CHEMICAL REVIEWS

REVIEW

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Transition Metal Catalyzed Enantioselective α-Heterofunctionalization of Carbonyl Compounds

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CONTENTS

1. INTRODUCTION

A prochiral (**1**, R^2 = H) or racemic (**1**, $R^2 \neq$ H) carbonyl compound can be activated toward electrophilic substitution via the formation of an enol or enolate intermediate, creating a tertiary or quaternary center at the α-carbon (Scheme 1). The use of a noncarbon electrophile leads to chiral α-heterofunctionalized products, and the generation of a new stereogenic center in this reaction makes it amenable to the development of asymmetric methodologies.

α-Heterofunctionalization of a carbonyl compound is a highly direct and strategically simple method for the synthesis of a large number of interesting molecules and synthetic building blocks, such as amino acids (by amination), α-hydroxy acids (by hydroxylation), and α-fluorinated products.

This review will cover key advances in the field of asymmetric α-heterofunctionalization of carbonyl compounds, where the enantioselectivity of the process is achieved by the use of chiral transition metal catalysts. Thus, strategies using chiral auxiliaries[1,2] or stoichiometric chiral electrophilic reagents[3,4] will not be included. The resurgence in interest in organocatalysis is an important contributor to this field of research in recent years but is beyond the remit of this thematic issue of *Chemical Reviews*; instead, the reader will be directed to accounts that exist elsewhere (vide infra). It is important to acknowledge earlier reviews on fluorination,[5] halogenation,[6] oxygenation, and amination reactions.[7] In our current discussion, we will aim to highlight the commonality, as well as to provide a comparison of the synthetic utility, scope, and limitations of the different catalytic systems used in these reactions.

2. HALOGENATION (FLUORINATION, CHLORINATION, AND BROMINATION) REACTIONS

Procedures for asymmetric fluorination, chlorination, and bromination of carbonyl compounds have all appeared in the past decade,[8] with fluorination attracting the greatest level of interest.[9] Success in this area can be attributed to the development of a number of highly efficient, electrophilic fluorinating agents; particularly *N*-fluorobenzene sulfonimide (NFSI), which has been adopted as an electrophile in the majority of asymmetric processes. Asymmetric electrophilic fluorination reactions formed part of a *Chemical Review* article by Ma and Cahard in 2004, on asymmetric fluorination, trifluoromethylation, and perfluoroalkylation.[10] Since then, various aspects of the asymmetric fluorination reaction have also been reviewed several times by others.[9] Thus, the discussion herein is by no means comprehensive but will focus on the three main classes of transition metal catalysts that have good generality and high enantioselectivity in these reactions, namely, Ti−TADDOLato; Pd- and Ni−diphosphine; and Cu, Ni, and Zn complexes derived

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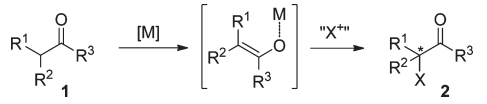
Scheme 1. Asymmetric α-Heterofunctionalization of Carbonyl Compounds



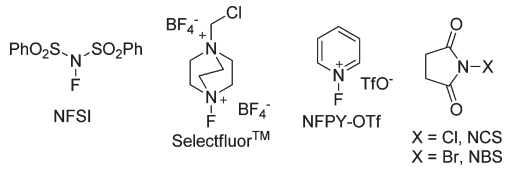


Figure 1. Common sources of electrophilic halogenation reagents.

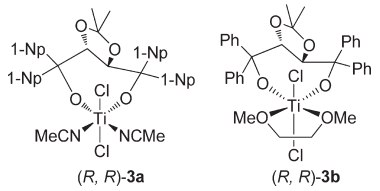


Figure 2. Ti−TADDOLato complexes.

from bis(oxazoline) ligands, finishing with a section containing more recent reports of new catalytic systems.

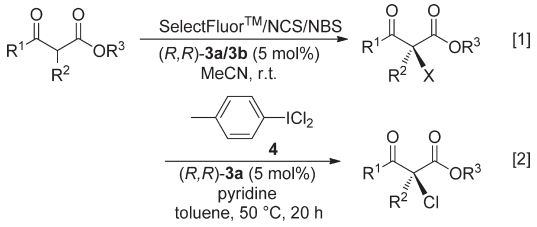
Because of the inherent electronegativity, stable sources of electrophilic halogens are limited. For fluorination, NFSI is most commonly used, although Selectfluor and NFPY are also deployed occasionally. For chlorination and bromination reactions, *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) are the most readily available sources of electrophilic chlorine and bromine, respectively (Figure 1).

Very often, the same or closely related catalysts can be used to accomplish more than one type of halogenation reactions of a particular class of carbonyl compounds. Thus, the discussion within this section will be organized by the type of metal catalysts and their specific scope and limitations.

2.1. Ti(TADDOLato)-Catalyzed α-Halogenations

The first catalytic asymmetric α-fluorination of β-ketoesters was reported by Hintermann and Togni in 2000, using isolated Ti−TADDOLato catalysts **3a** and **3b** (Figure 2),[11,12] which were found to be also applicable to chlorination and bromination of these substrates (Table 1).[12] Fluorination of β-ketoesters bearing bulky benzylic esters can be achieved with higher selectivities with the bis(acetonitrile) adduct **3a** using Selectfluor (entries 1−6). Use of NCS and NBS under these conditions also led to chlorinated and brominated products, respectively (entries 7−11), the latter with very low levels of stereoselectivity (entries 8 and 11). Subsequently, a hypervalent iodine reagent 4-(dichloroiodo)toluene (**4**) was employed with pyridine (to neutralize the HCl byproduct), to chlorinate α-methylacetoacetate

Table 1. Ti(TADDOLato)-Catalyzed Asymmetric Halogenation Reactions



entry	R^1	R^2	R^3	conditions	catalyst	X	time	yield[a] (%)	ee[b] (%)
1	Ph	Me	Et	[1]	**3a**	F	40 min	[c]	62
2	Ph	Me	$CHPh_2$	[1]	**3a**	F	1 d	[c]	82
3	Et	Me	$CHPh_2$	[1]	**3a**	F	20 min	[c]	81
4	Et	Me	Bn	[1]	**3a**	F	<7 min	[c]	71
5	Me	Me	$CH_2$1-Np	[1]	**3a**	F	<15 min	[c]	68
6	Et	Me	$CH_2(2,4,6\text{-}i\text{Pr}_3C_6H_3)$	[1]	**3a**	F	<15 min	[c]	90
7	Ph	Me	Et	[1]	**3a**	Cl	1 h	85	59
8	Ph	Me	Et	[1]	**3b**	Br	40 min	84	8
9	Me	Me	Bn	[1]	**3a**	Cl	<30 min	85	60
10	Et	Me	$CHPh_2$	[1]	**3a**	Cl	<1 h	94	88
11	Et	Me	$CHPh_2$	[1]	**3b**	Br	<30 min	90	23
12	Me	Me	Bn	[2]	**3a**	Cl	20 min	67	71
13	Ph	Me	Et	[2]	**3a**	Cl	45 min	83	15
14	Me	Bn	Bn	[2]	**3a**	Cl	20 min	82	16

[a] Isolated yield. [b] Determined by high-performance liquid chromatography (HPLC). [c] Unspecified, isolated yields reported to be "between 80 and >95%".

dx.doi.org/10.1021/cr100197z |*Chem. Rev.* 2011, 111, 1637–1656

Scheme 2. Ti(TADDOLato)-Catalyzed Heterodihalogenation of β-Ketoesters

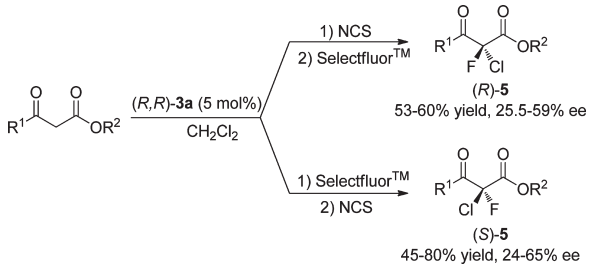
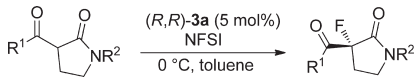


Table 2. Ti(TADDOLato)-Catalyzed Fluorination Reactions of α-Acyl-γ-Lactams



entry	R^1	R^2	yield (%)	ee (%)
1	Me	Bn	75	26
2	Ph	Bn	78	15
3	Ph	Me	75	6
4	Me	Ph	75	87
5	Cy	Me	60	50
6	*t*-Bu	Me	40	20

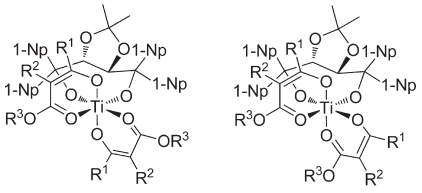


Figure 3. Major diastereomers of substrate-bound Ti(TADDOLato) complexes observed in solution.

with a better enantiomeric excess (ee) than the reaction using NCS ($R^1 = R^2 = Me$, entries 12 vs 9).[13] In this case, the choice of ester substituent had minimal bearing on the reaction outcome; however, small structural changes to the rest of the substrate (R^1 or $R^2 \neq Me$) resulted in a dramatic loss of enantioselectivity (entries 13 and 14). High concentrations of **4** were found to be detrimental to selectivity due to competing uncatalyzed reaction. Hence, the optimal protocol required the slow addition of the reagent, carried out at 50 °C.

An interesting extension to this work was the synthesis of chiral geminal heterodihalogenated products by sequential reactions performed in a one-pot procedure (Scheme 2).[14] First monochlorinating, and then asymmetrically fluorinating, β-ketoesters furnished products **5** with moderate yields and ee's. Reversing the order of these steps, thereby executing an asymmetric chlorination, allowed access to the opposite enantiomer with similar ee values.

Scheme 3. Cationic Pd(II)−Diphosphine Complexes and Formation of Activated Chelate Complexes

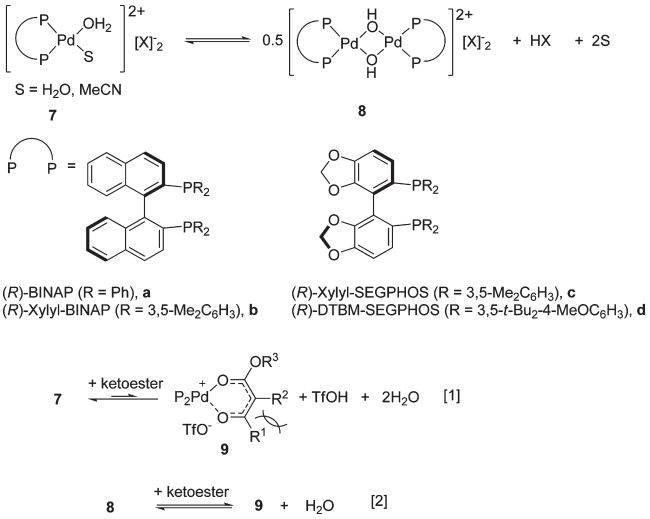
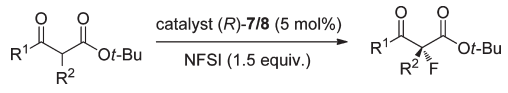
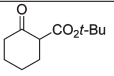
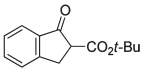
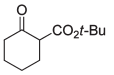
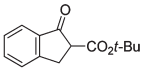


Table 3. Comparing Catalysts 7 and 8 in Asymmetric Fluorination of β-Ketoesters



Entry	Substrate R^1	Substrate R^2	Catalyst	Solvent	T (°C)	Time (h)	Yield (%)	ee (%)
1			**8b**·BF_4	EtOH	-10	20	91	94
2			**8b**·OTf	EtOH	-20	36	85	83
3	Ph	Me	**8b**·BF_4	EtOH	20	40	92	91
4			**7b**·SbF_6	MeOH	rt	0.5	93	99
5			**7b**·SbF_6	MeOH	rt	0.5	90	85
6	Ph	Me	**7b**·SbF_6	MeOH	rt	24	87	99

Ti(TADDOLato) catalyst **3a** has been employed in the fluorination of α-acyl-γ-lactams with up to 87% ee (Table 2). In this work, the reagent NFSI was found to give substantially higher ee's than other fluorinating agents investigated.[15]

It was believed that Ti-catalyzed halogenation reactions of β-ketoesters proceed via 2:1 substrate−catalyst intermediates. These can exist in six possible diastereomeric forms, four of which were isolated and characterized by X-ray and nuclear Overhauser effect (NOE) experiments.[15] The stereodefining atom transfer is determined by the orientation of the naphthyl groups, which provide steric shielding of the prochiral faces of the bound enolate. In solution, these complexes exist mainly in two

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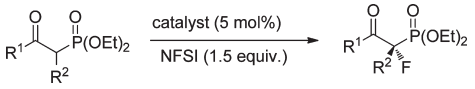
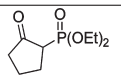
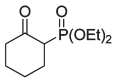
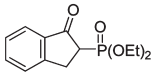
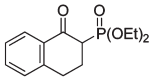
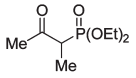
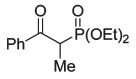
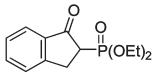
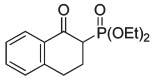
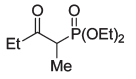
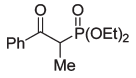
Table 4. Pd(II)-Catalyzed Fluorination of *β*-Ketophosphonates



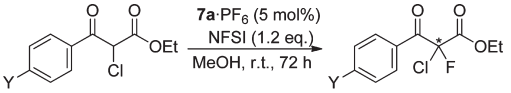
Entry	Substrate	Catalyst (mol%)	Solvent	T (°C)	t (h)	Yield (%)	ee (%)
1		**7b**·OTf (1)	EtOH	rt	12	82	95
2		**7b**·OTf (5)	EtOH	rt	8	93	96
3		**7b**·OTf (5)	EtOH	rt	3	84	95
4		**7b**·OTf (5)	EtOH	rt	3	97	94
5		**7c**·OTf (10)	EtOH	40	48	57	94
6		**7c**·OTf (10)	EtOH	40	48	38	95
7		**7c**·BF_4 (5)	MeOH	rt	3	91	97
8		**7c**·BF_4 (5)	MeOH	rt	8	93	97
9		**7c**·BF_4 (5)	THF	rt	90	65	87
10		**7c**·BF_4 (5)	THF	rt	94	62	91

diastereomeric forms, **6a** and **6b** (Figure 3). In the most abundant isomer, **6a**, both of the *Re* faces of the bound enolates are accessible to electrophilic attack, leading to the *S*-enantiomer, accounting for the observed stereochemistry. In the second most abundant isomer, **6b**, one of the ketoesters has its *Si*-face exposed, and it was proposed that this led to the degradation of the enantioselectivity.

2.2. Pd(II) and Ni(II) Diphosphine Complexes

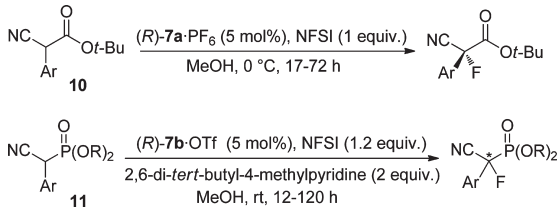
Over the past decade, chiral cationic Pd(II)−diphosphine complexes, containing noncoordinating counteranions (X = PF_6, BF_4, OTf, SbF_6), have been applied to a range of α-functionalization reactions, by providing a chiral template for chelating substrates, e.g., *β*-ketoesters.[16] Typically, axially chiral diphosphine ligands such as BINAP and SEGPHOS have been shown to be uniquely privileged in conferring generally high stereoselectivities in many catalytic reactions. These air- and moisture-stable Lewis acid catalysts can be utilized in one of two forms: monomeric complex **7**, prepared either as bisaqua species (S = H_2O) or acetonitrile adducts (S = MeCN). These are presumably displaced easily upon binding of the substrate (Scheme 3, eq 1), as the nature of the bound solvent has not been shown to affect the reactivity. Reaction of **7** with dilute sodium hydroxide or molecular sieves generates dimeric catalysts **8**, which contain bridging hydroxyl groups that can deprotonate the chelating substrate (Scheme 3, eq 2). Catalysts **8** are thus "bifunctional", acting as a Brønsted base and a Lewis acid simultaneously during the reaction.

Scheme 4. Pd-Catalyzed Asymmetric Fluorination of α-Chloro-*β*-ketoesters



Y = H, MeO, Me, Br, CF_3 79-94% yield, 63-77% ee

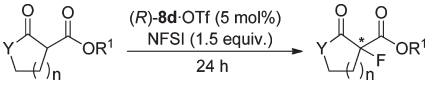
Table 5. Pd(II)-Catalyzed Fluorination of α-Aryl-α-cyanoacetates (10) and Phosphonates (11)



entry	substrate	Ar	R	time (h)	yield (%)	ee (%)
1	**10**	Ph		60	83	99
2	**10**	4-Cl−C_6H_4		17	94[a]	85
3	**10**	4-Tol		60	85	93
4	**10**	4-MeO−C_6H_4		72	85[b]	99
5	**10**	2-Np		60	88	93
6	**10**	9-anthracenyl		72	62[a,c]	93
7	**11**	Ph	Et	12	90	85
8	**11**	4-MeO−C_6H_4	Et	12	98	85
9	**11**	4-Cl−C_6H_4	Et	12	98	91
10	**11**	4-F−C_6H_4	Et	15	95	87
11	**11**	1-Np	Et	120	73	83
12	**11**	2-thienyl	Et	18	94	81

[a] Reaction conducted at room temperature (rt). [b] Reaction conducted using catalyst **9a**·BF_4. [c] Reaction conducted in THF/MeOH (1:1).

Table 6. Fluorination of Lactones and Lactams Catalyzed by 8d·OTf



entry	Y	*n*	R^1	solvent	additive	yield (%)	ee (%)
1	O	1	*t*-Bu	*i*-PrOH		75	98[a]
2	NBn	1	*t*-Bu	EtOH	2,6-lutidine	89	98
3	NMe	1	*t*-Bu	EtOH	2,6-lutidine	77	99
4	NCO_2CHPh_2	1	$CHPh_2$	EtOH	2,6-lutidine	45	99[b]
5	NH	2	*t*-Bu	EtOH	2,6-lutidine	74	94

[a] Using catalyst **8d**·OTf (2.5 mol %). [b] Using catalyst **8c**·OTf (5 mol %).

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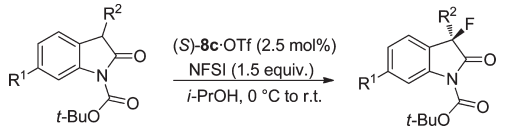
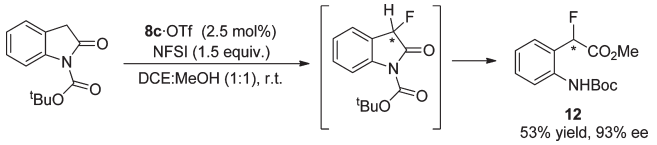
Table 7. Pd(II)-Catalyzed 3-Fluorination of Oxindoles



entry	R^1	R^2	t (°C)	T (h)	yield (%)	ee (%)
1	H	Ph	0	18	96	90
2	H	Me	rt	5	86	95
3	H	Bn	rt	4	72	80
4	CF_3	2-MeO−C_6H_4	rt	3	80	75
5	H	H	rt	43	29	21[a]

[a] Reaction conducted in THF.

Scheme 5. Catalytic Fluorination of Unsubstituted Oxindole, Followed by Methanolysis

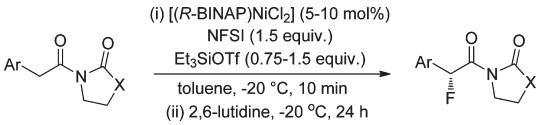


Pd-catalyzed enantioselective α-fluorination of β-ketoesters with NFSI was first demonstrated by Sodeoka and co-workers using dimeric complexes **8b** and **8c**,[17,18] to fluorinate a selection of cyclic and acyclic *tert*-butyl β-ketoesters with high yields and enantioselectivities (Table 3, entries 1−3); the Brønsted basicity of the catalyst was thought to promote the formation of the active Pd−enolate complex **9** in these reactions. However, these reactions have since been reexamined by Kim and co-workers with the monomeric catalyst **7b**·SbF_6 (Table 3, entries 4−6), which afforded similar results (e.g., entries 1 vs 4, 2 vs 5, 3 vs 6).[19] Notably, substantially shorter reaction times were involved using the monomeric catalyst, compared to the dimeric catalyst (entries 3 vs 6).

β-Ketophosphonates are good chelating substrates, and their fluorination reactions were also examined by the research groups of Sodeoka and Kim independently (Table 4), using different salts of the same monomeric palladium catalyst: **7b**·OTf (entries 1−6) and **7b**·BF_4 (entries 7−10), respectively. The reaction outcomes were virtually identical (entries 3 vs 7, 4 vs 8), implying the choice of counterion (TfO versus BF_4) has minimal bearing on the reaction outcome.[18−21] Reactions of cyclic substrates were extremely facile, complete within 12 h at room temperature using just 1 mol % of the catalyst, to afford products with excellent yields and selectivities (entry 1). In contrast, reactions with acyclic substrates were sluggish even at 40 °C, and 10 mol % of the more elaborate catalyst **7c**·OTf was required to obtain higher levels of selectivity (entries 5 and 6); without these enhancements, reactions were impractically slow and furnished moderate yields after 58−94 h (entries 9 and 10).

Further elaborations of these systems included the immobilization of catalyst **8b**·OTf in an ionic liquid [hmim][BF_4], which allowed the catalyst to be reused no less than 10 times in the fluorination of ketoesters, with no detectable erosion of its efficiency.[22] Similarly, the catalyst **7a**·BF_4 was immobilized in [bmim][BF_4] and used for the fluorination reactions of β-ketophosphonate substrates.[23] Recycling of up to 7 cycles was achieved, with only a marginal reduction in yield (∼5%) and ee (2%).

Table 8. Ni-Catalyzed Fluorination of α-Aryl Acetic Acid Derivatives



entry	X	Ar	[Cat] (mol %)	yield (%)	ee (%)
1	S	Ph	5	99	88
2	S	4-F−C_6H_4	5	90	83
3	S	4-MeO−C_6H_4	5	92	81
4	S	2-MeO−C_6H_4	10	87	78
5	S	1-Np	5	94	87
6	O	Ph	10	95	87
7	S	*n*-Pr	10	15	11

On the other hand, catalyst **7a**·PF_6 was used in the fluorination of α-chloro-β-ketoesters (Scheme 4),[24] with slightly better results than that previously achieved using the Ti(TADDOLato) catalyst (Scheme 2).

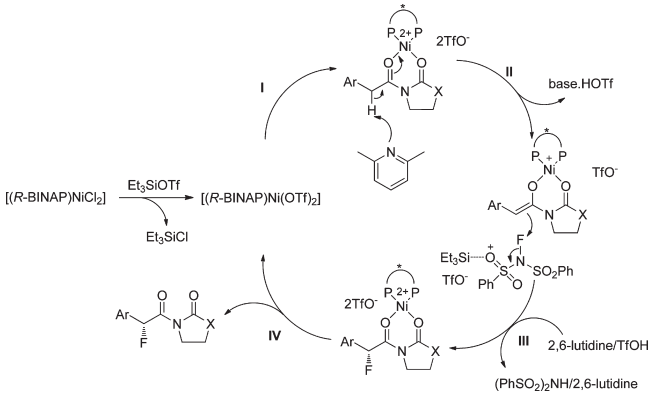
The fluorination of α-cyanoacetate affords a versatile class of synthetic intermediates, as the nitrile group can be readily reduced or hydrolyzed to a number of functional groups. In this regard, dicationic Pd(II) catalysts proved to be highly effective for the fluorination of *tert*-butyl α-aryl-α-cyanoacetates (**10**)[25] and α-aryl-α-cyanophosphonates (**11**);[26] reactions proceeded with excellent outcomes, although extended reaction times were required (Table 5). Using the catalyst **7a**·PF_6, the highest selectivities were observed in the reactions of *tert*-butyl esters of **10** (entries 1−6). The fluorination of α-aryl-α-cyanophosphonates **11**, on the other hand, required the presence of a hindered base and the bulkier catalyst **7b**·OTf (entries 7−12).

The scope of the Pd-catalyzed fluorination reactions has also been successfully extended to include lactones and lactams as substrates, using NFSI as the reagent and the Brønsted basic catalyst **8c**·OTf or **8d**·OTf (Table 6).[27] Fluorinated lactone products can be acquired in good yield and ee, as long as sterically bulky alcohols were employed as solvents to suppress competitive lactone ring-opening. The δ-lactone (Y = O, n = 2) was also examined, but its fluorinated product proved difficult to isolate—addition of $BnNH_2$ at the end of the reaction led to the ring-opened product, which was obtained in 35% yield with 97% ee. In comparison, δ-lactams were less acidic than lactones. For these substrates, the addition of a hindered base (2,6-lutidine, 0.5 equiv), was required to promote the formation of the palladium enolate. However, the product is less susceptible to ring-opening, so ethanol could be employed as solvent, to afford fluorinated lactams with excellent yields and enantioselectivity.

Further exploiting the affinity of 1,3-dicarbonyl moieties for these complexes, asymmetric fluorination of 3-substituted oxindoles was reported by Sodeoka and co-workers, using **8c**·OTf as catalyst.[28] *N*-Boc substrates were found to deliver the best performance, furnishing fluorinated 3-aryl and 3-alkyl substituted oxindoles with good enantioselectivities (Table 7, entries 1−4).

dx.doi.org/10.1021/cr100197z |*Chem. Rev.* 2011, 111, 1637–1656

Scheme 6. Proposed Catalytic Cycle for the Ni-Catalyzed Fluorination of α-Aryl Acetic Acid Derivatives



The reaction of the unsubstituted oxindole, however, proceeded slowly with low selectivity (entry 5). By adopting a mixture of solvents ($ClCH_2CH_2Cl$/MeOH, 1:1), the methanolysis product **12** was isolated in 53% yield and 93% ee (Scheme 5), i.e., the low ee observed for the fluorinated oxindole was attributed to product racemization. However, the methanolysis of the starting material also becomes competitive under these conditions, which limits the product yield of **12**.

An approach for the monofluorination of a prochiral methylene group was reported in 2007, wherein the fluorination of α-aryl acetic acid derivatives proceeded under a 3-component catalyst system of [(BINAP)$NiCl_2$]/Et_3SiOTf/2,6-lutidine (Table 8).[29] Moderate to good yields and enantioselectivities were achieved for all α-aryl substrates reported, and the nature of the heteroatom in the oxazolidinone/thiazolidinone ring did not appear to affect selectivity (entries 1−6). The only α-alkyl substrate reacted with poor yield and enantioselectivity (entry 7).

The unique combination of the catalytic components was specifically chosen to offer dual activation of the substrate and reagent (Scheme 6): the formation of the activated nickel−enolate complex is assisted by the presence of the noncoordinating Brønsted base (steps I and II), while the Lewis acidic Et_3SiOTf activates NFSI to become a stronger electrophile (step III), without interfering with the formation of the enolate. C−F bond formation results from the reaction between the activated substrate and the activated electrophile, prior to product release (step IV).

2.3. Lewis Acidic Complexes of Bis(oxazoline) Ligands

Bis(oxazoline) ligands constitute a unique class of privileged ligands that can be combined with a number of cationic metal centers to afford very effective stereocontrol in a number of Lewis acid catalyzed processes. There are three general classes of bis(oxazoline) ligands: BOX, PyBOX, and DBFOX, distinguished by their rigid backbones (Figure 4). These have been utilized extensively in asymmetric α-heterofunctionalization reactions.

The BOX−$Cu(OTf)_2$ complex had been investigated as a catalyst for the fluorination reaction of *tert*-butyl ketoesters using NFSI,[30−32] but selectivity was inferior to that previously achieved by palladium−diphosphine complexes (Table 3). On the other hand, using a combination of *t*-Bu−BOX with $Cu(OTf)_2$, chlorination and bromination of ketoesters by NCS and NBS

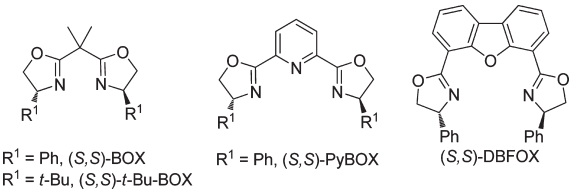


Figure 4. Commonly used bis(oxazoline) ligands in asymmetric catalysis.

can be realized with ee's of up to 77% and 82%, respectively (Table 9, entries 1−10).[33] Subsequently, Shibata, Toru, and coworkers were successful with the application of a Ni−DBFOX catalyst in the fluorination of β-ketoesters bearing bulky ester substituents (Table 9, entries 11−15), including several ee values of >90%.[34] Although only one acyclic substrate was reported, the yield and ee are high and can be achieved within a reasonable reaction time (18 h, entry 15). Using trifluoromethanesulfonyl chloride (CF_3SO_2Cl) as a mild chlorinating reagent, highly enantioselective chlorination of 2-carboxylate indanone and tetralone substrates can also be achieved in excellent selectivities using nickel(II) as the Lewis acid (entries 16−19). Notably, the choice of the metal salt (Cu or Ni) has been shown to afford opposite enantioselectivity in the fluorination of ketoesters.[35]

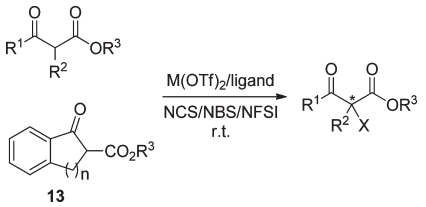
DBFOX complexes of nickel(II) and zinc(II) were also reported to be effective for asymmetric halogenation of other substrates (Table 10). These include fluorination and chlorination of *N*-Boc−oxindoles using NFSI and CF_3SO_2Cl, respectively, leading to ee's >90% for aryl- and alkyl-substituted products (entries 1−3).[34] Acyclic β-ketophosphonates may be subjected to zinc-catalyzed fluorination and chlorination reactions by NFSI and NCS, respectively (entries 4−12).[36] Lower catalytic loading was needed for the chlorination (10 mol %) than for the fluorination reaction (20 mol %). In contrast to previous catalytic systems, the best results were obtained for acyclic rather than cyclic substrates, which reacted slowly to give low yields (entries 7 and 12).

α-Aryl acetates were fluorinated with NFSI, using Ni$(ClO_4)_2 \cdot 6H_2O$ as the Lewis acid and 2,6-lutidine as a cocatalyst (Table 10, entries 13−16).[37] Compared to the previous results obtained with the Ni−BINAP complex (Table 8), the ee's of the Ni−DBFOX system are not as high, but the presence of Et_3SiOTf as a supplementary Lewis acid is unnecessary.

The fluorination of acyclic unsymmetrical malonates with NFSI has been reported with excellent results by using a catalyst generated from $Zn(OAc)_2$ (Table 10, entries 17−21).[38] Because the substrates are not as acidic as ketoesters, elevated reaction temperature (refluxing in CH_2Cl_2) was required for good yields, and the addition of molecular sieves provided high ee's for the reaction of a number of methyl *tert*-butyl malonates. Various heteroatoms may be accommodated at the α-position, leading to a number of interesting diheterofunctionalized products with ee's ≥ 90% (entries 19−21).

Two recent reports described the preparation and application of modified chiral oxazoline ligands **14** and **15** (Figure 5) for asymmetric fluorination and chlorination reactions, using Ni$(ClO_4)_2$ and CuOTf as metal precursors, respectively.[39,40] A limited number of cyclic ketoester substrates were included in these studies (Table 11); nevertheless, enantioselectivities of up to 99% and 85% can be attained in the fluorination and chlorination reactions, respectively. To suppress unproductive binding of the

Table 9. Asymmetric Halogenation of β-Ketoesters Catalyzed by Metal Complexes of Bis(oxazoline) Ligands



entry	R^1	R^2	R^3	X	M (mol %)	ligand (mol %)	solvent	*t* (h)	yield (%)	ee (%)
1	Me	Me	Et	Cl	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	98	77
2	Me	Bn	Et	Cl	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	98	61
3	Me	Et	Et	Cl	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	93	66
4	$(CH_2)_4$		Et	Cl	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	99	76
5	$(CH_2)_5$		Et	Cl	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	98	73
6	Me	Me	Et	Br	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	98	80
7	Me	Bn	Et	Br	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	99	66
8	Me	Et	Et	Br	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	90	70
9	$(CH_2)_4$		Et	Br	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	85	82
10	$(CH_2)_5$		Et	Br	Cu (9)	*t*-Bu−BOX (9)	Et_2O	16	80	71
11	**13** (*n* = 1)		*t*-Bu	F	Ni (10)	DBFOX (11)	CH_2Cl_2	3	76	99
12	**13** (*n* = 2)		Ad	F	Ni (10)	DBFOX (11)	CH_2Cl_2	3	88	95
13	$(CH_2)_3$		*t*-Bu	F	Ni (10)	DBFOX (11)	CH_2Cl_2	2	84	93
14	$(CH_2)_4$		*t*-Bu	F	Ni (10)	DBFOX (11)	CH_2Cl_2	2	86	99
15	Et	Me	$CHPh_2$	F	Ni (10)	DBFOX (11)	CH_2Cl_2	18	75	83
16[a]	**13** (*n* = 1)		*t*-Bu	Cl	Ni (10)	DBFOX (11)	CH_2Cl_2	10	72	97
17[a]	**13** (*n* = 1)		Ad	Cl	Ni (10)	DBFOX (11)	CH_2Cl_2	17	85	97
18[a]	**15** (*n* = 2)		Ad	Cl	Ni (10)	DBFOX (11)	CH_2Cl_2	45	61	98

[a] CF_3SO_2Cl (1.2 equiv) was used as the chlorinating reagent.

electrophile to the catalyst, slow introduction of the fluorinating reagent over the course of the reaction was essential to obtain good results.[41] It is interesting to note that the smaller ester substituents seemed to impart high selectivity in the copper-catalyzed chlorination reactions (entries 6 vs 7 and 8 vs 9), but the selectivity of the system is highly substrate dependent (entry 10).

2.4. Other Catalysts

In addition to the three main classes of catalysts described in previous sections, other catalytic systems have also found application in asymmetric halogenation reactions but are somewhat limited in substrate scope and achieved lower levels of enantioselectivities. These include the scandium−binaphthyl phosphate complex **17** (Figure 6), which can be used to fluorinate some cyclic and acyclic ketoesters bearing small ester substituents with up to 88% ee, using the commercially available fluorinating agent NFPY-OTf.[42]

On the other hand, Togni, Mezzetti, and co-workers achieved some success in asymmetric fluorination of cyclic and acyclic ketoesters, using the ruthenium catalyst **18** and NFSI.[43] However, reported ee's vary widely, and highly enolizable substrates are prone to uncatalyzed reaction under the adopted conditions, leading to poor selectivities.

More recently, chiral sulfoximes, such as **19**, have been used in combination with $Cu(OTf)_2$ for the halogenation of ethyl esters of β-ketoesters.[44] Using NFSI, fluorinated products can be obtained with modest ee's of 39−74%. However, chlorination and bromination reactions with NCS/NBS can be achieved with greater success, with up to 91% and 73% ee, respectively.

Interestingly, enantioselective fluorination of β-ketoesters can be attained with ee's up to 47%, and this has been achieved with DNA and a nonchiral Cu(II) complex. The chiral induction is attributed to the helical chirality of DNA and intercalation or groove binding of the catalyst−substrate complex.[45]

Overall, the field of asymmetric electrophilic halogenation reactions has been dominated by fluorination reactions, where several types of carbonyl substrates can be fluorinated with near-perfect enantioselectivities. The generation of tertiary stereogenic centers, however, remained challenging, as are chlorination and bromination reactions, where ee's of >90% are very rare.

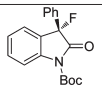
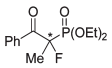
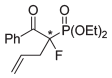
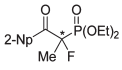
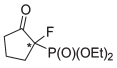
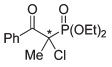
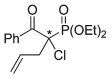
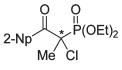
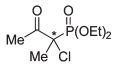
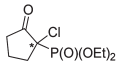
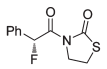
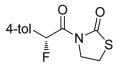
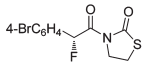
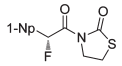
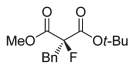
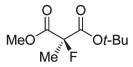
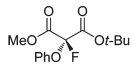
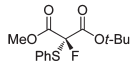
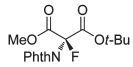
3. α-HYDROXYLATION REACTIONS

3.1. α-Hydroxylation of Ketones

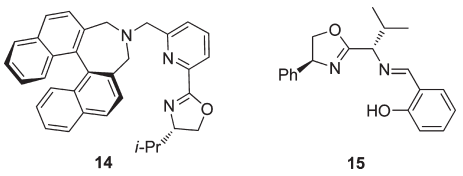
Keto−enol tautomerism generates a C=C bond, which can undergo epoxidation reactions to generate an unstable intermediate that rearranges to give an α-hydroxy ketone (Scheme 7). An attempt to achieve this catalytically was first reported in 2002, wherein 2-hydroxy ketones were subjected to conditions of the Sharpless asymmetric epoxidation reaction. Optically active hydroxylated products can be obtained with high ee's, but reactions were extremely slow—even by deploying an excess of the catalyst, very low conversions were obtained after several days (Scheme 8). The operation of competitive side reactions (e.g., Baeyer−Villiger oxidation) is also a significant problem in these reactions.[46,47]

dx.doi.org/10.1021/cr100197z |*Chem. Rev.* 2011, 111, 1637–1656

Table 10. Asymmetric Halogenation of Other Substrates Using Ni and Zn Complexes of DBFOX

Entry	Product	M (mol%)	DBFOX (mol%)	solvent	T (°C)	t (h)	Yield (%)	ee (%)	Ref
1		$Ni(OAc)_2$ (10)	11	CH_2Cl_2	rt	5	72	96	34
2		$Ni(OAc)_2$ (10)	11	CH_2Cl_2	rt	35	73	93	34
3		$Ni(OAc)_2$ (10)	11	CH_2Cl_2	rt	20	93	61	34
4		$Zn(ClO_4)_2$ (20)	22	CH_2Cl_2	reflux	60	86	88	36
5		$Zn(ClO_4)_2$ (20)	22	CH_2Cl_2	reflux	60	91	90	36
6		$Zn(ClO_4)_2$ (20)	22	CH_2Cl_2	rt	60	71	89	36
7		$Zn(ClO_4)_2$ (20)	22	CH_2Cl_2	rt	60	38	91	36
8		$Zn(SbF_6)_2$ (10)	11	CH_2Cl_2	rt	20	98	92	36
9		$Zn(SbF_6)_2$ (10)	11	CH_2Cl_2	rt	20	93	92	36
10		$Zn(SbF_6)_2$ (10)	11	CH_2Cl_2	rt	20	97	93	36
11		$Zn(SbF_6)_2$ (10)	11	CH_2Cl_2	rt	20	80	94	36
12		$Zn(SbF_6)_2$ (10)	11	CH_2Cl_2	rt	20	40	80	36
13[a]		$Ni(ClO_4)_2$ (10)	11	CH_2Cl_2	0	20	90	74	37
14[a]		$Ni(ClO_4)_2$ (10)	11	CH_2Cl_2	0	48	75	77	37
15[a]		$Ni(ClO_4)_2$ (10)	11	CH_2Cl_2	0	48	77	56	37
16[a]		$Ni(ClO_4)_2$ (10)	11	CH_2Cl_2	0	48	85	59	37
17		$Zn(OAc)_2$ (10)	11	CH_2Cl_2	reflux	15	90	98	38
18		$Zn(OAc)_2$ (10)	11	CH_2Cl_2	reflux	24	90	99	38
19		$Zn(OAc)_2$ (10)	11	CH_2Cl_2	reflux	15	85	98	38
20		$Zn(OAc)_2$ (10)	11	CH_2Cl_2	reflux	24	81	90	38
21		$Zn(OAc)_2$ (10)	11	CH_2Cl_2	reflux	18	91	93	38

[a] 2,6-Lutidine (1 equiv) included in the catalytic reaction.



14 15

Figure 5. Hybrid oxazoline ligands for asymmetric halogenation reactions.

3.2. Asymmetric Epoxidation of Enol Derivatives

Instead of relying on the keto−enol equilibrium to provide the C=C functionality, epoxidation reactions can be made more facile by employing enol derivatives, although this does introduce an additional step to the overall reaction. The application of osmium-catalyzed dihydroxylation procedure to methyl or silyl enol ethers was first reported by Sharpless and co-workers (Table 12):[48,49] employing AD-mix as catalyst/oxidant, several hydroxylated products can be obtained with >90% enantioselectivity. The stereoselectivity is defined by the catalyst, i.e., both *E*- and *Z*-isomers of the substrate gave the same enantiomer. Hence, high ee's can be achieved from *E*/*Z*-mixtures of substrates, although lower ee's were generally obtained with fully substituted enol ethers (Table 12, entries 5 and 8).

Conversion of silyl enol ethers to α-hydroxyketones can also be achieved asymmetrically using Mn−Salen epoxidation catalysts (Figure 7). This was first demonstrated by Reddy and Thornton, using catalyst **20** in combination with the terminal oxidant iodobenzene. A mixture of products (α-hydoxy and silyl ether ketones) was achieved, with low to moderate ee's of 14−62%.[50] In contrast to the Sharpless procedure, the stereoselectivities of these reactions are very much dependent upon the pattern of the substitution on the C=C bond.

Since then, synthetically more useful levels of ee's have been achieved using Mn(III) complexes **21a**−**c**, by employing NaOCl as the oxidant and the additive PPNO under aqueous conditions (Table 13). The substrate scope of this system includes silyl enol ethers as well as silyl ketene acetals, which furnish α-hydroxy ester products (entries 1−5).[51,52] Under very similar conditions, enol phosphonates can also be employed as substrates (entries 6−10), from which optically active α-hydroxy ketones can be obtained from the phosphonate products after treatment with TFA.[53] Compared to using the silyl enol ethers as substrates, products were obtained in much higher ee's, although yields were typically lower (entries 4 vs 6).

On the other hand, the oxidation of a number of cyclic alkyl enol ethers has been examined using Mn catalyst **22** and iodosobenzene as the oxidant (Table 14). As the racemization

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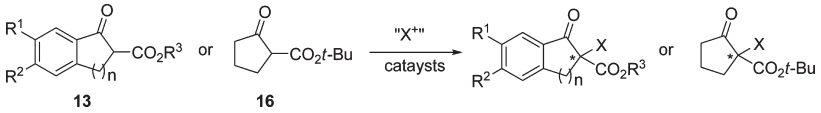
Table 11. Asymmetric Halogenation of β-Ketoesters Using Hybrid Ligands 14 and 15[a]



entry	substrate	X	R^1, R^2, R^3	*n*	time (h)	yield (%)	ee (%)
1	**13**	F	H, H, Bn	1	2	99	99
2	**13**	F	H, H, *t*-Bu	1	2	99	91
3	**13**	F	H, H, *t*-Bu	2	12	99	92
4	**16**	F			24	90	92
5	**13**	Cl	H, H, *i*-Pr	1	2	95	83
6	**13**	Cl	H, Cl, Me	1	2	99	74
7	**13**	Cl	H, Cl, *t*-Bu	1	2	99	70
8	**13**	Cl	MeO, MeO, Me	1	2	95	74
9	**13**	Cl	MeO, MeO, *t*-Bu	1	2	99	70
10	**16**	Cl			2	47	32

[a] General reaction conditions for fluorination (X = F): ketoester (1 equiv) and NFSI (1.1 equiv), 5 mol % of $Ni(ClO_4)_2$/**14** and MS4 Å in CH_2Cl_2, rt. General reaction conditions for chlorination (X = Cl): ketoester (1 equiv), NCS (1.2 equiv), 5 mol % of **15**-CuOTf·C_6H_6, CH_2Cl_2, 0 °C.

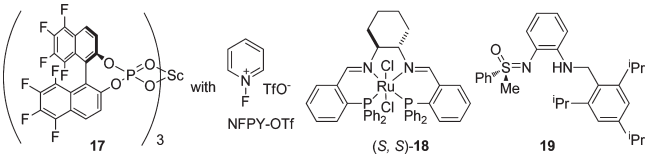
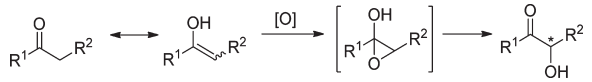


Figure 6. Other catalysts/ligands/reagents used in asymmetric halogenation reactions.

Scheme 7. Epoxidation of an Enol



of the α-hydroxy ketone products occurs under the reaction conditions, a dramatic improvement in the enantioselectivity can be achieved when reactions are conducted in alcoholic solvents, affording dialkyl ketals as optically active products.[54]

3.3. *O*-Nitroso Aldol Reaction of Tin Enolates and Silyl Enol Ethers

Nitrosobenzene can either be a source of *O*- or *N*-electrophile in nitroso aldol reactions. Under uncatalyzed conditions, tin enolates react with nitrosobenzene to give *N*-adducts.[55] In the presence of certain Lewis acid catalysts, however, selectivity can be reversed to form the *O*-adduct preferentially.[56] Momiyama and Yamamoto reported the application of a chiral Ag−diphosphine for the highly enantioselective *O*-selective nitro-aldol reactions (Table 15). Up to 95% ee can be attained with cyclic tin enolates, while the reaction of an acyclic substrate proceeded in lower regioselectivity, although the *O*-adduct was obtained with 94% ee (entry 5). It transpired that a 1:1 metal-to-ligand ratio is necessary to maintain *O*-selectivity; when this ratio is increased to >2:1, the reaction becomes *N*-selective (vide infra, section 4.3). The N−O bond of the products is readily cleaved by catalytic $CuSO_4$ without any loss of optical purity, giving optically active α-hydroxy ketones.

The reaction of silyl enol ethers with nitrosobenzene also proceed with high *O*-selectivity in the presence of certain Lewis acid catalysts.[57] An asymmetric process was developed using silver complexes generated from the chiral BINOL-derived phosphite ligand **23** with excellent results (Table 16).[58] Reactions were conducted at −78 °C and required slow addition of a fluoride source (CsF) over 16 h. High yields of the *O*-adduct with excellent ee's were observed with substrates containing 6-membered rings (entries 1−3 and 5). In comparison, reactions of substrates containing other ring sizes led to lower yields, due to competitive formation of the *N*-adducts (entry 4).

A recent paper reported an interesting way of generating tin enolates catalytically in situ, utilizing alkenyl trichloroacetates as substrates and a catalytic amount of $Bu_2Sn(OMe)_2$, in the presence of silver(I) acetate and a chiral diphosphine (Scheme 9, Table 17).[59] This nicely circumvents the use of stoichiometric tin reagent from the process. Moderate yields and regioselectivity can be achieved for cyclic substrates, although the *O*-adduct can be attained in extremely high ee's. Limitations of the reaction appear to be sterically hindered substrates (entry 5) and acyclic compounds (entries 8 and 9), which proceeded with poor regio- or enantioselectivity.

3.4. Ti(IV) and Ru(II)-Catalyzed α-Hydroxylation of β-Ketoesters

Because of their inherent acidity, reactions of β-ketoesters with electrophiles generally do not require the formation of metal enolates. A number of metal catalysts utilized earlier in asymmetric α-fluorination reactions were also found to be useful for the corresponding α-hydroxylation reactions. The precedent was set by Togni, Mezzetti, and co-workers in 2004,[60] wherein the Ti(TADDOLato) complex **3a** was reported to effect highly selective hydroxylation of β-ketoesters by using racemic 2-(phenylsulfonyl)-3-(4-nitrophenyl)oxaziridine **25a** as the oxidant, with ee's reaching 94% (Table 18). However, small changes

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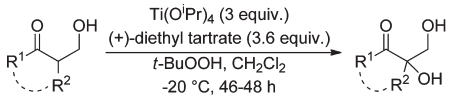
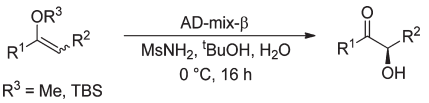
Scheme 8. Asymmetric α-Hydroxylation of 2-Hydroxy Ketones

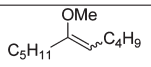
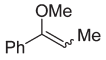
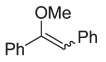
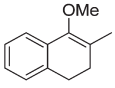
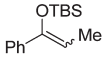
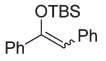
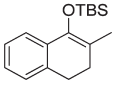


$R^1,R^2 = (CH_2)_4$, 37% yield, 97% ee
$R^1,R^2 = (CH_2)_5$, 58% yield, 86% ee
$R^1 = R^2 = Me$, 29% yield, 95% ee

Table 12. Hydroxylation of Enol Ethers with AD-mix Leading to α-Hydroxy Ketones



R^3 = Me, TBS

Entry	Substrate	*E*/*Z* ratio	Yield (%)	ee (%)
1		4/96	-	95
2		33/67	-	85
3		1/99	-	99
4		99/1	-	90
5		-	79-95	64
6		1/99	-	97
7		3/97	-	97
8		-	89-92	67

in substrate structure resulted in a large drop in ee. It was noted that substrates that exist largely in the enol form are prone to undergo uncatalyzed reactions, resulting in diminished ee (entries1 and 2 vs entries 3 and 4).

In the same study, the ruthenium salt **24** (the cationic form of complex **18**) was used in combination with hydrogen peroxide to effect the α-hydroxylation of these same substrates. Unlike **3a**, this oxidant does not react with enolized ketoesters in the absence of catalyst. However, yields were low and enantioselectivities of the reactions failed to exceed 47%.[61]

3.5. α-Hydroxylation Employing DBFOX Ligands

The DBFOX ligand had been used in combination with Lewis acids in a number of asymmetric α-hydroxylation reactions. Utilizing the racemic, saccharin-derived oxaziridine **25c** as oxidant, Toru, Shibata, and co-workers reported its use for the hydroxylation of cyclic ketoesters and oxindoles, by using Ni and Zn salts, respectively (Table 19, entries 1−11).[62] In these reactions, *tert*-butyl and 1-adamantyl esters gave >90% ee's; the only acyclic ketoester substrate reported gave only 27% yield

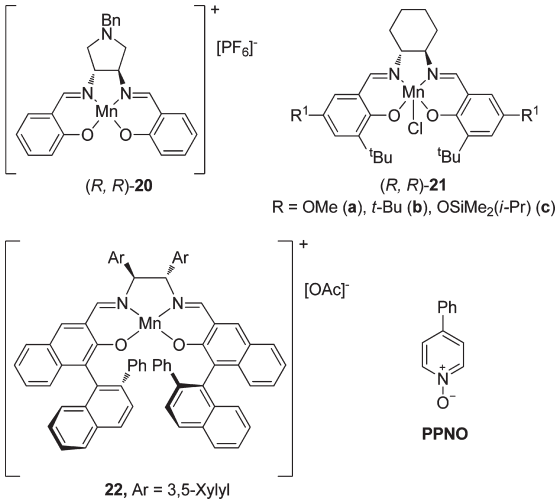


Figure 7. Catalysts and oxidant used in the Mn-catalyzed epoxidation of enol ethers.

after 50 h (entry 5), suggesting that this catalytic system is only suitable for hydroxylation of cyclic β-ketoesters with bulky ester substituents. Oxindoles with alkyl substituent at C-3 also afforded lower product yield and selectivity (entries 10 and 11) than aryl-substituted substrates (entries 6−8).

More recently, the procedure was successfully extended to the α-hydroxylation of unsymmetrical *tert*-butyl malonates (entries 12−17).[63] With these less reactive substrates, prolonged reaction times were required, even at reflux. Once again, the presence of a bulky *tert*-butyl ester was found to be necessary for high selectivity, as almost no enantioselectivity was observed with methyl ethyl malonates. The reaction is only catalyzed by Ni; the corresponding Zn complex was inactive.

3.6. Pd(II)−BINAP Catalyzed α-Hydroxylation of β-Ketoesters

Recently, we reported the application of the dicationic Pd(II)−BINAP catalyst **7a**·OTf to the α-hydroxylation of β-ketoesters (Table 20).[64,65] Dimethyldioxirane (DMD) was found to be the best oxidant for these reactions, generating cyclic α-hydroxylated β-ketoesters in short reaction times, in excellent yields, and with ee's of up to 98%. The scope of the reaction was extended to nitrogen heterocycles, providing hydroxylated 3-pyrrolidinones (entries 3 and 4), 2-pyrrolidinones (entries 5 and 6), and succinimides (entries 7 and 8) with significant ee's. Acyclic substrates were substantially less reactive, requiring several days to reach acceptable conversion in lower ee's. Compared to the previous catalysts, the Pd(II) catalyst is air- and moisture-stable; thus, reactions can be run under aerobic conditions without the need to exclude moisture.

In summary, early developments in asymmetric α-hydroxylation required multistep procedures, where the substrates were activated via enol and enolate intermediates. More recently, it has been demonstrated that the hydroxylation of β-ketoesters can be achieved directly, by using oxaziridines and DMD as oxidants.

4. α-AMINATION REACTIONS

Electrophilic α-amination of carbonyl compounds has been previously reviewed in 2004,[66] although not many asymmetric examples existed at that time. Since then, significant research activity has enabled different C−H groups to be substituted by nitrogen with impressive levels of enantioselectivity using either metal catalysis or organocatalysis. Compared to previously

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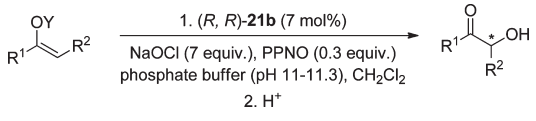
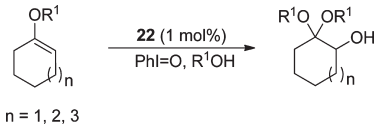
Table 13. Asymmetric Epoxidation of Silyl Enol Ethers Catalyzed by 21b



Entry	R^1	R^2	Y	T (°C)	Catalyst	Conversion (%)	ee (%)
1	Me	Ph	$SiMe_3$	rt	**21a**	99	89
2	Et	Ph	$SiMe_3$	rt	**21a**	72	87
3	*t*-Bu	Ph	$SiMe_3$	rt	**21a**	49	37
4	Ph	Me	$SiMe_3$	rt	**21a**	88	74
5	OMe	Ph	$SiMe_2$*t*-Bu	rt	**21a**	85	68
6	Ph	Me	$P(O)(OEt)_2$	0	**21b**	57	96
7	4-MeO-C_6H_4	Me	$P(O)(OEt)_2$	0	**21b**	56	89
8	Ph	Et	$P(O)(OEt)_2$	0	**21b**	50	93
9	Ph	*n*-Pr	$P(O)(Oi\text{-}Pr)_2$	0	**21b**	70	88
10			-	0	**21b**	37	89

Table 14. Epoxidation of Cyclic Silyl Enol Ethers Catalyzed by Complex 22



entry	*n*	R^1	yield (%)	ee (%)
1	1	Me	38	85
2	1	Et	58	89
3	2	Et	55	81
4	3	Et	68	88

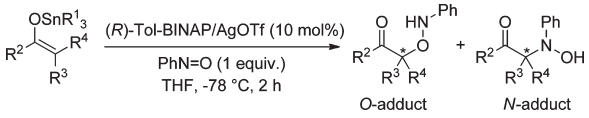
described halogenation and oxygenation reactions, the direct electrophilic α-amination of a simple carbonyl compound remains a challenging synthetic transformation. This is largely due to the lack of "naked" sources of electrophilic nitrogen, which can afford an amine or protected amine directly in a single step, thus requiring further functional group transformations. The following sections on metal-catalyzed reactions are organized according to the source of electrophilic nitrogen, subdivided by the type of keto-substrates.

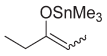
4.1. Azodicarboxylate as Electrophile

The vast majority of publications use an azodicarboxylate ($RO_2CN{=}NCO_2R$, where R = Me, Et, *i*-Pr, *t*-Bu, Bn) as the electrophile, generating chiral hydrazines as products, which can be transformed into chiral amines under hydrogenating or reducing conditions.

4.1.1. Amination of Silyl Enol Ethers. Reactions of a chelating azodicarboxylate **26** with silyl enol ethers proceeded enantioselectively in the presence of 5 mol % of [(*t*-Bu-BOX)Cu-$(OTf)_2$] (Scheme 10, Table 21).[67] The addition of 2,2,2-trifluoroethanol was essential for good catalyst turnover, and

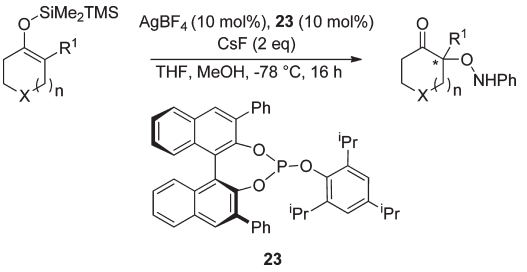
Table 15. *O*-Nitroso Aldol Reactions of Tin Enolates



Entry	Substrate	Yield[a] (%)	*O*-/*N*-adduct	ee (%)
1		95	>99/1	95
2		96	>99/1	95
3		93	>99/1	92
4		95	92/8	82
5		92	81/19	94

[a] Combined yield of both isomers.

Table 16. *O*-Nitroso Aldol Reactions of Silyl Enol Ethers



23

entry	R	X	*n*	yield (%)	ee (%)
1	H	CH_2	1	85	95
2	H	CMe_2	1	72	98
3	H	O	1	66	97
4	H	CH_2	0	41	90
5	Ph	CH_2	1	99	79

the *E*-/*Z*- geometry of the silyl enol ethers affects the stereochemistry of the products. Alkyl and aryl substituents are very well tolerated, furnishing >90% ee (entries 1−8). Thioester and acylpyrrole enol silanes may also be used as substrates (entries 9 and 10, respectively). These reactions are believed to occur via a hetero-Diels−Alder mechanism, where the intermediate **27** forms rapidly; product release and catalyst regeneration occurred upon addition of trifluoroethanol.

In the absence of a chelating moiety, the reaction of a silyl enol ether with dibenzyl azodicarboxylate may be achieved in 86% ee using a combination of AgOTf and BINAP (Scheme 11′).[68] Despite extensive optimization of the reaction

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Scheme 9. Catalytic Asymmetric Nitroso−Aldol Reaction of Alkenyl Trichloroacetates

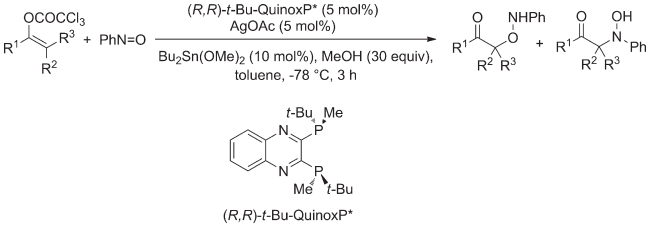
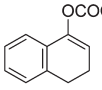
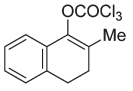
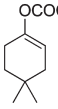


Table 17. Asymmetric Nitro−Aldol Reaction of Alkenyl Trichloroacetates (Scheme 9)

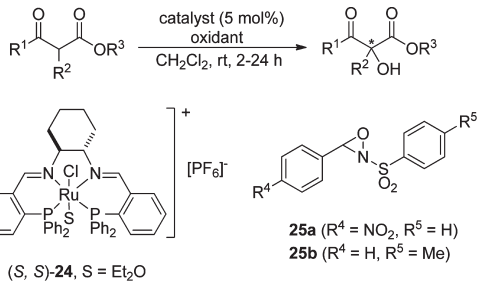
Entry	Substrate	Yield[a] (%)	*O*-/*N*-adduct	ee[b] (%)
1		81	76/24	97
2		65	89/11	99
3		72	68/32	96
4		92	>99/1	99
5		24	82/18	95
6		71	97/3	97
7		68	91/9	97
8	 (*E*/*Z* = 1/4)	8	51/49	92
9	 (*E*/*Z* = 1/4)	21	<1/99	3

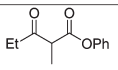
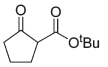
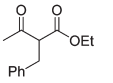
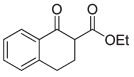
[a] Combined yield of both isomers. [b] Yield refers to *O*-adduct.

conditions, no other substrates were examined using this catalytic system.

4.1.2. Amination of Activated (Chelating) Carbonyl Compounds. α-Amination of *N*-acyloxazolidinones with azodicarboxylates was reported by Evans and co-workers, by using a chiral magnesium complex of a bis(sulfonamide) ligand **28**.[69] Catalytic turnover was improved by the presence of TsNHMe as an additive, leading to products with 80−90% ee.

Table 18. Asymmetric α-Hydroxylation Reactions Catalyzed by 3a and 24



Entry	Substrate	Enol (%)	Catalyst (*R*,*R*)-**3a**[a] Yield (%)	ee (%)	Catalyst (*S*,*S*)-**22**[b] Yield (%)	ee (%)
1		3	89	84	0	-
2		4	97	94	0	-
3		18	93	9	42	20
4		50	>99	4	53	36

[a] **23a** employed as oxidant. [b] 30% H_2O_2 employed as oxidant.

Because of the very low temperature required, the reactions required several days to reach completion, even at 10 mol % catalyst loading.

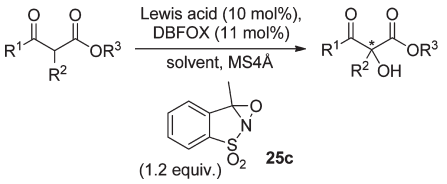
Unsurprisingly, catalysts and substrates used previously in asymmetric α-fluorination and hydroxylation reactions were also often used in α-amination reactions. Accordingly, the bis(oxazolidine) ligand (*S*,*S*)-BOX (Figure 4) has been used in several amination reactions (Table 23). Reactions with ketoesters were first reported by Jørgensen and co-workers.[70] Impressively, using just 0.5 mol % of the copper(II) catalyst, excellent results can be obtained with cyclic, as well as acyclic, substrates (entries 1−8), which had proved to be challenging in other α-functionalization reactions. The system was also used in the amination of some α-fluorinated ketoesters (entries 9−12), but reactions were slow, affording products with ee's of between 73−95%, including a β-ketoamide substrate (entry 12).[71] The absolute configurations of the products were not determined but were assigned in analogy with the previous work. Subsequently, amination of β-ketophosphonates was achieved using zinc(II) complexes (entries 13−20).[72] High ee's were achieved with both cyclic and acyclic substrates but required high catalytic loading (10 mol %) and extended reaction times. The absolute configuration was determined by the X-ray crystallographic structural elucidation of an oxazolidinone derivative of one of the products.

The copper-catalyzed amination methodology was used in tandem with palladium catalysis in the development of a 1-pot pyrazolidine synthesis (Scheme 12). Although the first step proceeded with an excellent 98% ee, the cyclization proceeded with low diastereoselectivity.[73]

Other oxazoline-based systems include *i*-Pr−PyBox/Eu(OTf)$_3$ for the amination of alkyl 2-carboxylate cyclopentanones[74] and a

dx.doi.org/10.1021/cr100197z |*Chem. Rev.* 2011, 111, 1637–1656

Table 19. Lewis Acid Catalyzed Hydroxylation Reactions Using DBFOX As a Chiral Ligand



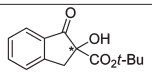
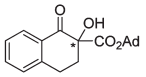
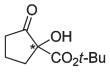
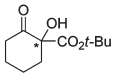
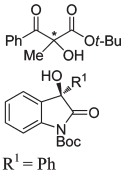
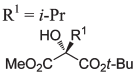
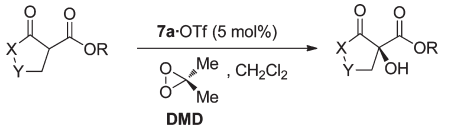
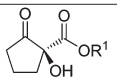
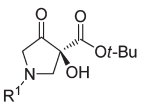
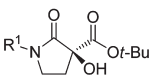
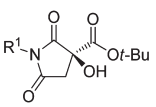
Entry	Product	Lewis acid	solvent	T (°C)	t (h)	Yield (%)	ee (%)	Ref
1		$Ni(ClO_4)_2$	CH_2Cl_2	rt	2	96	97	62
2		$Ni(ClO_4)_2$	CH_2Cl_2	rt	18	97	96	62
3		$Ni(ClO_4)_2$	CH_2Cl_2	rt	1	82	97	62
4		$Ni(ClO_4)_2$	CH_2Cl_2	rt	18	83	95	62
5		$Ni(ClO_4)_2$	CH_2Cl_2	rt	50	27	93	62
6	R^1 = Ph	$Zn(OAc)_2$	CH_2Cl_2	rt	6	82	93	62
7	R^1 = 4-Me-C_6H_4	$Zn(OAc)_2$	CH_2Cl_2	rt	15	84	94	62
8	R^1 = 4-F-C_6H_4	$Zn(OAc)_2$	CH_2Cl_2	rt	15	77	91	62
9	R^1 = C_6F_5	$Zn(OAc)_2$	CH_2Cl_2	rt	3	60	36	62
10	R^1 = Me	$Zn(OAc)_2$	CH_2Cl_2	rt	19	68	84	62
11	R^1 = *i*-Pr 	$Zn(OAc)_2$	CH_2Cl_2	rt	48	43	83	62
12	R^1 = Bn	$Ni(ClO_4)_2$	DCE	reflux	48	82	91	63
13	R^1 = Ph	$Ni(ClO_4)_2$	DCE	reflux	12	83	93	63
14	R^1 = Et	$Ni(ClO_4)_2$	DCE	reflux	16	84	98	63
15	R^1 = Et	$Ni(ClO_4)_2$	DCE	reflux	36	74	95	63
16	R^1 = Bu	$Ni(ClO_4)_2$	DCE	reflux	36	80	94	63
17	R^1 = *i*-Bu	$Ni(ClO_4)_2$	DCE	reflux	48	65	88	63

Table 20. Pd(II)-Catalyzed α-Hydroxylation of *β*-Ketoesters



Entry	Product	T (°C)	t (h)	Yield (%)	ee (%)
					
1	R^1 = Et	-20	0.5	89	87
2	R^1 = *t*-Bu	-20	0.5	88	98
					
3	R^1 = Cbz	-20	0.5	97	90
4	R^1 = Boc	-20	0.5	93	93
					
5[a]	R^1 = Bn	0	48	91	77
6	R^1 = Boc	0	18	99	96
					
7	R^1 = Bn	0	20	99	83
8[b]	R^1 = PMB	-10	1	92	87

[a] Reaction conducted with 20 mol % catalyst. [b] Reaction conducted with 10 mol % catalyst.

C_3-symmetrical *tris*(oxazoline) **29** with $Cu(OTf)_2$ for the amination of ethyl 2-methylacetoacetate[75] (Scheme 13). Although extremely high enantioselectivities can be observed, no other substrates were examined in these reports.

Palladium−diphosphine complex **7a**·PF_6 was assessed as a catalyst in the amination of *β*-ketoesters (Table 24, entries 1−6). Compared to the Cu- and Zn−oxazoline systems (Table 23), a range of azodicarboxylates can be used as aminating reagents, providing various substituted hydrazine products with very comparable ee's (Table 31). However, this system required higher catalyst loading (5 mol %), and reactions with acyclic substrates remained sluggish (entry 6).[76] Subsequently, the corresponding $[(BINAP)Ni(OH_2)_2]^{2+}[SbF_6]^-_2$ complex (**30**) and a nickel−diamine complex **31** (Figure 8) were also assessed in these reactions but were found to be generally less selective.[77] Complex **31** was used for the amination of α-fluoro-*β*-aryl-*β*-ketoesters[78] (Table 24, entries 7 and 8). Reactions were faster than that previously achieved using copper (Table 23, entries 9−12) but only offered moderate ee's of up to 78%.

The performance of nickel[79] and palladium[80] catalysts can be directly compared in the asymmetric amination of α-cyanoketones (Table 25). Overall, better results were achieved by employing Pd catalysts, with **7b**·BF_4 giving the higher selectivity for cyclic substrates (entries 1−4), and its Brønsted basic form **8b**·BF_4 is required to activate the less acidic acyclic substrate (entry 5).

A novel phenanthroline ligand **32** has been used in combination with $Cu(OTf)_2$ for the amination of a series of *β*-ketoesters derived from 1-indanone (Scheme 14).[81,82] The work is particularly notable for the excellent ee's attainable for methyl esters.

Other less common substrates have been examined in the amination chemistry. Shibasaki and co-workers developed a lanthanum-based ternary catalyst, consisting of a metal precursor, a valine-derived diamide ligand **33** and *tert*-butyl valine ester as a base, for the amination of a succinimide in high yield and 91% ee. The product is an intermediate for the synthesis of the aldose reductase inhibitor Ranirestat (Scheme 15).[83−85]

On the other hand, amination of α-aryl-α-cyanoacetates was reported by Ikariya and co-workers to proceed in the presence of a Cp*Ir(Tsdpen) complex **34**. By adding azodicarboxylate slowly

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Scheme 10. Cu-Catalyzed Reactions of Azodicarboxylate 26 with Silyl Enol Ethers

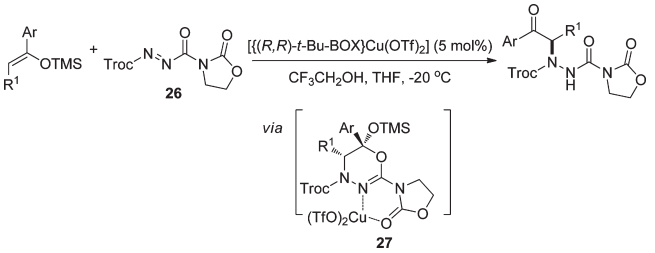
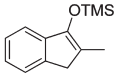


Table 21. Reactions of Azodicarboxylate 26 with Silyl Enol Ethers

Entry	Substrate		time	Yield (%)	ee (%)
	R^1	R^2			
1	Ph	Me	2 min	95	99
2	4-MeOC$_6$H$_4$	Me	<1 min	95	99
3	Ph	Et	30 min	93	98
4	Ph	allyl	2 h	92	97
5	Ph	*i*-Bu	2 h	92	98
6	Ph	*i*-Pr	3 h	86	99
7	4-MeOC$_6$H$_4$	Bn	3 min	88	91
8	4-MeOC$_6$H$_4$	Ph	2 h	95	91
9	S*t*-Bu	Me	overnight	85	96
10	1-pyrrole	Me	30 min	93	98[a]
11			30 min	90	86

[a] Reaction conducted with 1 mol % catalyst.

over the course of the reaction, ee's of between 91−96% can be achieved in 2 h (Table 26). The high reactivity of this catalyst was attributed to the Brønsted basic nature of the amine ligand, which is able to abstract a proton from the substrate, thereby promoting enolization of the process.[86]

The formation of chiral tertiary stereogenic centers is possible if product racemization can be suppressed. This was achieved using less acidic glycine-derived Schiff bases as nucleophiles.[87] The ferrocenyl ligand Taniaphos was used to promote a silver-catalyzed process, whereby excellent yields and ee's can be achieved with bulkier electrophiles and smaller substrates (Table 27, entries 1, 2, and 4).

4.1.3. Amination of Oxindoles. Shibasaki and co-workers reported an interesting class of Schiff base catalysts based on chiral binaphthyl diamine backbones.[88] These can coordinate to Ni to form mono- or bimetallic complexes **35a** and **35b**, respectively (Figure 9, Table 28). Interestingly, dependent on the metal-to-ligand ratio of the complex, opposite enantiofacial selectivity was observed for certain substrates with comparable yields and ee values (entries 1 vs 2, 3 vs 49 vs 10, and 13 vs 14).

Highly enantioselective α-aminations of oxindoles have also been recently achieved using a catalyst derived from Sc(OTf)$_3$ and a *N*,*N*′-dioxide ligand **36** (Table 29).[89] Reactions required

Scheme 11. Ag-Catalyzed Asymmetric Amination of a Silyl Enol Ether

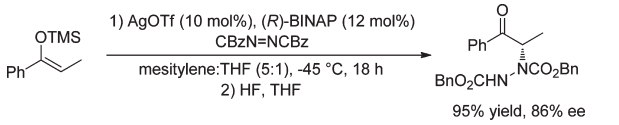
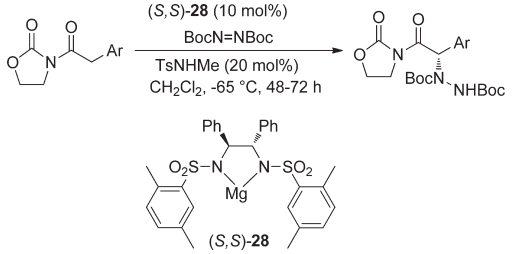


Table 22. Mg−Bis(sulfonamide) Catalyzed Amination of *N*-Acyloxazolidinones



entry	Ar	yield (%)	ee (%)
1	Ph	92	86
2	4-F−C$_6$H$_4$	97	90
3	4-OMe−C$_6$H$_4$	93	86
4	2-napthyl	87	82

several days to complete at −20 °C, which is considerably slower than the previous system. However, ee's in excess of 90% can be routinely achieved for alkyl-substituted oxindoles, with one example of an aryl-substituted substrate (entry 13). Even more impressively, the reaction outcome is insensitive to the ester substituent on the electrophile (R^4, entries 1 and 2) and the *N*-substituent (R^2 = H or Me, entries 14 and 15). On the basis of the observation of a positive nonlinear effect, the involvement of oligomeric aggregates of **36**-Sc(OTf)$_3$ in the transition state was suggested. The substrates were activated via the coordination of both carbonyl groups of the oxindole and the azodicarboxylate to the metal center.

4.2. Aziridination of Silyl Enol Ethers

Using phenyl iodinane TsN═IPh as the reagent, asymmetric aziridination of silyl enol ethers can be achieved to give optically active α-amino ketones. The first of such reports was described by Adam and co-workers, where copper(I) complexes of chiral Salen and BOX ligands were used as catalysts, with moderate ee's not exceeding 52% ee.[90] A few years later, Che and co-workers recorded greater success using the Ru(II) catalyst **37**, for the aziridination of limited examples of cyclic silyl enol ethers, with variable ee's of up to 97% (Scheme 16).[91]

Hashimoto and co-workers employed the dirhodium carboxylate catalysts **38a** and **38b** in combination with a more reactive iodinane reagent **39**, for the aziridination of a number of acyclic substrates (Table 30), including silyl ketene acetals (R^1 = OMe), with very high yields and ee's (entries 5 and 6).[92] The methodology has been applied successfully for the asymmetric synthesis of phenylglycine derivatives[93] and (−)-metazocine.[94]

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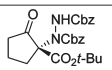
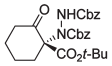
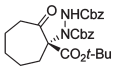
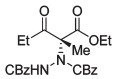
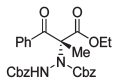
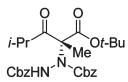
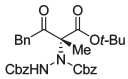
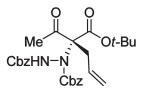
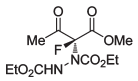
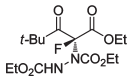
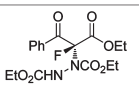
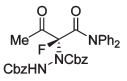
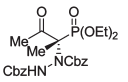
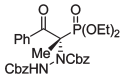
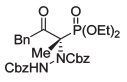
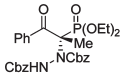
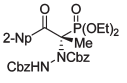
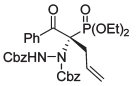
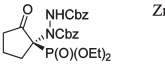
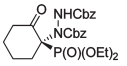
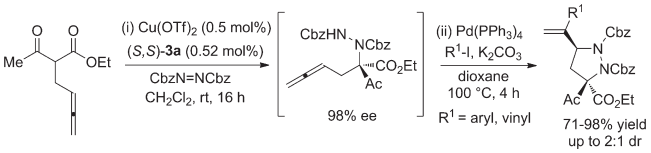
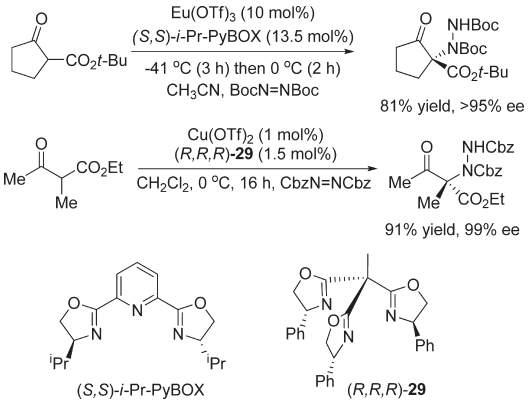
Table 23. Amination Reactions Catalyzed by Metal Complexes of the Bis(oxazoline) Ligand (*S,S*)-BOX

Entry	Product	Metal catalyst (mol%)	solvent	T (°C)	t (h)	Yield (%)	ee (%)	Ref
1		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	16	98	98	70
2		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	16	96	99	70
3		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	16	70	99	70
4		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	16	98	98	70
5		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	16	81	87	70
6		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	16	89	98	70
7		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	16	79	98	70
8		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	16	80	98	70
9		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	48	94	94	71
10		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	48	84	93	71
11		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	48	85	87	71
12		$Cu(OTf)_2$ (0.5)	CH_2Cl_2	rt	48	88	92	71
13		$Zn(OTf)_2$ (10)	CH_2Cl_2	rt	48	75	85	72
14		$Zn(OTf)_2$ (10)	CH_2Cl_2	rt	48	85	92	72
15		$Zn(OTf)_2$ (10)	CH_2Cl_2	rt	48	60	95	72
16		$Zn(OTf)_2$ (10)	CH_2Cl_2	rt	48	85	92	72
17		$Zn(OTf)_2$ (10)	CH_2Cl_2	rt	48	93	92	72
18		$Zn(OTf)_2$ (10)	CH_2Cl_2	rt	140	85	98	72
19		$Zn(OTf)_2$ (10)	CH_2Cl_2	rt	48	98	95	72
20		$Zn(OTf)_2$ (10)	CH_2Cl_2	rt	48	98	94	72

Scheme 12. One-Pot Amination-Cyclization Procedure for the Synthesis of Pyrazolidines



Scheme 13. Isolated Examples of α-Amination Reactions Catalyzed by Chiral Oxazoline Ligands



4.3. *N*-Nitroso Aldol Reactions

As previously discussed in section 3.3, the regioselectivity of the nitroso aldol reactions of tin enolates is highly dependent on the reaction conditions. Using a metal-to-ligand ratio of 2.5:1 and ethylene glycol as solvent, *N*-adducts were acquired with excellent yields and ee's (Table 31).[95]

To summarize, azodicarboxylates have been widely used as electrophiles in α-amination reactions, leading to hydrazine products often with excellent yields and ee's. This reaction has been extended to a wide range of carbonyl substrates, including oxindoles, whose lower acidity makes them more challenging substrates. In contrast, other sources of electrophilic nitrogen are much more limited; these include iodinanes and nitroso compounds, which have emerged in recent years.

5. SULFENYLATION REACTIONS

α-Sulfenylation received considerably less attention than other α-heterofunctionalization reactions. This is probably due to the inherent nucleophilicity of *S*-atoms, which can bind strongly to Lewis acidic metal centers (particularly late transition metals), thus inhibiting their catalytic activity. Employing

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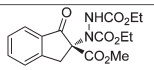
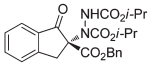
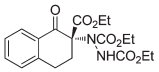
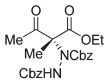
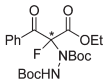
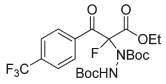
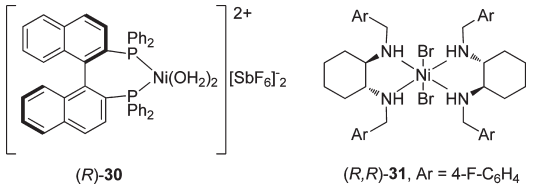
Table 24. Pd- and Ni-Catalyzed Amination of β-Ketoesters

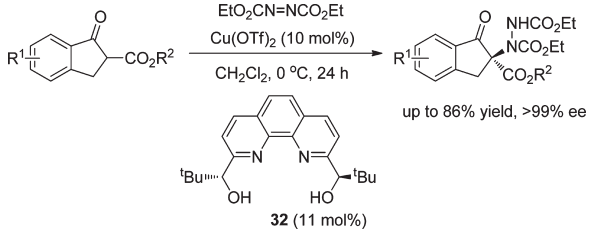
Entry	Product	Catalyst (mol%)	Time (h)	Yield (%)	ee (%)	Ref
1		**7a**·PF_6 (5)	0.5	94	99	77
2		**7a**·PF_6 (5)	0.5	99	94	77
3		**7a**·PF_6 (5)	1	73	93	77
4		**7a**·PF_6 (5)	9	93	93	77
5		**7a**·PF_6 (5)	1	75	91	77
6		**7a**·PF_6 (5)	62	57	95	78
7		**31** (5)	20	86	73	78
8		**31** (5)	26	81	74	78



(*R*)-**30** (*R,R*)-**31**, Ar = 4-F-C_6H_4

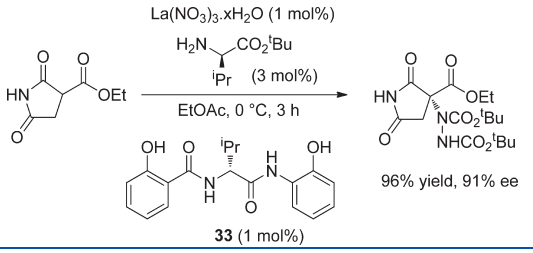
Figure 8. Ni complexes used as asymmetric amination catalysts.

Scheme 14. Asymmetric Amination with a Chiral Phenanthroline Ligand 32



Ti(TADDOLato) complex **3a** and the highly electrophilic reagent phthalamide *N*-sulfenyl chloride (**40**), phthalamide-protected thiol products (Z = phthalamide) were obtained with only moderate ee's (Table 32, entries 1−3).[96] Attributing the low enantioselectivities to the operation of a racemic uncatalyzed reaction, the less reactive electrophilic PhSCl was adopted as the *S*-electrophile.[97,98] Reaction times are considerably longer, but good results can be obtained for the sulfenylation of β-ketoesters and α-fluoro-β-ketoesters (Table 32, entries 4−8). The highest

Scheme 15. Amination of a Succinimide Derivative Using a Ternary Catalyst System



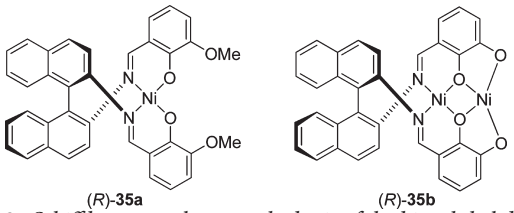
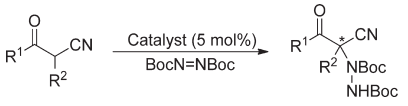
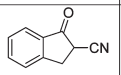
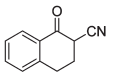


Figure 9. Schiff base complexes on the basis of the binaphthyl diamine backbone.

Table 25. Ni- and Pd-Catalyzed Amination of α-Cyanoketones



		Catalyst **31**[a]			Catalyst **7b**·BF_4[b]		
Entry	Substrate	Time (h)	Yield (%)	ee (%)	Time (h)	Yield (%)	ee (%)
1		0.5	91	81	0.17	95	92
2		0.5	92	83	0.17	95	95
3		1	93	73	0.17	95	85
4		3	85	75	2.5	90	83
5		12	84	78	20	87	86[c]

[a] Reactions were conducted in toluene at 0 °C. [b] Reactions were conducted in acetone at rt. [c] Reaction was conducted with catalyst **8b**·BF_4.

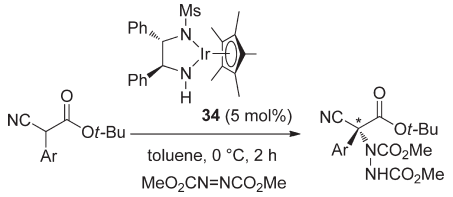
ee's were achieved with substrates containing bulky ester substituents (entries 4 vs 5).

The (*R,R*)-Ni−DBFOX complex was also applied to the sulfenylation of these substrates (Table 33).[99] Reactions of α-fluoro-β-ketoester substrates proceeded with higher yields using THF as solvent, while CH_2Cl_2 was optimal for the reaction of β-ketoesters.

6. CONCLUSION

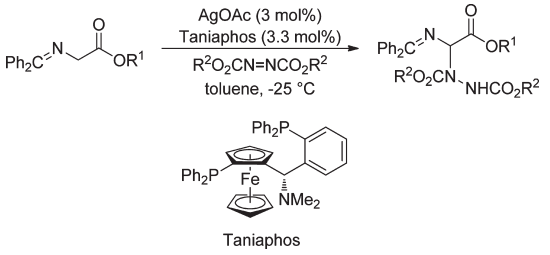
Metal-catalyzed electrophilic substitution at the α-carbon of a carbonyl compound by heteroatoms, particularly F, O, and N,

Table 26. Amination of α-Aryl-α-cyanoacetates



entry	Ar	R^1	yield (%)	ee (%)
1	Ph		99	95
2	4-MeO−C_6H_4		99	91
3	4-Cl−C_6H_4		99	95
4	4-Me−C_6H_4		99	96
5	2-thienyl		99	95

Table 27. Amination Reactions of Glycine-Derived Schiff Bases

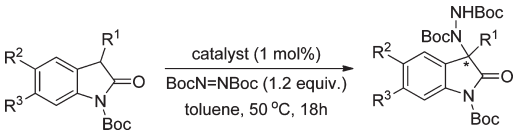


entry	R^1	R^2	yield (%)	ee (%)
1	Me	*t*-Bu	95	98
2	4-Br−$C_6H_4CH_2$	*t*-Bu	95	96
3	*t*-Bu	*t*-Bu	93	75
4	Me	*i*-Pr	98	92
5	Me	Bn	98	76

can be achieved with excellent yields and enantioselectivities. Related chlorination, bromination, and sulfenylation reactions have also been studied to a lesser extent, but the selectivities of these reactions are not yet at a synthetically useful level (ee's of >90% are rare). The majority of catalysts are Lewis acidic, which are particularly successful for the heterofunctionalization of certain β-functionalized carbonyl moieties, typically β-ketoesters, ketophosphonates, cyanoacetates, malonates, and Boc-protected oxindoles, which are able to form a chelate with the reactive metal center. Generally, Ni, Cu, and Zn complexes of bis(oxazolidine) ligands, diphosphine−palladium complexes, and Ti(TADDOLato) complexes also have a broad range of applicability across different substrates. Although other types of metal complexes have been found to display very good reactivities and selectivities, these tend to be restricted to a narrower range of substrates.

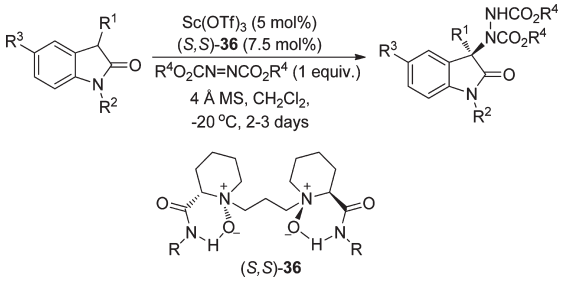
For the α-heterofunctionalization of less acidic carbonyl groups, such as aldehydes and ketones, preactivation of the α-carbon is necessary for metal catalysis and has so far been demonstrated via both enol ethers and metal (tin) enolates. This introduces an additional step to the synthesis, which is undesirable. In this regard, the emergence of proline-derived organocatalysts has enabled asymmetric α-heterofunctionalization of this type of substrate to be achieved in recent years, including

Table 28. α-Amination of Oxindoles Using Ni Catalysts



entry	R^1	R^2	R^3	catalyst	yield (%)	% ee (*R*/*S*)
1	Me	H	H	(*R*)-**35a**	99	94 (*S*)
2	Me	H	H	(*R*)-**35b**	99	99 (*R*)
3	allyl	H	H	(*R*)-**35a**	94	80 (*S*)
4	allyl	H	H	(*R*)-**35b**	99	97 (*R*)
5	(*E*)-cinnamyl	H	H	(*R*)-**35a**	95	92 (*S*)
6	(*E*)-cinnamyl	H	H	(*S*)-**35b**	86	91 (*R*)
7	Bn	H	H	(*R*)-**35a**	93	93 (*S*)
8	Bn	H	H	(*S*)-**35b**	93	99 (*R*)
9	Me	OMe	H	(*R*)-**35a**	96	98 (*S*)
10	Me	OMe	H	(*R*)-**35b**	91	94 (*R*)
11	Me	F	H	(*R*)-**35a**	91	87 (*S*)
12	Me	F	H	(*S*)-**35b**	95	96 (*R*)
13	CH_2CO_2Me	H	H	(*R*)-**35a**	96	91 (*S*)
14	CH_2CO_2Me	H	H	(*R*)-**35b**	98	96 (*R*)

Table 29. α-Amination of Oxindoles Using Sc Catalyst 36

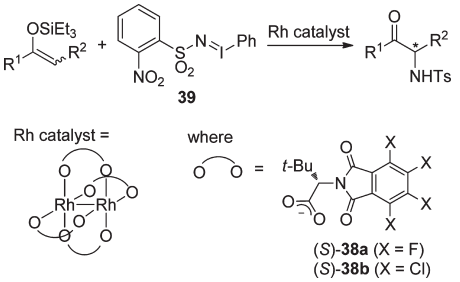


entry	R^1	R^2	R^3	R^4	yield (%)	% ee
1	Me	H	H	*i*Pr's	93	92
2	Me	H	H	Et	98	92
3	*n*-Pr	H	H	Et	78	98
4	*i*-Pr	H	H	Et	70	97
5	Bn	H	H	Et	91	98
6	2-$MeC_6H_4CH_2$	H	H	Et	81	98
7	4-$MeOC_6H_4CH_2$	H	H	Et	85	98
8	2-$ClC_6H_4CH_2$	H	H	Et	86	98
9	2,4-$Cl_2C_6H_3CH_2$	H	H	Et	94	97
10	1-$NpCH_2$	H	H	Et	80	98
11	2-$NpCH_2$	H	H	Et	80	98
12	2-thienylmethyl	H	H	Et	83	98
13	Ph	H	H	Et	85	93
14	Bn	Me	H	Et	85	95
15	Bn	Bn	H	Et	80	83

fluorination, amination, and oxygenation.[100−102] Thus, current methods in metal catalysts and organocatalysts are complementary with respect to their substrate scope in α-heterofunctionalization reactions.[7,100,103]

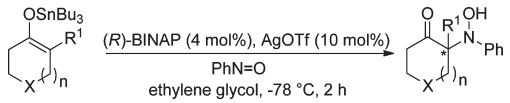
dx.doi.org/10.1021/cr100197z |*Chem. Rev.* 2011, 111, 1637–1656

Table 30. Rh-Catalyzed Aziridination of Silyl Enol Ethers and Silyl Ketene Acetals



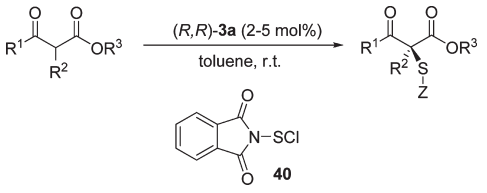
entry	R^1	R^2	catalyst (mol %)	T (°C)	t (h)	yield (%)	ee (%)
1	Me	Ph	(*S*)-**38a** (3)	−40	5	94	95
2	Me	Bn	(*S*)-**38a** (3)	−40	5	94	95
3	Ph	Me	(*S*)-**38a** (3)	−40	5−7	97	93
4	4-MeO-C_6H_4	Me	(*S*)-**38a** (3)	−40	5−7	98	95
5	OMe	Ph	(*S*)-**38b** (1)	rt	3	98	99
6	OMe	4-CF_3−C_6H_4	(*S*)-**38b** (1)	rt	3	95	97

Table 31. *N*-Nitroso Aldol Reactions of Sn Enolates



entry	R	X	n	*N*-/*O*- ratio	yield (%)	ee (%)
1	H	CH_2	0	97/3	90	86
2	H	CH_2	1	96/4	95	>99
3	H	CH_2	2	>99/1	96	97
4	Ph	CH_2	1	>99/1	94	77
5	H	CMe_2	1	>99/1	97	98

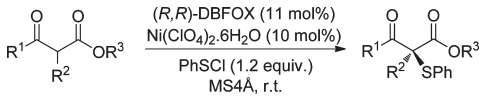
Table 32. Sulfenylation Reactions Catalyzed by 3a



entry	R^1	R^2	R^3	electrophile	t (h)	yield (%)	ee (%)
1	Me	Me	Bn	**40**	0.5	94	42
2	Ph	Me	Et	**40**	0.5	97	35
3		$(CH_2)_4$	Et	**40**	0.75	94	60
4	Me	Me	*t*-Bu	PhSCl	12	86	88
5	Me	Me	CMe_2(*i*-Pr)	PhSCl	14	82	97
6	Et	Me	*t*-Bu	PhSCl	12	80	87
7	Ph	Me	CMe_2Et	PhSCl	14	75	86
8	Me	F	CMe_2Et	PhSCl	14	60	89

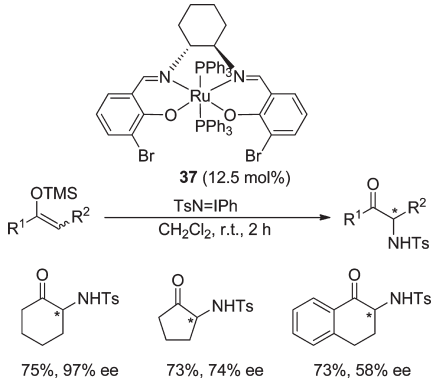
Overall, reactions that generate a quaternary stereogenic center are much more successful than the creation of tertiary

Table 33. Ni-Catalyzed Asymmetric Sulfenylation Reactions



entry	R^1	R^2	R^3	solvent	t (h)	yield (%)	ee (%)
1	Ph	F	*t*-Bu	THF	17	80	93
2	Me	F	*t*-Bu	THF	18	70	86
3	Et	F	*t*-Bu	THF	17	80	87
4	Me	Me	*t*-Bu	CH_2Cl_2	17	76	88
5	Et	Me	*t*-Bu	CH_2Cl_2	17	43	88
6		$(CH_2)_3$	*t*-Bu	CH_2Cl_2	30	61	59

Scheme 16. Ru-Catalyzed Aziridination of Silyl Enol Ethers



stereogenic centers. This is unsurprising, given that the substitution of a methylene group by a heteroatom will invariably lead to a product containing a CHX moiety that is more acidic than the precursor. Thus, competitive product racemization will be difficult to suppress. Another important limitation in the development of this subject area is the availability of electrophilic

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heteroatoms that are compatible with metal catalysts. Currently, these reagents are of comparatively high molecular weights (with respect to the heteroatom developed), which generates a stoichiometric amount of byproduct. Very often, extra functional group transformations are required, e.g., reduction of N−N and N−O bonds to the requisite amino or hydroxyl functionalities. Thus, one of the future challenges is to identify synthetically useful electrophiles that can be employed under catalytic conditions, to deliver optically active products with better atom- and step-economy.

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BIOGRAPHIES

Alex Smith was born in 1981 in Watford and grew up in St Albans, U.K. He graduated with an M.Sci. degree in Chemistry from Nottingham University in 2004. This was followed by a brief spell working as a medicinal chemist at Cancer Research Technology, London, before he embarked on his Ph.D. work at Imperial College in 2006, supervised by Dr. Mimi Hii, supported by an EPSRC studentship that was cosponsored by Pfizer. His research work involved the development of a new Pd-catalyzed methodology for the asymmetric hydroxylation of β-ketoesters using Pd catalysis. Having submitted his Ph.D. thesis in the summer of 2010, he is currently employed as a research scientist, working at Eli Lilly, U.K.

King Kuok (Mimi) Hii was born in Sarawak, Malaysia, in 1969. She graduated with First Class Honours with a B.Sc. degree from the University of Leeds, followed by a Ph.D. degree, for research performed under the supervision of Prof. Bernard L. Shaw, FRS. During her postdoctoral work at Oxford University with Dr. John M. Brown, FRS, she was awarded a Keeley Junior Research Fellowship by Wadham College. The award of a Ramsay Memorial Fellowship in 1997, cosponsored by ICI Strategic Funding, enabled her to initiate independent research back at Leeds, before the appointment to a lectureship at King's College London. She moved to a Senior Lectureship at Imperial College in 2003, where she was promoted to a Readership in Catalysis (2009). Her research interests are mainly in the area of homogeneous catalysis. In recent years, she has also initiated several projects with chemical engineering colleagues, on the development of sustainable catalytic processes for organic synthesis.

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