

Discovery of indium complexes as water-tolerant Lewis acids

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The work on development of organic reactions that are tolerant to air and moisture, especially that of carbon–carbon bond forming reactions, had only started in the early 1990s. Our laboratory had approached this subject when it was still in its infancy and had developed methodologies for that end. In this article, our decade of work on indium complexes as Lewis acids is summarised.

Introduction

The traditional approach to catalysis using Lewis acids is changing rapidly from single-use, air- and moisture-sensitive metal complexes such as AlCl_3 and TiCl_4 , to reusable and highly tolerant catalysts. Notably, salts from main group elements¹ are featured prominently in this progressive move towards mild and facile reactions, with sights set on the concept of “green chemistry”. Procedures that require organic solvents and toxic reagents are slowly being phased out. Above all, many laboratories are focussing on carbon–carbon bond forming reactions in the presence of air and water,^{2,3} building the backbone of complex molecules with methodologies not conceivable in Victor Grignard’s time. Very often, the total exclusion of organic solvents in every step of the synthesis protocol for most “green” methodologies is still not possible. However, the developments so far had established reaction procedures that are easy to execute, and such procedures often come with the added advantage of tolerance to many

functional groups. This dispenses with the need for protection and deprotection steps along the synthetic pathway, thus simplifying procedures and conserving materials.

Our laboratory has been interested in developing water-tolerant reactions since its establishment. For this purpose, we initially chose indium salts for their low toxicities and stability in air and water, properties that matched our research goal. In this article, we will outline our decade of work on the development of indium salts⁴ in carbon–carbon bond forming reactions.

Allylations

In our early studies on catalysis using water-tolerant Lewis acids for development into aqueous-based or water-based reactions, we had investigated the potential of lanthanide triflates⁵ to promote an In-mediated allylation⁶ of a glucose-derived aldehyde in aqueous media.⁷ The use of $\text{Yb}(\text{OTf})_3$ in our reaction system was found to effectively catalyse the reaction and imparted an appreciable increase in diastereoselectivity and yield (Table 1). The same catalyst was then applied to our work on the synthesis of enantiomerically pure β -aminoalcohols. This was done through either an In- or

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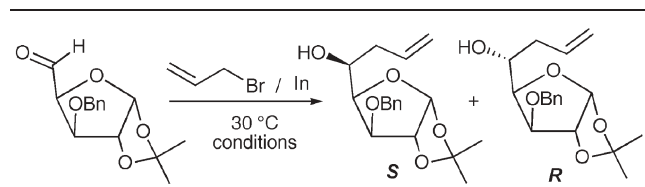
University. In 1994, he joined the National University of Singapore as a Lecturer, in 1999 as an Associate Professor and in 2004 as a full Professor. Professor Loh then moved to Nanyang Technological University in 2005 and is currently a Professor and



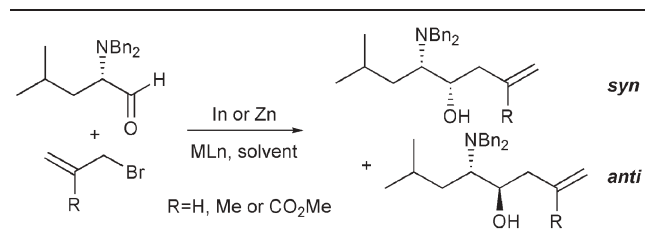
Guan-Leong Chua

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Table 1 Indium mediated allylation reaction


Entry	Conditions	Yield (%)	R:S
1	DMF–H ₂ O (6:4), 1 h, Yb(OTf) ₃ (1 eq.)	88	6:94
2	DMF–H ₂ O (6:4), 2 h	82	17:83
3	H ₂ O–THF (4:1), 10 h	72	24:76
4	H ₂ O, 10 h	66	41:59

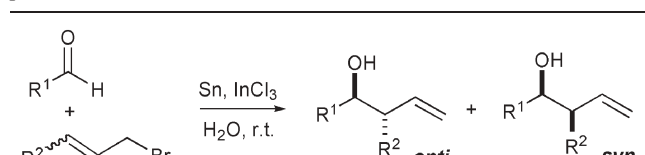
Table 2 Selected results (R = H) from indium mediated allylation of protected α -aminoaldehyde


Entry	Conditions	Yield (%)	anti:syn
1	DMF–H ₂ O (20:1), 0.5 h, In/La(OTf) ₃ (1 eq.)	88	92:8
2	DMF–H ₂ O (20:1), In, 5 h	82	87:13
3	H ₂ O, In, 24 h	82	73:27
4	DMF–H ₂ O (20:1), 0.5 h, Zn/La(OTf) ₃ (1 eq.)	94	91:9
5	DMF–H ₂ O (20:1), Zn, 5 h	88	90:10
6	H ₂ O, Zn, 24 h	Trace	—

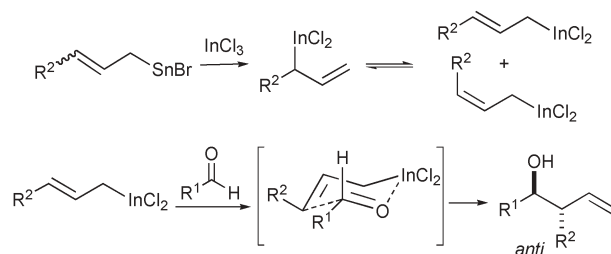
Zn-mediated allylation on protected α -aminoaldehydes.⁸ Although the rates of reactions were increased, we did not observe a significant contribution to yields and selectivities from added Yb(OTf)₃ and La(OTf)₃ (Table 2).

With emerging reports on novel Lewis acids derived from main group elements at that time, we had started investigating the use of indium complexes for developing allylation reactions in water. Earlier works by Marshall and Hinkle⁹ and Baba and co-workers¹⁰ suggested InCl₃ as a suitable candidate.

Our first application of InCl₃ is in the Sn-mediated allylation of carbonyl compounds in water (Table 3).¹¹ Yields were

Table 3 InCl₃-promoted Sn-mediated allylation of carbonyl compounds in water


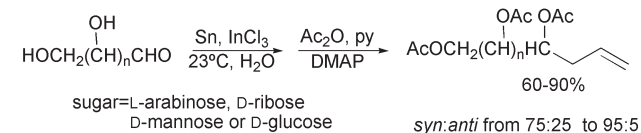
Entry	R ¹	R ²	Conditions	Yield (%)	anti:syn
1	Ph	Me	15 h	80	50:50
2	Ph	Ph	15 h	45	99:1
3	Ph	CO ₂ Et (<i>E</i>)	15 h	96	85:15
4	CH ₂ Br	CO ₂ Et (<i>E</i>)	15 h	55	80:20
5	3-C ₅ H ₄ N	CO ₂ Et (<i>E</i>)	24 h	51	80:20
6	cyclo-C ₆ H ₁₁	CO ₂ Et (<i>Z</i>)	15 h	65	68:32
7	cyclo-C ₆ H ₁₁	CO ₂ Et (<i>E</i>)	18 h (no InCl ₃)	60	85:15
8	cyclo-C ₆ H ₁₁	CO ₂ Et (<i>E</i>)	15 h	65	99:1

**Fig. 1** Proposed mechanism for the Sn/InCl₃ system for allylation of aldehydes in water.

moderate to high and high diastereoselectivities were observed for most of the substrates studied. Note that InCl₃ may only have moderate effects on the yields, but had significant influences on the final isomer ratios (entries 7 and 8, Table 3). The reactions were proposed to occur *via* transmetalation of the allyltin with the InCl₃, followed by preferential participation of the resulting *trans* intermediate in a cyclic complex to form the final product (Fig. 1). Such a transmetalation mechanism was also proposed by Marshall and Hinkle in their allylstannanes/InCl₃ system.¹² The *anti* products would have resulted from the most stable six-membered ring transition states whereby the bulky substituents on the aldehydes adopted the equatorial position. In the same piece of work, the convenient allylation of unprotected sugars¹³ was also studied and good to excellent yields were observed. Diastereoselectivities were generally excellent (Fig. 2). Note the strong *syn* preferences in these cases were attributed to a five-membered chelation transition state. The stereochemical outcome in this study drew a close parallel to the indium-mediated allylation system as observed by Paquette and Thomas.¹⁴

Our work in this new system of allylation converged with our interest in the synthesis of fluorinated compounds, especially compounds with CF₃ in place of CH₃. The CF₃ moiety, with its high C–F strength, electron-withdrawing properties, both hydro- and lipo-phobicities, often impart unique properties to the equivalent hydrocarbon counterpart.¹⁵ This is especially so for pharmacologically active compounds.

The Sn/InCl₃ allylation system was subsequently applied to the synthesis of trifluoromethylated homoallylic alcohols in water (Table 4).¹⁶ Results show that excellent yields and selectivities were accessible (entries 2–7), and that InCl₃ was indispensable (entry 1). This water-based methodology had allowed the convenient use of aqueous formaldehyde and



Proposed mechanism:

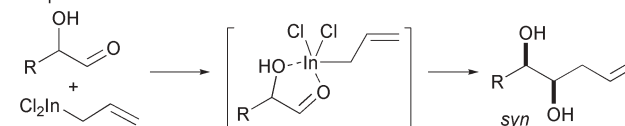
**Fig. 2** Allylation of unprotected sugars in water using the Sn/InCl₃ system.

Table 4 Selected results from reaction of aldehydes with 1,1,1-trifluorobut-2-ene

Entry	R	Condition	Yield (%)	<i>anti</i> : <i>syn</i>
1	Ph	Sn	0	—
2	Ph	Sn/InCl ₃	87 (91:9 γ : α , 60E:40Z)	95:5
3	H	Sn/InCl ₃	90 (only γ)	—
4	cyclo-C ₆ H ₁₁	Sn/InCl ₃	92 (only γ)	>99:<1
5	3-C ₅ H ₄ N	Sn/InCl ₃	95 (only γ)	92:8
6	2-C ₅ H ₄ N	Sn/InCl ₃	96 (only γ)	<1:>99
7	CO ₂ H	Sn/InCl ₃	83 (only γ)	<1:>99
8	Ph	In	87 (only γ)	92:8
9	H	In	86 (only γ)	—
10	cyclo-C ₆ H ₁₁	In	90 (only γ)	>99:<1
11	3-C ₅ H ₄ N	In	95 (only γ)	>99:<1
12	2-C ₅ H ₄ N	In	88 (only γ)	<1:>99
13	CO ₂ H	In	80 (only γ)	4:96

hydrated glyoxylic acid, substrates which are not possible with classical C–C bond forming systems. Crucially, the predominantly *anti* products supported the six-membered ring transition state previously proposed (Fig. 3). The notable reversals of stereochemical outcomes from 2-pyridinecarbaldehyde and glyoxylic acid (Table 4, entries 6, 7, 12 and 13) are explained through the bulky groups adopting the axial position as a result of the five-membered ring chelation with the In center. Our earlier proposal for an initial transmetalation of the allyltin with InCl₃ was supported by the similar yields and selectivities obtained with the solely In-mediated reactions (Table 4, entries 8–13).

The Sn/InCl₃ or In-only systems of allylation in water were particularly useful in our synthesis of α -trifluoromethylated alcohols from trifluoroacetaldehyde. Such an aldehyde is volatile and unstable, with its commercially available counterpart in the form of ethyl hemiacetal. Thus, a direct C–C bond formation using such a hemiacetal, not feasible with classical methods, would be a facile route to α -trifluoromethylated alcohols. In this regard, our water-based methodology was found to achieve good to excellent yields with moderate

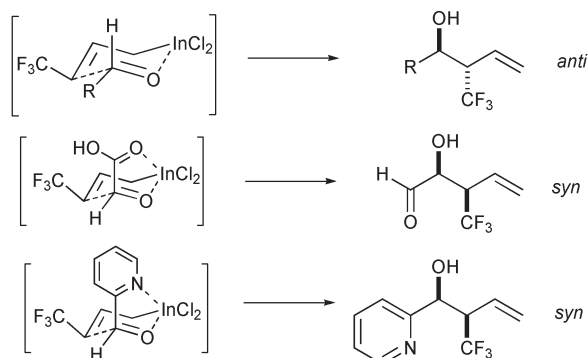


Fig. 3 Allylation of unprotected sugars in water using the Sn/InCl₃ system.

Table 5 InCl₃-promoted Sn-mediated or In-mediated allylation of trifluoroacetaldehyde in water

Entry	R ¹	R ²	R ³	Condition	Yield (%) (diastereomeric ratio)
1	Et	H	H	Sn/InCl ₃ (0.1 eq.)	Trace
2	Et	H	H	Sn/InCl ₃ (1 eq.)	85
3	Et	H	CO ₂ Me	Sn/InCl ₃ (1 eq.)	65
4	Et	Me	H	Sn/InCl ₃ (1 eq.)	72 (67:33)
5	Et	H	H	In	95
6	Et	H	CO ₂ Me	In	87
7	Et	Me	H	In	80 (65:35)
8	H	H	H	In	81
9	H	H	CO ₂ Me	In	82
10	H	Me	H	In	70 (68:32)
11	H	CO ₂ Et	H	In	0
12	H	CO ₂ E	H	In, Yb(OTf) ₃	0
13	H	Me	Br	In	0
14	H	Me	Br	In, Yb(OTf) ₃	0
15	H	H	Me	In	0
16	H	H	Me	In, Yb(OTf) ₃	0

diastereoselectivities even for trifluoroacetaldehyde hydrate (Table 5, entries 1–10). Note that unreactive allylic halides are unable to react even with the use of Yb(OTf)₃ (Table 5, entries 11–16). The absence of the ethoxy product could be due to the preference of the hard In center to coordinate with the hard OH base with OEt being the leaving group (Fig. 4). The comparable, if not moderately better, yields from In-only mediated reactions again reinforced our transmetalation proposal to account for our Sn/InCl₃ results.

Recently, we applied the use of InCl₃ in catalyzing the In-mediated one-pot allylation of dihydropyrans and dihydrofurans in water (Table 6).¹⁷ The InCl₃ catalysed the formation of the lactol *in situ* and subsequent allylation gave the corresponding 1,4- and 1,5-diols in good yields.

Current work on allylation is focused on the use of InCl₃ in asymmetric allylations in ionic liquids, with encouraging preliminary results.¹⁸

Aldol and related reactions

The aldol reaction is a powerful tool for the construction of carbon–carbon bonds that lends itself to acyclic stereocontrol.¹⁹ An important variant of the aldol reaction is the Mukaiyama aldol reaction²⁰ which is essentially a directed aldol reaction.

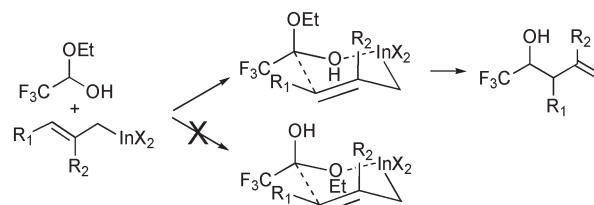


Fig. 4 Proposed mechanism of the allylation of trifluoroacetaldehyde ethyl hemiacetal.

Table 6 InCl₃ catalysed In-mediated allylation of dihydropyrans and dihydrofurans in water

Entry	Allyl bromide	n	Yield (%) (<i>anti:syn</i>)
1		1	83
2		2	83
3		1	77
4		2	68
5		1	53
6		2	64
7		1	60
8		2	58
9		1	83 (40:60)
10		2	78 (40:60)
11		1	49 (24:76)
12		2	52 (23:77)

Our laboratory has strong interest in exploring the chemistries of aldol reactions, especially the Mukaiyama aldol reaction. In particular, we envisioned protocols that would be tolerant of water and air, in contrast to the initially developed Mukaiyama aldol methodologies.

Kobayashi *et al.* pioneered the work in the adaptation of the Mukaiyama aldol reaction to work in aqueous media using lanthanide triflates as catalysts.^{21,22} We were interested at that time to investigate the feasibility of conducting the reaction in water with catalysis from InCl₃.²³ However, our results (Table 7) were found to be inconsistent, with effects from sequence of addition of reactants playing a part in the final

Table 7 Selected results from Mukaiyama aldol reaction in water

sequence A: 1 + InCl₃ then H₂O then 2 (15h)
 sequence B: 1 + InCl₃ then H₂O (15h) then 2
 sequence C: 1 + InCl₃ then 2 then H₂O (15h)

Entry	Aldehyde	Silyl enol ether	Sequence	Yield(s) (%)	<i>anti:syn</i>
1			A	51	48:52
2			B	74, 69	61:39
3			C	79, 55	52:48
4			C	82	40:60
12	HO ₂ CCHO·H ₂ O		C	80	56:44

Table 8 Aldol reaction of a glucose-derived silyl enol ether with aqueous formaldehyde

Entry	E:Z	Lewis acid (mol%)	Time	Yield (%)	R:S
1	80:20	InCl ₃ (40)	4–7 d	73	96:4
2	80:20	In(OTf) ₃ (40)	30 min	0 (decomp.)	—
3	80:20	In(OTf) ₃ (2)	0.5–1 d	38	93:7
4	80:20	Yb(OTf) ₃ (40)	2–3 d	40	88:12
5	0:100	InCl ₃ (40)	4–7 d	68	82:18
6	0:100	In(OTf) ₃ (2)	0.5–1 d	37	70:30
7	0:100	Yb(OTf) ₃ (40)	2–3 d	35	54:46

yield.²⁴ The heterogenous nature of the reaction would have also introduced inconsistencies in results from the varying efficiencies of mixing.

In our unpublished work on the synthesis of the core structure of zaragozic acids, we had devised a diastereoselective one carbon extension of a glucose derived silyl enol ether. This method uses the commercially available formaldehyde with InCl₃ as catalyst, giving good yields and excellent selectivities (Table 8).²⁵ Note that both *cis* and *trans* isomer of the silyl enol ether gave the same major isomer. The formaldehyde nucleophile was proposed to approach only in one direction due to the steric restrictions imposed by the rigid silyl enol ether. Product stereochemistry would then depend on the preferred conformation of the molecule. An *ab initio* calculation was done and we found that it corresponded well with our experimental results (Fig. 5). The use of water in this case is restricted to the quantities introduced by the 37%

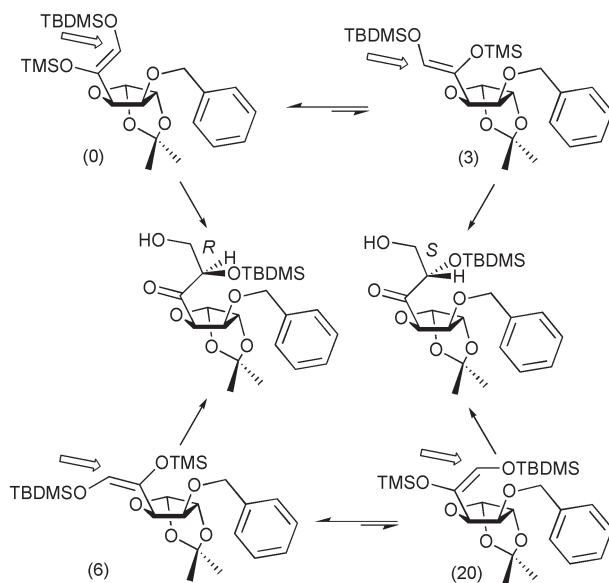


Fig. 5 Proposed mechanism for to account for the product stereochemistry. Numbers in parentheses denote the relative energies in kJ mol⁻¹.

Table 9 Selected results (R = Ph) from stereoselective aldol reaction of keto ester for the synthesis of 1,3-aminoalcohols

Entry	Silyl enol ether	Lewis acid	R:S (Yield, %)
1		BF ₃ ·H ₂ O	No reaction
2		La(OTf) ₃	Trace
3		Yb(OTf) ₃	90:10 (40)
4		InCl ₃ , H ₂ O	90:10 (40)
5		InCl ₃	90:10 (73)
6		InCl ₃	86:14 (72)
7		InCl ₃	99:1 (56)
8		InCl ₃	87:13 (58)
9		InCl ₃	99:1 (72)

formaldehyde solution. This tend to give more consistent results and subsequent studies on Mukaiyama aldol reactions were done with no solvent.

We proceeded to study the synthesis of 1,3-aminoalcohols through the Mukaiyama aldol reaction of a keto ester catalysed by InCl₃ under neat conditions.²⁶ Moderate to good yields were obtained (Table 9). Most importantly, high diastereoselectivities were observed that were explained through shielding of the carbonyl moiety by the phenyl group (Fig. 6). The proposal was supported by crystal structures of the keto ester. Note that π -stacking does not play a role as replacement of the phenyl group with cyclohexyl did not appreciably affect the stereoselectivity.

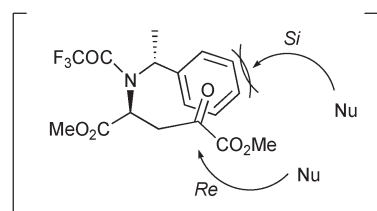


Fig. 6 Proposed mechanism to account for the stereochemical course of the Mukaiyama aldol reaction of the depicted keto ester.

Table 10 Direct aldol reaction of glyoxylic acid monohydrate with various ketones

Entry	Silyl enol ether	InCl ₃ (mol%)	Time/d	Yield (%) (<i>syn:anti</i>)
1		No InCl ₃	3	10 (73:27)
2		20	2	80 (60:40)
3		50	3	95 (59:41)
4		20	3	94
5		20	3d	91
6		20	2	80 (62:38)
7		20	4	95 (71:29)

The direct aldol reactions that circumvent the silyl enol ether intermediate were reported by several groups, and these procedures often require air- and moisture-sensitive Lewis acids.^{27,28} Our laboratory had applied the use of InCl₃ as a catalyst in the direct aldol reaction of glyoxylic acid with ketones without the use of solvents. Sonication is required and excellent yields with moderate diastereoselectivities were obtained (Table 10).²⁹ An open-chain antiperiplanar transition state was put forward to account for the product stereochemistry. Our laboratory had also used Montmorillonite K10 with success to catalyse similar Mukaiyama-aldol reactions in water.³⁰ These synthetic methodologies are useful to furnish building blocks for complex natural products through the synthesis of α -hydroxy acids.³¹

Mannich and related reactions

The Mannich reaction is an important reaction for the preparation of β -amino-ketones and -aldehydes.³² The products of such reactions are used in the synthesis of natural products and pharmaceuticals. An important variant of the Mannich reaction is the reaction between preformed imines from condensing aldehydes with amines, and silyl enol ethers generated from ketones. However, imines are frequently unstable, moisture sensitive and difficult to purify through distillation.

Encouraged by the expanding utility of InCl₃, we made use of its water-tolerance to devise a procedure to conduct the Mannich reaction in water. For such a methodology, we would need to generate the imine *in situ* and immediately

Table 11 InCl₃-catalysed one-pot Mannich reaction in water

$$R^1CHO + R^2NH_2 + \begin{array}{c} R^3 \\ \diagup \\ C \\ \diagdown \\ R^4 \end{array} \begin{array}{c} OTMS \\ \diagup \\ C \\ \diagdown \\ R^5 \end{array} \xrightarrow{InCl_3 (20 \text{ mol}\%), H_2O} \begin{array}{c} R^2 \\ | \\ NH \\ | \\ R^1 \\ | \\ C \\ / \quad \backslash \\ R^3 \quad R^4 \\ | \\ C \\ \diagup \quad \diagdown \\ R^5 \end{array}$$

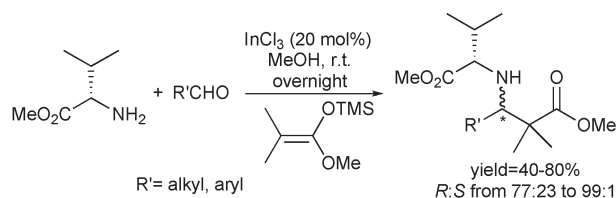
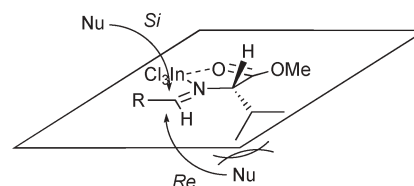
Entry	Aldehyde R ¹	Amine R ²	Yield (%) (<i>syn:anti</i>)			
1	H	Ph	30, 8 ^a	91	58	46
2	Ph	Ph	54	75	80 (57:43)	68 (59:41)
3	2-Py	Ph	92	94	70, 10 ^b (69:31)	60 (52:48)
4	H	4-ClPh	21	85	78	60
5	Ph	4-ClPh	23	60	26 (60:40)	17 (74:26)
6	2-Py	4-ClPh	90	91	55, 23 ^b (57:43)	35 (64:36)
7	H	4-MeOPh	35, 17 ^a	86	41, 5	20
8	Ph	4-MeOPh	30	40	45 (51:49)	11 (76:24)
9	2-Py	4-MeOPh	90	90	70, 11 ^b (66:34)	20 (76:24)
10	CO ₂ H	Ph	10	Decomp.	—	—
11	CO ₂ H	4-ClPh	31	63	—	—
12	CO ₂ H	4-MeOPh	10	Decomp.	—	—

^a Yield of: ^b Yield of aldol product.

react it with the silyl enol ether. We would thus need to investigate if the reaction with the imine would be faster than the competing aldol reaction.³³ Results show that this one-pot Mannich reaction produced moderate to excellent yields in most of the reactant combinations studied (Table 11). However, yields for enolizable imines, generated from aqueous formaldehyde in our study (entries 1, 4 and 7), were poor. Interestingly, there was a lack of deamination products as usually observed in conventional Mannich reactions. The expected competing aldol reactions were also not observed frequently. This suggests that the formation of Mannich products occur preferentially over the aldol products in our system. In fact, in the absence of InCl₃, the aldol products actually dominate, thus confirming the unique role that InCl₃ plays in this reaction. In the same paper, we had also reused the InCl₃ with no significant impact to the yield of product.

The above procedure was not successful for an enantioselective one-pot Mannich reaction using chiral amines. In addition, the procedure was limited to nonenolizable aldehydes and aromatic amines. However, further work shows that the use of MeOH as a solvent addressed these issues, resulting in moderate to high yields with good to excellent diastereoselectivities in a variety of substrates (Fig. 7).³⁴ Diastereoselectivity was attributed to the chelation of InCl₃ by the carbonyl group of the ester and the nitrogen. The resulting rigid bidentate structure allows bulky groups to effectively block one face, leading to high facial selectivities (Fig. 8).

An ionic liquid version of the one-pot Mannich procedure was also developed but shall not be discussed here.³⁵

**Fig. 7** A typical one-pot Mannich reaction in MeOH catalysed by InCl₃.**Fig. 8** Proposed mechanism to account for the diastereoselectivities in the one-pot Mannich reaction in MeOH catalysed by InCl₃.

Others

The Diels–Alder reaction is an important cycloaddition reaction for the construction of six-membered rings. Breslow had pioneered the study on carrying out the Diels–Alder reaction in water.³⁶ Our laboratory had studied the catalytic behaviour of InCl₃ for this pericyclic reaction and had demonstrated that significant improvements in yields and regioselectivities were observed in the presence of InCl₃ (Table 12).³⁷ InCl₃ was also demonstrated to improve the

Table 12 Selected results from InCl₃ catalysed Diels–Alder reaction in water

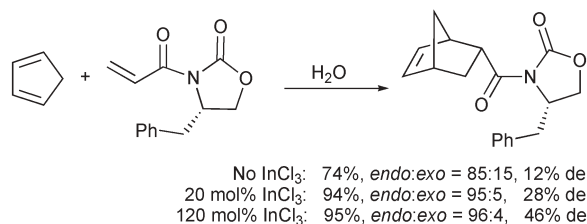
Entry	Reactants	Major product	Yield (%) (endo:exo)
1			89 (91:9)
2 ^a			60 (74:26)
3			85 (90:10)
4			99 (100:0)
5			88 (90:10)
6			95 (5:95)
7			88 (one regioisomer)

Conditions: water, room temperature, InCl₃ (20 mol%), 4 h. ^a No InCl₃.

selectivity of the Diels–Alder reaction using Evan's chiral auxiliary³⁸ from low to moderate (Fig. 9).

The direct synthesis of β-amino derivatives can be achieved through a conjugate addition of amines with α,β-ethylenic compounds. We were able to carry out such a reaction under mild conditions in water with the yield of the reaction increased by the addition of InCl₃.³⁹ Moderate to good yields, albeit with poor diastereoselectivities, were obtainable with a wide variety of substrates (Table 13). Note that the reaction can occur without the use of InCl₃ but suffers a yield penalty.

Related to our work on aldol reactions, we found that under neat conditions, InCl₃ catalyses the 1,4-addition of α,β-unsaturated carbonyl compounds with silyl enol ethers (Table 14).⁴⁰ Moderate to excellent yields were obtained in most of the reactant combinations. InCl₃ was proven to be an essential catalyst, without which no reaction can take place. InCl₃ can also be recovered and reused with no loss in catalytic activity.

**Fig. 9** Asymmetric Diels–Alder reaction catalysed by InCl₃.**Table 13** Selected results from the InCl₃ catalysed conjugate addition of amines to α,β-ethylenic compounds in water

Entry	Reactants	Conditions	Yield (%) (1:2 or de)
1		6 h	70 (33:67)
2		No InCl ₃ , 6 h	20 (35:65)
3		16 h	82
4		No InCl ₃ , 16 h	62
5		23 h	45 (14% de)
6		No InCl ₃ , 23 h	40 (15% de)
7		3 d	70 (7% de)
8		No InCl ₃ , 3 d	75
9		21 h	78 (60% de, 3R major)
10		No InCl ₃ , 21 h	63 (60% de, 3R major)

The versatility of the bifunctional cyanohydrins in the synthesis of complex molecules prompted us to develop synthetic methodologies that would realise these compounds with simple procedures. Evans *et al.* developed the use of TMSCN in place of traditional HCN as a safer source of CN for this addition reaction.⁴¹ Our intention was to study the scope and limitation of this reaction in water. We found that this reaction did not occur without Lewis acids but proceeded to give a good yield with InCl₃ (Table 15, entries 1–4).⁴²

Table 14 Selected results from the 1,4-addition of α,β-unsaturated carbonyl compounds with silyl enol ethers

Entry	α,β-Unsaturated carbonyl	Silyl enol ether	Conditions	Yield (%) (anti:syn)
1		1	No InCl ₃ , r.t. (1 h)	No reaction
2		1	r.t. (0.5 h)	67
3		2	0 °C to r.t.	82
4		3	r.t. (0.5 h)	86 (65:35)
5		4	r.t. (0.5 h)	90 (65:35)
6		5	0 °C (5 h), r.t. (2 h)	66
7		1	r.t. (2 min.)	68
8		2	0 °C (1 h)	12
9		3	r.t. (0.5 h)	51
10		4	−30 °C to r.t.	48
11		5	0 °C (0.5 h), r.t. (1 h)	18
12		1	r.t. (24 h)	64
13		2	r.t. (0.5 h)	90
14		4	r.t. (15 h)	14 (30:70)

Table 15 Selected results from the addition of TMSCN to aldehydes in water catalysed by InF₃

Entry	Aldehyde	Catalyst (mol%)	Yield (%)
1		—	No reaction
2		KF (100)	No reaction
3		TBAF (100)	No reaction
4		InCl ₃ (100)	60 (conversion)
5		InF ₃ (30)	95
6		InF ₃ (30)	80
7		InF ₃ (30)	85
8		InF ₃ (30)	80
9		InF ₃ (30)	75
10		InF ₃ (30)	75

Interestingly, use of InF₃ gave good to excellent yields for a variety of substrates, including the hemiacetal form of the volatile trifluoroacetaldehyde (entries 5–10). Competitive studies also show that the reaction is highly chemoselective towards aldehydes, with TMSCN unable to react with ketones under our reaction condition.

The formation of tetrahydropyran rings are often central to many syntheses of natural products. This Prins reaction is often performed under strong acidic conditions or, with water- and air-sensitive Lewis acids.⁴³ Prior to our work, Li and co-workers had achieved such a reaction using 100 mol% of InCl₃.^{44,45} Our group had further modified the reaction by using allylchlorosilane as allylating agent and conducting the reaction in CH₂Cl₂. With our protocol, we require only 20 mol% of InCl₃ (Fig. 10).⁴⁶ The tolerance of such a procedure to water was demonstrated by the equivalent yields and selectivities obtained in the presence of 1% water.

Chiral indium complexes

One of the most efficient way to effect asymmetric synthesis of enantiomerically pure compounds from achiral substrates is the use of chiral catalysts. However, most often these catalysts are moisture- and air-sensitive thus limiting their utility. Our laboratory had been studying the feasibility of a water-tolerant chiral catalyst and recently, we had developed the first catalytic chiral indium complex that is water-tolerant.

Prior to several attempts on developing asymmetric catalytic systems,⁴⁷ our initial work on a chiral indium complex was

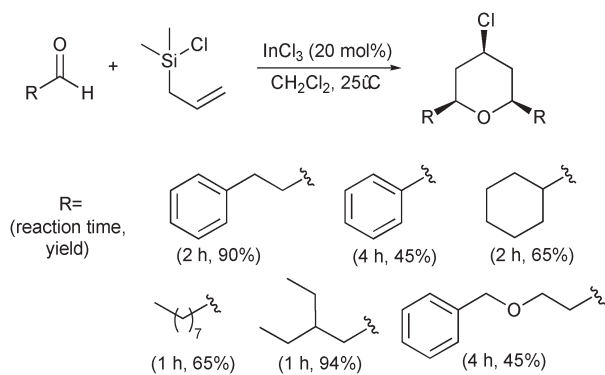


Fig. 10 Prins cyclisation reaction catalysed by InCl₃.

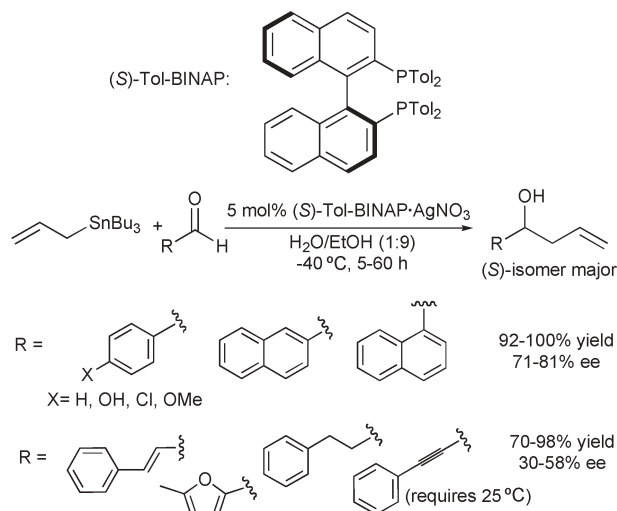


Fig. 11 Catalytic enantioselective allylation with (S)-Tol-BINAP-AgNO₃.

Table 16 Asymmetric allylation of benzaldehyde using (S)-BINOL-In(III) complexes

Entry	Indium reagent	Solvent	Equiv. of 1	Yield (%)	ee (%)
1	InF ₃	CH ₂ Cl ₂	1.0	0	—
2	In(O ⁱ Pr) ₃	CH ₂ Cl ₂	1.0	36	0
3	InBr ₃	CH ₂ Cl ₂	1.0	38	73
4	InCl ₃	CH ₂ Cl ₂	1.0	52	78
5	InCl ₃	CH ₂ Cl ₂	2.0	76	92
6	InCl ₃ (reduced MS)	CH ₂ Cl ₂	2.0	36	83
7	InCl ₃ (10 mol%)	CH ₂ Cl ₂	2.0	12	73
8	InCl ₃	CHCl ₃	2.0	52	90

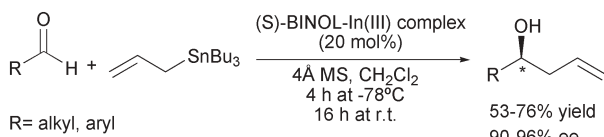


Fig. 12 Enantioselective allylation of aldehydes using BINOL–In(III) complex.

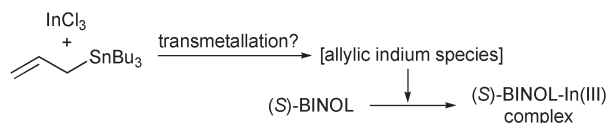
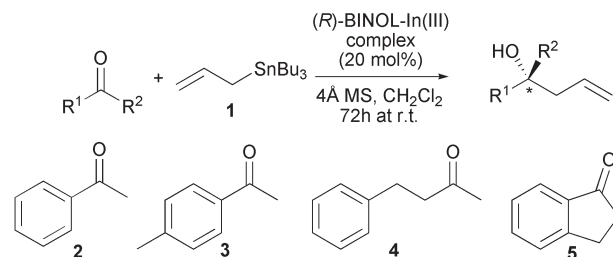


Fig. 13 Postulated process for the formation of chiral indium complex.

developed through the study on the asymmetric allylation of carbonyl compounds.⁴⁸ With the optimization of an early promising result, we found that InCl_3 , in the presence of 4Å molecular sieves in CH_2Cl_2 , reacts with the chiral ligand (*S*)-BINOL to give an active chiral indium complex. This BINOL–In(III) complex catalyzes the allylation of benzaldehyde in a highly enantioselective manner with excellent yields (Fig. 11, Table 16).⁴⁹ The study shows that InCl_3 with 2 equivalents of allyl tributylstannane gave the best allylation result. The quantity of molecular sieves (MS) is also critical (entry 6) and 20 mol% of the catalyst is required to maintain the high yields and enantioselectivities (entry 7). A variety of aldehydes were

Table 17 Selected results from the asymmetric allylation of ketones using (*R*)-BINOL–In(III) complexes

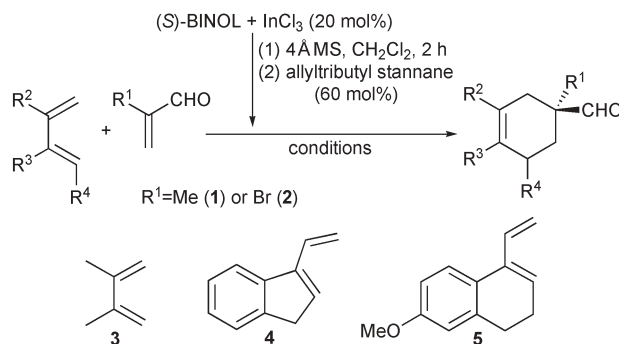


Entry	Indium reagent	Equiv. of 1	Temp/°C	Ketone	Yield (%)	ee (%)
1	InCl_3	2.0	–78 to r.t.	2	25	81
2	InCl_3	3.0	–78 to r.t.	2	46	81
3	InCl_3	3.0	r.t.	2	54	81
4	InBr_3	3.0	r.t.	2	76	82
5	InBr_3	3.0	r.t.	3	41	84
6	InBr_3	3.0	r.t.	4	60	80
7	InBr_3	3.0	r.t.	5	61	90

also allylated using this procedure and good yields with high enantioselectivities were obtained (Fig. 12).

The requirement for an excess allyltributyl stannane is actually surprising to us and our study shows that it is essential to form the final catalytic complex. Observations of several controlled experiments, including an NMR study, suggest its possible participation through transmetallation with InCl_3 .

Table 18 Selected results from asymmetric Diels–Alder reaction catalysed by (*S*)-BINOL–In(III) complex



Entry	Reactants	Conditions (°C, h)	Major product	R ¹	Yield (%)	ee (%)
1	3 + 1	r.t., 20		Me	63	98
2	3 + 2	–20, 20		Br	74	98
3	3 + 2	r.t., 20 + H ₂ O		Br	70	80
4	4 + 1	–20, 20		Me	71	98
5	4 + 2	–20, 20		Br	72	98
6	4 + 2	r.t., 20 + H ₂ O		Br	72	66
7	5 + 1	–20, 20		Me	75	97
8	5 + 2	–20, 20		Br	77	94
9	5 + 2	–20, 20 + H ₂ O		Br	61	94

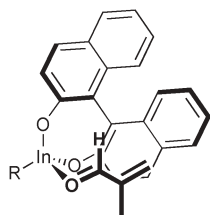


Fig. 14 Proposed assembly of the (*S*)-BINOL–In(III) complex with dienophile.

The resulting indium species then form the catalytic complex by reaction with (*S*)-BINOL (Fig. 13). Mechanistic study is still on-going to confirm this hypothesis.

An important aspect of the above protocol is the tolerance of the formed chiral indium complex to small amounts of water. We had attempted to develop this procedure towards an asymmetric allylation of aldehydes in water. However, we found that for a 30 mol% catalyst loading, 7.4 equivalents of water (relative to InCl₃) gave the best results in terms of yield without any penalty in enantioselectivities.⁵⁰ Further addition of water (above 22.2 equiv.) resulted in poor yields and enantioselectivities. These data, however, are only able to confirm the moisture tolerance of our methodology and efforts are still being directed towards an aqueous or water-only chiral catalytic system.

Extending an allylation methodology from aldehydes to ketones is usually not possible due to the lesser reactivities of ketones. Such allylations are normally carried out using the more reactive tetraallylstannanes.⁵¹ However, we are able to adopt the chiral BINOL–In(III) complexes to the allylation of ketones to give chiral tertiary alcohols (Table 17).⁵² In this procedure, the use of the stronger Lewis acid, InBr₃, is necessary for good to excellent yields and enantioselectivities in a variety of ketone substrates.

In broadening the scope of the BINOL–In(III) complexes even further, we had exploited their use in the asymmetric Diels–Alder reaction.⁵³ Experiments show that the BINOL–In(III) complex is equally applicable for such reactions, with moderate to good yields and high enantioselectivities (Table 18).⁵⁴ A possible assembly of catalyst and dienophile to account for the stereochemistry of the products was proposed (Fig. 14).

Conclusions

The exploration of the chemistry of In salts, since our laboratory's inception, has resulted in understanding of the applicability of such water-tolerant salts in many organic reactions. Work is still ongoing, especially in developing such chemistries in ionic liquids and to further refine the potential of such systems in enantioselective reactions. In particular, our future investigations are directed towards the design of new chiral Lewis acids that are effective in water. Focus on such catalysts is on indium as a catalytic centre. With the advent of organocatalysts, we also have an emerging program that aims to dispense with the need for metal centres, with functionalisation of biomolecules as a strategy towards new catalysts.

References

- Recent review: (a) T.-P. Loh and G.-L. Chua, in *Advances in Organic Synthesis*, ed. Atta-ur-Rahman and G. Jenner, Bentham Science Publishers Ltd, The Netherlands, 2005, vol. 1, p. 173.
- Recent review: C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095.
- S. Kobayashi, S. Nagayama and T. Busujima, *J. Am. Chem. Soc.*, 1998, **120**, 8287–8288.
- Recent reviews: (a) B. C. Ranu, *Eur. J. Org. Chem.*, 2002, 2347; (b) C. G. Frost and J. P. Hartley, *Mini-Rev. Org. Chem.*, 2004, **1**, 1.
- (a) Important pioneering work: S. Kobayashi, *Chem. Lett.*, 1991, 2187; (b) Recent review: S. Kobayashi, M. Sugiura, H. Kitagawa and W. W.-L. Lam, *Chem. Rev.*, 2002, **102**, 2227.
- Important pioneering work: C.-J. Li and T.-H. Chan, *Tetrahedron Lett.*, 1991, **32**, 7017.
- R. Wang, C.-M. Lim, C.-H. Tan and T.-P. Loh, *Tetrahedron: Asymmetry*, 1995, **6**, 1825.
- T.-P. Loh, R.-B. Wang, K.-L. Tan and K.-Y. Sim, *Main Group Met. Chem.*, 1997, **20**, 237.
- J. A. Marshall and K. W. Hinkle, *J. Org. Chem.*, 1995, **60**, 1920.
- M. Yasuda, T. Miyai, I. Shibata and A. Baba, *Tetrahedron Lett.*, 1995, **36**, 9497.
- X.-R. Li and T.-P. Loh, *Tetrahedron: Asymmetry*, 1996, **7**, 1535.
- J. A. Marshall and K. W. Hinkle, *J. Org. Chem.*, 1995, **60**, 1920.
- First reported allylation of sugars in aqueous media: W. Schmid and G. M. Whitesides, *J. Am. Chem. Soc.*, 1991, **113**, 6674.
- L. A. Paquette and T. M. Thomas, *J. Am. Chem. Soc.*, 1996, **118**, 1931.
- Organofluorine Chemistry*, ed. R. E. Banks, B. E. Smart and J. C. Tatlow, Plenum Press, New York and London, 1993.
- T.-P. Loh and X.-R. Li, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 980.
- S. Juan, Z.-H. Hao, S. Qi, S.-J. Jin and T.-P. Loh, *Synlett*, 2004, 829.
- J. Lu, S.-J. Ji, R. Qian, J.-P. Chen, Y. Liu and T.-P. Loh, *Synlett*, 2004, 534.
- C. H. Heathcock, in *Asymmetric Synthesis. Stereodifferentiating Reactions, Part B.*, ed. J. D. Morrison, AP, New York, 1984, vol. 3, p. 111.
- (a) T. Mukaiyama, K. Narasaka and T. Banno, *Chem. Lett.*, 1973, 1011; (b) T. Mukaiyama, T. Banno and K. Narasaka, *J. Am. Chem. Soc.*, 1974, **96**, 7503; (c) T. Mukaiyama, *Org. React.*, 1982, **28**, 203; (d) T. Mukaiyama, *Aldrichimica Acta*, 1996, **29**, 59.
- (a) S. Kobayashi and I. Hachiya, *J. Org. Chem.*, 1994, **59**, 3590; (b) S. Kobayashi, *Chem. Lett.*, 1991, 2187.
- Selected recent work: (a) A. Graven, M. Grotli and M. Meldal, *J. Chem. Soc., Perkin Trans. 1*, 2000, 955; (b) M. T. Reetz and D. Giebel, *Angew. Chem., Int. Ed.*, 2000, **39**, 2498; (c) Y. Mori, K. Manabe and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2001, **40**, 2815; (d) T. Nakagawa, H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, 2003, **32**, 696; (e) O. Munoz-Muniz, M. Quintanar-Audelo and E. Juaristi, *J. Org. Chem.*, 2003, **68**, 1622; (f) N. Aoyama, K. Manabe and S. Kobayashi, *Chem. Lett.*, 2004, **33**, 312.
- The use of InCl₃ was reported prior to our work: (a) T. Mukaiyama, T. Ohno, J.-S. Han and S. Kobayashi, *Chem. Lett.*, 1991, 949; (b) C. Scolastico, E. Conca, L. Prati, G. Guanti, L. Banfi, A. Berti, P. Farina and V. Valcari, *Synthesis*, 1985, 850.
- (a) T.-P. Loh, J. Pei and G.-Q. Cao, *Chem. Commun.*, 1996, 1819; (b) T.-P. Loh, J. Pei, K. S.-V. Koh, G.-Q. Cao and X.-R. Li, *Tetrahedron Lett.*, 1997, **38**, 3465.
- T.-P. Loh, G.-L. Chua, J. J. Vittal and M.-W. Wong, *Chem. Commun.*, 1998, 861.
- T.-P. Loh, J.-M. Huang, S.-H. Goh and J. J. Vittal, *Org. Lett.*, 2000, **2**, 1291.
- For examples: (a) H. F. Chow and D. Seebach, *Helv. Chim. Acta*, 1986, **69**, 604; (b) D. A. Evans, D. A. Rieger, M. T. Bilodeau and F. Urpi, *J. Am. Chem. Soc.*, 1991, **113**, 1047; (c) R. Mahrwald and B. Gundogan, *J. Am. Chem. Soc.*, 1998, **120**, 413.
- Early work on direct Aldol reaction using Lewis acids in water: (a) M. Nakagawa, H. Nakao and K. Watanabe, *Chem. Lett.*, 1985, 391; (b) P. T. Bounura, K. G. Rosauer and L. Dai, *Tetrahedron Lett.*, 1995, **26**, 4009; selected recent work: (c) T. Dewa, T. Saiki and Y. Aoyama, *J. Am. Chem. Soc.*, 2001, **123**, 502; (d) T. Darbre and M. Machuqueiro, *Chem. Commun.*, 2003, 1090.

- 29 (a) T.-P. Loh, L.-L. Wei and L.-C. Feng, *Synlett*, 1999, 1059; (b) T.-P. Loh, L.-C. Feng and L.-L. Wei, *Tetrahedron*, 2001, **57**, 4231.
- 30 T.-P. Loh and X.-R. Li, *Tetrahedron*, 1999, **55**, 5611.
- 31 Review: G. M. Coppola and H. F. Schuster, in *α -Hydroxy Acids in Enantioselective Synthesis*, VCH, Germany, 1997.
- 32 Recent review: N. Risch, M. Arend and B. Westermann, *Angew. Chem., Int. Ed.*, 1998, **37**, 1044.
- 33 (a) T.-P. Loh and L.-L. Wei, *Tetrahedron Lett.*, 1998, **39**, 323; (b) T.-P. Loh, S. B. K. W. Liung, K.-L. Tan and L.-L. Wei, *Tetrahedron*, 2000, **56**, 3227.
- 34 T.-P. Loh and S.-L. Chen, *Org. Lett.*, 2002, **4**, 3647.
- 35 S.-L. Chen, S.-J. Ji and T.-P. Loh, *Tetrahedron Lett.*, 2003, **44**, 2405.
- 36 (a) R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159; (b) R. Breslow, *Acc. Chem. Res.*, 2004, **37**, 471.
- 37 T.-P. Loh, J. Pei and M. Lin, *Chem. Commun.*, 1996, 2315.
- 38 D. A. Evans, K. T. Chapman and J. Bisha, *J. Am. Chem. Soc.*, 1988, **110**, 1238.
- 39 T.-P. Loh and L.-L. Wei, *Synlett*, 1998, 975.
- 40 T.-P. Loh and L.-L. Wei, *Tetrahedron*, 1998, **54**, 7615.
- 41 (a) D. A. Evans, J. M. Hoffman and L. K. Truesdale, *J. Am. Chem. Soc.*, 1973, **95**, 5822; (b) D. A. Evans, G. L. Carroll and L. K. Truesdale, *J. Org. Chem.*, 1974, **39**, 914.
- 42 T.-P. Loh, K.-C. Xu, D. S.-C. Ho and K.-Y. Sim, *Synlett*, 1998, 369.
- 43 Review: D. R. Adams and S. P. Bhatnagar, *Synthesis*, 1977, 61.
- 44 J. Yang, G. S. Viswanathan and C. J. Li, *Tetrahedron Lett.*, 1999, **40**, 1627.
- 45 More recent work: (a) C. C. K. Keh, V. V. Namboodiri, R. S. Varma and C. J. Li, *Tetrahedron Lett.*, 2002, **43**, 4993; (b) C. C. K. Keh and C. J. Li, *Green Chem.*, 2003, **5**, 80; (c) Y. S. Cho, H. Y. Kim, J. H. Cha, A. N. Pae, H. Y. Koh, J. H. Choi and M. H. Chang, *Org. Lett.*, 2002, **4**, 2025; (d) D. L. Aubele, C. A. Lee and P. E. Floreancig, *Org. Lett.*, 2003, **5**, 4521.
- 46 K.-P. Chan and T.-P. Loh, *Tetrahedron Lett.*, 2004, **45**, 8387.
- 47 Using cinchonidine: (a) T.-P. Loh, J.-R. Zhou and Z. Yin, *Org. Lett.*, 1999, **1**, 1855; T.-P. Loh, J.-R. Zhou and X.-R. Li, *Tetrahedron Lett.*, 1999, **40**, 9333; Ce(OTf)₄/PrPYBOX: (b) T.-P. Loh and J.-R. Zhou, *Tetrahedron Lett.*, 1999, **40**, 9115; Ag salt/(S)-Tol-BINAP: (c) T.-P. Loh and J.-R. Zhou, *Tetrahedron Lett.*, 2000, **41**, 5261.
- 48 Examples of enantioselective allylation: (a) R. Fornasier, F. Marcuzzi and D. Marton, *Main Group Met. Chem.*, 1998, **21**, 65; (b) A. Cunningham and S. Woodward, *Synlett*, 2002, 43; (c) S. Kobayashi, N. Aoyama and K. Manabe, *Chirality*, 2003, **15**, 124; (d) S. Singh, S. Kumar and S. S. Chimni, *Tetrahedron: Asymmetry*, 2002, **13**, 2679.
- 49 Y.-C. Teo, K.-T. Tan and T.-P. Loh, *Chem. Commun.*, 2005, 1318.
- 50 Y.-C. Teo, E.-L. Goh and T.-P. Loh, *Tetrahedron Lett.*, 2005, **46**, 6209.
- 51 Some recent examples of enantioselective allylation of ketones: (a) J.-K. Kim, K. M. Waltz, L. F. Garcia, D. Kwiatkowski and P. J. Walsh, *J. Am. Chem. Soc.*, 2004, **126**, 12580; (b) R. Wada, K. Oisaki, M. Kannai and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **125**, 8910; (c) K. Satoshi and M. Keiji, *Chirality*, 2003, **15**, 68; (d) K. M. Waltz, J. Gavenois and P. Walsh, *Angew. Chem., Int. Ed.*, 2002, **41**, 3697; (e) A. Cunningham and S. Woodward, *Synlett*, 2002, 43; (f) S. Yamasaki, K. Fujii, R. Wada, M. Kannai and M. Shibasaki, *J. Am. Chem. Soc.*, 2002, **124**, 6536; (g) H. Hanawa, S. Kii and K. Maruoka, *Adv. Synth. Catal.*, 2001, **1**, 57.
- 52 Y.-C. Teo, J.-D. Goh and T.-P. Loh, *Org. Lett.*, 2005, **7**, 2743.
- 53 Selected recent reviews on the enantioselective Diels–Alder reaction: (a) E. J. Corey, *Angew. Chem., Int. Ed.*, 2002, **41**, 1650; (b) D. A. Evans and J. S. Johnson, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobson, A. Pfaltz and H. Yamamoto, Springer, Berlin, 1999, vol. 3, p. 1177.
- 54 Y.-C. Teo and T.-P. Loh, *Org. Lett.*, 2005, **7**, 2539.