CHEMICAL REVIEWS

REVIEW

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Use of Nonfunctionalized Enamides and Enecarbamates in Asymmetric Synthesis

Kovuru Gopalaiah[†,‡] and Henri B. Kagan*[,‡]

[†]Department of Chemistry, University of Delhi, Delhi 110007, India

[‡]Institut de Chimie Moléculaire et des Matériaux d'Orsay (UMR 8182, CNRS), Laboratoire de Catalyse Moléculaire, Université Paris-Sud, 91405 Orsay, France

CONTENTS

1. INTRODUCTION

Enamine chemistry, pioneered by Stork in the 1950s, is very useful in synthesis.[1] Enamines **1** (Scheme 1) are nitrogen analogues of enols. The C_β position has nucleophilic properties and is prone to electrophilic attacks. For example, pyrrolidine enamine **4**, easily prepared from cyclohexanone and pyrrolidine, provided 2-methyl cyclohexanone **5** in high yield after hydrolysis. As opposed to the result from base-promoted methylation, only monosubstitution occurred using enamine alkylation. Enamides **2** are usually quite stable (with respect to enamines) and for a long time were not useful in synthesis. We had the opportunity to investigate the chemistry of enamides in the 1960s and subsequently published a short review on this class of compounds.[2] In 1972, we screened enamides in asymmetric hydrogenation as precursors of chiral amides and amines.[3] The relatively high enantiomeric excess observed with rhodium/DIOP catalysts made it reasonable to propose a mechanistic picture for the asymmetric hydrogenation of *N*-acyl dehydroamino acids where the chelation by the carbonyl of the acyl group was a key factor.[4] The hydrogenation of an enecarbamate **3** (R^1 = Et, R^2 = R^4 = R^5 = H, R^3 = Ph) was also briefly investigated.[5] In 1996, Burk successfully applied rhodium/DuPhos catalysts for the asymmetric hydrogenation of enamides.[6] There was subsequently a renewal of interest in the use of enamides as prochiral substrates in asymmetric hydrogenation. Enamides and enecarbamates were also used as substrates in other types of asymmetric catalytic reactions, for example, in various C–C bond formation processes. The present review is intended to cover most of the asymmetric reactions (catalytic) where enamides **2** and enecarbamates **3** are the key components. We will consider only structural units **2** and **3** that carry functional groups, which means that α- or β-dehydroamino acid derivatives are outside of the scope of the review. Catalytic enantioselective hydrogenations of enamides are detailed in section 2 of this review, and the nucleophilic addition reactions of enamides and enecarbamates are described in section 3. Then in sections 4–17, the numerous recently discovered stereoselective reactions that are promising in the area of asymmetric synthesis of nitrogen compounds are covered. The present review is mostly devoted to asymmetric catalysis, but stoichiometric synthesis

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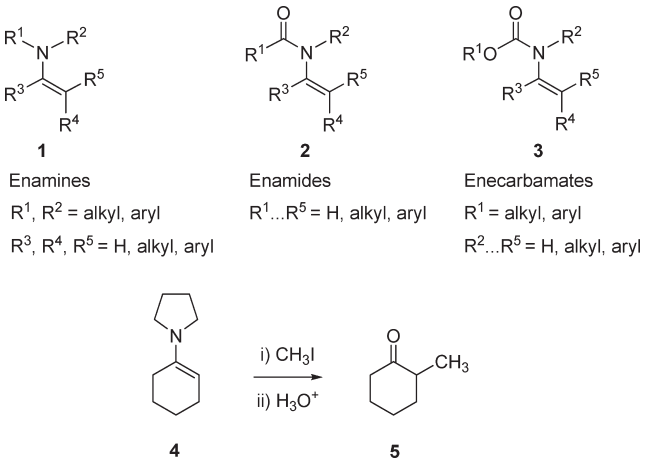
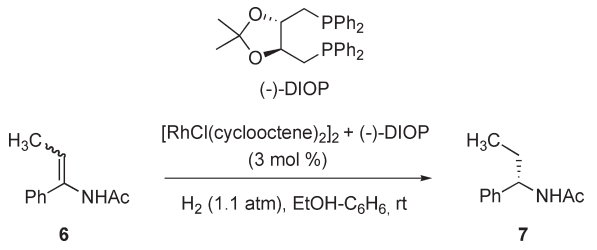
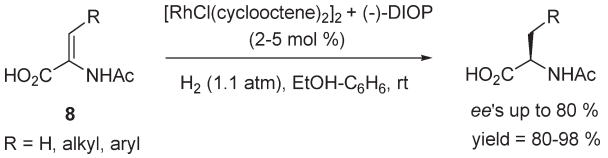
Scheme 1



Scheme 2



Scheme 3



are also included when the chiral auxiliary is not retained in the product or is potentially removable.

2. HYDROGENATION REACTIONS

2.1. Rhodium Catalysts

Chiral rhodium catalysts played a prominent role early in the development of asymmetric catalysis.[7] Asymmetric hydrogenation or asymmetric hydroformylation of C=C double bonds or asymmetric hydrosilylation of ketones or imines gave encouraging results in the early 1970s. Early results obtained in the asymmetric hydrogenation of enamides and enecarbamates, as well as more recent developments, are described in this section.

2.1.1. Chiral Bidentate or Multidentate Phosphorus Ligands. Asymmetric hydrogenation for a nonfunctionalized enamide was first studied using a DIOP/Rh(I) catalytic system[3] in our laboratory after the discovery of the enantioselective reduction of *N*-acyldehydroamino acid derivatives catalyzed by some rhodium complexes of chiral diphosphines.[8]

Scheme 4

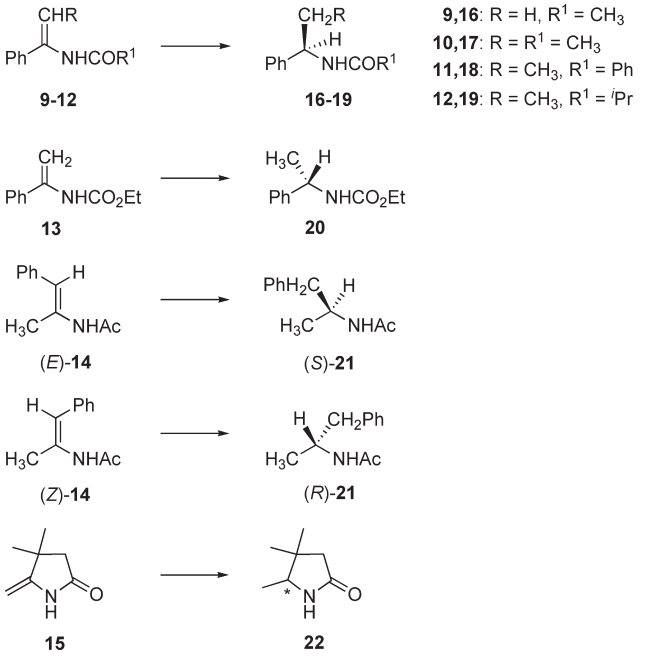


Table 1. (+)-DIOP/Rh Catalyzed Asymmetric Hydrogenation of Enamides 9−15[5]

enamide	[enamide]/[Rh][a]	product	conversion (%)	ee % (config)
9	50	**16**	100	45 (*R*)
10	50	**17**	100	83 (*R*)
11	25	**18**	≥95	73 ± 3 (*R*)
12	25	**19**	100	85 ± 4(*R*)
13	25	**20**	90	14.2 ± 0.4 (*S*)
(*E*)-**14**	25	**21**	93	15 (*S*)
(*Z*)-**14**	25	**21**	94	1.1 (*R*)
15	50	**22**	100	10[b]

[a] [Rh] = 4 mol %; DIOP/[Rh] = 1.1:1; C_6H_6/EtOH = 1:2. [b] Configuration not determined.

Hydrogenation of α-phenyl enamide **6** with (−)-DIOP/Rh catalyst in the presence of a hydrogen atmosphere gave (*S*)-*N*-acetyl α-phenylpropylamine (**7**) in 95% yield with 78% ee (Scheme 2).[3] This result was used as an argument to support the proposition that the good enantioselectivity of reduction of dehydroamino acids **8** was in part due to the presence of the NHAc function, which should chelate on the rhodium atom (Scheme 3). This chelation effect was later proven by other research groups.

We further studied the hydrogenation of the carbon−carbon double bond in a variety of enamides (**9**−**15**) (Scheme 4) with (+)-DIOP/Rh catalyst in ethanol−benzene mixture.[5] Low to moderate enantioselectivities were obtained for the amine derivatives **16**−**22** (Table 1). The solvent effect in the hydrogenation of enamide **9** was probed. In ethanol, the ee of the product was 42% with *R* configuration, whereas in pure benzene the ee of the product was 44% with *S* configuration. It was postulated that the cationic rhodium complex **23** (Figure 1) was the reactive species if the solvent is ethanol. For benzene solvent, a neutral rhodium complex was anticipated.

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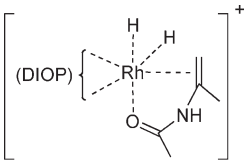

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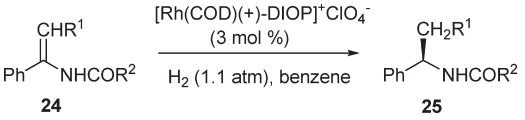
Figure 1. Proposed intermediate in the enamide hydrogenation catalyzed by a cationic rhodium complex.

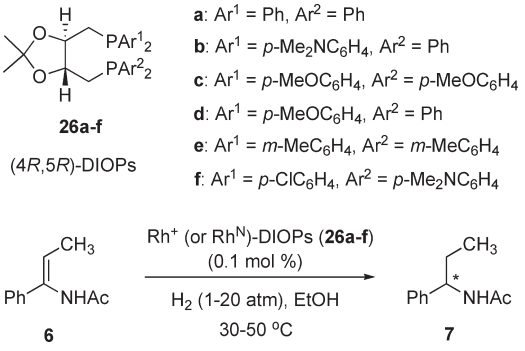
Table 2. [Rh(COD)(+)-DIOP]$^+$ClO$_4^-$ Catalyzed Hydrogenation of 24[9]



24 25

R^1	R^2	[enamide]/[Rh]	ee %
H	CH_3	100	68
CH_3	CH_3	100	92
CH_3	$CH(CH_3)_2$	50	90
C_2H_5	CH_3	50	90
C_6H_{11}	CH_3	50	82

Scheme 5



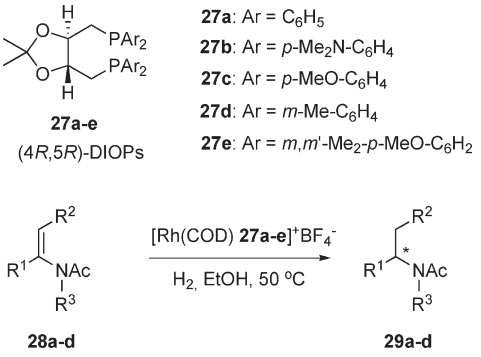
We disclosed in 1976 the screening of various neutral and cationic rhodium complexes for enamide **24** (R^1 = H, R^2 = CH_3) (Table 2) in both ethanol and benzene separately. The cationic complex [Rh(COD)(+)-DIOP]$^+$ClO$_4^-$ was more enantioselective in benzene.[9] The scope of this catalyst was explored for the enamides **24** (Table 2). It gave ee's up to 92% with quantitative conversion.

During 1992−1995, Achiwa et al. reported a series of results pertaining to the catalytic enantioselective hydrogenation of enamides.[10−12] They first studied the steric and electronic influences of the diarylphosphino groups of modified DIOPs on the enantioselectivity as well as the catalytic activity in the hydrogenation of enamide **6** (Scheme 5).[10] Reactions were performed in the presence of cationic (Rh^+) or neutral (Rh^N) rhodium complexes of (4*R*,5*R*)-DIOP (**26a**) and modified (4*R*,5*R*)-DIOPs (**26b**−**f**) bearing various substituents on the phenyl groups (Table 3). It was found that the cationic rhodium(I) complex of *p*-methoxy-substituted

Table 3. Asymmetric Hydrogenation of Enamide 6 Using Rh/26a−f Catalysts

entry	ligand	Rh	conversion (%)	ee (%)
1	**26a**	Rh^+	30	60
2		Rh^N	87	39
3	**26b**	Rh^+	89	50
4	**26c**	Rh^+	100	71
5		Rh^N	100	66
6	**26d**	Rh^+	73	72
7		Rh^N	65	47
8	**26e**	Rh^+	83	49
9	**26f**	Rh^+	40	41
10		Rh^N	79	43

Scheme 6



28,29	R^1	R^2	R^3
a	Ph	Me	H
b	Ph	H	Ph
c	*p*-$MeOC_6H_4$	H	Ph
d	*p*-$NO_2C_6H_4$	H	Ph

DIOP (**26c**) is the most efficient catalyst for the hydrogenation of enamide **6**.

The effect of the substituents of DIOPs (**27a**−**e**) on the enantioselectivity in the hydrogenation of α-aryl-substituted enamides **28a**−**d** using rhodium(I) complexes as catalysts was investigated (Scheme 6, Table 4).[11] Hydrogenation of **28b** with rhodium(I) complexes of **27a** and **27c** gave (*S*)-product **29b** in moderate ee's (Table 4, entries 6, 8), but the enantioselectivities with **27b** and **27d** were quite low (Table 4, entries 7, 9). Significantly, the rhodium(I) complex of **27e** showed a reversal of chirality affording (*R*)-product **29b** in high ee (Table 4, entry 10). The asymmetric hydrogenation of other enamides **28c**,**d** gave similar results.

The catalytic asymmetric hydrogenation of a cyclic enamide **30** affording the optically active *N*-acetylsalsolidine (**31**) (Scheme 7, Table 5) was studied using a variety of bisphosphine−rhodium(I) complexes.[12] A good enantioselectivity (80% ee) was accomplished with a new chiral bisphosphine ligand, MOCBP (**32**), synthesized by the same group.

RajanBabu et al. investigated the effect of substituent changes in the ligand backbone and the chelating phosphorus atoms of

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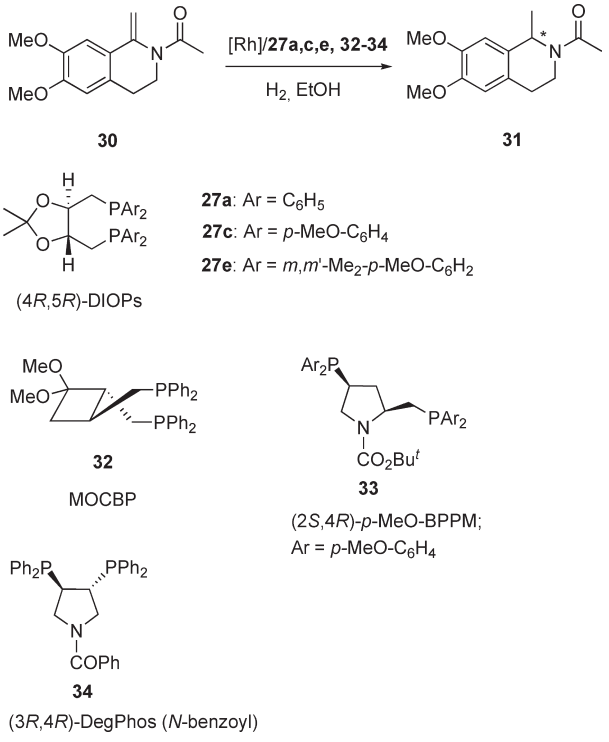
Table 4. Asymmetric Hydrogenation of Enamides 28a−d Catalyzed by Rh(I) Complexes of DIOPs (27a−e)

entry	enamide	ligand	substrate/catalyst	H_2 (atm)	time (h)	conversion (%)	ee % (config)
1	**28a**	**27a**	1000	5	4	30	60.0 (*S*)
2		**27b**	1000	5	4	100	24.0 (*S*)
3		**27c**	1000	5	4	100	71.0 (*S*)
4		**27d**	1000	5	4	83	49.0 (*S*)
5		**27e**	1000	5	4	90	9.0 (*R*)
6	**28b**	**27a**	200	1	20	100	59.5 (*S*)
7		**27b**	200	1	20	100	4.4 (*R*)
8		**27c**	200	1	20	100	42.4 (*S*)
9		**27d**	200	1	20	100	0.8 (*S*)
10		**27e**	200	1	20	100	76.7 (*R*)
11	**28c**	**27a**	200	1	20	100	60.7 (*S*)
12		**27c**	200	1	20	100	51.2 (*S*)
13		**27e**	200	1	20	100	53.5 (*R*)
14	**28d**	**27c**	200	1	20	100	28.4 (*S*)
15		**27e**	200	1	20	100	74.7 (*R*)

Scheme 7



the DIOP ligand on the enantioselectivity of Rh-catalyzed enamide hydrogenations.[13] Reactions were performed with the precatalysts prepared from various DIOP derivatives and analogues (Figure 2) for enamides **43** (Table 6). The electron-rich ligand systems **38**, **41**, and **42** gave quantitative yield and excellent selectivities, whereas **35** and the electron-deficient ligand **40** produced near-racemic products. A plausible explanation for the low selectivity of **35** compared with that of **27a** or **38** was proposed on the basis of the ground-state conformation of the rhodium−ligand complex (Figure 3). The methyl groups in **38** are in a quasiequatorial orientation and reinforce *one* stable ground-state conformation

Table 5. Asymmetric Hydrogenation of Enamide 30 Catalyzed by Bisphosphine/Rh(I) Complexes

ligand	Rh	substrate/catalyst	H_2 (atm)	conversion (%)	ee % (config)
27a	$Rh^+(COD)BF_4^-$	1000	5	72	40.5 (*S*)
27c	$Rh^+(COD)BF_4^-$	200	1	100	62.4 (*S*)
27e	$Rh^+(COD)BF_4^-$	200	1	100	29.1 (*S*)
32	$Rh^+(COD)BF_4^-$	200	1	100	80.6 (*R*)
	$Rh^+(COD)BF_4^-$	500	1	100	80.6 (*R*)
33	$Rh^+(NBD)ClO_4^-$	200	1	100	25.6 (*S*)
34	$Rh^+(NBD)ClO_4^-$	200	1	98	46.2 (*R*)

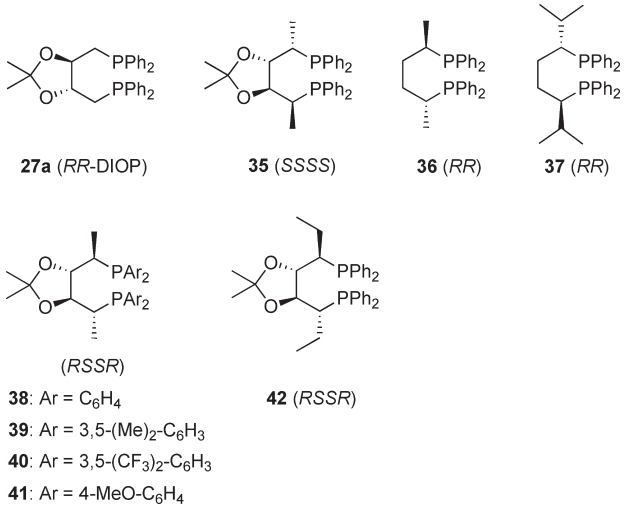


Figure 2. Some DIOP derivatives and analogues used for the enamide hydrogenations.

for the corresponding precatalyst. In **35**, the quasiaxial orientation of the two methyl groups destabilizes this conformation, resulting in the formation of a mixture of other conformers.

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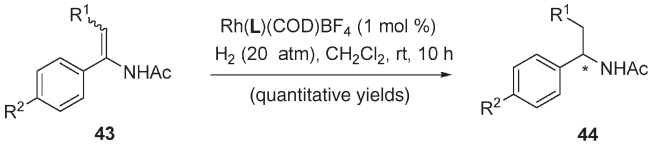
Table 6. Hydrogenation of Enamides 43 Using DIOP Analogues



		amides **44** (ee % (config))			
entry	ligand **L**	$R^1 = R^2 = H$	$R^1 = H$, $R^2 = Me$	$R^1 = H$, $R^2 = F$	$R^1 = Me$, $R^2 = H$
1	**27a**	53 (*S*)	68 (*S*)	71 (*S*)	92 (*S*)
2	**36**	91 (*R*)	93 (*R*)	97 (*R*)	96 (*R*)
3	**37**	95 (*S*)	93 (*S*)	94 (*S*)	77 (*S*)
4	**38**[a]	98 (*R*)	99 (*R*)	98 (*R*)	96 (*R*)
5	**39**	82 (*R*)	81 (*R*)	88 (*R*)	76 (*R*)
6	**41**	97 (*R*)	98 (*R*)	96 (*R*)	98 (*R*)
7	**42**	99 (*R*)	99 (*R*)	99 (*R*)	98 (*R*)

[a] SbF_6 and PF_6 ions also gave comparable ee's.

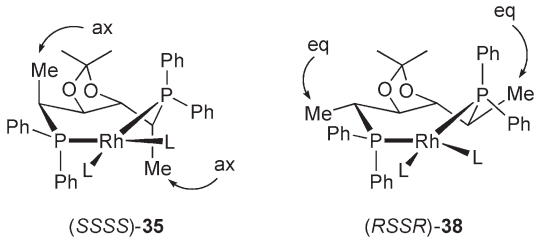
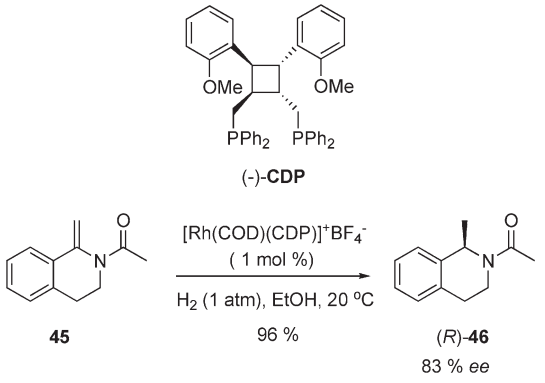


Figure 3. Effect of the α-substitution in (*SS*)-DIOP ligands.

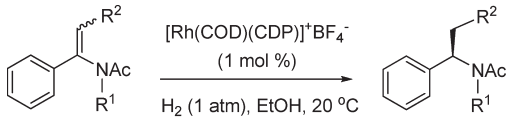
Scheme 8



A novel enantiopure bisphosphine ligand, (−)-CDP (Scheme 8), which is structurally related to MOCBP (**32**), was employed in the rhodium-catalyzed asymmetric hydrogenation of aryl enamides.[14] Reaction conditions were optimized with a cyclic enamide **45** using CDP/Rh catalyst to provide **46** in high enantioselectivity and yield. The generality of the CDP/Rh catalyst was studied for the hydrogenation of a variety of acyclic aryl enamides **47** (Table 7). The corresponding amides **48** were obtained in good to excellent yields with good enantioselectivity.

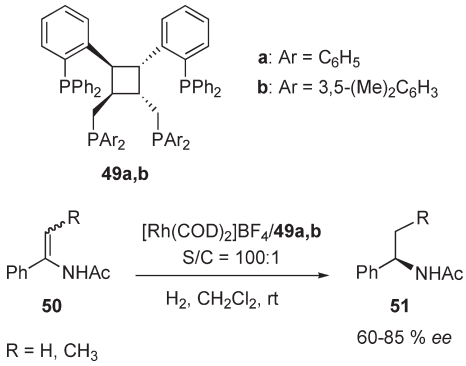
Ding et al. developed the novel C_2-symmetric tetraphosphine ligands **49a,b** for Rh-catalyzed asymmetric hydrogenation of α-aryl enamides **50** (Scheme 9).[15] These catalysts gave the amides **51** with excellent conversion (>99%) and moderate enantioselectivities.

Table 7. (−)-CDP/Rh-Catalyzed Asymmetric Hydrogenation of Enamides 47



R^1	R^2	time (h)	yield (%)	ee %
H	H	1	93	76
Ac	H	2	98	93
Bn	H	24	64	93
H	Me	1	99	92

Scheme 9



We explored the asymmetric hydrogenation of enamides **50a,b** with two novel chiral 1,2-diphosphines, namely, phellanphos (**52**) and nopaphos (**53**), as ligands in the cationic rhodium complexes $[Rh(COD)\mathbf{52}]^+PF_6^-$ and $[Rh(COD)\mathbf{53}]^+PF_6^-$, respectively (Scheme 10).[16]

The chiral ferrocene-based 1,3-bis(phosphanes) **54a−d**, which have planar chirality, were used as ligands in rhodium complexes of $[Rh(COD)\mathbf{54a-d}]X$ (where X = BF_4 or PF_6) for

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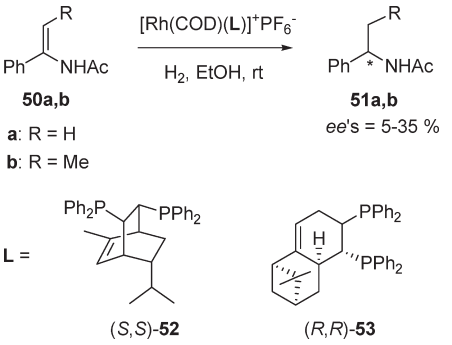
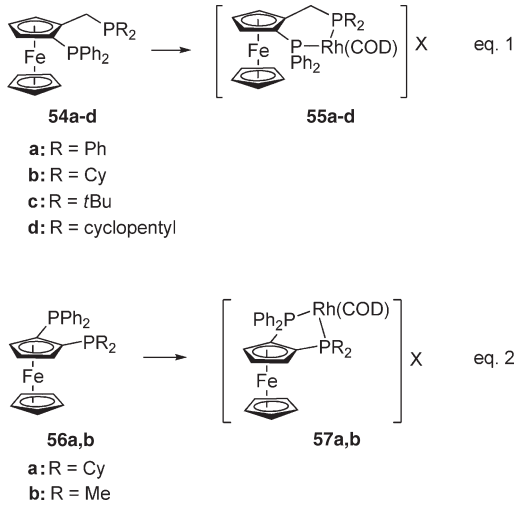
the hydrogenation of enamides **58** and **59** (Scheme 11, eq 1; Table 8).[17] The cationic complexes **55a**−**d** catalyzed the hydrogenation efficiently with 1 mol % of catalyst in methanol at atmospheric pressure and provided amides with up to 94% ee. Furthermore, the rhodium complexes of 1,2-bis(phosphanes) **56a,b** were employed in the hydrogenation of **58** and **59** (Scheme 11, eq 2).[18] Moderate enantioselectivities were obtained for the corresponding hydrogenated products.

The ferrocene-based 1,5-diphosphine ligands **60** and **61**, which bear a methoxy substituent at the α position, were investigated by

Scheme 10



Scheme 11



Scheme 12

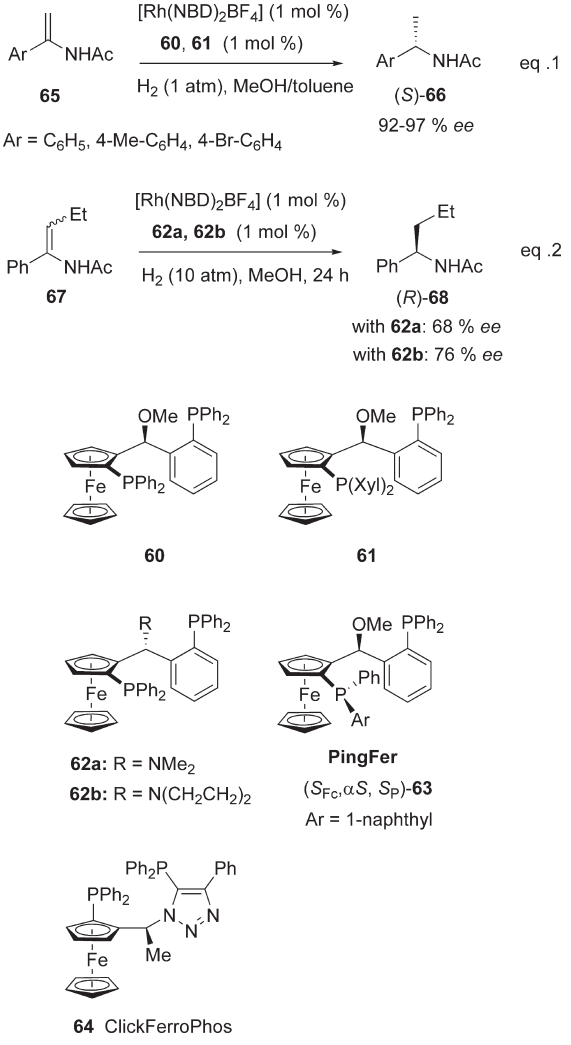
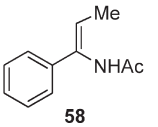
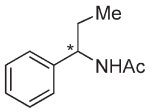
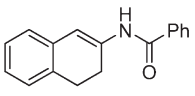
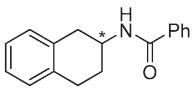


Table 8. Asymmetric Hydrogenation of Enamides 58 and 59 Catalyzed by Rhodium Complexes of 54a−d

Enamide	Bis(phosphane)[a]	H_2 (atm)	Product	Yield (%)	*ee* % (Config)
 **58**	**54a**	20		99	65 (*R*)
	54b	1		98	94 (*R*)
	54d[b]	10		95	82 (*S*)
 **59**	**54a**	20		95	26 (*S*)
	54b	5		93	36[c]
	54c	5		93	30[c]

[a] The rhodium catalyst was [Rh(COD)**54a**−**c**]BF_4. [b] [Rh(COD)**54d**]PF_6. [c] Configuration not determined.

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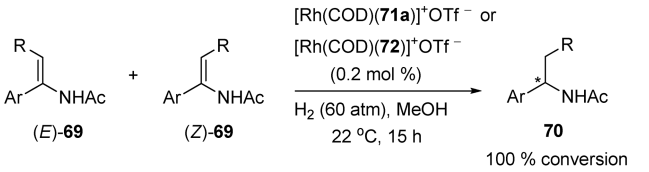
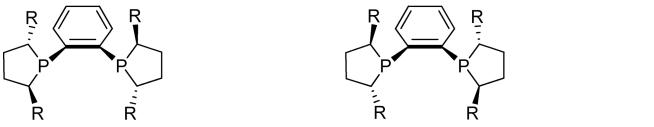
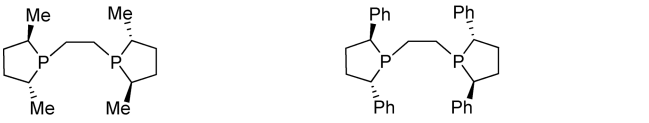
Knochel and co-workers as ligands for the Rh-catalyzed asymmetric hydrogenation of α-aryl enamides **65** (Scheme 12, eq 1).[19] These gave very high enantioselectivities for the amine derivatives **66**. Moderate enantioselectivities in the hydrogenation of **67** were obtained with the Rh catalysts of **62a,b** possessing an amino

Scheme 13





(*S*,*S*)-**71a**: (*S*,*S*)-Me-DuPhos, R = Me
(*S*,*S*)-**71b**: (*S*,*S*)-Et-DuPhos, R = Et
(*R*,*R*)-**71a**: (*R*,*R*)-Me-DuPhos, R = Me
(*R*,*R*)-**71b**: (*R*,*R*)-Et-DuPhos, R = Et

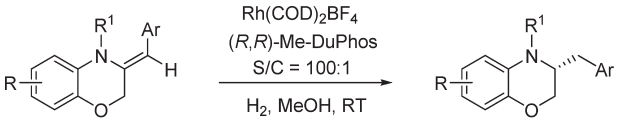


(*R*,*R*)-**72**: (*R*,*R*)-Me-BPE
(*R*,*R*)-**73**: (*R*,*R*)-Ph-BPE

Table 9. Rh-Catalyzed Asymmetric Hydrogenation of α-Aryl Enamides 69 (R = H)

Ar (**69**)	ligand	ee % (config)
C_6H_5	(*R*,*R*)-Me-BPE	95.2 (*R*)
p-CH_3-C_6H_4	(*R*,*R*)-Me-BPE	96.5 (*R*)
p-CF_3-C_6H_4	(*S*,*S*)-Me-DuPhos	95.6 (*S*)
p-CH_3O-C_6H_4	(*R*,*R*)-Me-BPE	95.3 (*R*)
p-F-C_6H_4	(*R*,*R*)-Me-BPE	95.0 (*R*)
p-MeS-C_6H_4	(*R*,*R*)-Me-BPE	96.3 (*R*)
m-Br-C_6H_4	(*S*,*S*)-Me-DuPhos	96.8 (*S*)
m-CH_3-C_6H_4	(*S*,*S*)-Me-DuPhos	94.9 (*S*)
o-F-C_6H_4	(*R*,*R*)-Me-BPE	95.7 (*R*)
2,6-$F_2C_6H_3$	(*R*,*R*)-Me-BPE	97.8 (*R*)
3,4,5-$(MeO)_3C_6H_2$	(*S*,*S*)-Me-DuPhos	95.6 (*S*)
2-naphthyl	(*S*,*S*)-Me-DuPhos	95.6 (*S*)
2-furanyl	(*S*,*S*)-Me-DuPhos	96.1 (*S*)
2-thienyl	(*S*,*S*)-Me-DuPhos	97.5 (*S*)

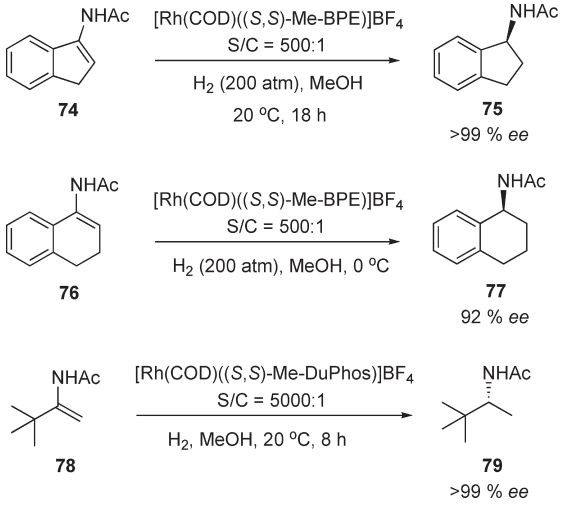
Table 10. (*R*,*R*)-Me-DuPhos/Rh-Catalyzed Asymmetric Hydrogenation of 80



80 **81**

entry	R	Ar	R^1	ee %
1	H	Ph	Ac	97.2
2	6-Me	Ph	Ac	98.0
3	6-MeO	Ph	Ac	97.2
4	6-Cl	Ph	Ac	98.2
5	7-Me	Ph	Ac	97.2
6	H	*p*-$MeOC_6H_4$	Ac	98.6
7	H	2-$MeOC_6H_4$	Ac	96.4
8	H	*p*-MeC_6H_4	Ac	98.2
9	H	2-MeC_6H_4	Ac	90.6
10	H	1-naphthyl	Ac	92.2
11	H	Ph	Bz	90.5

Scheme 14



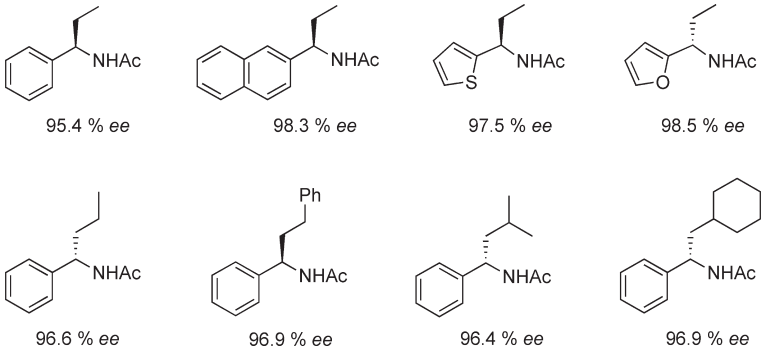


Figure 4. Catalytic asymmetric synthesis of α-arylalkylamine derivatives: (*R*)- and (*S*)-amines derived from (*R*,*R*)-Me-BPE/Rh and (*S*,*S*)-Me-DuPhos/Rh catalysts, respectively.

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 15

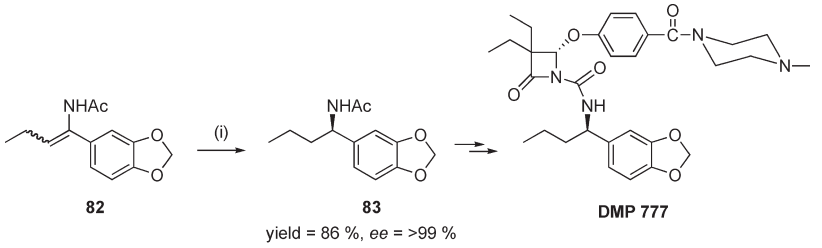
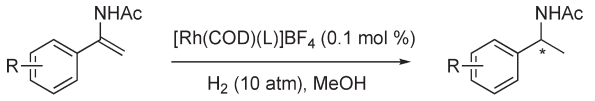


Table 11. Asymmetric Hydrogenation of α-Aryl Enamides 84



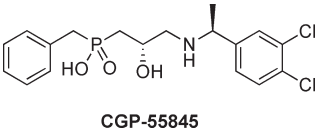
84 85

entry	R	ligand, L	temp (°C)	conv. (%)	ee % (config)
1	3,4-Cl_2	(*S*,*S*)-Et-DuPhos	40	>98	98 (*S*)
2	3-CO_2Me	(*S*,*S*)-Ph-BPE	40	>98	98 (*R*)
3	4-COMe	(*S*,*S*)-Et-DuPhos	30	>98	97 (*S*)
4	4-Cl	(*S*,*S*)-Ph-BPE	40	>98	99 (*R*)
5	4-CN	(*S*,*S*)-Ph-BPE	40	>98	99 (*R*)
6	2-Cl	(*S*,*S*)-Et-BPE	40	86	85 (*S*)

substituent at the α position (Scheme 12, eq 2).[20] The introduction of *P*-chirality in ligand **60** enhances the enantioselective discrimination of the catalyst when synergistic matching of the planar chirality is operating.[21] For example, hydrogenation of enamide **65** (Ar = C_6H_5) to the corresponding amine derivative **66** using the Rh catalyst derived from $Rh(COD)_2BF_4$ and *P*-chiral 1,5-diphosphanylferrocene ligand **63** produced 96% ee, while the Rh catalyst of $Rh(COD)_2BF_4$/**60** gave 86% ee. Recently, Fukuzawa and co-workers developed ClickFerrophos (**64**) for the Rh-catalyzed hydrogenation of enamide **65** (Ar = C_6H_5) (Scheme 12).[22] This gave **66** (Ar = C_6H_5) in 84% ee and 99% yield.

In 1996, Burk et al. used the rigid strongly electron-donating bis(phospholane) DuPhos **71** and BPE **72** ligands for the rhodium catalyzed hydrogenation of α-aryl enamides **69** (R = H) (Scheme 13).[6] This led to the amine products **70** (R = H) with very high enantioselectivities (≥90% ee). The general utility of DuPhos/Rh and BPE/Rh catalysts was thoroughly illustrated by the production of an array of amine derivatives **70** (R = H) (Table 9). An important feature of this system is the ability of these catalysts to hydrogenate mixtures of (*E*)- and (*Z*)-enamides with high enantioselectivities and thus obviate the need to prepare isomerically pure substrates.

The scope of Me-DuPhos/Rh and Me-BPE/Rh catalysts was further expanded to the hydrogenation of various α-aryl enamides possessing *β*-substituents (i.e., **69**, R ≠ H). This gave the corresponding amine derivatives with high enantioselectivities (≥95% ee) (Figure 4). Also, the cyclic enamides **74** and **76** were hydrogenated with BPE/Rh catalyst to the amine derivatives **75** and **77**, respectively, with excellent enantioselectivity (Scheme 14).[23] Interestingly, hydrogenation of enamide **78**, which is derived from a dialkyl ketone, with (*S*,*S*)-Me-DuPhos/Rh catalyst yielded product **79** (Scheme 14) with stereochemistry opposite to that of the (*S*)-phenylethyl amine **70** arrived from the hydrogenation of α-arylenamide **69** (Ar = Ph, R = H). Burk,[24] Gridnev et al.,[25] and Landis et al.[26] have independently studied the origin of this opposite stereoselection. After Burk's discovery of the Me-BPE ligand, a similar class of ligand, Ph-BPE (**73**), was synthesized by Pilkington et al.[27] The Rh-catalyst of **73** was employed in the hydrogenation of **69** (Ar = Ph, R = H) and led to the corresponding amine derivative **70** in 99% ee with 100% conversion.



CGP-55845

Figure 5. Drug candidate.

Zhou et al. explored the application of Me-DuPhos/Rh catalyst for the hydrogenation of exocyclic enamides **80** (Table 10), which are the building blocks of various biologically active molecules, such as levofloxacin, obscurinervine, etc.[28] Hydrogenations were carried out at 60 atm of hydrogen in methanol, giving high enantioselectivities (>97% ee) regardless of the substituents on the aromatic ring of the 1,4-benzoxazines. In the case of compounds with an *ortho* substituent of aryl on the exocyclic double bond, a lower enantioselectivity was obtained (Table 10, entries 9 and 10). Replacement of the *N*-Ac of (*Z*)-**80** with an *N*-Bz group led to a significant drop in the enantioselectivity (Table 10, entry 11 vs entry 4).

The Me-DuPhos/Rh catalytic system has been applied to the synthesis of amide **83**, a key component of DMP 777, which is used as an inhibitor of leukocyte elastase (Scheme 15).[29]

Meek et al. examined the efficacy of the rhodium catalysts of DuPhos and BPE ligands in the hydrogenation of a variety of α-aryl enamides **84** (Table 11).[30] The enantioselectivities for the obtained amine derivatives **85** were excellent. The synthetic potential of entry 1 (Table 11) opens the route to the drug candidate CGP-55845 (Figure 5), a GABA-B antagonist.

The C_2-symmetric polyhydroxyphospholane **86**, which has the backbone of DuPhos ligands, has been used for the rhodium-catalyzed asymmetric hydrogenation of acyclic and cyclic enamides (**87** and **74**) (Scheme 16).[31]

Asymmetric hydrogenation of the ene-trifluoroacetamides **89a**−**g** was studied using Me-BPE/Rh catalyst (Table 12).[32] Highly enantioenriched trifluoroacetamides **90** were obtained in good yields. The JosiPhos ligands **92** and **93** (Figure 6) were also tested for the rhodium-catalyzed hydrogenation of ene-trifluoroacetamides **89e,f** in various solvents. This gave 97% ee

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 16

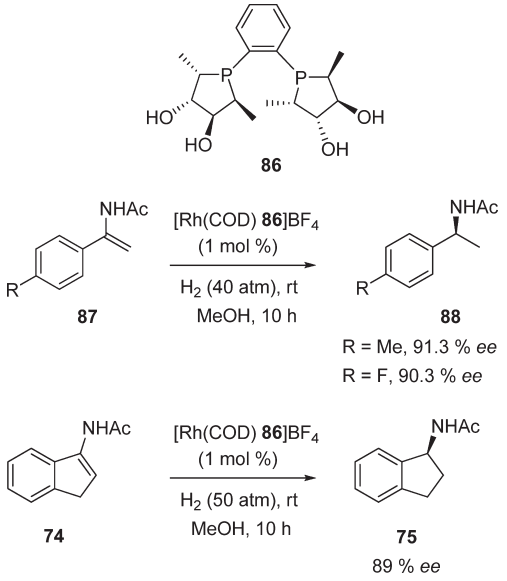
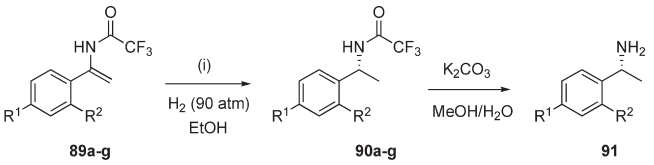


Table 12. Asymmetric Hydrogenation of Ene-trifluoroacet amides 89a−g Using Rh/Me-BPE Catalyst



(i) [Rh(COD)(Me-BPE)]BF_4 (0.75 mol %)

substrate	R^1	R^2	yield (%)(**90**)	ee (%)(**90**)
89a	H	H	80	96.5
89b	Br	H	91	94.4
89c	CO_2Me	H	95	96.2
89d	Ph	H	94	96.0
89e	CF_3	H	98	96.8
89f	Br	F	89	98.3
89g	OMOM	H	97	97.6

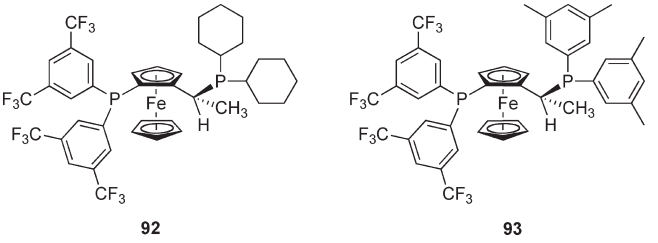


Figure 6. The JosiPhos ligands **92** and **93**.

for **90e** in isopropyl alcohol with **92** versus 92% ee for **90f** in 1,2-dichlorobenzene with **93**. The trifluoroamide functionality in **90** was easily deprotected under mild conditions into enantioenriched aryl amines **91**. Very recently, Hoelderich et al. published the heterogeneously catalyzed asymmetric

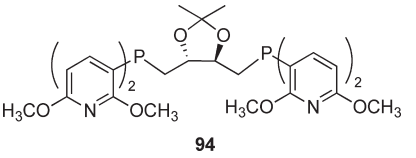
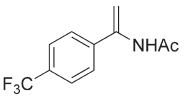
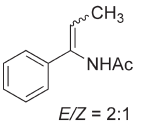
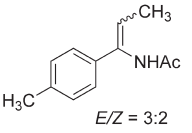
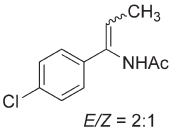
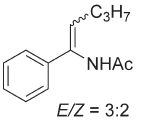


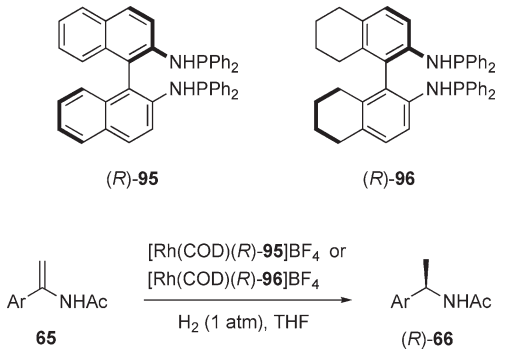
Figure 7. Chiral (*R,R*)-Py*-DIOP ligand **94**.

Table 13. Asymmetric Hydrogenation of Enamides Catalyzed by Rh/Py*-DIOP 94 and Rh/DIOP Complexes

Entry	Enamide	with Rh/Py*-DIOP[a] ee % (Config)	with Rh/DIOP[b] ee % (Config)
1		76 (*S*)	36 (*R*)
2	 *E/Z* = 2:1	84 (*S*)	87 (*R*)
3	 *E/Z* = 3:2	81 (*S*)	--
4	 *E/Z* = 2:1	81 (*S*)	--
5	 *E/Z* = 3:2	40 (*S*)	--

[a] Reactions were carried out in methanol with [Rh(COD)(Py*-DIOP)]BF_4 catalyst under 100 atm H_2 at room temperature. [b] Catalyst was [Rh(COD)(*S,S*)-DIOP]ClO_4, reaction conditions same as Rh(Py*-DIOP).

Scheme 17



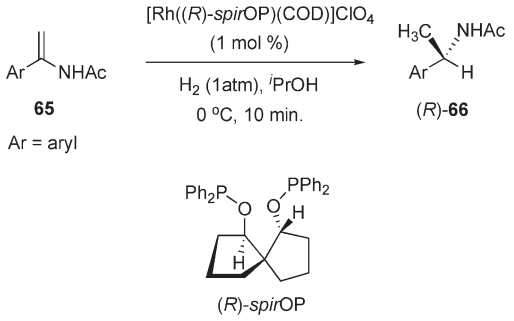
hydrogenation of α-aryl enamides over immobilized Rh-BPE and Rh-DUPHOS complexes on aluminum-containing M41S

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Table 14. Asymmetric Hydrogenation of 65 Catalyzed by Rh/95 or Rh/96 Complexes

Ar(**65**)	catalyst	conversion (%)	ee % ((*R*)-**66**)
C_6H_5	[Rh(COD) **95**]BF_4	100	92.9
C_6H_5	[Rh(COD) **96**]BF_4	100	96.8
p-$CF_3C_6H_4$	[Rh(COD) **95**]BF_4	100	95.1
p-$CF_3C_6H_4$	[Rh(COD) **96**]BF_4	100	99.0
p-$CH_3C_6H_4$	[Rh(COD) **95**]BF_4	97.6	95.1
p-$CH_3C_6H_4$	[Rh(COD) **96**]BF_4	100	97.0
p-ClC_6H_4	[Rh(COD) **95**]BF_4	100	94.9
p-ClC_6H_4	[Rh(COD) **96**]BF_4	100	97.0
m-$CH_3C_6H_4$	[Rh(COD) **95**]BF_4	93.4	94.8
m-$CH_3C_6H_4$	[Rh(COD) **96**]BF_4	100	97.7
2-furanyl	[Rh(COD) **95**]BF_4	100	96.1
2-furanyl	[Rh(COD) **96**]BF_4	100	98.4

Scheme 18



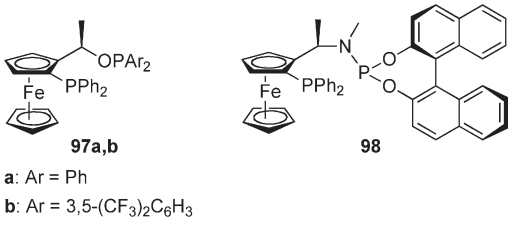
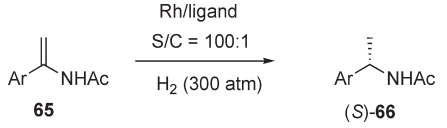


Figure 8. Some chiral ferrocene ligands.

Table 15. Enantioselective Hydrogenation of Enamides 65 with Rh/97a,b and Rh/98 Catalysts



ligand	Ar	solvent	temp (°C)	ee (%)
97a	C_6H_5	CH_2Cl_2	rt	72
97b	C_6H_5	CH_2Cl_2	rt	83
97b	*p*-$CF_3C_6H_4$	CH_2Cl_2	0	91
98	C_6H_5	CH_2Cl_2	rt	73
98	C_6H_5	THF	rt	77
98	C_6H_5	*i*-PrOH	rt	76

Scheme 19

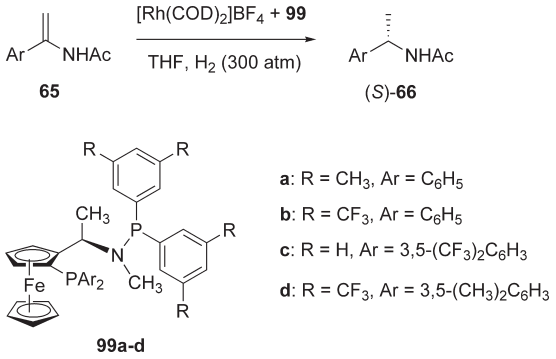


Table 16. Asymmetric Hydrogenation of Enamides 65 by Rh/99b Catalyst

Ar (**65**)	S/C	temp (°C)	time (h)	ee (%)
C_6H_5	1000	rt	16	95.8
C_6H_5	500	5	30	98.3
p-$CF_3C_6H_4$	500	5	30	98.6
p-BrC_6H_4	500	5	30	99.7
p-$CH_3C_6H_4$	500	5	30	99.4
p-$OCH_3C_6H_4$	500	5	30	99.3
m-$CH_3C_6H_4$	500	5	30	98.5
m-$OCH_3C_6H_4$	500	5	30	99.0

and SBA-15 type materials.[33] Chiral α-1-arylalkylamine derivatives were obtained in 99% conversion with enantioselectivities up to 99%.

Chan et al. published several papers on the rhodium-catalyzed asymmetric hydrogenation of enamides using a variety of phosphorus ligands.[34−38] The new chiral pyridyl diphosphine (*R,R*)-Py*-DIOP **94** (Figure 7) was applied to the Rh-catalyzed asymmetric hydrogenation of enamides (Table 13).[34] In comparison with the original DIOP, a higher ee value was obtained in the hydrogenation of a β-unsubstituted enamide using Py*-DIOP (Table 13, entry 1). The *E*/*Z* mixtures of β-substituted enamides were reduced with moderate to high enantioselectivities (Table 13, entries 2−5).

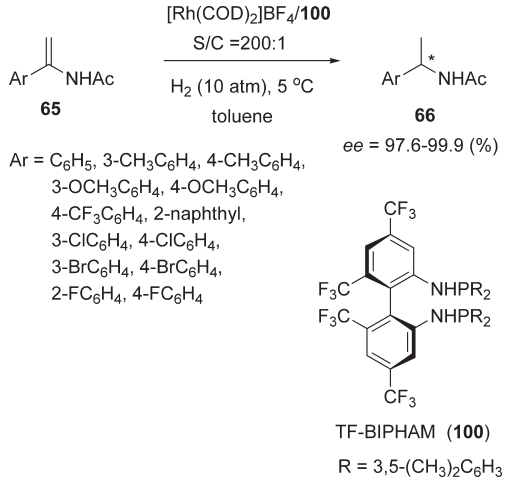
Rhodium catalysts derived from bisaminophosphine ligands (*R*)-**95** and (*R*)-**96** were employed in the asymmetric hydrogenation of enamides **65** (Scheme 17).[35] A variety of enamides **65** bearing *meta*- or *para*-substituents on the phenyl ring or heteroaryl groups were transformed to the corresponding enantiopure amines **66** with excellent yields and enantioselectivities (Table 14).

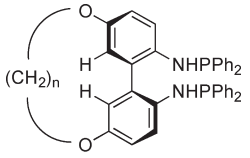
The utility of a rhodium complex of the spirocyclic phosphinite ligand *spir*OP was examined for the catalytic asymmetric hydrogenation of α-substituted enamides **65** (Scheme 18).[36] The importance of this catalytic system lies in its high catalytic activity. Amides **66** were obtained with ee's ranging from 85% to 97%.

The ferrocene-based chiral phosphine−phosphinite and phosphine−phosphoramidite ligands **97a,b** and **98**, respectively (Figure 8) were applied to the rhodium-catalyzed asymmetric hydrogenation of α-aryl enamides **65** (Table 15).[37] The catalysts were generated *in situ* from $[Rh(COD)_2]BF_4$ and **97a,b** or **98**. This gave the products (*S*)-**66** with moderate to good enantioselectivities.

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

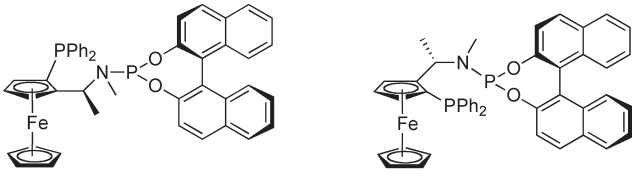
Scheme 20





(*S*)-**101a**: n = 8
(*S*)-**101b**: n = 10

Figure 9. Bisaminophosphines **101a,b**.

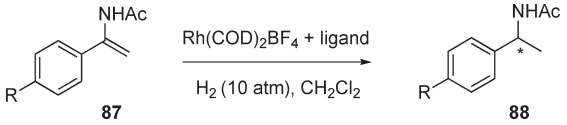


(S_c,R_p,S_a)-**102a**
(S_c,R_p,R_a)-**102b**
(S_c,S_p,R_a)-**102c**
(S_c,S_p,S_a)-**102d**
(S_c,R_p)-**102e**
(S_c,R_p)-**102f**

Figure 10. Phosphine−phosphoramidites **102a**−**f** used by Zheng and co-workers.[41]

Fluorinated ferrocenylphosphine−aminophosphine ligands **99a**−**d** were also developed and applied to the Rh-catalyzed asymmetric hydrogenation of enamides **65** (Scheme 19).[38] Promising results were given by **99b** in THF (96.5% ee, quantitative yield). Moreover, the ligand **99b** and its rhodium complex were stable in the presence of air or water. The scope of the Rh/**99b** catalyst in the hydrogenation of various α-aryl enamides **65** was explored (Table 16). This gives the reduced products (*S*)-**66** with high enantioselectivities in quantitative yields.

Table 17. Asymmetric Hydrogenation of Enamides 87 Catalyzed by Rh/102a−f Complexes



entry	ligand	R	Rh (mol %)	ee % (config)
1	(S_c,R_p,S_a)-**102a**	H	1	99.6 (*R*)
2	(S_c,R_p,R_a)-**102b**	H	1	10.6 (*S*)
3	(S_c,S_p,R_a)-**102c**	H	1	99.6 (*S*)
4	(S_c,S_p,S_a)-**102d**	H	1	82.6 (*R*)
5	(S_c,R_p)-**102e**	H	1	81.5 (*S*)
6	(S_c,R_p)-**102f**	H	1	78.1 (*R*)
7	(S_c,R_p,S_a)-**102a**	H	0.1	99.6 (*R*)
8	(S_c,R_p,S_a)-**102a**	F	0.1	98.7 (*R*)
9	(S_c,R_p,S_a)-**102a**	Cl	0.1	98.8 (*R*)
10	(S_c,R_p,S_a)-**102a**	Br	0.1	99.0 (*R*)
11	(S_c,R_p,S_a)-**102a**	CF_3	0.1	99.2 (*R*)

Wang et al. resolved the C_2-symmetric bis(aminophosphine) TF-BIPHAM (**100**) and applied it to the asymmetric hydrogenation of α-aryl enamides **65** (Scheme 20).[39] This gives the corresponding amine derivatives **66** with excellent enantioselectivities regardless of the position and the electronic properties of the substituents on the phenyl ring. Zhang and co-workers synthesized the atropisomeric 5,5′-linked biphenyl bisaminophosphine ligands **101a,b** (Figure 9) and checked for the hydrogenation of *N*-acetyl-α-phenylethenamine.[40] Low enantioselectivities (33−49% ee) for the reduced product were obtained.

Zheng et al. tested a new family of highly unsymmetrical phosphine−phosphoramidite ligands **102a**−**f** (Figure 10), which have a planar chiral ferrocenyl backbone and an axial-chiral binaphthyl moiety, in the Rh-catalyzed hydrogenation of α-aryl enamides **87** (Table 17).[41] Ligands **102a** and **102c** gave the highest enantioselectivity (Table 17, entries 1 and 3), but with opposite chirality. When the ligands **102e,f** of an achiral phosphoramidite moiety were used for hydrogenation of **87** (R = H), only moderate ee was obtained. This indicates that the binaphthyl moiety plays a crucial role in the enantioselectivity and controls the chirality of the hydrogenation products. The generality of the reaction using **102a** was explored for a variety of enamides **87** (Table 17, entries 8−11).

In parallel, a variety of novel H_8-BINOL-derived unsymmetrical hybrid ferrocenylphosphine−phosphoramidites **103**[42] and phosphine−phosphoramidite **104**[43] (Figure 11) were applied to the Rh-catalyzed hydrogenation of enamides **87**. Furthermore, the phosphine−phosphoramidite THNAPhos (**105**),[44] phosphine−aminophosphine (*R*)-HW-Phos (**106**),[45] and phosphine−phosphoramidite (*S*)-HY-Phos (**107**)[46] (Figure 11) were tested for the enantioselective Rh-catalyzed hydrogenation of enamides **69**. Excellent ee's and yields were obtained for the amine derivatives **70**.

Using a simple chiral 1,2-diphosphine **108** for the rhodium-catalyzed asymmetric hydrogenation of (*E*)- and (*Z*)-enamides **14** gave the reduced product **21** in 10% ee and 50% ee, respectively (Scheme 21).[47] The *Z* isomer hydrogenated much faster (relative rates 23:3); however, the enantiomer formed in excess from both isomers had the *R* configuration.

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

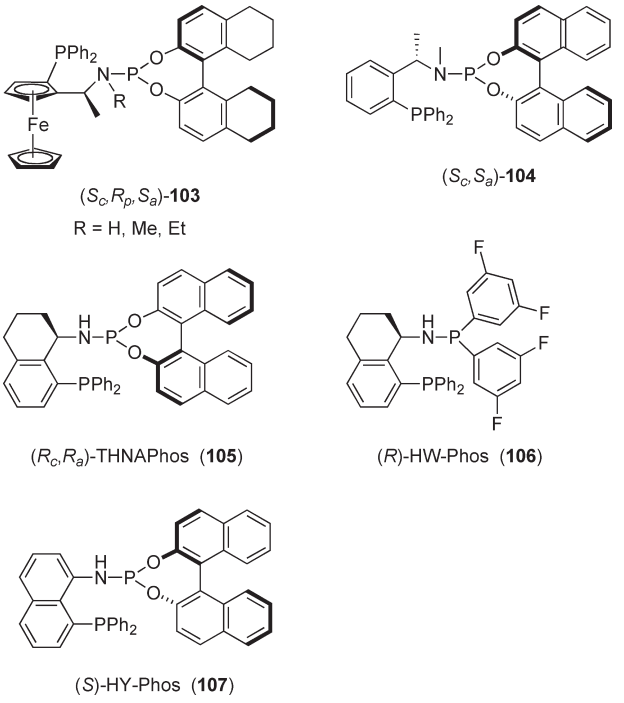
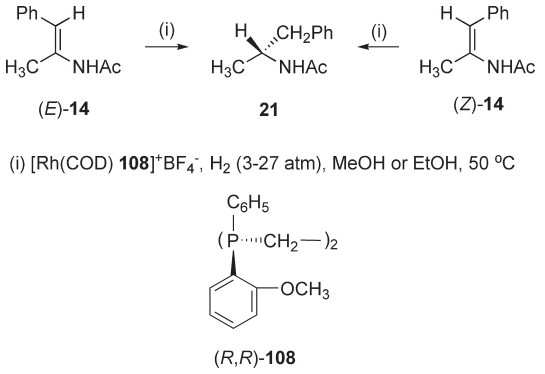


Figure 11. Ligands used by Zheng and co-workers.[42−46]

Scheme 21



Scheme 22

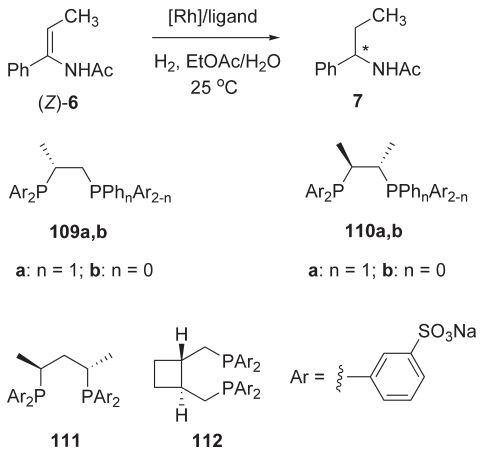


Table 18. Hydrogenation of Enamide (*Z*)-6

ligand	H_2 (atm)	EtOAc/H_2O	ee % (config)
109a + **109b**[a]	10	1/1	18 (*R*)
110a + **110b**[b]	10	1/1	39 (*S*)
111	5	1/1	13 (*R*)
112	10	1/1	26 (*S*)

[a] Mixture of 45% **109a** + 55% **109b**. [b] Mixture of 40% **110a** + 60% **110b**.

Scheme 23

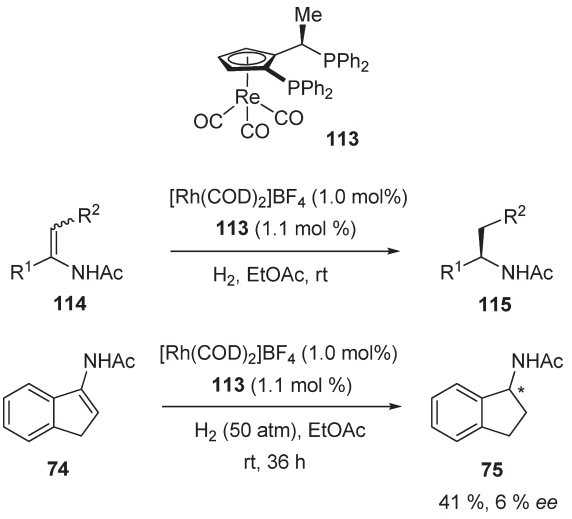


Table 19. Rh/113-Catalyzed Asymmetric Hydrogenation of Enamides 114

entry	R^1 (**114**)	R^2 (**114**)	time (h)	H_2 (atm)	conversion (%)	ee (%)
1	C_6H_5	H	16	10	100	93
2	4-Cl-C_6H_4	H	22	10	100	91
3	4-CF_3−C_6H_4	H	24	10	100	89
4	4-MeO-C_6H_4	H	20	20	100	85
5	4-Me-C_6H_4	H	22	10	100	88
6	4-Me-C_6H_4	CH_3	20	20	100	91
7	C_6H_5	CH_3	22	20	100	68

Rhodium(I) catalysts bearing water-soluble chiral sulfonated 1,2-, 1,3-, and 1,4-diphosphines (**109**−**112**) were used for the asymmetric hydrogenation of enamide (*Z*)-**6** in an aqueous−organic two-phase solvent system (Scheme 22, Table 18).[48] The catalysts were easily prepared by reacting the sulfonated phosphine with $[Rh(COD)Cl]_2$ or $[Rh(NBD)_2]BF_4$ in the ratio of 1.1:1 in water. The catalyst system could be recovered and reused without loss of enantioselectivity.

Bolm et al. demonstrated the application of novel cyrhetrene **113** in the rhodium-catalyzed asymmetric enamide hydrogenation (Scheme 23).[49,50] The α-aryl enamides **114** bearing either electron-withdrawing or -donating substituents on the aromatic ring gave the corresponding amine derivatives **115** with high enantioselectivity (85−93%) (Table 19, entries 1−5). The catalytic scope was expanded to the β-substituted α-aryl enamides **114** (entries 6 and 7). Isomeric mixtures of *E*/*Z*-enamides

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Scheme 24

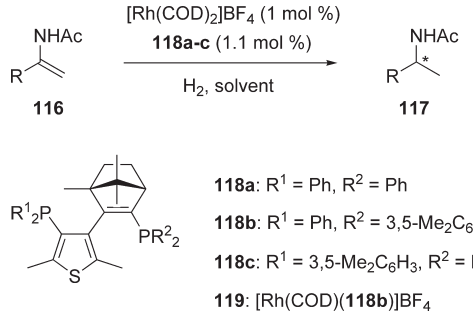


Table 20. Hydrogenation of Enamides 116 with Rh/118a−c Catalysts and Preformed Catalyst 119

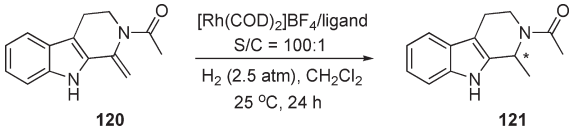
R (**116**)	ligand	solvent	H_2 (atm)	time (h)	ee % (config)
t-Bu	**118a**	CH_2Cl_2	50	3	87 (*S*)
t-Bu	**118b**	CH_2Cl_2	50	3	84 (*S*)
t-Bu	**118c**	toluene	50	3	66 (*S*)
Ph	**118a**	toluene	50	4	88 (*R*)
Ph	**118b**	MeOH	8	16	92 (*R*)
Ph	**118c**	MeOH	8	16	46 (*R*)
4-ClC_6H_4	**118a**	MeOH	50	3	84 (*R*)
4-ClC_6H_4	**118b**	MeOH	50	3	85 (*R*)
4-ClC_6H_4	**118c**	MeOH	50	3	56 (*R*)
2-$C_{10}H_7$	**118a**	toluene	50	4	94 (*R*)
2-$C_{10}H_7$	**118b**	toluene	50	4	98 (*R*)
2-$C_{10}H_7$	**118c**	toluene	50	4	44 (*R*)
3-$NO_2C_6H_4$	**118a**	MeOH	50	3	97 (+)
3-$NO_2C_6H_4$	**119**	toluene	5	1	99.7 (+)
3-$NO_2C_6H_4$	**118c**	MeOH	50	3	76 (+)

(2:1 ratio) were reduced to **115** in 68−91% enantioselectivities. The enantioselectivities are very low (3−5% ee) in the case of enamides **114** (R^1 = 2-Br-C_6H_4 or *t*-Bu), plausibly due to steric congestion. The 3-indenyl-*N*-acetyl amine **74** also gave only 6% ee because of the *E*-configured double bond, which inhibited proper coordination of the substrate.

Chiral diphosphine ligands **118a−c**, which have a bornene backbone, were used in the Rh-catalyzed hydrogenation of enamides **116** (Scheme 24).[51] The enantiomeric excesses for the amine derivatives **117** ranged from 84% to 99% when using ligands **118a,b** and preformed catalyst **119** (Table 20). The catalyst derived from **118c** gave lower asymmetric induction.

The Beller group from Rostock investigated the asymmetric hydrogenation of different enamides, in particular, the dihydro-β-carboline derivative **120**, with the use of rhodium catalysts.[52] The phospholane-based diphosphane cat*A*Sium MNXyF (**122**) was found to be the best ligand (Table 21, entry 1). Several structurally similar ligands (**123−128**) were tested in the asymmetric hydrogenation of compound **120** (Table 21, entries 2−7). It gave the reduced product **121** with ee's up to 97%. The enantioselectivity was further improved to 99% ee by using ethyl acetate as solvent. The scope of the rhodium catalysts of cat*A*Sium M ligands was explored for various benchmark enamides. Asymmetric hydrogenation of isoquinoline precursor **45** with Rh/**122−128** catalysts

Table 21. Hydrogenation of Enamide 120 with Various Phospholane-based Ligands (122−128)



120 → **121**

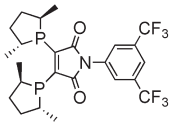
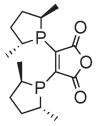
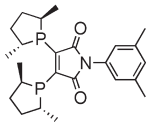
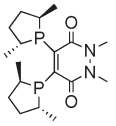
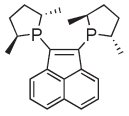
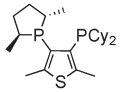
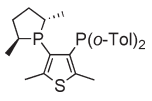
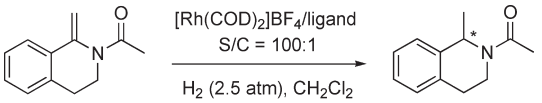
Entry	Ligand		Conversion (%)	*ee* (%)
1		(**122**)	>99	96 (-)
2		(**123**)	93	97 (-)
3		(**124**)	98	96 (-)
4		(**125**)	99	96 (-)
5		(**126**)	66	86 (-)
6		(**127**)	95	68 (-)
7		(**128**)	34	10 (-)

Table 22. Hydrogenation of Isoquinoline Substrate 45



45 → **46**

entry	ligand	conversion (%)	ee (%)
1	**122**	99	96 (−)
2	**123**	99	92 (−)
3	**124**	>99	94 (−)
4	**125**	98	88 (−)
5	**126**	99	84 (−)
6	**127**	99	50 (−)
7	**128**	99	58 (−)

gave moderate to high enantioselectivities (Table 22). Simple aryl, alkyl, and heteroaryl enamides **116** were hydrogenated using the

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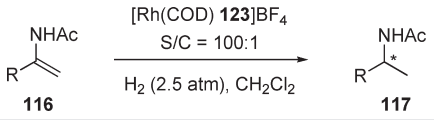
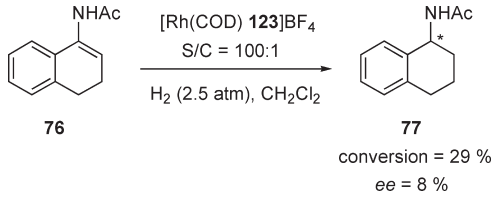
Table 23. Rh/123-Catalyzed Asymmetric Hydrogenation of Enamides 116

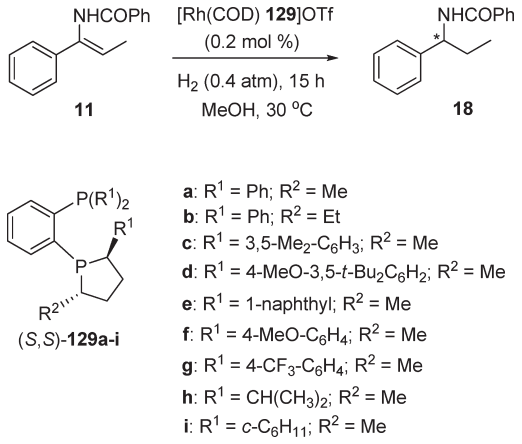


entry	R	conversion (%)	ee % (config)
1	C_6H_5	99	86 (*R*)
2	*p*-MeO-C_6H_4	>99	84 (*R*)
3	*m*-MeO-C_6H_4	>99	85 (*R*)
4	*o*-MeO-C_6H_4	99	80 (*R*)
5	*p*-CF_3-C_6H_4	>99	89 (*R*)
6	*t*-Bu	94	96 (+)
7	2-thiophene	>99	92 (+)

Scheme 25



Scheme 26



Rh/**123** catalyst (Table 23). The enantioselectivities of the reduced products **117** ranged from 80% to 96% ee. Finally, hydrogenation was carried out for endocyclic enamide **76** using the Rh/**123** catalyst. It gave a very low ee for amide **77** due to the shielding of the internal double bond (Scheme 25).

Saito et al. prepared a new class of C_1-symmetric phosphine−phospholane ligands **129a**−**i** and used them in the Rh-catalyzed hydrogenation of enamide **11** (Scheme 26, Table 24).[53] The ligands **129d**−**e** bearing a bulkier aryl substituent on the achiral phosphorus atom gave better asymmetric induction than C_2-symmetric DuPhos (Table 24, entries 4 and 5 vs 10). The utility of the Rh/**129a** catalyst for the hydrogenation of α-aryl enamides **87a**−**c** was further demonstrated by Pringle and co-workers (Figure 12).[54] The enantioselectivities obtained for the corresponding amine derivatives ranged from 70% to 96% ee.

Table 24. Asymmetric Hydrogenation of Enamide 11 with Rh/129a−i Catalysts

entry	ligand	conversion (%)	ee % (config)
1	**129a**	>99	94 (*S*)
2	**129b**	>99	81 (*S*)
3	**129c**	>99	95 (*S*)
4	**129d**	>99	99 (*S*)
5	**129e**	56	99 (*S*)
6	**129f**	>99	90 (*S*)
7	**129g**	4	6(*S*)
8	**129h**	>99	69 (*R*)
9	**129i**	>99	40 (*R*)
10	(*R*,*R*)-Me-DuPhos	25	78 (*R*)

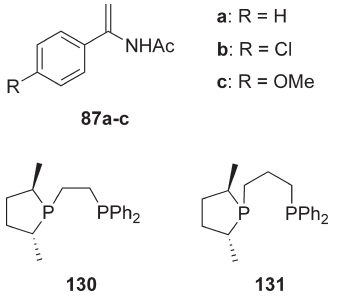


Figure 12. Enamides **87a**−**c** and ligands **130** and **131**.

Based on the structural features of ligand **129a**, this group

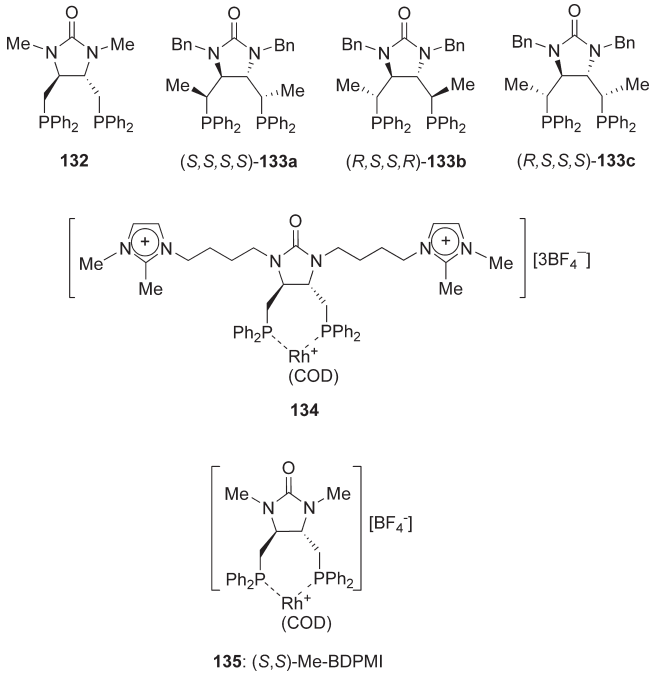


Figure 13. Ligands **132** and **133a**−**c** and rhodium complexes **134** and **135** used by Lee and co-workers.[56−58]

investigated the ligands **130** and **131** (Figure 12), which contain the same substituents (PPh_2 and 2,5-dimethylphospholane groups) but on more flexible backbones.[55] The Rh catalysts of

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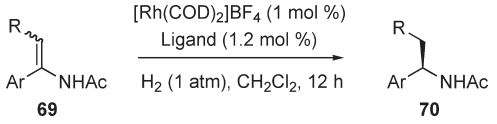
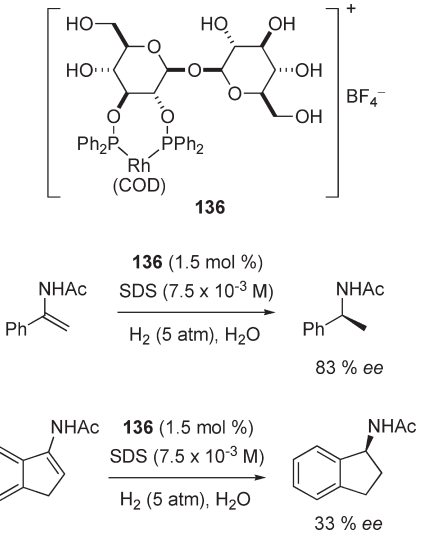
Table 25. Asymmetric Hydrogenation of α-Aryl Enamides 69 Catalyzed by Rh/132,133a−c Complexes



entry	ligand	Ar, R	conversion (%)	ee (%)
1	**132**	C_6H_5, H	100	98.5
2	**132**	*p*-MeC_6H_4, H	100	98.6
3	**132**	*p*-FC_6H_4, H	100	97.9
4	**132**	*p*-ClC_6H_4, H	100	97.8
5	**132**	*p*-$OMeC_6H_4$, H	100	99.0
6	**132**	2-naphthyl, H	100	>99.0
7	**132**	C_6H_5, Me	100	>99.0
8	**132**	C_6H_5, Et	100	>99.0
9	**132**	*p*-$OMeC_6H_4$, Me	100	>99.0
10	**132**	*p*-ClC_6H_4, Me	100	>99.0
11	**132**	*p*-MeC_6H_4, Me	100	99.0
12	**133a**	C_6H_5, H	100	50.6
13	**133b**	C_6H_5, H	100	95.1
14	**133c**	C_6H_5, H	100	98.6

Scheme 27



130 and **131** were employed in the hydrogenation of enamides **87a,b**, leading to the hydrogenated products with ee's up to 95%.

Lee et al. synthesized the chiral 1,4-diphosphines **132**[56] and **133a−c**[57] (Figure 13) with the backbone of imidazolidin-2-one and showed their utility as ligands in the rhodium-catalyzed hydrogenation of α-aryl enamides **69** (Table 25). The mixtures of *E*- and *Z*-enamides were also reduced with excellent enantioselectivities (Table 25, entries 7−11). Furthermore, hydrogenation of **69** (Ar = Ph, R = H) was investigated with the ionic liquid grafted chiral Rh complex **134** of 1,4-bisphosphine bearing two 1,2-dimethylimidazolium salt tags (Figure 13).[58] Catalyst **134** was reused several times in the hydrogenation without significant loss of catalytic efficiency (97.0% ee for the first run and 95.4% ee for the fourth run). The catalytic efficiency of **134** was compared with Rh/Me-BDPMI complex **135** in the [bmim][SbF_6]/*i*-PrOH two-phase system in the hydrogenation of enamide **69** (Ar = Ph, R = H). With catalyst **135**, the conversions and enantioselectivities were decreased significantly after two cycles (95.8% ee for the first run and 88.0% ee for the fourth run).

The water-soluble carbohydrate-based rhodium catalyst **136** bearing free hydroxy groups was tested in the asymmetric hydrogenation of *N*-acetyl-α-phenylethenamine and α-(*N*-acetylamido)indene in the presence of sodium dodecyl sulfate (SDS) in water (Scheme 27).[59]

Asymmetric enamide hydrogenations catalyzed by rhodium complexes of (*S,S*)-*t*-Bu-BisP* (**137**) and *t*-Bu-MiniPhos (**138**)

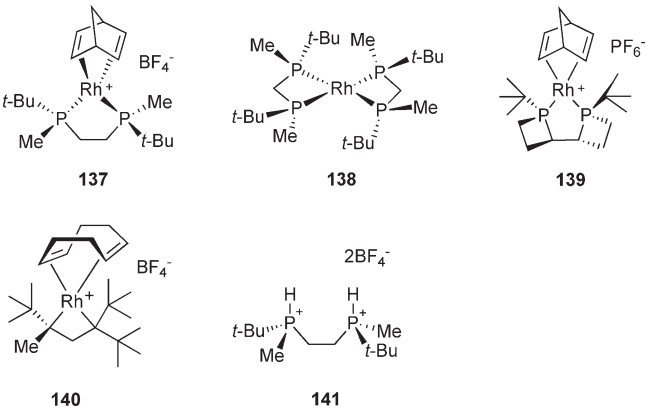
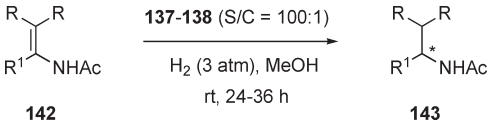


Figure 14. Preformed rhodium complexes **137**−**140**, and phosphonium salt **141** used by Imamoto and co-workers.[60−63]

Table 26. Enantioselective Hydrogenation of Aryl- and Alkylenamides 142 with Rhodium Catalysts 137 and 138

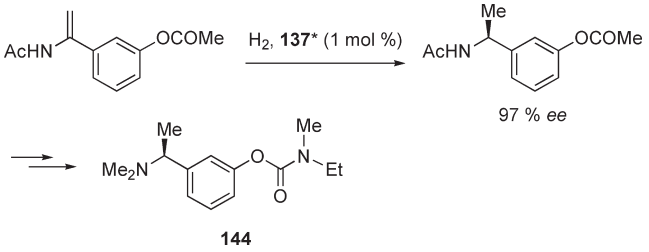


entry	R^1	R	catalyst	ee % (config)
1	C_6H_5	H	**137**	99 (*R*)
2	C_6H_5	H	**138**	66 (*R*)
3	3-$CH_3OC_6H_4$	H	**137**	97 (*R*)
4	3-$CH_3OC_6H_4$	H	**138**	87 (*R*)
5	4-$CH_3OC_6H_4$	H	**137**	96 (*R*)
6	4-$CH_3OC_6H_4$	H	**138**	86 (*R*)
7	3-ClC_6H_4	H	**137**	93 (*R*)
8	3-ClC_6H_4	H	**138**	71 (*R*)
9	4-ClC_6H_4	H	**137**	99 (*R*)
10	4-ClC_6H_4	H	**138**	88 (*R*)
11	3-$CH_3OCOC_6H_4$	H	**137**	99 (*R*)
12	3-$CH_3OCOC_6H_4$	H	**137***[a]	97 (*S*)
13	C_6H_5	Me	**137**	99 (*R*)
14	C_6H_5	Me	**138**	98 (*R*)
15	*t*-Bu	H	**137**	99 (*S*)
16	1-Adamantyl	H	**137**	99 (*S*)
17	1-Adamantyl	H	**138**	99 (*S*)

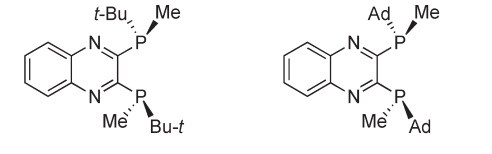
[a] **137*** is [Rh((*R,R*)-*t*-Bu-BisP*)]BF_4.

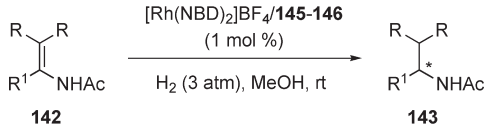
dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 28



Scheme 29





R^1	R	Ligand	*ee* % (Config)
Ph	H	**145**	99.9 (*R*)
1-adamantyl	H	**145**	96.3 (*S*)
Ph	Me	**146**	99.9 (*R*)

Scheme 30

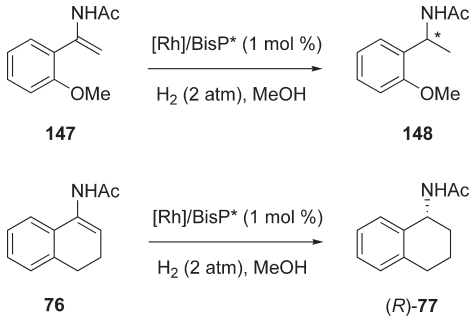
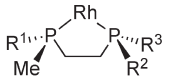


Table 27. Enantioselective Hydrogenation of Enamides 147 and 76



Entry	R^1	R^2	R^3	**148** *ee* % (Config)	**77** *ee* % (Config)
1	*t*Bu	*t*Bu	Me	50.4 (*R*)	8.5 (*R*)
2	Cp	Cp	Me	68.2 (*R*)	89.2 (*R*)
3	Cy	Cy	Me	73.1 (*R*)	57.2 (*R*)
4	Ad	Cp	Me	45.4 (*R*)	79.7 (*R*)
5	Ad	Cy	Me	61.6 (*R*)	68.5 (*R*)
6	Ad	*i*Pr	Me	50.8 (*R*)	59.9 (*R*)
7	*t*Bu	Cy	Me	68.4 (*R*)	68.3 (*R*)
8	Cy	Cp	Me	83.1 (*R*)	67.0 (*R*)
9	Ad	Ph	Ph	46.3 (*S*)	89.9 (*R*)
10	Ad	Ph	Me	40.3 (*R*)	73.0 (*R*)
11	*t*Bu	*i*Pr	Me	54.6 (*R*)	63.0 (*R*)

(Figure 14) were reported by Imamoto et al.[60] The BisP*-based catalyst **137** gave better results compared with **138** in the hydrogenation of a wide range of aryl- and alkyl-substituted enamides **142** (Table 26). The tetrasubstituted enamide also gave excellent ee's (Table 26, entries 13 and 14). Entry 12 in Table 26 demonstrates the applicability of the method to the asymmetric synthesis of acetylcholinesterase inhibitor SDZ-ENA-713 (**144**) (Scheme 28). Furthermore, the rhodium catalyst derived from $Rh(NBD)_2BF_4$ and the precursor of phosphonium salt **141**[63] (Figure 14) as well as the preformed catalysts **139**[61] and **140**[62] were tested in the hydrogenation of enamides **142**. These gave **143** in excellent yields (98−100%) and ee's up to 99%. Another class of ligands such as QuinoxP* (**145**)[64] and Ad-QuinoxP* (**146**)[65] were also employed in the rhodium-catalyzed hydrogenation of enamides **142** (Scheme 29). Recently, a marked deuterium isotope effect on the enantioselectivity in rhodium-catalyzed asymmetric hydrogenation of enamides was explored.[66] The strongest effects were noticed for the hydrogenation of aryl-substituted enamides having an *ortho* substituent that is capable of forming a hydrogen bond. The observed isotope effects were interpreted in terms of the competitive reactions of two dihydride intermediates and dideuteride intermediates that exist in equilibrium in the catalytic cycle.

Focusing on the BisP*/Rh catalysts developed by Imamoto and co-workers, Ohashi and co-workers synthesized a series of "unsymmetrical BisP*/Rh catalysts" and applied them to the hydrogenation of enamides **147** and **76** (Scheme 30, Table 27).[67] The ee values were compared with the symmetrical BisP* (Table 27, entries 1−3), which are in general lower than those obtained for the unsymmetrical BisP* (Table 27, entries 4−11), except for that of the symmetrical Cp-BisP*.

In a series of papers published since 1998, Zhang et al. have reported on several phosphorus ligands for rhodium-catalyzed asymmetric hydrogenation, which have been applied to enamide reduction.[68−85] Enamides **69** were hydrogenated with the rhodium catalyst generated *in situ* from $[Rh(COD)_2]OTf$ and bisphosphine BICP (**149**) (Figure 15), which led to the chiral amide derivatives **70** (Table 28).[68] The enantioselectivity of the reaction is not sensitive to the geometry of the starting enamides. Thus, a series of *Z*- and *E*-β-substituted enamide isomers were reduced in high yield and with high enantioselectivity. Additionally, the reaction is not sensitive to

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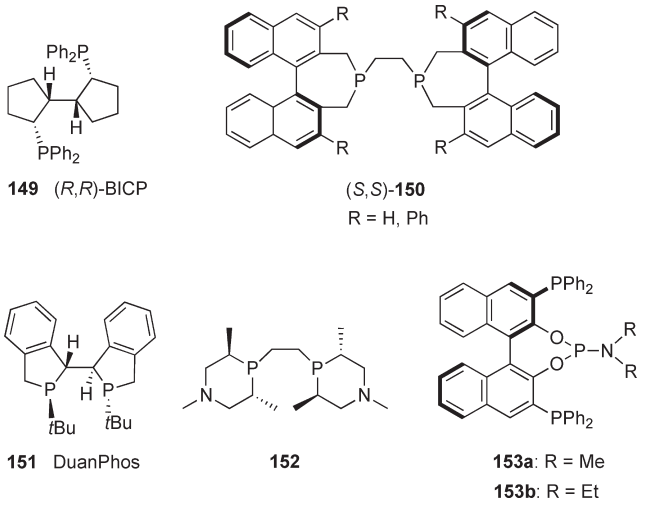
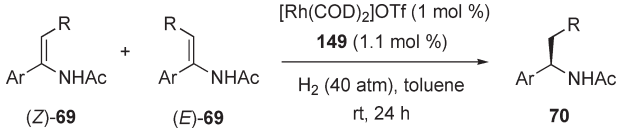


Figure 15. Some chiral phosphorus ligands used for the Rh-catalyzed asymmetric hydrogenation of enamides **69**.

Table 28. Asymmetric Hydrogenation of Enamides 69 Catalyzed by Rh/(*R*,*R*)-BICP (149)



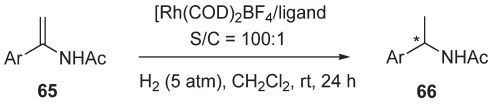
entry	Ar	R	ee (%)
1	C_6H_5	H	86.3
2	4-Me-C_6H_4	H	86.1
3	3-Me-C_6H_4	H	85.7
4	4-CF_3-C_6H_4	H	86.4
5	4-Ph-C_6H_4	H	93.0
6	4-MeO-C_6H_4	H	91.6
7	2-naphthyl	H	85.2
8	C_6H_5	CH_3	95.0
9	C_6H_5	$CH(CH_3)_2$	93.5
10	C_6H_5	CH_2Ph	90.5
11	4-MeO-C_6H_4	CH_3	95.2
12	4-CF_3-C_6H_4	CH_3	95.1
13	2-naphthyl	CH_3	93.6

electronic effects of substituents on the 1-aryl group. The catalytic system was expanded to the asymmetric hydrogenation of some cyclic enamides **30**, **74**, and **76**, for which it gave moderate enantioselectivities (60−78% ee).

Enamides **69** were hydrogenated with the rhodium catalyst derived from $Rh(NBD)_2SbF_6$ and ligands (*S*,*S*)-**150** (Figure 15).[69] This gave moderate enantioselectivities for the simple amides **70** (Ar = aryl, R = H). However, the isomeric mixture of *E*- and *Z*-β-substituted-α-aryl enamides gave high enantioselectivities (93−99%).

A highly electron-donating and conformationally rigid P-chiral phosphane ligand DuanPhos (**151**) (Figure 15) was synthesized.[70] It was used to prepare the cationic Rh complex {Rh(NBD)[(1*R*,1*R*′,2*S*,2*S*′)-**151**]}-SbF_6 for the catalytic asymmetric hydrogenation of α-aryl enamides and *E*/*Z*-mixtures of β-substituted-α-aryl enamides **69**. This gave the reduced products **70** with excellent enantioselectivities (97% to >99%).

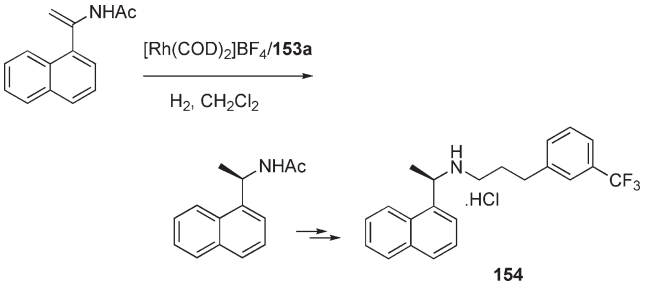
Table 29. Ligand Screening for the Asymmetric Hydrogenation of *ortho*-Substituted Aryl Enamides and 1-Naphthylenamides (65)



Ar	TangPhos[a] ee % (**66**) (config)	Et-DuPhos ee % (**66**) (config)	153a ee % (**66**) (config)	153b ee % (**66**) (config)
2-Me-C_6H_4	51.8 (*S*)	52.6 (*R*)	91.0(*R*)[b]	87.2 (*R*)
2-MeO-C_6H_4	54.4 (*R*)	51.4 (*R*)	99.4 (*R*)	99.0 (*R*)
2-F-C_6H_4	95.8 (*R*)	80.8 (*R*)	99.0 (*R*)	97.0 (*R*)
2-Cl-C_6H_4	9.4 (*R*)	55.6 (*R*)	99.6 (*R*)	98.2 (*R*)
2-NO_2-C_6H_4	88.0 (−)	85.8 (−)	98.2 (−)	98.2 (−)
2-CF_3-C_6H_4	68.8 (+)	88.4 (+)	93.8 (+)	94.2 (+)
1-naphthyl	74.8 (*S*)	51.8 (*R*)	92.4 (*R*)[c]	93.8 (*R*)[d]

[a] Rh(NBD)TangPhos]SbF_6 was used. [b] 0 °C, H_2 (25 atm). [c] 0 °C, H_2 (50 atm). [d] 2,2,2-Trifluoroethanol was used as solvent.

Scheme 31



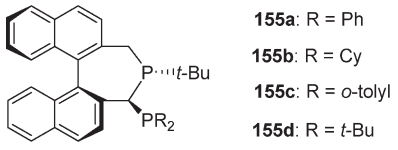


Figure 16. The C_1-symmetric bisphosphine ligands **155a**−**d**.

A six-membered bis(azaphosphorinane) ligand, **152**, was also synthesized by this group and used for the Rh-catalyzed asymmetric hydrogenation of enamides **69**.[71] Hydrogenation reactions were carried out at room temperature under 15 atm of H_2 in the presence of 1 mol % [Rh(**152**)(NBD)]SbF_6. A series of α-aryl enamides and isomeric *E*/*Z*-mixtures of β-substituted aryl enamides **69** were reduced to the corresponding amides **70** with excellent enantioselectivities (95−99%).

Triphosphorous bidentate phosphine−phosphoramidite ligands **153a,b** (Figure 15) were developed for the Rh-catalyzed asymmetric hydrogenation of enamides.[72] Several standard α-aryl enamides **69** were hydrogenated with the Rh catalyst prepared from [Rh(COD)]BF_4 and ligand **153a**. This gave the hydrogenated products **70** with excellent enantioselectivities (97−99%) in most cases. The scope of these ligands was further explored for the hydrogenation of

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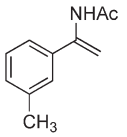
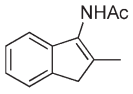
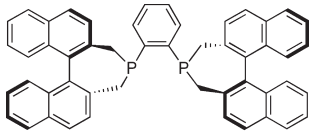
Table 30. Asymmetric Hydrogenation of Acyclic and Cyclic Enamides

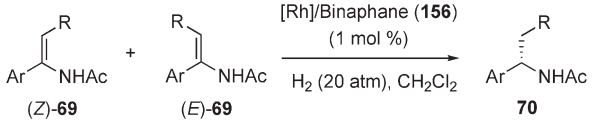
Enamide	Ligand	Conversion	*ee* % (Config)
	**155a**	100	53.5 (*R*)
	155b	100	79.7 (*R*)
	155c	100	53.7 (*S*)
	155d	100	71.8 (*S*)
	**155a**	100	37.1 (*S*)
	155b	100	31.5 (*S*)
	155c	60	69.7 (*R*)
	155d	100	84.5 (*R*)



156

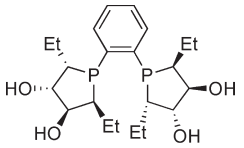
Figure 17. The ligand (*R*,*R*)-Binaphane.

Table 31. Rh/(*R*,*R*)-Binaphane (156) Catalyzed Enantioselective Hydrogenation of Enamides 69



entry	Ar, R	ee (%)
1	C_6H_5, H	90.0
2	3-MeC_6H_4, H	89.0
3	4-CyC_6H_4, H	90.0
4	2-naphthyl, H	89.5
5	C_6H_5, CH_3	99.1
6	4-OMeC_6H_4, CH_3	99.6
7	4-$CF_3C_6H_4$, CH_3	97.0
8	C_6H_5, CH_2CH_3	97.0
9	C_6H_5, CH_2Ph	95.0
10	C_6H_5, $CH(CH_3)_2$	97.6
11	2-naphthyl, CH_3	98.3

ortho-substituted aryl enamides and a 1-naphthylenamide **65** (Table 29). The enantioselectivities with the ligands **153a** and **153b** (Figure 15) were compared with the (1*S*,1*S*′,2*R*,2*R*′)-TangPhos (**168**) (Figure 22) and (*R*,*R*)-Et-DuPhos ((*R*,*R*)-**71b**, see Scheme 13 for structure) (Table 29). Interestingly, the ligands **153a** and **153b** gave excellent enantioselectivities in all cases compared with TangPhos and Et-DuPhos. The application of this methodology was extended to the synthesis of cinacalcet hydrochloride **154**, which is used for the treatment of hyperparathyroidism and hypercalcemia (Scheme 31).



157

Figure 18. Chiral tetrahydroxy phospholane ligand.

Scheme 32

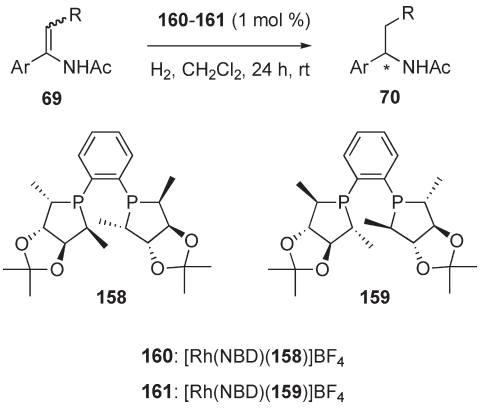
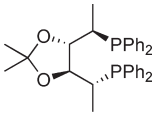


Table 32. Asymmetric Hydrogenation of Enamides 69 with Rhodium Catalysts 160 and 161

Ar (**69**)	R (**69**)	catalyst	ee % (config)
C_6H_5	$CH(CH_3)_2$	**160**	96 (*S*)
C_6H_5	H	**160**	92 (*S*)
p-$CF_3C_6H_4$	H	**160**	96 (*S*)
p-OMeC_6H_4	CH_3	**160**	97 (*S*)
p-$CF_3C_6H_4$	CH_3	**160**	97 (*S*)
C_6H_5	CH_3	**160**	98 (*S*)
C_6H_5	$CH(CH_3)_2$	**161**	93 (*R*)
C_6H_5	H	**161**	94 (*R*)
p-$CF_3C_6H_4$	H	**161**	93 (*R*)
p-OMeC_6H_4	CH_3	**161**	94 (*R*)



162

Figure 19. (*R*,*S*,*S*,*R*)-DIOP*.

The C_1-symmetric bisphosphine ligands **155a**−**d** (Figure 16) were used in the rhodium-catalyzed asymmetric hydrogenation of acyclic and cyclic enamides (Table 30).[73] The cationic rhodium complexes [Rh(COD)(**155a**−**d**)]BF_4 were used as precatalysts in MeOH under 150 atm H_2 pressure at room temperature. Moderate ee's were obtained for both enamides.

Asymmetric hydrogenation of enamides **69** with a rhodium catalyst generated in situ from $Rh(COD)_2PF_6$ and (*R*,*R*)-Binaphane (**156**) (Figure 17) led to the amine derivatives **70** with high enantioselectivities (Table 31).[74]

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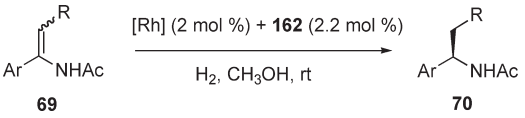
Table 33. Asymmetric Hydrogenation of Enamides 69 Catalyzed by a Rh/162 Complex



69 70

Ar	R	Rh	ee (%)
C_6H_5	H	$[Rh(COD)Cl]_2$	97.8
C_6H_5	H	$[Rh(COD)_2]SbF_6$	98.3
p-Ph-C_6H_4	H	$[Rh(COD)Cl]_2$	>99
p-Ph-C_6H_4	H	$[Rh(COD)_2]SbF_6$	>99
2-naphthyl	H	$[Rh(COD)Cl]_2$	>99
2-naphthyl	H	$[Rh(COD)_2]SbF_6$	99.0
C_6H_5	CH_3	$[Rh(COD)_2]SbF_6$	97.3
C_6H_5	*i*-Pr	$[Rh(COD)_2]SbF_6$	99.0
C_6H_5	Bn	$[Rh(COD)_2]SbF_6$	98.6
p-CF_3-C_6H_4	CH_3	$[Rh(COD)_2]SbF_6$	98.3
p-MeO-C_6H_4	CH_3	$[Rh(COD)_2]SbF_6$	98.0
2-naphthyl	CH_3	$[Rh(COD)_2]SbF_6$	>99

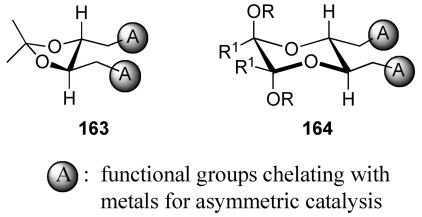


Figure 20. Chelating models of 1,4-bisphosphines.

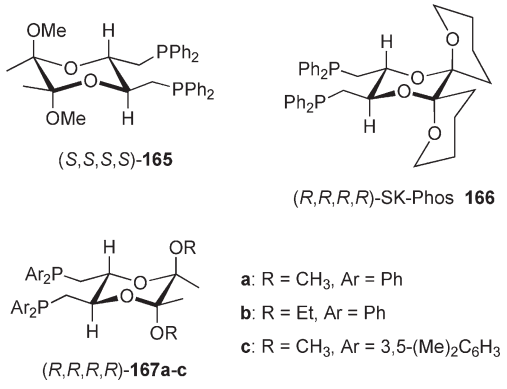


Figure 21. 1,4-Dioxane backbone based 1,4-bisphosphines.

A rhodium catalyst derived from $Rh(COD)_2PF_6$ and chiral hydroxyl phospholane **157** (Figure 18) was used in the hydrogenation of α-aryl enamides and isomeric (*E*)/(*Z*)-mixtures of *β*-substituted-α-aryl enamides **69**.[75] This gave the hydrogenated products **70** with high enantioselectivities (91−99%). Rhodium complexes of the bisphospholane ligand (*S*,*S*,*S*,*S*)-Me-ketalphos **158** and its diastereomer (*R*,*S*,*S*,*R*)-Me-ketalphos **159** were tested using the catalytic asymmetric hydrogenation of enamides **69** (Scheme 32, Table 32).[76] Complete conversions and high enantioselectivities were obtained.

A new bisphosphine ligand (*R*,*S*,*S*,*R*)-DIOP* (**162**) (Figure 19) was developed for the Rh-catalyzed asymmetric

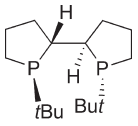


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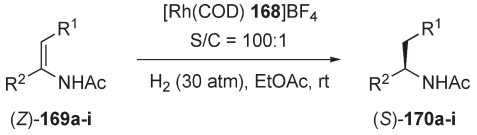
Figure 22. The ligand (1*S*,1*S*′,2*R*,2*R*′)-TangPhos.

Table 34. Asymmetric Hydrogenation of (*Z*)-169a−i with Rh/TangPhos (168) Catalyst



(*Z*)-**169a-i** (*S*)-**170a-i**

entry	enamide	R^1	R^2	ee (%)
1	**169a**	Ph	Me	99.3
2	**169b**	*o*-$MeOC_6H_4$	Me	99.0
3	**169c**	*p*-$MeOC_6H_4$	Me	96.6
4	**169d**	*m*-$MeOC_6H_4$	Me	99.1
5	**169e**	*m*-MeC_6H_4	Me	99.1
6	**169f**	*p*-MeC_6H_4	Me	98.8
7	**169g**	*o*-ClC_6H_4	Me	>99.9
8	**169h**	1-naphthyl-C_6H_4	Me	99.1
9	**169i**	Ph	Ph	98.3
10[a]	**169a**	Ph	Me	98.7

[a] Substrate/catalyst = 1000:1.

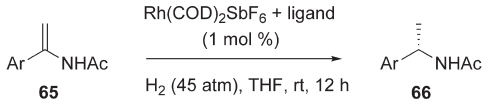
hydrogenation of a wide range of enamides **69** (Table 33).[77] In the ligand **162**, two stereogenic centers are close to the phosphorus, and the methyl groups orient themselves in equatorial positions in the seven-membered chelate ring. The rhodium catalyst was generated *in situ* from $[Rh(COD)Cl]_2$ or $[Rh(COD)_2]SbF_6$ and (*R*,*S*,*S*,*R*)-DIOP* (**162**). This catalyst gave the corresponding amine derivatives **70** with excellent enantioselectivities.

On the basis of these results, this group subsequently investigated chiral C_2-symmetric ligands containing a 1,4-dioxane backbone of the general structure **164** (Figure 20).[78] The 1,4-dioxane six-membered ring in **164** is conformationally rigid compared with the flexible 1,3-dioxolane five-membered ring in **163**. Asymmetric hydrogenation of α-aryl enamide (Ar = Ph, R = H) and various *E*/*Z* mixtures of *β*-substituted enamides **69** with rhodium catalysts generated *in situ* from $Rh(NBD)_2SbF_6$ and **165**−**167** (Figure 21) gave the products **70** with enantioselectivities ranging from 71% to 98%.

A 1,2-bisphospholane ligand, (1*S*,1*S*′,2*R*,2*R*′)-TangPhos (**168**) (Figure 22), was employed for the Rh-catalyzed asymmetric hydrogenation of enamides **69**.[79] The catalyst was generated *in situ* from $[Rh(NBD)_2]SbF_6$ (NBD = 3,5-norbornadiene) and **168** (1:1.1). A variety of α-aryl enamides and *β*-substituted isomeric enamide mixtures (*E*/*Z*)-**69** were hydrogenated to the corresponding amide derivatives **70** with excellent enantioselectivities (97% to >99%). Very recently, the utility of the Rh/TangPhos **168** catalytic system was further expanded to the hydrogenation of novel α-substituted *β*-aryl enamides (*Z*)-**169** (Table 34).[80] This allows the production of an array of amides **170** in excellent enantioselectivity. The substitution pattern on the α-phenyl ring generally has no appreciable effect on the enantioselectivity (Table 34, entries 2−4). Hindered enamides

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 33



BINAPO (R = H, Ar = Ph)

171 Me-*o*-BINAPO (R = Me, Ar = Ph)

172 Ph-*o*-BINAPO (R = Ph, Ar = Ph)

173 Xylyl-*o*-BINAPO (R = 3,5-$Me_2C_6H_3$, Ar = Ph)

174 Ph-*o*-Xylyl-BINAPO (R = Ph, Ar = 3,5-$Me_2C_6H_3$)

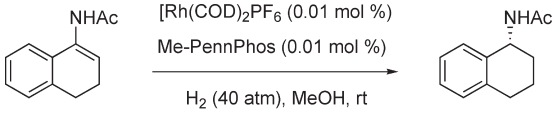
175 Ph-*o*-NAPHOS

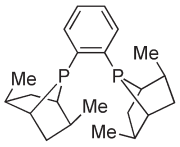
Table 35. Asymmetric Hydrogenation of Enamides 65 Using BINOL-derived Bisphosphorus Rhodium Catalysts

Ar (**65**)	ligand	ee (%)
C_6H_5	BINAPO	28.3
C_6H_5	**171**	67.2
C_6H_5	**172**	94.3
C_6H_5	**173**	89.4
C_6H_5	**174**	90.3
C_6H_5	**175**[a]	81.8
p-$CF_3C_6H_4$	**172**	96.7
m-MeC_6H_4	**172**	96.3
2-Naphthyl	**172**	94.1

[a] $Rh(COD)PF_6$ in methanol was used instead of $Rh(COD)_2SbF_6$ in THF.

Scheme 34



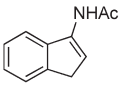
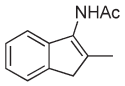
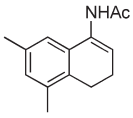
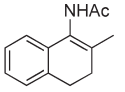
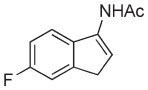
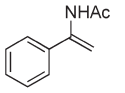
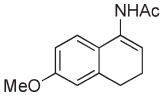
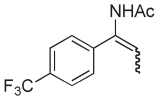
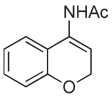
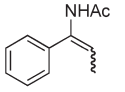
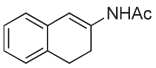


176 (*R*,*S*,*R*,*S*)-Me-PennPhos

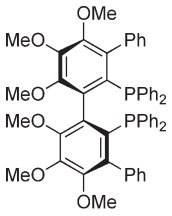
(*Z*)-**169h** and (*Z*)-**169i** were hydrogenated with excellent results (Table 34, entries 8 and 9). Notably, a much lower ee value (31%) was obtained for the *E*-configured enamide (*E*)-**169** (R^1 = Ph, R^2 = Me) with the Rh/TangPhos catalytic system.

Some novel *ortho*-substituted BINOL-derived bisphosphorus ligands (*o*-BINAPO and *o*-NAPHOS) **171**−**175** were synthesized from (*S*)-BINOL and used for the Rh-catalyzed asymmetric hydrogenation of enamides **65** (Scheme 33, Table 35).[81] These ligands form a nine-membered ring chelate with rhodium metal. The ligand **172** gave the highest enantioselectivities (94−96%).

Table 36. Me-PennPhos (176)/Rh-Catalyzed Asymmetric Hydrogenation of Cyclic and Acyclic Enamides

Entry	Substrate	*ee*[a] (%)	Entry	Substrate	*ee*[a] (%)
1		98	7		98
2		>99	8		73
3		>99	9		75
4		97	10		88
5		90	11		90
6		71			

[a] Configuration of the products as (*R*).



(*S*)-**177**

Figure 23. The ligand *o*-Ph-hexaMeO-BIPHEP.

To improve the enantioselectivity in the hydrogenation of cyclic enamides, this group investigated the reaction with PennPhos (**176**)/Rh catalyst (Scheme 34).[82] Several cyclic enamides derived from α-tetralones and α-indanones were hydrogenated with this protocol (Table 36, entries 1−8). This gave the corresponding amine derivatives with high enantioselectivities regardless of substitutions on the aromatic ring. Several acyclic enamides were also hydrogenated using PennPhos/Rh catalyst, which led to the corresponding reduced products with moderate enantioselectivities (Table 36, entries 9−11).

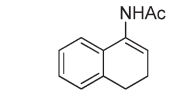
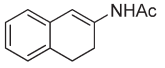
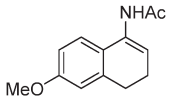
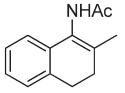
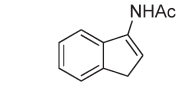
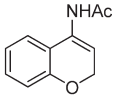
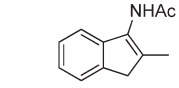
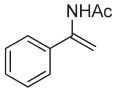
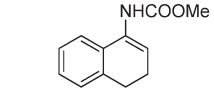
Subsequently, this group also developed a rhodium catalyst that is different from the $Rh(NBD)_2SbF_6$ catalyst in that it contains instead a substituted BIPHEP ligand, namely, *o*-Ph-hexaMeO-BIPHEP (**177**) (Figure 23), for the hydrogenation of cyclic enamides.[83] The various cyclic and acyclic enamides shown in Table 37 were hydrogenated to the corresponding amides with moderate to excellent ee's. A similar type of ligand, (*S*)-**178**, was also developed for the asymmetric hydrogenation of **76** (Scheme 35).[84]

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

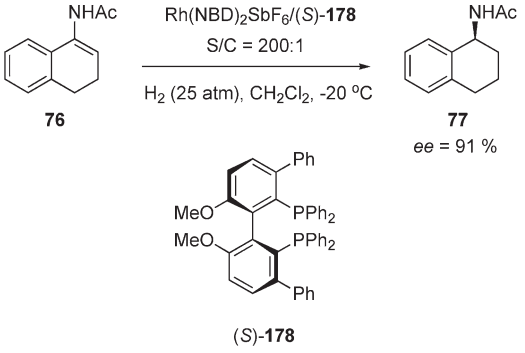
The asymmetric hydrogenation of *N*-phthaloyl enamides **179** with TangPhos/Rh catalysts was investigated recently (Scheme 36 and Table 38).[85] These reactions proceeded smoothly and gave high enantioselectivities for α-aryl enamides regardless of the electronic properties of the aromatic substituents. However, much lower ee's were reported for the substrates bearing an *ortho*-substituent on the aromatic ring.

The *N*-phthaloyl α-alkyl enamides gave very low enantioselectivity with the TangPhos/Rh catalyst. This methodology provides an easy synthesis of enantiopure primary amines **181** upon mild hydrolysis of the products **180**.

Table 37. Hydrogenation of Enamides and Enecarbamates Catalyzed by Rh/*o*-Ph-HexaMeO-BIPHEP System

Entry	Substrate	*ee* (%)	Entry	Substrate	*ee* (%)
1		98	6		45
2		98	7		37
3		96	8		66
4		99	9		70
5		96			

Scheme 35

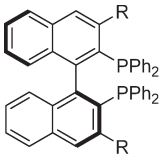


Keay et al. prepared a novel family of BINAP ligands (*S*)-**182a**−**e** with alkoxy- and acetoxy-derived substituents in the 3,3′-positions (Figure 24) and utilized them in the Rh-catalyzed hydrogenation of *N*-acetyl-phenylethenamide (Table 39).[86] The enantioselectivities in the presence of the 3,3′-substituted ligands were significantly higher than those for BINAP. Moreover, the 3,3′-disubstituted ligands provided product of the configuration opposite to that provided by BINAP.

The performance of a chiral bidentate phosphoramidite Me-BIPAM (**183**) for rhodium-catalyzed hydrogenation of α-aryl enamides **65** was tested by Miyaura and co-workers (Scheme 37, Table 40).[87] Both a preformed rhodium(I) catalyst (**184**) and a

Table 38. Asymmetric Hydrogenation of *N*-Phthaloyl Enamides 179 (Scheme 36)

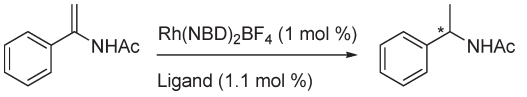
R (**179**)	ee % (180)
C_6H_5	98
4-ClC_6H_4	99
3-ClC_6H_4	99
2-naphthyl	99
2-(6-OCH_3-naphthyl)	99
4-$CH_3C_6H_4$	97
3-$CH_3C_6H_4$	98
4-FC_6H_4	98
4-$OCH_3C_6H_4$	98



(*S*)-**182a**: R = H
(*S*)-**182b**: R = *i*PrO
(*S*)-**182c**: R = MeO
(*S*)-**182d**: R = OC(O)*t*Bu
(*S*)-**182e**: R = BnO

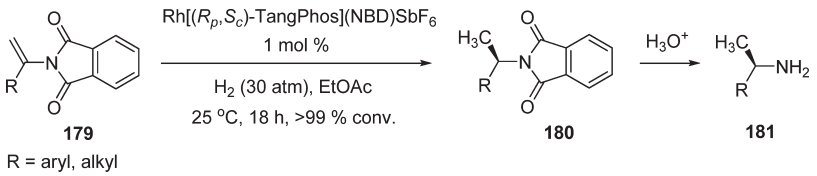
Figure 24. Ligands **182a**−**e** developed by Keay and co-workers.[86]

Table 39. Asymmetric Hydrogenation of *N*-Acetyl-phenylethenamide with Rh/(*S*)-182a−e Catalysts



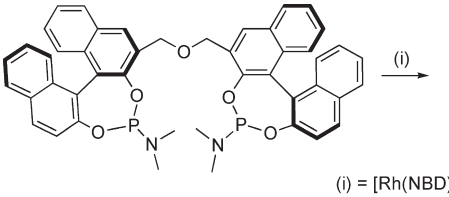
entry	ligand	ee % (config)
1	**182a**	10.7 (*R*)
2	**182b**	89.9 (*S*)
3	**182c**	26.9 (*S*)
4	**182d**	85.6 (*S*)
5	**182e**	59.6 (*S*)

Scheme 36

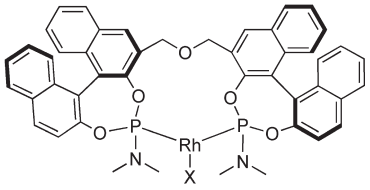


dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 37



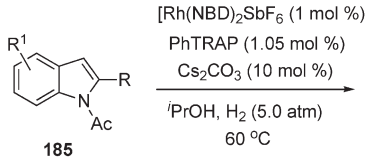
(*R*)-Me-BIPAM (**183**)



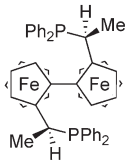
184

(X = (NBD)PF_6)

Scheme 38

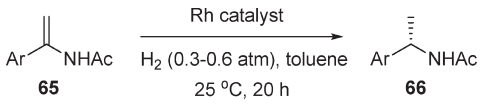


185 **186**



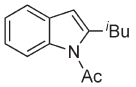
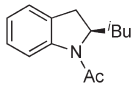
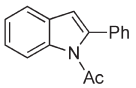
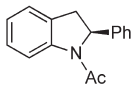
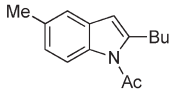
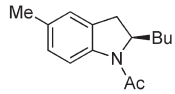
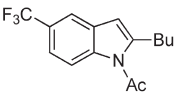
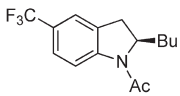
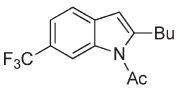
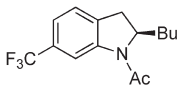
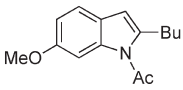
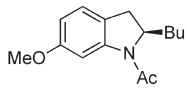
(*S*,*S*)-(*R*,*R*)-PhTRAP (**187**)

Table 40. Asymmetric Hydrogenation of Enamides 65 by 184 or Rh/183 Catalysts



entry	Ar	Rh catalyst (mol %)	conversion (%)	ee % (config)
1	Ph	$[Rh(NBD)_2]PF_6$/**183** (1)	50	95 (*S*)
2	Ph	$[Rh(NBD)_2]PF_6$/**183** (2)	>99	95 (*S*)
3	Ph	**184** (1)	72	93 (*S*)
4	Ph	**184** (1)	98	97 (*S*)
5	4-MeC_6H_4	**184** (1)	>99	85
6	3-MeC_6H_4	**184** (1)	>99	94
7	4-$MeOC_6H_4$	**184** (1)	83	77
8	4-BrC_6H_4	**184** (1)	>99	91
9	4-$CF_3C_6H_4$	**184** (1)	>99	91
10	4-$MeO_2CC_6H_4$	**184** (1)	92	86
11	2-naphthyl	**184** (1)	>99	94

Table 41. Catalytic Asymmetric Hydrogenation of 2-Substituted Indoles

Entry	Substrate **185**	Time (h)	Product **186**	Yield (%)	*ee* (%)
1		2		91	91
2		1		91	87
3		2		94	94
4		2		84	92
5		2		83	92
6		2		98	94

catalyst prepared *in situ* from **183** and $[Rh(NBD)_2]PF_6$ provided high yields and high enantioselectivity. Hydrogenation was highly sensitive to steric hindrance of *ortho*-substitutents on the aromatic ring (Table 40, entries 7 and 12). Aliphatic enamide, such as 2-acetamide-3,3-dimethyl-1-butene gave low conversion (15%).

Ito and co-workers reported the catalytic asymmetric hydrogenation of *N*-acetyl indoles **185** with rhodium complexes generated from $Rh(NBD)_2SbF_6$ and (*S*,*S*)-(*R*,*R*)-PhTRAP (**187**) (Scheme 38).[88] The presence of a base was essential for the hydrogenation to proceed, and among the several bases tested, Cs_2CO_3 was found to be effective. A variety of 2-substituted indoles were reduced to the corresponding indolines with high enantioselectivities in high yields (Table 41).

The Merck laboratories process research group made several biologically active compounds via syntheses in which enamide asymmetric hydrogenation is a key transformation. Taranabant (**188**), a cannabinoid-1 receptor inverse agonist for the treatment of obesity, was synthesized using a rhodium-catalyzed asymmetric hydrogenation of tetrasubstituted enamide **189** (Scheme 39).[89] A rhodium catalyst with a modified JosiPhos ligand **191** provided the product **190** in 94% yield and 99.7% ee. Another drug candidate, the bradykinin B1 antagonist **192**, which is used to treat pain and inflammation, was synthesized from enamide **193** (Scheme 40).[90] A variety of rhodium catalysts (**195**−**200**) were tested for the asymmetric hydrogenation of **193** (Table 42). Excellent ee's were obtained for amide **194** with the rhodium catalysts **199** and **200** derived from the BisP and TangPhos ligands, respectively.

2.1.2. Chiral Monodentate Phosphorus Ligands. The first example of Rh-catalyzed enantioselective hydrogenation of enamides with chiral monodentate phosphorus ligands was

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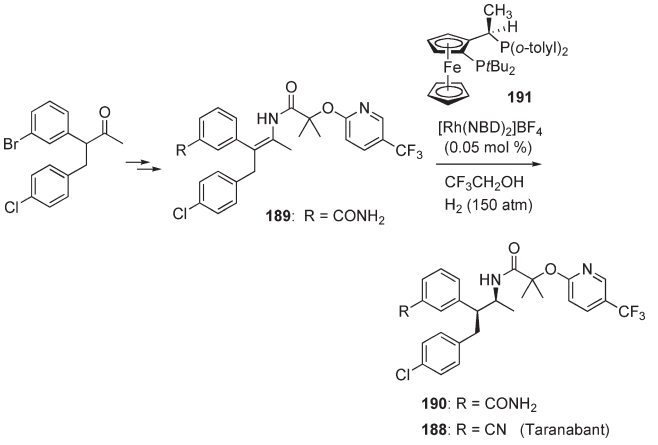
Scheme 39



Scheme 40

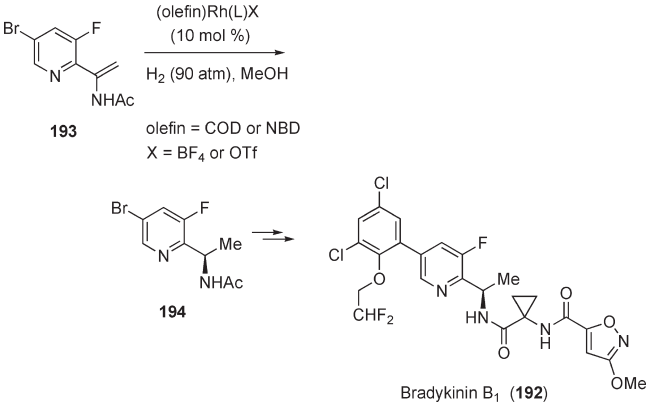
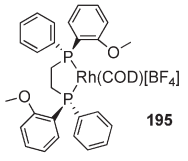
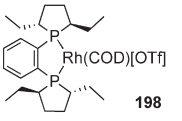
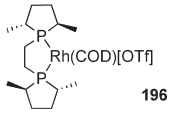
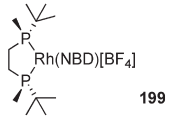
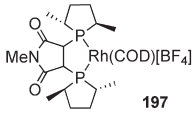
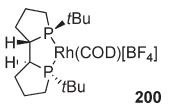


Table 42. Enantioselective Hydrogenation of Enamide 193 into 194

Entry	Catalyst	*ee* (**194**) (%)	Entry	Catalyst	*ee* (**194**) (%)
1	 **195**	84	4	 **198**	96
2	 **196**	92	5	 **199**	99
3	 **197**	94	6	 **200**	99

described by Zhou et al. in 2002.[91] The Rh catalyst prepared *in situ* from $Rh(COD)_2BF_4$ and the phosphoramidite **201a**,

Scheme 41

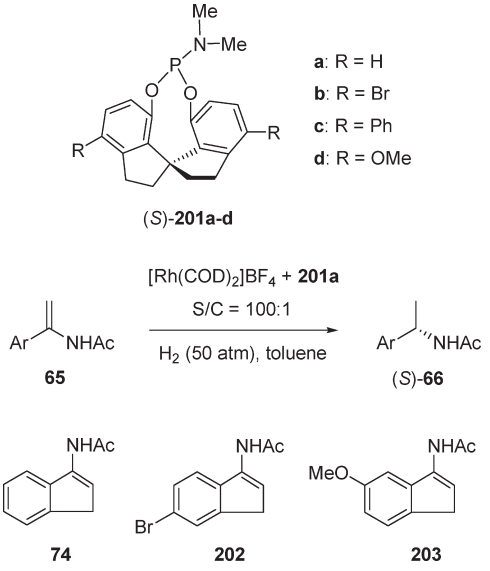


Table 43. Asymmetric Hydrogenation of 65 with Rh/(*S*)-201a Catalyst

Ar (**65**)	ee % ((*S*)-66)
C_6H_5	98.7
p-$CH_3C_6H_4$	99.7
m-$CH_3C_6H_4$	91.6
p-$CF_3C_6H_4$	98.9
p-FC_6H_4	99.1
o-FC_6H_4	91.1
p-ClC_6H_4	99.3
p-BrC_6H_4	99.5
2-furanyl	98.7
2-thienyl	95.8

which has a 1,1′-spirobiindane backbone, was employed in the hydrogenation of a variety of α-aryl enamides **65** (Scheme 41, Table 43). Cyclic enamides **74**, **202**, and **203** were also hydrogenated with Rh/**201a** catalyst in enantioselectivities of 94%, 88%, and 95%, respectively.[92] Moreover, using the related ligands **201b**−**d** in the hydrogenation of α-aryl enamides **65** (Ar = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4)[93] gave enantioselectivities ranging from 94% to 99%.

In a series of papers, Feringa and co-workers described the Rh-catalyzed enantioselective hydrogenation with a variety of monodentate phosphoramidite (**204**−**207**) and phosphine oxide (**208**) ligands (Figure 25).[94−98] Hydrogenation of enamides **209a**−**i** (Figure 26) with the Rh catalysts generated *in situ* from $Rh(COD)_2BF_4$ and 2 equiv of MonoPhos (**204**)[94,95]or its analogues, namely, PipPhos (**205**)[96] and MorfPhos (**206**),[96] in dichloromethane gave the corresponding acylated amines in high ee's and quantitative yields in most cases (Table 44). The Rh catalysts derived from the catechol-based phosphoramidite **207**[97] and the secondary phosphine oxide **208**[98] were also very effective for the hydrogenation of acyclic and cyclic enamides **209**. Quantitative yields and ee's up to 99% were obtained in all cases.

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

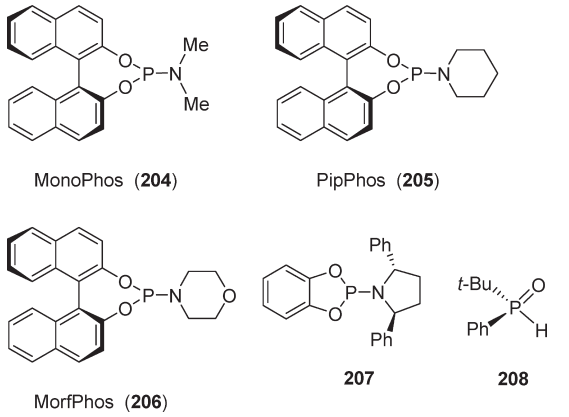


Figure 25. Monodentate phosphoramidite and phosphine oxide ligands used by Feringa and co-workers.[94−98]

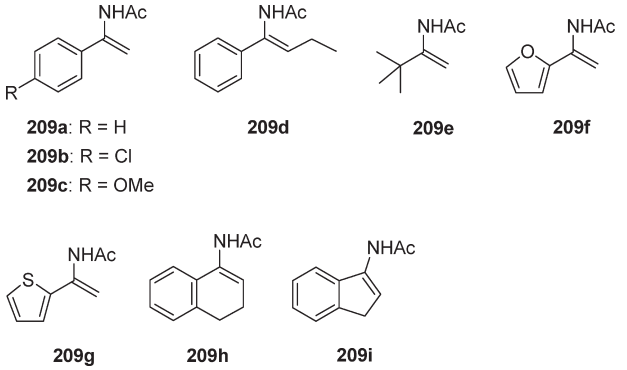


Figure 26. Some enamide substrates for the Rh-catalyzed asymmetric hydrogenation.

Table 44. Asymmetric Hydrogenation of Enamides 209a−i with Rh/204−206 Catalysts

entry	enamide	ligand	conversion (%)	ee (%)	config
1	**209a**	**204**	100	86	*S*
2		**205**	100	99	*R*
3		**206**	100	>99	*R*
4	**209b**	**204**	100	89	*S*
5		**205**	100	99	*R*
6		**206**	100	99	*R*
7	**209c**	**204**	100	86	
8		**205**	100	99	*R*
9		**206**	100	99	*R*
10	**209d**	**204**	100	84	*S*
11		**205**	100	96	*R*
12		**206**	100	98	*R*
13	**209e**	**204**	80	43	*S*
14		**205**	100	59	*S*
15	**209f**	**204**	100	85	*S*
16	**209g**	**204**	100	90	*S*
17	**209h**	**205**	100	84	*R*
18		**206**	100	87	*R*
19	**209i**	**205**	100	89	*R*
20		**206**	100	90	*R*

Scheme 42

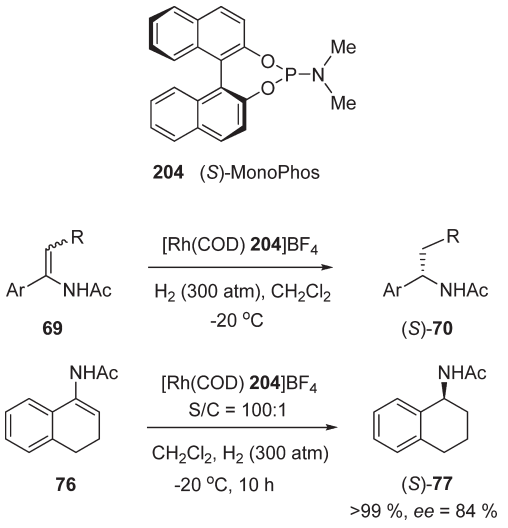


Table 45. Asymmetric Hydrogenation of Enamides 69 Catalyzed by Rh/(*S*)-MonoPhos (204)

Ar (**69**)	R (**69**)	S/C (mol/mol)	time (h)	yield (%)	ee (%)
C_6H_5	H	100	8	>99	95
p-CH_3-C_6H_4	H	100	8	>99	92
p-OCH_3-C_6H_4	H	100	8	>99	90
p-CF_3-C_6H_4	H	100	6	>99	96
1-naphthyl	H	50	18	20	70
C_6H_5	CH_3	100	18	25	89
p-Br-C_6H_4	H	100	8	>99	96
m-OCH_3-C_6H_4	H	100	8	>99	96
m-CH_3-C_6H_4	H	100	8	>99	93

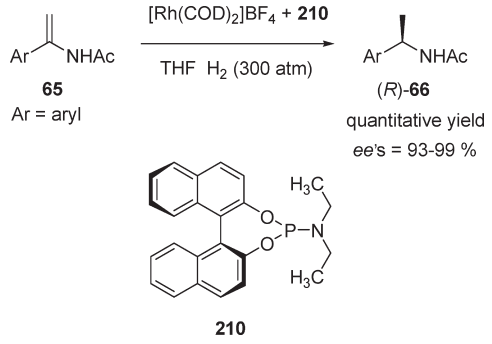
Chan et al. carried out a systematic study on the structural relationship of the MonoPhos ligands and the catalytic activities of their rhodium complexes in the hydrogenation of enamides **69** and **76** (Scheme 42, Table 45).[99] High enantioselectivities and excellent conversions were obtained in most cases. A rhodium catalyst containing phospholidine **210** (Scheme 43) gave significantly high ee's compared with the results from using MonoPhos.[100] With use of Rh/**210** catalyst (Scheme 43), a variety of α-aryl enamides **65** were hydrogenated in both excellent yield and high enantioselectivity except in the case of the hindered enamide **65** with Ar = 1-naphthyl, which gave a yield of 85% and an ee of 59%.

Rhodium catalysts of the monodentate phosphoramidite ligands **211**−**215** (Figure 27) derived from H_8-BINOL were used for the asymmetric hydrogenation of enamides **69**.[101] Screening experiments showed promising results with the ligand **211** bearing an *N*,*N*-dimethyl phosphoramidate group. A variety of enamides **69** were hydrogenated with the rhodium catalyst generated *in situ* from $[Rh(COD)_2]BF_4$ and **211** in THF under 300 atm of H_2 pressure. The ee values were found to be consistently 3% higher in most cases in comparison with those obtained with (*S*)-MonoPhos/Rh catalyst.

Ding et al. developed for hydrogenation reactions the supramolecular metal−organic polymer catalyst **216**[102] (Figure 28), the

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 43



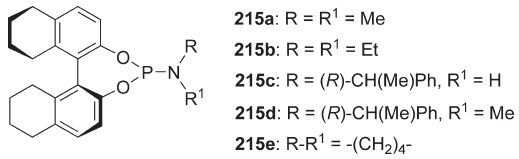


Figure 27. Monodentate phosphoramidite ligands **211**−**215**.

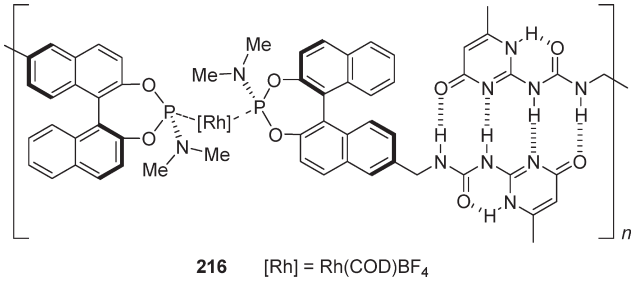
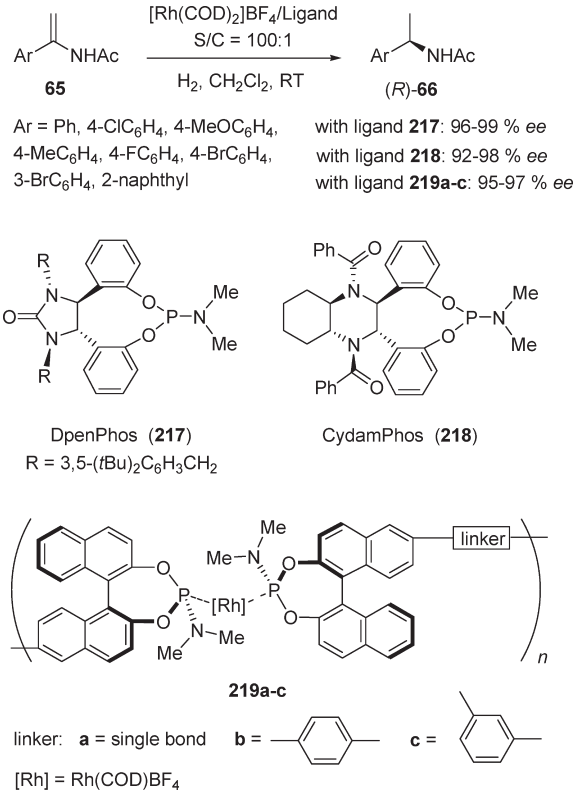


Figure 28. Supramolecular polymer catalyst.

monodentate phosphoramidite ligands DpenPhos (**217**)[103] and CydamPhos (**218**),[104] and linker attached monophosphoramidite ligands **219a**−**c**[105] (Scheme 44). With the catalyst **216**, enamide **65** (Ar = Ph) was hydrogenated in toluene under 40 atm of hydrogen to the corresponding amine derivative **66** in 91% ee with 99% yield. In parallel, the Rh catalysts of **217**−**219** were used for hydrogenation of a wide variey of α-aryl enamides **65** (Scheme 44).

Reetz et al. studied the utilility of BINOL-derived ligands of the types shown in **220** (Figure 29) for Rh-catalyzed hydrogenation of enamides **69** (Table 46).[106] The hydrogenation of enamide **69** (Ar = Ph, R = H) using [Rh(COD)(**221**)$_2$]BF$_4$ precatalysts derived from the novel BINOL-based *N*-phosphino sulfoximines **221** (Figure 30) leads to the amine derivative **70** (Ar = Ph, R = H) in quantitative yields with moderate to good enantioselectivities (64−87%).[107] Furthermore, a combinatorial exploration of asymmetric catalysts based on mixtures of BINOL-derived monodentate phosphates **220** and phosphonites **222a**−**c** for the Rh-catalyzed hydrogenation of enamides **65a**,**b** was carried out (Scheme 45).[108] For **65a**, two hits were found, one of which was a mixture of **220** (R = CH_2Ph) and **222b** to give 97.4% ee and the other of which was a combination of **220** (R = CH_3) and **222b** to give 95% ee. For the naphthyl substrate **65b**, the best enantioselectivity (97%) was obtained with a mixture of **222a** and **222b** or a combination of **220** (R = CH_3) and **222b**.

Scheme 44



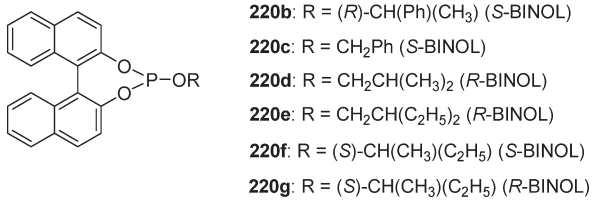


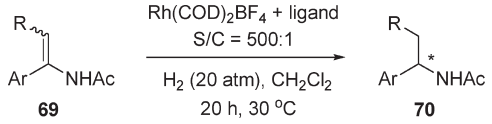
Figure 29. The BINOL-based ligands **220a**−**g**.

Recently, hydrogenation of **65a** was also performed with mixtures of the ligands **222a** and **222b**.[109] The homocombinations (*S*)-**222a** and (*S*)-**222b** gave a higher enantioselectivity (95%) than the other combinations.

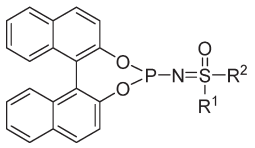
In a series of papers, Zheng and co-workers have reported the rhodium-catalyzed asymmetric hydrogenation of enamides using a variety of monodentate phosphine ligands.[110−114] Novel ferrocenylethylamine-derived monophosphoramidite **223**[110] and PEG monomethyl ether-derived polymer monophosphite **224**[111] (Figure 31) were synthesized for the hydrogenation of enamides **225** (Table 47). Excellent enantioselectivities were obtained in each case regardless of the electronic properties of the aryl group on the enamide (Table 47, entries 1−7). Notably, Rh/**223** and Rh/**224** complexes also exhibited high enantioselectivity for the hydrogenation of *E*/*Z* mixtures of *β*-substituted enamides **225** and gave the hydrogenation product with an ee of up to 97% (Table 47, entries 8−9). The ligand **224** has several advantages such as being air stable, recoverable from the reaction mixture, and conveniently recyclable several times.

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Table 46. Rh/220a−g Catalyzed Asymmetric Hydrogenation of Enamides 69



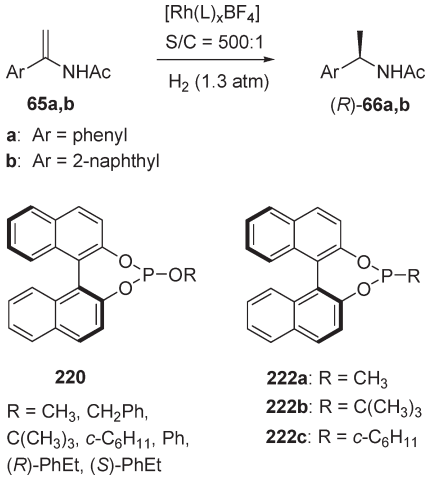
entry	Ar, R	ligand	conversion (%)	ee % (config)
1	2-naphthyl, H	**220a**	100	93.7 (*R*)
2	2-naphthyl, H	**220c**	100	94.3 (*R*)
3	2-naphthyl, H	**220d**	100	>92.0 (*S*)
4	2-naphthyl, H	**220e**	100	>93.0 (*S*)
5	2-naphthyl, H	**220f**	99.0	90.6 (*R*)
6	2-naphthyl, H	**220g**	99.5	>93.4 (*S*)
7	C_6H_5, H	**220a**	100	95.3 (*R*)
8	*p*-Cl-C_6H_4, H	**220b**	100	95.8 (*R*)
9	C_6H_5, Me (95% *Z*)	**220b**	100	97.0 (*R*)
10	C_6H_5, Me (84% E)	**220b**	69	76.2 (*R*)



221a: R_{BINOL}/S_{Sulf}; R^1 = Ph, R^2 = Me
221b: S_{BINOL}/S_{Sulf}; R^1 = Ph, R^2 = Me
221c: R_{BINOL}; $R^1 = R^2$ = Me
221d: R_{BINOL}; $R^1 = R^2$ = Ph

Figure 30. The ligands **221a−d**.

Scheme 45



Rhodium catalysts of the chiral monophosphites derived from a combination of carbohydrate and BINOL were used for the hydrogenation of α-aryl enamides **69** (Scheme 46).[112] For enamide **69** (Ar = Ph, R = H), the best enantioselectivities (95%) were found with ligands **227** and **228**, which bear the (*R*)-BINOL and (*S*)-BINOL matched carbohydrate backbone, respectively. With the rhodium catalyst derived from **227**, the scope of the reaction was expanded to various enamides **69** (Table 48). High enantioselectivities were obtained both for electron-withdrawing and electron-donating substituents on the phenyl group of the enamides. It is noteworthy that the ee values

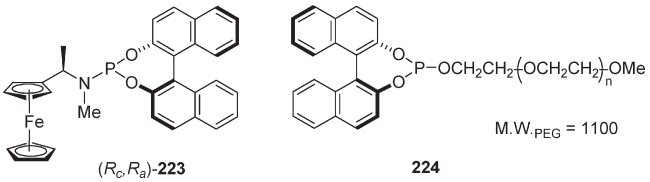
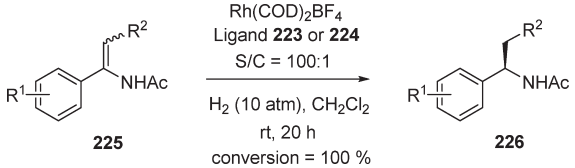


Figure 31. Monophosphoramidite **223** and polymer monophosphite **224** by Zheng and co-workers.[110,111]

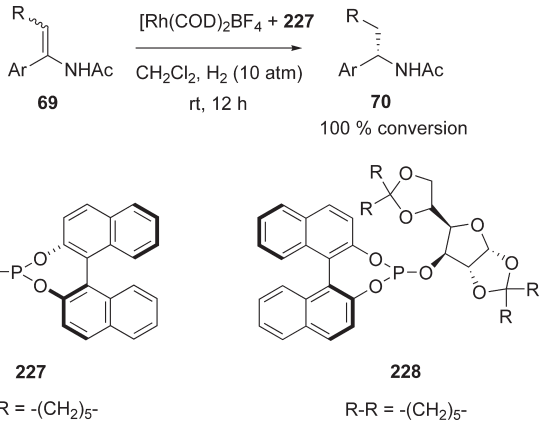
Table 47. Asymmetric Hydrogenation of Enamides 225 Catalyzed by Rh/223 and Rh/224 Complexes



entry	R^1	R^2	ligand **223**/ee % (**226**)	ligand **224**/ee % (**226**)
1	H	H	>99[a]	98
2	4-CF_3	H	99	97
3	4-Cl	H	99	98
4	4-Br	H	99	98
5	4-Me	H	>99	98
6	4-OMe	H	98	99
7	3-OMe	H	99.5	98
8	H	Me	94	97
9	H	Et	96	97

[a] Reaction performed in EtOAc.

Scheme 46



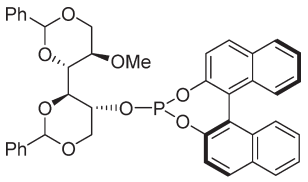
with **227** are higher than those obtained from Reetz's monophosphites[106] or modified MonoPhos.[100]

The monophosphite ligand **229** (Figure 32) was used in the Rh-catalyzed hydrogenation of α-aryl enamides **69** (Table 49).[113] Quantitative yields and high enantioselectivities were obtained in all cases except for the *ortho*-substituted enamide (Table 49, entry 5). Hydrogenation also proceeded smoothly for the β-substituted enamide mixture (*E*/*Z*) (entry 8) and the cyclic enamide (entry 9).

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Table 48. Rh/227 Catalyzed Asymmetric Hydrogenation of Enamides 69

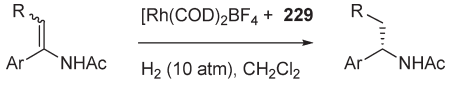
Ar, R (**69**)	ee % (*S*)-**70**
Ph, H	95.0
p-FC_6H_4, H	96.5
p-BrC_6H_4, H	98.5
p-$OMeC_6H_4$, H	95.9
p-$CF_3C_6H_4$, H	98.5
2-naphthyl, H	96.9
Ph, Me	96.7



229

Figure 32. Monophosphite **229** developed by Zheng and co-workers.[113]

Table 49. Rh/229 Catalyzed Asymmetric Hydrogenation of Enamides 69[a]



69 **70**

Entry	Ar, R	*ee* %
1	Ph, H	99.8
2	*p*-FC_6H_4, H	99.9
3	*p*-ClC_6H_4, H	99.7
4	*p*-$OMeC_6H_4$, H	99.5
5	*o*-ClC_6H_4, H	79.1
6	*p*-$CF_3C_6H_4$, H	99.9
7	2-naphthyl, H	99.5
8	Ph, Me	99.2
9[b]	Ph, Me	99.5

[a] Catalyst was 1 mol % [b] S/C = 1000:1.

Monophosphite ligands **230**−**232** (Figure 33) derived from carbohydrates and H_8-BINOL were tested for Rh-catalyzed asymmetric hydrogenation of enamide **69**.[114] The reactions proceeded smoothly in most cases and gave **70** with full conversion and excellent enantioselectivities with ee's often in the range 96−99%.

Reek et al. studied the high-throughput screening of a supramolecular catalyst library for the asymmetric hydrogenation of trisubstituted cyclic enamide **233** (Scheme 47).[115] The combination of

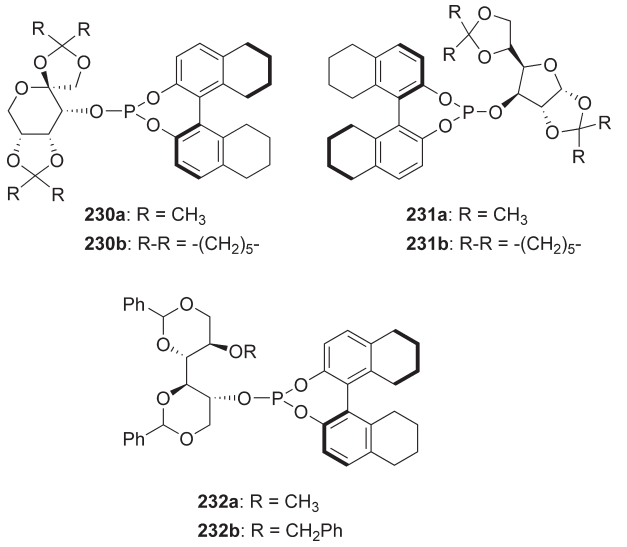
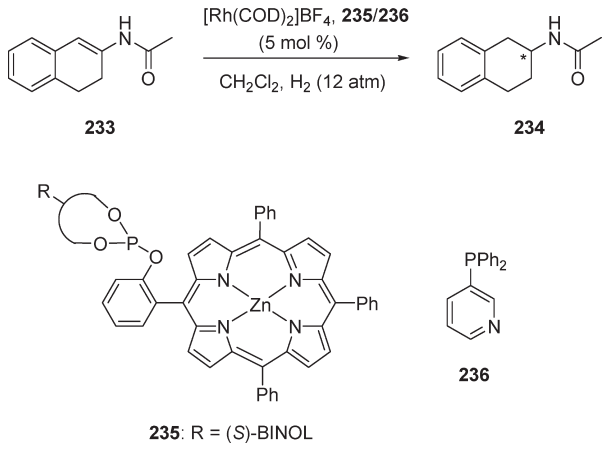


Figure 33. Carbohydrates and H_8-BINOL derived ligands by Zheng and co-workers.[114]

Scheme 47



porphyrin−phosphite **235** and pyridyl phosphorus **236** gave the best result (94% ee with 100% conversion) for the amine derivative **234**. In another report, the same group described the hydrogenation of **233** in low yield and 77% ee with a novel class of bidentate ligands that are formed by a self-assembly of urea appended two monodentate ligands.[116a] The rhodium catalyst $[Rh(NBD)(\mathbf{237a})_2]BF_4$ was derived from ligand **237a** (Figure 34). Very recently, a library of 12 new chiral urea-functionalized ligands **237b**−**m** that form supramolecular bidentate ligands in the presence of a rhodium catalyst precursor was tested on enamides **233** and **233a** (Figure 34).[116b] Enantioselectivities up to 66% and 72% for **233** and **233a**, respectively, were obtained.

New supramolecular chiral dendritic ligands (Figure 35) were applied to the Rh-catalyzed asymmetric hydrogenation of α-aryl enamides **65** (Table 50).[117] The catalysts were prepared *in situ* by reacting 2 equiv of the preformed second- and third-generation dendritic ligands $\mathbf{DG_2L_1}$ and $\mathbf{DG_3L_1}$ with $[Rh(COD)_2]BF_4$ in CH_2Cl_2. The hydrogenations

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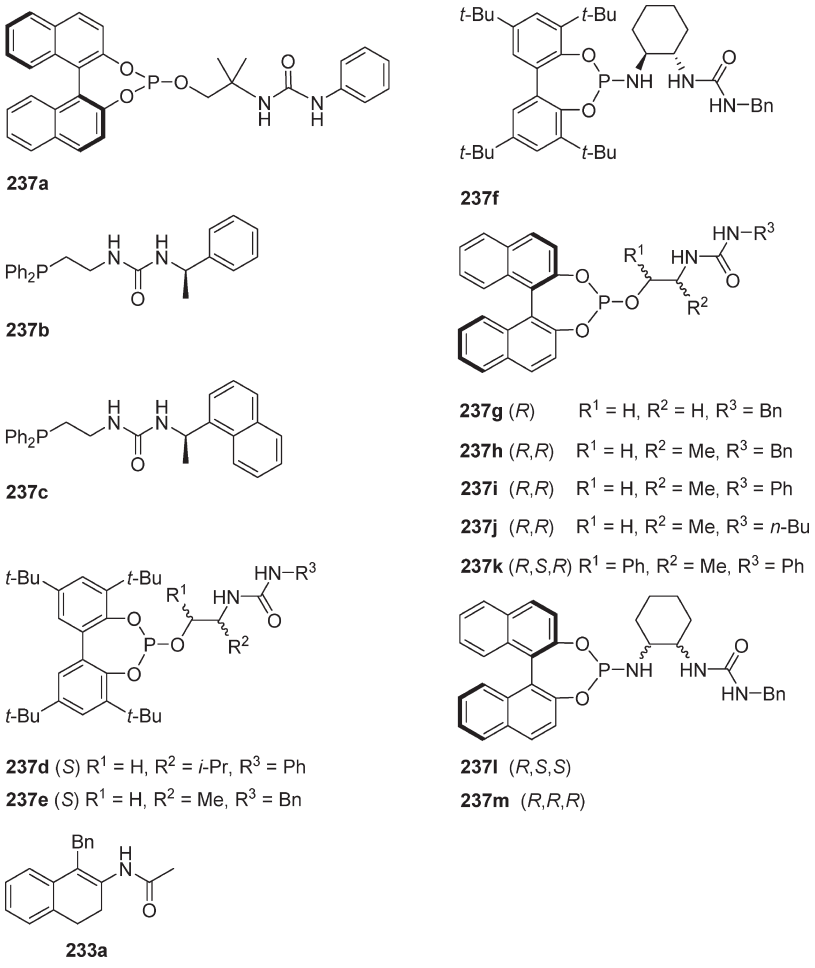

Figure 34. Urea appended phosphite ligands **237a**−**m** and enamide **233a**.

proceeded smoothly and provided the reduced products **66** with complete conversion and good enantioselectivity (83−90% ee). The supramolecular catalyst could be recycled and reused readily at least 5 times without obvious loss of enantioselectivity and reactivity.

The polymer-supported monodentate phosphite ligands **238a**−**e** (Figure 36) were developed by Chen et al. for Rh-catalyzed enantioselective hydrogenation of enamide **65** (Ar = Ph).[118] These reactions were carried out with catalysts generated *in situ* from $Rh(COD)_2OTf$ and ligands **238a**−**e** in CH_2Cl_2 under hydrogen at 200 atm. This gave the amide **66** (Ar = Ph) with excellent enantioselectivity (up to 96.4% ee) in quantitative conversion.

Gennari and co-workers synthesized a library of 10 chiral TROPOS phosphorus ligands **239**−**248** based on a flexible biphenol unit and a chiral P-bound alcohol (five phosphites) or a secondary amine (five phosphoramidites) (Figure 37).[119] These ligands were screened as a combination of two in the rhodium-catalyzed asymmetric hydrogenation of enamides **249a**, **b** (Table 51). Low to moderate enantioselectivities were obtained for the arylalkylamines **250a**,**b**.

Takacs et al. applied the ligand scaffolds of chiral triazole diphosphites **251** and **252** (Figure 38) to the rhodium-catalyzed asymmetric hydrogenation of enamides **65** (Table 52).[120] It was shown that the active catalyst is a 16-membered *P*,*P*-macrocyclic Rh(I) chelate.

Rampf et al. used the chiral phosphate ligand **254** for the rhodium-catalyzed asymmetric hydrogenation of acyclic and cyclic enamides **249a**,**b** and **76**, respectively (Figure 39).[121] This gave the reduced products in low to moderate enantioselectivities (8−81% ee).

Fiaud and Toffano et al. employed phospholanes **255**,[122] **256**,[123] and **257a**,**b**[124] for the hydrogenation of some cyclic and acyclic enamides (Scheme 48). Unfortunately, the enantioselectivities are low or moderate in all cases.

Beller et al. tested the chiral phosphepines **258** in the rhodium-catalyzed asymmetric hydrogenation of different acyclic and cyclic enamides (Scheme 49).[125] Enantioselectivity up to 95% was obtained with ligands **258a** and **258e** for the enamides **259b** and **259c** bearing electron-donating substituents (Table 53). The cyclic enamide **76** was hydrogenated using different catalysts [Rh]/(**258a**), [Rh]/(**258e**), and [Rh]/(**258i**) giving excellent yields (>99%) of **77** but in low enantioselectivities (Scheme 49, eq 2).

A few years ago Bruneau and co-workers briefly reviewed the application of monodentate phosphorus ligands for the rhodium-catalyzed asymmetric hydrogenation of a class of olefins comprising the *N*-(1-arylethenyl)acetamides and cyclic amides.[126]

2.2. Ruthenium Catalysts

In the early stages of the development of catalytic asymmetric hydrogenation, the rhodium/chiral phosphines were the

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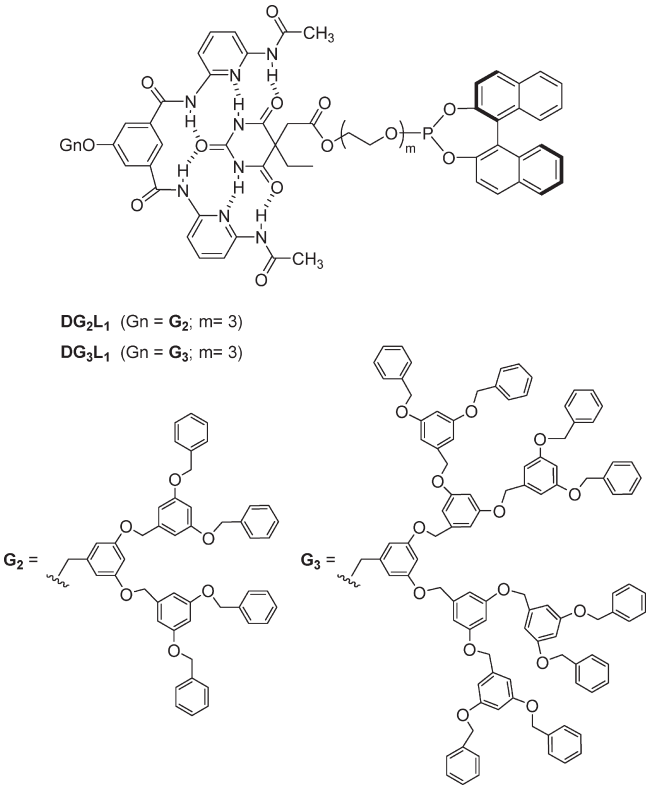

Figure 35. Supramolecular chiral dendritic monophosphite ligands assembled by hydrogen bonding.

Table 50. Asymmetric Hydrogenation of Enamides 65 Catalyzed by Supramolecular Dendritic Catalysts Rh/DG_2L_1 or Rh/DG_3L_1

ligands	Ar	ee (%)
DG_3L_1	C_6H_5	87
DG_2L_1	4-Cl-C_6H_4	83
DG_3L_1	4-Cl-C_6H_4	87
DG_2L_1	4-Br-C_6H_4	85
DG_3L_1	4-Br-C_6H_4	88
DG_2L_1	4-Me-C_6H_4	89
DG_3L_1	4-Me-C_6H_4	90

preferred catalysts, especially for C═C bond reductions. Since the mid-1980s spectacular advances have been seen using ruthenium/BINAP complexes.[127,128] The ability to prepare ruthenium complexes with a large variety of chiral phosphorus ligands to catalyze hydrogenation of C═C or C═O double bonds is especially useful. These catalysts are also useful in enantioselective enamide hydrogenation, as described below.

In work directed toward the goal of achieving asymmetric syntheses of some alkaloids, Noyori et al. have studied the catalytic asymmetric hydrogenation of the *N*-acyl-1-alkylidene-tetrahydroisoquinolines (*Z*)-**262a**−**d** and **264**−**266** by using

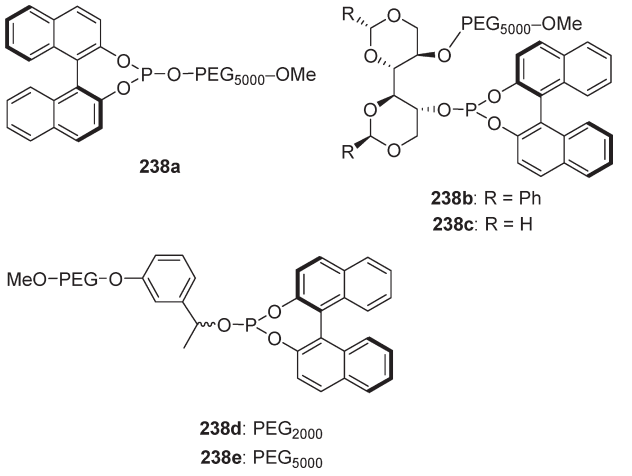

Figure 36. Polymer-supported chiral phosphite ligands **238a**−**e**.

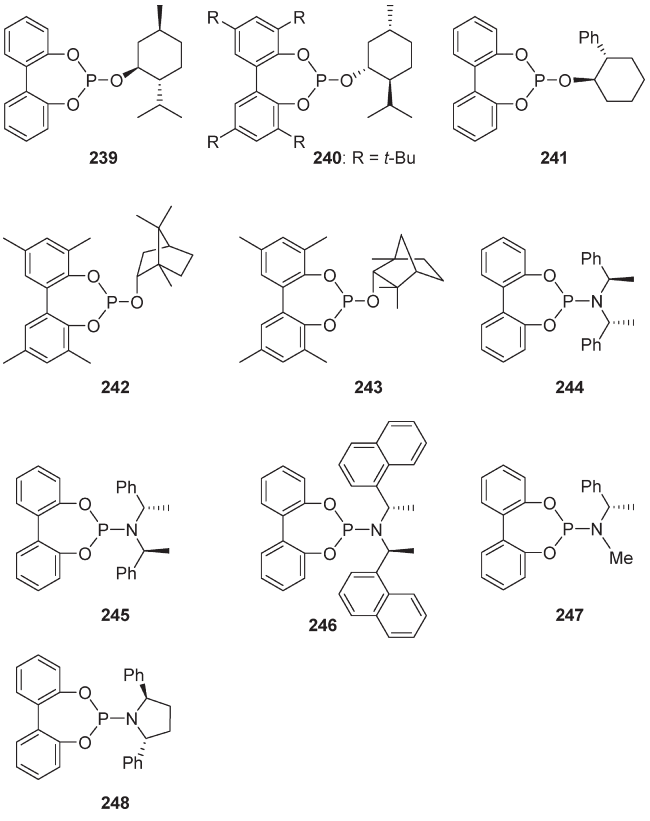

Figure 37. Library of 10 ligands, five phosphites (**239**−**243**) and five phosphoramidites (**244**−**248**).

ruthenium complexes bearing a chiral BINAP ligand, Δ-(*R*)-**261** and Λ-(*S*)- **261** (Scheme 50).[129] This gave tetrahydropapaverine derivatives in high yield with excellent enantioselectivity. The generality of the reaction is illustrated in Table 54. The *Z* enamide substrates (*Z*)-**262** having an appropriate *N*-acyl group proceeded smoothly to give the hydrogenated products, whereas *E* enamide substrates (*E*)-**262** were inert to the Ru-catalyzed hydrogenation conditions. The reaction using Δ-(*R*)-**261** as catalyst generally gave the 1*R* products predominantly, while the 1*S*

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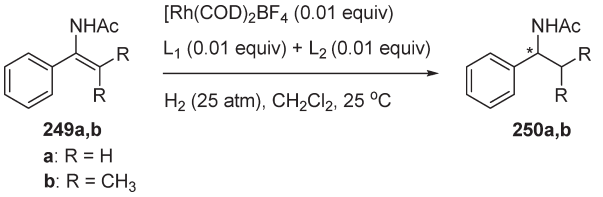
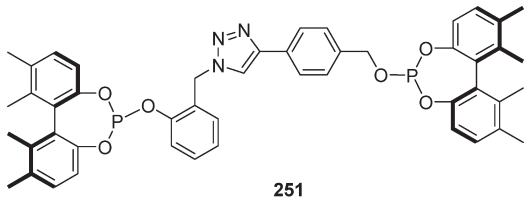
Table 51. Selective Results for the Hydrogenation of Enamides 249a,b



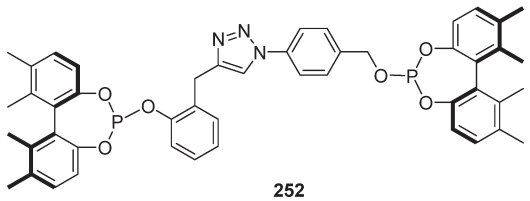
249a,b
a: R = H
b: R = CH_3

250a,b

substrate	L_1	L_2	conversion (%)	ee % (config)
249a	**241**	**241**	100	85(*S*)
249a	**243**	**243**	100	75(*S*)
249a	**239**	**248**	100	64(*S*)
249a	**241**	**245**	100	82(*S*)
249a	**241**	**246**	100	79(*S*)
249a	**240**	**247**	100	66(*S*)
249b	**239**	**248**	72	39
249b	**240**	**244**	55	36
249b	**242**	**248**	100	38
249b	**243**	**248**	100	47



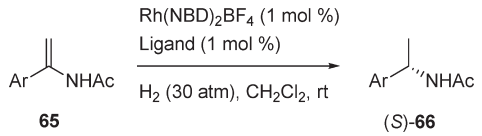
251



252

Figure 38. Click-connected ligand scaffolds by Takacs and co-workers.[120]

Table 52. Rh/251,252 Catalyzed Asymmetric Hydrogenation of Enamides 65

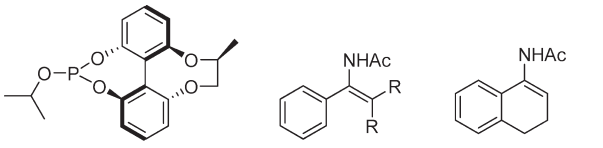


65

(*S*)-**66**

Ar	ligand	yield (%)	ee (%)
4-Cl-C_6H_4	**251**	99	96
C_6H_5	**252**	90	92
2-naphthyl	**252**	82	90

enantiomers were obtainable by the catalysis with Λ-(*S*)-**261**. Rhodium complexes such as [Rh(COD)(BINAP)]ClO_4 or [Rh(CH_3OH)$_2$(BINAP)]ClO_4 in the place of **261** did not give satisfactory results. The hydrogenation of (*Z*)-**262d** catalyzed by



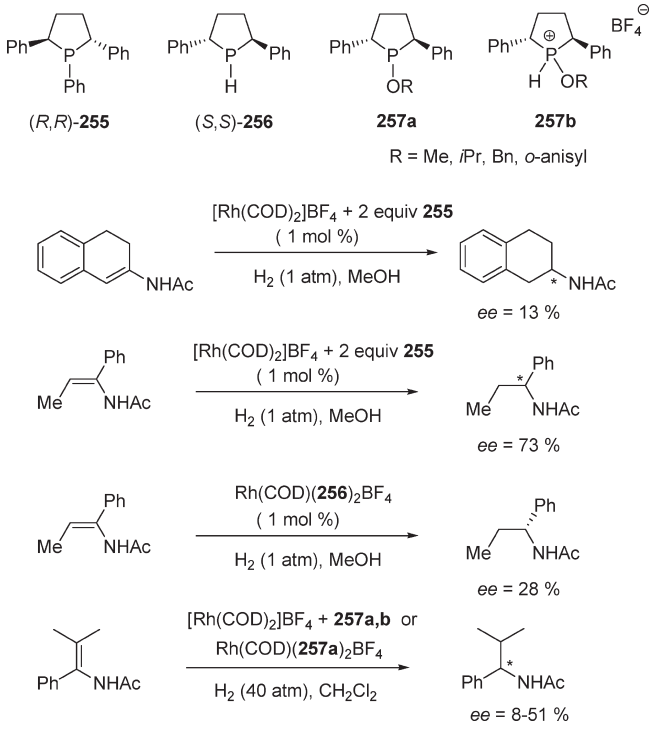
254

249a: R = H
249b: R = CH_3

76

Figure 39. Modentate phosphine ligand **254** and enamides **249a,b** and **76**.

Scheme 48



Δ-(*R*)-**261** and subsequent $LiAlH_4$ reduction produced (*R*)-laudanosine (**263**) in >99.5% ee. The Δ-(*R*)-**261**-catalyzed hydrogenation of the *Z* enamide **264** gave, after deacetylation and debenzylation, (*R*)-tretoquinol (**267**). In a similar manner, enamide **265** was converted into (*R*)-norreticuline (**268**) and was transformed into natural morphine. The catalytic reduction of the simple methylene derivative **266** afforded, after deacetylation, (*S*)-salsolidine (**269**) in 96% ee.

Chiral artificial morphines were synthesized via ruthenium-catalyzed enantioselective hydrogenation of enamides as a key transformation.[130] The (*Z*)-enamide **270a** with (*R*)-TolBINAP/Ru catalyst under 100 atm of hydrogen pressure afforded the (*R*)-**271a** in 98% ee and in 98% yield (Scheme 51). Hydrogenation of (*Z*)-enamide **270b** with (*S*)-TolBINAP/Ru catalyst gave (*S*)-**271b** in quantitative yield with 97% ee.

The BINAP/Ru(II) catalysts **261** were also applied to the asymmetric hydrogenation of the enamide functionality in a wide array of tetrahydroisoquinolines **272,273** and dihydroisoquinolines **274,275** (Scheme 52, Figure 40).[131] Hydrogenations were carried out in a 5:1 methanol− or ethanol−dichloromethane solution. This gave the hydrogenated products in excellent conversion

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and enantioselectivities (Table 55). The (*R*)-BINAP/Ru-catalyzed reaction of (1*Z*)-benzylidene substrates leads predominantly to the 1*R* benzylated products, whereas 1*S* enriched products are obtained by the reaction with (*S*)-BINAP/Ru catalyst.

The perfluoroalkyl-tagged (*S*)-BINAP **276** (Figure 41) was tested for the ruthenium-catalyzed asymmetric hydrogenation of *N*-acetyl-α-phenylethenamine in methanol.[132] It gave the hydrogenated product with 44% ee in 64% yield. The advantages of the Ru/**276** catalyst are the easy recovery, reusability, and low leaching of ruthenium.

Bruneau and co-workers published a series of papers on the ruthenium-catalyzed asymmetric hydrogenation of enamides.[133−136] Enantiopure *N*-acyloxazolidinones **278a−e** were synthesized by hydrogenation of oxazolidinones **277a−e** derived from cyclic carbonates (Scheme 53).[133] Tests of a variety of chiral ruthenium complexes containing the BINAP and BiPhemp diphosphine ligands showed these complexes to be very efficient in terms of activity and enantioselectivity (Table 56). The hydrogenated *N*-acyloxazolidinones were produced as the sole products in more than 85% yield. This method also suffices for the preparation of both enantiomers of *C*(5)-symmetrically disubstituted *N*-acyloxazolidinones. It was presumed that the excellent enantioselectivities related to the coordination of both the

Scheme 49

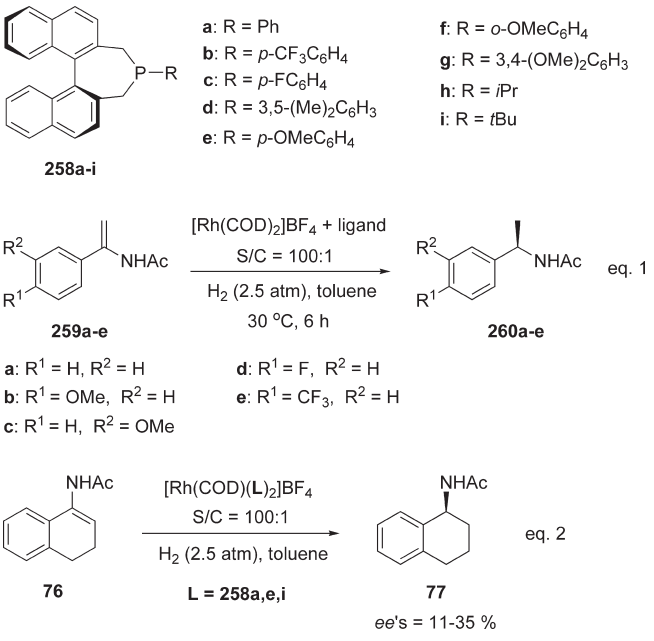
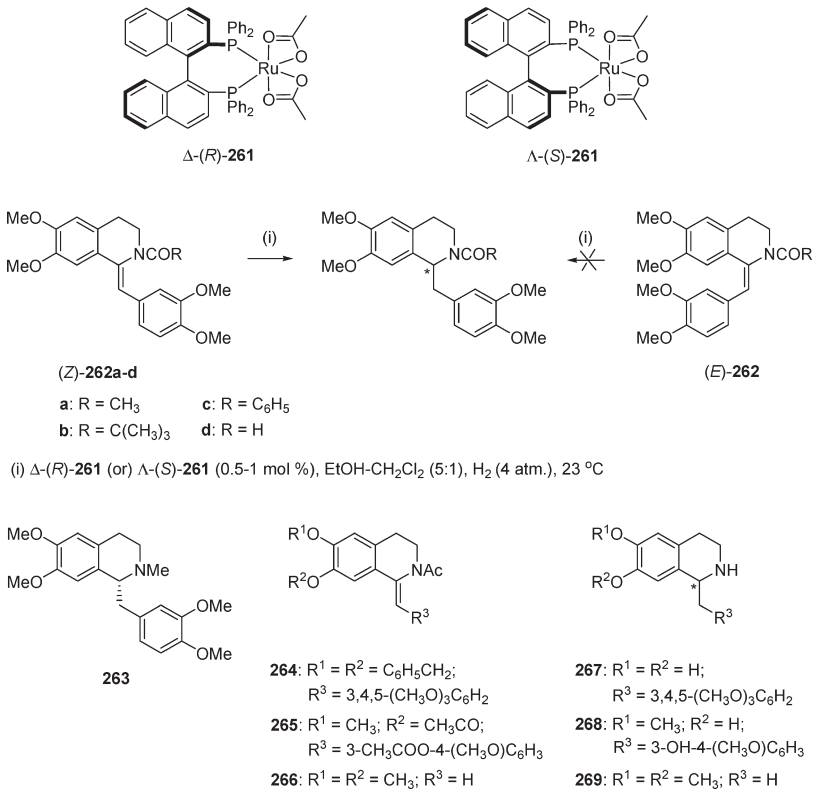


Table 53. Rh/258a−i Catalyzed Asymmetric Hydrogenation of Enamides 259a−e

ligand	*ee* % (**260a**) (config)	*ee* % (**260b**) (config)	*ee* % (**260c**) (config)	*ee* % (**260d**) (config)	*ee* % (**260e**) (config)
258a	93 (*R*)	91 (*R*)	95 (*R*)	86 (*R*)	78 (*R*)
258b	72 (*R*)	63 (*R*)	72 (*R*)	51 (*R*)	62 (*R*)
258c	88 (*R*)	79 (*R*)	84 (*R*)	71 (*R*)	73 (*R*)
258d	87 (*R*)	87 (*R*)	87 (*R*)	71 (*R*)	65 (*R*)
258e	93 (*R*)	92 (*R*)	89 (*R*)	86 (*R*)	78 (*R*)
258f	63 (*R*)	33 (*R*)	53 (*R*)	34 (*R*)	68 (*R*)
258g	90 (*R*)	89 (*R*)	89 (*R*)	83 (*R*)	85 (*R*)
258h	30 (*R*)	rac	26 (*R*)	4 (*R*)	44 (*R*)
258i	16 (*S*)	21 (*S*)	23 (*S*)	rac	25 (*S*)

Scheme 50

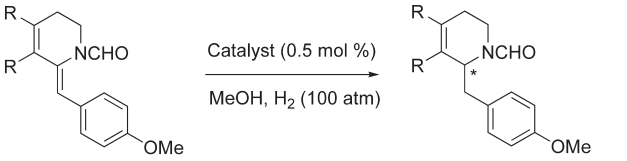


dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Table 54. Asymmetric Hydrogenation of (*Z*)-262a−d and 264−266 by Λ-(*S*)-261 Catalyst

		product		
substrate	time (h)	yield (%)	*ee* (%)	config
(*Z*)-**262a**	48	100	>99.5	*S*
(*Z*)-**262b**	48	100	50	*S*
(*Z*)-**262c**	158	100	96	*S*
(*Z*)-**262d**	48	100	>99.5	*S*
264	96	100	96	*S*
265	49	97	96	*S*
266	48	100	96	*S*

Scheme 51

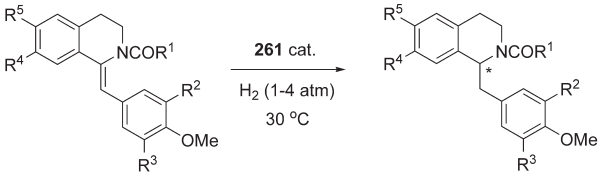


270a: R = CH_3
270b: R-R = -$(CH_2)_4$-

271a: R = CH_3
271b: R-R = -$(CH_2)_4$-

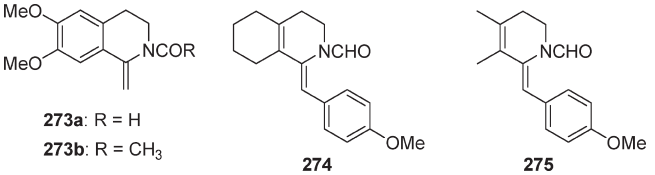
Catalyst = [Ru$(OCOCF_3)_2$(*R*)-TolBINAP] or [Ru$(OCOCF_3)_2$(*S*)-TolBINAP

Scheme 52



(*Z*)-**272a-i**

enamide	R^1	R^2	R^3	R^4	R^5
272a	H	OCH_3	H	OCH_3	OCH_3
272b	CH_3	OCH_3	H	OCH_3	OCH_3
272c	C_6H_5	OCH_3	H	OCH_3	OCH_3
272d	*p*-BrC_6H_4	OCH_3	H	OCH_3	OCH_3
272e	CH_3	OCH_3	OCH_3	$OCH_2C_6H_5$	$OCH_2C_6H_5$
272f	H	OH	H	OH	OCH_3
272g	CH_3	$OCOCH_3$	H	$OCOCH_3$	OCH_3
272h	H	$OCH_2C_6H_5$	$OCH_2C_6H_5$	H	OCH_3
272i	H	OH	H	H	OCH_3



273a: R = H
273b: R = CH_3

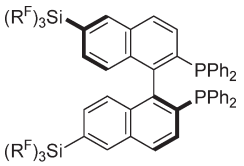
274 **275**

Figure 40. Some enamide substrates.

Table 55. Ru(II)/BINAP-Catalyzed Asymmetric Hydrogenation of Enamides

		product		
enamide	catalyst[a]	yield (%)	ee (%)	config
(*Z*)-**272a**	(*S*)-**261**	100	>99.5	*S*
(*Z*)-**272b**	(*S*)-**261**	100	>99.5	*S*
(*Z*)-**272c**	(*S*)-**261**	100	96	*S*
(*Z*)-**272d**	(*S*)-**261**	100	98	*S*
(*Z*)-**272e**	(*S*)-**261**	100	96	*S*
(*Z*)-**272f**	(*R*)-**261**	98	99	*R*
(*Z*)-**272g**	(*S*)-**261**	97	96	*S*
(*Z*)-**272h**	(*R*)-**261**	86	97	*R*
(*Z*)-**272i**	(*R*)-**261**	98	99	*R*
273a	(*S*)-**261**	100	97	*S*
273b	(*S*)-**261**	100	96	*S*
(*Z*)-**274**	Ru$(OCOCF_3)_2$[(*S*)-TolBINAP]	98	97	*S*
(*Z*)-**275**	Ru$(OCOCF_3)_2$[(*S*)-TolBINAP]	98	97	*S*

[a] Reactions were also performed with the enantiomeric catalyst.

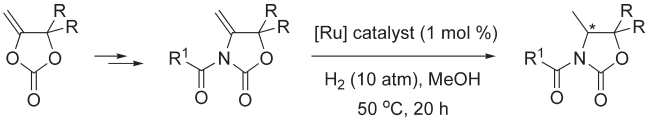


276

R^F = $CH_2CH_2C_8F_{17}$

Figure 41. Fluorous chiral BINAP ligand.

Scheme 53



277a-e **278a-e**

R = Me,
R-R = -$(CH_2)_5$-

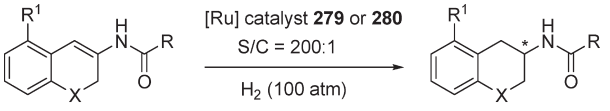
a: R^1 = Me, R = Me
b: R^1 = Me, R-R = -$(CH_2)_5$-
c: R^1 = Et, R = Me
d: R^1 = Et, R-R = -$(CH_2)_5$-
e: R^1 = Ph, R = Me

Table 56. Hydrogenation of 277a−e Catalyzed by Diphosphine/Ru(II) Complexes

substrate	catalyst	product	ee (%)
277a	((*R*)-BINAP)Ru$(OCOCF_3)_2$	*R*-(−)-**278a**	>99
277a	((*S*)-BiPhemp)Ru$(OCOCF_3)_2$	*S*-(+)-**278a**	99
277a	[((*R*)-BINAP)Ru$Cl_2]_2NEt_3$	*R*-(−)-**278a**	99
277b	((*R*)-BINAP)Ru$(OCOCF_3)_2$	*R*-(−)-**278b**	>99
277c	((*R*)-BINAP)Ru$(OCOCF_3)_2$	*R*-(−)-**278c**	98
277d	((*R*)-BINAP)Ru$(OCOCF_3)_2$	*R*-(−)-**278d**	98
277e	[((*R*)-BINAP)Ru$Cl_2]_2NEt_3$	*R*-(−)-**278e**	98

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 54



X = O, R^1 = OMe
281a: R = Me, **281b**: R = Ph

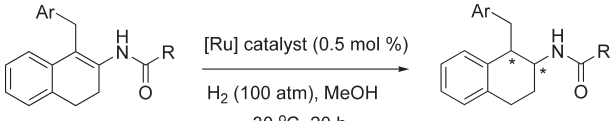
X = CH_2, R^1 = H
281c: R = Me, **281d**: R = CH_2Cl
281e: R = Et, **281f**: R = Ph

Table 57. Enantioselective Hydrogenation of Enamides 281a−f

enamide	catalyst	temp (°C)	reaction time (h)	yield (%)	ee (%)
281a	**279**	20	20	97	35
281a	**280**	20	20	95	8
281b	**279**	30	20	95	40
281c	**279**	20	20	95	90
281c	**279**	20	48	95[a]	90
281c	**280**	20	20	94	80
281d	**279**	60	20	95	64
281d	**280**	60	20	94	47
281d	**279**	20	20	95[b]	71
281e	**279**	20	20	95	90
281e	**280**	20	20	94	76
281f	**279**	20	20	95	96
281f	**280**	20	20	94	87

[a] Substrate/catalyst = 1000:1. [b] Substrate/catalyst = 100:1.

Scheme 55

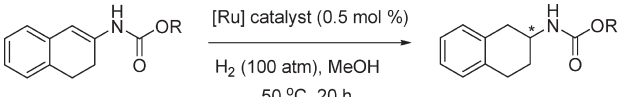


Ar = aryl
R = Me, Et

ees = 46-72 %

[Ru] catalyst: Diphosphine/(COD)Ru(methallyl)$_2$/HBF_4; molar ratio: 1/1/2
Diphosphine: Me-DuPhos, Me-BPE

Scheme 56



R = Me, Et, Bu, *n*-Bu, *i*-Bu, Ph

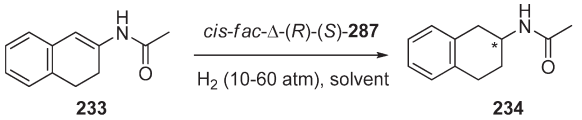
yield = 60-98 %
ee = 10-77 %

[Ru] catalyst: Diphosphine/(COD)Ru(methallyl)$_2$/HBF_4; molar ration: 1/1/2
Diphosphine: (*S*,*S*)-Me-DuPhos, (*S*,*S*)-Et-DuPhos, (*S*,*S*)-Me-BPE, (*S*,*S*)-Et-BPE

exocyclic C═C double bond and the acyl NCO group to the ruthenium center.

Enamides **281a−f** derived from 5-methoxy-3-chromanone and 2-tetralone were hydrogenated with BINAP ligands

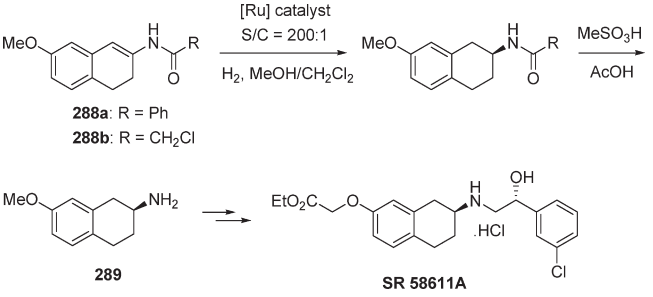
Scheme 57



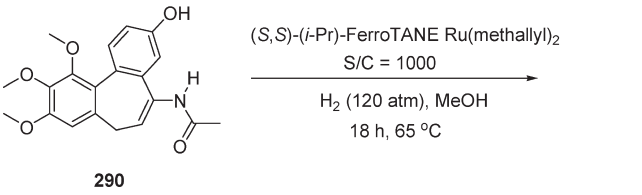
ee's up to 80 %

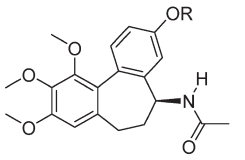
cis-fac-Δ-(*R*)-(*S*)-**287** = *cis-fac*-Δ-[Ru^{II}Cl {(*R*)-(bpea)} {(*S*)-(BINAP)}]BF_4
solvent = MeOH, *i*PrOH, THF, toluene

Scheme 58



Scheme 59





ee = 91.6 %

291: (*S*)-*N*-Acetylcolchinol, when R = H
ZD6126: R = PO_3H_2

((*R*)-BINAP)Ru(CO_2CF_3)$_2$ (**279**) and [NH_2Et_2][{RuCl((*S*)-BINAP)}$_2$(μ-Cl)$_3$] (**280**) (Scheme 54, Table 57).[134] This led to the corresponding products **282a−f**, which are valuable precursors for biologically active compounds such as (+)-S20499, MK-0499, and SR58611A. In general, the catalyst **279** gave higher enantioselectivities than **280**.

Catalysts **279** and **280** were ineffective with the more hindered enamides **283** (Scheme 55), and no hydrogenation was observed even for prolonged reaction times.[135] This group later investigated a novel *in situ* generated ruthenium catalytic system based on Me-DuPhos or Me-BPE ligands associated with Ru(COD)(methallyl)$_2$ and HBF_4, for the hydrogenation of tetrasubstituted enamides **283** (Scheme 55).[135] These reactions proceeded smoothly and produced the amides **284** as sole *cis*-diastereomers in good yields (95−98%) and moderate ee's.

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 60

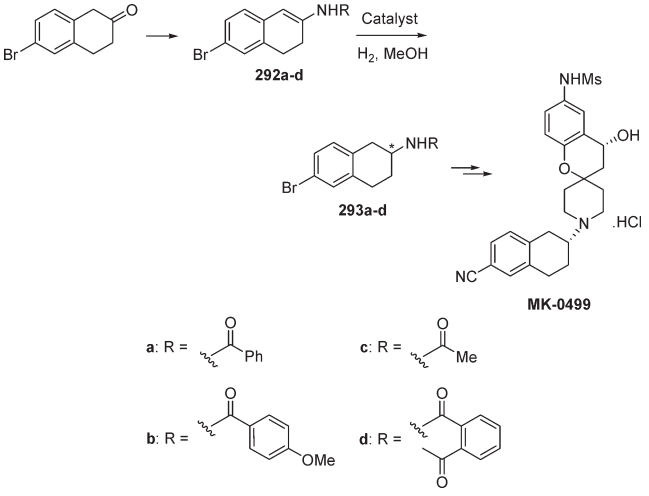
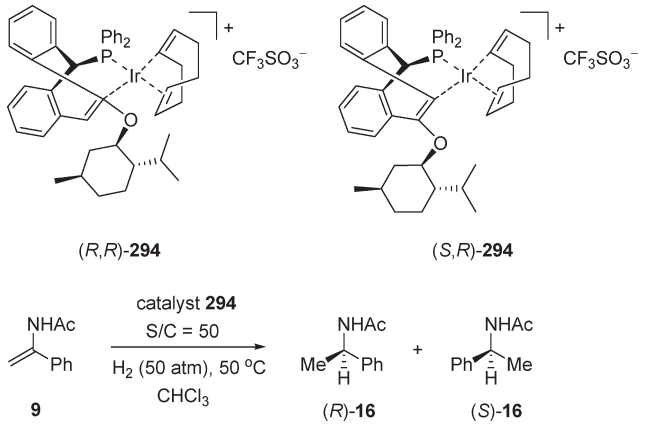


Table 58. Asymmetric Hydrogenation of Enamide 292a

			293a	
catalyst	catalyst (mol %)	reaction conditions	yield (%)	ee % (config)
Rh(*R*) BINAP ClO_4	10	20 °C/1500 atm + HCl	100	95 (*S*)
Ru(*R*) BINAP(Cym)Cl[a]	10	20 °C/1500 atm + HCl	92	90 (*S*)
Ru(*S*) BINAP(Cym)Cl[a]	10	20 °C/1500 atm + HCl	92	95 (*R*)
Ru(*S*) BINAP (Ph)Cl	10	20 °C/200 atm	95	98 (*R*)
Ru(*S*) BINAP(Ph)Cl	2	35 °C/150 atm	92	97 (*R*)

[a]Cym = cymene.

Scheme 61



The utility of the ruthenium complexes derived from Ru(COD)(methallyl)$_2$, HBF_4, and a diphosphine such as DuPhos or BPE was extended to the hydrogenation of enecarbamates **285** (Scheme 56).[136] The enantioselectivities were moderate for the carbamates **286**.

Rodríguez et al. tested the catalytic performance of the enantiopure ruthenium complex *cis-fac*-Δ-(*R*)-(*S*)-**287** in the hydrogenation of an endocyclic enamide **233** in a variety of solvents (Scheme 57).[137]

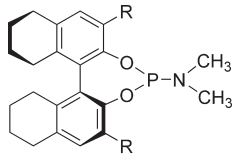


Figure 42. Monodentate 3,3′-substituted H_8-phosphoramidite **295** based on H_8-binaphthol.

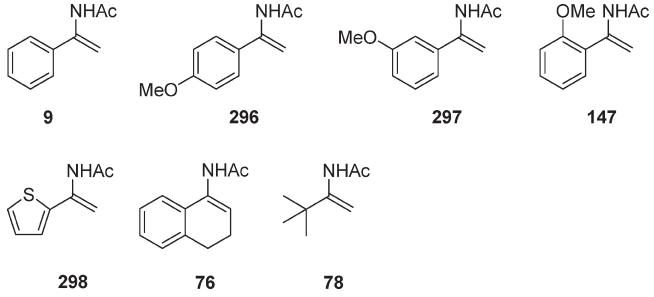


Figure 43. Some aryl- and alkyl-enamides.

Table 59. Selected Examples of Hydrogenation of Aryl- and Alkyl-enamides Using Ir/295 Catalyst[a]

entry	substrate	conversion (%)	ee % (config)
1	**9**	>99	93 (*S*)
2	**296**	>99	88 (*S*)
3	**297**	78	81 (*S*)
4	**147**	21	64 (*S*)
5	**298**	52	49(−)
6[b]	**298**	44	64(−)
7	**76**	17	60(−)
8	**78**	>99	70(+)
9[b]	**78**	>99	73(+)

[a] Reactions were carried out in toluene at 10 °C under H_2 (10 atm) for 16 h. [b] 2 mol % $NaBF_4$.

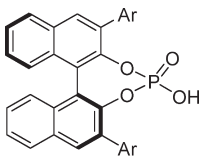


Figure 44. Catalyst (*S*)-**300** used for the hydrogenation of **116**.

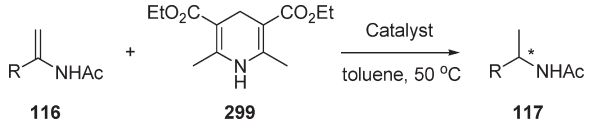
A chiral atypical β-adrenergic phenylethanolaminotetraline agonist SR58611A was synthesized by Agbossou and coworkers via ruthenium-catalyzed asymmetric hydrogenation (Scheme 58).[138] Using [Ru(*R*)-BINAP(C_6H_6)Cl]Cl or Ru{(*R*)-MeO-BiPhemp}Br_2 catalysts, the enamide **288a** gave excellent ee's (95−98%), whereas moderate ee's (69−78%) were obtained for the enamide **288b**.

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scientists at Dow Chemical and AstraZeneca in the United Kingdom have cooperated on the asymmetric enamide hydrogenation in the synthesis of (*S*)-*N*-acetylcolchinol (**291**), a key intermediate for ZD6126 (Scheme 59).[139] A wide range of enantioselective rhodium, ruthenium, and iridium catalysts were screened to find a suitable catalyst for the hydrogenation of enamide **290**. A ruthenium catalyst (*S*,*S*)-*i*Pr-FerroTANE Ru(methallyl)$_2$ and a rhodium catalyst [(*S*,*S*)-*t*Bu-FerroTANE Rh(COD)]BF$_4$, both based on FerroTANE ligands, gave the best results in terms of both selectivity and reactivity.

Researchers at Merck in New Jersey reported the asymmetric synthesis of MK-0499, a potent antiarrhythmia agent, via a rhodium- or ruthenium-catalyzed enantioselective hydrogena-

Table 60. Enantioselective Organocatalytic Hydrogenation of Enamides 116

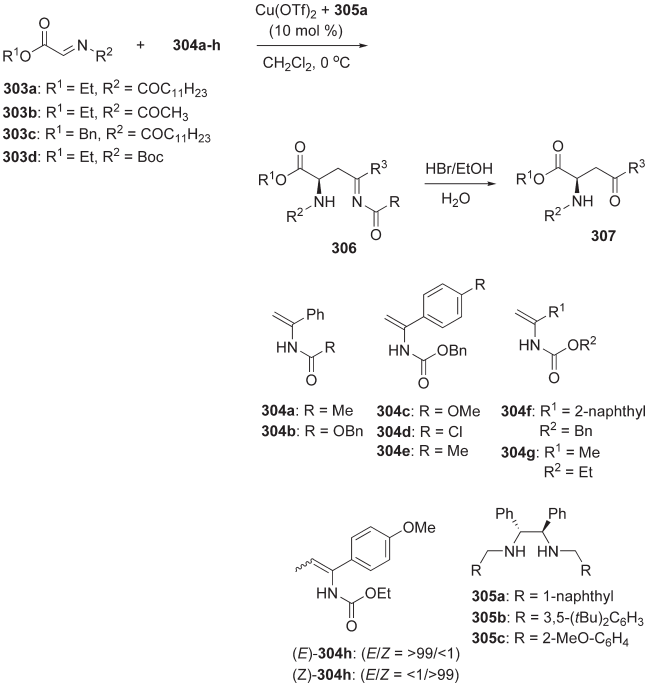


116 **299** **117**

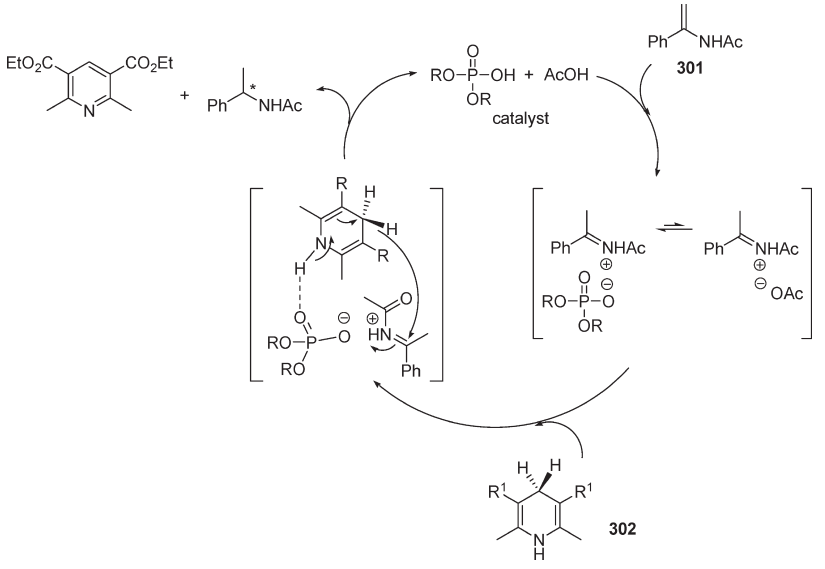
entry	R	catalyst[a]	time (h)	yield (%)	ee % (config)
1	Ph	A	117	39	91 (*R*)
2	Ph	B	15	97	91 (*R*)
3	4-MeC$_6$H$_4$	A	72	53	91 (*R*)
4	4-MeC$_6$H$_4$	B	24	93	90 (*R*)
5	4-ClC$_6$H$_4$	A	48	71	92 (*R*)
6	4-ClC$_6$H$_4$	B	17	88	91 (*R*)
7	4-FC$_6$H$_4$	A	72	90	90 (*R*)
8	4-FC$_6$H$_4$	B	17	96	89 (*R*)
9	4-CF$_3$C$_6$H$_4$	A	69	74	87 (*R*)
10	4-CF$_3$C$_6$H$_4$	B	40	96	87 (*R*)
11	4-MeOC$_6$H$_4$	A	15	96	95 (*R*)
12	*β*-naphthyl	A	48	91	94 (*R*)
13	*β*-naphthyl	B	14	99	92 (*R*)
14	α-naphthyl	A	94	31	89 (*S*)
15	α-naphthyl	B	44	43	78 (*S*)
16	3-MeOC$_6$H$_4$	A	47	90	74 (*R*)
17	3-MeOC$_6$H$_4$	B	18	98	71 (*R*)
18	2-MeOC$_6$H$_4$	A	40	90	42 (*S*)
19	2-MeOC$_6$H$_4$	B	15	96	41 (*S*)
20	*t*-butyl	A or B	48	-[b]	

[a] Catalyst A = (*S*)-**300** (1 mol %); catalyst B = (*S*)-**300** (1 mol %) + AcOH (10 mol %). [b] No desired product.

Scheme 63



Scheme 62



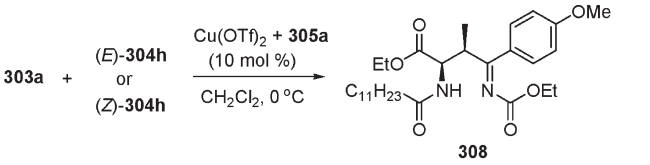
dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Table 61. Enantioselective Addition of Enamides and Enecarbamates 304 to Imines 303

			307	
entry	imine **303**	enamide/enecarbamate **304**	yield (%)	ee (%)
1	**a**	**a**	83	85
2	**a**	**b**	94	93
3[a]	**a**	**b**	92	93
4	**b**	**b**	72	94
5	**c**	**b**	89	91
6[b]	**d**	**b**	78	87
7	**a**	**c**	97	90
8	**b**	**c**	76	92
9	**a**	**d**	89	90
10	**a**	**e**	93	91
11	**a**	**f**	83	88
12	**b**	**f**	76	91
13	**c**	**g**	84	83
14[a]	**c**	**g**	81	84

[a] $Cu(OTf)_2$/**305b** catalyst was used. [b] $Cu(OTf)_2$/**305c** catalyst was used.

Scheme 64



308

(*E*)-**304h**: 77 %, *syn*/*anti* = 86/14, 94 % *ee* (*syn*)
(*Z*)-**304h**: 63 %, *syn*/*anti* = 68/32, 32 % *ee* (*syn*)

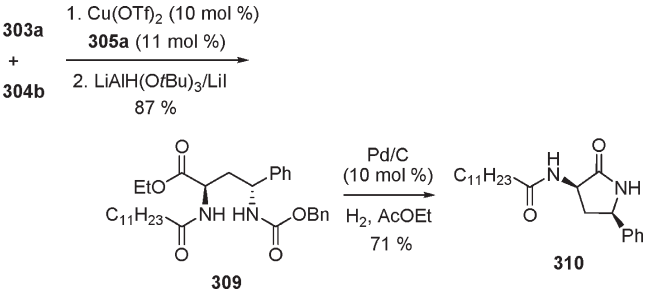
Table 62. (*R*)-311-Catalyzed Addition of Imine 312 (Ar = Ph) to Enamide 313a and Enecarbamates 313b−d

entry	**313**	S/C[a]	solvent	time (h)	yield (%)	ee (%)
1	**a**	50:1	CH_2Cl_2	0.5	77	69
2	**a**	50:1	$(CH_2Cl)_2$	0.5	61	70
3	**a**	50:1	Et_2O	0.5	71	80
4	**a**	50:1	toluene	0.5	90	86
5	**b**	50:1	toluene	1	94	60
6	**c**	50:1	toluene	1	55	83
7	**d**	50:1	toluene	1	85	95
8	**d**	1000:1	toluene	5	82	95
9	**d**	2000:1	toluene	5	85	93

[a] Molar ratio of imine **312**/catalyst **311**.

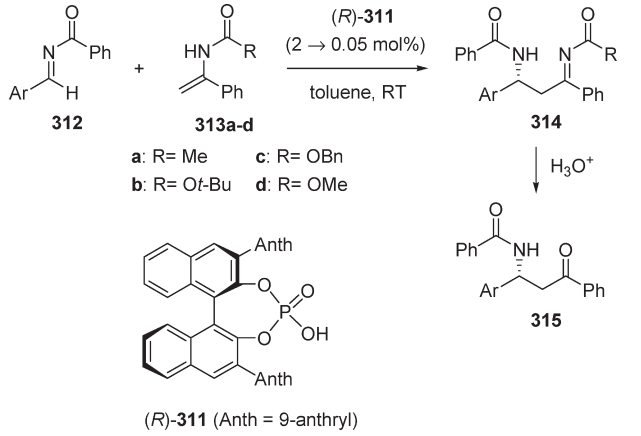
tion of enamide derivatives **292a**−**d** derived from 6-bromo-2-tetralone, as a key transformation (Scheme 60).[140] Several chiral catalysts were tested for the reduction of enamide **292a**, and the results are summarized in Table 58. The anisoyl enamide **292b** was hydrogenated with similar rate and selectivity as was **292a**. Enamide **292c** reacted much more slowly and the phthaloyl derivative **292d** could not be reacted at all under the reaction conditions used.

Scheme 65



309 **310**

Scheme 66



312 **313a-d** **314** **315**

(*R*)-**311** (Anth = 9-anthryl)

2.3. Iridium Catalysts

So far only three studies on the hydrogenation of enamides by iridium catalysts are known.[139b,141,142] In 2004, the first example appeared with the simple enamide *N*-(1-phenylvinyl)acetamide **9** using diastereomeric catalysts (*R*,*R*)-**294** and (*S*,*R*)-**294**, which led to the reduced products (*S*)-**16** (60% ee) and (*R*)-**16** (24% ee) respectively (Scheme 61).[141]

Researchers at AstraZeneca tested several iridium catalysts for asymmetric enamide hydrogenation in the synthesis of ZD6126, a potent vascular targeting agent (Scheme 59).[139b] Unfortunately, enantioselectivities for the amide **291** were low (≥10%) in all cases. Very recently, Beller and co-workers investigated the iridium-catalyzed asymmetric hydrogenation of nonfunctionalized enamides in the presence of 3,3′-substituted H_8-phosphoramidite **295** (Figure 42).[142] The catalytic system is sensitive to the addition of noncoordinating salts such as $NaClO_4$ and $NaBF_4$. A variety of aryl-substituted enamides, as well as sterically hindered alkyl-enamides (Figure 43), were selectively hydrogenated using 2 mol % $[Ir(COD)Cl_2]$/**295** as catalyst with 2 mol % $NaClO_4$ as an additive (Table 59).

2.4. Organocatalysts

Very recently, Antilla and co-workers developed an organocatalytic system for enantioselective hydrogenation of enamides using a dual-acid catalyst.[143] Reactions with a chiral phosphoric acid, (*S*)-**300** (Figure 44), were carried out in the presence of acetic acid and Hantzsch ester **299** as the reducing agent (Table 60). A variety of aromatic enamide substrates **116** were

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

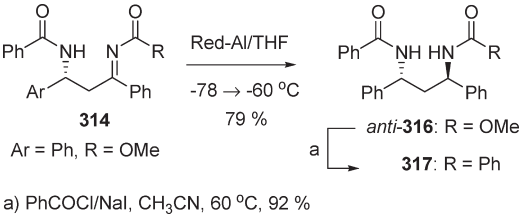
hydrogenated to the amine derivatives **117** (Table 60). In order to demonstrate the advantages of the dual-acid catalytic system, the corresponding reactions were conducted with the single chiral phosphoric acid (*S*)-**300** catalyst. As shown in Table 60, the dual-acid catalytic system significantly accelerated the hydrogenation reaction. The sterically hindered enamides **116** (R = α-naphthyl, 3-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$) gave lower enantioselectivities (Table 60, entries 15−19). Notably, these reaction conditions were completely ineffective for the aliphatic enamide **116** (R = *t*-Bu) (Table 60, entry 20). A plausible mechanism for the dual-acid catalyzed hydrogenation is shown in Scheme 62. In the presence of catalyst **302** and the cocatalyst acetic acid, the enamide **301** was transformed into an acyliminum intermediate, which was able to abstract a hydride from the Hantzsch ester. In the following step, only chiral phosphoric acid was active enough to catalyze the hydrogenation of the imine.

Table 63. (*R*)-311-Catalyzed Addition Reaction of Enecarbamate 313d with Various *N*-Benzoylimines 312[a]

entry	Ar (**312**)	yield (%)	ee (%)
1	*p*-Me-C$_6$H$_4$	90	95
2	*m*-Me-C$_6$H$_4$	83	93
3	*o*-Me-C$_6$H$_4$	61	93
4[b]	*o*-Me-C$_6$H$_4$	84	93
5	*p*-MeO-C$_6$H$_4$	82	92
6	*p*-Br-C$_6$H$_4$	89	96
7	*m*-Br-C$_6$H$_4$	85	95
8[c]	*o*-Br-C$_6$H$_4$	53	95
9[b]	*o*-Br-C$_6$H$_4$	82	96
10	*p*-F-C$_6$H$_4$	89	95
11	*p*-Cl-C$_6$H$_4$	84	95
12	*p*-NC-C$_6$H$_4$	97	98
13	1-naphthyl	88	95
14	2-naphthyl	91	95
15	(*E*)-C$_6$H$_5$−CH=CH-	81	93

[a] Reactions were carried out using 0.1 mmol % of imine **312** in toluene at rt for 5 h. Molar ratio **312**/**313d**/**311** = 1000:1200:1. [b] Molar ratio **312**/**313d**/**311** = 200:240:1. [c] Reaction time 12 h.

Scheme 67



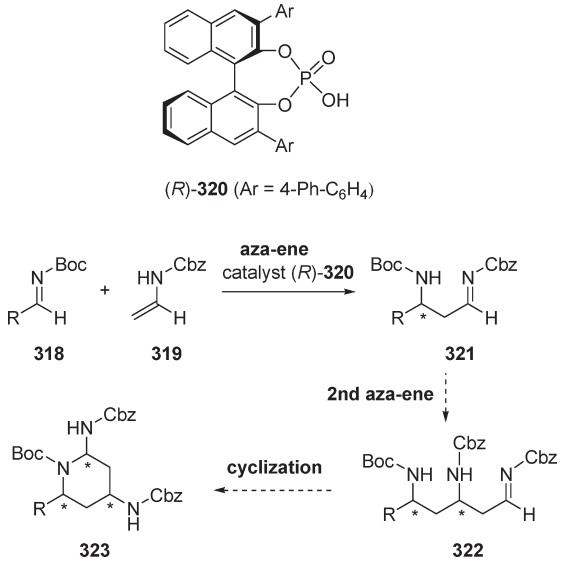
3. NUCLEOPHILIC ADDITION REACTIONS OF ENAMIDES AND ENECARBAMATES

In contrast to the frequent use of enamides and enecarbamates as substrates in catalytic asymmetric hydrogenation reactions, nucleophilic additions on these compounds are rare,[144−157] but the adducts so generated are electrophilic acylimines, which can be readily converted into complex molecules containing a nitrogen atom adjacent to an asymmetric center.

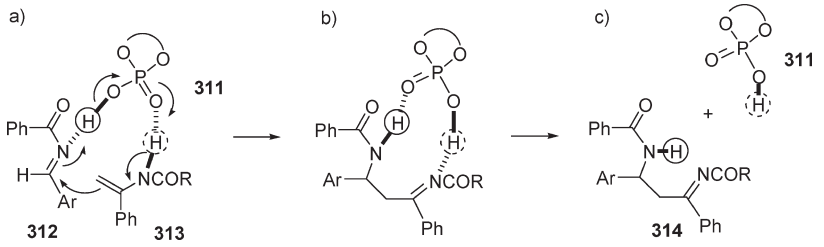
3.1. Addition of Enamides or Enecarbamates to Imines

The Kobayashi research group reported the first catalytic enantioselective nucleophilic addition of enamides and enecarbamates to imines.[145] Reaction of enamides **304a**−**g** with imines **303** in the presence of a chiral copper catalyst prepared from Cu(OTf)$_2$ and the chiral diamine **305a** gave the corresponding β-aminoimines **306** (Scheme 63). The yields and enantioselectivities were determined after conversion of **306** to β-amino ketones **307** by acidic hydrolysis (Table 61). The use of diamines **305b** and **305c** instead of **305a** were also effective. Reaction of (*E*)- and (*Z*)-2-methyl-substituted enamides (*E*)-**304h** and (*Z*)-**304h**

Scheme 69



Scheme 68



dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 70

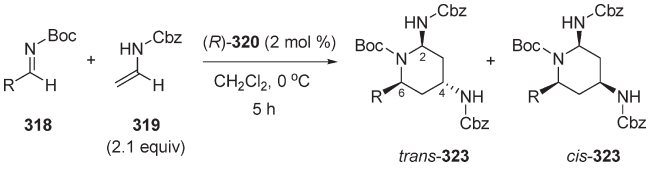
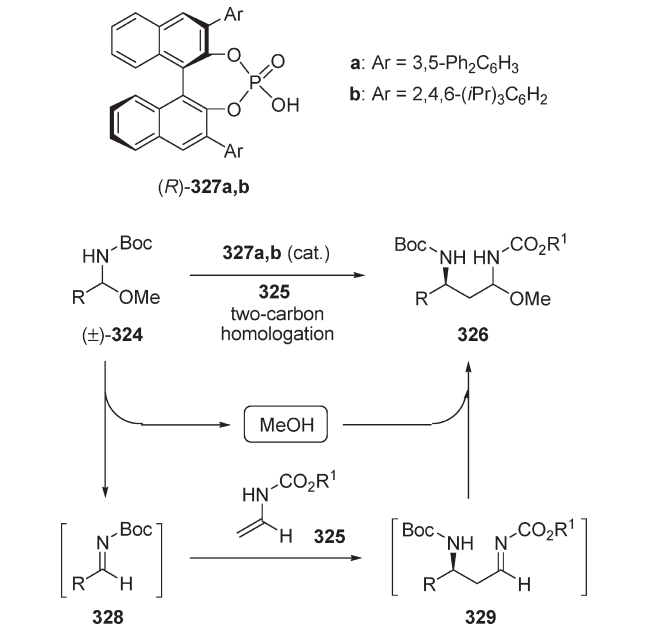


Table 64. (*R*)-320 Catalyzed Cascade Reaction of 318 with 319

R (318)	yield (%)	*trans*/*cis*	*trans*-323 ee (%)	*cis*-323 ee (%)
p-Br-C_6H_4	>99	94:6	99	23
p-Me-C_6H_4	>99	96:5	98	4
2-furyl	76	88:12	99	14
Ph−CH=CH	70	95:5	97	36
MeO_2C	84	88:12	98	
c-C_6H_{11}	68	94:6	97	48

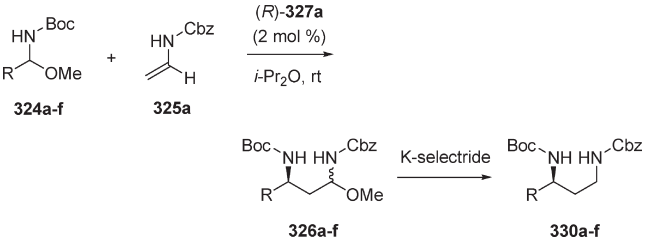
Scheme 71



with imine **303a** in the presence of chiral copper catalyst gave the adducts **308** in high yields with *syn* selectivity preferred in both cases (Scheme 64). The reaction of **303a** and **304b** with chiral copper catalyst followed by further treatment with LiAlH-$(OtBu)_3$ and LiI in the same pot afforded a 1,3-diamine **309** diastereoselectively (*syn*/*anti* = 14:86, Scheme 65). Diamine **309** was further transformed into lactam **310**. The authors postulated that the mechanism of this reaction is similar to the aza-ene-type pathway.

Terada and co-workers studied the catalytic enantioselective aza-ene-type reaction of enamides and enecarbamates **313** with

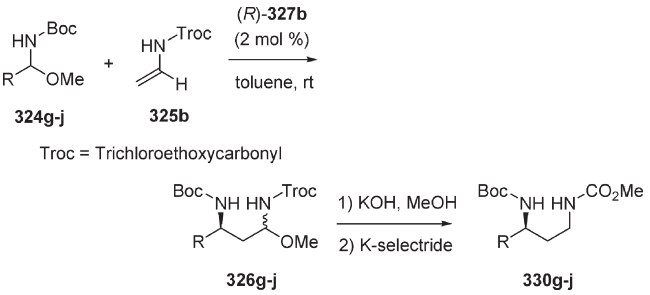
Table 65. (*R*)-327a Catalyzed Homologation of Aromatic Hemiaminal Ethers (324a−f) with 325a



		326		
entry	324 (R)	yield (%)	dr	330 ee (%)
1	**a** (C_6H_5)	74	50:50	94
2	**b** (2-MeC_6H_4)	74	33:67	91
3	**c** (4-MeC_6H_4)	90	59:41	90
4	**d** (4-$MeOC_6H_4$)	99	53:47	88
5	**e** (4-BrC_6H_4)	88	49:51	95
6[a]	**f** (4-NCC_6H_4)	44	54:46	84

[a] Reaction in toluene at 50 °C.

Table 66. (*R*)-327b Catalyzed Homologation of Aliphatic Hemiaminal Ethers (324g−j) with 325b



		326		
entry	324 (R)	yield (%)	dr	330 ee (%)
1	**g** (Et)	83	69:31	96
2	**h** (*i*-Pr)	56	50:50	98
3	**i** (*i*-Bu)	84	46:54	97
4	**j** (Me)	79	47:53	86

aldehyde-derived *N*-benzoylimines **312** using binaphthol-derived monophosphoric acid **311** as organocatalyst (Scheme 66).[146] The catalytic efficiency was screened with 2 mol % of **311** in the reaction of **312** (Ar = Ph) and **313a** in various solvents at room temperature (Table 62, entries 1−4). The yields and enantioselectivity were determined after the hydrolysis of imine adducts **314** to β-aminoketones **315** under the acidic workup. Toluene was the best among the solvents tested. The enecarbamates **313b−d** were examined in order to establish the effect of the steric bulk of the alkoxy moiety (Table 62, entries 5−7). The enantioselectivity increased with decreasing steric demand of the alkoxy moiety. The reactions were effective even with a decrease in the catalyst loading (0.05 mol %; Table 62, entry 9).

The applicability of this organocatalysis to a series of *N*-benzoylimines **312** reacting with enecarbamate **313d** was

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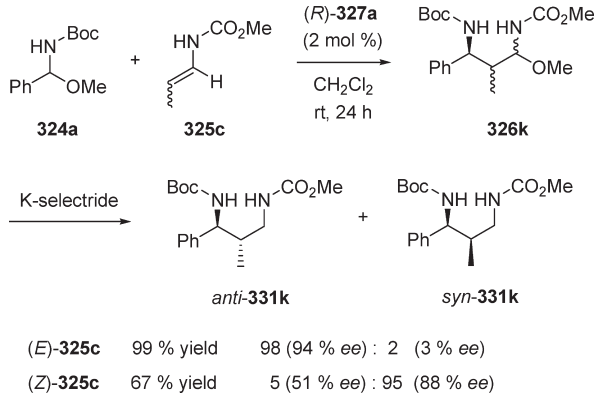
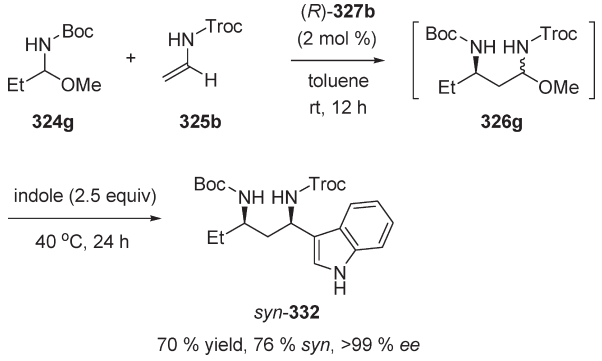
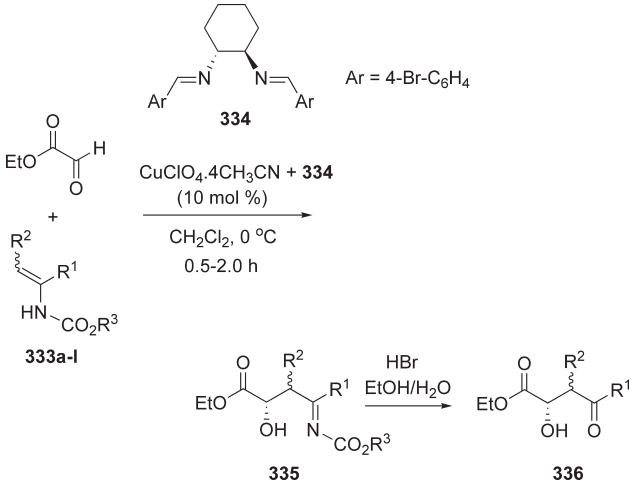
Scheme 72



Scheme 73



Scheme 74



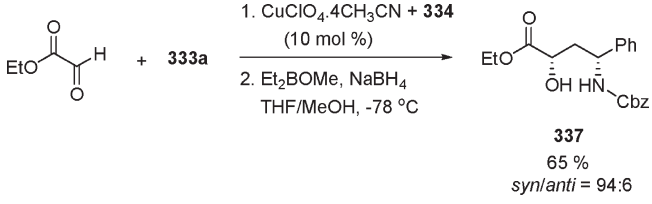
explored using 0.1 mol % of **311** (Table 63). These reactions proceeded smoothly and gave the corresponding β-aminoketones **315** in high yields with excellent enantioselectivity. Furthermore, the synthetic utility of this transformation was demonstrated by derivatization of **314** to C_2-symmetric 1,3-diamine **317**, which is a potentially useful chiral ligand (Scheme 67). The

Table 67. Cu^I-334 Catalyzed Addition of Enecarbamates 333a-l (R^3 = Bn) to Ethyl Glyoxylate (Scheme 74)

		336		
entry	333	yield (%)	*syn*/*anti*	ee (%)[a]
1	**333a** (R^1 = Ph, R^2 = H)	93		97
2	**333b** (R^1 = PMP, R^2 = H)	94		93
3	**333c** (R^1 = PCP, R^2 = H)	97		97
4	**333d** (R^1 = PMeP, R^2 = H)	quant		96
5	**333e** (R^1 = 2-Nap, R^2 = H)	91		96
6	(*E*)-**333f** (R^1 = Ph, R^2 = Me)	83	1:99	98
7[b,c]	(*E*)-**333f**	95	1:99	98
8	(*Z*)-**333f**	82	98:2	98
9[c]	(*Z*)-**333f**	96	98:2	98
10	(*E*)-**333g** (R^1 = PMP, R^2 = Me)	96	2:98	98
11	(*Z*)-**333g**	97	98:2	98
12	(*E*)-**333h** (R^1 = PMP, R^2 = Me)[d]	82	3:97	96
13	(*Z*)-**333h**[d]	96	99:1	98
14	(*E*)-**333i** (R^1 = PCP, R^2 = Me)	85	2:98	98
15	(*Z*)-**333i**	79	99:1	98
16	(*E*)-**333j** (R^1 = Ph, R^2 = Et)	58	1:99	98
17	(*Z*)-**333j**	92	99:1	98
18[b]	(*E*)-**333k** (R^1 = Et, R^2 = Me)	83	3:97	97
19[b]	(*Z*)-**333k**	89	92:8	98
20	**333l** (R^1–R^2 = $-(CH_2)_4-$)	85	16:84	94

[a] Value for the major diastereomer. [b] −20 °C. [c] Catalyst: 0.1 mol %. [d] R^3 = Et; PMP = *p*-methoxyphenyl; PCP = *p*-chlorophenyl; PMeP = *p*-methylphenyl; 2-Nap =2-naphthyl.

Scheme 75



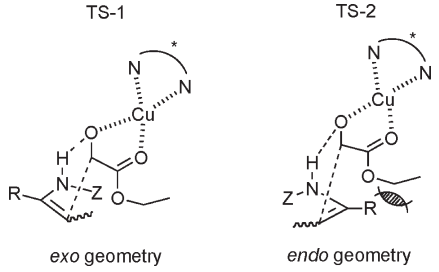


Figure 45. Proposed transition-state models.

authors proposed the mechanism shown in Scheme 68 for the organocatalytic reaction. The catalyst **311** participates in the aza-ene-type reaction of **312** with **313** through a hydrogen bonding network (Scheme 68a). The key aspect of catalysis is the dual function of the phosphoric acid moiety, which electrophilically

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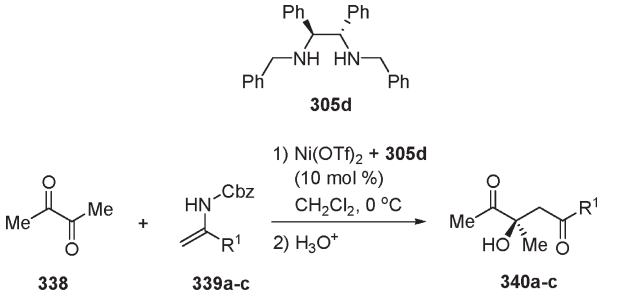
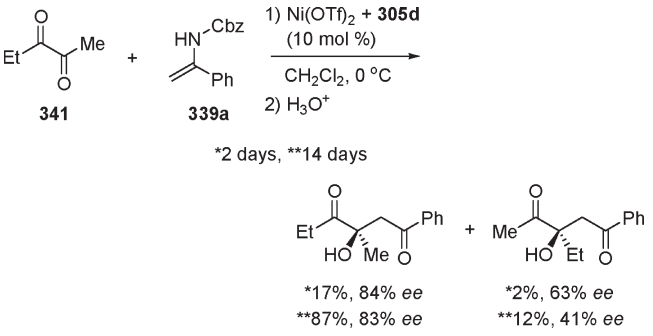
Table 68. 305d/Ni(OTf)$_2$ Catalyzed Reactions of 338 with 339a−c



a: R^1 = Ph
b: R^1 = *p*-OMe-C_6H_4
c: R^1 = *p*-Cl-C_6H_4

339	time (d)	product 340	yield (%)	ee (%)
a	2	a	67	76
a	14	a	94	84
b	2	b	47	45
b	14	b	59	65
c	2	c	20	75
c	14	c	90	82

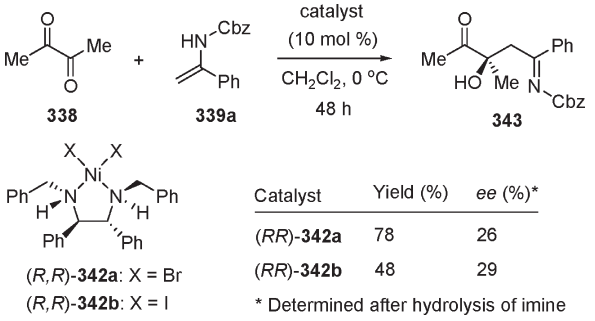
Scheme 76



activates **312** through the proton and accepts the NH proton of **313** through the Lewis basic phosphoryl oxygen atom. Subsequent bond recombination, which leads to the aza-ene-type product and regeneration of the catalyst **311**, would take place (Scheme 68b,c).

Subsequently, this group investigated the phosphoric acid derivative (*R*)-**320**-catalyzed tandem aza-ene type reaction/cyclization cascade transformation of monosubstituted enecarbamate **319** with aldimines **318** (Scheme 69).[147] This led to the piperidine derivatives **323** with multiple stereogenic centers. The aldimines **321** initially formed then underwent further aza-ene type reaction in a sequential process leading to the generation of aldimines **322**. The tandem aza-ene type reaction sequence would be terminated by intramolecular cyclization of **322** leading to the piperidine derivatives, with the trans isomer being the major one (Scheme 70, Table 64). The high diastereoselectivity was attributed to the double asymmetric induction arising from the matched combination of aldimine intermediate **322** and (*R*)-**320**. On the basis of experimental results, the stereochemical

Scheme 77



Catalyst	Yield (%)	ee (%)*
(*RR*)-**342a**	78	26
(*RR*)-**342b**	48	29

* Determined after hydrolysis of imine

outcome of the reaction was proposed to be that in which the catalyst (*R*)-**320** preferentially directs the attack of aldimines **318** to **321** onto the *Si* face, giving predominantly a 4,6-*trans* product. The final step of the stereoselective cyclization proceeded under substrate rather than catalyst control.

3.2. Addition of Enecarbamates to Hemiaminal Ethers

Very recently, the Terada research group developed an enantioselective two-carbon homologation method using enecarbamate derivatives **325** as an acetaldehyde anion equivalent through the activation of hemiaminal ethers **324** by chiral phosphoric acid catalysts **327** (Scheme 71).[148] The highly reactive aldimines **329** generated in the reaction are trapped by methanol allowing facile access to enantioenriched 1,3-diamine derivatives **326**. Reaction of enecarbamate **325a** with a series of aromatic hemiaminal ethers **324a−f** in the presence of catalyst **327a** gave excellent yields of the hemiaminal products **326a−f** as diastereomeric mixtures (Table 65). The configuration at the C3 position of **326a−f** was determined after reduction of the newly formed hemiaminal moiety by K-selectride, and the corresponding 1,3-diamine derivatives **330a−f** were obtained in enantioenriched form. The homologation was further applied to aliphatic hemiaminal ethers **324g−j** (Table 66). A high level of enantioselectivity was maintained for the reduced products **330g−i**, albeit with a slight decrease in enantioselectivity for the less bulky **330j** (R = Me; Table 66, entry 4).

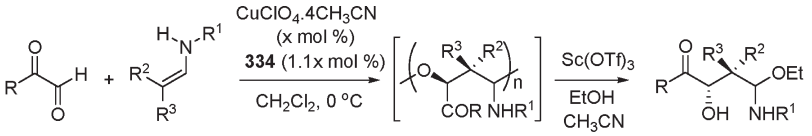
The homologation method was extended to a substituted enecarbamate **325c** (Scheme 72). Either *anti*- or *syn*-**331k** was obtained diastereoselectively from the respective (*E*)- or (*Z*)-isomer of **325c**, and each of the major diastereomers exhibited good to high enantioselectivity. Finally, a sequential transformation involving a homologation/Friedel−Crafts reaction was performed in one pot (Scheme 73). The 1,3-diamine derivative **332** was obtained in good yield in nearly enantiopure form, albeit with moderate *syn* diastereoselectivity. The extremely high enantioselectivity for *syn*-**332** was attributed to double asymmetric induction arising from an ideal matching between the configurations of the chiral hemiaminal product **326g** and the catalyst (*R*)-**327b**.

3.3. Addition of Enamides or Enecarbamates to Aldehydes or Ketones

Kobayashi et al. investigated addition reactions of enecarbamates to glyoxylic aldehydes, using chiral copper complexes.[149,150] In the screening of several chiral diamine ligands, box-type ligands, and diimine ligands, it was found that the higher reactivities and selectivities were delivered with the cyclohexyl diimine ligands

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Table 69. Cu^{I}-Catalyzed Addition of Enecarbamates 345a−f to Aldehydes 344

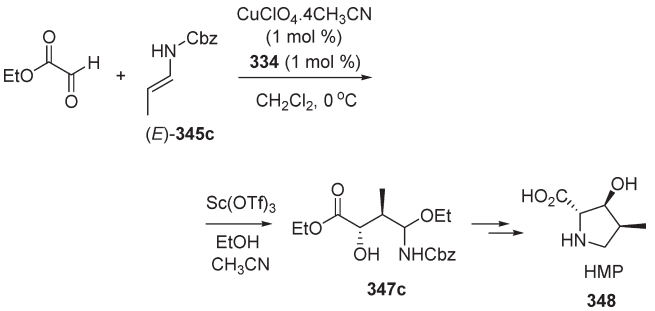


344 345a-f 346 347

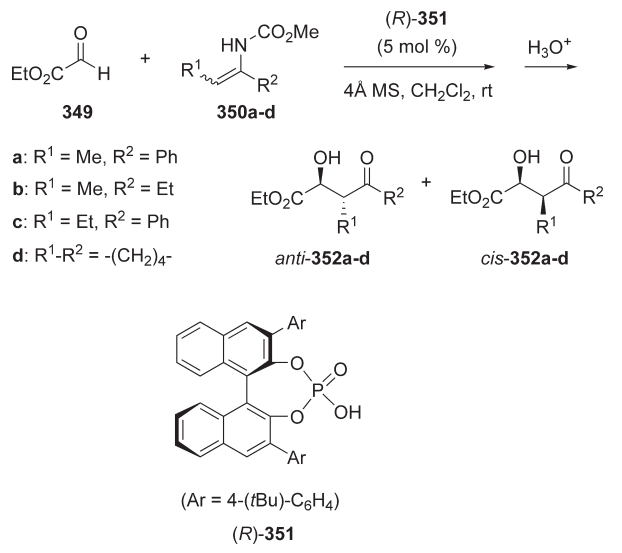
entry	R (344)	345	R^1, R^2, R^3	*x* (mol %)	time (h)	yield (%)	*syn*/*anti*	ee[a] (%)
1	OEt	**a**	Cbz, H, H	0.1	1	80		92
2	Ph	**a**		1	1.5	54		88
3	OEt	**b**	CO_2All, H, H	0.1	1	50		96
4	Ph	**b**		1	1.5	58		91
5	OEt	(*E*)-**c**	Cbz, H, Me	1	5.5	84	12/88	97
6	OEt	(*Z*)-**c**	Cbz, Me, H	1	28	79	92/8	95
7	OEt	(*E*)-**d**	Cbz, H, Et	1	5.5	87	9/91	98
8	OEt	(*Z*)-**d**	Cbz, Et, H	1	28	79	82/18	94
9	OEt	(*E*)-**e**	Cbz, H, Cl	1	24	50	5/95	96
10	OEt	**f**	Cbz, Me, Me	5	18	81		70
11	OEt	**f**		1	28	39		78

[a] Value for the major diastereomer. All = allyl group.

Scheme 78



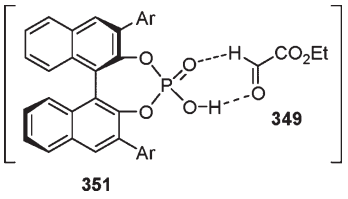
Scheme 79



possessing *para*-substituents on the phenyl group (Scheme 74, Table 67). Remarkably, the Cu^{I}-diimine ligand **334** gave

Table 70. Formation of 352a−d in Aza-ene Type Reaction between 350a−d and 349 Catalyzed by (*R*)-351

					ee (%)	
entry	enecarbamate	time (h)	yield (%)	*anti*/*syn*	*anti*	*syn*
1	(*E*)-**350a**	2	73	>99:<1	>99	53
2	(*E*)-**350b**	2	73	96:4	99	56
3	(*E*)-**350c**	4	75	99:1	99	74
4	**350d**	1	89	89:11	99	98
5	(*Z*)-**350a**	24	11	72:28	26	88
6	(*Z*)-**350b**	2	74	50:50	28	69
7	(*Z*)-**350c**	24	67	92:8	8	74



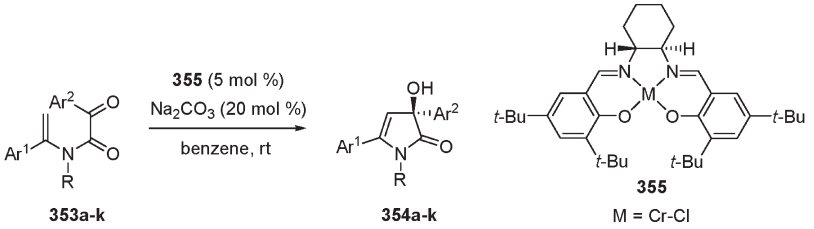
351

Figure 46. Hydrogen bonding interactions between the catalyst **351** and glyoxate **349**.

excellent levels of both diastereo- and enantioselectivity. Reaction of ethyl glyoxylate with α-unsubstituted enecarbamates **333a−e** gave the corresponding 1,3-iminoalcohol adducts **335** (Table 67, entries 1−5). The yields and ee's of the products were determined after conversion of **335** into the corresponding ketone **336**. The α-substituted enecarbamates **333f−l** reacted with ethyl glyoxylate smoothly in the presence of Cu^{I}-diimine ligand **334**. Moreover, the reactions proceeded stereospecifically: *E* enecarbamates gave *anti* adducts, whereas *Z* enecarbamates produced *syn* adducts with excellent enantioselectivities in most cases. The enecarbamate addition followed by diastereoselective reduction was also done in a

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

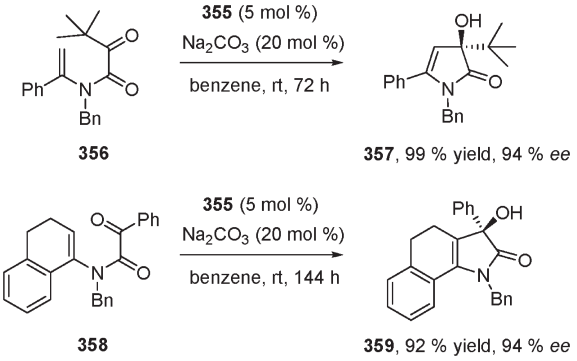
Table 71. Catalytic Enantioselective Cyclizations of Enamides 353



substrate **353**	R	Ar^1	Ar^2	time (h)	**354** yield (%)	**354** ee (%)
a	Bn	Ph	Ph	16	98	96
b	Bn	4-Me-C_6H_4	Ph	4	99	98
c	Bn	4-Cl-C_6H_4	Ph	114	99	96
c	Bn	4-Cl-C_6H_4	Ph	17[a]	93	97
d	Bn	4-Br-C_6H_4	Ph	96	97	99
e	Bn	Ph	4-Me-C_6H_4	68	98	97
f	Bn	Ph	4-F-C_6H_4	72	99	97
g	Bn	Ph	4-Cl-C_6H_4	16	98	97
h	PMB[b]	Ph	Ph	11	99	98
i	Allyl	Ph	Ph	15	99	94
j	Me	Ph	Ph	4	99	89
k	Ph	Ph	Ph	4	97	88

[a] 10 mol % **355** was used. [b] PMB = *p*-methoxy benzyl.

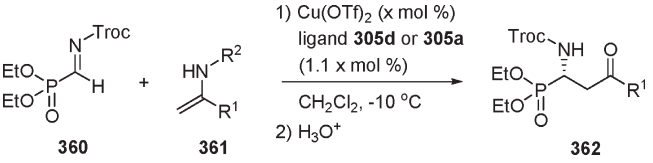
Scheme 80



one-pot process to furnish the *N*-Cbz-protected α-hydroxy-γ-amino acid ester **337** with high selectivity (Scheme 75). A concerted aza-ene-type mechanism was proposed to account for the stereochemical outcome of the formation of stereospecific products from the reaction of α-monosubstituted enecarbamates. Transition state TS-1 is preferred over TS-2 where there are unfavorable steric interactions between the bulky R group of the enecarbamate and the ester group of the ethyl glyoxylate or the bulky copper catalyst (Figure 45).

The above methodology was extended to the nucleophilic additions of enecarbamates **339a**−**c** to ketone **338** by using a diamine ligand **305d** with nickel(II) triflate as catalyst (Table 68).[151] This gave the corresponding tertiary alcohols **340a**−**c** after an acidic workup. Unsymmetrical ketone **341** with enecarbamate **339a** gave a mixture of products under the same reaction conditions (Scheme 76).

Table 72. Cu(II)-Catalyzed Reactions of 360 with 361[a]



entry	R^1	R^2	*x* (mol %)	yield (%)	ee (%)
1[b]	Ph	Cbz	10	86	89
2	Ph	Cbz	5	77	89
3	Ph	Bz	1.5	81	85
4	4-MeC_6H_4	Cbz	5	77	93
5	4-ClC_6H_4	Cbz	5	78	87
6[c]	4-ClC_6H_4	Bz	2	72	86
7	4-MeOC_6H_4	Cbz	5	77	94
8	2-naphthyl	Cbz	5	66	89
9[c]	3-MeC_6H_4	Bz	1.5	83	86

[a] Ligand **305d** was used unless otherwise mentioned. [b] Ligand **305a** was employed. [c] Enamide (1.5 equiv) was employed.

The nickel(II) complexes **342a** or **342b** catalyzed the nucleophilic addition reactions of enecarbamate **339a** to diketone **338** giving the imine adduct **343** with low ee's (Scheme 77).[152]

Subsequently, this group investigated the catalytic asymmetric addition reactions of aldehyde-derived enecarbamates **345a**−**f** with aldehydes **344** by using the Cu^I-catalyst of diimine **334** (Table 69).[153] Reactions of enecarbamates **345a**−**f** with ethyl glyoxylate in the presence of copper(I) catalyst initially gave polymeric material **346**. Further treatment with $Sc(OTf)_3$ produced the products **347** in moderate to high yields with excellent ee values in many cases. When phenylglyoxal was employed

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 81

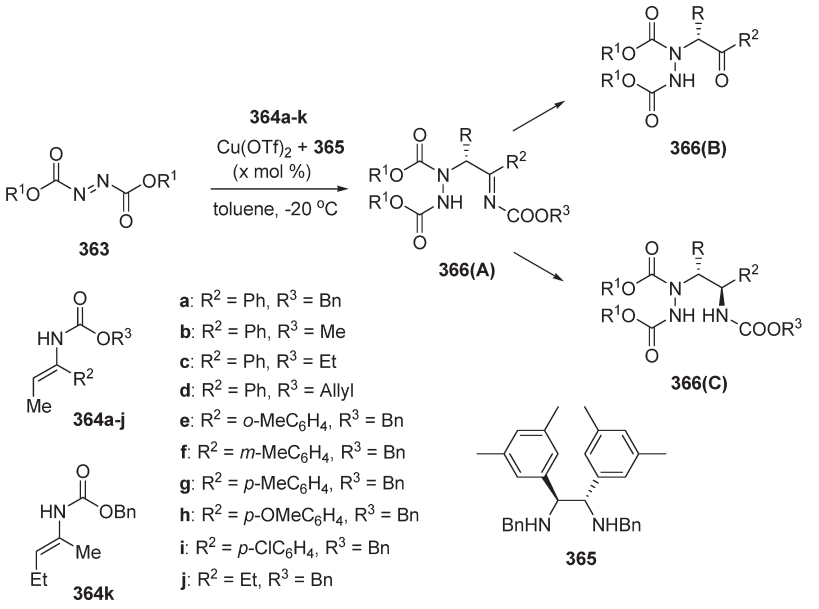


Table 73. Catalytic Asymmetric α-Amination of Enecarbamates[a]

entry	R^1 (363)	enecarbamate	x (mol %)	time (h)	yield (%)	ee (%)	product[b]
1[c]	*i*-Pr	**364a**	0.2	22	84	98	**366(C)**
2	*i*-Pr	**364b**	1	25	90	92	**366(B)**
3	*i*-Pr	**364c**	1	24	87	84	**366(B)**
4	*i*-Pr	**364d**	1	24	62	83	**366(B)**
5	Me	**364a**	3	24	83	82	**366(B)**
6	Et	**364a**	3	24	91	84	**366(B)**
7[d]	Bn	**364a**	10	6	99	85	**366(B)**
8	*i*-Pr	**364e**	5	20	84	96	**366(A)**
9	*i*-Pr	**364f**	1	24	93	97	**366(B)**
10	*i*-Pr	**364g**	5	10	90	94	**366(B)**
11[c]	*i*-Pr	**364h**	3	6	81	90	**366(C)**
12[c]	*i*-Pr	**364i**	0.2	24	79	96	**366(C)**
13[e]	*i*-Pr	**364j**	2	6	82[f]	82	**366(C)**
14[g]	*i*-Pr	**364k**	5	4	70	86	**366(C)**

[a] Reactions conducted with 1.1 equiv. of **363** relative to **364a**−**k**. [b] **A**: acylimine (no treatment); **B**: ketone by hydrolysis; **C**: 1,2-diamine derivative by reduction (*syn*/*anti* = <5:>95). [c] −10 °C. [d] MS (3 Å) were added. [e] Ligand **305a** was used. [f] *syn*/*anti* = 28:72. [g] MS (3 Å) were added.

instead of ethyl glyoxylate, it gave the desired *N*,*O*-acetal in reasonable yield and ee value (Table 69, entry 2). Substituted enecarbamates **345c**−**e** also reacted efficiently with ethyl glyoxylate (Table 69, entries 5−9). It is noteworthy that the *anti* and *syn* products were formed stereospecifically from the *E* and *Z* enecarbamates, respectively. Furthermore, the utility of this synthetic methodology was demonstrated in the preparation of (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline (HMP, **348**; Scheme 78), which is a nonproteinogenic amino acid.

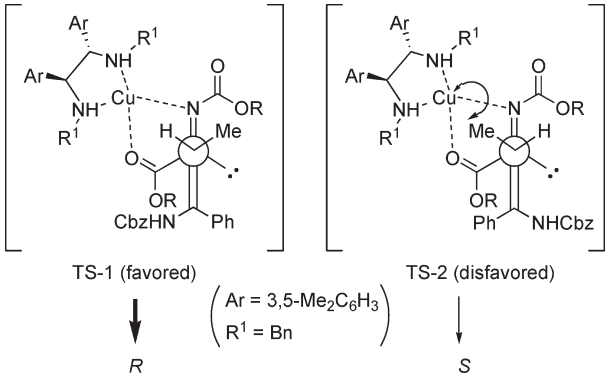
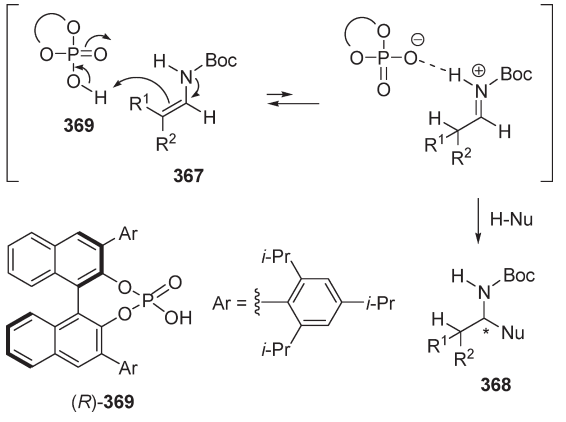


Figure 47. Proposed transition-state model.

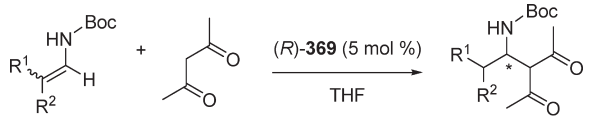
Scheme 82



Terada et al. reported the phosphoric acid (*R*)-**351** catalyzed aza-ene type reaction of glyoxate **349** with enecarbamates

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Table 74. Enantioselective Direct Mannich Reaction via Activation of Various Enecarbamates 367

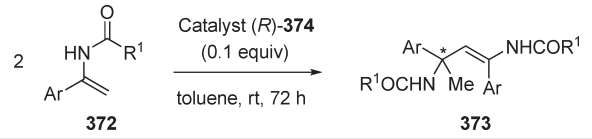


367a-g **370** **371a-g**

a: R^1 = H, R^2 = *i*-Pr (*E*/*Z* mixture)
b: R^1 = H, R^2 = Me
c: R^1 = H, R^2 = *n*-Bu (*E*/*Z* mixture)
d: R^1 = H, R^2 = *c*-Hex (*E*/*Z* mixture)
e: R^1 = Me, R^2 = Me
f: R^1 = H, R^2 = Bn (*E*/*Z* mixture)
g: R^1 = H, R^2 = Ph (*E* only)

entry	enecarbamate	conditions	yield of **371** (%)	ee (%)
1	**367a**	50 °C, 24 h	73	86
2	(*E*)-**367b**	50 °C, 24 h	49	49
3	(*Z*)-**367b**	50 °C, 24 h	63	49
4	**367c**	50 °C, 24 h	73	75
5	**367d**	50 °C, 24 h	67	89
6	**367e**	70 °C, 96 h	20	72
7	**367f**	50 °C, 24 h	56	61
8	**367g**	70 °C, 72 h	43	51

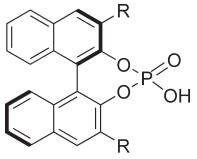
Table 75. Catalytic Asymmetric Self-Coupling of Enamides 372 by Using BINOL-Phosphate (*R*)-374



372 **373**

entry	R^1	Ar	yield (%)	ee (%)
1	Me	C_6H_5	79	96
2[a]	Me	2-ClC_6H_4		
3	Me	3-ClC_6H_4	15	88
4	Me	4-ClC_6H_4	82	>99
5	Me	4-$MeOC_6H_4$	83	88
6	Et	C_6H_5	70	85
7	Pr	C_6H_5	35	97
8	Pr	4-ClC_6H_4	63	>99

[a] No reaction



374
R = 4-NO_2-C_6H_4

Figure 48. (*R*)-BINOL-phosphate.

350a–d (Scheme 79).[154] Screening of a series of catalysts (**351**) bearing substituted phenyl rings showed that many para

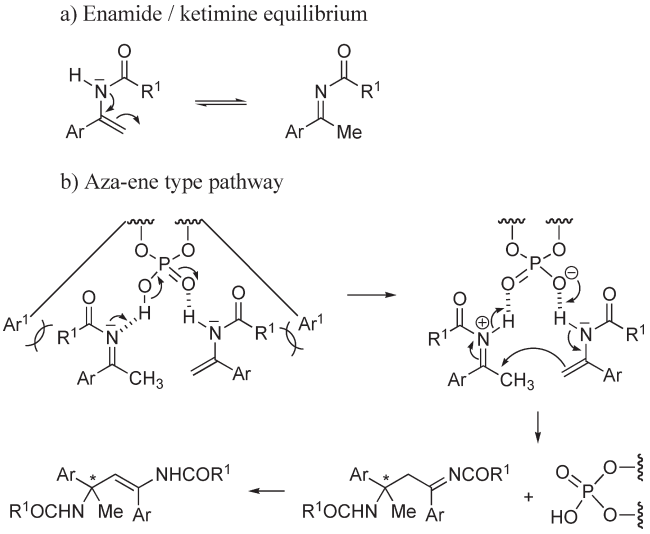
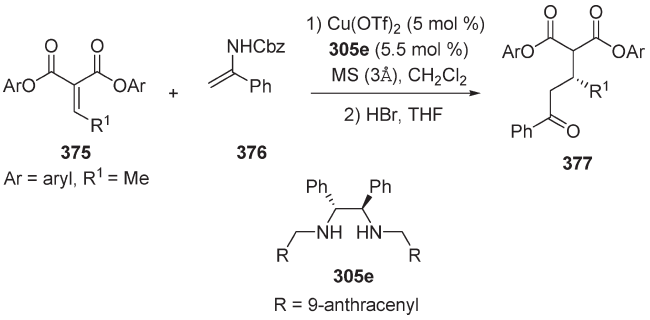


Figure 49. Mechanism for the self-coupling reaction of enamides.

Scheme 83



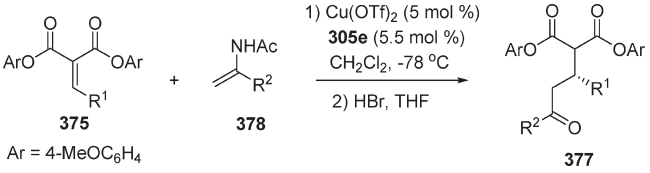
375
Ar = aryl, R^1 = Me

376

377

305e
R = 9-anthracenyl

Table 76. Catalytic Asymmetric Michael Reactions of Enamides 378



375
Ar = 4-$MeOC_6H_4$

378

377

entry	R^1	R^2	time (h)	yield (%)	ee (%)
1	Me	C_6H_5	10	90	90
2	Me	4-MeC_6H_4	24	80	88
3	Me	4-ClC_6H_4	22	92	90
4	Me	2-naphthyl	18	87	88
5	Me	Me[a]	10	35	80
6	Me	*i*-Pr[a]	10	88	83
7	Et	C_6H_5	24	85	94
8	Et	4-ClC_6H_4	46	64	93
9	Et	2-naphthyl	48	57	85
10	Et	2-thienyl	48	64	70
11[b]	*i*-Pr	C_6H_5	24	63	80

[a] The ethyl enecarbamate was used instead of the *N*-acetylenamine. [b] The reaction was conducted at −40 °C.

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substituents of the phenyl ring delivered high catalytic performance in terms of both activity and enantioselectivity in the reaction of **349** and **350** (R^1 = H, R^2 = Ph). The best results were obtained when Ar = 4-(*t*-Bu)-C_6H_4 in **351**. The scope of this catalyst was explored in the reaction of a variety of enecarbamates **350a**−**d** with **349** (Table 70). The initial aza-ene type products were hydrolyzed to the corresponding ketoalcohols **352a**−**d**. The reactions proceeded smoothly for (*E*)-enecarbamates and provided high enantioselectivities and *anti* selectivities (Table 70, entries 1−4). However, the (*Z*)-enecarbamates required longer reaction times and gave low enantioselectivities for the major *anti* isomer (Table 70, entries 5−7). DFT computational analysis of the complexation modes shows that the double hydrogen bonding interaction between the phosphoric acid and the glyoxylate is crucial in providing the high enantioselectivity (Figure 46).

Recently, Wang and co-workers investigated the Cr(III)-(salen)Cl **355** catalyzed enantioselective intramolecular addition of tertiary enamides to ketones (**353a**−**k**) to give highly functionalized 1*H*-pyrrol-2(3*H*)-one derivatives **354a**−**k** bearing a hydroxylated quaternary carbon center (Table 71).[155] The observed electronic effect was consistent with the nucleophilic attack of enamide at the carbonyl moiety. The increased electron density of the enamine double bond and the decreased electron density of the carbonyl led to an enhanced reaction rate. The configuration of the newly formed stereocenter in products **354** was determined as *S* by X-ray crystallography of an O-methylated derivative of **354d**, which indicated the nucleophilic attack of enamide at the *Re*-face of the carbonyl in the presence of **355**. The Cr(III)(salen)Cl-catalyzed enantioselective reaction was also applied to the enamides **356** and **358** (Scheme 80).

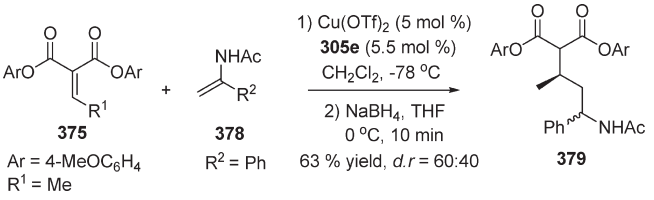
3.4. Addition of Enamides or Enecarbamates to Iminophosphonates

Kobayashi et al. reported the enantioselective additions of enecarbamates or enamides **361** to iminophosphonates **360** in the presence of a catalyst prepared from $Cu(OTf)_2$ and chiral diamine **305d** or **305a** (Table 72).[156] These reactions proceeded with high turnover frequency and α-amino phosphonates **362** were produced in excellent yields and enantioselectivities.

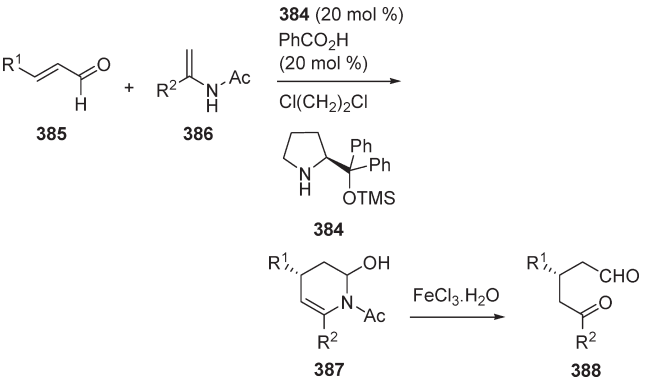
3.5. Addition of Enecarbamates to Azodicarboxylates

Kobayashi et al. reported the asymmetric amination of enecarbamates catalyzed by a Cu^{II} complex of chiral diamine **365** using azodicarboxylates (Scheme 81).[157] The scope of the catalytic asymmetric amination was explored for a wide range of azodicarboxylates **363** and enecarbamates **364** derived from aromatic and aliphatic ketones (Table 73), and they were found to give the corresponding desired products in good yields with high enantioselectivities. The initially formed acylimines **366(A)** were converted into ketone products **366(B)** after hydrolysis or 1,2-diamine derivatives **366(C)** after stereoselective reduction. The absolute configurations of the acylimine products were deter-

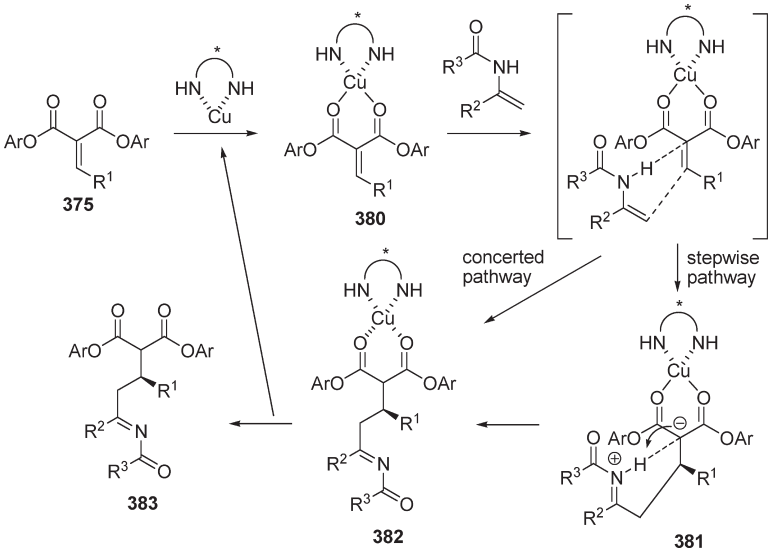
Scheme 84



Scheme 86



Scheme 85



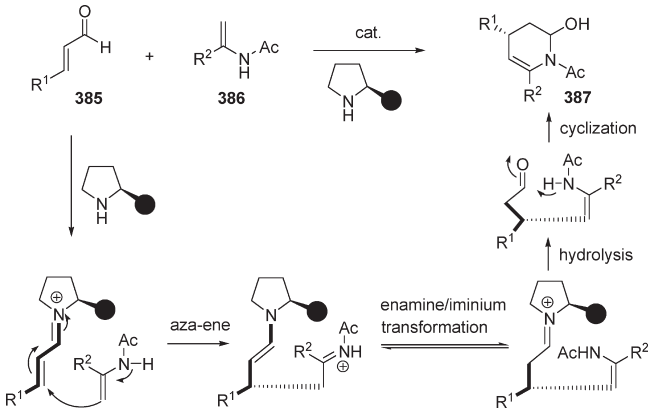
dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Table 77. Catalyst 384 Promoted Cascade Aza-ene-type Cyclization Reactions of α,β-Unsaturated Aldehydes (385) with Enamides (386)

entry	R^1 (385)	R^2 (386)	time (h)	yield (%) 387	yield (%) 388	ee (%) 388
1	4-$NO_2C_6H_4$	Ph	24	85	56	90
2	3-FC_6H_4	Ph	24	87	51	93
3[a]	2-$NO_2C_6H_4$	Ph	12	79	55	93
4[a]	4-$MeOC_6H_4$	Ph	10	77	53	95
5[a]	3-$MeOC_6H_4$	Ph	10	80	54	94
6[a]	1-naphthyl	Ph	10	82	53	97
7[a]	4-$MeOC_6H_4$	4-$MeOC_6H_4$	15	82	54	90
8[a]	4-$MeOC_6H_4$	4-FC_6H_4	15	80	53	92
9	4-$NO_2C_6H_4$	3-MeC_6H_4	14	80	51	94
10[a]	4-$MeOC_6H_4$	3-MeC_6H_4	14	73	50	94
11	4-$NO_2C_6H_4$	3-BrC_6H_4	40	45	50	90

[a] 2,4-Dinitrobenzoic acid used as additive instead of benzoic acid.

Scheme 87



mined to be *R*. To account for the stereochemical outcome of the reaction, the authors proposed an acyclic concerted transition-state model (Figure 47). It was presumed that a diamine ligand and azodicarboxylate coordinate to the copper in bidentate fashion and that the copper adopts a slightly distorted square-planar geometry. As for the facial selectivity of the enecarbamate, TS-1 and TS-2 in which the enecarbamate reacts with azodicarboxylate through an *antiperiplanar* transition state are reasonable to minimize steric repulsions between the enecarbamate and the copper catalyst or the carbamate group of the azodicarboxylate. TS-1, which gives the *R*-configured product, is more plausible because of the critical steric repulsion between the substituent of the enecarbamate and the copper catalyst in TS-2.

4. MANNICH REACTION

This reaction is one of the most widely utilized chemical transformations for the construction of enantiopure β-amino carbonyl compounds. Recently, Terada and co-workers published the enantioselective direct Mannich reaction via activation of enecarbamates **367** by a chiral monophosphoric acid catalyst **369** (Scheme 82).[158] Using acetylacetone **370** as a nucleophile, a variety of enecarbamates **367** having different β-substituents (R^1 and R^2) were reacted in THF to produce the corresponding β-alkyl-β-aminocarbonyl derivatives **371** in moderate to good enantioselectivities (Table 74). The absolute configuration of the Mannich product **371a** was determined as *R*.

5. SELF-COUPLING OF ENAMIDES

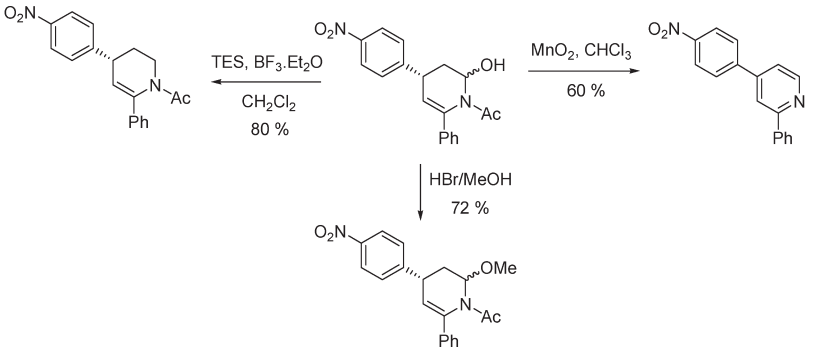
Tsogoeva et al. studied the enantioselective self-coupling of enamides **372** (Table 75) induced by BINOL-phosphate **374** catalyst (Figure 48).[159] The coupling products **373** possess a quaternary carbon center with a nitrogen atom. Enamides **372** bearing electron-withdrawing groups in the *ortho*- or *meta*-position in the aromatic ring rendered either no conversion or only low yield (entries 2 and 3 vs entry 1). On the other hand, good yields were obtained for enamides bearing electron-withdrawing or electron-donating groups in the *para*-position of the aromatic ring (entries 4 and 5). The reactivity and enantioselectivity was also altered by variation of the R^1 group. A plausible mechanism for the self-coupling reaction is shown in Figure 49. The first step (Figure 49a) concerns the equilibrium between enamide and ketimine in the presence of a chiral BINOL-phosphate. The next steps (Figure 49b) cause a coupling reaction due to the dual function of the phosphoric acid group. The application of the self-coupling reaction of enamides has been exploited for the synthesis of enantiopure β-alkyl-β-aminoketones.

6. MICHAEL REACTION

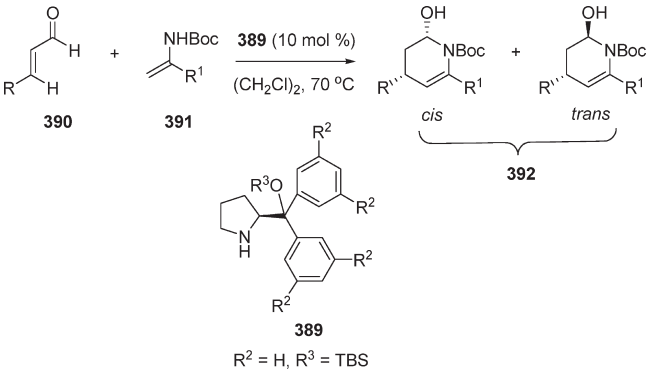
The usefulness of enamides and enecarbamates as nucleophiles in the Michael reaction was established by Kobayashi and co-workers.[160] Screening of a variety of chiral diamine ligands in the reaction of enecarbamate **376** and diaryl ethylidenemalonates **375** with $Cu(OTf)_2$ revealed diamine **305e** as very promising (Scheme 83). The yields and enantioselectivities were determined after hydrolysis of the initially formed Michael adducts to ketone products **377**. With the diamine **305e**, the Michael reaction was performed between a variety of alkylidenemalonates **375** and enamides **378** (Table 76). It gave the corresponding ketone products **377** in high yields and high enantioselectivities in most cases. The absolute stereochemistry of the products was determined to be the *S* configuration. The extension of this methodology was shown by the preparation of the amino ester **379** by reduction instead of hydrolysis of the initially formed imine Michael adduct

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

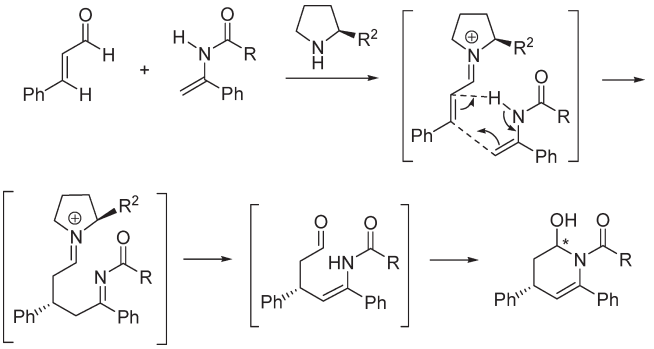
Scheme 88



Scheme 89



Scheme 90

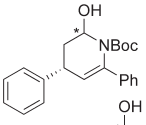
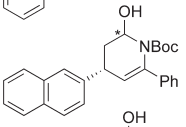
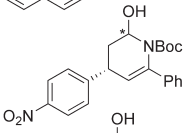
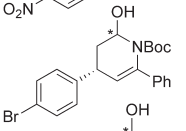
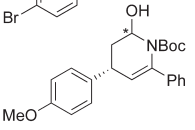
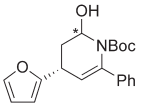
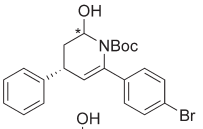
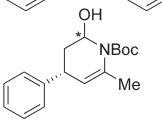


(Scheme 84). The authors proposed a mechanism for the reaction as shown in Scheme 85. The key intermediate could be generated by a concerted or a stepwise process.

7. CYCLIZATION REACTIONS

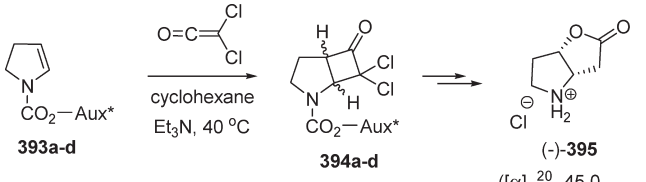
Wang and co-workers exploited the enantioselective cascade aza-ene-type cyclization reactions between α,β-unsaturated aldehydes **385** and enamides **386** (Scheme 86, Table 77) as catalyzed by the (*S*)-diphenylprolinol-TMS ether **384**.[161] These reactions proceeded in the presence of benzoic acid or 2,4-dinitrobenzoic acid as additives to give the enantioenriched six-membered ring hemiaminals **387**. Significantly, the cascade process involves an unprecedented multistep imminium/enamine transformation. The proposed cascade aza-ene-type cyclization sequence is shown in Scheme 87. Finally, the hemiaminals **387** were easily transformed to pyridines, enamides, and aminals (Scheme 88) in addition to 1,5-dicarbonyls **388** (Scheme 86).

Table 78. Asymmetric Formal Aza [3 + 3] Cycloaddition Between Enecarbamates and α,β-Unsaturated Aldehydes Using Diphenylprolinol Silyl Ether 389 Catalyst

Entry	Product **392**	Time (h)	Yield (%)	Ratio of *cis*:*trans*	*ee* (%) *cis*	*ee* (%) *trans*
1		34	90	34:66	94	93
2		38	83	29:71	91	90
3		22	83	29:71	95	97
4		22	88	31:69	91	92
5		48	73	19:81	97	97
6		96	80	27:73	99	99
7		29	89	26:74	90	88
8		23	85	19:81	90	90

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 91



a: Aux* = (-)-*endo*-bornyl

b: Aux* = (-)-menthyl

c: Aux* = (*R*)-1-(2,4,6-triisopropylphenyl)ethanol

d: Aux* = (-)-8-phenylmenthyl

Scheme 92

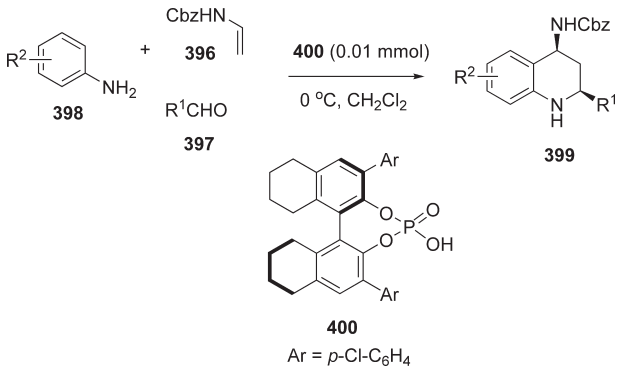


Table 79. Phosphoric Acid 400 Catalyzed Enantioselective Three-Component Povarov Reaction

entry	R^1 (**397**)	R^2 (**398**)	yield (%) (**399**)	ee (%) (**399**)
1	*p*-ClC_6H_4	*p*-OMe	74	99
2	*p*-PhC_6H_4	*p*-OMe	89	98
3	*p*-FC_6H_4	*p*-OMe	72	99
4	*p*-MeC_6H_4	*p*-OMe	64	>99
5	2-furyl	*p*-OMe	85	97
6	*p*-NCC_6H_4	*p*-OMe	75	>99
7	*p*-(*i*-Pr)C_6H_4	*p*-OMe	68	>99
8	*p*-$NO_2C_6H_4$	*p*-OMe	80	>99
9	*i*-$PrCH_2$	*p*-OMe	85	92
10	*i*-Pr	*p*-OMe	77	95
11	Et	*p*-OMe	82	92
12	*n*-propyl	*p*-OMe	90	92
13	Et	*p*-CF_3	57	93
14	Ph	H	74	99
15	Ph	*p*-Cl	89	>99

In parallel, Hayashi et al. discovered that the diphenylprolinol silyl ether **389** catalyzed a formal aza [3 + 3] cycloaddition reaction of enecarbamates **391** with α,β-unsaturated aldehydes **390**, leading to the enantiopure piperidine derivatives **392** (Scheme 89).[162] The one-pot transformation consists of four consecutive steps as described in Scheme 90. Reaction conditions were optimized by screening of diphenylprolinol catalysts **389** (R^2 = H, CF_3; R^3 = *tert*-butyldimethylsilyl, trifluoromethylsilyl, H)

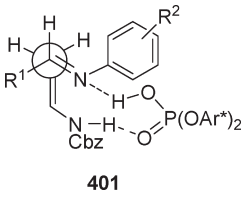
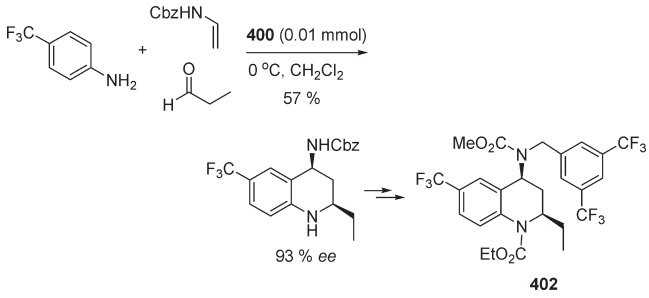
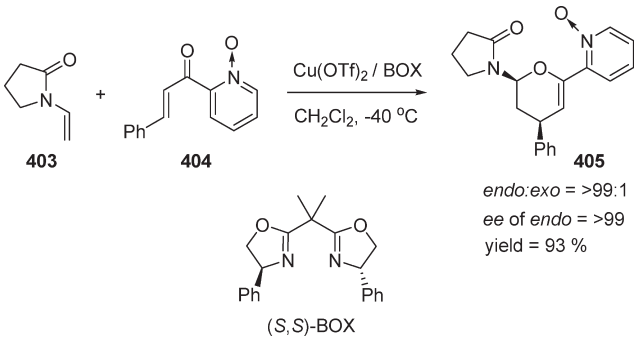


Figure 50. Proposed transition state.

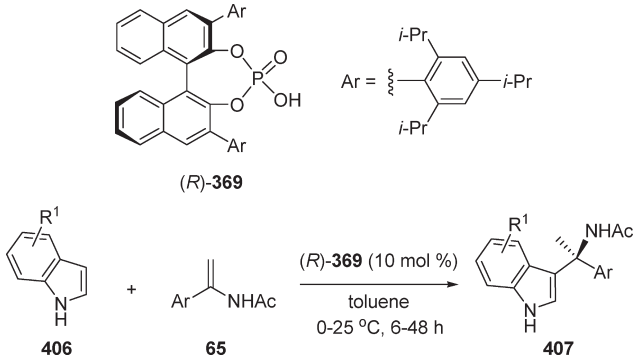
Scheme 93



Scheme 94



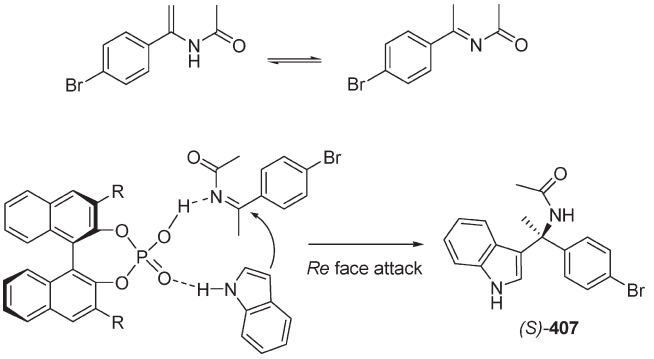
Scheme 95



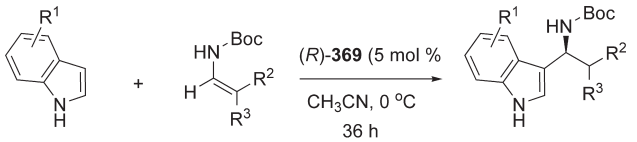
in various solvents. Best results were reported in dichloroethane at 70 °C. Reaction of **391** with a variety of acrolein derivatives in the presence of catalyst **389** led to the corresponding piperidine derivatives **392** in high yield with excellent enantioselectivity

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Scheme 96



Scheme 97



406a-f 408a-g 409

a: R^1 = H
b: R^1 = 5-MeO
c: R^1 = 5-Me
d: R^1 = 5-Br
e: R^1 = 6-Br
f: R^1 = 5-CO_2Me

a: R^2 = H, R^3 = H
b: R^2 = H, R^3 = Me (>99 % *E*)
c: R^2 = H, R^3 = *n*-Bu (1:1 *E*/*Z* mixture)
d: R^2 = H, R^3 = Bu (1:1 *E*/*Z* mixture)
e: R^2 = H, R^3 = *i*-Pr (1:1 *E*/*Z* mixture)
f: R^2 = H, R^3 = Ph (>99 % *E*)
g: R^2 = Me, R^3 = Me

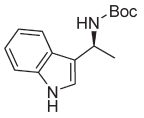
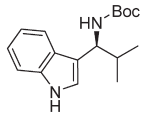
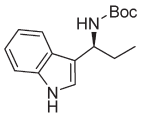
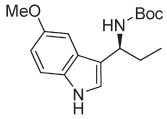
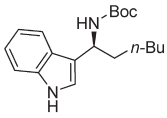
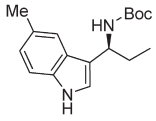
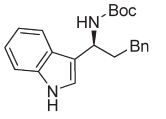
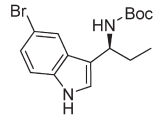
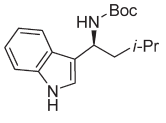
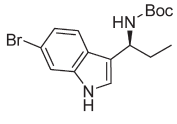
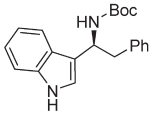
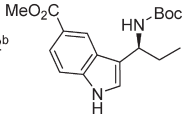
Table 80. (*R*)-369 Catalyzed Enantioselective Friedel−Crafts Reaction of Indole Derivatives 406 with α-Aryl Enamides 65

R^1 (**406**)	Ar (**65**)	yield (%) (**407**)	ee (%) (**407**)
H	C_6H_5	98	94
H	4-MeC_6H_4	99	92
H	4-$CF_3C_6H_4$	98	93
H	3-MeOC_6H_4	99	97
H	3-ClC_6H_4	99	92
H	3,4-$Me_2C_6H_3$	99	95
H	2-MeOC_6H_4	95	73
H	2-naphthyl	95	92
4-OH	C_6H_5	95	86
5-Br	C_6H_5	98	90
5-MeO	C_6H_5	99	92

(Table 78). The authors proposed that the ene component approaches opposite to the face with the bulky TBSO group.

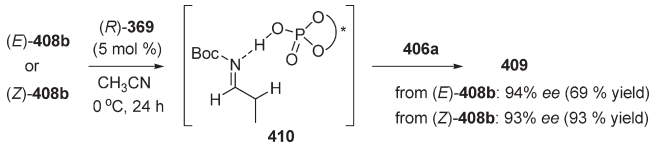
Correia et al. studied the [2 + 2] cycloaddition between dichloroketene and five-membered endocyclic enecarbamates **393a**−**d** (Scheme 91).[163] In these, the corresponding cycloadducts **394a**−**d** were produced in good yields but with low stereoselectivities (≥60% de). This methodology (stoichiometric asymmetric synthesis) was utilized for the synthesis of (−)-Geissman−Waiss lactone **395** from the major diastereomer of **394d** (Scheme 91).

Table 81. (*R*)-369 Catalyzed Enantioselective Friedel−Crafts Reaction of Indole Derivatives 406 with Enecarbamates 408

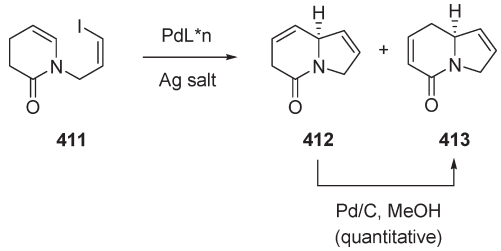
Entry	Product (**409**)	Yield % (*ee* %)	Entry	Product (**409**)	Yield % (*ee* %)
1[a]		95 (93)	7[c]		69 (94)
2		87 (94)	8		90 (90)
3		98 (94)	9		84 (93)
4[b]		82 (93)	10		91 (93)
5		80 9(1)	11		78 (96)
6[c]		63 (90)	12[b]		86 (93)

[a] Reaction run at −20 °C. [b] Reaction run at room temperature. [c] Reaction run at 50 °C.

Scheme 98



Scheme 99



8. POVAROV REACTION

Zhu et al. studied the chiral phosphoric acid **400** catalyzed enantioselective three-component Povarov reaction using enecarbamate **396**, aldehyde **397**, and functionalized anilines **398**

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

(Scheme 92).[164] This reaction produced the tetrahydroquinolines **399** in good yields with excellent enantioselectivity (Table 79). The absolute configuration of **399** (R^1 = Ph, R^2 = 4-Cl) was unambiguously determined by X-ray analysis to be (2*S*,4*R*). It was proposed that the phosphoric acid acted as a bifunctional catalyst that activates both the nucleophile and electrophile via transition state **401** (Figure 50) to allow a pseudointramolecular *Si*-face attack by **396** on the imine. The importance of this catalytic enantioselective three-component Povarov reaction was illustrated by the synthesis of torcetrapib **402** (Scheme 93).

9. HETERO-DIELS–ALDER REACTION

Recently, Blay et al. investigated an enantioselective inverse electron demand hetero-Diels–Alder reaction between enamide **403** and 2-alkenoylpyridine *N*-oxide **404** using a Cu(II)-BOX catalyst (Scheme 94).[165] The chiral dihydropyran **405** bearing a pyridine ring at the 6-position was obtained with very high yield and excellent stereoselectivity. The stereochemistry of the product revealed that the approach of alkene to the heterodiene occurs preferentially from the *Si* face of the double bond.

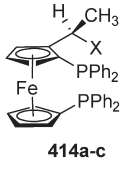
10. FRIEDEL–CRAFTS REACTION

The enamides and enecarbamates have generally been used as nucleophiles in acid-catalyzed reactions, while they can play the role of electrophile in the Friedel–Crafts reaction with indoles. Enantioselective Friedel–Crafts reactions of arenes with enamides or enecarbamates generate chiral amines with a quaternary carbon atom. In 2007, Zhou et al.[166] reported the BINOL-derived phosphoric acid (*R*)-**369** catalyzed enantioselective Friedel–Crafts reaction of indoles **406** with α-aryl enamides **65** as the electron-rich alkenes, while Terada et al[167] reported the same reaction with enecarbamates **408** as the electron-rich alkenes (Schemes 95 and 97). The scope and potential of the reaction was explored for a wide array of indole derivatives **406** and α-aryl enamides **65** in the presence of the catalyst (*R*)-**369** (Table 80). This gave the corresponding amine products **407** in excellent enantioselectivities and yields in most cases. However, by contrast, *ortho* substituents in the α-aryl enamides greatly diminished both the reactivity and enantioselectivity of the reaction. Noticeably, the Friedel–Crafts reaction did not occur with either *N*-methylindole or *N*-methyl α-aryl enamide. This shows that the hydrogen atom

Table 82. Ligand Effects on the Cyclization of 411[a]

entry	ligand	temp (°c)	time (h)	ratio **412**/**413**	yield (%)	ee (%) **413**
1	(*R*)-BINAP	90	46	1:3.3	67	34 (*R*)
2	**414c**	50	8.5	1:5.5	79	45 (*S*)
3	**414b**	50	14	1:12	62	52 (*S*)
4	**414a**	50	35	0:1	45	74 (*S*)

[a] Vinyl iodide **411** was treated with $Pd_2dba_3 \cdot CHCl_3$ (5 mol % Pd), ligand (12 mol %), Ag_3PO_4 (2 equiv), and $CaCO_3$ (2.2 equiv) in DMF.



414a-c

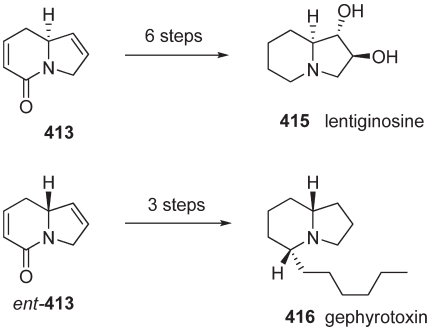
a: (*R*)-(*S*)-BPPFOH (X = OH)

b: (*R*)-(*S*)-BPPFOAc (X = OAc)

c: (*R*)-(*S*)-BPPFA (X = NMe_2)

Figure 51. Chiral ferrocene-based diphosphine ligands.

Scheme 100



Scheme 101

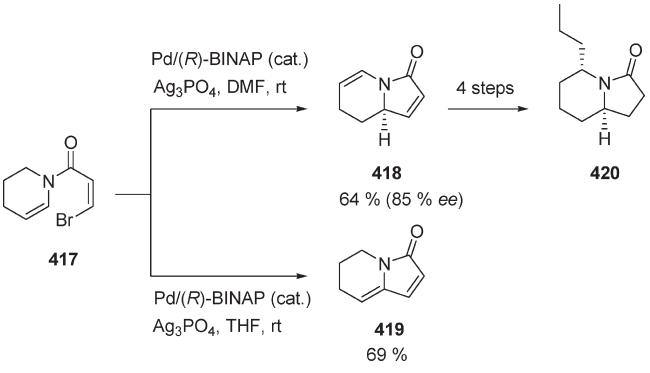


Table 83. Effect of Solvent, Silver Salt, and Temperature on Cyclization of 411

entry	silver salt	solvent	temp (°C)	time (h)	ratio of **412**/**413**	yield % **413**	ee % **413**
1	Ag_3PO_4	DMF	50	21	1:3.3	69	74
2	Ag_3PO_4	NMP	50	14.5	0:1	21	71
3	Ag_3PO_4	DMA	50	65	1:2.9	73	71
4	Ag_3PO_4	TMU	50	13	0:1	49	69
5	Ag_3PO_4	DMSO	23	7	1:2.5	82	81
6	Ag-exchanged zeolite	DMSO	23	3.3	1:4.5	58	79
7	Ag-exchanged zeolite	DMSO–DMF(1:1)	0	120	1:1.4	94	86

dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

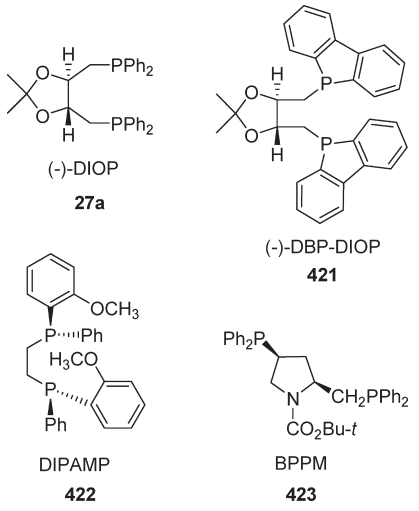
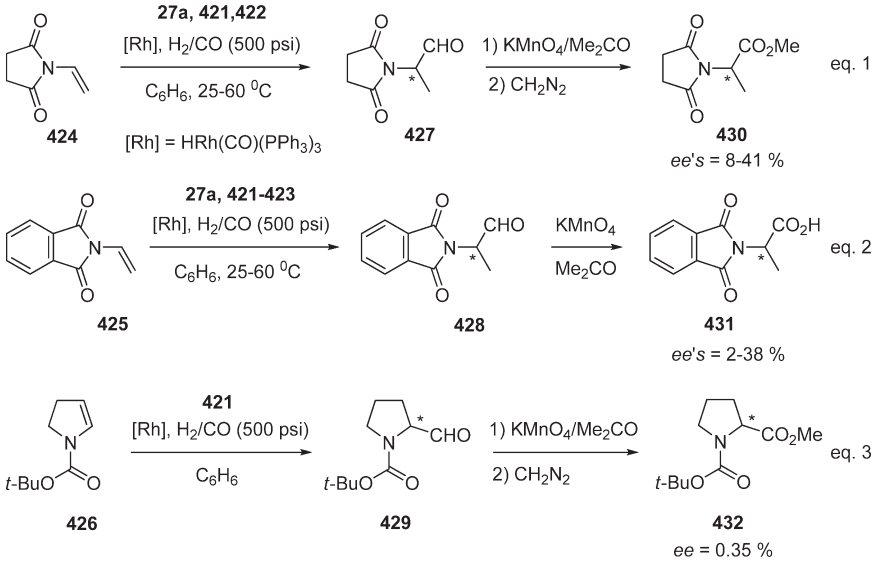


Figure 52. Chiral phosphine ligands used in the hydroformylation reactions of **424**−**426**.

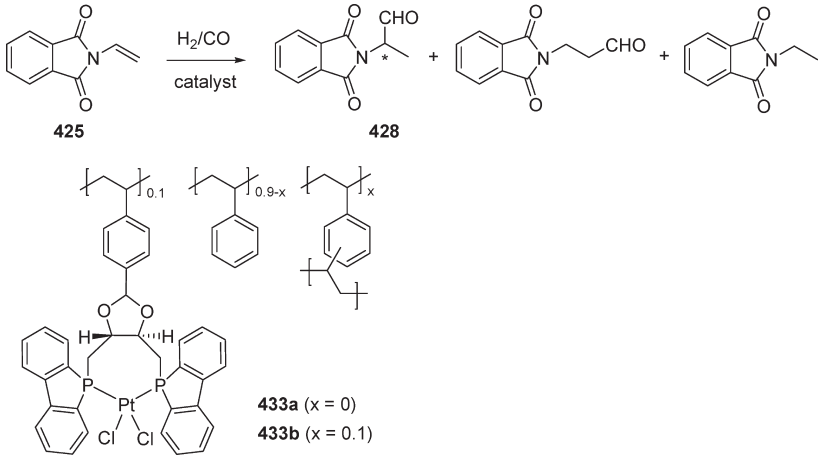
on the N atoms of both the indole and enamide moieties is crucial for the activation of the reactants by phosphoric acid catalyst. On the basis of these results the authors proposed the reaction model shown in Scheme 96. The chiral acid catalyst activates the indole and enamide moieties through two hydrogen bonds. The indole attacks the ketimine from the *Re* face, affording the Friedel−Crafts products with an *S* configuration.

The enantioselective Friedel−Crafts reaction of a variety of indoles **406a**−**f** with substituted enecarbamates **408a**−**g** catalyzed by chiral phosphoric acid (*R*)-**369** in acetonitrile leads to the enantioenriched 1-indolyl-1-alkylamine derivatives **409** (Scheme 97 and Table 81).[167] High enantioselectivities and chemical yields were often obtained. Furthermore, the isomeric (*E*)-**408b** and (*Z*)-**408b** gave the products **409** with the same level of enantioselectivity (Scheme 98). Based on these results, the authors presume that both reactions proceed through a common intermediate **410**, composed of **369** and an imine generated by the protonation of enecarbamates **408b**.

Scheme 102



Scheme 103



dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

Table 84. Asymmetric Hydroformylation of *N*-Vinylphthalimide 425 with Platinum Catalysts

run	catalyst	time (h)	conversion (%)	selectivity[a] (%)	b/n[b]	ee (%)
1	[(−)-DIPHOL]$PtCl_2$ + $SnCl_2.2H_2O$	60	60	37	6.0	68
2	[(−)-DIPHOL]$Pt(SnCl_3)Cl$	60	40	57	6.0	70
3	**433a** + $SnCl_2 \cdot 2H_2O$	70	52	45	3.5	62
4	**433b** + $SnCl_2 \cdot 2H_2O$	100	30	40	2.4	60
5[c]	**433b** + $SnCl_2 \cdot 2H_2O$	100	24	39	2.5	58
6[c]	**433b** + $SnCl_2 \cdot 2H_2O$	100	18	40	2.5	58
7[c]	**433b** + $SnCl_2 \cdot 2H_2O$	100	10	40	2.5	58

[a] Selectivity = hydroformylation products/total products. [b] Branched/normal ratio. [c] The catalyst was recycled from the previous run, and $SnCl_2 \cdot 2H_2O$ was added.

Scheme 104

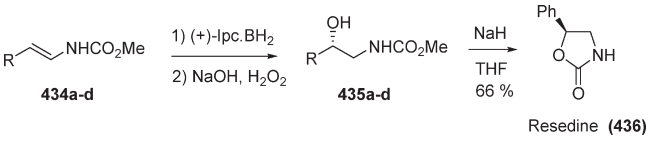
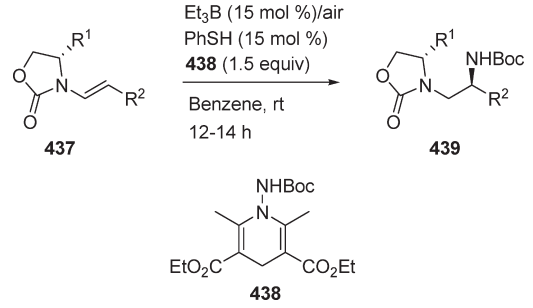


Table 85. Asymmetric Hydroboration of *trans*-434a−d

entry	enecarbamate *trans*-**434**	R	β-hydroxyamine **435**	yield (%)	ee (%)
1	**a**	Me	**a**	56	7
2	**b**	*i*-Pr	**b**	56	66
3	**c**	$Me(CH_2)_5$	**c**	92	60
4	**d**	Ph	**d**	94	70

Scheme 105



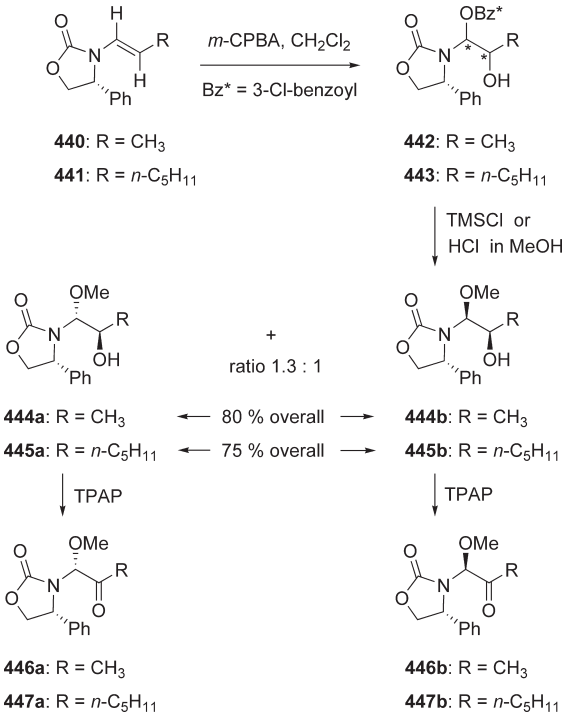
11. INTRAMOLECULAR HECK REACTION

Asymmetric Heck cyclizations have been employed in numerous ways for the construction of chiral nitrogen heterocycles. Enamides are interesting substrates for these reactions. For example, Shibasaki and co-workers described the asymmetric Heck cyclization of *N*-allylpyridones to give simple unsaturated indolizidines in useful enantiopurity.[168] Initial attempts to effect enantioselective cyclization of dihydropyridone vinyl iodide **411** using Pd/BINAP catalyst in the presence of Ag_3PO_4 gave a mixture of unsaturated indolizidine isomers **412** and **413** (Scheme 99). The minor isomer **412** could be converted quantitatively to the major α,β-unsaturated lactam **413** by subsequent reaction of the former with catalytic Pd/C in MeOH. The Pd/BINAP-catalyzed Heck cyclization of **411** proceeded slowly even at 90 °C, and

Table 86. Hydroamination of Chiral Enecarbamates

	437			
entry	R^1	R^2	yield (%) **439**	dr
1	*i*Pr	Et	47	13:1
2	*i*Pr	Bu	48	13:1
3	*i*Pr	*i*Pr	33	13:1
4	*i*Pr	*t*Bu	30	20:1
5	*i*Pr	PMB	40	13:1
6	*i*Pr	$(CH_2)_3Ph$	44	13:1
7	*i*Pr	$(CH_2)_3CO_2Et$	41	13:1
8	*i*Pr	$(CH_2)_2OAc$	48	13:1
9	Ph	Et	48	11:1
10	Ph	*i*Pr	34	11:1
11	*t*Bu	Et	48	14:1

Scheme 106



dx.doi.org/10.1021/cr100031f |*Chem. Rev.* 2011, 111, 4599–4657

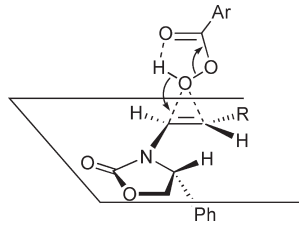
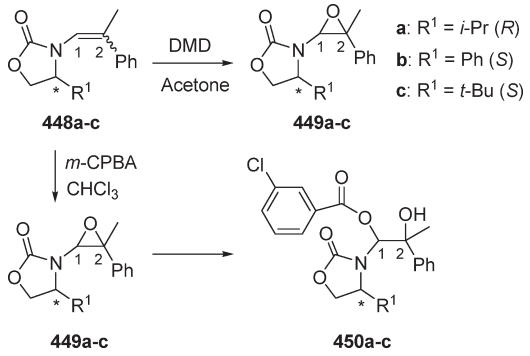


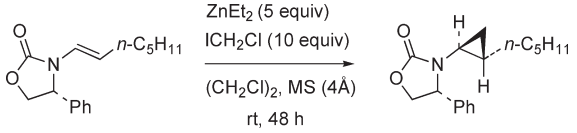
Figure 53. A π-facially differentiated chiral enecarbamate template.

Table 87. Diastereoselectivity in the Epoxidation of Enecarbamate 448a−c by DMD and *m*-CPBA



			diastereoselectivity of epoxide **449**
entry	reagent	substrate	1*S*:1*R*
1	DMD	(*Z*)-**448a**	60:40
2	*m*-CPBA	(*Z*)-**448a**	70:30
3	DMD	(*Z*)-**448b**	8:92
4	*m*-CPBA	(*Z*)-**448b**	8:92
5	DMD	(*Z*)-**448c**	7:93
6	*m*-CPBA	(*Z*)-**448c**	7:93
7	DMD	(*E*)-**448a**	53:47
8	*m*-CPBA	(*E*)-**448a**	50:50
9	DMD	(*E*)-**448b**	40:60
10	*m*-CPBA	(*E*)-**448b**	48:52
11	DMD	(*E*)-**448c**	25:75
12	*m*-CPBA	(*E*)-**448c**	21:79

Scheme 107



indolizidine **413** was obtained in only 34% ee (Table 82, entry 1). A survey of other chiral diphosphine ligands demonstrated that the optimum ligand for this transformation was (*R*)-(*S*)-BPPFOH (**414a**, Figure 51), which gave **413** as the only product in 45% yield and 74% ee (Table 82, entry 4). Hydrogen bonding of the hydroxyl group of ligand **414a** with the pyridone carbonyl group was suggested to account for the higher enantioselection observed with this ligand.

Further optimization of the Heck cyclization of **411** focused on the effects of solvent, silver salt, and temperature on asymmetric induction (Table 83). The best results were obtained using silver-exchanged zeolite in DMSO−DMF (1:1) at 0 °C (Table 83, entry 7). The utility of indolizidine intermediate **413** in natural product synthesis was demonstrated by its conversion to lentiginosine (**415**) and gephyrotoxin 209D (**416**) (Scheme 100).[169]

Sulikowski and co-workers also reported enantioselective Heck cyclizations of N-acylated tetrahydropyridine precursor **417** (Scheme 101).[170] In these studies, the selection of solvent proved to be critical for conversion of **417** to a chiral indolizidine derivative. Unsaturated indolizidine **418** was converted in four steps to **420**, a common intermediate in total syntheses of two indolizidine alkaloids: 5-epiindolizidine 167B[171] and 5*E*,9*Z*-indolizidine 223AB.[172]

12. HYDROFORMYLATION

In 1980, the Stille research group reported the first examples of asymmetric hydroformylation for a variety of enamides.[173] In the hydroformylation reactions, rhodium catalysts derived from the various phosphine ligands **27a** and **421**−**423** (Figure 52) were used. Reactions performed for *N*-vinylsuccinimide **424**, *N*-vinylphthalimide **425**, and *N*-acyl-2-pyrrolines **426** produced the formylated products **427**, **428**, and **429**, respectively (Scheme 102, eqs 1−3). These were further transformed to the corresponding acids or ester derivatives, and the enantioselectivities were measured. In all cases, the enantioselectivities were very low (2−41%).

Furthermore, the asymmetric hydroformylation of **425** was studied with the platinum catalyst [(−)-DBP-DIOP]Pt-($SnCl_3$)Cl and polymer-supported platinum catalysts **433a,b** (Scheme 103, Table 84).[174] These catalysts allowed a faster reaction with high ee (58−70%) but low aldehyde selectivity (37−57%). The hydroformylation of **425** in the presence of [(−)-BPPM]$PtCl_2$/$SnCl_2$ gave a 52% conversion to branched and normal aldehydes (b/n = 0.5) with relatively low aldehyde selectivity (85%).[175] The (*R*)-(+)-branched isomer was obtained in 72% ee.

13. HYDROBORATION

Matsumura et al. synthesized chiral β-hydroxyamines **435** via stoichiometric asymmetric hydroboration of enecarbamates **434** as shown in Scheme 104.[176] The hydroboration of *trans* enecarbamates **434b,c,d** using (+)-Ipc·BH_2 gave the corresponding β-hydroxyamines with moderate ee's (Table 85, entries 2−4), while the *trans*-**434a** gave **435a** with low ee (Table 85, entry 1). Finally, the usefulness of this methodology was demonstrated by a transformation of (*S*)-(+)-**435d** (70% ee) to resedine (**436**).

14. HYDROAMINATION

Hydroamination of chiral enecarbamates **437** derived from Evans oxazolidinones in the presence of *N*-aminated Hantzsch ester **438** lead to the protected vicinal diamines **439** (Scheme 105, Table 86).[177] The highest diastereoselectivity (dr = 20:1) was obtained for the *tert*-butyl-substituted carbamate (Table 86, entry 4). The relative configuration of the major isomer of **439** (R^1 = R^2 = *i*-Pr) was assigned by X-ray analysis. The stereoselectivity of the hydroamination reaction was explained by the preferred approach to the olefin by the carbamoyl radical from the side opposite to the shielding R^1

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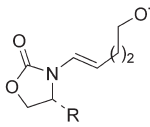
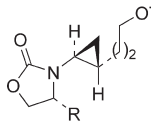
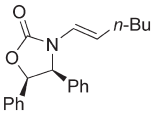
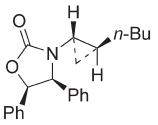
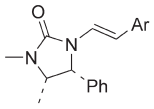
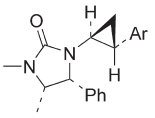
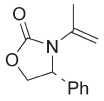
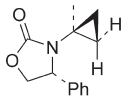
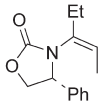
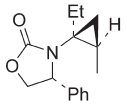
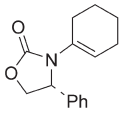
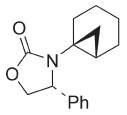
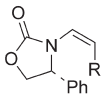
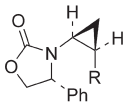
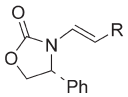
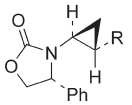
Table 88. Stereoselective Cyclopropanation of Chiral Enamides

Entry	Chiral Enamides	Cyclopropane Product	Time (h)	Yield (%)	*dr*
1	 **451**: R = Ph	 **463**: R = Ph	48	50	94:6
2	**452**: R = Bn	**464**: R = Bn	72	60	>95:5
3	 **453**	 **465**	48	61	>95:5
4	 **454**: Ar = PMB	 **466**: Ar = PMB	1	92	72:28
5	**455**: Ar = Ph	**467**: Ar = Ph	5	70	80:20
6	 **456**	 **468**	1	72	>95:5
7	 **457**	 **469**	72	40	88:12
8	 **458**	 **470**	24	80	>95:5
9	 **459**: R = *n*-C_6H_{13}	 **471**: R = *n*-C_6H_{13}	48	57	>95:5
10	**460**: R = Ph	**472**: R = Ph	48	64	>95:5
11	 **461**: R = *n*-C_5H_{11}	 **473**: R = *n*-C_5H_{11}	48	80	95:5
12	**462**: R = Ph	**474**: R = Ph	48	50	83:17

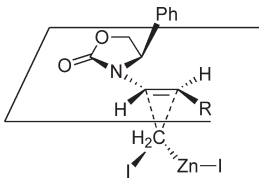


Figure 54. A π-facially differentiated chiral enamide template.

substituent. This reaction may generate chiral diamines after removal of the chiral auxiliary.

15. EPOXIDATION OF CHIRAL ENECARBAMATES

In 2002, Hsung et al. reported the epoxidations of chiral enecarbamates.[178] Reactions of **440** and **441** using *m*-CPBA in MeOH or in a $NaHCO_3$ buffer led to the aminals **444a/b** and **445a/b** as a mixture of diastereomers [1.3:1] (Scheme 106). Subsequent TPAP oxidation of **444a/b** and **445a/b** either as a mixture or as individual diastereomers led to α-keto hemiaminals **446a/b** and **447a/b**, respectively. The structure of aminal **444a** was unambiguously determined by X-ray analysis. The model shown in Figure 53 was proposed to explain the stereochemical control. The potential of the methodology was extended to generating chiral α-keto aminals as a viable source of chiral nitrogen stabilized oxyallyls in stereoselective [4 + 3] cycloadditions.

Bosio et al. studied the epoxidations of chiral oxazolidinone-substituted enecarbamates **448a−c** by dimethyldioxirane (DMD) as well as *m*-CPBA (Table 87).[179] The (*Z*)-enecarbamates **448a−c** (entries 1−6) gave higher diastereoselectivity than (*E*)-isomers (entries 7−12). In both DMD and *m*-CPBA reactions, the major diastereomer epoxide is the same; however, the epoxide was opened exclusively at the C1 position to the ester **450a−c** by the acid generated from *m*-CPBA. The absolute

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Scheme 108

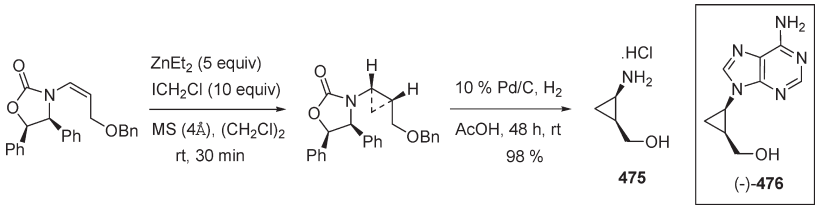
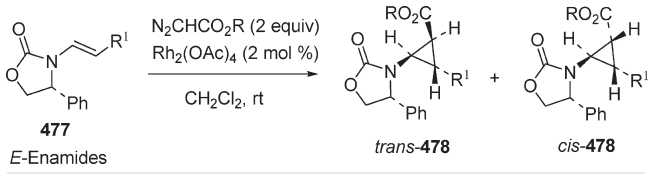


Table 89. Cyclopropanations of *E*-Enecarbamates



R^1	R	yield (%)	dr	*trans*/*cis*
CH_2CH_2OTBS	Et	74	>95:5	2.5:1
n-pent	Et	66	>95:5	2.5:1
n-pent	*t*-Bu	54	>95:5	2.5:1
Bn	Et	66	>95:5	4:1
Ph	Et	67	92:8	7:1
Ph	*t*-Bu	40	>95:5	7:1
c-hex	Et	67	>95:5	8:1
c-hex	*t*-Bu	62	>95:5	>19:1
i-Pr	Et	91	>95:5	9:1
i-Pr	*t*-Bu	78	>95:5	>19:1

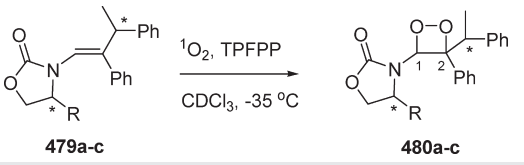
configurations of the epoxide **449c** and ester **450c** were determined as 1*R*,2*R* and 1*S*,2*R*, respectively.

16. SIMMONS–SMITH CYCLOPROPANATION

Hsung et al. reported the stereoselective Simmons–Smith cyclopropanation of chiral enecarbamates for the synthesis of chiral aminocyclopropanes (Scheme 107).[180] Reactions were conducted for a variety of chiral enecarbamates or eneimidazolones (**451**–**462**) using dihaloalkane ICH_2Cl as the methylidene source (Table 88). The configuration of the products was determined on the basis of the X-ray crystal structures of **466** and **472**, and it was found that both *E* and *Z* amides appeared to favor cyclopropanation at the same π-face (Figure 54). The Simmons–Smith cyclopropanation of chiral enecarbamates was applied for the synthesis of chiral aminocyclopropane **475**, which was used in the synthesis of the de novo cyclopropyl nucleoside (−)-**476** (Scheme 108).

This group also investigated a mutually π-facial selective cyclopropanation of chiral enecarbamates mediated by the dirhodium(II) carbenoids.[181] These reactions were carried out for a range of β-substituted *E*-enecarbamates using α-diazo esters in the presence of dirhodium(II) tetraacetate (Table 89). In all cases, the cycloaddition exhibits an excellent π-facial selectivity with respect to the enecarbamate. Furthermore, cyclopropanations were conducted for enecarbamates bearing α- as well as β-substituents. The observed π-facial selectivity is in accordance with the preferred conformation of chiral enecarbamate in which the oxazolidinone ring is coplanar with the olefin, thereby allowing a favorable approach of the metal carbene to the face of the enecarbamates *anti* to the phenyl substituent.

Table 90. Diastereoselective Dioxetane Formation in the Photooxygenation of Enecarbamates 479a–c



entry	479	R	dr
1	**a** (3*S*)	(*R*)-Me	>95:5 (1*S*,2*S*)
2	**b** (3*R*)	(*R*)-*i*-Pr	>95:5 (1*S*,2*S*)
3	**b** (3*S*)	(*R*)-*i*-Pr	>95:5 (1*S*,2*S*)
4	**c** (3*S*)	(*S*)-*i*-Pr	>95:5 (1*R*,2*R*)
5[a]	**b** (3*R*)	(*R*)-*i*-Pr	>95:5 (1*S*,2*S*)
6[b]	**b** (3*R*)	(*R*)-*i*-Pr	>95:5 (1*S*,2*S*)

[a] Used solvent mixture $CD_3OD/CDCl_3$ (4.1:1) [b] $CD_3COCD_3/CDCl_3$ (2.4:1)

17. PHOTOOXYGENATION OF CHIRAL ENECARBAMATES

The first example of a chiral-auxiliary-induced [2 + 2] cycloaddition between $^1O_2$ and oxazolidinone-functionalized enecarbamates **479a**–**c** was reported by Bosio, Turro, and coworkers (Table 90).[182] Photooxygenation was performed with 5,10,15,20-tetrakis(pentafluorophenyl)porphine (TPFPP) as sensitizer and an 800-W sodium lamp as light source and resulted in dioxetanes **480a**–**c** in excellent diastereoselectivity. When the configuration of the oxazolidinone stereogenic center was changed from *R* to *S*, the inverse configuration at the new stereogenic centers was obtained (Table 90, entries 3 and 4). The absolute configuration of the dioxetanes **480** was determined to be 1*S*,2*S* for the case in which the oxazolidinone stereogenic center is *R*-configured. It was established that the $^1O_2$ attacks exclusively from the top face in the [2 + 2] cycloaddition to the enecarbamates **479** and with complete π-facial control. On the basis of these interesting results, the authors further studied the photooxygenation for a variety of chiral oxazolidinone-functionalized *E*- and *Z*-enecarbamates.[183,184]

18. CONCLUSION

Enamides and enecarbamates are important substrates in asymmetric synthesis. This review considered only the C=C

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double bonds devoid of functional groups other than an *N*-acyl substituent.

The most important class of reactions (approximatively two-thirds of the review) is devoted to catalytic asymmetric hydrogenation, which allows the preparation of many types of amides or amines with very high enantiomeric excesses. This approach is applied in the pharmaceutical industry to the synthesis of biologically active compounds.

Asymmetric hydroformylation or intramolecular Heck reactions of prochiral enamides are less developed than enantioselective hydrogenation but give rise to interesting results.

A growing group of transformations is based on the nucleophilic addition of enamides on electrophilic reactants with the help of a chiral Lewis or Bronsted acid catalyst. Many asymmetric C−C bond formations are described, such as the enamide additions on aldehydes, ketones, or imines. The products are often formed in surprisingly high enantiomeric excesses. Hetero-Diels−Alder reactions or asymmetric aminations by enamide additions on N═N double bonds are also possible.

The stoichiometric enantioselective syntheses were less studied than the catalytic reactions. In this group of transformations, the enamide fragment is connected to some removable chiral auxiliaries or attacked by a chiral reagent. The diastereoselective or enantioselective functionalization of the enamide C═C double bond can be extremely efficient and provide final products in high ee's. This is detailed in sections 13−17 of the review.

In conclusion, the asymmetric transformations starting from enamides or enecarbamates provide a powerful and flexible tool to prepare complex nitrogen compounds in high enantiomeric excess.

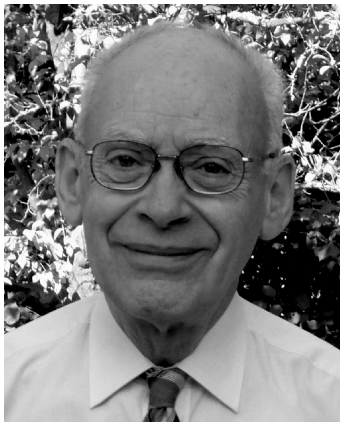
AUTHOR INFORMATION

Corresponding Author

*E-mail: henri.kagan@u-psud.fr.

BIOGRAPHIES

Kovuru Gopalaiah was born in Andhra Pradesh (India) in 1976. He earned his Masters Degree (M.Sc) in Organic Chemistry from Sri Venkateswara University, in 1998. He joined the Indian Institute of Science (IISc), Bangalore, for research, where he received his Ph.D in Chemistry in 2005 on "Novel Synthetic and Mechanistic Studies in Oxime and Amide Chemistry" under the supervision of Prof. S. Chandrasekhar. In 2006−2008, he worked with Prof. Henri B. Kagan at the Université Paris-Sud, France, as a Postdoctoral Fellow in the field of asymmetric synthesis. Currently, he is Assistant Professor at the University of Delhi, India. His research interests are focused on the development of metal-mediated chiral catalysts and organocatalysts for stereoselective reactions and asymmetric synthesis of biologically active compounds.



Henri B. Kagan was born in Boulogne-Billancourt (France) in 1930. He graduated from the Sorbonne and Ecole Nationale Supérieure de Chimie de Paris in 1954. He prepared his Ph.D. under the supervision of Dr. J. Jacques. He worked with Prof. A. Horeau at the Collège of France in Paris from 1962 as a research associate. He joined in 1968 the Université Paris-Sud, Orsay. He is emeritus Professor of the Université Paris-Sud since 1999. He is a member of the French Academy of Sciences. He developed investigations in various areas, such as asymmetric synthesis, asymmetric catalysis, and lanthanide reagents (for example, diiodosamarium). His awards include the Prelog Medal, the August-Wilhelm-von-Hofmann Medal, the Chirality Medal, the Nagoya Medal of Organic Chemistry, the Silver Medal of the RSC, the Tetrahedron Prize, the 2001 Wolf Prize for Chemistry (shared with K. B. Sharpless and R. Noyori), the 2002 Grand Prix de la Fondation de la Maison de la Chimie (shared with H. Yamamoto), the 2002 Ryoji Noyori Prize, the 2005 Bower award of the Franklin Institute, and the 2007 Horst-Pracejus award.

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NOTE ADDED IN PROOF

After the submission of the present manuscript, a review by Nugent and El-Shazly appeared (2010) in which chiral amine synthesis by enamide reduction, reductive amination, and imine reduction was described.[185] Two articles were also published, one on the asymmetric hydrogenation of enamides and enecarbamates using (*R*,*R*)-ChiraPhos/Rh[186] and the other on the enantioselective hydroformylation of enamides and enecarbamates with (*S*,*S*)-BisdiazaPhos/Rh.[187]