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Asymmetric synthesis using ketenes

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Contents

1. Introduction

Chemists have long used ketenes as useful intermediates in the synthesis of organic molecules. The seminal contributions of Staudinger to the field of organic synthesis included the discovery of ketene in 1908 and the addition of ketenes to imines to form β-lactams in 1912.[1] Since that time, numerous research groups have made advances both in the generation of ketenes and in their reactions. A particularly exciting area of ketene chemistry has been their use in stereoselective transformations. Ketenes have played a major role in the explosive development of new methods for acyclic stereocontrol in the period from 1960 until the present. Ketenes have been particularly amenable to catalytic reactions, most likely because of their ability to perform [2+2] and [4+2] cycloadditions (Fig. 1). These

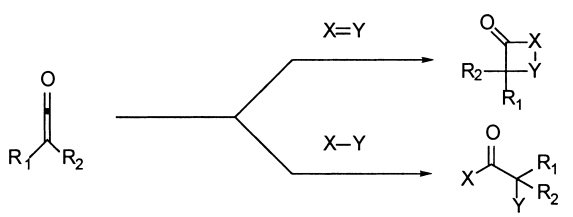

Figure 1. The general reactivity of ketenes.

Keywords: ketenes; asymmetric synthesis; organic molecules.

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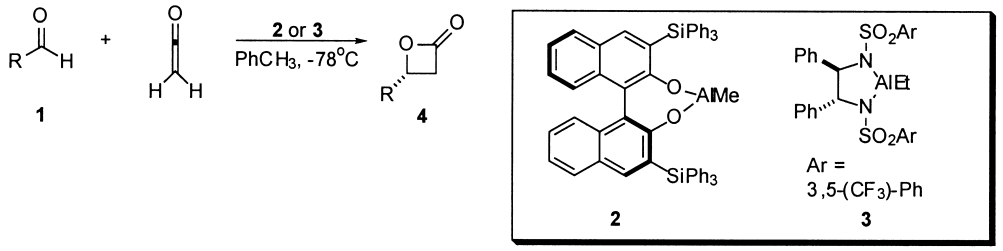
Table 1. Miyano's asymmetric lactone synthesis with stoichometric and catalytic amounts of lewis acid



Entry	R (**1**)	Lewis acid[a]	% yield[b] (**4**)	% ee (**4**)[c] (configuration)	Reference
1	Me	**2**	78	23 (*S*)	3a
2	Me	**3**	59	30 (*S*)	3b

[a] Chiral Lewis acid: **2**=1 equiv. and **3**=20 mol%.
[b] Determined using ASTEC Chiraldex G-TA column.
[c] Determined using ASTEC Chiraldex G-TA column.

additions leave no reactive functional groups to deactivate either an acidic or nucleophilic catalyst.

A number of excellent reviews have appeared on the general chemistry of ketenes, cycloadditions of ketenes, the addition of ketenes to aldehydes, and the addition of ketenes to imines.[2] Therefore, the current review will attempt to summarize advances in certain areas of ketene chemistry since the most recent review. As the general reactions of ketenes have been well covered, we will focus on use of ketenes in asymmetric synthesis. Finally, preference will be given to the use of auxiliary and catalyst control of ketene reactions, rather than substrate control.

Four particularly useful and stereoselective reactions of ketenes will provide the bulk of the material in this review: the addition of ketenes to aldehydes, the addition of ketenes to imines, rearrangements starting with ketenes, and the addition of alcohols to ketenes. This list is not meant to include every useful, asymmetric reaction of a ketene, but rather to serve as an entry into the literature for those interested in the field.

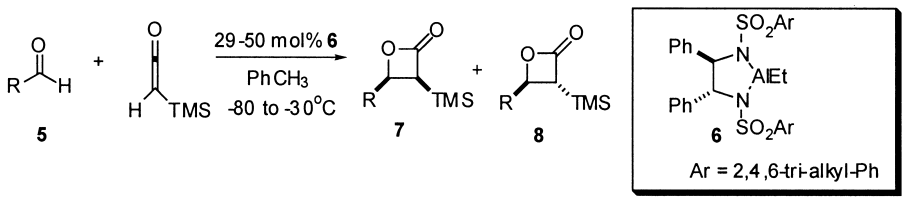
2. [2+2] Cycloadditions of ketenes and aldehydes

The addition of ketenes to aldehydes provides highly useful β-lactones. Not only do these lactones serve as the active component for a number of biologically active natural products, they also behave as masked aldol adducts. Therefore, a number of groups have employed this reaction as an equivalent to the aldol reaction, and one that is highly amenable to catalysis. The effect of aldehyde stereochemistry on the stereochemical outcome of the addition has been extensively studied and well reviewed, so we will focus here on catalyst controlled additions. As is typical with ketene reactions, nucleophiles or Lewis acids can catalyze this process.

2.1. Lewis acid-controlled additions

2.1.1. Results. In 1994, Miyano et al. reported the first use of a chiral aluminum–binaphthol complex as a promoter for the addition of preformed ketene to a variety of aldehydes (Table 1).[3] These authors then demonstrated that chiral aluminum–bissulfonamide complexes functioned as catalysts

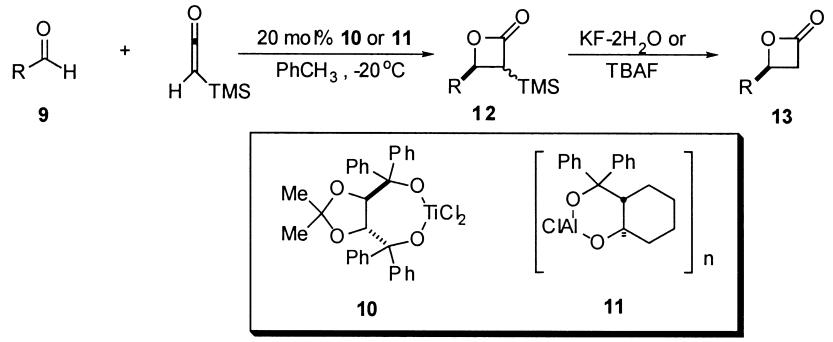
Table 2. Kocienski–Pons catalytic lactone formation utilizing silyl ketenes



Entry	R (**5**)	% yield (**7**)[a]	dr (**7**:**8**)[b]	% ee (**7**)[c]	Configuration (C3,C4)
1	$PhCH_2$	56	83: 17	83	3*S*,4*R*
2	$PhCH_2CH_2$	80	90: 10	44	3*S*,4*R*
3	*o*-Hex	32	85: 15	68	3*S*,4*R*
4	$C_{11}H_{23}$	67	94: 6	47[d]	3*S*,4*R*
5	*p*-MeO$PhCH_2$	77	99: 1	83[d]	3*S*,4*R*

[a] Isolated yields.
[b] *cis*/*trans* Determinded via NMR of crude reaction.
[c] Via HPLC.
[d] % Ee determined via ^{1}H NMR analysis of the CHTMS double let in the presence of 2 equiv. of (*R*)-(−)-2,2,2,-trifluro-1-(9-anthryl)-ethanol.

Table 3. Romo's optically active β-lactones prepared via [2+2] additions with silyl ketenes



Entry	R (**9**)	Catalyst	*cis*/*trans* (**12**)	% yield (**13**)[a]	% ee (**13**)[b] (configuration)	Reference
1	*n*-Bu	**10**	34:1	49	41 (ND)	5a
2	*p*-NO_2Ph	**10**	>19:1	71	21 (ND)	5a
3	Bn	**10**	9:1	58	9 (*R*)	5a
4	$PhCH_2CH_2$	**10**	>19:1	78	41 (*S*)	5a
5	*c*-Hex	**10**	>19:1	66	80 (*S*)	5a
6	$BnO(CH_2)_4$	**10**	19:1	76	45 (ND)	5a
7	*n*-Bu	**11**	>99:1	86	85 (*R*)	5a
8	Ph	**11**	>99:1	82	28 (ND)	5b
9	Bn	**11**	>19:1	45	75 (*R*)	5b
10	$PhCH_2CH_2$	**11**	>19:1	60	36 (*S*)	5b
11	*c*-Hex	**11**	>99:1	83	84 (*S*)	5b
12	$TBSO(CH_2)_5$	**11**	>19:1	55	46 (ND)	5b
13	$CH_2{=}CH(CH_2)_7$	**11**	>19:1	71	22 (ND)	5b
14	$(CH_3CH_2)CH$	**11**	>19:1	46	56 (ND)	5b

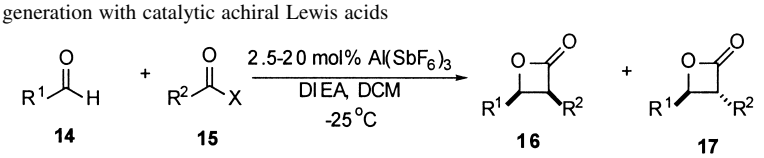
ND=not determined.
[a] Yield is for two steps.
[b] % ee was measured after desilylation.

for this process. Further work by the Kocienski–Pons group (Table 2)[4] and independently by the Romo group (Table 3),[5] showed that a variety of aluminum and titanium complexes catalyzed the addition of preformed TMS-ketene to aldehydes with moderate to good enantioselection.

In 1999, Nelson and co-workers discovered that the generation of ketene from acetyl chloride and a hindered tertiary amine base was compatible with some Lewis acid catalysts for the addition of ketene to aldehydes (Table 4).[6] They further demonstrated that aluminum–bissulfonamide complexes **19** and **20** were excellent asymmetric catalysts for the addition (Table 5). These workers have extended this chemistry to the addition of methylketene to aldehydes, and have extensively exploited the use of the β-lactone products in the synthesis of other chiral functional groups (Scheme 1).

2.1.2. Mechanism. The recent advances reported by the Nelson group shed light on the two key aspects of the ketene-aldehyde addition reaction: the generation of ketene, and the addition of ketene to aldehydes.[6b] Previous work had indicated that Lewis acids catalyzed the addition of preformed ketenes to aldehydes by coordination to and

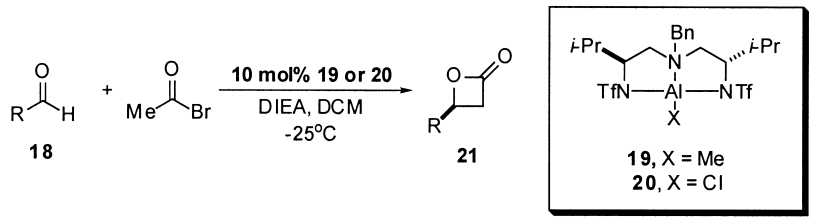
Table 4. Nelson's in situ ketene generation with catalytic achiral Lewis acids



Entry	R^1 (**14**)	R^2 (**15**)	X (**15**)	% yield (**16**; dr **16**:**17**)[a]
1	$PhCH_2CH_2$	Me	Cl	93
2	*i*-Bu	Me	Cl	82
3	$CH_2CH(CH_2)_8$	Me	Cl	81
4	*o*-Hex	Me	Cl	90
5	$BnOCH_2$	Me	Cl	83
6	$PhCH_2CH_2$	Me	Br	60
7	*o*-Hex	Me	Cl	82
8	$CH_2CH(CH_2)_8$	Et	Cl	80 (96:4)
9	*o*-Hex	Et	Cl	65 (97:3)

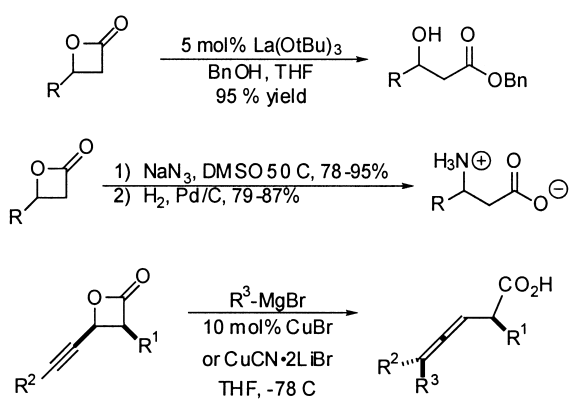
[a] Isolated yield.

Table 5. Nelson's asymmetric lactone synthesis using chiral aluminum complexes



Entry	R (**18**)	Catalyst (time (h), temperature (°C))	% yield (**21**)[a]	% ee (**21**)[b] (configuration)
1	$BnOCH_2$	**20** (8, −40)	91	92 (*R*)
2	$PhCH_2CH_2$	**19** (16, −50)	93	92 (s)
3	$PhCH_2CH_2$	**19** (72, −78)	89	95 (s)
4	$CH_2CH(CH_2)_8$	**20** (16, −50)	91	91 (*S*)
5	*i*-Bu	**19** (24, −50)	80	93 (*S*)
6	$BnOCH_2$	**20** (16, −40)	90	91 (*S*)
7	$TDBPSOCH_2$	**20** (16, −40)	74	89 (*R*)
8	$BnOH_2C$—≡—	**19** (16, −50)	86	93 (*R*)
9	*t*-Bu—≡—	**19** (16, −50)	91	85 (*R*)
10	*c*-Hex	**20** (24, −40)	56	54 (*R*)

[a] Isolated yields.
[b] Entries 1–6, and 8% ee determined via HPLC (Chiralcel OD-H column) and 4,5,9, and 10 via GC (Chiraldex G-TA column.



Scheme 1.

activation of the aldehyde, rather than the ketene. However, the formation of ketene in situ added further mechanistic issues to the analysis of Nelson's system. The Nelson group addressed these mechanistic issues using careful ^{13}C NMR studies, which revealed that the overall reaction did indeed proceed via a ketene intermediate, rather than a Lewis acid-bound enolate (Fig. 2). The studies also indicated that acetyl halides rapidly reacted with hindered tertiary amines to generate a mixture of ketene and starting halide at −78°C, even in the absence of Lewis acid (Fig. 3). Addition of an aluminum Lewis acid to this mixture did not affect the shift of the ketene resonances, indicating that the Lewis acid and ketene do not interact. Treatment of this mixture with an aldehyde and warming to −30°C afforded the β-lactone. Importantly, the β-lactone did not form in the absence of Lewis acid.

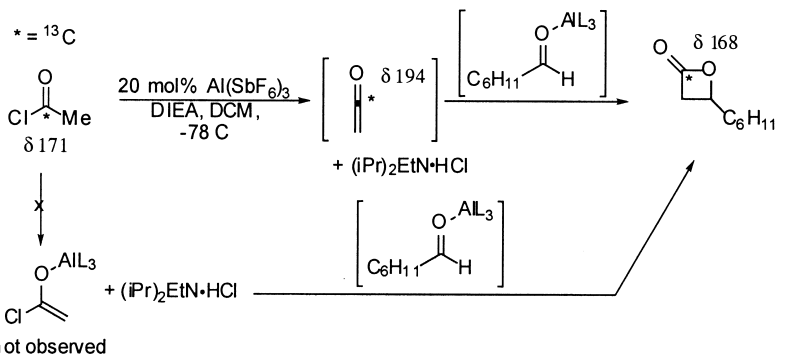


Figure 2. NMR Studies confirm a ketene-intermediate for Nelson's [2+2] reaction.

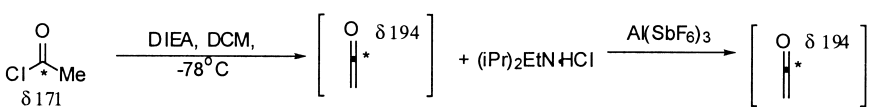
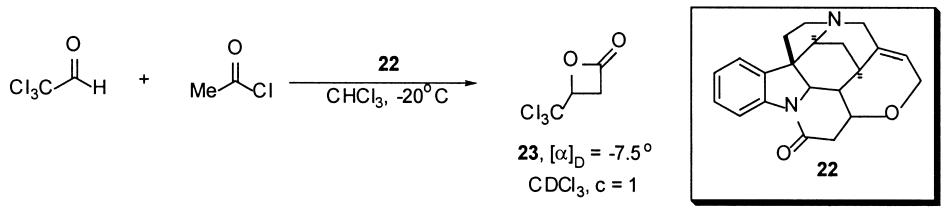


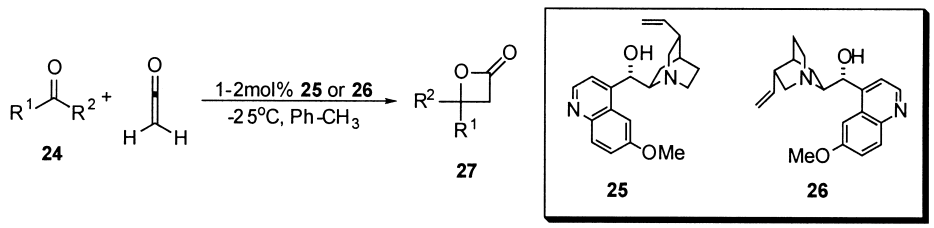
Figure 3. Addition of Lewis acid fails to alter the chemical shift of ^{13}C labeled ketene.



Scheme 2.

Nelson and co-workers further advanced the field by developing the first chiral Lewis acid catalyst to afford greater than 90% ee in the ketene–aldehyde addition. Although they did not provide a rationale for this superior induction, they did attribute the high activity of the catalyst to the distortion in geometry about the aluminum caused coordination of the tertiary amine. Use of the tridentate ligand would also be expected to project

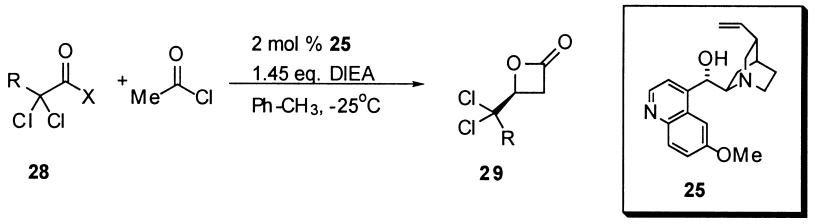
Table 6. Wynberg's quininine and quinidine catalysts for the asymmetric synthesis of lactones



Entry	R^1 (**24**)	R^2 (**24**)	Catalyst	% yield (**27**)[a]	% ee (**27**) (configuration)[b]
1	CCl_3	H	**25**	89	98 (*R*)
2	CCl_2H	H	**25**	67	45 (*R*)
3	CCl_2Me	H	**25**	95	91 (*R*)
4	CCl_2Et	H	**25**	87	89 (*R*)
5	CCl_2Ph	H	**25**	89	90 (*R*)
6	CCl_3	Me	**25**	72	94 (*R*)
7	CCl_3	*p*-Cl–Ph	**25**	68	90 (*R*)
8	CCl_3	*p*-NO_2–Ph	**25**	95	89 (*R*)
9	CCl_3	H	**26**	N/A	76 (*S*)
10	CCl_2H	H	**26**	N/A	N/A (*S*)
11	CCl_2Me	H	**26**	N/A	76 (*S*)
12	CCl_2Et	H	**26**	N/A	70 (*S*)
13	CCl_2Ph	H	**26**	N/A	68 (*S*)
14	CCl_3	Me	**26**	N/A	85 (*S*)
15	CCl_3	*p*-Cl–Ph	**26**	N/A	65 (*S*)
16	CCl_3	*p*-NO_2–Ph	**26**	N/A	65 (*S*)

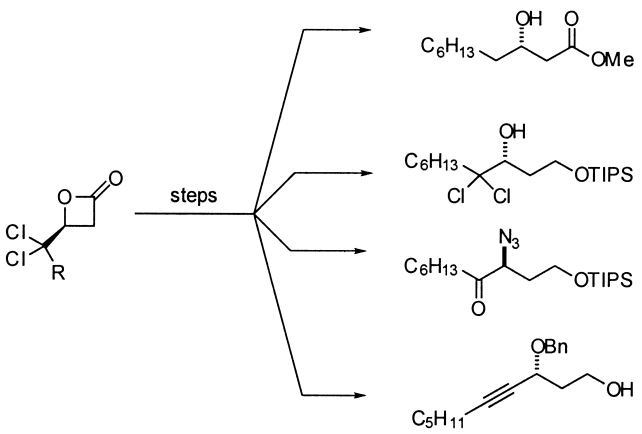
[a] Isolated yields.
[b] % Ee determined via ^{13}C NMR of the L-phenylethylamine amides or ^{19}F analysis of the Mosher esters of the hydroxyacids of the lactones. Configuration was determined by comparing the CD spectra with entries 1 and 9, which were converted to malic acid.

Table 7. Romo's lactone formation with chlorinated ketenes



Entry	R (**28**)	X (**28**)	% yield (**29**)[a]	% ee (**29**)[b]
1	Bn	H	85	94
2	*n*-Hex	H	73	93
3	$PivOCH_2CH_2$	H	80	94
4	*i*-Pr	H	40	98
5	Cl	Me	25	ND

[a] Isolated yields.
[b] GC Analysis with TBS-β-CD column.



Scheme 3.

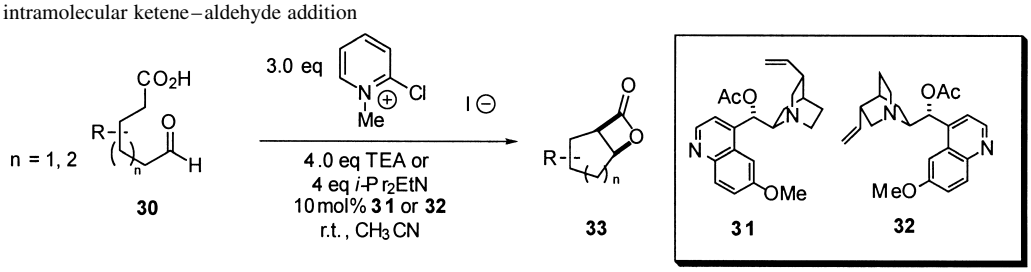
the asymmetry of the ligand further into the reaction sphere.

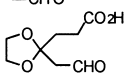
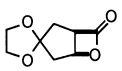
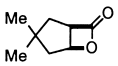
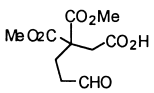
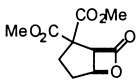
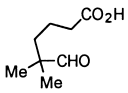
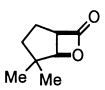
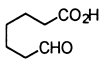
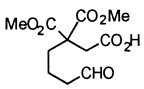
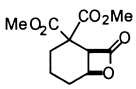
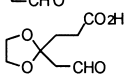
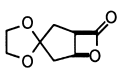
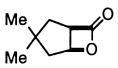
2.2. Nucleophile-catalyzed additions

2.2.1. Results. Borrmann and Wegler reported the first attempt at using chiral, non-racemic tertiary amine as the catalyst for the addition of a ketene to an aldehyde.[7] In the presence of Brucine (**22**), ketene added to chloral to afford β-lactone **23** (Scheme 2). Although they report that **23** so generated had an optical rotation, they did not quantify the extent of asymmetric induction realized in this reaction.

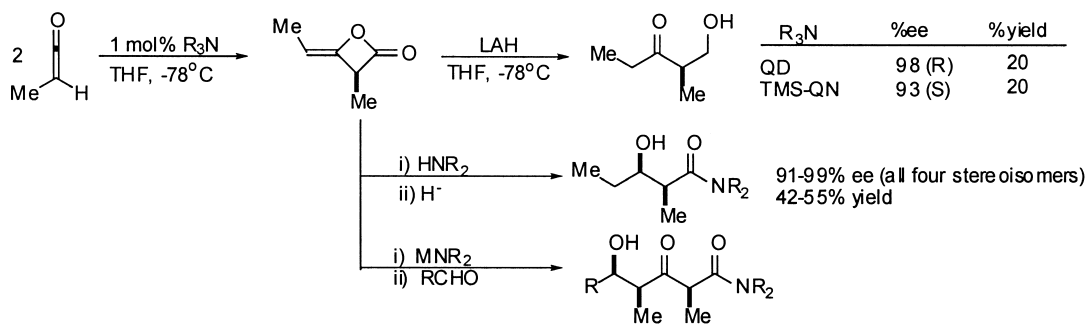
Wynberg and co-workers then demonstrated that the cinchona alkaloids quinidine (**25**) and quinine (**26**) afford excellent asymmetric induction in this reaction, and extended its scope to other highly electrophilic aldehydes and ketones (Table 6).[8] This reaction only proceeded when

Table 8. Romo's intramolecular ketene–aldehyde addition



Entry	Oxo-acid (**30**)	Catalyst	Lactone (**33**)	% yield (**33**)[a]	% ee (**33**)[b]
1		TEA		55	
2		TEA		66	
3		TEA		68	
4		TEA		62	
5		TEA		62	
6		TEA		36	
7		TEA		57	
8		**31**		54	92
9		**31** (**32**)[c]		37 (51)[c]	92 (86)[c]
10		**31**		45	90

[a] Isolated yields.
[b] % Ee determined via GC analysis.
[c] Values in parenthesis are for the enantiomer of lactone shown in entry 9.



Scheme 4.

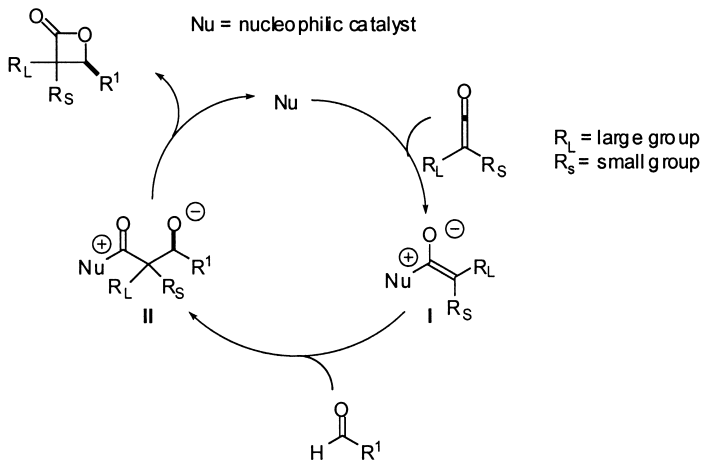


Figure 4. General mechanism for nucleophilic catalysis of ketene additions.

the electrophile bore at least two chlorine substituents on the carbon adjacent to the carbonyl.

Romo and co-workers later demonstrated that reactions employing ketene formed in situ from acetyl chloride and Hünig's base gave similar yields and selectivities to those using preformed ketene (Table 7).[9] This group also demonstrated a number of useful transformations of the chlorinated β-lactone products (Scheme 3).

In both the previous cases, the ketene–aldehyde addition only proceeded with highly electrophilic carbonyl compounds. However, Romo et al. discovered that aliphatic aldehydes did serve as electrophiles in the intramolecular version of this reaction.[9c] In this case, in situ activation of aldehyde acids with Mukaiyama's salt presumably led to aldehyde ketenes, which then underwent intramolecular β-lactone formation under the influence of *O*-acetyl quinidine (**31**) (Table 8).

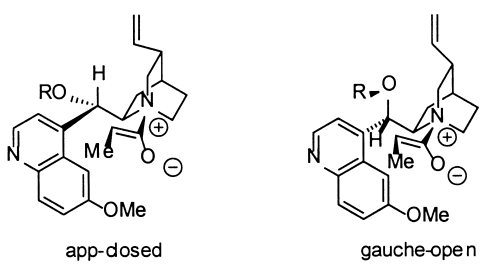
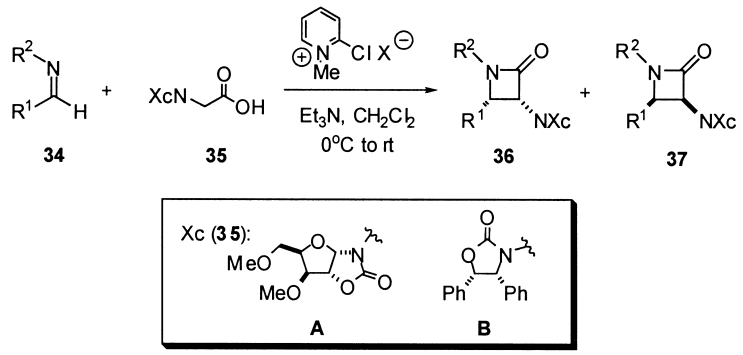


Figure 5. Two proposed ammonium enolates of quinidine.

In a reaction related to the ketene–aldehyde addition, Calter reported the dimerization of methylketene under the influence of cinchona alkaloid catalysts (Scheme 4).[10] This report was the first to demonstrate that *O*-silyl quinine derivatives could afford high enantioselectivity for the opposite enantiomer than that produced by quinidine diastereomers. Lack of high enantioselection from quinine-catalyzed reactions has been a chronic problem in the use of cinchona alkaloids as nucleophilic catalysts. Calter and co-workers later extensively exploited the methylketene dimer as a polypropionate synthon.

2.2.2. Mechanism. Addition of a tertiary amine to a ketene presumably generates ammonium enolate **I** (Fig. 4). This enolate can react with an electrophilic aldehyde, generating a second, zwitterionic intermediate, **II**. Cyclization of this intermediate generates the β-lactone and regenerates the amine catalyst. As **I** serves as the reactant in the stereochemistry-determining step, analysis of this intermediate should explain the asymmetric induction imparted by the catalyst. The catalyst sterically blocks attack on one π-face of the ammonium enolate, thereby setting the α-center (Fig. 5). The catalyst also controls the orientation of the approaching electrophile, necessarily through non-bonded interactions. However, the inability to observe the ammonium enolate has led to several proposed conformations for this species. Wynberg and Romo favor reaction from what Romo terms the *app-closed* conformation, while Calter proposes the *gauche-open* conformation as the reactive species. However, both models invoke shielding of the same face by C_9 and the quinoline substituent.

Table 9. Newly developed chiral auxiliaries for lactam synthesis



Entry	R^1 (**34**)	R^2 (**34**)	Xc (**35**)	X	dr (**36**:**37**)	% yield	Reference
1	PhCH=CH	Bn	**A**	I	>99:1	41	11b
2	PhCH=CH	Bn	**A**	TsO	>99:1	54	11b
3	PhCH=CH	Ph_2CH	**A**	I	81:19	85	11b
4	PhCH=CH	Ph_2CH	**A**	TsO	84:16	99	11b
5	PhCH=CH	*p*-MeOPh	**A**	TsO	94:6	97	11b
6	*p*-MeOPh	*p*-MeOPh	**A**	TsO	>99:1	91	11b
7	Ph	*p*-MeOPh	**A**	TsO	>99:1	94	11b
8	*p*-ClPh	*p*-MeOPh	**A**	TsO	>99:1	quant	11b
9	PhCH=CH	*p*-MeOPh	**A**	TsO	94:6	97	11b
10	PhC≡C	*p*-MeOPh	**A**	TsO	91:9	90	11b
11	Ph	Bn	**B**	I	1:>99	67	11c
12	Ph	*p*-MeOPh	**B**	I	1:>99	69	11c
13	PhCH=CH	Bn	**B**	I	1:>99	71	11c
14	PhCH=CH	*p*-MeOPh	**B**	I	1:>99	58	11c

3. [2+2] Cycloadditions of ketenes and imines

This addition reaction, also known as the Staudinger reaction, has seen intensive use in the synthesis of the biologically important β-lactams. A number of studies have explored the effect of ketene and imine stereochemistry on the stereochemistry of the β-lactams, and the review of Palomo summarizes this work well.[2d] We will focus here on the use of either auxiliaries or catalysts to control the absolute stereochemistry of β-lactam formation.

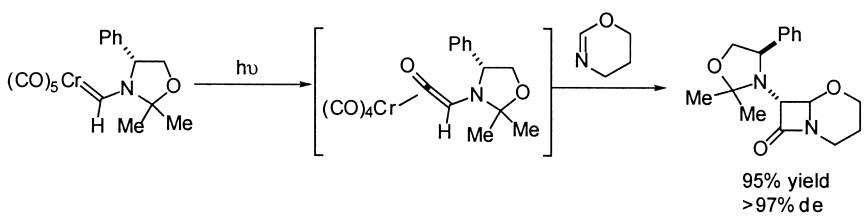
3.1. Auxiliary-controlled additions

The Staudinger reaction allows placement of a chiral auxiliary on the ketene or the imine component. Although the first strategy generally leads to higher stereocontrol, it limits one to the production of α-amino-β-lactams.

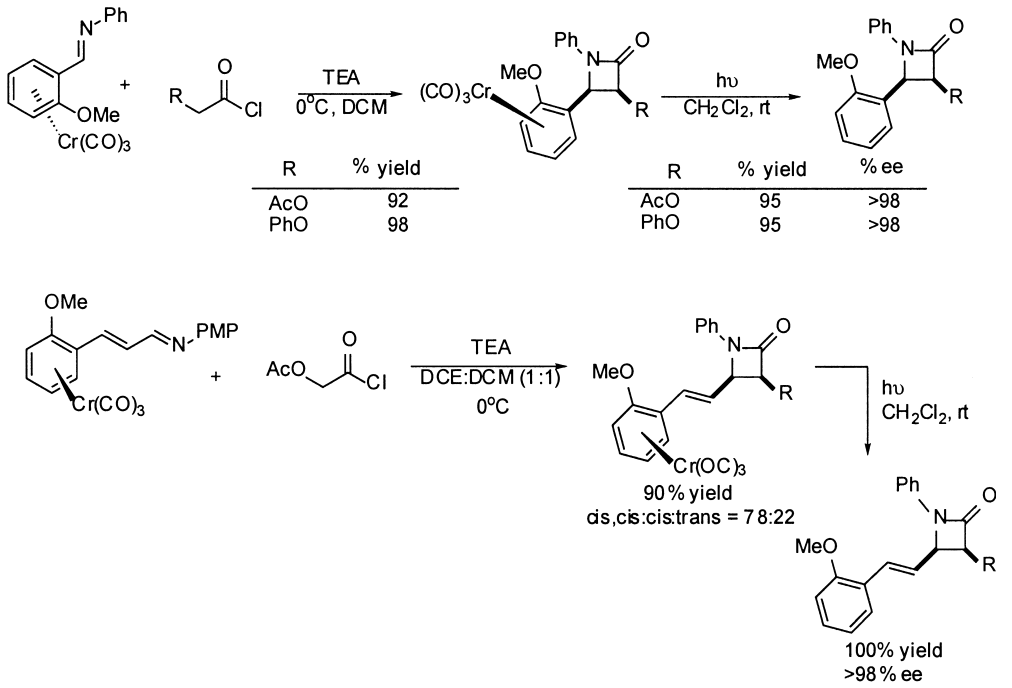
3.1.1. Ketene-bound auxiliaries. Since the discovery by Evans and Sjogren in 1985 that oxazolidinone auxiliaries effectively control the stereochemistry of β-lactam formation, several groups have developed new oxazolidinones with improved properties.[11] D-xylose[11b] and *erythro*-2-amino-1,2-diphenylethanol[11c] derived auxiliaries give excellent levels of stereocontrol in the Staudinger reaction, and benefit from facile preparations (Table 9). However, the continued lack of a non-destructive method for auxiliary removal continues to plague the use oxazolidinone auxiliaries in this reaction.

Hegedus and co-workers developed an interesting strategy for generating and stereoselectively reacting ketenes.[12] They used carbene complexes of chromium carbonyls as precursors to ketenes bearing a chiral oxazolidine auxiliary (Scheme 5). Photolysis of the carbene complex generated the metal-bound ketene, which then reacted with imidates to form β-lactones with high levels of diastereoselectivity.

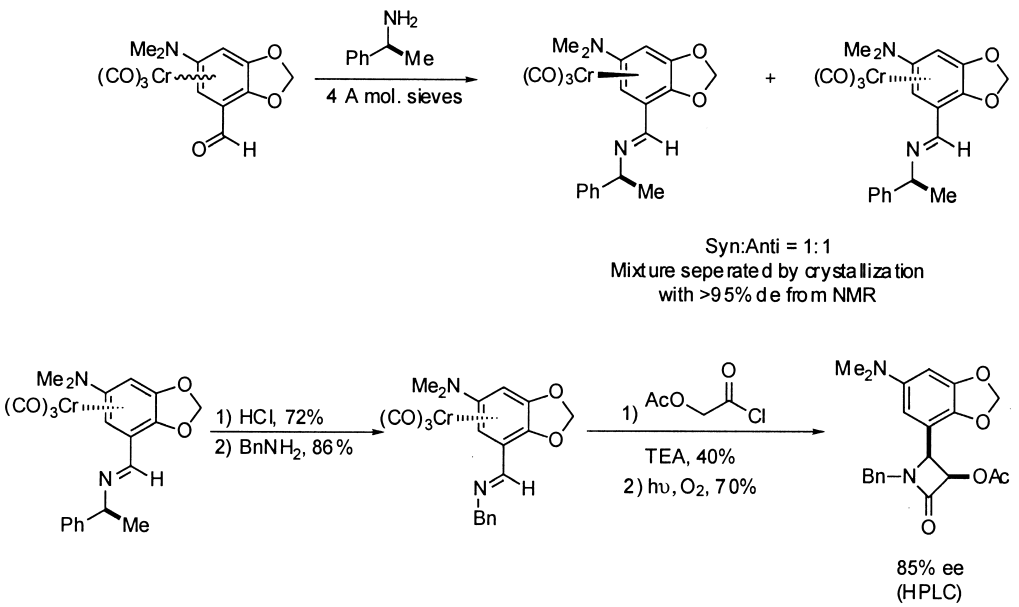
3.1.2. Imine-bound auxiliaries. Auxiliaries to the imine attached through nitrogen generally afford low induction and require destructive methods for removal. An attractive strategy for imine-bound auxiliary control developed by Del Buttero, Maiorana et al. involves the use of planar chiral chromium(0) complexes of aromatic imines (Scheme 6).[13] The metal differentiates the faces of the imine, and then decomplexes under mild, oxidative conditions. Da Costa, Damas and co-workers recently extended this methodology to more highly substituted aromatic imines (Scheme 7).[14]



Scheme 5.



Scheme 6.



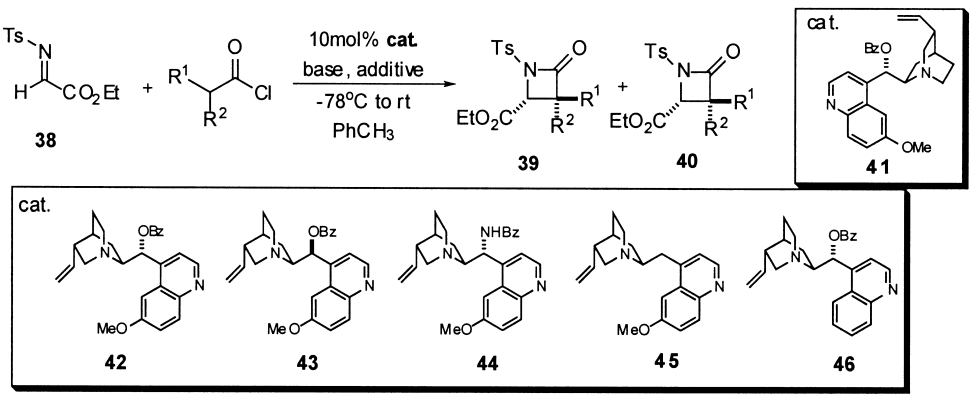
Scheme 7.

3.2. Catalyst-controlled additions

Although the Staudinger reaction generally can proceed without catalysis, recent studies prove that nucleophilic catalysts can provide excellent levels of enantioselectivity. Both cinchona alkaloid derivatives and planar-chiral, nucleophilic metal complexes give efficient asymmetric catalysis.

3.2.1. Cinchona alkaloid-catalyzed reactions. Lectka and co-workers demonstrated that benzoyl quinidine (**41**) catalyzed the addition of several ketenes to tosyl imine **38** to form β-lactams in 95–99% ee (Table 10).[15] These workers further discovered that the alkaloid also catalyzed the formation of the ketenes from acid chlorides and proton sponge. This group went on to develop a number of practical advances in this reaction, including the use of solid supported reagents and catalysts, and the use of inorganic bases such as potassium carbonate or sodium hydride as replacements for proton sponge. Further, the combination of a Lewis acid with the nucleophilic catalyst led to higher yields of the β-lactam products, without reduction in the enantioselectivity of the reaction. However, one limitation of this method was the requirement for highly electrophilic imines such as **38** or the related benzoyl imine **48** (Table 11). Lectka proposed a nucleophilic mechanism for the catalysis.

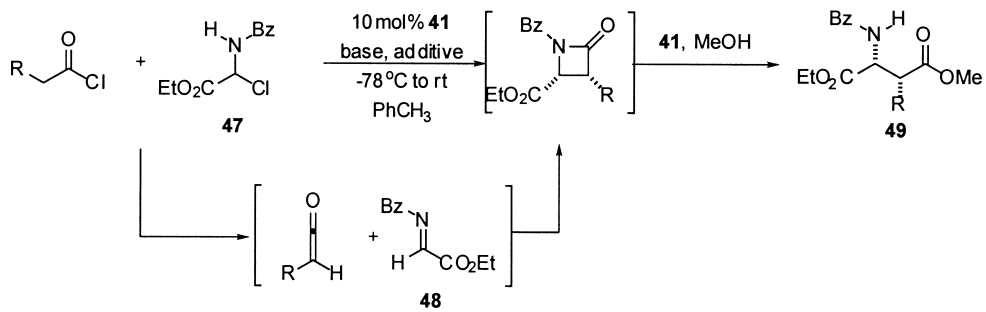
Table 10. Leckta's cinchona alkoloids for lactam formation



Entry	R^1 (**38**)	R^2(**38**)	Base	Catalyst	Additve	% yield (**39**)[a]	dr (**39**:**40**)[b]	%ee (**39**)[c]	Reference
1	Ph	Ph	PS	**41**	None	36	–	99	15j
2	Et	H	PS	**41**	None	57	99/1	99	15j
3	Oph	H	PS	**41**	None	45	99/1	99	15j
4	Oac	H	PS	**41**	None	61	>99/1	98	15j
5	Bn	H	PS	**41**	None	60	33/1	96	15j
6	CH_2Oph	H	PS	**41**	None	53	50/7	>95	15j
7	$CH{=}CH_2$	H	PS	**41**	None	58	99/1	98	15j
8	N_3	H	PS	**41**	None	47	25/1	97.5	15j
9	Br	H	PS	**41**	None	61	98/2	96	15j
10	BnO	H	PS	**41**	None	65	99/1	96	15j
11	BnO	H	BEMP	**41**	None	60	99/1	99	15j
12	BnO	H	PS	**41**	None	57	99/1	99	15j
13	BnO	H	K_2CO_3	**41**	None	56	8/1	93	15j
14	BnO	H	NaH/15-crown-5	**41**	None	60	25/1	99	15j
15	Ph	H	PS	**41**	None	65	99/1	96	15i
16	Ph	H	PS	**41**	$Sc(OTf)_3$	80	N/A	N/A	15i
17	Ph	H	PS	**41**	$Zn(OTf)_2$	85	N/A	N/A	15i
18	Ph	H	PS	**41**	$In(OTf)_3$	95	60/1	98	15i
19	Ph	H	PS	**42**	None	NR	99/1	99 (*ent*)	15j
20	Ph	H	PS	**43**	None	NR	99/1	99 (*ent*)	15j
21	Ph	H	PS	**44**	None	NR	10/1	89 (*ent*)	15j
22	Ph	H	PS	**45**	None	NR	2/1	72 (*ent*)	15j
24	Ph	H	PS	**46**	none	NR	5/1	5 (*ent*)	15j

[a] Isolated yield.
[b] Determined by ^{1}H NMR of crude residue.
[c] *ent*=enantiomer of product.

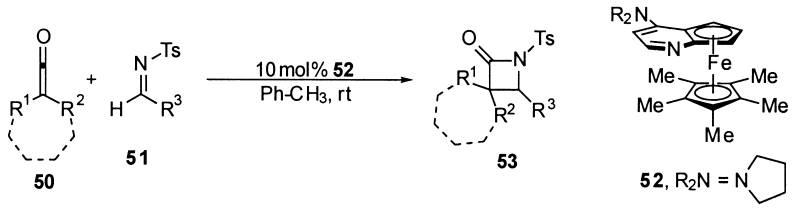
Table 11. Leckta's β-aminoester synthesis

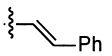
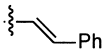
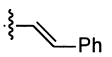


Entry	R (**47**)	% yield (**49**)[a]	dr (**49**)[b]	% ee (**49**)[c]
1	Ph	62	12/1	95
2	PhO	63	14/1	95
3	*p*-MeOPh	62	10/1	94
4	*p*-ClPh	60	12/1	94
5	*p*-MeOPhO	53	11/1	96

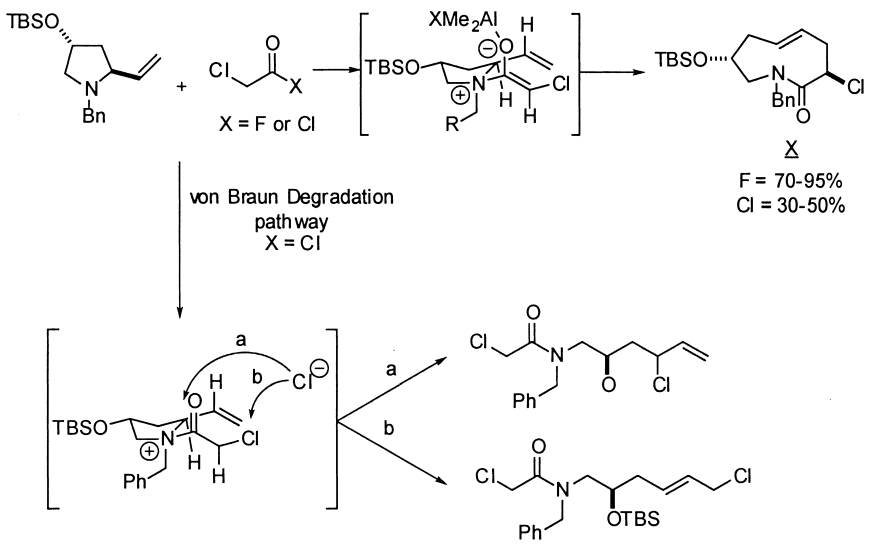
[a] Isolated yield.
[b] Determined by ^{1}H NMR of crude reaction mixture.
[c] Determined via chiral HPLC.

Table 12. Fu's azoferrocene complex catalyzes the Staudinger reaction



Entry	R^1 (**50**)	R^2 (**50**)	R^3 (**51**)	% yield (**53**)[a]	dr (**53**)[a]	% ee (**53**)[a]
1	$-(CH_2)_6-$		Ph	84		81
2	$-(CH_2)_6-$			90		92
3	$-(CH_2)_6-$			82		91
4	$-(CH_2)_6-$			89		94
5	$-(CH_2)_6-$			76		94
6	Et	Et		93		92
7	Et	Et		93		92
8	Ph	*i*-Bu	Ph	88	8:1	98
9	Ph	*i*-Bu		97	11:1	98
10	Ph	*i*-Bu		95	10:1	98
11	Ph	*i*-Bu		88	15:1	89
12	Ph	Et		97	9:1	95
13	Ph	Et		98	10:1	98

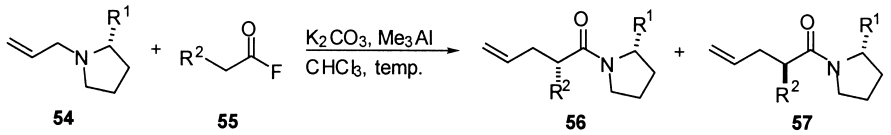
[a] Average of two runs.



Scheme 8.

3.2.2. Metal complex-catalyzed reactions. In 2001, Fu and Hodous demonstrated that azaferrocene complex **51** catalyzes the addition of disubstituted ketenes to tosyl imines with high levels of enantiocontrol (Table 12).[16] The reaction tolerated a variety of substituents on both the ketene and imine reactants. Unsymmetric, disubstituted ketenes yielded products with excellent diastereoselectivity, leading to the creation of adjacent quaternary and tertiary centers. Fu

Table 13. Nubbemeyer's Zwitterionic aza-claisen using proline and prolinol auxilaries



54 55 56 57

Entry	R^1 (**54**)	R^2 (**55**)	Temperature (°C)	% yield (**56**)	**56**:**57**
1	CO_2Me	$N(BOC)CH_2CH(OEt)_2$	20	73[a]	15:1
2	CO_2Me	NPht	0	74	1:1
3	CO_2Me	N_3	20	77	4:1
4	CO_2Me	N_3	0	77	7:1
5	CO_2Me	N_3	−20	77	9.5:1
6	$CH_2OTBDMS$	$N(BOC)CH_2CH(OEt)_2$	0	51[b]	15:1
7	$CH_2OTBDMS$	$N(BOC)CH_2CH(OEt)_2$	0	75	15:1
8	$CH_2OTBDMS$	N_3	0	77	15:1
9	CH_2OBn	$N(BOC)CH_2CH(OEt)_2$	0	47[a]	15:1

[a] Yield determined after cyclization.
[b] Yield after four steps.

proposed that the metal complex functions as a nucleophilic catalyst, in line with other asymmetric reactions catalyzed by **52** and its relatives.

4. Ketene-based rearrangements

Several rearrangements proceed through ketene intermediates. Recent work in this area has focused on the aza-Claisen rearrangement proceeding via ketenes and allylic amines. Both chiral auxiliaries and Lewis acids effectively control the stereochemical outcome of this reaction.

4.1. Auxiliary-controlled rearrangements

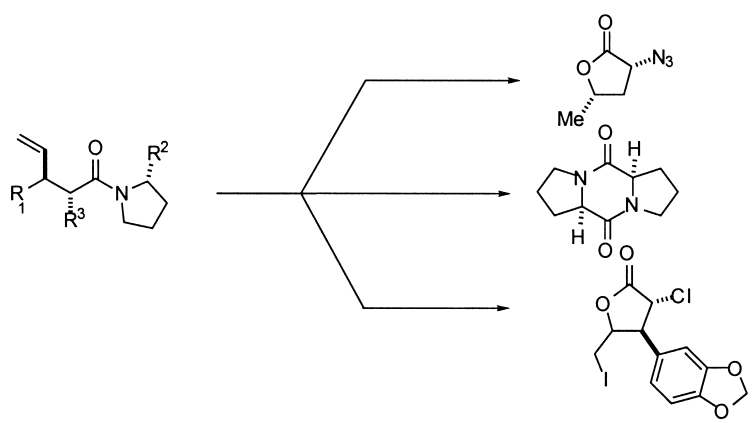
Nubbemeyer and co-workers extensively explored the zwitterionic aza-Claisen rearrangement starting with allylic amines and acid halides.[17] They demonstrated that acid fluorides led to much higher yields than the corresponding acid chlorides, as the fluorides were much less prone to generating von Braun degradation side products (Scheme 8). After demonstrating that the reaction displayed the same types of stereospecificity and 1,2-, 1,3-, and 1,4-stereocontrol common for [3,3]-rearrangements, the Nubbemeyer group also showed that certain auxiliaries afforded high levels of diastereoselectivity. In particular, proline-derived auxiliaries such as that present in **54** gave rearranged products in greater than 90% de (Table 13). The group then used the γ,δ-unsaturated amides in the synthesis of a variety of nitrogen containing products (Scheme 9).

4.2. Lewis acid-controlled rearrangements

MacMillan et al. developed a very convenient variation of the ketene initiated aza-Claisen rearrangement (Table 14).[18] This reaction employed allylic amines and acid chlorides in combination with a hindered tertiary amine and a Lewis acid. The reaction also gave very high levels of stereospecificity and 1,3-relay of stereochemistry (Table 15). MacMillan and Yoon further demonstrated that supra-stoichiometric amounts of certain chiral Lewis acids afforded high levels of enantiospecificity in the rearrangement (Table 16).

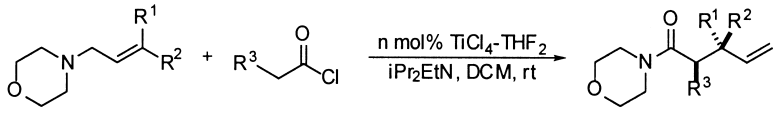
5. Miscellaneous

In addition to the classes of reactions discussed above, ketenes serve as key intermediates in a number of



Scheme 9.

Table 14. MacMillan's aza-Claisen rearrangement

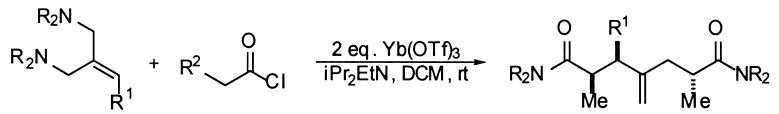


58 59 60

Entry	R^1 (**58**)	R^2 (**58**)	R^3 (**59**)	Mol% catalyst	% yield (**60**)	*syn*:*anti* (**60**)[a,b]
1	H	Me	Me	5	92	>99:1
2	H	Ph	Me	10	76	>99:1
3	H	Cl	Me	10	95	>99:1
4	H	H	Me	10	95	–
5	Me	H	Me	20	74	5:95
6	H	Me	NPht	10	77	>99:1
7	H	Me	SPh	10	81	92:8
8	H	Me	OBn	10	91	86:14
9	H	Cl	OBn	10	83	90:10
10	Cl	H	OBn	10	70	10:90

[a] Product ratios determined by GLC using a Bodman CC 1701 column.
[b] Relative configuration assigned by single-crystal X-ray analysis or chemical correlation to a know compound.

Table 15. MacMillan's tandem aza-Claisen rearrangement



61 62 63

Entry	NR_2 (**61**)	R^1 (**61**)	R^2 (**62**)	% yield (**63**)	*syn*–*anti*/*anti*–*anti*[a,b]
1	Morpholine	Me	Me	97	98:2[c]
2	Pyrrolidine	Me	Me	90	95:5
3	Piperidine	Me	Me	99	96:4
4	Morpholine	Cl	Me	98	99:1
5	Morpholine	OBz	Me	86	91:9[c]
6	Morpholine	CN	Me	78	97:3[c,d]
7	Morpholine	SPh	Me	70	93:7[d]
8	Morpholine	Me	Me	97	98:2[c]
9	Morpholine	Me	Bn	99	92:8
10	Morpholine	Me	NPhth	98	95:5[c]
11	Morpholine	Me	OPv	97	97:3[d]
12	Morpholine	OBz	OPv	71	92:8[d,e]
13	Morpholine	Cl	OPv	84	95:5[d]

[a] Ratios determined by GLC, HPLC, or ^{1}H NMR.
[b] The *syn*–*syn* and *anti*–*syn* isomers were isolated in <1% yield.
[c] Relative configurations assigned by X-ray analysis.
[d] Using $TiCl_4$–THF_2.
[e] *syn*–*syn* Isomer 2% isolated yield.

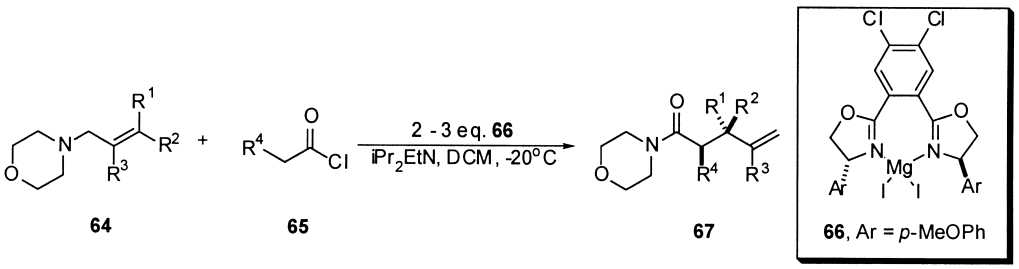
asymmetric reactions. We discuss several of these reactions below: the additions of alcohols to ketenes, the formation of α-halocarboxylates from ketenes, and some examples of auxiliary-controlled [2+2] additions of a ketene to an alkene.

5.1. Additions of alcohols to ketenes

This addition reaction has a venerable history as a method for synthesizing chiral carboxylate derivatives. The first example of the use of chiral alcohol to control the configuration of the newly formed stereocenter dates for 1919. The susceptibility this reaction to both nucleophilic and basic catalysis has also led to one of the first examples of the use of a cinchona alkaloid as a catalyst for the reaction of a ketene.

5.1.1. Auxiliary-controlled additions. The addition of a chiral alcohol to an unsymmetrically substituted ketene produces diastereomeric ester products. As hydrolysis of the resulting ester leads to recovery of the original chiral alcohol, the alcohol can be considered a chiral auxiliary. Almost a century of research has led to the development of such auxiliaries with ever increasing levels of diastereoselectivity. In 1989, a group from Merck reported the most selective example of this type of reaction (Table 17).[19] The addition of certain α-hydroxy esters to methylaryl ketenes resulted in the formation of aryl-propionic esters with diastereomeric excesses over 90%. Later experimental and theoretical studies of this reaction indicated that tertiary amine used to generate the ketene also played a key role in the addition reaction (Scheme 10).[19c]

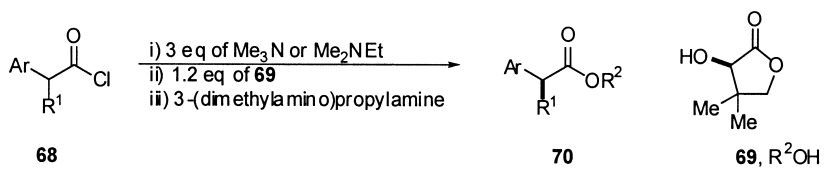
Table 16. The asymmetric aza-Claisen rearrangement using 2–3 equiv. of chiral Lewis acid



Entry	R^1 (**64**)	R^2 (**64**)	R^3 (**64**)	R^4 (**65**)	% yield (**67**)	*syn*:*anti*[a]	% ee (**67**)[a]
1	H	H	H	OAc	44	–	37
2	H	H	H	OTBS	67	–	38
3	H	H	H	O(*p*-ClPh)	59	–	71
4	H	H	H	OPh	48	–	78
5	H	H	H	OMe	28	–	80
6	H	H	H	OBn	80	–	91
7	H	H	H	OBn	80	–	91
8	H	H	Me	OBn	78	–	91
9	H	H	Ph	OBn	79	–	90
10	H	CH_2OBz	H	OBn	86	92:8	86
11	H	*p*-NO_2Ph	H	OBn	82	99:1	97
12	H	CO_2Et	H	OBn	84	97:3	96
13	H	Cl	H	OBn	95	98:2	91
14	Cl	H	H	OBn	74	3:97	91
15	Me	CO_2Et	H	OBn	75	94:6	97

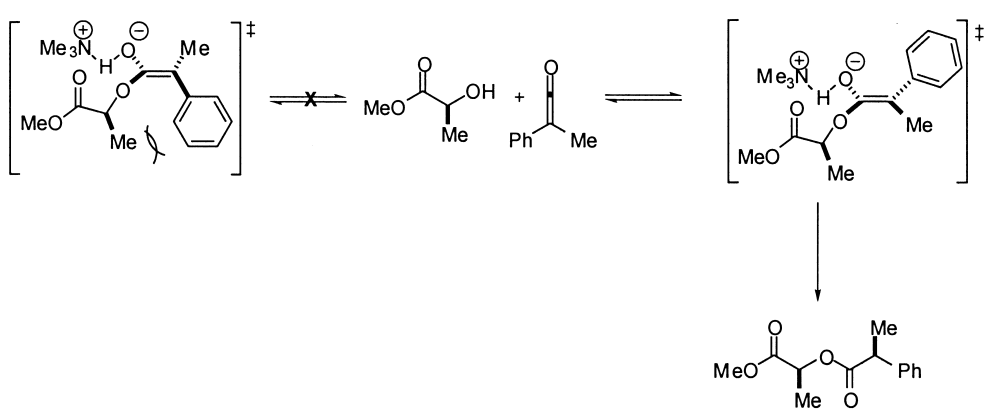
[a] Ratios determined by chiral GLC or HPLC. Absolute stereochemistry determined by chemical correction or by analogy.

Table 17. Merck's addition of chiral alcohols to ketenes

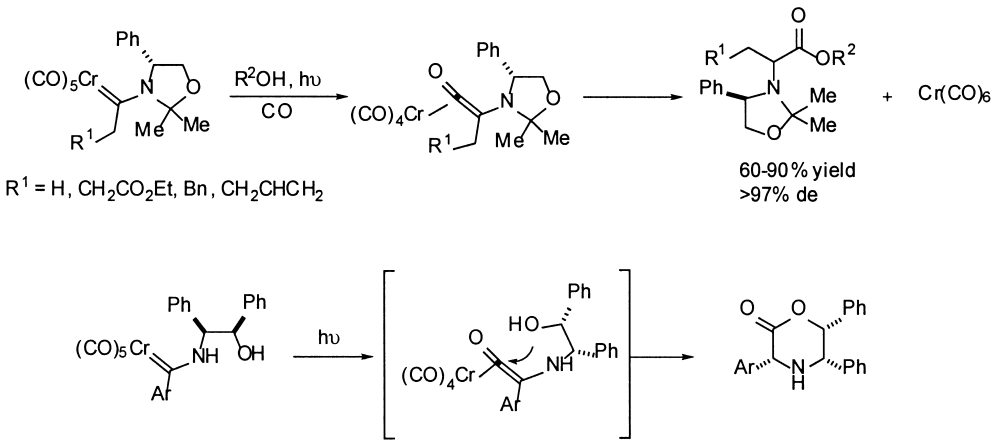


Entry	R^1 (**68**)	Ar (**68**)	% yield (**70**)	% de (**70**)[a]
1	Me	Ph	91	>99
2	Me	*p*-MeOph	90	>99
3	Et	Ph	93	>99
4	Bn	Ph	90	>99
5	Allyl	*p*-MeOph	65	>99

[a] Determined via ^{1}H NMR analysis.

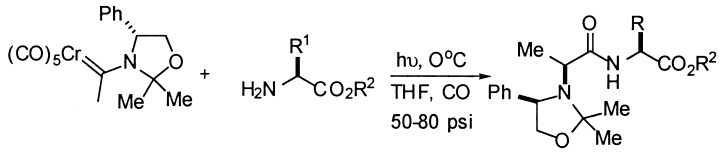


Scheme 10.



Scheme 11.

Table 18. Additions of amines to chromium bound ketenes

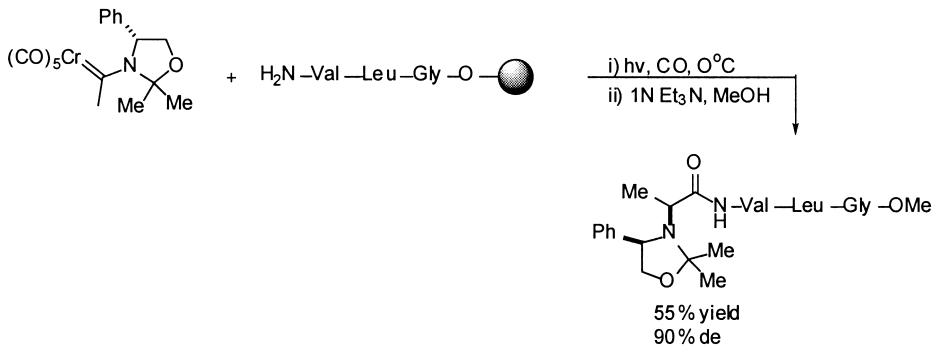


71 **72**

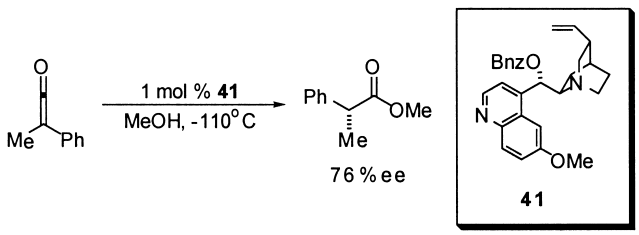
Entry	R^1 (**71**)	% yield (**72**)	dr (**72**)
1	Me	88	98:2
2	H	68	94:6
3	Bn	72	97:3
4	Ph	86	98:2
5	Ipr	65	86:14
6	$CH_3CH(OH)$	56	95:5
7	3-indoyl	60	90:10
8	CH_2OH	61	98:2
9	CH_2SH	32	92:8
10	$(CH_2)_2CO_2Me$	75	98:2
11	*p*-HO–$PhCH_2$	64	94:6
12	CH_2CO_2Me	64	95:5
13	$CH_2CH_2SCH_3$	68	95:5

Hegedus and co-workers have extended their chromium carbenoid methodology to control over the diastereoselectivity of the addition of alcohols and amines to ketenes.[12] Both types of nucleophile added to give the resulting α-amino esters (Scheme 11) or amides (Table 18) with excellent levels of diastereocontrol. The amine addition provided a method for peptide formation in the absence of any coupling agents (Scheme 12).

5.1.2. Catalyst-controlled additions. The seminal work of Pracejus and co-workers indicated that chiral catalysts could indeed induce some asymmetry in the addition of alcohols to ketenes.[20] In the most selective reaction to originate from this study, benzoyl quinine catalyzed the addition of methanol to phenylmethyl ketene to afford the phenyl propionic ester in 76% ee (Scheme 13). These authors postulated a



Scheme 12.



Scheme 13.

nucleophilic mechanism for the catalysis of the addition.

Simpkins and co-workers recently discovered that silylketenes function as superior substrates for the related addition of thiols to ketenes.[21] The benzoyl derivatives of quinine and quinidine both afforded greater than 90% ee of a variety of α-silylthioesters (Table 19). Subsequent refunctionalization reactions afforded several useful synthons (Scheme 14).

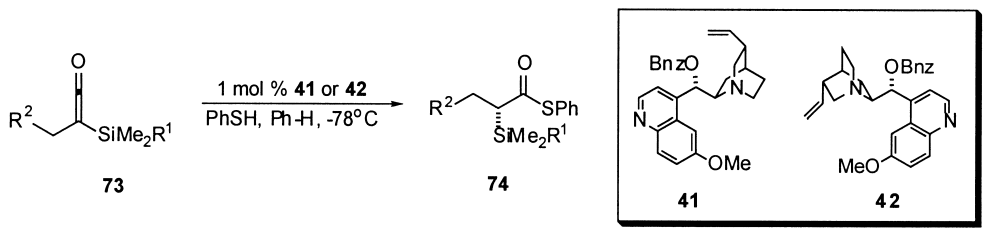
Fu and co-workers extended the scope of the catalyzed addition reaction by employing planar-chiral azaferrocenes as catalysts.[22] Although these catalysts afforded similar enantioselectivities those shown by cinchona alkaloid derivatives in the addition of methanol to phenylmethylketene, complex **76** was a much more selective catalyst than benzoylquinine for the addition to phenyl-α-*o*-trimethyleneketene (Table 20). These authors also favored a nucleophilic mechanism for the catalysis. The use of a pyrdinium triflate co-catalyst increased the enantioselectivity of the process by 20%, presumably by changing the species involved in the stereochemistry-determining protonation step.

5.2. α-Halocarboxylate synthesis

Several methods recently developed for the synthesis of α-halocarboxylates pass through ketene intermediates. Although these methods differ mechanistically, we will discuss them together.

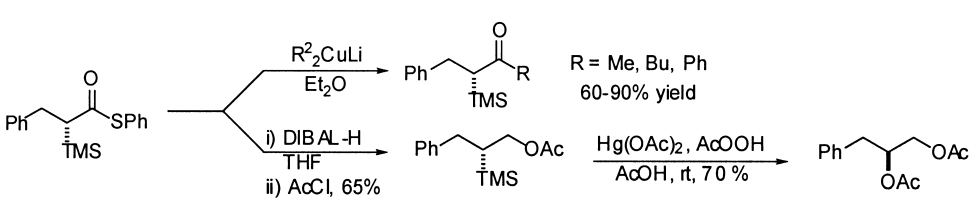
5.2.1. Auxiliary-controlled syntheses. Koh and Durst demonstrated that the addition of pantolactone to α-alkyl-α-haloketenes yields the corresponding α-haloesters with high levels of diastereocontrol (Table 21).[23] High diastereoselectivity depended on rapid warming of the reaction mixture and short reaction times, as the product epimerized by deprotonation or halide displacement. The sense of induction observed in this reaction aligned with that observed in earlier addition reactions, if the halogen assumed the role of the larger ketene substituent. Later work from this group demonstrated that the α-haloesters reacted with secondary amines to produce α-aminoacid derivatives by an interesting dynamic, kinetic resolution (Scheme 15).

Table 19. Simpkins addition of thiols to silylketenes



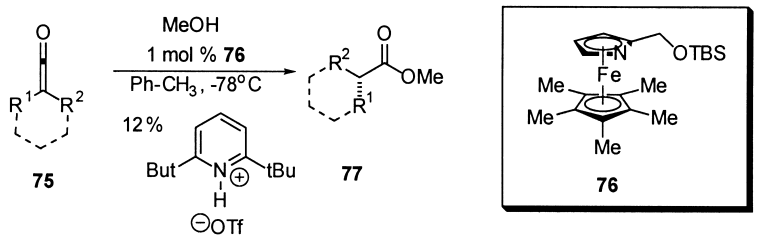
Entry	R^1 (**73**)	R^2 (**73**)	Catalyst	% yield (**74**)	% ee (**74**)[a]
1	Me	Ph	42	97	91
2	Me	Ph	41	99	91
3	Me	2-Naphthyl	42	99	93
4	Me	2-Naphthyl	41	99	94
5	Me	*n*-Pr	42	99	89
6	Me	Bn	42	86	89
7	Ph	Ph	42	94	82
8	Ph	Ph	41	84	79
9	Ph	$(CH_2)CH{=}CH_2$	42	86	84[b]
10	Ph	$(CH_2)CH{=}CH_2$	41	84	82[b]

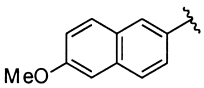
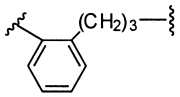
[a] Determined via HPLC.
[b] Approximate values due to incomplete enantiomer separation.



Scheme 14.

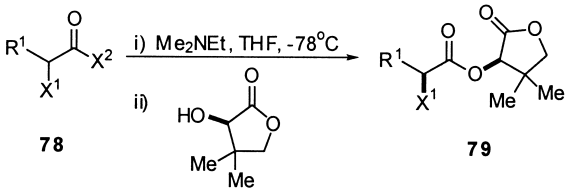
Table 20. Fu's azaferrocene's for addition of alcohols to ketenes



Entry	R^1 (**75**)	R^2 (**75**)	% yield (**77**)[a]	% ee (**77**)[a]
1	Ph	Me	87	77
2	*p*-(*i*-Bu)–Ph	Me	88	77
3		Me	80	75
4	*m*-PhOPh	Me	96	74
5	Ph	Et	92	68
6			97	80

[a] All data are the average of two runs.

Table 21. Koh and Durst's α-haloester synthesis



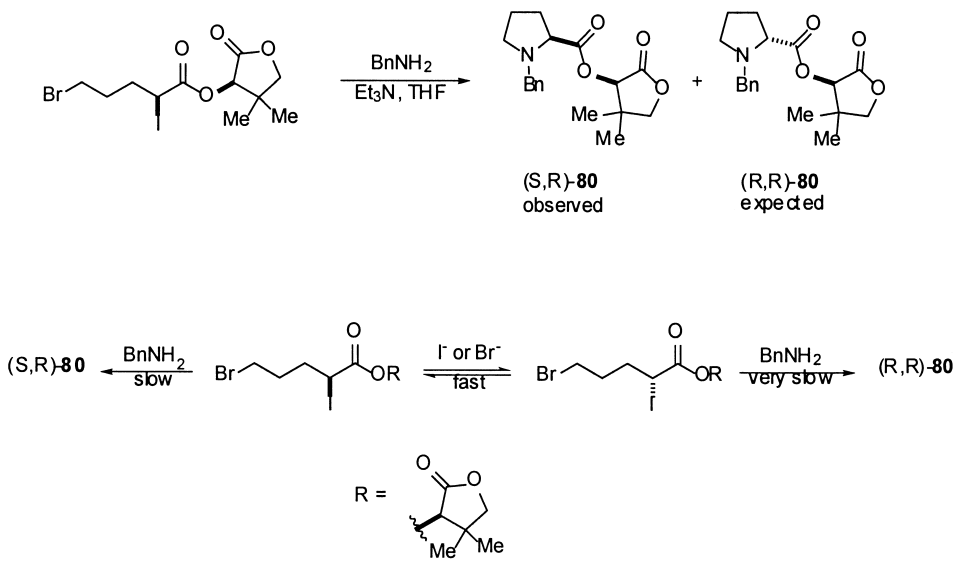
Entry	R^1 (**78**)	X^1 (**78**)	X^2 (**78**)	Warming period (h)	% yield[a] (**79**)	% de (**79**)
1	*t*-Bu	Br	Cl	20	79	87
2	*i*-Pr	Br	Cl	0.25	78	78
3	*i*-Pr	I	Cl	4.5	71	85
4	*c*-Pentyl	I	Cl	4.5	73	91
5	Bn	I	Cl	0.25	51	88
6	$(Ph)_2CH$	I	Cl	4.5	52	>95
7	*c*-HexCH_2	I	Cl	0.25	48	75
8	Et	Br	Br	0.25	84	83
9	Et	Br	Cl	0.25	63	75

[a] Isolated yields after chromatography.

5.2.2. Catalyst-controlled syntheses. Lectka and co-workers recently extended their method for in situ ketene generation and alkaloid-catalyzed addition to an elegant method for the preparation of α-haloesters.[24] Generation of a variety of ketenes in the presence of halogenating agents **82** or **83** and a catalytic amount of benzoyl quinidine led to the corresponding α-haloesters with optical purities of 80–99% (Table 22). The success of this reaction depended on the use of a solid-supported base for the generation of the ketene, as the use of proton sponge led undesired byproducts (Scheme 16). This group has since employed sodium carbonate and sodium hydride as alternative, inexpensive bases for the generation of ketenes for the halogenation reaction.

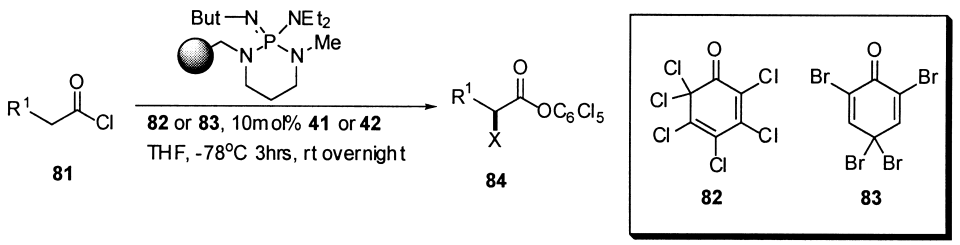
5.3. [2+2] Additions of ketenes to alkenes

Several groups have developed auxiliaries and substrates for the [2+2] cycloadditions of ketenes and alkenes to afford chiral cyclobutanones. Greene and co-workers demonstrated that vinylethers derived from 2-phenylcyclohexanol or (2,4,6-triisopropyl)ethanol reacted with dichloroketene to afford cyclobutanones with diastereoselectivities greater than 95% (Scheme 17).[25] This group used these products in the syntheses of α-cuparenone and methylenolactocin. Correia et al. employed an 8-phenylmenthol auxiliary to control the ketene–alkene addition in the course of a synthesis of the Geissman–Waiss lactone (Scheme 18).[26] Finally, Sugimura and co-workers

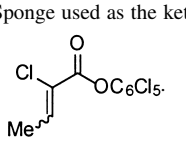


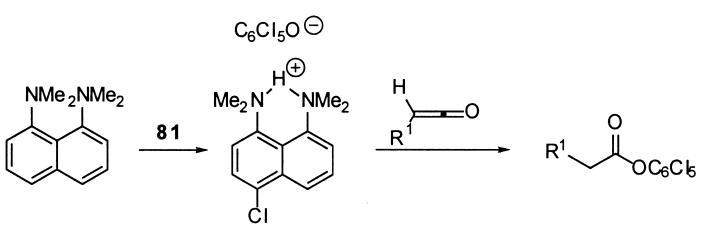
Scheme 15.

Table 22. Leckta's α-halogenation using solid supported base

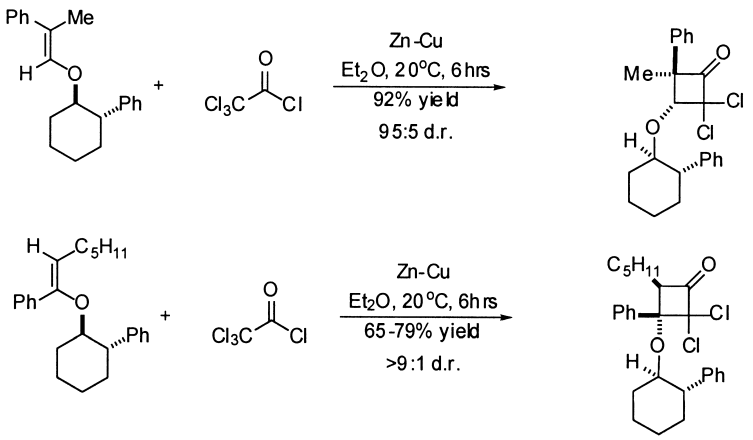


Entry	R^1 (**81**)	Halogenating agent	Catalyst	X (**84**)	% yield[a] (**84**)	% ee (**84**) (configuration)
1	Ph	**82**	42	Cl	40[b]	95 (*S*)
2	Ph	**82**	42	Cl	80	99 (*S*)
3	Ph	**82**	41	Cl	81	99 (*R*)
4	$PhOCH_2$	**82**	42	Cl	57	97 (*S*)
5	$PhOCH_2$	**82**	41	Cl	60	96 (*R*)
6	$PhOCH_2$	**82**	42	Br	50	99 (*S*)
7	1-Np	**82**	42	Cl	57	95 (*S*)
8	2-Np	**82**	42	Cl	63	94 (*S*)
9	1-Thiophene	**82**	42	Cl	66	80 (*S*)
10	CH_2=CH	**82**	42	Cl	65	–[c]
11	Br	**82**	42	Cl	51	97 (*S*)

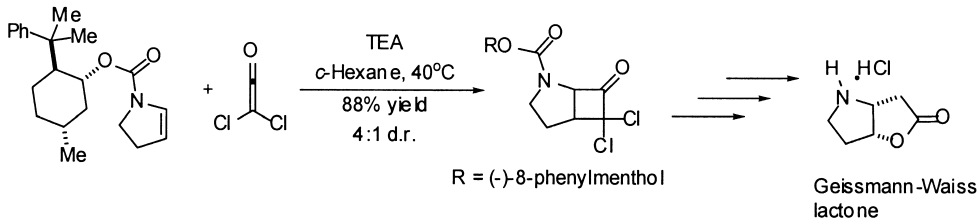
[a] Isolated yields after column chromatography.
[b] Proton Sponge used as the ketene forming base.
[c] Product: 



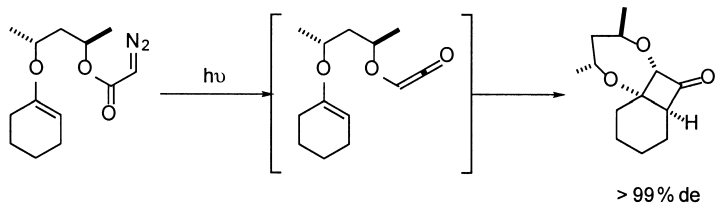
Scheme 16.



Scheme 17.



Scheme 18.



Scheme 19.

showed that 2,4-pentanediol tethers control the intramolecular ketene–alkene cycloaddition to form cyclobutanones in greater than 99% diastereomeric excess (Scheme 19).[27]

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Biographical sketch

Robert K. Orr was born in Cherry Hill, NJ. He received his BS degree in chemistry from Richard Stockton College in 1998, while conducting research with Professor Kenneth Overly. After moving to the University of Rochester, he began his doctorate research into the in situ generation and dimerization of ketenes, and into bifunctional catalysts for the direct aldol reaction. After completion of his degree, he will begin post-doctoral studies with Professor Steven M. Weinreb at the Pennsylvania State University.

Michael A. Calter was born in Huntington, NY, and obtained his BS in Chemistry from the University of Vermont in 1988. His graduate studies were carried out at Harvard University under the direction of Professor David A. Evans. After completing his doctorate in 1993, he worked for Professor Larry E. Overman at the University of California, Irvine as an American Cancer Society Postdoctoral Fellow. In 1995, he began at Virginia Tech as an assistant professor of chemistry. In 1999, he moved to the University of Rochester, where he is currently an associate professor. His research interests lie in the discovery and exploitation of tertiary amine catalyzed, asymmetric reactions. The main project in his labs involves the use of the ketene dimerization reaction to produce precursors for polyketide synthesis.