amino functionalities in complex **288d** are partially or fully protonated, preventing the formation of zwitterionic enolates (Figure 17; complex **292**). In that case, only the *Lewis* acid would be available for activation of the aldehyde **207** and the transition state would less organized than desired.

In an alternative potentially competing mode of action the protonated amino functionality might form a hydrogen bond to the coordinated aldehyde thereby further increasing the substrate's electrophilicity (Figure 17; complex **293**). The protonated amino functionalities could thus act as chiral *Brönsted* acids.

Figure 17. Potential activation modes of the protonated complex **288d**.

To prevent protonation of the amino functionalities in complex **288d** the same amount of base and acetyl bromide (3.0 equiv. each) was added (Table 55, entry 1). Interestingly, the increased amount of base led to a diminished reaction rate (entry 5), but no difference in enantioselectivity was observed (34% *ee*). With an inversed order of addition, i.e. first the base, then acetyl bromide, no reaction at all took place (entry 2). Under these conditions the amino functionalities would be expected to remain unprotonated throughout the whole reaction but the catalyst is apparently deactivated. This might point to anintermolecular amine coordination to aluminum resulting in the formation of oligomers thus completely blocking the *Lewis* acid. Protonation (alternatively acylation) of the amino moieties is hence essential for catalytic activity. As depicted in Figure 17, the aldehyde coordination might not only be rigidified through the formation of a proton bridge, but would also be even more activated explaining the acceleration of the reaction rate. A smaller excess of acetyl bromide relative to the base provided similar data (entries 3 and 4). In the case of the thioether donor in **291**, acylation rather than protonation is more likely (low basicity, high nucleophilicity of thioethers) to occur, possibly explaining the somewhat diminished enantioselectivity by a less organized transition state as a result of the absence of an additional rigidifying hydrogen bond element.

Table 55. Influence of the AcBr / *Hünig*'s base ratio.[a]

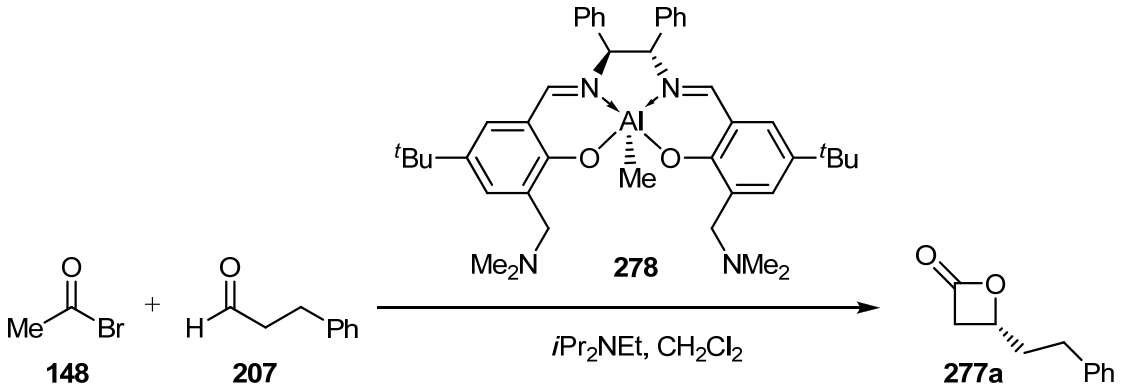


Entry	Ratio AcBr/base	Time [h]	Conversion [%]	*ee*[b] [%]
1[c]	3 : 3	68	34	34
2[d]	3 : 3	45	0	-
3[d]	3 : 2.9	45	31	36
4[d]	3 : 2.8	45	39	36
5[d]	3 : 2.5	45	39	34

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –20 °C with 10 mol% catalyst. The ketene was formed *in situ.*The catalyst was preformed for 24 h at ambient temperature. [b] *ee* determined by HPLC on a chiral support. [c] AcBr added before the base. [d] Base added before AcBr.

Studies with complex **278** revealed a similar behavior as for **288**. As before, using 2.5 equiv. of base resulted in the highest reaction rate (Table 56, entry 1). When the amount of base was increased the reaction rate was diminished (entries 2 to 4) whereas in all cases the same enantioselectivity was attained. This observation confirmed the assumption that in all reactions the selectivity originates from the same active species. The concentration of these species seems to be highly dependent on the amount of base. With an excess of base the reaction was completely inhibited by catalyst deactivation (entry 5).

Table 56. Influence of the AcBr / *Hünig*'s base ratio.[a]

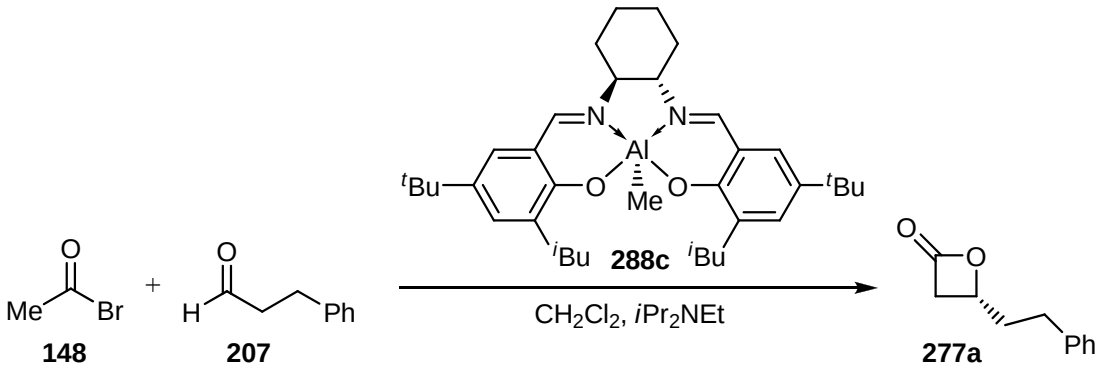


Entry	Ratio AcBr/base	Time [h]	Conversion [%]	*ee*[b] [%]
1	3 : 2.5	93	45	24
2	3 : 2.8	93	39	24
3	3 : 3	93	31	24
4	3 : 3.5	93	0	-

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –20 °C with 10 mol% catalyst. The ketene was formed *in situ.*The catalyst was preformed for 1 h at ambient temperature. [b] *ee* determined by HPLC on a chiral support. AcBr was added before the base.

Control experiments with complex **288c** further revealed that by an excess of *Hünig*'s base the catalyst is completely inhibited (Table 57, entry 3). An equal amount of base and acetyl bromide drastically diminished the reaction rate (entry 2) as compared to a 3 : 2.5 ratio of acetyl bromide and base (entry 1). These results clearly show that the sterically hindered *Hünig*'s base, usually considered to be non-nucleophilic, apparently also inhibits the catalyst by coordination.

Table 57. Influence of the AcBr / *Hünig*'s base ratio with control catalyst system **288c**.[a]



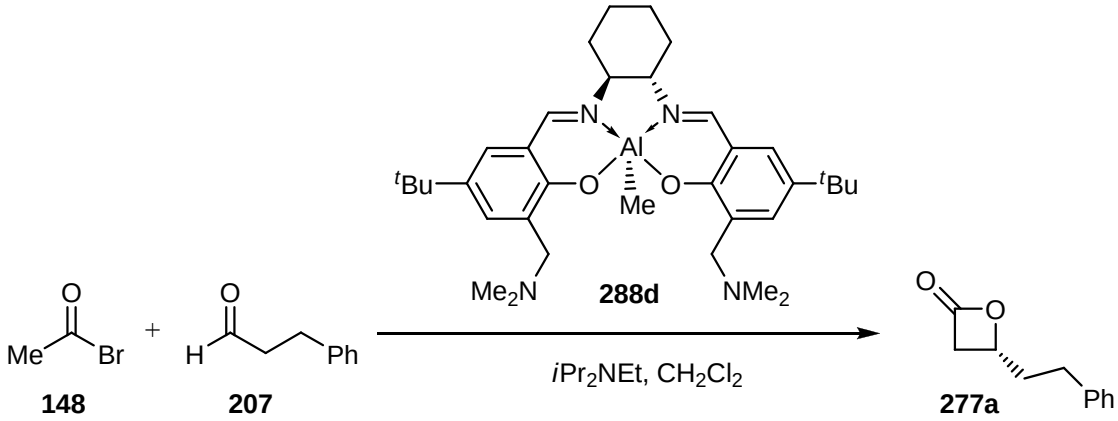
Entry	Ratio AcBr/base	Time [h]	Conversion [%]	*ee*[b] [%]
1	3 : 2.5	48	95	6
2	3 : 3	48	42	4
3	3 : 3.5	24	0	-

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –20 °C with 10 mol% catalyst. The ketene was formed *in situ.*The catalyst was preformed for 1 h at ambient temperature. [b] *ee* determined by HPLC on a chiral support. AcBr was added before the base.

8.2.15 Influence of the Base

To avoid the problematic inhibition of the catalyst by *Hünig*'s base, alternative even less nucleophilic bases such as PMP or 1,8-bis(dimethylamino)naphthalene (proton sponge) were investigated. However, reactions promoted by PMP using an excess of AcBr resulted in a decrease in turnover (Table 58, entry 1), whereas with equimolar amounts of acetyl bromide and base again no reaction at all was observed (entry 2). When proton sponge was utilized as base neither with an excess of acetyl bromide (entry 3) nor with equimolar amounts of base and acetyl bromide (entry 4) the targeted product was furnished. Reasoning that with proton sponge, due to its kinetic inertness for C-H deprotonations,[156] it might be necessary to use a second more rapidly reacting auxiliary base in catalytic amounts, which deprotonates acetyl bromide and then delivers the proton to the stoichiometric, thermodynamically stronger base thus acting as a proton carrier, proton sponge was studied in combination with *Hünig*'s base, yet did not provide any targeted product (entries 5 and 6).

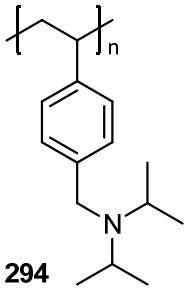
Table 58. Variations of the base.[a]



Entry	Base	Ratio AcBr/Base	Time [h]	Conversion [%]	*ee*[b] [%]
1	PMP	3 : 2.5	48	35	49
2	PMP	3 : 3	48	0	-
3	proton sponge	3 : 2.5	18	0	-
4	proton sponge	3 : 3	18	0	-
5	proton sponge/*Hünig*'s base	3 : 2.5 : 0.1	26	0	-
6	proton sponge/*Hünig*'s base	3 : 2.5 : 0.2	26	0	-

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde at –20 °C with 10 mol% catalyst. The ketene was formed *in situ.*The catalyst was preformed for 24 h at ambient temperature. [b] *ee* determined by HPLC on a chiral support. AcBr was added before the base.

Another approach to avoid inhibition of the catalyst was the application of a polymer bound immobilized tertiary amine base **294**. The ketene was preformed in a separate *Schlenk* tube at –20 °C and added *via* canula to the reaction mixture, while the polymer bound base **294** was not transferred. For the formation of ketene, 7 equiv. of acetyl bromide and 6 equiv. of base were utilized.



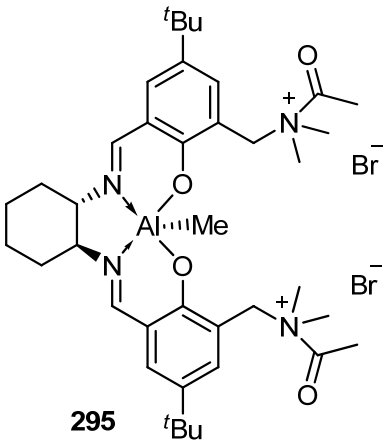
294

5 h after addition of the ketene solution, no conversion to the desired product could be detected.

To control if a low ketene concentration was the problem, an additional amount of acetyl bromide (3 equiv.) and non-immobilized *Hünig'*s base (2.5 equiv.) was added. Astonishingly, after another 3 h, a very high conversion of 93% to the product with 46% *ee* was obtained. The polymer bound base **294** proofed to be unsuitable probably as a consequence of its lower basicity as compared to *Hünig'*s base thus resulting in insufficient ketene formation.

Reasoning that with a larger excess of acetyl bromide (approx. 10 equiv.) the concentration of free base is significantly lower, coordination of base to the catalyst is strongly suppressed. This observation confirmed the conclusion that, although still no alternative to *Hünig'*s base was at hand, the activity of the catalyst could be drastically increased by using a large excess of acetyl bromide relative to *Hünig'*s base.

By a high concentration of acetyl bromide, the ligand's amino functionalities might be either protonated (Figure 17) or acylated (Figure 18). The acylium moiety cannot be deprotonated due to the large excess of acetyl bromide.

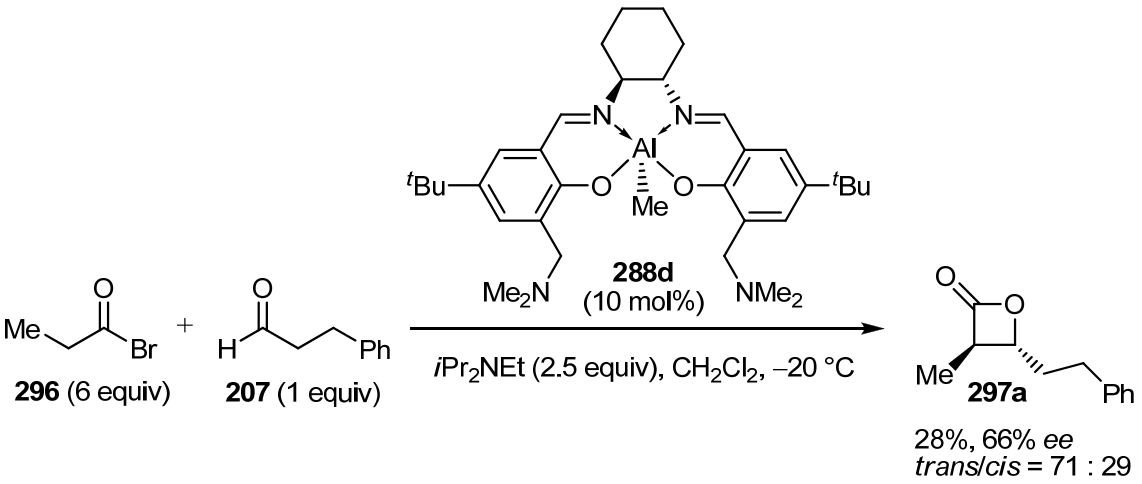


295

Figure 18. Acylated catalyst **295**.

On the other hand, the bromide counteranion present is still a relatively good nucleophile possibly resulting in the equilibrium formation of an acyl bromide enolate from the generated ketene. This enolate might interact with the positively charged ammonium moieties by forming a contact ion pair. The enolate could then react with the aldehyde to form the *trans*-configured β-lactone **297a** if propionylbromide (**296**) is used as ketene source (Scheme 100). The first reaction with such a system confirmed this assumption. The *trans*-configured β-lactone (**297a**) was preferably formed (*trans*/*cis* = 71:29) with a promising *ee* of 62%. In this experiment the catalyst was preformed for 24 h at ambient temperature.

Although a low conversion of 58% and a yield of only 28% was observed this first result confirmed the initiative hypothesis.



Scheme 100

Similar interactions which lead to the formation of a contact ion pair are especially exploited in phase transfer catalysis. But so far no system is known where *Lewis* acid catalysis and phase transfer catalysis are combined in one catalyst.

Since at least two reactive catalyst systems possessing either acylated or protonated ammonium functionalities are present arguably exhibiting a different selectivity profile, in the following Chapters the influence of structurally defined positively charged aprotic ammonium moieties on the reaction was further investigated.

9 Contact Ion Pair Directed *Lewis* Acid Catalysis

9.1 Concept

In this work a novel concept within the context of dual activation catalysis was developed. It combines the concepts of *Lewis* acid and phase transfer catalysis (Figure 19).

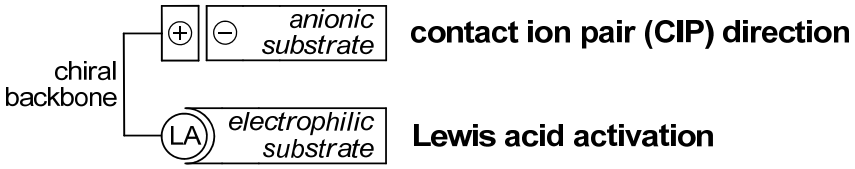
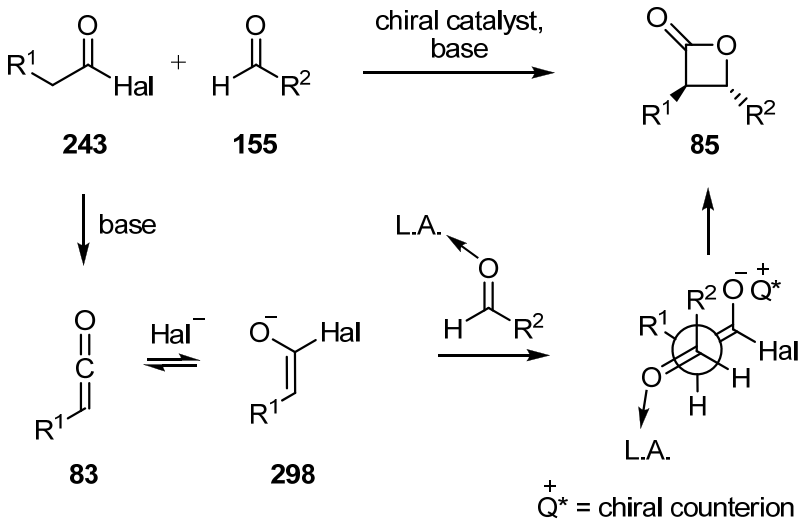


Figure 19. The concept of CIP directed *Lewis* acid catalysis.

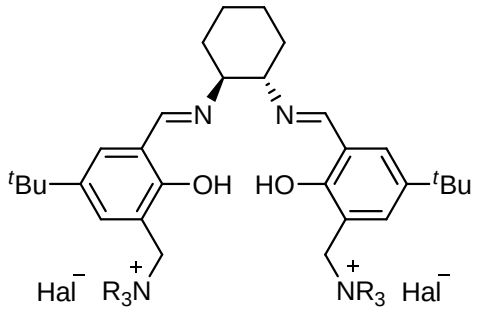
As already outlined in Chapter 7 (Background) the development of a *trans*-selective catalytic asymmetric [2+2] cyclocondensation of acyl halides **243** and aliphatic aldehydes **155** might be achieved if enolate **298**, and not ketene **83**, represents the reactive intermediate (Scheme 101). A possible way to achieve this goal could be the use of a catalyst that includes a *Lewis* acid (L.A.) moiety for aldehyde activation and a positively charged aprotic functionality (Q^{*+}) within the ligand system which could direct the anionic enolate by formation of a contact ion pair (CIP). The enolate could then undergo an enantioselective aldol addition to the aldehyde which is activated by complexation to the chiral monocoordinating *Lewis* acid. The key aspect being that the enolate could react faster than the ketene intermediate **83** itself. Since this preference is usually not observed, the instable enolate would have to be generated in the catalyst sphere, by attack of the halide counteranion to the ketene intermediate, as well as stabilized by the contact ion pair formation with the aprotic cationic functionalty Q^{*+}.



Scheme 101. Working hypothesis for the *trans*-selective formation of β-lactones (L.A. = *Lewis* acid).

The resulting acyl halide alcoholate could then cyclize to form the thermodynamically more stable *trans*-configured product.

As a ligand system **299** capable to contact ion pair (CIP) formation, quaternary ammonium moieties could, e.g., be utilized.

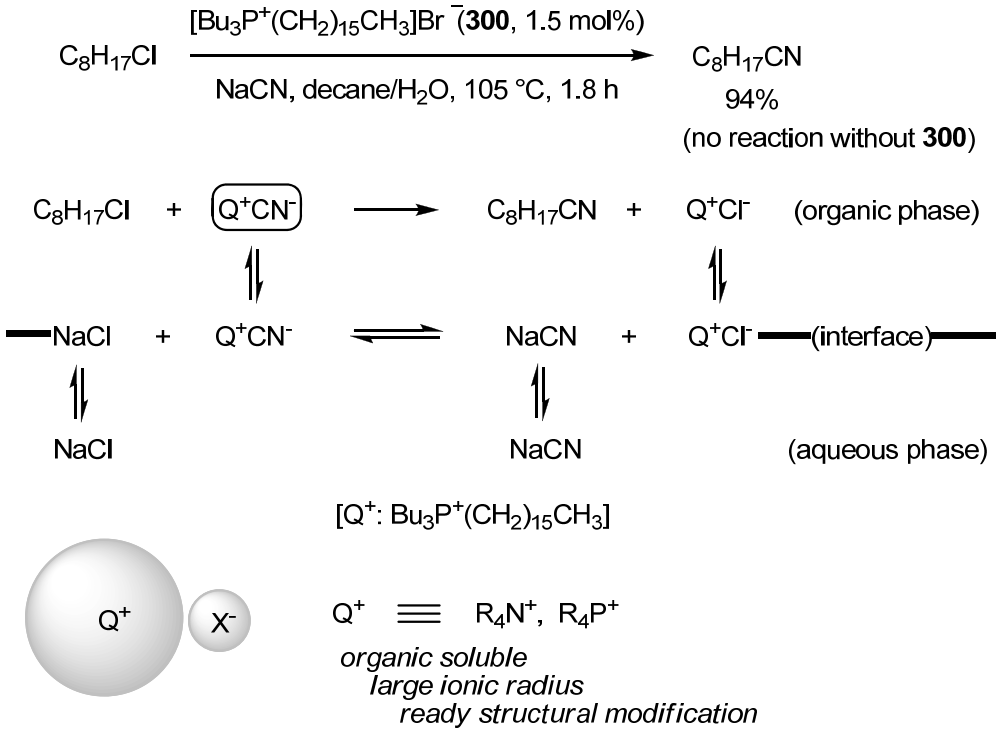


299 R = alkyl

In contrast to the charged aprotic functionality, protic cations might quench either the anionic nucleophile or the *Lewis* acid after deprotonation by a base which is required to generate the enolate intermediate.[157] The new concept would thus have the principal advantage – as compared to a bifunctional *Lewis* acid/*Lewis* base catalyst[136,148b] – that the cationic functionality does not deactivate the *Lewis* acid by a self-quenching process and the strategy would implement a cooperative combination of the two concepts of phase transfer catalysis[160c,d] (PTC) and *Lewis* acid catalysis.

9.2 General Aspects of Phase Transfer Catalysis

In 1971, *Starks* introduced the term "phase transfer catalysis" to explain the critical role of tetraalkylammonium or phosphonium salts (Q^+X^-) in the reactions between two substances located in different immiscible phases.[158] For example, the displacement reaction of 1-chlorooctane with aqueous sodium cyanide is accelerated many thousandfold by the addition of hexadecyltributylphosphonium bromide (**300**) as a phase transfer catalyst (Scheme 102). Key to this tremendous enhancement in reactivity is the generation of aquaternary phosphonium cyanide, which makes the cyanide anion soluble in organic solvents and sufficiently nucleophilic. The high rate of displacement is mainly attributed to two of the three characteristic features of the pairing cation (Q^+): high lipophilicity and the large ionic radius, both resulting in an almost naked nucleophile (see Scheme 102).



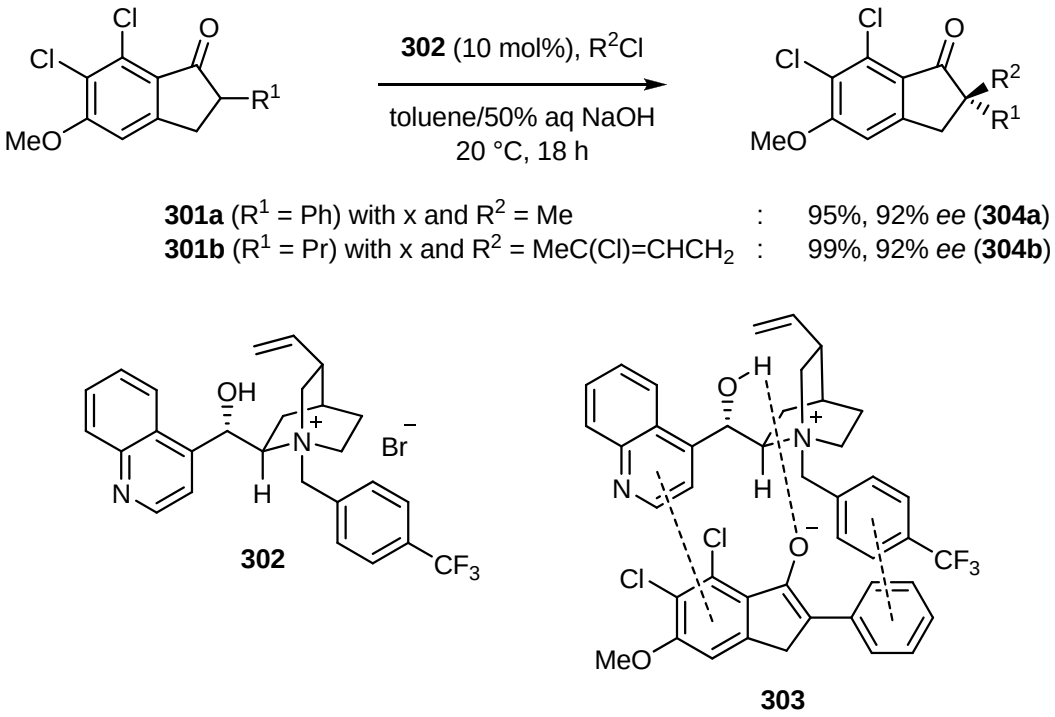
Scheme 102

Although it was not the first observation of the catalytic activity of quaternary onium salts,[159] the foundations of phase transfer catalysis were laid by *Starks* together with *Makosza* and *Brändström* in the mid to late 1960s. Since then, phase transfer catalysis as a practical methodology for organic synthesis has seen an exponential growth. The advantages of this method are its simple experimental procedures, mild reaction conditions, inexpensive and

environmentally benign reagents and solvents, and the possibility of conducting large-scale preparations.

On the other hand, the development of asymmetric phase transfer catalysis based on the use of structurally well-defined chiral, non-racemic catalysts has progressed rather slowly, despite its potential to create a new area of asymmetric catalysis by taking full advantage of structurally and stereochemically modifiable tetraalkyl onium ions (Q^+). However, recent efforts toward this direction have resulted in notable achievements, thus permitting to perform various bond-forming reactions under the mild conditions typically used in phase-transfer catalysis. In this introduction only a few examples out of the wide field of asymmetric phase transfer catalysis will be provided. More information about the topic can be found in several reviews.[160]

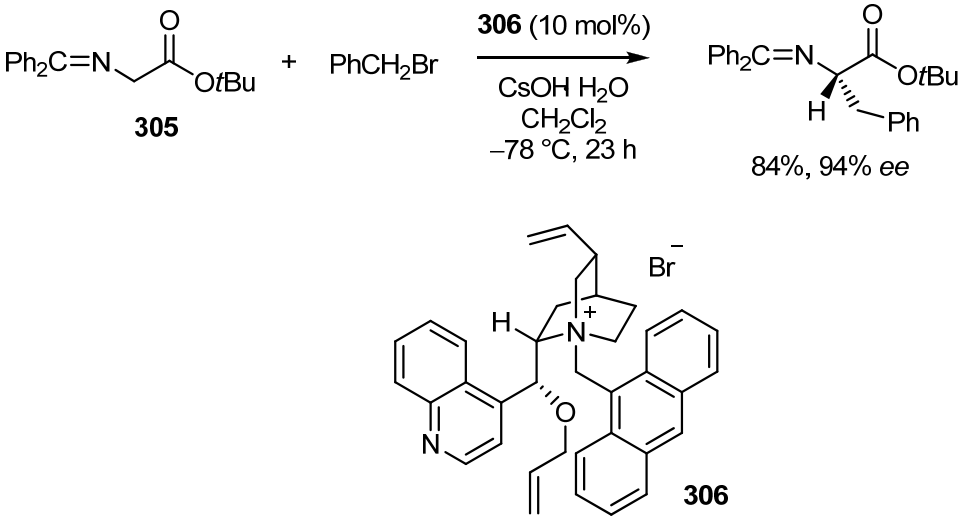
The enantioselective alkylation of active methylene compounds occupies the central position in the field of asymmetric phase transfer catalysis, and its development was triggered by the pioneering work of a *Merck* research group in 1984.[161] *Dolling* and co-workers utilized the cinchonine-derived quaternary ammonium salts **302** as catalyst for the methylation of phenylindanone derivative **301** under phase transfer conditions (toluene/50% aq NaOH solution) and succeeded in obtaining the corresponding alkylated product **304** in excellent yield and high enantiomeric excess (Scheme 103).[162] The authors made systematic studies of this reaction, and proposed the tight ion pair intermediate **303**, formed through hydrogen bonding as well as electrostatic and π-π stacking interactions, to account for the result. To confirm that the formation of an ion pair is essential, the CF_3-substituent on the *N*-benzyl group was changed for substituents (CH_3O, CH_3, F, Cl) with less electron-withdrawing power. And indeed, with these substituents lower *ee*'s in the range of 60-80% were obtained.



301a (R^1 = Ph) with x and R^2 = Me : 95%, 92% *ee* (**304a**)
301b (R^1 = Pr) with x and R^2 = MeC(Cl)=CHCH$_2$: 99%, 92% *ee* (**304b**)

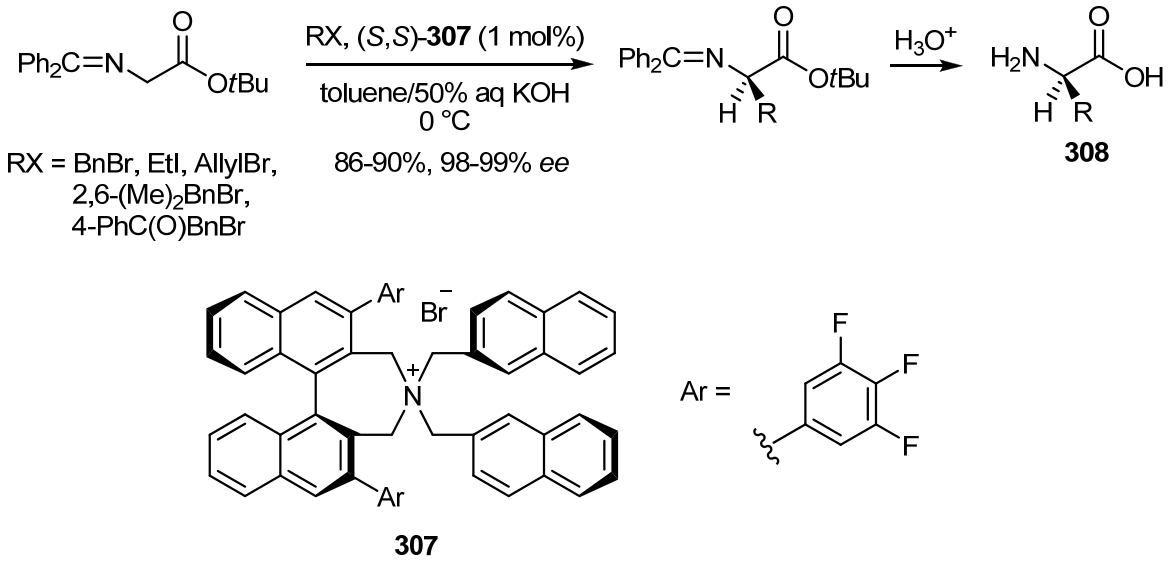
Scheme 103. Asymmetric phase-transfer-catalyzed alkylation of indanone derivatives.

A new class of cinchona alkaloid derived catalysts bearing an *N*-anthracenylmethyl group have opened up a new era of asymmetric phase-transfer catalysis. In 1997 *Corey* and co-workers prepared *O*-allyl-*N*-anthracenylmethyl cinchonidium salt **306**.[163] By using solid cesium hydroxide monohydrate (CsOH·H2O) at very low temperature, they achieved a high asymmetric induction in the enantioselective alkylation of **305** (Scheme 104).



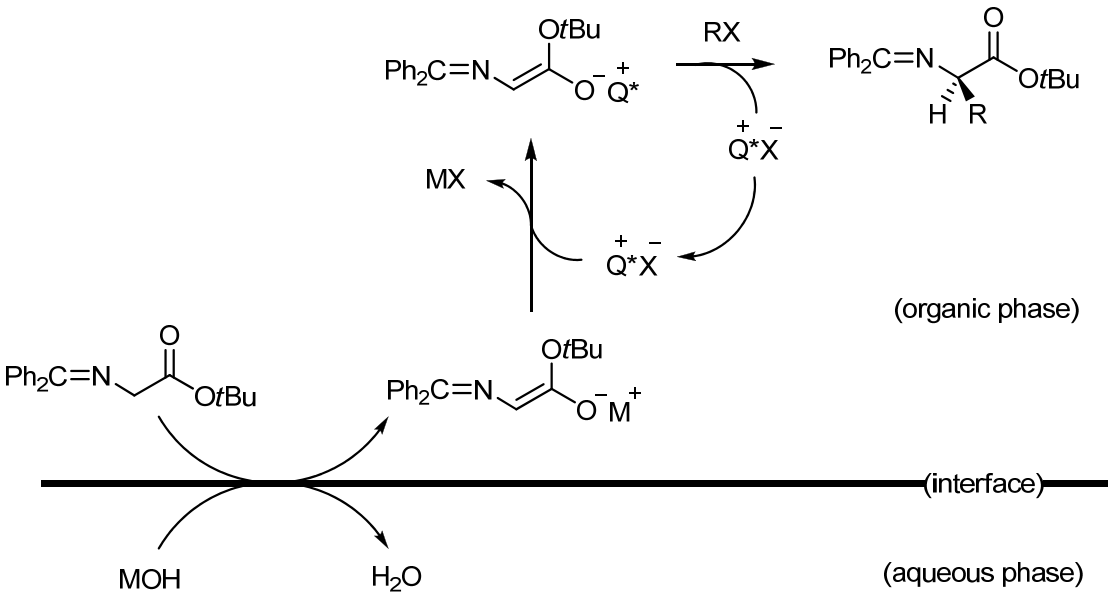
Scheme 104

While most applications of asymmetric PTC rely on inexpensive cinchona alkaloid derived ammonium salts which, however, offer only limited room for structural modification and optimization, *Maruoka* and co-workers prepared the structurally rigid, chiral spiroammonium salt **307**, derived from commercially available (*S*)-1,1'-bi-2-naphthol in five steps, as a new C_2-symmetric phase transfer catalyst and successfully applied it to the preparation of a variety of essential α-amino acids **308** (Scheme 105).[164]



Scheme 105

In general the phase transfer catalysis is only succesful if the chiral onium cation can lead to the generation of highly reactive chiral onium enolates through sufficiently fast ion-exchange and effective shielding of one of the two enantiotopic faces of the enolate anion (Scheme 106). The former minimizes the intervention of the direct alkylation of metal enolate to give racemic product, and the latter controls the absolute stereochemistry. Side reactions like saponification can be prevented by appropriate choice of protecting groups.



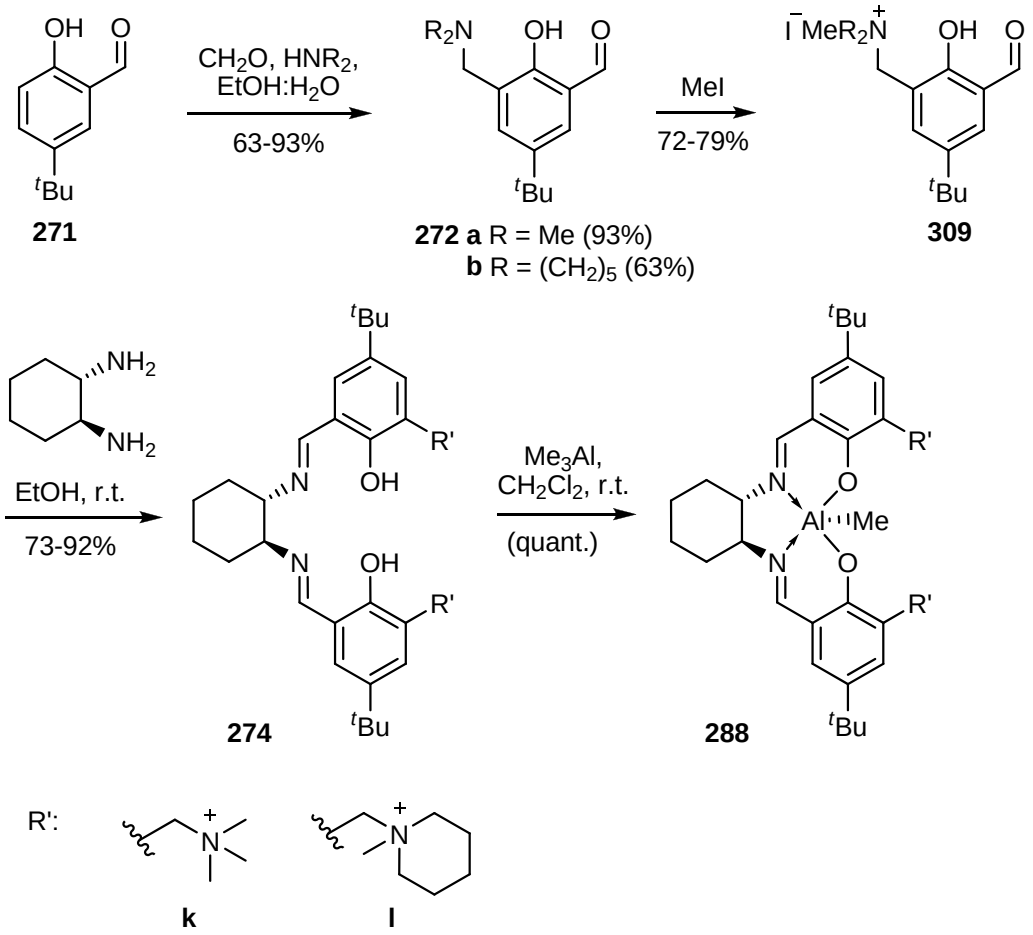
Scheme 106

9.3 Development of a *trans*-Selective Catalyst

9.3.1 Ligand Synthesis

9.3.1.1 Formation of Ammonium Ligands ***274 k-l***

To establish proof of principle, salen ligands were again selected. As mentioned above, salen ligands are often readily available from salicylaldehyde derivatives and diamines and are typically air-stable crystalline solids. Enantiopure dicationic Al-salene[155b,165] complexes **288** can be synthesized in only four steps, starting from the commercially available salicylaldehyde (**271**) (Scheme 107).[143] A *Mannich* reaction of **207** with imoniums generated *in situ* from formaldehyde and a secondary amine provides amino aldehyde **272**, which is then reacted with methyl iodide leading to the ammonium functionalized aldehyde **309**. Subsequent condensation with (*S,S*)-cyclohexanediamine, followed by complexation with Me_3Al, gives rise to complex **288**.



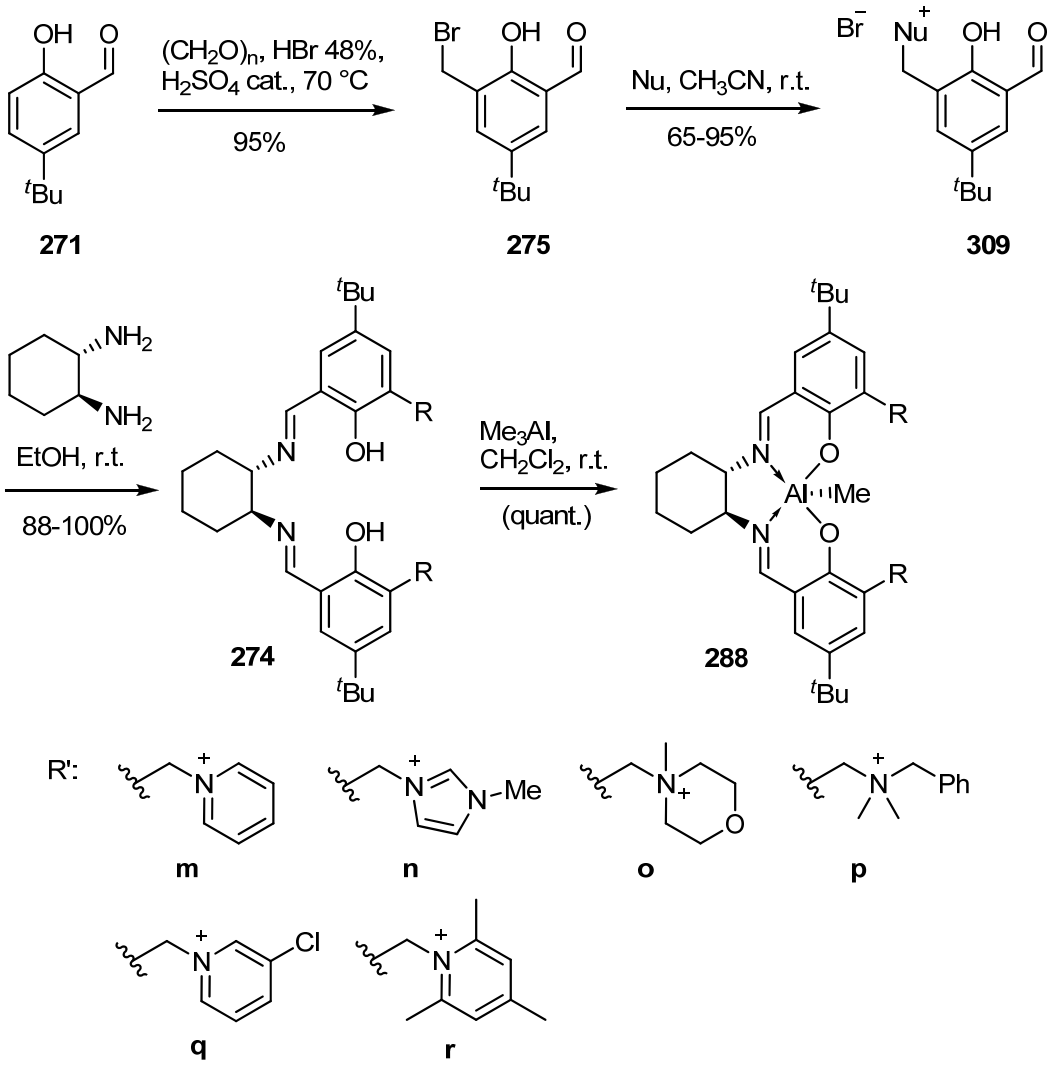
Aldehyde **309**	Yield [%]	Ligand **274**	Yield [%]
k	79	**a**	92
l	72	**d**	73

Scheme 107. Formation of Al-salen complexes **288**.

*9.2.1.1 Formation of Ligands **274 m-r***

In addition to the cationic ammonium ligands **274 k-l** attempts were made to synthesize ligands **274 m-n** and **q-r** bearing *N*-heterocyclic functionalities. Al-salene complexes **274 m-r** can be conveniently synthesized in four steps, starting from the commercially available salicylaldehyde (**271**) (Scheme 108). Reaction with paraformaldehyde in aqueous HBr provided bromomethyl aldehyde **275** in high yield, which was then reacted with the corresponding nucleophile. The nucleophilic substitution worked well with all nucleophiles (see Table in Scheme 108), whereas the following condensation step with (*S,S*)-cyclohexanediamine worked only well for substrates **274 m-p** but proofed to be problematic for **274 q-r**.

Condensation with **309 q-r** led to substantial amounts of side products probably due to the tendency of electron poor pyridine derivatives to undergo nucleophilic aromatic substitution or addition reactions. The synthesis and the purification of the complex product mixtures were not further optimized in these cases.

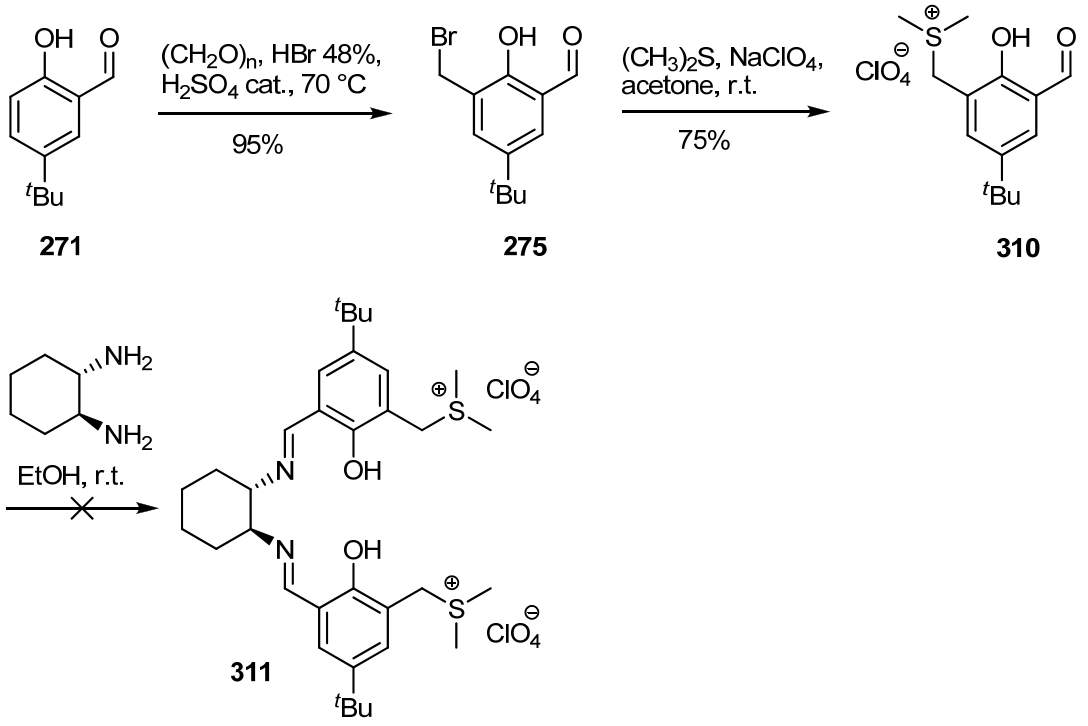


Aldehyde **309**	Nu	Yield [%]	Ligand **274**	Yield [%]
m	pyridine	92	**m**	quant.
n	1-methylimidazole	86	**n**	quant.
o	*N*-methylmorpholine	95	**o**	88
p	*N*,*N*-dimethylbenzylamine	87	**p**	91
q	3-chloropyridine	90	**q**	not isolated
r	2,4,6-trimethylpyridine	65	**r**	not isolated

Scheme 108. Formation of catalyst **288**.

9.2.1.2 Attempts to Form Sulfonium Ligand ***311***

Treating bromomethyl aldehyde **275** with dimethylsulfide gave very little amounts of sulfonium aldehyde **310** (yield < 20%) (Scheme 109). As the bromide is as well a good nucleophile the equilibrium was apparently mainly on the side of the starting material. Conducting the nucleophilic substitution in acetone in the presence of sodium perchlorate improved the outcome significantly because of the low solubility of sodium bromide. However, the following condensation with (*S,S*)-cyclohexanediamine failed since the sulfonium moiety was too prone to nucleophilic substitution reactions and therefore a lot of side products were obtained. The reaction or purification of the complex product mixture was not further optimized.



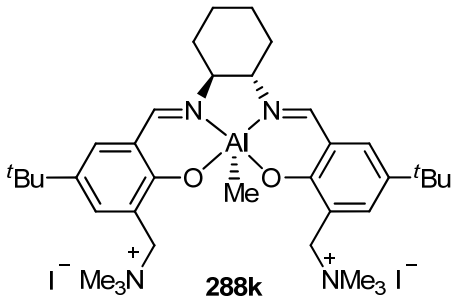
Scheme 109. Formation of sulfonium ligand **311**.

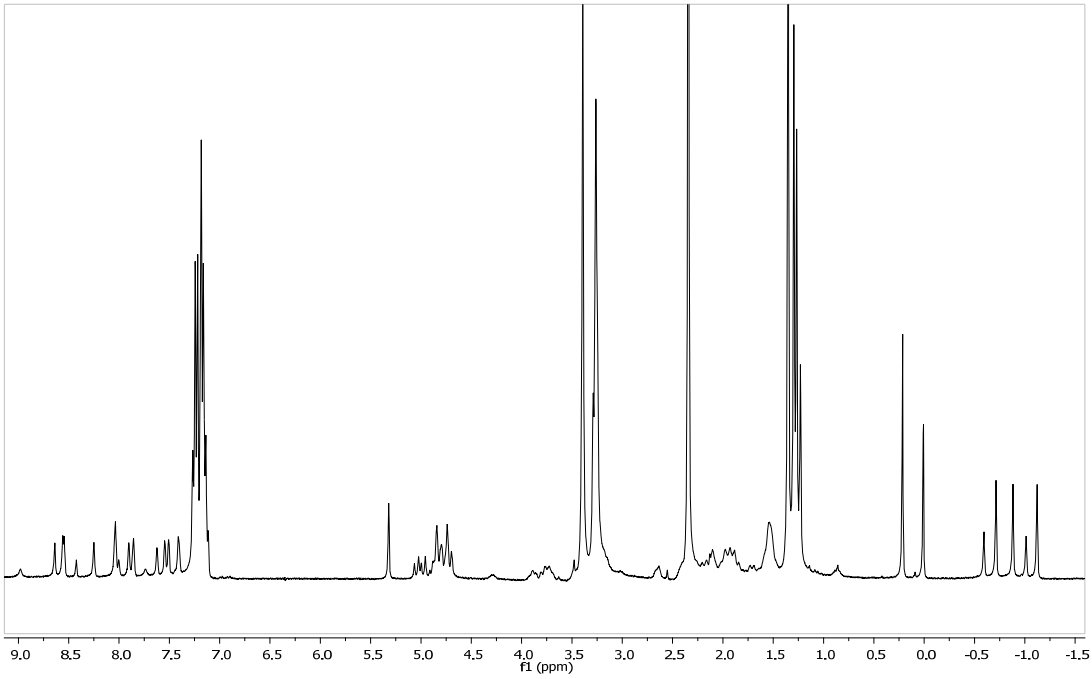
9.3.2 NMR Studies on the Formation of the Catalyst

In order to obtain more detailed information about the complex formation, ^{1}H-NMR experiments were conducted. In a typical procedure the NMR tube was charged with ligand **274k** under nitrogen and CD_2Cl_2 was added. The solution was then treated with Me_3Al (2M in toluene) and the sample was analyzed in distinct intervals.

Spectrum 7 was measured after 15 min and shows that complexation to form a uniform species of the catalyst is not yet complete.

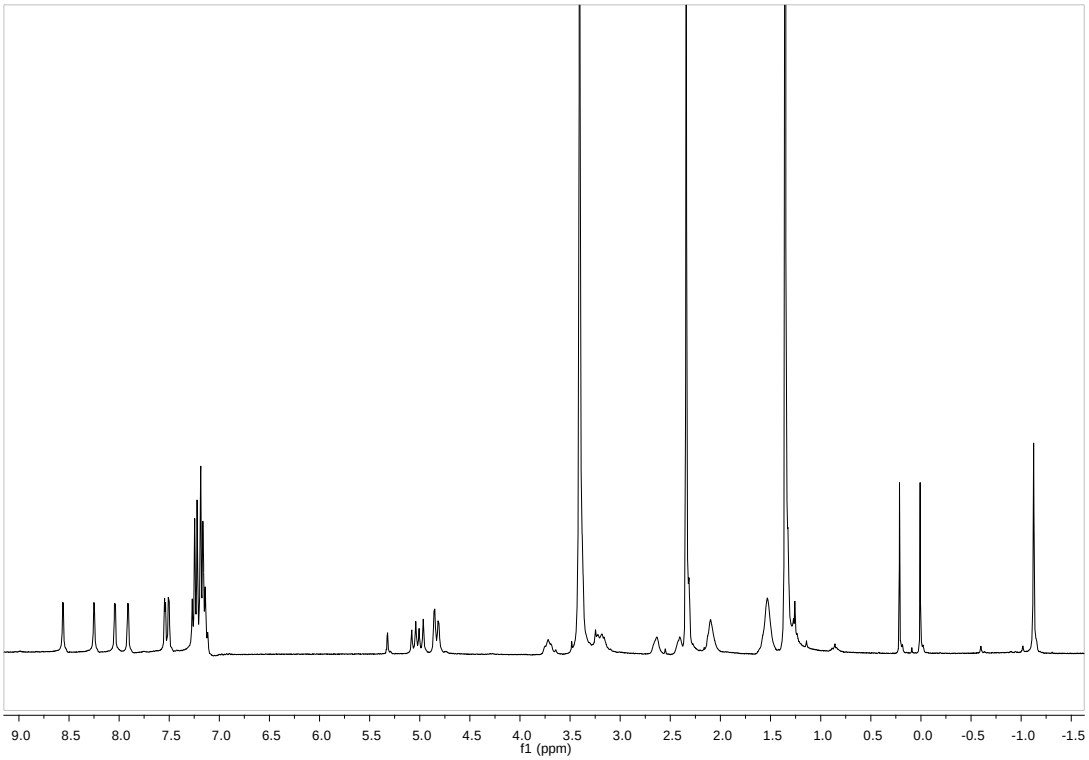
Spectrum 7. Complexation 15 min after addition of Me_3Al (300 MHz, 21 °C).





Spectrum 8 was measured 3 h after the addition of Me_3Al indicating complete conversion. After 24 h, no changes could be observed. Therefore, for all subsequent experiments, if not otherwise indicated, the catalyst was consequently formed for 3 h at 23 °C.

Spectrum 8. Complex **288k** 3 h after addition of Me_3Al (300 MHz, 21 °C).

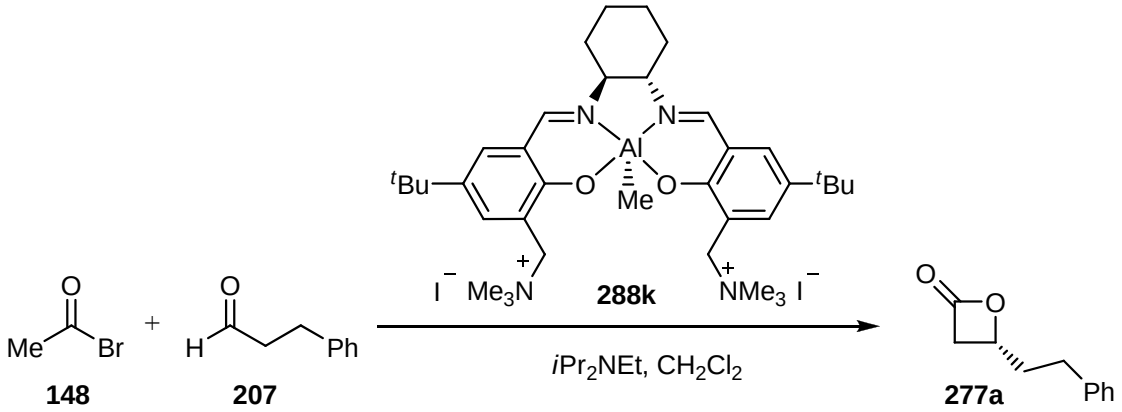


9.3.3 Studies with Unsubstituted Ketene

9.3.3.1 Influence of the Aldehyde Concentration

The model reaction of acetyl bromide and dihydrocinnamaldehyde catalyzed by the readily available bistrimethylammonium system **288k** was investigated at different aldehyde concentrations at −60 °C revealing an only marginal dependency of reaction rate as well as selectivity on the concentration (Table 59, entries 1 to 4). Further decreasing the temperature provided the best results at a standard concentration of 0.25 mol/L, but the differences are again only minute (entries 5 to 7).

Table 59. Influence of the aldehyde concentration on yield and selectivity.[a]



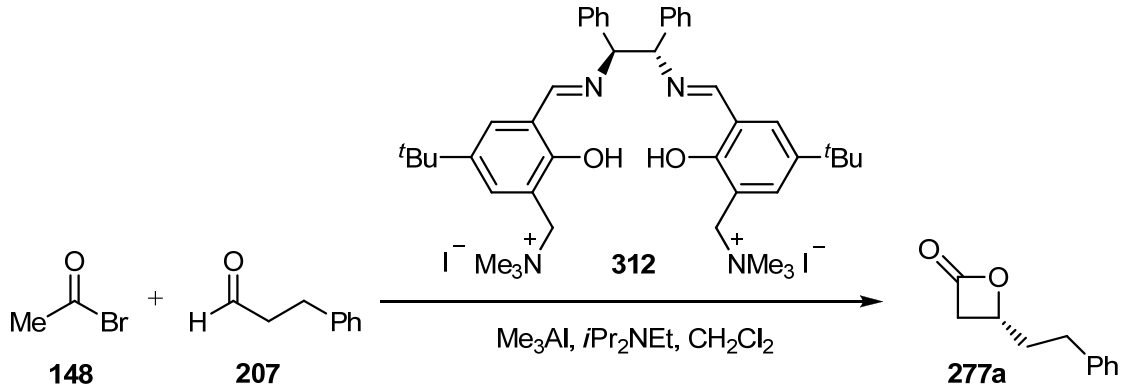
Entry	Conc. [mol/L]	Temp. [°C]	Time [h]	Conversion [%]	Yield [%]	*ee*[b] [%]
1	0.50	−60	4	94	65	64
2	0.40	−60	4	93	64	64
2	0.33	−60	4	95	67	63
3	0.25	−60	4	92	66	64
4	0.50	−85	24	38	28	82
5	0.25	−85	25	39	32	84
6	0.17	−85	25	30	25	82

[a] All reactions were performed with 10 mol% of the ligand and the aluminum source at –60 °C. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] *ee* determined by HPLC on a chiral support.

9.3.3.2 Studies with Ligand 312

Compared to cyclohexane-1,2-diamine derived ligand **274**, reactions with ligand **312** possessing a 1,2-diphenyl ethylene-1,2-diamine backbone resulted in inferior enantioselectivity and therefore no further studies with this system were conducted (Table 60).

Table 60. Studies with ligand **312**.[a]



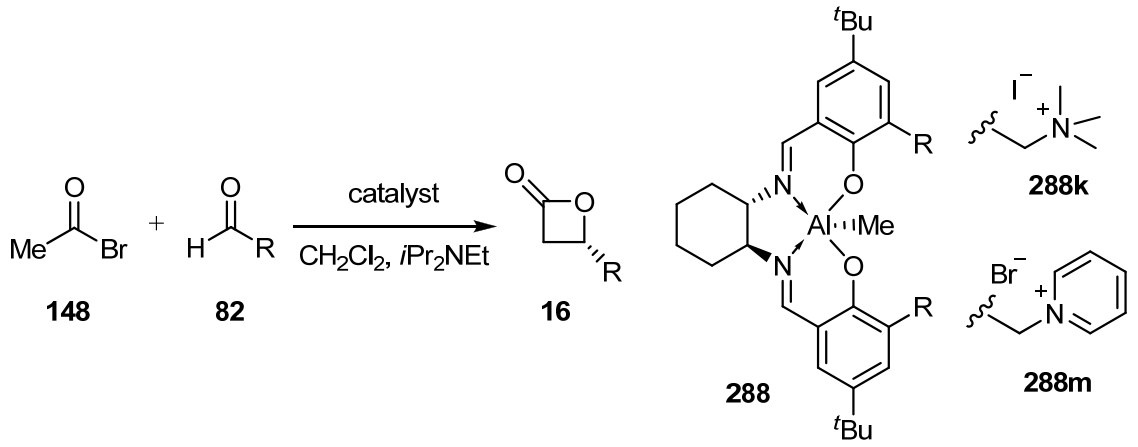
Entry	Backbone	Temp. [°C]	Time [h]	Conversion [%]	Yield [%]	*ee*[b] [%]
1	cyclohexyl	−85	24	38	28	82
2	1,2-diphenyl	−85	24	22	16	43

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and the aluminum source. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 10 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] *ee* determined by HPLC on a chiral support.

9.3.3.3 Influence of the Temperature

At −20 °C catalyst **288a** furnished β-lactone **16** with moderate enantioselectivity (50% *ee*) and, although full conversion was noticed, only a moderate yield was obtained (62%, Table 61, entry 1). Therefore, to attain synthetically useful enantioselectivities, the reaction temperature had to be further decreased. While at −70 °C the selectivity could be increased to moderate 70% *ee* (entry 2), the reaction at −85 °C led to good 82% *ee* (entry 3). Unfortunately, at such a low temperature the β-lactone formation proceeded very slowly, probably because of the poor solubility of catalyst **288a**. With bispyridinium catalyst **288b** at −85 °C, neither yield (28%) nor selectivity (81% *ee*) were largely influenced (entry 4). In contrast, the α-branched cyclohexylcarboxaldehyde furnished product **16** with high enantioselectivity (88% *ee*) and good yield (82%, entry 5), even at −40 °C.

Table 61. Influence of the temperature.[a]



Entry	Catalyst 288	R	Temp. [°C]	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]
1	**k**	CH_2CH_2Ph	−20	2	100	62	50
2	**k**	CH_2CH_2Ph	−70	22	93	76	70
3	**k**	CH_2CH_2Ph	−85	25	30	25	82
4	**m**	CH_2CH_2Ph	−85	24	35	28	81
5	**m**	$^cC_6H_{11}$	−40	21	89	82[d]	88

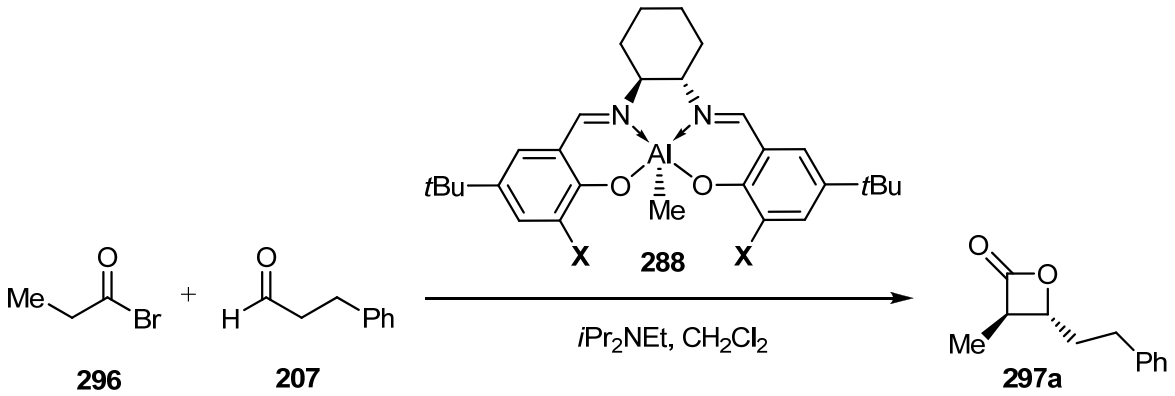
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and the aluminum source. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. AcBr and 2.5 equiv. *Hünig*'s base. [b] Yield after aqueous workup determined by ^{1}H NMR using acetophenone as an internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Yield of isolated product.

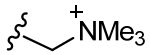
9.3.4 Studies with Substituted Ketenes: *Trans*-Selective Catalytic Asymmetric Synthesis of β-Lactones

9.3.4.1 Proof of Concept

To establish proof of principle complexes **288** with different substituents **X** in the 6-position of the phenol ring were chosen (Table 62). The most simple catalyst system **288b** with X = H produced β-lactone **297a** with moderate *cis*-selectivity in almost racemic form (entry 1). For the more bulky salen **288c** carrying isobutyl substituents (entry 2), both reduced reactivity and *cis*-selectivity were noted, while *tert*-butyl substituents in **288a** completely impeded any product formation (entry 3), presumably for steric reasons. In contrast, catalyst **288k** possessing a positively charged ammonium substituent at the phenol 6-position led to enhanced reactivity (entry 4). Moreover, the enantioselectivity was significantly improved with an inverted absolute configuration for the major enantiomer.

Table 62. Development of a contact ion pair / *Lewis* acid catalyst.[a]



Entry	288	Temp. [°C]	Time [h]	Yield[b] [%]	*ee*[c] [%]	*trans*/*cis*[d]
1	H	−20	2	42	12	21 : 79
2	*i*Bu	−20	2	28	-23	25 : 75
3	*t*Bu	−20	2	0	-	-
4		−20	2	59	59	91 : 9

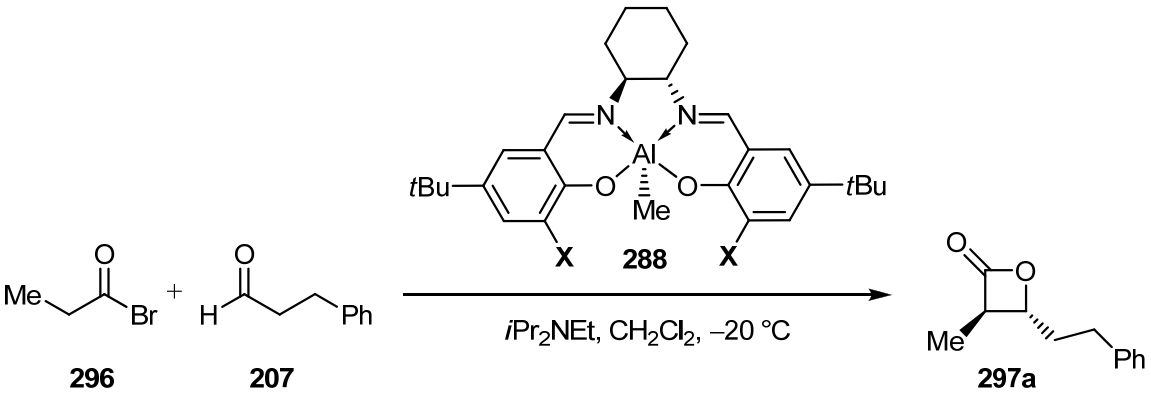
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and the aluminum source. The catalysts were preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Ratio determined by ^{1}H NMR spectroscopy.

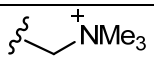
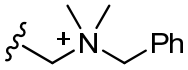
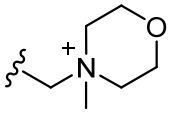
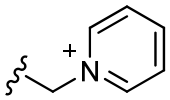
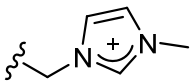
9.3.4.2 Ligand Screening

For a further catalyst screening complexes **288** differing in the substituents X at the 6-position of the phenol rings were chosen (Table 63). To compare the effect of the substituents X, the reactions presented in Table 63 were performed in DCM at −20 °C and stopped after 2 h, if not indicated otherwise.

All catalysts **288** with cationic ammonium or heterocyclic functionalities provided high *trans*-selectivities (entries 1-5). As a general trend, the enantioselectivity was slightly reduced with increased steric bulk of the cationic moiety. The planar pyridinium system **288m** possessing an sp^2-N was the most selective catalyst so far. This might be explained by a more efficient contact ion pair formation as compared to ammonium functionalities. Imidazolium derivative **288n**, in which the positive charge is delocalized over two N-atoms, led to significantly lower enantio- and diastereoselectivity as a consequence of a less stable contact ion pair due to a wider charge distribution.

Table 63. Development of a contact ion pair / *Lewis* acid catalyst.[a]



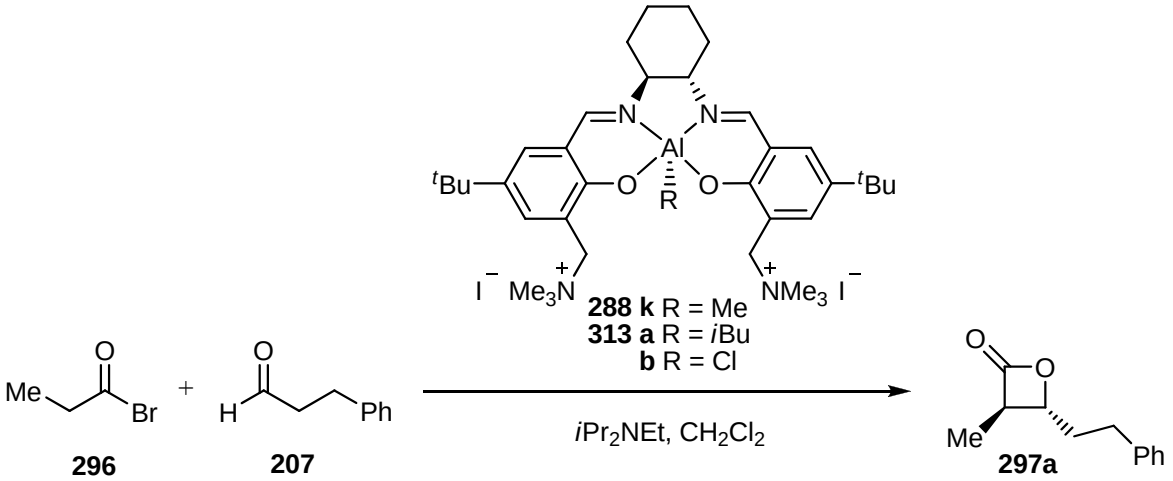
Entry	X	Time [h]	Yield[b] [%]	*ee*[c] [%]	*trans*/*cis*[d]
1		2	59	59	91 : 9
2		2	68	40	85 : 15
3		2	69	50	92 : 8
4		2	65	66	90 : 10
5		2	51	60	86 : 14

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and the aluminum source at –20 °C for 24 h. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Ratio determined by ^{1}H NMR spectroscopy.

9.3.4.3 Influence of the Aluminum Source

For initial studies the complex was preformed with different aluminum sources for 3 h at ambient temperatures (Table 64, entries 1 and 2). Attempts to form the catalyst with Et_2AlCl failed because shortly after addition of a solution of the Al source (1 M in hexane) a precipitation of the catalyst occurred. The best result for the model reaction with dihydrocinnamaldehyde (**207**) was obtained with Me_3Al (60% *ee*, entry 1). Dibal (30% *ee*, entry 2) led to an inferior enantioselectivity. With both Me_3Al (95%, entry 1) and Dibal (93%, entry 2) conversions were almost identical.

Table 64. Influence of the aluminum source.[a]



296 207 297a

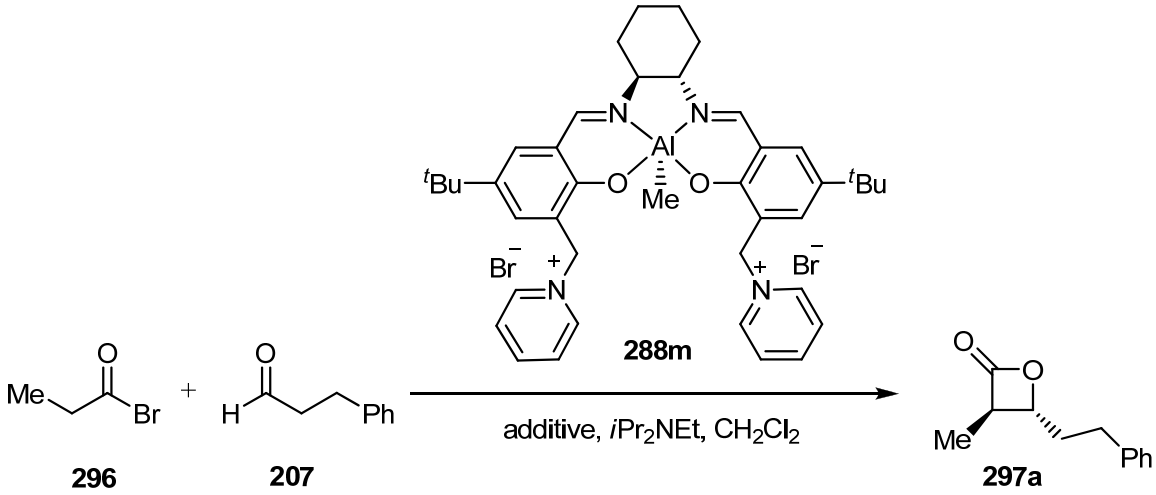
Entry	Al source	Temp. [°C]	Time [h]	Conversion [%]	Yield [%]	*ee*[b] [%]
1	Me_3Al	−20	2	95	75	60
2	Dibal	−20	2	93	73	30

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and the aluminum source. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] *ee* determined by HPLC on a chiral support.

9.3.4.4 Influence of an Increased Nucleophile Concentration

Assuming that an increased nucleophile concentration might also increase the concentration of the enolate, an additional amount of different ammonium halide salts was added (Table 65). Compared to the standard reaction (entry 1), with tetrabutylammonium bromide (TBABr) as nucleophilic additive (entry 2) the yield slightly dropped while the enantioselectivity remained identical. In contrast, with tetrabutylammonium iodide (TBAI) lower values in terms of both yield and enantioselectivity were obtained (entry 3). These results indicate that the reacting enolate is probably generated directly in the catalyst sphere by attack of the catalyst's halide counteranion to the ketene. Therefore, additional amounts of halide salts would just increase the chance that the moisture sensitive catalyst is partially quenched or inhibited by halide coordination.

Table 65. Influence of an increased nucleophile concentration.[a]



Entry	Nucleophile source	Temp. [°C]	Time [h]	Conversion [%]	Yield [%]	*ee*[b] [%]
1	-	−70	44	73	67	86
2	TBABr (1 equiv.)	−70	44	62	60	86
3	TBAI (1 equiv.)	–70	44	56	46	83

TBABr = tetrabutylammonium bromide; TBAI = tetrabutylammonium iodide

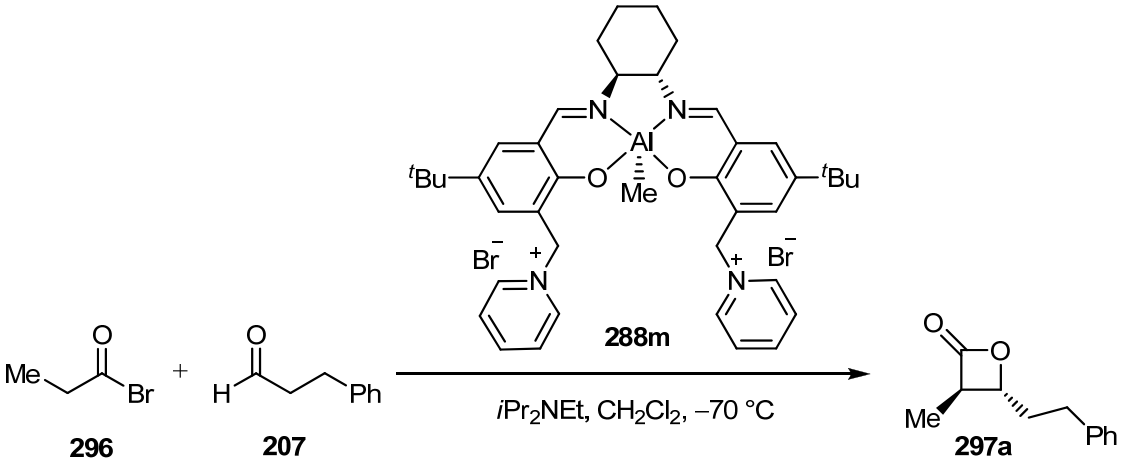
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and Me_3Al as the aluminum source. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] *ee* determined by HPLC on a chiral support.

9.3.4.5 Attempts to Increase the Yield of the Model Reaction

The best yield obtained so far for the model reaction with ligand **288m** at –70 °C was 67% at a rather low conversion of 73% (Table 66, entry 1). By an extended reaction time of more than 5 days selectivity and yield decreased (entry 2). To determine if the ketene intermediate decomposes thus stopping the reaction after more or less one day, propionyl bromide and base were added in two portions (entries 3 and 4). The second portion of acid bromide and base was added after 24 h. Although the conversion was higher (80 and 88%) the reactions led to reduced selectivities and yields.

Another explanation for the moderate yields could be decomposition of the catalyst. However, an experiment where an additional amount of the catalyst (10 mol%) was added after 25 h (entry 5) led to similar results as obtained for the standard reaction (entry 1).

Table 66. Catalyst formation.[a]

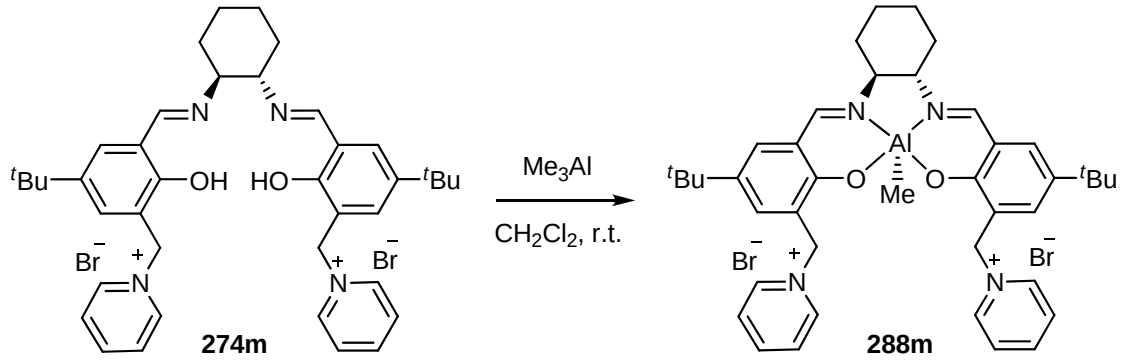


Entry	Bromide (equiv.)	Base (equiv.)	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]	*trans*/*cis*[d]
1	6	2.5	44	73	67	86	95 : 5
2	6	2.5	138	67	41	79	90 : 10
3	4+2	1.5+1	48	80	58	83	92 : 8
4	6+4	2.5+1.5	48	88	56	80	93 : 7
5	6	2.5	40	74	59	86	93 : 7

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and Me_3Al as the aluminum source at –70 °C. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ*. [b] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Ratio determined by ^{1}H NMR spectroscopy.

9.3.4.6 Formation of the Catalyst

So far the catalyst had been prepared *in situ* as follows: to a solution of ligand **274** (0.21 mmol) in CH_2Cl_2 (3.5 mL) a solution of Me_3Al in toluene (2 M, 0.21 mmol) was added and the mixture was stirred for 3 h at ambient temperature. The catalyst solution was then cooled to the indicated temperature and all other reagents were added subsequently (Scheme 110).

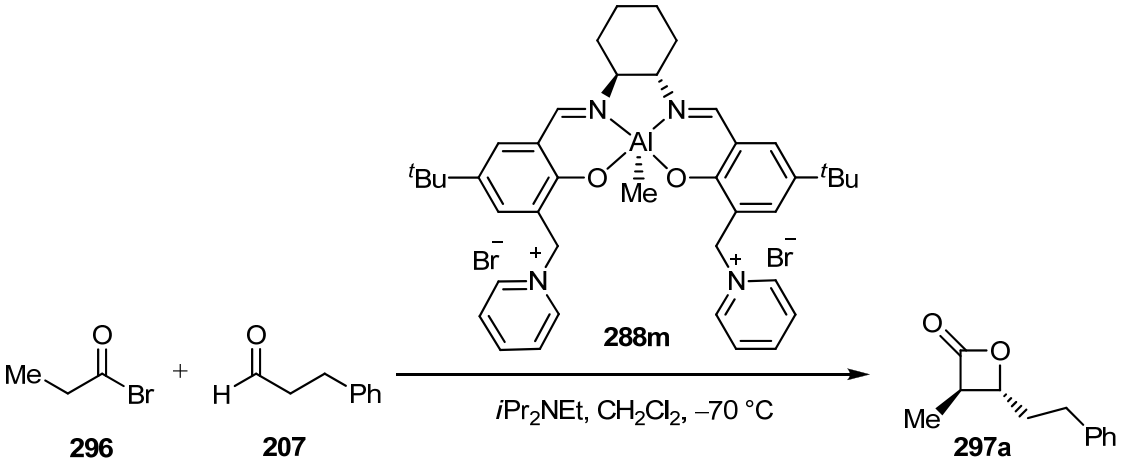


Scheme 110

For the new procedure a washing step was introduced after the complexation for 3 h (the following steps were carried out in a glove box): pentane (5 mL) was added to fully precipitate complex **288** and the mixture was filtered. Washing the filter cake with an additional amount of pentane (5 mL) and drying *in vacuo* afforded the catalyst as bright yellow powder in quantative yield.

Reactions conducted with the isolated catalyst **288m** provided not only higher selectivities but also a higher yield (Table 67, entry 2) as compared to the initial procedure (entry 1). By the washing step unreacted parts of the achiral aluminum source can be removed, which otherwise might lead to lower selectivities.

Table 67. Influence of the catalyst formation.[a]

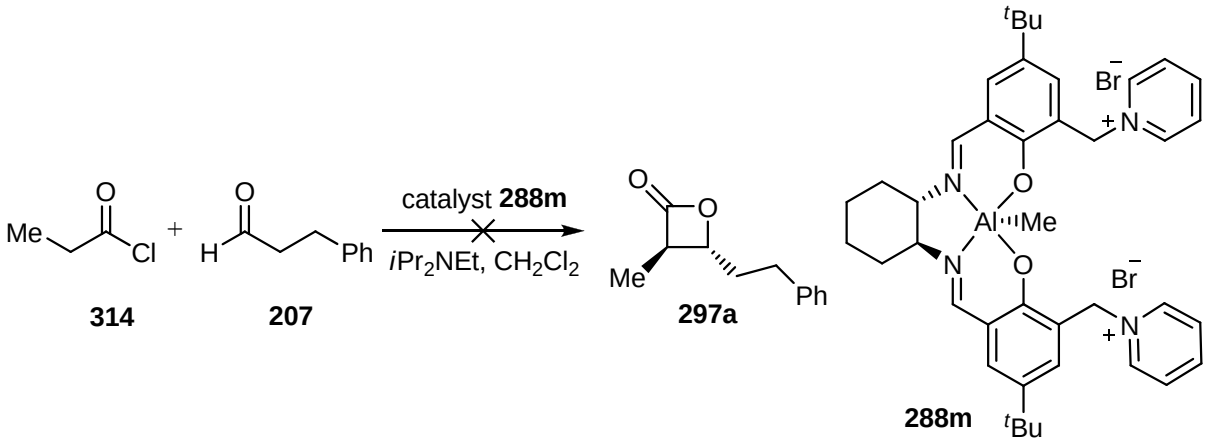


Entry	Formation procedure	Time [h]	Conversion [%]	Yield[b] [%]	*ee*[c] [%]	*trans*/*cis*[d]
1	old	24	80	63	86	95 : 5
2	new	24	89	82	88	97 : 3

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and Me_3Al as the aluminum source at −70 °C. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Ratio determined by ^{1}H NMR spectroscopy.

9.3.4.7 Influence of the Ketene Precursor

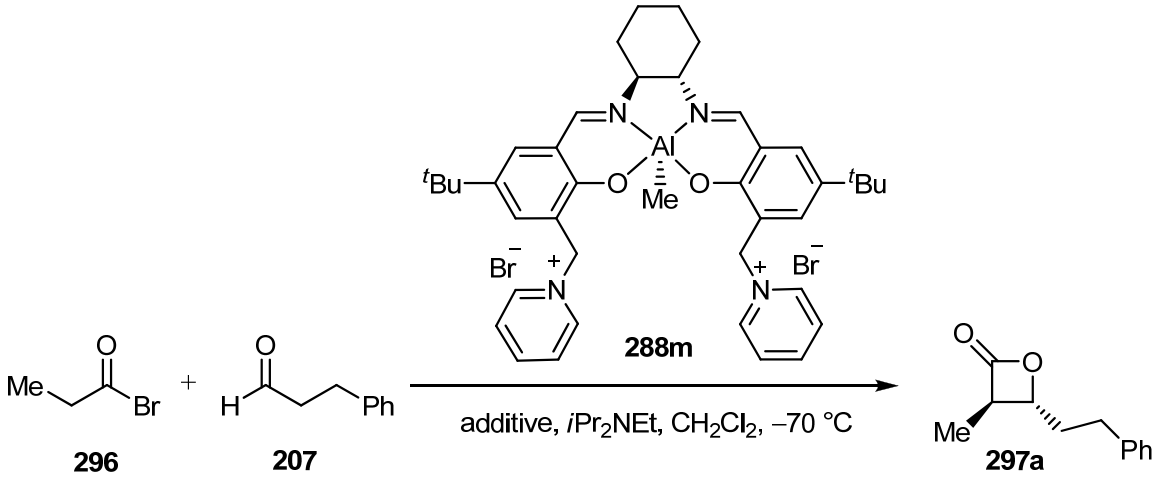
With the use of propionyl chloride instead of propionyl bromide no reaction was observed, probably because the generated chloride anion is less nucleophilic than bromide and hence less acyl halide enolate is formed as reactive intermediate (Scheme 111). Alternatively, the harder chloride might also inhibit the catalyst by coordination to the hard Al center. Interestingly, with an additional amount of tetrabutylammonium bromide (1 equiv.) still no product was provided.



Scheme 111

To test if the chloride inhibits the catalyst a reaction with propionyl bromide as ketene source and tetrabutylammonium chloride as chloride source was carried out. The procedure was as follows: to a solution of preformed catalyst **288m** (0.025 mmol) in CH_2Cl_2 (2 mL) was added at −70 °C dihydrocinnamaldehyde (0.25 mmol), propionyl bromide (1.50 mmol), *Hünig*'s base (0.625 mmol) and tetrabutylammonium chloride (0.25 mmol). Compared to the reaction without a chloride source (Table 68, entry 1) the reaction with the ammonium salt leads to a lower yield and to a slightly diminished diastereoselectivity (entry 2). This experiment supports the hypothesis that the chloride inhibits the catalyst.

Table 68. Influence of an additional chloride source.[a]



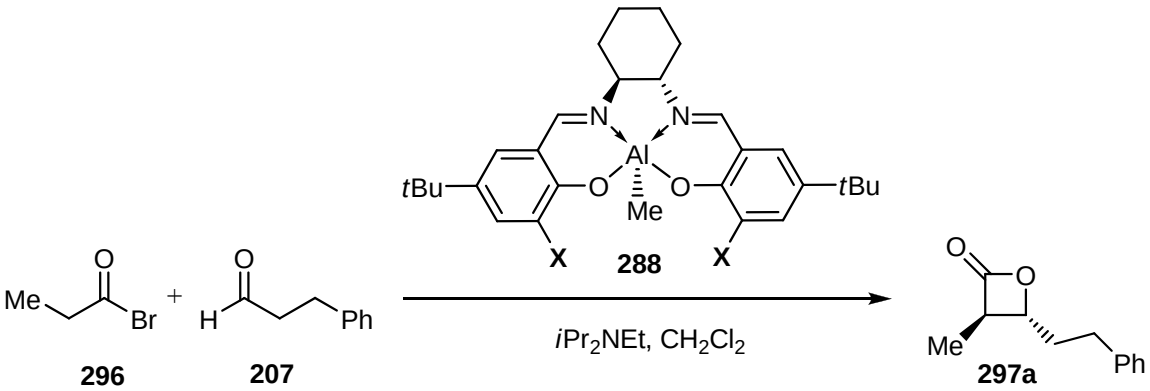
Entry	Additive	Time [h]	Yield[b] [%]	*ee*[c] [%]	*trans*/*cis*[d]
1	no additive	24	82	88	97 : 3
2	Bu_4NCl	24	60	88	95 : 5

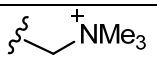
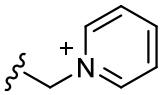
[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and the aluminum source at –70 °C for 24 h. The catalyst was preformed for 3 h at ambient temperature and isolated. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Ratio determined by ^{1}H NMR spectroscopy.

9.3.4.8 Influence of the Temperature

To attain synthetically useful enantioselectivities, the reaction temperature had to be further decreased. While the reaction catalyzed by trimethylammonium system **288k** was extremely slow at −50 °C as a result of poor catalyst solubility (Table 69, entry 2), the pyridinium catalyst **288m** is significantly more reactive (entries 3 to 5) and renders high enantio- and *trans*-selectivity (88%, 97:3) and good yield (82%) at –70 °C (entry 5).

Table 69. Influence of the temperature.[a]



Entry	X	Temp. [°C]	Time [h]	Yield[b] [%]	*ee*[c] [%]	*trans*/*cis*[d]
1		−20	2	59	59	91 : 9
2		−50	24	22	83	92 : 8
3		−20	2	65	66	90 : 10
4		−50	5	72	80	92 : 8
5		−70	24	82	88	97 : 3

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and the aluminum source. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Ratio determined by ^{1}H NMR spectroscopy.

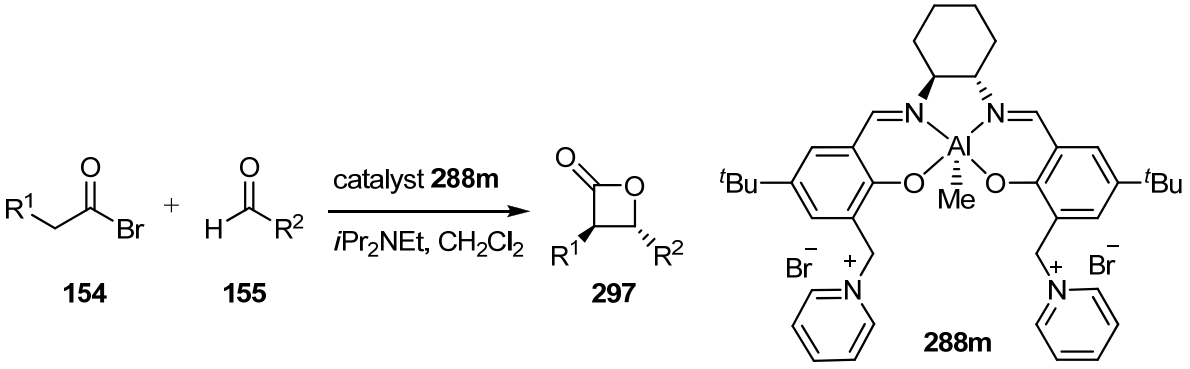
9.3.4.9 Substrate Scope

The reaction generally provided high *trans*-selectivities with aliphatic aldehydes (Table 70). The enantioselectivity did not significantly depend on the aldehyde and almost identical results were obtained with substrates possessing long aliphatic side chains (entries 2-4, 10), with or without a C=C double bond, β-branched aldehydes such as isovaleraldehyde (entries 8, 14) or sterically undemanding aldehydes like propanal, butanal or pentanal (entries 5-7, 11-13). In particular these latter results are remarkable, since high enantioselectivities have previously never been reported for very small aldehydes in alternative catalytic asymmetric cycloadditions with acylhalides or ketenes. Utilization of the α-branched aliphatic cyclohexylcarboxaldehyde afforded only very little conversion to the β-lactone at −70 °C (24% after 48 h) and a very low yield (5%, *ee* was not determined).

Therefore the temperature had to be increased to –40 °C providing the product with good selectivity (80% *ee*, *trans*/*cis* = 87:13) and yield (78%, entry 9).

Both yields and enantioselectivities were further increased with valeroylbromide as compared to propionylbromide (entries 10-15). It is expected that the corresponding ketene with a bulkier substituent is less reactive and hence a background reaction, in which the pyridinium moiety is not involved, should be less favorable employing such a larger acyl bromide.

Table 70. Substrate scope (Part A).[a]

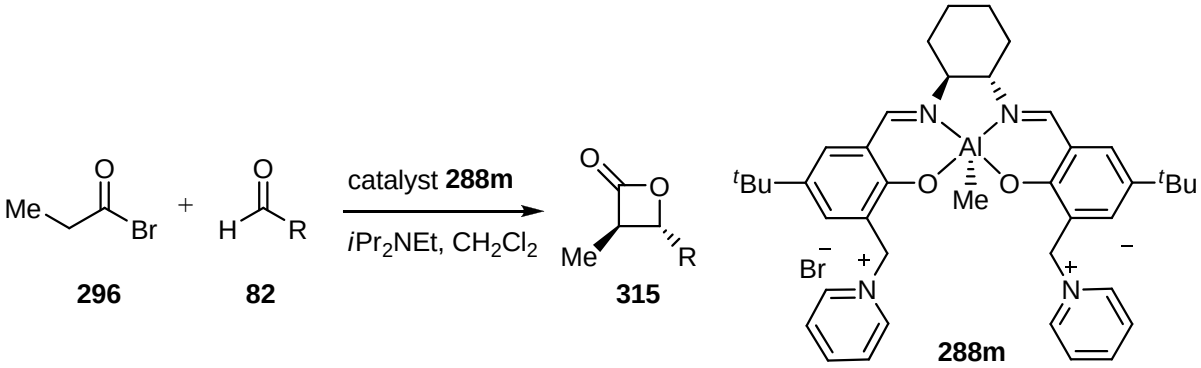


Entry	297	R^1	R^2	Yield [%][b]	*ee*[c] [%]	*trans* : *cis*[d]
1	**a**	Me	$(CH_2)_2Ph$	82[e]	88	97 : 3
2	**b**	Me	*n*Hept	77	87	96 : 4
3	**c**	Me	$(CH_2)_3CH{=}CH_2$	74[e]	88	96 : 4
4	**d**	Me	$(CH_2)_8CH{=}CH_2$	62	87	94 : 6
5	**e**	Me	Et	76[e]	87	95 : 5
6	**f**	Me	*n*Pr	67	93	97 : 3
7	**g**	Me	*n*Bu	64	89	97 : 3
8	**h**	Me	*i*Bu	76[e]	87	94 : 6
9[f]	**i**	Me	*c*Hex	78[e]	80	87 : 13
10	**j**	*n*Pr	$(CH_2)_2Ph$	91	94	98 : 2
11	**k**	*n*Pr	$(CH_2)_3CH{=}CH_2$	96	95	98 : 2
12	**l**	*n*Pr	Et	63	94	97 : 3
13	**m**	*n*Pr	*n*Pr	93	95	98 : 2
14	**n**	*n*Pr	*n*Bu	92	93	96 : 4
15	**o**	*n*Pr	*i*Bu	76	94	96 : 4

[a] All reactions were performed at a concentration *c* = 0.25 mol/L of the aldehyde with 10 mol% catalyst at –70 °C for 24 h if not indicated otherwise. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] Isolated yield. [c] *ee* determined by HPLC on a chiral support. [d] Ratio determined by ^{1}H NMR spectroscopy. [e] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [f] Reaction performed at –40 °C.

With benzaldehyde as substrate no product formation was observed at –20 °C. Other substrates like benzyloxyacetaldehyde (Table 71, entry 1), 2-octynal (entry 2) or 4-nitrobenzaldehyde led to diminished enantioselectivities.

Table 71. Substrate scope (Part B).[a]



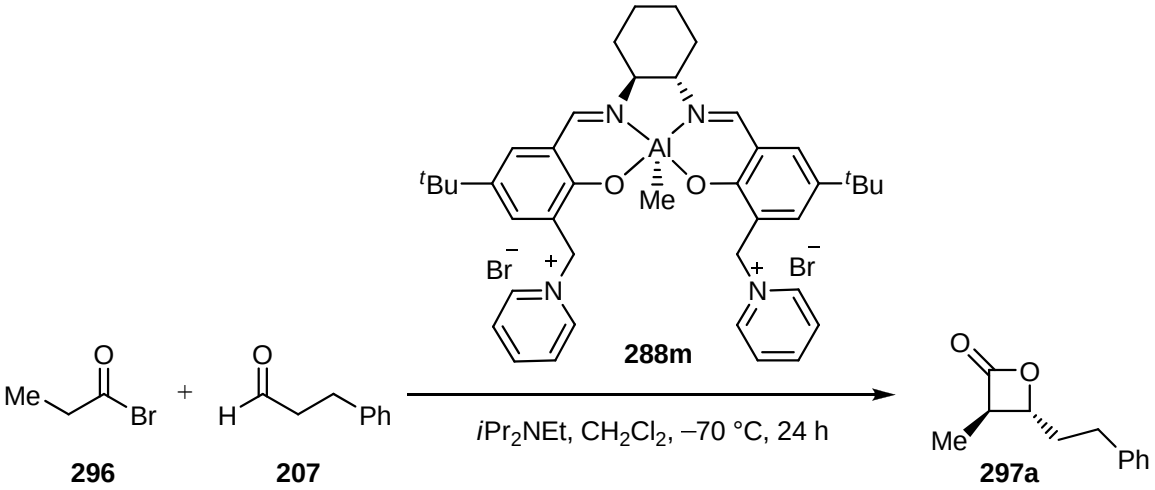
Entry	R	Temp. [°C]	Time [h]	Conversion [%]	Yield [%]	*ee*[b] [%]	*trans* : *cis*[c]
1	CH_2OBn	−20	5	100	n.d.	43	86 : 14
2	C≡C*n*pentyl	−20	4	100	n.d.	38	85 : 15
3	4-$NO_2C_6H_4$	−70	42	60	n.d.	63	87 : 13

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% catalyst. The catalyst was preformed for 3 h at ambient temperature and was used without purification. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] *ee* determined by HPLC on a chiral support. [c] Ratio determined by ^{1}H NMR spectroscopy.

9.3.4.10 Influence of the Amount of Catalyst

So far all experiments were performed with 10 mol% catalyst **288m**. In an experiment conducted with 5 mol% catalyst **288m** (Table 72, entry 2) the yield (77%) and diastereoselectivity (*trans*/*cis* = 96:4) dropped slightly compared to the experiment with 10 mol% catalyst (entry 1) with a yield of 78% and a *trans*/*cis* ratio of 97:3. When the catalyst amount was further reduced to 2.5 mol% the yield was diminished to 53% and the diastereoselectivity dropped to a *trans*/*cis* ratio of 94:6 (entry 3).

Table 72. Influence of the amount of catalyst.[a]



Entry	Catalyst amount [mol%]	Yield[b] [%]	*ee*[c] [%]	*trans*/*cis*[d]
1	10	78	88	97 : 3
2	5	77	88	96 : 4
3	2.5	53	88	94 : 6

[a] All reactions were performed at a concentration c = 0.25 mol/L of the aldehyde with 10 mol% of the ligand and Me_3Al as the aluminum source at –70 °C for 24 h. The catalyst was preformed for 3 h at ambient temperature. The ketene was formed *in situ* from 6 equiv. propionylbromide and 2.5 equiv. *Hünig*'s base. [b] Yield determined by ^{1}H NMR spectroscopy using acetophenone as internal standard. [c] *ee* determined by HPLC on a chiral support. [d] Ratio determined by ^{1}H NMR spectroscopy.

9.3.4.11 Working Model

The proposed mode of operation is depicted in Figure 20. The aldehyde is assumed to bind with its sterically more accessible lone pair to the only available Al coordination site to form an octahedral complex. Since the unstable acylbromide enolate is expected to be present in only minute concentrations, it is likely that the reacting intermediate is generated directly in the catalyst sphere by attack of the catalyst's bromide counteranion to the ketene. This attack would be expected to occur selectively *trans* to the residue R^1 to minimize repulsive interactions thus selectively forming the *E*-configured enolate contact ion pair. This reactive species should nucleophilically attack the aldehyde *via* an open transition state adopting a staggered conformation. Our model is in agreement with the products' (*R*,*R*)-configurations obtained. The absolute configuration was determined for **297f** by comparison of the specific optical rotation with literature data.[166] Since a uniform reaction pathway can be assumed, the configuration has been assigned to all β-lactones **297**.

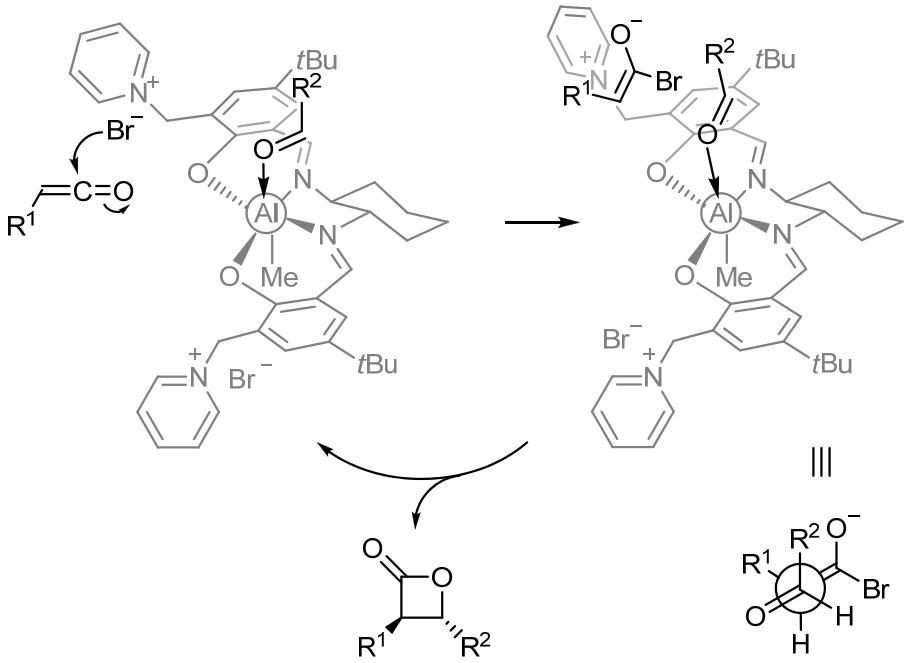


Figure 20. Working model.

10 Conclusion and Outlook

β-Lactones readily undergo nucleophilic ring-opening reactions as a result of their intrinsic ring strain and therefore behave as activated aldol equivalents. Consequently, the development of catalytic asymmetric [2+2] cycloadditions of ketenes and aldehydes offers an alternative to catalytic asymmetric ester and amide aldol reactions, which in most cases require the preformation and isolation of enolate equivalents such as silyl ketene acetals.

Additionally, β-lactones also represent a structural motif in a number of important natural and synthetic bioactive products. The large majority of these bioactive compounds have a *trans*-configuration about the heterocyclic system.

The aim of the present work was to develop a *trans*-selective catalytic asymmetric [2+2] cyclocondensation of acyl halides and aliphatic aldehydes. To achieve this goal, a novel concept within the context of dual-activation catalysis that combines the cooperative action of aprotic contact ion pair and *Lewis* acid catalysis was introduced (Figure 21).

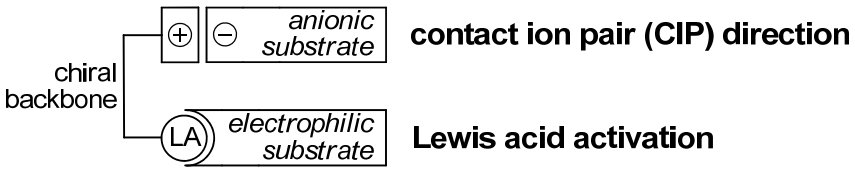
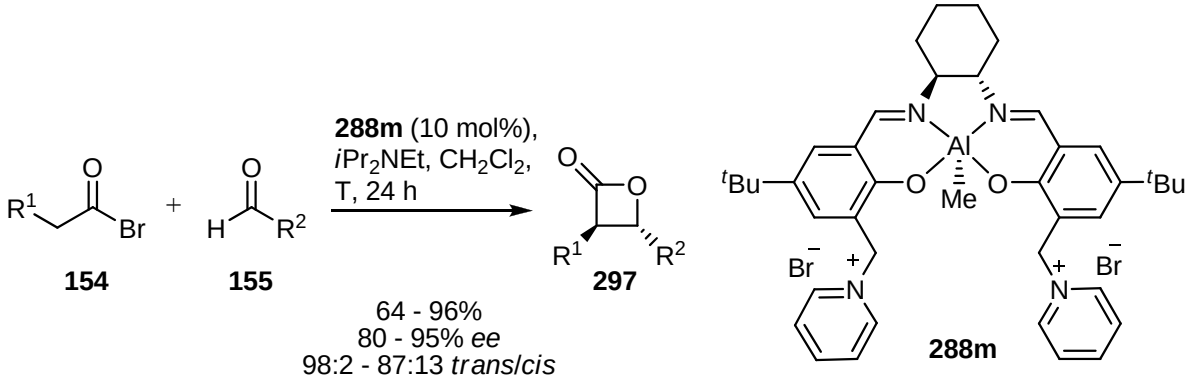


Figure 21. The concept of contact ion pair directed *Lewis* acid catalysis.

With this concept the first *trans*-selective [2+2] cyclocondensation of acyl halides with aliphatic aldehydes, furnishing 3,4-disubstituted β-lactones with high stereoselectivity, was developed and thus represents an alternative to the rare type of catalytic asymmetric *anti*-aldol additions (Scheme 112).



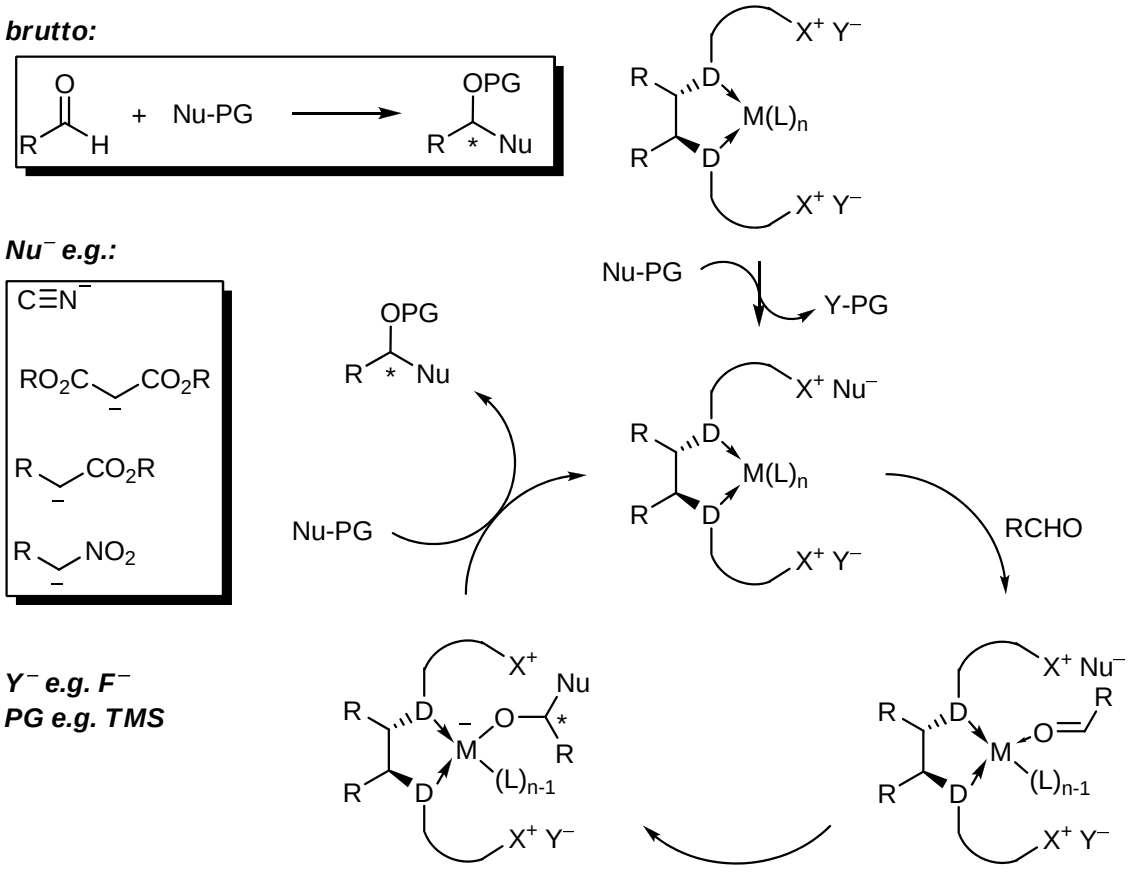
Scheme 112

As a general trend, the enantioselectivity was slightly reduced with increased steric bulk of the cationic moiety of the catalyst. The planar pyridinium system **288m** possessing an sp^2-hybridized N atom was the most selective catalyst. One explanation might be that formation of the contact ion pair with **288m** might be more efficient than with ammonium functionalities.

The reaction generally provided high *trans* selectivities with α-unbranched aliphatic aldehydes (*trans*/*cis* = 94:6 to 98:2). With the α-branched cyclohexylcarboxaldehyde a lower *trans* selectivity was obtained (*trans*/*cis* = 87:13). The enantioselectivity did not significantly depend on the aldehyde, and almost identical results were obtained with α-unbranched substrates possessing long aliphatic side chains with or without a C=C bond, with β-branched aldehydes such as isovaleraldehyde, and with sterically undemanding aldehydes like propanal, butanal or pentanal.

Especially the results with sterically undemanding aldehydes are remarkable since high enantioselectivities have previously never been reported for very small aliphatic aldehydes in other catalytic asymmetric cycloadditions with acyl halides or ketenes.
Both yields and enantioselectivities were further increased when valeroyl bromide was used instead of propionyl bromide.

This novel dual activation concept might be of general utility for the addition of anionic nucleophiles to electrophiles such as aldehydes, ketones or imines (Scheme 113). Therefore various alternative applications such as the addition of cyanide, malonates, nitronates or ester enolates to aldehydes are envisaged. One could still argue that the anionic nucleophile might deactivate the *Lewis* acid by coordination. However, the strategy should be to form the active nucleophile *in situ* in the direct catalyst environment to maintain low concentrations of this *Lewis* basic concept.



Scheme 113. Proposed applications of the principle of contact ion pair directed *Lewis* acid catalysis.

11 Experimental Part

Except as otherwise indicated, all reactions were carried out in oven or flame dried glassware under a positive pressure of argon. Toluene was dried by passage over activated alumina under nitrogen atmosphere. Dichloromethane was purified by distillation and dried by a passage over activated alumina under nitrogen atmosphere. All aldehydes and *N,N*-diisopropylethylamine (Acros, >99.5%) were distilled from CaH_2 under nitrogen. Aldehydes **236** and **238** were prepared from the commercially available alcohols according to published procedures.[167] Aldehyde **237** was synthesized from 2-methyl-2-penten-1-ol according to literature procedures.[167,168] Aldehydes **272a-e** and ligands **274a-e** were prepared according ot published procedure.[143d] Enantiomerically pure (*S*,*S*)-1,2-diaminocyclohexane was generously donated by *Reuter Chemische Apparatebau KG* (RCA; Freiburg, Germany). Enantiomerically pure 1,2-diamino-1,2-diphenylethane was prepared according to literature.[169] (*1S*,*2S*)-1,2-*N*,*N'*-Bis(*p*-toluenesulfonylamino)cyclohexane (**222h**, Aldrich, 98%), (*1R*,*2R*)-1,2-*N*,*N'*-bis(trifluoromethylsulfonylamino)cyclohexane (**222k**, Aldrich, 97%), 5-*tert*-butyl-2-hydroxy-benzaldehyde (Aldrich, 98%), (*S*,*S*)-(+)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (**274h**, Aldrich, 98%), propionyl bromide (Aldrich, 98%), *n*-valeroyl bromide (TCI Europe, >98%), pyridine (Fluka, >99.8%), anhydrous pentane (Fluka, over molecular sieves, >99.5%), methanol (Fluka, HPLC grade), *n*-hexane (Fluka, UV quality), cyclohexane (Thommen & Furler), ethyl acetate (Thommen & Furler), diethyl ether (Fluka) and triethylamine (Fluka, >99.5%) were used as purchased. All other laboratory chemicals were purchased from *ABCR*, *Acros*, *Aldrich*, *Fluka*, *J.T. Baker* or *Merck* and were used without purification. For work-up procedures and flash chromatography, distilled technical grade solvents were used. Unless otherwise indicated, all liquids were added *via* syringe, solids were added neat against an argon flow. Solvents were removed at a heating bath temperature of 40 °C and 800 - 30 mbar pressure by rotary evaporation. Non-volatile compounds were dried *in vacuo* at 0.01 mbar. Except as otherwise indicated, reactions were magnetically stirred and monitored either by ^1H NMR spectra or thin layer chromatography (TLC) using silica gel plates from *Merck* (silica gel 60 F_{254}). Visualization occurred by fluorescence quenching under UV light and by staining with aqueous $KMnO_4$ / NaOH. Purification by flash chromatography was performed on silica gel 60 Å, 32-62, provided by *Fluka,* using a forced flow of eluent at 0.2-0.4 bar pressure.

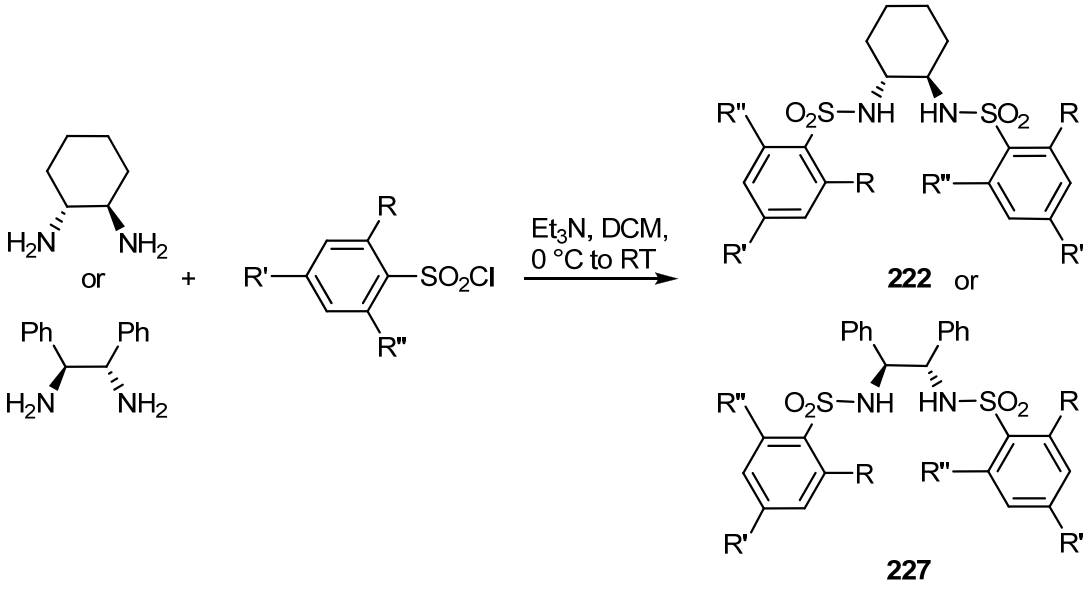
NMR-spectra were recorded on a *Varian Gemini 300*, a *Varian Mercury 300* spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C) and on a *Bruker DRX400* spectrometer operating at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts δ are referred in terms of ppm and *J*-coupling constants are given in Hz. Abbreviations for multiplicity are as follows: *s* (singulet), *d* (doublet), *t* (triplet), *q* (quadruplet), *m* (multiplet), *b* (broad signal). IR-spectra were recorded on a *Perkin Elmer Spectrum One FT-IR* with a *Universal ATR Sampling Accessory* and the signals are given by wave numbers (cm^{-1}). Optical rotation was measured on a *Jasco DIP-100 digital polarimeter* operating at the sodium D line with a 100 mm path length cell. Melting points were measured using a *Büchi 535* melting point apparatus in open glass capillaries and are uncorrected. Mass spectra were obtained from the ETH Zürich MS Service. High resolution EI mass spectra were performed on a *Micromass AutoSpec Ultima* and were calibrated with perfluorotributylamine (PFTBA) prior to data acquisition. High resolution ESI mass spectra were performed on an *Ion Spec Ultima 2 FTICR*. ESI mass spectra were performed on a *Finnigan TSQ7000*. Combustion analysis was performed by the Mikroelementaranalytisches Laboratorium at ETH Zürich. Analytical gas chromatography (GC) was performed on a *Hewlett Packard HP6890 Series gas chromatograph* with a flame ionization detector using a *Supelco GammaDex^{TM} 120 Fused Silica Capillary Column* (30 m x 0.25 mm x 0.25 μm film thickness). Hydrogen was used as the carrier gas at the indicated pressure. Analytical high performance liquid chromatography (HPLC) was performed on a *Hitachi LaChrom Elite liquid chromatograph* equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using a *Daicel Chiralcel^{TM} OD-H column* (25 x 0.46 cm). HPLC grade isopropanol and hexanes were used as the eluting solvents.

11.1 Part A: *Lewis* Acid Catalysis

11.1.1 Part A1: Catalysis with Ligands 222 and 227

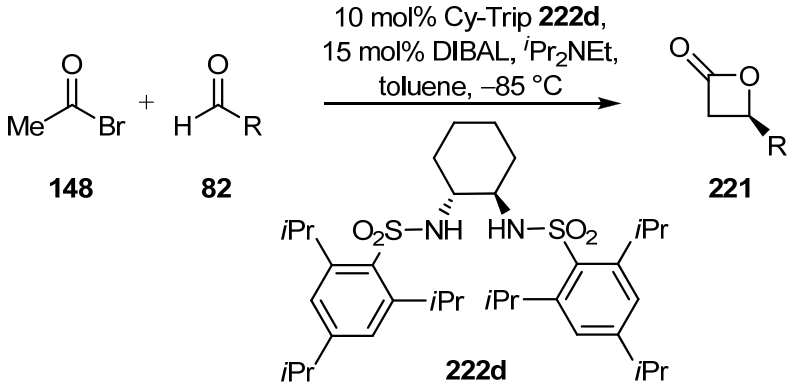
11.1.1.1 General Procedures

General procedure for the formation of bis(*N*-sulfonylamino)-1,2-diphenylethane ligands and bis(*N*-sulfonylamino)cyclohexane-ligands (GPA1-1)[170]



To a solution of the corresponding diamine (2 mmol, 1 equiv.) in DCM (20 mL) at 0 °C the corresponding sulfonyl chloride (4 mmol, 2 equiv.) and triethylamine (6 mmol, 3 equiv.) were added. The solution was stirred for 30 min at 0 °C. Subsequently, the solution was stirred at ambient temperature until complete conversion as monitored by TLC (typically 20 h). The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (cyclohexane/ethyl acetate).

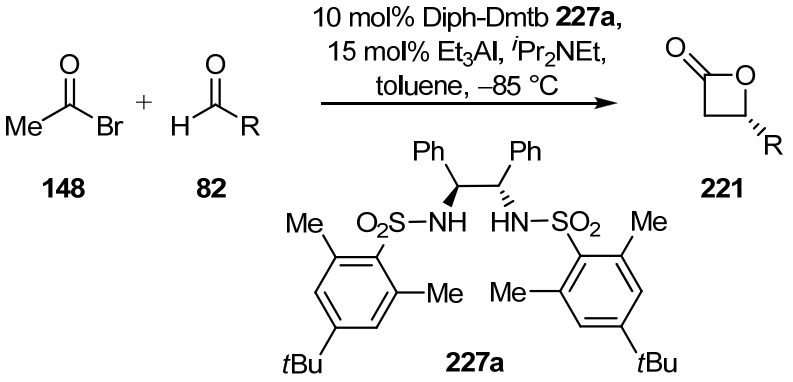
General procedure for the formation of β-lactones 221 from α-unbranched aldehydes using bissulfonamide ligand 222d (GPA1-2)



To a mixture of ligand **222d** (0.05 mmol, 0.1 equiv.) in toluene (2 mL) was slowly added at ambient temperature a solution of Dibal (1.0 M in hexane, 0.075 mmol, 0.15 equiv.). The mixture was heated to 80 °C and stirred for 4 h. Subsequently, the solution was stirred for 1 h at ambient temperature. The catalyst solution was then cooled to −85 °C and the corresponding α-unbranched aldehyde **82** (0.5 mmol, 1 equiv.), acetyl bromide **148** (1.5 mmol, 3 equiv.) and diisopropylethylamine (1.25 mmol, 2.5 equiv.) were successively added. The resulting heterogeneous mixture was stirred at −85 °C until complete conversion as monitored by ^{1}H-NMR (24-140 h). The reaction mixture was poured into aqueous 1 M HCl (20 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic phase was dried over $MgSO_4$, filtered and diethyl ether was removed *in vacuo*. The yield was determined by ^{1}H-NMR using acetophenone as internal standard.

The crude product mixtures of **221a,f** were purified by flash chromatography (pentane/diethyl ether). The solutions of the crude products were directly added to the column without prior removal of toluene.

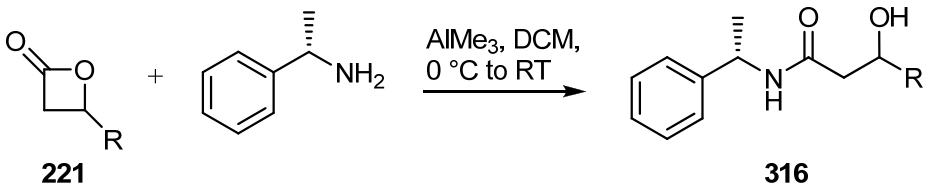
General procedure for the formation of β-lactones 221 from α-branched aldehydes using bissulfonamide ligand 227a (GPA1-3)



To a mixture of ligand **227a** (0.05 mmol, 0.1 equiv.) in toluene (2 mL) was slowly added at ambient temperature a solution of Et_3Al (1.0 M in hexane, 0.075 mmol, 0.15 equiv.). The mixture was heated to 80 °C and stirred for 4 h. Subsequently, the solution was stirred for 1 h at ambient temperature. The catalyst solution was then cooled to −85 °C and α-branched aldehyde **82** (0.5 mmol, 1 equiv.), acetyl bromide (**148**, 1.5 mmol, 3 equiv.) and diisopropylethylamine (1.25 mmol, 2.5 equiv.) were successively added. The resulting heterogeneous mixture was stirred at −85 °C until complete conversion as monitored by ^{1}H-NMR (25-136 h). The reaction mixture was poured into aqueous 1 M HCl (20 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic phase was dried over $MgSO_4$, filtered and diethyl ether was removed *in vacuo*. The yield was determined by ^{1}H-NMR using acetophenone as internal standard.

The crude product mixture of **221b** was purified by flash chromatography (pentane/diethyl ether). The solution of the crude product was directly added to the column without prior removal of toluene.

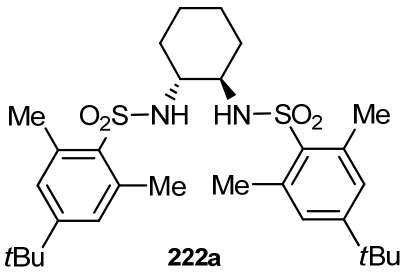
General procedure for the ring opening of monosubstituted β-lactones 221 with (GPA1-4)



To a solution of (*S)*-1-phenylethylamine (1.09 mmol, 2 equiv.) in dichloromethane (1.5 mL) at 0 °C was slowly added a solution of trimethylaluminum in hexane (2.0 M, 523 µL, 1.05 mmol, 1.9 equiv.). The mixture was stirred at ambient temperature for 2 h. A solution of the lactone **221** (0.55 mmol) in DCM (1.5 mL) was added dropwise. The reaction was stirred at ambient temperature until complete conversion as monitored by TLC (24 h). The reaction mixture was diluted with dichloromethane (3 mL) and poured into an ice cooled saturated solution of potassium sodium tartrate (10 mL). The mixture was transferred into a separatory funnel and the layers were separated. The aqueous phase was extracted with DCM (5 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (cyclohexane/ethyl acetate).

11.1.1.2 Ligand Synthesis

(*1R*,*2R*)-1,2-*N*,*N*'-Bis(4-*tert*-butyl-2,6-dimethylbenzenesulfonylamino)cyclohexane 222a



222a

Bissulfonamide **222a** was prepared according to GP1 from (*1R,2R*)-cyclohexane-1,2-diamine and 4-*tert*-butyl-2,6-dimethylbenzene-1-sufonyl chloride. Purification by flash chromatography (cyclohexane/ethyl acetate 4:1) gave title compound **222a** as a white solid (1.07 g, 1.89 mmol, yield: 95%).

$C_{30}H_{46}N_2O_4S_2$, **MW:** 562.83 g/mol.

Mp: 157-160 °C.

[α] $_D^{22.1°C}$ (c = 5.060 , $CHCl_3$) = +4.5 ± 0.2.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.12 (*s*, 4 H, C*H*$_{Ar}$); 4.86 (*d*, *J* = 5.9, 2 H, N*H*); 2.88 (*m*, 2 H, C*H*-N); 2.65 (*s*, 12 H, $C_{Ar}CH_3$); 1.88 (*m*, 2 H, $(CH_2)_{ring}$); 1.55 (*m*, 2 H, $(CH_2)_{ring}$); 1.30 (*s*, 18 H, $C(CH_3)_3$); 1.11 (*m*, 4 H, $(CH_2)_{ring}$).

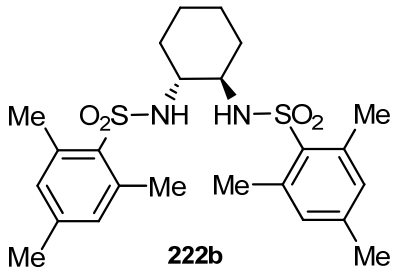
^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 155.1, 138.6, 134.3, 128.5, 56.3, 34.6, 33.1, 30.9, 24.2, 23.5.

IR (ATR): 3287, 2956, 2866, 1595, 1558, 1450, 1406, 1315, 1172, 1143, 1052, 895, 870, 751, 646.

HRMS (EI) *m/z*: Calc. for [M^+]: 562.2899. Found: 562.2899.

Anal. Calcd. for $C_{30}H_{46}N_2O_4S_2$: C, 64.02; H, 8.24; N, 4.98; O, 11.37; S, 11.39. Found: C, 64.10; H, 8.25; N, 4.98.

(*1R*,*2R*)-1,2-*N*,*N*'-Bis(2,4,6-trimethylbenzenesulfonylamino)cyclohexane 222b



222b

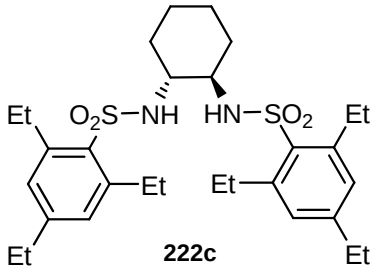
Bissulfonamide **222b** was prepared according to GP1 from (*1R,2R*)-cyclohexane-1,2-diamine and 2,4,6-trimethylbenzene-1-sulfonyl chloride. Purification by flash chromatography (cyclohexane/ethyl acetate 8:1) gave title compound **222b** as a white solid (884 mg, 1.85 mmol, yield: 92%).

$C_{24}H_{34}N_2O_4S_2$, **MW:** 478.67 g/mol.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 6.95 (*s*, 4 H, C*H*$_{Ar}$); 4.90 (*d*, *J* = 5.7, 2 H, N*H*); 2.82 (*m*, 2 H, C*H*-N); 2.61 (*s*, 12 H, CH_3); 2.30 (*s*, 6 H, CH_3); 1.85 (*m*, 2 H, (CH_2)$_{ring}$); 1.54 (*m*, 2 H, (CH_2)$_{ring}$); 1.08 (*m*, 4 H, (CH_2)$_{ring}$).

All other analytical data are in accordance with the literature.[171]

(*1R*,*2R*)-1,2-*N*,*N*'-Bis(2,4,6-triethylbenzenesulfonylamino)cyclohexane 222c



222c

Bissulfonamide **222c** was prepared according to GP1 from (*1R,2R*)-cyclohexane-1,2-diamine and 2,4,6-triethylbenzene-1-sulfonyl chloride. Purification by flash chromatography (cyclohexane/ethyl acetate 9:1) gave title compound **5c** as a white solid (913 mg, 1.62 mmol, yield: 81%).

$C_{30}H_{46}N_2O_4S_2$, **MW:** 562.83 g/mol.

Mp: 136-137 °C.

[α] $_D^{22.1°C}$ (c = 5.115 , $CHCl_3$) = –6.3 ± 0.1.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.01 (*s*, 4 H, C*H*$_{Ar}$); 4.75 (*d*, *J* = 5.8, 2 H, N*H*); 3.02 (*m*, 8 H, C$_{Ar}$CH_2); 2.86 (*m*, 2 H, C*H*-N); 2.63 (*m*, 4 H, C$_{Ar}$CH_2); 1.85 (*m*, 2 H, (CH_2)$_{ring}$); 1.53 (*m*, 2 H; (CH_2)$_{ring}$); 1.27 (*m*, 18 H, CH_3); 1.07 (*m*, 4 H, (CH_2)$_{ring}$).

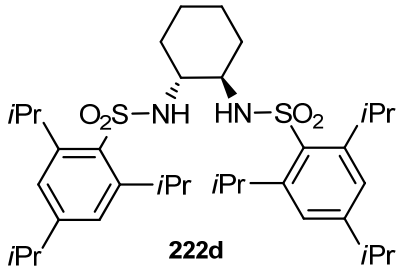
^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 148.6, 145.5, 133.6, 129.4, 56.4, 33.4, 28.5, 28.4, 24.3, 16.9, 14.9.

IR (ATR): 3289, 2966, 2934, 2874, 1600, 1562, 1452, 1419, 1312, 1151, 1071, 1048, 954, 903, 875, 658, 632.

HRMS (EI) *m/z*: Calc. for [M^+]: 562.2899. Found: 562.2901.

Anal. Calcd. for $C_{30}H_{46}N_2O_4S_2$: C, 64.02; H, 8.24; N, 4.98; O, 11.37; S, 11.39. Found: C, 64.14; H, 8.01; N, 5.07.

(*1R*,*2R*)-1,2-*N*,*N*'-Bis(2,4,6-triisopropylbenzenesulfonylamino)cyclohexane 222d



222d

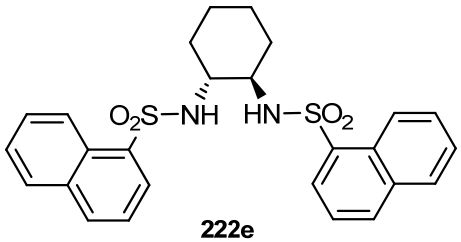
Bissulfonamide **222d** was prepared according to GP1 from (*1R,2R*)-cyclohexane-1,2-diamine and 2,4,6-triisopropylbenzene-1-sulfonyl chloride. Purification by flash chromatography (cyclohexane/ethyl acetate 12:1) gave title compound **222d** as a white solid (1.23 g, 1.90 mmol, yield: 95%).

$C_{36}H_{58}N_2O_4S_2$, **MW:** 646.99 g/mol.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.15 (*s*, 4 H, CH_{Ar}); 5.03 (*d*, *J* = 5.7, 2 H, N*H*); 4.16 (*m*, 4 H, C*H*(CH_3)$_2$); 3.13 (*m*, 2 H, C*H*-N); 2.90 (*m*, 2 H, C*H*(CH_3)$_2$); 1.85 (*m*, 2 H, (CH_2)$_{ring}$); 1.56 (*m*, 2 H, (CH_2)$_{ring}$); 1.27 (*d*, *J* = 6.8, 24 H, CH_3); 1.25 (*d*, *J* = 6.9, 12 H, CH_3); 1.10 (*m*, 4 H, (CH_2)$_{ring}$).

All other analytical data are in accordance with the literature.[171]

(*1R*,*2R*)-1,2-*N*,*N*'-Bis(1-naphthylsulfonylamino)cyclohexane 222e



222e

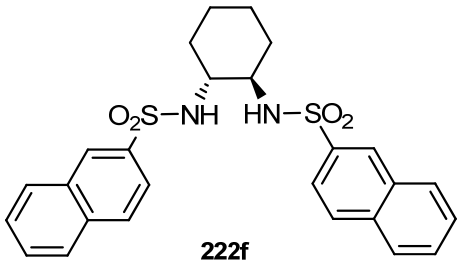
Bissulfonamide **222e** was prepared according to GP1 using naphthalene-1-sulfonyl chloride, but using 2.50 mmol of (*1R,2R*)-cyclohexane-1,2-diamine in 30 mL DCM. Purification by flash chromatography (cyclohexane/ethyl acetate 2:1) gave title compound **222e** as a white solid (1.14 g, 2.31 mmol, yield: 92%).

$C_{26}H_{26}N_2O_4S_2$, **MW:** 494.63 g/mol.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 8.52 (*dd*, *J* = 8.5, 0.9, 2 H, CH_{Ar}); 8.25 (*dd*, *J* = 7.4, 1.3, 2 H, CH_{Ar}); 8.08 (*d*, *J* = 8.3, 2 H, CH_{Ar}); 7.96-7.94 (*m*, 2 H, CH_{Ar}); 7.70-7.66 (*m*, 2 H, CH_{Ar}); 7.63-7.59 (*m*, 2 H, CH_{Ar}); 7.56-7.52 (*m*, 2 H, CH_{Ar}); 5.07 (*d*, *J* = 5.4, 2 H, N*H*); 2.79 (*m*, 2 H, C*H*-N); 1.58 (*m*, 2 H, (CH_2)$_{ring}$); 1.36 (*m*, 2 H, (CH_2)$_{ring}$); 0.99-0.86 (*m*, 4 H, (CH_2)$_{ring}$).

All other analytical data are in accordance with the literature.[171]

(*1R*,*2R*)-1,2-*N*,*N*'-Bis(2-naphthylsulfonylamino)cyclohexane 222f



222f

Bissulfonamide **222f** was prepared according to GP1 using naphthalene-2-sulfonyl chloride, but using 2.50 mmol of (*1R,2R*)-cyclohexane-1,2-diamine in 30 mL DCM.

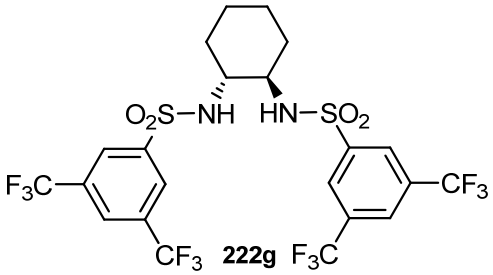
Purification by flash-chromatography (cyclohexane/ethyl acetate 3:1) gave title compound **222f** as a white solid (1.06 g, 2.15 mmol, yield: 86%).

$C_{26}H_{26}N_2O_4S_2$, MW: 494.63 g/mol.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 8.45 (*m*, 2 H, CH_{Ar}); 7.91 (*m*, 8 H, CH_{Ar}); 7.63 (*m*, 4 H, CH_{Ar}); 4.98 (*d*, *J* = 6.2, 2 H, N*H*); 2.82 (*m*, 2 H, C*H*-N); 1.85 (*m*, 2 H, (CH_2)$_{ring}$); 1.50 (*m*, 2 H, (CH_2)$_{ring}$); 1.17-0.97 (*m*, 4 H, (CH_2)$_{ring}$).

All other analytical data are in accordance with the literature.[171]

(*1R*,*2R*)-1,2-*N*,*N*'-Bis(3,5-trifluoromethylbenzenesulfonylamino)cyclohexane 222g



222g

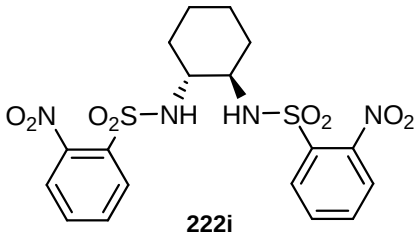
Bissulfonamide **222g** was prepared according to GP1 from (*1R,2R*)-cyclohexane-1,2-diamine and 3,5-bis(trifluoromethyl)benzene-1-sulfonyl chloride. Purification by flash chromatography (cyclohexane/ethyl acetate 2:1) gave title compound **222g** as a white solid (1.09 g, 1.64 mmol, yield: 82%).

$C_{22}H_{18}F_{12}N_2O_4S_2$, MW: 666.50 g/mol.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 8.31 (*s*, 4 H, CH_{Ar}); 8.08 (*m*, 2 H, CH_{Ar}); 5.06 (*s*, 2 H, N*H*); 2.98 (*m*, 2 H, C*H*-N); 1.81 (*m*, 2 H, (CH_2)$_{ring}$); 1.67 (*m*, 2 H, (CH_2)$_{ring}$); 1.30-1.15 (*m*, 4 H, (CH_2)$_{ring}$).

All other analytical data are in accordance with the literature.[172]

(*1R*,*2R*)-1,2-*N*,*N*'-Bis(2-nitrobenzenesulfonylamino)cyclohexane 222i



222i

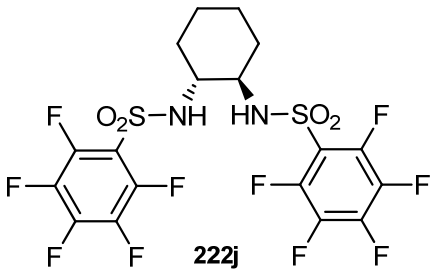
Bissulfonamide **222i** was prepared according to GP1 from (*1R,2R*)-cyclohexane-1,2-diamine and 2-nitrobenzene-1-sulfonyl chloride. Purification by flash-chromatography (cyclohexane/ethyl acetate 1:1) gave title compound **222i** as a white solid (1.12 g, 2.30 mmol, yield: 92%).

$C_{18}H_{20}N_4O_8S_2$, MW: 484.51 g/mol.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 8.12 (*m*, 2 H, C*H*$_{Ar}$); 7.84 (*m*, 2 H, C*H*$_{Ar}$); 7.34 (*m*, 4 H, C*H*$_{Ar}$); 5.38 (*m*, 2 H, N*H*); 3.27 (*m*, 2 H, C*H*-N); 1.90 (*m*, 2 H, (C*H*$_2$)$_{ring}$); 1.61 (*m*, 2 H, (C*H*$_2$)$_{ring}$); 1.36-1.20 (*m*, 4 H, (C*H*$_2$)$_{ring}$).

All other analytical data are in accordance with the literature.[172]

(*1R*,*2R*)-1,2-*N*,*N*'-Bis(pentafluorobenzenesulfonylamino)cyclohexane 222j



222j

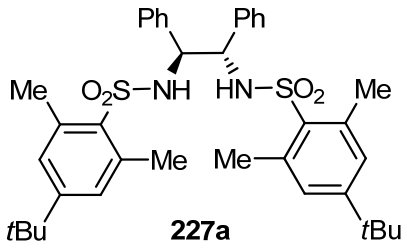
Bissulfonamide **222j** was prepared according to GP1 using pentafluorobenzene-1-sulfonyl chloride, but using 2.50 mmol (*1R,2R*)-cyclohexane-1,2-diamine in 30 mL DCM. Purification by flash-chromatography (cyclohexane/ethyl acetate 8:1) gave title compound **222j** as a white solid (863 mg, 1.50 mmol, yield: 75%).

$C_{18}H_{12}F_{10}N_2O_4S_2$, MW: 574.41 g/mol.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 5.46 (*m*, 2 H, N*H*); 3.32 (*m*, 2 H, C*H*-N); 1.92 (*m*, 2 H, $(CH_2)_{ring}$); 1.72 (*m*, 2 H, $(CH_2)_{ring}$); 1.44-1.21 (*m*, 4 H, $(CH_2)_{ring}$).

All other analytical data are in accordance with the literature.[171]

(*1S*,*2S*)-1,2,-*N*,*N*'-Bis(4-*tert*-butyl-2,6-dimethylbenzenesulfonylamino)-1,2-diphenylethylendiamine 227a



227a

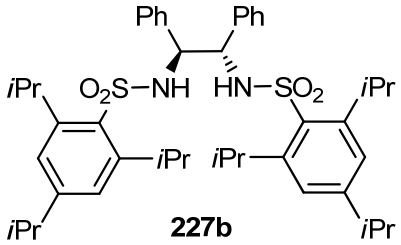
Bissulfonamide **227a** was prepared according to GP1 from (*1S,2S*)-1,2-diphenylethane-1,2-diamine and 4-*tert*-butyl-2,6-dimethylbenzene-1-sulfonyl chloride. Purification by flash chromatography (cyclohexane/ethyl acetate 8:1) gave title compound **227a** as a white solid (1.17 g, 1.78 mmol, yield: 89%).

$C_{38}H_{48}N_2O_4S_2$, MW: 660.93 g/mol.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 6.94-6.79 (*m*, 10 H, CH_{Ar}); 6.58 (*m*, 4 H, CH_{Ar}); 5.78 (*m*, 2 H, N*H*); 4.36 (*m*, 2 H, C*H*-N); 2.48 (*s*, 12 H, CH_3); 1.23 (*m*, 18 H, CH_3).

All other analytical data are in accordance with the literature.[173]

(*1S*,*2S*)-1,2-*N*,*N*'-Bis(2,4,6-triisopropylbenzenesulfonylamino)-1,2-diphenylethylendiamine 227b



227b

Bissulfonamide **227b** was prepared according to GP1 from (*1S,2S*)-1,2-diphenylethane-1,2-diamine and 2,4,6-triisopropylbenzene-1-sulfonyl chloride. Purification by flash-chromatography (cyclohexane/ethyl acetate 10:1) gave title compound **227b** as a white solid (1.15 g, 1.55 mmol, yield: 78%).

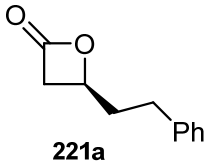
$C_{44}H_{60}N_2O_4S_2$, MW: 745.09 g/mol.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 6.99-6.87 (*m*, 10 H, C*H*$_{Ar}$); 6.58 (*m*, 4 H, C*H*$_{Ar}$); 5.71 (*m*, 2 H, N*H*); 4.47 (*m*, 2 H, C*H*-N); 4.00 (*m*, 4 H, C*H*$(CH_3)_2$); 2.83 (*m*, 4 H, C*H*$(CH_3)_2$); 1.18 (*m*, 24 H, CH_3); 1.05 (*d*, *J* = 6.7, 12 H, CH_3).

All other analytical data are in accordance with the literature.[174]

11.1.1.3 β-Lactone Synthesis

(*S*)-4-Phenylethyl-oxetan-2-one 221a



221a

β-Lactone **221a** was prepared according to GP2 using aldehyde **207** (reaction time: 48 h) and was furnished as solution in toluene (0.47 mmol, yield: 93%, *ee* = 88%). The *ee* value was determined by HPLC (Chiralcel OD-H, 97:3 *n*-hexane/*i*PrOH, 1.0 mL/min, 210 nm).
To determine the isolated yield, **221a** was prepared according to GP2, but using 1.50 mmol aldehyde **207** in 6 mL toluene.

Purification by flash chromatography (pentane → pentane/ diethyl ether 4:1) gave **221a** as colorless oil (230 mg, 1.30 mmol, 87%, *ee* = 88%). Spectral data for the (*R*)-enantiomer has been reported earlier.[175]

$C_{11}H_{12}O_2$, MW: 176.21 g/mol.

[α] $_D^{21.1°C}$ (c = 0.915, $CHCl_3$) = −48. 8 ± 0.3.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.25 (*m*, 5 H, CH_{Ar}); 4.50 (*m*, 1 H, C*H*-O); 3.48 (*dd*, *J* = 16.3, 5.8, 1 H, C*H*H-C(O)); 3.03 (*dd*, *J* = 16.3, 4.3, 1 H, CH*H*-C(O)); 2.77 (*m*, 2 H, $CH_2CH_2C_{Ar}$); 2.13 (*m*, 2 H, $CH_2CH_2C_{Ar}$).

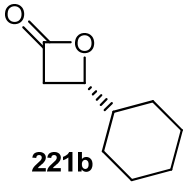
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 167.9, 139.9, 128.5, 128.2, 126.3, 70.4, 42.9, 36.4, 31.3.

IR (ATR): ν = 3028, 2933, 1817, 1603, 1131, 1110 827, 748, 699.

HRMS (EI) *m/z*: Calc. for [M^+]: 176.0832. Found: 176.0833.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; O, 18.16. Found: C, 74.84; H, 6.95.

(*S*)-4-Cyclohexyl-oxetan-2-one 221b



221b

β-Lactone **221b** was prepared according to GP3 using aldehyde **226** (reaction time: 25 h) and was furnished as solution in toluene (0.44 mmol, yield: 88%, *ee* = 90%). The *ee* value was determined by GC (GammaDex™, 145 °C, 2.0 mL/min).
To determine the isolated yield **221b** was prepared according to GP3, but using 1.50 mmol of aldehyde **226** in 6 mL toluene.

Purification by flash chromatography (pentane → pentane/diethyl ether 8:1) gave **221b** as colorless oil (209 mg, 1.35 mmol, yield: 90%, *ee* = 90%). Spectral data for the (*S*)-enantiomer has been reported earlier.[176]

$C_9H_{14}O_2$, MW: 154.21 g/mol.

[α] $_D^{25.0°C}$ (c = 0.605, $CHCl_3$) = +18.8 ± 1.0.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.19 (*ddd*, *J* = 8.2, 5.8, 4.4, 1 H, C*H*-O); 3.42 (*dd*, *J* = 16.3, 5.8, 1 H, C*H*H-C(O)); 3.10 (*dd*, *J* = 16.3, 4.4, 1 H, CH*H*-C(O)); 1.93 (*m*, 1 H, C*H*$(CH_2)_2$); 1.82-1.54 & 1.23 & 1.00 (3 x *m*, 10 H, 5 x $(CH_2)_{ring}$).

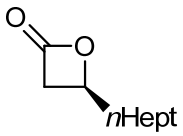
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 168.4, 74.8, 42.0, 41.0, 28.2, 27.1, 26.0, 25.4, 25.2.

IR (ATR): ν = 2926, 2854, 1818, 1450, 1275, 1117, 948, 866, 853, 833.

HRMS (EI) *m/z*: Calc. for [M^+]: 154.0988. Found: 154.0992.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; O, 20.75. Found: C, 70.15; H, 9.40.

(*S*)-4-*n*Heptyl-oxetan-2-one 221c



221c

β-Lactone **6c** was prepared according to GP2 using aldehyde 4c (reaction time: 63 h), but using 1.00 mmol of aldehyde **235** in 4 mL toluene. **221c** was furnished as solution in toluene (0.82 mmol, yield: 86%, *ee* = 84%). The *ee* value was determined by HPLC (Chiralcel OD-H, 95:5 *n*-hexane/*i*PrOH, 1.0 mL/min, 210 nm) after ring opening with (*S*)-1-phenylethylamine (*vide infra*).

$C_{10}H_{18}O_2$, MW: 170.25 g/mol.

[α] $_D^{23.8°C}$ (c = 1.660, $CHCl_3$) = –24.8 ± 0.7.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.50 (*m*, 1 H, C*H*-O); 3.50 (*dd*, *J* = 16.3, 5.8, 1 H, C*H*H-C(O)); 3.05 (*dd*, *J* = 16.3, 4.3, 1 H, CH*H*-C(O)); 1.93-1.68 (*m*, 2 H, CH_2CH_2CH); 1.50-1.28 (*m*, 10 H, $(CH_2)_5CH_3$); 0.88 (*m*, 3 H, CH_3).

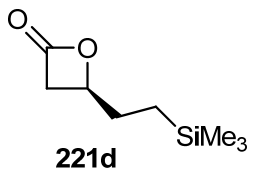
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 168.2, 71.3, 42.9, 34.7, 31.7, 29.2, 29.1, 25.0, 22.7, 14.2.

IR (ATR): ν = 2926, 2856, 1822, 1464, 1124, 946, 860, 813.

MS (EI) *m/z*: 43.0 (100), 128.1 [M^+-C_3H_7] (10).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66; O, 18.80. Found: C, 70.62; H, 10.67.

(*R*)-4-(2-Trimethylsilanyl-ethyl)-oxetan-2-one 221d



221d

β-Lactone **221d** was prepared according to GP2 using aldehyde **236** (reaction time: 62 h) and was furnished as solution in toluene (0.41 mmol, yield: 82%, *ee* = 84%). The *ee* value was determined by GC (GammaDex^{TM}, 100 °C, 2.0 mL/min).

$C_8H_{16}O_2Si$, **MW:** 172.30 g/mol.

[α] $_D^{25.4°C}$ (c = 1.140, $CHCl_3$) = –13.3 ± 0.4.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.45 (*m*, 1 H, C*H*-O); 3.47 (*dd*, *J* = 16.3, 5.7, 1 H, C*H*H-C(O)); 3.03 (*dd*, *J* = 16.3, 4.3, 1 H, CH*H*-C(O)); 1.92-1.64 (*m*, 2 H, $CHCH_2$); 0.64-0.41 (*m*, 2 H, CH_2Si); 0.02 (*s*, 9 H, 3 x CH_3Si).

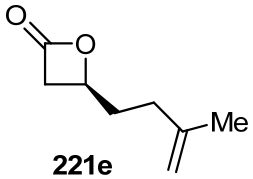
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 168.3, 73.0, 42.3, 29.2, 11.1, –1.8.

IR (ATR): ν = 2954, 2898, 1824, 1739, 1414, 1248, 1124, 834, 762, 691.

HRMS (EI) *m/z*: Calc. for [MH^+]: 173.0998. Found: 173.0993.

Anal. Calcd. for $C_8H_{16}O_2Si$: C, 55.77; H, 9.36; O, 18.57; Si, 16.30. Found: C, 55.81; H, 9.34.

(*S*)-4-(3-Methyl-but-3-enyl)oxetan-2-one 221e



221e

β-Lactone **221e** was prepared according to GP2 using aldehyde **237** (reaction time: 140 h) and was furnished as solution in toluene (0.46 mmol, yield: 92%, *ee* = 88%). The *ee* value was determined by GC (GammaDex™, 90 °C, 2.0 mL/min).

$C_8H_{12}O_2$, MW: 140.18 g/mol.

[α] $_D^{24.2°C}$ (c = 1.450, $CHCl_3$) = –23.4 ± 0.7.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.75 (*d*, *J* = 18.3, 2 H, C*H*$_2$-C); 4.52 (*m*, 1 H, C*H*-O); 3.52 (*dd*, *J* = 16.3, 5.8, 1 H, C*H*H-C(O)); 3.08 (*dd*, *J* = 16.3, 4.3, 1 H, CH*H*-C(O)); 2.23-1.84 (*m*, 4 H, C*H*$_2$C*H*$_2$); 1.75 (*s*, 3 H, C*H*$_3$).

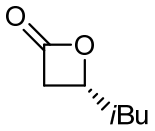
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 168.0, 143.5, 111.0, 70.8, 42.9, 33.0, 32.7, 22.4.

IR (ATR): ν = 2970, 2938, 1819, 1650, 1444, 1132, 1111, 885, 830.

HRMS (EI) *m/z*: Calc. for [M^+]:140.0832. Found: 140.0831

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.55; H, 8.63; O, 22.83. Found: C, 68.72; H, 8.85.

(*R*)-4-Isobutyl-oxetan-2-one 221f



221f

β-Lactone **221f** was prepared according to GP3 using aldehyde **230** (reaction time: 26 h), but using Dibal instead of Et_3Al and ligand 22**7b**. **221f** was furnished as solution in toluene (0.49 mmol, yield: 98%, *ee* = 85%). The *ee* value was determined by GC (GammaDex^{TM}, 100 °C, 2.0 mL/min).

To determine the isolated yield the crude product was purified by flash chromatography (pentane → pentane/ diethyl ether 4:1) giving **221f** as colorless oil (57 mg, 0.43 mmol, yield: 85%, *ee* = 85%). Spectral data for the (*S*)-enantiomer has been reported earlier.[175]

$C_7H_{12}O_2$, MW: 128.17 g/mol.

[α] $_D^{25.9°C}$ (c = 0.920, $CHCl_3$) = +19.3 ± 0.8.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.58 (*m*, 1 H, C*H*-O); 3.54 (*dd*, *J* = 16.2, 5.6, 1 H, C*H*H-C(O)); 3.05 (*dd*, *J* = 16.5, 4.2, 1 H, CH*H*-C(O)); 1.79 & 1.58 (2 x *m*, 3 H, $CH_2CH(CH_3)_2$); 0.95 (*d*, *J* = 6.6, 6 H, 2 x CH_3).

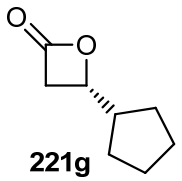
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 168.2, 70.2, 43.6, 43.4, 25.4, 22.8, 22.2.

IR (ATR): ν = 2960, 2874, 1820, 1118, 881, 805.

MS (EI) *m/z*: 128.1 [M^+] (6), 43.1 (100).

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44; O, 24.96. Found: C, 65.50; H, 9.45.

(*S*)-4-Cyclopentyl-oxetan-2-one 221g



221g

β-Lactone **221g** was prepared according to GP3 using aldehyde **238** (reaction time: 84 h) and was furnished as solution in toluene (0.41 mmol, yield: 90%, *ee* = 80%). The *ee* value was determined by GC (GammaDex^{TM}, 100 °C, 2.0 mL/min).

$C_8H_{12}O_2$, MW: 140.18 g/mol.

[α] $_D^{23.3°C}$ (c = 1.770, $CHCl_3$) = +27.7 ± 0.5.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.37 (*ddd*, *J* = 8.0, 5.8, 4.3, 1 H, C*H*-O); 3.47 (*dd*, *J* = 16.3, 5.8, 1 H, C*H*H-C(O)); 3.07 (*dd*, *J* = 16.3, 4.3, 1 H, CH*H*-C(O)); 2.23 (*m*, 1 H, C*H*$(CH_2)_2$); 1.72 & 1.45 & 1.26 (3 x *m*, 8 H, 4 x $(CH_2)_{ring}$).

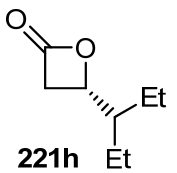
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 168.3, 74.2, 43.5, 41.8, 28.4, 27.7, 25.7, 25.6.

IR (ATR): ν = 2954, 2869, 1816, 1277, 1123, 857.

MS (EI) *m/z*: 140.1 [M^+] (3), 67.1 (100).

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.55; H, 8.63; O, 22.83. Found: C, 68.72; H, 8.79.

(*S*)-4-(1-Ethyl-propyl)-oxetan-2-one 221h



221h

β-Lactone **221h** was prepared according to GP3 using aldehyde **228** (reaction time: 136 h) and was furnished as solution in toluene (0.47 mmol, yield: 94%, *ee* = 80%).

The *ee* value was determined by GC (GammaDex^{TM}, 100 °C, 2.0 mL/min).

$C_8H_{14}O_2$, MW: 142.20 g/mol.

[α] $_D^{26.0°C}$ (c = 1.000, $CHCl_3$) = +13.7 ± 0.7.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.37 (*ddd*, *J* = 8.3, 5.7, 4.5, 1 H, C*H*-O); 3.47 (*dd*, *J* = 16.3, 5.8, 1 H, C*H*H-C(O)); 3.12 (*dd*, *J* = 16.3, 4.4, 1 H, CH*H*-C(O)); 1.55 + 1.36 (2 x *m*, 5 H, C*H*(CH_2)$_2$); 0.93 (*m*, 6 H, 2 x CH_3).

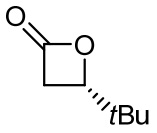
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 168.3, 73.8, 44.7, 41.7, 21.6, 21.0, 11.1, 10.4.

IR (ATR): ν = 2965, 2878, 1825, 1462, 1277, 1119, 862.

HRMS (EI) *m/z*: Calc. for [M^+]: 142.0988. Found: 142.0987.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92; O, 22.50. Found: C, 67.52; H, 9.68.

(*S*)-4-*tert*-Butyl-oxetan-2-one 221i



221i

β-Lactone **221i** was prepared according to GP3 using aldehyde **229** (reaction time: 135 h) and was furnished as solution in toluene (0.42 mmol, yield: 83%, *ee* = 78%) The *ee* value was determined by HPLC (Chiralcel OD-H, 97:3 *n*-hexane/*i*PrOH, 1.0 mL/min, 210 nm) after ring opening with (*S*)-1-phenylethylamine (*vide infra*). Spectral data for the (*S*)-enantiomer has been reported earlier.[104]

$C_7H_{12}O_2$, MW: 128.17 g/mol.

[α] $_D^{24.4°C}$ (c = 0.825, $CHCl_3$) = +18.3 ± 0.8.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.25 (*dd*, *J* = 6.0, 4.5, 1 H, C*H*-O); 3.32 (*dd*, *J* = 16.5, 6.0, 1 H, C*H*H-C(O)); 3.16 (*dd*, *J* = 16.5, 4.5, 1 H, CH*H*-C(O)); 1.00 (*s*, 9 H, 3 x CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 168.2, 77.9, 38.2, 32.9, 24.1.

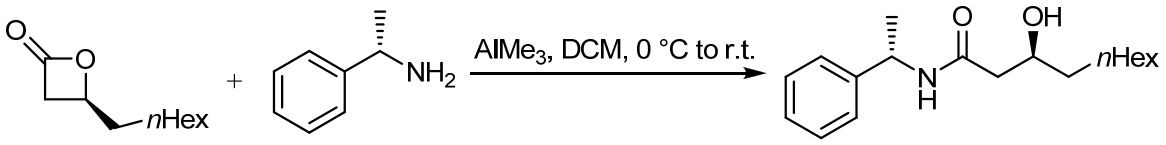
IR (ATR): ν = 2963, 2875, 1823, 1129, 944, 866.

HRMS (EI) *m/z*: Calc. for [M^+]: 128.0832. Found: 128.0828.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44; O, 24.97. Found: C, 65.49; H, 9.29.

11.1.1.4 Ring Opening Reactions

(*S*)-3-Hydroxy-decanoic acid ((*S*)-1-phenyl-ethyl)amide 316c



221c **316c**

Amide **316c** was prepared according to GP4 using 4-*n*heptyl-oxetan-2-one **221c** (0.21 mmol) in DCM (1.2 mL). Purification by flash chromatography (cyclohexane/ethyl acetate 2:1) gave title compound **316c** as a white solid (54 mg, 0.19 mmol, yield: 89%). The *dr* value of the crude product was determined by HPLC (Chiralcel OD-H, 97:3 *n*-hexane/*i*PrOH, 1.0 mL/min, 210 nm).

$C_{18}H_{29}NO_2$, MW: 291.43 g/mol.

MP: 87-88 °C ((*S*)-3-hydroxy isomer).

[α] $_D^{25.9°C}$ ((*S*)-3-hydroxy isomer, c = 0.875, $CHCl_3$) = 57.5 ± 0.5.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C, mixture of (*S*)- and (*R*)-3-hydroxy isomers): δ = 7.37-

7.23 (*m*, 5 H, C*H*$_{Ar}$); 6.03 (*m*, 1 H, N*H*); 5.14 (*m*, 1 H, C*H*-N); 3.98 (*m*, 1 H, C*H*-O); 3.53 (*m*, 1 H, O*H*); 2.40-2.21 (*m*, 2 H, C*H*$_2$-C(O)); 1.49 (*d*, *J* = 6.8, 3 H, C*H*$_3$-CH); 1.42-1.26 (*m*, 12 H, C*H*$_2$); 0.87 (*m*, 3 H, C*H*$_3$-CH$_2$).

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C, (*S*)-3-hydroxy isomer): δ = 7.36-7.23 (*m*, 5 H, C*H*$_{Ar}$); 6.17 (*d*, *J* = 7.4, 1 H, N*H*); 5.12 (*m*, 1 H, C*H*-N); 3.97 (*m*, 1 H, C*H*-O); 3.58 (*d*, *J* = 3.6, 1 H, O*H*); 2.36 (*dd*, *J* = 15.3, 2.9, 1 H, C*H*H-C(O)); 2.24 (*dd*, *J* = 15.3, 8.9, 1 H, CH*H*-C(O)); 1.48 (*d*, *J* = 6.9, 3 H, C*H*$_3$-CH); 1.42-1.26 (*m*, 12 H, C*H*$_2$); 0.87 (*m*, 3 H, C*H*$_3$-CH$_2$).

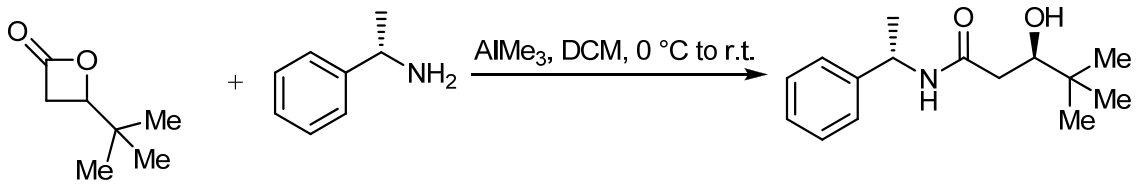
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.5, 143.0, 128.7, 127.4, 126.0, 68.7, 48.7, 42.5, 36.9, 31.7, 29.5, 29.2, 25.4, 22.6, 21.9, 14.1.

IR (ATR): ν = 3292, 3204, 2921, 2851, 1635, 1540, 1470, 1453, 1376, 1129, 1085, 1019, 694.

HRMS (ESI) *m/z*: Calc. for [MNa$^+$]: 314.2091. Found: 314.2087.

Anal. Calcd. for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81; O, 10.98. Found: C, 74.42; H, 10.07; N, 4.81.

(*S*)-3-Hydroxy-4,4-dimethyl-pentanoic acid ((*S*)-1-phenyl-ethyl)amide 316i



221i **316i**

Amide **316i** was prepared according to GP4 using 4-*tert*-butyl-oxetan-2-one (0.55 mmol) **221i** in DCM (3 mL). Purification by flash chromatography (cyclohexane/ethyl acetate 2:1) gave title compound **316i** as an amorphous colorless solid (102 mg, 0.41 mmol, yield: 75%, *ee* = 79%).

The *dr* value of the crude product was determined by HPLC (Chiralcel OD-H, 97:3 *n*-hexane/*i*PrOH, 1.0 mL/min, 210 nm).

$C_{15}H_{23}NO_2$, **MW:** 249.35 g/mol.

MP: 66-67 °C ((*S*)-3-hydroxy isomer).

$[\alpha]_D^{25.7°C}$ ((*S*)-3-hydroxy isomer, c = 0.995, $CHCl_3$) = 87.3 ± 0.4.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C, (*S*)-3-hydroxy isomer): δ = 7.37-7.23 (*m*, 5 H, CH_{Ar}); 6.18 (*m*, 1 H, N*H*); 5.13 (*m*, 1 H, C*H*-N); 3.66 (*m*, 1 H, C*H*-O); 3.57 (*d*, *J* = 3.1, 1 H, O*H*); 2.34 (*dd*, *J* = 15.3, 2.2, 1 H, C*H*H-C(O)); 2.21 (*dd*, *J* = 14.9, 10.3, 1 H, CH*H*-C(O)); 1.49 (*d*, *J* = 6.9, 3 H, CH_3-CH); 0.90 (*s*, 9 H, CH_3-C).

^{13}C NMR (75 MHz, $CDCl_3$, 21 °C, (*S*)-3-hydroxy isomer): δ = 172.0, 142.8, 128.6, 127.3, 126.0, 76.1, 48.8, 37.7, 34.5, 25.7, 21.9.

IR (ATR): ν = 3466, 3283, 3066, 2962, 2871, 1641, 1623, 1539, 1387, 1375, 1362, 1078, 1013, 761, 697.

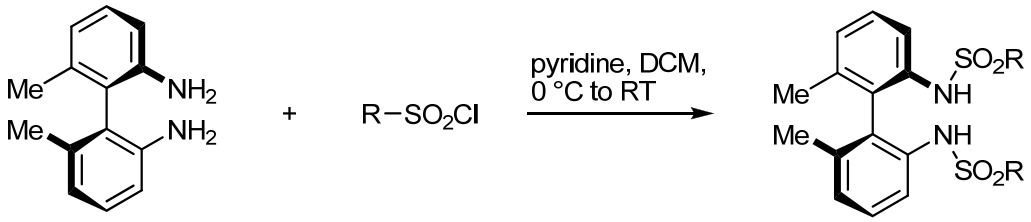
HRMS (ESI) *m/z*: Calc. for [MNa^+]: 272.1621. Found: 272.1627.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62; O, 12.83. Found: C, 72.09; H, 9.33; N, 5.56.

11.1.2 Part A2: Catalysis with Ligand 224

11.1.2.1 General Procedures

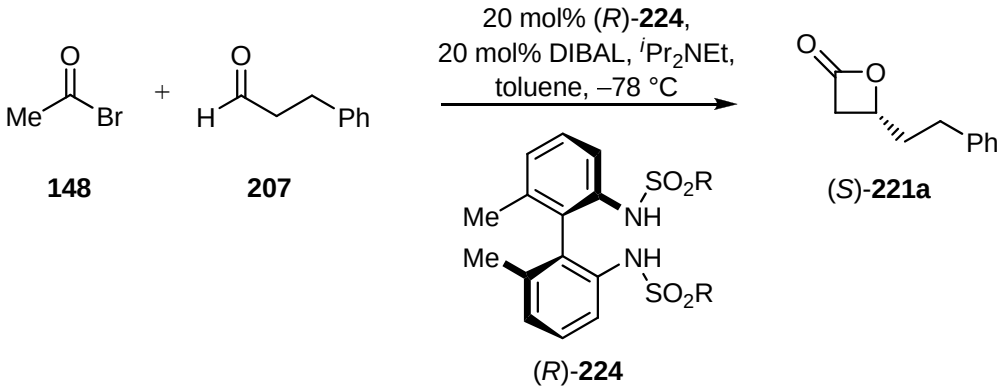
General procedure for the formation of bis(*N*-sulfonylamino)-6,6'-dimethylbiphenyl-2,2'-diamine ligands (*R*)-224 (GPA2-1)[170]



317 **215** (*R*)-**224**

To a solution of the diamine **317** (1 equiv.) in DCM (7 mL) at 0 °C pyridine (6-6.5 equiv.) was added, followed by a solution of the corresponding sulfonyl chloride **215** in DCM. The solution was stirred at ambient temperature and the conversion was monitored by HPLC.
The reaction was quenched with 10 mL 1M HCl and extracted with DCM (2x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography.

General procedure for the formation of β-lactone (*R*)-221a (GPA2-2)



148 **207** (*S*)-**221a**

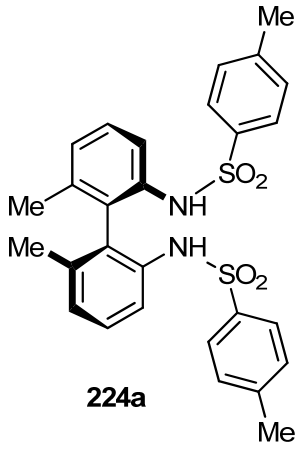
(*R*)-**224**

To a mixture of ligand **224** (0.10 mmol, 0.2 equiv.) in toluene (4 mL) was slowly added at ambient temperature a solution of Dibal (1.0 M in hexane, 0.10 mmol, 0.2 equiv.).

The mixture was heated to 80 °C and stirred for 2 h. Subsequently, the solution was stirred for 1 h at ambient temperature. The catalyst solution was then cooled to −78 °C and dihydrocinnamaldehyde (**207**) (0.5 mmol, 1 equiv.), acetyl bromide (**148**, 1.5 mmol, 3 equiv.) and diisopropylethylamine (1.25 mmol, 2.5 equiv.) were successively added. The resulting heterogeneous mixture was stirred at −78 °C until complete conversion as monitored by ^{1}H-NMR (26-72 h). The reaction mixture was poured into aqueous 1 M HCl (20 mL) and extracted with cyclohexane (3 x 15 mL). The combined organic phase was dried over $MgSO_4$, filtered and cyclohexane was removed *in vacuo*. The yield was determined by ^{1}H-NMR using pyridine as internal standard.

11.1.2.2 Ligand Synthesis

(*R*)-*N*,*N*'-(6,6'-dimethylbiphenyl-2,2'-diyl)bis(4-methylbenzenesulfonamide) 224a



224a

Bissulfonamide **224a** was prepared according to GPA2-1 (reaction time: 8 h) from (*R*)-6,6'-dimethylbiphenyl-2,2'-diamine (**317**) (151 mg, 0.71 mmol, 1 equiv.), pyridine (517 µL, 6.40 mmol, 9 equiv.) and 4-methylbenzene-1-sulfonyl chloride (434 mg, 2.28 mmol, 3.2 equiv.). After 1 h an additional amount of the sulfonyl chloride (135 mg, 0.71 mmol, 1 equiv.) and pyridine (57 µL, 0.71 mmol, 1 equiv.) was added. Purification by flash chromatography (cyclohexane/ethyl acetate 20:1) gave title compound **224a** as a light orange solid (0.34 g, 0.65 mmol, yield: 91%).

$C_{28}H_{28}N_2O_4S_2$, **MW:** 520.66 g/mol.

MP: 152.7-153.8 °C.

[α] $_D^{25.1°C}$ (c = 0.363, $CHCl_3$) = –27.4° ± 0.1.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.65 (*m*, 4H, C*H*$_{Ar}$), 7.55 (*d*, *J* = 8.1 Hz, 2H, C*H*$_{Ar}$), 7.27 (*m*, 6H, C*H*$_{Ar}$), 6.99 (*m*, 2H, C*H*$_{Ar}$), 5.76 (*s*, 2H, N*H*), 2.40 (*s*, 6H, C*H*$_3$), 1.57 (*s*, 6H, C*H*$_3$).

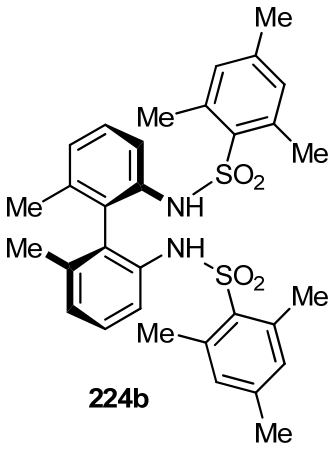
^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 144.5, 138.1, 136.0, 135.2, 129.9, 129.8, 127.2, 126.2, 123.4, 115.7, 21.6, 19.3.

IR ($CHCl_3$): ν = 3347, 3033, 2925, 1598, 1582, 1464, 1384, 1326, 1164.

LRMS (EI) *m/z*: Calc. for [M^+]: 520.1. Found: 520.2.

Anal. Calcd. for $C_{28}H_{28}N_2O_4S_2$: C, 64.59%; H, 5.42%; N, 5.38%. Found: C, 64.32%; H, 5.51%; N, 5.34%.

(*R*)-*N*,*N*'-(6,6'-dimethylbiphenyl-2,2'-diyl)bis(2,4,6-trimethylbenzenesulfonamide) 224b



224b

Bissulfonamide **224b** was prepared according to GPA2-1 (reaction time: 55 h) from (*R*)-6,6'-dimethylbiphenyl-2,2'-diamine (**317**) (204 mg, 0.96 mmol, 1 equiv.), pyridine (465 µL, 5.77 mmol, 6 equiv.) and 2,4,6-trimethylbenzene-1-sulfonyl chloride (542 mg, 1.92 mmol, 2.0 equiv.) in DCM (7 mL). After 27 h an additional amount of the sulfonyl chloride (271 mg, 0.96 mmol, 1 equiv.) and pyridine (233 µL, 2.88 mmol, 3 equiv.) was added.

Purification by flash chromatography (DCM/ethyl acetate 100:1) gave title compound **224b** as a light purple solid (0.51 g, 0.89 mmol, yield: 92%).

$C_{32}H_{36}N_2O_4S_2$, MW: 576.77 g/mol.

MP: decomposition above 200 °C.

[α] $_D^{25.3°C}$ (c = 0.368, $CHCl_3$) = +29.1° ± 0.1.

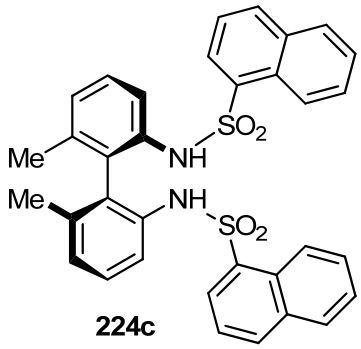
^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.20 (*m*, 4H, CH_{Ar}), 7.01 (*d*, *J* = 7.30, 2H, CH_{Ar}), 6.93 (*s*, 4H, CH_{Ar}), 6.14 (*s*, 2H, N*H*) 2.45 (*s*, 12H, CH_3), 2.30 (*s*, 6 H, CH_3), 1.64 (*s*, 6H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 139.2, 138.4, 135.5, 134.6, 132.2, 131.7, 129.5, 126.9, 126.5, 118.4, 22.9, 22.6, 21.0, 19.6.

IR ($CHCl_3$): ν = 3358, 3033, 2942, 1603, 1581, 1463, 1374, 1326, 1157.

HRMS (EI) *m/z*: Calc. for [M^+]: 576.2116. Found: 576.2111.

(*R*)-*N*,*N*'-(6,6'-dimethylbiphenyl-2,2'-diyl)dinaphthalene-1-sulfonamide 224c



224c

Bissulfonamide **224c** was prepared according to GP1 (reaction time: 49 h) from (*R*)-6,6'-dimethylbiphenyl-2,2'-diamine (**317**) (134 mg, 0.63 mmol, 1 equiv.), pyridine (332 µL, 4.11 mmol, 6.5 equiv.) and naphthalene-1-sulfonyl chloride (316 mg, 1.39 mmol, 2.2 equiv.).

After 3.5 h an additional amount of the sulfonyl chloride (143 mg, 0.63 mmol, 1 equiv.) and pyridine (153 µL, 1.89 mmol, 3 equiv.) was added. Purification by flash chromatography (cyclohexane/ethyl acetate 20:1) gave title compound **224c** as a yellow solid (0.35 g, 0.59 mmol, yield: 93%).

$C_{34}H_{28}N_2O_4S_2$, **MW:** 592.73 g/mol.

MP: 98.3-99.2 °C.

[α] $_D^{25.3°C}$ (c = 0.363, $CHCl_3$) = +122.3° ± 0.1.

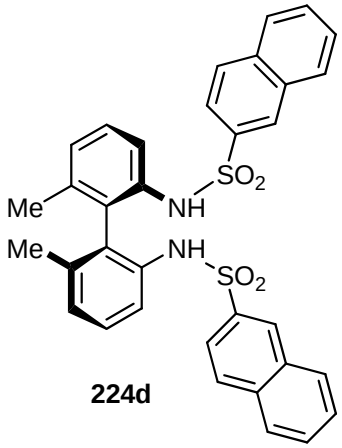
^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 8.27 (*dd*, *J* = 7.4, 1.3, 2H, C*H*$_{Ar}$), 8.16 (*dd*, *J* = 8.6, 0.9 , 2H, C*H*$_{Ar}$), 8.04 (*d*, *J* = 8.3, 2H, C*H*$_{Ar}$), 7.90 (*m*, 2H, C*H*$_{Ar}$), 7.57 (*m*, 2H, C*H*$_{Ar}$), 7.50 (*m*, 4H, C*H*$_{Ar}$), 7.39 (*m*, 2H, C*H*$_{Ar}$), 7.14 (*m*, 2H, C*H*$_{Ar}$), 6.72 (*m*, 2H, C*H*$_{Ar}$), 6.13 (*s*, 2H, N*H*), 1.09 (*s*, 6H, C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 138.1, 134.9, 134.3, 134.2, 130.0, 129.5, 129.1, 128.8, 127.0, 126.5, 124.5, 124.0, 123.8, 116.8, 19.0.

IR ($CHCl_3$): ν = 3348, 3034, 1581, 1508, 1464, 1384, 1328, 1165, 1136.

LRMS (EI) *m/z*: Calc. for [MNa^+]: 615.1. Found: 615.2.

(*R*)-*N*,*N*'-(6,6'-dimethylbiphenyl-2,2'-diyl)dinaphthalene-2-sulfonamide 224d



224d

Bissulfonamide **224d** was prepared according to GP1 (reaction time: 38 h) from (*R*)-6,6'-dimethylbiphenyl-2,2'-diamine (**317**) (131 mg, 0.62 mmol, 1 equiv.), pyridine (324 µL, 4.02 mmol, 9 equiv.) and naphthalene-2-sulfonyl chloride (308 mg, 1.36 mmol, 2.2 equiv.). After 15 h an additional amount of the sulfonyl chloride (140 mg, 0.62 mmol, 1 equiv.) and pyridine (150 µL, 1.86 mmol, 3 equiv.) was added. Purification by flash chromatography (cyclohexane/ethyl acetate 100:1) gave title compound **224d** as a white solid (0.27 g, 0.45 mmol, yield: 73%).

$C_{34}H_{28}N_2O_4S_2$, **MW:** 592.73 g/mol.

MP: 92.8-93.7 °C.

[α] $_D^{25.7°C}$ (c = 0.400, $CHCl_3$) = –13.2° ± 0.1.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 8.42 (*d*, *J* = 2.1, 2H, CH_{Ar}), 7.95 (*dd*, *J* = 7.5, 1.2 , 2H, CH_{Ar}), 7.92 (*d*, *J* = 8.4, 2H, CH_{Ar}), 7.89 (*dd*, *J* = 7.7, 1.3, 2H, CH_{Ar}), 7.69 (*dd*, *J* = 8.7, 2.0, 2H, CH_{Ar}), 7.61 (*m*, 4H, CH_{Ar}), 7.54 (*d*, *J* = 8.0, 2H, CH_{Ar}), 7.25 (*t*, *J* = 8.0, 2H, CH_{Ar}), 6.96 (*m*, 2H, CH_{Ar}), 6.02 (*s*, 2H, N*H*), 1.51 (*s*, 6H, CH_3).

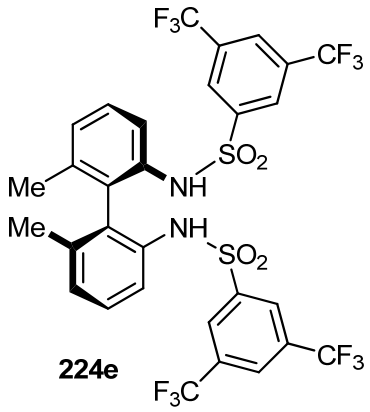
^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 138.2, 136.0, 135.1, 135.1, 132.0, 129.9, 129.8, 129.3, 129.0, 128.0, 127.6, 126.4, 123.8, 122.1, 116.0, 19.3.

IR ($CHCl_3$): ν = 3347, 3061, 3034, 1582, 1464, 1384, 1327, 1163.

LRMS (EI) *m/z*: Calc. for [MNa^+]: 615.1. Found: 614.8.

Anal. Calcd. for $C_{34}H_{28}N_2O_4S_2$: C, 68.90%; H, 4.76%; N, 4.73%. Found: C, 68.73%; H, 4.88%; N, 4.58%.

(*R*)-*N*,*N*'-(6,6'-dimethylbiphenyl-2,2'-diyl)bis(3,5-bis(trifluoromethyl)benzenesulfonamide) 224e



224e

Bissulfonamide **224e** was prepared according to GP1 (reaction time: 93 h) from (*R*)-6,6'-dimethylbiphenyl-2,2'-diamine (**317**) (134 mg, 0.63 mmol, 1 equiv.), pyridine (332 µL, 4.11 mmol, 6.5 equiv.) and 3,5-bis(trifluoromethyl)benzene-1-sulfonyl chloride (435 mg, 1.39 mmol, 2.2 equiv.). After 17 h an additional amount of the sulfonyl chloride (198 mg, 0.63 mmol, 1 equiv.) and pyridine (153 µL, 1.89 mmol, 3 equiv.) was added. Purification by flash chromatography (CH_2Cl_2) gave title compound **224e** as a white solid (0.40 g, 0.52 mmol, yield: 82%).

$C_{30}H_{20}F_{12}N_2O_4S_2$, **MW:** 764.60 g/mol.

MP: 61.8-64.1 °C.

[α] $_D^{25.9°C}$ (c = 0.401, $CHCl_3$) = –14.4° ± 0.1.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 8.21 (*m*, 4H, C*H*$_{Ar}$), 8.08 (*s*, 2H, C*H*$_{Ar}$), 7.36 (*m*, 4H, C*H*$_{Ar}$), 7.10 (*m*, 2H, C*H*$_{Ar}$), 6.02 (*s*, 2H, N*H*), 1.59 (*s*, 6H, C*H*$_3$).

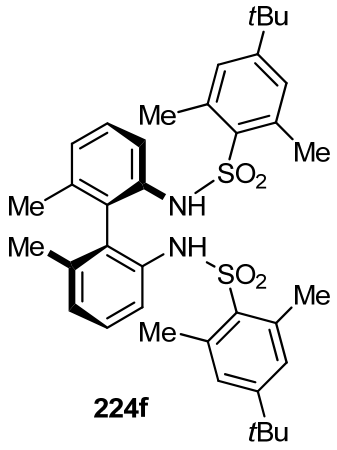
^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 142.3, 138.4, 133.9, 133.7, 133.3, 133.0, 132.7, 130.3, 128.0, 127.5, 127.4, 127.1, 127.0, 127.0, 125.9, 123.7, 121.0, 117.9, 19.3.

IR ($CHCl_3$): ν = 3339, 3086, 1581, 1463, 1397, 1359, 1280, 1224, 11.88, 1169, 1150, 1109.

LRMS (EI) *m/z*: Calc. for [MNa^+]: 787.1. Found: 787.0.

Anal. Calcd. for $C_{30}H_{20}F_{12}N_2O_4S_2$: C, 47.13%; H, 2.64%; N, 3.66%. Found: C, 46.99%; H, 2.75%; N, 3.61%.

(*R*)-*N*,*N*'-(6,6'-dimethylbiphenyl-2,2'-diyl)bis(3,5-bis(trifluoromethyl)benzenesulfonamide) 224f



224f

Bissulfonamide **224f** was prepared according to GP1 (reaction time: 7 d) from (*R*)-6,6'-dimethylbiphenyl-2,2'-diamine (**317**) (27 mg, 0.13 mmol, 1 equiv.), pyridine (66 µL, 0.81 mmol, 6.2 equiv.) and 4-*tert*-butyl-2,6-dimethylbenzene-1-sufonyl chloride (72 mg, 0.28 mmol, 2.2 equiv.) in CH_2Cl_2 (2 mL). After 54 h an additional amount of the sulfonyl chloride (33 mg, 0.13 mmol, 1 equiv.) and pyridine (10 µL, 0.13 mmol, 1 equiv.) was added. Purification by flash chromatography (CH_2Cl_2/ethyl acetate 20:1) gave title compound **224f** as a white solid (48 mg, 0.08 mmol, yield: 58%).

$C_{38}H_{48}N_2O_4S_2$, **MW:** 660.93 g/mol.

MP: 213.2-214.0 °C.

$[\alpha]_D^{26.1°C}$ (c = 0.424, $CHCl_3$) = –4.5° ± 0.2.

^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 7.23 (*m*, 4H), 7.09 (*s*, 4H), 7.00 (*ddd*, *J* = 6.9, 1.8, 0.7, 2H), 6.19 (*s*, 2H), 2.47 (*s*, 12H, CH_3), 1.58 (*s*, 6H, CH_3), 1.30 (*s*, 18H, C(CH_3)$_3$).
^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 155.4, 138.9, 138.4, 135.5, 134.8, 129.4, 128.6, 126.9, 126.7, 11.8, 34.6, 30.9, 23.3, 19.5.

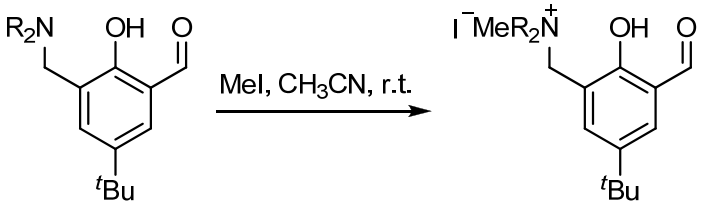
IR ($CHCl_3$): ν = 3356, 3034, 2966, 1594, 1581, 1558, 1463, 1375, 1327, 1175, 1146.

HRMS (EI) *m/z*: Calc. for [M^+]: 660.3055. Found: 660.3058.

11.2 Part B: Dual Activation Catalysis

11.2.1 General Procedures

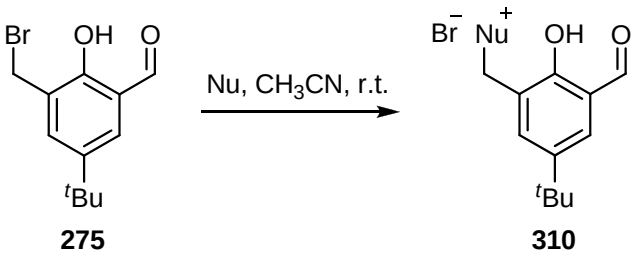
General procedure for the formation of aldehydes 309 (GPB-1)



272 **309**

Aldehyde **272** (1equiv.) was dissolved in dry acetonitrile and MeI (1 equiv.) was added. The mixture was stirred for 14 h at ambient temperature. Et_2O was added and the suspension was filtered. After washing with Et_2O the product was dried *in vacuo* to give **309**. If not otherwise mentioned no further purification step was carried out.

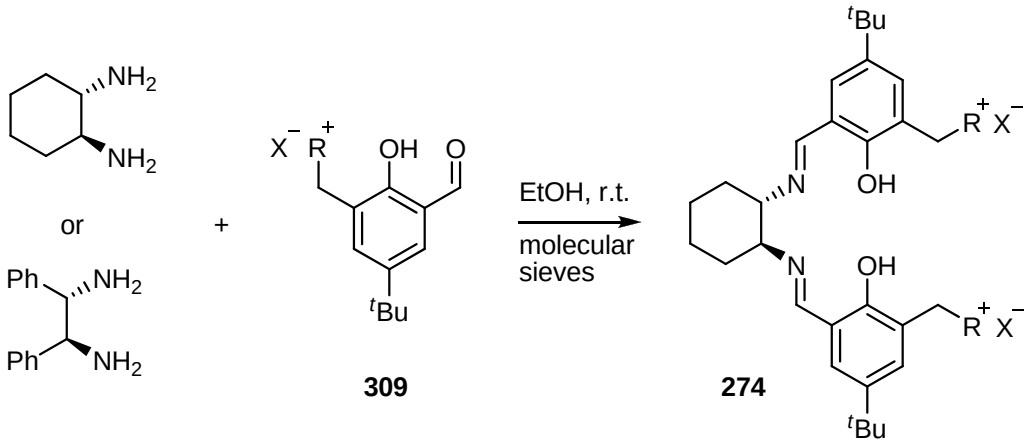
General procedure for the formation of aldehydes 310 (GPB-2)



275 **310**

3-Bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (**275**)[177] (1equiv.) was dissolved in dry acetonitrile and the corresponding nucleophile (Nu, 1 equiv.) was added. The suspension was stirred for 14 h at ambient temperature. Et_2O was added and the mixture was filtered. After washing with Et_2O the product was dried *in vacuo* to give **310**. If not otherwise mentioned no further purification step was carried out.

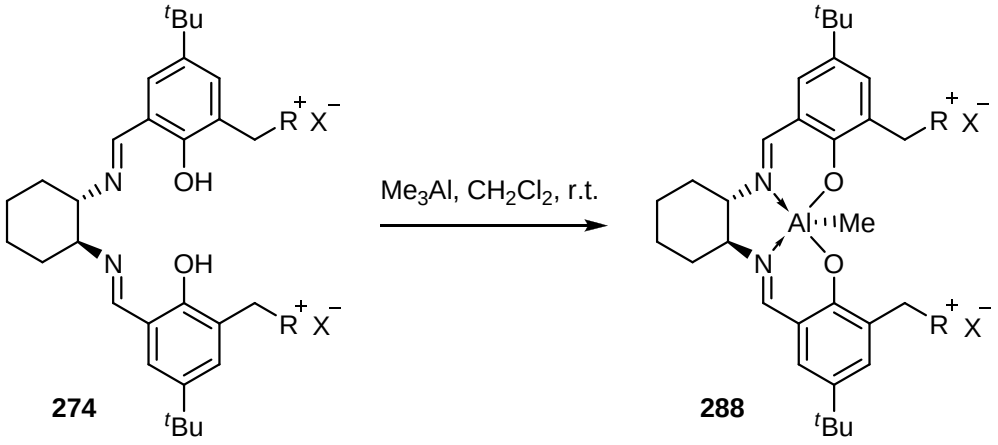
General procedure for the formation of ligands 274 k-p (GPB-3)



309 **274**

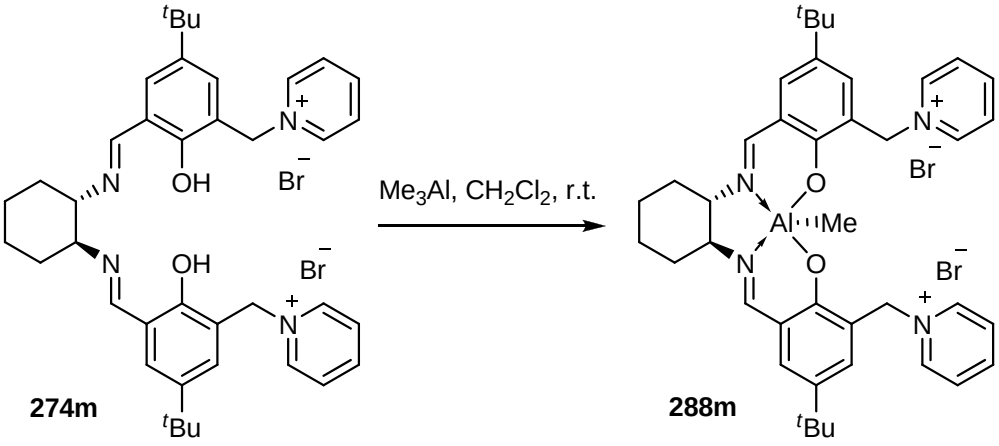
To a solution of (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (1 equiv.) in ethanol at ambient temperature aldehyde **309** (2 equiv.) and molecular sieves (4Å) were added. The mixture was stirred for 14 h at ambient temperature. After filtration, EtOH was removed *in vacuo*. Subsequent repetitive azeotropic removal of residual EtOH with DCM gave **274** as a solid. If not otherwise mentioned no further purification step was carried out.

General procedure for the formation of catalysts 288 k-p (GPB-4)



To a solution of diimine **274** (0.21 mmol, 1 equiv.) in DCM (3.5 mL) a solution of Me_3Al in toluene (2 M, 0.10 mL, 0.21 mmol, 1 equiv.) was added. The mixture was stirred for 3 h at ambient temperature.

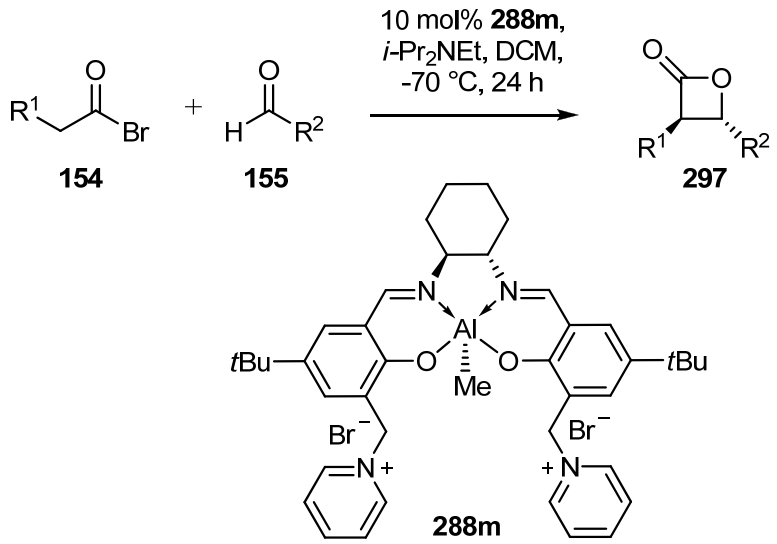
General procedure for the formation of the active catalyst 288m



To a solution of diimine **274m** (0.16 g, 0.21 mmol, 1 equiv.) in DCM (3.5 mL) a solution of Me_3Al in toluene (2 M, 0.10 mL, 0.21 mmol, 1 equiv.) was added. The mixture was stirred for 3 h at ambient temperature. Pentane (5 mL) was added to fully precipitate complex **288m** and the mixture was filtered under nitrogen. Washing the filter cake with an additional amount of pentane (5 mL) and drying *in vacuo* afforded the active catalyst as bright yellow powder in quantitative yield.

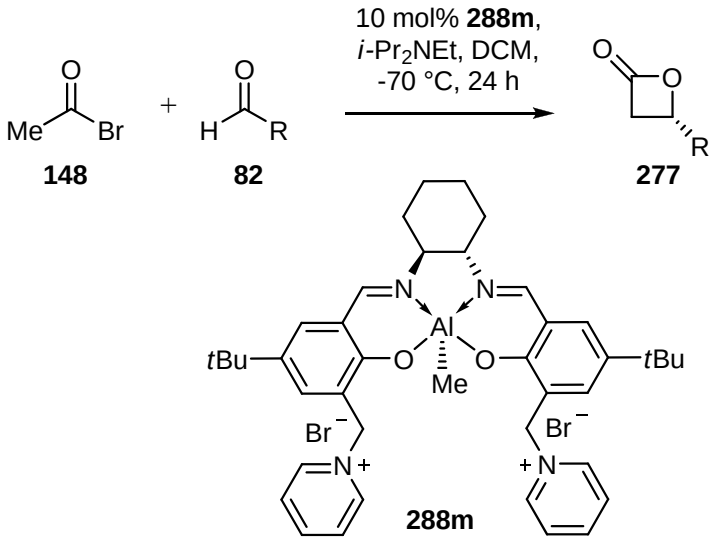
To avoid decomposition, the complex was synthesized at the same day as the catalysis was carried out.

General procedure for the asymmetric formation of *trans*-configured β-lactones 297 (GPB-5)



To a mixture of complex **288m** (0.075 mmol, 0.1 equiv.) in DCM (3 mL) was successively added at −70 °C aldehyde **155** (0.75 mmol, 1 equiv.), acid bromide **154** (4.5 mmol, 6 equiv.) and diisopropylethylamine (1.875 mmol, 2.5 equiv.). The resulting heterogeneous mixture was stirred at −70 °C for 24 h. The reaction mixture was poured into aqueous 1 M HCl (30 mL) and extracted with DCM (2 x 20 mL). The combined organic phase was dried over $MgSO_4$ and filtered through a short plug of silica gel. DCM was subsequently removed *in vacuo*. For β-lactones **297a**, **c**, **e** and **h** the yield was determined by ^{1}H-NMR using acetophenone as internal standard. The crude product mixtures of all other β-lactones were purified by flash chromatography.

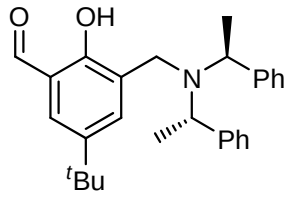
General procedure for the asymmetric formation of β-lactones 277 (GPB-6)



To a mixture of complex **288m** (0.05 mmol, 0.1 equiv.) in DCM (2 mL) was successively added at −70 °C aldehyde **82** (0.50 mmol, 1 equiv.), acid bromide **148** (3.0 mmol, 6 equiv.) and diisopropylethylamine (1.25 mmol, 2.5 equiv.). The resulting heterogeneous mixture was stirred at −70 °C for 24 h. The reaction mixture was poured into aqueous 1 M HCl (20 mL) and extracted with DCM (2 x 20 mL). The combined organic phase was dried over $MgSO_4$ and filtered through a short plug of silica gel. DCM was subsequently removed *in vacuo*. For β-lactone **277** the yield was determined by ^{1}H-NMR using acetophenone as internal standard. The crude product mixtures of all other β-lactones were purified by flash chromatography.

11.2.2 Synthesis of the Ligand Precursor

5-*tert*-Butyl-2-hydroxy-3-((bis((*S*)-1-phenylethyl)amino)methyl)benzaldehyde (272f)



272f

Aldehyde **272f** was prepared according to GPB-2 using 3-bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (**275**) (0.26 g, 0.95 mmol, 1 equiv.) and (–)-bis((*S*)-1-phenylethyl)amine (0.43 g, 1.90 mmol, 2 equiv.) in 5 mL acetonitrile, but instead of adding Et_2O and subsequent filtration the solvent was removed *in vacuo*. The residue was dissolved in Et_2O (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by flash-chromatography (cyclohexane/ethyl acetate 14:1) gave title compound **272f** as yellow oil (0.33 g, 0.80 mmol, yield: 84%).

$C_{28}H_{33}NO_2$, MW: 415.57 g/mol.

[α] $^{25.0°C}_{D}$ (c = 1.600, $CHCl_3$) = –18.1 ± 0.1.

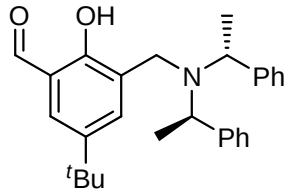
^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 11.51 (*bs*, 1 H, $C_{Ar}OH$); 10.06 (*s*, 1 H, C*H*O); 7.56 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.41 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.29 (*m*, 8 H, CH_{Ph}); 7.23 (*m*, 2 H, CH_{Ph}); 4.12 (*d*, *J* = 15.8, 1 H, $C_{Ar}CH$); 4.04 (*q*, *J* = 6.9, 2 H, C*H*CH_3); 3.60 (*d*, *J* = 15.8, 1 H, $C_{Ar}CH$); 1.42 (*d*, *J* = 6.9, 6 H, CHCH_3); 1.29 (*s*, 9 H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 194.4, 158.3, 143.3, 142.1, 133.8, 129.2, 128.4, 128.2, 127.3, 125.8, 121.0, 58.8, 45.7, 34.3, 31.5, 18.6.

IR (ATR): ν = 2964, 1650, 1451, 1265, 1213, 728, 698.

HRMS (EI) *m/z*: Calc. for $[M]^+$: 415.2506. Found: 415.2504.

5-*tert*-Butyl-2-hydroxy-3-((bis((*R*)-1-phenylethyl)amino)methyl)benzaldehyde (272g)



272g

Aldehyde **272g** was prepared according to GPB-2 using 3-bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (**275**) (0.26 g, 0.95 mmol, 1 equiv.) and (+)-bis((*R*)-1-phenylethyl)amine (0.43 g, 1.90 mmol, 2 equiv.) in 5 mL acetonitrile, but instead of adding Et_2O and subsequent filtration the solvent was removed *in vacuo*. The residue was dissolved in Et_2O (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by flash-chromatography (cyclohexane/ethyl acetate 14:1) gave title compound **272g** as yellow oil (0.30 g, 0.71 mmol, yield: 75%).

$C_{28}H_{33}NO_2$, **MW:** 415.57 g/mol.

[α] $_D^{25.0°C}$ (c = 1.490, $CHCl_3$) = +20.5 ± 0.1.

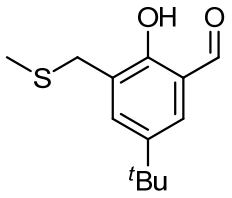
^{1}H NMR (400 MHz, CD_2Cl_2, 21 °C): δ = 11.41 (*s*, 1 H, $C_{Ar}OH$); 10.04 (*s*, 1 H, C*H*O); 7.58 (*d*, *J* = 2.6, 1 H, CH_{Ar}); 7.41 (*d*, *J* = 2.6, 1 H, CH_{Ar}); 7.29 (*m*, 8 H, CH_{Ph}); 7.21 (*m*, 2 H, CH_{Ph}); 4.05 (*m*, 3 H, $C_{Ar}CH$, $CHCH_3$); 3.60 (*d*, *J* = 15.8, 1 H, $C_{Ar}CH$); 1.42 (*d*, *J* = 6.9, 6 H, $CHCH_3$); 1.29 (*s*, 9 H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, CD_2Cl_2, 21 °C): δ = 194.5, 158.3, 143.7, 142.3, 134.1, 128.7, 128.5, 128.4, 127.4, 126.0, 121.2, 58.8, 45.6, 34.4, 31.4, 18.3.

IR (ATR): ν = 2964, 1650, 1450, 1265, 1212, 727, 697.

HRMS (ESI) *m/z*: Calc. for $[MH]^+$: 416.2584. Found: 416.2592.

5-*tert*-Butyl-2-hydroxy-3-(methylthiomethyl)benzaldehyde (272h)



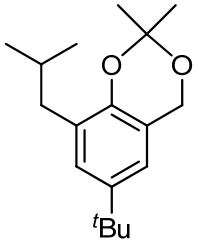
272h

Aldehyde **272h** was prepared according to GPB-2 using 3-bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (**275**) (0.65 g, 2.38 mmol, 1 equiv.) and sodium methanethiolate (0.17 g, 2.38 mmol, 2 equiv.), but instead of acetonitrile THF (50 mL) was used and the reaction was quenched with water (50 mL) followed by extraction with CH_2Cl_2 (3 x 40 mL). The organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Purification by flash-chromatography (cyclohexane/ethyl acetate 14:1) gave title compound **272h** as light yellow oil (0.16 g, 0.66 mmol, yield: 28%).

$C_{13}H_{18}O_2S$, **MW:** 238.35 g/mol.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 11.21 (*s*, 1 H, $C_{Ar}OH$); 9.88 (*s*, 1 H, C*H*O); 7.55 (*d*, *J* = 2.4, 1 H, CH_{Ar}); 7.43 (*d*, *J* = 2.4, 1 H, CH_{Ar}); 3.76 (*s*, 2 H, $C_{Ar}CH_2$); 2.08 (*s*, 3 H, SCH_3); 1.34 (*s*, 9 H, $C(CH_3)_3$).

6-*tert*-Butyl-8-isobutyl-2,2-dimethyl-4*H*-benzo[1,3]dioxine (285)



285

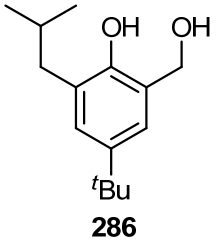
Acetonide **285** was prepared according to published procedure[143d] using 8-(bromomethyl)-6-*tert*-butyl-2,2-dimethyl-4*H*-benzo[1,3]dioxine (2.09 g, 6.68 mmol, 1 equiv.), isopropylmagnesiumchloride (2M in Et_2O, 3.65 mL, 8.02 mmol, 1.2 equiv.) and Li_2CuCl_4 (1M in THF, 4.01 mL, 0.40 mmol, 0.06 equiv.) in THF (60 mL). Purification by flash chromatography (cyclohexane/ethyl acetate 150:1) afforded **285** as a light yellow oil (1.06 g, 3.81 mmol, 57%).

$C_{18}H_{28}O_2$, **MW:** 276.41 g/mol.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 6.97 (*d*, *J* = 2.2, 1 H, CH_{Ar}); 6.79 (*d*, *J* = 2.2, 1 H, CH_{Ar}); 4.83 (*s*, 2 H, CH_2OH); 2.43 (*d*, *J* = 7.1, 2 H, $C_{Ar}CH_2$); 1.87 (*m*, 1 H, CH(CH_3)$_2$); 1.53 (*s*, 6 H, C(CH_3)$_2$); 1.27 (*s*, 9 H, C(CH_3)$_3$); 0.89 (*d*, *J* = 6.6, 6 H, CH(CH_3)$_2$).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21; O, 11.58. Found: C, 77.96; H, 10.48.

4-*tert*-Butyl-2-(hydroxymethyl)-6-isobutylphenol (286)



286

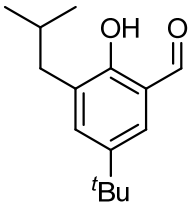
Diol **286** was prepared according to published procedure[143d] using 6-*tert*-butyl-8-isobutyl-2,2-dimethyl-4*H*-benzo[1,3]dioxine (**285**, 0.63 g, 2.28 mmol, 1 equiv.) and aq. HCl (1M, 17 mL) in THF (17 mL). Purification by flash chromatography (cyclohexane/ethyl acetate 14:1) afforded **286** as a colorless oil (0.27 g, 1.16 mmol, 51%).

$C_{15}H_{24}O_2$, MW: 236.35 g/mol.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.11 (*s*, 1 H, $C_{Ar}OH$); 7.05 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 6.88 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 4.84 (*d*, *J* = 5.9, 2 H, CH_2OH); 2.50 (*d*, *J* = 7.1, 2 H, $C_{Ar}CH_2$); 2.08 (*t*, *J* = 5.9, 1 H, CH_2OH); 1.94 (*m*, 1 H, $CH(CH_3)_2$); 1.25 (*s*, 9 H, $C(CH_3)_3$); 0.93 (*d*, *J* = 6.6, 6 H, $CH(CH_3)_2$).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23; O, 13.54. Found: C, 76.18; H, 10.42.

5-*tert*-Butyl-2-hydroxy-3-isobutylbenzaldehyde (287)



287

Aldehyde **287** was prepared according to published procedure[143d] using 4-*tert*-butyl-2-(hydroxymethyl)-6-isobutylphenol (0.27 g, 1.13 mmol, 1 equiv.) and MnO_2 (0.76 g, 7.88 mmol, 7 equiv.) in CH_2Cl_2 (14 mL). Purification by flash chromatography (cyclohexane/ethyl acetate 40:1) afforded **287** as a yellow oil (0.14 g, 0.59 mmol, 52%).

$C_{15}H_{22}O_2$, MW: 234.33 g/mol.

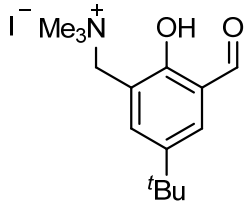
^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 11.10 (*s*, 1 H, $C_{Ar}OH$); 9.86 (*s*, 1 H, C*H*O); 7.39 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.35 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 2.53 (*d*, *J* = 7.2, 2 H, $C_{Ar}CH_2$); 1.96 (*m*, 1 H, $CH(CH_3)_2$); 1.32 (*s*, 9 H, $C(CH_3)_3$); 0.92 (*d*, *J* = 6.6, 6 H, $CH(CH_3)_2$).

^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 197.0, 158.0, 142.0, 136.2, 129.9, 127.6, 119.7, 38.9, 34.3, 31.6, 28.8, 22.8.

IR (ATR): ν = 2955, 1650, 1463, 1267, 1210, 717.

HRMS (ESI) *m/z*: Calc. for $[M]^+$: 234.1615. Found: 234.1617.

1-(5-*tert*-Butyl-3-formyl-2-hydroxyphenyl)-*N*,*N*,*N*-trimethylmethanaminium iodide (309k)



309k

Aldehyde **309k** was prepared according to GPB-1 using 5-*tert*-butyl-3-((dimethylamino)methyl)-2-hydroxybenzaldehyde (0.50 g, 2.12 mmol, 1 equiv.) and methyl iodide (0.13 mL, 2.12 mmol, 1 equiv.) in 15 mL acetonitrile. Et_2O (25 mL) was added and the mixture was filtered. After washing with Et_2O (10 mL) the product was dried *in vacuo* to give **309k** as a light yellow solid (0.64 g, 1.67 mmol, yield: 79%).

$C_{15}H_{24}INO_2$, MW: 377.26 g/mol.

Mp: decomposition above 212 °C.

^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 11.61 (*s*, 1 H, $C_{Ar}OH$); 9.95 (*s*, 1 H, C*H*O); 8.36 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.78 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 5.01 (*s*, 2 H, $C_{Ar}CH_2$); 3.36 (*s*, 9 H, $N(CH_3)_3$); 1.39 (*s*, 9 H, $C(CH_3)_3$).

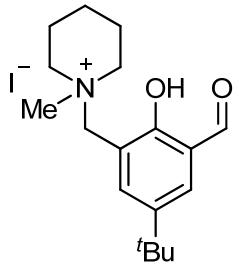
^{13}C NMR (100 MHz, DMSO, 21 °C): δ = 196.9, 157.9, 142.3, 139.4, 132.2, 121.3, 116.5, 61.9, 52.2, 33.9, 30.8.

IR ($CHCl_3$): ν = 3608, 3426, 2964, 1659, 1618, 1483, 1469.

HRMS (ESI) *m/z*: Calc. for $[M\text{-}Br]^+$: 250.1803. Found: 250.1802.

Anal. Calcd. for $C_{15}H_{24}INO_2$: C, 47.76; H, 6.41; N, 3.71; O, 8.48; I, 33.64. Found: C, 47.83; H, 6.48; N, 3.80.

1-(5-*tert*-Butyl-3-formyl-2-hydroxybenzyl)-1-methylpiperidinium iodide (309l)



309l

Aldehyde **309l** was prepared according to GPB-1 using 5-*tert*-butyl-2-hydroxy-3-(piperidin-1-ylmethyl)benzaldehyde (0.30 g, 1.10 mmol, 1 equiv.) and methyl iodide (69 µL, 1.10 mmol, 1 equiv.) in 5 mL acetonitrile. Et_2O (15 mL) was added and the mixture was filtered. After washing with Et_2O (5 mL) the product was dried *in vacuo* to give **309l** as a light yellow solid (0.33 g, 0.79 mmol, yield: 72%).

$C_{18}H_{28}INO_2$, **MW:** 417.12 g/mol.

Mp: decomposition above 213 °C.

^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 11.63 (*s*, 1 H, $C_{Ar}OH$); 9.94 (*s*, 1 H, C*H*O); 8.43 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.75 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 5.04 (*s*, 2 H, $C_{Ar}CH_2$); 3.76 (*m*, 2 H, $N(CH_2)_{ring}$); 3.51 (*m*, 2 H, $N(CH_2)_{ring}$); 3.20 (*s*, 3 H, NCH_3); 2.10-1.65 (*m*, 6 H, $(CH_2)_{ring}$); 1.40 (*s*, 9 H, $C(CH_3)_3$).

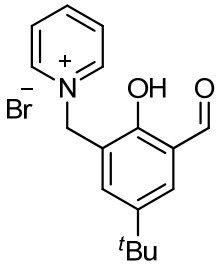
^{13}C NMR (100 MHz, CH_3CN, 21 °C): δ = 199.2, 159.8, 144.4, 140.9, 135.0, 122.0, 116.2, 62.9, 62.0, 47.5, 35.1, 31.5, 21.7, 20.8.

IR ($CHCl_3$): ν = 3410, 2958, 2869, 2435, 1658, 1617, 1469, 1454, 1280.

HRMS (ESI) *m/z*: Calc. for $[M-I]^+$: 290.2115. Found: 290.2110.

Anal. Calcd. for $C_{18}H_{28}INO_2$: C, 51.81; H, 6.76; N, 3.36; O, 7.67; I, 30.41. Found: C, 51.78; H, 6.60; N, 3.47.

1-(5-*tert*-Butyl-3-formyl-2-hydroxybenzyl)pyridinium bromide (309m)[178]



309m

Aldehyde **309m** was prepared according to GPB-2 using 3-Bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (6.07 g, 22.4 mmol, 1 equiv.) and pyridine (1.90 mL, 22.4 mmol, 1 equiv.) in 80 mL acetonitrile. Et_2O (50 mL) was added and the mixture was filtered. After washing with Et_2O (50 mL) the product was dried *in vacuo* to give **309m** as a white solid (7.20 g, 20.6 mmol, yield: 92%).

$C_{17}H_{20}BrNO_2$, MW: 350.25 g/mol.

Mp: >250 °C.

^{1}H NMR (300 MHz, DMSO, 21 °C): δ = 11.16 (*s*, 1 H, $C_{Ar}OH$); 10.05 (*s*, 1 H, C*H*O); 9.14 (*d*, *J* = 5.5, 2 H, *o*-CH_{Pyr}); 8.60 (*tt*, *J* = 7.6, 1.3, 1 H, *p*-CH_{Pyr}); 8.15 (*m*, 2 H, *m*-CH_{Pyr}); 8.09 (*d*, *J* = 2.6, 1 H, CH_{Ar}); 7.88 (*d*, *J* = 2.6, 1 H, CH_{Ar}); 5.89 (*s*, 2 H, $C_{Ar}CH_2$); 1.22 (*s*, 9 H, $C(CH_3)_3$).

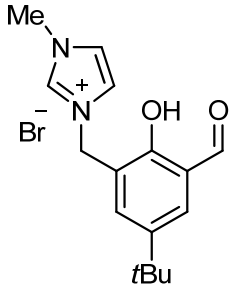
^{13}C NMR (75 MHz, DMSO, 21 °C): δ = 196.3, 156.7, 145.9, 145.0, 142.8, 136.3, 130.7, 128.1, 121.9, 121.2, 58.9, 34.1, 30.9.

IR ($CHCl_3$): ν = 3372, 2959, 2868, 2450, 1660, 1635, 1619, 1488, 1481, 1277.

HRMS (ESI) *m/z*: Calc. for $[M\text{-}Br]^+$: 270.1489. Found: 270.1489.

Anal. Calcd. for $C_{17}H_{20}BrNO_2$: C, 58.30; H, 5.76; N, 4.00; O, 9.14; Br, 22.81. Found: C, 58.36; H, 5.69; N, 4.06.

3-(5-*tert*-butyl-3-formyl-2-hydroxybenyl)-1-methyl-1*H*-imidazol-3-ium bromide (309n)



309n

Aldehyde **309n** was prepared according to GPB-2 using 3-Bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (0.70 g, 2.58 mmol, 1 equiv.) and 1-methylimidazole (0.20 mL, 2.58 mmol, 1 equiv.) in 5 mL acetonitrile. Et_2O (10 mL) was added and the mixture was filtered. After washing with Et_2O (5 mL) the product was dried *in vacuo* to give **309n** as a white solid (0.91 g, 2.58 mmol, yield: 86%).

$C_{16}H_{21}BrN_2O_2$, **MW:** 353.25 g/mol.

Mp: >250 °C.

^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 11.41 (*s*, 1 H, $C_{Ar}OH$); 10.73 (*s*, 1 H, C*H*O); 9.91 (*s*, 1 H, NC*H*N_{Imid}); 8.36 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.65 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.56 (*t*, *J* = 1.8, 1 H, NCH_{Imid}); 7.16 (*t*, *J* = 1.8, 1 H, NCH_{Imid}); 5.68 (*s*, 2 H, $C_{Ar}CH_2$); 3.98 (*s*, 3 H, NCH_3); 1.37 (*s*, 9 H, C(CH_3)$_3$).

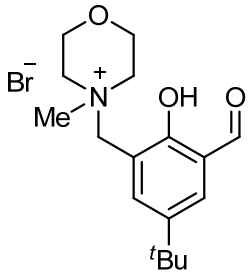
^{13}C NMR (75 MHz, DMSO, 21 °C): δ = 196.8, 156.4, 142.6, 136.6, 135.6, 130.4, 123.7, 122.4, 122.3, 121.0, 47.1, 35.8, 34.0, 30.9.

IR ($CHCl_3$): ν = 3376, 2962, 2445, 1658, 1619, 1471, 1276.

HRMS (ESI) *m/z*: Calc. for $[M\text{-}Br]^+$: 273.1598. Found: 273.1598.

Anal. Calcd. for $C_{16}H_{21}BrN_2O_2$: C, 54.40; H, 5.99; N, 7.93; O, 9.06; Br, 22.62. Found: C, 54.29; H, 5.99; N, 8.01.

4-(5-*tert*-Butyl-3-formyl-2-hydroxybenzyl)-4-methylmorpholin-4-ium iodide (309*o*)



309o

Aldehyde **309*o*** was prepared according to GPB-2 using 3-Bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (0.26 g, 0.95 mmol, 1 equiv.) and N-methylmorpholine (0.10 mL, 0.95 mmol, 1 equiv.) in 4 mL acetonitrile. The mixture was filtered without prior addition of Et_2O and after washing with CH_3CN (5 mL) the product was dried *in vacuo* to give **309*o*** as a white solid (0.34 g, 0.90 mmol, yield: 95%).

$C_{17}H_{26}BrNO_3$, MW: 372.30 g/mol.

Mp: decomposition above 216 °C.

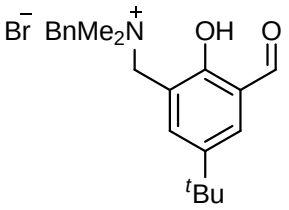
^{1}H NMR (400 MHz, DMSO, 21 °C): δ = 11.38 (*bs*, 1 H, $C_{Ar}OH$); 10.16 (*s*, 1 H, C*H*O); 8.01 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.98 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 4.77 (*s*, 2 H, $C_{Ar}CH_2$); 3.99 (*m*, 4 H, $(CH_2)_{ring}$); 3.57 (*m*, 2 H, $(CH_2)_{ring}$); 3.41 (*m*, 2 H, $(CH_2)_{ring}$); 3.12 (*s*, 3 H, N(CH_3)); 1.33 (*s*, 9 H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, DMSO, 21 °C): δ = 196.8, 157.9, 142.4, 139.8, 132.3, 121.5, 115.5, 61.5, 59.9, 58.8, 45.6, 34.0, 30.9.

IR ($CHCl_3$): ν = 3416, 2961, 2873, 2435, 1659, 1617, 1473.

HRMS (ESI) *m/z*: Calc. for $[M-Br]^+$: 292.1907. Found: 292.1909.

***N*-Benzyl-1-(5-*tert*-butyl-3-formyl-2-hydroxyphenyl)-*N*,*N*-dimethylmethanaminium bromide (309p)**



309p

Aldehyde **309p** was prepared according to GPB-2 using 3-Bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (0.26 g, 0.95 mmol, 1 equiv.) and N-benzyldimethylamine (0.14 mL, 0.95 mmol, 1 equiv.) in 4 mL acetonitrile. Addition of Et_2O (15 mL) led to precipitation of the product as an oil. The solvent was decanted and the residue was triturated with Et_2O (2 x 20 mL) whereupon the oil became a solid. The product was dried *in vacuo* to give **309p** as a light-yellow solid (0.34 g, 0.83 mmol, yield: 87%).

$C_{21}H_{28}BrNO_2$, MW: 406.36 g/mol.

Mp: decomposition above 110 °C.

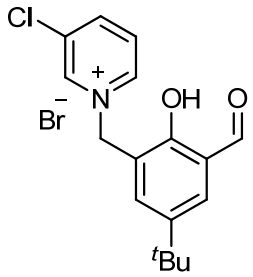
^{1}H NMR (400 MHz, CH_3CN, 21 °C): δ = 11.46 (*bs*, 1 H, $C_{Ar}OH$); 10.03 (*s*, 1 H, C*H*O); 8.16 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.94 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 7.64 (*m*, 2 H, CH_{Ph}); 7.52 (*m*, 3 H, CH_{Ph}); 4.84 (*s*, 2 H, $C_{Ar}CH_2$); 4.86 (*s*, 2 H, $C_{Ar}CH_2$); 3.01 (*s*, 6 H, $N(CH_3)_2$); 1.35 (*s*, 9 H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, CH_3CN, 21 °C): δ = 198.8, 159.7, 144.4, 141.3, 134.5, 134.3, 131.6, 130.1, 129.1, 122.2, 116.8, 68.8, 62.2, 49.8, 35.1, 31.5.

IR ($CHCl_3$): ν = 3609, 3397, 2965, 2438, 1659, 1617, 1477.

HRMS (ESI) *m/z*: Calc. for $[M\text{-}Br]^+$: 326.2115. Found: 326.2116.

1-(5-*tert*-Butyl-3-formyl-2-hydroxybenzyl)-3-chloropyridinium bromide (309q)



309q

Aldehyde **309q** was prepared according to GPB-2 using 3-Bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (0.40 g, 1.48 mmol, 1 equiv.) and 3-chloropyridine (0.14 mL, 1.48 mmol, 1 equiv.) in 5 mL acetonitrile. Et_2O (10 mL) was added and the mixture was filtered. After washing with Et_2O (5 mL) the product was dried *in vacuo* to give **309q** as a white solid (0.51 g, 1.33 mmol, yield: 90%).

$C_{17}H_{19}BrClNO_2$, **MW:** 384.70 g/mol.

Mp: >250 °C.

^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 11.52 (*s*, 1 H, $C_{Ar}OH$); 9.91 (*s*, 1 H, C*H*O); 9.89 (*d*, *J* = 6.1, 1 H, *o*-CH_{Pyr}); 9.68 (*s*, 1 H, *o*-CH_{Pyr}); 8.82 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 8.36 (*d*, *J* = 8.8, 1 H, *p*-CH_{Pyr}); 8.00 (*m*, 2 H, *m*-CH_{Pyr}); 7.70 (*d*, *J* = 2.5, 1 H, CH_{Ar}); 6.38 (*s*, 2 H, $C_{Ar}CH_2$); 1.39 (*s*, 9 H, $C(CH_3)_3$).

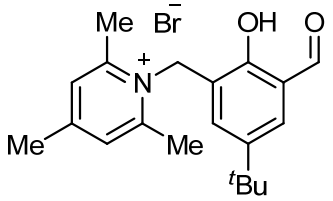
^{13}C NMR (100 MHz, DMSO, 21 °C): δ = 196.3, 156.8, 145.7, 143.8, 142.8, 136.3, 133.9, 131.0, 128.8, 121.3, 121.2, 60.0, 34.1, 30.9.

IR ($CHCl_3$): ν = 3411, 2957, 2928, 2855, 2399, 1654, 1465.

HRMS (ESI) *m/z*: Calc. for $[M\text{-}Br]^+$: 304.1099. Found: 304.1095.

Anal. Calcd. for $C_{17}H_{19}BrClNO_2$: C, 53.08; H, 4.98; N, 3.64; O, 8.32; Cl, 9.22; Br, 20.77. Found: C, 52.91; H, 5.01; N, 3.63.

1-(5-*tert*-Butyl-3-formyl-2-hydroxybenzyl)-2,4,6-trimethylpyridinium bromide (309r)



309r

Aldehyde **309r** was prepared according to GPB-2 using 3-bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (0.82 g, 3.01 mmol, 1 equiv.) and 2,4,6-collidine (0.40 mL, 3.01 mmol, 1 equiv.) in 15 mL acetonitrile. Et_2O (8 mL) was added and the mixture was filtered. Purification by flash chromatography (CH_2Cl_2/CH_3OH 9:1) gave **309r** as a light yellow solid (0.77 g, 1.96 mmol, yield: 65%).

$C_{20}H_{26}BrNO_2$, **MW:** 392.33 g/mol.

Mp: decomposition above 124 °C.

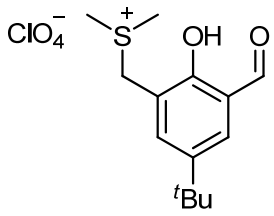
^{1}H NMR (300 MHz, CH_2Cl_2, 21 °C): δ = 11.18 (*s*, 1 H, $C_{Ar}OH$); 9.91 (*s*, 1 H, C*H*O); 7.72 (*d*, *J* = 2.4, 1 H, CH_{Ar}); 7.63 (*d*, *J* = 2.4, 1 H, CH_{Ar}); 7.54 (*s*, 2 H, CH_{Ar}); 6.09 (*s*, 2 H, $C_{Ar}CH_2$); 2.91 (*s*, 6 H, $C_{Ar}CH_3$); 2.57 (*s*, 3 H, $C_{Ar}CH_3$); 1.32 (*s*, 9 H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, CD_2Cl_2, 21 °C): δ = 197.5, 158.8, 157.4, 156.4, 144.3, 134.3, 131.3, 129.0, 121.1, 120.1, 34.7, 31.3, 22.8, 22.0.

IR ($CHCl_3$): ν = 3612, 3392, 2968, 2438, 1658, 1641, 1479.

HRMS (ESI) *m/z*: Calc. for $[M-Br]^+$: 312.1958. Found: 312.1954.

(5-*tert*-Butyl-3-formyl-2-hydroxybenzyl)dimethylsulfonium perchlorate (310)



310

Aldehyde **310** was prepared according to published procedure[179] using 3-bromomethyl-5-*tert*-butyl-2-hydroxy-benzaldehyde (0.70 g, 2.58 mmol, 1 equiv.), dimethylsulfide (0.42 mL, 5.68 mmol, 2.2 equiv.) and sodium perchlorate (0.32 g, 2.58 mmol, 1 equiv.) in 3 mL acetone. The mixture was stirred for 24 h at ambient temperature. Et_2O (15 mL) was added and the mixture was filtered. After washing with Et_2O (5 mL) the product was dissolved in hot acetone, pentane (15 mL) was added and the mixture was filtered. After washing with pentane (5 mL) the product was dried *in vacuo* to give **310** as a white solid (0.51 g, 1.44 mmol, yield: 56%).

$C_{14}H_{21}ClO_6S$, **MW:** 352.83 g/mol.

Mp: decomposition above 192 °C.

^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 11.50 (*s*, 1 H, $C_{Ar}OH$); 9.94 (*s*, 1 H, C*H*O); 7.92 (*d*, *J* = 2.4, 1 H, CH_{Ar}); 7.74 (*d*, *J* = 2.4, 1 H, CH_{Ar}); 4.75 (*s*, 2 H, $C_{Ar}CH_2$); 2.96 (*s*, 6 H, $S(CH_3)_2$); 1.35 (*s*, 9 H, $C(CH_3)_3$).

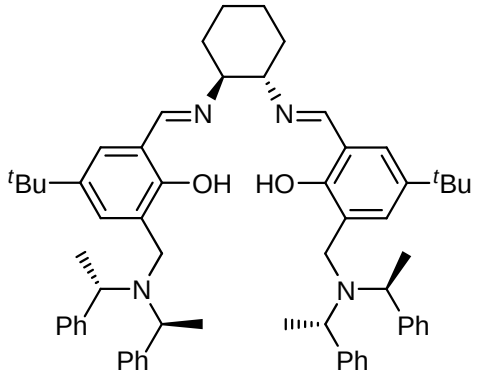
^{13}C NMR (100 MHz, CD_3CN, 21 °C): δ = 199.2, 158.7, 144.8, 138.2, 134.2, 121.9, 116.0, 42.3, 35.1, 31.4, 25.4.

IR ($CHCl_3$): ν = 3436, 3014, 2975, 2399, 1653, 1558.

HRMS (ESI) *m/z*: Calc. for $[M\text{-}ClO_4]^+$: 253.1257. Found: 253.1255.

11.2.3 Ligand Synthesis

(*S*,*S*)-(+)-N,N'-Bis(3-*tert*-butyl-5-((bis((*S*)-1-phenylethyl)amino)-1-ylmethyl)salicylidene)-1,2-cyclohexane-diamine (274f)



274f

Ligand **274f** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (43 mg, 0.38 mmol, 1 equiv.) and bis((*S*)-1-phenylethyl)amine (**272f**) (0.31 g, 0.75 mmol, 2 equiv.) in 3 mL ethanol, but instead of adding Et_2O the suspension was filtered and washed with cold ethanol (2 mL). The residue was dissolved in DCM, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to give **274f** as a yellow solid (0.23 g, 0.25 mmol, 67%).

$C_{62}H_{76}N_4O_2$, **MW:** 909.29 g/mol.

Mp: 85-88 °C.

[α] $_D^{25.0°C}$ (c = 1.120, $CHCl_3$) = +199.2 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 13.41 (*bs*, 2 H, $C_{Ar}OH$); 8.28 (*s*, 2 H, N=C*H*C_{Ar}); 7.82 (*d*, *J* = 2.3, 2 H, C*H*$_{Ar}$); 7.28 (*m*, 16 H, C*H*$_{Ar}$); 7.16 (*m*, 4 H, C*H*$_{Ar}$); 6.99 (*d*, *J* = 2.4, 2 H, C*H*$_{Ar}$); 4.06 (*d*, *J* = 16.6, 2 H, $C_{Ar}CH_2$); 3.96 (*q*, *J* = 6.8, 4 H, C*H*CH_3); 3.58 (*d*, *J* = 16.5, 2 H, $C_{Ar}CH_2$); 3.26 (*m*, 2 H, (C*H*)$_{ring}$-N); 1.93-1.57 (*m*, 4 H, $(CH_2)_{ring}$); 1.56-1.38 (*m*, 4 H, $(CH_2)_{ring}$); 1.31 (*d*, *J* = 6.8, 12 H, CHCH_3); 1.27 (*s*, 18 H, C(CH_3)$_3$).

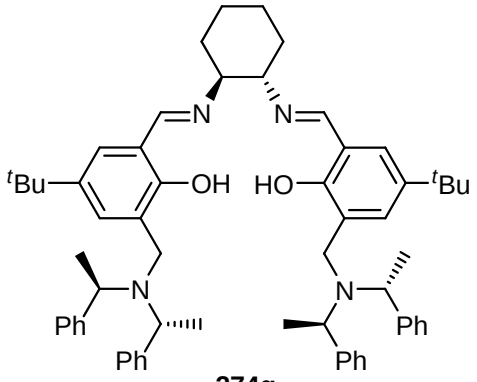
^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 165.4, 156.2, 144.9, 140.7, 130.1, 130.0, 128.2, 128.1, 126.7, 125.7, 117.4, 72.9, 58.7, 42.8, 34.2, 33.6, 31.7, 24.5, 19.5.

IR ($CHCl_3$): ν = 3616, 2968, 2864, 1630, 1451.

HRMS (ESI) *m/z*: Calc. for $[MH]^+$: 909.6041. Found: 909.6057.

Anal. Calcd. for $C_{62}H_{78}N_4O_2$: C, 81.90; H, 8.42; N, 6.16; O, 3.52. Found: C, 81.61; H, 8.50; N, 6.08.

(*S*,*S*)-(+)-N,N'-Bis(3-*tert*-butyl-5-((bis((*R*)-1-phenylethyl)amino)-1-ylmethyl)salicylidene)-1,2-cyclohexane-diamine (274g)



274g

Ligand **274g** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (35 mg, 0.31 mmol, 1 equiv.) and bis((*S*)-1-phenylethyl)amine (**272g**) (0.25 g, 0.61 mmol, 2 equiv.) in 3 mL ethanol, but instead of adding Et_2O the suspension was filtered and washed with cold ethanol (2 mL). The residue was dissolved in DCM, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to give **274g** as a yellow solid (0.21 g, 0.23 mmol, 74%).

$C_{62}H_{76}N_4O_2$, **MW:** 909.29 g/mol.

Mp: 89-91 °C.

[α] $_D^{25.0°C}$ (c = 0.550, $CHCl_3$) = +248.7 ± 0.3.

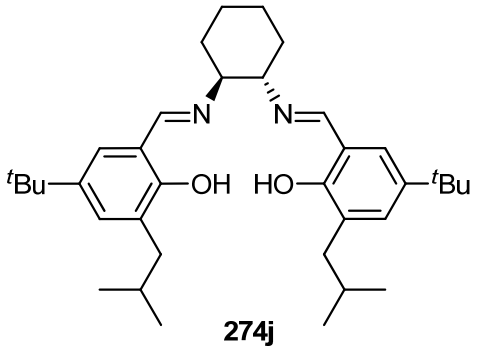
^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 13.38 (*bs*, 2 H, $C_{Ar}OH$); 8.21 (*s*, 2 H, N=C*H*C_{Ar}); 7.66 (*d*, *J* = 2.0, 2 H, C*H*$_{Ar}$); 7.24 (*m*, 16 H, C*H*$_{Ar}$); 7.14 (*m*, 4 H, C*H*$_{Ar}$); 6.91 (*d*, *J* = 2.1, 2 H, C*H*$_{Ar}$); 4.08 (*d*, *J* = 16.2, 2 H, $C_{Ar}CH_2$); 3.96 (*q*, *J* = 6.8, 4 H, C*H*CH_3); 3.52 (*d*, *J* = 16.2, 2 H, $C_{Ar}CH_2$); 3.25 (*m*, 2 H, (C*H*)$_{ring}$-N); 1.88 (*m*, 4 H, (CH_2)$_{ring}$); 1.70 (*m*, 2 H, (CH_2)$_{ring}$); 1.46 (*m*, 2 H, (CH_2)$_{ring}$); 1.33 (*d*, *J* = 6.8, 12 H, CHCH_3); 1.19 (*s*, 18 H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 165.3, 156.3, 144.9, 140.7, 130.3, 129.7, 128.1, 128.0, 126.6, 125.8, 117.3, 72.9, 58.2, 42.5, 34.2, 33.5, 31.6, 24.5, 18.9.

IR ($CHCl_3$): ν = 3616, 2969, 2864, 1630, 1450.

HRMS (ESI) *m/z*: Calc. for $[MH]^+$: 909.6041. Found: 909.6024.

(*S*,*S*)-(+)-N,N'-Bis(3-*tert*-butyl-5-(*iso*-butyl)salicylidene)-1,2-cyclohexane-diamine (274j)



274j

Ligand **274j** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (29 mg, 0.25 mmol, 1 equiv.) and 5-*tert*-butyl-2-hydroxy-3-isobutylbenzaldehyde (**287**) (0.12 g, 0.51 mmol, 2 equiv.) in 2 mL ethanol and was obtained as an orange oil (0.14 g, 0.25 mmol, 100%).

$C_{36}H_{54}N_2O_2$, MW: 546.83 g/mol.

[α] $_D^{25.0°C}$ (c = 1.600, $CHCl_3$) = +199.0 ± 0.1.

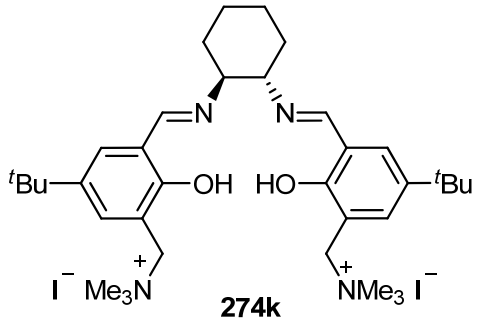
^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 13.37 (*bs*, 2 H, $C_{Ar}OH$); 8.24 (*s*, 2 H, N=$CH C_{Ar}$); 7.09 (*d*, *J* = 2.4, 2 H, CH_{Ar}); 6.96 (*d*, *J* = 2.4, 2 H, CH_{Ar}); 3.29 (*m*, 2 H, $(CH)_{ring}$-N); 2.49 (*d*, *J* = 7.2, 4 H, $C_{Ar}CH_2$); 1.93 (*m*, 6 H, $CH(CH_3)_2$, $(CH_2)_{ring}$); 1.72 (*m*, 2 H, $(CH_2)_{ring}$); 1.43 (*m*, 2 H, $(CH_2)_{ring}$); 1.23 (*s*, 18 H, $C(CH_3)_3$); 0.91 (*dd*, *J* = 1.2, 6.6, 12 H, $CH(CH_3)_2$.

^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 165.4, 157.0, 140.3, 131.0, 128.6, 125.7, 117.5, 72.7, 39.3, 33.8, 33.3, 31.4, 28.4, 24.3, 22.7, 22.6.

IR (ATR): ν = 2953, 2864, 1627, 1465, 1270, 757, 733.

HRMS (ESI) *m/z*: Calc. for $[MH]^+$: 547.4258. Found: 547.4253.

(*S*,*S*)-(+)-*N*,*N*'-Bis(3-*tert*-butyl-5-(*N*,*N*,*N*-trimethyl-1-ylmethyl)salicylidene)-1,2-cyclohexane-diamine diiodide (274k)



274k

Ligand **274k** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (64 mg, 0.56 mmol, 1 equiv.) and 1-(5-*tert*-butyl-3-formyl-2-hydroxyphenyl)-*N*,*N*,*N*-trimethylmethanammonium iodide (**309k**) (0.42 g, 1.12 mmol, 2 equiv.). Recrystallisation from hot EtOH gave **274k** as a yellow solid (0.43 g, 0.52 mmol, 92%).

$C_{36}H_{58}I_2N_4O_2$, MW: 832.68 g/mol.

Mp: decomposition above 213 °C.

[α] $_D^{25.0°C}$ (c = 1.055, acetonitrile) = +264.3 ± 0.7.

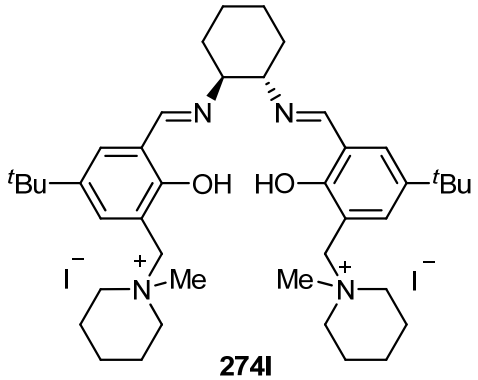
^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 14.26 (*bs*, 2 H, $C_{Ar}OH$); 8.42 (*s*, 2 H, N=CHC_{Ar}); 7.81 (*d*, *J* = 2.4, 2 H, CH_{Ar}); 7.42 (*s*, 2 H, CH_{Ar}); 4.87 (*d*, *J* = 12.5, 2 H, $C_{Ar}CH_2$); 4.69 (*d*, *J* = 12.5, 2 H, $C_{Ar}CH_2$); 3.50 (*m*, 2 H, $(CH)_{ring}$-N); 3.26 (s, 18 H, $N(CH_3)_3$); 1.97 (*m*, 4 H, $(CH_2)_{ring}$); 1.71 (*m*, 2 H, $(CH_2)_{ring}$); 1.51 (*m*, 2 H, $(CH_2)_{ring}$); 1.29 (*s*, 18 H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, CD_3CN, 21 °C): δ = 166.5, 160.9, 142.1, 136.3, 132.3, 119.4, 116.2, 72.2, 64.5, 53.8, 34.8, 33.4, 31.6, 24.8.

IR ($CHCl_3$): ν = 3610, 3428, 2957, 1633, 1602, 1483, 1470.

HRMS (ESI) *m/z*: Calc. for $[M^{2+}\text{-}I^-]^+$: 705.3599. Found: 705.3594.

(*S*,*S*)-(+)-*N*,*N*'-Bis(3-*tert*-butyl-5-((*N*-methyl)piperidinium-1-ylmethyl)salicylidene)-1,2-cyclohexane-diamine diiodide (274l)



274l

Ligand **274l** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (95 mg, 0.83 mmol, 1 equiv.) and 1-(5-*tert*-butyl-3-formyl-2-hydroxybenzyl)-1-methylpiperidinium iodide (**309l**) (0.62 g, 1.66 mmol, 1 equiv.) and was obtained as an orange solid (0.55 g, 0.83 mmol, 100%).

$C_{42}H_{66}I_2N_4O_2$, MW: 912.81 g/mol.

Mp: decomposition above 185 °C.

[α] $_D^{25.0°C}$ (c = 0.945, acetonitrile) = +253.5 ± 0.2.

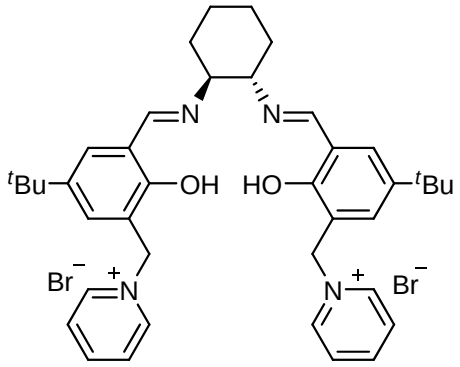
^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 14.28 (*bs*, 2 H, $C_{Ar}OH$); 8.41 (*s*, 2 H, N=C*H*C_{Ar}); 7.83 (*d*, *J* = 2.5, 2 H, C*H*$_{Ar}$); 7.38 (*d*, *J* = 2.5, 2 H, C*H*$_{Ar}$); 4.91 (*d*, *J* = 12.6, 2 H, $C_{Ar}CH_a$); 4.71 (*d*, *J* = 12.6, 2 H, $C_{Ar}CH_b$); 3.64 (*m*, 4 H, N(C*H*$_2$)$_{ring}$); 3.46 (*m*, 6 H, N(C*H*$_2$)$_{ring}$/N(C*H*)$_{ring}$); 3.07 (*s*, 6 H, NC*H*$_3$); 2.08-1.45 (*m*, 20 H, (C*H*$_2$)$_{ring}$); 1.29 (*s*, 18 H, C(C*H*$_3$)$_3$).

^{13}C NMR (100 MHz, DMSO, 21 °C): δ = 165.8, 160.2, 139.9, 135.7, 130.9, 117.7, 115.0, 69.7, 61.3, 60.0, 46.3, 33.7, 32.2, 31.0, 23.5, 20.6, 19.4.

IR ($CHCl_3$): ν = 3611, 3429, 2958, 1633, 1602, 1479.

HRMS (ESI) *m/z*: Calc. for $[M^{2+}\text{-}I^-]^+$: 785.4225. Found: 785.4213.

(*S*,*S*)-(+)-N,N'-Bis(3-*tert*-butyl-5-(pyridinium-1-ylmethyl)salicylidene)-1,2-cyclohexane-diamine dibromide (274m)



274m

Ligand **274m** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (0.20 g, 1.78 mmol, 1 equiv.) and 1-(5-*tert*-butyl-3-formyl-2-hydroxybenzyl)pyridinium bromide (**309m**) (1.25 g, 3.56 mmol, 1 equiv.) and was obtained as an orange solid (1.38 g, 1.78 mmol, 100%).

$C_{40}H_{50}Br_2N_4O_2$, MW: 778.66 g/mol.

Mp: decomposition above 195 °C.

[α] $_D^{24.3°C}$ (c = 1.100, acetonitrile) = +320.5 ± 0.1.

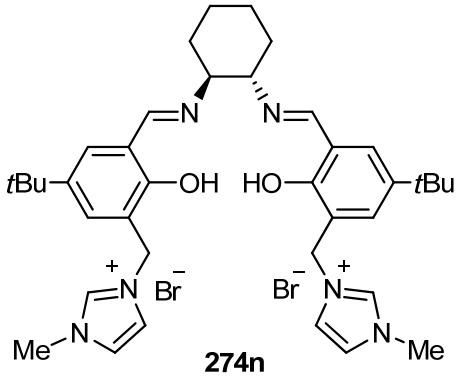
^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 14.16 (*bs*, 2 H, $C_{Ar}OH$); 9.55 (*d*, *J* = 5.5, 4 H, *o*-CH_{Pyr}); 8.46 (*t*, *J* = 7.8, 2 H, *p*-CH_{Pyr}); 8.38 (*s*, 2 H, N=CHC_{Ar}); 8.22 (*d*, *J* = 2.5, 2 H, CH_{Ar}); 7.99 (*m*, 4 H, *m*-CH_{Pyr}); 7.32 (*d*, *J* = 2.5, 2 H, CH_{Ar}); 6.13 (*dd*, 4 H, $C_{Ar}CH_2$); 3.43 (*d*, *J* = 9.5, 2 H, $(CH)_{ring}$-N); 1.90 (*m*, 4 H, $(CH_2)_{ring}$); 1.67 (*m*, 2 H, $(CH_2)_{ring}$); 1.47 (*m*, 2 H, $(CH_2)_{ring}$); 1.27 (*s*, 18 H, $C(CH_3)_3$).

^{13}C NMR (75 MHz, CD_2Cl_2, 21 °C): δ = 164.9, 159.1, 145.4, 145.3, 142.0, 133.0, 130.3, 128.1, 120.7, 118.2, 71.6, 60.1, 34.6, 33.2, 31.6, 24.5.

IR ($CHCl_3$): ν = 3609, 3399, 2962, 2866, 1633, 1602, 1481.

HRMS (ESI) *m/z*: Calc. for $[M^{2+}\text{-}Br^-]^+$: 697.3112. Found: 697.3114.

(*S*,*S*)-(+)-N,N'-Bis(3-*tert*-butyl-5-((1-methyl-1*H*-imidazol-3-ium)-1-ylmethyl)salicylidene)-1,2-cyclohexane-diamine dibromide (274n)



274n

Ligand **274n** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (100 mg, 0.88 mmol, 1 equiv.) and 3-(5-*tert*-butyl-3-formyl-2-hydroxybenyl)-1-methyl-1*H*-imidazol-3-ium bromide (**309n**) (0.62 g, 1.76 mmol, 2 equiv.) and was obtained as an orange solid (0.69 g, 0.88 mmol, 100%).

$C_{38}H_{52}Br_2N_6O_2$, MW: 784.67 g/mol.

Mp: decomposition above 188 °C.

[α] $_D^{25.0°C}$ (c = 1.060, acetonitrile) = +267.5 ± 0.2.

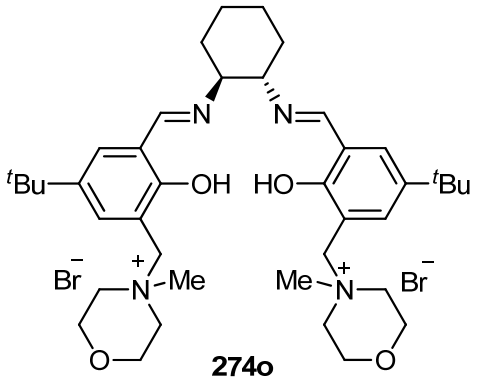
^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 14.00 (*bs*, 2 H, $C_{Ar}OH$); 10.47 (*s*, 2 H, $NCHN_{Imid}$); 8.41 (*s*, 2 H, $N{=}CHC_{Ar}$); 7.83 (*d*, *J* = 2.5, 2 H, CH_{Ar}); 7.30 (*m*, 4 H, NCH_{Imid}/CH_{Ar}); 7.22 (*t*, *J* = 1.8, 2 H, NCH_{Imid}); 5.49 (*s*, 4 H, $C_{Ar}CH_2$); 3.99 (*s*, 6 H, NCH_3); 3.45 (*m*, 2H, $(CH)_{ring}$-N); 1.93 (*m*, 4 H, $(CH_2)_{ring}$); 1.72 (*m*, 2 H, $(CH_2)_{ring}$); 1.51 (*m*, 2 H, $(CH_2)_{ring}$); 1.27 (*s*, 18 H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, DMSO, 21 °C): δ = 165.8, 158.1, 140.4, 136.5, 131.3, 129.2, 123.5, 122.4, 121.3, 117.4, 70.1, 47.4, 35.8, 33.7, 32.5, 31.0, 23.6.

IR ($CHCl_3$): ν = 3610, 3402, 2965, 1633, 1602, 1480, 1448.

HRMS (ESI) *m/z*: Calc. for $[M^{2+}\text{-}Br^-]^+$: 703.3330. Found: 703.3327.

(*S*,*S*)-(+)-*N*,*N*'-Bis(3-*tert*-butyl-5-((*N*-methyl)morpholinium-1-ylmethyl)salicylidene)-1,2-cyclohexane-diamine dibromide (274*o*)



274o

Ligand **274*o*** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (26 mg, 0.23 mmol, 1 equiv.) and 4-(5-*tert*-butyl-3-formyl-2-hydroxybenzyl)-4-methylmorpholin-4-ium bromide (**309*o***) (0.17 g, 0.46 mmol, 2 equiv.) in 6 mL ethanol and was obtained as an orange solid. The raw product was dissolved in DCM (3 mL) and addition of Et_2O (10 mL) led to precipitation of the product. The solvent was decanted and the residue was triturated with Et_2O (2 x 20 mL). The product was dried *in vacuo* to give **274*o*** as a yellow solid (0.16 g, 0.20 mmol, 88%).

$C_{40}H_{62}I_2N_4O_4$, MW: 916.75 g/mol.

Mp: decomposition above 205 °C.

[α] $_{D}^{25.0°C}$ (c = 0.730, acetonitrile) = +247.9 ± 0.1.

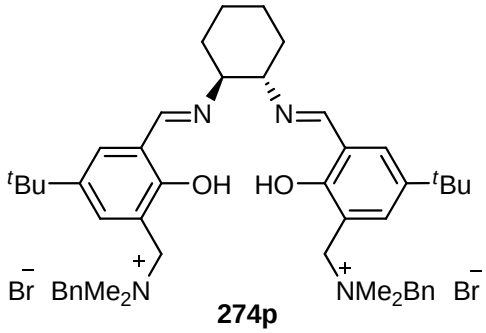
^{1}H NMR (400 MHz, CD_2Cl_2, 21 °C): δ = 14.36 (*bs*, 2 H, $C_{Ar}OH$); 8.42 (*s*, 2 H, N=C*H*C_{Ar}); 7.98 (*d*, *J* = 2.4, 2 H, C*H*$_{Ar}$); 7.39 (*d*, *J* = 2.4, 2 H, C*H*$_{Ar}$); 5.10 (*d*, *J* = 12.6, 2 H, $C_{Ar}CH_a$); 4.99 (*d*, *J* = 12.6, 2 H, $C_{Ar}CH_b$); 4.05 (*m*, 8 H, $(CH_2)_{morph}$-O); 3.67 (*m*, 8 H, $(CH_2)_{morph}$-N); 3.48 (*m*, 2 H, $(CH)_{ring}$-N); 3.41 (*s*, 6 H, NCH_3); 2.06-1.39 (*m*, 8 H, $(CH_2)_{ring}$); 1.27 (*s*, 18 H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, CD_2Cl_2, 21 °C): δ = 165.2, 160.4, 142.2, 137.0, 131.7, 119.0, 114.9, 71.8, 62.3, 61.5, 59.9, 54.4, 48.4, 34.6, 33.3, 31.7, 24.7.

IR ($CHCl_3$): ν = 3610, 3401, 2965, 1632, 1602, 1477, 1450.

HRMS (ESI) *m/z*: Calc. for $[M^{2+}\text{-}I^-]^+$: 789.3810. Found: 789.3810.

(*S*,*S*)-(+)-*N*,*N*'-Bis(3-*tert*-butyl-5-((*N*-benzyl-*N*,*N*-dimethyl)-1-ylmethyl)salicylidene)-1,2-cyclohexane-diamine dibromide (274p)



274p

Ligand **274p** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (24 mg, 0.21 mmol, 1 equiv.) and *N*-benzyl-1-(5-*tert*-butyl-3-formyl-2-hydroxyphenyl)-*N*,*N*-dimethylmethanammonium bromide (**309p**) (0.17 g, 0.42 mmol, 2 equiv.) in 5 mL ethanol and was obtained as an orange solid. The raw product was dissolved in DCM (3 mL) and addition of Et_2O (10 mL) led to precipitation of the product as an oil. The solvent was decanted and the residue was triturated with Et_2O (2 x 20 mL) whereupon the oil became a solid. The product was dried *in vacuo* to give **274p** as a yellow solid (0.17 g, 0.19 mmol, 91%).

$C_{48}H_{66}Br_2N_4O_2$, MW: 890.87 g/mol.

Mp: decomposition above 202 °C.

[α] $_D^{25.0°C}$ (c = 0.865, acetonitrile) = +273.3 ± 0.2.

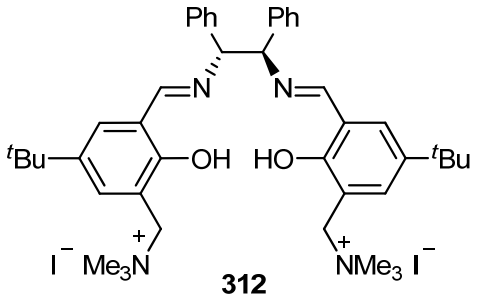
^{1}H NMR (400 MHz, CD_2Cl_2, 21 °C): δ = 14.15 (*bs*, 2 H, $C_{Ar}OH$); 8.37 (*s*, 2 H, N=$CH$$C_{Ar}$); 7.89 (*d*, *J* = 2.2, 2 H, CH_{Ar}); 7.68 (*m*, 4 H, CH_{Ph}); 7.48 (*m*, 6 H, CH_{Ph}); 7.34 (*d*, *J* = 2.2, 2 H, CH_{Ar}); 5.05 (*m*, 6 H, $C_{Ar/Ph}CH_2$); 4.87 (*d*, *J* = 12.4, 2 H, $C_{Ar}CH_2$); 3.43 (*m*, 2 H, $(CH)_{ring}$-N); 3.11 (*s*, 6 H, NCH_3); 3.07 (*s*, 6 H, NCH_3); (1.91 (*m*, 4 H, $(CH_2)_{ring}$); 1.67 (*m*, 2 H, $(CH_2)_{ring}$); 1.44 (*m*, 2 H, $(CH_2)_{ring}$); 1.25 (*s*, 18 H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, CD_2Cl_2, 21 °C): δ = 165.3, 160.0, 142.2, 136.5, 133.9, 131.6, 131.1, 129.7, 128.5, 119.0, 115.5, 72.3, 68.5, 62.7, 54.4, 49.5, 34.6, 33.5, 31.7, 24.6.

IR ($CHCl_3$): ν = 3610, 3398, 2960, 1633, 1602, 1477.

HRMS (ESI) *m/z*: Calc. for $[M^{2+}\text{-}Br^-]^+$: 809.4364. Found: 809.4367.

(*R*,*R*)-(+)-*N*,*N*'-Bis(3-*tert*-butyl-5-(*N*,*N*,*N*-trimethyl-1-ylmethyl)salicylidene)-1,2-diphenylethane-1,2-diamine diiodide (312)



312

Ligand **312** was prepared according to GPB-3 from (1*R*,2*R*)-(–)-1,2-diphenylethane-1,2-diamine (95 mg, 0.45 mmol, 1 equiv.) and 1-(5-*tert*-butyl-3-formyl-2-hydroxyphenyl)-*N*,*N*,*N*-trimethylmethanammonium iodide (**309k**) (0.34 g, 0.90 mmol, 2 equiv.). Recrystallisation from hot EtOH gave **312** as a yellow solid (0.37 g, 0.39 mmol, 88%).

$C_{44}H_{60}I_2N_4O_2$, MW: 930.78 g/mol.

Mp: decomposition above 229 °C.

[α] $_{D}^{25.0°C}$ (c = 0.555, acetonitrile) = –70.6 ± 0.3.

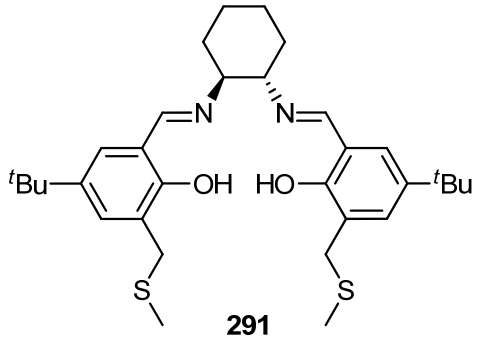
^{1}H NMR (300 MHz, CD_2Cl_2, 21 °C): δ = 14.20 (*bs*, 2 H, $C_{Ar}OH$); 8.32 (*s*, 2 H, N=$CH$$C_{Ar}$); 7.84 (*d*, *J* = 2.2, 2 H, CH_{Ar}); 7.35 (*d*, *J* = 2.2, 2 H, CH_{Ar}); 7.26 (*m*, 10 H, CH_{Ph}); 4.97 (*m*, 4 H, $C_{Ar}CH_2$/$C_{Ph}CH$); 4.75 (*d*, *J* = 12.9, 2 H, $C_{Ar}CH_2$); 3.33 (s, 18 H, $N(CH_3)_3$); 1.30 (*s*, 18 H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, CD_3CN, 21 °C): δ = 167.2, 158.7, 140.8, 139.0, 135.3, 131.1, 128.3, 127.9, 127.6, 118.1, 115.3, 76.6, 62.5, 52.2, 33.7, 30.9.

IR ($CHCl_3$): ν = 3608, 3428, 2960, 2399, 1631, 1602, 1483, 1471.

HRMS (ESI) *m/z*: Calc. for $[M^{2+}\text{-}I^{-}]^{+}$: 803.3756. Found: 803.3740.

(*S*,*S*)-(+)-N,N'-Bis(3-*tert*-butyl-5-(methylthiomethyl)salicylidene)-1,2-cyclohexane-diamine (291)



291

Ligand **291** was prepared according to GPB-3 from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (38 mg, 0.34 mmol, 1 equiv.) and 5-*tert*-butyl-2-hydroxy-3-(methylthiomethyl)benzaldehyde (**272h**) (0.16 g, 0.67 mmol, 2 equiv.) in 3.5 mL ethanol. The crude product mixture was purified by flash chromatography (*n*hexanes/ethyl acetate 95:5 to 4:1) to give **291** as a yellow oil (48 mg, 0.09 mmol, 26%).

$C_{32}H_{46}N_2O_2S_2$, **MW:** 554.85 g/mol.

[α] $_D^{25.0°C}$ (c = 0.550, $CHCl_3$) = +235.2 ± 0.3.

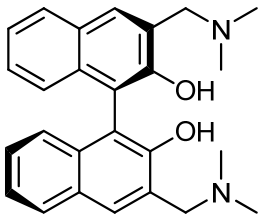
^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 13.58 (*s*, 2 H, $C_{Ar}OH$); 8.27 (*s*, 2 H, N=$CH$$C_{Ar}$); 7.23 (*d*, *J* = 2.4, 2 H, CH_{Ar}); 7.05 (*d*, *J* = 2.4, 2 H, CH_{Ar}); 3.76 (*d*, *J* = 13.0, 2 H, $C_{Ar}CH_2$); 3.69 (*d*, *J* = 13.0, 2 H, $C_{Ar}CH_2$); 3.30 (*m*, 2 H, $(CH)_{ring}$-N); 2.05 (*s*, 6 H, SCH_3); 1.90 (*m*, 4 H, $(CH_2)_{ring}$); 1.72 (*m*, 2 H, $(CH_2)_{ring}$); 1.45 (*m*, 2 H, $(CH_2)_{ring}$); 1.24 (*s*, 18 H, $C(CH_3)_3$).

^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 165.1, 156.9, 140.7, 130.4, 127.1, 125.0, 118.0, 72.8, 34.2, 33.6, 32.8, 31.7, 24.5, 15.8.

IR (ATR): ν = 2954, 2860, 2236, 1628, 1598, 1470, 1273, 1220, 907, 728.

HRMS (ESI) *m/z*: Calc. for $[MH]^+$: 555.3073. Found: 555.3059.

(*R*)-3,3'-Bis((dimethylamino)methyl)-1,1'-binaphthyl-2,2'-diol (269)



269

Ligand **269** was prepared according to published procedure[180] and was obtained as a yellow solid (0.47 g, 1.16 mmol, 68%).

$C_{26}H_{28}N_2O_2$, **MW:** 400.51 g/mol.

Mp: >240 °C.

[α] $_D^{25.0°C}$ (c = 0.630, CH_3CN) = +184.5 ± 0.3.

^{1}H NMR (400 MHz, CD_2Cl_2, 21 °C): δ = 7.77 (*d*, *J* = 8.0, 2 H, C*H*$_{Ar}$); 7.63 (*s*, 2, C*H*$_{Ar}$); 7.24 (*ddd*, *J* = 8.1, 6.7, 1.4, 2 H, C*H*$_{Ar}$); 7.17 (*ddd*, *J* = 8.0, 6.7, 1.4, 2 H, C*H*$_{Ar}$); 7.09 (*m*, 2 H, C*H*$_{Ar}$); 4.02 (*d*, *J* = 13.7, 2 H, $C_{Ar}CH_2$); 3.79 (*d*, *J* = 13.7, 2 H, $C_{Ar}CH_2$); 2.35 (*s*, 12 H, $N(CH_3)_2$).

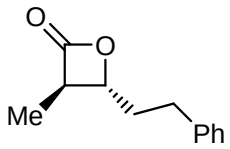
^{13}C NMR (100 MHz, CD_2Cl_2, 21 °C): δ = 154.5, 134.3, 128.5, 128.0, 127.7, 126.2, 125.4, 124.9, 123.1, 116.8, 63.6, 44.5.

IR ($CHCl_3$): ν = 3010, 2957, 2832, 2788, 1630, 1603, 1580, 1507, 1470, 1437, 1419.

HRMS (ESI) *m/z*: Calc. for $[MH]^+$: 401.2224. Found: 401.2230.

11.2.4 β-Lactone Synthesis

(3*R*,4*R*)-*trans*-3-Methyl-4-(2-phenylethyl)oxetan-2-one (297a)



297a

β-Lactone **297a** (0.41 mmol, yield: 82%, *ee* = 88% *dr* = 97:3) was prepared from propionylbromide (**296**) and 3-phenylpropionaldehyde (**207**) according to the general procedure, but using 0.50 mmol of **207** in 2 mL of DCM. The *dr* value was determined by ^{1}H-NMR and the *ee* value by HPLC (Chiralcel OD-H, 97:3 *n*-hexane/*i*PrOH, 1.0 mL/min, 210 nm). An analytically pure sample was obtained as colorless oil by flash chromatography (pentane / diethyl ether 20:1). Spectral data for the racemate have been reported earlier.[181]

$C_{12}H_{14}O_2$, MW: 190.24 g/mol.

[α] $_D^{25.9°C}$ (c = 1.280, $CHCl_3$) = +67.4 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.34-7.17 (*m*, 5 H, C*H*$_{Ar}$); 4.16 (*ddd*, *J* = 7.5, 5.9, 4.0, 1 H, C*H*-O); 3.20 (*qd*, *J* = 7.5, 4.0, 1 H, C*H*-C(O)); 2.77 (*m*, 2 H, $CH_2CH_2C_{Ar}$); 2.13 (*m*, 2 H, $CH_2CH_2C_{Ar}$); 1.32 (*d*, *J* = 7.5, 3 H, CH_3).

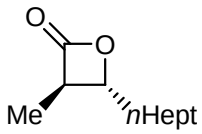
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.6, 139.9, 128.5, 128.2, 126.3, 78.6, 50.8, 35.6, 31.4, 12.5.

IR (ATR): ν = 2935, 1816, 1603, 1124, 840, 698.

HRMS (EI) *m/z*: Calc. for [M^+]: 190.0988. Found: 190.0989.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; O, 16.82. Found: C, 75.85; H, 7.53.

(3*R*,4*R*)-*trans*-3-Methyl-4-heptyloxetan-2-one (297b)



297b

β-Lactone **297b** was prepared from propionylbromide (**296**) and octanal according to the general procedure. Purification by flash chromatography (pentane / diethyl ether 20:1) gave **297b** as colorless oil (107 mg, 0.58 mmol, 77%, *ee* = 87% *dr* = 96:4). The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (ThermoFinnigan TraceGC, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C, ramp @ 5 °C/min to 180 °C, hold 20 min). Spectral data for the racemate has been reported earlier.[181]

$C_{11}H_{20}O_2$, MW: 184.28 g/mol.

[α] $_D^{26.4°C}$ (c = 1.175, $CHCl_3$) = +45.6 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.17 (*td*, *J* = 6.6, 4.0, 1 H, C*H*-O); 3.21 (*qd*, *J* = 7.5, 4.0, 1 H, C*H*-C(O)); 1.93-1.68 (*m*, 2 H, CH_2CH_2CH-O); 1.39 (*d*, *J* = 7.5, 3 H, $CHCH_3$) 1.49-1.28 (*m*, 10 H, $(CH_2)_5CH_3$); 0.88 (*t*, *J* = 6.6, 3 H, CH_2CH_3).

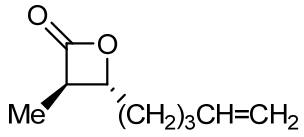
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.9, 79.5, 50.7, 34.2, 31.7, 29.2, 29.1, 25.0, 22.6, 14.1, 12.6.

IR (ATR): ν = 2927, 1821, 1123.

HRMS (EI) *m/z*: Calc. for $[M-H]^+$: 183.1380. Found: 183.1382.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94; O, 17.36. Found: C, 71.55; H, 10.80.

(3*R*,4*R*)-*trans*-3-Methyl-4-(4-pentenyl)oxetan-2-one (297c)



297c

β-Lactone **297c** (0.37 mmol, yield: 74%, *ee* = 88%, *dr* = 96:4) was prepared from propionylbromide (**296**) and 5-hexenal according to the general procedure, but using 0.50 mmol of aldehyde in 2 mL DCM The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (Hewlett Packard HP6890, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C for 2 min, ramp @ 5 °C/min to 150 °C, hold 0.75 min, ramp @ 8 °C/min to 200 °C). An analytically pure sample was obtained as colorless oil by flash chromatography (pentane / diethyl ether 20:1). Spectral data for the racemate has been reported earlier.[181]

$C_9H_{14}O_2$, MW: 154.21 g/mol.

[α] $_D^{21.8°C}$ (c = 1.025, $CHCl_3$) = +58.7 ± 0.3.

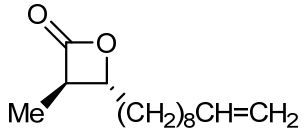
^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 5.78 (*ddt*, *J* = 16.9, 10.2, 6.7, 1 H, CH_2CH=CH_2); 5.07-4.97 (*m*, 2 H, CH=CH_2); 4.18 (*ddd*, *J* = 7.3, 6.1, 4.0, 1 H, C*H*-O); 3.23 (*qd*, *J* = 7.5, 4.0, 1 H, C*H*-C(O)); 2.12 (*m*, 2 H, CH_2CH=CH_2); 1.93-1.71 (*m*, 2 H, CH_2CH_2CH-O); 1.64-1.42 (*m*, 2 H, $CH_2CH_2CH_2$); 1.39 (*d*, *J* = 7.5, 3 H, $CHCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.9, 137.6, 115.3, 79.3, 50.7, 33.4, 33.1, 24.1, 12.4.

IR (ATR): ν = 2936, 1817, 1641, 1123.

HRMS (EI) *m/z*: Calc. for [M^+]: 154.0989. Found: 154.0991.

(3*R*,4*R*)-*trans*-3-Methyl-4-(9-decenyl)oxetan-2-one (297d)



297d

β-Lactone **297d** was prepared from propionylbromide (**296**) and undecylenic aldehyde according to the general procedure. Purification by flash chromatography (pentane / diethyl ether 20:1) gave **297d** as colorless oil (104 mg, 0.47 mmol, 62%, *ee* = 87%, *dr* = 94:6). The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (ThermoFinnigan TraceGC, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C, ramp @ 5 °C/min to 180 °C, hold 20 min).

$C_{14}H_{24}O_2$, MW: 224.34 g/mol.

[α] $_D^{27.0°C}$ (c = 1.245, $CHCl_3$) = +40.5 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 5.81 (*ddt*, *J* = 16.8, 10.1, 6.7, 1 H, CH_2CH=CH_2); 5.03-4.91 (*m*, 2 H, CH=CH_2); 4.17 (*ddd*, *J* = 7.1, 6.3, 4.0, 1 H, C*H*-O); 3.22 (*qd*, *J* = 7.5, 4.0, 1 H, C*H*-C(O)); 2.04 (*m*, 2 H, CH_2CH=CH_2); 1.93-1.68 (*m*, 2 H, CH_2CH_2CH-O); 1.45-1.25 (*m*, 12 H, $CH_2(CH_2)_6CH_2$); 1.39 (*d*, *J* = 7.5, 3H, CHCH_3).

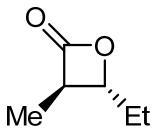
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.9, 139.0, 114.1, 79.5, 50.7, 34.2, 33.8, 29.4, 29.3, 29.2, 29.1, 28.9, 25.9, 12.6.

IR (ATR): ν = 2926, 1821, 1640, 1122.

HRMS (EI) *m/z*: Calc. for [M^+]: 224.1776. Found: 224.1776.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78; O, 14.26. Found: C, 75.06; H, 10.56.

(3*R*,4*R*)-*trans*-3-Methyl-4-ethyloxetan-2-one (297e)



297e

β-Lactone **297e** (0.76 mmol, yield: 76%, *ee* = 87% *dr* = 95:5) was prepared from propionylbromide (**296**) and propanal according to the general procedure, but using 1.00 mmol of aldehyde in 4 mL of DCM. The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (ThermoFinnigan TraceGC, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C, ramp @ 5 °C/min to 180 °C, hold 20 min). An analytically pure sample was obtained as light-yellow oil by flash chromatography (pentane / diethyl ether 20:1).

$C_6H_{10}O_2$, MW: 114.14 g/mol.

[α] $_{D}^{25.5°C}$ (c = 1.625, $CHCl_3$) = +55.0 ± 0.1.

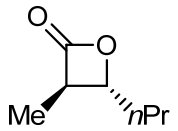
^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.13 (*td*, *J* = 6.6, 4.0, 1 H, C*H*-O); 3.23 (*qd*, *J* = 7.5, 4.0, 1 H, C*H*-C(O)); 1.97-1.72 (*m*, 2 H, CH_3CH_2CH-O); 1.39 (*d*, *J* = 7.5, 3 H, CHCH_3); 1.02 (*t*, *J* = 7.5, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.8, 80.5, 50.3, 27.3, 12.7, 9.1.

IR (ATR): ν = 2937, 1816, 1125, 848.

HRMS (EI) *m/z*: Calc. for $[M-H]^+$: 113.0597. Found: 113.0592.

(3*R*,4*R*)-*trans*-3-Methyl-4-propyloxetan-2-one (297f)



297f

β-Lactone **297f** was prepared from propionylbromide (**296**) and butanal according to the general procedure. Purification by flash chromatography (pentane / diethyl ether 20:1) gave **297f** as colorless oil (64 mg, 0.50 mmol, 67%, *ee* = 93%, *dr* = 97:3). The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (Hewlett Packard HP6890, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C for 2 min, ramp @ 5 °C/min to 150 °C, hold 0.75 min, ramp @ 8 °C/min to 200 °C). Spectral data for **297f** has been reported earlier.[182]

$C_7H_{12}O_2$, MW: 128.17 g/mol.

[α] $_D^{23.2°C}$ (c = 1.005, $CHCl_3$) = +65.5 ± 0.1.

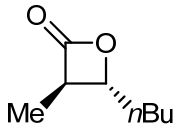
^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.19 (*ddd*, *J* = 7.4, 6.1, 4.0, 1 H, C*H*-O); 3.23 (*qd*, *J* = 7.5, 4.0, 1 H, C*H*-C(O)); 1.92-1.68 (*m*, 2 H, CH_2CH_2CH-O); 1.55-1.35 (*m*, 2 H, CH_2CH_3); 1.39 (*d*, *J* = 7.5, 3H, $CHCH_3$); 0.99 (*t*, *J* = 7.4, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.8, 79.3, 50.7, 36.1, 18.4, 13.7, 12.5.

IR (ATR): ν = 2962, 1817, 1124, 872, 814.

HRMS (EI) *m/z*: Calc. for [M^+]: 128.0832. Found: 128.0832.

(3*R*,4*R*)-*trans*-3-Methyl-4-butyloxetan-2-one (297g)



297g

β-Lactone **297g** was prepared from propionylbromide (**296**) and pentanal according to the general procedure, but using 1.00 mmol of aldehyde in 4 mL of DCM. Purification by flash chromatography (pentane / diethyl ether 20:1) gave **297g** as colorless oil (91 mg, 0.64 mmol, 64%, *ee* = 89%, *dr* = 97:3). The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (ThermoFinnigan TraceGC, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C, ramp @ 5 °C/min to 180 °C, hold 20 min). Spectral data for the racemate has been reported earlier.[183]

$C_8H_{14}O_2$, MW: 142.20 g/mol.

[α] $_D^{28.3°C}$ (c = 1.080, $CHCl_3$) = +58.0 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.18 (*ddd*, *J* = 7.1, 6.3, 4.0, 1 H, C*H*-O); 3.22 (*qd*, *J* = 7.5, 4.0, 1 H, C*H*-C(O)); 1.94-1.69 (*m*, 2 H, CH_2CH_2CH-O); 1.48-1.30 (*m*, 2 H, CH_2CH_3); 1.39 (*d*, *J* = 7.5, 3 H, $CHCH_3$); 0.93 (*t*, *J* = 7.1, 3 H, CH_2CH_3).

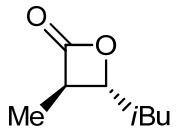
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.9, 79.5, 50.7, 33.8, 27.1, 22.4, 13.9, 12.6.

IR (ATR): ν = 2934, 1818, 1124, 840.

HRMS (EI) *m/z*: Calc. for $[M-H]^+$: 141.0910. Found: 141.0911.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92; O, 22.50. Found: C, 67.41; H, 9.72.

(3*R*,4*R*)-*trans*-3-Methyl-4-*iso*-butyloxetan-2-one (297h)



297h

β-Lactone **297h** (0.38 mmol, yield: 76%, *ee* = 87%, *dr* = 94:6) was prepared from propionylbromide (**296**) and isovaleraldehyde according to the general procedure, but using 0.50 mmol of aldehyde in 2 mL of DCM. The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (Hewlett Packard HP6890, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C for 2 min, ramp @ 5 °C/min to 150 °C, hold 0.75 min, ramp @ 8 °C/min to 200 °C). An analytically pure sample of **297h** was obtained as colorless oil by flash chromatography (pentane / diethyl ether 20:1).

$C_8H_{14}O_2$, MW: 142.20 g/mol.

$[\alpha]_D^{27.4°C}$ (c = 1.000, $CHCl_3$) = +59.9 ± 0.1.

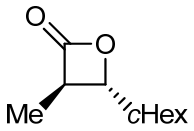
^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.25 (*ddd*, *J* = 7.5, 5.9, 4.0, 1 H, C*H*-O); 3.21 (*qd*, *J* = 7.5, 4.0, 1 H, C*H*-C(O)); 1.85-1.71 (*m*, 2 H, CHCH_2CH-O); 1.67-1.56 (*m*, 1 H, C*H*$(CH_3)_2$); 1.39 (*d*, *J* = 7.5, 3 H, CHCH_3); 0.97 (*d*, *J* = 6.5, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.9, 78.5, 51.2, 43.0, 25.4, 22.8, 22.3, 12.5.

IR (ATR): ν = 2959, 1817, 1120, 882.

HRMS (EI) *m/z*: Calc. for [M^+]: 142.0988. Found: 142.0988.

(3*R*,4*R*)-*trans*-3-Methyl-4-cyclohexyloxetan-2-one (297i)



297i

β-Lactone **297i** (0.59 mmol, yield: 78%, *ee* = 80%, *dr* = 83:17) was prepared from propionylbromide (**296**) and cyclohexylcarboxaldehyde according to the general procedure, but using 0.75 mmol of aldehyde in 3 mL of DCM. The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (GammaDex^{TM}, 120 °C, 2.0 mL/min). An analytically pure sample of **297i** was obtained as colorless oil by flash chromatography (pentane / diethyl ether 20:1). Spectral data for the racemate have been reported earlier.[181]

$C_{10}H_{16}O_2$, MW: 168.23 g/mol.

[α] $_{D}^{25.0°C}$ (c = 0.800, $CHCl_3$) = +47.4 ± 0.2.

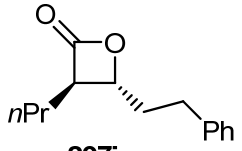
^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 3.86 (*dd*, *J* = 8.4, 4.1, 1 H, C*H*-O); 3.28 (*qd*, *J* = 7.5, 4.1, 1 H, C*H*-C(O)); 1.94 (*m*, 1 H, (C*H*)$_{c\text{Hex}}$); 1.83-1.56 (*m*, 5 H, (CH_2)$_{c\text{Hex}}$); 1.37 (*d*, *J* = 7.5, 3 H, CHCH_3); 1.32-1.18 (*m*, 3 H, (CH_2)$_{c\text{Hex}}$); 1.02 (*m*, 2 H, (CH_2)$_{c\text{Hex}}$).

^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 172.2, 83.3, 48.9, 41.9, 28.5, 27.2, 26.0, 25.4, 25.1, 12.9.

IR (ATR): ν = 2926, 2853, 1818, 1450, 1125, 856.

HRMS (EI) *m/z*: Calc. for [MH^+]: 169.1223. Found: 169.1222.

(3*R*,4*R*)-*trans*-3-Propyl-4-(2-phenylethyl)oxetan-2-one (297j)



297j

β-Lactone **297j** was prepared from valerylbromide and 3-phenylpropionaldehyde according to the general procedure. Purification by flash chromatography (DCM / pentane 3:1, then pentane / diethyl ether 40:1) gave **297j** as colorless oil (149 mg, 0.68 mmol, 91%, *ee* = 94%, *dr* = 98:2). The *dr* value was determined by ^{1}H-NMR and the *ee* value by HPLC (Chiralcel OD-H, 97:3 *n*-hexane/*i*PrOH, 1.0 mL/min, 210 nm).

$C_{14}H_{18}O_2$, MW: 218.29 g/mol.

$[\alpha]_D^{26.4°C}$ (c = 1.300, $CHCl_3$) = +59.2 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.33-7.16 (*m*, 5 H, C*H*$_{Ar}$); 4.22 (*ddd*, *J* = 7.9, 5.5, 4.0, 1 H, C*H*-O); 3.19 (*ddd*, *J* = 8.4, 6.9, 4.0, 1 H, C*H*-C(O)); 2.75 (*m*, 2 H, $CH_2CH_2C_{Ar}$); 2.11 (*m*, 2 H, $CH_2CH_2C_{Ar}$); 1.70 (*m*, 2 H, CH_2CH-C(O)); 1.41 (*m*, 2 H, $CH_3CH_2CH_2$); 0.92 (*t*, *J* = 7.3, 3 H, CH_3).

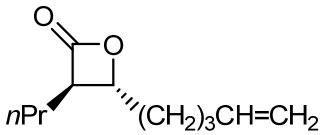
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.1, 140.0, 128.5, 128.2, 126.2, 77.1, 56.0, 36.2, 31.4, 29.8, 20.3, 13.8.

IR (ATR): ν = 2931, 1813, 1603, 1114, 838, 748, 698.

HRMS (EI) *m/z*: Calc. for $[M]^+$: 218.1301. Found: 218.1300.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; O, 14.66. Found: C, 77.22; H, 8.38.

(3*R*,4*R*)-*trans*-3-Propyl-4-(2-phenylethyl)oxetan-2-one (297k)



297k

β-Lactone **297k** was prepared from valerylbromide and 5-hexenal according to the general procedure. Purification by flash chromatography (pentane / diethyl ether 40:1) gave **297k** as colorless oil (131 mg, 0.72 mmol, 96%, *ee* = 95%, *dr* = 98:2). The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (ThermoFinnigan TraceGC, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C, ramp @ 5 °C/min to 180 °C, hold 20 min).

$C_{11}H_{18}O_2$, MW: 182.26 g/mol.

[α] $_{D}^{22.6°C}$ (c = 1.280, $CHCl_3$) = +38.6 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 5.78 (*ddt*, *J* = 16.9, 10.2, 6.7, 1 H, CH_2CH=CH_2); 5.07-4.97 (*m*, 2 H, CH=CH_2); 4.23 (*ddd*, *J* = 7.5, 5.8, 4.0, 1 H, C*H*-O); 3.19 (*ddd*, *J* = 8.7, 6.6, 4.0, 1 H, C*H*-C(O)); 2.12 (*m*, 2 H, CH_2CH=CH_2); 1.92-1.69 (*m*, 4 H, CH_2CH_2CH-O/ CH_2CH-C(O)); 1.64-1.37 (*m*, 4 H, $CH_2CH_2CH_2$/ $CH_3CH_2CH_2$); 0.96 (*t*, *J* = 7.3, 3 H, CH_3).

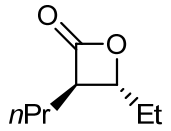
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.3, 137.6, 115.3, 77.9, 56.0, 33.8, 33.2, 30.0, 24.3, 20.4, 13.9.

IR (ATR): ν = 2933, 1814, 1641, 1120.

HRMS (EI) *m/z*: Calc. for $[M-H]^+$: 182.1301. Found: 182.1304.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; O, 17.56. Found: C, 72.71; H, 9.98.

(3*R*,4*R*)-*trans*-3-Propyl-4-ethyloxetan-2-one (297l)



297l

β-Lactone **297l** was prepared from valerylbromide and propanal according to the general procedure, but using 0.50 mmol of aldehyde in 2 mL of DCM. Purification by flash chromatography (pentane / diethyl ether 40:1) gave **297l** as light-yellow oil (45 mg, 0.32 mmol, 63%, *ee* = 94%, *dr* = 97:3). The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (ThermoFinnigan TraceGC, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C, ramp @ 5 °C/min to 180 °C, hold 20 min). Spectral data for the racemate has been reported earlier.[184]

$C_8H_{14}O_2$, MW: 142.20 g/mol.

$[\alpha]_D^{24.5°C}$ (c = 1.215, $CHCl_3$) = +25.8 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.18 (*td*, *J* = 6.6, 4.0, 1 H, C*H*-O); 3.19 (*ddd*, *J* = 8.8, 6.6, 4.0, 1 H, C*H*-C(O)); 1.96-1.64 (*m*, 4 H, CH_3CH_2CH-O/ CH_2CH-C(O)); 1.54-1.36 (*m*, 2 H, $CH_3CH_2CH_2$); 1.02 (*t*, *J* = 7.5, 3 H, CH_3); 0.96 (*t*, *J* = 7.3, 3 H, CH_3).

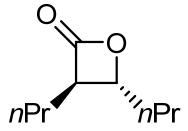
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.4, 79.1, 55.5, 30.0, 27.5, 20.4, 13.8, 9.2.

IR (ATR): ν = 2964, 1813, 1125, 849.

HRMS (EI) *m/z*: Calc. for $[M]^+$: 142.0988. Found: 142.0988.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92; O, 22.50. Found: C, 67.85; H, 9.88.

(3*R*,4*R*)-*trans*-3-Propyl-4-propyloxetan-2-one (297m)



297m

β-Lactone **297m** was prepared from valerylbromide and butanal according to the general procedure. Purification by flash chromatography (pentane / diethyl ether 40:1) gave **297m** as colorless oil (109 mg, 0.70 mmol, 93%, *ee* = 95%, *dr* = 98:2). The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (ThermoFinnigan TraceGC, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C, ramp @ 5 °C/min to 180 °C, hold 20 min).

$C_9H_{16}O_2$, MW: 156.22 g/mol.

$[\alpha]_D^{22.3°C}$ (c = 1.630, $CHCl_3$) = +36.8 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.22 (*ddd*, *J* = 7.4, 5.9, 4.0, 1 H, C*H*-O); 3.18 (*ddd*, *J* = 8.7, 6.6, 4.0, 1 H, C*H*-C(O)); 1.90-1.63 (*m*, 4 H, CH_2CH_2CH-O/ CH_2CH-C(O)); 1.53-1.34 (*m*, 4 H, 2x $CH_3CH_2CH_2$); 0.96 (*m*, 6 H, 2x CH_3).

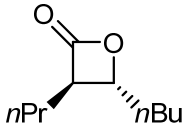
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.4, 77.9, 55.9, 36.5, 29.9, 20.3, 18.4, 13.8.

IR (ATR): ν = 2960, 1813, 1125, 818.

HRMS (EI) *m/z*: Calc. for $[M\text{-}C_2H_5]^+$: 127.0754. Found: 127.0754.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32; O, 20.48. Found: C, 69.26; H, 10.29.

(3*R*,4*R*)-*trans*-3-Propyl-4-butyloxetan-2-one (297n)



297n

β-Lactone **297n** was prepared from valerylbromide and pentanal according to the general procedure, but using 0.50 mmol of aldehyde in 2 mL of DCM. Purification by flash chromatography (pentane / diethyl ether 40:1) gave **297n** as colorless oil (78 mg, 0.46 mmol, 92%, *ee* = 93%, *dr* = 96:4). The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (ThermoFinnigan TraceGC, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C, ramp @ 5 °C/min to 180 °C, hold 20 min).

$C_{10}H_{18}O_2$, MW: 170.25 g/mol.

[α] $_{D}^{26.9°C}$ (c = 1.135, $CHCl_3$) = +30.5 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.22 (*ddd*, *J* = 7.3, 6.1, 4.0, 1 H, C*H*-O); 3.18 (*ddd*, *J* = 8.7, 6.6, 4.0, 1 H, C*H*-C(O)); 1.93-1.61 (*m*, 4 H, CH_2CH_2CH-O/ CH_2CH-C(O)); 1.52-1.29 (*m*, 6 H, $CH_3CH_2CH_2CH$/ $CH_3CH_2CH_2CH_2$); 0.94 (*m*, 6 H, 2x CH_3).

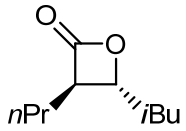
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.4, 78.1, 55.9, 34.1, 30.0, 27.1, 22.4, 20.4, 13.9, 13.8.

IR (ATR): ν = 2958, 1814, 1125, 837.

HRMS (EI) *m/z*: Calc. for $[M-H]^+$: 169.1223. Found: 169.1224.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66; O, 18.80. Found: C, 70.71; H, 10.49.

(3*R*,4*R*)-*trans*-3-Propyl-4-*iso*-butyloxetan-2-one (297*o*)



297*o*

β-Lactone **297*o*** was prepared from valerylbromide and isovaleraldehyde according to the general procedure, but using 0.50 mmol of aldehyde in 2 mL of DCM. Purification by flash chromatography (pentane / diethyl ether 40:1) gave **297*o*** as colorless oil (65 mg, 0.38 mmol, 76%, *ee* = 94%, *dr* = 96:4). The *dr* value was determined by ^{1}H-NMR and the *ee* value by GC (ThermoFinnigan TraceGC, Chrompac Chirasil-Dex CB column 25 m x 0.25 mm, flow rate 1.1 mL/min, method: 60 °C, ramp @ 5 °C/min to 180 °C, hold 20 min).

$C_{10}H_{18}O_2$, MW: 170.25 g/mol.

[α] $_{D}^{24.9°C}$ (c = 1.600, $CHCl_3$) = +47.4 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.30 (*ddd*, *J* = 8.0, 5.2, 4.0, 1 H, C*H*-O); 3.17 (*ddd*, *J* = 8.4, 6.9, 4.0, 1 H, C*H*-C(O)); 1.88-1.36 (*m*, 6 H, CHCH_2CH-O/ $CH_3CH_2CH_2$CH-C(O)); 0.93 (*m*, 6 H, 2x CH_3).

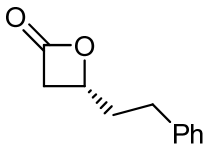
^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.4, 76.9, 56.4, 43.5, 29.9, 25.4, 22.8, 22.4, 20.3, 13.8.

IR (ATR): ν = 2958, 1815, 1116.

HRMS (EI) *m/z*: Calc. for $[M-C_4H_9]^+$: 113.0597. Found: 113.0596.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66; O, 18.80. Found: C, 70.71; H, 10.59

(*R*)-4-(2-phenylethyl)oxetan-2-one (*R*)-221a



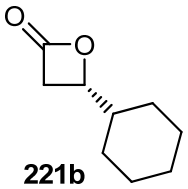
(*R*)-**221a**

β-Lactone (*R*)-**221a** (0.14 mmol, yield: 28%, *ee* = 82%) was prepared from acetylbromide (**148**) and 3-phenylpropionaldehyde (**207**) according to the general procedure. The *ee* value was determined by HPLC (Chiralcel OD-H, 97:3 *n*-hexane/*i*PrOH, 1.0 mL/min, 210 nm). An analytically pure sample was obtained as colorless oil by flash chromatography (pentane / diethyl ether 15:1). Analytical data for the (*S*)-enantiomer have been reported earlier.[175]

$C_{11}H_{12}O_2$, MW: 176.21 g/mol.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.25 (*m*, 5 H, CH_{Ar}); 4.50 (*m*, 1 H, C*H*-O); 3.48 (*dd*, *J* = 16.3, 5.8, 1 H, C*H*H-C(O)); 3.03 (*dd*, *J* = 16.3, 4.3, 1 H, CH*H*-C(O)); 2.77 (*m*, 2 H, $CH_2CH_2C_{Ar}$); 2.13 (*m*, 2 H, $CH_2CH_2C_{Ar}$).

(*S*)-4-Cyclohexyloxetan-2-one (221b)



221b

β-Lactone **221b** was prepared from acetylbromide (**148**) and cyclohexylcarboxaldehyde (**226**) according to the general procedure. Purification by flash chromatography (pentane / diethyl ether 15:1) gave **221b** as colorless oil (63 mg, 0.41 mmol, 82%, *ee* = 88%).The *ee* value was determined by GC (GammaDex^{TM}, 145 °C, 2.0 mL/min). Analytical data have been reported earlier.[176]

$C_9H_{14}O_2$, MW: 154.21 g/mol.

[α] $_D^{25.0°C}$ (c = 2.950, $CHCl_3$) = +18.5 ± 0.1.

^{1}H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 4.19 (*ddd*, *J* = 8.2, 5.8, 4.4, 1 H, C*H*-O); 3.42 (*dd*, *J* = 16.3, 5.8, 1 H, C*H*H-C(O)); 3.10 (*dd*, *J* = 16.3, 4.4, 1 H, CH*H*-C(O)); 1.93 (*m*, 1 H, C*H*$(CH_2)_2$); 1.82-1.54 & 1.23 & 1.00 (3 x *m*, 10 H, 5 x $(CH_2)_{ring}$).

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13 Curriculum Vitae

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Aug 1992 - Oct 1996	Laboratory Assistant at Ciba-Geigy AG (Pharmaceutical Chemistry – Metabolic Risk Factors Unit)
Nov 1996 - Dec 2000	Chemistry studies (Diploma as Chemist FH) at the University of Applied Sciences Zürich
Jan 2001 - Mar 2004	Chemistry studies (Diploma as Chemist ETH) at ETH Zürich - Internship at Novartis, Basel (3 months) - Internship at F. Hoffmann La-Roche, Basel (4 months)
Spring 2004	Diploma thesis ("Approach towards the synthesis of (*1R**, *2'S**)-N-(Phenylacetyl)-1,2,3,4-tetrahydro-1-(2-hydroxypropyl)isochinoline as a model for a precursor of an *Iboga*-Alkaloid") under the supervision of *Stefan Höck* in the group of Prof. Dr. *Hans-Jürg Borschberg* at ETH Zürich
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During my Ph.D. thesis, I was teaching assistant for the lecture "Allgemeine Chemie II (OC)" as well as for the lecture "Organic Synthesis and Method Strategies, OC IV".

Zürich, September 2008 Thomas Kull