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Reductions of 1,3-dicarbonyl systems with ruthenium–biarylbisphosphine catalysts

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Abstract: A variety of biarylbisphosphine-based ligands for ruthenium have been used to catalyze the asymmetric hydrogenation of β-dicarbonyl systems. The method of preparation of the catalyst system plays an important role in the stereochemical outcome of the reaction as well as the reaction conditions required. The mechanism of the reaction has not been fully elucidated, but some insight has been gained. © 1997 Published by Elsevier Science Ltd

1. Introduction

The desire to produce enantiomerically pure pharmaceuticals and other fine chemicals has advanced the field of asymmetric catalytic technologies. Since the independent discoveries of Knowles and Horner,[1,2] the number of innovative asymmetric catalyses for hydrogenation and other reactions has mushroomed. Initially, Nature was the sole provider of enantiomeric and diastereoisomeric compounds; these form what is known as the "chiral pool". This pool comprises of relatively inexpensive, readily available, optically active natural products, such as carbohydrates, hydroxy acids, and amino acids, that can be used as starting materials for asymmetric synthesis.[3,4] With the advances in catalytic reactions, both chemical and enzymatic, the chiral pool has widened to include compounds that are not common in Nature, but are available at scale and low cost.[4]

Prior to 1968, early attempts to mimic Nature's biocatalysis through noble metal asymmetric catalysis primarily focused on heterogeneous systems that employed chiral supports,[5] such as quartz,

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natural fibers, and polypeptides. An alternative strategy was hydrogenation of substrates modified by a chiral auxiliary.[6] Knowles[1] and Horner[2] separately discovered homogeneous asymmetric catalysts based on rhodium complexes bearing a chiral monodentate tertiary phosphine. Continued efforts in this field have produced hundreds of asymmetric catalysts with a plethora of chiral ligands,[7] dominated by chelating bisphosphines, that are highly active and enantioselective. These catalysts are beginning to rival biocatalysis in asymmetric organic synthesis. Their evolution has been chronicled in several reviews.[8–12]

Asymmetric catalysis possesses many advantages over stoichiometric and enzymatic methodologies. The most important benefit in favor of asymmetric catalysis, when compared to methods that employ a stoichiometric reagent, is chiral multiplication. A single chiral catalyst molecule can generate thousands of new stereogenic centers.

Stoichiometric methods utilize resolution of racemates, or start from chiral pool materials. Resolutions require the use of a resolving agent to form diastereoisomers that then must be separated. This process can be quite wasteful since the undesired diastereoisomer of the racemate has to be either racemized or discarded. Recovery of the resolving agent also has to be considered. Utilization of the chiral pool in asymmetric synthesis can be limited by the availability of the inexpensive reagents that possess the correct stereochemistry and structure similarities to the final target.[4]

Enzymes cannot perform the range of reactions that organometallic catalysts can, and may be susceptible to degradation caused by heat, oxidation, and pH. Substrates not recognized by enzymes can be used with asymmetric catalysts, where optimization of the enantioselectivity and overall chirality can be easily modified by change of the chiral ligands on the catalyst.[13] It is the ligand that provides the chiral environment and enantioselctivity through differentiation of the possible diastereoisomeric transition states.[14]

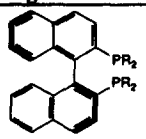
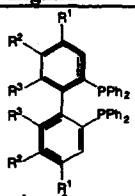
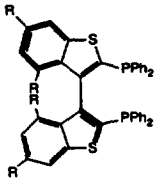
Asymmetric catalysis has been most prevalent in the area of homogeneous hydrogenations. As previously stated, the advantages to produce considerable amounts of a single enantiomer or diastereoisomer from a small amount of chiral catalyst has a huge industrial impact. Natural and unnatural amino acids, particularly L-DOPA, have been produced by this method.[15,16] Catalysts based on rhodium and ruthenium have enjoyed the most success.

Asymmetric catalysis undertook a quantum leap with the discovery of ruthenium and rhodium catalysts based on the atropisomeric bisphosphine BINAP (**1**). The use of a cationic Rh(BINAP) complex was found to reduce enamides with good enantioselectivities,[17–19] but Ru(BINAP) derivatives have wider application.[17] These catalysts have displayed remarkable versatility in the asymmetric reduction and isomerization of α-, β-, γ-keto esters, functionalized ketones, allylic alcohols, α,β-unsaturated carboxylic acids, and enamides.[17] The key feature of BINAP is the rigidity of the ligand when coordinated to a transition metal center, which is critical during enantioface selection of the substrate by the catalyst. This effect has been invoked in similar types of catalytic reactions with other bisphosphine ligands and metals.[15,20–29]

Effort has continued to improve Ru(BINAP) systems. Studies in this field have included the synthesis of preformed and *in situ* formation of ruthenium catalysts bearing BINAP and structurally similar biphenyl atropisomeric bisphosphines (Table 1). A significant number of reactions with Ru(BINAP) species have been patented by Takasago,[30–33] especially as they have been used for the commercial synthesis of the α-tocopherol side chain and β-lactam intermediates (see Section 6).[34] This commercial exploitation is a result of a collaboration between Takasago and Professors Noyori, Takaya, and Saburi.[17] Other companies do have patents on Ru(BINAP) compounds and their usage.[35] Many of the derivatives of BINAP given below have arisen from studies that not only tried to improve the efficiency of catalytic systems derived from BINAP, but to find alternative systems that would not be encumbered for commercial practice.

The purpose of this review will focus on the affects due to changes in catalyst preparation, atropisomeric arylphosphine ligands, and anionic ligands on the reactivity and stereoselectivity during

Table 1. Bisarylbisphosphine ligands

Cmpd	Ligand[a]	Acronym	Cmpd	Ligand[a]	Acronym
					
1	R = Ph	BINAP	10	$R^1 = R^3 = Me$, $R^2 = OMe$	BIMOP
2	R = *c*-C_6H_{11}	Cy-BINAP	11	$R^1 = R^3 = CF_3$, R^2 = OMe	FUPMOP
3	R = *p*-MeC_6H_4	*p*-tol-BINAP	12	$R^1 = R^3 = CF_3$, $R^2 = H$	BIFUP
4	R = *m*-MeC_6H_4	*m*-tol-BINAP	13	$R^1 = R^2 = H$, $R^3 = Me$	BIPHEMP
5	R = *p*-$MeOC_6H_4$	*p*-MeO-BINAP	14	$R^1 = R^2 = H$, $R^3 = OMe$	MeO-BIPHEP
6	R = *p*-FC_6H_4	*p*-F-BINAP			
7	R = *p*-ClC_6H_4	*p*-Cl-BINAP	15	R = Me	tetraMe-BITIANP
8	R = 3,5-$(Me)_2C_6H_3$	3,5-diMe-BINAP	16	R = H	BITIANP
9	R = 3,5-$(t\text{-}Bu)_2C_6H_3$	3,5-$(t\text{-}Bu)_2$-BINAP			

[a] Ligands have been shown in the *S*-configuration.

the reduction of 1,3-dicarbonyl systems. Other ligands and catalyst systems, which can be considered to be related to BINAP, such as Duphos, have been employed with substrates that are also reduced by Ru(BINAP) catalysts. These are not discussed.

2. Catalysts

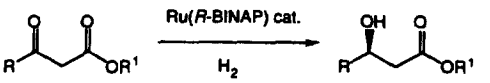
One of the many impressive processes of Ru(BINAP)-type catalysts, summarized in Table 2, is the reduction of carbonyl groups that includes functionalized ketones, α-, β-, γ-keto esters, and dynamic kinetic resolutions. The intricacies of catalyst preparation are most evident in these asymmetric reductions. A slight variation in the procedure can result in large differences in reactivity and stereoselectivity. The mechanism for Ru(BINAP) reduction of 1,3-dicarbonyl systems is not fully understood and most studies have been empirical in nature (see Section 5). It should be noted that many of the catalysts give rise to the same intermediates in the catalytic cycle, yet small changes in catalyst preparation conditions can result in significant reactivity differences.

Asymmetric reductions of methyl acetoacetate (**39a**), and other β-keto esters (Scheme 1) illustrate the effects of these subtle variations since a number of catalysts have been reported to catalyze this reduction. Variations of Ru(BINAP) catalyst systems, which include a combination of anionic ligands, such as halogens, acetates, acetoacetonato, and cyclopentadienyls, along with modified bisphosphine ligands, and the reaction conditions employed, that include hydrogen pressure, solvent, and pH, on reactivity and enantioselectivity are summarized in Table 3.[†]

[†] This Table, and subsequent ones, summarize a large number of reactions to enable comparisons between changes in the reaction parameters. Obviously, reaction conditions have been improved over time — this is discussed in the text. In many cases, the structure of the catalytic species is not known; for simplicity, we will refer to the Ru(BINAP) species added to the hydrogenation reaction as "the catalyst". In addition, it should be noted that the catalyst turnover number is sensitive to the exact experimental conditions. Thus, comparison of a "one-off" experiment with an optimized process should not be taken as rigorous.

Table 2. Ru(BINAP) catalyst systems

Cmpd	Catalyst system	Cmpd	Catalyst system
17	$Ru(OAc)_2(BINAP)$	**28**	$[RuCl_2(BINAP)(DMF)]_n$
18	$[RuCl_2(BINAP)]$	**29**	$[RuCl_2(BINAP)\cdot 3(SbPh_3)$
19	$[RuBr_2(BINAP)]$	**30**	$[Ru(\eta^3\text{-2-Me-allyl})_2(BINAP)]$
20	$[RuI_2(BINAP)]$	**31**	$RuCl_2(PhCN)_2(BINAP)$
21	$[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$	**32**	$RuCl_2(2\text{-}FrCN)_2(BINAP)$
22	$[RuCl(C_6H_6)(BINAP)]Cl$	**33**	$RuCl_2(C_6F_5CN)_2(BINAP)$
23	$[RuBr(C_6H_6)(BINAP)]Br$	**34**	[CpRuCl(BINAP)]
24	$[RuI(C_6H_6)(BINAP)]I$	**35**	[(MeCp)RuCl(BINAP)]
25	$[Ru(C_6H_6)(BINAP)]BF_4$	**36**	$[CpRu(BINAP)]PF_6$
26	[Ru(*p*-cymene)(BINAP)]Cl	**37**	$[Ru(O_2CCF_3)_2(BINAP)]$
27	[RuI(*p*-cymene)(BINAP)]I	**38**	$[RuCl(PPh_3)(BINAP)]_2(\eta\text{-}Cl)_2$



39 **40**

a, R = Me, R^1 = Me
b, R = Et, R^1 = Me
c, R = Pr, R^1 = Me
d, R = Bu, R^1 = Me
e, R = C_9H_{19}, R^1 = Me
f, R = $C_{11}H_{23}$, R^1 = Me
g, R = $C_{15}H_{31}$, R^1 = Me
h, R = Ph, R^1 = Me
i, R = Me, R^1 = Et
j, R = Me, R^1 = Bu-*t*
k, R = Me, R^1 = Pr-*i*
l, R = Et, R^1 = Et
m, R = $PhCH_2$, R^1 = Me
n, R = H_2C=CH-CH_2, R^1 = Me
o, R = *E*-MeCH=CH-CH_2-CH_2, R^1 = Me
p, R = Me_2C=CH-CH_2-CH_2, R^1 = Me
q, R = $MeCH_2CH$=CH-CH_2, R^1 = Me

Scheme 1.

Table 3. Summary of reaction conditions and product stereoselectivity as shown in Scheme 1 with BINAP-based catalysts

Entry	Cat.	Cat config	Prep.[a]	Sub	Solvent	H_2 Press. (psig)	Temp. (°C)	S/C ratio	Time (h)	Conv (%)	ee (%)	Prod config	Ref.
1	17	*R*	—	39l	MeOH	1500	25	200	48	41	4	*R*	36
2	18	*R*	A	39l	EtOH	1500	25	1000	58	100	99	*R*	36
3	18	*R*	A	39j	MeOH	1000	25	1000	34	100	98	*R*	36
4	18	*R*	A	39a	MeOH	1500	25	2000[b]	36	99.96	>99	*R*	36
5	18	*S*	A	39a	MeOH	1200	25	1400	40	100	>99	*S*	36
6	19	*R*	A	39l	EtOH	1290	20-32	1260	51	100	>99	*R*	37
7	19	*R*	A	39k	MeOH	1100	25	1100	34	100	98	*R*	36
8	19	*R*	A	39a	MeOH	1500	25	2100[b]	43	99.96	>99	*R*	36
9	19	*R*	A	39b	MeOH	1400	25	1200	52	100	99	*R*	36
10	20	*S*	A	39a	MeOH	1500	25	1400	40	100	>99	*S*	36
11	21	*R*	—	39a	MeOH	1500	25	1400	40	100	>99	*S*	36
12	21	*S*	—	39a	MeOH	1500	35	1000	40	100	98	*S*	38
13	21	*S*	—	39a	MeOH	1500	50	1000	48	100	98	*S*	39,40
14	21	*R*	—	39a	MeOH	300	50	100	48	100	96	*R*	41
15	22	*S*	—	39a	MeOH	1400	17	2000	44	100	98	*S*	42
16	22	*S*	—	39a	MeOH	1500	55	1950	24	100	96	*S*	43
17	22	*S*	—	39a	MeOH	1500	20	3000	50	73	97	*S*	43
18	24	*S*	—	39a	CH_2Cl_2	1500	50	2100	35	100	97	*S*	42
19	24	*S*	—	39a	MeOH	1500	20	2400	24	100	99	*S*	43
20	25	*S*	—	39a	MeOH	1300	20	3000	92	—	98	*S*	43
21	26	*S*	—	39a	MeOH	1300	20	2000	55	0	—	—	43
22	26	*S*	—	39a	MeOH	1500	60	2000	22	0.4	—	—	43
23	27	*S*	—	39a	MeOH	1500	30	2500	35	100	99	*S*	42
24	27	*S*	—	39a	MeOH, H_2O[c]	1500	30	2200	35	100	98	*S*	42
25	27	*S*	—	39a	MeOH	1500	30	2500	35	97	99	*S*	43
26	27	*S*	—	39a	MeOH, H_2O[c]	1500	30	2200	48	100	98	*S*	43
27	27	*S*	—	39a	CH_2Cl_2, H_2O[c]	1500	50	2100	48	100	98	*S*	43
28	27	*S*	—	39a	MeOH, CH_2Cl_2, H_2O[d]	45	30	610	90	100	98	*S*	43
29	28	*R*	B	39a	MeOH	1500	25	1950	40	100	99	*R*	44
30	28	*R*	B	39a	MeOH	1500	100	1950	0.5	100	99	*R*	44
31	28	*S*	B	39a	MeOH	60	100	1470	6	100	98	*S*	44
32	28	*S*	C	39a	MeOH	1500	25	1490	40	100	99	*S*	44
33	29	*S*	C	39a	MeOH	1500	100	1490	0.5	100	99	*S*	44
34	29	*S*	C	39a	MeOH	60	100	1990	6	100	98	*S*	44
35	21	*S*	D	39c	MeOH[e]	50	80	1300	5.5	100	98	*S*	45,46
36	21	*S*	D	39d	MeOH[e]	50	80	650	5.5	100	97	*S*	45,46
37	21	*R*	E	39a	MeOH	40	40	5000	8	97	>97	*R*	47
38	30	*R*	—	39a	MeOH	1500	25	100	48	0	—	—	41
39	19	*R*	G[f]	39a	MeOH	150	80	100	1	100	98	*R*	41
40	19	*S*	G[f]	39a	MeOH	300	40	100	12	100	>99	*S*	41
41	19	*S*	H[g]	39a	MeOH	300	50	100	48	100	>99	*S*	41
42	38	*R*	J	39a	MeOH	1500	24	2000	40	99	97.5	*R*	48
43	38	*R*	J[h]	39a	MeOH	1500	24	2000	40	99	97.6	*R*	48
44	31	*S*	—	39a	MeOH	1500	35	1000	40	0	—	—	38
45	32	*R*	—	39a	MeOH	1500	35	1000	40	0	—	—	38
46	33	*S*	—	39a	MeOH	1500	35	1000	40	0	—	—	38
47	31	*S*	—	39a	MeOH	1500	50	1000	40	0	—	—	38
48	32	*R*	—	39a	MeOH	1500	50	1000	40	40[i]	92	*R*	38
49	33	*S*	—	39a	MeOH	1500	50	1000	40	62[j]	95	*S*	38
50	31	*S*	—	39a	MeOH	1500	50	100	40	17[k]	—	—	38
51	32	*R*	—	39a	MeOH	1500	50	100	40	30[l]	94	*R*	38
52	33	*S*	—	39a	MeOH	1500	50	100	40	92[m]	97	*S*	38
53	35	*S*	—	39a	MeOH, H_2O[n]	1000	100	600	18	100	76	*S*	49

Entry	Cat.	Cat config	Prep.[a]	Sub	Solvent	H_2 Press. (psig)	Temp. (°C)	S/C ratio	Time (h)	Conv (%)	ee (%)	Prod config	Ref.
54	34	*S*	—	**39a**	MeOH, H_2O^n	1000	100	600	4.5	100	78	*S*	49
55	35	*S*	—	**39a**	MeOH, H_2O^n	1000	60	600	90	100	94	*S*	49
56	35	*S*	—	**39a**	MeOH, H_2O^n	1000	60	600	40	100	76	*S*	49
57	35	*S*	—	**39a**	MeOH, H_2O^n	400	100	600	16	100	62	*S*	49
58	35	*S*	—	**39i**	EtOH, H_2O^n	1000	100	600	18	100	58	*S*	49
59	35	*S*	—	**39i**	EtOH, H_2O^n	1000	60	600	63	100	91	*S*	49
60	36	*S*	—	**39a**	MeOH, H_2O^n	1000	100	600	16	100	0	—	49
61	36	*S*	—	**39a**	MeOH	1000	100	600	24	100	8	*R*	49

[a] Procedures: A: Preformed solid from the addition of 2 eq. of HCl, HBr, or Me_3SiI to $Ru(OAc)_2$(Bisphosphine) in CH_2Cl_2 then removal of volatiles; B: $[RuCl_2(C_6H_6)]_2$ and bisphoshine (Ru:bisphosphine = 1:1.05) is heated at 100 °C in DMF for 10 minutes followed by removal of volatiles; C: $RuCl_2(Sb(Ph_3))_3$ and bisphosphine are heated in *o*-dichlorobenze at 160 °C for 10 minutes followed by removal of volatiles; D: A toluene solution of $[RuCl_2(COD)]_n$ and bisphosphine is heated at 140 °C in a closed vessel until the solution is homogeneous followed by removal of volatiles. The catalyst is slurried in THF; E: A toluene solution of $[RuCl_2(COD)]_n$ and bisphosphine is heated at 140 °C in a closed vessel. The homogeneous solution is cooled to room temperature with vigorous stirring and the solid separated by filtration. The catalyst mixture is acidified with 0.1 mole% of HCl; F: $[RuI_2(p\text{-cymene})]_2$ and bisphosphine in CH_2Cl_2 are heated with stirring for 30 minutes. Catalyst solution is prepared just prior to hydrogenation; G: To $Ru(\eta^3\text{-}2\text{-Me-allyl})_2$(bisphosphine) in acetone is added 2.2 eq. of methanolic HBr, is stirred for 30 minutes, followed by removal of the volatiles; H: Methanolic HBr (2.2 eq.) is added to an acetone solution of $Ru(\eta^3\text{-}2\text{-Me-allyl})_2$(COD) and bisphosphine, stir for 30 minutes, followed by removal of volatiles; I: A solution of bisphosphine in MeOH or CH_2Cl_2 is added to $[RuCl_2(COD)]_2$(MeCN), stirred for 90 minutes, then 2 eq. of HCl in MeOH was added, and the mixture stirred for 60 minutes. The catalyst is used as a solution; J: Prepared from $[RuCl(PPh_3)_2(dma)]_2(\eta\text{-}Cl)_2$; K: 2 equiv. of HCl, HBr, or TFA is added to $Ru(OAc)_2$(Bisphosphine) in acetone or toluene; L: The hydrogenation vesel is charged with substrate, $[Ru(COD)(\eta^3\text{-}2\text{-Me-allyl})_2]$ and the bisphosphine. [b] At a concentration of 50%. [c] As a 95:5 mixture. [d] As a 65:30:5 mixture. [e] Dowex-50 was also present. [f] The catalyst was preformed. [g] The catalyst was used *in situ*. [h] The catalyst was exposed to air for 10 days. [i] Accompanied by 60% acetal formation. [j] Accompanied by 38% acetal formation. [k] Accompanied by 83% acetal formation. [l] Accompanied by 70% acetal fromation. [m] Accompanied by 8% acetal fromation. [n] As a 97:3 mixture.

2.1. *Halogen systems*

Ru(BINAP)-type catalysts bearing halogen ligands are generally more reactive than catalysts bearing anionic oxygen ligands. For example, $Ru(OAc)_2$(BINAP) (**17**) slowly hydrogenates the ethyl ester **39i** at high‡ hydrogen pressure (Table 3; entry 1). The addition of two equivalents of a strong acid, such as HCl, HBr, or Me_3SiI, produces unidentified oligomeric catalytic species, $[RuX_2(BINAP)]$ (**18–20**), that exhibit an increase in activity and stereoselectivity. Reductions with high substrate to catalyst ratios (S/C) of 10,000 can be achieved with these catalytic systems. In fact, concentrations of 50% by weight **39a** or **39i–k** are hydrogenated without affecting the stereoselectivity (Table 3; entries 2–10).[36,37] The use of these catalysts at low pressures and higher temperatures has not been reported.

Other halogen containing Ru(BINAP)-type catalysts for the asymmetric reduction of **39** are anionic $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**),¶[50,51] which has been formally postulated as

‡ High hydrogen pressure is defined as operating pressures ≥1000 psig. Moderate hydrogen pressures is defined as the operating pressures in the range of 100–1000 psig, while low hydrogen pressures are ≤100 psig.

¶ This representation will be used for consistency even when the alternative, triethylamine, form has been used in the orginal citation. The structure of an analogue has been characterized by X-ray diffraction.[50]

$[RuCl_2(BINAP)]_2(NEt_3)$[36,39] (*vide infra*) (Table 3; entries 11–14) and cationic [RuX(arene)(BINAP)]X (**22–27**)[42,43] (Table 3; entries 15–28). Both classes of catalysts exhibit reactivities and enantioselectivities similar to $[Ru(BINAP)X_2]$ generated from $Ru(OAc)_2$(BINAP) (**14**).

Another procedure that produces a highly reactive, stereoselective Ru(BINAP) catalyst capable of carbonyl reduction of β-keto esters at low hydrogen pressures is the combination of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ and BINAP in DMF at 100°C for 10 minutes (Table 3; entries 29–31).[44] By contrast, if the catalyst is prepared in an analogous manner but at 50–55°C in ethanol–benzene (8:1) the cationic complex, $[RuCl(\eta^6\text{-}C_6H_6)(BINAP)]Cl$ (**22**), is produced.[52] The change of solvent to DMF and heat treatment at 100°C in the catalyst preparation allows complete exchange of the arene ligand with the bisphosphine and results in the formation of a mixture of $RuCl_2(BINAP)(DMF)_2$ and $[RuCl_2(BINAP)(DMF)]_n$ (**28**).§ Extended periods of heat treatment result in the formation of ruthenium–carbonyl complexes through insertion into the formamide group of DMF.[53]

Another convenient synthesis of the Ru(BINAP) catalyst **29** capable of the reduction of **39a** under a low hydrogen pressure is to heat equimolar amounts of the air stable $RuCl_2[Sb(Ph)_3]_3$ and BINAP in 1,2-dichlorobenzene at 160°C for 10 minutes (Table 3; entries 32–34).[44]

A slight change in the preparation of $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) produces a catalyst that is capable of reducing β-keto esters, **39c–d**, at 50 psig hydrogen and 80°C without loss in the enantioselectivities (Table 3; entries 35–36),[45,46] and can leave remote di- and trisubstituted olefins intact (*vide infra*). A ^{31}P NMR analysis of the catalyst showed a complex mixture of ruthenium of which one component was **21**.[54] This is, perhaps, the most useful member of this class of catalyst as the reaction conditions are so mild.

The original preparation of $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) involved the reaction of $[RuCl_2(COD)]_n$, BINAP, and triethylamine (NEt_3) in toluene heated to reflux, to yield **21** with a small amount of $HRuCl(BINAP)_2$.‖[55] The authors offer no explanation as to why the catalyst contains diethylamine rather than triethylamine. Attempts to prepare catalysts with diethylamine or diethylammonium chloride failed. The secondary amine is presumably formed by degradation of the triethylamine. Initial ligand exchange produces an unidentified crystalline material, that was found to be ineffective as a catalyst at 50 psig hydrogen pressure and 80°C. The reaction mixture eventually becomes a red, homogeneous solution upon further heat treatment. Toluene is removed from the homogenous, red reaction mixture *in vacuo*, and the residue is slurried in THF. This catalyst system is introduced to the reduction substrate as a THF stock solution. Unfortunately, this catalyst system produces slightly lower turnovers than $[RuCl_2(BINAP)]$ species; however, treatment of the THF slurry with washed DOWEX-50 enhances the catalytic activity without affecting the enantioselectivity, and substrate to catalyst ratios of 1300 are achieved.

$[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) crystallizes from the homogeneous toluene solution described above by slow cooling to room temperature with vigorous stirring, followed by simple filtration. The crystallization removes all the other ruthenium species present in solution to give just **21**. This material can catalyze reduction of **39a** up to 5,000 turnovers at low hydrogen pressure when elevated temperatures are used in conjunction with a strong acid (Table 3; entry 37).[47]

The reaction conditions of 40°C and 40 psig hydrogen with 0.1 mole% HCl (based on substrate) are mild enough to hydrogenate the *tert*-butyl ester **39j** in MeOH with only 3% transesterification. The effect of acid on the catalyst is reversible. The addition of NEt_3 will stop the hydrogenation, but upon re-acidification, the original reaction rates are re-established. An acid dependence is also observed with $[RuCl(\eta^6\text{-}C_6H_6)(BINAP)]Cl$ (**22**), a catalyst without endogenous amine. The presence of low-level basic impurities in the substrates (or even in the catalyst) may be the reason that some keto esters are difficult to hydrogenate. The use of DOWEX-50 to enhance the reactivity in previous

§ The exact ratio is not given by authors. The mixture of ruthenium species was identified by ^{31}P NMR and conductivity measurements. The catalyst will be classified as $[RuCl_2(BINAP)(DMF)]_n$ (**28**).

‖ The ruthenium species was identified by ^{31}P NMR, but the authors do not report the ratio of ruthenium species present.

examples support this argument (*vida supra*). Higher amounts of acid present in the system do not enhance or hinder the reactivities.[47]

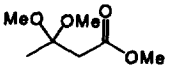
Ru(η^3-2-Me-allyl)$_2$(BINAP) (**27**) is not an effective catalyst for the reduction of **39a** (Table 3; entry 38). However, the addition of two equivalents of HBr to **30** in acetone produces [RuBr$_2$(BINAP)] (**19**), which can be used to hydrogenate **39a** with reasonable rates (Table 3; entry 39). These rates are highly dependent on temperature (Table 3; entry 40), but stereoselectivities are not. The hydrogenation of **39a** is roughly four times faster if the [RuBr$_2$(BINAP)] (**19**) is preformed compared to *in situ* preparation (Table 3; entry 41).[41]

Another catalyst that has been found to be useful is [RuCl(PPh$_3$)(BINAP)]$_2$(μ-Cl)$_2$ (**38**), which is prepared by the heat treatment of [RuCl(PPh$_3$)$_2$(dma)]$_2$(μ-Cl)$_2$ and BINAP. This catalyst shows excellent stability as a solid as there was no loss of reactivity or selectivity after exposure to air for 10 days (Table 3; entries 42–43).[48]

Catalysts derived from [RuX$_2$(BINAP)] seem to be the most efficacious for the reduction of 1,3-dicarbonyl compounds.

2.2. *Nitrile systems*

[NH$_2$Et$_2$]$^+$[{RuCl(BINAP)}$_2$(μ-Cl)$_3$]$^-$ (**21**) can be converted to discrete mononuclear ruthenium species by treatment with aryl nitriles at elevated temperatures. Ruthenium BINAP species of the general formula RuCl$_2$(ArCN)$_2$(BINAP) (**31–33**), where ArCN is benzonitrile, 2-furancarbonitrile, or pentafluorobenzonitrile, have been synthesized. Attempted hydrogenation of **39a** in the presence of **31** at 35°C results in the complete formation of the acetal **41**. The lack of reduction with these catalytic precursors is believed to due to competing binding in favor of the nitrile over the substrate. The nitrile dissociation can be improved by raising the hydrogenation temperature to 50°C as evidenced by reduction of **39a** to **40a**; however, the acetal byproduct **41** is still formed (Table 3; entries 44–52). The relative reactivities for the hydrogenation of **39a** catalyzed by the RuCl$_2$(ArCN)$_2$(BINAP) series coincide with the observed dissociation of the respective ArCN (pentafluorobenzonitrile>2-furancarbonitrile>benzonitrile) established by ^{31}P NMR.[38]



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2.3. *Cyclopentadienyl systems*

The substitution of one halogen ligand for the sterically more encumbered anionic η^5-cyclopentadienyl (Cp) ligand, [CpRuCl(BINAP)] (**34**), produces low catalytic activity yet moderate to good enantioselectivities for the asymmetric reduction of the substrates, **39a** and **39i**, at temperatures in the range of 60–100°C (Table 3; entries 53–59). Acceptable reaction rates occur at 100°C, but this is to the detriment of stereoselectivity. The importance of the halogen ligand for stereoselectivity is evident in hydrogenations with the cationic complex [CpRu(BINAP)]PF$_6$ (**36**) of the ethyl ester **39i** to ethyl 3-hydroxybutyrate (**40i**) where only 0–8% ee was attained (Table 3; entries 60–61). Catalysts with MeCp ligand have shown 2 hour induction periods. The authors proposed "catalyst activation begins with liberation of Cp or MeCp with corresponding formation of a catalytic intermediate. Retention of the chloride ligand in this intermediate apparently provides the necessary molecular template to promote catalysis mechanism which generates product of high enantiomeric purity".[49] The possibility of Cp or MeCp liberation seems very speculative.

2.4. *Arene analogues*

Catalyst reactivity can be varied by modification of the ligands on the metal. In the reduction of **39a** with [RuX$_2$(BINAP)] (**17–20**) and [RuX(η^6-C$_6$H$_6$)(BINAP)]X (**22–24**) classes of catalysts, the reactivity and enantioselectivity vary little when X is Cl, Br, or I at high hydrogen pressures (Table 3; entries 3–10 and 15–19). [RuX(η^6-C$_6$H$_6$)(BINAP)]X with the non-coordinating counteranion

Table 4. Catalyst systems with modified phosphorus ligands

Cmpd	Catalyst system
42	$[NH_2Et_2]^+[RuCl(p\text{-MeO-BINAP})_2(\mu\text{-Cl})_3]^-$
43	[RuI(*p*-cymene)(*p*-MeO-BINAP)]I
44	[RuI(*p*-cymene)(*p*-Tol-BINAP)]I
45	[RuI(*p*-cymene)(*m*-Tol-BINAP)]I
46	[RuI(*p*-cymene)(3,5-(*t*-Bu)$_2$-BINAP)]I
47	[RuI(*p*-cymene)(*p*-Cl-BINAP)]I
48	[RuI(*p*-cymene)(*p*-F-BINAP)]I
49	[RuI(*p*-cymene)(3,5-(Me)$_2$-BINAP)]I
50	[RuI(*p*-cymene)(H_8-BINAP)]I
51	[RuI(*p*-cymene)(BIMOP)]I
52	[RuI(*p*-cymene)(FUMOP)]I
53	[RuI(*p*-cymene)(BIFUP)]I
54	[RuI(*p*-cymene)(BIPHEM)]I
55	[RuI(*p*-cymene)(MeO-BIPHEP)]I
56	[$RuCl_2$(tetraMe-BITIANP)$(DMF)_n$]
57	[$RuCl_2$(BITIANP)$(DMF)_n$]
58	[$RuBr_2$(BIPHEMP)]
59	[$RuBr_2$(MeO-BIPHEMP)]
60	[$RuCl_2$(BINAP)]$_2$(MeCN)
61	[$RuCl_2$(*p*-TolBINAP)]$_2$(MeCN)
62	[$RuCl_2$(MeO-BIPHEP)]$_2$(MeCN)
63	[$RuCl_2$(BIPHEP)]$_2$(MeCN)
64	[$RuCl_2$(BIPHEMP)]$_2$
65	[Ru(η^3-2-Me-allyl)$_2$(MeO-BiPHEP)]

BF_4^- gave high enantioselectivities in the reduction of **39a** (Table 3; entry 20), but the authors did not report the amount of conversion. Changes in these anionic ligands coupled with changes in the reaction solvent has a dramatic effect on diastereoselectivities during dynamic kinetic resolutions (See Section 4). Differences in rate and enantioselectivity due to anionic ligands are observed more readily within the [RuX(arene)(bisphosphine)]X series when the η^6-arene ligand is *p*-cymene instead of benzene. [RuCl(*p*-cymene)(BINAP)]Cl (**26**) is inactive even at 60°C and high pressure, whereas the iodo-derivative **24** is quite active as a catalyst in the reduction of **39a** (Table 3; entries 18–28). The decrease in activity upon changing the η^6-arene ligand from benzene to *p*-cymene has been attributed to the stability of [RuX(*p*-cymene)(BINAP)] toward hydrogen under the reaction conditions.[43] η^6-Benzene within the [RuX(arene)(bisphosphine)]X series is liberated more easily than η^6-cymene. In fact, [RuI(η^6-C_6H_6)(BINAP)]I (**24**) is difficult to isolate due to loss of benzene, whereas [RuI(*p*-cymene)(BINAP)]I (**26**) can be isolated in pure form.[42]

2.5. *BINAP analogues*

In addition to the bisaryl moieties, the phosphorus groups can be modified through the phenyl groups (Table 4). The introduction of substituents can modify the electron density of the aromatic rings, and this, in turn, alters the electron density at phosphorus. Catalysts prepared from these modified systems can have different reaction rates and selectivities when compared to the parent BINAP system (eg., Table 3; entry 13 and Table 5; entry 1).[50]

Modification of the $-PPh_2$ moiety on the bisphosphine ligand with various electron withdrawing or donating groups results in loss of enantioselectivity for reductions with [RuI(*p*-cymene)(bisphosphine)]I that contain the following electron modifying groups: $-P(C_6H_4OMe\text{-}p)_2$ (**5**), $-P(tol\text{-}p)_2$ (**3**), $-P[C_6H_3(Bu\text{-}t)\text{-}3,5]_2$ (**9**), $-P(C_6H_4F\text{-}p)_2$ (**6**), and $-P(C_6H_{11})_2$ (**2**) (Table 5; entries 2–6).[43] [RuI(*p*-cymene)(bisphosphine)]I that contain bisphosphine ligands within the biphenyl backbone series with various substituents (**10–14**) result in similar reactivities and enantioselectivities compared to

Table 5. Summary of reaction conditions and product stereoselectivity as shown in Scheme 1 with BINAP-based catalysts

Entry	Cat.	Cat config	Prep.[a]	Sub	Solvent	H_2 Press. (psig)	Temp. (°C)	S/C ratio	Time (h)	Conv (%)	ee (%)	Prod config	Ref.
1	42	*R*	—	39a	MeOH, CH_2Cl_2	1500	30	4000	27	100	99	*R*	50
2	43	*S*	—	39a	MeOH, CH_2Cl_2[b]	1350	30	1900	40	100	94	*S*	43
3	44	*S*	—	39a	MeOH, CH_2Cl_2[b]	1300	30	2200	40	100	97	*S*	43
4	46	*R*	—	39a	MeOH, CH_2Cl_2[b]	1500	30	2100	39	83	93	*R*	43
5	48	*S*	—	39a	MeOH, CH_2Cl_2[b]	1250	30	2440	40	100	97	*S*	43
6	50	*R*	—	39a	MeOH, CH_2Cl_2[b]	1250	30	1400	40	81	93	*R*	43
7	27	*S*	F[c]	39a	MeOH, CH_2Cl_2[d]	150	30-40	1000	20	100	>99	*S*	56
8	27	*S*	F[c]	39a	MeOH, CH_2Cl_2[d]	150	30-40	2000	20	100	>99	*S*	56
9	51	*R*	F[c]	39a	MeOH, CH_2Cl_2[d]	440	30-40	1000	20	100	99	*R*	56
10	51	*R*	F[c]	39a	MeOH, CH_2Cl_2[d]	150	30-40	2000	20	100	100	*R*	56
11	52	*S*	F[c]	39a	MeOH, CH_2Cl_2[d]	440	30-40	1000	20	100	100	*S*	56
12	52	*S*	F[c]	39a	MeOH, CH_2Cl_2[d]	150	30-40	1000	20	100	>99	*S*	56
13	52	*S*	F[c]	39a	MeOH, CH_2Cl_2[d]	150	30-40	2000	20	100	>99	*S*	56
14	53	*S*	F[c]	39a	MeOH, CH_2Cl_2[d]	1300	30-40	1000	20	13	95	*S*	56
15	55	*S*	H[e]	39a	MeOH	300	50	100	48	100	>99	*R*	41
16	54	*S*	G[f]	39a	MeOH	150	80	100	1	100	>99	*S*	41
17	54	*S*	G[f]	39a	MeOH	75	50	200	60	100	>99	*S*	41
18	56	*R*	B	39i	MeOH	1500	70	1000	2	95	>99	*R*	57
19	19	*R*	G[f]	39b	MeOH	300	40	1000	65	100	>99	*R*	41
20	19	*R*	H[e]	39b	MeOH	300	40	1000	16	100	>99	*R*	41
21	58	*S*	G[f]	39b	MeOH	300	40	1000	65	100	>99	*S*	41
22	58	*S*	H[e]	39b	MeOH	300	40	1000	16	100	>99	*S*	41
23	18	*S*	B	39m	MeOH	50	75		24	12–25[g]	93	*S*	59
24	57	*S*	B	39m	MeOH	1500			2	93	>98	*S*	59

[a] Procedures: (As Table 3) B: $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ and bisphoshine (Ru:bisphosphine = 1:1.05) is heated at 100 °C in DMF for 10 minutes followed by removal of volatiles; F: $[RuI_2(p\text{-cymene})]_2$ and bisphosphine in CH_2Cl_2 are heated with stirring for 30 minutes. Catalyst solution is prepared just prior to hydrogenation; G: To $Ru(\eta^3\text{-2-Me-allyl})_2$(bisphosphine) in acetone is added 2.2 eq. of methanolic HBr, is stirred for 30 minutes, followed by removal of the volatiles; H: Methanolic HBr (2.2 eq.) is added to an acetone solution of $Ru(\eta^3\text{-2-Me-allyl})_2$(COD) and bisphosphine, stir for 30 minutes, followed by removal of volatiles. [b] As a 3:1 mixture. [c] The catalyst was probably used *in situ*—see original citation.. [d] As a 1:1 mixture. [e] The catalyst was used *in situ*. [f] The catalyst was preformed. [g] The addition of trace HCl caused decarboxylation (70%).

[RuI(*p*-cymene)(BINAP)]I for the reduction of **39a** provided the bisphosphine biphenyl backbone contains at least one electron-donating group regardless of whether electron-withdrawing groups are present (Table 5; entries 7–13). Reactivity is severely hampered when both phenyls in the backbone contain only electron-withdrawing groups, and the stereoselectivity also drops slightly (Table 5; entry 14).[56] Catalysts with an electron-rich biphenyl backbone, such as BIPHEMP (**13**) and MeO-BIPHEP

(**14**), show little change in catalytic reactivity with respect to Ru(BINAP) under comparable reaction conditions (Table 3; entries 39–41 and Table 5; entries 15–17).

The backbone of the ligand does not have to be simply phenyl or naphthyl. An asymmetric homogeneous ruthenium catalyst based on diheteroaryl-bisphosphine ligands, such as **15**, have been reported. The ruthenium complex was prepared by heat treatment of $[RuCl_2(\eta^6\text{-}C_6H_6)]_n$ and the bisphosphine DMF at 100°C to produce an unidentified [$RuCl_2$(tetraMe-BITIANP)](DMF)] (**56**) complex mixture. This catalyst system efficiently hydrogenates the ethyl ester **39i** (Table 5; entries 18–24).[57,58]

Overall the most efficient catalyst systems contain the [RuX_2(BINAP)] core. Certainly the use of biaryl systems other than BINAP shows little benefit other than circumvention of patent encumberences.

3. The β-keto substrate

Generally, β-keto esters are hydrogenated to 3-hydroxy esters in high enantiomeric purity in the presence of a Ru(BINAP) catalyst. As mentioned in numerous literature references and several reviews,[8,10–12,17,53,60] [Ru(BINAP-like)] catalysts can hydrogenate β-keto esters that contain a variety of functionalities, including amides and various esters, with high stereoselectivities. Enantioselectivities for β-keto esters are 97–99% ee when the alkyl group at C-4 ranges from C_1 to C_9 (eg, **39b–e**, Table 6; entry 1), but enantioselectivities drop to 94–97% ee as the alkyl group becomes larger (**39f–g**, Table 6; entries 2–10). Notably, reduction of **39m** failed to produce **40m** with Ru(BINAP) catalysts. The addition of HCl to the reaction results in 12–25% conversions along with 70% yield of 4-phenyl-2-butanone via hydrolysis of the ester followed by decarboxylation (Table 5; entry 23). High conversion of **39m** to **40m** is achieved with high enantioselectivity when the reduction is catalyzed by **57** (Table 5; entry 24).

Generally, the enantioselectivities for various catalysts previously discussed for the asymmetric reduction of **39** are similar, but relative rates of the catalyst are more dependent upon catalyst preparation. [$RuBr_2$(BINAP)] (**19**) when prepared *in situ* in acetone shows higher reactivities in comparison to preformed **19** for the asymmetric reduction of **39b** (Table 5; entries 19–20), contrary to that observed for the reduction of **39a**. The same rate observations are seen with ruthenium catalysts containing *S*-BIPHEMP (**13**) (Table 5; entries 21–22).[41]

For the reduction of **39f**, turnovers of 50,000 are observed at 500 psig hydrogen pressure and 80°C catalyzed by *in situ* [$RuCl_2$(bisphosphine)]$_2$(MeCN) catalysts (**60–63**) (Table 6; entries 2–5). Extremely high catalyst activities are observed if the catalyst is prepared by the addition of two equivalents of HCl to $Ru(OAc)_2$(BIPHEMP) (Table 6; entry 6).[62]

In some cases, the mildness of the reaction conditions allow the asymmetric reduction of β-keto esters without reduction of remote di- and trisubstituted olefins. Most examples are for the methyl esters, but other esters, such as Et, *i*-Pr, and *t*-Bu, are also reduced efficiently with high stereoselectivities. Examples of β-keto amides reductions have been reported to give high enantioselectivities.[71]

Chemoselectivity of a catalyst can be observed by the hydrogenation of β-keto esters that contain a remote olefin. $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**), prepared by heating at 140°C in toluene, was able to hydrogenate selectively the 3-oxo group of substrates that contained di- and trisubstituted alkenes, **39o–p**, with good catalytic turnovers (Table 6; entries 11–13).[45,63] In the case of the disubstituted alkene β-keto ester **39o**, the reaction can be stopped after 30 minutes to give **40o** in 98% ee. Unfortunately, the terminal olefin reduces faster than the 3-oxo group during the hydrogenation of **39n** (Table 6; entry 14). Another catalyst that reports good chemoselectivity for **39o** is [$RuBr_2$(BIPHEMP)] (**57**), but extended reaction times do result in reduction of the disubstituted olefin (Table 6; entries 15–17). β-Keto esters with a disubstituted δ,ε-olefin, such as **39q**, are selectively hydrogenated with **58** in 99% ee (Table 6; entries 18–22).[41] Low hydrogen pressure is essential for

Table 6. Summary of reaction conditions and product stereoselectivity with BINAP-based catalysts

Entry	Cat.	Cat config	Prep.[a]	Sub	Solvent	H_2 Press. (psig)	Temp. (°C)	S/C ratio	Time (h)	Conv (%).	ee (%)	Prod config	Ref.
1	19	*R*	A	39e	MeOH	1500	23	100	40	100	>99	*R*	61
2	60	*R*	I[b]	39f	MeOH, CH_2Cl_2[c]	500	80	50,000	20	99	95.8	*R*	62
3	61	*R*	I[b]	39f	MeOH, CH_2Cl_2[c]	500	80	50,000	20	93	94.8	*R*	62
4	62	*R*	I[b]	39f	MeOH, CH_2Cl_2[c]	500	80	50,000	20	97	97.1	*R*	62
5	63	*R*	I[b]	39f	MeOH, CH_2Cl_2	500	80	50,000	20	99	97.3	*R*	62
6	64	*R*	A	39f	MeOH, CH_2Cl_2[c]	500	80	50,000	20	99[d]	97.0	*R*	62
7	19	*R*	G[e]	39g	CH_2Cl_2	750	50	100	48	100	94	*R*	41
8	19	*R*	H[b]	39g	CH_2Cl_2	750	50	100	48	100	96	*R*	41
9	57	*S*	H[b]	39g	CH_2Cl_2	750	30	100	48	100	95	*S*	41
10	57	*S*	H[b]	39g	CH_2Cl_2	220	30	100	48	19	94	*S*	41
11	21	*S*	D	39o	MeOH[f]	50	80	1300	0.5	100	98	*S*	45
12	21	*S*	D	39p	MeOH	50	80	650	6	100	98	*S*	45
13	21	*S*	D	39p	MeOH	50	80	650	6	100	99	*S*	63
14	21	*S*	D	39n	MeOH	50	80	650	—[g]	nd	nd	—	45
15	58	*S*	G[e]	39o	MeOH	88	80	200	0.08	100[h]	99	*S*	41
16	58	*S*	H[b]	39o	MeOH	60	80	500	0.25	95[i]	99	*S*	41
17	58	*S*	G[e]	39o	MeOH	88	80	200	0.5	100[j]	99	*S*	41
18	58	*S*	G[e]	39q	MeOH	90	80	330	0.5	100[k]	99	*S*	41
19	58	*S*	G[e]	39q	MeOH	90	80	200	0.25	100[l]	99	*S*	41
20	60	*S*	H[b]	39q	MeOH	60	80	500	0.25	95	99	*S*	41
21	58	*S*	H[b]	39q	MeOH	90	80	330	0.5	100	99	*S*	64
22	58	*R*	H[b]	39q	MeOH	90	80	330	0.5	100	99	*R*	64
23	21	*R*	—	39o	MeOH	1400	25	300	48	92[l]	98	*S*	65
24	58	*S*	G[e]	39o	MeOH	300	40	330	65	100[m]	99	*S*	41
25	17	*S*	—	66a	EtOH	1500	25		25-40	100	<70	*R*	66
26	n	*S*	A	66a	EtOH	1500	25		25-40	100	<70	*R*	66
27	17	*S*	—	66a	EtOH	1500	100	200	0.08	100	97	*R*	66
28	n	*S*	A	66a	EtOH	1500	100	200	0.08	100	97	*R*	66
29	28	*R*	B	66a	EtOH	60	100	2060	6	100	93	*R*	44
30	19	*S*	H	66a	EtOH	1000	93	1665	1	100	89	*S*	41
31	30	*S*	—	66a	EtOH	1500	80		75	95	90	*S*	41
32	58	*S*	G	66a	EtOH	1000	93	1665	1	100	81	*S*	41
33	19	*S*	A	66b	EtOH	1500	28	700			78	*S*	41
34	28	*R*	B	66b	EtOH	60	100	1500	12	100	97	*S*	67
35	21	*R*	—	66c	MeOH	1500	50	1000	48	85	94	*R*	40
36	21	*R*	—	66d			25				97		60
37	19	*S*	A	66e	MeOH, THF[o]	1500	20-32	290	86	100	95	*R*	37
38	21	*S*	—	66g	MeOH	1450	25	100	70	90	>95	*S*	68
39	19	*S*	A	66f	EtOH	1500	28	700			98	*S*	37
40	21	*R*	—	66h	MeOH	1500	25		68	75	96	*S*	41
41	58	*S*	G	66h	MeOH	1500	25		72	90	80	*R*	41
42	19	*R*	—	71a	EtOH	1500	18-21	500	145	97	99	*threo*	69
43	19	*R*	—	71b	EtOH	1500	18-21	500	60-180	99	97	*threo*	69
44	19	*R*	—	71c	EtOH	1500	18-21	500	60-180	92	100	*threo*	69
45	19	*S*	—	71a	EtOH	1500	18-21	500	60-180	96	>99	*erythro*	69
46	19	*R*	—	71d	EtOH	1500	29	500	33	100	87	*R*	69
47	21	*S*	—	71a	MeOH	1500	35	500	48	5	—	—	39,40
48	21	*S*	—	71a	MeOH	1500	25	500	48	0	—	—	39,40
49	21	*R*	—	74b	MeOH	1500	50	500	48	100	77	R^p	39,40
50	21	*S*	—	74b	MeOH	1500	50	500	48	100	78	S^p	39,40
51	21	*R*	—	74c	MeOH	1500	50	500	48	100	78	R^p	40
52	21	*S*	—	74c	MeOH	1500	50	500	48	100	81	S^p	40

Entry	Cat.	Cat config	Prep.[a]	Sub	Solvent	H_2 Press. (psig)	Temp. (°C)	S/C ratio	Time (h)	Conv (%).	ee (%)	Prod config	Ref.
53	21	*R*	—	**71d**	MeOH	1500	50	500	48	100	70	*S*[p]	40
54	21	*S*	—	**71d**	MeOH	1500	50	500	48	100	71	*R*[p]	40
55	21	*R*	—	**84a**[q]	MeOH	1500	50	500	48	100	20	*syn*	39,40
56	21	*R*	—	**84b**[q]	MeOH	1500	50	500	48	100	14	*syn*	40
57	21	*R*	—	**84c**[q]	MeOH	1500	50	500	48	100	64	*syn*	40
58	21	*S*	—	**84a**[q]	MeOH	1500	50	500	48	100	90	*anti*	39,40
59	21	*S*	—	**84b**[q]	MeOH	1500	50	500	48	100	56	*anti*	40
60	21	*S*	—	**84c**[q]	MeOH	1500	50	500	48	100	88	*anti*	40
61	19	*R*	A	**87**	EtOH	1500	25	760	106	100	85	*S*	36
62	56	*R*	B	**87**	CH_2Cl_2	1500	25	1000	100	92	90	*S*	57
63	21	*R*	—	**87**	MeOH	750	50	500	20	98	98	*R*[s]	70
64	21	*R*	—	**87**	MeOH	1500	100	500	20	58	99	*R*[t]	70

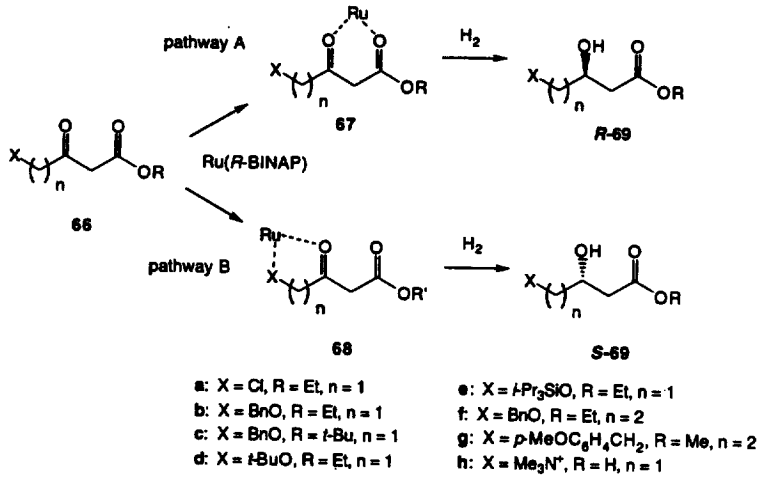
[a] Procedures: (As Table 3) A: Preformed solid from the addition of 2 eq. of HCl, HBr, or Me_3SiI to $Ru(OAc)_2$(Bisphosphine) in CH_2Cl_2 then removal of volatiles; B: $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ and bisphoshine (Ru:bisphosphine = 1:1.05) is heated at 100 °C in DMF for 10 minutes followed by removal of volatiles; D: A toluene solution of $[RuCl_2(COD)]_n$ and bisphosphine is heated at 140 °C in a closed vessel until the solution is homogeneous followed by removal of volatiles. The catalyst is slurried in THF; G: To $Ru(\eta^3\text{-allyl})_2$(bisphosphine) in acetone is added 2.2 eq. of methanolic HBr, is stirred for 30 minutes, followed by removal of the volatiles; H: Methanolic HBr (2.2 eq.) is added to an acetone solution of $Ru(\eta^3\text{-2-Me-allyl})_2$(COD) and bisphosphine, stir for 30 minutes, followed by removal of volatiles; I: A solution of bisphosphine in MeOH or CH_2Cl_2 is added to $[RuCl_2(COD)]_2$(MeCN), stirred for 90 minutes, then 2 eq. of HCl in MeOH was added, and the mixture stirred for 60 minutes. The catalyst is used as a solution. [b] The catalyst was used *in situ*; [c] As a 96:4 mixture; [d] There was 75% conversion after 1h; [e] The catalyst was preformed; [f] Dowex-50 was also present; [g] The alkene reduces faster than the keto group; [h] The saturated product (~4%) was also observed; [i] The saturated product (<5%) was also observed; [j] The saturated product (20%) was also observed.; [k] No alkene reduction was observed at 0.5 h, but 10% saturation had occurred at 50 min; [l] No alkene reduction was observed; [m] The alkene was reduced completely; [n] The citation gives $[RuX_2(BINAP)]$, where X = Cl or Br as the catalyst; [o] MeOH:THF = 5:2; [p] At C–5; [q] As *R*-isomer; [r] **89**:**90**:**88** = 2:0:98 ; [s] **89**:**90**:**88**= 89:9:2.

selectivity. $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) and $[RuCl_2(BINAP)]$ (**18**) completely reduce **39q** at high hydrogen pressures (Table 6; entry 23),[63,65] while preformed $[RuBr_2(BIPHEMP)]$ (**58**) completely reduces the hydroxy olefin to **40q** at moderate hydrogen pressures (Table 6; entry 24).[41]

β-Keto esters that contain functionality in the γ-position can affect the stereocontrol of the catalyst upon reduction due to competing coordination modes (Scheme 2). Poor enantioselectivities are observed in the reduction of **66a** at 25°C and high hydrogen pressures with $Ru(OAc)_2$(BINAP) (**17**) or $[RuX_2(BINAP)]$ (X=Cl, Br) (Table 6; entries 25–26). An increase in reaction temperature to 100°C results in the formation of **69a** (97% ee) (Table 6; entries 27–28).[66] The increase in enantioselectivities is attributed to a decrease in the formation of **68a**, which is temperature dependent.

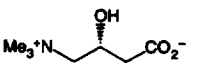
Other catalysts that are capable of achieving good enantioselectivity for the reduction of **66a** are $[RuCl_2(BINAP)(DMF)]_n$ (**28**)[44], *in situ* $[RuBr_2(BINAP)]$ (**19**), $Ru(\eta^3\text{-2-Me-allyl})_2$(BINAP) (**30**), and preformed $[RuBr_2(BIPHEMP)]$ (**58**) (Table 6; entries 29–32).[41]

A similar temperature dependence on the enantioselectivities is observed when the γ-functionality is a benzyloxy group, as in **66b**. An increase in temperature from 25°C to 100°C increases the selectivities in the formation of **69b** from 78% to 97–98% ee with $[RuBr_2(BINAP)]$ (**16**)[37] or $[RuCl_2(BINAP)(DMF)]_n$ (**28**)[67] as the catalyst (Table 6; entries 33–34). $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) reduces **66c** with 94% ee at 50°C (Table 6; entry 35).[40] An increase in the steric bulk of the ether functionality with *tert*-Bu- (**66d**) or *i*-Pr_3Si- (**66e**) groups improves the selectivities to 95–97% ee at low temperature (Table 6; entries 36–37).[37,60] The higher homologues, **66f–g**, are also reduced at 25°C, albeit slowly, with comparable enantioselectivites (Table 6; entries 38–39).[37,68] The coordination of Ru(BINAP) to the ester group in pathway A (Scheme 2) prevails as the alkoxy or siloxy groups hinder the formation of the complex **68** necessary for pathway B to be followed.



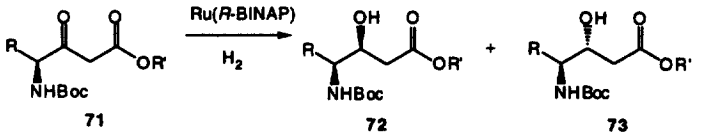
Scheme 2.

Competitive ligation of β-ketoesters with an ammonium salt at the γ-position, **66h**, does not occur. Carnitine (Vitamin B_T) (**70**) is produced directly from the reduction of **66h** with $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) or preformed $[RuBr_2(BIPHEMP)]$ (**58**) at 25°C in 96% ee and 80% ee, respectively (Table 6; entries 40–41).[41]



70

β-Keto esters with a γ-amide group show the effects of double asymmetric induction when the γ-position is a stereogenic center. The outcome of the stereochemistry at the 3-hydroxy position is determined by the configuration of the ligand on the catalyst. In the statine series, **72** (Scheme 3), reduction of *S*-**71a–c** in the presence of $[RuBr_2(R\text{-BINAP})]$ (*R*-**19**) gave the isomer **72** (de >98%, ee 97–100%) (Table 6; entries 42–44). The product **72** is also formed (de 82%, ee >99%) upon reduction of *S*-**71a** with $[RuBr_2(S\text{-BINAP})]$ (*S*-**19**) (Table 6; entry 45). Unfortunately, these reductions require extended reaction times (60–180 hrs). If the γ-position is not a stereogenic center, as with **71d**, lower enantioselectivity (87% ee) results (Table 6; entry 46).[69]



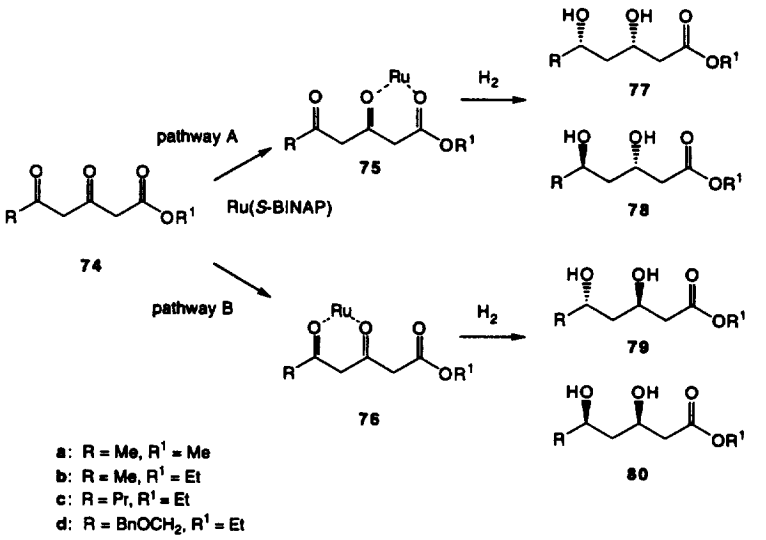
Scheme 3.

Once again high enantioselectivities and yields are obtained with the $[RuCl_2(BINAP)]$ motif.

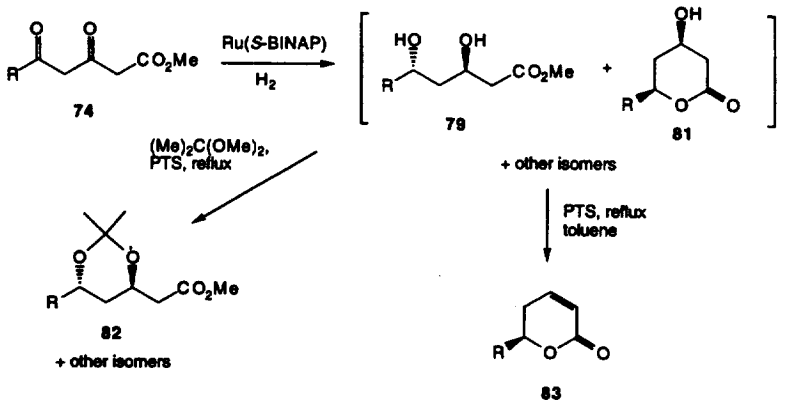
3.1. *Diketo esters*

β-Ketoesters with an additional δ-carbonyl group can give rise to multiple ligation possibilities with Ru(BINAP) (Scheme 4) that may affect the stereochemical outcome of the reduction. β,δ-Diketoesters, **74**, can be reduced with Ru(BINAP) catalysts to form the β,δ-dihydroxyesters; however,

this transformation is not straightforward. The catalyst, which is directed by the ester carbonyl oxygen in the reduction of γ-functionalized β-ketoesters (*vide supra*), can also ligate to the C-5 carbonyl oxygen. Reduction of **74** with Ru(*S*-BINAP) catalyst gives a mixture of the *syn* (**77,80**) and *anti* (**78,79**) diastereoisomers, where the latter predominates, and lactone **81**, which is derived from **79** (Scheme 5). The *syn*:*anti* ratio was determined by acetonization with 2,2′-dimethoxypropane to give **82**, while the optical purity at C-5 was determined through the unsaturated lactone, **83**, formed upon heat treatment of the mixture of **78** and **81** with acid. Conversions of 0–5% are observed if the reduction of **74a** is performed in the presence of $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) at 25–35°C (Table 6; entries 47–48). An increase in temperature to 50°C provides 100% conversion with **74b–c** and a 60–62% de in favor of the *anti* isomers (Table 6; entries 47–52). Reduction of **74c**, which contains an additional ether group proceeds with 0% de, but 70–71% ee at C-5 (Table 6; entries 53–54). The poor diastereoselectivity is attributed to significant competitive ligation of the benzyloxy group during the coordination to the catalyst.[40]

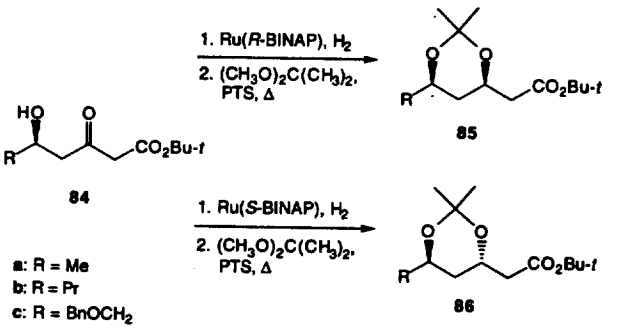


Scheme 4.



Scheme 5.

The question of whether the reduction of **74** with $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) reduces C-3 or C-5 initially has been addressed by the reduction of **84** with known configuration at C-5 (Scheme 6). $[NH_2Et_2]^+[\{RuCl(R\text{-}BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (*R*-**21**) reduction of *R*-**84a–c** followed by acetonization produces the *syn* (**85**) and *anti* (**86**) products with diastereoselectivities of 20, 14, and 64%, respectively, in favor of the *syn* diastereoisomer (**85**), not the *anti*-diastereoisomer (**86**) as observed in the direct reduction of **74** (Table 6; entries 55–57). The reduction of *R*-**84a–c** with catalyst of the opposite antipode, (*S*-**21**), produces the *anti* diastereoisomer of **86** with 90, 56, and 88% de (Table 6; entries 58–60).[40] Although the authors state that the reduction of **74a–b** proceeds by initial reduction at C-3, the complex **76** is inferred to lie on the major reaction pathway (Scheme 4; pathway B). Subsequent reduction at C-5 then forms the *anti* dihydroxy ester **78**. These results suggest that the Ru(BINAP) complexes preferentially to the ester and β-carbonyl groups rather than to the β- and δ-oxygens. However, due to the number of metal complexes and the problems associated with predictions around matched and mismatched pairs during the second reduction, this can only be considered a rationalization until all of the isomer permutations have been investigated on an individual basis.

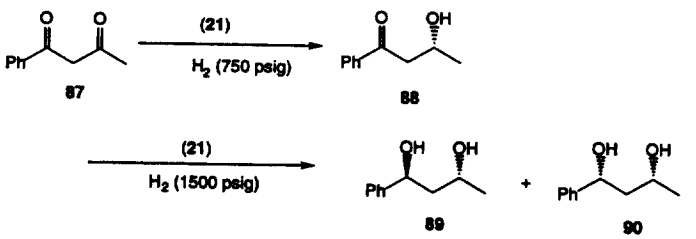


Scheme 6.

Again, there have been no significant enhancements in the usage of the basic $[RuCl_2(BINAP)]$ system for the reductions of this class of compounds.

3.2. *γ-Phenyl-1,3-dicarbonyl compounds*

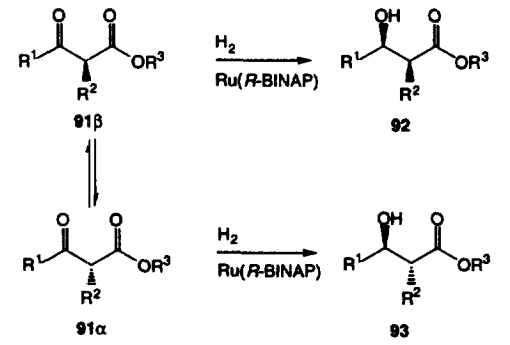
γ-Phenyl-1,3-dicarbonyl compounds are not easy to reduce with Ru(BINAP) catalysts, and require high hydrogen pressures (Table 6; entries 61–62)[36,57] as illustrated with 1-benzoylacetone (**87**) and $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) that produces 1-phenyl-3-hydroxy-2-butanone (**88**) (Table 6; entry 63). Increasing the hydrogen pressure to 1500 psig and temperature to 100°C produces **89** and **90** with 58% conversion and reasonable diastereoselectivity (89:9:2 **89**:**90**:**88**), but high enantioselectivity at C-3 of **89** (Table 6; entry 64) (Scheme 7).[70]

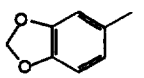
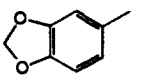


Scheme 7.

4. Dynamic resolution

The phenemenon of dynamic kinetic resolution is an important consideration for the reduction of β-dicarbonyl compounds, and has already been reviewed.[8,60,72] Dynamic kinetic resolution for substrates with epimerizable substituents at the α-position is successful if racemization of enantiomers **91α** and **91β** is rapid with respect to the Ru(BINAP)-catalyzed reduction (Scheme 8). Deuterium labelling experiments have confirmed the rapid equilibrium of epimers at C-2.[73] Generally, the configuration of C-3 is governed by the chirality of BINAP, whereas the configuration at C-2 is substrate specific. Also, diastereoselectivities are always more efficient when the reductions are performed in CH_2Cl_2 compared to a protic solvent, although reaction rates and stereoselectivies at C-3 are slightly reduced. Several examples of various dynamic kinetic resolution are summarized in Table 7.



	R^1	R^2	R^3
a:	Me	Me	Et
b:	Me	NHCOMe	Me
c:	Me	NHCOMe	t-Bu
d:	Me	NHCOi-Pr	Me
e:		NHCOMe	Me
f:		NHCOPh	Me
g:	Me	$CH_2NHCOPh$	Et
h:	Me	Cl	Me
i:	Ph	Cl	Et
j:	p-MeOPh	Cl	Me

Scheme 8.

Simple α-alkyl-substituted β-keto esters give rise to high enantioselectivity at C-3 but with poor diastereoselectivity as illustrated by the [$RuBr_2$(BINAP)] catalyzed reduction of racemic **91a** that gives a ~1:1 mixture of diastereoisomers, **92a** and **93a** (Table 7; entry 1).[36] A similar result is observed with [RuCl(η^6-C_6H_6)(BINAP)]Cl (**22**) (Table 7; entry 2). The *syn* and *anti* isomers of the product are not interconvertible under these reaction conditons. Diastereoselectivities increase slightly to about 2:1 in favor of the *syn* isomer when the hydrogenation is performed in CH_2Cl_2, although enantioselectivities drop slightly (Table 7; entry 3).[74]

β-Keto esters with amide or carbamate functionality, **91b–f**, at C-2 give high *syn*-diastereoselectivity upon reduction with [$RuBr_2$(BINAP)] (Table 7; entry 4).[73] High diastereoselectivities (98% *syn*) are maintained when R^1 is a 3,4-methylenedioxyphenyl group with 94% ee at C-3 (Table 7; entry 5). A slight decrease in enantioselectivity at C-3 (92% ee) is observed upon changing the substitution in the

Table 7. Summary of reaction conditions and product selectivity for dynamic resolutions

Entry	Cat.	Cat. config	Prep.[a]	Sub	Solvent	H_2 Press. (psig)	Temp. (°C)	S/C ratio	Time (h)	Conv (%)	de (%)	Config	ee (%)	Config[b]	Ref.
1	19	*R*	A	91a	EtOH	1500	25	1200	40	100	2	*syn*	96	*R*	36
2	22	*R*	—	91a	EtOH	1500	50	550-1250	60-80	100	1.4	*syn*	97	*R*	74
3	22	*R*	—	91a	CH_2Cl_2	1500	50	550-1250	60-80	100	36	*syn*	94	*R*	74
4	19	*R*	A	91b	CH_2Cl_2	1500	15	270	50	100	98	*syn*	98	*R*	73
5	19	*R*	A	91e	CH_2Cl_2	1500	50	260	120	100	98	*syn*	94	*R*	73
6	19	*R*	A	91f	CH_2Cl_2	1500	50	230	96	100	98	*syn*	92	*R*	73
7	18	*R*	K	91b	MeOH	1350-1500	20	100	48-72	90	52	*syn*	95	*R*	75
8	18	*R*	K	91c	MeOH	1350-1500	20	100	48-72	75	54	*syn*	85	*R*	75
9	18	*R*	K	91d	MeOH	1350-1500	20	100	48-72	90	54	*syn*	92	*R*	75
10	21	*R*	—	91b	HOAc	1350-1500	20	100	48-72	90	24	*syn*	42	*R*	75
11	37	*R*	K	91b	CH_2Cl_2	1350-1500	20	100	48-72	21	90	*syn*	51	*R*	75
12	21	*R*	—	91g	CH_2Cl_2	1500	50	100	20	100	88	*syn*	98	*R*	43
13	21	*R*	—	91g	MeOH	1500	50	100	—	100	60	*syn*	nd	–	43,
14	27	*S*	—	91g	CH_2Cl_2	735	50	100	40	44	nd	–	nd	–	43
15	27	*S*	—	91g	CH_2Cl_2[c]	735	50	100	40	98	88	*syn*	97	*S*	43
16	22	*R*	—	91g	CH_2Cl_2[c]	735	55	100	40	91	74	*syn*	90	*R*	52
17	22	*R*	—	91g	MeOH	735	55	100	40	100	0		77	*R*	52
18	23	*R*	—	91g	CH_2Cl_2[c]	735	55	100	40	91	79	*syn*	98	*R*	52
19	23	*R*	—	91g	MeOH	735	55	100	40	95	9	*syn*	80	*R*	52
20	27	*S*	—	91g	CH_2Cl_2[c]	1500	50-60	100	40	100	87	*syn*	98	*S*	43
21	27	*S*	—	91g	CH_2Cl_2[c]	735	55	100	40	98	88	*syn*	97	*S*	52
22	27	*S*	—	91g	MeOH	735	55	100	40	100	51	*syn*	97	*S*	52
23	27	*R*	—	91g	CH_2Cl_2, MeOH[d]	735	55	1000	21	91	84	*syn*	99	*R*	52
24	45	*S*	—	91g	MeOH	735	55	1000	20	94	67	*syn*	91	*S*	52
25	43	*R*	—	91g	MeOH	735	50-60	1000	20	97	67	*syn*	91	*R*	43
26	44	*S*	—	91g	MeOH[c]	735	50-60	1000	20	47	48	*syn*	95	*S*	43
27	50	*S*	—	91g	MeOH	800	65	800	20	53	71	*syn*	93	*S*	76
28	50	*S*	—	91g	CH_2Cl_2	800	65	800	20	74	85	*syn*	99	*S*	76
29	50	*S*	—	91g	CH_2Cl_2, MeOH[d]	800	65	800	20	80	92	*syn*	99	*S*	76
30	50	*S*	—	91g	CH_2Br_2, MeOH[d]	800	65	800	20	73	87	*syn*	99	*S*	76
31	50	*S*	—	91g	CH_2Br_2, MeOH[d]	800	65	800	20	100	52	*syn*	97	*S*	76
32	48	*S*	—	91g	MeOH[c]	735	50-60	1000	20	20	39	*syn*	94	*S*	43
33	47	*S*	—	91g	MeOH	735	50-60	1000	20	39	72	*syn*	96	*S*	43
34	49	*S*	—	91g	MeOH	735	55	1000	43	73	73	*syn*	91	*S*	52
35	49	*S*	—	91g	CH_2Cl_2, MeOH[d]	735	55	1000	46	72	91	*syn*	98	*S*	52
36	49	*S*	—	91g	CH_2Cl_2[c]	735	55	100	40	68	95	*syn*	99	*S*	52
37	46	*R*	—	91g	CH_2Cl_2, MeOH[d]	735	55	1000	40	55	98	*syn*	99	*R*	52
38	46	*R*	—	91g	MeOH	735	55	500	20	91	92	*syn*	92	*R*	52
39	30	*R*	L	91h	EtOH	440	27	100	20	100	4	*anti*	93	*R*	77
40	46	*R*	L	91h	CH_2Cl_2	1300	80	200	5	100	98	*anti*	99	*R*	77
41	65	*S*	L	91h	CH_2Cl_2	1300	80	200	4	90		*anti*	96[e]	*S*	77
42	65	*R*	L	91h	CH_2Cl_2	1300	80	200	4	90		*anti*	96[e]	*R*	77
43	19	*R*	H	91i	EtOH	440	27	100	20	100	81	*syn*	5	*R*	77
44	65	*R*	L	91i	CH_2Cl_2	880	50	100	60	90	35	*anti*	84	*R*	77
45	59	*R*	H	91i	CH_2Cl_2	880	50	100	60	90	44	*anti*	90	*R*	77
46	30	*S*	L	91i	CH_2Cl_2	1300	80	200	3	64	92	*anti*	83	*S*	77

Entry	Cat.	Cat. config	Prep.[a]	Sub	Solvent	H_2 Press. (psig)	Temp. (°C)	S/C ratio	Time (h)	Conv (%)	de (%)	Config	ee (%)	Config[b]	Ref.
47	30	*R*	L	91i	MeOH	74	50	200	16	100)	83	*syn*	15	*R*	77
48	30	*S*	L	91j	CH_2Cl_2	1200	80	100	17	90	92	*anti*	94	*S*	77
49	24	*S*	B	95	MeOH	60	25	1877	100	100	80[f]	*syn*	98	*S*	78
50	22	*R*	—	97a	CH_2Cl_2	1500	50	550-1250	60-80	100	97	*anti*	92	*R*	74
51	22	*R*	—	97a	CH_2Cl_2	1500	50	1170	70	100	98	*anti*	92	*R*	73
52	27	*S*	—	97a	CH_2Cl_2[c]	1500	50		40	100	98	*anti*	95	*S*	43
53	22	*R*	—	97b	CH_2Cl_2	1500	50	550-1250	60-80	100	90	*anti*	90	*R*	74
54	19	*S*	G	97b	CH_2Cl_2	300	80	100	3	100	47	*anti*	91	*S*	79
55	22	*R*	—	97c	CH_2Cl_2	1500	50	550-1250	60-80	100	86	*anti*	93	*R*	74
56	22	*R*	—	97a	MeOH	1500	50	550-1250	60-80	100	63	*anti*	88	*R*	74
57	19	*R*	H	97a	MeOH	1500	80	100	48	100	92	*anti*	85	*R*	79
58	57	*R*	B	97a	MeOH	1500	70	1000	100	92	86	*anti*	>99	*R*	57
59	22	*R*	—	97b	EtOH	1500	50	550-1250	60-80	100	3	*anti*	88	*R*	74
60	19	*R*	G	97b	MeOH	300	80	100	2	100	8	*syn*	88	*R*	79
61	21	*S*	D	97d	MeOH[g]	50	80	1300	5.5	100	0	—	96	*S*	45
62	19	*R*	G	97a	MeOH	300	80	100	2	50	94	*anti*	94	*R*	79
63	22	*R*	—	97l	MeOH	1500	50	550-1250	60-80	100	95	*syn*	93	*R*	74
64	27	*S*	—	97l	CH_2Cl_2, MeOH[d]	1500	50	1485	40	100	98	*syn*	97	*S*	43
65	27	*S*	—	97e	CH_2Cl_2, MeOH[d]	1400	60	nd	120	100	54	*trans*	98	*S*	80
66	27	*S*	—	97f	CH_2Cl_2, MeOH[d]	1400	60	nd	120	100	61	*trans*	97	*S*	80
67	22	*S*	—	97g	CH_2Cl_2	1500	55	182	22	81	nd	—	97	*S*	81
68	22	*R*	—	97h	CH_2Cl_2	1500	50	278	42	32[h]		*anti*	86	*R*	74
69	19	*R*	H	97i	MeOH	150	80	32	48	100	95	*anti*	83	*R*	79
70	19	*R*	H	97i	CH_2Cl_2	150	80	32	48	95	97	*anti*	96	*R*	79
71	21	*R*	—	97i	CH_2Cl_2	150	80	32	48	90	87	*anti*	87	*R*	79
72	19	*R*	H	97i	MeOH	150	80	32	48	85	97	*anti*	95	*R*	79
73	19	*S*	H	97i	MeOH	150	80	32	48	93	93	*anti*	86	*S*	79
74	19	*S*	G	97j	MeOH	150	25	50	48	60	97	*anti*	92	*S*	79
75	19	*S*	G	97j	MeOH	75	80	70	48	100	96	*anti*	88	*S*	79
76	21	*S*	D	97k	MeOH[i]	52	80-85	83	14	98.4	—	*trans*	44.7	*S*	82
77	21	*S*	D	97k	MeOH[j]	52	80-85	83	14	43.5	—	*trans*	96	*S*	82
78	21	*S*	D	97k	MeOH[k]	52	80-85	83	14	33	—	*trans*	100	*S*	82
79	21	*S*	D	97k	MeOH[l]	52	80-85	83	14	29.9	—	*trans*	100	*S*	82

[a] Procedures: A: Preformed solid from the addition of 2 eq. of HCl, HBr, or Me_3SiI to $Ru(OAc)_2$(Bisphosphine) in CH_2Cl_2 then removal of volatiles; B: $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ and bisphoshine (Ru:bisphosphine = 1:1.05) is heated at 100 °C in DMF for 10 minutes followed by removal of volatiles; D: A toluene solution of $[RuCl_2(COD)]_n$ and bisphosphine is heated at 140 °C in a closed vessel until the solution is homogeneous followed by removal of volatiles. The catalyst is slurried in THF; G: To $Ru(\eta^3\text{-2-Me-allyl})_2$(bisphosphine) in acetone is added 2.2 eq. of methanolic HBr, is stirred for 30 minutes, followed by removal of the volatiles; H: Methanolic HBr (2.2 eq.) is added to an acetone solution of $Ru(\eta^3\text{-2-Me-allyl})_2$(COD) and bisphosphine, stir for 30 minutes, followed by removal of volatiles; K: 2 equiv. of HCl, HBr, or TFA is added to $Ru(OAc)_2$(Bisphosphine) in acetone or toluene; L: The hydrogenation vesel is charged with substrate, $[Ru(COD)(\eta^3\text{-2-Me-allyl})_2]$ and the bisphosphine. [b] At C-3. [c] 0.5% (v/v) water added. [d] As a 7:1 mixture. [e] The final reaction product is 94 (Scheme 9). [f] Dehalogenation (15%) also occurred. [g] In the presence of Dowex-50. [h] 25% of the (*3R,4R*)-ketoester was recovered. Other products were also present. [i] In the presence of 13 mole % HCl. [j] In the presence of 9.5 mole % HCl. [k] In the presence of 8.1 mole % HCl. [l] In the presence of 6.2mole % HCl.

amide group from methyl (**91e**) to benzyl (**91f**) although the diastereoselectivities are not affected for the reductions in CH_2Cl_2 (Table 7; entries 5–6). These hydrogenations are very slow with low catalyst turnovers.

High *syn*-diastereoisomer formation is attributed to a transition state that is stabilized by hydrogen bonding between the amide hydrogen and ester moiety. Protic solvents no longer stabilize the hydrogen bonding in the transition state, and hydrogenations performed in protic solvents result in dismal diastereoselectivities (52–54% *syn*) (Table 7; entries 7–9). The reduction of racemic **91b** in HOAc with $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) gives the *syn* isomer **92b** in 24% de (Table 7; entry 10). $Ru(O_2CCF_3)_2$(BINAP) (**37**), generated from $Ru(OAc)_2$(BINAP) and CF_3CO_2H, reduces racemic **91b** in CH_2Cl_2 with 90% de but 51% ee (Table 7; entry 11); however, the rate is poor.[75]

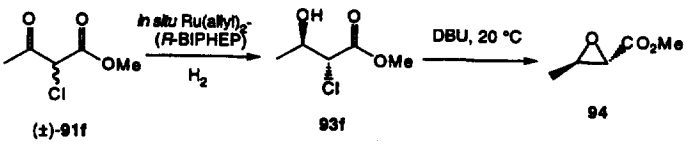
2-Benzamidomethyl-3-oxobutanoates, such as **91g**, have been reduced with several catalysts as the product, **92g**, is an important intermediate for carbapenem antibiotics. Few variations, such as substitution on the bisphosphines ligands, within each Ru(BINAP) catalyst series, have been investigated except for the [RuX(arene)(BINAP)]X series. Anionic $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) and the cationic [RuX(arene)(BINAP)]X series have both reduced **91g** with high diastereoselectivities and enantioselectivities (Table 7; entries 12–13).

Solvent has a large effect on the diastereoisomeric ratio in the reduction of **91g**. Diastereoselectivities of **92g** are higher for reductions performed in CH_2Cl_2 than in MeOH, but the reaction rates are very slow in anhydrous CH_2Cl_2. The addition of small amounts of water or protic solvents, such as MeOH, to CH_2Cl_2 improves the catalytic activity, but at the expense of the diastereoselectivities.

The nature of the halogen ligand coordinated to ruthenium affects the diastereoselectivities in the reduction of **91g**, the highest being attained with iodo as compared to chloro or bromo (Table 7; entries 14–23).

Variation of the substituents on BINAP provides a means to fine-tune the diastereoselectivity, enantioselectivity, and the rate in the reduction of **91g**. Ruthenium catalysts bearing electron donating groups, such as methyl or methoxy, at the *meta* or *para* positions of the diphenylphosphino moieties of BINAP had little effect on the diastereoisomeric ratio or enantioselectivities when the reduction was performed in MeOH (Table 7; entries 24–26). An increase in diastereoselectivity is observed when the "backring" of the naphthylene of BINAP is reduced (Table 7; entries 27–29); however, a decrease in diastereoselectivity is observed when the co-solvent is changed to CH_2Br_2 from CH_2Cl_2 (Table 7; entries 30–31). Decreased catalytic activities and stereoselectivities are observed for ruthenium catalysts bearing electronegative substituents in the *para* position of the diphenylphosphino groups (Table 7; entries 32–33). Although a single *meta*-methyl group on the phenyl rings had little effect on the diastereoselectivity and enantioselectivity (Table 7; entry 24), 3,5-disubstituted aryl rings analogues of BINAP produce catalysts that reduce **81g** with the high diastereo- and enantioselectivities (Table 7; entries 34–38). Considerable effort has been expended on the [RuX(arene)(BINAP)]X series to achieve 98% de (*syn*) and 99% ee with 55% conversion (Table 7; entry 37).[43] The authors did not elaborate if extended reaction times would produce higher conversions.

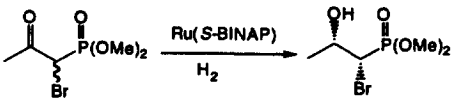
Dynamic kinetic resolution can also be observed for β-keto esters with halogens at C-2. Reductions of **91h–j** with Ru(BINAP) catalysts in CH_2Cl_2 produce *anti*-**93h–j** whereas reductions performed in protic solvents give predominantly *syn*-**92h–j** (Table 7; entries 39, 40, 43–48). Non-halogenated catalysts, Ru(2-Me-allyl)$_2$(bisphosphine), prepared *in situ*, gave the highest diastereoselectivities and enantioselectivities compared to halogen containing Ru(BINAP) catalysts. When R^1 is a methyl group, the reduction catalyzed by *in situ* Ru(2-Me-allyl)$_2$(BINAP) (**30**), prepared from the combination of Ru(COD)(2-Me-allyl)$_2$ to BINAP in acetone, proceeds with the formation of **92h** (98% de syn and 99% ee) (Table 7; entry 39). *E*-Methylglycidate (**94**), an important intermediate for the taxol side chain, can be prepared in a two-step, one-pot sequence through dynamic kinetic resolution (Scheme 9) (Table 7; entries 41–42).[77]



(±)-91f 93f 94

Scheme 9.

The dynamic kinetic resolution approach has been extended to the synthesis of α-bromo-β-hydroxy phosphonates (Scheme 10). $[RuCl_2(BINAP)(DMF)]_n$ (**28**) reduces **95** with *syn* diastereoselectivity (80% ds, 98% ee) (Table 7; entry 49). Unfortunately, 15% dehalogenation accompanies the reduction.[78]



95 96

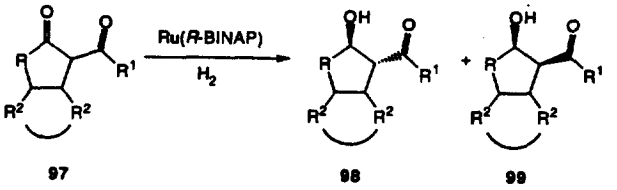
Scheme 10.

Cyclic α-alkyl β-keto esters and lactones (Schemes 11 and 12) are reduced with higher diastereoselectivites than acyclic examples, but maintain high stereoselectivities at the carbonyl group that is reduced. The *anti*-diastereoisomer is produced in the reduction of **97** with Ru(BINAP) catalysts. Hydrogenations of **97** with several Ru(BINAP) catalyts in CH_2Cl_2 give reasonable diastereoselectivies (Table 7; entries 50–55) and good enantioselectivities (91–95%). Diastereoselectivities drop to 3–63% when the hydrogenations are performed in alcohol solvents (Table 7; entries 56–61), with the exception of the reduction of **97a** with preformed $[RuBr_2(BINAP)]$ (**19**) (Table 7; entry 54).[79] Ruthenium catalyst prepared from a heteroaryl phosphosphine ligand, **15**, can reduce **97a** in MeOH with 86% de (*anti*) and >99% ee (Table 7; entry 58).[57] Improved diastereoselectivity, compared to those obtained with **91a**, can be attributed to steric interaction between the diphenylphosphino moiety of the BINAP and the rigid cyclic backbone.[74] Unlike cyclic β-keto esters, solvent effects on diastereoselectivies and enantioselectivities are not prevalent in the reduction of lactone **97l** (Table 7; entries 63–64).[43,74]

Other unique ring β-keto esters, **97d–j** have been reduced in the presence of Ru(BINAP) catalysts (Table 7; entries 61, 65–75). Cyclopentanone-2-carboxylates with two configurationally stable stereocenters, **97e–f** form only two diastereoisomers when reduced by [RuI(cymene)(BINAP)]I (**27**), with the *trans* hydroxy ester (**98e–f**) as the major product (Table 7; entries 65–66). The authors state that **97e** does not racemize under catalytic conditions, unlike other similar unsubstituted cyclopentanone-2-carboxylates **97a–d**, and does not belong to dynamic kinetic resolution.[80]

It has been suggested that one enantiomer of racemic **97k** hydrogenates faster than the other due to the twist of the BINAP ligand in the presence of known amounts of HCl to yield **98k**. The amount of HCl present is critical to the resolution. Conversions of 90% (43% overall conversions) of the "matched" keto ester can be reduced with $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) (Procedure D) with 96% ee in the presence of 9.5 mole% HCl. Reductions that are performed with less HCl selectively produce the single enantiomer at low overall conversions while high HCl concentration in the reduction produces higher overall conversions to the hydroxyester with lower enantioselectivity of the desired diastereomer (Table 7; entries 76–79).[82]

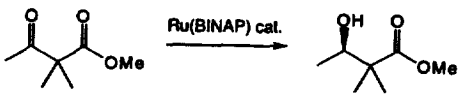
The hydrogenations of spiro[4.4]nonane-1,6-dione (**100**) with $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**) provide the corresponding *cis,trans*-diol with high selectivity, but this is compromised by a significant side reaction where the starting material undergoes ring opening.[83]



97 98 99

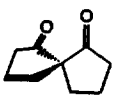
a: R = CH_2; R^1 = OMe, R^2 = H
b: R = $(CH_2)_2$; R^1 = OEt, R^2 = H
c: R = $(CH_2)_3$; R^1 = OMe, R^2 = H
d: R = $(CH_2)_4$; R^1 = OMe, R^2 = H
e: R = CH_2; R^1 = OMe, R^2 = *m*-ClPh (all trans)
f: R = CH_2; R^1 = OMe, R^2 = *o*-ClPh (all trans)
g: R = $-CH_2C(O)-$; R^1 = OEt, R^2 = H
h: R = CH_2; R^1 = OMe, R^2 =
i: R = R^1 = OEt, R^2 = H
j: R = R^1 = OEt, R^2 = H
k: R = CH_2 R^1 = OMe, R^2 =
l: R = O R^1 = Me, R^2 = H

Scheme 11.



101

Scheme 12.



100

When searching for a catalyst to reduce functionalized keto esters, the halo compound **21** provides a useful entry point. However, if large scale reactions are envisoned, then optimization of the ligands, including the use of biaryls other than BINAP could be advantageous.

5. Mechanism

No specific mechanism for the Ru(BINAP) catalyzed reduction of β-keto esters has been proposed. The large difference between catalysts that contain halogen as opposed to anionic ligands in the reduction of 1,3-dicarbonyl substrates has not been directly addressed. One possible explanation is attributed to the ability of halogen ligands to bridge more than one metal center. Although the metal center is stabilized by these facile bridging halide ligands in [Ru(BINAP)X_2], the metal centers are still reactive toward hydrogen; whereas, the reactivity toward hydrogen by Ru(BINAP) systems that

contain anionic oxygen ligands may be proportional to the dissociation of that oxygen ligand (See Section 5).

The reductions of β,δ-diketo esters suggest that the metal has a preference to complex with the ester moiety and the β-carbonyl group when the reduction is effected (*vide supra*). As reaction times can be somewhat extended for these reductions, it is somewhat surprising that the presence of an additional γ-functional group that can ligate to the reaction center does not have a significant affect on the reaction outcome — α-substituted carbonyl systems are readily reduced under comparable conditions.[4,10,60]

Smooth catalytic reduction of 2,2-dimethyl-3-oxobutyrate (**101**) (Scheme 12) indicates that the catalyst is capable of reduction of the keto form of the substrate.[36,73] General consensus is that β-dicarbonyl compounds are reduced by Ru(BINAP) catalysts in the keto form; however, the possibility for more than one reduction mechanism may exist with these substrates.

A detailed ^{31}P and ^{1}H NMR study shows that the catalytic reactitivity enhancement by the addition of a strong acid. $[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$ (**21**), formed a single new, unidentified Ru(BINAP)-species that exhibits two doublets in the ^{31}P NMR upon acidification with methanesulfonic acid in CD_2Cl_2/MeOD. Addition of 8 psig hydrogen to the catalyst solution results in a complex mixture of Ru(BINAP)-species as indicated by ^{31}P NMR. Six broad hydride resonances are observed in the ^{1}H NMR. Addition of **39a** to this mixture shows an immediate disappearence of hydride resonances in the ^{1}H NMR. The disappearence takes 1 hour if the solvent is CD_2Cl_2. The ruthenium hydride formation is dependent upon the presence of an acid medium. The rate determining step in the catalytic cycle for the reduction of β-keto esters is hydrogen activation of Ru(BINAP) catalyst precursors.[51] The main body of data listed in the Tables also suggests that the hydrogen activation is highly dependent on temperature. Catalytic activity usually increases with temperature without loss of enantioselectivity. As many of the Ru(BINAP) compounds give rise to the same active catalytic species, a multitude of parameters can be invoked to account for the observed variations.

A mechanism for the asymmetric reduction of acetylacetone (Scheme 13) has been proposed and may be extended to the reduction of β-keto esters.[84] The study focused on the mononuclear complex $RuCl_2(PPh_3)$(BIPHEMP) (**102**), while several Ru(BINAP) and Ru(BIPHEMP) intermediates believed to be involved in the catalytic cycle were synthesized and studied under hydrogenation conditions. The optimal hydrogen activation is achieved when the ruthenium catalyst contains two chloride ligands in the catalyst precursor. Also, the catalytic activity is hindered by the addition of PPh_3 (to **102**) and base (NEt_3), slightly enhanced to a limited extent by the addition of HCl (methanolic solutions), and not at all by chloride ions (*vida infra*).

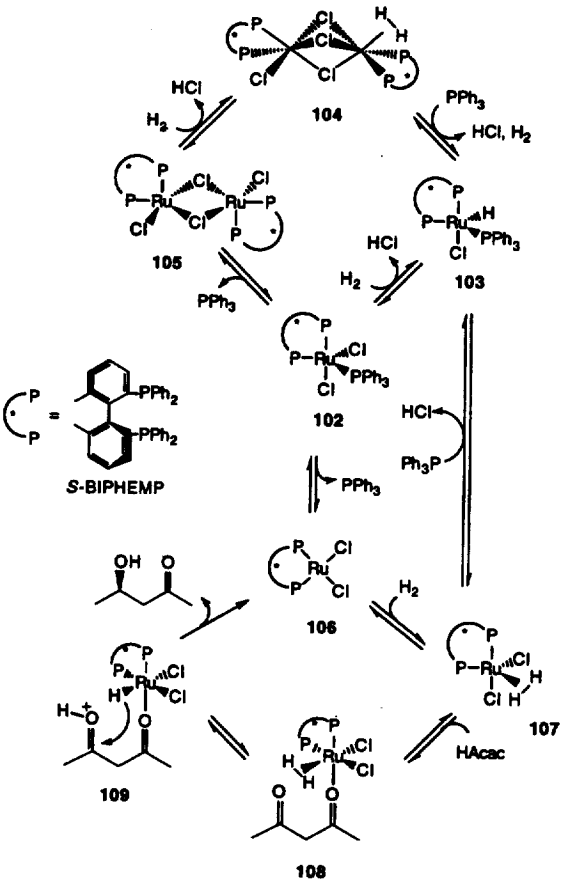
The proposed mechanism can be divided into two sections: the catalytic cycle (**106–109**), and nonproductive intermediates that have been observed in the reaction mixture (**102–105**).

The key species in the catalytic cycle is proposed as a mononuclear 14 electron, highly unsaturated [$RuCl_2$(BIPHEMP)] species, **106**, which would account for the rapid activation of hydrogen to form **107**. NMR studies of the hydrogenation mixture show that **103** and **104** are always present during the reaction and indicate that heterolytic splitting of hydrogen by **102** to give **103** is faster than the hydrogenation. This statement is contrary to observations made by King in the NMR study with β-keto esters where ruthenium hydride species immediately disappeared upon addition of substrate. The proposed mechanism for the reduction of acetylacetonate is not conclusive without detailed kinetic studies.

6. Examples in synthesis

There are a number of examples of syntheses that rely on the asymmetric hydrogenation of 1,3-dicarbonyl systems to establish stereogenic centres within the target molecule.

The preparation of carnitine has already been discusses through the reduction of **66g** (Table 6; entries 40–41).[41] This vitamin is also accessible through reduction of the δ-chloro compound and subsequent displacement.[66]

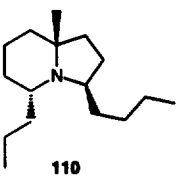


Scheme 13.

In the synthesis of statine, the control of the catalyst bonding to the ester group in the substrate **71b** far outweighs the effect of the γ-stereogenic center (Scheme 3) (Table 6; entry 43).[69]

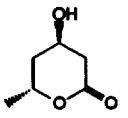
β-Lactam antibiotics are accessible by the reduction of the α-(2-amidomethyl) β-keto esters (**91g**), followed by cyclization and oxidation.[52,85]

The reduction of **39c** with catalyst prepared from the *in situ* combination of BINAP with $Ru(COD)Cl_2$ in the presence of triethylamine has been used in a synthesis of (−)-indolizidine 223AB (**110**).[46]

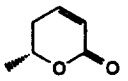


110

A key building block for the synthesis of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors is the hydroxy lactone **111**, that, in turn, can be prepared from the unsaturated lactone **112** (*cf.* Scheme 5).[39,86–91]

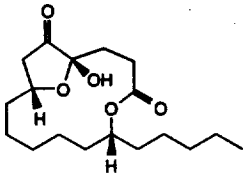


111



112

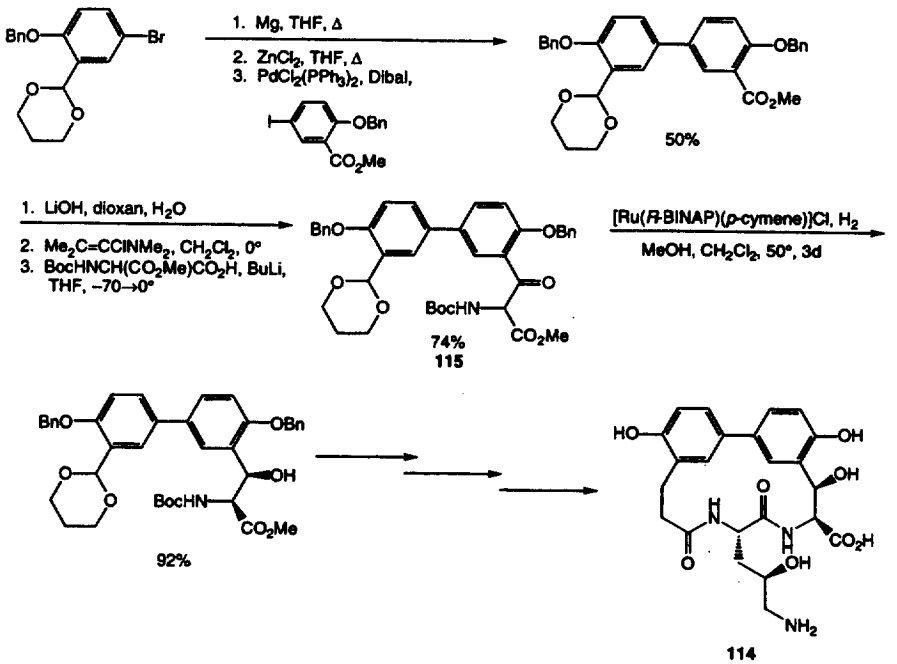
As part of a synthesis of the spore germination autoinhibitor gleosporone (**113**), which also corrected the original structural assignment, a comparison of an asymmetric hydrogenation of the unsaturated keto ester **39o** to a baker's yeast reduction showed that the β-hydroxy ester was formed in higher yield (92%, 98% ee) by the chemical method as opposed to the biochemical conditions (45%, 75% ee) (*cf.* Scheme 2). However, the latter did not reduce the isolated alkene.[65]



113

Reduction of the keto ester **66g** provided the β-hydroxy ester **67g** (*cf.* Scheme 2), whose stereogenic center was used to set up four new stereocenters in the C_{20}–C_{34} fragment in a convergent synthesis of the natural product FK 506 which inhibits T-cell activation genes.[68,92]

In a synthesis of the cyclopeptide antibiotic, biphenomycin A (**114**), two of the stereogenic centers are derived from the reduction of an α-amino-β-ketoester (**115**) (Scheme 14).[93]



Scheme 14.

7. Conclusion

The versatility of ruthenium catalysts that contain atropisomeric bisphosphines in the reduction of various prochiral substrates are well known. Ru(BINAP) catalysts, which are prepared by various

methods, display various reactivities and enantioselectivities in the reduction of β-keto esters. The slight differences in all the catalysts discussed in the reduction of β-keto esters may be the result of the formation of metal clusters and oligomers similar to **105**, as evident by complex ^{31}P NMR resonances, and appear to be consistent with the basis of the proposed mechanism for the reduction of acetylacetone. The optimal catalysts for the reduction of β-keto esters contain two halogens. Also, involvement of reactants, such as MeCN, NEt_3, etc., in each catalyst preparation may shift the equilibrium of Ru(BINAP) catalyst to unreactive Ru(BINAP) species. The pH of the reaction mixture is critical; residual base in the reaction mixture can result in the formation of unreactive Ru(enolato)(BINAP) species. Acidification by HX or DOWEX-50 can eliminate inhibitions caused by base impurities and re-establish original reaction rates. The affect of the counteranion or countercation in Ru(BINAP)-catalyzed reductions is not understood. In the [RuX(arene)(bisphosphine)]X series, coordination of the halide counterion in the catalytic cycle may possibly aid the reactivity and enantioselectivity during the reduction of β-keto esters.

β-Keto esters with γ-functionality can affect the enantioselectivities of the catalyst by competitive ligation of the ruthenium metal center with either the ester carbonyl oxygen or by the γ-functionality. Ru(BINAP) catalysts generally prefer coordination to the ester moiety.

β-Keto esters that contain labile stereogenic centers in the α-position are capable of dynamic kinetic resolution—the preferential formation of a single diastereoisomer amongst four possible diastereoisomers. In general, Ru(bisphosphine) catalysts that contain halogens are very efficient in the dynamic resolution of β-keto esters with epimerizable α-substituents, such as functionalized or cyclic alkyls, amides, halides, and lactones, but the highest diastereoselectivities are obtained in the reduction of these β-keto esters with [RuI(*p*-cymene)(bisphosphine)]I catalysts.

The general approach has been used to introduce stereogenic centers in a number of syntheses. As the methodology is amenable to scale up, coupled with our expanding understanding of the parameters that determine the stereochemical outcome of the reaction, the usage of this methodology should continue to grow.

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